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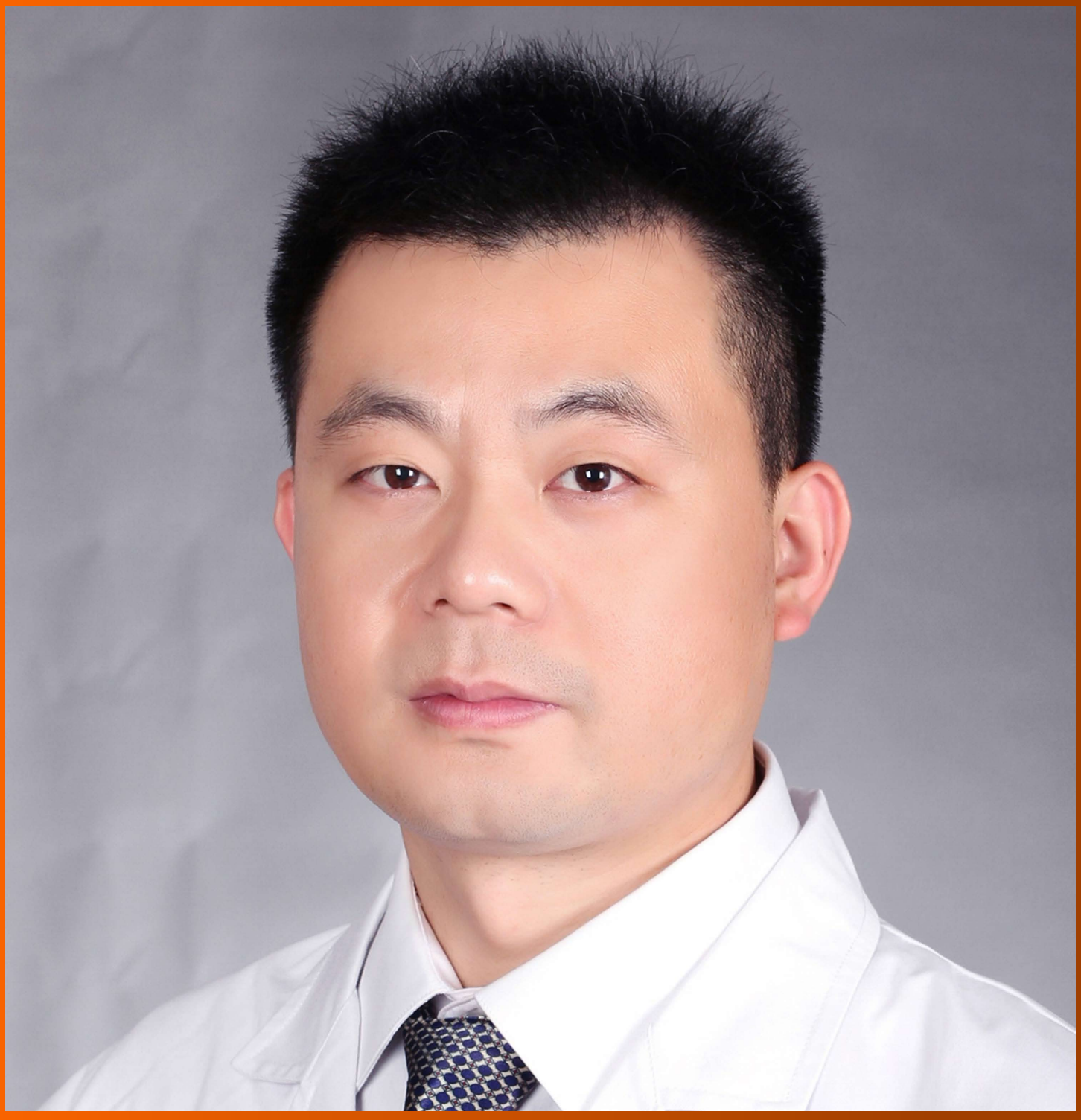

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AIM AND SCOPE

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ORIGINAL ARTICLE

Basic Study

Inverse correlation between CD8$^+$ inflammatory cells and E-cadherin expression in gallbladder cancer: Tissue microarray and imaging analysis

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Abstract

AIM

To investigated the association between the tumor cells' expression of E-cadherin and the numbers of several types of inflammatory cells infiltrating into the invasive portion of gallbladder cancer (GBC).

METHODS

We analyzed 50 GBC cases for which a sufficient amount of tumor tissues for tissue microarray (TMA) had been saved. Three tissue cores (3.0 mm) of invasive lesion from each case were used for the TMA. The 4-μm cut sections on slides were immunostained using primary antibodies including E-cadherin for cancer cells, leukocyte common antigen for leukocyte, myeloperoxidase for neutrophils, CD3 for T cells, CD4 for helper T cells, CD8 for killer T cells, CD20 for B cells and CD68 for macrophages. The immunostained slides were digitally analyzed by imaging analysis software.

RESULTS

A significant inverse correlation between the number of infiltrating CD8$^+$ cells at invasive areas and the expression of E-cadherin by cancer cells was observed (P = 0.0001), although the degree of this correlation was relatively weak (R = 0.32). The number of CD8$^+$ cells and the cancer cells' E-cadherin expression were also significantly correlated with tumor differentiation (well-differentiated *vs* poorly differentiated) (P = 0.0467 and P = 0.0294, respectively). Inverse correlation of T-stage

and the number of CD8$^+$ cell infiltration was observed with statistical significance in comparison of T2 and T3 cases (P = 0.0324).

CONCLUSION

Our findings indicate an inverse correlation of CD8$^+$ T cell infiltration and cancer cells' E-cadherin expression at invasive areas of GBC. Further analyses are essential to test these findings.

Key words: E-cadherin; Inflammation; CD8; Gallbladder cancer; Tissue microarray

Core tip: We analyzed the association between the expression of E-cadherin in tumor cells and the type and amount of inflammatory cells infiltrating into the invasive portion of gallbladder cancer, using tissue microarray and imaging analyses. The results indicated an inverse correlation of CD8$^+$ T cell infiltration and E-cadherin expression by cancer cells at invasive areas of gallbladder cancer. Further analyses are essential to test these results.

Kai K, Masuda M, Aishima S. Inverse correlation between CD8$^+$ inflammatory cells and E-cadherin expression in gallbladder cancer: Tissue microarray and imaging analysis. *World J Clin Cases* 2017; 5(1): 1-8 Available from: URL: http://www.wjgnet.com/2307-8960/full/v5/i1/1.htm DOI: http://dx.doi.org/10.12998/wjcc.v5.i1.1

INTRODUCTION

Gallbladder cancer (GBC) often shows the dedifferentiation or clustering of tumor cells (tumor budding) at the areas of infiltration, and a high degree of inflammatory response usually accompanies these findings[1]. Dedifferentiation is often associated with increased aggressiveness of a tumor. Although genetic heterogeneity, genome instability and epithelial-mesenchymal transition are considered mechanisms of dedifferentiation, the mechanism of dedifferentiation has not been established[2,3]. The concept of tumor budding was first established in colorectal cancer and was considered to be associated with the initial phase of tumor invasion and then with metastatic activity and prognostic outcome in various types of solid tumors[1,4,5], but the mechanism underlying tumor budding has not been clearly demonstrated.

Cell-cell adhesion participates in histogenesis and the maintenance of cell polarity and tissue structure. It has long been known that the mutual adhesiveness of cancer cells is significantly weaker than that of the corresponding normal cells[6,7]. Reduced cell-cell adhesiveness allows cancer cells to destruct of the histological structure of tumor tissue, resulting in the dedifferentiation of the tumor. E-cadherin is a well-known cell adhesion molecule composed of a series of components, each comprised of approximately 110 amino acid residues. E-cadherin forms a complex with three cytoplasmic proteins (alpha-, beta- and gamma-catenins), and the E-cadherin-catenin complex plays a key role in cellular adhesion; the loss of this function has been associated with tumor dedifferentiation and metastasis[8].

The microenvironment of cancer changes dramatically in relation to invasion into the stroma due to the changes of blood flow, metabolism and the direct interaction of inflammatory cells. We speculated that the type or amount of inflammatory cells that infiltrate into invasive areas may play some roles in the loss of E-cadherin function, and that tumor-infiltrating inflammatory cells thus contribute to the dedifferentiation of GBC. The purpose of this study was to determine the association between the expression of E-cadherin in tumor cells and the type and amount of inflammatory cells infiltrating into the invasive portion of GBC.

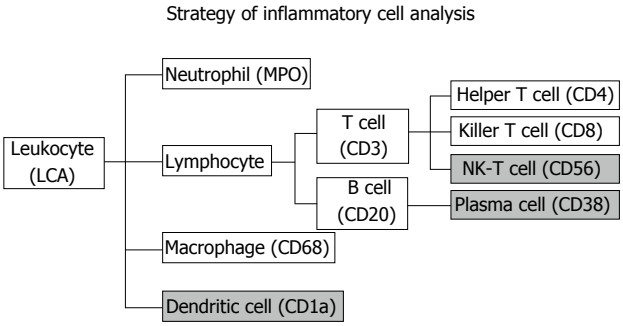

Figure 1 The inflammatory cell analysis strategy. Gray filled shows items which was not able to analyze by Tissue studio (because of positive stain of tumor cells). LCA: Leukocyte common antigen; MPO: Myeloperoxidase.

MATERIALS AND METHODS

Patients and tissue microarray preparation

We selected a total of 50 GBC cases for which a sufficient amount of formalin-fixed, paraffin-embedded tumor tissues for tissue microarray (TMA) had been saved from resection of the primary lesion at Saga University Hospital between 1994 and December 2010. Three tissue cores (3.0 mm) of the invasive lesion from each case were used for the TMA. Written informed consent for the use of resected tissue and clinical information was obtained from all patients, and the study protocol was approved by the Ethics Committee of the Faculty of Medicine at Saga University (approval No. 27-19). Clinical and histopathological staging were based on the TNM Classification of Malignant Tumors by the International Union against Cancer (7th edition)[9].

The inflammatory cell analysis strategy and immunohistochemical stains

The inflammatory cell analysis strategy is summarized in Figure 1. The labels that were initially considered for inflammatory cells were as follows: Leukocyte common antigen (LCA) for leukocytes, myeloperoxidase (MPO) for

Table 1 The primary antibodies used for immunohistochemistry

Antibody	Dilution	Clone	Manufacturer
LCA	Prediluted	PD7/26, 2B11	Nichirei Biosciences, Tokyo
MPO	1:200	Polyclonal	DakoCytomation, Glostrup, Denmark
CD3	Prediluted	PS1	Nichirei Biosciences
CD4	Prediluted	4B12	Nichirei Biosciences
CD8	1:50	C8/144B	DakoCytomation
CD20	1:50	L26	DakoCytomation

LCA: Leukocyte common antigen; MPO: Myeloperoxidase.

neutrophils, CD3 for T cells, CD4 for helper T cells, CD8 for killer T cells, CD56 for natural killer T cells, CD20 for B cells, CD38 for plasma cells, CD68 for macrophages and CD1a for dendritic cells. Among them, CD56, CD38 and CD1a were excluded from the analysis because the imaging analysis software could not accurately detect inflammatory cells due to positive staining of the tumor cells. The primary antibodies used are summarized in Table 1. The 4-μm cut sections on slides were heated in EDTA (pH 9.0) by a microwave for antigen retrieval. The Envision+® System (Dako Cytomation, Glostrup, Denmark) was used as the secondary antibody. The slides were visualized by diaminobenzidine tetrahydrochloride, and nuclei were counterstained with hematoxylin. An Autostainer plus® automatic stainer (Dako Cytomation) was used for staining.

Imaging analysis

Immunostained tissue microarray slides were digitally scanned by the NanoZoomer 2.0-HT digital slide scanner (Hamamatsu Photonics, Hamamatsu, Japan) with 20 × magnification for the imaging analysis. The numbers of positively stained inflammatory cells were automatically counted by the imaging analysis software, Tissue Studio (Definiens, München, Germany) (Figure 2). The membranous expression of E-cadherin was assessed by the histological score that was automatically calculated by Tissue Studio (Figure 3). Tissue Studio digitally evaluated the membranous expression of E-cadherin and categorized the expression into three grades (high, medium and low), and the histological score was calculated by the following formula: 1 × %Low + 2 × %Medium + 3 × %High.

Statistical analysis

We used JMP ver. 12 software (SAS Institute, Cary, NC, United States) for all statistical analyses. The comparisons of two groups were performed using a simple linear regression analysis, and each pair was analyzed using Student's *t*-test as appropriate. Probability values < 0.05 were considered significant.

RESULTS

The population of inflammatory cells at the invasive sites of GBC

The numbers of inflammatory cells per TMA core are summarized in Table 2. Many acute inflammatory cells such as MPO$^+$ neutrophils and CD68$^+$ macrophages (average numbers/core were 2692.39 and 2452.99, respectively) were infiltrated into invasive sites of the GBCs. Regarding the composition of infiltrating lymphocytes, CD8$^+$ killer T cells showed the largest number, followed by CD4$^+$ helper T cells; CD20$^+$ B cells were the least in number (avg. nos./core were 919.44, 583.01 and 467.95). All of the types of inflammatory cells showed a large standard deviation, indicating that the number and composition of inflammatory cells were quite different in each case.

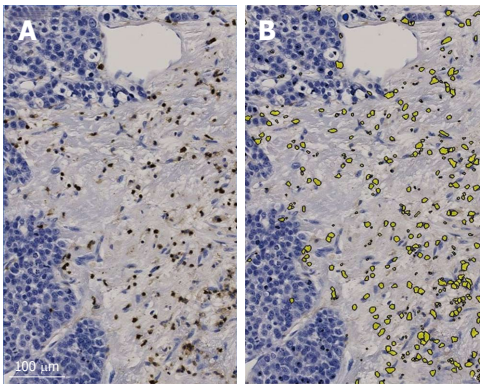

Figure 2 Images of CD8$^+$ lymphocytes. A: Original image of CD8-immunostained slide of an invasive area; B: The software Tissue Studio detects the positive cells and counts them automatically.

Correlation between E-cadherin expression and the type of inflammatory cells

The results of our single linear regression analysis between E-cadherin expression and the type of inflammatory cells are summarized in Table 3. The immunohistochemical markers of inflammatory cells that were shown to be significantly correlated with the expression of E-cadherin were LCA ($P = 0.0482$), CD3 ($P = 0.011$) and CD8 ($P = 0.0001$). The linear regression models of these factors are demonstrated in Figure 4. An inverse correlation between the number of CD8$^+$ cells and the expression of E-cadherin was observed, but the degree of this correlation was relatively weak (R = 0.32).

Clinicopathological data and correlations with pathologically assessed differentiation

The clinicopathological data, number of CD8$^+$ cells (means of analyzable cores in each case) and E-cadherin histological score (means of analyzable cores in each cases) of the 50 GBC cases are presented in Table 4. The numbers of cases in which the pathologically assessed differentiation of invasive front was observed were as follows. G1 (well-differentiated), 16 cases (32.0%); G2 (moderately differentiated), 19 cases (38.0%); G3 (poorly differentiated), 15 cases (30.0%). The median ± SD of CD8$^+$ cells was 580.0 ± 1154.5, and the E-cadherin histological score was 114.3 ± 37.8.

Figure 5 illustrates the correlations of pathologically assessed differentiation with the number of infiltrating

Table 2 The numbers of inflammatory cells per tissue microarray core

	Maximun positive cell counts/core	Minimun positive cell counts/core	Average/core	Standard deviation/core	No. of analyzable cores
LCA	13962	73	3108.27	2734.79	136
MPO	10911	388	2692.39	1830.47	131
CD3	14702	74	1967.06	2058.45	130
CD4	6583	0	583.01	934.52	134
CD8	5572	10	919.44	1034.35	131
CD20	7097	4	467.95	834.74	133
CD68	11355	97	2452.99	2043.92	135

LCA: Leukocyte common antigen; MPO: Myeloperoxidase.

Table 3 Single linear regression analysis of the relationship between E-cadherin expression and the type of inflammatory cells

Cells	Regression equation	Adjusted R^2	R	Standard error	*P*-value
LCA	EHS = 117.67879 − 0.0029223 × LCA	0.0216	0.15	46.5793	0.0482
CD20	EHS = 112.37344 − 0.0083497 × CD20	0.0153	0.12	45.8466	0.083
CD3	EHS = 119.86794 − 0.0050479 × CD3	0.0421	0.21	45.7107	0.011
CD4	EHS = 109.63264 − 0.0003939 × CD4	< 0.0001	n/a	47.1913	0.9285
CD8	EHS = 121.37735 − 0.0146326 × CD8	0.1011	0.32	43.6707	0.0001
MPO	EHS = 104.23773 + 0.0012811 × MPO	−0.00523	n/a	46.9647	0.5701
CD68	EHS = 113.83072 − 0.0023317 × CD68	0.0029	0.05	46.8666	0.2412

EHS: E-cadherin histological score; n/a: Not available; LCA: Leukocyte common antigen; MPO: Myeloperoxidase.

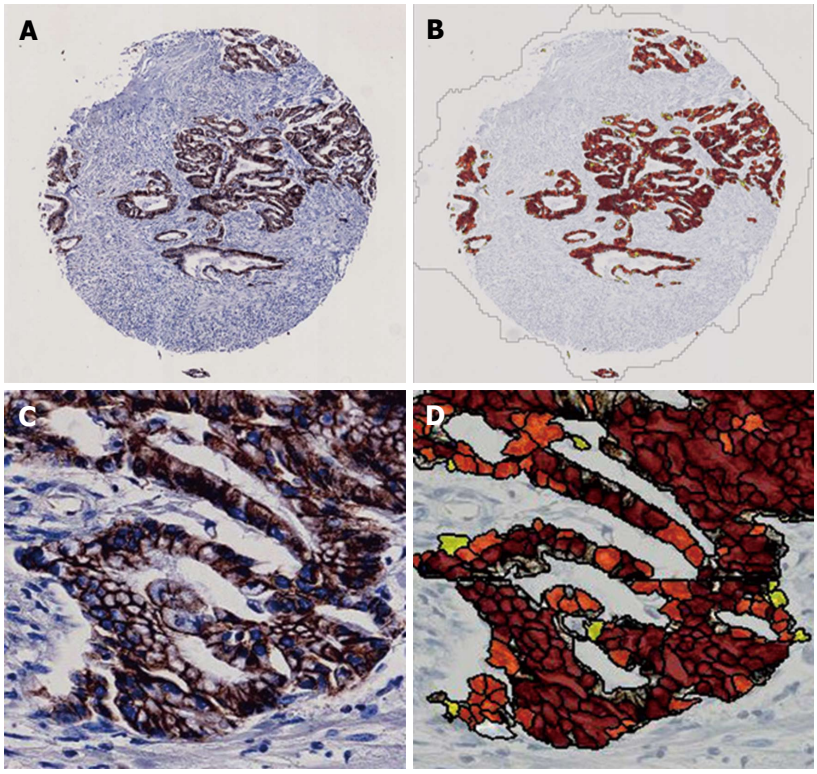

Figure 3 Images of E-cadherin expression in cancer cells. A: Low-magnification image of an E-cadherin-immunostained TMA core; B: Low-magnification image of E-cadherin-immunostained TMA core analyzed by Tissue Studio; C: High-magnification (× 400) image of an E-cadherin-immunostained TMA core; D: High-magnification (× 400) image of an E-cadherin-immunostained TMA core analyzed by Tissue Studio. The membranous expression of E-cadherin was assigned to three categories of the degree of expression: High (brown), medium (orange) and low (yellow). The histological score was calculated by the following formula: 1 × %Low + 2 × %Medium + 3 × %High. TMA: Tissue microarray.

CD8$^+$ cells in each case or with the E-cadherin histological score in each case, with each pair analyzed by Student's *t*-test. A significant difference was observed in the comparison of G1 and G3 cases according to the number of CD8$^+$ cells (P = 0.0467) and according to the E-cadherin histological score (P = 0.0294).

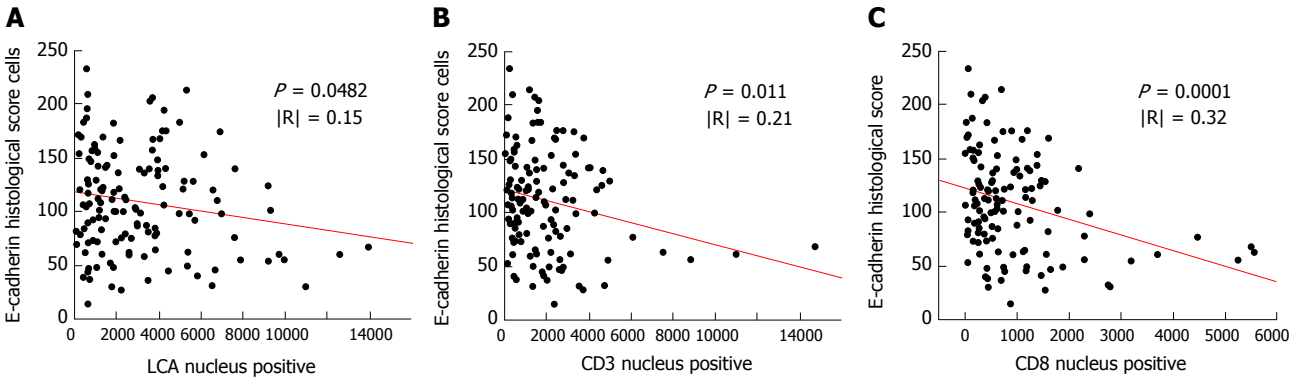

Figure 4 The single linear regression models of the relationship between E-cadherin expression (histological score) and the numbers of cells. The cells were positively immunostained by LCA (A), CD3 (B) and CD8 (C) antibodies.

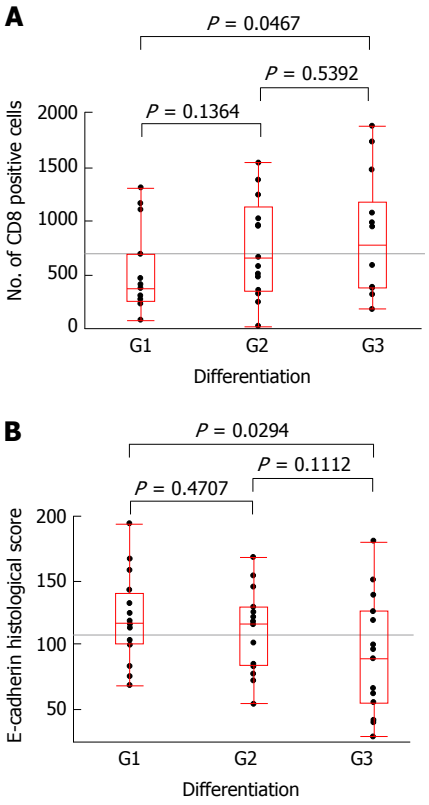

Figure 5 The box-and-whisker plots regarding pathologically assessed differentiation and the number of CD8$^+$ cells (A) and the E-cadherin histological score (B). Significant differences were observed in the comparison of G1 and G3 cases according to the number of CD8$^+$ cells (P = 0.0467) and according to the E-cadherin histological score (P = 0.0294), respectively.

Relationship between TMN-stage and E-cadherin expression or CD8$^+$ cell infiltration

No distant metastasis (M1) case was involved in this study. The mean ± SD of number of infiltrating CD8$^+$ cells with T2, T3 and T4 tumors were 1489.05 ± 1607.22, 747.33 ± 719.87 and 506.92 ± 336.37, respectively. The mean ± SD of E-cadherin histological score with T2, T3 and T4 tumors were 101.69 ± 37.90, 108.27 ± 37.04 and 133.75 ± 42.30, respectively. Figure 6 illustrates the correlations of T-stage with the E-cadherin histological score in each case or with the number of infiltrating CD8$^+$ cells in each case. A significant difference was observed in the comparison of T2 and T3 cases according to the number of CD8$^+$ cells (P = 0.0324).

Table 4 Clinicopathologic features of the patients with gallbladder cancer (n = 50) n (%)

Age	Mean ± SD	68.7 ± 8.4
Gender	Male	15 (30.0)
	Female	35 (70.0)
Differentiation of invasive front	G1	16 (32.0)
	G2	19 (38.0)
	G3	15 (30.0)
T-stage	T2	18 (36.0)
	T3	28 (56.0)
	T4	4 (8.0)
N	N0	17 (34.0)
	N1	33 (66.0)
No. of CD8-positive cells (means of analyzable cores in each case)	Median ± SD	580.0 ± 1154.5
E-cadherin histological score	Median ± SD	114.3 ± 37.8

The mean ± SD of number of infiltrating CD8$^+$ cells of N0 and N1 cases was 1109.10 ± 1618.16 and 936.39 ± 849.25, respectively. The mean ± SD of E-cadherin histological score of N0 and N1 cases was 117.73 ± 9.11 and 102.90 ± 6.54, respectively. Figure 7 illustrates the N-stage with the E-cadherin histological score in each case or with the number of infiltrating CD8$^+$ cells in each case. No significant difference was observed in each comparison.

DISCUSSION

This study analyzed the association between the expression of E-cadherin at tumor cells and inflammatory cells infiltrating into the invasive area of GBC, using the TMA technique and imaging analysis software. Our observation that relatively large numbers of acute inflammatory cells such as neutrophils and macrophages had infiltrated into invasive areas seems reasonable, since the gallbladder frequently develops acute inflammation manifested as acute cholecystitis. Although neutrophils have the potential for cell damage/destruction by the degranulation of their arsenal of cytotoxic chemicals

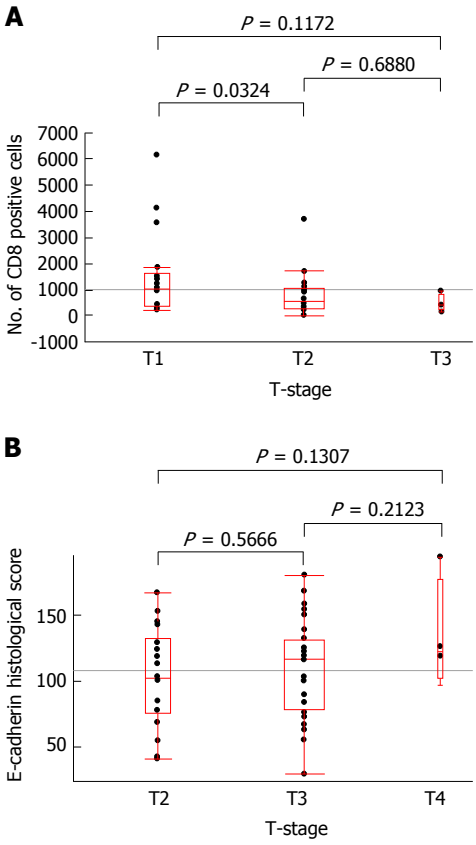

Figure 6 The box-and-whisker plots regarding T-stage and the number of CD8+ cells (A) and the E-cadherin histological score (B). A significant difference was observed in the comparison of T2 and T3 cases according to the number of CD8+ cells ($P = 0.0324$).

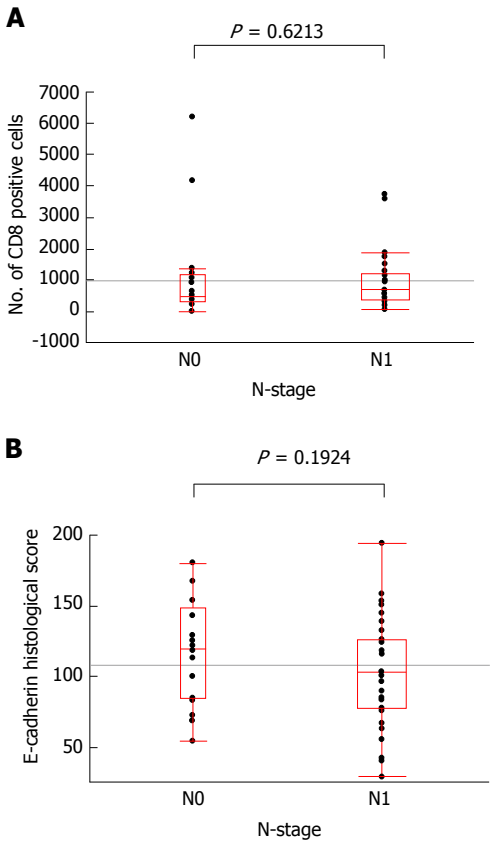

Figure 7 The box-and-whisker plots regarding N-stage and the number of CD8+ cells (A) and the E-cadherin histological score (B). No significant difference was observed in each comparison.

and enzymes[10], we observed no association between neutrophil infiltration and the E-cadherin expression of the tumor cells in this study.

Among the analyzed inflammatory cells, significant associations with E-cadherin expression by tumor cells were observed in the infiltration of leukocytes (LCA), T cells (CD3) and CD8+ T cells. In light of the degree of statistical correlation and theoretical considerations, we interpret our present findings as showing that CD8+ T cells are involved in the loss or attenuation of E-cadherin expression in GBC.

Generally, CD8+ T cells have been considered manifestations of host immune reactions against cancer cells, and favorable prognostic impacts of CD8+ T cells have been found in a wide variety of solid cancer tissues[11-18]. Regarding GBC, the prognostic impact of CD8+ T cell has been less investigated, and it remains controversial[19,20]. Herein we investigated the correlation between the invasion of CD8+ T cells or E-cadherin expression of tumor cells and the prognosis of GBC cases (disease free survival, overall survival and disease specific survival), and no significant relationship was found (data not shown).

It is interesting finding that the number of infiltrating CD8+ cells were significantly fewer in T3 cases than that of T2 cases. Although it is not statistically significant, the number of infiltrating CD8+ cells were fewer in T4 cases than that of T3 cases. Similar results, namely inverse correlation of T-stage and the density of CD8+ cell infiltration has been reported in colorectal cancer[21]. It is hypothesized that progressive decrease of CD8+ cell densities along with tumor invasion could indicate a progressive immune escape and the magnitude of the immune reaction at the early stage of the disease could be a major determinant for controlling the evolution of colorectal cancer[21].

Same as other sites of cancer, a reduced expression of E-cadherin by cancer cells compared to non-tumorous epithelium has been reported in GBC[22]. The major finding of the present study is the inverse correlation of CD8+ T-cell infiltration and E-cadherin expression by cancer cells. This result might be interpreted in the following two ways. The first interpretation is that the expression of E-cadherin by tumor cells is initially reduced by unknown causes, and then the tumor invaded stroma and CD8+ T-cell infiltration is an immune response to the invading tumor. If this is so, it gives rise to the hypothesis that the more reduced the E-cadherin expression of the tumor is, the greater the amount of CD8+ T cells attracted will be.

A second interpretation of the results of the present study is that infiltrating CD8+ T cells affects the reduced expression of E-cadherin. The mechanisms of the inactivation of the E-cadherin are: (1) a consequence of genetic alterations of E-cadherin; (2) genetic alterations of beta-catenin; and (3) a loss of the interaction of beta-catenin and E-cadherin due to the tyrosine phosphorylation

of beta-catenin[8]. If $CD8^+$ T cells reduce E-cadherin expression, the focus of investigation should be to determine whether $CD8^+$ T cells affect any or all of the above-described mechanisms for the inactivation of E-cadherin.

Either way, our results do not adequately establish the relationship between $CD8^+$ T cell and E-cadherin expression. It also remains in doubt whether the results of a TMA analysis truly reflect the status of the entire tumor. In addition, the microenvironment of a tumor is not composed of only inflammatory cells but also extracellular matrix and surrounding blood vessels; a degree of hypoxia and tumor-associated fibroblasts also contribute to the tumor microenvironment and interact with each other in a complex manner. We found no study in the English literature that provides evidence that the loss of E-cadherin expression promotes $CD8^+$ T-cell infiltration, or evidence that $CD8^+$ T cells reduce the E-cadherin expression in cancer cells, which would support our results. Therefore, a prudent validation by different research methods is essential to establish the correlation between $CD8^+$ T cells and E-cadherin expression in cancer cells.

In conclusion, the results of the present study indicate an inverse correlation of $CD8^+$ T-cell infiltration and E-cadherin expression by cancer cells at invasive areas of GBC. However, our data are not enough to establish the above interaction, and further experimental and clinicopathological analyses are needed to test our results.

COMMENTS

Background

Gallbladder cancer (GBC) often shows the dedifferentiation or clustering of tumor cells at the areas of infiltration. The author speculated that the type or amount of inflammatory cells that infiltrate into invasive areas of GBC may play some roles in the loss of E-cadherin function, and that tumor-infiltrating inflammatory cells thus contribute to the dedifferentiation of GBC.

Research frontiers

This study quantitatively assessed the type and amount of inflammatory cells infiltrating into invasive front of GBC using tissue microarray technique and latest imaging analysis software.

Innovations and breakthroughs

The results of present study indicate an inverse correlation of $CD8^+$ T cell infiltration and cancer cells' E-cadherin expression at invasive areas of GBC. No previous study in the English literature provides evidence that the loss of E-cadherin expression promotes $CD8^+$ T cell infiltration, or evidence that $CD8^+$ T cells reduce the E-cadherin expression in cancer cells. Their results also indicate the inverse correlation of T-stage and the number of $CD8^+$ T cell infiltration.

Applications

The goal of the study is to clarify the correlation of $CD8^+$ T cell infiltration and E-cadherin expression of cancer cells. These results would be applicable to clarify the mechanism of dedifferentiation and metastasis of cancer. However, further analyses are essential for conclusive result for the correlation of $CD8^+$ T cell infiltration and E-cadherin expression of cancer cells.

Terminology

E-cadherin is a well-known cell adhesion molecule and the E-cadherin-catenin complex plays a key role in cellular adhesion; the loss of this function has been associated with tumor dedifferentiation and metastasis. A $CD8^+$ T cell was known as cytotoxic T cell or killer T cell that kills cancer cells, cells that are infected (particularly with viruses), or cells that are damaged in other ways.

Peer-review

This study investigates the association between the expression of E-cadherin and the numbers of several types of inflammatory cells infiltrating into the invasive portion of GBC.

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CASE REPORT

Cardiac papillary fibroelastoma: The need for a timely diagnosis

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Author contributions: Yandrapalli S, Mehta B, Mondal P, Gupta T and Goldberg R identified the cases, collected patient data, and drafted a preliminary report; Khattar P and Fallon J were involved in the pathological diagnoses, provided histopathological slides and provided guidance regarding the pathological aspects of the condition; Sule S and Aronow WS reviewed the paper and made critical changes.

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Abstract

Cardiac papillary fibroelastomas (CPFs) are the second most common primary cardiac tumors and the most common cardiac valvular tumors. Although they are histologically benign and usually asymptomatic, CPFs can lead to serious and life-threatening complications like myocardial infarction, stroke, pulmonary embolus, cardiac arrest etc. CPFs represent a rare entity in clinical medicine and literature regarding their management is limited. We report two cases which illustrate such complications arising from undiagnosed CPFs on the aortic valve. We further stress on the importance of identifying CPFs early so that they can be managed appropriately based on recommendations from the available literature.

Key words: Lambl's excrescences; Aortic valve; Cardiac tumors; Cardiac papillary fibroelastoma; Sudden cardiac death

Core tip: The cases illustrate serious complications that can arise from an undiagnosed cardiac papillary fibroelastoma. The importance of continued investigation

with a transesophageal echo when there is high clinical suspicion is explained. Current management strategies have been outlined based on available literature.

Yandrapalli S, Mehta B, Mondal P, Gupta T, Khattar P, Fallon J, Goldberg R, Sule S, Aronow WS. Cardiac papillary fibroelastoma: The need for a timely diagnosis. *World J Clin Cases* 2017; 5(1): 9-13 Available from: URL: http://www.wjgnet.com/2307-8960/full/v5/i1/9.htm DOI: http://dx.doi.org/10.12998/wjcc.v5.i1.9

INTRODUCTION

Primary cardiac tumors are rare and have a very low prevalence of based on 22 large autopsy studies[1]. Cardiac papillary fibroelastomas (CPFs) are the second common primary cardiac tumors[2]. For decades, CPFs were thought to be asymptomatic and incidental autopsy findings. However, in the past two decades they have gained importance as they have the potential to cause fatal and life-threatening complications. They represent a rare entity in clinical medicine and literature regarding their management is limited. We report two cases of CPFs presenting with cardiovascular and neurological complications and outline the importance of having a clinical suspicion for these tumors, in an effort to prevent further serious complications.

CASE REPORT

Case 1

A 64-year-old man was transferred to our institution for further management of congestive heart failure, acute kidney injury and lower gastrointestinal bleeding. He initially presented to the other institution with worsening dyspnea and orthopnea. His medical history was significant for hypertension, congestive heart failure, and non-ST elevation myocardial infarction (NSTEMI). Prior coronary angiography was significant for non-obstructive coronary artery disease (CAD). At the other institution, a chest roentgenogram showed moderately large right-sided effusion. Transthoracic echocardiography (TTE) showed moderately reduced left ventricular systolic function with an ejection fraction of 35%-40% and severely reduced right ventricular systolic function. A diagnosis of acute decompensated heart failure was made and he was started on intravenous furosemide. Hospital course was complicated by acute kidney injury and lower gastrointestinal bleeding. The patient refused blood product transfusion as he was a Jehovah's Witness. He did not improve clinically and was transferred to our institution. At the time of transfer to our institution, his hemoglobin was 6.3 g/dL and blood pressure was 90/40 mmHg. In our institution, ECG did not reveal ischemic changes, troponin I was elevated at 1.10 ng/mL, and brain natriuretic peptide level was elevated at 533 pg/mL.

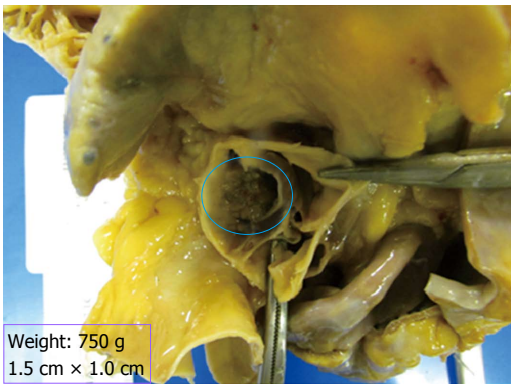

Figure 1 Autopsy specimen of the heart demonstrating a cardiac papillary fibroelastoma on the aortic valve. Note the large bulky tan-white non-encapsulated, rubbery, firm lesion with short pedicle and multiple papillary fronds on the aortic valve measuring 1.5 cm × 1.0 cm in size, completely occluding the right coronary ostium (blue circle).

He was admitted to the medical intensive care unit for further management. Approximately 4 h after admission he developed severe hypotension which rapidly progressed to cardiac arrest with asystole. Despite resuscitative measures, patient expired.

Autopsy showed cardiomegaly (750 g), old inferior wall infarct and healing acute right ventricular myocardial infarct. There was a large bulky tan-white non-encapsulated, rubbery, firm lesion with short pedicle and multiple papillary fronds on the aortic valve measuring 1.5 cm × 1.0 cm in size, completely occluding the right coronary ostium (Figure 1). Histological section of the mass shows benign papillary lesion comprised of a single layer of endocardial cells overlies a thin layer of mucopolysaccharide matrix and underlying, almost acellular, avascular stroma composed predominantly of elastic fibers. Elastin stain reveals concentric elastin fibres within the papillary excrescences (Figure 2). Immunohistochemical stains reveal lining endothelial cells are positive for S100, CD34 and Factor Ⅷ. Coronary artery atherosclerosis of the left anterior descending artery (10%-20% occlusion), the left circumflex artery (10%-20%), and the right coronary artery (20%-30% occlusion) was seen. Coronary emboli were not noted. Based on the autopsy findings, the immediate cause of death was acute myocardial infarction secondary to papillary giant fibroelastoma of aortic valve completely occluding the right coronary ostium.

Case 2

A 53-year-old female with a history of diabetes mellitus and NSTEMI presented with sudden onset tingling and numbness on her left side of her face, mouth, upper and lower extremities. Symptoms resolved spontaneously in one hour with no sequelae. Computed tomography (CT) scan of the head and CT angiography of cerebral and carotid arteries were unremarkable. Magnetic resonance imaging of the brain did not show signs of acute infarction. Based on these findings, she was diagnosed

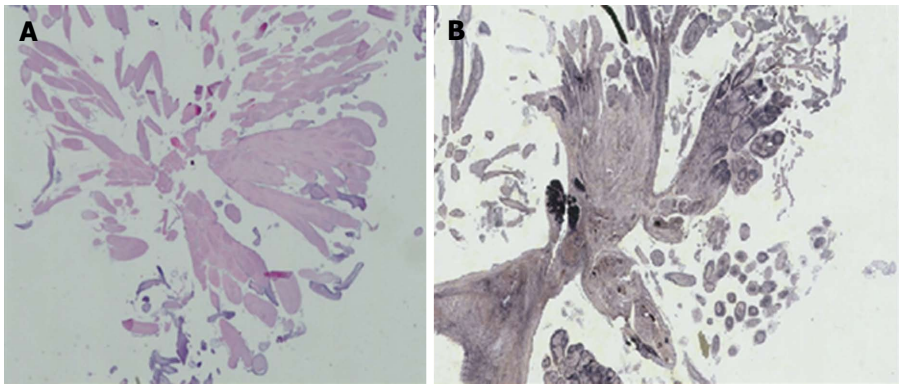

Figure 2 Microscopic photograph of the cardiac papillary fibroelastoma. A: Histological section of the mass shows benign papillary lesion comprised of a single layer of endocardial cells overlies a thin layer of mucopolysaccharide matrix and underlying, almost acellular, avascular stroma composed predominantly of elastic fibers; B: Elastin stain reveals concentric elastin fibres within the papillary excrescences.

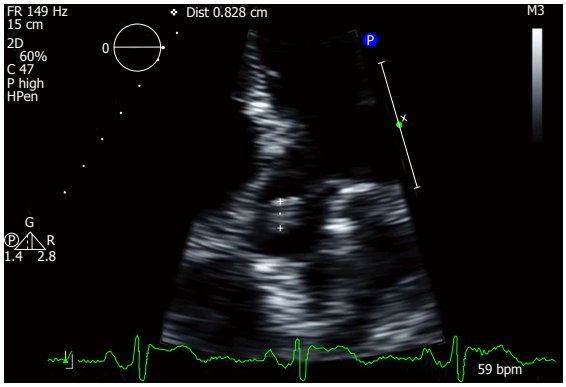

Figure 3 Transthoracic echocardiogram showing a cardiac papillary fibroelastoma on the aortic valve (marked).

with a transient ischemic attack (TIA). Further stroke workup with a TTE showed a mobile mass on the aortic valve (Figure 3) which was later confirmed by a transesophageal echocardiography (TEE). A mobile, pedunculated, 1.2 cm round mass on the aortic side of the non-coronary cusp of a tri-leaflet aortic valve was seen in the TEE, with an appearance most consistent with a fibroelastoma. She was afebrile and blood cultures were negative, ruling out endocarditis. Attributing the TIA symptoms to embolization from the fibroelastoma, she was referred for surgical removal. Pathological exam of the resected mass confirmed a fibroelastoma. She was discharged and remained symptom free.

DISCUSSION

The first case illustrates a fatal outcome associated with an undiagnosed CPF, and the second case illustrates the benefit of early detection of a CPF to prevent further complications.

Primary cardiac tumors are very rare and have an approximate prevalence of 0.02% based on autopsy studies[1]. Myxomas were reported to be the most common, and CPFs stand second[2]. Gowda *et al*[3] used the term "papillary fibroelastoma" for the first time in a case report of myocardial infarction in the absence of coronary atherosclerosis.

CPFs, the most common cardiac valvular tumors, are benign endocardial papillomas, with highest prevalence in the 6th to 8th decade of life[3,4]. CPFs are predominantly valvular with 80% arising from the valvular endocardium. The aortic valve is the most commonly involved with prevalence between 35% and 63%, followed by the mitral valve (9% to 35%), the tricuspid valve (6%-15%), and the pulmonary valve (0.5%-8%)[3-5]. In a large single center review of highly-selected referral population, CPF was more prevalent (0.089% of all echocardiograms) than cardiac myxoma[4]. The pathogenesis of CPF is unclear. Papillary fibroelastomas have been described as neoplasms, hamartomas, organizing thrombi, or post-traumatic tumors[6]. Some authors believe that CPFs represent gaint form of Lambl's excrescence, evolving from a thrombotic phenomenon due to traumatization of the endothelial cells at the level of the valves which have an increased pressure gradient[5]. Grossly, CPFs have a sea anemone appearance with a gelatinous surface and a stalk with multiple papillary projections[5]. Microscopically, CPFs are avascular and are composed of collagen, elastic, and reticulin[5].

Most patients with CPFs are asymptomatic and these are incidental findings during echocardiography, cardiac surgery, or autopsies[3]. However, the past three decades have witnessed reported cases with life-threatening cardiac and neurological symptoms, including TIA, angina, syncope, stroke, blindness, myocardial infarction and sudden death, heart failure, among many others. Cerebrovascular events are the most common presenting symptom in symptomatic patients[4]. In their meta-analysis of 725 CPF cases, Gowda *et al*[3] postulated that tumor mobility was the only independent predictor of CPF related death or nonfatal embolization. However, in the study by Tamin *et al*[4] echocardiographic characteristics of CPFs (size, location, and mobility) were not significantly associated with a cerebrovascular accident. CPFs can cause symptoms by embolization of either the tumor

fragments or a thrombus that has formed on the surface of the tumor. This mechanism can explain the TIA symptoms in our second case. Direct obstruction by the tumor mass resulting in acute myocardial infarction can also occur, as in our first case. Our first patient had a NSTEMI prior to this admission with non-obstructive CAD on prior cardiac catheterization. Autopsy revealed an old inferior wall infarct and non-obstructive CAD. These findings suggest that the aortic valve CPF was causing intermittent obstruction of the right coronary ostium resulting in recurrent myocardial infarction and subsequent heart failure.

The advent of higher-resolution imaging especially TEE facilitates rapid ante-mortem diagnosis in symptomatic patients. Currently, depending on symptoms and tumor mobility either surgical resection or anticoagulation/antiplatelet agents are offered to patients. Based on available data, surgical resection is strongly recommended in symptomatic patients to prevent further cardiovascular or embolic events[3,7]. This was the rationale for surgical resection of the CPF in our second patient. She had a mobile, pedunculated fibroelastoma on her aortic valve causing a TIA (Figure 3). Curative surgical resection was done to prevent further complications. In asymptomatic patients, there is a debate between anticoagulation *vs* surgical excision. Increased cerebrovascular accidents and mortality were observed in patients with echocardiographically suspected CPF who did not undergo surgical removal[4]. Ikegami *et al*[7] recommend surgical excision in asymptomatic patients with incidental CPF finding taking into account the friability, mobility and location of the CPF. Literature suggests that successful complete resection of CPF is curative with an excellent long-term prognosis and a lower stroke risk[3,4].

Given the potential to cause fatal outcomes and the availability of successful therapies, CPF should be a diagnostic consideration in elderly patients with myocardial infarction with normal coronaries or non-obstructive CAD after other potential causes of myocardial injury and other confounding diagnoses have been ruled out. Diagnostic evaluation begins with a TTE, but it is advisable to further evaluate with TEE when clinical suspicion for CPF is high, as TTE can miss a third of CPF's evident on a TEE[4]. It must be noted that the TTE of our first patient did not reveal a CPF. Surgical resection should be offered for symptomatic patients and also to asymptomatic patients with high risk CPFs. Close monitoring and follow-up is recommended if medical management is pursued. Randomized studies are needed to make valid recommendations as most of the available studies are single center experiences.

COMMENTS

Case characteristics

Case 1: A 64-year-old man with sudden cardiac arrest; Case 2: A 53-year-old female with sudden onset tingling and numbness on her left side of her face, mouth, upper and lower extremities.

Clinical diagnosis

Case 1: Acute myocardial infarction leading to sudden cardiac arrest; Case 2: Acute cerebrovascular event/transient ischemic attack (TIA).

Differential diagnosis

Case 1: Coronary thromboembolism from atherosclerosis, acute blood loss anemia causing cardiac demand ischemia, coronary occlusion secondary to vasculitis/arteritis, aortic dissection, with retrograde involvement of the coronary arteries, coronary artery emboli, secondary to cholesterol, air, or the products of sepsis, drugs (cocaine, *etc.*); Case 2: Endocarditis, cardiac myxoma, cardiac papillary fibroelastomas (CPFs), organized thrombus, valvular lipoma, *etc.*

Laboratory diagnosis

Case 1: Acute myocardial infarction; Case: All labs were within normal limits.

Imaging diagnosis

Case 2: Transthoracic echocardiography (TTE) showing a cardiac papillary fibroelastoma on the aortic valve.

Pathological diagnosis

CPF.

Treatment

Case 2: Complete surgical excision of the CPF.

Related reports

Traditionally though to be asymptomatic, the past three decades have witnessed reported cases of CPFs with life-threatening cardiac and neurological symptoms, including TIA, angina, syncope, stroke, blindness, myocardial infarction and sudden death, heart failure, among many others.

Term explanation

CPFs are benign endocardial papillomas and are the most common cardiac valvular tumors. They have the propensity to cause life-threatening cardiac and neurologic complications. Surgical resection should be considered in symptomatic patients and in asymptomatic patients with high risk feautures.

Experiences and lessons

TTE can miss a third of the CPFs. A transesophageal echocardiography should be considered when there is high clinical suspicion. Early detection is necessary to prevent life-threatening cardiac and neurologic complications. Surgical resection can be curative.

Peer-review

The paper is well written.

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CASE REPORT

Intra-abdominal abscess and intractable sinus - a rare late complication after splenectomy

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Author contributions: Both authors contributed to the acquisition of data, writing, and revision of this manuscript.

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Abstract

Intra-abdominal abscess and an intractable abdominal wall sinus forty years after splenectomy is rare, which has not been described previously in the surgical literature. We report the management of a patient who had presented with an intractable sinus on his left hypochondrium forty years after having undergone splenectomy and cholecystectomy, which persisted for more than two years despite repeated surgery and courses of antibiotics and compromised quality of life significantly from pain. A sinogram and computerised tomographic scan followed by exploration and laying open of the sinus delivered multiple silk sutures used for ligation of splenic pedicle, led to complete resolution of the sinus. It is important to avoid using non-absorbable silk sutures during splenectomy when splenectomy is undertaken in a contaminated field. Appropriate imaging and exploration is mandatory for its resolution.

Key words: Abscess; Intractable; Late presentation; Splenectomy; Sinus

Core tip: An intra-abdominal abscess and a sinus 40 years following splenectomy is rare, which should be investigated with a computerised tomographic scan and a sinogram and treated by exploration. Non-absorbable silk sutures, which act as nidus for bacteria, should be avoided if splenectomy is undertaken simultaneously with surgery on a hollow viscus.

Shrestha B, Hampton J. Intra-abdominal abscess and intractable sinus - a rare late complication after splenectomy. *World J Clin Cases* 2017; 5(1): 14-17 Available from: URL: http://www.wjgnet.com/2307-8960/full/v5/i1/14.htm DOI: http://dx.doi.

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INTRODUCTION

Splenectomy is performed for a wide range of medical conditions such as haematological disorders, portal hypertension and trauma, which can be attended by complications, principally infectious and thromboembolic[1]. Splenectomy is also performed in association with surgery of other abdominal viscera, particularly in multiply injured trauma victims, where contamination of abdominal cavity is present[2]. Chronic intra-abdominal sepsis can compromise the quality of life significantly and be challenging from diagnostic and treatment perspectives. We describe the management challenges posed by the late presentation of a patient with intra-abdominal abscess followed by an intractable abdominal wall sinus 40 years after splenectomy and review pertinent literature.

CASE REPORT

A 62-year-old male was referred to our general surgical clinic from the dermatology department for a second opinion and management of a persistently discharging sinus on the left hypochondrium of two years duration, which was associated with severe eczematous changes on the skin around the sinus, unresponsive to topical steroid creams. He experienced continuous pain in the left upper abdomen, which compromised his sleep and work, and was on regular diazepam 5 mg nocte, morphine sulphate solution 5-10 mg PRN, sustained-release morphine sulphate (Zomorph®) 10 mg 12 hourly and oral phenoxymethylpenicilln 250 mg twice daily.

Aged 19, he had undergone a cholecystectomy and splenectomy for gallstones and portal hypertension through an upper midline incision. Forty years after the surgery, he presented with a painful lump on his left hypochondrium with clinical features suggestive of an intra-abdominal abscess. The abscess, containing thick pus, was drained through a transverse subcostal incision. Although the operation record described that the omentum was herniating through a 1 cm diameter defect in the muscles, which was closed with interrupted 0 prolene sutures; in retrospect, the omentum was walling off the abscess, which was mistaken for an incisional hernia. After four weeks, a discharging sinus developed through the middle of the scar, which refused to heal despite debridement on three occasions, regular dressings and courses of flucloxacilln. Over the following two years, the pain and the sinus persisted and caused severe disability. Due to the extensive excoriation of the skin surrounding the sinus, he was referred to a dermatology clinic.

On examination, the skin around the sinus showed severe eczematous changes and the sinus was adherent to the left costal margin in the mid-axillary line the white blood cell count was 16 × 10^9/L and the C-reactive protein was 21 units/mL culture of the pus grew *Staphylococcus aureus* sensitive to flucloxacilln. A plain computerised tomographic (CT) scan showed a septated extraperitoneal collection in the left upper abdomen measuring 85 mm × 25 mm × 20 mm with adjacent inflammatory changes (Figure 1A). A sinogram delineated the tract under the ribs towards the upper quadrant. There was no communication with the bowel. A CT scan of the abdomen, following the sinogram, after the administration of oral water and intravenous contrast, showed the contrast in the cavity (5 cm × 15 cm in maximum axial dimensions) lying in the extraperitoneal space, which extended from the opening under lower edge of the rib cage to the under surface of the diaphragm cranially. The splenic flexure and the descending colon lay close to the cavity without communication between them (Figure 1B).

The sinus was explored under general anaesthesia. Using a 6 Fr feeding tube, methylene blue dye was injected into the cavity. Through a generous subcostal incision, the sinus tract was followed cranially keeping the dissection close to the rib cage and laid it fully open. The cavity contained thick pus and free-floating braided black silk sutures (15 in number), it was thoroughly curetted with a Volkmann's spoon and washed with copious amount of saline and hydrogen peroxide solution. The wound was closed in layers after inserting a 16 Fr Robinson's drain, which was removed after 7 d and the patient was discharged home. The specimens from the sinus contained multiple pieces of fibrous tissue, largest measuring 20 mm in maximum dimension. The histology of the sinus tract showed chronically inflamed fibrous tissue with no evidence of granulomatous inflammation or neoplastic disease. On a routine follow-up after three weeks, the wound has healed with no sign of recurrence of the sinus. The patient has stopped taking analgesia or tranquillizers. On a telephone enquiry two years following the surgery, he remained well, pain free and not on any drugs, with no signs of recurrence of sinus.

DISCUSSION

The spleen is crucial in regulating immune homoeostasis through its ability to link innate and adaptive immunity and in protecting against infections[3]. Asplenic patients have a lifelong risk of overwhelming post-splenectomy infection and have been reported to have low numbers of peripheral blood IgM memory B cells[4]. Immunisation and prophylactic antibiotics help preventing post-splenectomy opportunistic infections.

Presentation with an intra-abdominal abscess and a non-healing sinus, 40 years following splenectomy, is rare and unreported in the surgical literature. Surgical treatment of acute cholecystitis or appendicitis, is known to be associated with a higher risk of late abscess formation, due to retained stones in the abdominal cavity/wall or contamination of the wound at the time of surgery, respectively[5,6]. The differential diagnosis of a non-healing sinus includes tuberculosis, malignancy, presence

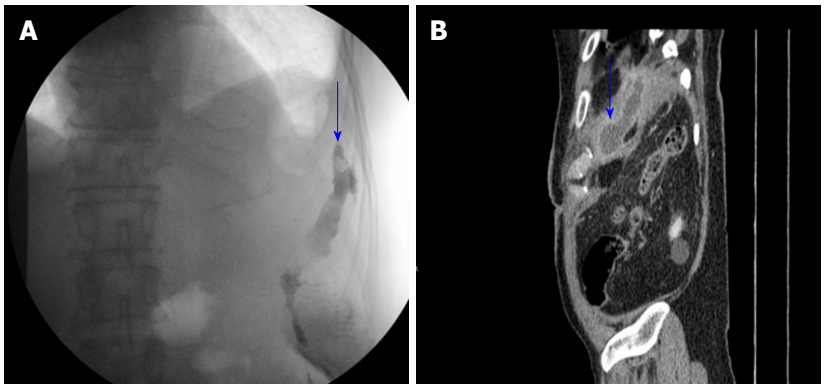

Figure 1 Contrast in the sinus tract extending up into the left upper quadrant (arrow) (A) and abscess cavity in the left upper quadrant (arrow) (B).

of foreign bodies and communication with abdominal organs to the skin surface. Moreover, mesh repair of an incisional or inguinal hernia, as well as the use of silk yarn in surgical sutures, are associated with late abscess formation. The silk acts as a foreign body and a nidus for latent infection, which can manifest with sinuses several years after the primary surgery as in our case[7].

Intra-abdominal abscesses can also occur due to injury to the stomach, pancreas or intestine during splenectomy, but the incidence reported is less than 1 percent and the presentation is usually early during the post-operative period[8,9]. Splenectomy performed for splenic abscess can present with intra-abdominal abscess due to contamination of peritoneal cavity and post-splenectomy immunosuppressed state[10]. Bacterial translocation is the invasion of indigenous intestinal bacteria through the gut mucosa to normally sterile tissues and internal organs, which could lead to delayed infection as in our case[11].

Our patient had undergone a splenectomy with ligation of the splenic vessels with silk sutures and a cholecystectomy in the same sitting. It is highly likely that contamination of the splenic bed containing silk sutures with the organisms present in the gall bladder had led to this delayed presentation with a splenic bed abscess and persistent sinus. Resolution of the sinus after removal of the infected silk sutures, emphasises the need for avoidance of using braided silk sutures during surgery, particularly, when splenectomy is performed together with resection of hollow abdominal viscera or when an immunosuppressed state is likely to follow, such as after splenectomy and organ transplantation. Utilisation of absorbable and non-braided sutures can potentially prevent this complication. Polyglactin 910 is considered to be the optimum suture in preventing the formation of adhesions and abscesses[12]. A sinogram and CT scan followed by early exploration, removal of the sutures and complete excision of the sinus tract through adequate surgical access are essential for a permanent cure and amelioration of prolonged suffering of the patient.

COMMENTS

Case characteristics

A 62-year-old man with history of undergoing splenectomy 40 years ago presented with presented with a 2-year history of a sinus following drainage of an intra-abdominal abscess, which refused to heal despite repeated surgical interventions.

Clinical diagnosis

A discharging sinus on the left hypochondrium with excoriation of skin.

Differential diagnosis

A chronic sinus due to tuberculosis, malignancy, presence of foreign body or a fistula communicating to intra-abdominal organs.

Laboratory diagnosis

There was leucocytosis and raised C-reactive protein. *Staphylococcus aureus* was isolated from the discharge emanating from the sinus.

Imaging diagnosis

A plain computerised tomographic (CT) scan showed a septated extraperitoneal collection in the left upper abdomen measuring 85 mm × 25 mm × 20 mm with adjacent inflammatory change. A sinogram delineated the tract under the ribs towards the upper quadrant. There was no communication with the bowel.

Pathological diagnosis

The histology of the sinus tract showed chronically inflamed fibrous tissue with no evidence of granulomatous inflammation or neoplastic disease.

Treatment

Exploration of the sinus, removal of retained silk sutures and curettage of the sinus led to complete healing.

Related reports

Intra-abdominal abscess and infections following use of non-absorbable sutures have been reported in the past. But a case like this presenting 40 years after having undergone splenectomy has not been reported in the past.

Experiences and lessons

The case emphasizes the need for appropriate investigations with a sinogram and CT imaging followed by early exploration of the sinus. Use of non-absorbable sutures should be avoided to prevent such complications.

Peer-review

This is a very rare case indeed. The case report is correctly structured, well written, the case is well and completely described. It is indeed useful as a case report for clinical practice.

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CASE REPORT

Local advanced rectal cancer perforation in the midst of preoperative chemoradiotherapy: A case report and literature review

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Author contributions: Yamashita K and Sumi Y operated on the patient and designed the report; Hasegawa H, Yamamoto M, Kanaji S, Matsuda Y, Matsuda T, Oshikiri T, Nakamura T and Suzuki S drafted the paper; Koma YI, Komatsu M, Sasaki R and Kakeji Y critically revised the paper with an important conceptual and editorial input.

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Abstract

Standard chemoradiotherapy (CRT) for local advanced rectal cancer (LARC) rarely induce rectal perforation. Here we report a rare case of rectal perforation in a patient with LARC in the midst of preoperative CRT. A 56-year-old male was conveyed to our hospital exhibiting general malaise. Colonoscopy and imaging tests resulted in a clinical diagnosis of LARC with direct invasion to adjacent organs and regional lymphadenopathy. Preoperative 5-fluorouracil-based CRT was started. At 25 d after the start of CRT, the patient developed a typical fever. Computed tomography revealed rectal

perforation, and he underwent emergency sigmoid colostomy. At 12 d after the surgery, the remaining CRT was completed according to the original plan. The histopathological findings after radical operation revealed a wide field of tumor necrosis and fibrosis without lymph node metastasis. We share this case as important evidence for the treatment of LARC perforation in the midst of preoperative CRT.

Key words: Local advanced rectal cancer; Preoperative chemoradiotherapy; Rectal perforation; 5-fluorouracil; Tumor necrosis

Core tip: Standard chemoradiotherapy (CRT) for local advanced rectal cancer (LARC) rarely induces rectal perforation. This case report presents a case of rectal perforation in a patient with LARC in the midst of 5-fluorouracil-based preoperative CRT. We decided to complete CRT according to the original plan after supporting emergency recovery. The histopathological findings after radical operation revealed a wide field of tumor necrosis and fibrosis without lymph node metastasis, suggesting the efficacy of the CRT. We believe that establishing a standard treatment for CRT-related LARC perforation may improve the prognosis of such cases.

Takase N, Yamashita K, Sumi Y, Hasegawa H, Yamamoto M, Kanaji S, Matsuda Y, Matsuda T, Oshikiri T, Nakamura T, Suzuki S, Koma YI, Komatsu M, Sasaki R, Kakeji Y. Local advanced rectal cancer perforation in the midst of preoperative chemoradiotherapy: A case report and literature review. *World J Clin Cases* 2017; 5(1): 18-23 Available from: URL: http://www.wjgnet.com/2307-8960/full/v5/i1/18.htm DOI: http://dx.doi.org/10.12998/wjcc.v5.i1.18

INTRODUCTION

Currently, the best proven approach to local advanced rectal cancer (LARC) is a combination of surgery and preoperative chemoradiotherapy (CRT)[1,2]. Compared to preoperative radiotherapy (RT) alone, the incidence of local recurrence at 5 years was significantly lower in the preoperative CRT group[3]. We previously reported that the pathological response to preoperative 5-fluorouracil (FU)-based CRT may be a useful predictor of LARC survival[4]. However, preoperative CRT is associated with various adverse effects that can be life-threatening. Among the life-threatening side effects, CRT-related perforation of colorectal cancer is not well understood. We herein report a case of perforated LARC associated with preoperative CRT.

CASE REPORT

A 56-year-old Japanese male was transported to our facility with chief complaints of fever and general malaise. Though he had had anemia 3 years prior, he did not seek medical attention. He had used alcohol for at least 34 years. His serum level of carcino embryonic antigen was increased to 21.0 ng/mL (normal < 2.5). The colonoscopy examination revealed a low anterior circumferential rectal lesion (Figure 1A).

An endoscopic biopsy histologically confirmed the clinical diagnosis of adenocarcinoma. Magnetic resonance imaging (MRI) findings revealed LARC with involvement of perirectal fat, the prostate and the seminal vesicles (Figure 1B). Some of the lymph nodes in the tumor area were enlarged (Figure 1C) and 18-fluorodeoxyglucose (FDG)-positron emission tomography (PET)/computed tomography (CT) showed metabolically active foci in the left obturator lymph node (Figure 1D). No evidence of distant spread was seen.

The patient was scheduled for preoperative 5-FU-based CRT. Administration of a fixed dose of tegafur/uracil (UFT) (300 mg/body per day) and leucovorin (LV) (75 mg/body per day) was planned for days 1-28. Concurrent RT administration to the whole pelvis (Figure 2A) was planned in fractions of 1.8 Gy/d, 5 d a week for 5 wk (45 Gy in 25 fractions). However, the patient developed a typical fever at 25 d after starting CRT (36 Gy in 20 fractions received). The CT findings revealed rectal perforation with air-fluid around the left side of the seminal vesicle adjacent to the rectum (Figure 2B), and the colonoscopic examination also showed the perforation of the tumor wall (Figure 2C). The patient underwent construction of a sigmoid colostomy as an emergency surgery.

At 12 d after the surgery with no inflammatory findings, the remaining CRT was commenced, and was completed safely according to plan. The patient underwent abdominoperineal resection of the rectum including the prostate and seminal vesicle with a laparoscopic technique as minimally invasive surgery. The histopathological findings revealed that a wide area of tumor tissue had been replaced by necrotic tissue and fibrous tissue, suggesting that chemoradiation had been effective (Figure 3). The Union for International Cancer Control (UICC) TNM staging[5] of the tumor was pT3, N0 (0/34), M0. No evident disease recurrence has been observed in the patients for 8 mo.

DISCUSSION

RT is one of the useful modalities for various cancers including rectal cancer. Currently, more than 50% of cancer patients receive RT with or without chemotherapy[6]. RT gives rise to various cellular responses including both DNA and membrane damage[7]. The DNA damage leads to cell cycle arrest, apoptosis, stress and the activation of DNA repair processes through coordinating intracellular signal pathways involving poly ADP ribose polymerase, ERK1/2, p53 and ataxia telangiectasia mutated[7,8]. Concerning pelvic RT with concurrent 5-FU-based chemotherapy, 5-FU can increase radiation sensitivity[3,9]. However, RT

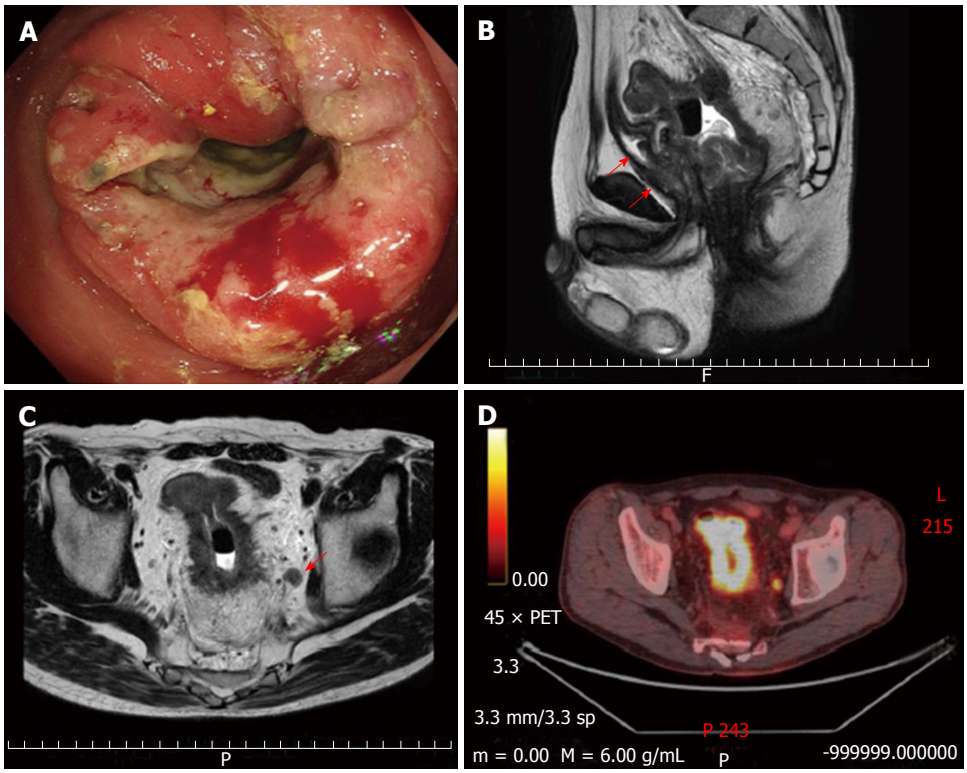

Figure 1 Evaluation of clinical findings. Colonoscopy showed a circumferential mass at the lower rectum (A); Sagittal magnetic resonance imaging (MRI) of the pelvis showed rectal mass with involvement prostate and seminal vesicles (red arrows) (B), and perirectal fat (C); The enlarged lymph node in the left obturator detected by coronal MRI (red arrow) showed obvious metabolically active foci 18-fluorodeoxyglucose-positron emission tomography/computed tomography evaluation (D).

causes various side effects that damage healthy cells and tissues near the treatment area.

Radiation-related tissue injuries are well known to occur in the gastrointestinal tract. Acute radiation-related small bowel toxicity often occurs during RT for LARC. The overall incidence of acute Grade 3-4 diarrhea was 16%-39% in prospective studies of preoperative RT[10]. Concerning the rectum, radiation proctitis is generally classified as acute or chronic phase by the timeframe of the symptoms, and chronic proctitis may include acute proctitis defined as an inflammatory process. However, the detailed pathogenesis of RT-induced proctitis is not yet clear. Acute proctitis including symptoms of diarrhea, nausea, cramps, tenesmus, urgency, mucus discharge and minor bleeding occurs within 6 wk after the start of RT[11]. Severe bleeding, strictures, perforation, fistula and bowel obstruction occur in the chronic phase, which may not become apparent for months to years[12]. Concerning pelvic RT with concurrent 5-FU-based chemotherapy, severe acute small-bowel toxicity was found to be associated with radiation in a dose-dependent manner[13,14].

Colorectal perforation is a life-threatening complication. The causes of rectal perforation include fecal impaction, enema, and cancer and its therapy, including RT, chemotherapy and molecular-targeted therapy. Among them, rectal perforation from pelvic RT is an extremely rare adverse event. The mechanisms of radiation-related perforation, especially the difference in responses between normal rectal tissue and LARC tissue, remain elusive. RT-induced normal tissue perforation is generally caused by accumulation of radiation-induced irreversible ischemic mechanisms with submucosal fibrosis and obliteration of small blood vessels[15]. In addition to the ischemic change, cancer tissue with high radiation sensitivity results in massive necrotic death, which in turn triggers an inflammatory reaction analogous to a wound-healing response[15-17].

There is general agreement that radiation-induced gastrointestinal injuries are associated with the dose of radiation. Late normal tissue reactions are more dependent on the dose per fraction than acute reactions[18]. Still, Do *et al*[12] reported that a total dose of 45 to 50 Gy delivered to the pelvis for adjuvant or neoadjuvant treatment for rectal malignancies generally causes very few acute and late morbidities.

However, total treatments of > 70 Gy cause significant and long-standing injury to the surrounding area[12,19]. In the present case, the main cause of the standard 5-FU-based CRT-related rectal perforation was thought to be not direct radiation morbidity but a secondary effect of the tumor necrosis. In addition to excessive treatment effects of CRT, the potential risks for CRT-related LARC perforation may include the presence of diverticula, collagenosis and tumor ulceration. Khan *et al*[20] also argue that the biological behavior of the tumor may have a large influence on whether an event occurs because all transrectal tumors have the potential for perforation. Pathological and immunohistochemical analyses of various factors in colorectal tumor perforation

Table 1 Characteristics of perforated local advanced rectal cancer associated with 5-fluorouracil-based preoperative chemoradiotherapy

Case	Ref.	Sex Age	Time to perforation Total dose of RT (Gy/fr)	Surgical intervention (additional surgery)	TNM Classification[1]	Outcome
1	Lee *et al*[22]	F 67	5 D after planned CRT 50 Gy/28 fr	LAR	cT4, NX, MX pT4, N2, M0	Alive
2	Lee *et al*[22]	F 78	Immediately after planned CRT 54 Gy/unknown	Ileostomy	cT4, NX, MX	Alive
3	Lee *et al*[22]	M 72	2 W in the middle of planned CRT 21.6 Gy/unknown	Colostomy	cT3, NX, MX	Perioperative death
4	Lee *et al*[22]	M 76	4 W in the middle of planned CRT 36 Gy/unknown	Colectomy with ileostomy	cT3, NX, MX	Perioperative death
5	Khan *et al*[20]	M 47	1 W after planned CRT 50.45 Gy/28 fr	LAR	cT3, N1, M0 pT3, N2, M0	Alive
6	ElGendy *et al*[23]	F 55	2 W after planned CRT 45 Gy/unknown	LAR	cT3, N1, M0 pT3, N2, M0	Alive
7	Our case	M 56	25 D in the middle of planned CRT 36 Gy/20 fr	Colectomy (APR after remaining planned CRT)	cT4, N2, M0 pT3, N0, M0	Alive

[1]According to the TNM classification by Union for International Cancer Control (UICC)[5]. The following cases searched common literature search engines (PubMed, Medline, Google Scholar) through August 2016, using search terms related to rectal cancer, perforation and chemoradiotherapy. LAR: Low anterior resection; APR: Abdominoperineal resection; CRT: Chemoradiotherapy; RT: Radiotherapy; F: Female; M: Male.

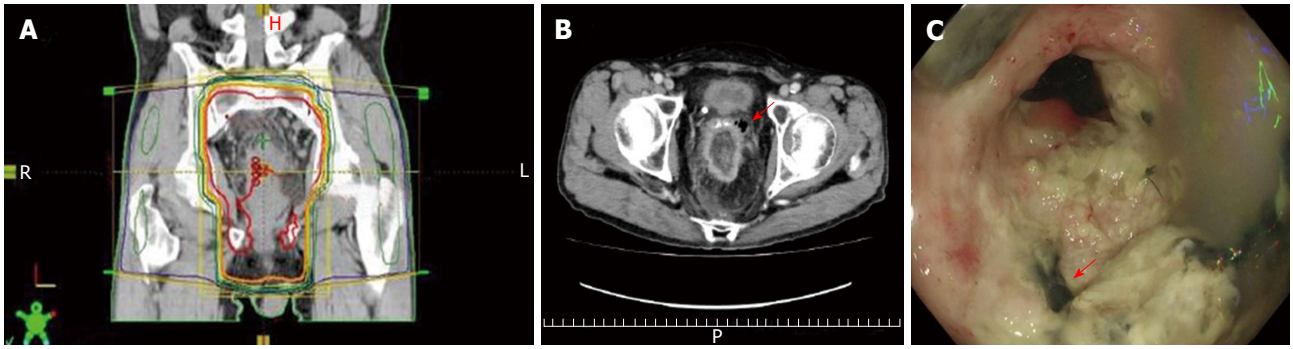

Figure 2 Rectal tumor perforation suggestive of chemoradiationdamage. Radiotherapy was delivered to the whole pelvis through three (one posterior-anterior and two lateral) or four (one anterior-posterior, one posterior-anterior and two lateral) fields using a 10-MV linear accelerator in the prone position (A); Coronal computed tomography findings showed a small bubble of extra-luminal gas (red arrow) (B); Preoperative colonoscopicfindings for radical surgery showed excavation with mucosa necrosis (red arrow) suggestive of chemoradiationdamage in the rectal tumor (C).

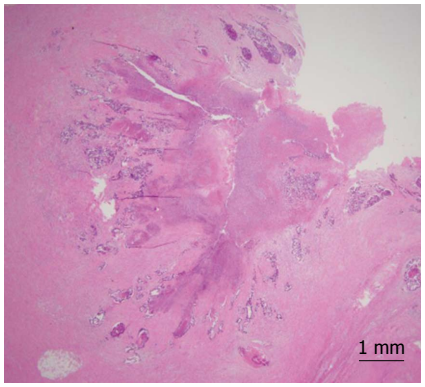

Figure 3 Histological findings of the resected specimen showed a wide field of tumor necrosis with fibril formation (H-E stain).

compared with non-perforated tumor showed significant associations of tumor location and cell differentiation[21].

We searched all common literature search engines (PubMed, Medline, Google Scholar). To our knowledge, only 6 cases of perforated LARC associated with 5-FU-based preoperative CRT have been reported[20,22,23] (Table 1). Among them, the cases of perforation in the midst of preoperative CRT were only 2 in number. Furthermore, completion of preoperative CRT according to the original plan after supporting emergency recovery for CRT-related rectal perforation has never before been described.

In recent years, various molecularly targeted agents have been used clinically for colorectal cancer. However, the spread of molecularly targeted therapies including combination RT has resulted in more cases of agent-induced gastrointestinal perforation[24,25]. Gastrointestinal perforation has occurred in both non-tumor tissue and tumor tissue including rectal cancer[26]. To avoid severe complications related to CRT, such as LARC perforation, regimens of chemotherapy as well as methods of radiation therapy should be carefully considered.

In conclusion, we documented an extremely rare case of LARC that developed preoperative rectal perforation in the midst of 5-FU-based preoperative CRT. We share this case as important evidence for the treatment for

LARC perforation in the midst of preoperative CRT. Our case findings imply that completing preoperative CRT after supporting emergency recovery may enhance the anti-tumor effect, resulting in a better prognosis for such cases.

COMMENTS

Case characteristics

A 56-year-old male with locally advanced rectal cancer (LARC) developed preoperative rectal perforation in the midst of 5-fluorouracil (FU)-based pre-operative chemoradiotherapy (CRT).

Clinical diagnosis

Colonoscopy and imaging tests resulted in a clinical diagnosis of LARC with direct invasion to adjacent organs and regional lymphadenopathy.

Differential diagnosis

Inflammatory associated rectal perforation.

Laboratory diagnosis

Preoperative serum level of carcino embryonic antigen was increased to 21.0 ng/mL (normal < 2.5).

Imaging diagnosis

The computed tomography findings revealed rectal perforation with air-fluid around the left side of the seminal vesicle adjacent to the rectum.

Pathological diagnosis

A wide area of tumor tissue was replaced by necrotic tissue and fibrous tissue, suggesting that chemoradiation had been effective.

Treatment

The patient completed preoperative CRT after supporting emergency recovery.

Related reports

To our knowledge, only 6 cases of perforated LARC associated with 5-FU-based preoperative CRT have been reported.

Experiences and lessons

The authors share this case as important evidence for the treatment of LARC perforation in the midst of preoperative CRT.

Peer-review

This case report demonstrated that completing preoperative CRT after supporting emergency recovery may enhance the anti-tumor effect, resulting in a better prognosis.

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Conscience imperative of providing information and knowledge in hepatology: The Portuguese approach

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Abstract

The last 25 years have been a thrilling time for the Portuguese hepatologists. Our national meetings have been providing the forum for the exchange of scientific ideas and the presentation of clinical research in clinical Hepatology, a growing world of knowledge in medical care. Bridging the gaps between technology and clinical daily practice, the latest development and the almost humble bedside care, has been a challenge for the increasing numbers of doctors devoted to the diagnostic and treatment of liver disease. We have been trying to be very persuasive among the Portuguese medical community in demonstrating that cultural vectors may influence the origin and pattern of liver disease among us. Viral hepatitis and alcoholic liver disease are paradigms of this assumption. Chronic liver disease is responsible for 3% of the deaths in Portugal, which accounts for the top ten causes of death in our country. The recognition by public health authorities of this fact along with the national net of hepatology outpatient consultation in public hospitals, has brought liver diseases under the lights of doctors concerns and an increased public awareness of its dimension.

Key words: Alcohol; Cirrhosis; Hepatology; Liver; Public health

Core tip: The last 25 years have been a thrilling time for the Portuguese Hepatologists. Nowadays our main efforts are devoted both at the level of training and pregraduate teaching, especially in the large university hospitals but also in addressing the public directly, aiming essentially in giving information on three major topics: Alcohol, viral hepatitis and the obesity epidemics.

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TO THE EDITOR

The last 25 years have been a thrilling time for the portuguese hepatologists. Our national meetings, either the portuguese association for the study of liver disease annual meeting or the portuguese digestive disease week, have been providing the forum for the exchange of scientific ideas and the presentation of clinical research in clinical hepatology, a growing world of knowledge in medical care. Bridging the gaps between technology and clinical daily practice, the latest development and the almost humble bedside care, has been a challenge for the increasing numbers of doctors devoted to the diagnostic and treatment of liver disease.

Nowadays our main efforts are devoted both at the level of training and pregraduate teaching, especially in the large University Hospitals but also in addressing the public directly, aiming essentially in giving information on three major topics: Alcohol, viral hepatitis and the obesity epidemics.

We have been trying to be very persuasive among the Portuguese medical community in demonstrating that cultural vectors may influence the origin and pattern of liver disease among us. Viral hepatitis and alcoholic liver disease are paradigms of this assumption. Chronic liver disease is responsible for 3% of the deaths in Portugal, which accounts for the top ten causes of death in our country[1]. The recognition by Public Health authorities of this fact along with the national net of hepatology outpatient consultation in public hospitals, has brought liver diseases under the lights of doctors concerns and an increased public awareness of its dimension. Furthermore, although liver transplantation only begun 20 years ago, there are about 250 patients yearly transplanted, in 3 centers, serving a ten million population[2].

It is true that alcoholic liver disease is a dominant concern in this country and several reasons may contribute to this fact: Portugal, with temperate climate from Atlantic and Mediterranean origins, has a rich tradition in wine processing, and for years, many rural communities were actively involved in those processes. Alcohol consumption is thus a widespread habit, and in the traditional good-eating-and-drinking land (many times advertised abroad), it became a deep cultural characteristic lasting for decades. This creates a great challenge for us doctors, while trying to explain everyone, the risks, the facts and the fancies about chronic alcohol consumption.

If we accept WHO reports claiming for recent evidence suggesting association between alcohol abuse induced disorders and HIV/AIDS[3,4], it is easy to extrapolate that this may also play a role and background for viral hepatitis liver injury. Binge drinking for example is associated with non-protected, unexpected and multiple partners sex behaviour[3]. So prevention has been a major task for public health authorities concerning alcohol abuse, under the judicious guidance and advice of hepatologists. The social and individual impact of more than 50 alcohol-induced disorders, obviously remain as a leading topic for medical attention.

Interestingly many other features related to viral hepatitis have had a significant change in the last years in Portugal. If we take hepatitis A, 25 years ago, we had a high level of endemicity, and several reports showed that the adult anti hepatitis A virus (HAV) prevalence was above 90%: Infection was almost universal at around 5-6 years old[5,6]. The profound changes in basic hygienic and sanitary conditions of both urban and rural population, made now a different reality, with only a seroprevalence less than 35% of anti HAV in modern adolescents[5]. Although we know that if acquired in adult it may have a fulminant course with 2% mortality[1], in the meantime universal vaccination and its inclusion in the National Vaccination Program has not been advocated. Our policy is checking anti-HAV previously to vaccination, if considered after the age of 15.

Hepatitis B also has changed recently among us. At the end of the millennium, HBsAg prevalence was shown to the 1.25%[6], bringing Portugal to a low prevalence area. Recently it has been claimed to be less than 1%, in a national serological survey[7], with an anti HBs prevalence of 47%, reflecting the vaccination policy adopted years ago. The overall prevalence of anti-HBc is now of 6%[8]. Among us, hepatitis B virus vaccine is included in the National Vaccination Program since 1993 for adolescents aged 10-13, and for all newborns since year 2000. The ongoing strategy is vaccination, of all newborns and adolescents, with additional recommendation of risk group vaccination as defined by regulatory ministerial documentation. Recent challenges however have been brought up by the intensive immigration from eastern European countries where Hbs Ag prevalence shifts between 1%-7%[9] reproducing the same scenario as 40 years ago, when Angola and Mozambique citizens came back to mainland.

Still the predominant form of chronic hepatitis B is the negative chronic hepatitis, accounting for more than 80% of the cases, as a recent nationwide hospital survey showed, underlining our Mediterranean connections[1]. Despite the vaccination Program regularly undertaken, the fact is that there is a growing interest on this topic, related to the increased identification of long standing "carriers", now truly reclassified as chronic hepatitis patients, and to the questions raised by the immunosuppressive drugs regimen (*e.g.,* biologics, chemotherapy), urging the need for appropriate prophylaxis.

Hepatitis C also, has clearly gained full media and patient attention in recent years. Our estimated anti-hepatitis C virus (HCV) prevalence (based on blood donors statistics, and many clinical observations ranges between 1% and 1.5% (100000-150000 subjects)[2]. Interesting cultural and historical facts made a significant contribution for this: Sports, for example. Portuguese people share with Brazilians not only the language and many cultural roots, but also an overriding enthusiasm about soccer. It is the national Portuguese sport, practiced all over the country, with passionate supporters following major Portuguese teams' performances and

successes in European champion leagues. After thorough questionnaires and observations, we found several cases of young, otherwise healthy adults who had, as a single risk factor for HCV infection, the sharing of needles or glass reusable syringes by the paramedics of amateur soccer clubs in the eighties and nineties[1]. This occurred whenever multivitamin complexes were intravenously administered (sometimes weekly!) or when anti-inflammatory drugs were repeatedly given intramuscularly. We found that it was a widespread habit, to strengthen athletes' performance. However, other sources for percutaneous transmission of HCV, such as contaminated instruments and equipment, should always be kept in mind when we deal with our patients. Many Portuguese, as young people, had prolonged sojourns in Africa and were involved in the colonial war of late 1960s and early 1970s. In those days, mass vaccination programs for prophylaxis in Portuguese troops going to Africa, did not use disposable needles, and tattooing with device sharing was also very common. Also, in the wake of the 1974 Portuguese Revolution, almost 1 million people returned from Africa, creating new sociological challenges in main land, at the same time fuelled by proper stimuli from the brave new world of musical scene which paved the way for youth contestation movements to include the adoption of high-risk behaviours such as sporadic (nowadays "forgotten") intravenous drug use. Furthermore, bizarre and folk medical practices such as intravenous gammaglobulin use for "immune strength" or as "memory inducers" and intravenous calcium for chronic asthenia and tetany, without proper aseptic use of needles and syringes, may have given a significant contribution to the estimated 150000 infected people[2]. Nowadays, special attention has been given on the risk of further iatrogenic exposures to the transmission of HCV infection, beyond the overall care of health providers and the educational tools given to those involved in cosmetic procedures (tattooing, body piercing), trying to avoid what has been seen recently in developed countries from Europe, United Stated or Australia: Preparation and delivery of injectable medications, particularly in the anaesthetics setting, has been intensively addressed by those concerned with HCV epidemiological new unexpected features.

Portuguese Hepatologists have been trying to discuss the viability of creating a National Strategy Plan for prevention and control of hepatitis C. This ambitious plan stands on the tripod base of quality information, reinforced prevention and cost-effective modalities, and intend to gather many society vectors like health related authorities, scientific societies - beyond the conventional gastroenterology and hepatology association - pharmaceutical companies, patients organizations, and of course, politicians and the media. This tremendous effort set the stage and the pace for a unique agreement between health authorities and Industry, allowing the recent access of thousands of patients exclusively to all-oral hepatitis c treatment agents.

Step by step we have managed to reach public interest and media attention: In 2010 spring time, we promoted the "Liver on Tour", a special Project devoted to increase public awareness on Liver health and Liver disease. All counties in Portugal were visited in a road show, with lots of simple, reliable and practical information on liver problems. Members of the Portuguese Association for the study of liver diseases board of directors were literally on the road, claiming for attention and protection for the liver. In 2011-2015 another several "out of the box" meetings addressed this anthropological insight of liver Health: Sports and the liver (along with major conferences from well-known Portuguese sportsmen), sexuality and liver health, with two more symposia on the liver and Social Exclusion, showing how liver diseases promote exclusion and how exclusion itself is a vector for liver diseases.

Building these projects, we show clearly that silence will not be an option for those devoted in Portugal in caring for liver problems: Information and knowledge will remain to be, as demonstrated in these busy and passionate last years, a conscience imperative.

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The primary task of *WJCC* is to rapidly publish high-quality Autobiography, Case Report, Clinical Case Conference (Clinicopathological Conference), Clinical Management, Diagnostic Advances, Editorial, Field of Vision, Frontier, Medical Ethics, Original Articles, Clinical Practice, Meta-Analysis, Minireviews, Review, Therapeutics Advances, and Topic Highlight, in the fields of allergy, anesthesiology, cardiac medicine, clinical genetics, clinical neurology, critical care, dentistry, dermatology, emergency medicine, endocrinology, family medicine, gastroenterology and hepatology, geriatrics and gerontology, hematology, immunology, infectious diseases, internal medicine, obstetrics and gynecology, oncology, ophthalmology, orthopedics, otolaryngology, pathology, pediatrics, peripheral vascular disease, psychiatry, radiology, rehabilitation, respiratory medicine, rheumatology, surgery, toxicology, transplantation, and urology and nephrology.

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MINIREVIEWS

Externalized conductors and insulation failure in Biotronik defibrillator leads: History repeating or a false alarm?

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Abstract

Conductor externalization and insulation failure are frequent complications with the recalled St. Jude Medical Riata implantable cardioverter-defibrillator (ICD) leads. Conductor externalization is a "unique" failure mechanism: Cables externalize through the insulation ("inside-out" abrasion) and appear outside the lead body. Recently, single reports described a similar failure also for Biotronik leads. Moreover, some studies reported a high rate of electrical dysfunction (not only insulation failure) with Biotronik Linox leads and a reduced survival rate in comparison with the competitors. In this paper we describe the case of a patient with a Biotronik Kentrox ICD lead presenting with signs of insulation failure and conductor externalization at fluoroscopy. Due to the high risk of extraction we decided to implant a new lead, abandoning the damaged one; lead reimplant was uneventful. Subsequently, we review currently available literature about Biotronik Kentrox and Linox ICD lead failure and in particular externalized conductors. Some single-center studies and a non-prospective registry reported a survival rate between 88% and 91% at 5 years for Linox leads, significantly worse than that of other manufacturers. However, the preliminary results of two ongoing multicenter, prospective registries (GALAXY and CELESTIAL) showed 96% survival rate at 5 years after implant, well within industry standards. Ongoing data collection is needed to confirm longer-term performance of this family of ICD leads.

Key words: Implantable cardioverter defibrillator; Biotronik implantable cardioverter defibrillator lead; Externalized conductors; Insulation failure

Core tip: Conductor externalization and insulation failure are frequent complications with the recalled St. Jude Medical Riata implantable cardioverter-defibrillator leads. Cables can externalize through the insulation ("inside-out" abrasion) and appear outside the lead body. Recently similar failure mechanisms have also been described for Biotronik leads. Some studies reported a high rate of electrical dysfunction (including insulation

failure) with Biotronik Linox leads and a survival rate between 88% and 91% at 5 years, significantly worse than that of other manufacturers. However, the preliminary results of two ongoing multicenter, prospective registries showed 96% survival rate at 5 years, well within industry standards.

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INTRODUCTION

Implantable cardioverter-defibrillator (ICD) is a well established life-saving therapy for patients at risk of sudden cardiac death from ventricular arrhythmias. "Achille's heel" of the ICD system is the lead, because of its susceptibility to mechanical and electrical defects[1]. Incidence of lead failure can be as high as 0.58%/year, increasing with time (up to 10%-15% at 10 years of follow up)[2,3]. Lead failure has a broad range of clinical presentations and outcomes, the most dreaded being potentially lethal proarrhythmia and inability to interrupt spontaneous ventricular arrhythmias.

Conductors fracture and insulation failure are the main mechanisms responsible for lead failure[1-3]: Two classical examples are the recalled Medtronic Sprint Fidelis leads and the St. Jude Riata leads family.

Sprint Fidelis leads (Medtronic Inc., St. Paul, Minnesota, United States) were recalled from the market, in October 2007, because of a high failure rate due to conductor fracture. On the other side, Riata family of ICD silicone leads (St. Jude Medical, Sylmar, California, United States) underwent class I recall by the Food and Drug Administration, in December 2011, because of insulation failure. In particular, Riata leads are susceptible to a unique failure mechanism: The conductor cables can externalize through the silicone insulation ("inside-out" abrasion) and appear outside the lead body[3].

Recently, single case reports described a "Riata like" insulation failure mechanism also for Biotronik Kentrox and Linox ICD leads (Biotronik, Berlin, Germany)[4-9]. Moreover, some single-center studies and a non-prospective registry reported a high rate of electrical dysfunction (including but not limited to insulation failure) with Biotronik Linox leads and a reduced survival rate in comparison with the competitors[10-12]. Nevertheless, the preliminary results of two ongoing multicenter, prospective registries (GALAXY and CELESTIAL) showed 96% survival rate at 5 years after implant, well within industry standards and not different from that of other manufacturers[13].

In this paper, we describe (beyond the already published case reports) a patient, managed at our institution, with a Biotronik Kentrox ICD lead presenting with signs of insulation failure and conductor externalization at fluoroscopy. Subsequently, we review currently available literature about Biotronik ICD lead failure and in particular insulation failure with externalized conductors.

ANATOMY OF A DEFIBRILLATOR LEAD

General concepts

Each ICD lead has several components[3]: Conductor, insulation material, defibrillation coil, electrode, fixation mechanism to myocardium, division point of single conductors and connector. Most manufacturers use similar materials, even if assembled in different ways. All modern ICD leads have a multi-lumen design. High-voltage shock conductors include a low-resistance core of silver-platinum and are coated with polytetrafluoroethylene and ethylenetetrafluoroethylene (ETFE); they lie in a silicone cylinder with 3-6 lumens. Low-voltage conductors are made of alloy of cobalt, nickel, chromium silver and molybdenum. A central coil conductor used for the pacing-sensing cathode (tip) allows for stylet insertion and extension/retraction of the fixation helix. Conductors for the pacing-sensing anode (ring) and high voltage coils are built in parallel cables around the central coil (Figure 1). Lead design may vary among manufacturers: Coils can be placed in symmetric or asymmetric manner; compression lumens can be present or not, *etc*. All leads, anyway, will have minimum one distal right ventricular (RV) shock coil, necessary for the delivery of high-voltage shock therapy. Dual-coil leads have another shock coil, usually located in the superior vena cava (SVC). Dual-coil leads may ensure greater defibrillation efficacy, expecially in right-sided implants, but they involve greater procedural difficulties and risks, when extraction is required, due to fibrotic tissue around the proximal coil (Figure 2).

Last generation ICD leads use a DF-4 connection, that has replaced the old, multicomponent yokes (DF-1/IS-1). DF-4 connection has the pace-sense conductors and the defibrillation conductor(s) connected to a single pin. The new connection has the advantage of a reduced pocket bulk and prevents the accidental reversal of high-voltage connections during implantation or replacement procedures.

ICD leads always have bipolar sensing and the tip electrode is always used as a cathode. However two types of sensing design exist. The dedicated bipolar lead has a ring electrode as sensing dedicated anode. On the other side, the integrated bipolar lead has the RV defibrillation coil, integrated within the shock circuit, as the anode. Therefore, a dedicated bipolar lead is more complex because it requires two conductors, versus one in an integrated bipolar lead. Dedicated and integrated leads show no difference regarding

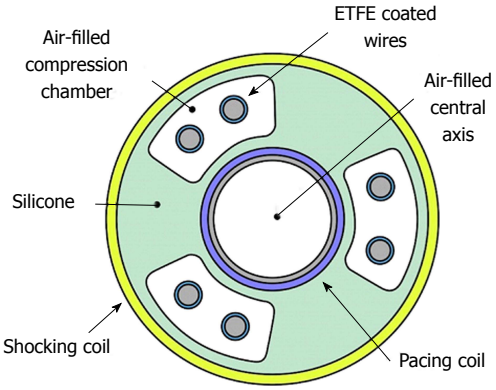

Figure 1 Cross-section design of a modern implantable cardioverter-defibrillator lead. ETFE: Ethylenetetrafluoroethylene.

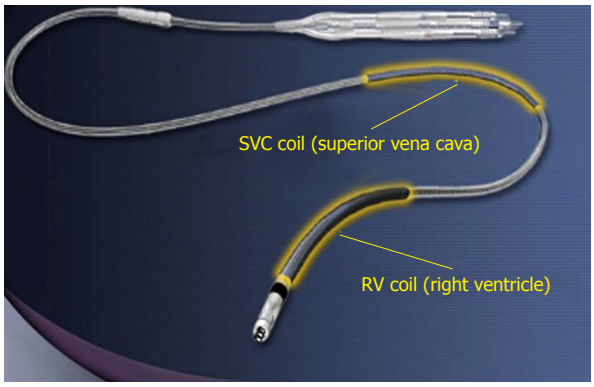

Figure 2 A typical transvenous implantable cardioverter-defibrillator lead with DF-1 connection and dual-coil design. SVC: Superior vena cava.

sensing of ventricular fibrillation (VF). However, an integrated bipolar lead has a larger "antenna", more prone to oversensing of diaphragmatic myopotentials, electromagnetic interference (EMI) and atrial "far field" signals. Dedicated bipolar leads are more prone to oversense the T wave. Current ICD leads diameters vary from 6.3 to 8.6 French.

Biotronik Kentrox and Linox leads

Kentrox SL (marketed from 2001 to 2005) is a 9.3 French, passive fixation ICD lead with an isodiametric design, coated with fractal iridium. The sensing is dedicated bipolar. The lead is insulated with silicone rubber similar to first generation Riata leads insulation. In contrast to Riata lead, Kentrox does not present a "redundant" design that can facilitate the movement of the cables within the lumen (and was supposed to be implied in "inside-out" abrasion)[6]. Nevertheless, the mechanism of Kentrox externalization described in literature (see next paragraphs) seems to be very similar to that of Riata leads: "Inside-out" abrasion (movement of the conductors within the insulation, leading to cable externalization through the outer layer) rather than "outside-in" (contact with another lead or anatomic structures, *e.g.*, tricuspid valve).

Linox family leads (marketed in 2005) are 7.8 French with an isodiametric design and dedicated bipolar sensing. The cross-section of Linox lead is comparable to that of Kentrox and, although having a smaller diameter, the thickness of the silicone layer is equal. Moreover, Linox is equipped with integrated flat-wire shock coil (Protek®) which reduces fibrotic tissue ingrowth.

Linox^{Smart} lead (marketed in 2009, from 2012 proMRI model) is additionally treated with Silglide®, a surface treatment which ensures lubricious coating, improved gliding, low friction and reduces the risk of abrasion (Figure 3). In a similar manner, Riata ST and Durata St. Jude Medical models were provided with an additional abrasion-resistant silicone-polyurethane co-polymer (Optim™). Silicone rubber is inert and more biostable compared to polyurethane, but has a higher coefficient of friction and is more vulnerable to abrasion and breaches. On the other side, polyurethane is too stiff to be used as the only insulation material in ICD leads. That is why each manufacturer attempted to "reinforce" silicone with different proprietary solutions.

Finally, Protego family leads (marketed in 2013) are almost identical to Linox, their new feature is the introduction of a DF-4 connection.

CASE REPORTS

The case managed in our center

A 71-year-old man, with ischemic dilated cardiomyopathy, was evaluated in our center for a suspect ICD malfunction. He had been implanted, 10 years before, with a Biotronik defibrillator and a Kentrox dual-coil lead as primary prevention. In 2013 the device was replaced (normal battery depletion) and an Ellipse St. Jude defibrillator was implanted and connected to the old Kentrox lead. Early in 2016 at device interrogation we found abnormally low pacing impedance values (< 200 Ohm) and repetitive nonphysiological high-rate sensed events on sensing channels (both near and far field), suggesting an insulation defect. These episodes were of brief duration, therefore they did not trigger inappropriate shocks (Figure 4). At fluoroscopy conductor externalization was evident just proximal to the ventricular coil (Figure 5). Due to a deemed high risk of extraction we decided to implant a new lead, abandoning the damaged one; reimplant was uneventful. Subsequent defibrillation testing on induced VF was performed successfully.

In our center we have followed a total of 35 patients with Biotronik ICD leads: 5 Kentrox, 27 Linox and 3 Protego models, implanted between 2005 and 2016. The above-mentioned case is the only failure we had to face so far.

Published case reports of Biotronik ICD leads (insulation) failure

Shoemaker *et al*[4] was the first to report the phenomenon of conductor externalization in a Linox lead.

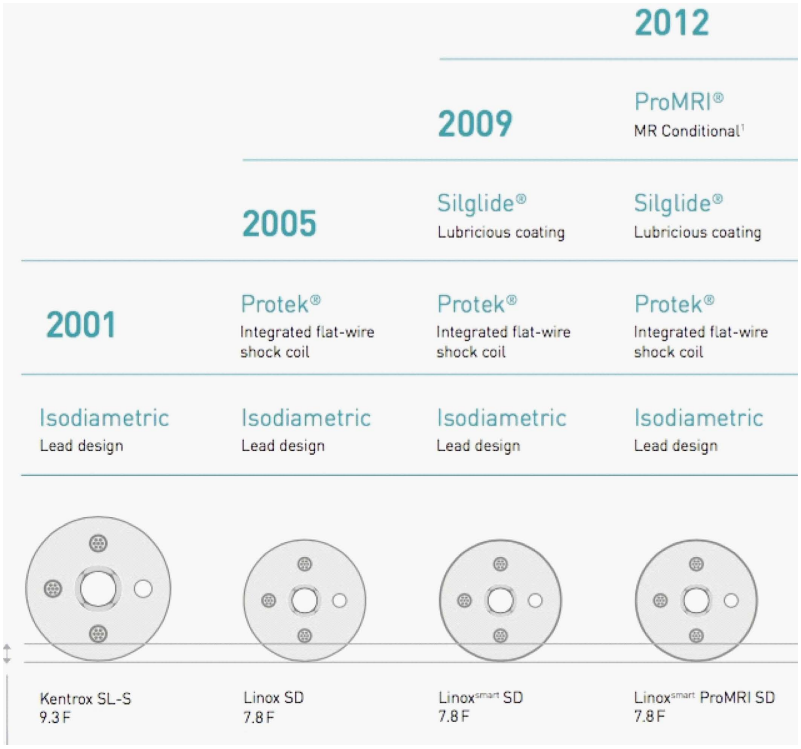

Figure 3 Overview of Kentrox and Linox Biotronik leads. Courtesy of Biotronik Italia.

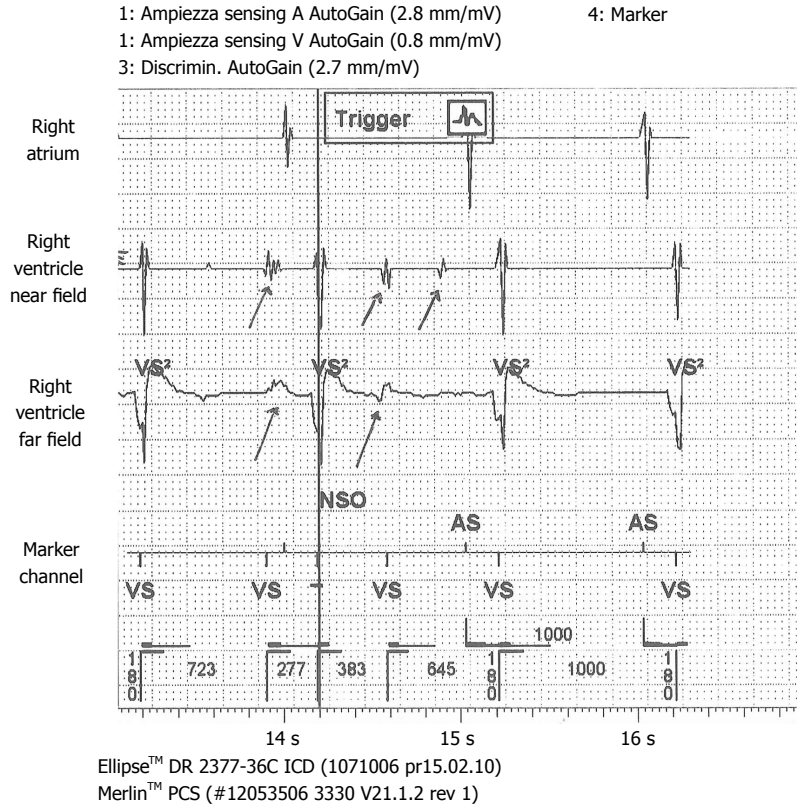

Figure 4 Intracardiac electrogram recording of non-physiological sensed events due to insulation failure in the patient managed in our center. NSO: Non sustained oversensing; AS: Atrial sensing; VS: Ventricular sensing.

The lead was dual-coil, implanted 4 years before, in a patient with a persistent left and absent right SVC. The externalized conductors, proximal to the caval coil, were incidentally discovered during a coronary angiogram. There was no change in baseline electrical performance of the lead which was, however, extracted. It is notewhorty that a lead with externalized conductors may still function normally because high-voltage and pace-sense ring cables are covered with ETFE, which serves as a second insulation. However, if ETFE abrades, electrical short circuits can occur during shock delivery with inability to defibrillate and catastrophic consequences.

In a successive paper, Manfredi *et al*[5] described

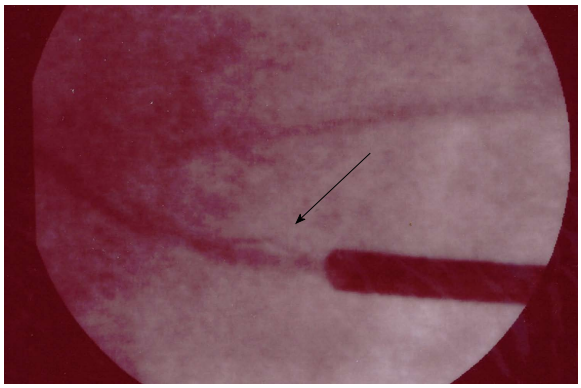

Figure 5 Fluoroscopy image of Kentrox conductor externalization just proximal to the ventricular coil in the patient managed in our center.

a dual-coil Linox lead, implanted 8 years before, in a 53-year-old man with ischemic dilated cardiomyopathy for primary prevention. During an electrophysiological study, the lead had conductor wires protruding outside the body lead, between caval and ventricular coil. Also in this case, device interrogation revealed normal baseline electrical values. The patient was not pacing dependent and had never received appropriate or inappropriate ICD therapy; therefore, it was decided to follow the lead closely without extracting or replacing it.

Abi-Saleh *et al*[6] were the first to describe externalized conductor in a Kentrox lead. The dal-coil lead had been implanted, 7 years before, in a 38-year-old man with Brugada syndrome after cardiac arrest from VF. The patient presented with multiple inappropriate shocks due to noise which was evident on intracardiac electrogram (suggesting insulation failure); moreover, device check also revealed high pacing and shock impedance (suggesting concomitant conductors fracture). Fluoroscopy showed externalized conductors at the level of tricuspid valve. The patient underwent Kentrox extraction and reimplantation of a new ICD lead.

Another case of Kentrox failure was described by Bogossian *et al*[7]. The paper reports the first evidence of conductor externalization in a single-coil Biotronik lead, which had been implanted, 11 years before, in a 14-year-old boy after cardiac arrest from idiopathic VF. The lead presented externalized conductors at the region of tricuspid valve. Electrical measurements of the lead showed a significant decrease of sensing values, as well as a high-voltage shock impedance > 300 Ohm (suggesting both insulation failure and conductor fracture). The malfunctioning lead was explanted and a subcutaneous ICD was implanted.

In the case report by Reichlin *et al*[8], a Linox dual-coil lead presented with multiple inappropriate shocks due to noise on the sensing channel, suggesting insulation failure. Baseline electrical parameters (sensing values, pacing threshold and impedances) were normal. The lead had been implanted, 8 years before, in a 54-year-old man with non-ischemic dilated cardiomyopathy. At fluoroscopy externalized conductor cables were seen just proximal to the ventricular coil. The lead was extracted and visual inspection confirmed the externalization of pace-sense cables, putative source of noise.

Finally, Wutzler *et al*[9] described the case of a 31-year-old man with VF which was not interrupted by his ICD. The device was explanted: An area of burn marks on the surface with a small hole in the titanium can was found. Further analysis by the manufacturer showed a defect of the defibrillator output stage, indicating shock delivery via a low impedance shock path and premature battery discharge. These findings suggest an isolation defect of the ICD lead (Biotronik Linox^{Smart}).

SINGLE-CENTER STUDIES AND A NON-PROSPECTIVE REGISTRY

Given this background and the published case reports, some centers started to systematically review all Biotronik leads implanted in their institutions.

Howe *et al*[10] reviewed all Biotronik ICD leads implanted in Royal Victoria Hospital, Belfast, United Kingdom, between 2006 and 2014. They included Vigila and Volta ICD leads marketed by Sorin (Sorin Group, Milan, Italy) but produced by Biotronik and identical to Linox. A total of 98 leads were included in their retrospective analysis (86 Linox and 12 Vigila/Volta). The authors identified a total of 4 lead failures, corresponding to 4% of all Biotronik leads. The failed leads presented with signs of insulation failure: 3 cases of nonphysiological high rate noise sensing leading to VF detection; 1 case with a significant decrease in pacing lead impedance. Only 1 case of externalized conductors was evident at fluoroscopy. All malfunctional leads were subsequently replaced.

Noti *et al*[11] reported their experience with Biotronik ICD leads, implanted in their center (University Hospital of Bern, Switzerland) between 2006 and 2014. They retrospectively compared performance of all Linox/Vigila leads (n = 93) with that of all Boston Scientific Endotak Reliance integrated bipolar leads (n = 190) and Medtronic Sprint Quattro dedicated bipolar lead (n = 202), implanted during the same period. Moreover, all Linox/Vigila leads were screened with fluoroscopy for conductor externalization. Lead failure was defined as follows: Recurrent nonphysiological high-rate sensing unrelated to EMI or T-wave oversensing; a sudden rise in pacing or shock impedance unrelated to perforation or dislodgment; sudden increase in pacing threshold and/or sudden decrease in R-wave sensing; visual evidence of fracture or insulation failure or externalization. The authors identified 9 cases of lead failure in Biotronik leads (9.7%): 2 cases of externalization, 6 cases of nonphysiological high rate noise sensing (5 cases with

inappropriate shocks), 1 case of high-voltage conductor fracture. All failures concerned Linox leads (not Vigila). Lead failure was about 1% for Boston and Medtronic leads. Notably, lead survival at 5 years was 88% for Biotronik, 97.5% for Boston, 100% for Medtronic leads. Moreover, the median time from implant to failure was shorter with Biotronik leads (46 mo) compared with Boston and Medtronic (60 mo). A total of 10 patients died during the study period but circumstances of death were not systematically evaluated. The authors concluded that survival of Biotronik ICD leads was significantly worse than that of other leads; insulation failure was the most common presentation even if conductor externalization was seen only in a minority of failed leads. Younger age was found to be and independent predictor of failure.

In 2015, Padfield *et al*[12] published the results of a multicenter retrospective ICD registry, performed in British Coumbia (BC) region of Canada. Following the introduction of Linox leads the authors began to observe cases of early failure, some of which associated with conductors externalization. Therefore, they systematically evaluated the long term performance of all Linox leads implanted in BC, using St. Jude Medical Durata ICD leads (implanted during the same period) as comparator. This retrospective analysis included a total of 477 Linox and 838 Durata leads, implanted between 2008 and 2014. Definition of lead failure was almost identical to the above-mentioned paper of Noti *et al*[11]. Over a median of 39 (27-50) mo Linox leads had a higher failure rate than the Durata: 16/477 cases of Linox failure *vs* 4/838 for Durata (3.4% *vs* 0.4%). Linox failure type in detail was as follows: 11 cases of recurrent nonphysiological high-rate sensing; 7 cases of sudden impedance rise consistent with lead fracture; insulation failure was confirmed in 6 cases (exposed conductors in the pocket, insulation abrasion, "outside-in" abrasion, *etc*). Notably, no clear case of "Riata like" externalized conductor was evident at fluoroscopy, but systematic radiographic analysis was not performed. Survival rate at 5 years was 91.6% for Linox *vs* 99.4% for Durata ($P < 0.0001$). Failure occurred earlier with Biotronik leads compared to Durata. Female sex was the only independent risk factor for Linox failure in this study ($P = 0.004$). Patient survival analysis was not an end-point of the study and not reported.

Taken togheter these 3 studies[10-12] (with the limitations that we will discuss thereafter) analyzed 668 Biotronik ICD leads and showed a worrisome incidence of Linox leads failure, ranging from 3.4% to 9.7% (*vs* 1% of Endotak Reliance and Sprint Quattro leads and 0.4% of Durata). Survival rate at 5 years (88%-91%) was significantly lower in comparison with the competitors. Failure occurred earlier with Biotronik leads compared to the others. Insulation defect was the main mechanism of failure, while conductor fracture was less frequent but not negligible. Conductor externalization was present only in a minority of cases but fluoroscopic screening was not performed systematically in all studies.

BIOTRONIK PRODUCT PERFORMANCE REPORT

In contrast to the above-mentioned studies, Linox survival rate was 96%-97% at 5 years of follow-up in a product performance report published by Biotronik in July 2015 (http://www.biotronik.com/files/38E6-CFB4E275DE2CC1257EC800531F89/$FILE/Product_Performance_Report_July_2015.pdf), well within industry standards. Anyway, it is well known that reported failure rates from manufacturers are frequently based on voluntary product return and not on systematic data collection, so they are prone to under-reporting bias.

ONGOING PROSPECTIVE REGISTRIES

Conflicting results of spontaneous studies *vs* Biotronik report prompted to evaluate post-market, long-term performance of Linox leads in 2 ongoing large, multi-center, *prospective*, non-randomized, independent registries GALAXY (NCT00836589) and CELESTIAL (NCT00810264)[13].

GALAXY registry was designed to obtain long-term safety and reliability data on Linox family leads implanted in 98 United States sites. Enrollment started in 2009 end was completed in 2011, a total of 1997 patients being included. CELESTIAL post-approval registry was originally designed to evaluate long-term performance of Biotronik Corox family of bipolar left ventricular leads. However many Linox were implanted and included in the study of this ICD lead. The enrollment (2499 patients in 97 United States sites) started in 2008 and was completed in 2013.

A total of 3.933 Linox leads were implanted for both registries and included in the analysis. All patients were implanted with a Biotronik ICD or biventricular defibrillator. The GALAXY and CELESTIAL registry protocols collected adverse events (AEs) related to the implanted system or procedure. A "system-related" AE was defined as follows: (1) an event related to the implanted system occurred; and (2) an action was taken to address the event, or lead use was continued despite a known performance issue, which would have otherwise implicated an action to be taken (*e.g*., patient too ill for extraction).

The median follow-up was 3.6 years for Linox models and 2.3 years for Linox^{Smart}. The analysis of Linox leads showed an excellent performance over time: The estimated cumulative survival rate probability was 96.3% at 5 years after implant for Linox models and 96.6% at 4 years for Linox^{Smart} leads. A relatively low rate of chronic AEs was observed (2.31%). The most common AEs were: Oversensing (23, 0.58%); conductor fracture (14, 0.36%); failure to capture (13, 0.33%); insulation breach (10, 0.25%); high pacing impedance (8, 0.20%).

The authors concluded that Linox leads are safe, reliable and rarely associated with lead-related adverse events, with a clinically acceptable estimated survival

probability that is well within industry standards. Data collection is still ongoing an will be updated in the near future.

DISCUSSION AND CONCLUSION

Transvenous ICD leads are prone to failure over time, representing the weakest link of a defibrillation system. Lead models from various manufacturers have different performance records. Endotak Reliance (Boston), Sprint Quattro (Medtronic) and Durata (St. Jude Medical) have a very low incidence of failure (between 0.4% and 1%); this is expecially true for the leads marketed from a longer time and with longer follow-up duration (Endotak and Sprint Quattro). On the opposite site, other leads have been withdrawn from the market because of a very high rate of failure, and this is the case of Medtronic Sprint Fidelis (over 268000 leads implanted worldwide) and St. Jude Riata (over 227000 implants worldwide).

Recent case reports[4-9] and some studies[10-12]. have raised doubts about the performance of Biotronik ICD leads too. Over 140.000 Biotronik ICD leads have been marketed worldwide (including Kentrox, Linox and Vigila/Volta) so it is of utmost importance to have a high level of awareness and attention when following patients with these leads. For this reason expert consensus exists that systematic post-market surveillance of (all) ICD leads is essential to evaluate their long-term performance.

Linox and Riata leads share some structural similarities: Silicone insulation without outer coating, a coaxial lead design, a rather small diameter. The unique insulation defect described for Riata leads ("inside-out" abrasion) has been consistently reported also for Kentrox and Linox leads. The exact failure mechanism of Biotronik lead is not fully clear, but it is plausible that it is very similar to Riata. While case reports focused the attention on conductors externalization, other studies have shown that this phenomenon was present only in a minority of cases, even if fluoroscopic screening was not always performed systematically. More importantly, insulation defect was the main mechanism of failure for Biotronik leads (independently from conductor externalization). Conductor fracture was less frequent but (differently from Riata) not negligible.

A very important point is to explain the discrepancies existing between single-center studies plus the Canadian retrospective registry[10-12] on one side, and the results of the United States prospective registries (CELESTIAL and GALAXY)[13] on the other side. The former showed a worrisome incidence of Linox leads failure (from 3.4% to 9.7% *vs* 0.4%-1% of competitors) with a significantly lower lead survival rate at 5 years (88%-91%). The latter (CELESTIAL and GALAXY registries) substantially confirm the results of product performance report published by Biotronik, with a 96% survival rate at 5 years and a relatively low rate of chronic adverse events (2.3%). First of all, single-center and retrospective studies have a relatively small sample size (a total of 668 leads) compared to the 2 United States prospective registries (3.933 leads), so it is harder to draw conclusions with smaller numbers. Secondly, the 2 United States registries[13] have a prospective design and a more complete protocol which are best suited to address the question of lead performance. Finally, in the BC Canadian registry Linox leads were predominately connected to a Medtronic device, while most Durata leads were connected to a St. Jude Medical ICD. This is important because each manufacturer has its own proprietary sensing filters and algorithms. Medtronic devices have a proprietary Lead Integrity Alert (LIA™) which is sensitive to nonphysiological short V-V sensing intervals: this algorithm can be useful to assess lead performance, including Linox[14], but when used with non-Medtronic leads it can potentially overestimate the incidence of failure.

In conclusion CELESTIAL and GALAXY registries are quite reassuring, even if Linox performance seems to be slightly inferior to Endotak Reliance, Durata and Sprint Quattro. Data collection from the registries is still ongoing an will be updated in the near future to confirm longer-term performance of this family of ICD leads. Meantime, Biotronik leads can be managed according to usual clinical practice. Literature data do not support the need for a routine fluoroscopic screening, but (in our opinion) it is reasonable to have the lead connected to a Biotronik device whenever possible. Finally, remote monitoring should be activated for early detection of potential nonphysiological high-rate sensing before the occurrence of inappropriate shocks.

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This statement is to certify that all authors have seen and approved the manuscript being submitted, have contributed significantly to the work, attest to the validity and legitimacy of the data and its interpretation, and agree to its submission to the Journal. We attest that the article is the Authors' original work, has not received prior publication and is not under consideration for publication elsewhere. On behalf of all Co-Authors, the corresponding Author shall bear full responsibility for the submission. Any changes to the list of authors, including changes in order, additions or removals will require the submission of a new author agreement form approved and signed by all the original and added submitting authors. Patient's consent was obtained. The authors report no relationships that could be construed as a conflict of interest.

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CASE REPORT

Fatality in Kikuchi-Fujimoto disease: A rare phenomenon

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Abstract

Kikuchi-Fujimoto disease (KFD), also known as histiocytic necrotizing lymphadenitis, is an uncommon condition, typically characterized by lymphadenopathy and fevers. It usually has a benign course; however, it may progress to fatality in extremely rare occasions. The diagnosis is made *via* lymph node biopsy and histopathology. Our patient was a young female who presented with shortness of breath, fever, and malaise. Physical examination revealed significant cervical and axillary lymphadenopathy. Chest X-ray displayed multilobar pneumonia. She required intubation and mechanical ventilation for progressive respiratory distress. Histopathology of lymph nodes demonstrated variable involvement of patchy areas of necrosis within the paracortex composed of karyorrhectic debris with abundant histiocytes consistent with KFD. After initial stabilization, the patient's condition quickly deteriorated with acute anemia, thrombocytopenia and elevated prothrombin time, partial prothrombin time, and D-dimer levels. Disseminated intravascular coagulopathy (DIC) ensued resulting in the patient's fatality. DIC in KFD is not well understood, but it is an important cause of mortality in patients with aggressive disease.

Key words: Kikuchi-Fujimoto disease; Disseminated intravascular coagulopathy; Histiocytic necrotizing lymphadenitis; Lymphadenopathy; Fatality

Core tip: Kikuchi-Fujimoto disease (KFD), or histiocytic necrotizing lymphadenitis, is an uncommon condition, typically characterized by lymphadenopathy and fevers. KFD is an extremely rare disease. With this case we wish to highlight that KFD carries a risk of mortality in the setting of acute, aggressive disease, which is in contrast to the benign, self-limiting condition that has been classically documented in literature. The patient emphasizes the importance of recognizing this as we present the fourth case of disseminated intravascular coagulopathy as a cause of fatality in these patients.

Barbat B, Jhaj R, Khurram D. Fatality in Kikuchi-Fujimoto

disease: A rare phenomenon. *World J Clin Cases* 2017; 5(2): 35-39 Available from: URL: http://www.wjgnet.com/2307-8960/full/v5/i2/35.htm DOI: http://dx.doi.org/10.12998/wjcc.v5.i2.35

INTRODUCTION

Kikuchi-Fujimoto disease (KFD), or histiocytic necrotizing lymphadenitis, is a rare, self-limiting condition characterized by regional lymphadenopathy, fevers, night sweats, and upper respiratory symptoms. Although a viral or autoimmune pathogenesis has been suggested, the etiology continues to remain unknown. Diagnosis is based on histologic features noted on excisional biopsy. A majority of cases have a benign course; rarely does KFD result in death. After performing a wide literature search, we only found three other documented cases that resulted in death from disseminated intravascular coagulopathy (DIC). This disease was initially thought to have a predilection for Asian women between the ages of 20 and 35 years. However, new cases of KFD have also been described in non-Asian ethnicity and young age groups in the United States[1]. Recognition of KFD is essential because it can easily be mistaken for lymphoma, tuberculosis, or carcinoma[2]. Here we report a case of a patient with KFD who died secondary to DIC.

CASE REPORT

The patient was a previously healthy, 21-year-old female who presented with a two-day history of dyspnea, fever, and malaise. Initial set of vitals revealed a blood pressure of 109/57 mmHg, temperature of 38.2 ℃, heart rate of 118 bpm, respiratory rate of 24 breaths/min, and oxygen saturation of 78% on room air. On 4 liters of nasal cannula, her oxygen saturation improved to 97%. A chest X-ray demonstrated multifocal pneumonia. Treatment for community-acquired pneumonia was initiated with ceftriaxone and azithromycin. On physical examination, she was noted to have significant axillary, cervical and inguinal lymphadenopathy. Her respiratory status continued to decline despite supplemental oxygen therapy and antibiotics, requiring emergent endotracheal intubation with mechanical ventilation. A computerized tomography (CT) chest, abdomen, and pelvis was performed, which revealed significant cervical and axillary lymphadenopathy, bilateral lung consolidation, and a moderate pericardial effusion (Figure 1).

As the patient's presentation was very severe, a comprehensive differential was considered. Among the entire laboratory data that was performed HIV, streptococcus pneumonia, legionella, histoplasma, brucella, aspergillus, tuberculosis, influenza, respiratory syncytial virus were negative. There was a mild elevation in mycoplasma IgM and chlamydia antibody titer. The patient's antibiotic therapy was tailored to include a broader spectrum of organisms. Bronchoscopy with bronchoalveolar lavage was performed given the above CT findings. There was no evidence of mucus plugs, active bleeding, endobronchial lesions or anatomical abnormalities. Pathology of the fluid revealed presence of acute inflammatory cells. A transthoracic echocardiogram revealed normal systolic function with a moderate pericardial effusion without tamponade physiology.

Due to the significant lymphadenopathy, pericardial effusion, and an elevated LDH of 2319 unit/L, a concern for lymphoma was raised. Therefore, a cervical lymph node biopsy was performed. Histopathology demonstrated variable involvement of patchy small to large areas of necrosis within the paracortex. The necrotic areas were composed of karyorrhectic debris with abundant histiocytes consistent with KFD (Figure 2).

Septic work up consisting of blood, sputum and urine cultures remained negative throughout her admission. Despite aggressive antibiotic therapy, high dose steroids, and supportive care, the patient's condition continued to decline. She required increasing pressure support to maintain oxygenation. Intravenous immune globulin (IVIG) was given without any improvement in the patient's symptoms. The hemoglobin level began to precipitately decrease without any active sites of bleeding. A hemolytic work up was initiated, which revealed a haptogobin < 10 mg/dL and schistocytes on peripheral smear. She then developed significant thrombocytopenia with platelet level recorded as low as 26 K/mcL. Partial thromboplastin time, prothrombin time levels and D-dimer levels started to rise. Fresh frozen plasma was transfused for impending DIC. The patient's clinical condition and laboratory parameters continued to deteriorate despite resuscitative efforts in the intensive care unit. Unfortunately, she expired secondary to development of DIC.

DISCUSSION

KFD, or histiocytic necrotizing lymphadenitis, is rare and usually has a benign self-limiting course. The etiology of this disease has not been established yet, but there are viral origins including HHV-6, HHV-8, and EBV that have been theorized[3]. One study found that apoptotic cell death plays a role in the pathogenesis of KFD[4]. The most common symptoms include, but are not limited to lymphadenopathy, fatigue, fevers, night sweats and weight loss.

There are no specific laboratory values that are pathognomonic for this disease. A case review of 244 patients with KFD revealed laboratory values that were unremarkable except for an elevated ESR, mild neutropenia, and lymphocytosis in some cases[5]. Imaging can aid in limiting the differential diagnosis. CT and magnetic resonance imaging can be useful for evaluating patients with cervical lymphadenopathy. CT features may mimic those of lymphoma; however, lymph nodes in KFD are not as large as those in

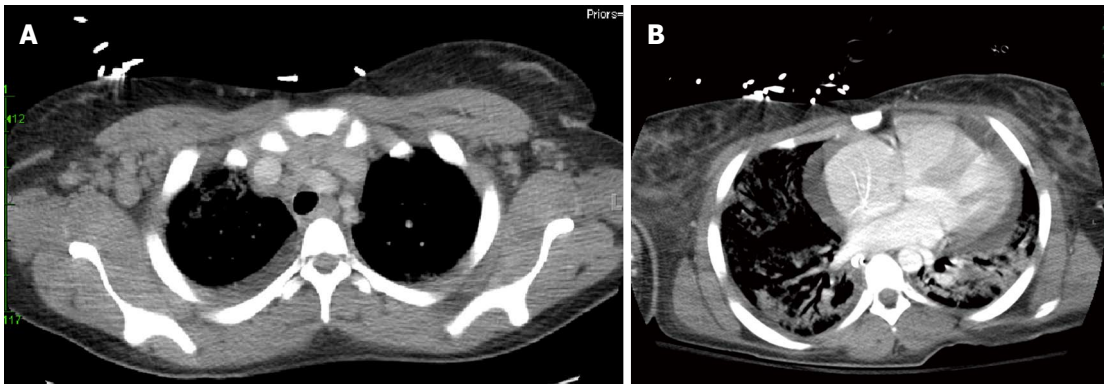

Figure 1 Computerized tomography chest. A: Computerized tomography (CT) chest demonstrating significant axillary lymphadenopathy; B: CT chest revealing bilateral lung consolidation, and a moderate pericardial effusion.

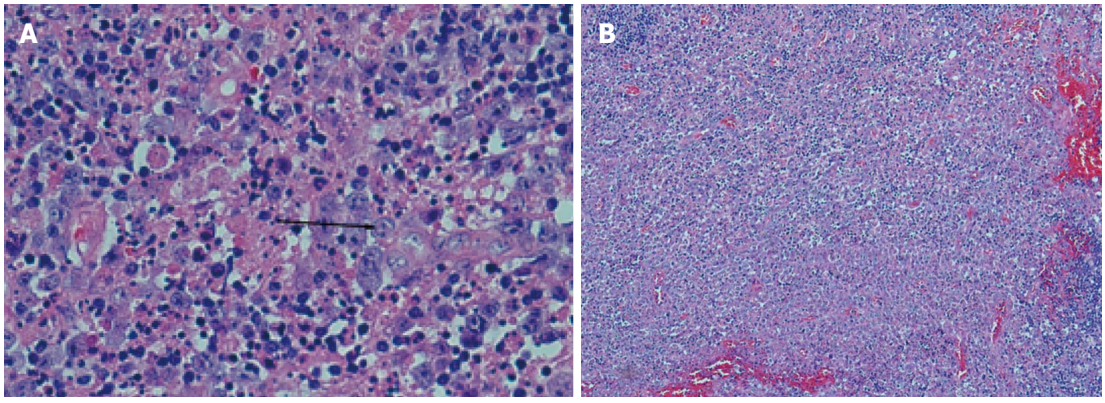

Figure 2 Histopathology. A: High magnification view with arrow revealing histiocyte. Histiocytes are derived from blood monocytes and digest debris; B: Sample of a cervical node biopsy revealing multiple areas showing necrotic foci.

lymphoma[6].

A definite diagnosis of KFD is made by biopsy, typically excisional, but fine needle aspiration has also been used. There are some characteristic histologic features of KFD including patchy necrotizing areas primarily in the paracortical regions that contain fibrinous material with karyorrhexis. A distinctive mottled appearance may be noted, as immunoblasts tend to border necrotic zones[7]. Early diagnosis is important as the clinical and laboratory presentations can imitate situations needing time-consuming and expensive interventions[5]. KFD can be easily misdiagnosed; literature estimates as high as 40% of the time with lymphoma being the most commonly mistaken diagnosis[8].

Once the diagnosis is made, symptomatic and supportive treatment is usually adequate. When symptomatology requires treatment, a short course of corticosteroids is preferred. Currently, there are no recommendations on exact dosage or route of administration[9]. In severe cases, high dose intravenous steroids have been shown to be effective and aid in symptom reduction[10]. IVIG has been shown to be successful in several, critical cases. Once again, no formal recommendations on dosing and duration exist. IVIG has been routinely implemented as empiric therapy in autoimmune and inflammatory processes secondary to its immunomodulatory properties[11]. In individuals with a benign hospital course, it is important to have adequate follow up as patients have an increased risk of relapse. One study showed that hydroxychloroquine could be used in the treatment of relapsed KFD[12]. On rare instances, despite these treatment modalities, KFD may progress to mortality such as the patient we presented.

Our patient is unique as she had an extremely progressive course of Kikuchi lymphadenitis with subsequent multiorgan failure and death from DIC. In our review of literature, we found three other documented cases of death in KFD as a result of DIC (Table 1)[13,14]. Other causes of death included hemophagocytic syndrome and severe infection[15], pulmonary hemorrhage[16] and acute heart failure[17].

The precise mechanism of DIC in KFD is unknown. A proposed mechanism involves a massive cytokine release during the acute phase of the disease, mainly consisting of tumor necrosis factor-alpha, interleukin-1, and interleukin-6. These cytokines result in significant endothelial damage and activation of the thrombosis and anticoagulation cascade pathognomonic for DIC[13].

Table 1 Fatalities in Kikuchi-Fujimoto disease

Ref.	Presentation	Presence of autoantibodies	Cause of death
Uslu *et al*[13], 2014	A 32-year-old female with fever, fatigue, chest and abdominal pain for 15 d	Not mentioned	DIC
Sharma *et al*[14], 2015	A 57-year-old fever with fever and UTI	Yes: ANA, anti-La, anti-RNP	Septic shock and DIC
Sharma *et al*[14], 2015	A 55-year-old female with fever, dizziness, loss of balance, decreased hearing, diarrhea, vomiting and a non-blanching rash over the upper arms and thighs	Yes: Anti-Ro and anti-La	DIC

DIC: Disseminated intravascular coagulopathy; UTI: Urinary tract infection; ANA: Antinuclear antibody; anti-RNP: Anti-ribonucleoprotein.

In our patient, all other potential causes of DIC including sepsis and acute myeloid leukemia were negative, supporting the association of DIC and KFD.

KFD is an extremely rare disease. With this case we wish to highlight that KFD carries a risk of mortality in the setting of acute, aggressive disease, which is in contrast to the benign, self-limiting condition that has classically been documented in literature. Our patient emphasizes the importance of recognizing this fact as we present the fourth case of DIC as a cause of fatality in these patients.

COMMENTS

Case characteristics

The patient is a 21-year-old female who presented with symptoms of malaise and fevers.

Clinical diagnosis

The main clinical findings included cervical and axillary lymphadenopathy.

Differential diagnosis

Differential diagnosis included lymphoma, viral syndrome and bacterial infections. Computerized tomography scan findings confirmed the lymphadenopathy as well as bilateral lung consolidation, and a moderate pericardial effusion. Histopathology of the lymph node biopsy revealed findings consistent with Kikuchi-Fujimoto disease (KFD).

Treatment

In most cases, supportive treatment is adequate. In severe cases and relapsing cases, intravenous immune globulin and hydroxychloroquine have been used, respectively.

Related reports

Unfortunately, our patient expired secondary to disseminated intravascular coagulopathy (DIC). The exact mechanism of how DIC occurs in KFD is unknown; however, it has been proposed that cytokine release plays a role. With this case we wish to highlight that KFD carries a risk of mortality in the setting of acute, aggressive disease, which is in contrast to the benign, self-limiting condition that has classically been documented in literature.

Term explanation

KFD: Kikuchi-Fujimoto disease.

Peer-review

KFD is an extremely rare disease. The authors highlighted that KFD carries a risk of mortality in the setting of acute, aggressive disease, which is in contrast to the benign, self-limiting condition that has been classically documented in literature. This set of cases emphasizes the importance of recognizing the fact of DIC as a cause of fatality in these patients.

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CASE REPORT

Aggressive restenosis after percutaneous intervention in two coronary loci in a patient with human immunodeficiency virus infection

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Abstract

A 54-year-old black African woman, 22 years human immunodeficiency virus (HIV)-positive, presented with an acute coronary syndrome. She was taking two nucleoside reverse transcriptase inhibitors and two protease inhibitors. Viral load and CD4 count were stable. Angiography revealed a right coronary artery lesion, which was treated with everolimus eluting stent. She also underwent balloon angioplasty to the first diagonal. She re-presented on three different occasions and technically successful coronary intervention was performed. The patient has reported satisfactory compliance with dual anti platelet therapy throughout. She was successfully treated with surgical revascularisation. The patient did not experience any clinical recurrence on follow up. This case demonstrates exceptionally aggressive multifocal and recurrent instent restenosis in a patient treated for HIV infection, raising the possibility of an association with HIV infection or potentially components of retro viral therapy.

Key words: Coronary artery disease; Restenosis; Human immunodeficiency virus

Core tip: With an increasing burden of cardiovascular disease in patients with human immunodeficiency virus (HIV), a subgroup of patients may emerge in whom this represents a significant clinical challenge. Better understanding of the responsible mechanisms may allow more tailored pharmacotherapy for susceptible individuals. We report an exceptionally aggressive and recurrent case of coronary stent restenosis in HIV positive patient. Numerous percutaneous interventions were performed but eventually patient was treated successfully with surgical revascularisation.

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INTRODUCTION

Restenosis is encountered after coronary revascularisation and it is attributed as part of the arterial healing process in response to stents[1]. It had been a major drawback when using balloon angioplasty and bare metal stents but was reduced using drug eluting stents[2]. Procedural-related factors, such as stent malposition, coronary anatomy (*e.g.,* ostial disease) and patient-specific considerations (*e.g.,* diabetes) increase risk of instent restenosis (ISR)[1].

Human immunodeficiency virus (HIV) has been linked to increase risk of future cardiovascular events[3,4]. Contrary to earlier reports[5], restenosis was found to be comparable between patients with and without HIV infection[3,4]. The increase use of drug eluting stents may have contributed to the reduction in ISR in HIV population[6].

We have encountered a case of aggressive and recurrent restenosis in HIV patient despite using second-generation drug eluting stent. Below we described the details of this case with brief review of the literature.

CASE REPORT

A 54-year-old black African female was diagnosed HIV-positive 22 years prior to presentation with an acute coronary syndrome (ACS). She had been managed with combination of two nucleoside reverse transcriptase inhibitors (Lamivudine and Abacavir) in addition to two protease inhibitors (Lopinavir and Ritonavir). The CD4 count had been stable of 250 cells/mm^3 with a viral load of 150-250 copies/mL. There was a history of treated hypertension and treated hypercholesterolemia.

Her cardiac history (below) spans 20 mo. Initial presentation was with an episode of chest pain at rest associated with inferolateral ST segment depression on the ECG. Angiography revealed a 70% right coronary artery (RCA) lesion, which was treated with a 3.0 mm × 23 mm Xience (Abbott Vascular) Everolimus drug eluting stent (DES), post dilated with a 3.0 Quantum non-compliant balloon (Boston Scientific) (Figure 1A and B). In addition, she underwent balloon angioplasty to the first diagonal branch with 3.0 × 12 Maverick balloon (Boston Scientific) (Figure 1C and D).

She represented 7 mo later with stable angina and was found to have a *de novo* lesion in the mid left anterior descending artery (LAD) with satisfactory result to the diagonal branch but severe in stent restenosis (ISR) in the previously stented RCA. The ISR segment was predilated with Maverick balloon (Boston Scientific) and a paclitaxel-eluting balloon was inflated to 18 atmosphere for 45 s (Figure 2A and B). The LAD lesion was stented with 3.5 mm × 23 mm Xience stent and post dilated with 3.5 × 12 Quantum non-complaint balloon (Figure 2C and D).

Eight months later, she presented again with an acute coronary syndrome. Repeat angiography demonstrated severe ISR in both the RCA and LAD stents. Following lesion preparation with a 3.0 cutting balloon, both RCA and LAD were stented - with 3.0 mm × 28 mm and 3.5 mm × 28 mm Xience stents respectively (Figure 3). Stents were post dilated to high pressure with 3.5 Quantum balloon. The end angiographic result was excellent in both arteries.

Yet, within 4 mo she was experiencing recurrent exertional chest discomfort. A further coronary angiogram showed subtotal occlusion of the LAD with TIMI2 flow and both antegrade and retrograde filling, from RCA. The occluded segment was within the distal portion of the stent. The RCA was sub totally occluded by severe ISR in the stented segment (Figure 4). It is worth noting that patient has reported satisfactory compliance with her dual anti platelets therapy throughout her multiple interventional procedures. She was referred for surgical revascularisation.

DISCUSSION

This case demonstrates exceptionally aggressive multifocal and recurrent instent restenosis in a patient treated for HIV infection. Restenosis can occur as part of an arterial healing response after injury following coronary stenting[1]. Neointimal hyperplasia occurs due to proliferation of smooth muscle cells and has been successfully ameliorated by the use of drug-eluting stents[2]. In contemporary series, the restenosis rate in first generation DES ranged between 0% and 16% depending on complexity of targeted lesions[7], while the rate of recurrent restenosis was 11%[8]. Factors associated with increased risk of ISR include: Diabetes mellitus, small calibre vessel disease, ostial disease and vein graft stenosis[1].

Treatment options are balloon catheter angioplasty, implantation of a second, coated or uncoated stent,

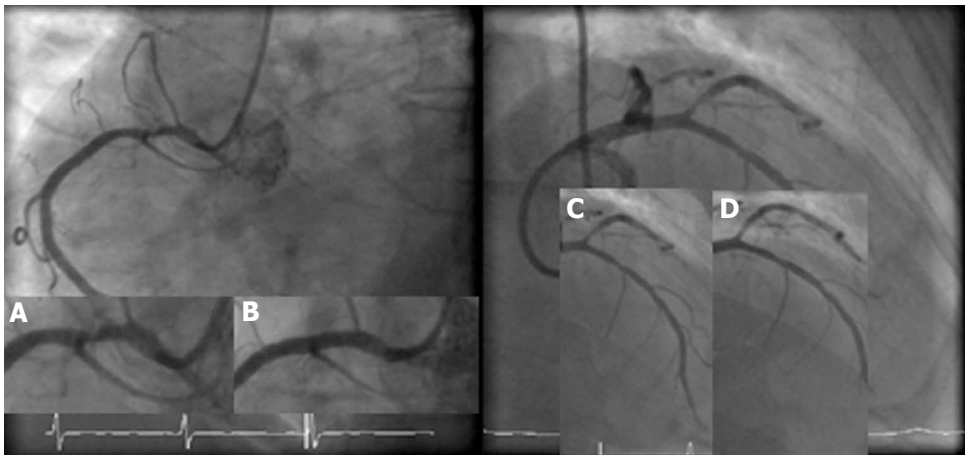

Figure 1 Initial coronary angiogram showing proximal right coronary and first diagonal stenoses. A, B: Right coronary artery pre- and post-stenting with 3.0 Xience Everolimus drug eluting stent, respectively; C, D: Pre- and post-balloon angioplasty to first diagonal, respectively.

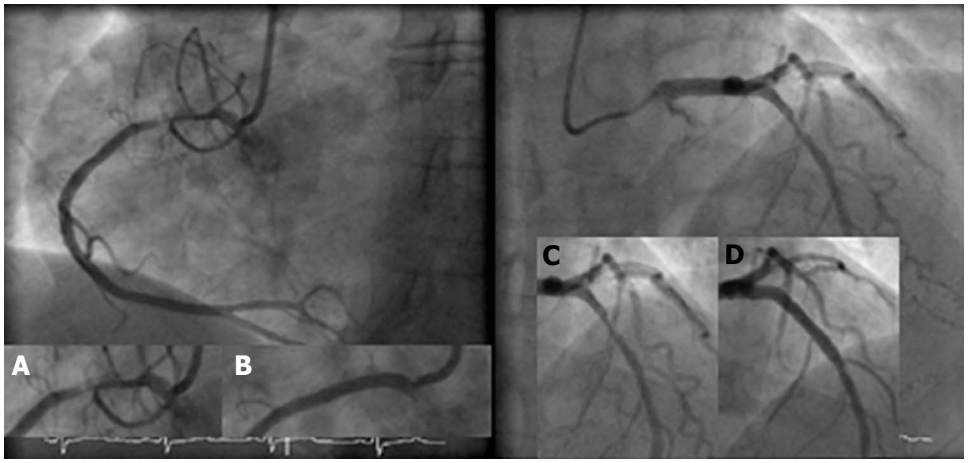

Figure 2 Second coronary angiogram following presentation with stable angina. A, B: Severe instent restenosis in the proximal segment of RCA and result post-Paclitaxel drug eluting balloon; C, D: Severe stenosis in mid LAD segment stented and subsequently stented with 3.5 Xience Everolimus drug eluting stent. LAD: Left anterior descending artery; RCA: Right coronary artery.

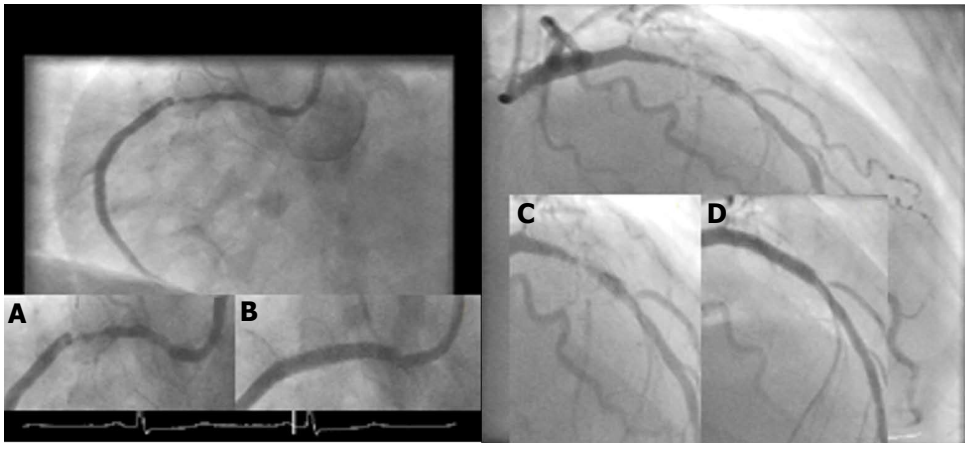

Figure 3 Coronary angiogram performed following second acute coronary syndrome event. A, B: Severe recurrent instent restenosis within the proximal segment of RCA and subsequent Xience stent; C, D: Severe ISR within mid LAD stented segment and subsequent Xience stent. LAD: Left anterior descending artery; RCA: Right coronary artery; ISR: In stent restenosis.

mechanical debulking (*e.g.,* rotablation), intracoronary irradiation (brachytherapy) and drug eluting balloon.

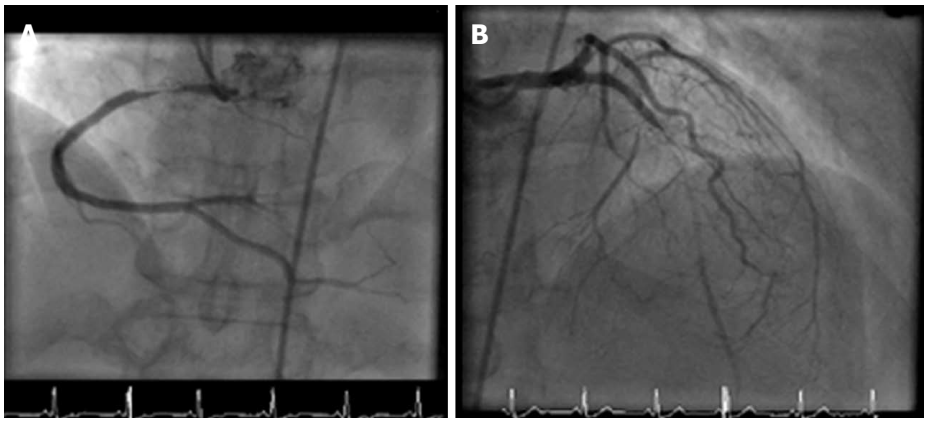

Figure 4 Further coronary angiogram following intractable angina symptoms. A: Sub totally occluded proximal RCA within stented segment; B: Sub totally occluded LAD with antegrade filling. LAD: Left anterior descending artery; RCA: Right coronary artery.

These approaches have various rates of success[9].

In an HIV-positive population, a higher rate of ischemic heart disease compared to general population has been reported[10]. Although there was no difference in morbidity or mortality during hospital admission between HIV and general population, it was noted that on long term follow up there was an increased risk of recurrent ischemic events in HIV compared to non HIV presenting with ACS[3,4]. There was no difference in the rate of clinical restenosis between two groups[4]. Although it has previously been reported that target vessel revascularization and ISR were higher in HIV population[5], this trend was diminished in more contemporary studies[3,4]. This may be explained by the high rate of stenting in the latter studies with drug eluting stents leading to 60% fewer major adverse cardiovascular events in HIV population[6].

Antiretroviral therapy (ART) is a potential atherosclerotic risk in HIV patients[11]. Although this therapy has improved the care of HIV infection, metabolic side effects have been observed, including dyslipidaemia and insulin resistance[11]. The combination therapy was independently associated with increased rate of myocardial infarction[11]. Moreover, the incidence of myocardial infarction rose after the introduction of protease inhibitors[12]. This risk was still significant for protease inhibitor after adjustment for lipid concentration[10].

Nucleoside reverse transcriptase inhibitors did not show similar cardiovascular risk profile as protease inhibitors[13]. No associations between the rate of myocardial infarction and cumulative or recent use of zidovudine, stavudine, or lamivudine. On the other hand, recent, but not cumulative, use of Abacavir or Didanosine was associated with increase rate of myocardial infarction[14]. Interestingly, neither drug is thought to have substantial effect on metabolic profile[14].

In this case, patient was non-diabetic and both LAD and RCA stents were deployed at high pressure with satisfactory angiographic results. Everolimus eluting stents were persistently used to treat the restenosis in this case. It is unlikely that using another stent with different drug such as zotarolimus or biolimus may have changed the outcome. Recent meta-analysis demonstrated that although second generation stents carry lower risk of target vessel revascularisation compared to first generation stents (which eluted sirolimus or paclitaxel), there was no difference among everolimus, zotarolimus or biolimus drug eluting stents[15]. Whether HIV status may have influence on drug eluting stent outcome is not well documented and further research is warranted.

In this case, the HIV therapy had been stable and has not changed over the period of coronary intervention, and nor had the viral load or CD4 count. Yet, we observed aggressive restenosis raising the possibility of an association with her HIV infection or potentially components of her ART therapy. Although HIV infection causes attenuated inflammatory response to infections, it causes profound functional alterations of the endothelium, resembling the subclinical inflammation in atherosclerosis[16]. Leukocyte adherence to endothelium is enhanced as the expression of cell adhesion molecules increases[16]. Higher levels of soluble adhesion molecules have been found before the introduction of ART[17]. Moreover, ART has a stimulator effect on some of these molecules, enhancing HIV effect on endothelial function[17]. Furthermore, HIV infection can stimulate proliferation of human vascular smooth muscle cells and therefore promote atherosclerosis[10]. Although it has been reported that risk of restenosis in HIV corresponds to level of viral load[18], it is not clear whether smooth muscle cell proliferation and the accumulation of extracellular matrix, which are the main processes involved in in-stent restenosis, may be induced by protease inhibitors or by the HIV itself[19]. The chronic low-level inflammation in HIV patients may also contribute to their high rate of restenosis[5]. HIV patients have higher levels of C-reactive protein than their age and sex-matched controls[5].

This case shows exceptionally aggressive restenosis after PCI. As cardiovascular disease becomes more prevalent in patients with HIV, a subgroup of patients may emerge in whom this represents a significant clinical challenge. Better understanding of the responsible mechanisms may allow more tailored pharmacotherapy for susceptible individuals.

COMMENTS

Case characteristics

A 54-year-old lady with 22 years history of human immunodeficiency virus (HIV) on antiretroviral therapy.

Clinical diagnosis

Coronary artery disease with recurrent in-stent restenosis.

Differential diagnosis

Stent thrombosis.

Laboratory diagnosis

Rise in cardiac enzymes, including troponin.

Imaging diagnosis

Diagnostic angiogram confirming restenosis of coronary stents.

Treatment

Despite attempts with percutaneous revascularisation, patient was eventually and successfully treated with surgical revascularisation.

Term explanation

ISR: In-stent restenosis.

Peer-review

The authors report a clinical case of a patient with HIV infection on antiretroviral therapy with recurrent in-stent restenosis requiring several percutaneous intervention and finally coronary artery bypass graft. The case is interesting and well written.

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CASE REPORT

Unexpected challenging case of coronary sinus lead extraction

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Author contributions: Bontempi L contributed to the conception and design of the work, drafting the article, final approval; Tempio D, De Vito R, Cerini M, Salghetti F, Dasseni N, Villa C, Raweh A, Inama L, Vassanelli F, Luzi M, Curnis A contributed to the drafting and critical revision of the work, final approval.

Institutional review board statement: The ethics committee approval is not required by the regulations for case report.

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Abstract

An 84-year-old woman implanted with cardiac resynchronization therapy defibrillator underwent transvenous lead extraction 4 mo after the implant due to pocket infection. Atrial and right ventricular leads were easily extracted, while the attempt to remove the coronary sinus (CS) lead was unsuccessful. A few weeks later a new extraction procedure was performed in our center. A stepwise approach was used. Firstly, manual traction was unsuccessfully attempted, even with proper-sized locking stylet. Secondly, mechanical dilatation was used with a single inner sheath placed close to the CS ostium. Finally, a modified sub-selector sheath was successfully advanced over the electrode until it was free of the binding tissue. The post-extraction lead examination showed an unexpected fibrosis around the tip. No complications occurred during the postoperative course. Fibrous adhesions could be found in CS leads recently implanted requiring non-standard techniques for its transvenous extraction.

Key words: Cardiac resynchronization therapy; Coronary sinus lead; Transvenous lead extraction; Cardiac pacing; Fibrosis

Core tip: Coronary sinus lead extraction is a safe procedure with complication rates comparable to those of the extraction of other leads in experienced centers. The main difficulties may be related to the thickness of the coronary sinus structure and the fibrotic adhesions along it. In this case report we describe an unusual case of persistent fibrosis at the tip of a coronary sinus lead only 4 mo after implantation and the non-standard techniques adopted to achieve successful extraction.

Bontempi L, Tempio D, De Vito R, Cerini M, Salghetti F, Dasseni N, Villa C, Raweh A, Inama L, Vassanelli F, Luzi M, Curnis A. Unexpected challenging case of coronary sinus lead extraction. *World J Clin Cases* 2017; 5(2): 46-49 Available from: URL: http://www.wjgnet.com/2307-8960/full/v5/i2/46.htm DOI: http://dx.doi.org/10.12998/wjcc.v5.i2.46

INTRODUCTION

As the number of cardiac resynchronization therapy (CRT) devices increases, so does the need for coronary sinus (CS) lead extraction, especially because patients with CRT are among those with the highest risk of device related complications[1]. Although there are potential risks of complications associated with the thin wall of the CS and of the afferent branches, CS lead extraction is a safe procedure when performed by experienced professionals due to the generally low rate of adhesions along the coronary vein[2]. We shall describe an uncommon case of fibrotic adhesions at the tip of the CS lead a few months after the implant and the transvenous techniques adopted to successfully extract the lead.

CASE REPORT

An 84-year-old woman implanted with CRT defibrillator for idiopathic cardiomyopathy underwent a transvenous lead extraction (TLE) 4 mo after the implant due to a local pocket infection with chronic positive blood culture of *Staphylococcus Pseudintermedius*. Atrial and right ventricular leads were easily extracted, while the attempt to remove the CS lead (Attain® Performa™ Model 4298, Medtronic, Minneapolis, MN, United States) was unsuccessful in the referral center. The patient was then brought to our attention to complete the extraction of the CS lead, in accordance with the current guidelines which set a class I indication to complete system removal in case of device-related infection[3]. The procedure was carried out, under local anesthesia, in our laboratory by two expert interventional electrophysiologists and a cardiac surgeon on standby. Before the procedure, contrast material was administered through the intravenous line, ipsilateral to the site of placement to assess the patency of the subclavian vein. The CS lead was visually examined by fluoroscopy (Figure 1). Two unsuccessful attempts of gentle manual traction (MT) were subsequently performed: The first after the introduction of an Attain Hybrid guidewire (Medtronic) and the second with a locking stylet LLD E (Lead Lock Device Spectranetics, Colorado, United States or Cook Intravascular Inc, IN, United States) advanced as distal as possible. Mechanical dilatation (MD) was then used through a single polypropylene inner sheath with an internal diameter of 8.5 Fr (Cook Intravascular Inc.) advanced up to the CS ostium. Stable traction of the locking stylet still failed to detach the lead; all movements were carefully coordinated in order to avoid injury to the vessel, and especially to the superior vena cava.

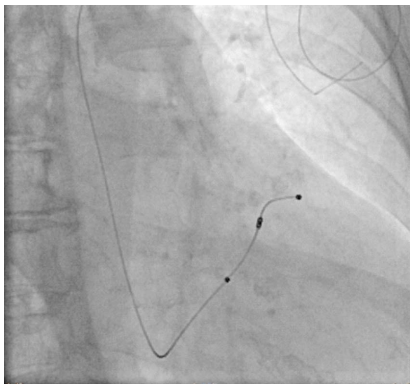

Figure 1 Coronary sinus lead position before cardiac lead extraction.

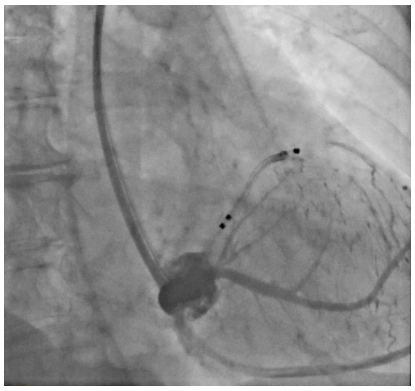

Figure 2 Coronary sinus angiography, by Attain Command™ Delivery system.

Afterwards, CS was cannulated using an Attain Command™ Delivery System (Medtronic), but due to the inability to reach the tip of the lead, an Attain Select™ sub-selector (Medtronic) was added and advanced inside the CS branch. After both sheaths were successfully inserted, angiographies were performed to verify the integrity of the vascular system (Figure 2). At the sub-selective CS venography, the vessel of the electrode was not visualized. A distal branch occlusion

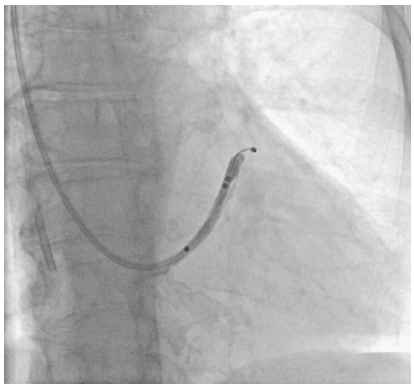

Figure 3 Coronary sinus subselective angiography by Attain Select™ sub-selection catheter.

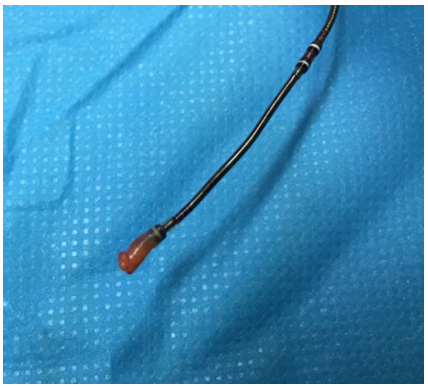

Figure 4 Extracted electrode with fibrotic adhesions at the distal tip.

was present, probably due to the development of fibrotic processes (Figure 3).

In order to give more cutting force and increase the shear strength, we decided to cut the sub-selector sheath 1.5 cm from the distal part. With the modified delivery system, the lead was disengaged and pulled back into the sheath.

Despite the short implantation period, the post-extraction examination showed an extended fibrosis on the surface of the lead body (Figure 4). No CS dissection was observed and the postoperative course was uneventful.

DISCUSSION

We are reporting a difficult CS TLE a few months after the implant, which required challenging MD up to the distal tip of CS lead using both conventional sheaths and modified CS lead delivery due to fibrotic adherence.

Recently, HRS published an expert consensus statement[3] which asserts that the infection of the pocket, device, and/or lead is the most frequent Class I indication for lead removal.

Lead extraction is still a challenging procedure requiring specific expertise. HRS recommends at least 40 cases experience for the physician acting as first operators, whereas a minimum number of 20 annual extractions should be requested[4,5].

A frequent issue found during the lead extraction is the presence of fibrotic processes on body leads, both in vascular and endocardial side. This problem is much more sporadic in the CS, where the only region easily affected by fibrosis is the ostium. However, there is still a great concern about CS extraction because of the potential risk of cardiac tamponade due to CS dissection.

CS leads can be often successfully extracted with direct traction only, as reported by a recent study on 125 leads[6], but literature is not exhaustive.

Nevertheless, in a small percentage of cases, major and possibly life-threatening complications are related to the extraction tools used in the weak CS structure in unfavourable anatomical positions, raising questions regarding the possible need of tools specifically designed for this structure.

In addition, CS leads have different designs, having a smaller body diameter than atrial or ventricular leads with less physical resistance to traction and a higher risk of rupture. In order to avoid lead damage the counter pressure or countertraction maneuvers have to be applied with special care.

Our procedure consisted in the following phases: (1) manual traction was attempted; (2) a locking stylet (LLD E) was put forward along the lumen and locked at the distal part of the lead, then MT was attempted again; (3) as traction was unsuccessful due to unexpected fibrosis, a modified delivery sheath was advanced over the lead until the lead was disengaged from all the tissue at the distal tip of CS lead. Despite our experience in lead extraction[7], in this case removing a CS lead was unexpectedly difficult, not only by MT but also performing MD.

To date, there are no tools specifically designed for CS lead extraction. In order to complete the procedure successfully we had to directly modify a standard CS delivery system to obtain a non-traumatic dissection of local fibrosis.

This case highlights the importance of approaching each single procedure with caution as even a potentially simple case may be challenging for an expert operator.

In conclusion, persistent fibrosis at the tip of a CS lead was found during the extraction procedure 4 mo after implant. A tailored technique consistent of locking stylet MT with a modified sub-selector delivery sheath advanced over the lead in the CS branch was successful.

COMMENTS

Case characteristics

An 84-year-old woman implanted with cardiac resynchronization therapy defibrillator had persistent fevers.

Clinical diagnosis

The patient presented a pocket infection.

Differential diagnosis

The patient underwent transvenous lead extraction 4 mo after the implant, but difficulties were found in the coronary sinus lead extraction.

Laboratory diagnosis
The infection presented persistent positive blood culture of *Staphylococcus Pseudintermedius*.

Imaging diagnosis
At the sub-selective coronary sinus venography, the vessel of the electrode was not visualized; a distal branch occlusion was present, probably due to the development of fibrotic processes.

Pathological diagnosis
The post-extraction examination showed an extended fibrosis on the surface of the lead body.

Treatment
A modified sub-selector sheath was successfully advanced over the electrode until it was free of the binding tissue.

Related reports
Coronary sinus leads can be often successfully extracted with direct traction only, the presence of fibrotic processes on body leads is uncommon in the coronary sinus, in particular after few months from the implant.

Term explanation
A sub-selector sheath is a tool used during resynchronization therapy defibrillator implant to reach and deliver the electrode in the target vessel of the coronary venous system.

Experiences and lessons
Persistent fibrosis at the tip of a coronary sinus lead might be found also few months after implant, a tailored technique with a modified sub-selector delivery sheath advanced over the lead in the coronary sinus branch allowed to complete the extraction procedure.

Peer-review
This is a rare case report about coronary sinus lead extraction using new techniques. This manuscript is nicely structured and well written.

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CASE REPORT

Rapunzel syndrome is not just a mere surgical problem: A case report and review of current management

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Abstract

Recurrent Rapunzel syndrome (RRS) is a rare clinical presentation with fewer than six cases reported in the PubMed literature. A report of RRS and literature review is presented. A 25-year-old female was admitted to hospital with a 4-wk history of epigastric pain and swelling. She had a known history of trichophagia with a previous admission for Rapunzel syndrome requiring a laparotomy nine years earlier, aged 16. Psychological treatment had been successfully achieved for nine years with outpatient hypnotherapy sessions only, but she defaulted on her last session due to stressors at home. The abdominal examination demonstrated an epigastric mass. Computer tomography scan revealed a large gastric bezoar and features of aspiration pneumonia. The patient underwent emergency open surgical laparotomy for removal as the bezoar could not be removed endoscopically. The bezoar was cast in a shape that mimicked the contours of the stomach and proximal small bowel, hence the diagnosis of RRS. The patient was seen by a psychiatrist and was commenced on Quetiapine before discharge. She continues to attend follow-up.

Key words: Trichobezoars; Rapunzel syndrome; Recurrence; Obsessive compulsive disorders; Case report

Core tip: There remain to be clear guidelines on the management of trichotillomania associated disorders. Here we report that Rapunzel syndrome requires a comprehensive and long-term psychiatric follow-up as it is not a primary surgical condition. A late relapse of the condition is possible and recognizing this as a clinical possibility can intensify efforts in relapse prevention during the follow-up period. This approach is important in eliminating the need for recurrent surgical

interventions and associated morbidity. Multidisciplinary health care teams headed by a psychiatrist as well as family support play a key role in the prevention of recurrence.

Obinwa O, Cooper D, Khan F, O'Riordan JM. Rapunzel syndrome is not just a mere surgical problem: A case report and review of current management. *World J Clin Cases* 2017; 5(2): 50-55 Available from: URL: http://www.wjgnet.com/2307-8960/full/v5/i2/50.htm DOI: http://dx.doi.org/10.12998/wjcc.v5.i2.50

INTRODUCTION

A bezoar is a collection of foreign material in the gastrointestinal tract. A trichobezoar is a bezoar formed by the ingestion of hair and occurs typically in patients with trichotillomania. The latter is defined as an irresistible desire to pull out one's hair and it has been included in the 2013 Diagnostic Statistical Manual (DSM-5) of the American Psychiatry Association as an obsessive compulsive disorder[1].

Rapunzel syndrome is a rare manifestation of a trichobezoar, which occurs when strands of swallowed hair extend beyond the pylorus of the stomach, into the intestine as a tail[2]. It was first described by Vaughan *et al*[3] in 1968. Primary or recurrent cases of trichobezoars may lead to complications such as intussusception[4,5], pancreatitis[6] and bile duct dilatation[4]. Significant other complications such as gastric perforation[7,8], peritonitis[9], and even death[10] have also been reported. Despite the potential for significant complications and mortality, there is still a lack of any specific and comprehensive guidelines on appropriate postoperative follow-up for patients with Rapunzel syndrome to reduce the risk of recurrence[11].

In this case report, we present a rare case in which Rapunzel syndrome represented nine years following an initial laparotomy. This manuscript is written in accordance with the case report (CARE) guidelines[12]. The clinical management dilemmas in this case, including those accounting for the recurrent Rapunzel syndrome (RRS), have been reported to inform guidelines on appropriate postoperative follow-up of patients with Rapunzel syndrome.

CASE REPORT

A 25-year-old female was admitted to hospital with a 4-wk history of epigastric pain, swelling and early satiety. The symptoms, while initially intermittent, had become more constant and severe over the four days prior to admission. She denied any nausea, vomiting, weight loss or change in bowel habit. She had a known history of trichophagia (compulsive ingestion of hair) with a previous admission for Rapunzel syndrome requiring an anterior gastrotomy nine years earlier, aged 16. She had been referred to a psychiatry service following this episode and was successfully managed with a non-pharmacological treatment strategy in the form of behavioural therapy for nine years. The patient reported finding initial outpatient hypnotherapy sessions very beneficial, however, she admitted to later defaulting on follow-up appointments due to stressors at home.

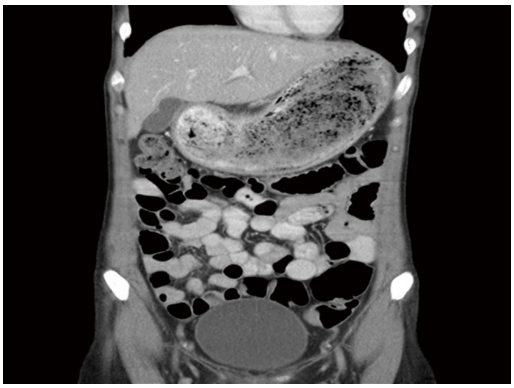

Figure 1 Computed tomographyscan of the abdomen revealing a large gastric bezoar.

On examination, she was anaemic, and her abdomen was distended with an upper midline laparotomy scar visible, consistent with her previous surgery. A firm abdominal mass, which extended from her left subcostal region to her umbilicus, was palpable. At this point, the differential diagnosis included an enlarged spleen, recurrence of the trichobezoar or Rapunzel syndrome. Her blood work revealed a microcytic hypochromic anaemia with a haemoglobin level of 9.1 g/dL. Blood urea, creatinine, electrolytes, blood glucose, serum amylase and liver function tests were normal. An abdominal CT showed a grossly distended stomach and pylorus filled with debris (Figure 1), with infiltrates within the right lower lung lobe. Following this, the patient consented to the removal of the foreign body under general anaesthesia (Figure 2).

The patient was brought to the theatre, intubated, and under general anaesthesia, a diagnostic upper gastrointestinal endoscopy was performed. The endoscopy showed that the stomach and pylorus were filled with a large mass of hair (Figure 3). The greater curvature of the stomach was also ulcerated. The high density of the hair conglomerate precluded successful endoscopic extraction, and surgical exploration was performed through a 7-cm upper midline incision. The adhesions from her previous surgery were divided and an Alexis® O Wound Protector (Applied Medical, United States) was used to protect the wound. A gastrotomy (5 cm) was made in the anterior stomach away from the pylorus. The foreign body was visualised, grasped, and carefully extracted from the stomach. The trichobezoar weighed 850 g and was cast in a shape that mimicked the contours of the stomach and proximal small bowel, hence the diagnosis of RRS (Figure 4). The gastrotomy was closed in two layers, and this was followed by

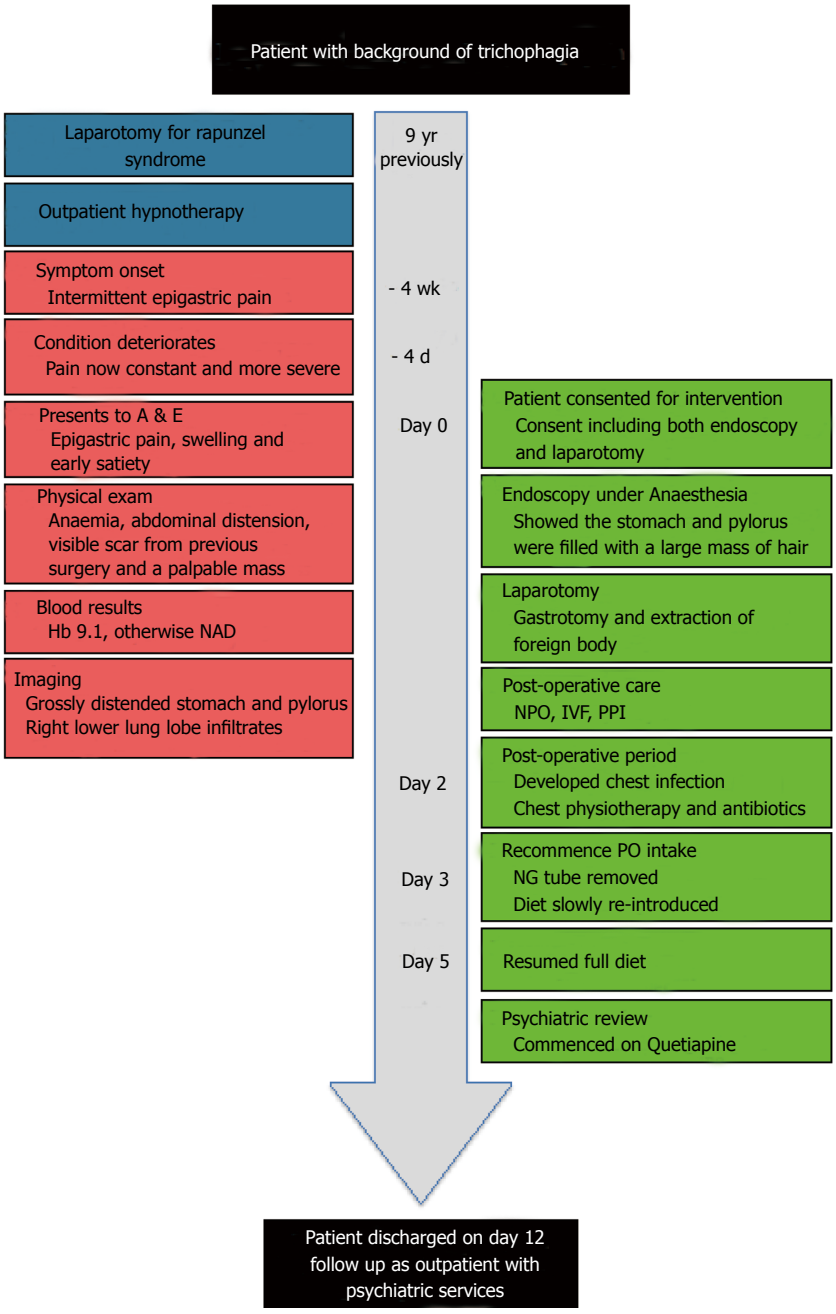

Figure 2 Timeline.

fascial and skin closure.

Postoperatively, the patient received analgesia and was kept nil by mouth for three days. She received intravenous fluids and proton pump inhibitors during this period. The postoperative period was complicated by a chest infection on day 2. The infection necessitated chest physiotherapy and an extended duration of prophylactic antibiotics to a full 7-d course. Of note, the chest infection was apparent at the time of pre-operative diagnosis. The nasogastric tube was removed on day 3, and her diet was slowly re-introduced. She had resumed full diet by day 5 and was also commenced on haematinics. She was reviewed by a psychiatrist and was started on Quetiapine 25 mg daily before discharge on day 12. Outpatient follow-up for further management of her mood symptoms and cognitive behavioural therapy was arranged.

DISCUSSION

Rapunzel syndrome is not a primary surgical condition. Treating the underlying trichotillomania is critical in preventing a relapse, but this can be challenging in clinical practice. Clinical dilemmas and valuable lessons learned from the management of this rare case of recurrence are described herein.

Firstly, laparotomy is the recommended approach of choice for removal of the trichobezoar in Rapunzel syndrome[11,13]. Enzymatic degradation, pharmacotherapy, endoscopic fragmentation and laparoscopy have been shown to be ineffective in these cases as the tail often extends into the jejunum[13,14]. The

Table 1 Management of cases of recurrent Rapunzel syndrome in the literature[1]

Ref.	Year published	Age (S1)	Psychiatric management	Age (S2)	Psychiatric management	Interval (recurrence)	Reason for recurrence
Memon *et al*[2]	2003	10	Advised treatment of her emotional disturbances	12	Supervised psychiatric treatment[2]	2 yr	Unresolved emotional stress factor (ignored psychiatric treatment, continued to eat hairs of females neighbours)
Eryilmaz *et al*[23]	2004	12	Psychiatric treatment[2]	19	Supervised treatment with family counselling	7 yr	Underlying depressive personality disorder
Morales-Fuentes *et al*[22]	2010	16	No treatment mentioned	22	Psychiatric treatment[2]	6 yr	Inadequate initial treatment Obsessive disorder Pleasure feeling of how the hair scrapped the throat
Jones *et al*[6]	2010	35	No treatment mentioned	37	Quetiapine Habit reversal training with family and neighbours involvement	2 yr	Inadequate initial treatment
Tiwary *et al*[18]	2011	10	Behavioural therapy Clomipramine after 1 mo Follow-up × 6/12	15	Supervised psychiatric treatment[2]	5 yr	Lack of psych follow-up Defaulted after 6/12
Current study	2016	16	Behavioural therapy	25	Supervised behavioural therapy Quetiapine 25 mg	9 yr	Defaulted follow-up due to stressors at home

[1]All cases involved female patients; [2]Details not specified. S1: First surgical intervention; S2: Second surgical intervention.

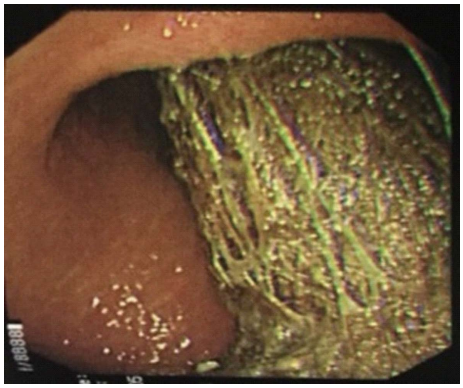

Figure 3 Gastroscopy showing the obstructing trichobezoar.

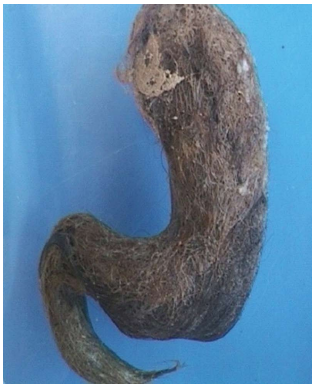

Figure 4 The fully extracted giant gastric trichobezoar with a tail.

major drawback of the open surgical technique is the high incidence of postoperative infection[13]. However, the chest infection in this case report was arguably present due to aspiration at the time of diagnosis and was evident on the preoperative CT imaging. The site of incision, the wound protection technique, and the outlined postoperative care all limited the morbidities in this case. The pre-morbid anaemia and gastric ulceration were also well managed using haematinics and proton pump inhibitors.

Secondly, this case showed that cognitive behaviour therapy in the form of exposure and response prevention, although useful in the initial management may become limited in the long-term prevention of relapse of trichotillomania. For this behavioural therapy to be effective, there needs to be a comprehensive home support network with family or friends also monitoring treatment compliance at home[6,15]. Randomised control trials have shown that patients who respond to psychotherapy might still be stigmatized or be socially rejected[16]. Such stigmatization and rejection may lead to depression, the latter has been described as an independent predictor of quality of life deficits in patients with trichotillomania[17]. The involvement by the family helps to reinforce treatment and facilitates early detection of relapse. Despite these efforts in the management of our case, the presence of home stressors was subtle and was undetected in the outpatient setting. The result was a delay in diagnosis of a relapse, an emergency presentation and morbidity at presentation.

Thirdly, a comprehensive and long-term psychiatric follow-up is needed in all cases as late relapse is possible. An ideal psychiatric follow-up approach is one which can early detect relapse, or highlight those who require closer monitoring and more aggressive treatment.

Furthermore, patients who are on pharmacological therapy should be monitored by a psychiatrist. Continued surveillance by carers for adverse events while on medication is also advisable. Close monitoring is especially important during the times of adjustment of dosage regimens. Adjunctive investigations such as biannual abdominal imaging during the follow-up period has been proposed by some authors[6], while others advocate routine ultrasound[11] or upper GI endoscopy at 6, 12 and 24 mo[18]. The use of trichotillomania severity scales as a way of assessing treatment response may prove useful in the future[19]. All these proposals are however yet to be universally adopted in clinical practice.

Currently, there are no Food and Drug Administration approved treatments for trichotillomania, which makes it difficult for clinicians to select an appropriate therapeutic plan[20]. When effective, long-term treatment with an SSRI may be a reasonable first-line option to prevent relapse[21]. Clomipramine, quetiapine or augmenting an SSRI with an atypical antipsychotic have been used for treatment-resistant cases[6,21]. However, all cases in which a drug treatment is considered should be referred to a psychiatrist who then makes a decision on the appropriate therapy[21]. In this case report, quetiapine was recommended. Furthermore, patients on drug treatment should be carefully monitored as treatment may be associated with psychiatric comorbidity and suicidal ideation in later life[21]. It is clear that new targets are warranted to ensure a clinically supported effective pharmacological approach to treat this condition[20].

Recurrence of Rapunzel syndrome is extremely rare and fewer than six cases have been reported in the PubMed database[2,6,18,22,23]. Management of the condition can be challenging even in experienced hands. Our patient did well on cognitive therapy alone for nine years without any issues, and this justified the continued non-pharmacological management in the first instance. As mentioned earlier, pharmacological treatment may be limited and is not without risks, but this had to be instituted following the relapse. So far, the cases of recurrence have been recorded in females with variable times of between two and nine years between the initial surgical treatment and presentation with relapse (Table 1). Our review of the management also showed that RRS occurs when the underlying psychological trigger is under-diagnosed or treated. With specific reference to the index case report, it was principally due to an inadequate supervision by carers and subsequent failure of the patient to attend follow-up sessions.

In conclusion, this case report is relevant as it clearly describes important clinical lessons learned from the psychological and surgical management of a case of RRS which, to our knowledge, represents the longest published interval between initial treatment and presentation with relapse of the condition. The key message is that although surgery is the initial treatment, a comprehensive and long-term postoperative psychiatric follow-up is needed in patients with Rapunzel Syndrome as a late relapse is possible. Multidisciplinary health care teams headed by a psychiatrist as well as family support play a key role in the prevention of recurrence. It is hoped that our shared experience will inform the management of similar cases.

COMMENTS

Case characteristics

A 25-year-old lady with a previous history of gastrotomy for Rapunzel syndrome presented with a 4 wk history of epigastric pain, swelling and early satiety.

Clinical diagnosis

Trichophagia and finding of a firm abdominal mass, which extended from her left subcostal region to her umbilicus.

Differential diagnosis

Recurrent Rapunzel syndrome (RRS), gastric trichobezoar; also consider an enlarged spleen (splenomegaly) if the history of trichophagia is not apparent.

Laboratory diagnosis

The only abnormal laboratory finding was microcytic hypochromic anaemia.

Imaging diagnosis

Computed tomography showed a grossly distended stomach and pylorus filled with debris.

Pathological diagnosis

RRS.

Treatment

Gastrotomy with complete removal of the trichobezoar, psychotherapy, pharmacological treatment and long-term psychiatric follow-up.

Related reports

Relapse of Rapunzel syndrome following initial surgery classically occur within the first seven years of initial treatment and have very rarely been reported beyond this time frame. Stigmatization or social rejection of patients who respond to psychotherapy can lead to depression and relapse.

Term explanation

Rapunzel syndrome is a benign entity that classically occurs when strands of swallowed hair extend beyond the pylorus of the stomach, into the intestine as a tail. It is known to be difficult to remove with pharmacotherapy or endoscopic fragmentation and requires a gastrotomy for removal.

Experiences and lessons

Rapunzel syndrome requires a comprehensive and long-term psychiatric follow-up as it is not a primary surgical condition. A late relapse of the condition is possible and recognizing this as a clinical possibility can intensify efforts in relapse prevention during the follow-up period, thereby eliminating the need for multiple surgical interventions and morbidity. Multidisciplinary health care teams headed by a psychiatrist as well as family support play a key role in the prevention of recurrence.

Peer-review

An interesting case, focusing on surgical as well as psychiatric treatment of RRS. Albeit a rare condition, the paper provides a thorough review of the literature and adequate advice on the management.

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CASE REPORT

Rhabdomyolysis following severe hypokalemia caused by familial hypokalemic periodic paralysis

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Abstract

Rhabdomyolysis continues to appear with increasing frequency and represents a medical emergency requiring rapid appropriate treatment. One of the unusual causes of nontraumatic rhabdomyolysis is hypokalemic periodic paralysis without secondary causes. Primary hypokalemic periodic paralysis is a rare genetic disease characterized by episodic attacks of muscle weakness due to decreases in serum potassium. A 30-year-old woman who had 3 episodic attacks of hypokalemic periodic paralysis was admitted in emergency room with sudden onset symmetrical muscle weakness. After several hours, she started to complain myalgia and severe ache in both calves without any changes. Laboratory test showed markedly elevated creatine phosphokinase, lactic dehydrogenase levels with hypokalemia, rhabdomyolysis resulting from hypokalemia was diagnosed. Here, we report an unusual case of rhabdomyolysis caused by severe hypokalemia, which was suggested a result of familial hypokalemic periodic paralysis.

Key words: Rhabdomyolysis; Hypokalemia; Familial hypokalemic periodic paralysis

Core tip: Familial hypokalemic periodic paralysis is characterized by periodic attacks of muscle weakness due to decreases in serum potassium, caused by genetic defect of potassium-sensitive muscle membrane excitability with familial occurrence. Rhabdomyolysis following severe hypokalemia as the manifestation of familial hypokalemic periodic paralysis is rare, but it occasionally develops acute kidney injury, disseminated intravascular coagulation, arrhythmia as a potentially life threatening complication promptly recognized by the treating physician. The authors pointed to early detection of rhabdomyolysis as a serious complication of severe

hypokalemia, and ruling out other causes of hypokalemia by step-wise approach, finally reached the diagnosis with the familial hypokalemic periodic paralysis.

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INTRODUCTION

Nontraumatic rhabdomyolysis is a polyetiological disease that continues to appear with increasing frequency and represents a medical emergency, that it occasionally develops acute kidney injury, disseminated intravascular coagulation and cardiac arrhythmia as a potentially life threatening complication[1,2]. One of the most interesting causes of nontraumatic rhabdomyolysis is potassium deficiency caused by a variety of reasons. Familial hypokalemic periodic paralysis is a rare genetic disease characterized by periodic attacks of muscle weakness due to decreases in serum potassium without other detectable causes[3]. Rhabdomyolysis following severe hypokalemia as the manifestation of primary hypokalemic periodic paralysis is extremely rare[4]. Here, we report an unusual case of rhabdomyolysis caused by severe hypokalemia, which in turn was the result of primary hypokalemic periodic paralysis.

CASE REPORT

A 30-year-old woman was brought to the emergency room with sudden-onset, rapidly symmetrical flaccid weakness in the proximal lower extremity muscles after excessive intake of carbohydrates. She did not complain of nausea, vomiting, diarrhea, fever or rash, and there was no history of medication use, nor had she experienced any trauma or vigorous exercise. Her menstrual cycle was regular and she was married and nulliparous. The patient reported a history of 3 similar episodes of weakness in the past year. All episodes occurred after consuming excessive carbohydrates and drinking alcohol. Each time she was admitted to a hospital emergency room and muscle weakness improved after intravenous potassium administration. There was no detectable reason for her hypokalemia whenever she did it. Unusual point was her family history that included the sudden cardiac death of her father, paternal uncle and brother without determination of the exact cause. On physical examination, her blood pressure was 120/80 mmHg, heart rate was 78 beats/min and body temperature was 36.4 ℃. Cardiopulmonary examination was unremarkable. Neurological examination revealed symmetrical flaccid muscle paralysis involving predominantly the thighs and calves, areflexia without sensory involvement and positive Trousseau sign. Initial laboratory investigations demonstrated markedly severe hypokalemia (K 1.6 mEq/L) with hypophosphatemia (phosphorus 0.8 mg/dL), while other routine chemistry including total calcium level, liver function and hematological laboratory values were normal. Plasma renin activity, aldosterone and thyroid hormone levels were within normal range (Table 1). ABG analysis revealed the following: pH 7.48, $PaCO_2$ 29 mmHg, PaO_2 106 mmHg, bicarbonate 22.3 mEq/L and oxygen saturation 98.8%. This respiratory alkalosis was considered as results of hyperventilation due to her complaints. Urinary excretion of potassium was 2.5 mmol/L and urinary osmolarity was 326 mOsm/kg; the transtubular potassium gradient was 1.67. Blood and urine cultures were all negative, and serology for viruses including hepatitis B virus, hepatitis C virus, human immunodeficiency virus and resilient packet ring was also negative, so no recent infections were suspected. Electrocardiogram revealed a Q-T interval elongation pattern corresponding to hypokalemia-related changes (Figure 1). After 6 h of potassium administration, the patient suddenly developed tetany and a severe ache in both calves without corresponding physical exertion. Initially she complained only of weakness without pain, but she began to show new symptoms including severe muscle tenderness, myalgia. Also, her urine color changed to dark-brown, described as "tea-colored" and the amount of urine decreased. We suspected rhabdomyolysis and laboratory tests showed elevated creatine phosphokinase (45720 IU/L) and lactic acid dehydrogenase (LDH 1686 U/L) and low serum potassium (2.2 mmol/L) (Table 1). We sought to determine the cause of hypokalemic rhabdomyolysis using a step-wise approach. Rhabdomyolysis was accompanied by episodic muscle weakness with severe hypokalemia and no other causes, including thyrotoxicosis, hyperaldosteronism, renal loss or gastrointestinal loss. Based upon these clinical features, a diagnosis of primary hypokalemic periodic paralysis was made due to a positive family history of unexpected sudden cardiac death and hypokalemia during paralytic attacks without other detectable causes. We diagnosed the patient with rhabdomyolysis following severe hypokalemia caused by familial hypokalemic periodic paralysis. DNA analysis and muscle biopsy was planned for exact diagnosis (sporadic or familial), but we could not perform, because she refused further tests. After treatment *via* hydration, potassium replacement and medication with spironolactone, the patient's creatine phosphokinase and potassium levels normalized and her symptoms improved. The patient described in the case report exhibited characteristic clinical features of rhabdomyolysis caused by profound potassium deficiency associated with primary hypokalemic periodic paralysis.

DISCUSSION

Rhabdomyolysis is a pathological condition involving

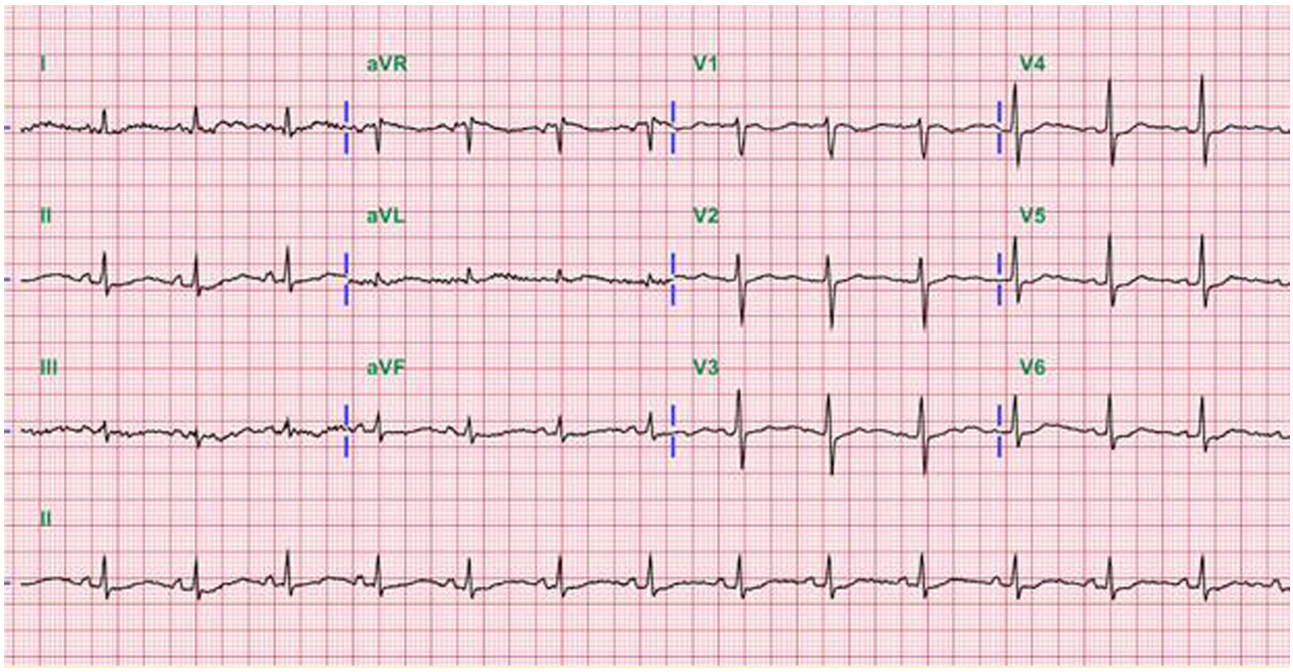

Figure 1 Q-T interval elongation.

Table 1 Clinical course of the patient

HD	#1	#2	#3	#4	#5	#6
Potassium (mmol/L)	1.9	2.2	3.7	3.2	3.9	4.6
Na (mmol/L)	143	146	145	146	144	145
CPK (U/L)	110	45720	41200	37700	10899	1933
LDH (U/L)		1686	496	342	242	186

CPK: Creatine phosphokinase; LDH: Lactic dehydrogenase.

skeletal muscle cell damage leading to the release of toxic intracellular material into the blood circulation. It ranges from an asymptomatic illness to a life-threatening condition associated with acute kidney failure, disseminated intravascular coagulation, and critical arrhythmia as complications of rhabdomyolysis[1]. There are multiple causes of rhabdomyolysis, which can be classified as physical (traumatic) and non-physical (nontraumatic) causes. One major cause of rhabdomyolysis is muscular trauma, and less common causes include muscle enzyme deficiency, electrolyte abnormality, infection, toxins, endocrinopathy, and drugs including β-mimetics, insulin, laxatives or diuretics such as thiazides. One of the most interesting causes of non-traumatic rhabdomyolysis is electrolyte abnormalities including potassium deficiency[2]. The mechanism of the hypokalemia-induced rhabdomyolysis is still not clear, but it may be related to the fact that hypokalemia may induce muscle injury or frank necrosis as a consequence of relative ischemia[4].

Potassium plays an important role in regulating muscle blood flow, and local potassium levels in capillaries are essential regulators of vascular tension. Changes in potassium distribution across the cellular membrane might affect excitability and contractile force of muscle tissue[3]. Normally during exercise, muscles release intracellular potassium, causing local pockets of hyperkalemia, which in turn trigger vasodilation and increase perfusion to active myocytes[3]. Effect of total body potassium depletion decreases local hyperkalemia preventing vasodilation and leads to tissue hypoxia. Severe hypokalemia contracts capillaries, reduces muscle blood supply and results in muscle cell damage[3,5]. The clinical manifestations of potassium depletion vary, because hypokalemia affects the function of several organs including cardiovascular system, neurologic system, muscles, and kidneys. The severity of the clinical symptom depends on the degree of hypokalemia, more severe hypokalemia may lead to progressive weakness, hypoventilation and even complete paralysis. Also, the occurrence of side effect (or complication) of hypokalemia, for example like rhabdomyolysis, is related to the severity of pre-existing potassium deficiency and the underlying disease state[5,6]. For the accurate treatment of these symptoms of hypokalemia, it requires correct identification of the cause. Among the various causes of hypokalemia, drugs such as diuretics, laxatives or insulin are the most common cause of potassium depletion, which induced by abnormal losses of potassium, or redistribution within cells. Thus, the first step in the management of hypokalemia is to review the patient's drug record. In the absence of an inciting drug, hypokalemia can result from an acute shift of potassium from the extracellular compartment to cells, from inadequate intake, or from abnormal losses through the kidney and intestinal losses by diarrhea[3]. This diagnosis is readily made from the

history under most conditions. In situations where the cause of hypokalemia is not obvious, measurement of urinary potassium excretion and blood pressure as well as assessment of acid-base balance are often helpful. In the presence of hypertension, Cushing syndrome or aldosteronism should be suspected in any patient with the triad of hypertension, hypokalemia and metabolic alkalosis[6]. Rare hereditary defects in renal salt transport, such as Bartter syndrome or Gitelman syndrome, can cause hypokalemia without hypertension in a manner similar to that of diuretics. Potassium loss can also occur due to diabetic ketoacidosis and renal tubular acidosis[7]. Severe hypokalemia can occur, although rarely, in association with thyrotoxicosis, resulting in a clinical syndrome characterized by the sudden onset of severe muscle weakness and paralysis[3]. Signs and symptoms of thyrotoxic periodic paralysis usually accompany acute episodic attacks of muscle weakness and paralysis, and it is clinically identical to hypokalemic periodic paralysis, so the misdiagnosis may be made[8,9].

Hypokalemic periodic paralysis leads to randomly-spaced attacks or episodes of weakness that range from mild to flaccid paralysis triggered by falls in serum potassium, and involve several or all of the skeletal muscles with complete recovery between attacks[8,9]. It is categorized as primary, due to a genetic defect with familial or sporadic occurrence or as secondary, due to drugs, suprarenal gland disease[9]. Primary hypokalemic periodic paralysis can be associated with mutations in genes encoding for subunits of the muscular sodium channel, calcium channel and potassium channel[8,10]. Diagnosis is based on patient history and can be confirmed by evaluation of serum electrolytes and trans-tubular potassium concentration gradient during an attack using the CMAP amplitude test (Exercise EMG) or by DNA analysis and muscle biopsy[9]. Negative DNA test results are not conclusive[10]. Triggers for paralysis may be a carbohydrate-rich diet such as consumption of sweet and starchy, alcohol or strenuous physical activity. Other precipitating factors include stress related to infections, menstruation, lack of sleep or certain drugs such as b-mimetics, insulin or corticosteroids[9]. Appropriate management includes a diet low in sodium and simple carbohydrates. Patients should avoid over-exertion and becoming chilled, and should take supplemental potassium. Acetazolamide is highly effective for prevention of paralytic attacks and some patients require potassium supplementation in order to achieve complete control of episodes. Acetazolamide is a carbonic anhydrase inhibitor, causing the accumulation of carbonic acid, however the mechanism of the therapeutic effects of the drug in hypokalemic periodic paralysis is not clear and appears to be independent of carbonic anhydrase inhibition. It is reported that acetazolamide is expected to trigger calcium-activated potassium channels on skeletal muscle and make sarcolemma channel activity intense, and restore the serum K^+ levels to control values[11-14]. Patients who fail to respond to acetazolamide, may respond well to potassium sparing diuretics including spironolactone.

This case report has two limitations. First, genetic analysis and muscle biopsy for diagnostic confirmation was not done because of patient's reluctance. However, it is known that negative result of genetic analysis and muscle biopsy are not conclusive, we could approach the final diagnosis based on the clinical course and family history of patient. Second, on the suspicious of rhabdomyolysis, myoglobin levels as a sensitive marker of muscle damage was not measured. However, tea-colored urine showed myoglobinuria, and it suggested that myoglobin was released into the circulation.

In summary, primary hypokalemic periodic paralysis is a rare genetic muscle disease leading to periodic muscle weakness and hypokalemia without other detectable causes. Rhabdomyolysis presenting with severe hypokalemia as the first manifestation of primary hypokalemic periodic paralysis is extremely rare and represents a medical emergency requiring rapid diagnosis and appropriate treatment. We report a case of rhabdomyolysis following severe hypokalemia caused by familial hypokalemic periodic paralysis. This case acts as a reminder of the risk of rhabdomyolysis among patients with familial hypokalemic periodic paralysis.

COMMENTS

Case characteristics

A 30-year-old woman, who had 3 episodic attacks of hypokalemic periodic paralysis was admitted in emergency room with sudden onset symmetrical muscle weakness. After several hours, she started to complain myalgia and severe ache in both calves without any changes.

Clinical diagnosis

Initial symptoms included episodic attacks of muscle weakness due to decreases in serum potassium. Later she complained myalgia and severe ache in both calves, and her urine color was changed to dark-brown.

Differential diagnosis

Drug-induced hypokalemia, thyrotoxic periodic paralysis, Cushing syndrome, hyperaldosteronism, Conn syndrome, Bartter syndrome, Gitelman syndrome, Liddle syndrome, diabetic ketoacidosis, renal tubular acidosis.

Laboratory diagnosis

Laboratory examinations showed markedly decreased in serum potassium, elevated creatine phosphokinase, lactic dehydrogenase levels.

Treatment

Intravenous hydration, potassium replacement and medication with spironolactone.

Related reports

Nontraumatic rhabdomyolysis is a polyetiological disease, and one of the most interesting causes of nontraumatic rhabdomyolysis is potassium deficiency. Hypokalemia is resulted in the various causes such as thyrotoxocosis, cushing syndrome, hyperaldosteronism, Conn syndrome.

Term explanation

Familial hypokalemic periodic paralysis is characterized by periodic attacks of muscle weakness due to decreases in serum potassium, caused by genetic defect of potassium-sensitive muscle membrane excitability with familial occurrence. Nontraumatic rhabdomyolysis is a polyetiological disease, and one of the most interesting causes is severe hypokalemia.

Experiences and lessons

Rhabdomyolysis following severe hypokalemia as the manifestation of familial hypokalemic periodic paralysis is rare, but it occasionally develops a potentially life threatening complication. The authors pointed to early detection of rhabdomyolysis as a serious complication of hypokalemia, and ruling out other causes of hypokalemia by step-wise approach, finally reached the diagnosis with the familial hypokalemic periodic paralysis.

Peer-review

The paper is well-written.

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CASE REPORT

Indolent lung opacity: Ten years follow-up of pulmonary inflammatory pseudo-tumor

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Author contributions: Degheili JA and Nasser MJ have contributed equally to this work; both have been involved in the acquisition of patient's data, literature review, and writing of initial draft; Koubaissi SA assisted in literature review and revision of the edited manuscript; Kanj NA is the senior author and has been involved in the revision of the different manuscript's versions.

Institutional review board statement: The study was reviewed and approved by the Institutional Review Board at the American University of Beirut-Medical Center.

Informed consent statement: The patient highlighted in this case report gave his consensus prior to study enrollment, authorizing the use and disclosure of his protected health information.

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Abstract

Inflammatory pseudotumor (IPT) has always been considered a diagnostic challenge. Its rarity and resemblance to other more common pathological entities imposes that neither clinical nor radiological characteristics can lead to a definitive diagnosis. The surgical excision of the lesion is the ultimate approach for accurate diagnosis and cure. Moreover the true nature of IPT, its origin as a neoplastic entity or an over-reactive inflammatory reaction to an unknown trigger, has been a long debated matter. Surgery remains the treatment of choice. IPT is mostly an indolent disease with minimal morbidity and mortality. Local invasion and metastasis predict a poor prognosis. We hereby present a unique case of pulmonary IPT that was surgically excised, but recurred contralaterally, shortly thereafter. Despite no medical or surgical treatment for ten years, the lesion has remained stable in size, with neither symptoms nor extra-pulmonary manifestations.

Key words: Inflammatory pseudotumor; Anaplastic lymphoma kinase; Inflammatory myofibroblastic tumor; Plasma cells granuloma; IgG4-related sclerosing disease

Core tip: Inflammatory pseudotumor is considered a diagnostic challenge, with no one-self explained pathophysiology. Over-reactive inflammatory response to various triggering agents or even an entity with malignant potentials represents the two-sided pendulum. Accurate pathological identification lies on adequate tissue acquisition, which often occurs during surgical resection; the preferred treatment approach. Even though both local recurrence and metastasis represent a poor prognosis, its indolent course is not a well-known property, which we do here highlight in our patient with a 10-year follow up, possessing a stable and indolent disease.

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INTRODUCTION

Inflammatory pseudotumor (IPT) of the lung had been first described by Brunn[1] in 1939 and the term had been coined by Umiker *et al*[2] in 1954. Most commonly IPT presents in the lung and orbit. Other less common locations include: Liver, spleen, stomach[3], breast, esophagus, salivary glands[4], and the central nervous system[5]. It accounts for less than 1% of all lung specimens' pathologies[6].

Given the heterogeneity in its true pathogenesis, several interchangeable terms have been linked to IPT such as: Plasma cell granuloma, inflammatory myofibroblastic tumor (IMT), xanthoma, fibroxanthoma, and histiocytoma[7]. This resulted in some confusion among the medical societies regarding IPT true definition and description. A simple and clear classification has been reported which divided the spectrum of IPT into non-neoplastic versus neoplastic variants, the latter including IMT[8].

CASE REPORT

A 43-year-old female, smoker with a history of left tuberculous pleuritis treated in 1997, presented 6 years later to our clinic complaining of exertional shortness of breath of one year duration.

Computed tomography (CT) of the chest revealed the presence of a left upper lobe mass 3.0 cm × 3.0 cm, along with prominent bilateral hilar and mediastinal lymph nodes. Pulmonary function tests showed mild restrictive disease. She underwent left lateral mini-thoracotomy followed by wedge resection of the lesion with mediastinal lymph node biopsy. Grossly, no parietal pleural involvement was noted, and no frozen section was sent, at that time, for intra-op identification. Pathology came out to be acute and chronic non-specific inflammation along with fibrosis (Figure 1). No treatment was initiated, and the patient was discharged home, advising close follow-up.

Ten years following her thoracotomy, the patient presented back for asymptomatic right middle lobe opacity, not resolving on several antibiotic regimens.

CT chest revealed a right middle lobe mass extending to the right lower lobe, with mediastinal and hilar lymphadenopathy (Figure 2).

A CT-guided core biopsy of the middle lobe mass was performed. Histopathological examination revealed a matrix of spindle cells consistent of fibroblasts and myofibroblasts, intermixed with inflammatory cells including leukocytes, plasma cells, and histiocytes (Figure 3). A low mitotic activity was noted among cells, with no dysplasia. These findings highly suggest a pulmonary IPT of the lymphoplasmacytic subtype. Anaplastic lymphoma kinase (*ALK*) gene mutation was absent on the tissues, and serum IgG4 level was 0.279 g/L (0.052-1.25 g/L). Pathologic reexamination of the previously resected left upper lobe lesion confirmed similar histopathological findings. Given the indolent course of the disease and the asymptomatic status, along with a financial burden on the patient, a watchful waiting approach was elected, instead of surgical resection, with CT of the chest, to be done, every 2 to 3 years.

DISCUSSION

Pulmonary IPT represents a distinct group of pathologies ranging from benign lesions as plasma cell granuloma to lesions with more malignant potentials as IMTs[9]. IPT of the lung is a rare entity, constituting around 0.7% of all lung tumors, and approximately 0.04% to 1.2% of all thoracotomies[10]. Most of IPT lesions occur in younger age groups, with no sex predilection[11]. In fact, IPT in the pediatric age group is mostly of neoplastic form (IMT). The more benign forms of IPT usually occur in the adult population[8].

Pathogenesis

The predominant infectious/inflammatory etiology: The pathogenesis of IPT is elusive. Inflammation in IPT has been attributed to a metabolic disturbance, pulmonary infection, and/or antigen-antibody interaction to an unknown agent[7]. Thirty percent of IPT cases are reported to be preceded by recurrent respiratory tract infections. Isolated pathogens include: Human Herpes Virus, Epstein Barr Virus, Nocardia, Mycoplasma, and Actinomycetes[4,12]. Repetitive respiratory insults will call for inflammatory cells to migrate to the insult site. Subsequently over-reactive inflammation results in proliferation and infiltration of inflammatory cells, including lymphocytes, plasma cells, and histiocytes. This could explain the persistent elevation in serum

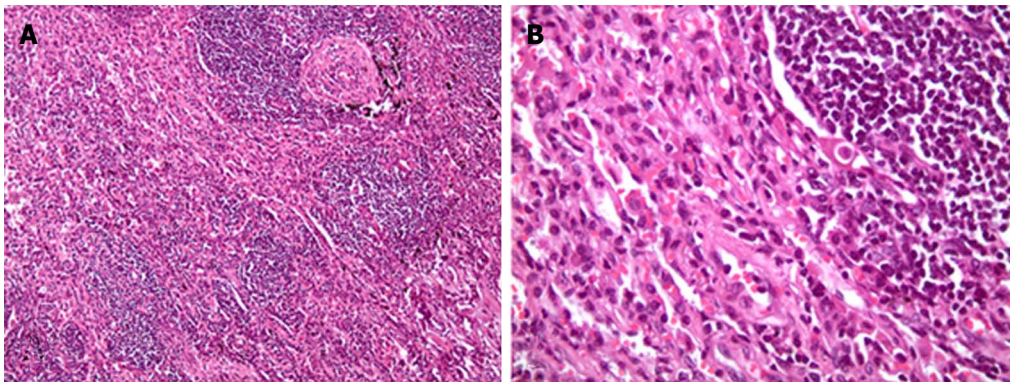

Figure 1 Initial lung resection revealing diffuse infiltration of inflammatory cells and undifferentiated fibroblasts, representing acute and chronic non-specific inflammation, along with fibrosis (A: 10 ×; B: 40 × magnification).

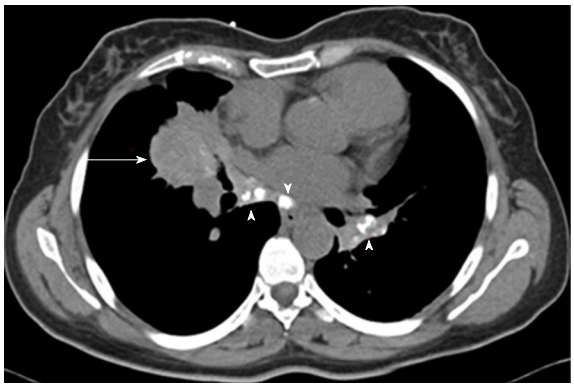

Figure 2 Computed tomography of the chest revealing a right middle lobe mass (arrow), with multiple calcified hilar and mediastinal lymph nodes (arrow heads).

inflammatory biomarkers, as C-reactive protein and erythrocytes sedimentation rate[10].

The genetic postulate: *ALK* gene has been used as a molecular surrogate to differentiate benign IPT from malignant IMT. *ALK* gene is present on chromosome 2p2. The gene encodes for tyrosine kinase receptors, and the resultant derangement will cause *ALK* protein over-expression and cell proliferation[4]. *ALK* positivity is only observed in IMT patients. Approximately half of IMT patients stain positive for *ALK*; yet show a great variation with age[8]. In contrast to other tumors that stain positive for *ALK*, *ALK*-positive IMT is associated with better prognosis than *ALK*-negative IMT, as the latter is associated with higher rate of metastasis[13].

Malignant potentials of IMT have been attributed to the derangement of *ALK*[14]. This proves to be pivotal in the medical treatment of IPT, as certain drugs can competitively inhibit such receptors and prohibit proliferation[15].

IPT *vs* IgG4-related diseases: A subset of IPT has been correlated with IgG4-related diseases[16]. "IgG4-related" sclerosing disease, a new disease entity, reflects the presence of abundant IgG4-plasma cells in the tissues[17,18]. IgG4 is the least abundant of all IgG subclasses, and accounts for less than 6% of the total IgG subclasses in the serum[19]. Serum IgG4 is elevated in certain pathological entities such as atopic dermatitis, pemphigus vulgaris, and sclerosing pancreatitis[10]. The IgG4-related IPT behaves differently than isolated IPT, as it responds greatly to steroids, precluding the need for surgical resection[8]. To confirm the diagnosis of IgG4-related pulmonary IPT, histological analysis is needed. A recent study reported the presence of IgG4-positive plasma cells in Plasma Cell Granuloma, a type of Pulmonary IPT[20]. This is contrary to serum IgG4 which is not always elevated[17]. Obliterative vasculitis also raises the probability of IPT over IMT[18]. The ratio of IgG4 over IgG-positive plasma cells, within tissue specimens, acts as a surrogate for diagnosis of IgG4-related IPT. A ratio greater than 50% is usually diagnostic[13].

Histopathology

Histologically, IPT consists of proliferation of fibroblasts and myofibroblasts intermingled with varying numbers of inflammatory cells including: Lymphocytes, polyclonal plasma cells, macrophages, and histiocytes[8]. Various histological classifications have been inaugurated, describing IPT. The most commonly used is that of Matsubara *et al*[21], and that of the World Health Organization (WHO)[22]. The former classifies IPT, according to dominant component cells and main histological characteristics, into 3 subtypes: Organizing Pneumonia, Fibrohistiocytoma, and Lymphoplasmacytic type; each constituting 44%, 44% and 12%, respectively. The WHO classification, on the other hand, divides IPT into compact spindle cell and hypocellular fibrous patterns[22].

Clinical presentation

Almost 70% of IPT cases are discovered incidentally. Such patients are either asymptomatic or complain of symptoms of other diseases[12]. Symptoms such as cough, hemoptysis, shortness of breath, and chest pain occur in 25% to 50% of patients[11]. Fever is not

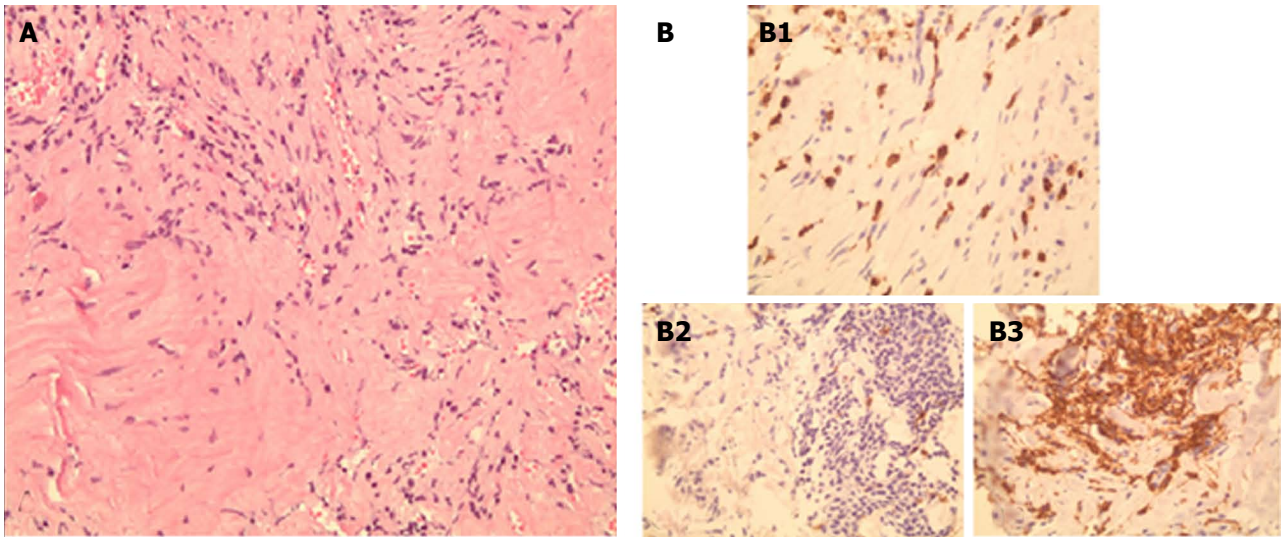

Figure 3 (A) Heavy infiltration of lymphocytes, plasma cells, and histiocytes, within a background of spindle-shaped fibroblasts and myofibroblasts, arrayed in fascicles (B). Immunostaining of tissues showing positivity for CD3 (B1), negativity for CD20 (B2), and positivity for CD138 (B3), respectively.

uncommon[22], mainly due to interleukins' production (*e.g.*, IL-1β, IL-6)[23].

Radiologic manifestations

Well-circumscribed solitary nodules, with peripheral lower lobar predilection, constitute the usual radiologic manifestation of IPT. In one study, this has been reported to occur in 87% of patients[24]. Multiple nodules do present in only 5% of cases[25]. Calcifications and lymphadenopathy are seen in 15% and 7% of cases, respectively[26]. Cavitary lesions and pleural effusions are quite rare findings[4]. Based on the radiological mode of presentation, it is difficult to differentiate IPT from other entities such as lung tumor or pulmonary tuberculosis; thus rendering IPT a clinical and a radiological challenge[11].

Diagnosis

Transbronchial lung biopsy (TBLB) is not a favored diagnostic tool in IPT due to the small size of pieces, taken during the procedure, which renders the diagnosis a difficult call[11]. In fact, only 6.3% of IMT or IPT cases are diagnosed using TBLB[27]. Moreover, not uncommonly, lung tumors are surrounded by chronic inflammation because of the resulting insult to normal tissue, thus rendering diagnosis even more staggering. Definitive diagnosis of IPT is mainly achieved by surgical resection, which if complete, will lead to definitive cure in most cases.

Prognosis

The prognosis of IPT/IMT is variable. It usually depends on the tumor size and the magnitude of surgical resection[27]. Tumors greater than 3 cm are usually not amenable to complete resection. This implies a drop in long-term survival to less than 50%[12]. After complete resection, prognosis is favorable, with 5- and 10-year survival of 91% and 77%, respectively[28]. Metastatic lesions of IPT have approximately a 30-fold increase in recurrence rate, and are associated with a poor prognosis[12]. Positive margins after incomplete resection result in recurrence rate from 5% to 25%[10,13]. Pulmonary IMT, when not excised, shows continuum growth in approximately 8% of cases with a 5% risk of distant metastasis[13].

Treatment

As previously stated, complete resection represents the most favorable and recommended diagnostic and therapeutic approach for pulmonary IPT. Patients who witness disease recurrence or those who do not fit for surgery may rarely benefit from other approaches including corticosteroids, chemo, and/or radiotherapy. Those modalities can also be used as adjuncts to suspected incomplete resection[29]. Radiotherapy has little to offer for these slow-growing lesions; hence radiation may cause more damage than cure. Corticosteroids' use has shown contradictory results, though certain case reports showed complete regression after prolonged treatment[12]. Interestingly, many IPT lesions resolve completely after core biopsy. Such paradoxical behavior termed "spontaneous resolution", is not a well understood phenomenon[13]. Methotrexate was used in some cases with modest results[30]. Crizotinib, a newly synthesized ALK inhibitor, has been used on a patient with pulmonary IMT, and showed sustained partial response[31].

In conclusion, this case, to the best of our knowledge, represents the longest reported follow up in an IPT patient. The absence of symptoms and the relative stability of the lesion, after 10 years, stipulate the natural and the benign behavior of this slowly-growing entity. The true outcome of IPT clearly requires further investigation. Greater capabilities in deciphering the

diagnosis and approach to this disease, without relying on *en bloc* excision, lie on top of these investigations.

COMMENTS

Case characteristics

A 43-year-old woman, smoker, with history of left upper lobe mass resection, discovered after investigation for one year history of exertional dyspnea. Pathology back then showed acute and chronic non-specific inflammation with fibrosis. Ten years later, follow up on non-resolving right middle lobe opacity, despite multiple antibiotic regimens, resulted in a computed tomography (CT)-guided biopsy to be performed. Matrix of spindle cells intermixed with inflammatory cells was noticed.

Clinical diagnosis

Diagnosis of pulmonary inflammatory pseudotumor (IPT) was established from the core-guided biopsy.

Differential diagnosis

Differential diagnosis of pulmonary IPT includes lung carcinoma and pulmonary tuberculoma; two entities that needed to be taken into consideration while suspecting pulmonary IPT.

Laboratory diagnosis

In most isolated cases, laboratory data is normal except, in some cases, where pulmonary IPT is associated with IgG4 disease, for which the serum IgG4 subclass would be elevated.

Imaging diagnosis

Pulmonary IPT is difficult to diagnose, based on different radiological modalities alone. Its radiological resemblance with other entities, such as pulmonary tumor and tuberculosis, renders IPT a radiological challenge.

Pathological diagnosis

Histological examination of the CT-guided core biopsy revealed a matrix of spindle cells consistent with fibroblasts and myofibroblasts, intermixed with inflammatory cells, composed of lymphocytes, plasma cells, and histiocytes.

Treatment

En-bloc surgical resection with negative margins represents the core treatment for pulmonary IPT. Patients, who are ineligible for surgical intervention, can benefit from other suboptimal modalities including corticosteroids and chemo-radiation. The novel use of Crizotinib has proven its efficacy in IPT patients possessing anaplastic lymphoma kinase-positivity.

Related reports

The present case report represents the longest follow-up, extending over a decade period, in a patient with pulmonary IPT, with no current or previous treatment. This highlights the indolent course of this disease entity, despite some other data reports evidence of local invasion or metastasis, even.

Term explanation

Pulmonary IPT constitutes less than 1% of all lung malignancies, and involves a spectrum of diseases, exhibiting benign behavior to more malignant potentials, as described by the inflammatory myofibroblastic tumors (IMT). Histologically, IPT constitutes of spindle cells intermingled with inflammatory cells, which are arrayed in fascicles.

Experiences and lessons

IPT of the lung is a rare disease entity, for which observation is regarded as a valid option, to be taken, but closely, into consideration.

Peer-review

The review is well structured and current enough. The article provides information that is useful for application to clinical practice.

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CASE REPORT

Multiple perforations and fistula formation following corticosteroid administration: A case report

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Author contributions: He JN and Li HY designed the report; He JN, Yao X and Liu Y collected the patient's clinical data; He JN, Yu Y and Liu JG collected the relevant literature; He JN and Tian Z analyzed the data and wrote the paper.

Institutional review board statement: The subject gave written informed consent to the study protocol, which was approved by the ethics committee of Shengjing Hospital.

Informed consent statement: This patient gave his written informed consent before this case report was written.

Conflict-of-interest statement: The authors declare that they have no conflicts of interest.

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Abstract

Eosinophilic granulomatosis with polyangiitis (EGPA) is a rare systemic small- and medium-sized-vessel vasculitis. The literature contains only a few reports of gastrointestinal perforation with this condition. We report a patient with EPGA treated with high-dose steroid who underwent emergency surgery for intestinal perforations. We performed a simple repair of the 11 perforations. Intestinal fistulas developed 8 d postoperatively; they healed well after 60 d of continuous washing and negative pressure suction. The clinical data of 14 additional patients with EGPA or Churg-Strauss syndrome complicated with gastrointestinal perforation, which were reported from 1996 to 2014, were also collected and compared. The formation of multiple perforations and fistulas following high dosage steroid administration can have a good outcome with appropriate management. Meticulous attention to abdominal symptoms and appropriate interventions can result in timely management. Corticosteroid administration remains a very important perioperative procedure for EPGA.

Key words: Vasculitis; Eosinophilic granulomatosis with polyangiitis; Churg-Strauss syndrome; Gastrointestinal perforation; Surgery

Core tip: Eosinophilic granulomatosis with polyangiitis (EGPA) complicated with intestinal perforation is very rare. It needs urgent surgical intervention but hormone administration usually covers up the situation and

delays the prognosis. We report a 43-year-old male diagnosed with EGPA by biopsy who experienced high-dose hormone administration, 11 intestinal perforations, postoperative intestinal fistula, and eventually recovered. This article aims to share the treatment course and experience.

He JN, Tian Z, Yao X, Li HY, Yu Y, Liu Y, Liu JG. Multiple perforations and fistula formation following corticosteroid administration: A case report. *World J Clin Cases* 2017; 5(2): 67-72 Available from: URL: http://www.wjgnet.com/2307-8960/full/v5/i2/67.htm DOI: http://dx.doi.org/10.12998/wjcc.v5.i2.67

INTRODUCTION

Eosinophilic granulomatosis with polyangiitis (EGPA) is a rare type of necrotizing vasculitis affecting small to medium-sized vessels. It is typically characterized by asthma, lung infiltrates, necrotizing granulomas, and hypereosinophilia. It is an uncommon form of vasculitis with a prevalence that ranges from 10.7 to 13 cases/million[1]. Gastrointestinal involvement has been reported to occur in approximately 50% of EGPA patients. Symptoms include abdominal pain, vomiting and diarrhea[2]. Although EGPA very easily involves the digestive system, the chance of digestive tract perforation is very low and only a handful of cases have been reported. We report a case of EGPA with 11 intestinal perforations, and discuss the subsequent treatment.

CASE REPORT

A 43-year-old male with a 3-mo history of asthma was admitted to the Rheumatoid Immune Department of Shengjing Hospital in July 2013. The patient complained of a cough of one-month duration, blood-stained sputum, 14-d peripheral purpura, 3-d diarrhea, and an oral ulcer. His height was 176 cm and weight was 72 kg when admission. His temperature was 37.2 ℃, his pulse was 78 per minute, and his blood pressure was 128/78 mmHg. Multiple skin purpura was found in the physical examination. Heart sounds were clear and regular with no murmur. A few moist rales were heard with lung auscultation. Abdominal examination was unremarkable. Laboratory studies revealed leukocytosis (15600/mm^3) with eosinophilia (20.3%), a marked increase in inflammatory indices (ESR: 69 mm at the first hour; CRP: 176 mg/L), rheumatoid factor (656 UI/mL), and positive pANCA antibody. A pulmonary computed tomography (CT) scan revealed multiple low-density oval shadows, with the largest one measuring about 3.2 cm × 2.6 cm (Figure 1). A diagnosis of vasculitis was made. A biopsy of the nasal mucosa revealed an eosinophilic infiltration. We diagnosed EGPA according to the revised international Chapel Hill nomenclature. The patient received methylprednisolone (120 mg intravenously daily) and ifosfamide for the treatment of the pulmonary lesions. The patient's condition exacerbated during the first three days following admission; the methylprednisolone dose was increased to 500 mg (intravenously daily × 2) and then was gradually tapered. On the 13th day after admission (160 mg methylprednisolone intravenously daily), he experienced a sudden onset of fever and abdominal pain. The physical examination revealed generalized abdominal tenderness without apparent rebound tenderness, and muscle tension. No specific treatment was given. After 11 h, the abdominal pain exacerbated and peritonitis developed. An abdominal CT scan showed an amount of free gas in the abdominal cavity (Figure 2). A laparotomy was performed immediately, which revealed scattered eleven perforations in the intestine. The proximal one was located approximately 150 cm distal from the ligament of Treitz ligament, and the distal one located approximately 50 cm from the ileocecal valve, with the largest measuring about 3 cm × 3 cm (Figure 3). Considering the high risk of short bowel syndrome, we made a simple repair of the intestinal perforations. Histopathological examination did not reveal either eosinophilic infiltration or granuloma formation of the vessels (Figure 4).

Continued intravenous therapy with intermittent ifosfamide as well as somatostatin and esomeprazole was administered postoperatively. The hormone dosage was tapered from 160 mg downward. On postoperative day 6, when the steroid was reduced to 80 mg, the patient's vasculitis exacerbated and he developed fever and new purpura on the entire body. Eight days postoperatively, an intestinal fistula developed, which was confirmed by fistulography (Figure 5). With continuous saline washing through a double-lumen cannula connected to a negative pressure suction apparatus, the drainage was about 300 mL intestinal fluid daily; the fistula slowly healed. The patient began eating on postoperative day 45. Gastric retention occurred after eating; it was treated with decompression *via* a nasogastric tube, total parenteral nutrition, and a gastric motility stimulating agent. The patient resumed eating about two months postoperatively, and the drainage was minimal. When the steroid dosage was reduced to 60 mg intravenously, the fistula healed and the patient was discharged.

Unfortunately, four months later, an intestinal fistula and vasculitis recurred. Although the amount was 5 mL daily, he was readmitted and underwent continuous washing and negative pressure suction. The fistula healed slowly during one month. When last seen in the outpatient clinic in March 2014, he was in good health without any symptoms or eosinophilia. Laboratory analysis revealed 0.1% eosinophils and negative pANCA antibodies.

DICUSSION

EGPA, formerly named churg-strauss syndrome (CSS),

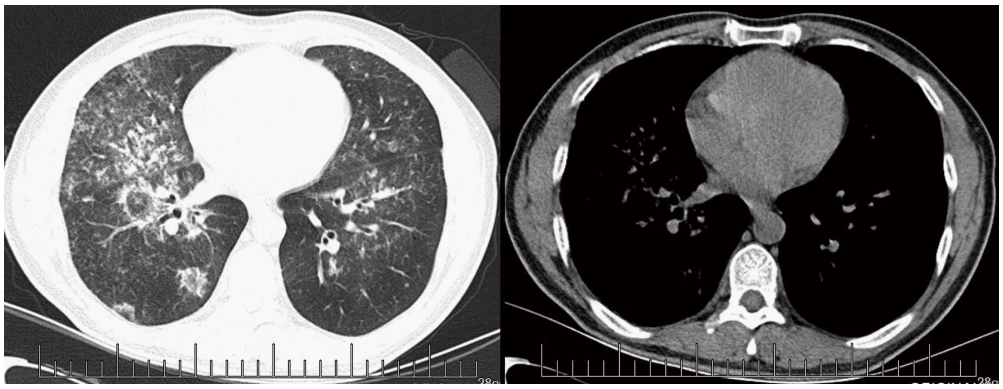

Figure 1 Pulmonary computed tomography images showing bilateral consolidation with air-bronchogram, especially in the right lung with multiple ground glass low-density shadows.

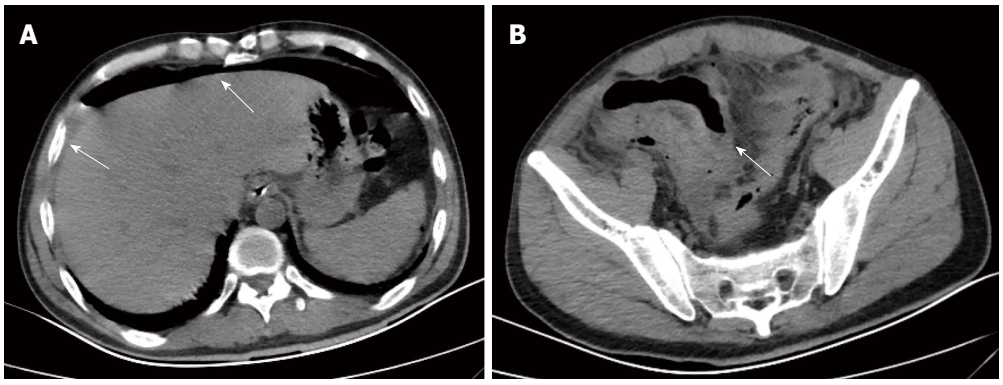

Figure 2 Abdominal transverse computed tomography images. A: Free air in the abdomen and fluid around the liver; B: Intestinal wall thickening in the right lower quadrant and seepage, scattered with free air.

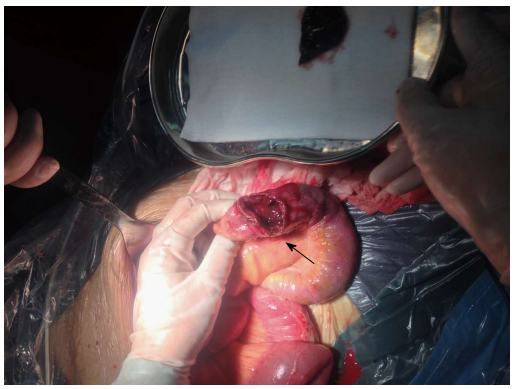

Figure 3 Introperative findings. There were 11 perforations in the intestine. The arrow points to the bigger one measuring about 3 cm × 3 cm.

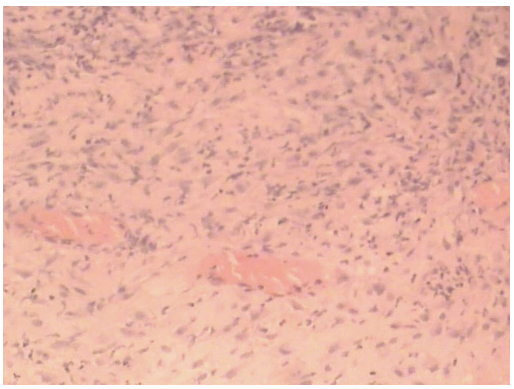

Figure 4 Histopathological examination showing a large number of infiltrated inflammatory cells (HE staining, × 100).

is characterized by the presence of severe asthma as well as blood and tissue eosinophilia. It is an uncommon form of vasculitis, with a prevalence that ranges from 10.7 to 13 cases/million. Although it is classified as vasculitis, the affected tissue usually does not show necrotizing vasculitis or granulomata, rather an apparently nondestructive infiltration of the vessel walls by eosinophils; in fact, only 40%-60% of patients with CSS have anti-neutrophil cytoplasmic antibodies (ANCAs)[3]. For this reason the diagnostic criteria remain clinical.

Gastrointestinal involvement is present in 32.6% of CSS patients. In 29.11% of the cases, the large bowel is involved, in 53.5%, the small bowel is involved, in 16.6%, the gastroduodenal region is involved, and in 6.3%, pancreatitis and cholecystitis occur. The mortality rate is 11.9%[4-6]. Although gastrointestinal symptoms are common, perforated ulcers are relatively uncommon and only a small number of cases have been documented in the literature[7]. Because multiple organs are involved and peritonitis symptoms are not typical, complicated clinical manifestations occur, which delays

Table 1 Summary of cases of Churg-Strauss syndrome/eosinophilic granulomatosis with polyangiitis with digestive perforation in the English literature

Ref.	year	Age/ sex	Initial symptoms	WBC (/mm^3)	Eosino (%)	Hormone	Perforation	treatment	Histology	Second perforation	Pro-gnosis
Ikoma *et al*[10]	2014	19/ female	Asthma	24700	39	Yes	Ileum	Anastomosis	Transmural infiltration of numerous eosinophils with thrombosis and extensive involvement of small arteries	No	Alive
Kaul *et al*[11]	2014	58/ male	Low-grade fever	94000	42	Yes	Ileo-caecal junction	Ileostomy	Transmural inflammation of sub-mucosal and serosal vessels with perivascular infiltrate comprising of lymphomononuclear cells and eosinophils	No	Alive
Assmann *et al*[12]	2014	32/ male	Dyspnea, fatigue, fever and chest pain	-	5500/1	Yes + cyclophos-phamide	Middle part of jejunum	Anastomosis	-	No	Alive
Assmann *et al*[12]	2014	36/ male	Dyspnea, fatigue, fever and chest pain	-	4900/1	Yes + cyclophos-phamide	Colon transversum	Anastomosis	Eosinophilic infiltration and thrombotic vessel occlusion	No	Alive
Çiledağ *et al*[8]	2012	35/ male	Anorexia	-	35	Yes	Small intestine	Repair	-	No	Died
Venditti *et al*[13]	2011	69/ male	Abdominal pain	-	-	Yes	Right and transverse colon	Ileostomy	Multiple ulcers, extravasal granulomas and mucosal pseudopolyps	No	Alive
Zanaboni *et al*[14]	2008	43/ male	Asthma	32000	65	Yes	Small intestine	Anastomosis	Necrotizing ischemic vasculitis with inflammatory granulomatous infiltrates of lymphocytes, polymorphonuclear cells and eosinophils	Yes	Alive
Rolla *et al*[15]	2007	55/ male	Asthma	15500	21	Yes	Ileum	Anastomosis	Granulomatous vasculitis with eosinophilic infiltration	No	Alive
Murakami *et al*[5]	2004	51/ female	Asthma	27650	62	Yes	Ileum	Anastomosis	Angiitis of small vessels surrounded by eosinophilic infiltration and granuloma of the vessels	No	Died
Nagashima *et al*[16]	2002	67/ male	Asthma	18500	65	Yes	Intestine	Anastomosis	Vasculitis in the small arteries and arterioles characterized by thrombotic occlusion with fibrinoid necrosis of the vascular wall and prominent inflammatory cell infiltration in the perivascular region	No	Alive
Nakamura *et al*[17]	2002	31/ male	Epigastralgia	19700	40	Yes	Jejunum and ileum	Anastomosis	Multiple ulcerative lesions with remarkable eosinophilic infiltration and thrombosis obstruction of small vessels	No	Alive
Alvarez *et al*[18]	2002	64/ female	Urticaria, recurrent rhinitis, and asthma	10000	34	Yes	Intestine	Anastomosis	Wall ulcerations, vascular thrombosis with fibrinoid necrosis, and eosinophilic infiltrates	Yes	Died
Kim *et al*[4]	2000	72/ female	Asthma	6600	14	Yes	Sigmoid colon	Anastomosis	Ulceration with heavy infiltrations of eosinophils, neutrophils and lymphoplasma cells	-	-

Sharma *et al*[19]	1996	16/ male	Low-grade, continuous fever and wheezing sounds in the chest	12600	70	Yes	Jejunum	Anastomosis	Necrotizing vasculitis with marked eosinophilic infiltration of medium-to-small blood vessels and extravascular granulomas	No	Died

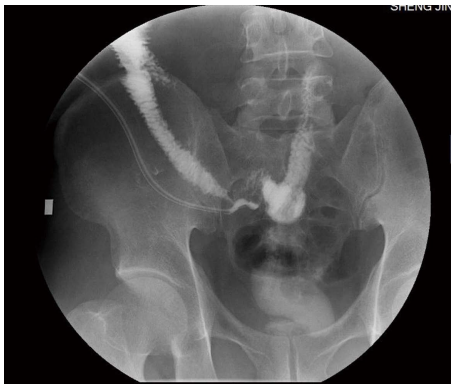

Figure 5 Fistulography showing that after injection of contrast agents, the intestine of the right lower quadrant abdomen developed a fistula.

treatment and results in a poor prognosis.

A systematic review of the literature was performed using the keywords "Churg-Strauss syndrome/eosinophilic granulomatosis with polyangiitis" and "gastrointestinal perforation" in PubMed to search articles from 1951 to December 2014. In China, CSS/EGPA with gastrointestinal perforation is very rare, and there is no relevant report. The articles were restricted to English language only. Duplicate reports and papers with important data missing were excluded. We included the papers on digestive tract perforation with CSS/EGPA, and compared the characteristics (Table 1). The average patient age was 46.3 years (range: 16-72 years; males: 10; females: 4). A half of the patients were complicated with the symptom of asthma, and all of them had received corticosteroid treatment. Their prognosis was poor, with 4/13 (30.77%; case 13 was unknown) dying during hospitalization, although the causes of death were very different. A second perforation of the digestive system occurred in 2 (15.38%) of 13 patients (case 13 was unknown).

Ulceration, perforation, and stenosis of the gastrointestinal tract are assumed to be the results of ischemia caused by vasculitis. The small intestine is the most commonly affected site[8]. Immunosuppressive therapy, especially large-dosage corticosteroids, may play an important role in the development of an intestinal perforation. However, sometimes, it is difficult to distinguish clinically whether the intestinal perforation is due to vasculitis itself or immunosuppression[9].

Treatment of a gastrointestinal perforation in patients with active vasculitis can be challenging. A delayed diagnosis may lead to a delayed cure, as in our patient. First, we did not pay adequate attention to the digestive symptoms: Sour regurgitation, heartburn, and abdominal pain. Second, the symptoms of peritonitis are often atypical in patients receiving long-term administration of glucocorticoids. Third, when the digestive tract perforation occurred, the patient was in the rheumatic ward. As a result of consultation, diagnosis, and department transference, treatment delay can occur. Fourth, the gastrointestinal perforation may occur during a clinical remission. The perforation of this case occurred during the process of steroid tapering. Pathologic examination of the perforated bowel revealed no significant eosinophil infiltration.

In conclusion, improved awareness of gastrointestinal symptoms may allow for timely management of a perforation. Multiple perforations and fistulas caused by high dosage steroids can have a good outcome with appropriate management. Prompt surgical treatment is necessary. The choice of the appropriate surgical approach should be based on the time the perforations occurred, their size, numbers, and sites. Adequate steroid administration and intensive care play an important role during perioperative treatment.

COMMENTS

Case characteristics

A 43-year-old male with a 3-mo history of asthma, a cough of one-month duration, blood-stained sputum, 14 d of peripheral purpura, 3 d of diarrhea, and an oral ulcer. On the 13th day after admission, the patient experienced a sudden onset of fever and abdominal pain. And the abdominal pain exacerbated and peritonitis developed rapidly.

Clinical diagnosis

History of asthma, peripheral purpura, and peritonitis.

Differential diagnosis

Granulomatosis with polyangiitis, microscopic polyangitis, and polyarteritis nodosa.

Laboratory diagnosis

Laboratory studies revealed leukocytosis (15600/mm^3) with eosinophilia (20.3%), a marked increase in inflammatory indices (ESR: 69 mm at the first hour; CRP: 176 mg/L), rheumatoid factor (656 UI/mL), and positive pANCA antibody.

Imaging diagnosis

A pulmonary computed tomography (CT) scan revealed multiple low-density oval shadows, with the largest one measuring about 3.2 cm × 2.6 cm. An abdominal CT scan showed free air in the abdomen.

Pathological diagnosis

A biopsy of the nasal mucosa revealed an eosinophilic infiltration.

Treatment

Continued intravenous hormone therapy with intermittent ifosfamide

perioperatively, and intestinal perforation repair.

Related reports

Eosinophilic granulomatosis with polyangiitis (EGPA) is a rare type of necrotizing vasculitis affecting small to medium-sized vessels; it is typically characterized by asthma, lung infiltrates, necrotizing granulomas, and hypereosinophilia. Gastrointestinal involvement even perforation is more unusual and results in a poor prognosis.

Term explanation

EGPA with multiple intestinal perforations is very rare. Prompt surgical treatment is necessary. Adequate steroid administration and intensive care play an important role during perioperative treatment.

Experiences and lessons

Reasonable amount of hormone administration is the key point during the treatment. Excess hormone may induce intestinal perforation while insufficient amount could induce disease relapse and intestinal fistula postoperatively.

Peer-review

This is an interesting case report and the paper is well written.

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THERAPEUTIC ADVANCES

Guidance on opioids prescribing for the management of persistent non-cancer pain in older adults

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Abstract

Many older adults suffer from persistent pain but prevalence studies consistently showed high levels of untreated or under-treated pain in old population. Both persistent pain and pain under-treatment adversely affect independence and quality of life in geriatric patients. Pain management is challenging in this age-group because of the declining organ function, the presence of concurrent diseases and polypharmacy. For all the above reasons, persistent pain in the elderly should be considered a geriatric syndrome per se and effective approaches are warranted. Current guidelines and consensus statements recommend opioid therapy for older adults with moderate-to-severe persistent pain or functional impairment and diminished quality of life due to pain. However clinicians and patients themselves have some concerns about opioids use. Age-related decline in organs functions and warnings about risk of addiction and drug misuse/abuse also in geriatric patients need particular attention for safe prescribing. On the basis of clinical evidence, these practical recommendations will help to improve the competence on opioid role in persistent pain management and the likelihood of a successful analgesic trial in older patients.

Key words: Chronic pain; Opioids; Pain management; Elderly

Core tip: Persistent pain (pain that lasts more than three months) is a common issue in older adults. Pain management requires a multidisciplinary approach and the knowledge of analgesic drugs is fundamental for effective and safe outcomes. Current guidelines for geriatric patients recommend opioid-use as a first-line agent for moderate-to-severe persistent pain. However some concerns about opioid-use in this age-group are present. Nevertheless opioid epidemic needs attention for safe prescribing. This manuscript addresses to data that will likely help to improve the competence on opioids use and the likelihood of a successful analgesic trial in older adults.

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INTRODUCTION

Persistent pain and opioid use in geriatrics: The thin line between love and hate

Pain is an unpleasant sensory and affective experience, that is the complex sum of injuries and sensory stimuli mediated by individual emotions and expectations. In accordance with the definition proposed by the Commission of Acute Pain in Elderly People of the American Geriatric Society, persistent pain is a pain lasting more than three months that may or may not have an evident causal disease process[1].

There are several reasons why managing persistent non-cancer pain in older persons is a priority in healthcare agenda. First, the prevalence of pain in older adults is high. Approximately 45%-85% of the older population complain about chronic pain in different settings[2,3]. In particular, prevalence studies show that from 25% to 76% of older people living in community and from 85% to 93% of those living in residential care suffer from persistent pain[4].

Musculoskeletal disorders are common in later life and osteoarthritis is the main cause of persistent pain in older adults[5]. Other non-cancer causes include neuropathies, vertebral compression fractures, end-stage organ failures and stroke[6].

Besides persistent pain is disabling in later life and high costly for healthcare[7]. Chronic pain in older adults determines, through a multifactorial pathway, disabling condition, affecting proper ability to maintain independence and leading to a decline in social activities and isolation[8]. Moreover relationship with mental distress, anxiety, depression, sleep disturbance and cognitive decline is well known[9]. For all those reasons, we have to consider persistent pain in older people as a geriatric syndrome per se resulting in several sequelae (loss of mobility and independence, sarcopenia and decline in strength, inappetence, *etc.*).

Current approaches recommend that in older adults pharmacological interventions for persistent pain should be always part of a comprehensive and multidisciplinary approach (*i.e.,* psychological intervention, physical activity and complementary therapy); in this regard, opioid therapy should be considered in older patients with moderate-to-severe persistent pain or pain-related functional impairment or diminished quality of life due to pain.

As a matter of fact concerns about opioids use to treat chronic pain in older adults is present from both patients and providers side. Some old people believe that using analgesic medication invariably results in adverse events and that long-term use is associated with an unacceptable high risk of addiction[10]; the belief that chronic pain is a natural part of aging and it only could get worse over time[11], and that any possible treatment is not likely to provide any meaningful benefit[12]. Moreover, since older adults are more prone to drugs adverse events, clinicians sometimes are reluctant to prescribe opioids in this frail patients. Comorbidities and agerelated changes in organ functions determine major concerns for opioids prescribing.

Nevertheless the rise in opioid prescribing - and consequent increasing risk of abuse, addiction, misuse or diversion - is actually a major concern in many countries, with reports coming from Australia[13], United States[14] and Norway[15]. United States, Canada, Australia, and some Western European countries show very high levels of opioids use (over 43800 defined daily doses per million people per day in United States in the years 2011-2013), and in the period 2011-2013, use in North America increased in absolute terms from about 2.4 billion to about 5.3 billion defined daily doses per annum[16], thus justifying more stringent strategies to improve communication between clinicians and patients about the risks and benefits of opioid therapy for chronic pain, reducing the risks associated with long-term opioid therapy[17].

DISCOVERING OPIOIDS

What are opioids?

Opioids are a group of compounds that act by binding to opioid receptors which are distributed in the brain, spinal chord and periferal tissues. In general opioids are rapidly absorbed in the gut, have a high rate of first pass in the liver, are conjugated in the liver, have metabolites and vary in distribution based on their specific protein affinity, and are finally excreted through gastrointestinal or urinary tract. Opioids can act as agonists, antagonists and partial agonists/antagonists at peripheral and central opioid receptors. Fentanyl, hydromorphone, methadone, morphyne and oxycodone are opioid agonists and buprenorphine is a partial agonist/antagonist. Tapentadol has a multiple mechanism, acting as an opioid agonist and noradrenalin and serotonine reuptake inhibitor[18].

Opioids are the most powerful pain reliever-drugs and in general opioid prescribing is supposed to respond to the clinical needs of older adults who require effective relief from moderate-to-severe persistent pain.

OPIOIDS USE AND OLDER ADULTS

Opioids and age-related organs functions' changes

Organs functions progressively decline with aging. The age-related changes in drug metabolism occuring in the old population shall be considered. Aging decreases hepatic blood flow and volume, which influence opioids metabolism[19]; opioids clearance can be also altered because of age-related reduction in renal blood flow and

glomerular filtration rate (GFR)[20]. For those opioids with a primary renal clearance - such as morphine, tapentadol and hydromorphone - decrease in GFR could lead to more side effects. Thereby an estimation of creatinine clearance and hepatic function is always needed to guide clinicians in dosage adjustments.

Common geriatric conditions, like malnutrition, under-weight and sarcopenia, can lower serum albumen concentration, thus increasing the free fraction of opioids which are protein-bound; it prompts to potentially increasing side effects.

Of note, in geriatric patients the chronic - and highly prevalent - use of proton pump inhibitors H_2-receptor antagonist could alter drug absorption by increasing gastric environment pH[21].

Polypharmacy and comorbidities: Never forget them in the elderly

Persistent pain in older patients often occurs in the setting of multiple comorbidities and it limits treatment options. In fact, elderly people suffer from several chronic conditions[22] and they often are under polypharmacy. The attendant risk of drug-drug interactions increases exponentially with the number of medication taken[23]. Moreover drug interactions are likely to increase by the consumption of over-the-counter (OTC) medications, which patients often perceive to be not important, tending to omit to their physicians[24]. Interactions between drugs can lead to either serious adverse events or a reduction in therapeutic effect. Thus, it is fundamental to be aware of all the medications that the patient is taking, including OTC drugs, and the doses of each preparation.

CURRENT APPROACHES TO PAIN MANAGEMENT IN OLDER ADULTS: THE ROLE OF OPIOIDS

When managing persistent non-cancer pain in older adults, clinicians are supported by recommendations provided by national guidelines[25] - those by American Geriatric Society (AGS)[26] and British Geriatric Society (BGS)[4] are the best known - and several consensus statements[27-29].

Both AGS and BGS guidelines recommend to consider rarely and with extreme caution anti-inflammatory drugs (NSAIDs) and COX-2 selective inhibitors use in older adults with persistent pain, owing to risk of gastrointestinal bleeding[30] - which increases in frequency with age[31] - cardiovascular and kidney dysfunction[32,33]. Thereby all patients taking NSAIDs should be assessed for gastrointestinal and renal toxicity, hypertension, heart failure and potential drug-drug interactions; in general short-term NSAIDs use at low effective dosage is allowed in the old population[4,26].

Acetaminophen is recommended for mild-to-moderate pain of musculoskeletal origin[25-27], even though limited effectiveness of acetaminophen compared to placebo and other analgesics has been shown. In knee and hip osteoarthritis, as well as for the treatment of severe low back pain, acetaminophen does not seem to confer any demonstrable effect or benefit, irrespective of dose[34].

Current guidelines recommend that opioid therapy should be considered for old patients with moderate-to-severe persistent pain, pain-related functional impairment or diminished quality of life due to pain[25].

According to these guidelines a lower than normal initial dose should be used when prescribing opioids to older patients, in particular in those who are drug-naive; longer dosing intervals and slow adjustments of the dosage are also recommended to achieve the optimum therapeutic effect in safety[4,25-27].

Despite authoritative indications, management of persistent pain in older adults still lacks in everyday practice. As example, a national Canadian study documented that only 7% of older adults with disabling moderate-to-severe pain were receiving opioids stronger than codeine[35]. Of note, older people commonly use OTC analgesics and 40% of them do not experience any relief from pain from these medications[10]. In this regard, around the clock pain control *vs* "on demand" methods are preferable[21].

However we should not forget what's so relevant when treating persistent pain, especially in older adults: opioid therapy - and in general any pharmacological treatment - is likely to be more effective when it is part of a comprehensive and multidisciplinary approach (*e.g.,* psychological intervention, physical activity and complementary therapy); in fact relevant studies show that older people generally feel more comfortable with a multimodal treatment approach.

ARE OPIOIDS FOR CHRONIC-NON-CANCER PAIN EFFECTIVE IN OLDER ADULTS? CLINICAL EVIDENCE BETWEEN MYTH AND REALITY

Theoretically, all opioids may be suitable for older and frail adults; however because of inter-patient variability, opioid rotation or switching may result in better tolerability and efficacy for some patients.

A meta-analysis by Furlan *et al*[36] stated that opioids have better outcome than placebo in reducing pain and improving functional activites, as well as being more effective for both nociceptive and neuropathic pain[37]. In 2010 a meta-analysis of 43 treatment studies examining the effects of opioid-use among older adults mostly suffering from musculoskeletal pain demonstrated positive effect sizes for reductions in pain and physical disability, but not for improvement in quality[38].

Evidence from trials show that opioid therapy for geriatric patients can be safe and effective with appropriate cautions, including lower starting doses, slower titration, longer dosing interval and more frequent moni-

toring[4]. As example, in a large population (n = 13179 patients) transdermal buprenorphine proved to be effective and well tolerated in the treatment of chronic pain, irrespective of the patient's age[39].

Even though the belief that neuropathic pain (wich accounts for many chronic intractable conditions) is not responsive to opioids, opioid analgesics are recommended as generally second-line treatments in neuralgia; remarkably they also can be considered for first-line use in select clinical circumstances, such as severe or acute pain[40]. Moreover, combination analgesic therapy with opioids and anticonvulsivants has been shown effective for treating neuropathic pain[41]. In particular, the combination treatment with morphine or oxycodone, and gabapentin or pre-gabalin resulted in a greater reduction in pain than did anticonvulsivants or opioids alone, with beneficial effects on mood, pain-related interference with daily activities, and quality of life: Of note especially in geriatrics, these results were yielded with lower doses of each medication than each did alone[42].

Long-term opioids use generally raises concerns in clinicians because of inconsistent clear positive risk-benefit-ratio. A recent 52-wk extension phase-open-label study showed that prolonged-release oxycodone-naloxone achieved satisfying analgesic effect in older adults (mean age 81.7 years) in absence of major adverse events or addiction[43]. A prolonged longitudinal study among nursing home residents (n = 10372) with persistent pain revealed that long-acting opioids use may be a relatively safe option in the elderly population, yielding benefits in functional status and social engagements[44].

However taking medications to reduce pain should be part of a global approach to pain in older adults. Being involved in physical activity and participating into programmes that aim at improving social and psychological functioning are essential. Only in this regard, appropriate opioids use may synergistically allow old patients to achieve their goals.

IS PRESCRIBING OPIOID SAFE IN FRAIL OLDER ADULTS?

Although there aren't generally absolute contraindications to opioid use for managing chronic non-cancer pain in older adults, caution is needed to minimize side effects and risks, in particular in those with several comorbidites and polypharmacy.

Opioids have side effects that could be prevented and are manageable with some cautions. In older adults opioids-related adverse effects could differ from those in younger patients, in particular for clinical relevance as schematically described below. Constipation: The most common adverse effect of opioid therapy. It is experienced by around 40% of patients taking opioids for chronic non-cancer pain Contrary to other adverse effects, tolerance to opioid-induced constipation (OIC) does not develop. To prevent or reduce opioid-induced bowel dysfunction laxatives should be initiated preventively at the same time when an opioid therapy is started[16]. Alternatively, prolonged-release formulation of oxycodone/naloxone is a suitable approach in older adults to prevent OIC[4]. Due to its very low systemic bioavailability, it predominantly antagonizes opioid receptors in the gastrointestinal tract, thereby preventing bowel dysfunction[45,46]. Nausea: It is among the most frequently reported adverse events during opioid therapy[47]. It occurs at the beginning of the treatment and it can be prevented by slower titration to the effective dosage and, if needed, antiemetics. Central nervous system (CNS): Sedation is another common adverse effect associated with opioid use in the elderly. It generally occurs at the beginning of an opioid trial and disappears after a few days[48]. Combinations of opioids and CNS depressant drugs - such as antipsychotics or benzodiazepines - may have an additive role in sedation and it should be avoided. Mental confusion and hallucinations could appear in older adults during opioid therapy; these adverse events were reported less frequently in oxycodone group than in the morphine group[49]. Of note, observational studies revealed that opioids do not influence cognitive functions in elderly patients[44,47]. Delirium: In older adults opioids are associated with an increased risk of delirium; in the case of opioid therapy caution should be tempered with the observation that untreated severe pain can itself cause delirium[50]. Low-doses and slow titration may prevent older adults from developing delirium. Falls and fractures: Opioids use has been associated with a substantially increased risk of falls and hip fractures in geriatric patients[51]. Clinicians should be aware that this risk is dose-dependent and higher for short-acting opioids than long-acting opiods, especially during the first two weeks of therapy[52]. It is generally believed that fracture-risk results from dizziness and sedation leading to falls, but some researchers suggested that opioids might also interfere with bone formation through suppression of endogenous sexual hormones production. Respiratory depression: It is rare with long-term treatment and occur with dosing changes, errors or misuse. Respiratory depression doesn't occur if low drug-doses and slow titration are used during treatment initiation. Immunosuppression: Opioid-induce immunosuppression is a phenomenon mediated by the presence of μ-opioid receptors in immune cells in the CNS. Morphine and fentanyl appear to have higher immunosuppressive effects[53]. Selection of an opioid drug for long-term treatment should consider this effect in the older adults. Overdose: The recent marked increase of opioid overdose cases in the United States and Northern Europe is a major concern. Inadvertent overdose could be common in older patients, often related to insufficient care-giver support and practitioner expertise with rapid dose titration and failure to appreciate the inter-individual variability in dose requirements and response. Other potential causes of overdose in the elderly include concurrent use of alcohol, inadequately treated pain and

Table 1 Management of opioid-related adverse effects in older adults

Adverse effect	Frequency	Management
Constipation	+++	Prescribe laxatives when starting opioids Consider oxycodone/naloxone preparation
Nausea	+++	Low doses and slow titration To treat with antiemetics
Sedation, mental confusion	+	Careful review of medications (benzodiazepines, antidepressants, *etc.*) Low doses and slow titration
Delirium	+	Careful review of medications (benzodiazepines, antidepressants, *etc.*) Low doses and slow titration
Falls, fractures	+/-	To monitor walking instability and fall risk when initiating opioids Careful review of medications To prefer long-acting opioids
Respiratory depression	Very rare	Low doses and slow titration
Immunosuppression	Rare	To consider in long-term therapy
Addiction	Very rare	Abuse history Use tools to assess risk Monitoring patient

depression, particularly when compounded by awareness of dismal prognosis and hopelessness[54]. Addiction: Risk of addiction is possible in the elderly but it is lower than in middle-aged patients[55]. Clinicians should ask all patients about any substance abuse history. Screening questionnaires can be helpful in determining a patient's risk of opioid misuse and addiction. As example, the Opioid Risk Tool is the simplest and most widely used of the screening tools[56].

Higher rates of adverse effects are observed with initiation of opioids, but data also suggest that these may be preventable if monitored closely. Few available studies on prolonged opioids therapy in older adults find no significative incidence of long-term adverse events[45,46].

Common opioid-related adverse effects in older adults and their management are resumed in Table 1.

BRINGING EVIDENCE TO PRACTICE: PRESCRIBING OPIOIDS IN OLDER ADULTS

Existing guidelines for managing persistent pain in older adults recommend that opioid therapy for elderly patients can be safe and effective in patients with moderate-to-severe pain with appropriate cautions[4,24-27]. Despite these recommendations nowadays in clinical practice NSAIDs continue to be one of the most commonly prescribed and consumed analgesic agents in the elderly[57]. It is estimated that over 100000 hospitalizations occur annualy on account of NSAIDs-induced gastrointestinal and renal toxicity[58] and that approximately 20% of all congestive heart failure admissions can be attributed to NSAIDs use[59]. NSAIDs prolonged-use is particularly hazardous in older adults with hypertension, peptic ulcer disease or impaired renal function.

When using opioids in older adults, some recommendations should be followed before, when and after prescribing them.

Before prescribing opioids: Proper assessment is essential

Older adults with persistent pain vary in their response to opioids and their risk of complications; assessment of concurrent medications, cognitive and behavioral status and social support should be encouraged before starting a opioid trial.

Before prescribing opioids in the oldest, some factors must be taken into account (Table 2): As physiologic changes due to aging could lead to altered drug metabolism, renal and hepatic functions assessment is fundamental; polypharmacy: Assessment of medications is essential in this population. Concurrent use of over-the-counter NSAIDs, benzodiazepines or other sedatives place patients at higher risk for morbidity or mortality[60]; multimorbidity: Chronic conditions - such as disorders of gait and balance, kidney and cardiovascular diseases - should always be taken into account; tools to assess risk of addiction or abuse are strongly recommended; even though risk of opioids misuse/abuse is unfrequent in the elderly population, additional prescribing information and prescribing tools shall be regularly used in addressing any concerns about opioid risks and addiction[31]; shared decision-making: Planning treatment and monitoring outcomes is recommended; it is important to establish realistic treatment goals, focusing on functional issues such as increased mobility or independence rather than pain intensity[61]; drug prescribing for chronic pain in older adults should be part of a comprehensive management, that includes exercise and psychological interventions.

When prescribing opioids in older adults

When trialing an opioid treatment for an older patient the adage "start low and go slow" is recommended. Advise patients that treatment will start with a trial period of about four weeks. Opioids should be titrated slowly, using half the starting dose used for younger adults. A 3-d tolerance check is recommended after initiation or dose increase to assess for excess sedation or confusion[25].

Staying too slow is unacceptable and could contribute

Table 2 Before prescribing opioid treatment in older adults

Consider age-related physiological changes (creatinine clearance, hepatic function, serum albumen)
Assess polypharmacy (over-the-counter analgesics, benzodiazepines, antidepressants, antipsychotic drugs)
Consider multimorbidity
Use tools to assess risk of addiction
Share realistic treatment goals and make therapeutic plan
Consider exercise and psychological interventions

Table 3 When prescribing opioids in older adults

Beginning at the lowest possible dose and titrating upwards base on tolerability and efficacy
Longer dosing interval and regular monitoring are recommended
Switching to another opioid might be indicated in cases of unacceptable side effects of insufficient analgesia
The oral route may be the most convenient
Low-doses of strong opioids should be preferred to weak opioids because of its effectiveness and safety
Strong opioids generally recommended in frail old population are buprenorphine, hydromorphone and oxycodone (including oxycodone/naloxone formulation)
Controlled-release formulation and transdermal formulations are generally preferred (low risk of addiction and adverse effects)
Considering laxatives or oxycodone/naloxone to prevent constipation
Over-the-counter analgesics use should be avoided

to under-treatment. In fact, if treatment goals are not met and the patient tolerates the therapy, advancing dose is reasonable before moving on to another intervention[62]. Switching to another opioid might be indicated in cases of unacceptable side effects or insufficient analgesia.

The least invasive route of administration should be used; the oral route may be the most convenient and it can rapidly provide relatively steady blood concentrations; transdermal administration may be preferred in the context of opioid rotation or switching (paying attention to equivalent doses), or for uncompliant patients, and those unable to swallow, also to reduce staffing requirements in residential and nursing homes. Given the high potency of transdermal fentanyl, it should not be used for opioid initiation[4]. Sudden opioids withdrawal should be avoided.

In general low-dose of strong opioids should be preferred to weak opioids (tramadol and codeine) because of its effectiveness and safety[21,22]. Prescribing weak opioids could require higher dosage to reach adequate analgesia and high doses are likely to determine harmful adverse events in the old population.

Tramadol has a different mode of action to other opioids as it inhibits the neuronal reuptake of both norepinephrine and serotonin. Particulary when used in combination with selective seretonin-reuptake inhibitors, tramadol has the potential to cause life-threatening events such as serotonin toxicity or serotonin syndrome. This is a clear limitation to tramadol use in the elderly because of the high concurrent rates of depression in this age-group. Furthermore, there should be recognition that there is individual variability in codeine's efficacy dependent upon drug metabolism into its active metabolites. Up to 30% of the population has been reported to be poor hydroxilators of debrisoquine required for codeine activation.

Buprenorphine, hydromorphone and oxycodone (including oxycodone and naloxone formulation) are the strong opioids more studied in geriatric patients[37,38,43,45]. Morphine instead should be use with extreme caution in older patients with renal impairment.

On the contrary, actually the evidence to support tapentadol still lacks in specific old population. True efficacy and side effects profiles of tapentadol in this age-group are largely unknown, especially for long-term use[59,61-63]. However, as tapentadol does not undergo significant metabolism by cytochrome P-450 system, the potential for drug-drug interactions is supposed to be lower than other opioids.

Since OIC is the most frequent side effect, prophylactive laxative therapy should be initiated in nearly all patients using opioids. A proper approach to reduce OIC in the frail elderly is the fixed-dose combination oxycodone/naloxone because of its peculiar biochemical profile[43,45,46].

Finally in order to improve the convenience for elderly patients and avoid the risk of addiction, the controlled-release formulation and transdermal formulations are generally preferred[63], whereas OTC analgesics use should be avoided (Table 3).

After precribing opioids: Addiction and side effects monitoring

If an opioid trial is undertaken, it is important to closely monitor whether treatment goals are met or adverse effects occur (arranging regular phone contacts or visits during the initiation and dose titration phase of treatment). When monitoring older adults using opiods clinicians must ensure that patients is adhering to treatment plan. On each contact "the four As" - analgesia, activites of daily living, adverse events and aberrant drug taking - should be regularly evaluated. In particular, any signs of misuse, abuse or drug diversion have to be assessed and regularly

(at least every 3 mo) monitored.

CONCLUSION

Managing persistent pain in older adults is a complex task, as the relevant presence of multiple comorbidities, polypharmacy and physiological vulnerability in this age-group. Formulating an effective treatment plan for older adults with persistent pain requires a clear understanding of comorbidities and psycho-social situation. However, common opioid-related harms can be minimized with an individualized approach to opioid prescribing tailored to patients' health status and risk factors.

Given the established opioids use-related risks, the potential negative effects must always be weighed against the consequences of untreated or partially treated pain. In fact, the consequences of inadequately treated pain itself can determine impaired function, decreased independence in daily activities and depression.

Beginning at the lowest possible dose and titrating upwards base on tolerability and efficacy, longer dosing interval and frequent monitoring are strongly recommended[4,24-27]. Prescribing opioids to older adults can be very gratifying when clinicians are adequately trained in pain management. Of note, even relatively low doses of strong opioids can be effective and safe; in our experience old subjects seem more prone to achieve therapeutic goals at low opioids-dosage than younger patients[43,46]. This age-related feature is so remarkable as summarized by the adage "the lower effective opioids dose, the lower adverse effect".

In conclusion, when approaching an old patient with persistent pain the risk-benefit-ratio should address our approach to opioid-use, supported by recommendations from current guidelines and by evidence from clinical observations.

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MINIREVIEWS

Decoding white coat hypertension

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Abstract

There is arguably no less understood or more intriguing problem in hypertension that the "white coat" condition, the standard concept of which is significantly blood pressure reading obtained by medical personnel of authoritative standing than that obtained by more junior and less authoritative personnel and by the patients themselves. Using hospital-initiated ambulatory blood pressure monitoring, the while effect manifests as initial and ending pressure elevations, and, in treated patients, a low daytime profile. The effect is essentially systolic. Pure diastolic white coat hypertension appears to be exceedingly rare. On the basis of the studies, we believe that the white coat phenomenon is a common, periodic, neuro-endocrine reflex conditioned by anticipation of having the blood pressure taken and the fear of what this measurement may indicate concerning future illness. It does not change with time, or with prolonged association with the physician, particularly with advancing years, it may be superimposed upon essential hypertension, and in patients receiving hypertensive medication, blunting of the nighttime dip, which occurs in about half the patients, may be a compensatory mechanisms, rather than an indication of cardiovascular risk. Rather than the blunted dip, the morning surge or the widened pulse pressure, cardiovascular risk appears to be related to elevation of the average night time pressure.

Key words: White coat; Ambulatory blood pressure; Triggers; Hypertension; Neuro-endocrine reflex; Nighttime dip; Morning surge; Conditioned reflex

Core tip: White coat hypertension is a poorly understood and significantly common ambulatory blood pressure finding. This study defines blood pressure during various periods of the day and night, analyzes nighttime dip and morning surge, provides insight into the triggers of the episode, and discusses the possible neuro-endocrine causes. It is a permanently conditioned reflex from anticipation and fear that blood pressure measurement may indicate future illness. Recognition of this condition reduces the patient's worry, relieves them both of a lifetime of unnecessary medication and the side effects of the otherwise ever-increasing dosages, and diminishes the frustration of the attending physician.

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INTRODUCTION

There is arguably no less understood or more intriguing problem in hypertension than the "white coat" condition, the standard concept of which is a significantly higher blood pressure reading obtained by medical personnel of authoritative standing than that obtained by more junior and less authoritative personnel and by the patients themselves.

The whole subject is infused with uncertainties and contradictions beginning with the lack of a clear enunciation of the definition upon which the diagnosis rests. This presently depends on a strict definition, recognized by the international cardiological community narrowly as "an office pressure of greater than 140/90 mmHg with a home or ambulatory measurement of less than 135/85 mmHg", although some authorities recognize wider limits[1-5]. The measurements are based largely on recognition of the Korotkof sounds, a technique unchanged for over a century and rarely measured over a period greater than 10 s. Moreover, the recorded pressure is subject to diurnal variation, activity, rest, emotional state and current medications as well as individual measurement technique, size of cuff, personal auditory acuity and environmental noise levels. Such variety exists in the methods of defining white coat hypertension (WCH)[2,5-8] that the incidence is quoted as low as 10% of the hypertensive population and as high as 40%[9-12].

Normal variation

Almost all adults have a higher systolic blood pressure when taken in a doctor's office than when taken by ambulatory blood pressure monitoring (ABPM) or by the patients themselves[3]. It has been recognized for two decades that averaged multiple office readings are as much as 10/5 mmHg higher than ABP measurements. Some of these pressures will reduce to normal values with repeated office measurements following rest. Generally, the difference is so small that it lies within the normal daily variation, does not influence the diagnosis in regard to the blood pressure or require a change in management[3].

It is only when the pressure difference is significant and the ABPM configuration is characteristic, that a diagnosis of WCH is warranted. The degree of pressure elevation in susceptible patients is also physician dependent, some physicians causing a higher white coat effect than others.

To add further confusion to the concept, a recent recommendation of the British Heart Society suggested that patients originally thought to have elevated pressures but were found to be normotensive on ambulatory monitoring be classified as "white coat hypertensives" while true hypertensives with further elevation in the presence of the doctor be considered to show the "white coat effect". A more understandable distinction would be to designate the elevation of pressure as the "white coat effect" and the person manifesting this effect as a "white coat hypertensive".

A representative graphic printout of a typically normal 24 h ABPM recording is shown in Figure 1 and the advent of this diagnostic tool has drastically altered the appreciation and understanding of hypertension as a whole and WCH in particular. The use of ABPM has demonstrated that the generally accepted definition of WCH is far too narrow and superficial and does not recognize the complexities revealed by analysis of this technique in susceptible persons. The present review examines the data from decades of ambulatory recording, providing a more comprehensive description of the four characteristic periods in the 24 h recordings, exploring the triggers of the white coat episode, considering the complex implications of the night-time pressure dip and postulating the continuing benign nature of the white coat experience.

Greater understanding of clinical hypertension will only evolve from widespread utilization of 24 h blood pressure monitoring, which is not yet current practice in the United States. It is as important to clinical hypertension as the 24 h Holter has become to clinical arrhythmia and it is indispensable for the understanding of WCH.

Diagnostic tests

The recognition of the inherent inaccuracy of the definition in both clinical practice and hypertension research necessitated the search for other clinical and laboratory measures to describe WCH. A "slow breathing test" causing a fall in pressure after one minute[13], was supposed to indicate WCH. A rise in pressure determined by an unknown and un-introduced physician (the White Coat Test) or the response to public speaking to an audience of strangers[14], were to also confirm the white coat diagnosis. None of these tests have become standards.

In the clinical setting, repeated office pressures in the severe hypertensive range for many years without the evidence of left ventricular hypertrophy, retinal arterial changes or albuminuria, strongly suggests that the recorded pressure is not sustained. Furthermore, office measurements of systolic pressure are known to quickly settle to reduced values on repeated estimation[4] while white coat systolic pressures tend to vary up-and-down by large amounts on repeated measurements.

The vast proportion of patients referred for ABPM have been unsuccessfully treated for office-perceived hypertension and present while taking usually large amounts of medication. A further clue that the elevated pressure may be due to the white coat effect is the observation that, despite increasing medication, generally little change is elicited in the office in the systolic and

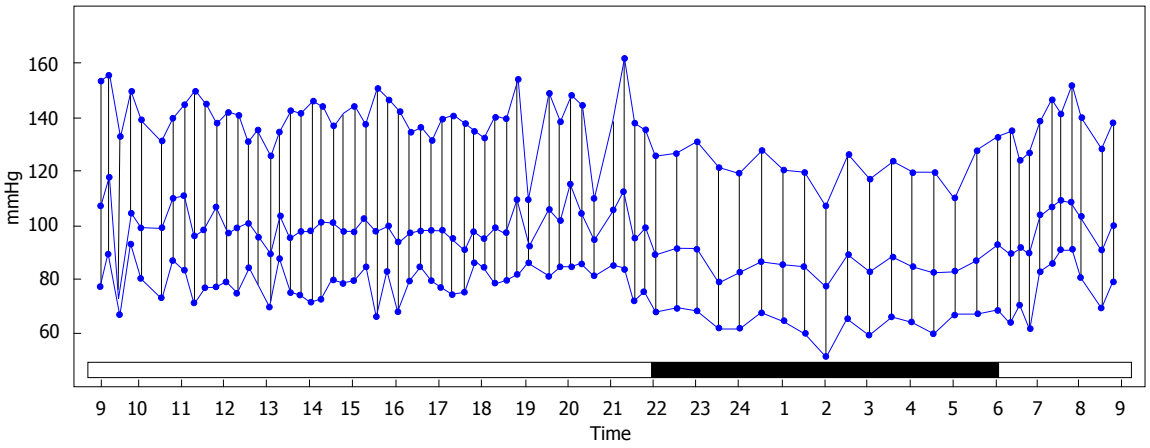

Figure 1 Normal 24 h ambulatory blood pressure recording. In all the figures, the simultaneous systolic and diastolic blood pressure values are connected by vertical lines. The blue line within the verticals is the mean blood pressure. The recorded pressure in mmHg is noted on the vertical axis. At the time of recording, recognized normal values, represented by light horizontal lines, were 135 mmHg systolic and 85 mmHg diastolic during the daytime and 120 mmHg systolic and 70 mmHg diastolic during sleep. The 24 h time of recording is noted on the horizontal axis. The solid black horizontal bar represents the sleep period.

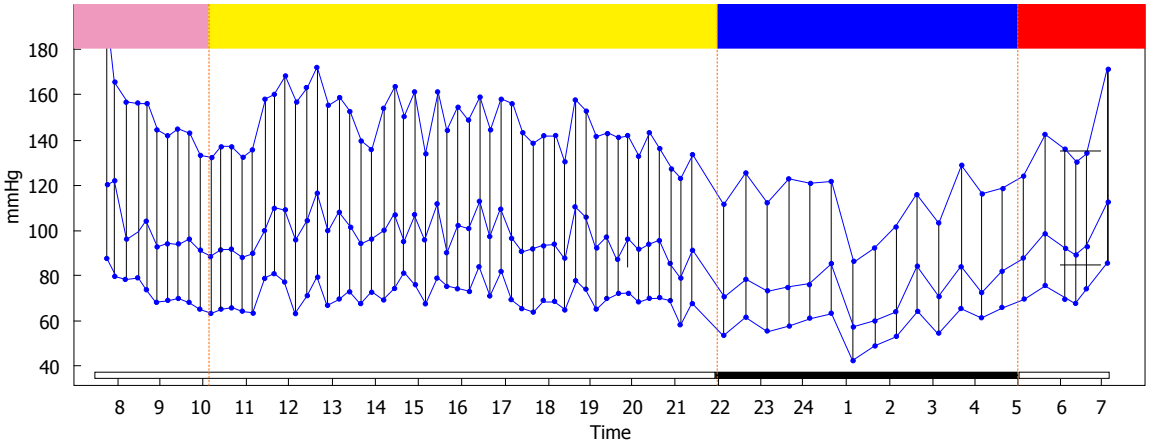

Figure 2 The four time segments of the recording.

diastolic pressures. In true recalcitrant hypertension, by comparison, the medication usually affects some lowering of pressure although not to an acceptable level. The majority of patients in our study were taking between one and four hypertensive medications at the time of their ABP measurement.

RESEARCH

The ambulatory recordings can be analyzed to identify almost 30 specific measurements and provide a profile of the white coat effect that greatly expands the understanding of the conditions that define it.

The figures used to illustrate this review were obtained using the Spacelabs equipment (Del Mar-Pressurometer P6 and more recently Sentinal). The studies begin in the morning with the recorder attached in the EKG department of the community hospital. Pressures are recorded continually through the day, through sleep and in the following morning up until the time that the recorder is removed again in the same hospital department. The data is analyzed using the Spacelabs reporting software.

The 24 h blood pressure recordings can be considered in a number of segments: The initial recordings taken at the time of attachment of the recording device and extending for three or four hours, a second segment encompassing the remaining morning hours and through the afternoon and evening until bedtime, a third segment during sleep and a final segment, upon awakening and until the recorder is removed. Each segment has a unique pattern defining its white coat character (Figure 2).

ANALYSIS

The initial application in the hospital

The hospital department and the application of the recorder in that setting provide the environment to trigger the white coat effect. Precipitated by the attachment of the ABP monitor, the pressure is usually high and is recorded at or near the office pressure. The hook-up is not performed by a white-coated physician but by a casually dressed technician so the stimulus appears to be related to the hospital environment and the patient's concern about

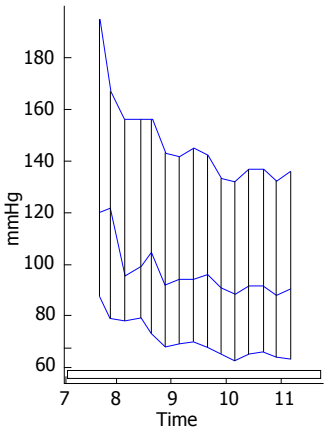

Figure 3 The hospital-induced bimodal blood pressure fall of the white coat effect.

what the test results might portend. These conditions and its effect have been reported elsewhere[15,16], identifying this response to be universal and not specific for this particular hospital.

In the first minutes of recording, the systolic and diastolic pressures usually reach the highest levels in the entire 24 h. The next 30 min shows the steepest fall of pressure but it rarely falls to the eventual daytime values. This pattern, illustrated in Figure 3, has been recognized and used by others as a supplemental factor in the diagnosis[17]. During the next 2 to 3 h, the pressure falls more slowly to usually the lowest daytime value[18].

This bimodal pattern suggests that either the sympathetic stimulus responsible for the initial pressure elevation does not quickly dissipate or that it is accompanied by an endocrine stimulus with a slower rate of decline. This neuro-endocrine mechanism may not be only specific for blood pressure as a case has been reported of a white coat hypertensive who was also a white coat hyperglycemic as his laboratory-obtained blood sugar was always elevated while his home level and his Hemoglobin A1C were always normal[19].

In this initial segment, the pulse pressure tends to be wider as the systolic pressure is elevated disproportionately to the diastolic. This observation has also been used as an indicator of the white coat effect[20-22]. Using the standard office/home pressure difference to identify the white coat effect, a positive correlation was found with pulse pressures of 60 mmHg or greater.

The daytime period

This segment is characterized by a plateau which is sustained with only minor variations. As the vast majority of the patients were receiving multiple hypertensive medications, this level may, in fact, be below normal. Three variations have been seen in this segment.

The first variation occurs when the patient exercises. The response is normal for exercise with elevation of the systolic and less elevation of the diastolic pressure. Following the exercise, the pressure falls back rapidly (unlike the dissipation of the white coat elevation) to the previous plateau level (Figure 4). This pattern probably mimics that of recovery after a stress test, when the heart rate and the blood pressure normally fall to the resting level within 12 min. However, the recording frequency of the ABPM is usually set at no shorter than 30 min in the daytime so this information is often not recorded. A similar rise and fall of the pressure can be seen with episodes of anxiety, excitement and anger but neither these nor the exercise elevations reach the magnitude of the white coat episodes.

A second variation occurs when the patient experiences another incident which provokes the white coat response. An expanded discussion of the "triggers" of the white coat episodes will be presented and discussed later.

A third variation occurs when the patient actually has essential hypertension complicated by the white coat effect. With a relatively high occurrence of these two conditions in the older adult population, the coincidence is not unusual. In this instance, pressure rises through the afternoon and evening in the normal diurnal manner and the pressures eventually reach abnormally high levels (Figure 5). In the past, WCH has been described as part of a continuous spectrum, beginning with normal blood pressure, ending with true essential hypertension with white coat intermediate between the two[23-25]. This was part of the widely held concept that WCH was not a benign disorder, retaining the capacity to morph into true, sustained hypertension[7,26-32]. Interestingly, the vast majority of papers supporting this concept have used the narrow and possibly contentious definition (> 140 mmHg office with < 135 mmHg home) to diagnose WCH.

Our present view is that as both benign white coat and pathological essential hypertension are common conditions, the occasion frequently arises when the two will exist together and, as time passes, the true pressure elevation of older age eventually dominates but does not obscure the white coat effect (Figure 6). This concept is supported by many authors[33-39].

The period of sleep

The circadian fall in blood pressure during sleep has been fully examined only since the advent of ABP monitoring and its occurrence in WCH has not been generally elucidated.

This physiological nighttime dip in pressure occurs in approximately half of the hypertensive adult population[40]. It occurs in approximately the same proportion in treated white coat hypertensives. When this happens, the pressure may be significantly lowered by the medication but this tends to be without symptoms or complications (Figure 7). The understanding of the "night-time dip" is complex and its significance is controversial. Although no definition of its calculation is standardized, the generally utilized method is to subtract the average night-time systolic pressure from the average daytime systolic pressure and express that value as a percentage of the daytime figure. It is generally agreed that it is normal for the mean systolic pressure to fall to a level

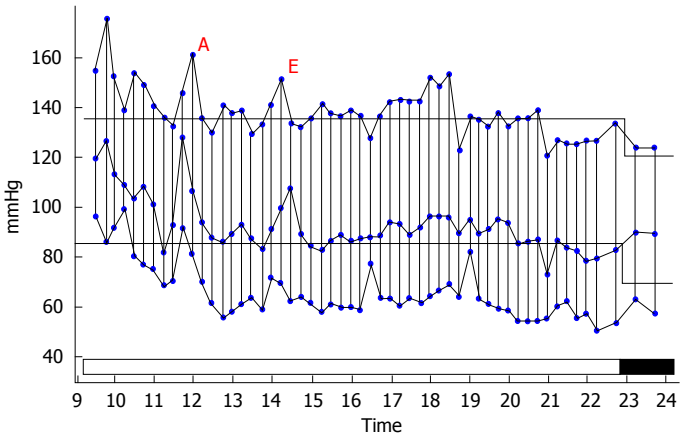

Figure 4 The pressure elevation from exercise (E) and strenuous activity (A).

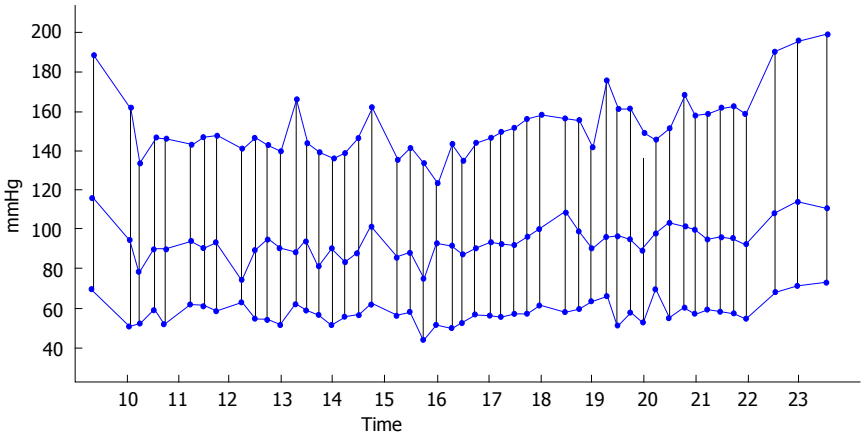

Figure 5 White coat hypertension with superimposed essential systolic hypertension reflected in the rising pressure in the afternoon and evening.

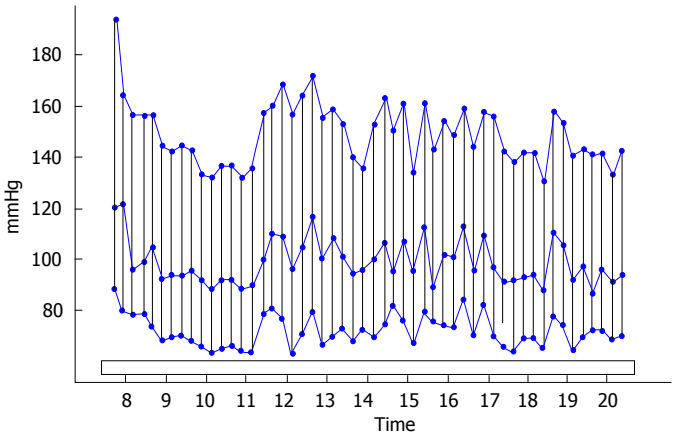

Figure 6 Essential hypertension with an initial classical white coat configuration.

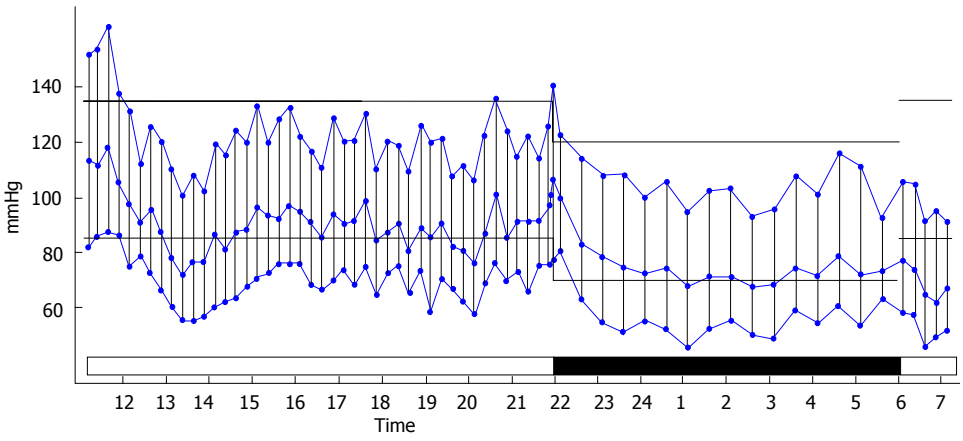

Figure 7 The night-time dip. A classical white coat pattern during day time with a normal sleep time pressure dip of 20 mmHg.

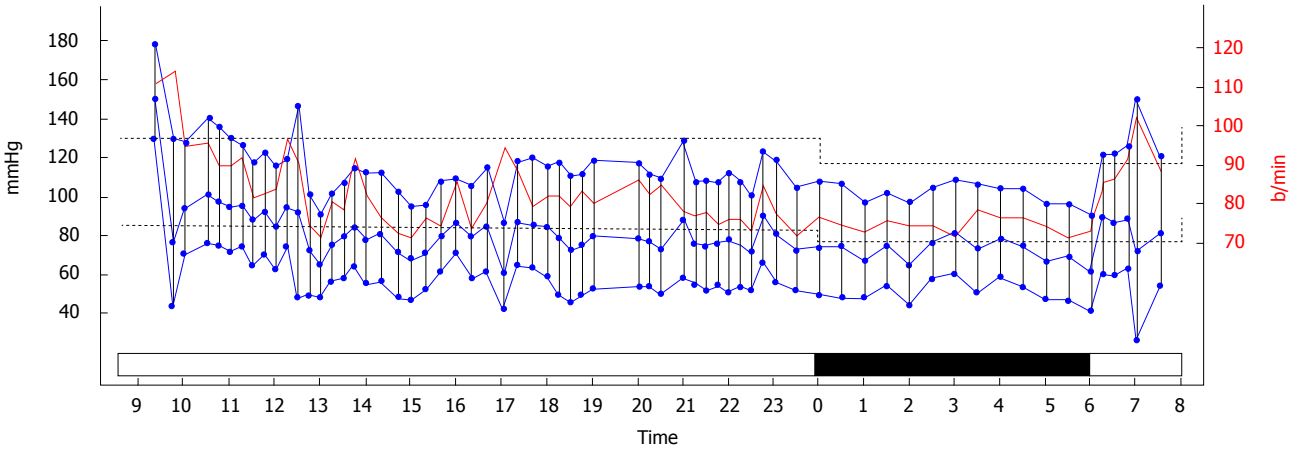

Figure 8 White coat hypertension with a blunted night time dip. The recorded pressure in mmHg is noted on the left vertical axis. The pulse pressure in beats per minute is noted on the right vertical axis. The 24 h time of recording is noted on the horizontal axis. The solid black horizontal bar represents the sleep period.

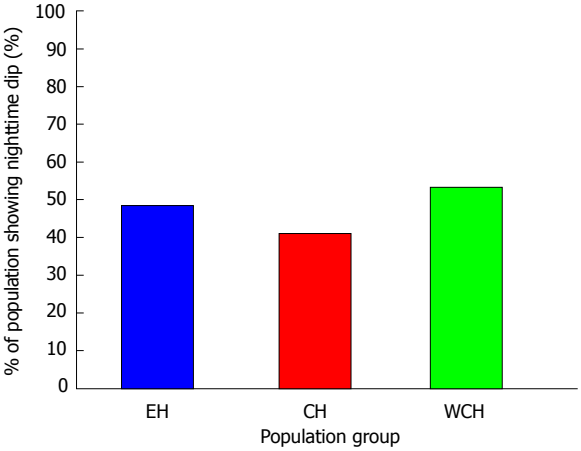

Figure 9 Similar percentage of blunted nighttime dippers in medicated but uncontrolled essential hypertensives, medicated controlled hypertensives, and medicated white coat hypertensives. EH: Essential hypertensives; CH: Controlled hypertensives; WCH: White coat hypertensives.

10%-20% lower than the mean daytime systolic pressure. Those whose pressure falls less than 10% are known as "non-dippers" or as having a "blunted" dip. Essential hypertensive patients are understood to lose the night time dip.

The concept of "blunted" dipping of the pressure (Figure 8) has been linked to the increased risk of cardiovascular disorders[41-45] but these studies have almost always been conducted in patients not on hypertensive medication[46]. Half of the white coat patients in this series had blunting or absence of the nighttime dip, but because they had neither sustained hypertension, left ventricular hypertrophy, albuminuria or optic fundal arterial changes for many years, it was difficult to believe that they were at enhanced cardiovascular risk. To further elucidate this issue, medicated but uncontrolled essential hypertensives, medicated controlled hypertensives and medicated white coat hypertensives were compared in regard to the nighttime dip. While the three groups were significantly different in multiple modalities of blood pressure, they were not significantly different in regards to their percentage of nighttime dippers (Figure 9)[46]. It was concluded that, in contrast to the reported findings in un-medicated white coat hypertensives, the nighttime dip could not be used as a predictor of cardiovascular risk in medicated white coat patients although this cannot be substantiated due to the lack of follow up information.

One possible explanation of benign non-dipping in medicated patients is that the body's auto-regulatory systems may not permit the night-time pressure to "dip" further when it is already reduced to very low levels with hypertensive drugs. In both treated and untreated hypertensives, blunting was associated with advanced age, obesity, diabetes mellitus and overt cardiovascular or renal disease, suggesting that blunting may be merely a marker of high cardiovascular risk rather than a cause[40]. However, if the actual average night-time systolic pressure is considered rather than the "dip", a strong correlation with cardiovascular risk has been shown[47].

Pressures may also rise during the night (Figure 10). This can be caused by episodes of obstructive sleep apnea and superimposed essential hypertension. Dreams and particularly nightmares are also implicated (Figure 11). Waking to empty the bladder does not usually cause a significant elevation. None of these pressure elevations mimic the white coat episode.

The final segment

This segment, representing the time of awakening and the subsequent couple of hours, is characterized by a normal circadian rise in pressure continuing until the recording device is removed. In our series, this provoked another white coat episode. In most cases the pressure does not reach the same peak as was recorded when the monitor was initially attached at the beginning of the study and, on rare occasions, it is not seen at all. When exaggerated, this pressure rise is designated "the

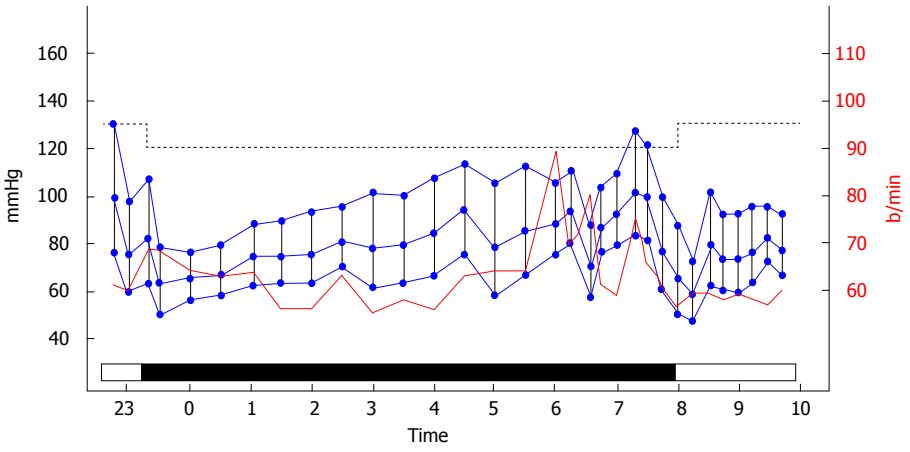

Figure 10 Elevated nighttime blood pressure and pulse rate. The recorded pressure in mmHg is noted on the left vertical axis. Right axis shows the recorded pulse rate in beats per minute. Horizontal axis displays the 24 h time with black bar indicates the sleep period.

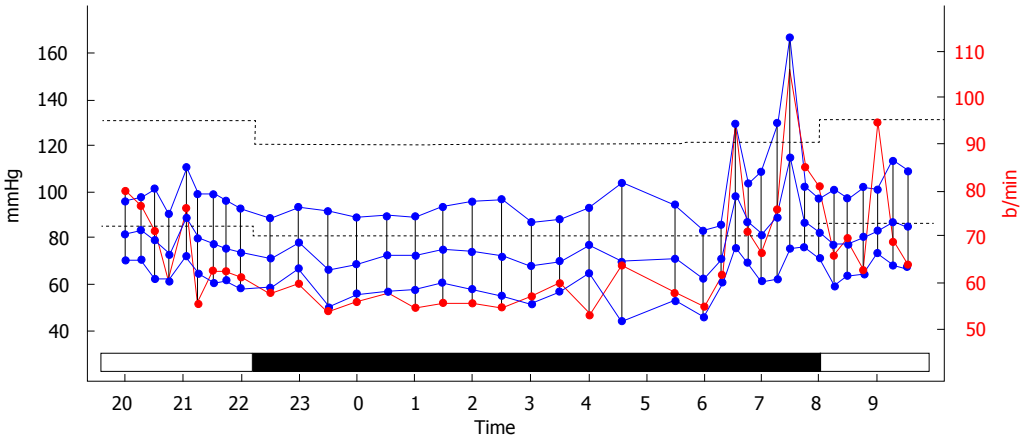

Figure 11 Pressure and pulse rate rise during a nightmare at 7:30 am.

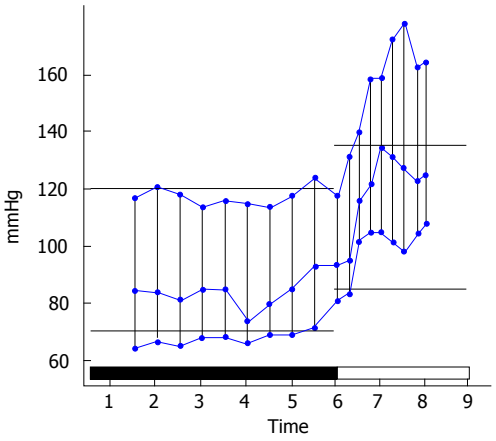

Figure 12 The "morning surge" upon awakening.

morning surge" (Figure 12) and it has been considered the cause of the increased incidence of acute myocardial infarction in the morning hours. In treated white coaters with pre-awakening depressed pressure, this rise may be further exaggerated. However in our series, there were frequent instances at other times during the day when the blood pressure "surge" was greater than in the morning (Figure 13), but no myocardial infarction was experienced in the whole series while the ABPM was recording.

In non-dippers, the morning rise may be diminished. Clearly the "dip" and the "surge" are dependently linked and while they share the time course of increased cardiovascular episodes, the cause of these events seems to have been shown to be due principally to the average nighttime systolic pressure[47].

Further white coat characterization

Widening of the pulse pressure has been recognized as a risk factor in cardiovascular disease, particularly as it is usually associated with systolic hypertension, aortic regurgitation or thyrotoxicosis, risk factors in themselves. The white coat effect raises the systolic pressure either exclusively or by a far greater magnitude than the diastolic and widening of the pulse pressure occurs with every episode. As such, it has been recognized as a marker of this condition[20-22]. The relationship or interdependence of the systolic and diastolic pressures in WCH, as measured by the correlation coefficient, has not been shown to be unique or different from that of regular essential hypertension. No cases of acute myocardial infarction occurred while the patients were being monitored and no symptoms of angina were reported during the white coat periods.

White coat elevation in blood pressure is essentially

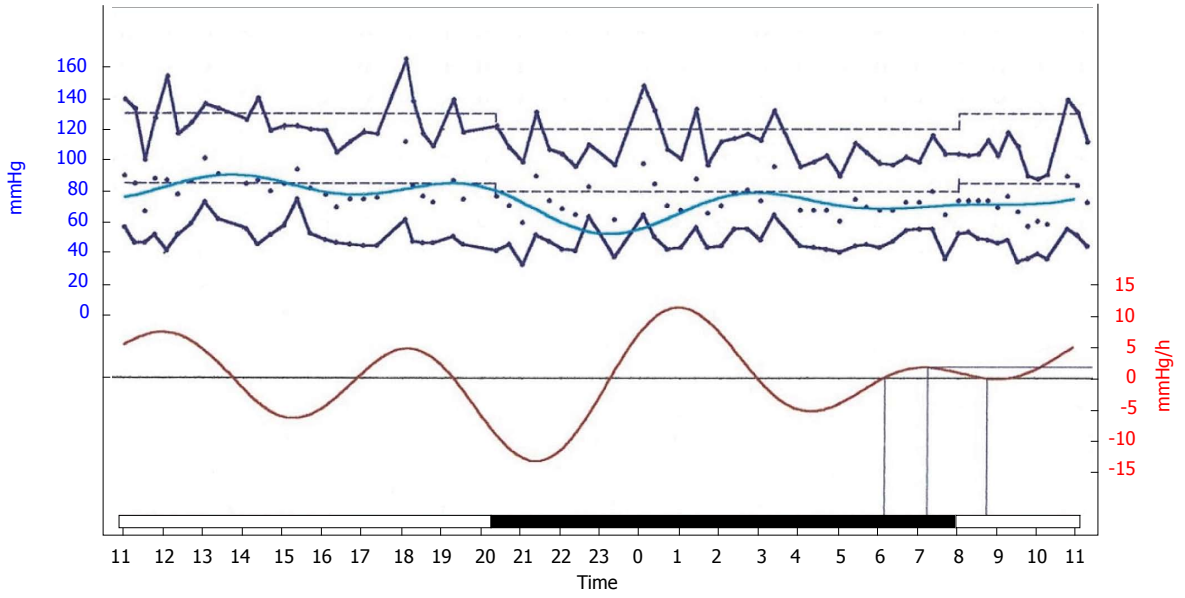

Figure 13 Rate of rise and fall of systolic pressure during the 24 h. The rate is shown by the red line with the mmHg rise/hour noted on the right vertical axis.

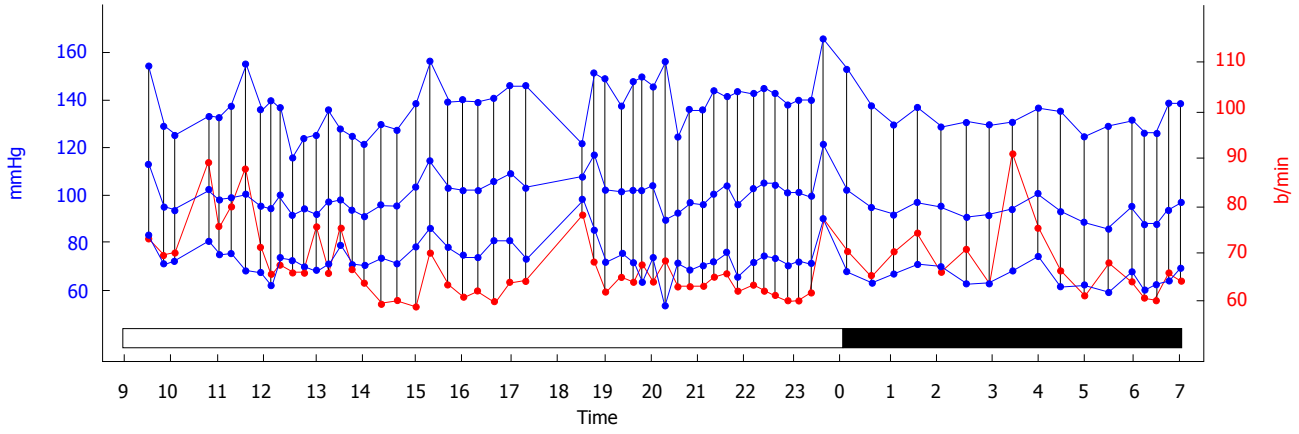

Figure 14 Diastolic white coat hypertension. Office blood pressure recorded repeatedly over two years ranged from 130-140 mmHg systolic and 95-100 mmHg diastolic. Ambulatory blood pressure monitoring shows stable systolic pressure while the diastolic pressure falls into the 60-70 mmHg range.

systolic and another feature of the white coat effect is the apparent rarity of pure diastolic WCH which we can define as a significant diastolic difference between office and home or ABPM pressure with a sustained normal systolic pressure. There is a modest related increase in the diastolic pressure during a white coat episode, such as happens with an exercise stress test, but no case of pure and isolated diastolic WCH with sustained normal systolic pressure has been previously reported. Only two such cases have been observed in this series. One example is shown in Figure 14. The other patient had office diastolics 25-30 mmHg higher than on the ABP monitor. This may result from diastolic pressure being related to a different proportion of neuro and endocrine control of the peripheral arteriolar constriction than systolic WCH. However, both patients, post menopausal women, had prior strokes, one due to undiagnosed atrial fibrillation, the other with temporal arteritis and both fully recovered at the time of white coat diagnosis. The relationship of the neurological and cardiac conditions is unknown. A relationship with diastolic WCH has been demonstrated with polymorphisms of angiotensinogen, angiotensin-converting enzyme and protein G[45].

Apart from Mancia's study[48] observing the appearance of the physician at the patient's bedside, no detailed examination of the process that triggers the white coat event has been reported. Possible factors include anxiety linked to anticipation of having the blood pressure measured, arriving at the doctor's office, entering into the examining room, undergoing the preceding physical examination, or the actual recording of the blood pressure. In a study to clarify this issue, known white coat hypertensives were recruited and underwent the aforementioned sequence of events while wearing an ambulatory blood pressure recording device[49].

Attachment of the monitor in the hospital setting and each of the afore-mentioned stages of a doctor's visit provoked a white coat episode. Anticipation of the visit

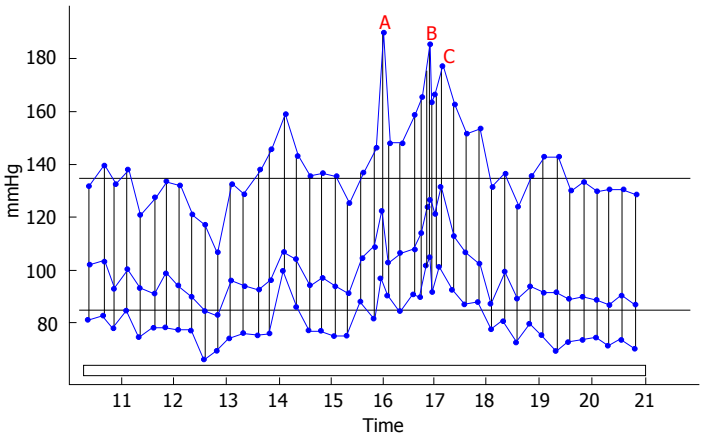

Figure 15 Triggers and aggravation. "A" represents pressure upon arriving at the doctor's office, "B" on entering the consulting room, and "C" on applying the pressure cuff to the arm and recording the blood pressure. The pressure peak at 1400 h represented a prolonged argument with the patient's cable TV company.

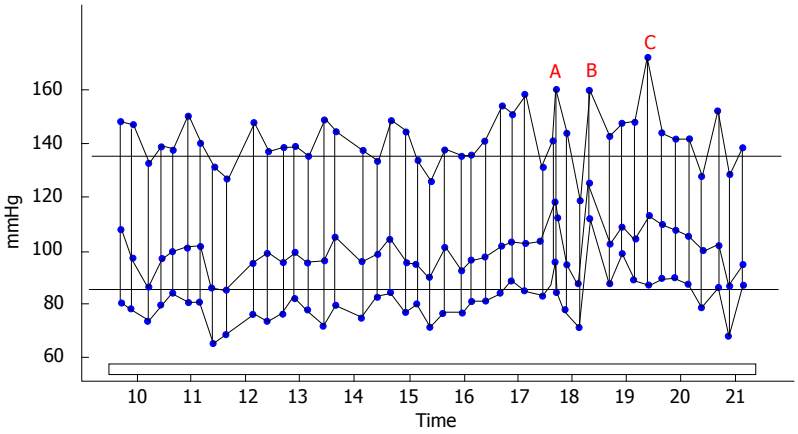

Figure 16 Triggers and anxiety. The pressures indicated by A, B and C represent the same activity as shown in figure 15. The preceding multiple pressure peaks represent the anticipatory anxiety and concern regarding the visit to the doctor.

evoked some blood pressure elevation but arrival at the doctor's office produced a full-blown white coat episode, indicated by the letter A in the subsequent figures. While waiting for the doctor, this peak tended to resolve to some extent. This time course has been previously reported and has been suggested as a characteristic of the episodes. Admission to the consulting room (letter B in the figures) caused another pressure rise and manually taking the blood pressure by cuff and mercury manometer produced the highest peak (letter C). Placement of the cuff but not inflating it to record a manual pressure produced the same blood pressure response as if it had actually been taken, reinforcing the "anticipation" concept. Recorded episodes of exercise, aggravation (Figure 15) and anxiety (Figure 16) produced less pressure elevations than the white coat episodes.

Much has been written concerning the mechanism of WCH in terms of pathophysiology, personality, interpersonal interactions and the influence of authority. Anxiety elevates blood pressure but does not appear to be the trigger for the white coat episodes[50] as white coat patients have been subjected to anxiety testing and have not been shown to be different to non-white coat persons[51,52]. Mental stress has been considered as a trigger for the white coat episode[53], but this could not be confirmed by other researchers[54]. Reactivity to public peaking has been advanced as a cause[55] but this clearly could not be a trigger for real life office pressure measurement. Anticipation not only of actually taking the blood pressure but the interpretation of the result by the doctor and its imagined significance on the health status seems to be the main stimulus of the white coat effect. Anticipation ranks more highly than anxiety.

Jhalani *et al*[56] considered the mechanism to be due to a conditioned reflex that, once established persisted for visit after doctor's visit, year upon year. Even when the fear of an adverse finding was eliminated by repeated examinations over the years, the white coat response persisted[56]. This process has been described with severe, prolonged nausea, provoking anticipation about further cyclical vomiting attacks, facilitating conditioning in a self-perpetuating manner.

CONCLUSION

On the basis of the studies, we believe that the white coat phenomenon is a common, periodic, neuro-endocrine reflex conditioned by anticipation of having the blood pressure taken and the fear of what this measurement may indicate concerning future illness. It does not change with time or with prolonged association with the physician.

Particularly with advancing years, it may be superimposed upon essential hypertension and, in patients receiving hypertensive medication, blunting of the nighttime dip, which occurs in about half the patients, may be a compensatory mechanism rather than an indication of cardiovascular risk. Rather than the blunted dip, the morning surge or the widened pulse pressure, cardiovascular risk

appears to be related to elevation of the average night time pressure.

On hospital initiated ABPM, the white coat effect manifests as initial and ending pressure elevations and, in treated patients, a low daytime profile. The effect is essentially systolic. Pure diastolic WCH appears to be exceedingly rare.

Recognition of this condition reduces patient's worry, relieves them both of a lifetime of unnecessary medication and the side effects of the otherwise ever-increasing dosages and diminishes the frustration of the attending physician.

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MINIREVIEWS

Bayés syndrome and acute cardioembolic ischemic stroke

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Abstract

Bayés syndrome is an under-recognized clinical condition characterized by advanced interatrial block. Bayés syndrome is a subclinical disease that manifests electrocardiographically as a prolonged *P* wave duration > 120 ms with biphasic morphology ± in the inferior leads. The clinical relevance of Bayés syndrome lies in the fact that is a clear arrhythmological syndrome and has a strong association with supraventricular arrhythmias, particularly atypical atrial flutter and atrial fibrillation. Likewise, Bayés syndrome has been recently identified as a novel risk factor for non-lacunar cardioembolic ischemic stroke and vascular dementia. Advanced interatrial block can be a risk for embolic stroke due to its known sequelae of left atrial dilation, left atrial electromechanical dysfunction or atrial tachyarrhythmia (paroxysmal or persistent atrial fibrillation), conditions predisposing to thromboembolism. Bayés syndrome may be responsible for some of the unexplained ischemic strokes and shall be considered and investigated as a possible cause for cryptogenetic stroke. In summary, Bayés syndrome is a poorly recognized cardiac rhythm disorder with important cardiologic and neurologic implications.

Key words: Bayés syndrome; Cardioembolic stroke; Electrophysiological processes; Cardiovascular risk factors; Heart conduction system

Core tip: Bayés syndrome is an under-recognized cardiac rhythm disorder with significant cardiologic and neurologic implications. It constitutes a genuine arrhythmological syndrome characterized by advanced interatrial block. Bayés syndrome is a key predictor of higher risk of new-onset atrial fibrillation and it is independently associated with an increased risk for non-lacunar cardioembolic stroke. Likewise, can be the cause of some cryptogenic strokes, and be related to clinically silent cerebral ischemia and vascular cognitive impairment, or even, vascular dementia.

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INTRODUCTION

Bayés syndrome is an under-recognized cardiological condition characterized by advanced interatrial block. Although it has yet to receive adequate coverage in textbooks and remains poorly perceived in clinical practice, Bayés syndrome represents a novel risk factor for cardioembolic ischemic stroke[1,2].

The principal goal of this mini-review is to expand and update knowledge of the little-known relationship between Bayés syndrome and acute ischemic cardioembolic stroke.

It should be noted that cardioembolic ischemic stroke accounts for one-quarter of all cerebral infarcts[3], is the most severe ischemic stroke subtype with a low prevalence of absence of neurological dysfunction at hospital discharge and a non-negligible risk of early embolic recurrence (1%-10%)[4-7], and has the highest in-hospital mortality (6%-27%)[3,4,8].

Compared to non-cardioembolic stroke, the percentage of female sex (54.3% *vs* 34.6%) and very old patients (≥ 85 years) (28.5% *vs* 18.3%) is more frequent. This may be explained by the increasing prevalence of atrial fibrillation with age. In the Framingham study, a growing population attributable risk of stroke due to atrial fibrillation with age was found, with a prevalence of atrial fibrillation of 1.8% in patients aged 60-69 years, 4.8% in those aged 70-79 years, and 8.8% in the 80 to 90 year group[9]. Similarly, the increased frequency of cardioembolic infarcts in women compared to non cardioembolic, which are more frequent in men, may also be related to increasing age observed in the industrialized societies, where women represent the majority of elderly people due to their higher life expectancy[10].

In the Sagrat Cor Hospital of Barcelona Stroke Registry (Table 1), which is one of the first stroke data banks of Catalonia and Spain, the short prognosis of patients with cardioembolic cerebral infarction is poorer compared to other subtypes of cerebral infarction with higher in-hospital mortality (21.9% *vs* 8.2%), whereas symptom free at discharge are less frequent (14.3% *vs* 19.9%)[7].

Recent studies have shown that Bayés syndrome is a key independent factor of cardioembolic cerebral ischemia[1,2], although there is still a need of high level of clinical suspicion in order to diagnose it. Early and proper diagnosis of Bayés syndrome is desirable and necessary, since patients will require closer clinical surveillance, and possibly accompanying antiarrhythmic and antithrombotic preventive therapies.

CONCEPT AND DEFINITIONS

In analogy to other cardiac conduction delays, atrial conduction abnormalities should be divided into partial and advanced interatrial blocks (aIAB) or Bayés syndrome. The syndrome of advanced interatrial conduction block due to conduction impairment in Bachmann's bundle, results in delayed and retrograde activation of the left atrium that signifies a conduction delay between the left and right atria, and it is associated with a high incidence of atrial tachyarrhythmias, especially a particular and specific form of atypical atrial flutter or atrial fibrillation[11,12].

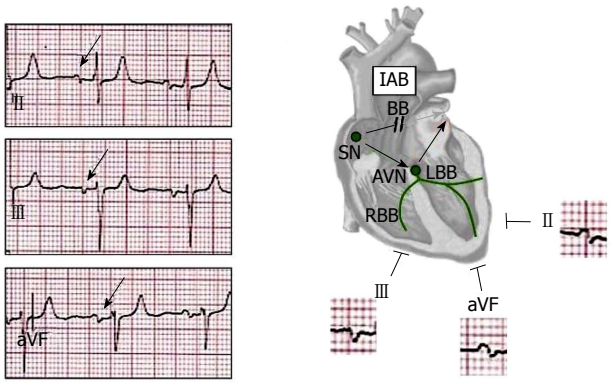

Figure 1 Scheme of the anatomo-electrophysiologic features of the Bayés syndrome[27]. AVN: AV node; BB: Bachmann bundle; IAB: Interatrial block; LBB: Left bundle branch; RBB: Right bundle branch; SN: Sinus node.

The first case of inter-atrial block was described by Bachmann[13] in 1941. Later, in 1971, Castillo and Vernant[14] emphasized that when a *P* wave with plus/min (biphasic) morphology is observed in leads Ⅱ, Ⅲ, and avF, the atrial stimulus is blocked in the upper part of the septum. Finally, between 1979 and 1985, Bayes de Luna *et al*[15,16] precisely analyzed the prevalence, pathological associations, and profile of the arrhythmias associated with aIAB, thereby defining a distinct and well-defined anatomo-electrical entity. Dr. Bayés de Luna contribution was fundamental in demonstrating the association between advanced interatrial block and supraventricular arrhythmias, thus confirming a well-defined arrhythmic syndrome. The consensus of naming this association with the eponymous Bayés syndrome has recently been accepted by the scientific community in honor of Dr. Antoni Bayés de Luna, the great Catalan master of clinical electrocardiography[1,17,18], for his contribution to the understanding of the natural history of this cardiac syndrome. However, Bayés syndrome remains an under-recognized clinical condition.

Bayés de Luna described the electrocardiographic pattern for identifying IAB and classified the types of block that occur at the atrial level. The distinction is based on the *P*-wave duration, and more important, the *P*-wave morphology: A partial block, indicated by a *P*-wave duration of 120 ms or more, and bifid *P* wave (notched *P*-wave) in leads Ⅱ, Ⅲ and aVF (Figure 1). If the interatrial block is advanced, also, the *P* wave is prolonged (duration 120 ms or more), but the second part of the P wave in inferior leads becomes negative (biphasic pattern or *P*-wave plus/min morphology) because of the retrograde activation of the left atrium (*P*-wave ± in Ⅱ, Ⅲ, and aVF) (Figure 2)[19-21].

It should be noted that, initially, IAB may occur

Table 1 Demographic, cerebrovascular risk factors, neuroimaging and outcome in the first-ever cardioembolic stroke *vs* first-ever non-cardioembolic cerebral infarct population

Variable	Cardioembolic stroke *n* = 575	Non-cardioembolic cerebral infarct[1] *n* = 1507	*P* value
Age, yr, mean (SD)	78.96 (9.39)	73.45 (12.8)	0.0001
Age strata, yr			0.0001
< 65	44 (7.6)	285 (18.9)	
65-74	116 (20.2)	405 (26.9)	
75-84	251 (43.7)	557 (37.0)	
⩾ 85	164 (28.5)	260 (17.3)	
Sex			0.0001
Males	199 (34.6)	788 (52.3)	
Females	373 (65.4)	719 (47.7)	
Hypertension	291 (50.6)	835 (55.4)	0.049
Diabetes	103 (17.9)	368 (24.4)	0.002
Atrial fibrillation	433 (75.3)	176 (11.7)	0.0001
Heavy smoking (> 20 cigarettes/d)	23 (4.0)	184 (12.2)	0.0001
ACM vascular topography	391 (68.0)	703 (46.6)	0.0001
Echocardiography	363 (63.1)	598 (39.7)	0.0001
Symptom-free at discharge	82 (14.3)	300 (19.9)	0.003
In-hospital death	126 (21.9)	123 (8.2)	0.0001
Transfer to convalescent/rehabilitation units	89 (15.5)	154 (10.2)	0.001
Length of stay, days, median (interquartile range)	15 (10-24)	11 (8-19)	0.0001
Prolonged hospital stay > 12 d	330 (57.4)	650 (43.1)	0.0001

Data expressed as numbers and percentages in parenthesis. [1]Atherothrombotic, *n* = 565; lacunar, *n* = 566; essential, *n* = 280; unusual, *n* = 96.

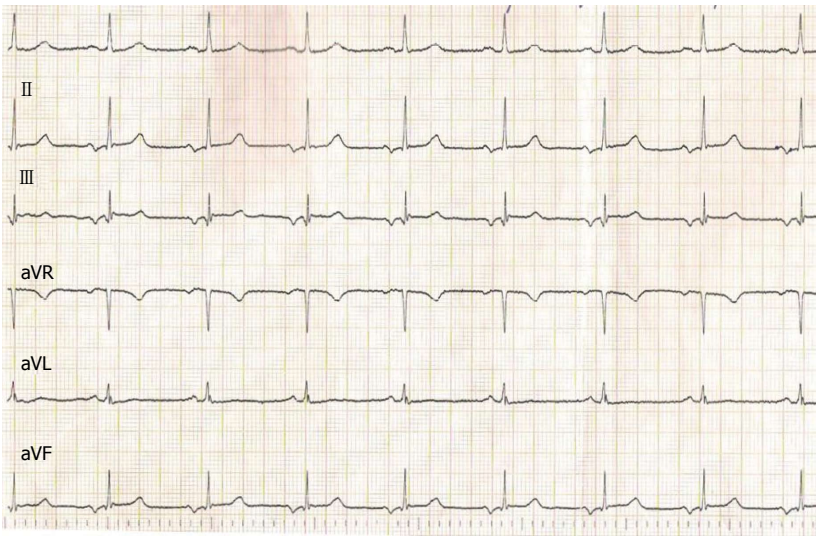

Figure 2 A 55-year-old male diagnosed with Bayés syndrome, with a history of paroxysmal atrial fibrillation showing normal values of echocardiographic measurements, except for a discrete left atrial enlargement (40 mm). ECG shows the presence of advanced interatrial block. *P*-wave duration is wide (120 ms) and biphasic in inferior leads (Ⅱ, Ⅲ and aVF). ECG: Electrocardiogram.

transiently and may be reversible. It may be classified as first-degree (partial), second-degree (transient interatrial block or atrial aberrancy), or third-degree (advanced). There is consensus on considering transient interatrial block as a marker of electromechanical dysfunction of the left atrium and a risk factor for recurrence of atrial fibrillation[11,15].

Although the diagnosis of interatrial block is frequently associated with left atrial enlargement (LAE), there are some cases, especially of first-degree IAB, without this association. Therefore, it should be noted that IAB is a separate entity from atrial enlargement[11,22].

The prevalence of interatrial block is age-dependent, increasing from 5.4% at < 20 years old to 60% at > 50; in the same way, advanced IAB increases from 0.1% to 2% in patients with heart valve disease and cardiomyopathy[23,24]. The increased age-related risk may be probably due to atrial fibrosis which would result in impaired atrioventricular conduction through the atria. However, the exact pathogenesis has not been elucidated and various comorbidities, including coronary heart disease, arterial hypertension, and diabetes mellitus, have been proposed. The cause of IAB may be likely degenerative because of the increased incidence with age[11].

ASSOCIATION OF INTERATRIAL BLOCK WITH SUPRAVENTRICULAR ARRHYTHMIAS

The Bayés syndrome is a clear arrhythmological syn-

Table 2 Main studies of interatrial block as a cerebrovascular risk factor or as a predictor for acute ischemic stroke (period 1979-2016)

Ref.	Study type	*n*	Age (yr)	Gender	Inclusion criteria	Exclusion criteria	Confounding factors	Parameters evaluated	Results
Wu *et al*[32]	Retrospective cohort	1046	63 ± 10	612 males 434 females	Patients hospitalized in Zhengzhou University People's Hospital for diagnosis and treatment between March 1 and March 31 of 2010 ECG Presence of IAB	History of AF Patients under anticoagulant treatment Missing data for calculation of $CHADS_2$ and CHA_2DS_2-VASc scores Lost to follow-up	Congestive Heart Failure Hypertension Diabetes Mellitus Previous strokes/ TIA Coronary Artery Disease PCI during index admission CABG during index admission Tobacco consumption LVEF LA diameter Medication Use	Conduction lengths $CHADS_2$ and CHA_2DS_2-VASc scores Apparition of Stroke (Hemorrhagic or Ischemic)	Mean follow-up of 4.9 ± 0.7 yr 0.8% hemorrhagic stroke 5.3% presented ischemic stroke or TIA Ischemic stroke or TIA increased with $CHADS_2$ score: 0.37, 0.85, 0.96 and 1.92 per 100-person years for scores of 0, 1, 2, and > 3 respectively CHA_2DS_2-VASc scores correlated with Ischemic stroke or TIA (0.19, 0.59, 0.76, 0.88, and 2.0 for scores of 0, 1, 2, 3, and > 4 respectively) Cut-off points: > 3 for $CHADS_2$, > 4 for CHA_2DS_2-VASc Conclusion: $CHADS_2$ and CHA_2DS_2-VASc scores may be predictors of risk of ischemic stroke or TIA in patients with IAB without atrial fibrillation
Martinez-Selles *et al*[40]	Case-control	80	101.4 ± 1.5	21 males 59 females	Patients from the Cardiac and Clinical Characterization of Centenarians (4C) Registry	Hospitalized patients	Dementia Perceived health status score Previous stroke Mitral regurgitation Systolic dysfunction Left atrial diameter > 40 mm	Conduction lengths ECG measurements Short Portable Mental Status Questionnaire Premature atrial beats	IAB group showed higher rate of previous stroke than normal P wave and AF groups Premature atrial beats were more frequent in advanced IAB than normal P-wave Mitral regurgitation could play an important role in IAB Conclusion: Advanced IAB is a pre-atrial fibrillation condition associated with premature atrial beats. Atrial arrhythmias and IAB occurred more frequently in centenarians than in septuagenarians.
O'Neal *et al*[24]	Retrospective cohort	14716	54 ± 5.8	6622 males 8094 females	Patients enrolled in the ARIC Study Recruited between 1987 and 1989	Patients with prevalent stroke or AF at baseline Race other than black or white Black participants from Washington County and Minneapolis	Black Tobacco use Diabetes LDL cholesterol level BMI Hypertension Antihypertensive medication Coronary heart disease Heart failure	Conduction lengths Presence of stroke Stroke type	Incidence rate of ischemic stroke was higher in aIAB (8.05/1000 person-years *vs* 3.14; $P < 0.0001$) Conclusion: aIAB was associated with incident ischemic stroke

O'Neal *et al*[29]	Retrospective cohort	14625	54 ± 5.8	6581 males 8044 females	Patients enrolled in the ARIC Study Recruited between 1987 and 1989	Participants with AF at baseline Missing baseline covariates Missing follow-up data Race other than black or white Black participants from Washington County and Minneapolis	Black Tobacco consumption Diabetes LDL cholesterol level BMI Hypertension Antihypertensive medication	Conduction lengths	Total of 262 aIAB (69 baseline, 193 new) 1929 AF cases were identified aIAB patients presented an AF incidence of 29.8/1000 *vs* 6.8/1000 of non-aIAB; HR = 3.09 (P < 0.0001) Conclusion: aIAB is a useful marker to identify high risk subjects for developing atrial fibrillation
Pirinen *et al*[41]	Case-control	690	15-49	438 males 252 females	Correct diagnosis of IS Part of the Helsinki Young Stroke Study	Unknown stroke date Outpatient treatment only No ECG OR only take on the day of stroke in ER OR no ECG between day of stroke and 14 d after	Coronary heart disease Heart failure Obesity Hypertension Tobacco use Dyslipidemia CHF Preexisting AF #VALUE	Arrhythmia types Conduction lengths Stroke etiology	Most Common ECG abnormalities: T-wave inversion (LVH (14%), prolonged *P*-wave (13%), prolonged QTc (12%). Most ECG abnormalities in the Stroke Etiology Subgroups: HRCE, LAA and SVD Conclusion: Routine ECG provides useful information for directing the work-up of a young IS patient. In addition to AF, P-terminal force in particular showed a strong association with etiology of high-risk source of cardioembolism
Enriquez *et al*[42]	Prospective cohort	187	67 ± 10.7	Not reported	Patients with typical atrial flutter (AFI) with no prior history of AF referred for CTI ablation	Patients that had received repeat ablations or did not demonstrate a bidirectional block	Composite of Cardiovascular Disease not reported	Conduction lengths Ejection fraction Holter monitoring	Advanced IAB was detected in 18.2% of patients Left atrium was larger in aIAB (46.2 ± 5.9 mm *vs* 43.1 ± 6.0 mm; P = 0.01) 35.8% of patients developed new-onset AF
Cotter *et al*[31]	Retrospective cohort	51	17-73	28 males 23 females	ILR implanted after unexplained ischemic stroke Brain imaging consistent with embolism Arterial imaging Structural cardiac imaging and rhythm monitoring 50 d of continuous monitoring	TIA Documented cause of stroke before ILR implantation Intrinsic small-vessel disease cause Atheromatosis stenosis > 50% or dissection High-risk cardiac embolic source No AF detected in 24 h - Holter	Not reported	Rhythm monitoring ECG Conduction lengths $CHADS_2$ and CHA_2DS_2-VASc scores	25.5% of cases had AF IAB more prevalent in patients with AF (P = 0.02) AF patients larger LA volumes (P = 0.025) Mean AF duration was 6 min Conclusion: In patients with unexplained stroke atrial fibrillation was detected by implantable loop recorders in 25.5%. IAB was an independent predictor of AF
Cotter *et al*[30]	Case-control	78	24-55	49 males 29 females	⩽ 55 yr at time of stroke Index cerebral infarct with no cause found	Poor quality data	Not reported	Conduction lengths PFO status A-S-C-O Classification	IAB more frequent in cases than controls (40% *vs* 13%) (P < 0.05) 74.6% of stroke showed PFO (70.3% large)

					CT or MRI imaging, cervical vascular imaging, ECG and rhythm monitoring				No statistical difference of *P*-wave length (with *vs* without PFO) Conclusion: In young patients with unexplained stroke, particularly those with patent foramen ovale atria l dysfunction is a possible mechanism of stroke
Ariyarajah *et al*[43]	Case-control	66	60-87	39 males 27 females	Definitive acute or subacute cerebral infarct Probable embolic origin	No 12-lead ECG during 14 d post infarct Non-sinusal rhythm detected in ECG	Hypertension Valvulopathies Cardiomyopathies Tobacco Use Dyslipidemia Diabetes Mellitus Hyper/ Hypothyroidism COPD Florid Heart Failure Cardiac Catheterization Myocardial Infection Valvuloplasty Previous strokes/ TIA History of AF/ Flutter CAD	Echocardiogram Conduction lengths	61% IAB prevalence CAD paroxistically more present in control, perhaps due to atherosclerotic origin LA more prevalent in IAB group, with greater LA thrombi (83% *vs* 0%) Conclusion: IAB could be a risk factor for embolic stroke due to its known sequelae of left atrial dilation and electromechanical dysfunction that predispose to thrombosis
Ariyarajah *et al*[2]	Case-control	228	30-102	118 males 110 females	Studied for suspicion of stroke with CT Scan and MRI	No 12-lead ECG during 14 d post infarct	Hypertension Valvulopathies Cardiomyopathies Tobacco Use Dyslipidemia Diabetes Mellitus Hyper/ Hypothyroidism COPD Florid Heart Failure Cardiac Catheterization Myocardial Infection Valvuloplasty Previous strokes/ TIA History of AF/ Flutter CAD	Conduction lengths Stroke etiology	61% IAB embolic *vs* 40% non-embolic (P = 0.006) Hypertension for embolic stroke (P < 0.0001) Conclusion: IAB could be a novel risk for embolic stroke
Ariyarajah *et al*[12]	Prospective cohort	32	66-94	15 males 17 females	Saint Vincent Hospital general patients (December 15, 2004 to January 14, 2005) Resting ECG obtained on admission Existing 2-dimensional transthoracic echocardiograms Sinus rhythm	Not reported	Mitral or tricuspid valvular disease Hypertension Coronary artery disease Hyperlipidemia Diabetes mellitus History of AF/ Flutter ACEI use Beta-blocker use Statins use	Conduction lengths LA dimension LVEF Cardiovascular events (heart failure, peripheral embolism, transient ischemic attack, stroke, atrial tachyarrhythmias)	Coronary disease was more prevalent in the IAB group Cardiovascular events were overall most significant in IAB, except for stroke, TIA, peripheral arterial embolism and atrial flutter Conclusion: In patients with comparable echocardiographic parameters, IAB remained associated with atrial fibrillation after 15-mo follow-up

Lorbar *et al*[33]	Retrospective cohort	104	22-101	58 males 46 females	St Vincent Hospital (January 2000 to December 2001) patients with ICD codes for embolic stroke Diagnosis of embolic ischemic stroke or TIA by a neurologist with or without imaging techniques	Cerebrovascular events non ICD codes Dementia, seizure, hypertensive encephalopathy, subdural hematoma, dizziness, vertigo, psychosis, and headache	Not reported	Conduction lengths ECG patterns	41% history of AF, or newly diagnosed AF 80% normal sinus rhythm patients showed IAB on concurrent ECG Conclusion: IAB may represent a new factor for stroke
Jairat *et al*[23]	Prospective cohort	1000	24-94	585 males 415 females	Saint Vincent Hospital general patients	Not reported	Not reported	Conduction lengths ECG patterns	32.8% of all patients showed IAB 41.1% of sinus rhythm patients showed IAB Conclusion: Patients with IAB must be followed for atrial enlargement, potential thrombosis, and the onset of atrial fibrillation

ACEI: Angiotensin converting enzyme inhibitor; AF: Atrial fibrillation; aIAB: Advanced intraatrial block; BMI: Body mass index; CABG: Coronary artery bypass grafting; CAD: Coronary artery disease; COPD: Chronic obstructive pulmonary disease; CHF: Chronic heart failure; CT: Computed tomography; CTI: Cavotricuspid isthmus; DM1: Diabetes mellitus 1; DM2: Diabetes mellitus 2; ECG: Electrocardiogram; ER: Emergency room; HR: Hazard ratio; HRCE: High-risk source of cardioembolism; IAB: Intraatrial block; ILR: Implantable loop recorder; IS: Ischemic stroke; LA: Left atrium; LAA: Large artery atherosclerosis; LDL: Low density lipoprotein; LVEF: Left ventricular ejection fraction; LVH: Left ventricle hypertrophy; MRI: Magnetic resonance imaging; PCI: Percutaneous coronary intervention; PFO: Permeable foramen ovale; SVD: Small-vessel disease; TIA: Transient ischemic attack; ARIC: Atherosclerosis Risk in Communities.

drome. Advanced IAB is a key predictor for high risk of new-onset atrial fibrillation after a successful cavo-tricuspid isthmus ablation in patients with typical atrial flutter[11,25].

A clinical study reported that 90% of patients with atrial fibrillation recurrence at one year had advanced IAB, and multivariate analysis demonstrated that persistent IAB was a predictor of AF recurrence. Advanced IAB is a useful marker to identify subjects who are at high risk for developing atrial fibrillation, and is a pre-atrial fibrillation condition associated with premature atrial beats[24].

Practical consequences and clinical implications of Bayés syndrome are the high incidence of atrial extrasystoles and paroxysmal supraventricular tachyarrhythmia, especially in patients with valvular heart disease or cardiomyopathy. A control group of patients with similar clinical states and left atrial size by echocardiography showed much lower incidence of these arrhythmias[11]. Bayés de Luna *et al*[26] also suggested that antiarrhythmic treatment prevents recurrences of atrial tachyarrhythmia in these cases.

There are currently no evidence-based recommendations on the most appropriate therapeutic approach for Bayés syndrome in any of the different cardiologic or neurologic guidelines for primary or secondary prevention of cerebral ischemia. A clinical case of a patient with Bayés syndrome reported antiarrhythmic treatment with amiodarone and anticoagulant administration with acenocoumarol[27].

Prolonged QRS duration is an independent predictor of cardiovascular mortality in patients with underlying structural heart disease. Similarly, the relation between sudden death and QT prolongation is an established fact[11]. Increased P wave duration is the only *P* wave index significantly associated with increased cardiovascular mortality. Therefore, IAB as a subclinical disease merits elucidation as a marker of risk for adverse outcomes.

A NEW RISK FACTOR FOR CEREBRAL INFARCT AND VASCULAR DEMENTIA

Recently, Bayés syndrome has been shown to be a predictor of cardioembolic stroke[28]. There are three main consequences of advanced IAB: Firstly, IAB is a substrate for sustained AF, and the association between AF and advanced IAB has been demonstrated. Secondly, IAB results in poor left atrium (LA) contractility due to a delayed depolarization which can result in LA dysfunction. Such a delay has hemodynamic consequences including raised LA pressure and LA dilatation, which again is a substrate for AF. Thirdly, IAB may be associated with structural factors as a result of left atrium enlargement, although it may occur in patients with normal left atrium size[11].

As a result, advanced IAB could be a risk for embolic stroke due to its known sequelae of left atrial dilation, LA electromechanical dysfunction or atrial tachyarrhythmias, conditions which predispose to the formation of echo-contrast, and may serve as a nidus for thrombi or microthrombi, and thus increase the risk for cardioembolic events. Because IAB predicts atrial fibrillation, patients with IAB may intermittently be in atrial fibrillation (paroxysmal atrial fibrillation), causing embolization[3,11].

Ariyarajah *et al*[2] analyzed 293 patients with cerebral

infarct, 85 of them cardioembolic, and reported that 88% of cardioembolic infarcts showed sinus rhythm and 61% of these had advanced IAB, concluding that IAB could be a novel risk factor for embolic stroke.

In an analysis of ARIC (Atherosclerosis risk in Communities Study) advanced IAB was independently associated with an increased risk for ischemic stroke, thus definitively confirming IAB as a novel risk factor for cardioembolic ischemic stroke[29].

Cotter *et al*[30] reported an increased incidence of interatrial block in younger adults with cryptogenic stroke and patent foramen ovale, suggesting atrial arrhythmias as a possible cause of unexplained ischemic stroke in these patients. In another study, atrial fibrillation detected by implantable loop recorders in unexplained stroke was identified in 25.5% of cases, and AF was independently associated with interatrial conduction block[31].

In a clinical study the $CHADS_2$ and $CHADS_2DS_2$-VASCc scores could predict the risk of ischemic stroke or TIA in patients with IAB without atrial fibrillation[32].

However, the association of Bayés syndrome and ischemic stroke is limited to non-lacunar cardioembolic infarcts[33,34]. Lacunar infarcts are an ischemic stroke subtype related mainly to hypertension and diabetes[35,36]. Ischemic stroke of unusual causes accounted for 5% of ischemic strokes and the association of advanced IAB in this ischemic stroke subtype is improbable[37].

By contrast, it is important to highlight that about 10%-30% of ischemic strokes remain cryptogenic despite reasonably thorough evaluations[38,39]. A possible explanation for this is that IAB may be responsible for some of the unexplained strokes.

Furthermore, atrial fibrillation is independently associated with an increased risk of vascular dementia. In a clinical study conducted in centenarians, the rate of dementia was 48% in subjects with a normal *P* wave, 60% in those with partial IAB, and 81% in those with advanced IAB and 90% in those with atrial fibrillation[40].

Table 2 shows the most relevant published studies about IAB as a cardiovascular risk factor and acute ischemic stroke[41-43].

FUTURE RESEARCH

Recognition of Bayés syndrome is not merely an academic issue. It allows selecting high-risk patients for which pharmacological therapy could be beneficial. Open questions remain to be addressed with well-designed clinical trials including whether antiarrhythmic and/or anticoagulant drugs could be used in patients with advanced IAB without atrial tachyarrhythmias to prevent both AF and embolic stroke.

Additional epidemiological studies would be needed to define the possible connection between Bayés syndrome and clinically silent cerebral infarctions, small vessel disease, cognitive impairment of vascular type or dementia.

CONCLUSION

Bayés syndrome is a poorly recognized cardiac rhythm disorder with important clinical implications. Bayés syndrome is a pre-atrial fibrillation condition and should be considered a novel and important risk factor for cardioembolic stroke and vascular cognitive impairment.

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ORIGINAL ARTICLE

Observational Study

Surveillance of Australian Hajj pilgrims for carriage of potentially pathogenic bacteria: Data from two pilot studies

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Abstract

AIM

To estimate the pharyngeal carriage rate of *Neisseria meningitidis* (*N. meningitidis*), *Streptococcus pneumoniae* (*S. pneumoniae*) and *Staphylococcus aureus* (*S. aureus*) among Australian Hajj pilgrims.

METHODS

In 2014, surveillance was conducted in two phases among Australian Hajj pilgrims: The first phase during Hajj in Mina, and the second phase soon after returning home to Australia. Nasopharyngeal or oropharyngeal swabs were taken from participants then tested, firstly by nucleic acid testing, and also by standard culture.

RESULTS

Of 183 participants recruited in the first phase, 26 (14.2%) tested positive for *S. pneumoniae*; 4 had received pneumococcal conjugate vaccine (PCV13). Only one tested positive for *N. meningitidis* (W). Of 93 2nd phase samples cultured, 17 (18.3%) grew *S. aureus*, all methicillin sensitive, 2 (2.2%) grew *N. meningitidis* (on subculture; one serotype B, one negative), and 1 (1%), from an unvaccinated pilgrim, grew *S. pneumoniae*.

CONCLUSION

Relatively high carriage of *S. pneumoniae* and little meningococcal carriage was found. This indicates the importance of a larger study for improved infection surveillance and possible vaccine evaluation.

Key words: Carriage; Conjugate vaccine; *Staphylococcus aureus*; *Neisseria meningitidis*; *Streptococcus pneumoniae*; Hajj

Core tip: We conducted this pilot study to understand the impact of mass gatherings on pharyngeal carriage of potentially pathogenic bacteria and to assess the burden of pathogenic microorganisms resistant to antimicrobial agents among travellers returning to Australia following an overseas travel. This study demonstrates that a larger study is feasible and important to inform public health measures to prevent the transmission and limit emergence of antimicrobial resistant pathogens at mass gathering events such as the annual Hajj pilgrimage.

Azeem MI, Tashani M, Badahdah AM, Heron L, Pedersen K, Jeoffreys N, Kok J, Haworth E, Dwyer DE, Hill-Cawthorne G, Rashid H, Booy R. Surveillance of Australian Hajj pilgrims for carriage of potentially pathogenic bacteria: Data from two pilot studies. *World J Clin Cases* 2017; 5(3): 102-111 Available from: URL: http://www.wjgnet.com/2307-8960/full/v5/i3/102.htm
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INTRODUCTION

Hajj is one of the world's largest annual mass gatherings, attracting approximately 2-3 million people each year from around the globe. During Hajj there is a high risk of communicable diseases, primarily due to overcrowding, shared accommodation and mingling of local and international pilgrims[1,2]. The importation of pathogens from arriving pilgrims may result in local transmission of infection within the Kingdom of Saudi Arabia (KSA). Similarly, there may be further dissemination of infectious diseases after pilgrims return home.

Respiratory infections are of particular concern at Hajj; transmission may occur from symptomatic individuals or asymptomatic carriers[3,4]. In susceptible populations, the pharyngeal colonisation of pathogens may contribute to serious bacterial infections, including pneumonia, sepsis and meningitis[5]. Localised meningococcal outbreaks and their further dissemination have been linked to international travel, migration, attendance at Hajj and participation in sporting events[6-11]. Intercontinental spread of serogroup A meningococcal disease in 1987 affected thousands of Hajj pilgrims globally; mandating bivalent meningococcal (A and C) vaccine for all Hajj pilgrims helped with disease control[7]. Investigation of the 1992 meningococcal outbreak in Makkah, KSA showed an extremely high meningococcal carriage rate of 86% among devotees who attended congregational prayers in the Holy Mosque[12]. Following the Hajj-associated outbreaks of *Neisseria meningitidis* (*N. meningitidis*) W in 2000 and 2001, visas for entry into KSA for Hajj and Umrah pilgrims were changed to require the quadrivalent meningococcal vaccine (covering serogroups A, C, W and Y)[13,14].

Currently, respiratory infections are the most common illnesses during Hajj[15,16]. Cough is almost de rigeur, occurring virtually in all Hajj pilgrims[17,18]. Pneumonia is the leading cause of hospital admission during Hajj, with the commonest causative organisms being *Streptococcus pneumoniae* (*S. pneumoniae*), *Haemophilus influenzae, Klebsiella pneumoniae* and *Mycobacterium tuberculosis*[19-21].

In a study of samples from nares, axilla, groins and open wounds of Hajj pilgrims, a 20.9% carriage rate of *Staphylococcus aureus* (*S. aureus*) was found. Of

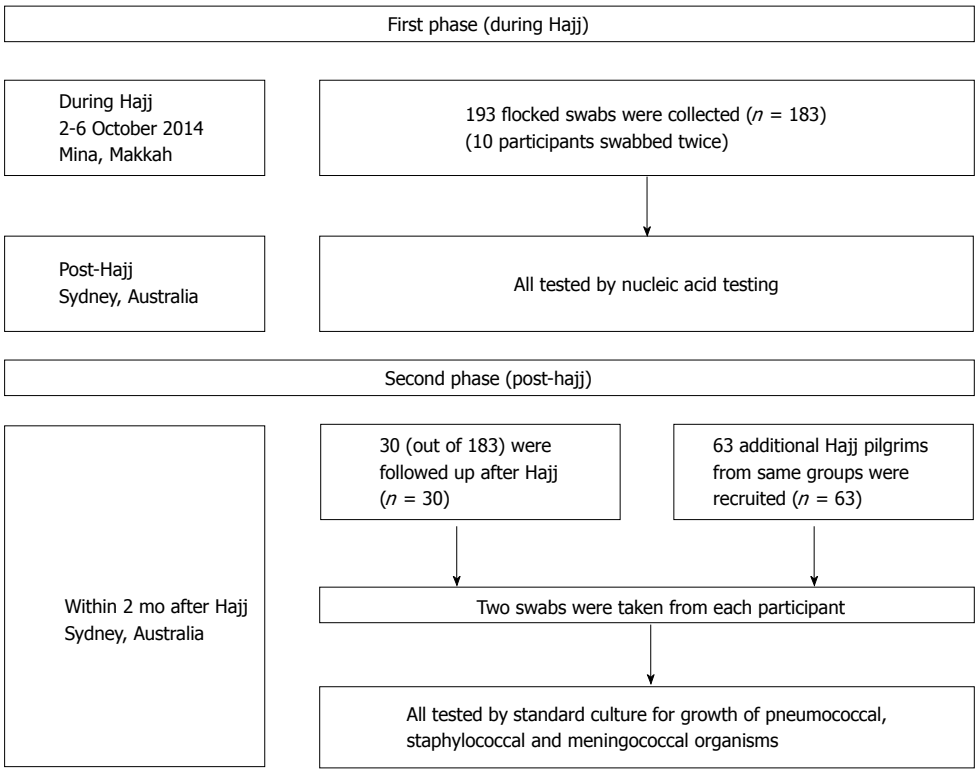

Figure 1 Schematic diagram showing recruitment of pilgrims.

these about 1.5% were methicillin resistant *S. aureus* (MRSA)[22]. In another study in four Makkah hospitals spanning twelve months from 2004-2005 that included the Hajj season, MRSA accounted for 199 of 512 (39%) *S. aureus* clinical isolates[23].

Inappropriate antimicrobial use during Hajj could result in the emergence of drug-resistant organisms, and antibiotic resistant respiratory organisms have been frequently isolated from Hajj pilgrims[24-26]. The potential for worldwide outbreak of infectious diseases caused by resistant microorganisms such as ciprofloxacin-resistant *N. meningitidis*, penicillin-resistant *S. pneumoniae*, MRSA and extended-spectrum beta-lactamase (ESBL) producing Gram negative bacteria is increasingly recognised[27-30]. Recently, there was a worrying report of the acquisition of extended-spectrum cephalosporin- and colistin-resistant *Salmonella enterica* in a returned French Hajj pilgrim[31].

The pharyngeal carriage of bacterial pathogens among Australian pilgrims has not been evaluated. Therefore, we performed two pilot studies, during and after Hajj, to estimate the pharyngeal carriage rate of *N. meningitidis*, *S. pneumoniae* and *S. aureus* among Australian Hajj pilgrims who attended Hajj in 2014, assessed antimicrobial susceptibility patterns and investigated the possible impact of preventive measures such as pre-travel vaccination and facemasks use.

MATERIALS AND METHODS

Enhanced surveillance was conducted in two phases among Australian pilgrims: The first phase involved recruiting pilgrims during their tent stay in Mina, Makkah, KSA in the peak period of the Hajj 2014, and the second phase involved recruiting pilgrims after their return from Hajj to Australia (Figure 1).

First phase (during Hajj)

This study was explained to pilgrims in their tents. From those who consented, nasopharyngeal or oropharyngeal swabs were collected while in Mina from all participants on the fifth day of their stay in tents; in a subset of pilgrims who had respiratory symptoms (cough, sore throat and/or rhinorrhoea), swabs were also collected on the first day of recruitment. Following collection, flocked swabs were placed in universal transport medium (UTM) (Vircell). The swabs were transported approximately 5 km on ice to the collaborating laboratory in Makkah where they were stored at -20 ℃ before being shipped under similar conditions to the testing laboratory in Australia. This carriage study was nested within an ongoing randomised controlled trial examining the efficacy of facemasks against respiratory viruses; this methodology is published[32].

Second phase (post-Hajj)

Within 2 mo of their return from Hajj, Australian pilgrims were consented for follow-up swabbing. Oropharyngeal swabs were collected in mosques, community centres, local events (such as "family fun" days) and participants' residences in Greater Sydney, New South Wales. From each pilgrim, 2 oropharyngeal swabs were obtained

Table 1 The primer sequences for *Neisseria meningitidis*

Serotype	Gene target	Primer sequences	Product size (bp)
A	*orf-2*	F: CGCAATAGGTGTATATATTCTTCC; R: CGTAATAGTTTCGTATGCCTTCTT	400
B	*siaD*	F: GGATCATTTCAGTGTTTTCCACCA; R: GCATGCTGGAGGAATAAGCATTAA	450
C	*siaD*	F: TCAAATGAGTTTGCGAATAGAAGGT; R: CAATCACGATTTGCCCAATTGAC	250
W135	*siaD*	F: CAGAAAGTGAGGGATTTCCATA; R: CACAACCATTTTCATTATAGTTACTGT	120
Y	*siaD*	F: CTCAAAGCGAAGGCTTTGGTTA; R: CTGAAGCGTTTTCATTATAATTGCTAA	120

Orf2: Open reading frame 2; *siaD*: Polysialyltransferase gene.

using charcoal and non-charcoal Copan Amies agar gel swabs and transported to the laboratory on ice within four hours of collection.

Phenotypic identification of N. meningitidis, S. pneumoniae and S. aureus

Swabs collected during the second phase were directly plated onto mannitol aztreonam methicillin salt, chocolate and nalidixic acid (Oxoid, Basingstoke, England) and modified New York City (Becton Dickinson, Sparks, MD, United States) agar plates. Bacterial colonies growing following 24-48 h of incubation in 5% CO_2 at 37 ℃ were identified using the Bruker Microflex LT (Bruker Daltonics Inc., Billerica, MA, United States) matrix-assisted laser desorption-ionization time-of-flight (MALDI-TOF) mass spectrometer. Antimicrobial susceptibility testing was performed using E-test (AB BIODISK, Solna, Sweden) or the BD Phoenix (Becton Dickinson) automated microbiology system. Serotyping of *N. meningitidis* was performed on all isolates using agglutination serum (Remel Europe Ltd., Dartford, England).

Nucleic acid test for N. meningitidis and S. pneumoniae

Swabs collected during Hajj were vortexed in 3 mL of UTM. Nucleic acid (NA) was extracted from 250 μL of UTM sample using the Qiagen EZ1 Virus Mini kit on the Qiagen EZ1 Advanced XL instrument. NA was eluted in a final volume of 60 μL and stored at -80 ℃ prior to nucleic acid testing (NAT).

NAT of S. pneumoniae

S. pneumoniae was detected using a modified version of an assay previously described[33], targeting a 101 base-pair segment of the autolysin-encoding (*lytA)* gene [forward primer, 5′-ACGCAATCTAGCAGATGAAGC-3′; reverse primer, 5′-TGTTTGGTTGGTTATTCGTGC-3′; probe, 5′-6-carboxy-fluorescein (FAM)-TTTGCCG AAAACGCTTGATACAGGG-BHQ-1-3′].

Baseline fluorescence was determined using a fluorescence reader (FluorTracker™, Stratagene, La Jolla, CA, United States) before amplification in the Mastercycler Gradient thermocycler (Eppendorf, Hamburg, Germany). The reaction mix was amplified at 95 ℃ × 15 min (96 ℃ × 10 s; 63 ℃ × 1 min) for 45 cycles and 72 ℃ × 2 min for one cycle. End point fluorescence was then determined using FluorTracker™, positive samples were defined as a minimum of 2 × increase in fluorescence. These results were confirmed by agarose gel electrophoresis on a 2% gel run at 200 volts for 40 min and stained with SYBR-Safe.

NAT of N. meningitidis

N. meningitidis was detected using a previously described assay[34], that uses a single amplification real-time PCR targeting a 110 base-pair segment of the meningococcal capsular transfer gene, *ctrA* [forward primer, 5′-GCTGCGGTAGGTGGTTCAA-3′; reverse primer, 5′-TTGTCGCGGATTTGCAACTA-3′; probe, 5′-6-carboxy-fluorescein (FAM)-CATTGCCACGTGTCAGCTGCACAT-BHQ-1-3′]. The reaction mix was amplified in a Roche LightCycler® 480 (Roche Diagnostics GmbH, Mannheim, Germany) at 95 ℃ × 5 min (95 ℃ × 15 s, 60 ℃ × 1 min) × 45; 40 ℃ × 30 s with detection on the 640 nmol/L channel during elongation at 60 ℃.

NAT of N. meningitidis serogroup

Samples where *N. meningitidis* was detected were further evaluated using a previously described molecular serotyping method[35]. Samples were tested using five single-plex conventional assays targeting different regions of the *orf-2* and *siaD* genes which are specific for serotypes A, B, C, W and Y. The primer sequences are listed in Table 1. The reaction mixes were amplified at 95 ℃ × 15 min (95 ℃ × 30 s; 50 ℃/55 ℃ × 1 min; 72 ℃ × 30 s) for 40 cycles and 72 ℃ × 5 min for one cycle. The resultant products were visualised by agarose gel electrophoresis on a 2% gel run at 200 volts for 40 min and stained with SYBR-Safe.

Ethical approval

Ethics approval was granted by the Hunter New England Human Research Ethics Committee (HREC), Australia (Ref: HREC/13/HNE/265). To verify the vaccination records of pilgrims, data were cross-checked with another ongoing trial by our team with a separate ethics approval from the Hunter New England HREC (Ref13/05/15/3.05).

Table 2 Demographics of participants (during and post-Hajj, *n* = 246)

Attributes	During Hajj *n* (%)	Post-Hajj *n* (%)
Gender		
Female	111 (60.7)	30 (32.3)
Male	72 (39.3)	63 (67.7)
Age in years		
0-18	0	1 (1)
19-34	38 (20.8)	17 (18.3)
35-49	58 (31.7)	52 (55.9)
50-64	28 (15.3)	8 (8.6)
≥ 65	1 (0.6)	0
Did not disclose	58 (31.7)	15 (16.1)
Meningococcal vaccine uptake		
Not vaccinated	0	4 (4.3)
Meningococcal polysaccharide vaccine	144 (78.7)	48 (51.6)
Meningococcal Conjugate vaccine	39 (21.3)	41 (44.1)
Pneumococcal vaccine uptake		
Not vaccinated	145 (79.2)	55 (59.1)
Pneumococcal conjugate vaccine (PCV13)	38 (20.8)	38 (40.9)
Facemasks use		
Used facemasks	76 (41.5)	32 (34.4)
Did not use facemasks	92 (50.3)	59 (63.4)
Did not disclose	15 (8.2)	2 (2.2)

PCV13: Pneumococcal conjugate vaccine 13-valent.

RESULTS

A total of 246 pilgrims were recruited to this study: 183 in the first phase during Hajj and 93 in the second phase after Hajj; 30 appeared in both groups (Figure 1). The median age for pilgrims was 40 years (range 12-67), 126 (51.2%) were women (Tables 2 and 3).

First phase (during Hajj)

One hundred and ninety three samples were collected from 183 study participants. Ten participants provided two swabs, the first collected on their first day in Mina when symptomatic and second collected on their 5th day.

Twenty-six (14.2%) participants had *S. pneumoniae* detected by NAT (Table 3). Thirty-eight (20.8%) participants had a confirmed history of receiving 13-valent pneumococcal conjugate vaccine (PCV13) within six months prior to travel. Of the 26 pilgrims who were PCR-positive for *S. pneumoniae,* 4 reported receiving PCV13 and the other 22 reported not receiving the vaccine.

Of the 183 study participants only one (0.6%) tested positive for *N. meningitidis* (serogroup W). Receipt of quadrivalent polysaccharide meningococcal vaccine was reported by 144 (78.7%) participants - 39 (21.3%) reported receiving quadrivalent meningococcal conjugate vaccine. The pilgrim with positive *N. meningitidis* PCR reported receiving the polysaccharide vaccine. Seventy-six (41.5%) participants reported using a facemask, while 92 (50.3%) reported not using a facemask at anytime during Hajj; the other 15 (8.2%) did not disclose

Table 3 Carriage rate of *Streptococcus pneumoniae, Neisseria meningitidis and Staphylococcus aureus*

	During Hajj		Post-Hajj	*P*[1]
	First day of Mina (NAT)	Last day of Mina (NAT)	Standard culture	
S. pneumoniae	1/10	26/183	1/93	< 0.01
N. meningitidis	--	1/183	2/93	0.26
S. aureus	--	--	17/93	

[1]*P* value is for the difference in carriage detection rates for the last day of Mina *vs* post-Hajj by standard culture. NAT: Nucleic acid testing; *N. meningitidis*: *Neisseria meningitidis*; *S. pneumoniae*: *Streptococcus pneumoniae*; *S. aureus*: *Staphylococcus aureus*.

if they used a facemask. The pneumococcal carriage rate was similar in those who used a facemask compared to those who did not [14.1% (13/92) *vs* 14.5% (11/76), *P* = 0.95]. There was no statistically significant difference in pneumococcal carriage rates based on age < 50 years (16.7% *vs* 11.5%, *P* = 0.3) or gender (female *vs* male = 17.1% *vs* 9.7%, *P* = 0.2). The only pilgrim with positive *N. meningitidis* PCR reported not using a facemask during Hajj.

Second phase (post-Hajj)

Of the oropharyngeal samples collected from 93 pilgrims, *S. aureus* was isolated in 17 (18.3%), and all were methicillin susceptible (Table 3). *N. meningitidis* was isolated in two (2.2%) samples; on subculture, one was serotype B and sensitive to benzylpenicillin and cefotaxime, the other was negative on subculture. Both pilgrims reported receiving the quadrivalent meningococcal polysaccharide vaccine. In this group 89 (95.7%) reported receiving meningococcal quadrivalent vaccine before travelling to Hajj: 48 (51.6%) polysaccharide vaccine and 41 (44.1%) conjugate vaccine. Four (4.3%) did not recall their vaccination history but having attended Hajj before, were likely to have been vaccinated previously.

S. pneumoniae was isolated from one pilgrim and it could not be serotyped and sensitivity was not done; this pilgrim had not been vaccinated against pneumococcus. Of the 93 participants in this group, 38 (40.9%) reported receiving pneumococcal vaccine, PCV13 in all. Thirty-two (34.4%) reported using a facemask, 59 (63.4%) reported not using a facemask during Hajj and the other 2 (2.2%) did not disclose whether they used a facemask or not. Of 32 pilgrims who used a facemask, *S. aureus* was isolated from 8 (25%), and of 59 pilgrims who did not use a facemask *S. aureus* was isolated from 9 (15%) (*P* = 0.27). Both pilgrims from whom meningococci were isolated reported using a facemask, the pilgrim from whom pneumococcus was recovered did not disclose whether a facemask was used or not. There was no statistically significant difference in staphylococcal carriage rates based on age < 50 years (17.5% *vs* 23%, *P* = 0.6) or gender (male *vs* female = 20% *vs* 13%, *P* = 0.4). Sixteen (17.2%)

Table 4 Pneumococcal carriage rates according to the uptake of 13-valent pneumococcal conjugate vaccine in first phase of study

	PCR positive for pneumococci *n* (%)	PCR negative for pneumococci *n* (%)	Total
PCV13	4 (10.5)	34 (89.5)	38
No PCV13	22 (15.2)	123 (84.8)	145
Total	26 (14.2)	157 (85.8)	183

PCV13: Pneumococcal conjugate vaccine 13-valent.

participants had taken antibiotics (either amoxicillin, amoxicillin/clavulanic acid and/or roxithromycin) while at Hajj; however, none had taken antibiotics within 2 wk prior to swab collection. *S. aureus* was isolated from two of those who reported using antibiotics during Hajj and *S. pneumoniae* from another one.

DISCUSSION

We found a 14.2% pneumococcal carriage rate in pilgrims during the Hajj 2014, which is moderately high. About 2 in 5 received conjugate pneumococcal vaccine before travel. Carriage was similar irrespective of whether pneumococcal vaccine had been given, reflecting the likelihood that many pilgrims were already colonised before being vaccinated and that vaccination is more potent in preventing acquisition than in extinguishing carriage.

Prevalence of pneumococcal carriage was almost double the rate reported among French pilgrims during the early phase of the Hajj 2012 (7.3%), but lower than the rate (19.5%) found a few days before the pilgrims' departure from KSA[36]. In a study of 3203 pilgrims (1590 at the beginning, and 1613 at the end of Hajj), Memish *et al*[37] demonstrated that, although the overall carriage rate of pneumococci among African and Asian pilgrims in the early weeks of the Hajj 2011 and 2012 was 4.4%, the prevalence of PCV13 vaccine-serotypes was only 1.1%. In the same cross-sectional investigation, the overall carriage rate was 7.5% during the later phase of Hajj and 3.6% belonged to PCV13 vaccine-serotypes[37]. Subsequently the investigators conducted a prospective cohort study during the Hajj 2013 demonstrating that 1.8% pilgrims before and 7.1% ($P < 0.01$) pilgrims immediately after the conclusion of Hajj carried pneumococci; 35.5% serotypes are covered by PCV-13[38]. However, the carriage rates reported in all studies including ours, was much lower than the high carriage rate of 62% found by Benkouiten *et al*[39] among French pilgrims during the Hajj 2013.

The pneumococcal carriage rate in the post-Hajj phase was very low (1.1%). We are unaware of any other pneumococcal carriage study in pilgrims after return to their home countries for comparison. High PCV13 uptake (39%) in the post-Hajj cohort may have reduced the carriage rate or it could be an effect of antibiotic use (17.2% reported receiving antibiotics while at Hajj). Also, there was a time difference of up to two months between collection of Hajj and post-Hajj samples, enough time for most pilgrims to have lost carriage of Hajj-associated pneumococci. The diagnostic tests used differed between our study phases (PCR was used for first phase, and standard culture for the second phase) which may explain the low detection rate in the post-Hajj phase.

The uptake of PCV13 in the first cohort of our study, 21%, and in the second cohort (post-Hajj), 40.9%, was higher than any other report. This reflects pilgrims' participation in a vaccine trial involving PCV13. However, we did not find significant difference in pneumococcal carriage rate between vaccinated and unvaccinated pilgrims. Although not significant, it was lower in the vaccinated group (Table 4), possibly because of the small sample size or because a large proportion of the serotypes were not covered by PCV13. Although serotype characterisation was not performed in our pilot study, other studies suggest that between a quarter and half of the serotypes at Hajj are not covered by PCV13. None of the pilgrims in our cohorts reported having received pneumococcal polysaccharide vaccine, because only a few (3.3%) suffered from chronic diseases for which pneumococcal vaccination is recommended, and only one was aged over 65 years. In another study, overall pneumococcal polysaccharide vaccine uptake among Australian pilgrims ranged between 14% and 29%[40]. International studies have shown that the overall uptake of pneumococcal vaccine in Hajj pilgrims ranged between 2.5% and 36%[41-43].

The low meningococcal carriage rate of 0.6% during Hajj is not surprising because of more universal vaccination, nearly half with quadrivalent conjugate vaccine. During Hajj 2012 and 2013, Benkouiten *et al*[39] failed to detect *N. meningitidis* in nasal and/or throat swabs collected from French pilgrims. However, a study conducted in Mina during Hajj 2003 among 344 pilgrims from 29 different nations identified a carriage rate of 3.2%[44], following the 2000-2001 W epidemic.

The post-Hajj meningococcal carriage rate of 1.1% is less than in other studies. After the worldwide meningococcal W outbreak following 2000 Hajj, the carriage among Singaporean pilgrims two weeks after the Hajj 2001 was 15% for serogroup W with 55% persisting as carriers for 5-6 mo[45]. During the following year, El Bashir *et al*[8] demonstrated a carriage rate of 6.3% among United Kingdom pilgrims for all serogroups 2-6 wk after the pilgrims' return from Hajj. Twenty one percent of the pilgrims reported receiving antibiotics for respiratory illnesses during Hajj[8]. This high rate of antibiotic use compares with 17.2% reported by participants in our study. In 2010, Ceyhan *et al*[46] reported that 27% of returned Turkish Hajj pilgrims were positive for meningococcal carriage, mostly W-135. Airport-based surveillance studies conducted in 2001 in Thailand[47] and the United States[48] demonstrated a meningococci carriage rate of 0% and 2.6%, respectively. This is similar to the 1.4% carriage rate in a more contemporary study in Iran in 2012[49]. In the

latter two studies respectively, 15% and 58.5% pilgrims reported using antibiotics during Hajj[48,49]. Other studies conducted in Iran and Kuwait demonstrated that a single dose of ciprofloxacin before travel essentially eradicated meningococcal carriage[50,51]. The low carriage rate several weeks after Hajj in our study could possibly be indicative of the effect of a fairly high uptake (44.1%) of conjugate meningococcal vaccine. By contrast, the reported uptake of conjugate meningococcal vaccine among international pilgrims at Hajj 2013 was only 0.2%[42]. Worldwide, few pilgrims receive the conjugate vaccine because of its costs. In a surveillance study conducted in 2009 involving 1400 Hajj pilgrims of 14 nationalities, Ashgar *et al*[28] found the carriage rate of meningococci among arriving Hajj pilgrims to be 5.9%, increased by the end of the pilgrimage to 11.1% (P = 0.03)[28]. They also reported circulation of meningococcal strains resistant to azithromycin, ceftriaxone, ciprofloxacin, levofloxacin, meropenem and rifampicin[28].

Due to the public health significance, monitoring of antimicrobial susceptibility of clinical specimens for meningococci and pneumococci is important[52], particularly since pilgrims from high-risk countries in the African meningitis belt are routinely given ciprofloxacin prophylaxis on arrival for pilgrimage into KSA. Transnational dissemination of multi-drug resistant organisms has been reported[28]. This is relevant in the context of pneumococcal disease since about 20% of the pneumococcal isolates at Hajj are penicillin resistant[53]. Circulation of drug resistant pneumococci has been of concern in other mass gatherings, such as the reporting of pathogenic multi-drug resistant strains of *S. pneumoniae* circulating in Spain at the time of Barcelona Olympic in 1992 (however, the Olympic Organising Committee did not recommend pneumococcal vaccine for visitors)[54,55]. Today, antibiotic resistance is widespread and, considering the high incidence of pneumonia, the high carriage rate of pneumococci and circulation of multi-drug-resistant pneumococci, vaccination is recommended for all high-risk pilgrims and the conjugate vaccine is preferred[20,37,53].

The effect of facemasks use on pharyngeal bacterial carriage at Hajj has not been established yet, although a large trial is underway to examine the effectiveness of facemasks against viral infections[32]. In other settings such as among healthcare workers, the effectiveness of facemasks against pharyngeal bacterial colonisation, including *S. pneumoniae* was evaluated but no significant effect was observed[56]. Even though we did not find any significant effect of facemasks use on the pharyngeal/nasopharyngeal carriage rate of *S. pneumoniae* or *S. aureus*, interestingly a prospective study conducted in the Netherlands among pig farmers demonstrated that the use of facemasks was significantly associated with lower MRSA nasal carriage[57]. Perhaps a larger facemask study could demonstrate its true effect on pharyngeal colonisation of bacteria. We found an 18% carriage rate of *S. aureus* in the second (post-Hajj) phase of the study, but did not detect MRSA. This compares with a nasal carriage rate of 25% among arriving international pilgrims and 20.9% among departing pilgrims during the Hajj 2009[58] and similar to the nasal carriage rate of methicillin-susceptible *S. aureus* (28%) elsewhere in Australia[59,60].

To our knowledge, this is the first Australian carriage surveillance study for potentially pathogenic bacteria such as pneumococci, meningococci and *S. aureus* among Hajj pilgrims. We were able to validate pneumococcal and meningococcal conjugate vaccine uptake from a parallel trial. In the Hajj 2009, roughly one in five to seven *S. aureus* isolates were MRSA[58]. *S. aureus* has been cultured from sputum samples (between 3.8% to 7.7% isolates) among Hajj pilgrims with respiratory infections but MRSA was not cultured[15,59]. However, MRSA was isolated in samples collected from various body sites in about 1.5% pilgrims during the Hajj 2004[22].

Limitations of our study include a relatively small sample size and an inconsistent sampling site (*i.e.*, mostly nasopharyngeal in the first phase and oropharyngeal in the second phase). Different diagnostic methods were employed in the two different phases of the study with NAT in first phase of the study and phenotypic methods in the second phase which did not allow us to compare two datasets directly, and because of the differences in study designs it was not possible to make valid comparison with the reports of other investigators, so we limited the discussion to only narrative synthesis. In addition, only a few strains of carriage organisms were studied, especially we did not assess for other potentially vaccine preventable pathogens such as *H. influenza,* and pneumococcal isolates were not serotyped. The discordance in the number of participants between first and second phase was due to unavailability of some participants for post-Hajj sampling within 2 mo after Hajj, because often pilgrims make side trips to other countries after Hajj and do not return to Australia directly. To address these limitations, a larger study is currently underway.

In conclusion, this study found a moderately high carriage rate of *S. pneumoniae* amongst pilgrims during the Hajj 2014 in the background of a conjugate pneumococcal vaccine trial, but a low meningococcal carriage rate. This pilot study demonstrates that a larger study is feasible and important to inform public health measures to prevent the transmission and limit the impact of significant infectious diseases at mass gathering events such as the annual Hajj pilgrimage. Further information on the serotype of circulating pneumococcal isolates will optimise the use of pneumococcal vaccination in pilgrims.

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through a multidisciplinary Approach".

COMMENTS

Background

Pharyngeal acquisition of pathogenic microorganisms during Hajj, one of the world's largest mass gatherings, is a known risk. Before this study, the carriage rate of common bacterial pathogens among Australian pilgrims had not been investigated.

Research frontiers

There is high risk of acquiring a carriage of potentially pathogenic bacteria during Hajj, the author propose investigating this at a larger scale.

Innovations and breakthroughs

This study emphasises that international travel, including mass gatherings, is a significant risk factor for the acquisition of and subsequent colonisation or infection with bacteria.

Applications

This pilot study demonstrates that a larger study is feasible and important to inform public health measures to prevent the transmission and limit the impact of significant infectious diseases at mass gathering events such as the annual Hajj pilgrimage. Further information on the serotype of circulating pneumococcal isolates will optimise the use of pneumococcal vaccination in pilgrims.

Terminology

Carriage: The harbouring or transporting of a microorganism for example in the human body; Hajj: The Muslim pilgrimage to Mecca, which takes place in the last month of the arabic calendar and which all Muslims are expected to make at least once during their lifetime if they can afford to do so. It is one of the Five Pillars of Islam; Pilgrimage: A pilgrimage is a journey of spiritual significance; Pilgrim: A person who journeys to a sacred place for religious reasons.

Peer-review

It is an interesting surveillance study for carriage of pathogenic bacteria, the first one among Hajj pilgrims.

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CASE REPORT

Pulmonary embolism and internal jugular vein thrombosis as evocative clues of Lemierre's syndrome: A case report and review of the literature

Alfredo De Giorgi, Fabio Fabbian, Christian Molino, Elisa Misurati, Ruana Tiseo, Claudia Parisi, Benedetta Boari, Roberto Manfredini

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Abstract

Lemierre's syndrome (LS) is an uncommon condition with oropharyngeal infections, internal jugular vein thrombosis, and systemic metastatic septic embolization as the main features. Fusobacterium species, a group of strictly anaerobic Gram negative rod shaped bacteria, are advocated to be the main pathogen involved. We report a case of LS complicated by pulmonary embolism and pulmonary septic emboli that mimicked a neoplastic lung condition. A Medline search revealed 173 case reports of LS associated with internal jugular vein thrombosis that documented the type of microorganism. Data confirmed high prevalence in young males with Gram negative infections (83.2%). Pulmonary embolism was reported in 8.7% of cases mainly described in subjects with Gram positive infections (OR = 9.786; 95%CI: 2.577-37.168, *P* = 0.001), independently of age and gender. Only four fatal cases were reported. LS is an uncommon condition that could be complicated by pulmonary embolism, especially in subjects with Gram positive infections.

Key words: Lemierre's syndrome; Pulmonary embolism; Fusobacterium species; Internal jugular vein thrombosis; Systemic septic embolization

Core tip: We report a case of Lemierre's syndrome (LS) complicated by pulmonary embolism (PE) that mimicked

a neoplastic lung condition. The case was related to previously reported cases in Medline that documented the type of microorganism. We associated PE with LS due to Gram positive infections.

De Giorgi A, Fabbian F, Molino C, Misurati E, Tiseo R, Parisi C, Boari B, Manfredini R. Pulmonary embolism and internal jugular vein thrombosis as evocative clues of Lemierre's syndrome: A case report and review of the literature. *World J Clin Cases* 2017; 5(3): 112-118 Available from: URL: http://www.wjgnet.com/2307-8960/full/v5/i3/112.htm DOI: http://dx.doi.org/10.12998/wjcc.v5.i3.112

INTRODUCTION

Lemierre's syndrome (LS) is an uncommon condition characterized mainly by oropharyngeal infections complicated with internal jugular vein (IJV) thrombosis and subsequently metastatic infections secondary to septic emboli. This syndrome was first reported by Andrè Lemierre in 1936 in a personal experience describing 20 patients[1].

Primary sites of infection in these patients are the tonsils (palatine tonsils or peritonsillar tissue), pharynx and lower respiratory tract[2]. Fusobacterium represents the most common micro-organism related to this syndrome (about 90% of cases). Fusobacterium spp. are strictly anaerobic Gram-negative rod shaped bacteria, mainly isolated from the oral cavity[3]. The mechanisms underlying virulent clinical conditions are not known, and Fusobacterium is considered a rare cause of head and neck infections[4].

After local proliferation, neck infection is associated with IJV thrombosis and then hematogenous spread to other peripheral organs could happen such as the lung, joints, soft tissue, abdominal parenchyma, and central nervous system[5].

We report a case of LS complicated by pulmonary embolism and pulmonary septic emboli after IJV thrombosis.

CASE REPORT

A 53-year-old man presented to emergency department because of a history of occipital headache, malaise, hacking cough, chest pain exacerbated by inspiration, and fever for one month. He had a history of smoking, hypertension, hyperuricemia, and gastro-esophageal reflux. His general practitioner treated him unsuccessfully with clarithromycin and ceftriaxone. Blood chemistry panel showed increasing inflammatory indexes, such as white blood cells (WBC) 16.560/mm^3, C-reactive protein (CRP) 13.60 mg/dL, and erythrocyte sedimentation rate (ESR) 70 mm. Chest X-ray did not show parenchymal lesions, and either spinal column X-ray or encephalic nuclear magnetic resonance (NMR) was unremarkable.

On admission, the physical examination was unremarkable except that pharyngeal and tonsil hyperemia was detected. He was diagnosed with chronic tonsillitis by an otorhinolaryngologist. Pharyngeal packing with cultural exam identified saprophytic flora. Levofloxacin and nebulizer therapies were prescribed.

Further laboratory tests showed WBC = 11.070/mm^3, CRP = 3.70 mg/dL, ESR = 53 mm, fibrinogen = 706 mg/dL, and D-dimer = 773 ng/mL. Immunoglobulin-A was 559 mg/dL. Chest X-ray showed parenchymal and pulmonary consolidation associated with pleural effusion. Bronchoscopy with broncho-alveolar lavage (BAL) including microbiology and cytology was negative.

A chest computed tomography (CT) scan showed left pleural effusion, contralateral sub-pleural fibrosis and, above all, an important ovular lesion at the level of medial right lobe measuring 25.7 mm with central cavitation. Further three lesions of 5-6 mm at the superior right lobe, and enlargement of pulmonary hilar lymph nodes were evident (the largest was 13.4 mm). Since these images were suggestive of pulmonary neoplastic lesions (Figure 1A), a brain CT scan was planned. The latter detected a deficit of right sigmoid sinus and bulb of jugular vein filling, which were suggestive of thrombosis of the right jugular vein (Figure 2A). Doppler ultrasonography of upper and lower limbs and echocardiography were negative. A further careful re-evaluation of chest CT supported the hypothesis of septic pulmonary outbreaks, and filling defect in the upper and middle branches of the right pulmonary artery suggested pulmonary embolism (Figure 1B). A diagnosis of LS associated with IJV thrombosis secondary to tonsillitis and pulmonary emboli was made, and low molecular weight heparin (LMWH) was added to levofloxacin. Eleven days later, the patient was discharged in good general conditions. One month after discharge, a cerebral magnetic resonance angiogram (MRA) showed the complete re-canalization of the IJV (Figure 2B).

DISCUSSION

LS is an oropharyngeal infection complicated with IJV thrombosis and subsequently metastatic infections due to septic emboli[1]. LS represent an uncommon condition, and its prevalence is 0.6-2.3 cases per million population. Mortality rate is 4%-18%[6]. LS incidence is higher in people aged 14-24, and its annual rate is 14.4 cases per million people per year. Mean age of patients is reported to be 18-20 years[6,7]. Male patients seen to be at higher risk, especially in autumn and winter[5].

The most common etiology of LS is infection due to *Fusobacterium necrophorum*, an anaerobic, non-motile, filamentous and non-spore forming Gram negative rod, which is described in 80% of cases. Several other organisms have been reported, isolated as single pathogen (5% of cases) or in association with *Fusobacterium necrophorum* (10.1%), such as many bacteria of Bacteroides family, Group B and C Streptococcus, *Streptococcus oralis*, *Staphylococcus epidermidis*, *Klebsiella pneumoniae*,

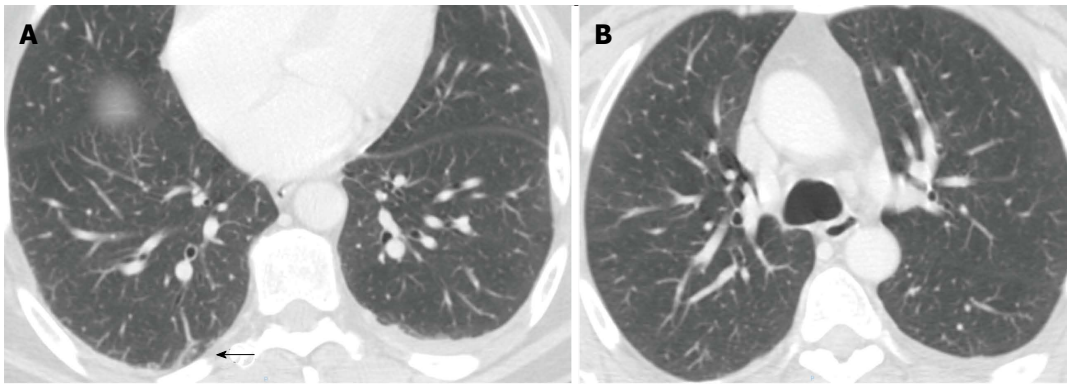

Figure 1 Chest computed tomography showing pulmonary lesions in the posterior region of the right lung (A) associated with left pulmonary embolism (B).

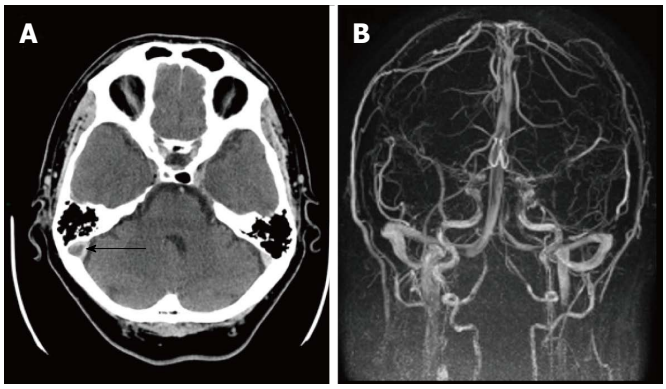

Figure 2 Internal jugular vein thrombosis (arrow) showed by brain TC (A), and further complete re-canalization demonstrated by cerebral magnetic resonance angiogram after antibiotic and anticoagulant therapy (B).

Enterococcus sp., *Proteus mirabilis*, Eubacterium sp., *Eikenella corrodens*, lactobacilli and Candida sp. On the other hand, culture results are negative in 12% of cases[7].

The main site of infection is palatine tonsils (87.1% of cases) and it could lead to exudative tonsillitis and peritonsillar tissue ulcer. However, it has been reported that only hyperemia or grey pseudo-membrane could be detected. Moreover, odontogenic infections, mastoiditis, parotitis, sinusitis, otitis, and skin or subcutaneous tissue infection of the head or neck may represent the primary infection site. Finally, the disease could happen even if the appearance of the pharynx was not remarkable[5-7].

Pulmonary embolism is not frequently described in LS. Lesions of the lungs are due to haematogenous spread of bacteria from the IJV, and necrotic cavitary lesions, infiltrates, pleural effusions or empyema, abscesses, pneumo-thoraces, or necrotising mediastinitis have been reported[5].

We performed a Medline literature search to identify papers reporting cases with LS associated with IJV thrombosis. The following search terms were used: "Lemierre syndrome" in combination with "internal jugular vein thrombosis" and "vein thrombosis". We found that isolation of microorganism was available in 173 cases (Table 1). LS was described more frequently in males (61.3%), aged 25.5 ± 14 years. Gram negative bacteria (84.3%), particularly *Fusobacterium spp* (76.3%), were related to it. Multiple microorganisms were reported in 8.7% of cases. Complications such as IJV thrombosis, arterial thrombosis, and pulmonary embolism were reported in 71.7%, 2.9% and 8.7% of cases, respectively. Only four fatal cases (2.3%) were described. Univariate analysis (Table 2) showed that pulmonary embolism was more frequent in patients with Gram positive bacteria. This finding was further confirmed by multivariate analysis and we calculated an odd ratio of 9.786 (95%CI: 2.577-37.168, P = 0.001). The relationship was independent from age, gender, and site of thrombosis.

In conclusion, LS is a rare condition that can mimic a neoplastic disease. However, the careful evaluation of clinical evolution should suggest a correct diagnosis. Moreover, the presence of pulmonary embolism represents a serious complication, and should be suspected when infection is due to Gram positive bacteria.

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COMMENTS

Case characteristics

A 53-year-old man with a history of smoking, hypertension, hyperuricemia, and gastro-esophageal reflux presented with occipital headache, malaise, hacking cough, chest pain exacerbated by inspiration, and fever.

Table 1 Reported cases of Lemierre's syndrome with internal jugular vein documenting microbiology

Ref.	Pathogen
Vogel *et al*, *Am J Dis Child* 1980	FN
	FN
Sinave *et al*, *Medicine* (Baltimore) 1989	FN
	FN, *Staphy. epidermidis*
Jones *et al*, *Postgrad Med J* 1990	FN
Blok *et al*, *Ned Tijdschr Geneeskd* 1993	FN
	FN
	FN
Ahkee *et al*, *Ann Otol Rhinol Laryngol* 1994	FN
Bader-Meuiner *et al*, *Eur J Pediatr* 1994	FN
Dykhuizen *et al*, *Eur Respir J* 1994	FN and *Bacteroides fragilis*
Hughes *et al*, *Clin Infect Dis* 1994	Multiple microrganisms
Kubota *et al*, *Nihon Kyobu Shikkan Gakkai Zasshi* 1994	FN
Alvarez *et al*, *Pediatrics* 1995	FN
Gupta *et al*, *Clin Pediatr* (Phila) 1995	FN and *Staphy. epidermidis*
Karanas *et al*, *Ann Plast Surg* 1995	FN
Bhagat *et al*, *Infect Dis Clin Pract* (Baltim Md) 1996	*Klebsiella pneumoniae*
De Sena *et al*, *Pediatr Radiol* 1996	FN
	FN
Harar *et al*, *ORL J Otorhinolaryngol Relat Spec* 1996	FN
Lee *et al*, *South Med J* 1997	*Strepto. viridans*
Bouton *et al*, *Rev Med Brux* 1998	FN
Dhawan *et al*, *Indian J Pediatr* 1998	*Peptostrepto. anaerobius, Bacteroides fragilis, Eikenella corrodens*
Williams *et al*, *Int J Pediatr Otorhinolaryngol* 1998	*Strepto. viridians*
	Strepto. viridians
Gong *et al*, *Eur Radiol* 1999	FN
Stokroos *et al*, *Arch Otolaryngol Head Neck Surg* 1999	FN
Agarwal *et al*, *J Laryngol Otol* 2000	FN
Alifano *et al*, *Ann Thorac Surg* 2000	FS and Propionibacterium
Chemlal *et al*, *Presse Med* 2000	*Strepto. intermedius*
Edibam *et al*, *Crit Care Resusc* 2000	FN
Gowan *et al*, *Can Respir J* 2000	FN
Ockrim *et al*, *J R Soc Med* 2000	FN
Shaham *et al*, *Clin Imaging* 2000	FS
Abele-Horn *et al*, *Eur J Clin Microbiol Infect Dis* 2001	FN
De Vos *et al*, *Neth J Med* 2001	FN
Singhal *et al*, *South Med J* 2001	FN
Turay *et al*, *Respirology* 2001	FN
Chirinos *et al*, *Medicine* (Baltimore) 2002	FN
	FN
Hoehn *et al*, *Crit Care Med* 2002	FN
Hope *et al*, *J Laryngol Otol* 2002	FN
Nguyen-Dinh *et al*, *J Neuroradiol* 2002	Strepto. species
Boo *et al*, *Ir Med J* 2003	FN
Dalamaga *et al*, *Anaerobe* 2003	FN
de Lima *et al*, *Pediatr Radiol* 2003	FN
Figueras *et al*, *Acta Paediatr* 2003	FN
Hodgson *et al*, *Undersea Hyperb Med* 2003	FN
Jarmeko *et al*, *CMAJ* 2003	FN
Velez *et al*, *J Oral Maxillofac Surg* 2003	FN
Williams *et al*, *J Clin Microbiol* 2003	FN
Ramirez *et al*, *Pediatrics* 2003	FN
	FN
	FN
	FN
	FN
Ahad *et al*, *Eye* (Lond) 2004	FN
Bentham *et al*, *Pediatr Neurol* 2004	FN
Giridharan *et al*, *J Laryngol Otol* 2004	FN
	FN
	FN
Lai *et al*, *N Engl J Med* 2004	FN
Litterio *et al*, *Anaerobe* 2004	FN
Ritter *et al*, *Ultraschall Med* 2004	FN
Aliyu *et al*, *Eur J Clin Microbiol Infect Dis* 2005	FN
Charles *et al*, *J Vasc Surg* 2005	FN
Dool *et al*, *Eur Arch Otorhinolaryngol* 2005	FN
	FN
	FN

Kuduvalli *et al*, *Acta Anaesthesiol Scand* 2005	FN
Libeer *et al*, *Acta Clin Belg* 2005	FN
	FN and *Bacteroides spp*
Masterson *et al*, *Int J Pediatr Otorhinolaryngol* 2005	FN
Min *et al*, *Angiology* 2005	*Staphy. haemolyticus* and *himinis*
Morizono *et al*, *Intern Med* 2005	*Porphyromonas asaccharolytica*
Nadkarni *et al*, *J Emerg Med* 2005	FN
Nakamura *et al*, *Angiology* 2000	FN
Ochoa *et al*, *Acad Emerg Med* 2005	FN
Peng *et al*, *J Formos Med Assoc* 2005	FN
Rivero Marcotegui *et al*, *An Med Interna* 2005	*Mycoplasma pneumoniae*
Schmid *et al*, *Pediatrics* 2005	FN
Shah *et al*, *J Ayub Med Coll Abbottabad* 2005	FN
	FN
Touitou *et al*, *Eur J Neurol* 2006	FN
Venkateswaran *et al*, *Ann Acad Med Singapore* 2005	FS and *Bacteroides fragilis*
Varkey Maramattom *et al*, *Cerebrovasc Dis* 2005	FN
Hochmair *et al*, *Wien Klin Wochenschr* 2006	FN
Fleskens *et al*, *Ned Tijdschr Geneeskd* 2006	FN
	FN
Constantin *et al*, *BMC Infect Dis* 2006	FN
Ravn *et al*, *Scand J Infect Dis* 2006	FN
Morris *et al*, *Ir Med J* 2006	FN
Olson *et al*, *Br J Ophthalmol* 2006	FN
Park *et al*, *J Bone Joint Surg Br* 2006	FN
Perović *et al*, *Acta Med Croatica* 2006	FN
Singaporewalla *et al*, *Singapore Med J* 2006	*Klebsiella pneumoniae*
Boga *et al*, *J Thromb Thrombolysis* 2007	*Staphy. aureus*
Brown *et al*, *J Laryngol Otol* 2007	FN
Chiu *et al*, *Australas Radiol* 2007	FN
Cholette *et al*, *Pediatr Pulmonol* 2007	FN
	FN
Juárez Escalona *et al*, *Med Oral Patol Oral Cir Bucal* 2007	*Strepto. intermedius* and *Bacteroides fragilis*
Thompson *et al*, *Infect Dis Obstet Gynecol* 2007	*Peptostrepto. anaerobius*, *Bacteroides fragilis*, and *Eikenella corrodens*
Wang *et al*, *Anaesth Intensive Care* 2007	FN
Westhout *et al*, *J Neurosurg* 2007	FN
Garimorth *et al*, *Wien Klin Wochenschr* 2008	FN
Georgopoulos *et al*, *J Laryngol Otol* 2008	FN
Kadhiravan *et al*, *J Med Case Rep* 2008	*Staphy. aureus*
Bentley *et al*, *J Emerg Med* 2009	*Staphy. aureus*
Goyal *et al*, *Neurol Sci* 2009	FN
Lee *et al*, *J AAPOS* 2009	*Strepto. viridans and salivarius*
Lu *et al*, *J Am Board Fam Med* 2009	FN
	FS
	FS
Takazono *et al*, *Jpn J Infect Dis* 2009	FN
van Wissen *et al*, *Blood Coagul Fibrinolysis* 2009	FN
	FN
Castro-Marín *et al*, *J Emerg Med* 2010	FN
Chacko *et al*, *J Laryngol Otol* 2010	FN
Herek *et al*, *J Emerg Med* 2010	*Staphy. aureus*
Courtin *et al*, *Ann Fr Anesth Reanim* 2010	FN
Bonhoeffer *et al*, *Klin Padiatr* 2010	FN
Lim et al, *Auris Nasus Larynx* 2010	*Staphy. aureus*
Nakayama *et al*, *Auris Nasus Larynx* 2010	FN
Ridgway *et al*, *Am J Otolaryngol* 2010	FN
Vargiami *et al*, *Eur J Pediatr* 2010	*Abiotrophia defective*
Vincent *et al*, *J Pediatr* 2010	FN
Gülmez *et al*, *Mikrobiyol Bul* 2011	FN
Huynh-Moynot *et al*, *Ann Biol Clin* (Paris) 2011	FN
Maalikjy Akkawi *et al*, *Neurol Sci* 2001	*Klebsiella pneumoniae*
Naito *et al*, *Nihon Kokyuki Gakkai Zasshi* 2011	FN
O'Dwyer *et al*, *Ir J Med Sci* 2011	FN
Yamamoto *et al*, *Nihon Rinsho Meneki Gakkai Kaishi* 2011	FN
Garbati *et al*, *J Med Case Rep* 2012	*Klebsiella pneumoniae*
Hile *et al*, *J Emerg Med* 2012	*Peptococcus anaerobius*
Kuppalli *et al*, *Lancet Infect Dis* 2012	FN
Lee *et al*, *J Microbiol Immunol Infect* 2012	*Klebsiella pneumoniae*
Lim *et al*, *Med J Malaysia* 2012	*Klebsiella pneumoniae*
Teai *et al*, *J Formos Med Assoc* 2012	*Klebsiella pneumoniae*

Teng *et al*, *J Emerg Med* 2012	FN
Tsai *et al*, *J Formos Med Assoc* 2012	*Klebsiella pneumoniae*
Abhishek *et al*, *Braz J Infect Dis* 2013	*Staphy. aureus*
Blessing *et al*, *Int J Pediatr Otorhinolaryngol* 2013	FN
Khan *et al*, *Indian J Pediatr* 2013	FN
Klein *et al*, *Heart Lung* 2013	*Mycoplasma pneumoniae*
Marulasiddappa *et al*, *Indian J Crit Care Med* 2013	*Staphylococcus aureus*
Nguyen *et al*, *Malays J Med Sci* 2013	*Klebsiella pneumoniae*
Phua *et al*, *Int J Angiol* 2013	*Klebsiella pneumoniae*
Righini *et al*, *Head Neck* 2014	FN
	FN
	FN
	Strepto. costellatus
	Enterococcus faecalis
	Strepto. anginosus
	Neisseria species
	FN
	FN
Gunatilake *et al*, *Int J Emerg Med* 2014	*Staphy. aureus*
Asnani *et al*, *J Fam Pract* 2014	FN
Galyfos *et al*, *Scand J Infect Dis* 2014	FN
Aslanidis *et al*, *Pan Afr Med J* 2014	*Candida albicans*, *Staphy. epidermidis*, and *Klebsiella pneumonia*
Karnov *et al*, *Open Forum Infect Dis* 2014	FN
Choi *et al*, *Tuberc Respir Dis* (Seoul) 2015	*Staphy. epidermidis*
Chuncharunee *et al*, *Hawaii J Med Public Health* 2015	*Klebsiella pneumoniae*
Croft *et al*, *Respir Med Case Rep* 2015	FN
Fischer *et al*, *Infect Dis Rep* 2015	FN
He *et al*, *BMJ Case Rep* 2015	FN
Kempen *et al*, *Eur Spine J* 2015	*Strepto. milleri* and FS
Prakashchandra *et al*, *J Clin Diagn Res* 2015	FN
Oya *et al*, *Intern Med* 2015	FS
Takano *et al*, *BMC Res Notes* 2015	FN
Wong *et al*, *J Am Board Fam Med* 2015	FN
Habert *et al*, *Rev Mal Respir* 2016	FN

FN: *Fusobacterium necrophorum*; FS: Fusobacterium species; Strepto: Streptococcus; Staphy: Staphylococcus.

Table 2 Univariate analysis comparing cases of Lemierre's syndrome with and without pulmonary embolism

	No pulmonary embolism (n = 158)	Pulmonary embolism (n = 15)	P
Female, n (%)	61 (38.8)	6 (38.5)	NS
Male, n (%)	97 (61.2)	9 (61.5)	
Age, (yr)	25.5 ± 14.1	26.2 ± 13.6	NS
Gram positive bacteria, n (%)	21 (13.3)	6 (40)	0.006
Gram negative bacteria, n (%)	137 (86.7)	9 (60)	
Multiple microrganisms, n (%)	14 (8.9)	1 (6.7)	NS
Only jugular vein thrombosis, n (%)	113 (71.5)	11 (73.3)	NS
Arterial thrombosis, n (%)	5 (3.2)	0	NS
Fatal cases, n (%)	4 (2.5)	0	NS

NS: Not significant.

Clinical diagnosis
Physical examination showed only pharyngeal and tonsil hyperemia related to chronic tonsillitis in the patient with a history of gastro-esophageal reflux.

Differential diagnosis
Pulmonary infection with slow resolution, pulmonary abscess, and pulmonary neoplasia.

Laboratory diagnosis
Laboratory work-up showed increased white blood cells, C-reactive protein, and erythrocyte sedimentation rate.

Imaging diagnosis
Chest X-ray was negative for parenchymal lesions at first, but then it showed parenchymal and pulmonary consolidation associated with pleural effusion confirmed by a computed tomography scan. Moreover, filling defect in the upper and middle branches of the right pulmonary artery suggestive of pulmonary embolism was detected. A brain computed tomography scan excluded parenchymal lesions, but a deficit of the right sigmoid sinus and bulb of jugular vein filling suggestive of thrombosis of right jugular vein were shown.

Pathological diagnosis
Tonsillitis related to Fusobacterium infection complicated with internal jugular vein thrombosis and pulmonary embolism.

Treatment
The patient was treated with levofloxacin and low molecular weight heparin.

Related reports
Lemierre's syndrome is a rare condition characterized by oropharyngeal infection

complicated by internal jugular vein thrombosis and pulmonary embolism.

Experiences and lessons

Lemierre's syndrome could mimic a neoplastic process. A careful follow-up of this condition is necessary.

Peer-review

The paper is well written.

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CASE REPORT

Unicentric Castleman's disease associated with end stage renal disease caused by amyloidosis

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Author contributions: Eroglu E and Oymak O designed the report; Unal A and Sipahioglu MH performed the kidney biopsy; Eroglu E and Kaynar L collected the patient's clinical data; Akgun H reported the biopsy specimens; Eroglu E and Kocyigit I analyzed the data and wrote the paper; all the authors contributed to this article.

Institutional review board statement: Not applicable due to the case report format.

Informed consent statement: Informed consent was obtained from the patient included in the case report.

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Abstract

Castleman's disease (CD), also known as angiofolicular lymph node hyperplasia, is a rare heterogenous group of lymphoproliferative disorders. Histologically, it can be classified as hyaline vascular type, plasma cell type, or mixed type. Clinically two different subtypes of the CD are present: Unicentric and multicentric. Unicentric CD is generally asymptomatic and associated with hyaline vascular type, and its diagnoses depend on the localized lymphadenopathy on examination or imaging studies. However, multicentric CD presents with generalized lymphadenopathy and systemic symptoms including malaise, fever, night sweats, weight loss, and it is associated with the plasma cell type and mix type. Herein, we report a patient with unicentric CD of the plasma cell type without systemic symptoms, who developed end stage renal failure caused by amyloidosis 6 years after onset of CD.

Key words: Castleman's disease; Amyloidosis; Plasma cell; Inflammation; End stage renal disease

Core tip: Castleman's disease (CD), also known as angiofolicular lymph node hyperplasia, is a heterogeneous group of lymphoproliferative disorders. The clinically unicentric

form is generally asymptomatic and often associated with hyaline vascular type. The unicentric form of the disease often shows mild to moderate clinical prognosis, however the multicentric form is a more severe form. After the complete surgical removal of the lymph node, remission is achieved in many cases and complications are very rare. However, this case of unicentric CD of the plasma cell type is unique due to the fact that it presented with amyloidosis and end stage renal disease six years after the onset of the disease.

Eroglu E, Kocyigit I, Unal A, Sipahioglu MH, Akgun H, Kaynar L, Tokgoz B, Oymak O. Unicentric Castleman's disease associated with end stage renal disease caused by amyloidosis. *World J Clin Cases* 2017; 5(3): 119-123 Available from: URL: http://www.wjgnet.com/2307-8960/full/v5/i3/119.htm DOI: http://dx.doi.org/10.12998/wjcc.v5.i3.119

INTRODUCTION

Castleman's disease (CD), firstly described in 1956 by Castleman *et al*[1] as giant lymphoid hyperplasia or angiofolicular lymph node hyperplasia, is a heterogeneous group of lymphoproliferative disorders. It is divided anatomically into unicentric and multicentric forms and histologically into plasma, hyaline vascular, and mixed cell types.

Unicentric Castleman's disease (UCD) is mostly asymptomatic and is discovered when an enlarged lymph node is determined on physical examination or by imaging studies[2,3]. Conversely, multicentric Castleman's disease (MCD) is a systemic disease with generalized peripheral lymphadenopathy, hepatosplenomegaly, malaise, fever, night sweats, and weight loss. Eighty to ninety percent of CD cases develop the hyaline vascular histological type, and it is commonly associated with UCD and clinically presents as a mediastinal or mesenteric mass. The plasma cell type (10%-20% of CD cases) accounts for the majority of multicentric cases and clinically presents with systemic symptoms due to increased inflammatory activity[3,4].

The pathogenesis of CD has not yet been completely clarified. The histopathological changes in lymph nodes resemble to the reactive changes that can be seen in response to normal antigenic stimuli. It has been shown that increased production of interleukin-6 (IL-6) might be related with the systemic inflammatory symptoms of CD. Unlike UCD, MCD is strongly associated with immunosuppression and human herpesvirus-8 (HHV-8) infection. The diagnosis is generally confirmed by excisional biopsy of the affected lymph node. Treatment of UCD is generally completed by resection of the lymph node; however, some cases need chemotherapy or immunotherapy[4,5].

Herein, we present the case of a male patient with UCD of the plasma cell type, which was diagnosed in 2010, with the excision of a paraaortic lymph node. Complete surgical resection was performed, and the patient was followed in a remission state for 3 years. Three years after he was lost to follow-up, the patient was admitted to hospital with increased creatinine levels, overt proteinuria, and increased inflammatory markers. A kidney biopsy showed AA-type amyloidosis. The patient was given hemodialysis due to end stage renal disease. Although the disease was in remission in imaging studies, this case presented with sudden kidney failure caused by amyloidosis, a rare complication of UCD of the plasma cell type.

CASE REPORT

A 69-year-old man was admitted to hospital with abdominal discomfort, tenderness, and dyspeptic complaints in August 2010. Abdominal ultrasonography revealed paraaortic lymphadenopathy and the patient was referred to the hematology department. He had no history of hypertension, diabetes mellitus, smoking, or alcohol use. The physical examination showed no sign of peripheral lymphadenopathy or hepatosplenomegaly. Laboratory results showed hypochromic microcytic anemia with a hemoglobin level of 11.9 g/dL, mean corpuscular volume (MCV) of 78 fl, erythrocyte sedimentation rate of 66 mm/h, and C-reactive protein level of 64 mg/L (normal range: 0-6 mg/L). The reticulocyte count was normal. There was no iron, folic acid, or vitamin B12 deficiency according to the laboratory results. All biochemical parameters were within normal range. Serologic tests for hepatitis, human immunodeficiency virus, Brucella, cytomegalovirus, Epstein-Barr virus, and HHV-8 were all negative. Serum immunoelectrophoresis demonstrated polyclonal hyperglobulinemia. Bone marrow aspiration and biopsy revealed normocellular findings. A computed tomography scan demonstrated a paraaortic lymphadenopathy (6 cm in diameter). Total lymph node excision was performed and the result of the pathologic specimen was reported as Castleman's disease of the plasma cell type (Figure 1). After operation, the patient was followed until July 2013, and he was in remission state according to laboratory and imaging studies. Follow-up laboratory results in 2011 showed that the erythrocyte sedimentation rate was 55 mm/h and the C-reactive protein was 25 mg/L. Follow-up laboratory results in 2012 showed that the erythrocyte sedimentation rate was 35 mm/h and the C-reactive protein level was 9.6 mg/L. During the patient's last hematology visit in 2013, a physical examination revealed normal findings. Laboratory parameters showed that his hemoglobin level was 13.7 g/dL, the erythrocyte sedimentation rate was 33 mm/h, and the C-reactive protein level was 9.6 mg/L. All biochemical parameters were within normal range. Serum immunoelectrophoresis and protein electrophoresis were normal. Radiologically, there were millimetric lymph nodes in the paraaortic area. The patient stopped routine follow-up hematology visits after July 2013 and was not seen for three years due to the lack of complaints. In June 2016,

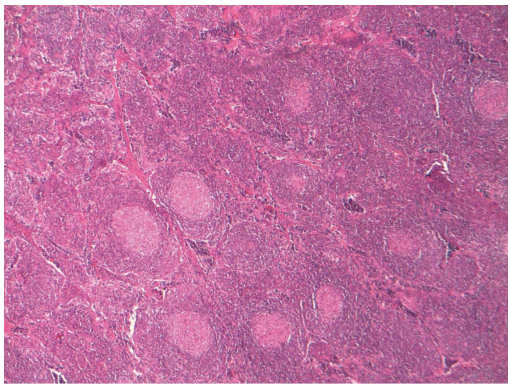

Figure 1 Light microscopy (HE × 400) demonstrates that reactive lymphoid follicles and the reactive germinal centers are radially penetrated by blood vessels in the lymph node specimen.

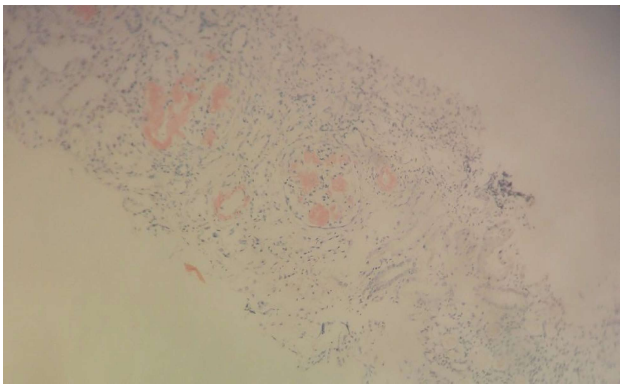

Figure 2 Light microscopy (HE × 400) demonstrates Congo red positive amyloid deposits in a glomerulus in the renal biopsy specimen.

the patient was admitted to the hematology department with complaints of nausea, vomiting, abdominal pain, and edema in the distal extremities. A physical examination revealed pale skin and conjunctiva without hepatosplenomegaly. Laboratory examinations revealed normochromic normocytic anemia (Hct, 25.7%; Hb, 9.6 g/dL; MCV, 87 fl) and elevated erythrocyte sedimentation rate (80 mm/h) and C-reactive protein (76 mg/L). The results of the laboratory findings were as follows: Glucose 95 mg/dL, BUN 75 mg/dL, creatinine 6.2 mg/dL, Na 139 mmol/L, K 5.0 mmol/L, Ca 8.2 mmol/L, phosphorus 5.2 mmol/L, uric acid 6.6 mg/dL, total cholesterol 223 mg/dL, LDL 126 mg/dL, GGT 15 U/L, ALP 97 U/L, AST 10 U/L, ALT 6 U/L, total protein 5.9 g/dL, albumin 2.4 g/dL, LDH 213 U/L, CPK 20 U/L, and serum iPTH level 151 pg/mL (15-65). The urine stick test revealed a positive result for protein (+++), but there were no erythrocyte or leukocyte casts in the microscopic evaluation of the urine sediment. The 24-h urine protein level was 10 g. ANA, anti-ds DNA, anti-GBM and ANCA profiles were all negative. The patient did not have any chronic inflammatory conditions such as tuberculosis, malaria, rheumatoid arthritis, or familial Mediterranean fever. The patient was referred to the nephrology department. An abdomen ultrasonography noted normal sized kidneys and a normal parenchymal thickness with increased grade 2 renal cortical echogenicity. All other findings were normal. A kidney biopsy was performed, which suggested AA-type amyloidosis (Figure 2). Metabolic acidosis and uremic symptoms had occurred, oliguria developed, and creatinine clearance was decreased to 10 mL/dk. The patient was admitted for veno-venous hemodialysis intervention *via* a double-lumen dialysis catheter in the jugular vein. Hematologic assessment demonstrated that CD was in remission according to imaging studies. A PET-CT scan only reported multiple millimetric lymph nodes without FDG uptake in the paraaortic area. Hemodialysis intervention was continued three times a week due to progressive deterioration of kidney functions. The patient was discharged from hospital two weeks later with a hemodialysis catheter and followed weekly. Two months later, he was considered to have end stage renal disease and underwent routine hemodialysis intervention *via* a created arteriovenous fistula.

DISCUSSION

Although renal involvement is a potential complication of CD, this rare case of UCD of the plasma cell type presented with renal failure caused by amyloidosis 6 years after the onset of the disease.

UCD is generally asymptomatic and sometimes comes to clinical attention if an enlarged lymph node is demonstrated on physical examination or in imaging studies. UCD more frequently affects one lymph node area. Systemic symptoms (*i.e.*, malaise fever, night sweats, and weight loss) are generally limited to patients with the less common plasma cell type[2,3]. Although 10% to 20% of UCD cases are of the plasma cell type, MCD is generally associated with the plasma cell type and closely linked to systemic inflammatory symptoms and renal complications[2,6]. Interestingly, our patient with UCD of the plasma cell type had no constitutional symptoms but was complicated by secondary amyloidosis 6 years after diagnosis and remission. This case illustrates the unexpected clinical course of CD.

Leung *et al*[7] reported a patient with MCD of the plasma cell type, who developed acute-on-chronic renal failure caused by renal amyloidosis 15 years after onset of CD and ultimately end stage renal disease. In UCD, surgical resection of the tumor results in a resolution of systemic symptoms and normalization of laboratory abnormalities. However, repeated renal biopsies show no evidence of regression of amyloid deposits in cases with UCD[8]. Androulaki *et al*[9] described a patient with UCD complicated with systemic AA-type amyloidosis which regressed with surgical resection. In contrast, Gaduputi *et al*[10] reported a case with UCD in a submandibular mass that was complicated by systemic amyloidosis and surgical resection failed to regress the amyloidosis. Intriguingly, our patient presented with amyloidosis 6 years after surgical resection of the localized disease. However, his disease was in remission radiologically, and we believe that low-grade inflammation may be responsible for the amyloidosis in this patient. We speculate that low-grade inflammation exists in patients

with CD of the plasma cell type.

Renal manifestations associated with CD are heterogeneous, including, minimal change disease, membranous, mesangio-proliferative, crescentic, membrano-proliferative glomerulonephritis, interstitial nephritis, and amyloidosis[11]. El Karoui *et al*[12] investigated the renal involvement by kidney biopsy of 19 French patients and found 20% of the patients (4/19) had renal amyloidosis. They concluded that the most common renal histologic findings were small-vessel lesions. Xu *et al*[13] recently reported the renal involvement in 76 Chinese patients with CD and they concluded that CD of the multicentric type, plasma cell type or mixed types is often associated with renal complications. Although previous case reports have showed that in patients with CD and renal manifestations, 25 of 64 patients had amyloidosis according to the current English literature, they did not report any patients with CD and renal amyloidosis in their cohort. They also demonstrated that thrombotic microangiopathy-like lesions are the most common pathological characteristics[13]. These findings suggest that amyloidosis may be histologically rare but clinical presentation of amyloidosis in patients with CD is more severe than other renal involvements.

This UCD case of the plasma cell type is unique due to renal failure caused by amyloidosis having occurred after 6 years of disease onset while the patient was in remission radiologically. In conclusion, physicians should be careful in terms of the presence of an inflammatory state and amyloidosis although a patient may be in radiological remission.

COMMENTS

Case characteristics

A 69-year-old man with Castleman's disease (CD) presented with nausea, vomiting, abdominal pain, and edema in the distal extremities.

Clinical diagnosis

There were pale skin and conjunctiva without hepatosplenomegaly and also, pitting edema in distal extremities.

Differential diagnosis

Nephrotic syndrome, lymphoma, and congestive heart failure.

Laboratory diagnosis

Increased serum creatinine, erythrocyte sedimentation rate, C-reactive protein, decreased hemoglobin and albumin levels were revealed in laboratory examinations.

Imaging diagnosis

A positron-emission tomography-computed tomography (PET-CT) scan only reported multiple millimetric lymph nodes without fluorodeoxyglucose (FDG) uptake in the paraaortic area.

Pathological diagnosis

AA-type amyloidosis.

Related reports

Previous case reports of patients with CD and renal manifestations have documented 25 of 64 patients had amyloidosis according to the current English literature. Amyloidosis may be histologically rare but clinical presentation of amyloidosis in patients with CD is more severe than other renal involvements.

Term explanation

CD is a heterogeneous group of lymphoproliferative disorders, which is described by Benjamin Castleman *et al*. Clinically two different subtypes of the CD are present, unicentric CD (UCD) and multicentric CD (MCD). UCD presents with localized lymphadenopathy. MCD, however, presents with generalized lymphadenopathy and systemic symptoms. PET-CT is used to determine lesions and FDG is a radiolabeled sugar molecule which is taken by lesion/lesions.

Experiences and lessons

UCD of the plasma cell type may present with renal failure caused by amyloidosis while the disease is in remission radiologically. Physicians should be careful in terms of the presence of an inflammatory state and amyloidosis development in patients with CD.

Peer-review

In this manuscript, the authors report on a case of unicentric CD associated with end stage renal disease caused by amyloidosis. This case report is clinically interesting.

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CASE REPORT

Neurostimulation for fecal incontinence after correction of repair of imperforate anus

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Author contributions: Bougie A contributed to the conception and design of the report; all authors contributed to the collection of the patient's clinical data as well as the writing, revision and approval of the article.

Institutional review board statement: The study was reviewed and approved by the Centre Hospitalier Universitaire de Sherbrooke (CHUS) Institutional Review Board.

Informed consent statement: The patient gave informed, written consent for publication of this case report.

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Abstract

We are reporting the case of a 32-year-old female who had suffered from fecal incontinence (FI). She was born with an imperforate anus and a recto-vaginal fistula; she underwent repair at 6 mo of age. At 29 years of age, she was still fecally incontinent despite extensive pelvic floor reeducation. A magnetic resonance imaging and an anal electromyography were performed. Because her symptoms were considered to be probably due to extra-sphincteric implantation of the neo-anus, a redo was performed of the recto-neo-anal intra-sphincteric anastomosis. A neurostimulator device was subsequently implanted for persistent incontinence. Solid and liquid FI resolved, and her quality of life improved markedly. Combining surgery to correct the position of the neo-anus within the anal sphincter complex and neurostimulation could thus become a new approach in cases of refractory FI for patients with imperforate anus as a newborn. Follow-up into adulthood after pediatric imperforate anus surgery should be recommended for adult patients with persistent FI.

Key words: Fecal incontinence; Congenital malformation; Neuromodulation; Neurostimulation; Imperforate anus

Core tip: Fecal incontinence is frequent among young adults who have suffered from an imperforate anus. This condition needs to be better understood by adult surgeons, and evaluation of the repair is necessary.

This case report describes exams done to confirm the abnormal position of the anus in relation to the sphincter complex and what was done to improve the condition of the patient. Surgery and neurostimulation were complementary and dramatically improved the quality of life of this patient.

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INTRODUCTION

Surgeries in the first years of life for imperforate anus can lead to lifelong problems with fecal incontinence (FI) with a great impact on quality of life[1], largely due to the neo-anus in relation to the anal sphincter position and integrity. Despite successful surgery, results for fecal continence and quality of life can be disappointing.

Sacral neurostimulation (SNS) is a new modality to help restore fecal continence when patients are refractory to standard treatment[2]. The feasibility of SNS has been explored for adult patients with anorectal malformations[3]. To continue to advance the indications for SNS within the context of FI, we describe how a patient's continence was fully restored with SNS, subsequent to a second intra-sphincteric bowel re-transposition, 30 years after the first attempt.

CASE REPORT

A 24-year-old woman presented herself to the perineology unit for a history of FI, soiling, uncontrolled flatulence and urgent defecation worsening for 2 years and recent symptoms of dyschezia. She complained of constipation, the longest period without stools being 3 d. For at least 1 year, bowel emptying of small stools was always incomplete.

She was born by vaginal delivery as a full-term baby with an imperforate anus and a recto-vaginal fistula. She was treated with dilatations until definitive surgery. She was brought to surgery at the age of 6 mo and anal transposition with repair of the fistula was performed. She was brought back to surgery 2 mo later for a recurrence of the fistula, and an anoplasty with repair of the fistula was performed. After the second surgery, the fistulous tract remained patent for days and eventually closed spontaneously without diversion.

Initial manometry showed that the resting pressure of the anal canal was normal: In cmH_2O, rectal pressure was 12; upper anal canal (UAC) pressure was 67; and lower anal canal (LAC) pressure was 51. Voluntary contractions were very weak (only 21 in the UAC, and 13 in the LAC) and of short duration. There was also a decrease in the amplitude of the recto-anal inhibitory reflex (RAIR). Its presence indicated, in retrospect, that the initial congenital lesion was probably a low rather than a high lesion[4]. The recto-anal contractile reflex was absent up to 50 mL of rectal distension by inflating a rectal balloon. She also had a micro-rectum: The maximum tolerable volume was only 90 mL (normal adult values are between 140 and 320 mL).

Pelvic magnetic resonance imaging was performed and showed a normal internal sphincter but a narrow external sphincter and puborectalis on the left side only. There was also a suspicion of a fistulous tract to the vagina (without any clinically evident symptoms). An anal echo-endoscopy was performed, which showed a distorted anus with a narrow recto-vaginal space with the same observations for the external sphincter and a possible fistulous tract. Despite extensive pelvic floor reeducation, the symptoms remained and her quality of life was poor for the following 5 years.

She was referred to surgery for an evaluation for SNS. She was wearing daily protective pads and her Jorge-Wexner score for FI was 15/20[5]. A rectal examination showed that the anal cutaneo-sphincteric reflex was absent, anal tone was poor, and a superficial contraction posterior to the surgical neo-anus was elicited by voluntary anal contraction.

Percutaneous nerve stimulation (PNS) was performed for 1 wk (model 3057, Medtronic). The term PNS is used by analogy to SNS with a permanent InterStim device but with a temporary electrode for Percutaneous Nerve Evaluation (PNE) that can last, with care, for up to three weeks. Unfortunately, successful results were not achieved. After left stimulation, her Jorge-Wexner score remained at 15/20. She had no liquid stools, wore a pad daily (which was constantly dirty) and leaked solid stools almost daily. Similar results were obtained with PNS on the right. Anal electromyography (EMG) showed no response on the right side, where the external sphincter should be located, poor activity on the left and anterior sides, and a better response on the posterior part. There were polyphasic motor units potentials. The neurologist performed the EMG twice, before and after the PNS; he made the additional and previously unreported remark that, anteriorly, he only found scar tissue and very few muscle fibers, in contrast to posterior to the anus. The pudendal nerve latency (PNTML) was normal (1.8 ms) on both sides, as well as the sacral arc at 33 ms.

Because her symptoms were considered to be probably due to extra-sphincteric implantation of the neo-anus, she was brought back to surgery at the age of 30. A dissection of her neo-anus was carried out proximally for 10 cm passing along the posterior vaginal wall. Resection of the neo-anus, which had visibly been implanted anterior to the sphincter, was completed until normal rectal mucosa was found. Intra-operative neurostimulation was used to implant the recto-neo-anal intra-sphincteric anastomosis. A loop colostomy was performed to protect the repair. Post-operative manometry showed

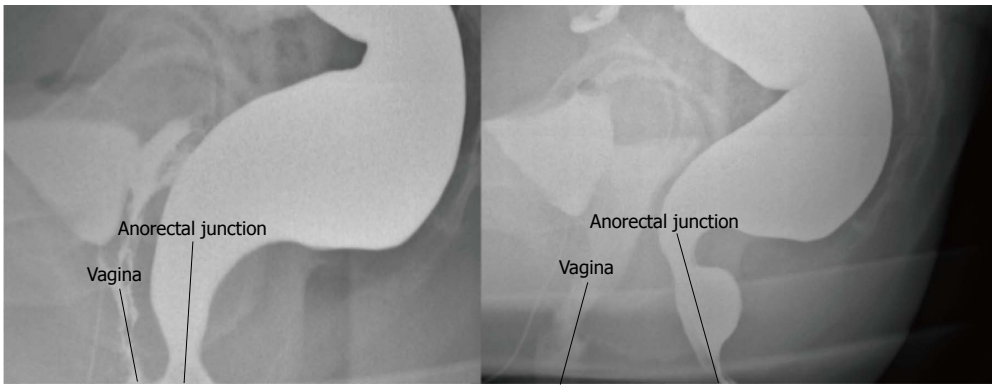

Figure 1 Pre- and post-operative defecographies. Both results show the evolution of the anorectal anatomy after repositioning of the neo-anus in the intra-sphincteric position. There is a widening of the space between the vagina and the anal canal and an improvement of the anorectal angle.

a normal, unchanged (12, 59 and 60 cmH_2O) resting pressure of the anal canal with persistently (even if slightly stronger) weak voluntary contractions, despite a subjective improvement based on a digital examination by the surgeon. EMG showed significantly better results with clear activity of the external sphincter on both sides of the anus. Motor units, however, were still polyphasic and prolonged at 30-40 ms. There was evidence of satellite potentials and conduction block indicating re-innervation. The sacral arc and PNTML remained normal. There was no anismus (recto-sphincteric dyssynergia). The colostomy was later closed. The Jorge-Wexner score for FI was still 11/20 at 4 mo after surgery, and she still complained of losing stools at least once a week and of remaining constipated.

Post-operative defecography showed an impressive difference with her pre-operative defecography (Figure 1). There was a marked widening of the space between the vagina and the anal canal and an improvement of the anorectal angle.

PNS was thus reattempted for 1 wk on the right side without improvement of her score of 11/20, but solid FI stopped. On the left side, her score dropped to 10/20, and stimulation also worked for solid FI. Offered with a choice, she opted for a left permanent SNS.

The first stage of SNS was performed, implanting the tined lead electrode (Medtronic Model 3093-28) on the left side. The neurostimulator device (Medtronic Model 3023, InterStim Neurostimulator) was implanted 3 wk later. One month after definitive surgery her Jorge-Wexner score for FI fell to 2/20; the 2 points were for wearing pads out of fear of soiling. Solid and liquid FI resolved, and her quality of life improved markedly. On her own, she decided to shut off the InterStim at night.

Her remaining complaints were skin tags at the anal margin impeding defecation. Even if she defecated daily, radiopaque markers were not all defecated 1 wk after ingestion of 20 markers. Removal of skin tags partially solved the problem. Slight anismus was corrected by biofeedback. She also scored, understandably with her life history, positive for constipated irritable bowel syndrome (IBS-C) on the basis of the Rome Ⅲ criteria; this was addressed and solved through long interviews with the treating surgeon (GD). Her Jorge-Wexner score, 2 years after SNS, was 0/20 with only 0.7 V of stimulation. The active electrode was the 0 electrode as the negative pole, and electrode 3 was the positive one. Impedance was 1026 ohms.

Her next visit to check the electronic system was at age 33 and she claimed she had remained fully continent. However, impedance of two of the four electrodes was unacceptably high, above 4000 ohms. She denied any fall or trauma to the buttock, but spontaneously expressed the fact that, encouraged by her full continence, she had become much more physically active. Before, because of her poor quality of life, she was very sedentary. She also complained of some persistent IBS symptoms. Her program was modified. Electrode 2 was selected as the negative pole. The InterStim case became the positive pole. Impedance was 523 ohms; the amplitude of stimulation was slightly higher at 1.65 V. The frequency was set at 21 Hz; on and off stimulation were 25 and 5 s respectively. The current was below 15 μA.

DISCUSSION

Intensive pelvic floor reeducation is the main treatment for FI in patients who had imperforate anus surgery. Unfortunately, FI frequently persists in adulthood[1]. Adult colorectal surgeons do not see these patients very often, as follow-up may not be recommended by pediatric surgeons.

Despite intensive pelvic floor reeducation, the quality of life of the patient described in this report remained poor until recognition of an extra-sphincteric implantation of her bowel into the neo-anus. The evaluation process took many years as she presented first at the perineology unit for pelvic floor reeducation, which was 5 years before a transfer to surgery.

A first attempt, with neurostimulation only, failed to correct the problem. Her Jorge-Wexner score improved, but she was left with frequent episodes of FI and persistent constipation.

Correction of the surgical error failed to restore fe-

cal continence. Pudendal neuropathy is often present in patients with FI, and this established the basis for successful treatment of this patient. It is our belief that because her external sphincter never worked correctly, resection of the neo-anus and re-implantation of the rectum in the external sphincter did not achieve optimal results, showing the complexity of the problem. As a second PNS attempt showed better results, SNS was performed. Improvement was beyond the surgeon's expectations and the patient's quality of life improved dramatically.

Neurostimulator settings need to be personalized to each patient. The first electrode selected may not be optimal for the entire lifespan of the neurostimulator. Dislodgment of the electrode because of physical activity or fibrosis may alter the contact of the electrode with sacral nerves. Resistance and settings are usually periodically verified: The position on the electrode is selected that offers the best sensation at the anus to improve anal function; and the lowest voltage possible is selected to extend the battery life of the neurostimulator.

The patient could turn off her neurostimulator at night without interfering with the functional results. We always suggest that patients do so to increase the battery life of the neurostimulator.

This report shows that not only should the initial surgical treatment be followed up years later but, in addition, the electrical activity of the anus should be evaluated.

Indications of SNS for FI are growing. We demonstrate here a successful case to correct FI in an adult female in the context of chronic problems of congenital origin. Combining surgery to correct the position of the neo-anus in relation to the anal sphincters and SNS could thus become a new approach in cases of refractory FI. Follow-up into adulthood after pediatric imperforate anus surgery is recommended for adult patients with persistent FI; patients who respond to SNS could then be treated accordingly.

COMMENTS

Case characteristics

A 32-year-old female born with an imperforate anus who suffered from fecal incontinence (FI) despite extensive pelvic floor reeducation.

Clinical diagnosis

She complained of FI, soiling, uncontrolled flatulence, urgent defecation and constipation.

Differential diagnosis

Her FI was considered to be due to extra-sphincteric implantation of the neo-anus and to be neurogenic.

Laboratory diagnosis

An anal electromyography helped for repositioning of the neo-anus and concluded in the neurogenic aspect of the sphincters.

Imaging diagnosis

Magnetic resonance imaging and pre-operative defecography demonstrated the erroneous position of the anus. Post-operative defecography showed the widening of the space between the vagina and the anal canal and an improvement of the anorectal angle.

Treatment

A redo was performed of the recto-neo-anal intra-sphincteric anastomosis. A neurostimulator device was subsequently implanted for persistent incontinence.

Related reports

Few studies reported use of neurostimulation in case of FI in patients with a history of imperforate anus.

Term explanation

Sacral neurostimulation stimulates the pudendal nerve which is responsible for perineal sensitivity and motor response of the anus.

Experiences and lessons

Follow-up into adulthood after pediatric imperforate anus surgery should be recommended for adult patients with persistent FI.

Peer-review

This is a very interesting case report showing sacral neuromodulation works in a fecal incontinence patient after erroneous repair of imperforate anus. The case report is well written.

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MINIREVIEWS

Prosthetic reconstruction of the trachea: A historical perspective

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Abstract

This review discusses the history of tracheal reconstruction; from early work to future challenges. The focus is primarily on prosthetic tracheal reconstruction in the form of intraluminal stents, patch repairs, circumferential repairs and replacement of the trachea. A historical perspective of materials used such as foreign materials, autografts, allografts, xenografts and techniques, along with their advantages and disadvantages, is provided.

Key words: Tracheal stenosis; Trachea; Prostheses and implants; Stents

Core tip: Reconstruction of tracheal defects has historically been difficult, predominantly due to the lack of an intrinsic blood supply. Direct anastomosis is generally considered to be the best option. For larger defects, stenting and prosthetic reconstruction remain the primary methodologies. In light of the recent scandal surrounding tracheal replacement, this article aims to give a historical review of tracheal reconstruction methods.

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INTRODUCTION

Tracheal reconstruction has been widely researched over the last 50 years. There are numerous indications for tracheal reconstruction, most frequently post-intubation injuries, idiopathic stenosis, neoplasia and re-stenosis following surgery[1].

Following tracheal resection, primary reconstruction with direct anastomosis of the patient's own tracheobronchial tissue is generally accepted as the best

option[2-7]. Anatomical studies suggest that up to half of the trachea can be resected in adults and directly anastomosed, without undue tension, by implementing mobilisation techniques such as suprahyoid release incisions and/or dissection of the hilum and pulmonary ligament[8]. This has been corroborated in large studies, with acceptable safety profiles and good long-term results, although the limits vary depending upon the patient's age, body habitus, local anatomy, co-morbidities and previous treatments[1,9-12].

In patients with very extensive pathology, direct anastomosis following resection is not possible and as such, either stenting or replacement with a prosthesis remain the two principle options. This provides a significant subset of patients. For example, long-segment defects (greater than 50% of the trachea) constitute approximately half of tracheal stenosis cases, although more recently this has been innovatively and successfully managed *via* a slide tracheoplasty procedure[13,14]. A range of materials have been attempted and no ideal prosthesis has yet been developed. The ideal prosthesis is airtight, of adequate consistency to prevent collapse, well accepted by the host thus causing minimal inflammatory reaction, impervious to fibroblastic and bacterial invasion of the lumen and allows ingrowth of respiratory epithelium along the lumen[15,16].

In this review article we will provide a historical overview of tracheal reconstructive trends.

EARLY WORK

In the late 1890s and into the twentieth century, interest in tracheal reconstruction evolved[17-20]. Initially, as with many surgical specialities, a knowledge base was formed principally through isolated case reports. The focus at this time was autogenous replacements such as skin alone, or skin and fascial grafts[21,22]. Daniel *et al*[23] heralded the advent of a more scientific approach with experimental animal studies. Throughout this period there was a transition from autogenous materials to solid prostheses such as tantalum, polyethylene, acrylic and steel tubes[24-27]. No ideal prosthesis was found and outcomes were variable. Indeed, often composite approaches were taken, usually in the form of a solid prosthesis with fascia lata grafts. The level of evidence remained low.

1950s TO THE POROUS PROSTHESIS

Following this initial interest and *in vivo* work (Table 1), Gebauer was amongst the first to develop porous prostheses to counteract some of the drawbacks of solid prostheses[28,29]. It was found that a porous prosthesis more closely approximates the function of tracheal cartilages as compared to a solid prosthesis[30]. However complications including strictures, granulation formation, chronic infection, pressure necrosis from the prosthesis and dislodgement remained problematic. Erosion of the brachiocephalic artery was also not infrequent. The porous structure was calculated to permit ingrowth of host connective tissue thus incorporating the prosthesis into the tracheal site; it was found that a minimal porosity of 40 to 60 μm is necessary for capillary ingrowth[31]. There was a proliferation of literature and animal studies in this field during the 1950s and 1960s[32-36]. This culminated in a better understanding of an ideal prosthesis in that the graft should be airtight, have adequate consistency, be well accepted by the host, cause minimal inflammatory reaction, be impervious to fibroblastic and bacterial invasion into the lumen but ideally allow ingrowth of respiratory epithelium along the lumen[15,33,35]. The decision of material to trial was often dependent upon industrial and commercial advances and availability, ranging from steel wire, tantalum, marlex, PTFE, dacron and teflon[2,29-36]. Combinations of materials were often employed. Towards the end of this period, as a result, prosthetic reconstruction of the trachea was being performed in human patients[37,38]. The most promising outcomes were with Silicone prostheses. The Neville group pioneered this approach and developed the Neville prosthesis, a silicone based mould under high compression available as straight or bifurcated tubes[15,16]. In this series of 62 patients, outcomes were reported to be good and the use of silicone was explicated by its resilience, non-reactivity, smooth inner surface and ability to be readily moulded[15,39]. This, therefore, fulfilled all the criteria for an ideal graft except for ciliated epithelium traversing the inner surface. Suture line granulomas remained problematic and were treated endoscopically[15,16,37]. This connective tissue ingrowth initially serves to fix and integrate the porous prostheses but this continued proliferation leads to scar tissue, obstruction and stenosis alongside with resultant chronic infection[31].

At this time, progress was also being made in surgical techniques, led by Grillo's team in Boston. Anatomic studies indicated that up to half the trachea in adults can be resected and closed primarily with an end to end anastomosis[8]. The same group has validated this with resulting large case series with low morbidity and mortality[3,4,9-11,13,31]. Slide tracheoplasty and other mobilisation techniques including suprahyoid release incisions, dissection of the hilum and pulmonary ligament have all been successfully used to achieve primary closure. Undoubtedly this remains the gold standard management of tracheal resection. However, it is not always possible and is dependent upon the patient's age, body habitus, local anatomy, extent of disease, co-morbidities and previous treatments such as radiotherapy[3,4,9-11,13,31].

These studies therefore established that primary repair remains the method of choice and should be employed wherever possible. In addition, it was concluded that an entirely satisfactory tracheal graft will never be available[31,35]. The silicone airway is at least as satisfactory as any prosthesis yet fashioned for tracheal replacement and any alternative must be wholly dependable with minimal morbidity and mortality[31]. This remains the

Table 1 Tracheal reconstruction methodology over time

Year	First author	Category[1]	Material	Study type (number)
1898	Bruns[17]		Prosthesis unknown	Human
1911	Hohmeier[18]	Autogenous	Fascia lata	Animal
1912	Levit[19]	Autogenous	Fascia	Human (1)
1927	Fairchild[20]	Autogenous	Skin	Human (1)
1935	LeJeune[21]	Autogenous	Split thickness skin graft	Human (2)
1945	Crafoord[22]	Autogenous	Cutaneous and costal cartilage	Human (1)
1946	Belsey[24]	Solid prosthesis	Steel with fascia lata	Human (1)
1948	Clagett[25]	Solid prosthesis	Polyethylene	Human (1)
1948	Daniel[23]	Solid prosthesis	Fascia, Metal Tube	Animal
1948	Longmire[26]	Solid prosthesis	Acrylic tube	Human (1)
1949	Rob[27]	Solid prosthesis	Tantalum with fascia lata	Human (4)
1949	Kergin	Autogenous	Pericardium and bronchus	Human (1)
1950	Jarvis	Solid prosthesis	Stainless Steel	Human (1)
1950	Gebauer[29]	Porous prosthesis	Wire-enforced dermal graft	Human (11)
1951	Bucher[30]	Porous prosthesis	Stainless steel wire mesh	Animal
1952	Cotton[2]	Solid prosthesis	Stainless steel tube	Human (2)
1953	Edgerton	Solid prosthesis	Split grafts with foam rubber	Human (12)
1953	Pressman[32]	Autogenous	Decalcified bone	Animal
1955	Morfit	Solid prosthesis	Polyethylene	Animal
1962	Beall[35]	Solid prosthesis	Polyethylene	Animal
1964	Aletras	Solid prosthesis	Teflon frame with pericardium	Animal
1967	Graziano[33]	Porous prosthesis	Silicon with dacron	Animal
1968	Pearson[34]	Porous prosthesis	Marlex (Polyethylene)	Animal
1973	Monk	Autogenous	Dermal grafts	Human (6)
1973	Demos	Porous prosthesis	Silicone	Animal
1974	Montgomery[38]	Porous prosthesis	Silicone t tube	Human (94)
1974	Pearson	Porous prosthesis	Marlex (Polyethylene)	Human (6)
1976	Neville[37]	Porous prosthesis	Silicone	Human (26)
1977	Lindholm	Autogenous	Bone/periosteum/muscle	Human (2)
1982	Neville[15]	Porous prosthesis	Neville prosthesis (silicon with dacron rings)	Human (54)
1982	Westaby	Porous prosthesis	Bifurcated silicone stent	Human (1)
1985	Toomes[6]	Porous prosthesis	Neville prosthesis (silicon with dacron rings)	Human (9)
1986	Scherer[67]	Tissue engineering	Bioprosthesis	Animal
1989	Har-El	Autogenous	Alloplast implanted muscle flap	Animal
1990	Neville[39]	Porous prosthesis	Silicone tubes	Human (62)
1990	Cull	Porous prosthesis	PTFE	Animal
1990	Jorge	Porous prosthesis	PTFE	Animal
1990	Kato[66]	Autogenous	Oesophagus and Silicone T tube	Animal
1990	Letang[65]	Homograft	Jejunum and Silicone T tube	Animal
1990	Varela	Porous prosthesis	Stainless steel wire mesh	Human (5)
1992	East[64]	Autogenous	Composite fascia, septum	Human (1)
1994	Okumura[63]	Porous prosthesis	Collagen and Marlex mesh	Animal
1996	Sharpe	Porous prosthesis	Marlex and pericardium	Human (1)
1996	Elliott[62]	Homograft	Homograft	Human (5)
1997	Kiriyama[61]	Homograft	Oesophageal autograft	Animal
1997	Teramachi[60]	Porous prosthesis	Marlex with collagen	Animal
2000	Sekine[59]	Porous prosthesis	Marlex	Animal
2003	Pfitzmann[58]	Homograft	Oesophagus	Human (1)
2004	Kim[57]	Porous prosthesis	Skin and polypropylene mesh	Animal
2005	Martinod[56]	Homograft	Allogenic aorta	Animal
2005	Shi[55]	Porous prosthesis	Polyprophyelene mesh with polyurethane/collagen	Animal
2006	Jaillard[54]	Homograft	Allograft aorta	Animal
2008	Sato[53]	Porous prosthesis	Polyprophyelene mesh with collagen	Animal
2008	Macchiarini[79]	Homograft	Stem cell seeded homograft	Human
2009	Nakamura[51]	Porous prosthesis	Polyprophlene with additional collagen, stem cells	Animal
2010	Makris[50]	Homograft	Allograft aorta	Animal
2010	Sato[49]	Tissue engineering	Bioprosthesis	Animal
2010	Tsukada[74]	Tissue engineering	Bioprosthesis	Animal
2011	Yu[47]	Autogenous/prosthesis	Radial forearm flap with PTFE or polyethlene	Human (7)
2011	Jungebluth[48]	Tissue engineering	Stem cell bioartificial scaffold	Human (1)
2012	Elliott[46]	Tissue engineering	Stem cell bioartificial scaffold	Human (1)
2012	Gray[45]	Tissue engineering	Stem cell bioartificial scaffold	Animal
2012	Tani	Tissue engineering	Collagen scaffold with FGF	Animal
2012	Wurtz[77]	Homograft	Allograft aorta with fascial graft and external cartilage	Animal
2014	Chang[40]	Tissue engineering	Stem cell bioartificial (3D Printed) scaffold	Animal
2016	Delaere[78]	Allotransplant	Vascularised allograft	Human

[1]A number of these are composite strategies. PTFE: Polytetrafluoroethylene; FGF: Fibroblast growth factor.

case today.

1990s ONWARDS

Further avenues of research have evolved in the last few decades. This has focussed on homografts, various composite strategies (including further work on porous prostheses) and latterly, tissue engineering[1,5,9,10,12,14,40-67].

Scherer *et al*[67] were first to experiment with bioprostheses by transplanting tracheas from various animals as autografts, allografts and xenografts. Rejection seemed to be avoided[31,67]. This preceded a plethora of animal studies, particularly transplantation studies, and in the last few years, attempts to translate this to patients[40,41,43,44,49,50,54,56,61]. Recently, research has focused on tracheal stem cell regeneration. Despite initial positive results, the outcomes have been generally poor and as such should be used with caution[42]. Pedicled flaps may serve to implant and maintain the stem cell generated trachea prior to reconstruction[41]. A recent pilot study has used three-dimensional printing of an artificial tracheal graft[40]. In addition, there has been some focus on the use of intestinal (either jejunal or oesophageal) tubes to replace the trachea[66]. This autogenous tissue reconstruction can be categorised into free grafts with and without foreign material support (*e.g.*, the composite wire and fascia or dermal grafts); vascularised tissue flaps (*e.g.*, pedicled intercostal muscle) and autogenous tube construction (*e.g.*, oesophagus)[31]. Autologous tracheal replacement using radial forearm fasciocutaneous free flap has also demonstrated positive outcomes[68].

Further homografts include pericardium and aorta[50,54,56]. Patch repair of the trachea using pericardial allografts[69] and xenografts[70] have been shown to have good outcomes[71]. More recently, aortic homografts used as a bioprosthetic device for patch repair have also shown favourable results[72,73]. Circumferential replacement of the trachea using aortic allografts has shown poorer results, in both animal[74] and human[75] models. Wurtz demonstrated that silicone-stented aortic allografts have no cartilage regeneration, probably due to ischaemia prior to neoangiogenesis[76]. This led to proposals of a composite, fascial flap-wrapped allogeneic aortic graft with external cartilage ring support[77]. Again, no reconstruction has been as successful as direct anastomosis, or even silicone prostheses alone.

CONTROVERSIES AND FUTURE DEVELOPMENTS

The intriguing yet unsolved surgical dilemma of tracheal replacement remains a challenge to clinicians. Currently, work from the Leuven group (Delaere *et al*[78]) have shown promising results with the judicious use of allotransplants. Surgical ingenuity will lead to novel approaches to these problems[3]. However, it is important to note that these techniques should not create more problems than they solve and patients are to be treated as an individual with a duty of care attached to that. As a corollary to this, it is worth highlighting that where a series of animal experiments are successful, application of these procedures to humans almost inevitably presents greater issues and a higher failure rate[3]. Work on tracheal regeneration using stem-cell implanted scaffolds[44,48,79], which has been the centre of recent controversy, showed questionable data and ultimately poor results.

CONCLUSION

Direct revascularisation of the trachea is unsuitable due to its lack of an intrinsic blood supply. Its anatomical features (proximity to major vessels, segmental blood supply) and the presence of a variety of different tissue types (respiratory epithelium, cartilage, blood vessels) make reconstruction difficult. Recent attempts with tissue-engineered transplants have all failed due to this reason[80]. Tracheal reconstruction is optimal when primary anastomosis is possible with undue tension. Patients requiring reconstruction should be managed in a multidisciplinary team at a high volume tertiary referral centre to optimise treatment. Tracheal replacement can be divided into prosthesis, homograft and autogenous tissue reconstruction, or a combinatorial methodology. None have proven ideal conduits as tracheal replacements. The most convincing evidence has historically been silicone based prostheses, and more recently revascularised tracheal homografts and allotransplants. Stenting of the trachea has shown poor results. In emergent situations, endobronchial debulking and laser is preferable over stenting as this may prevent primary surgery.

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ORIGINAL ARTICLE

Retrospective Study

Esophageal squamous papilloma lacks clear clinicopathological associations

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Author contributions: Chan CHY designed the study and supervised manuscript preparation; Wu Y acquired study data; Weltman M supervised manuscript preparation; Jideh B acquired study data, reviewed the literature and wrote the paper.

Institutional review board statement: Nepean Hospital institutional review board gave ethics approval of study design and protocol.

Informed consent statement: This was a retrospective study; some of the patients had deceased. Patient consent was not obtained but the presented data are anonymized and the risk of identification is low/nil. The study design was approved by Nepean Hospital institutional review board.

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Abstract

AIM

To determine the prevalence of esophageal squamous papillomas (ESPs) in a tertiary teaching hospital and to assess for any clinical associations, including relations with esophageal squamous cell carcinomas (SCCs).

METHODS

Data from a total of 6962 upper gastrointestinal endoscopies over a five year period were retrospectively obtained and analysed.

RESULTS

ESP was found in sixteen patients (0.23%). Eight (50%) patients had a high body mass index, seven (44%) had history of cigarette smoking. Reflux esophagitis was found in four (25%) patients. All ESPs were solitary with a mean endoscopic size of 3.8 mm and located in the mid to lower esophagus. Human papilloma virus (HPV) was tested in three (19%) patients and was negative. Esophageal SCC was found in seven patients (0.10%) during the same period. None of the specimens were tested for HPV, and none had associated papillomatous changes.

CONCLUSION

ESP is an uncommon tumour with unclear clinical associations and malignant potential.

Key words: Esophagus; Papilloma; Gastroesophageal reflux disease; Human papilloma virus; Squamous cell

carcinoma

Core tip: Esophageal squamous papilloma is a rare endoscopic finding with uncertain clinicopathological associations. They are usually asymptomatic and their aetiology is unknown. A high body mass index and a history of cigarette smoking, both risk factors for gastroesophageal reflux disease, were the most prevalent patient characteristic in our cohort with esophageal squamous papillomas (ESPs), however no definite associations can be established. None of the esophageal squamous cell carcinomas during the same study period progressed from ESP. Long-term longitudinal studies would be valuable to clarify clinical associations and the malignant potential of ESPs in order to establish appropriate management and surveillance strategies.

Jideh B, Weltman M, Wu Y, Chan CHY. Esophageal squamous papilloma lacks clear clinicopathological associations. *World J Clin Cases* 2017; 5(4): 134-139 Available from: URL: http://www.wjgnet.com/2307-8960/full/v5/i4/134.htm DOI: http://dx.doi.org/10.12998/wjcc.v5.i4.134

INTRODUCTION

Esophageal squamous papilloma (ESP) is a rare tumour of the esophagus with a reported prevalence of 0.01% to 0.45%[1-5]. Lesions rarely cause symptoms, and are usually an incidental finding on endoscopy. Typical endoscopic appearance is that of a small, less than 5mm sessile wart-like fleshy nodule (Figure 1) located predominantly in the middle to lower esophagus[1,2]. Larger lesions with a more raised, erythematous appearance have also been described[6]. The aetiology has not yet been established; proposed factors include chronic gastroesophageal reflux disease (GERD), human papilloma virus (HPV) and mucosal trauma[5,7-13]. The clinical associations and malignant potential of these lesions is unknown. Currently, there is no consensus on appropriate management and surveillance strategies for ESPs. In this study we aimed to identify the prevalence of ESPs in an Australian tertiary hospital cohort and to assess for possible clinical associations. We also attempted to assess its association with esophageal squamous cell carcinoma (SCC).

MATERIALS AND METHODS

All patients between June 2010 and March 2015 with ESP and esophageal SCC at a tertiary teaching hospital (Nepean Hospital) were retrospectively identified using the electronic pathology department database. Over this period a total of 6962 upper gastrointestinal endoscopies were performed. Patients were identified and their medical records and endoscopic reports were reviewed and analysed. The clinical information assessed included age, gender, body mass index (BMI), cigarette smoking history and use of acid suppression therapy [proton pump inhibitor (PPI)]. The endoscopic findings comprised the location, size and number of lesions; presence of a hiatus hernia, and presence of reflux esophagitis. Results of HPV testing were noted when performed; histology reports for patients with esophageal SCC during the same period were carefully perused for any papillomatous changes.

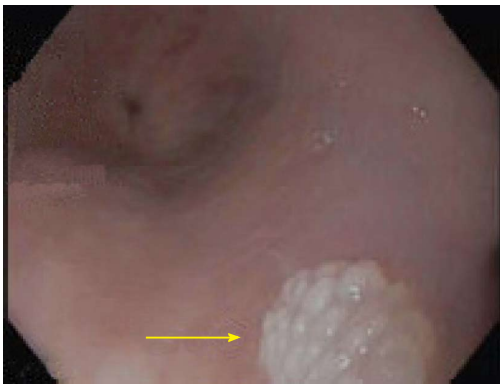

Figure 1 Esophageal squamous papilloma on upper endoscopy. A well demarcated soft wart-like sessile nodule with an estimated endoscopic size of 3 mm.

RESULTS

Among the 6962 upper gastrointestinal endoscopies performed over the study period, sixteen patients were found to have ESPs giving a prevalence of 0.23%. Patient characteristics are summarised in Table 1.The patients with ESPs comprised of ten (62.5%) females with mean age of 52 ± 16 (SD) years (range 33-83 years). Eight (50%) patients were overweight or obese having BMIs between 25-39; seven (44%) patients were cigarette smokers; three (19%) patients were using regular acid suppression therapy (PPIs). The indications for the endoscopic procedure varied with two of the sixteen patients having the procedure for investigation of GERD and one patient for dysphagia. One patient had evidence of a hiatus hernia, which was small. Reflux esophagitis was found in four (25%) of the sixteen patients. All patients had solitary papillomas; mean endoscopic size of lesions was 3.8 ± 3.2 (SD) mm (range 1-12 mm) and the mean size of histological specimens was 2.9 ± 1.5 (SD) mm (range 1-7 mm). All the papillomas were found in the middle to lower esophagus. Seven (44%) of them were biopsied; seven (44%) were removed with a polypectomy snare and details of the remaining two were not documented. Patients that had lesions biopsied did not have a repeat gastroscopy within the same study period for definitive resection of the lesion. Two (13%) patients had repeat endoscopies following endoscopic snare resection within the same study period and there was no evidence of papilloma recurrence. *Helicobacter*

Table 1 Patient characteristics with esophageal squamous papilloma

Patient No.	Age (yr)	Sex (M/F)	Cigarette smoking (Y/N)	BMI	PPI use (Y/N)	Indication for endoscopy	Location of ESP from incisors	No. of ESPs	Endoscopic size of ESP (mm)	Histological size of ESP specimen (mm)	Hiatus hernia (Y/N)	Reflux esophagitis (Y/N)	*Helicobacter pylori* (positive/ negative)	HPV test (positive/ negative)	Method of ESP resection/sampling
1	57	F	Y	20	N	Upper GI bleed	Distal	1	Small	2	N	N	Negative	n/a	n/a
2	83	F	N	19	Y	Dyshpagia	20	1	3	3	N	Y	Negative	n/a	Snare polypectomy
3	66	M	N	24	N	Abdominal pain	32	1	Small	4	N	N	Negative	n/a	Snare polypectomy
4	74	M	N	36	N	Abdominal pain	39	1	Small	5	N	N	n/a	n/a	Hot biopsy
5	60	F	N	34	Y	GERD	33	1	4	3	Y (3 cm)	Y	Negative	n/a	Snare polypectomy
6	39	M	N	30	N	GERD	38	1	3	3	N	Y	Negative	Negative	Snare polypectomy
7	39	F	N	24	N	Bloating	28	1	3	2	N	N	Negative	n/a	Biopsy
8	33	F	N	21	N	Anaemia	27	1	Small	3	N	Y	Negative	n/a	Snare polypectomy
9	49	M	Y	30	N	Abdominal pain, family history CRC	Distal	1	Small	3	N	N	Negative	n/a	n/a
10	37	F	N	24	N	Family history of gastric cancer	32	1	1	1	N	N	Negative	Negative	Biopsy
11	54	F	Y	23	N	Variceal screen	35	1	2	4	N	N	n/a	n/a	Biopsy
12	39	M	Y	34	N	Abdominal pain	39	1	4	2	N	N	Negative	n/a	Biopsy
13	81	F	Y	28	N	Diarrhoea	25	1	Small	2	N	N	Negative	n/a	Biopsy
14	45	M	Y	31	Y	Abdominal pain	Upper third	1	2	2	N	N	Negative	n/a	Snare polypectomy
15	38	F	Y	n/a	N	Bloating, abdominal pain	25	1	n/a	1	n/a	n/a	Negative	n/a	Biopsy
16	41	F	N	27	N	Abdominal pain	35	1	12	7	N	N	Negative	Negative	Snare polypectomy

BMI: Body mass index; PPI: Proton pump inhibitor; CRC: Colorectal cancer; GERD: Gastroesophageal reflux disease; HPV: Human papilloma virus; n/a: Not available; ESP: Esophageal squamous papilloma; M: Male; F: Female; Y: Yes; N: No.

pylori was not evident on microscopy in any of the patients. HPV testing was performed on only three patient and all were negative.

Seven patients were observed to have esophageal SCC in the same period, giving a prevalence of 0.10%. Patient characteristics are summarised in Table 2. The group comprised of five (71%) females and with mean age of 71 ± 15 (SD) years (range 50-92 years). Two (29%) patients were overweight, one (14%) patient was underweight with a BMI of 18, and the remaining four (57%) patients had BMIs within healthy range. Three (43%) patients were cigarette smokers. HPV was not tested on any of the specimens. There were no reported papillomatous changes on histological examination.

DISCUSSION

In our study the prevalence of ESPs was 0.23% which is consistent with previously published studies[1-5]. The majority of the patients were middle-aged also similar to previous studies in the literature. The female predominance in our cohort is an inconsistent observation compared to previous reports on ESPs[1,7,8,14]. Although GERD has been postulated to be a factor in the aetiology of ESP[5,9,15], only two (12.5%) of our study patients underwent upper endoscopy for GERD. However, we cannot ascertain with any certainty that the other patients did not have GERD. This is supported by the finding of reflux esophagitis in two (12.5%) patients who had the procedure for an indication other than GERD (one for the investigation of anaemia and the other for dysphagia, Table 1).

A high BMI was the most prevalent of the assessed patient characteristics in our study with 50% of patients having a BMI in the overweight-obese range. An association between BMI and ESPs has not been previously demonstrated. However, an elevated BMI is an established risk factor for GERD[16]. The second most prevalent clinical characteristic in the studied patients was a history of cigarette smoking found in seven (44%) patients. Cigarette smoking was not found to be associated with ESP in a previous study[14], but similar to a high BMI, cigarette smoking is a risk factor for the development of GERD[17]. Hiatus hernia is another risk factor for GERD which was observed in one (6.25%) patient in our cohort and it was small-sized.

Table 2 Patient characteristics with esophageal squamous cell carcinoma

Patient No.	Age (yr)	Sex (M/F)	Cigarette smoking (Y/N)	BMI	Indication for endoscopy	Location of SCC from incisors (cm)	HPV test (positive/ negative)	Papillomatous changes on histopathology	Management of SCC
1	50	M	Y	21	Dysphagia, B/G achalasia	40	n/a	No	Ivor-Lewis esophagectomy
2	92	F	N	29	Dysphagia	32	n/a	No	Palliation
3	62	F	Y	25	n/a	Middle	n/a	No	Ivor-Lewis esophagectomy
4	86	F	N	20	Dysphagia	15	n/a	No	Radiation therapy, Palliation
5	76	F	N	20	n/a	Middle	n/a	No	Neoadjuvant Chemo-Radiation, Ivor-Lewis esophagectomy
6	59	F	N	18	n/a	Middle	n/a	No	Ivor-Lewis esophagectomy, Chemotherapy, Palliation
7	72	M	Y	20	Dyspnoea. B/G achalasia	Distal	n/a	No	Radiation therapy, PEG tube feeding, Palliation

BMI: Body mass index; HPV: Human papilloma virus; SCC: Squamous cell carcinoma; n/a: Not available; M: Male; F: Female; Y: Yes; N: No.

The mean size and location of ESPs were consistent with previous observations[1,2]. They were all solitary and appeared as rounded well delineated sessile wart-like lesions (Figure 1) as traditionally described. Multiple lesions have been observed in some studies[18-20].

ESPs were not all removed with therapeutic intent, which is the general recommendation, despite the ambiguity about their malignant potential[21]. Histological diagnosis remains important due to the endoscopic resemblance to other pathologies including glycogenic acanthosis, verrucoid border of SCC, and verrucous carcinoma[2,21]. Case reports of alternative ablative techniques including radiofrequency ablation have been described[22]. Recurrence after definitive endoscopic removal is thought to be low[2]. This was true for the two patients in our series that had repeat gastroscopies within the same study period and no evidence of papilloma recurrent was found. It is unclear whether other lesions not endoscopically removed were not followed due to lack of well-established management and surveillance guidelines.

Three patients in our cohort had testing for HPV (serotype 16) in the ESP specimen and the results were all negative. Although HPV infection is a proposed aetiological factor since the demonstration of HPV antigens in ESPs[23], the extent of the contribution is controversial and most reported lesions, similar to our study, are found in the absence of HPV[2,13,14,24,25]. *Helicobacter pylori* has not been proposed to have any association in any of the previous ESP studies, and in our cohort the bacterium was not detected on microscopy in any of the patients.

The prevalence of esophageal SCC in this study was 0.10%. Most patients (71%) were females and generally older than the cohort with ESPs years. The risk of esophageal SCC, unlike esophageal adenocarcinomas, is not generally increased with obesity[26] and this was true in our cohort with five (71%) patients having BMIs within healthy range. Cigarette smoking is an established risk factor for esophageal SCC and in our group three (43%) patients had a history of cigarette smoking.

HPV was not tested in any of the esophageal SCC specimens in our cohort, neither were any papillomatous changes reported. Whilst HPV infection and papilloma formation are considered a precursor in cervical and oropharyngeal squamous carcinoma[27,28], the relation between HPV and esophageal SCC is controversial with conflicting results across multiple studies. Several systematic reviews and meta-analyses have addressed this relation, two of the most recent by Li *et al*[29] and who Petrick *et al*[30] concluded that further studies are needed to clarify the association.

This study has several limitations. The study is a retrospective assessment of results which can lead to the possibility of inaccurate and incomplete data. It was performed in a single, tertiary-care institution which can introduce a selection bias. Most patients with ESP did not have follow-up gastroscopies to assess for ESP clearance or recurrence. Finally, the analysis of results is largely descriptive given the low prevalence and small absolute numbers of patients with ESPs making it difficult to draw conclusions on any clinical associations.

In summary, ESPs remains a rare endoscopic finding with uncertain clinicopathological associations. They are usually asymptomatic and their aetiology is unknown. Whilst a high BMI and a history of cigarette smoking, both risk factors for GERD, were the most prevalent patient characteristic in our cohort with ESP, no definite associations can be established. None of the esophageal SCCs during the same study period progressed from ESP. Long-term longitudinal studies would be valuable to clarify clinical associations and the malignant potential of ESPs in order to establish appropriate management and surveillance strategies.

COMMENTS

Background

Esophageal squamous papilloma (ESP) is a rare tumour with a reported prevalence of 0.01% to 0.45%. It is usually asymptomatic and discovered incidentally on upper endoscopy. The aetiology, clinical associations along with its malignant potential are unknown. The aim of this study was to determine the prevalence of ESPs in a tertiary teaching hospital and to assess for any clinical associations, including relations with esophageal squamous cell carcinomas (SCCs).

Research frontiers

There are limited studies on ESPs. Gastroesophageal reflux disease (GERD),

human papilloma virus (HPV) and mucosal trauma are proposed aetiological factors. No studies have assessed associations between ESPs and SCCs.

Innovations and breakthroughs

This study identified certain clinical features to be prevalent in patients with ESP including high body mass index and cigarette smoking, which have not been previously described. Also, the SCCs in the study period did not seem to progress from ESPs which may suggest ESP are benign.

Applications

This study contributes to the body of hypotheses surrounding ESP. Large longitudinal studies are required to help clarity clinicopathological associations of ESPs and their malignancy potential in order to establish appropriate management and surveillance strategies.

Peer-review

The authors aimed to identify the prevalence of ESPs in an Australian tertiary hospital cohort and to assess for possible clinical associations and to assess its association with esophageal SCC whose large data from a total of 6962 upper gastrointestinal endoscopies. Well written, well balanced.

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ORIGINAL ARTICLE

Retrospective Study

Efficacy of intragastric balloon on weight reduction: Saudi perspective

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Abstract

AIM

To evaluate the safety and efficacy of intragastric balloon (IGB) in weight reduction in obese patients referred to a tertiary hospital in the Kingdom of Saudi Arabia.

METHODS

Three hundred and one consecutive obese individuals, who underwent IGB placement during January 2009 to May 2015, were analyzed. The subjects aged 18 to 60 years and had a minimum body mass index (BMI) of 27 kg/m^2. The IGB was placed under conscious sedation and kept for 6 mo. Anthropometric measurements were recorded during and after 6 mo of IGB removal.

RESULTS

The body weight, excess body weight, and BMI were significantly reduced at the time of IGB removal and 6 mo later. Body weight loss > 10% was achieved in 224 subjects at removal of IGB. End of treatment success and long-term success were both significantly observed in women (70 *vs* 11) (71 *vs* 12.5) respectively. Excess BMI loss was significantly higher in subjects retaining the IGB for over 6 mo both at the removal [43.44 ± 19.46 (n = 221) *vs* 55.60 ± 28.69 (n = 80); t = 4.19, P = 0.0001] as well as at the end of 6 mo' follow-up [46.57 ± 24.89 (n = 221) *vs* 63.52 ± 31.08 (n = 80); t = 4.87, P = 0.0001]. Within 3 d of IGB placement, two subjects developed pancreatitis and one subject developed cardiac arrhythmia. Intestinal obstruction due to displacement of IGB occurred in two subjects. All

these subjects recovered uneventfully after immediate removal of the IGB.

CONCLUSION

IGB was effective in our cohorts. The observed weight reduction was maintained for at least 6 mo post IGB removal. IGB placement was safe with a satisfactory tolerance rate.

Key words: Weight reduction; Intragastric balloon; Saudi

Core tip: Intragastric balloon (IGB) is a minimally invasive option for weight reduction. Several studies have demonstrated its superiority to lifestyle changes in reducing the morbidity and mortality associated with morbid obesity. This study evaluated the safety and efficacy of Medsil IGB in weight reduction of patients referred for weight reduction to a tertiary center in the Kingdom of Saudi Arabia. Endoscopic placement and keeping the Medsil IGB in situ for six months was proven to be safe, well tolerated and very effective for short and long term weight loss.

Almeghaiseeb ES, Ashraf MF, Alamro RA, Almasoud AO, Alrobayan AA. Efficacy of intragastric balloon on weight reduction: Saudi perspective. *World J Clin Cases* 2017; 5(4): 140-147 Available from: URL: http://www.wjgnet.com/2307-8960/full/v5/i4/140.htm DOI: http://dx.doi.org/10.12998/wjcc.v5.i4.140

INTRODUCTION

Obesity, a medical condition in which body fat is accumulated in excess leading to severe negative health effects including reduced lifespan, affects an estimated 700 million people worldwide[1]. This pandemic health problem is much more serious threat to public health even when compared to alcohol consumption or tobacco smoking. Obesity decreases life expectancy by 6 to 7 years[2], while a body mass index (BMI) of 30-35 kg/m^2 and > 40 kg/m^2 reduces life expectancy by 2 to 4 years and by 10 years respectively[3]. Some estimates have even predicted that a BMI of > 40 reduces life expectancy by almost 20 years[4]. In addition to decline in the lifespan, this preventable cause of death also leads to quality of life deterioration owing to severe cardiologic, respiratory, dermatological, gastrointestinal, urinary, reproductive and psychiatric complications[5]. A recent estimate published in 2013 has put the overall prevalence of obesity at 28.7% (body mass index $\geqslant$ 30 kg/m^2) in the Kingdom of Saudi Arabia, with women much more prone than men (33.5% *vs* 24.1%)[6].

Advanced cases of obesity require surgical interventions with drastic lifestyle modifications. Alternatively, mild to moderately obese subjects can achieve 5%-10% weight loss through exercise and dietary changes[7]. However, the weight gain recurs at high rates on cessation of these weight loss programs[8]. Further, pharmacological agents have not been found to be any better than dietary and exercise programs. The therapeutic or lifestyle management of obesity is a long-term and arduous undertaking. Literature shows that long-term treatments, both dietary regimens and weight-loss programs following pharmacotherapy remain largely ineffective[9]. Further, conservative treatment is clearly ineffective in morbid obesity (BMI $\geqslant$ 40 kg/m^2)[10], while bariatric surgery remains the only option with promising long-term results. However, subjects who are unwilling to consent for or do not qualify for the bariatric surgery end up having intragastric balloon as the best possible alternative[11].

These factors have fostered a spurt in interest in the utility of intragastric balloon (IGB) to achieve weight loss in excess of 10%. While earlier studies have documented the utility of various intragastric balloons in Saudi subjects[12,13], data on newer variants of balloons is lacking. Hence, this study is an attempt to evaluate the end of treatment success rates (ETS) and long-term treatment success rates (LTS) for recently introduced, GOST R certified intragastric balloon MEDSIL® in obese patients referred to a tertiary health clinic in the Kingdom of Saudi Arabia.

MATERIALS AND METHODS

Subjects

Three hundred and one subjects, consecutively opting for IGB therapy for weight loss at The Prince Sultan Military Medical City Hospital, Kingdom of Saudi Arabia between January 2009 and May 2015 were included in the study. Both men and women aged 14 to 65 years with a minimum BMI of 27 kg/m^2 and medically free from or with one or two of the comorbidities namely diabetes mellitus, hypertension, bronchial asthma, back pain, or Knee joint complains were included. In general, patients rated only up to ASA class Ⅱ were preferred. Further, subjects without active endocrine diseases and ability to tolerate the procedure were selected for the procedure. Patients classified into $\geqslant$ ASA category were excluded from the procedure. Baseline characteristics of the study subjects are presented in Table 1.

All the subjects underwent a routine clinical examination where information on anthropometrics and medical history was collected. Weight and height was measured with patients wearing no shoes and light clothing. Fasting blood sample was collected in the morning for the estimation of blood glucose concentration. Subsequent to the clinical evaluation of these results and after obtaining an informed written consent, MEDSIL® IGB was placed in the stomach through endoscopy.

Intragastric balloon implantation and removal

All the subjects were treated with MEDSIL® IGB, silicon based saline filled bioenetric intragastric balloon (BIB) with a maximal volume of 700 mL (CSC MEDSIL, Russia). Patients were explained all the risks including perforation,

Table 1 Baseline characteristics of the subjects (n = 301) included for intragastric balloon therapy

Characteristics	Average (mean ± SD)[1]	Range
Age (yr)	34.34 ± 10.38	14-65
Female (%)	67	
Body weight (kg)	94.73 ± 16.38	67-203
Height (cm)	161.52 ± 6.11	150-179
BMI (kg/m^2)	36.24 ± 5.24	27.10-70.24
Excess body weight (ideal BMI 25)	29.42 ± 14.61	5.6-130.8
Fasting blood glucose (mg/dL)	100.15 ± 29.26	69-240

[1]Applicable to all the values except % females. BMI: Body mass index.

bleeding, infection and adverse effects to the medicine, as well as the benefits and alternatives to the procedure prior to obtaining the informed written consent. All the patients understood the details and stated so.

For insertion of balloon, the patient was connected to monitoring devices and placed in left lateral position. In 297 patients, the device was implanted under procedural sedation and analgesia, with midazolam and fentanyl or pethidine. In 4 patients, the device implantation was done by inducing anesthesia using midazolam and intravenous propofol. Oxygen was provided continuously through a nasal cannula. Intravenous medications were administered through an indwelling cannula. After adequate conscious sedation was achieved, the patient was intubated and the endoscope was advanced under direct visualization to the duodenum.

Endoscope was withdrawn after complete examination for the presence of grossly anatomical contraindications. Balloon was inserted into the oral cavity and pushed into the stomach with a trocar followed by re-introduction of the endoscope. Under direct visualization, balloon was adjusted for proper placement followed by retraction of the push trocar wire. Balloon was then inflated with 400 mL to 700 mL of saline mixed with methylene blue. On achieving the desired inflation, the balloon catheter was gently pulled out leaving the balloon in stomach. The scope was gently retracted with careful examination of the colour, texture, anatomy, and integrity of the mucosa on the way out. The patient was subsequently transferred to the recovery area for observation.

The IGB was removed on completion of 6 mo, with the duration extending by one or more months in some subjects owing to various reasons. Anthropometric measurements were recorded during and after 6 mo of IGB removal. Overnight fasting blood specimen was collected at removal for the estimation of blood concentration. Patients were also provided with walk in follow-ups/clinic appointments on quarterly basis, but two third of the patients were seen on the fixed appointment only.

Similar protocol was followed for the removal of the balloon. After achieving adequate conscious sedation, the patient was intubated and the scope was advanced under direct visualization to the Stomach. After confirming absence of food or organic particles, an aspiration needle was inserted into the balloon followed by complete withdrawal of the fluid. The fully deflated balloon was withdrawn using a toothed forceps along the scope followed by routine follow up procedures.

Patients remained on their regular food without prescription of a hypocaloric diet. Post-insertion fasting blood glucose level estimation were scheduled and followed up to ensure that it was done as soon as treatment duration is completed.

Measurements and statistics

Weight loss variables like body weight (kg), BMI, body weight loss (BWL%) and excess BMI loss (EBL%) were measured at baseline, and during and after 6 mo of IGB removal. A BWL value of > 10% at the time of IGB removal and after 6 mo of IGB removal was considered an ETS and LTS respectively. EBL% was calculated using the formula [(Baseline BMI-Current BMI)/(Baseline BMI-25)] × 100. All the descriptive data are expressed as mean ± SD. Paired *t*-test was used to compare baseline and outcome variables for individuals, whereas unpaired *t*-test was used for gender and age based comparisons. Fisher's exact test was used to evaluate the occurrence of number of patients with BWL% > 10 between groups. The association of initial BMI and age with BWL% and EBL% was measured through Pearson correlation coefficient. A two-tailed P value of < 0.05 was considered statistically significant. Statistical Package for the Social Sciences (SPSS v. 18) was used for all the statistical tests.

RESULTS

Apart from the expected post procedure symptoms like nausea, vomiting and upper abdominal discomfort, and no serious complications were observed during recovery from IGB placement. Balloon was removed a day to week earlier than 6 mo in 20 subjects, at the completion of 6 mo in 201 subjects and after a week to few months over 6 mo in 80 subjects. In addition to the removal of IGB in 221 subjects owing to completion of the treatment duration, balloons were removed due to numerous other reasons as listed in the Table 2.

At the end of treatment, body weight, excess body weight, and BMI were significantly lowered as compared to initial measurements (Table 3 and Figure 1). The ETS rate, represented by number of patients with BWL% of > 10 was 74% (224 of 302 subjects). The fasting blood glucose remained statistically similar to the initial measurements. At the end of 6 mo after IGB removal, the body weight, excess body weight and BMI still remained significantly lower (Table 3). The BWL and BMI loss continued during post IGB removal phase, resulting in significantly higher measurements after 6 mo of removal as compared to the measurements taken during IGB removal. The LTS rates remained similar to ETS with just 2 more subjects added to the > 10% weight loss by the end of 6 mo IGB post-removal.

Statistical sub-analysis revealed different outcome

Table 2 Reasons for removal of the intragastric balloon

Reason for removal	No.	Reason for removal	No.
TDC	221	Intolerance	4
Abdominal pain	1	Vomition	1
Miscellaneous	2	TDC and intolerance	1
TDC and abdominal pain	19	TDC and vomition	10
TDC and discomfort	24	TDC and other reasons	2
Intolerance and abdominal pain	4	Intolerance and vomition	2
Intolerance and other reason	1	Abdominal pain and vomition	3
Abdominal pain and other reason	1	Discomfort and other reason	1
TDC, abdominal pain and vomition	1	Intolerance, abdominal pain and vomition	2
TDC, abdominal pain and discomfort	1		

Abdominal discomfort was a state of tolerable uneasiness without pain; Abdominal pain involved a state of colic; Vomition was a state of uncontrolled expulsion of gastric contents; Intolerance was a state wherein subjects experienced a mix of side effects and were unable to tolerate. Other reasons were a variety of situations that did not show a consistent pattern. TDC: Treatment duration complete.

Table 3 Weight related measurements at intragastric balloon removal and after 6 mo of removal

Characteristics	At removal (mean ± SD)[a]	After 6 mo of removal
Body weight (kg) (Min-Max)	82.25 ± 14.73[b] (55-181)	81.06 ± 14.84[b] (53-181)
BWL (kg) (Min-Max)	12.48 ± 5.16 (0-30)	13.67 ± 6.65[b] (-1-42)
BWL (%) (Min-Max)	13.08 ± 4.81 (0-35.29)	14.30 ± 6.12[b] (-0.85-32.14)
No. of patients with BWL% > 10	224	226
Excess body weight (ideal BMI 25) (Min-Max)	16.93 ± 13.44[b] (-10.61-108.75)	15.74 ± 13.73[b] (-12.72-107.04)
BMI (kg/m^2) (Min-Max)	31.49 ± 4.88[b] (20.96-62.63)	31.04 ± 5.01[b] (20.44-63.14)
BMI loss (kg/m^2) (Min-Max)	4.75 ± 1.87 (0-11.43)	5.20 ± 2.40[b] (-0.36-15.43)
EBMIL% (Min-Max)	46.67 ± 22.88 (0-161.09)	51.07 ± 27.66[b] (-2.12-195.53)
Fasting blood glucose (mg/dL) (Min-Max)	98.67 ± 20.28 (71-187)	--

[a]$P < 0.05$ *vs* [b]$P < 0.001$. BWL: Body weight loss; BMI: Body mass index; EBMIL: Excess BMI loss.

Table 4 Association of gender and exercise on end of treatment success and long term success

Characteristics	At removal (mean ± SD)[a]				After 6 mo of removal	
	Gender		Exercise		Gender	
	Male (n = 72)	Female (n = 229)	Yes (n = 131)	No (n = 170)	Male (n = 72)	Female (n = 229)
BWL (%)	14.99 ± 4.72	12.48 ± 4.68[b]	15.22 ± 4.81	11.43 ± 4.11[b]	16.71 ± 6.72	13.53 ± 5.72[b]
Number of patients with BWL% > 10	8	160[b]	113	111[b]	9	163[b]
Body mass index loss (kg/m^2)	5.56 ± 1.92	4.49 ± 1.78[b]	5.47 ± 1.85	4.19 ± 1.68[b]	6.19 ± 2.72	4.89 ± 2.20[b]
EBMIL%	51.61 ± 24.75	45.12 ± 22.09[a]	55.66 ± 25.12	39.74 ± 18.24[b]	57.48 ± 30.27	49.06 ± 26.53[a]
Fasting blood glucose reduction (%)	-0.59 ± 13.29	-0.92 ± 13.14	-0.37 ± 13.10	-1.25 ± 13.22	--	--

[a]$P < 0.05$ *vs* [b]$P < 0.001$. ETS: End of treatment success; LTS: Long term success; BWL: Body weight loss; EBMIL: Excess body mass index loss.

when patients where compared according to gender and exercise habits (Table 4). The BWL%, BMI loss, and excess BMI loss (EBMIL%) was significantly lesser in women at the end of treatment as well as after 6 mo of removal. However, significantly higher proportion of women achieved ETS (70 *vs* 11) and LTS (71 *vs* 12.5) rates. As expected, BWL%, BMI loss and EBMIL% was significantly higher in exercising cohort at the end of treatment. Fasting blood glucose level changes remained statistically similar with gender and exercise habit.

Age was not correlated with initial BMI or EMBIL% at initial or later phases of the study (Table 5). However, initial BMI was strongly correlated with BMI as well as EBMIL% measured at IGB removal as well as 6 mo after removal.

The duration of IGB removal was also important in determining the EBMIL% (Figure 2). The EBMIL% was significantly higher in subjects retaining the IGB for over 6 mo both at the removal [43.44 ± 19.46 (n = 221) *vs* 55.60 ± 28.69 (n = 80); t = 4.19, P = 0.0001] as well as at the end of 6 mo follow-up [46.57 ± 24.89 (n = 221) *vs* 63.52 ± 31.08 (n = 80); t = 4.87, P = 0.0001]. Duration of the IGB was also important in determining adverse complications in some of the individuals as outlined below.

In addition to the routine adverse events associated with IGB therapy, some of the patients experience unusual complication of spontaneous deflation and passage out of the digestive system. It must be noted that most of these patients had the balloon beyond the treatment duration. Out of five such cases, 2 women who had undergone IGB insertion at other institute, consulted us for removal after

Table 5 Correlation of age and initial body mass index with weight-linked parameters

	Age	Initial BMI	BMI at removal	EBMIL% at removal	BMI after 6 mo of removal	EBMIL% after 6 mo of removal
Age	1	0.074	0.082	-0.108	0.082	-0.108
Initial BMI	0.074	1	0.934[b]	-0.413[b]	0.891[b]	-0.376[b]

Values are Pearson Correlation Coefficient (r); [b]$P < 0.01$. BMI: Body mass index; EBMIL: Excess BMI loss.

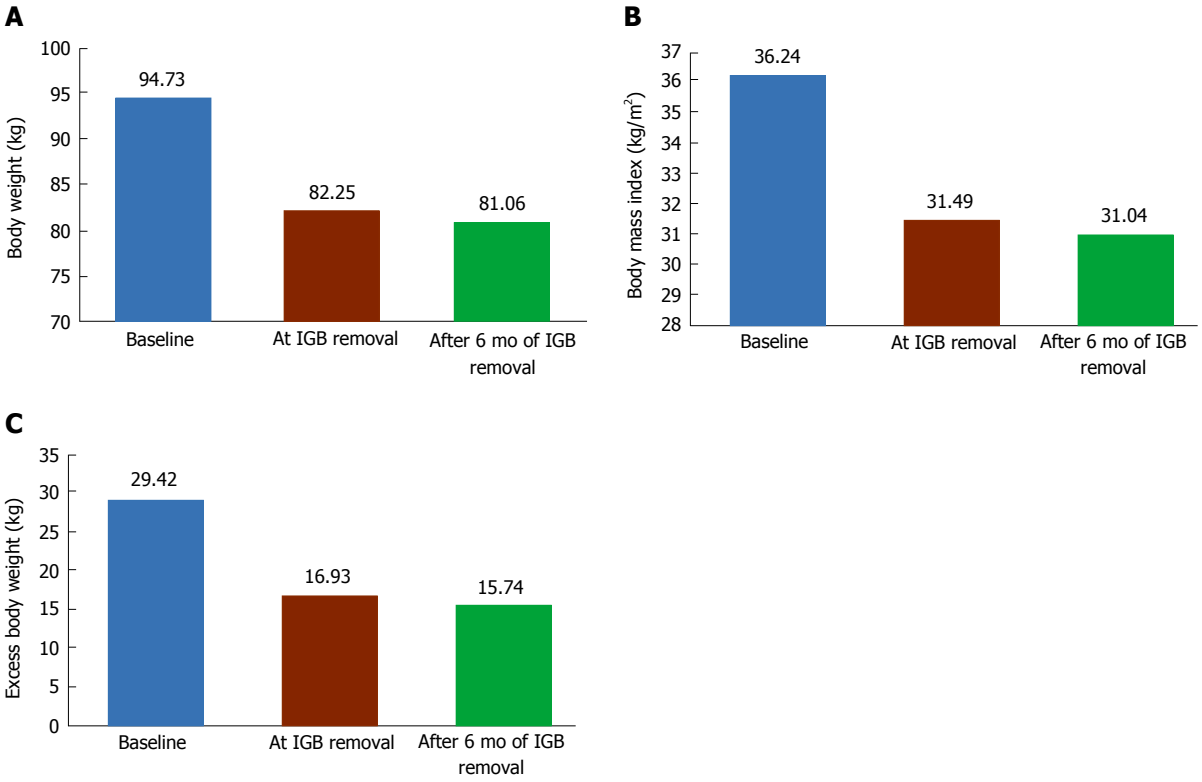

Figure 1 From baseline to 6 mo follow-up. A: Body weight changes. Both the measurements were significantly lower than baseline values; B: Body mass index changes. Both the measurements were lower than baseline values; C: Excess body weight changes. Both the measurements were significantly than baseline values. IGB: Intragastric balloon.

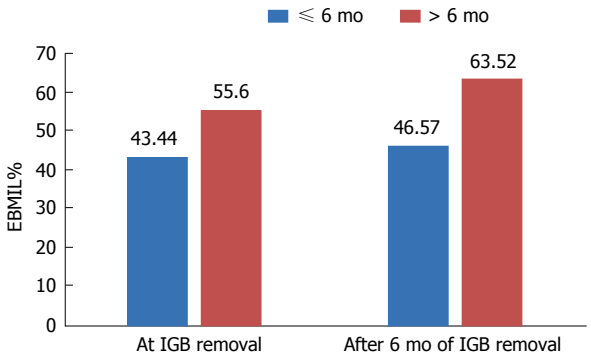

Figure 2 Influence of duration at intragastric balloon removal excess body mass index loss%. The red bars are statistically larger than bars. IGB: Intragastric balloon. IGB: Intragastric balloon.

1 year of insertion and three women operated at our clinic approached for removal at 8 mo. These five women underwent gastroscopy using X-ray and CT scan, which failed to reveal any traces of the IGB in the GI tract. The only plausible explanation for this is spontaneous rupture and excretion of the IGB without any knowledge of these patients.

One woman and one man developed clinical and biochemical pancreatitis on third day post IGB insertion. These symptoms subsided completely after immediate removal of IGB. One man developed arrhythmia 2 d post IGB insertion and recovered fully following immediate removal of IGB.

A woman with IGB got pregnant before the due date of removal and approached us at the end of first trimester with symptoms correlating intestinal obstruction. Esophagogastroduodenoscopy failed to detect balloon in the stomach. Imaging showed that balloon was lodged in middle of the jejunum. This IGB was surgically removed. The woman completed pregnancy without complications and gave birth to a normal offspring. Another man developed intestinal obstruction due to IGB dislodgement 7 mo post insertion that was detected through abdominal CT scan. This man recovered completely and uneventfully

Table 6 Studies reporting outcomes in body composition after placement of intragastric balloon

Study	Weight loss at removal (duration of placement in months)	Weight loss at follow-up (duration of follow-up in months)
Mathus-Vliegen *et al*[26], 2005	21.3 (12)	12.6 (12)
Herve *et al*[27], 2005	12.0 (6)	8.6 (12)
Doldi *et al*[28], 2004	15.5 (6)	-1.3 (14)
Melissas *et al*[29], 2006	41.6% EWL (6)	23.9% EWL (6-30)
Angrisani *et al*[30], 2006	32.9% EWL (6)	27.1% EWL
Ganesh *et al*[31], 2007	4.4 (6)	1.5 (6-12)
Ohta *et al*[32], 2009	12 (6)	6.4 (12)
Gümürdülü *et al*[33], 2013	12.4 (6)	9.7 (6)
Bužga *et al*[20], 2014	18.4 (6)	-
Present study	13.08 (6)	14.30 (6)

Weight in kilograms; EWL: Excess weight loss.

after laparoscopic surgery.

DISCUSSION

Subsequent to their introduction in 1982[14], numerous studies showed that IGBs are an effective and low cost method to achieve temporary weight loss in morbidly obese individuals, leading to significant decrease in morbidity and mortality rates[15,16]. The promising outcomes have fuelled the development of numerous fluid or air filled IGBs over the years. The newer variants are becoming much less invasive compared to surgical interventions in morbid obesity, though latter options remain primary approach in super-obese patients with a BMI over 50[17]. IGBs are also employed as a preoperative tool in bariatric surgery as its weight reducing effects significantly reduces the mortality, morbidity and risks associated with this invasive surgery[18].

Variety of intragastric balloons have been studied in numerous studies for safety and efficacy in Saudi subjects[12,19]. However, the newer variant of intragastric balloon Medsil remains to be tested in this population. In this study, we tested the end of the treatment and long term success rates for this device in a large Saudi cohort. Similar to a 2014 report on Czech subjects[20], these balloons were well tolerated in Saudi subjects analysed in this study.

This study demonstrated a clear benefit of Medsil balloon on body composition, as six mo placement of the balloon lead to significant reduction in body weight. The mean BMI loss (4.75 and 5.20 kg/m^2) and BWL (13.08 and 14.30 kg) at IGB removal and after six months of removal were comparable to both the results of using other balloons or Medsil balloons. These studies have reported a BMI loss of 5.7-6.7 kg/m^2 and weight loss of 14.7-17.8 kg[16,21,22], with one study using the same device reporting a BMI loss of 5.5 kg/m^2 and weight loss of 18.4 kg[20]. Table 6 presents a comparison showing the similarities of outcomes in body composition reported by earlier studies. It must be noted that the BMI loss which corresponds to weight-loss was on the higher end as compared to other studies after one year of completion of the treatment.

Two reviews have extensively evaluated the weight loss due to IGBs. Dumonceau[21] 2008 analysed 4877 patients from 30 studies and recorded a mean weight loss of 17.8 kg (or a BMI loss of 4-9 kg/m^2). Another systematic review reported similar outcomes and revealed that, combined with lifestyle changes, IGBs provide an effective means for achieving a significant temporary weight loss, though the long term outcomes remain yet to be understood[16]. Our results of a significant weight loss and a large number of patients achieving and maintaining > 10% BWL from the IGB removal to follow-up after 6 mo, clearly suggests that long term results can be achieved through this method. In addition to the balloon, initial BMI, adherence to the lifestyle changes and patients level of motivation are highly likely to play an important role in achieving long term results.

Bioenetric intragastric balloons, which are now known as Orbera Intragastric Balloon (Apollo Endosurgery, Austin, TX, United States) are the most commonly used balloons. A comparison with the existing literature showed that BWL was less than expected, however not too less (Table 7).

The number of individuals achieving > 10% BWL increased from 224 to 226 from balloon removal to at 6 mo follow-up. This amounts to an increase in the number of patients achieving > 10% BWL during follow-up. These results are highly impressive as two of the earlier studies have showed that only 48%[23] or 55%[24] of the patients went on to continue losing weight from balloon removal to follow-up at 1 year. Our study results are very promising in this aspect.

The fasting blood glucose level remained statistically similar both during balloon removal as well as after 6 mo of follow-up. Bužga *et al*[20] 2014 also reported a similar result, though they demonstrated a positive effect of the balloon on glucose tolerance. On the contrary, earlier studies by Mathus-Vliegen and Konopko-Zubrycka have demonstrated a statistically significant reduction in fasting blood glucose levels through intragastric balloons[11,24]. These contradictory findings remain to be evaluated by meta-analysis to reveal the actual association.

Our study, though of higher strength due to large sample size, had a few limitations. A follow-up period of more than six months (at least 1 year) including tracking of comorbidities along with body conversion parameters would have been more insightful. The evaluation of fasting blood glucose levels could have been more meaningful if glucose tolerance and glycated hemoglobin levels were also included. Compared to earlier report of maintenance of > 10% weight loss in about 25% of patients for almost 30 mo[25], 75% of the subjects who achieved this result after 6 mo follow-up in our study seem to be responding much better. Looking at the similarities of BIB and Medsil balloons, it is highly likely that our subjects will be able to maintain weight loss for long term. However, it must be noted that our study provides the first report on the follow-up parameters for

Table 7 Comparison of weight-loss with other types of intragastric balloons

Balloon	Type (volume)	Material	Weight loss (EOT in months)	Ref.
Medsil BIB	Fluid-supplied (400-700 mL saline)	Silicone	12.48 ± 5.16 kg (6 mo)	This study
Orbera (Apollo Endosurgery)	Fluid-supplied (400-700 mL saline)	Silicone	16.9 ± 0.9 kg (6 mo)	Gaur *et al*[34], 2015
The Elipse™ (Allurion Technologies)	Fluid-supplied (450-550 mL filling fluid)	NA	2.4 kg (6 wk)	Machytka *et al*[35], 2016
ReShape Duo® Integrated DualBalloon System (ReShape medical)	Fluid-supplied (900 mL; 450 mLX2 saline)	Silicone	25.1 ± 1.6% EWL (6 mo)	Ponce *et al*[36], 2015
Spatz Adjustable Balloon system (Spatz FGIA)	Fluid-supplied (400-600 mL saline)	Silicone	24 kg (at 12 mo)	Brooks *et al*[37], 2014
Heliosphere BAG® (Helioscopie)	Air-supplied (950 mL air)	Polyurethane and silicone	16 ± 7 kg (6 mo)	Giardiello *et al*[38], 2012
Obalon® Gastric Balloon (Obalon Therapeutics)	Air-supplied (250 mL air, nitrogen)	NA	5 kg (12 wk)	Mion *et al*[39], 2013

EOT: End of treatment; EWL: Excess weight loss; NA: Not available; BIB: Bioenetric intragastric balloon.

Medsil balloons.

In conclusion, it could be concluded that Medsil intragastric balloons are safe and effective for Saudi subjects and more than three fourth of the subjects can be expected to achieve long term weight loss.

COMMENTS

Background

Obesity is a major pan-endemic health problem in the Kingdom of Saudi Arabia affecting about 30% of the population. Literature shows that dietary regimens and weight-loss programs following pharmacotherapy remain largely ineffective. Bariatric surgery is the most effective long term option, however the majority are either reluctant to undergo surgery or do not qualify for medical reasons.

Research frontiers

Intragastric balloons are of proven benefit as an alternative or a bridge to surgery, however the evidence for its utility particularly the newer version such as the intragastric balloon (IGB) MEDSIL® in the Kingdom of Saudi Arabia is lacking.

Innovations and breakthroughs

This study is an attempt to evaluate its long-term treatment success rate in obese patients referred to a tertiary health clinic in the Kingdom of Saudi Arabia. Endoscopic placement and keeping the Medsil IGB in situ for six months was proven to be safe, well tolerated and very effective for short and long term weight loss.

Applications

The intragastric balloons are well tolerated and are effective in weight reduction.

Peer-review

It is a retrospective study but of a very big cohort and the IGB is a new commercialized one. It is a well done paper and the language is good too.

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CASE REPORT

Incidental echocardiographic finding: Fractured inferior vena cava filter

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Abstract

Inferior vena cava filters have gained increasing popularity in recent decades and knowledge on rare complications becomes vital to practicing physicians. A 30-year-old African American male with diabetes mellitus, hypertension, end-stage renal disease, history of deep venous thrombosis and placement of venacaval filter who was seen in the cardiology clinic for cardiac risks stratification prior to renal transplant. Patient denied any cardiac symptoms. A transthoracic echocardiogram was performed and showed two linear echoes bright densities in the right atrium and right ventricle embedded which was later found to be fractured filter struts by computed tomography. We discuss the various outcomes associated with non-retrieval of retrievable inferior vena cava filters.

Key words: Inferior vena cava filter; Fractured inferior vena cava filter; Cardiac foreign body; Metal in heart; Incidental echocardiographic finding

Core tip: Retrievable vena cava filters as indicated by the name, is temporary and should be retrieved timely. However noncompliance to follow-up and retrieval has been associated with numerous complications which could also be life threatening in extreme cases. We are writing this case with the intent to enlighten physicians on various types of available filters, complications associated with it and the challenges associated with delayed retrieval of filters. This case report also emphasizes the challenges associated with delayed retrieval of the filters and the management of the complications associated with inferior vena cava filters.

Sivasambu B, Kabirdas D, Movahed A. Incidental echocardiographic finding: Fractured inferior vena cava filter. *World J Clin Cases* 2017; 5(4): 148-152 Available from: URL: http://www.wjgnet.com/2307-8960/full/v5/i4/148.htm DOI: http://dx.doi.org/10.12998/wjcc.v5.i4.148

INTRODUCTION

Intracardiac foreign bodies have been described in the literature with the first case described in 1954. Various post traumatic and iatrogenic cardiac foreign bodies have been implicated with catheters fragments, needles, pacemaker electrodes, and stents being the commonest. We describe an asymptomatic patient who was found to have an intra cardiac foreign body on a transthoracic echocardiogram done for preoperative evaluation for renal transplant. On further evaluation it was confirmed as inferior vena cava (IVC) filter fragments.

Vena cava filters have gained increasing popularity in recent decades with the simplicity of the procedure, and the expansion of the indications including prophylactic insertion especially in patients following trauma with high risk for venous thromboembolism. Thus knowledge about the possible complications associated with IVC filters becomes vital for practicing physicians. Fracture of IVC filters and intra cardiac embolization can lead to potentially life threatening complications.

CASE REPORT

A 30-year-old African American male with diabetes mellitus, hypertension and end-stage renal disease was seen in the cardiology clinic for cardiac risk stratification prior to renal transplant. Patient denied any cardiac symptoms and stated to have good functional status. One year prior he had sustained a motor vehicle accident with extensive burn injuries and fracture of the left tibia and fibula for which he had an external fixation performed. His hospital course was complicated by deep venous thrombosis (DVT) for which he underwent placement of an IVC filter. On examination pulse rate was 78, arterial pressure was 140/88 mmHg and respiratory rate was 14. Physical examination was remarkable for scars in chest and extremities from prior burns treated with skin graft. Cardiovascular examination revealed normal heart sounds with no gallops or murmurs and no volume over load. Electrocardiogram showed normal sinus rhythm. The transthoracic echocardiogram showed two linear echo bright densities in the right atrium (Figure 1) and ventricle embedded in the wall (Figures 2 and 3) otherwise unremarkable. Non-contrast computed tomography of the chest confirmed the presence of the foreign bodies which was identified to be the fractured limbs of the IVC filter (Figures 4 and 5). IVC filter was in place with the missing limbs evident on imaging (Figure 6). As patient was asymptomatic and the objects were found to be embedded in the myocardium vena cava filter retrieval was not advocated. Though the indication for IVC filter placement was transient patient had lost to follow-up and now presented with an incidental intra cardiac foreign body.

DISCUSSION

The Mobin-Uddin umbrella filter[1] was the initial filter of historical value followed by the Greenfield filter which was introduced in 1973 by Greenfield *et al*[2] and still remains the standard to which other filters are compared. Vena cava filter is utilized as a treatment option of venous thromboembolism in specific situations. Venous thrombo embolism (VTE) comprises of deep venous thrombosis and pulmonary embolism (PE). VTE is known to be associated with increased morbidity and mortality. The gold standard treatment for DVT and PE is anticoagulation. However in the presence of contraindication for anticoagulation or if significant risk of bleeding persists vena cava filters are the safest treatment modality[3,4]. Vena cava filters can also be placed for treatment failure of anticoagulation and recurrent thrombosis despite therapeutic levels of anticoagulation and development of new contraindications after initiation of anticoagulation. In the latter however the decision of placement depends on the required duration of anticoagulation and the risk of thrombosis on cessation of anticoagulation.

Vena cava filters (IVC filters) are commonly placed in the IVC below the level of renal veins owing to the high prevalence of lower extremity thrombosis and subsequent pulmonary embolism. Even in the absence of demonstrable Lower extremity thrombosis in pulmonary embolism, IVC filters are placed if anticoagulation is contraindicated as thrombus in the pelvis or calf veins may be undetected or can form later. Nevertheless in the context of upper extremity thrombosis IVC filters are not beneficial and superior vena cava filters should be placed.

Utilization of IVC filters for DVT varies widely and has been recently evaluated in a study in 263 hospitals. Approximately 15% of the patients with venous thromboembolism received filter placement with a wide range between 0% to 39%. The characteristics associated with the wide variability in filter placement were acute bleeding at the time of admission, major operation after admission, presence of metastatic cancer, more severe illness, small hospital, and rural location.

Various types of IVC filters are available for use currently and can be classified as permanent and retrievable filters. The Society of Interventional Radiology guidelines recommends that the decision to select between the permanent and retrievable filter should be based on required duration of treatment for venous thromboembolism and the risks associated with anticoagulation therapy[5]. Complications are associated with both type of filters but the prevalence of complications varies with each specific type of IVC filter. Complications could be directly associated with the insertion of the filter such as bleeding or infection at the puncture site, allergic reactions to contrast or

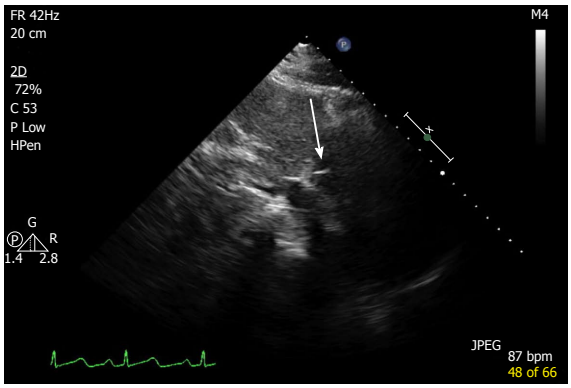

Figure 1 Echocardiography - modified subcostal view showing liner foreign body in the right atrium.

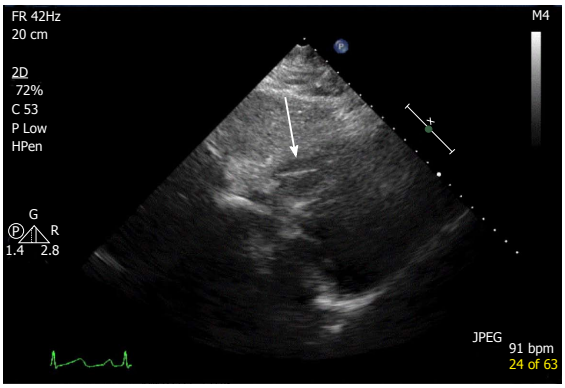

Figure 2 Echocardiography subcostal view showing liner foreign body in the right ventricle.

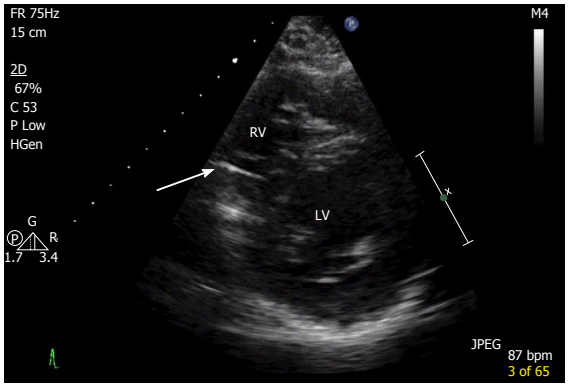

Figure 3 Echocardiography short axis view showing liner foreign body in the right ventricle.

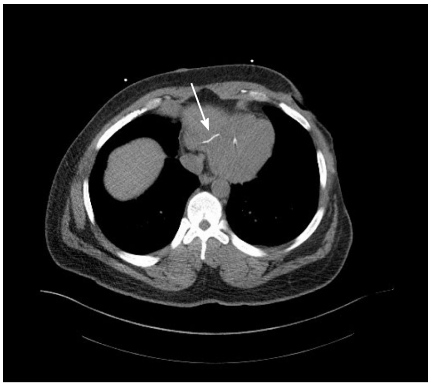

Figure 4 Computed tomography of the chest showing liner foreign body in the right ventricle.

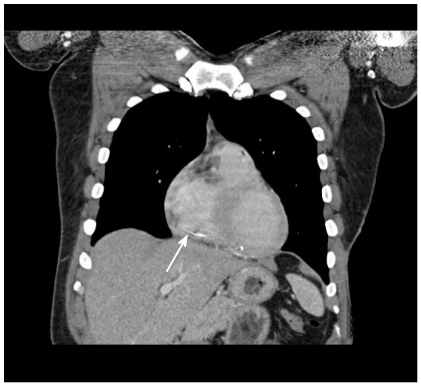

Figure 5 Computed tomography of the chest showing liner foreign body in the right ventricle.

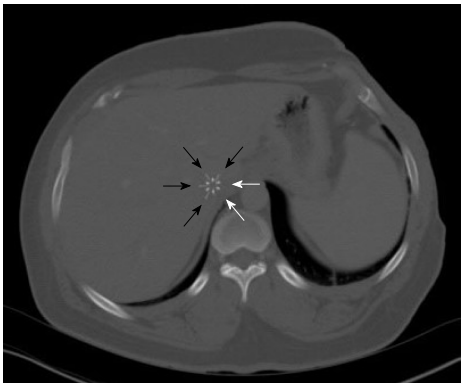

Figure 6 Computed tomography of the abdomen showing missing limbs of the filter. Black arrows showing 4 outer limbs and white arrows showing the position of missing outer limbs.

other medications used during placement, misplacement of the filter and entrapment of the guidewire within the filter. Late complications include fracture, migration, limb embolization, tilt, IVC penetration, VTE and IVC thrombus[6,7].

A review of data from the United States Food and Drug Administration Manufacturer and User Facility Device Experience (MAUDE) from January 2009-December 2012 reveled 1606 reported AEs involving 1057 IVC filters were identified. Of reported AEs, 1394 (86.8%) involved retrievable IVC filters, and 212 (13.2%) involved permanent IVC filters ($P < 0.0001$). Reported AEs included fracture, migration, limb embolization, tilt, IVC penetration, venous thromboembolism and pulmonary embolism, IVC thrombus, and malfunctions during placement.

IVC filters mechanically provide protection from lower extremity DVT migration to the lungs however does not protect against thrombosis at or below the filter. Knowledge on management of IVC filter thrombosis

is limited to experience with small group of patients. Various techniques have been utilized with endovascular treatment being more successful. Other techniques such as catheter-directed thrombolysis, power pulse spray, various mechanical devices, judicious use of tPA or stent placement have also been used in case by case basis.

Though the most reported complication with retrievable filter was fracture according to the MAUDE database[8] other studies revealed significantly varying fracture risk according to the brand of filter with the Celect filters having a very low fracture rate and the Bard Recovery filters having the highest as high as 25%[9].

Fracture of a filter strut and intracardiac embolization[10] has been reported in literature to be a devastating complication in some patients. An intracardiac strut can be asymptomatic as in our patient or present with a clinical picture similar to PE with shortness of breath pleuritic chest pain, non-sustained ventricular tachycardia and life threatening cardiac tamponade. The use of IVC filter is trending up and the availability of various types with different risk profile mandates physicians to have knowledge regarding types of filters and clinical implications associated with each type to recognize the complications and institute timely appropriate management. The choice of filter should take into consideration individual risks of the filter, clinical indication for the filter and the required duration of treatment to avoid unnecessary complications.

Timely retrieval of retrievable filter can prevent the sequelae of fracture and embolization and the subsequent complications. In systematic review by Angel *et al*[11] the retrieval rate was as low as 34%. As a consequence of reported low retrieval rates the Food and Drug Administration in the United States has recommended that "the implanting physicians and clinicians responsible for the ongoing care of patients with retrievable IVC filters consider removing the filter as soon as protection is no longer needed"[12].

Optimum management of intracardiac foreign bodies depends on the size and shape of the foreign body and the symptoms. Asymptomatic patients with a foreign body that is smoothly shaped and less than 5-10 mm can be managed conservatively. Our patient did not demonstrate any high risk features and thus was managed conservatively.

In conclusion, IVC filters are increasingly utilized in the clinical practice albeit with low retrieval rates of temporary filters which could result in potentially life threatening preventable complications. Timely retrieval of IVC filter is vital to prevent the unwanted sequelae associated with filter strut fracture and embolization. This case was written to highlight the importance of timely retrieval of filters and to enlighten physicians on rare complications associated with non-retrieval.

COMMENTS

Case characteristics

A 30-year-old African American male presented to the cardiology clinic for cardiac risks stratification prior to renal transplant.

Clinical diagnosis

Physical examination was remarkable for scars in chest and extremities from prior burns treated with skin graft otherwise unremarkable.

Differential diagnosis

Foreign body in right atrium suspected either a fractured inferior vena cava (IVC) filter or a metal travelling intravascularly to heart following car accident.

Laboratory diagnosis

Unremarkable other than elevated creatinine due to end stage renal failure.

Imaging diagnosis

The transthoracic echocardiogram showed two linear echo bright densities in the right atrium and ventricle embedded in the wall. Non-contrast computed tomography of the chest confirmed the presence IVC filter was in place with the missing limbs evident on imaging.

Treatment

As patient was asymptomatic and the objects were found to be embedded in the myocardium vena cava filter retrieval was not advocated.

Related reports

Fracture of a filter strut and intracardiac embolization has been reported in very few case reports to be a devastating complication in some patients. However rates of IVC filter removal remains low.

Term explanation

IVC filters are used in patients with deep venous thrombosis of lower extremities with contraindications for anticoagulation's.

Experiences and lessons

Timely retrieval of IVC filter is vital to prevent the unwanted sequelae associated with filter strut fracture and embolization.

Peer-review

The authors describe an interesting and well documented complication of cava filter and give a nice review of literature.

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CASE REPORT

Ominous lung cavity "Tambourine sign"

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Author contributions: Verma R, Bhalla AS and Goyal A had contributed in imaging and radiological work-up; Loganathan N and Guleria R evaluated the patient clinically and provided treatment (chemotherapy); Jain D helped in making histopathological diagnosis; all authors have contributed in complete patient care.

Institutional review board statement: Isolated case reports are exempt from review and approval at our institution.

Informed consent statement: Verbal informed consent was taken at the time of conducting investigations that the case may be used in academic and teaching purpose maintaining identity and confidentiality of the patient.

Conflict-of-interest statement: Nil.

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Abstract

Mucinous adenocarcinoma represents a rare subtype of adenocarcinoma of the lung, which is frequently invasive and has a poorer prognosis. Of its wide range of imaging appearances, air-space consolidation is the most frequent pattern while cavitary form has only rarely been reported. Despite imaging advancements, the differentiation of benign and malignant cavitary lung lesions sometimes remains imperfect. We propose "Tambourine" sign on computed tomography to raise the suspicion of mucinous adenocarcinoma in a lung cavity, under appropriate clinical settings. The sign indicates an irregular cavity with undistorted prominent thick walled bronchioles within the wall and draping along thereby resembling the musical instrument "tambourine". Adjacent ground glass and internal septations may also be seen.

Key words: Lung cavity; Tambourine; Adenocarcinoma mucinous; Tomography; X-ray

Core tip: Lung cavities are commonly encountered in routine chest imaging and diagnosis may become a challenge in certain cases despite advances in imaging techniques. Imaging points have been described in literature to differentiate benign from malignant cavities that help in diagnosing most of the cases, however some lesions are still difficult to interpret and accurately diagnose. Tambourine sign has been introduced by us for a relative thin walled lung cavity where undistorted smaller bronchi with thickened and prominent walls are seen to be entering and draping along the cavity walls. This imaging sign resembles the musical instrument tambourine, and this is ominous and point towards a

more sinister lesion as in our case and in similar cases reported in literature. Hence in appropriate clinical and imaging background this sign should be carefully looked at and appropriate workup should be done for timely diagnosis.

Verma R, Bhalla AS, Goyal A, Jain D, Loganathan N, Guleria R. Ominous lung cavity "Tambourine sign". *World J Clin Cases* 2017; 5(4): 153-158 Available from: URL: http://www.wjgnet.com/2307-8960/full/v5/i4/153.htm DOI: http://dx.doi.org/10.12998/wjcc.v5.i4.153

INTRODUCTION

Lung cancer is the most common cause of malignancy-related mortality in both sexes[1]. In the recent decades, there has been a substantial increase in the proportion of adenocarcinomas, making it the most common type. The spectrum of lung adenocarcinoma ranges from atypical adenomatous hyperplasia to frankly invasive lesion[2]. Invasive mucinous adenocarcinoma (IMAC) is a special subtype of adenocarcinoma lung that was earlier termed as mucinous broncho-alveolar carcinoma (BAC) and is known to be more aggressive than conventional adenocarcinoma[3]. IMAC may have a wide range of imaging appearances, of which air-space consolidation is the most common[2] pattern.

We present a case of 37-year female who presented with a thin-walled left lower lobe (LLL) lung cavity six years ago, but remained undiagnosed despite adequate workup, till a final diagnosis of IMAC was made. Review of literature focussing on radiological findings of this unusual cavitary appearance of IMAC is discussed.

CASE REPORT

A 37-year non-smoker female presented to our institute with history of cough, sputum, shortness of breath, loss of weight and episodic hemoptysis in November 2014. Her problem began in 2008 with an episode of cough, streaky hemoptysis and copious sputum production, which was treated with antibiotics as respiratory tract infection. Multiple subsequent hospital admissions and extensive clinical/radiological workup was done (Figure 1) for similar complaints but was inconclusive (Figures 2 and 3).

The laboratory investigations in the current admission were again non-contributory (Figure 1). Contrast-enhanced computed tomography (CECT) was done and it revealed multiple cavitary lesions in bilateral lungs with the largest in LLL showing large enhancing solid component. Many of the cavitary lesions in current CT showed a peculiar imaging appearance: Irregular inner and outer walls with thick walled bronchioles seen near the edge and within the walls of the cavities. No surrounding ground glass opacity (GGO) was seen in the current CT. There was no pleural effusion or mediastinal adenopathy. The included sections of upper abdomen were unremarkable.

Review of the prior imaging (Figures 2 and 3) demonstrated progression over the last six years. The lesion began (in 2008) as a thin-walled (4 mm) well-defined cavity in superior segment of LLL (Figure 2A-C). Both the inner and outer margins of the wall showed irregularity. Adjacent thick walled prominent undistorted bronchioles (dotted arrows) were seen near the edge and within the wall of cavity. Mild surrounding GGO was also seen. There was an additional smaller cavitating nodule in right upper lobe (RUL) with subtle surrounding GGO (not shown). Combining clinical and laboratory data, patient was presumed to have respiratory infection and treated for the same. Subsequent imaging in 2010 (Figure 2D-F) showed increase in size and wall thickness of the LLL cavity. Imaging done in 2012 depicted multiple new cavitating nodules in RUL (Figure 3A and B) and increase in size of LLL cavity, along with development of internal septations. No GGO or consolidation was seen and there was no solid component in any of these cavities.

Current CECT images showed further increase in the size of the lesions and development of significant soft tissue component in LLL cavity (Figure 3C-E). Many of the cavitary lesions in the current CT showed multiple internal septations. Considering disease progression and development of solid component, malignancy was kept as the first differential. Other possibilities included atypical infections (fungal, atypical mycobacterial, nocardia, *etc*.) and vasculitis. However, long disease course (approximately 6 years) was unusual for both infection and malignancy.

USG-guided biopsy was done from the LLL mass (solid component) that showed atypical glands in the background of abundant mucin with areas of frank invasion suggestive of well-differentiated IMAC (Figure 4A and B). Analysis for ALK and EGFR mutation was negative. 18F-FDG PET-CT was done to rule out lung metastasis from extrathoracic primary which did not reveal any other primary site and the lung lesions showed patchy foci of mild FDG uptake (Figure 4C). The patient was started on chemotherapy (Pemetrexed and Carboplatin) but she continued to progress and developed bone metastases and soon became bedridden.

DISCUSSION

Lung cavities are commonly encountered in routine radiology practice. While in most cases the distinction between benign and malignant cavities is straightforward, some of the lesions may pose a diagnostic challenge. Differential diagnosis of acquired cavitary lung lesions include pyogenic infections such as lung abscess, necrotising pneumonia, septic emboli; granulomatous infections like tuberculosis, fungal; vasculitis including granulomatosis with polyangitis (Wegener's) and Churg Strauss; connective tissue diseases like rheumatoid disease, ruptured hydatid and malignancy. A constellation of imaging features including wall thickness, number of lesions, distribution/site,

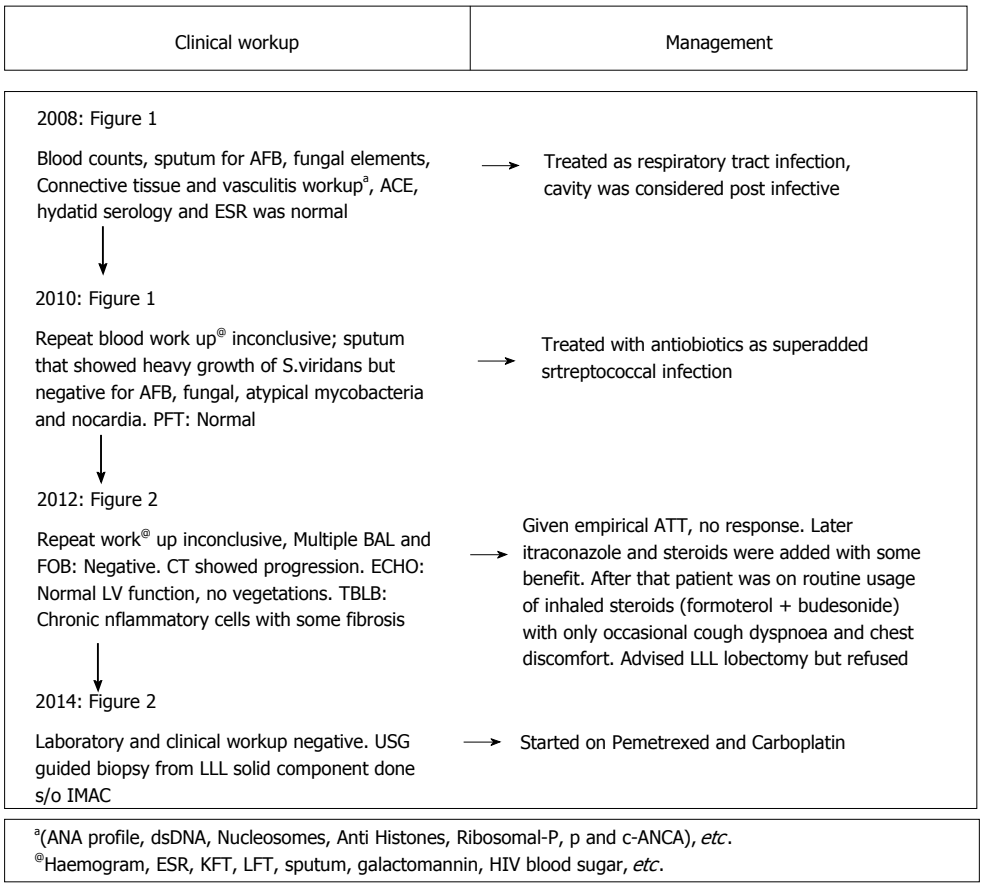

Figure 1 The clinical work-up and evaluation from onset till diagnosis. BAL: Bronchoalveolar lavage; TBLB: Transbronchial lung biopsy; ACE: Angiotensin converting enzyme; EGFR: Epidermal derived growth factor receptor; PFT: Pulmonary function test; AFB: Acid fast bacilli; ESR: Erythrocyte sedimentation rate; GGO: Ground glass opacity; ATT: Anti tubercular therapy.

adjacent GGO/nodules/consolidation, satellite lesions, internal contents, fluid level and the background lung need to be considered to reach a diagnosis.

Amongst lung malignancies, squamous cell carcinoma is the most common type to present as cavitary mass while adenocarcinomas rarely show true cavitation due to lack of frank necrosis and relative preservation of lung architecture. Adenocarcinomas however show areas of pseudocavitation due to presence of air in the patent smaller bronchi and preserved intra-alveolar air[4]. IMAC is a special subtype of invasive adenocarcinoma lung that is more common in females, non-smokers and presents at a younger age. When these tumors are multifocal, they are frequently mutilobar and lower lobe predominance is seen[2,5].

On CT, IMAC usually appear as consolidation with air bronchogram (commonest) or multifocal solid and subsolid (ground glass) nodules or masses which tend to be bronchocentric[2,6]. Due to abundant mucin production, large areas of pseudocavitation may be seen. They have low FDG uptake[7] due to large amount of mucin and for same reason show less contrast enhancement frequently depicting the "CT angiogram sign".

Previously IMAC was termed as Mucinous Broncho-alveolar Carcinoma however the term BAC has now been removed from recent adenocarcinoma classification. BAC by definition was for non-invasive tumors while IMAC though predominantly show lepidic spread, frequently have areas of frank invasion. GGO is an indicator of lepidic spread while the solid component correlates with invasion. IMAC are frequently EGFR negative and may show *k-RAS* mutation, therefore having a poorer prognosis[8].

IMAC presenting as cavity is rare and to the best of our knowledge only two cases have been described previously[9,10]. Cavitation in adenocarcinoma may be caused by obstruction of the distal bronchus by tumour cells creating a check-valve mechanism or alveolar rupture due to tumour proliferation or mucus retention[9]. A detailed review of the previously reported cases and all the imaging studies of our case enabled us to come up with a peculiar finding common to all, which we intend to refer to as the "Tambourine sign".

"Tambourine" sign refers to an irregular cavitary lesion with adjacent thick walled undistorted bronchioles within wall of the lesion and adjacent to it. The appearance resembles the musical instrument tambourine where the irregular cavity wall corresponds to the ring of the instrument, while the thick walled dilated bronchioles within the wall correspond to the metallic jingles. The cavity wall itself though irregular, may not be thick (as in

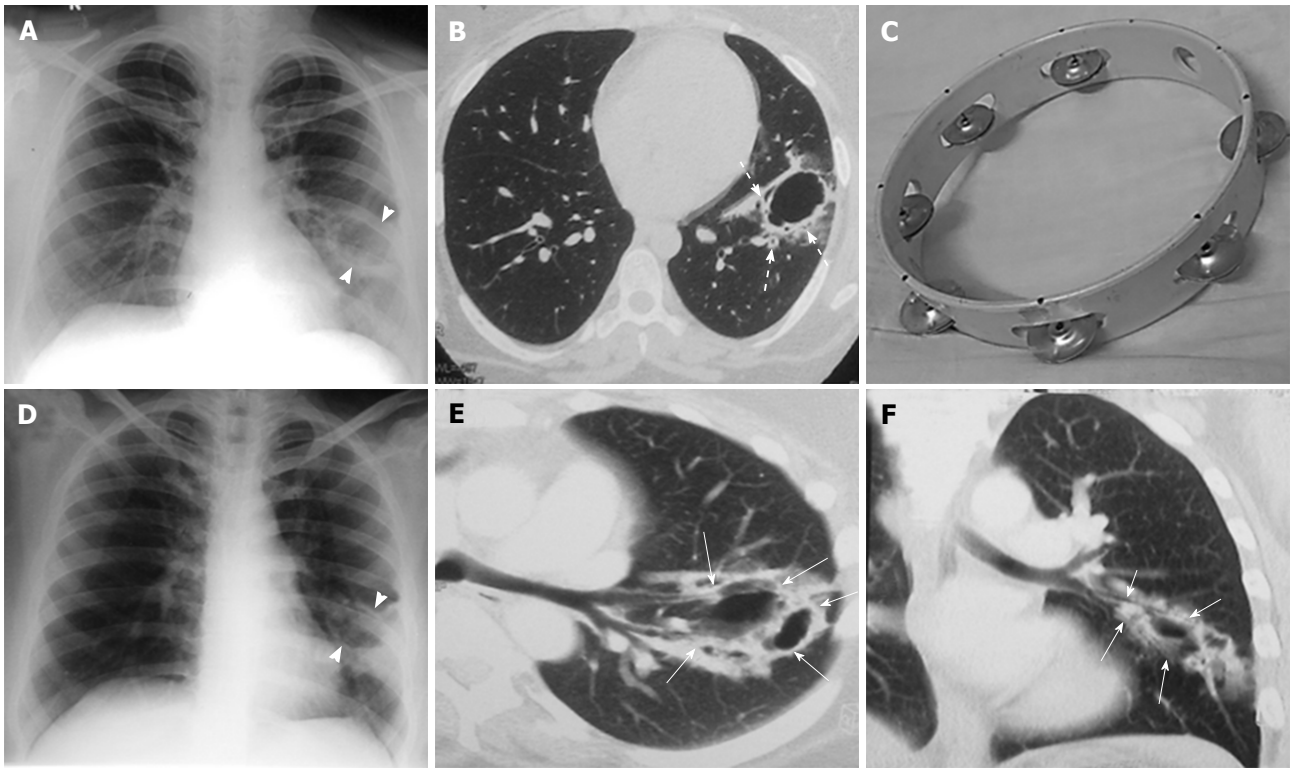

Figure 2 Initial and two year follow-up computed tomography imaging. Chest radiograph (A) and CT (B) in 2008 (first study) show well-defined thin-walled (4 mm) irregular cavitary lesion (arrow head) in superior segment of left lower lobe. Thick walled bronchioles (dotted arrows) are seen near the edge and within the wall of cavity with adjacent ground glass giving rise to "Tambourine" sign; (C) depicts the musical instrument "tambourine" for comparison; subsequent radiograph (D) and CT (E and F) in 2010 shows increase in size and wall thickness of the cavity. Note the adjacent bronchioles (thin white arrows) entering into the cavity wall. CT: Computed tomography.

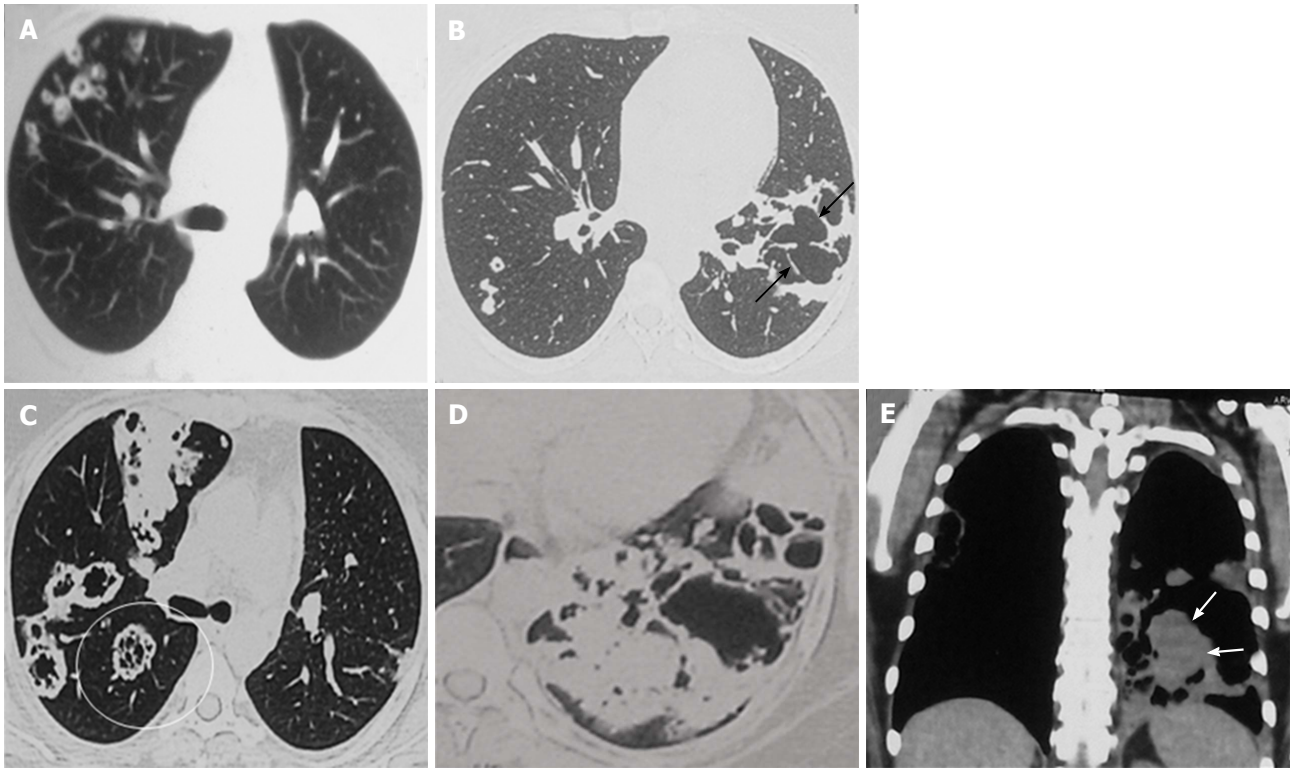

Figure 3 Disease progression with development of soft tissue. Chest CT study of 2012 lung window (A and B) shows multiple new cavitating nodules in RUL (A) and increase in size of LLL cavity with development of internal septations (arrows) (B). No solid nodules or GGO or consolidation is seen. Current CECT images (2014: C to E) demonstrate further increase in size of the lesions and multiple new lesions having internal septations and development of significant soft tissue component in LLL cavity (solid arrows). Also note the "Tambourine" sign in RLL cavities as well (encircled cavity in C). LLL: Left lower lobe; RUL: Right upper lobe; GGO: Ground glass opacity; CECT: Contrast-enhanced computed tomography.

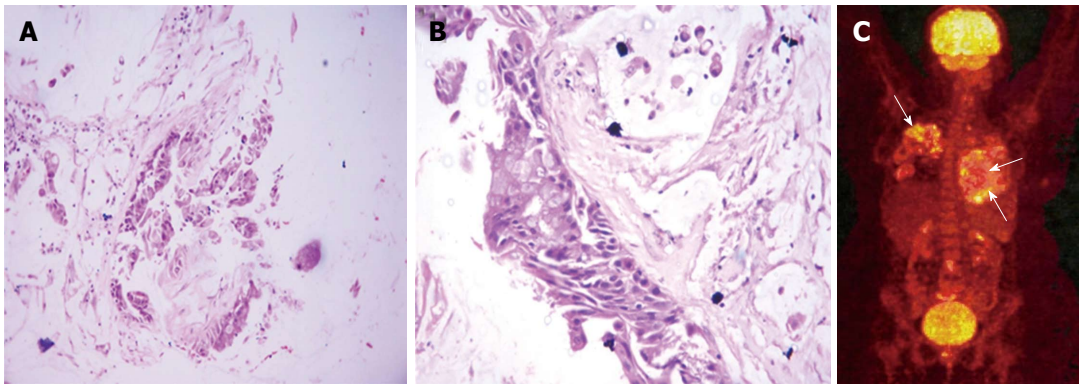

Figure 4 Histopathology and positron emission tomography findings. A and B: Histological photomicrograph shows fragments of tumor with mucinous epithelium H and E × 40. Higher magnification (C) shows invasive mucinous adenocarcinoma with pools of extracellular mucin H and E × 400; C: Whole-body PET-CT image shows patchy mild uptake of FDG within the lung lesions. No evidence of extrathoracic primary site of malignancy is there. PET-CT: Positron emission tomography-computed tomography; FDG: 2-[fluorine-18] fluoro-2-deoxy-D-glucose.

Table 1 Confounding factors leading to delay in diagnosis in the index case

Young age of presentation
Lack of significant soft tissue component and thin walls initially
Multifocality favoured a systemic infection/disease (vasculitis) rather than primary lung malignancy
Increase in wall thickness in second CT was suspicious, but interpretation was confounded by heavy growth of streptococcus.
Waxing and waning symptoms.
Repeated negative BAL and FOB

CT: Computed tomography; BAL: Bronchoalveolar lavage; FOB: Fiberoptic bronchoscopy.

Table 2 Learning points

IMAC is more common in non-smokers and females and has poor prognosis
It has lower lobe predominance and is frequently multifocal
IMAC may be missed on repeated cytology and biopsies due to relative paucity of malignant cells and large amount of mucin
"Tambourine" sign in appropriate clinical setting identifies lung cavity suspicious for malignancy, especially IMAC
IMAC may show unusual slow growth and only mild uptake on PET

IMAC: Invasive mucinous adenocarcinoma; PET: Positron emission tomography.

the initial CT in the index case). Prominent thick walled undistorted bronchi are caused by tumour cell infiltration and desmoplastic reaction. Presence of internal septations and surrounding GGO (indicating lepidic spread of the tumor) further increase the likelihood of malignancy in such a lesion. When viewed in retrospect, both of the previously described cases as well as our patient showed "Tambourine" sign in all the CT examinations.

Paucity of malignant cells in such large amount of mucin[11] may make IMAC difficult to detect on BAL cytology as well as on TBLB. Though adenocarcinomas are usually aggressive, unusually slow growing lesions have also been reported[12,13]. This along with other confounding factors (Table 1) delayed the diagnosis in the index case. Adenocarcinoma may develop in a pre-existing cavity; however the index case was likely to be harbouring malignancy right from the onset. This is because the LLL cavity showed suspicious features on the first CT itself (tambourine sign) and progressively increased in size and wall thickness on subsequent imaging, along with development of multifocal lesions. The unusual feature in our case was atypical radiological appearance of the lesion as a thin-walled cavity, repeated negative cytology/biopsy and unusual slow growth.

Summary and conclusion

The purpose of this article is to highlight an additional radiological sign which could raise suspicion of malignancy in a lung cavity. An irregular cavitary lesion with adjacent thick walled undistorted bronchioles within wall of the lesion and adjacent to it ("Tambourine" sign) is suspicious for malignancy and needs extensive work-up even if the cavity is relatively thin walled. Internal septations, surrounding GGO, lower lobe location, multifocality, normal background lung without any obvious airway disease, fibrosis and scarring may further point towards underlying malignancy (IMAC), provided the work-up for other differentials is negative (as in our case). Any increase in size or wall thickness prompts aggressive management by early surgical removal even when repeated BAL or biopsy is negative (Table 2).

COMMENTS

Case characteristics

Cough, shortness of breath and occasional hemoptysis.

Clinical diagnosis

Respiratory tract infection.

Differential diagnosis

Reactivated kochs.

Laboratory diagnosis

Was confusing and non contributory.

Imaging diagnosis
Initially lung cavity with tambourine sign initially later developed soft tissue.

Pathological diagnosis
Invasive mucinous adenocarcinoma.

Treatment
Premetrexed and carboplatin combination chemotherapy and radiotherapy for bone metastasis.

Related reports
Being thin walled cavity with no significant soft tissue repeat biopsies may be negative hence surgical excision may be considered when extensive workup is inconclusive.

Term explanation
The cavity resembles "Tambourine" on computed tomography, that refers to the musical instrument seen as thin walled cavity in background of normal lung with prominent and thick walled undistorted bronchi draping and entering the cavity walls.

Experience and lesson
This imaging finding has been retrospectively observed in previous similar reported cases of Invasive mucinous adenocarcinoma presenting as cavity and hence the classical appearance need to be focussed and re-emphasised. Close follow-up is very helpful in such cases.

Peer-review
Nice case and also well drafted.

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REVIEW

Evolution, current status and advances in application of platelet concentrate in periodontics and implantology

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Abstract

Platelet concentrates (PC) [platelet-rich plasma (PRP) and platelet-rich fibrin (PRF)] are frequently used for surgical procedures in medical and dental fields, particularly in oral and maxillofacial surgery, plastic surgery and sports medicine. The objective of all these technologies is to extract all the elements from a blood sample that could be used to improve healing and promote tissue regeneration. Although leukocyte rich and leukocyte poor PRP's have their own place in literature, the importance of non-platelet components in a platelet concentrate remains a mystery. PC have come a long way since its first appearance in 1954 to the T-PRF, A-PRF and i-PRF introduced recently. These PC find varied applications successfully in periodontics and implant dentistry as well. However, the technique of preparation, standing time, transfer process, temperature of centrifuge, vibration, *etc*., are the various factors for the mixed results reported in the literature. Until the introduction of a proper classification of terminologies, the PC were known by different names in different countries and by different commercial companies which also created a lot of confusion. This review intends to clarify all these confusion by briefing the exact evolution of PC, their preparation techniques, recent advances and their various clinical and technical aspects and applications.

Key words: Platelet concentrates; Platelet rich plasma; Platelet-rich fibrin; Pure-platelet-rich fibrin; Leukocyte- and platelet-rich fibrin; Sticky bone; Platelet derived growth factors; Fibrin glue

Core tip: Platelets concentrates are known to be a rich source of growth factors with added antimicrobial efficacy due to incorporations of leukocytes. But does that mean that platelets or platelet poor/depleted plasma do not have any antimicrobial role? Are the mixed results reported in the literature due to deviations from the manufacturing protocols and nomenclature of platelet concentrates (PC)? Does technical factors related to centrifuge speed, time, temperature, vibrations, resonance, *etc.*, affect the biological quality of the resultant platelet concentrate? A thorough knowledge evolution, preparation and applications of various PC will help clinicians to use this arsenal more efficiently.

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INTRODUCTION

An average baseline platelet count in humans is 200000 ± 75000/μL with a half-life of 7-10 d. Platelets are irregularly shaped, small (2-4 μm) anuclear cells, derived from fragmentation of precursor megakaryocytes. They contain few mitochondria, many granules and 2 prominent membrane structures, the dense tubular system and the surface connected canalicular system. Activated platelets trigger their major effects by substances located in one of the three different types of platelet granules: A-granules, dense granules, and lysosomes. Alpha granules are the most abundant type and contain many different bioactive mediators. They are spherical or oval structures (200 to 500 nm), enclosed by a unit membrane. Upon contact with exposed endothelium (due to damage tissue or wound) the platelets get activated and are known to release key wound healing factors: Platelet derived growth factor (PDGF), vascular endothelial growth factor (VEGF), transforming growth factor (TGF) and epidermal growth factor (EGF). Platelets begin to actively secrete these proteins within 10 min after clotting, with more than 95% of the pre synthesized growth factor secreted within 1 h. For the balance of their life (5 to 10 d), the platelets synthesize and secrete additional proteins. As the direct platelet influence begins to subside, macrophages, which arrive by means of vascular ingrowth stimulated by the platelets, assume responsibility for wound-healing regulation by secreting their own factors. Thus, the platelets at the repair site ultimately set the pace for wound repair.

Platelet concentrates (PC) [platelet-rich plasma (PRP) and platelet-rich fibrin (PRF)] are frequently used for surgical procedures in many medical fields[1], particularly in oral and maxillofacial surgery[2,3], plastic surgery[4] and sports medicine[5,6]. The objective of all these technologies is to extract (through centrifugation) all the elements from a blood sample that could be useful to improve healing and promote tissue regeneration[7], particularly: The platelets (rich in growth factors)[8], the fibrin (supporting matrix)[9] and in some cases the cell content (mostly leukocytes)[9]. A natural blood clot contains 95% red blood cells, 5% platelets, less than 1% white blood cells, and numerous amounts of fibrin strands. A PRP blood clot contains 4% red blood cells, 95% platelets, and 1% white blood cells. The literature on these products is quite confusing and controversial due to the lack of proper characterization of these many different products[10,11]. Compared to application of single, supra-physiological concentrations of recombinant growth factors, PC has the advantage of offering multiple, synergistically working growth factors at the wound site and in concentrations that are physiologically and biologically more relevant. But the question is whether it is only the platelet in PC's that plays lead role or are the non-platelet components equally important when considering the clinical applications. Some authors have in-fact suggested that RBC's and WBC's could be pernicious as they may contribute in inflammatory reactions leading to damage of the treated tissues[12-14]. Until these controversies are resolved in clinical literature, a big question still persists whether the non-platelet cellular components of PC have any role in their biological activities such as platelet activation and subsequent release of growth factors?

The natural healing process in any wound starts as blood coagulation leading to fibrin/platelet clot and matrix. PC's were introduced to reinforce this natural wound healing process. For example fibrin glues which are being used as surgical adjuvants since > 40 years. Over the period, this idea evolved to a more refined concept of tissue regeneration which was enhanced by the cells and the growth factors contained in these preparations. Initially used as surgical adjuvant, the PRP/PRF became the new glorified regenerative medicine approach. Platelets, leukocytes, fibrin, growth factors and other cells are the primary active players in the physiological wound healing process. Combined together they form a kind of engineered tissue which is derived from the blood circulation. However, this complex combination is ultimately decisive for the optimal performance. Therefore, the L-PRF clot, *i.e.*, Leukocyte-and PRF, was commonly known as an "optimized blood clot".

EVOLUTION OF PC

1954

Kingsley[15] first used the term PRP to earmark thrombocyte concentrate during experiments related to blood coagulation.

1970

"Fibrin glue" was introduced by Matras[16] which improved healing of skin wounds in rat models. Fibrin glue was made by polymerizing fibrinogen with thrombin and calcium. However, due to low concentration of fibrinogen in donor plasma, the quality and stability of fibrin glue was suboptimal.

1975-1978

Numerous research works suggested an enhanced concept for using blood extracts and designated them as "platelet-fibrinogen-thrombin mixtures"[17].

1979

Another author called it "gelatin platelet - gel foam". This new proposition asserted the performance of platelets, and demonstrated exquisite preliminary results in general surgery, neurosurgery and ophthalmology. However till then all these products were used primarily for their "gluey

effect", without consideration of effects of growth factors or their healing properties.

1986

Knighton *et al*[18] first demonstrated that PC successfully promote healing and they termed it as "platelet-derived wound healing factors (PDWHF)", which was successfully tested for the management of skin ulcers.

1988, 1990

Kingsley *et al*[15] and Knighton *et al*[19] used a slightly different term "platelet-derived wound healing formula (PDWHF)".

1997

Whitman *et al*[20] named their product PRP during preparation but when the end product had a consistency of a fibrin gel and therefore labeled it as "platelet gel".

1998

The development of these techniques continued slowly until the article of Marx *et al*[21], which started the craze for these techniques. However, all these products were designated as PRP without deliberation of their content or architecture, and this paucity of terminology continued for many years. Some commercial companies, in lieu of better visibility, started labeling their products with distinct commercial names.

1999

One of the popular methods advertised on large scale to prepare pure platelet rich plasma was commercialized as plasma rich in growth factors (PRGF) or also called as preperation rich in growth factors (Endoret, Victoria, Biotechnology Institute BTI, Spain). However, because of lack of specific pipetting steps and also lack of ergonomics, there were significant issues with this technique[11]. Another widely promoted technique for P-PRP was commercialized by the name Vivostat PRF (Alleroed, Denmark). However, as the name implies it is not a PRF but produces a PRP product.

2000

Simultaneously, Choukroun *et al*[22] developed another form of PC in France which was labeled as PRF, based on the strong fibrin gel polymerization found in this preparation. It was stamped as a "second-generation" platelet concentrate because it was obviously different from other PRPs. This proved an important milestone in the evolution of terminology.

2006

Bielecki *et al*[23] and Cieslik-Bielecka *et al*[24,25] proposed to define PRP as inactive substance, while PRG (Platelet Rich Gel) was a more biologically activated fibrin matrix rich in platelets, leukocytes and relative active molecule.

Sacco[26] introduced a new concept of CGF (concentrated growth factors). For making CGF from venous blood, rpm in range of 2400-2700 was used to separate cells. The fibrin rich blocks that were obtained were much larger, richer and denser.

2008

Everts *et al*[27,28] focused on the leukocyte component of the platelet concentrate and the two forms, *i.e.*, non-activated and activated. The inactivated/non-activated product was called "platelet-leukocyte rich plasma (P-LRP) and activated gel was labeled platelet-leukocyte-gel" (PLG).

2009

The first classification about platelet concentrate was proposed by Dohan Ehrenfest *et al*[11]. This classification defined 4 main families based on separation of the products using 2 key parameters: The cellular content (primarily leukocytes) and the fibrin architecture: (1) Pure platelet-rich plasma (P-PRP) - or leukocyte-poor platelet-rich plasma (LP-PRP); (2) Leukocyte-and platelet-rich plasma (L-PRP); (3) Pure PRF (P-PRF) - or leukocyte-poor PRF; and (4) Leukocyte- and platelet-rich fibrin (L-PRF).

2010

Concept of sticky bone (autologous fibrin glue mixed with bone graft) was introduced by Sohn[29] in 2010.

2012

Mishra *et al*[30] proposed another classification which was limited to PRP and applicable to sports medicine only. They stated 4 types of PRP based on presence or absence of leukocytes and whether or not the PRP is activated and all types can fall into 2 sub-types: A: Platelets > 5 × baseline or B: Platelets < 5 × baseline. In all the following types "solution" means non-activated PRP and gel means activated PRP. Type 1: L-PRP solution; Type 2: L-PRP gel; Type 3: P-PRP solution; Type 4: P-PRP gel.

At about the same time DeLong *et al*[31] introduced another classification system called PAW (Platelets quantity, Activation mode, White cells presence). However it again was only restricted to PRP families and was similar to classification by Mishra *et al*[30].

2014

Choukroun[32] introduced an advanced PRF called A-PRF (claimed to contain more monocytes). Tunalı *et al*[33] introduced a new product called T-PRF (Titanium-prepared PRF).

2015

Mourão *et al*[34] gave detailed technical note on preparation of i-PRF.

EVOLUTION IN PREPARATION TECHNIQUES

Fibrin glues, fibrin sealants or fibrin tissue adhesives are derivatives of human plasma that resemble the final stages

of blood coagulation wherein a fibrin clot is formed, available commercially in Europe since late 1970's. There are two types of fibrin sealants: Homologous and autologous. Homologous/commercial variant was prepared by mixing 2 components, *i.e.*, fibrinogen component containing factor XIII and the thrombin component containing calcium ions. Homologous fibrinogen concentrates were prepared from plasma cryoprecipitate or from Cohn fraction I. However, due to the risk of transmitting infections, later fibrin sealants were prepared from autogenous whole plasma and polymerization was instituted using bovine thrombin.

True concentrate of platelets, was termed PRP, which can be manufactured by using two techniques. Both these techniques differ in their technical aspects: (1) General-purpose cell separators; and (2) Platelet-concentrating cell separators.

The former technique (general-purpose cell separators) requires about 450 mL of blood and also usually requires a hospital setting. Blood is drawn into a citrate-phosphate-dextrose anticoagulant containing collection bag. In the first cycle it is centrifuged at 5600 rpm to separate RBCs, platelet poor plasma (PPP) and PRP. Subsequently the speed of the centrifuge is reduced to 2400 rpm to get a final separation of about 30 mL of PRP from the RBCs. A major advantage of this technique is that the remaining PPP and RBCs can be restituted to the patient's circulation or can be discarded. The ELMD-500 (Medtronic Electromedic, Auto Transfusion System, Parker, CO, United States) cell separator is widely used for this technique. The second technique, Platelet-concentrating cell separators, is more widely used since this equipment can be accommodated in a dental clinic setup. This technology permits the procurement of PRP using smaller quantities of blood. Currently, two such systems are approved by FDA and commercially available: Harvest SmartPrep Platelet Concentrate System (HSPCS; Harvest Technologies, Plymouth, MA, United States) and the 3i Platelet Concentrate Collection System (3i PCCS; 3i Implant Innovations, Palm Beach Gardens, FL, United States). Several studies have been performed to compare the efficacy of these systems[6-8]. Although, traditionally a double-spin technique has been used, authors such as Eby[35] have proposed the use of a single spin technique. The preparation and processing of PRP is quite similar in most of the platelet-concentrating systems, however the anticoagulant used and the speed and duration of centrifugation may differ.

An important evolution of terminology appeared when several authors, particularly the groups of Dohan Ehrenfest *et al*[8,36] pointed out that the PC were also associated with various forms of circulating cells, particularly leukocytes, and labeled it as L-PRP (Leukocyte rich platelet rich plasma). Large number of commercial or experimental systems exists for the preparation of L-PRP. In past years many automated protocols have been developed that require minimum handling of blood products, for example Biomet GPS III (Biomet Inc., Warsaw, IN, United States) and Harvest Smart-PreP (Harvest Technologies, Plymouth, MA, United States). There are also other kits which require more handling of blood products, for example Regen PRP (RegenLab, Le Mont-sur-Lausanne, Switzerland) or Plateltex (Prague, Czech Republic). Rutkowski *et al*[37] (2008) demonstrated single spin centrifugation for 10 min at 1350 g for preparation of PRP and they reported six-times enrichment of platelet concentrate. Interestingly they also reported that platelet morphology changes over a period of 6 h bench set time. In fact, even after 2 h the platelets in PRP started to appear less normal. They concluded that PRP bench set times should not exceed 2 h to maintain maximal levels of growth factors, TGFb1 and of platelet morphology. Akhundov *et al*[38] (2012) claimed to introduce a cost effective technique for procuring PRP. They harvested patient's blood using syringe/Vacutainer tubes containing 10 mmol/L 3.8% citrate. This citrate treated blood was transferred to 50 mL Falcon centrifuge tube and centrifuged for 15 min at 280 g at room temperature. After centrifuge, platelets and plasma were removed using 5 mL pipette and transferred to a new 50 mL Falcon centrifuge tube and centrifuged again for 15 min at 280 g at room temperature. The pellet with 1-2 mL of plasma was transferred to new syringe for use in patient for injection or topical application.

Fukaya *et al*[39] (2014) reported an innovative yet economic technique for preparing PRP which consisted of a modification of a(disposable) 5-mL syringe that was inserted into a regular centrifuge. The syringe was positioned in the centrifuge in such a manner that the platelet rich plasma separated adjacent to the tip of the syringe. They also highlighted that instead of heparin or EDTA (ethylene diamine tetra acetic acid), majority of commercial kits adopt dextrose solution A (ACD-A) as an anticoagulant. Even though coagulation and platelet aggregation are very different and anticoagulants never suppress platelet aggregation, no commercial kits consider adding platelet aggregation inhibitor. It's known that aggregated platelets attach to the wall of syringes and are unable to detach from them easily. However their primary aggregation is reversible and the platelets detach from the syringe wall and float in the plasma again after many hours. But in routine clinical practice we cannot wait so long. Therefore authors have suggested addition of platelet aggregation inhibitor "prostaglandin E1 (PGE1)" to anticoagulant ACD-A for preparation of PRP with dense PDGF-BB.

The sole product in the family of P-PRF is the fibrinet PRFM (Platelet-Rich Fibrin Matrix, Cascade Medical, NJ, United States). These are high-density fibrin network preparation with poor leukocyte content. They exist purely in a strongly activated gel form that cannot be injected or used like conventional fibrin glues but instead can be manipulated like a real solid material for other applications. However an important disadvantage of this technique is its high cost and relative complexity of the procedure as compared to the other forms of PRF available such as the L-PRF. The L-PRF was developed and evaluated as a one-step centrifugation without anti-coagulation or blood activator[40]. However, currently the sole commercially available, FDA approved system for making L-PRF, is the

Intra-Spin L-PRF (Intra-Lock Inc., FL, United States). It has something called "Xpression preparation box", which allows the production of generous quantities of membranes and fibrin in relatively small time. Mazzucco *et al*[41] (2016) compared the mechanical properties of PRF against PRGF and found that the former was stronger. It should be noted that the early protocol to produce L-PRF was 3000 rpm/10 min, while since many years the 2700 rpm/12 min protocol is mostly used that gives much better polymerized L-PRF and therefore stronger membranes than the 3000 rpm/10 min protocol. The original L-PRF system now exists only in one CE/FDA cleared form that is termed Intra-Spin L-PRF as stated above. A brief compilation of different types and techniques of platelet concentrate is presented in Table 1[22,26,29,32-34,41-50].

RECENT ADVANCES

After PRF a concept of "Concentrated Growth Factors (CGF)" was introduced in 2006 by Sacco[26]. A special centrifuge called Medifuge (Italy), is used to prepare CGF, similar to PRF, but with a different centrifugation speed which allows the separation of a fibrin matrix which is much denser, larger and richer in growth factors. CGF has been shown to have a greater versatility and better regenerative capacity, as reported for alveolar ridge and sinus augmentation (Sohn *et al*[51], 2009). In a study, Rodella *et al*[52] could demonstrate the presence of VEGF and TGF-b1in RBC and CGF layers. This suggests that improved CGF procedure could enhance the quantity of growth factors in the CGF layer or, alternatively, a possible use of RBC layer in clinical applications. In addition to this, the existence of CD34 positive cells, within the CGF network, could lead to investigation of their clinical implications in future.

Ample evidence has emerged recently on the role of monocytes on the vessels growth and bone regeneration. Monocytes play an important role in vascularization, bone growth and production of VEGF. Monocytes are known to have BMP receptors and recently it was discovered that they produce BMP-2. In an attempt to incorporate the monocytes within the PRF, Choukroun[32] introduced an advanced PRF called A-PRF™. They have discovered earlier soft tissue growth, more release of BMPs, greater and faster vascularization and more cytokine release than conventional PRF.

A concept of fabricating growth factors-enriched bone graft matrix (also known as "sticky bone") using autologous fibrin glue has been demonstrated since 2010[29]. Sticky bone provides stabilization of bone graft in the defect, and therefore, accelerates tissue healing and minimizes bone loss during healing period. To obtain autologous fibrin glue, 20-60 CC of venous blood is centrifuged at 2400-2700 rpm using a specific centrifuge (Medifuge, Silfradentsrl, Sofia, Italy) for 2 min. Out of the two layers obtained, the deeper layer is RBC's and the superficial layer is AFG. This AFG is then extracted using a syringe and mixed with particulate bone powder and allowed to rest for 5-10 min for polymerization, which results in a yellow colored mass called "sticky bone"[53]. Sohn *et al*[53] also noted that the polymerization can be accelerated by adding the exudates obtained after compression that they used to make CGF membrane. These exudates contained growth factors and autologous thrombin in RBC layer due to which the auto-polymerization completed faster[53]. The resultant sticky bone is moldable, prevents micro and macro movement of grafted bone, entraps platelets and leukocytes in its fibrin network, is natural and prevents ingrowth of soft tissues in graft.

Mourão *et al*[34] (2015) described a technique to obtain an injectable form of PRF called i-PRF. In this technique a short centrifuge for 2 min at 3300 rpm gave an orange color fluid which can be injected or mixed with bone graft to give a well agglutinated "steak" for bone grafting.

Although successful procedures have been reported extensively using Choukran's L-PRF, physicians such as O' Connell[54] had raised concern regarding possible health hazard with the particles of silica in the glass tubes. In spite of the fact that the silica particles are sufficiently dense so as to sediment along with the RBC's, they are small enough so that a fraction of them will remain colloidally suspended in the platelet-poor plasma layers, buffy coat and fibrin and might eventually reach the patient during treatment. In this context a study was done by Dohan Ehrenfest *et al*[9] in 2010 evaluating the cell composition and 3D organization of L-PRF persuaded by different types of collection tubes (such as glass-coated plastic tubes or dry glass) and compression techniques (soft or forcible) on the final L-PRF-membrane architecture. Authors demonstrated that there was no influence of the type of tested tube on the architecture of this second generation PC. However Tunalı *et al*[33] in 2014, introduced a new product called T-PRF (Titanium-prepared PRF). The use of titanium tubes for collection and centrifugation instead of glass tubes was established on the hypothesis that titanium may be a more efficient platelet activator than silica, for preparing L-PRF. Based on light, scanning electron and fluorescence microscopy analysis, Tunalı *et al*[33] concluded that T-PRF has immensely organized network along with a continuous integrity and even the fibrin network was thicker and also it covered larger area.

Anitua *et al*[55] (2015) in an *in-vitro* study, evaluated the outcome of different ozone treatments on biologic properties of PRGF. They found that using "continuous flow protocol" of ozone treatment of PRGF, fibrin scaffold formation, growth factor levels along with proliferative potential was drastically reduced. In contrast, ozone treatment using "syringe method" had no effect on the biological outcomes of this autologous therapy, so ozone therapy in combination with PRGF can be effectively used.

APPLICATION OF PC IN PERIODONTICS AND IMPLANT DENTISTRY

Various *in vitro* studies have demonstrated that PRP exerts

Table 1 Compilation of different platelet concentrates, their discovery and different protocols available

Platelet concentrate type	Method (automated/manual)	Highlights
P-PRP	Cell separator PRP (Automated) Weibrich *et al*[50]	PRP collected by discontinuous method where patient is connected to machine continuously, around 300 mL PRP can be collected. When PRP is obtained from a blood bag of 450 mL, 40 mL of PRP can be obtained per bag. Differential ultracentrifugation employed (3000 g)
	Vivostat PRF (Automated) Leitner *et al*[42]	Type of advanced cell separator designed to produce fibrin sealant It is cumbersome, expensive, have low and damaged platelet yielding capacity
	Anitua's PRGF# (Manual) Anitua[43]	Citrated blood is collected in 5 mL tubes and softly centrifuged for 8 min at 460 g Platelet poor layer (1 mL) is discarded and the PRGF layer above buffy coat layer is pipetted out from all tubes and collected in one tube. Calcium chloride is added for clotting. However there are problem in ergonomy and reproducibility of the procedure
	Nahita PRP (Manual) Tamimi *et al*[44]	Protocol similar to Anitua's PRGF
L-PRP	PCCS PRP (Automated) Weibrich *et al*[45]	Consists of two compartments, citrated blood is transferred into first compartment and centrifuged for a short time. Using air pressure, upper layer PPP and buffy coat are transferred into second compartment and centrifuged for a longer time. PPP is transferred back to first compartment and final product - leukocyte and PRP is left behind. It is no longer available
	SmartPReP PRP (Automated) Weibrich *et al*[46]	It also has two compartments, but requires less manipulation It is a multifunctional system which can also be used to concentrate stem cells from bone marrow transplant
	Megalian APS PRP (Automated) Christensen *et al*[47]	This advanced cell separator had optical reader. It has compact size, designed for small blood samples (upto 50 mL). Although, platelet collection efficacy is high but cell preservation is yet to be known
	GPS PRP (Automated) Martovits *et al*[48]	Another variation of 2 chambers, 2 stage centrifuge protocol PPP is discarded and second centrifuge is with RBC layer. Final PRP is aspirated from the surface of RBC layer
	Friadent PRP (Manual) Weibrich *et al*[46]	Both these techniques employ classical method of 2 stage centrifuge. First soft spin that gives three layers. PPP and buffy coat transferred to another tube and after hard spin the PPP is discarded leaving behind PRP
	Curasan PRP (Manual) Weibrich *et al*[50]	Depending on technique of collecting buffy coat, one can randomly get either P-PRP or L-PRP
	AutoloGel (Automatic) Driver *et al*[49]	The final product was called as "autologous platelet-rich plasma gel"
	Regen PRP (Manual) Plateltex PRP (Manual) Mazzucco *et al*[41]	Both these techniques uses specific jellifying agents such as calcium gluconate and lyophilized purified batroxobin, an enzyme that cleaves fibrino-peptide to induce fibrin polymerization without bovine thrombin and gelling in about 10 min[47] The Regen method also employs a separator gel within the centrifugation tubes to improve collection of platelets and leucocytes
	Ace PRP (Manual) Tamimi *et al*[44]	Similar protocol but with variation in centrifugation force and time and types of anticoagulant
P-PRF	Fibrinet PRFM (Manual) (PRFM Kit, Cascade Medical, New Jersy, United States) Leitner *et al*[42]	Consists of two tubes, one for blood collection and another for PRFM clotting. Around 9 mL blood is collected in a tube containing tri-sodium citrate anticoagulant and a separator gel and centrifuged for 6 min at high speed. Buffy coat and PPP are transferred in second tube containing calcium chloride and centrifuged for 15 min and then stable PRFM clot can be collected. Very low amount of leucocytes are obtained due to the specific separator gel used, however the fibrin matrix is more denser and stable than PRP's
L-PRF	Choukroun's PRF (Manual) Choukroun *et al*[22]	Considered second generation platelet concentrate obtained by natural process without any anticoagulants or jellifying agents Venous blood collected and centrifuged at low speed yielding and RBC layer, PRF clot in middle and acellular plasma top layer The PRF clot can be pressed between guage to make a strong membrane
	Intra-Spin[9] (Manual) (Intra-lock, United States)	The only FDA approved kit for PRF. It employs 9 mL glass coated plastic tube, centrifuged at room temperature at 2700 rpm (around 400 g) for 12 min. Contains and Xpression kit to compress the clot to make membranes
	Titanium-prepared PRF (experimental) (Manual) Tunalı *et al*[33]	The platelet activation by using titanium tubes instead of glass tubes seems to offer some high characteristics to T-PRF The PRF obtained was highly organized and with continuous integrity. The fibrin meshwork is thicker and covers larger area
	Other non FDA cleared centrifuge to produce L-PRF: Salvin 1310 (Salvin Dental) and LW-UPD8 (LW Scientific)	Studies have shown that as compared to Intra-spin, these 2 machines produces more vibration and resonance

CGF	Medifuge, Silfradent srl, Italy Sacco[26]	Permits the isolation of a much larger, denser fibrin matrix which is richer in growth factors Demonstrates presence of TGF-b, VEGF and $CD34^+$
Sticky Bone	Sohn[29]	Autologous fibrin glue mixed with bone graft
T-PRF	Tunalı *et al*[33]	Titanium tubes were used for collection and centrifugation instead of glass tubes
A-PRF	(Advanced PRF Process, France) Choukroun[32]	Earlier vascularization, faster soft tissue growth, more cytokines and release of BMPs
i-PRF	Mourao *et al*[34]	Blood collected in 9 mL tube without any additive, centrifuged for 2 min at 3300 rpm, the resultant orange color fluid in the tube is the i-PRF

PCCS: Platelet concentrate collection system; APS: Autologous platelet separator; PRP: Platelet-rich plasma; PRGF: Plasma rich in growth factors; PRF: Platelet-rich fibrin; TGF: Transforming growth factor; VEGF: Vascular endothelial growth factor; GPS: Gravitational platelet separation system.

positive effects on gingival fibroblasts[56], oral osteoblasts[57], and periodontal ligament (PDL) fibroblasts[58], making it an ideal candidate to facilitate complete periodontal regeneration. PRP may also benefit surgical sites and wound healing *via* its antibacterial properties. This antimicrobial effect has been reported against bacteria such as *Staphylococcus aureus*[59], *Escherichia coli*[60], and *Klebsiella pneumonia*[61]. PRP was also found to be active against oral microorganisms, including *Enterococcus faecalis, Candida albicans, Streptococcus agalactiae,* and *Streptococcus oralis*[62], reinstating that PRP is a potentially useful substance in fighting postoperative infections.

Applications in periodontics

Application of PRP to bone graft material has demonstrated earlier bone regeneration and soft tissue healing[21]. PRP can also retard epithelial migration by infusing it into resorbable barrier membranes. This will also provide localized source of growth factors that will accelerate soft tissue and hard tissue maturation[63]. Agrawal and Gupta[64] (2014) in a split mouth study concluded that a combination of PRP with DFDBA was more efficient than DFDBA with saline for the management of non-contained intrabony defects. In addition to this, a combination of PRP with bovine porous bone mineral and GTR membrane also showed good clinical response[65]. Combination of PRF and bone graft has also reported exceptional results in periodontic-endodontic furcation defect[66]. However, Choi *et al*[67] questioned the benefits of mixing PRP and bone graft material, expressing their concern that it interfere new bone formation. According to the authors, growth factors when present in high concentrations at inappropriate times for prolonged duration can negatively affect the cell behavior. They further affirmed that proliferation and viability of alveolar bone cells are quashed by high PRP concentrations but are accelerated by low PRP concentrations[68].

PRF is a powerful healing biomaterial with inherent regenerative capacity and can be used in various procedures such as periodontal intrabony defects[69,70], treatment of furcation[71], sinus lift procedures[72] and as application in the field of tissue engineering, it can be used as a scaffold for human periosteal cells *in vitro*[73]. Eren and Atilla[74] in 2012 treated bilateral gingival recession with (CAF) coronally advanced flap and (SCTG) subepithelial connective tissue graft on one side and CAF with PRF on other side. They found improvement in all parameters with both the techniques. Since use of PRF was practical and simple to perform and also eliminates the requirement of donor site wound, they suggested that CAF + PRF as a better alternative to CAF + SCTG. Anilkumar *et al*[75], reported PRF as a probable but innovative approach for root coverage in treating gingival recession in mandibular anterior region using combination of PRF membrane and laterally positioned flap technique. Aroca *et al*[76] in a randomized clinical trial concluded that addition of a PRF membrane placed under the MCAF (modified coronally advanced flap) provided additional gain in gingival/mucosal thickness but inferior root coverage over 6 mo follow up period compared to the conventional therapy.

Applications in implantology

Choi *et al*[77] in 2006 conducted an animal study to compare the sinus lining perforation repair using either the (AFG) autologous fibrin glue or the collagen membrane. Their histological evaluation found that in repaired wounds, where AFG was used, demonstrated newly regenerated continuous epithelium across the original perforation site as compared to collagen membrane treated site where there was no epithelium, inflammatory infiltration was seen along with extensive fibrosis even after 2-wk of healing. Literature reports the applications of PRP in continuity defects[78], sinus lift augmentation[79,80], vertical/horizontal ridge augmentations[81], ridge preservation[82], periodontal/peri-implant defects[83]. Several articles have reported the use of L-PRF membranes for the stimulation of bone and gingival healing during sub-antral sinus augmentations[72] and global rehabilitations using dental implants[84,85]. The effect of these membranes on soft tissue healing and maturation is particularly significant[86]. In yet another case report, Del Corso *et al*[87] in 2012 used L-PRF in immediate implant replacement of maxillary central incisor and reported excellent healing and esthetics. Choukroun *et al*[88] studied the effect of PRF with (FDBA) freeze-dried bone allograft to augment bone regeneration in direct sinus lifting and found accelerated bone regeneration.

Simonpieri *et al*[84,85], in a two-part publication, reported an innovative technique for maxillary reconstruction using PRF membranes, FDBA and 0.5% metronidazole solution. A 0.5% metronidazole solution (10 mg) in small quantity provides an effective shielding of the bone graft material against unavoidable bacterial contamination[89]. The membrane component of PRF was used to guard the surgical site and enhance the soft tissue healing.

However the PRF fragments were blended with the graft particles. They also suggested that the PRF membranes can be trimmed into fragments (millimeter size) and added to graft material, functioning as a "biological connector" between the different elements of the graft, and will form a matrix which will promote the migration of osteoprogenitor cells to the center of the graft, neo-angiogenesis and capture of stem cells[90,91]. Using the protocol reported in the literature, they frequently observed a greater degree of gingival maturation post-healing. They also noticed thickening of keratinized gingival tissues that eventually enhanced the esthetic integration and final result of their prosthesis. Moreover, all their clinical experiences highlighted that the use of PRF seemed to reduce postoperative edema and pain, and even minor chances of infectious phenomena[85]. PRF can be condensed to make plugs which can be positioned in the implant osteotomy site to promote sinus floor elevation using a crestal core elevation (CCE) procedure[92] or osteotome-mediated sinus floor elevation (OMSFE) with simultaneous implant placement[93]. PRF can not only be used as a substitute for particulate grafting to predictably elevate the sinus floor using a crestal approach, but PRF can also provide protection for the sinus membrane during the use of an osteotome. Even in case of sinus membrane perforation, the fibrin matrix can aid in wound closure[77,94]. PRF plugs can also be indicated in management of residual extraction sockets[95]. A technique in which autologous PRF is used in extracted socket after immediate bone augmentation using titanium membranes applied to the socket walls and achieving primary closure, was found to be feasible and safe with adequate bone filling after 8 wk or above for implant fixation[96]. Hafez *et al*[97] in 2015 demonstrated that PRF membrane maintains particulate autogenous bone graft and help achieve primary coverage over immediately placed implants. Sohn *et al*[53] compared CGF membrane and collagen membrane for alveolar ridge augmentation. Their bone biopsy results showed favorable new bone formation along mineral allograft without sign of inflammation. They also evaluated three dimensional ridge augmentation using sticky bone with or without use of titanium mesh, and found favorable augmentation even without the use of titanium mesh[53].

The use of platelet and immune concentrate during bone grafting offers the following 4 advantages[85]: Firstly, the fibrin clot plays an important mechanical role, wherein the PRF membrane maintains and protects the bone graft and its fragments, when incorporated in the body of bone graft, serving as biological connectors between bone particles. Secondly, the fibrin network promotes cellular migration, particularly for endothelial cells which are necessary for the neo-angiogenesis[40], vascularization and survival of the graft. Thirdly, the platelet cytokines (PDGF, TGF-beta, IGF-1) are creating a perpetual process of healing gradually released as the fibrin matrix is resorbed[84,98]. Lastly, the leukocytes and cytokines in the fibrin network play a significant role in the self-regulation of inflammatory and infectious phenomena within the grafted material[99].

DISCUSSION

In preparation of PRP, the choice of anticoagulant used is an important parameter in its capability of preserving the platelets' best possible functionality, integrity and morphology. In particular do Amaral *et al*[100] (2016) concluded that the use of (EDTA) ethylene-diamine-tetra-acetic acid yielded more platelet in whole blood; however, it increased the mean platelet volume (MPV) following the blood centrifugation steps required for obtaining PRP. Authors also discovered that the use of (ACD) anticoagulant citrate dextrose and sodium citrate (SC) significantly induced mesenchymal cell (MSC) proliferation. Moreover, PRP obtained in sodium citrate anticoagulant not only presented higher platelet recovery after the first centrifugation step but also had a minimal change in MSC gene expression. Citrate seems to be a suitable anticoagulant, because it has been recently shown that thrombin-activated PRP releases all growth factor at the same time in a bolus, while non-activated PRP uses the platelets as a sustained delivery system, exhibiting the best wound healing effects[101]. PRP is not routinely used nowadays because of complicated preparation techniques, expensive procedure and offer quite mixed clinical results[2,3]. On the other hand, the L-PRF family has developed very fast over the last years, as the technique is very simple and useful in daily practice, it is user friendly and relatively inexpensive[11].

One logical question that comes to a clinician is how much rich is PRP or PRF? What is the difference of richness in these PC's? Literature reports a range of less than 2 fold to around 8.5 fold increase in platelets. In a classification of PRP, Mishra *et al*[30] suggested a sub-classification of PRP into A and B, where a 5-fold platelet concentrate may be a relevant baseline for definition of PRP (it should also be noted that concentrations greater than 5-fold gave better clinical results). Another aspect of this definition is that this baseline is not universal and may not be valid for all clinical applications. Weibrich *et al*[102] suggested that different individuals may require different platelet concentration ratios to achieve comparable biological effect.

Although leukocyte rich and leukocyte poor PRP's have their own place in literature, the importance of non-platelet components in a platelet concentrate remains a mystery. Parrish *et al*[103] 2016, in an *in-vitro* study demonstrated that leukocyte poor PRP (LP-PRP) showed poor coagulation and poor platelet growth factor release compared to whole blood and leukocyte rich PRP (LR-PRP). They also checked tendon cell proliferation *in-vitro* using serum from LP-PRP and LR-PRP and found greater advantages with the later. LP-PRP was inferior even to whole blood. Thus they concluded that cellular components other than platelet, that are usually eliminated during the course of PRP preparation, are important for efficient functioning of platelets including its thrombin generation, growth factor release and capacity for cell proliferation[103]. However, these findings need to be confirmed *in-vivo* to make them more justifiable. In addition to this, difference in the

age of patient from who's blood PRF is made also differs structurally and qualitatively. In a recent study, Yajamanya *et al*[104] (2016) evaluated fibrin network pattern changes of PRF in young and old age groups using a cell-block cytology method. They found that in progressing age groups there was significant decrease in dense and increase in loose fibrin network. They also discovered reduction in the number of platelets and WBC's entrapped within fibrin network with increasing age groups.

It has always been a common thought that L-PRP or L-PRF would give an additional advantage over P-PRP or P-PRF due to the presence of immune cells, *i.e.*, leukocytes. Does that mean that platelets do not have any role to play in immunity? Numerous studies have emphasized that human platelets are a good source of antimicrobial peptides such as: Thymosin β4, platelet basic protein, platelet factor 4, connective tissue activating peptide Ⅲ, fibrino-peptides A and B and chemokine (C-C motif) ligand 5[105]. There are special receptors on the platelets that are known to aggregate with bacteria. Platelets also participate in generating oxygen metabolites, including hydrogen peroxide, superoxide, and hydroxyl free radicals[106]. Largely, platelets demonstrate impressive activities against the blood-borne pathogens and also play an important role in the innate host defense against the initiation and progression of infections[106]. In fact Garraud *et al*[107] in 2015 claimed that "platelets are innate and inflammatory cells and do not only assist immunity but are immune cells themselves". Anitua *et al*[61] demonstrated that even if an additional dose of leukocytes was present it did not significantly enhance the antimicrobial properties of PRP. Yang *et al*[108] (2015) in a study evaluated the antimicrobial activity of four plasma preperations: PRP, platelet poor plasma (PPP), platelet depleted plasma (PDP) and PRF. Using haemocytometer, they found leucocytes only in PRP and not in other preparations. However, their results showed that all plasma preparations were efficient enough to inhibit bacterial growth for > 24 h with PRP as the strongest antimicrobial agent. In terms of time-kill assay, authors discovered that PRP, PPP and PDP had similar effect on *F. nucleatum* indicating that it was sensitive to the antibacterial agents in plasma. The poor antimicrobial effect of PRF was attributed to the fact that a mesh of fibrin was formed in PRF, which adsorbed these agents and thus exerted less minimal effect on the growth inhibition of this microorganism. However, one should note that the technique of PRF preparation was not according to the L-PRF protocol given by Choukroun *et al*[22] in 2000. To make PRF, Yang *et al*[108] used fraction of PRP and activated it by 23 mmol/L of calcium chloride for 30 min and centrifuged again at 6000 g for 30 min to recover "fibrin-free supernatant" which they labeled as PRF. Hence, although their experiment highlighted the antimicrobial effect of plasma, regardless of platelet and leukocyte concentration, their conclusion of PRF should be read with caution. The basic biological difference between PRP and PRF is that in PRP the polymerization is artificially provoked and there is extrinsic growth factor enmeshment, whereas in PRF there is natural polymerization with intrinsic growth factors enmeshment. When compared *in-vitro*[109] studies have revealed that most of the growth factors from P-PRP gel are released in the first hours after preparation and get completely dissolved in the medium after 3-d. In contrast the L-PRF membrane not only remained intact and solid after 7-d but also continuously released large quantities of growth factors. These growth factors are sustainably released for at least 1 wk up to 28 d[110]. This allows PRF to stimulate the environment for a significant time during wound healing. As a general concern, at the time of any surgery, platelets will start collecting at the surgical site to initiate clotting and healing, which may reduce the whole blood platelet count[111]. As such, it is recommended that blood should be drawn before the surgery starts because the surgery itself might cause platelet activation and that may eventually interfere with preparation of platelet concentrate[112,113]. Also the massive release of TSP-1 from PRF membrane has opened up a new range of application for this membrane[8].

Considering technical aspects for preparation of PRP, for the first centrifuge it is best to keep the speed and time to the shortest that will separate the RBC's and plasma clearly. In the second centrifuge the time and speed should be sufficiently high so that more platelets will precipitate without destroying them[39]. Ehrenfest *et al*[114], claimed that for small table centrifuges, the most relevant parameters to be logically evaluated was the vibrations of those centrifuge, the vibration shocks at the time of acceleration and the eventual resonance. All these mechanical properties may impede with the quality and biological signature of the final L-PRF product. The authors tested 4 different centrifuges; *viz*: The original L-PRF centrifuge (Intra-Spin, Intra-Lock) and 3 other laboratory centrifuges: Salvin 1310 (Salvin Dental), LW - UPD8 (LW Scientific) and the A-PRF 12 (Advanced PRF, Process). They demonstrated even if the centrifuges were used in the same conditions and at the same speed there was a significant discrepancy in their vibration levels and 3 out of four quickly reached a threshold of resonance. They found "Intra-Spin" to be the most stable machine tested. At the traditional speed of production of L-PRF, the level of undesirable vibration was between 4.5 and 6 times lower with this machine than with other centrifuges. Moreover, Intra-Spin always stayed under the threshold of resonance, as compared to the other three tested machines[114].

CONCLUSION

There have already been many technological advancement in preparing and understanding the various types of PC from random single spin centrifugation to fully automated commercially available systems. However, the characterization of such complex products seems to remain incomplete due to the number of parameters involved. Apart from presence or absence of leukocytes, whether or not the activation is carried out, other

parameters that should be taken into consideration are the quantity or rate of platelet collection, the quantity and rate of leukocyte collection, cell composition and preservation during collection, transportation and centrifugation. As discussed earlier, the parameters particular to the centrifuge used are also important such as: Its size, vibration, the duration of centrifugation. Other than that, the cost involved, ergonomics, the form and volume of final product, *etc*., also need to be taken into consideration while evaluating newer techniques, commercial products, classification systems or indications for their application in medicine and dentistry. With L-PRF being more user friendly and economic, this arsenal is finding wider applications in surgical field. The introduction of i-PRF will also find suitable applications, where injectable form of platelet concentrate is required. Looking at the current trends PRP and L-PRF are most commonly used and have been researched upon. Newer advances such as A-PRF, i-PRF, t-PRF, CGF and sticky bone concept have been reported in single or few cases but no long term or controlled trial have been done to prove the advantage of their advancement over conventional PRP and PRF. So clinicians should use the advancements with caution.

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ORIGINAL ARTICLE

Observational Study

Robotic single-site supracervical hysterectomy with manual morcellation: Preliminary experience

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Abstract

AIM

To evaluate the feasibility, safety and peri- and post-operative outcomes of robotic single-site supracervical hysterectomy (RSSSH) for benign gynecologic disease.

METHODS

We report 3 patients who received RSSSH for adenomyosis of the uterus from November 2015 to April 2016. We evaluated the feasibility, safety and outcomes among these patients.

RESULTS

The mean surgical time was 244 min and the estimated blood loss was 216 mL, with no blood transfusion necessitated. The docking time was shortened gradually from 30 to 10 min. We spent 148 min on console operation. Manual morcellation time was also short, ranging from 5 to 10 min. The mean hospital stay was 5 d. Lower VAS pain score was also noted. There is no complication during or after surgery.

CONCLUSION

RSSSH is feasible and safe, incurs less postoperative pain and gives good cosmetic appearance. The technique of in-bag, manual morcellation can avoid tumor dissemination.

Key words: Robotic surgery; Single-site; Supracervical

hysterectomy; Single port; Subtotal hysterectomy

Core tip: Robotic single-site surgery (RSS) is feasible and safe in performing supracervical hysterectomy for benign gynecologic disease. Less pain and cosmetic value are important advantages of RSS. Manual morcellation can be done through single port setting.

Ding DC, Hong MK, Chu TY, Chang YH, Liu HW. Robotic single-site supracervical hysterectomy with manual morcellation: Preliminary experience. *World J Clin Cases* 2017; 5(5): 172-177 Available from: URL: http://www.wjgnet.com/2307-8960/full/v5/i5/172.htm DOI: http://dx.doi.org/10.12998/wjcc.v5.i5.172

INTRODUCTION

The first laparoscopic subtotal hysterectomy (LSH) was reported in 1991[1]. Retaining the cervix may preserve sexual, urinary and bowel function[2].

LSH is approached in the same manner as total laparoscopic hysterectomy (LTH). After uterine vessels are secured, the cervix is transected at the level of internal os. However, the ascending branch of uterine vessel is sometimes hard to approach. During transection, severe bleeding may occur. Amputation of the cervix is also a time-consuming procedure. The loop is also designed for cervical amputation and could save 80% of the time required for performing this procedure[3]. Retrieval of uterine corpus after the transection was achieved by mechanical or manual morcellation through an extended abdominal port[4]. The mean surgical time of LSH ranged from 70 min to 134 min[5]. Complications and outcomes are comparable with those of LTH. Above all, the technique involved in LSH is more difficult than LTH because of the time required for amputation of cervix.

Robotic assisted hysterectomy (RAH) has been increased from 0.5% in 2007 to 9.5% in 2010[6,7]. Although RAH is a safe approach to hysterectomy, but the longer surgical time required[8-10]. Compared to open surgery, RAH provides advantages for reduced length of hospital stay and blood transfusions[11].

Laparo-endoscopic single-site surgery (LESS) offered a new way to perform minimally invasive gynecological surgery[12-14]. The advantages of LESS included less postoperative pain, lower dosage of analgesic required[13], greater cosmetic satisfaction[14], lower morbidity and comparable outcomes compared with those of standard laparoscopic surgery[14,15]. Nevertheless, LESS involves technical challenges such as loss of port triangulation, clashing of instruments and long learning curve. Robotic single-site surgery (RSS) may provide advantages to overcome these shortages[16,17].

Table 1 Characteristics of patients received robot single-site supracervical hysterectomy

Patient	1	2	3	Mean
Diagnosis	Adenomyosis	Adenomyosis	Adenomyosis	
Age (yr)	44	43	48	45
BMI (kg/m^2)	22.5	23.6	26.6	24.2
Previous surgery	Partial oophorecotmy	Nil	C/S	
Largest diameter of uterus (cm)	8	10	11.9	10
Total op time (min)	200	233	300	244.3
Docking time (min)	30	20	10	20
Console time (min)	120	160	165	148.3
Morcellated time (min)	5	5	10	6.7
Blood loss (mL)	100	300	250	216.7
VAS (1 h)	3	4	4	3.7
VAS (24 h)	3	4	2	3
VAS (48 h)	0	2	0	0.7
Hospital stay (d)	4	4	4	4
Complication	0	0	0	0

VAS: Pain score; BMI: Body mass index.

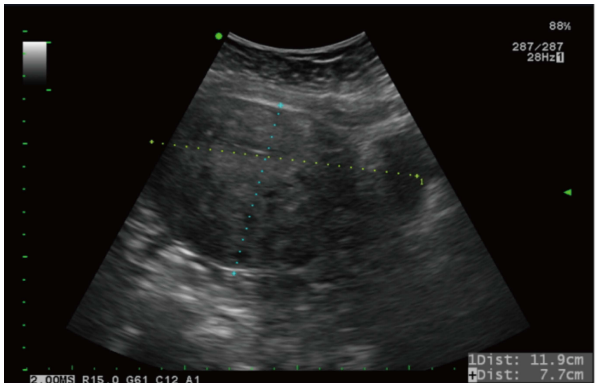

Figure 1 Ultrasound of adenomyosis of uterus. The largest diameter of uterus measured was 11.9 cm.

Here we described supracervical hysterectomy performed with single-site da Vinci Surgical System (Si version, Intuitive Surgical, Sunnyvale, CA, United States) in three patients affected by adenomyosis of the uterus.

MATERIALS AND METHODS

Three women presented with adenomyosis of the uterus complicated with menorrhagia and dysmenorrhea. Two patients had previous history of abdominal surgery. One woman had anemia (Hb: 10.3 g/dL) (Table 1).

Abdominal ultrasound was performed for all patients; their maximum diameters of uterus were listed in Table 1. Figure 1 shows the uterus of the largest diameter of 11.9

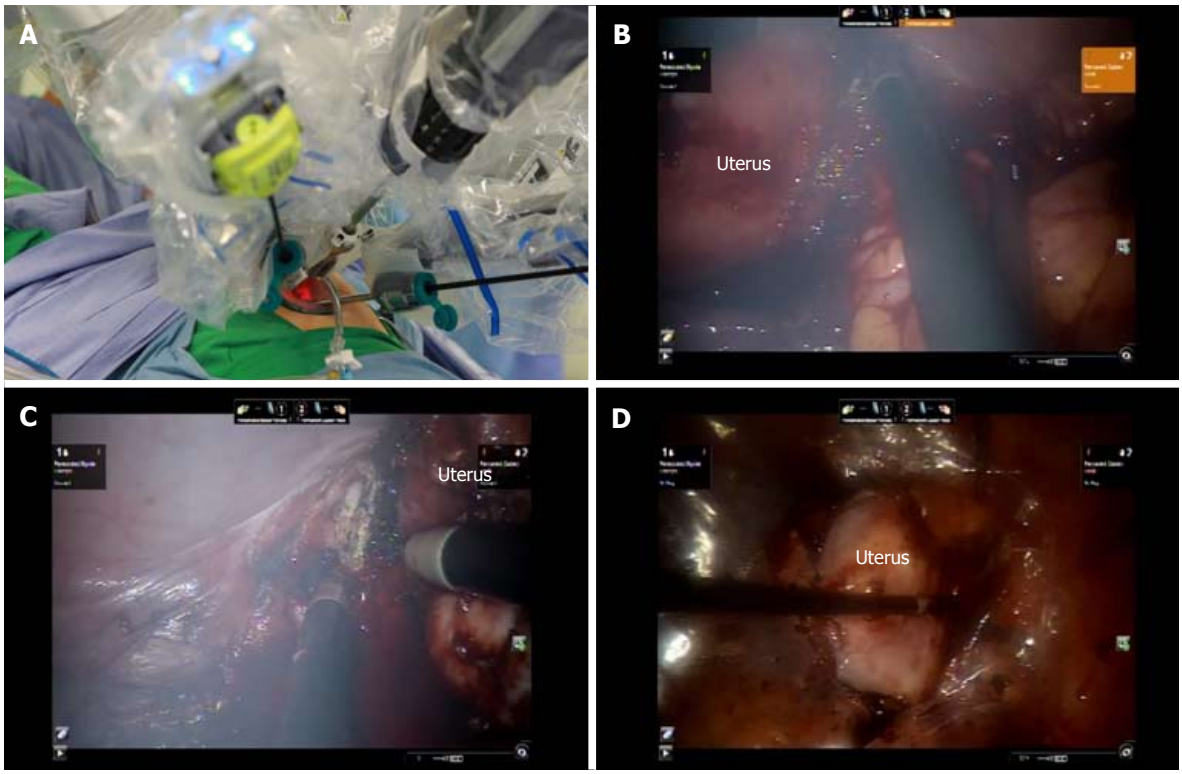

Figure 2 Intraoperative view of supracervical hysterectomy. A: Placement of robotic trocars using a single-site device; B: Cutting right cervical region; C: Cutting left cervical region; D: Amputated uterus placed into tissue bag.

cm with the suspected lesion of adenomyosis located at the posterior uterine wall.

The patients were then scheduled for robotic-assisted supracervical hysterectomy. The single-port device is a multichannel non-reusable specific port with space for four cannulas and an insufflation valve. A target anatomy arrow indicator is marked on the cannula. Two 25-cm curved cannulas for robotic instruments, one cannula for the high-definition three-dimensional endoscope, and one 5-mm assistant cannula were used in the surgery.

The uterine manipulator was placed to adjust the uterine position. After catching the bilateral skin along the umbilicus with two Allis clamps, a 2-cm midline umbilical skin incision was made. Through this incision, a wound retractor (Lagis, Taichung, Taiwan) was introduced into the abdominal cavity, then a single-site port (da Vinci Surgical System) was introduced into the abdominal cavity grasped by an atraumatic clamp through the wound retractor.

The patient was placed supine in lithotomy position with 30° Trendelenburg position, and the robotic patient cart was positioned between the patient's legs. Then the robotic arms were opened in the opposite position. The 30° endoscope was placed in camera trocar and a watchful inspection of total abdominal cavity was performed.

Then the other three cannulas were inserted through the port and their positions were adjusted according to the scope view and mark. The remaining cannula was placed in front of the uterus and then held still to allow docking. Finally, robotic instruments including fenestrated bipolar and hook unipolar instruments were introduced (Figure 2A). One Veress needle (COVIDIEN) was inserted at suprapubic region under direct vision by endoscope for evacuation the smoke. After cutting both right and left endocervical regions (Figure 2B and C), the amputated uterus was rolled and placed into a tissue bag (Cook, Figure 2D). Then the robot was undocked and the tissue bag was grasped to the umbilical port using an assistant port grasper. Then the uterus was manually morcellated from the umbilical wound (Figure 3A) and all morcellated pieces were placed onto a plate (Figure 3B). Then one sheet of Seprafilm was cut into four pieces and placed with or without docking robot arms onto surgical sites to prevent adhesion (Figure 3C). After all robotic procedures were completed, the umbilical wound was closed using interrupted 0 Vicryl for the fascia layer and 3-0 Vicryl for the subcutaneous layer (Ethicon, Figure 3D).

Statistical analysis

Statistics using Student's *t*-test was performed when compare pain score of the two groups, and the differences between the groups were considered significant at $P < 0.05$.

RESULTS

The mean operative time was 244 min and the estimated blood loss was 216 mL (Table 1), with no blood transfusion necessitated. The docking time was shortened gradually

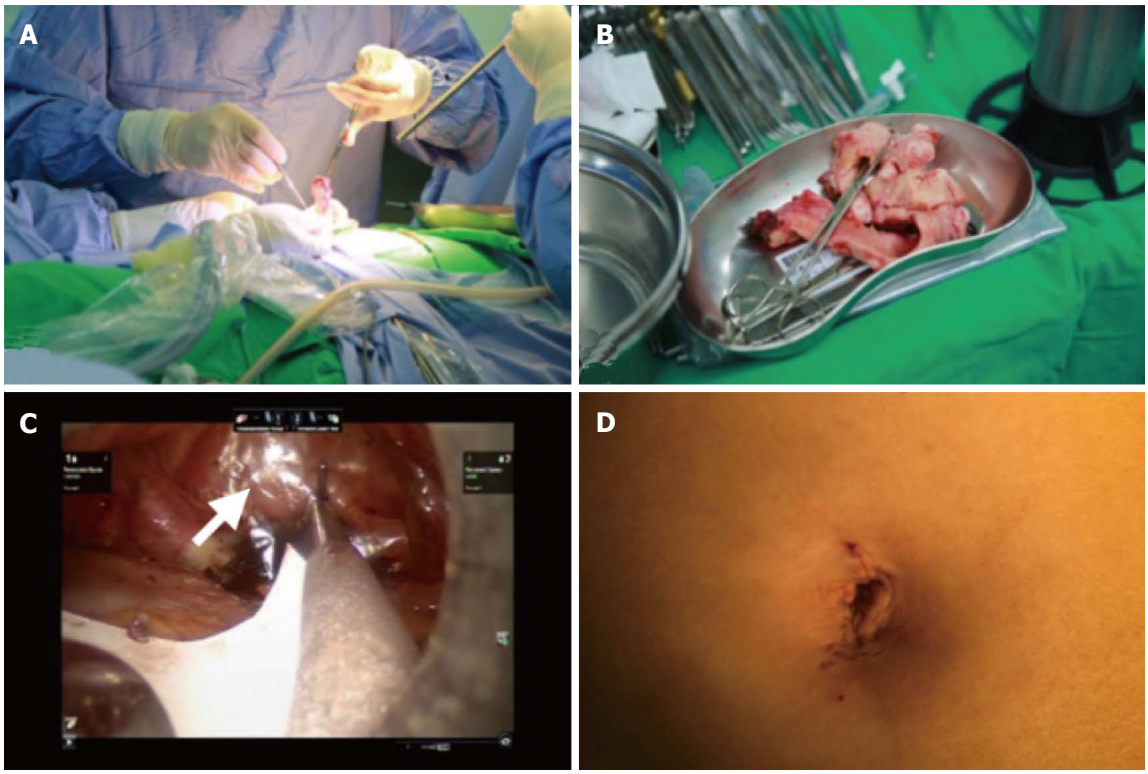

Figure 3 Intraoperative view of manual morcellation of the uterus and the placement of seprafilm. A: Manual morcellation of uterus through the single-site wound; B: Morcellated uterus; C: Seprafilm placed onto surgical sites (arrow); D: Postoperative umbilical scar.

from 30 to 10 min. We spent 148 min on console operation. Manual morcellation time was also short, ranging from 5 to 10 min. The post-operative course was uneventful and all patients were discharged 3 d after operation. The VAS pain score was 3.7, 3.0 and 0.7 at 1, 24 and 48 h, respectively. The mean hospital stay was 4 d. The surgical specimens conformed adenomyosis of the uterus. There is no complication during or after surgery.

DISCUSSION

Single-site surgery has become popular due to improved cosmetic appearance, multiple incisions avoided, and minimal post-operative pain and recovery time[13,14]. Nevertheless, LESS surgery is characterized by longer surgical time and technical challenge. Robotic single-site surgery (RSS) is the same as LESS, but the instrument was more ergonomic compared with other single-site methods[18,19]. In our experience, RSS supracervical hysterectomy (SH) is a valid alternative to laparoscopic and standard robotic SH and provides the same surgical outcome.

There is only one study report on the RSSSH experience in gynecology[20]. However, there is no detailed information regarding RSSSH except the number of patients while there are several reports on RSS hysterectomy (RSSH)[16,18,21-23]. RSSH was first reported in 2011[23] and concluded to be feasible offering several advantages such as smaller scar, less pain and the same outcome compared with standard robotic surgery[23]. Moreover, in preclinical models of human cadavers, the RSS technique is effective and reproducible in various gynecological surgeries[24].

There is a more surgical time in RSSSH than in RSSH. The total surgical time is 134 min in RSSH but 244 min in RSSSH[19]. The cause of more surgical time may be attributed to our initial experience and the type of surgery performed. The pelvic adhesiolysis have also contributed to longer operating time. A lot of surgical time was spent in the endocervical ring cutting. The cutting efficiency of robot hook is not efficient. Coagulate the bleeding caused by cutting the endocervical ring is also time consuming. However, we assume the surgical time can be shortened after more surgical experiences.

There is more blood loss after RSSSH than after RSSH[19]. The mean blood loss is 50 mL in RSSH but 240 mL in RSSSH. The cause of greater blood loss may be attributed to our initial experience and the type of surgery performed. In RSSH, the vagina is cut after securing the uterine vessels. However, in RSSSH, the ascending branch of uterine vessels cannot be easily secured using a bipolar instrument. Therefore, after cutting the bilateral endocervical region, bleeding can sometimes be vigorous. This condition is the same for LESS supracervical hysterectomy[25].

The advantage of RSS is less post-operative pain, thus necessitating less pain control[13,14]. This study also demonstrated these advantages. The VAS pain score was 3.7, 3.0 and 0.7 at 1, 24 and 48 h, respectively. In contrast, the VAS in LESS hysterectomy was 5.6, 3.7 and

Table 2 Comparison of postoperative pain

Time	LESS hysterectomy (n = 36)	RSSSH (n = 3)	P value
VAS pain score			
0-2 h	5.68 ± 2.11	3.7 ± 0.6	< 0.05
24 h	3.75 ± 1.61	3.0 ± 1.0	> 0.05
48 h	2.25 ± 1.59	0.7 ± 1.6	< 0.05

LESS: Laparoendoscopic single-site surgery; RSSSH: Robot single-site supracervical hysterectomy; VAS: Visual analog scale.

2.2 at 1, 24 and 48 h, respectively (Table 2)[13], indicating significantly lower VAS pain score in RSSSH than in LESS hysterectomy at 1 and 48 h (P < 0.05). Infiltration wound with ropivacaine or other long-acting local anesthetics also provide good pain control[19,26].

The mean hospital stay in this study is 4 d. Nevertheless, the hospital stay is only 3 d in the previous study[19]. The long hospital stay in our study is due to the health insurance in our country. The insurance offers the patient can stay in hospital for 4 d.

Power morcellation had been widely used in laparoscopic surgery to speed removal of specimen[27]. However, owing to the risk of leiomyosarcoma dissemination after power morcellation, removal of specimen in a bag was suggested[28,29]. Therefore, techniques for safe specimen removal have been reported[30]. We also developed a technique of manual morcellation[31]. In this study, we used the same technique for placing the specimen into a tissue bag and for manual morcellation through the single-port wound. This morcellation method is relatively safe without tumor cell or tissue dissemination.

The use of Seprafilm as adhesion barrier was approved by the FDA in 1996. However, Seprafilm is seldom used in laparoscopic surgery because it easily breaks and sticks[32]. We applied a simple technique (using wet gauze and paper roll) for rapid and safe placement of Seprafilm onto the surgical sites[33].

Another problem encountered during RSS is surgical smoke that could influence the vision. With RSS using both unipolar and bipolar energies, there is no additional port for passage of smoke in the single-port device. To overcome this problem, a small Veress needle is used for smoke release, thus achieving good vision outcome.

In conclusion, we demonstrated that RSSSH is feasible and safe in gynecologic patients. Less postoperative pain and greater cosmetic satisfaction were the major advantages of RSSSH. The technique of in-bag, manual morcellation could avoid tumor dissemination. Nevertheless, randomized study and the outcome of long-term follow-up are still needed in the future.

COMMENTS

Background

Minimally invasive surgery has been popular in gynecologic surgery. Therefore, despite conventional multi-port laparoscopic surgery, laparoscopic single-site surgery (LESS) emerges since 2009. However, there are some technical difficulties and instrument design hurdling the progress of LESS. Nevertheless, Robotic single-site surgery (RSSS) solves the technical and instrument problems in LESS.

Research frontiers

RSSS is in its beginning stage. Although there are several papers discussing the RSSS, there is still a lot of space to improve the RSSS on supracervical hysterectomy (SH). The authors attempted to use RSSS to perform SH and to test if RSSS is a feasible and safe method to perform SH.

Innovations and breakthroughs

The present study demonstrated RSSSH is a feasible and safe method for the patients with adenomyosis of the uterus.

Applications

The data in this study suggested that RSSSH could be a feasible and safe modality for patients with adenomyosis of the uterus.

Terminology

Adenomyosis of the uterus is a condition of endometrial glands presented in the myometrium and enlarged of the uterus. The symptoms of adenomyosis are including dysmenorrhea and menorrhagia that cause the major reason for women receiving hysterectomy.

Peer-review

The authors investigated the feasibility of RSSSH for adenomyosis of the uterus and found that this approach is safe and acceptable in the management of the similar patients in the future based on the analysis of outcome from the 3 patients.

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CASE REPORT

Ticagrelor therapy and atrioventricular block: Do we need to worry?

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Informed consent statement: The patients involved in this study gave their oral informed consent authorizing use and disclosure of their protected health information. At our Institution informed oral consent is regarded as sufficient for case reports/editorial.

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Abstract

Ticagrelor is a potent, direct P2Y12 antagonist with rapid onset of action and intense platelet inhibition, indicated in patients with acute coronary syndromes (ACS). This drug is usually well tolerated, but some patients experience serious adverse effects: Major bleeding; gastrointestinal disturbances; dyspnoea; ventricular pauses > 3 s. Given the unexpected high incidence of bradyarrhythmias, a PLATO substudy monitored this side effect, showing that ticagrelor was associated with an increase in the rate of sinus bradycardia and sinus arrest compared to clopidogrel. This side effect was usually transient, asymptomatic and not associated with higher incidence of severe atrioventricular (AV) block or pacemaker needs. A panel of experts from Food and Drug Administration did not consider bradyarrhythmias a serious problem in clinical practice and, accordingly, current labeling of the drug does not give any precaution or contraindication regarding this issue. However, recently some articles have described ACS patients with high-degree, life-threatening, AV block requiring drug discontinuation and, in some cases, pacemaker implantation. In this paper, we describe and discuss five published case reports of severe AV block following ticagrelor therapy and two other cases managed in our Hospital. The analysis of literature suggests that, although rarely, ticagrelor can be associated with life-threatening AV block. Caution and careful monitoring are required especially in patients with already compromised conduction system and/or treated with AV blocking agents. Future studies, with long-term rhythm monitoring, would help to define the outcome of patients at higher risk of developing this complication.

Key words: Ticagrelor; Atrioventricular block

Core tip: Ticagrelor is a potent, direct antiplatelet agent with rapid onset of action and intense platelet inhibition, indicated in patients with acute coronary syndromes (ACS). Even if well tolerated, some patients experience bradyarrhythmias complications, especially sinus bradycardia and sinus arrest. This effect is usually transient, asymptomatic and not associated with higher incidence of severe atrioventricular block. However, recent articles have described ACS patients with high-degree atrioventricular block requiring drug discontinuation and, in some cases, pacemaker implantation. In this paper, we describe and discuss five published reports and two other cases managed in our Hospital. We conclude that, although rarely, ticagrelor can be associated with life-threatening atrioventricular block. Caution and careful monitoring are required especially in patients with already compromised conduction system and/or treated with atrioventricular blocking agents. Future studies, with long-term rhythm monitoring, would help to define the outcome of patients at higher risk of developing this complication.

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INTRODUCTION

Ticagrelor is a potent, direct P2Y12 antagonist with rapid onset of action and intense platelet inhibition. Unlike clopidogrel and prasugrel, it is not a thienopyridine and is not a prodrug. In patients with acute coronary syndromes (ACS) ticagrelor was superior to clopidogrel in reducing major adverse cardiac events and had a similar efficacy compared to prasugrel[1].

Ticagrelor is usually well tolerated, but some patients can experience serious adverse effects: Major bleeding (but rates are lower compared with other potent antiplatelet agents); gastrointestinal disturbances; dyspnoea; ventricular pauses > 3 s[1].

Given the unexpected high incidence of ventricular pauses in the landmark PLATO trial, this side effect was monitored by a prospectively designed, continuous electrocardiograph (ECG) monitoring substudy, including about 3000 patients[2]. In this study ticagrelor was associated with an increase in the rate of ventricular pauses > 3 s compared to clopidogrel (5.8% *vs* 3.6%, RR = 1.61, P = 0.01), mainly due to sinoatrial nodal pauses. This finding was only seen during the first week of therapy, while the incidence at 30 d was very low and similar between the two groups. Moreover, the great majority of pauses was asymptomatic and - even more important - there was no differences in the incidence of atrioventricular (AV) block or pacemaker need between groups[2].

As a consequence of this study[2] and after an "*ad hoc*" Food and Drug Administration meeting in 2011[3], a panel of experts concluded that the overall benefit of ticagrelor was superior to the risk of ventricular pauses, which appeared to be devoid of serious clinical consequences. Accordingly, current labeling of the drug does not give any precaution or contraindication regarding bradyarrhythmic effects.

CASE REPORT

Five published case reports of high-degree AV block after ticagrelor therapy

Recently, 5 reports of ACS patients in a "real world clinical scenario" have been published, describing cases of severe bradyarrhythmias due to AV block requiring intensive care, temporary pacing and sometimes the implant of a permanent pacemaker.

The first article was published by Goldberg *et al*[4] in 2015. A 52-year-old diabetic man with ACS and severe stenosis of ostial left anterior descending (LAD) artery underwent 2 bare metal stents implantation. Baseline ECG showed complete right bundle branch block (RBBB). Left ventricular ejection fraction (LVEF) was preserved. The patient, already taking bisoprolol 1.25 mg, was also treated with a loading dose of ticagrelor 180 mg. A few hours later, several episodes of paroxysmal AV block occurred, with pauses > 11 s and syncope, requiring the insertion of a temporary pacing system. Subsequently, bisoprolol was stopped and ticagrelor replaced with clopidogrel. After 3 d, the AV block resolved and temporary pacing was removed without implanting a permanent pacemaker. At 6 mo follow up, no AV block or other bradyarrhythmias were recorded.

Ünlü *et al*[5] reported about a patient who developed symptomatic Mobitz type Ⅱ AV block four days after receiving ticagrelor therapy in the context of ACS and left circumflex artery (LCA) stenting. The patient was already on beta-blocker therapy (bisoprolol 1.25 mg) before this acute event and baseline ECG showed first-degree AV block with narrow QRS. Ticagrelor and beta-blocker were withdrawn, but AV block still persisted after ten days, so a dual-chamber permanent pacemaker was implanted.

Goldberg *et al*[6] published the case of a 71-year-old female patient with ACS and proximal LAD occlusion, treated with thrombus aspiration and stent implantation. On ECG, she had complete left bundle branch block (LBBB) and was not taking beta-blockers. LVEF was moderately decreased. Ticagrelor was soon started, with recommended loading dose of 180 mg and continued with 90 mg twice a daily. Two days later, bisoprolol was started at 1.25 mg and after three hours complete AV block appeared, associated with sinus bradycardia, pauses up to 14 s and syncope. Temporary pacing was soon initiated, ticagrelor and bisoprolol were stopped. In two days AV block disappeared and temporary pacemaker was removed. A permanent pacemaker was not implanted and, at 6 mo follow up, no recurrence of AV

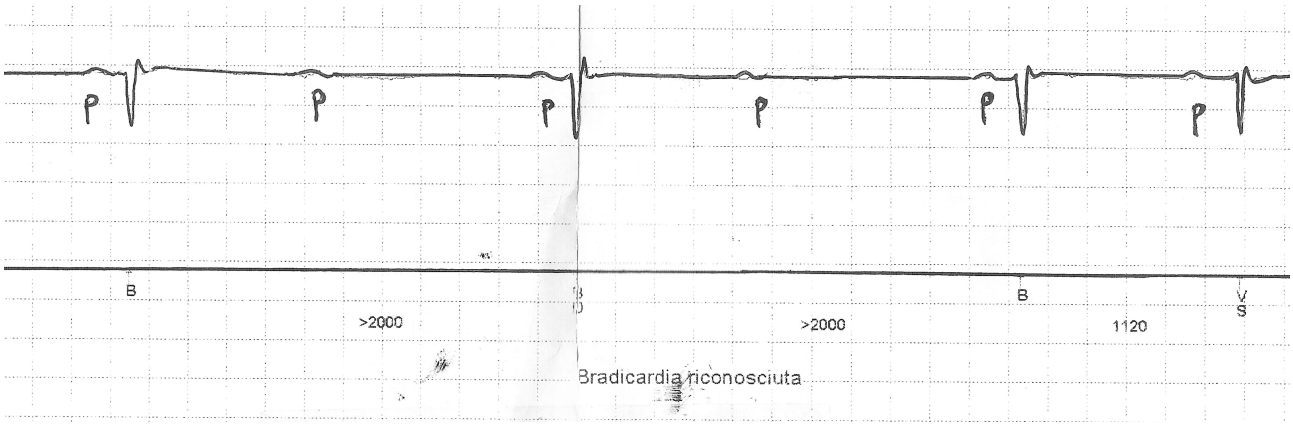

Figure 1 Patient #1. Continuous electrocardiograph monitoring showing paroxysmal episodes of 2:1 atrioventricular block with narrow QRS and lengthening of PP interval (associated sinus bradycardia).

block or other bradyarrhythmias were seen.

In the paper by Ozturk *et al*[7], a 62-year-old male diabetic patient (already on beta-blocker therapy) was admitted because of ACS and treated with right coronary artery (RCA) angioplasty. Baseline ECG showed first-degree AV block with narrow QRS. Seven hours after starting the 180 mg ticagrelor loading dose, a second-degree Mobitz Ⅱ type AV block appeared, associated with sinus bradycardia. The bradyarrhythmia was asymptomatic and well tolerated. Beta-blocker was stopped but AV block persisted up to seven days, so ticagrelor was replaced with prasugrel. On the third day after ticagrelor withdrawal, AV block disappeared. The patient was discharged and after one month he did not experience any other bradycardia.

Lastly, Baker *et al*[8] described a 56-year-old male diabetic patient with ACS and severe proximal LAD stenosis, treated with drug-eluting stent (DES) implantation. At baseline ECG PR interval and QRS complex were normal. One hour after starting ticagrelor loading dose, PR interval increased to 204 ms, so beta-blocker was not started. After additional three hours, the patient experienced nausea, diaphoresis and lightheadedness, with telemetry strip showing severe sinus bradycardia, sinus arrests and paroxysms of AV block. An emergent coronary angiography revealed a widely patent LAD stent and a temporary pacing system was inserted. Ticagrelor was discontinued and replaced with prasugrel; after 12 h bradyarrhytmias completely resolved. After some days, low dose beta-blocker was introduced and subsequent clinical course was uneventful.

Two further cases managed at our hospital

Here we describe two cases of ACS patients managed at our hospital, both with severe AV block following initiation of ticagrelor therapy.

The first was an 82-year-old male patient admitted with ACS and severe proximal LAD stenosis, who was treated with DES implantation and ticagrelor. He was already taking bisoprolol 1.25 mg. At baseline ECG PR interval was prolonged (about 280 ms) and QRS complex was narrow. A few days after discharge, the patient was admitted again because of several syncopal episodes without prodromes. Continuous ECG monitoring showed several paroxysmal episodes of 2:1 AV block associated with lengthening of PP interval (associated sinus bradycardia); these episodes persisted even after bisoprolol discontinuation (Figure 1), but did not require temporary pacing. It was decided to replace ticagrelor with clopidogrel: After some days AV block resolved, without the need of a pacemaker, and bradycardia did not recur over 6 mo follow up.

The second patient was a 76-year-old diabetic male with a recent DES implantation for LCA stenosis, in the setting of ACS hospitalization. Ticagrelor was started at usual doses just before angioplasty, while he was not taking beta-blocker because his baseline ECG displayed complete RBBB, left anterior hemiblock and a PR interval of 200 ms. Two weeks after starting ticagrelor, the patient was evaluated for recurrent syncopal episodes. A 24-h Holter ECG showed several episodes of paroxysmal complete AV block associated with PP interval lengthening (Figure 2). The patient was hospitalized and ticagrelor was replaced with prasugrel. During the following days, bradyarrhythmic phenomena were clearly reduced but did not completely disappear, so a permanent dual-chamber pacemaker was implanted.

DISCUSSION

The occurrence of ventricular pauses is a well-known side effect of ticagrelor, but it has been considered a transient phenomenon without serious clinical consequences. In this context, the most commonly reported arrhythmias are sinus bradycardia, sinus arrest and phases of junctional rhythm, usually fading away without symptoms. High-degree AV block occurred in a healthy volunteer after a large dose of the drug in a dose-finding study[1], but it was not considered a serious issue in the normal clinical setting[3]. It is only recently that some reports have described cases of high-degree, life-threatening, AV block requiring drug discontinuation[4-8], in patients with ACS.

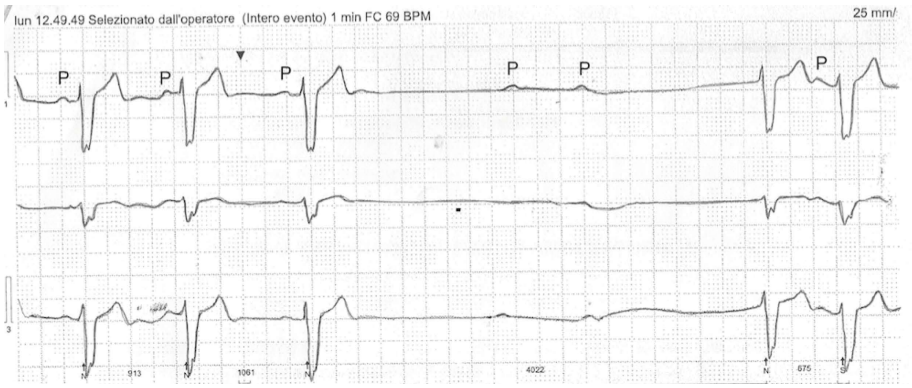

Figure 2 Patient #2. Holter electrocardiograph monitoring showing episodes of paroxysmal complete atrioventricular block associated with PP interval lengthening. Baseline wide QRS complex.

The exact mechanisms of bradyarrhythmic effect of ticagrelor, leading to AV block, are not fully clear. It has been hypothesized a direct effect of the drug on cardiac automaticity and conduction, but the most plausible explanation is the increase in adenosine plasma concentration due to the inhibition of its cellular uptake[9]. Adenosine has a potent AV blocking effect and also a negative influence on the activity of the sinoatrial node[1,3,9]. Almost all the patients, in the above-described reports, displayed AV block associated with sinus node inhibition, manifesting as sinus bradycardia (PP interval lengthening during the block) or sinus arrest.

A total of seven ACS patients with severe bradyarrhythmia have been described in this paper (including our two cases) and six of them presented at baseline with an already diseased conduction system (first-degree AV block, LBBB, RBBB), which is a known risk factor for developing high-degree AV block. The insertion of a temporary pacing system was necessary in three patients with severe clinical picture. A permanent pacemaker was implanted in two patients with persistent high-degree AV block (one with pre-existing long PR interval, the other with baseline RBBB + left anterior hemiblock). Moreover, five patients out seven were taking beta-blocker therapy, which obviously increases the risk of bradyarrhythmias.

It is interesting to note that four patients of this series suffered from diabetes and it has been reported that cardiac conduction abnormalities occur more frequently in diabetic patients[10], even subclinically. The patient described by Baker *et al*[8] had normal PR interval and QRS duration but he was a diabetic. It is unclear how many patients had pre-existing conduction system disease in PLATO trial, while diabetes was present in 25% of the population[8]. In the PLATO substudy investigating the incidence of bradyarrhytmias[2], the majority of patients with ventricular pauses were also taking beta-blocker therapy.

There are several reasons why ticagrelor can reasonably be considered the offending agent in this series of ACS patients: (1) high-degree AV block appeared briefly after the drug was started; (2) high-degree AV block disappeared (or improved) after its discontinuation; (3) not all patients were taking beta-blocker therapy and - when prescribed - doses were low; (4) AV block did not resolve after beta-blocker withdrawal; and (5) there was no other clear explanation for such an acute arrhythmic event and coronary lesions involved all major arteries.

These observations suggest that ticagrelor can have life-threatening, although rare, bradyarrhythmic effects in patients with ACS. Caution and careful monitoring are required especially in patients with already compromised conduction system and/or treated with AV blocking agents (even if these conditions are not currently considered as contraindications to ticagrelor therapy). Moreover, it remains to be established whether ticagrelor treated patients with more stable cardiovascular diseases (chronic stable coronary artery disease, peripheral artery disease)[11,12] or with cerebral ischemia[13] have a lower risk of bradyarrhythmias compared to ACS patients.

Future studies, with long-term rhythm monitoring, would help to define the outcome of patients at higher risk of developing this complication, including the potential association with diabetes and the risk of bradyarrhytmias in clinical settings other than acute coronary events.

COMMENTS

Case characteristics

Two patients with acute coronary syndrome were treated with ticagrelor and developed high-degree atrioventricular block; drug was discontinued but one patient required permanent pacing anyway.

Clinical diagnosis

Acute coronary syndrome and iatrogenic atrioventricular block.

Differential diagnosis

Primary atrioventricular block.

Laboratory diagnosis

Troponin elevation, all other blood exams were within normal limits.

Imaging diagnosis

Atrioventricular block at electrocardiograph.

Pathological diagnosis

Non-ST-elevation myocardial infarction.

Treatment
Drug discontinuation, pacemaker implant.

Related reports
Recent articles have described patients with acute coronary syndrome treated with ticagrelor who developed high-degree atrioventricular block requiring drug discontinuation and, in some cases, pacemaker implantation.

Term explanation
Acute coronary syndrome is a condition with myocardial ischemia due to acute coronary occlusion; high degree atrioventricular block is a life-threatening bradyarrhythmia due to impaired conduction of atrial impulses to the ventricles.

Experiences and lessons
Ticagrelor can have life-threatening, although rare, bradyarrhythmic effects in patients with acute coronary syndrome. Caution and careful monitoring are required especially in patients with already compromised conduction system and/or treated with atrioventricular blocking agents.

Peer-review
Comprehension and explanation of the problem is sound and the case-report is interesting.

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CASE REPORT

Unusual presentation of nasopharyngeal carcinoma with rectal metastasis

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Author contributions: Vogel M and Kourie HR initiated and wrote this case; Piccart M and Lalami Y reviewed and commented on this paper.

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Informed consent statement: The involved person in this case report gave his verbal informed consent prior to study and that was mentioned in the computerized medical file.

Conflict-of-interest statement: The authors confirm that they do not have any conflict of interest.

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Abstract

Nasopharyngeal carcinoma (NPC) is a rare tumour that mainly metastasizes in lymph nodes, bones, lungs and liver. Colorectal metastases of NPC are extremely rare phenomenon and associated with a poor prognosis. We reported here a case of NPC with rectal metastasis, we discussed the treatment modalities and the prognosis after reviewing the similar cases described in the literature.

Key words: Nasopharyngeal carcinoma; Prognosis; Rectal metastasis; Treatment

Core tip: This is a rare case of nasopharyngeal carcinoma with rectal metastasis. After reporting the similar cases in the literature, we discussed the prognosis and the treatment of this rare phenomenon.

Vogel M, Kourie HR, Piccart M, Lalami Y. Unusual presentation of nasopharyngeal carcinoma with rectal metastasis. *World J Clin Cases* 2017; 5(5): 183-186 Available from: URL: http://www.wjgnet.com/2307-8960/full/v5/i5/183.htm DOI: http://dx.doi.org/10.12998/wjcc.v5.i5.183

INTRODUCTION

Nasopharyngeal carcinoma (NPC) is a head and neck cancer starting in the upper part of the throat, behind

Table 1 Three cases of colorectal metastases from nasopharngeal carcinoma

Ref.	Age (yr)	Sites of metastasis	Other metastasis	Colorectal metastases treatment	Follow-up
Lahuri *et al*[9] (2015)	61	Ascending colon	Right adrenal gland, supraclavicular lymph nodes, liver, lungs	Right hemicolectomy	Patient died 2 mo later
Suppiah *et al*[8] (2006)	64	Rectum	Abdominal lymph nodes	None	Patient died 15 d later
The present case	65	Rectum	Lung, adrenal glands, bones, lymph nodes, epiduritis, peritoneal carcinomatosis	None	Patient died 1 mo later

the nose (nasopharynx). This tumor has different distribution and incidence worldwide with endemic regions: The incidence of NPC is lower than 1/100000 in most countries; however, in the southern part of China (including Hong Kong), its incidence is higher and can reach 15 to 20/100000. Otherwise, the incidence of NPC is higher in males, the sex ratio being 2-3:1[1,2].

Genetic susceptibility, Epstein-Barr chronic virus infection, and environmental factors (*e.g.*, carcinogens and dietary factors) are risk factors associated to NPC[3,4]. NPC is divided into 3 subtypes by the World Health Organisation (WHO): Keratinizing squamous cell carcinoma, non-keratinizing carcinoma and undifferentiated carcinoma[5].

NPC has a tendency to metastasize to cervical lymph nodes, due to the abundant lymphatic network under the nasopharyngeal mucosa. At the time of diagnosis, 60%-85% of patients already have cervical metastasis[6]. The common distant metastasis are bones (65.9%), lungs (26.9%), liver (30.7%) and distant lymph nodes (28.5%). Other rare metastatic sites are described (2.4%) like spleen, kidney, pleura, breast gland, abdominal wall and thyroid gland[7]. The treatment of a non-metastatic patient is based on radiation therapy and/or chemotherapy. In metastatic NPC, the treatment is usually chemotherapy.

We report in this paper a rare presentation of NPC metastasizing to the rectum. We review the rare similar cases described in the literature about this association and discuss prognosis and treatment modalities of this unusual clinical presentation.

CASE REPORT

A 65-year-old smoker Caucasian patient presented to our department in July 2015 with stage IVc (T3N3bM1) non keratinizing undifferentiated NPC (WHO type Ⅲ). The diagnosis was established by computed tomography (CT) requested for the investigation of chronic nasal obstruction and multiple cervical nodes. The tumour measured 7.2 cm in diameter. Multiple lymph nodes were palpable in the supra clavicular fossa. Further investigations with a positron emission tomography-computed tomography (PET-CT) showed metastatic lesions in bones and lungs. The patient was treated with radiotherapy therapy, because he refused the Cisplatin-5FU chemotherapy regimen and bisphosphonates for his bone metastasis. A post radiotherapy PET-CT showed a moderate metabolic response of the nasopharyngeal tumour and cervical lymph nodes, but also a metabolic progression in the distant metastatic lesions. A close follow-up was advised. A new progression in the adrenal glands, Th10-Th11 epiduritis and peritoneal carcinomatosis were reported after 7 mo. Epiduritis was treated with radiation therapy.

A follow-up PET-CT, after one year of the diagnosis, showed a suspicious lesion in the rectum (Figure 1). Before including the patient into a phase I protocol, it was necessary to document this lesion. The work-up included a colonoscopy revealing a rectal mass, and a biopsy documenting a metastatic lesion from the well-known nasopharyngeal non-keratinizing undifferentiated carcinoma (Figure 2). It was decided to start a palliative chemotherapy but the patient died one month without receiving any treatment.

DISCUSSION

Rectum and colon metastases of NPC are extremely rare entities. To our knowledge, there are only two similar cases described in the literature: One with rectal metastasis[8] and another with colon metastases[9]. These lesions are usually asymptomatic and diagnosed on complementary imaging tests.

Thus, Two out of three patients were asymptomatic; the only symptomatic patient was reported by Suppiah *et al*[8] and presented with rectal bleeding and abdominal pain. In the reported cases the patients had multiple other metastases before the diagnosis of the colorectal metastases. In the 3 cases, the patient shortly died after the diagnosis. In the case reported by Lahuri *et al*[9], the metastasis was interpreted first as rectal adenocarcinoma, leading to a right hemicolectomy. Chemotherapy was planned but the patient died rapidly (Table 1).

Differentiating between a secondary lesion and another primary in front of a rectal lesion in the context of NPC is essential to guide therapy. The diagnosis cannot be confirmed without a pathological exam including immune-histochemical staining to further characterize the lesion. In case of a confirmed secondary lesion, systemic chemotherapy is indicated, while in case of a rectal primary, a loco-regional treatment is prioritized.

Usually, the treatment for non metastatic NPC at early stages is radiotherapy, including both sides

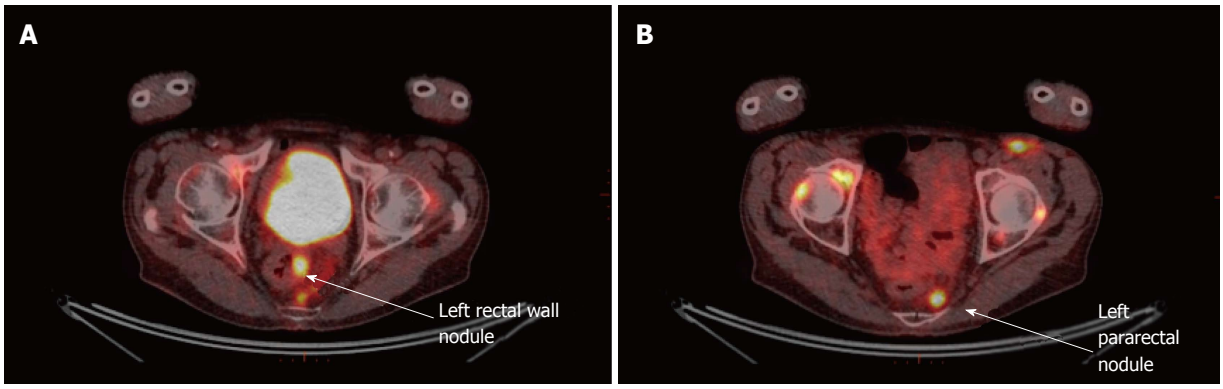

Figure 1 The positron emission tomography-computed tomography: Left rectal wall nodule (A) and left pararectal nodule (B).

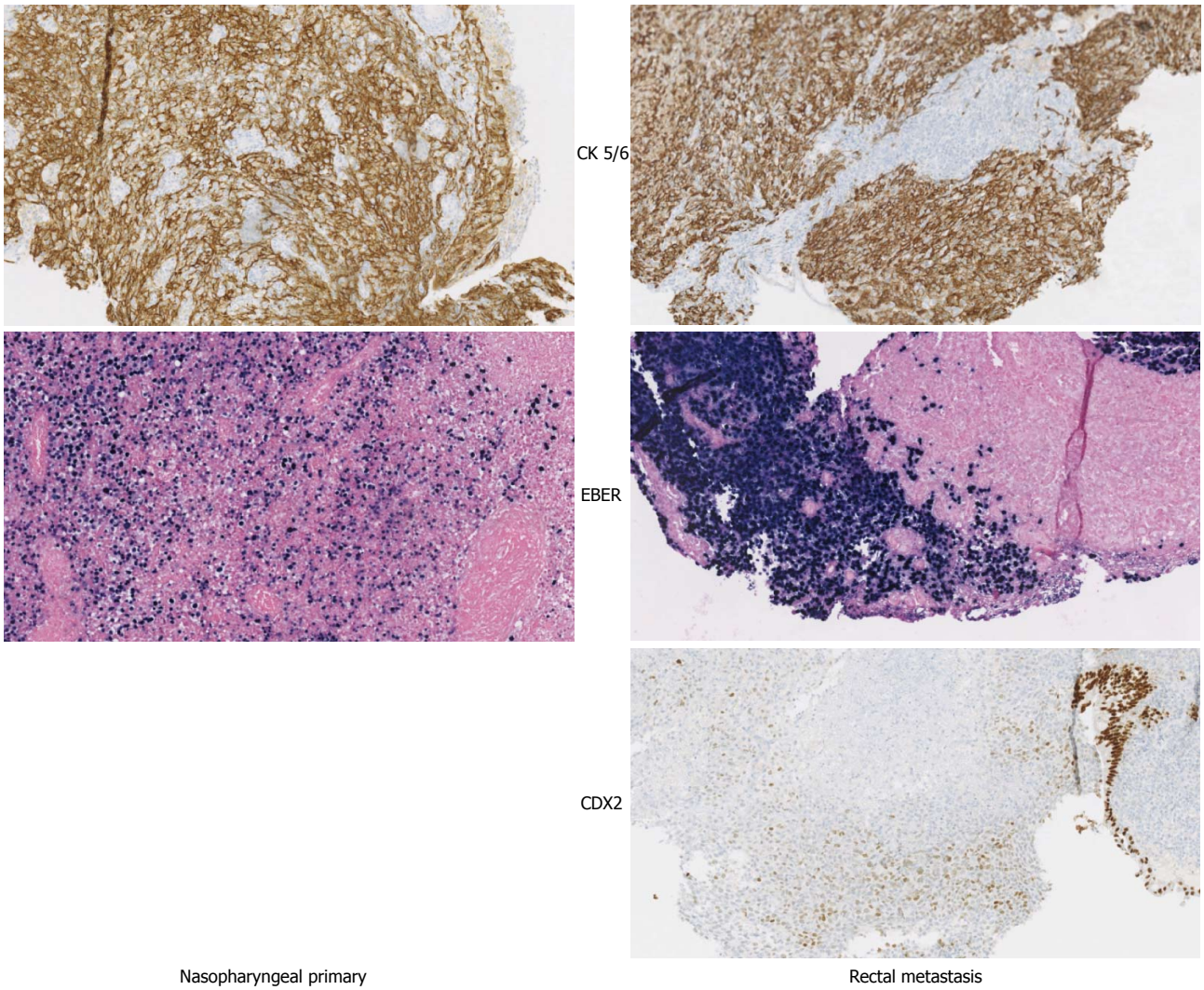

Figure 2 The nasopharyngeal primary and rectal metastasis are positive for CK 5/6 (confirming the epithelial origin) and EBER (confirming Epstein-Barr virus positivity). CDX2 the marker of colorectal origin is negative in the rectal lesion, confirming that it is a metastasis.

of the neck and retropharyngeal nodes. For locally advanced stages, the treatment guidelines advocate the combination of chemotherapy and radiotherapy. According to the response, surgery or brachytherapy can be considered as consolidation treatments[10]. In case of a metastatic NPC, the recommended first-line treatment is a platinum-based regimen and, more specifically, 5FU-cisplatin chemotherapy. In second line treatment, another chemotherapy can be proposed; the selection of which depends usually on the first-line treatment[11]. In the new era of checkpoint inhibitors, pembrolizumab, an anti-PD1 agent, showed remarkable

results in advanced multitreated NPC with response rates of 26% and disease control rate of 77%[12].

To conclude, the diagnosis of rectal metastases originated of NPC is necessary to orient the treatment modality and to determine the prognosis of the disease.

COMMENTS

Case characteristics

The patient did not present particular symptoms at the diagnosis of rectal metastasis of nasopharngeal carcinoma.

Clinical findings

The clinical examination of the patient was normal.

Differential diagnosis

A rectal primary adenocarcinoma was a possible differential diagnosis.

Laboratory findings

A moderate anemia was the only laboratory test abnormality.

Imaging diagnosis

A follow-up positron emission tomography-computed tomography, after one year of the diagnosis of pharyngeal adenocarcinoma, showed a suspicious lesion in the rectum.

Pathological diagnosis

The work-up included a colonoscopy revealing a rectal mass, and a biopsy documenting a metastatic lesion from the well-known nasopharyngeal non-keratinizing undifferentiated carcinoma.

Treatment

Palliative care was initiated because of the alteration of the performance status of the patient.

Experiences and lessons

It is very important to confirm the pathology of unusual localization of a suspicious lesion in a patient developing cancer to differentiate between a metastasis and a second primary. The prognosis and the treatment of a rectal metastasis of nasopharyngeal carcinoma and rectal primary is very different.

Peer-review

The manuscript is of interest and well written.

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CASE REPORT

Elizabethkingia miricola: A rare non-fermenter causing urinary tract infection

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Institutional review board statement: The present case report has been retrospectively reviewed and reported and it didn't require any institutional ethics committee approval.

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Abstract

Elizabethkingia miricola (*E. miricola*) is a gram-negative non-fermentative bacterium which is rarely encountered. It is usually misidentified or considered as a contaminant in routine microbiology laboratories due to the limitations in conventional biochemical techniques. However, with the advent of the matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF-MS), the identification of non-fermenters has become easy and this has led to enhanced understanding of the clinical significance of these uncommonly isolated microorganisms. The genus *Elizabethkingia* has only two species *E. meningoseptica* and *E. miricola*. Both of these organisms are known to be multi-drug resistant and therefore, their accurate identification and antimicrobial susceptibility testing are necessary prior to the initiation of appropriate therapy. In the world literature till date, only 3 cases of sepsis caused by *E. miricola* have been reported. We present the first case of *E. miricola* association with urinary tract infection.

Key words: *Elizabethkingia miricola*; Antibiotics; Urinary tract infections; Matrix-assisted laser desorption ionization time-of-flight; Non-fermenters

Core tip: Non-fermenters except *Pseudomonas* and *Acinetobacter* are less commonly associated with urinary tract infection (UTI). But recently an upsurge in a number of reported cases has been noted due to the use of MALDI-TOF which is an easy and reliable identification technique. Till date in literature, there is no reported case of *Elizabethkingia miricola* (*E. miricola*) causing UTI, although its significance in blood and sputum samples of sepsis patients has been demonstrated earlier. This is the first case report showing a clinical association of *E. miricola* with symptomatic UTI and also demonstrating the multidrug resistance nature of this organism.

Gupta P, Zaman K, Mohan B, Taneja N. *Elizabethkingia miricola*: A rare non-fermenter causing urinary tract infection. *World J Clin Cases* 2017; 5(5): 187-190 Available from: URL: http://www.wjgnet.com/2307-8960/full/v5/i5/187.htm DOI: http://dx.doi.org/10.12998/wjcc.v5.i5.187

INTRODUCTION

Urinary tract infections (UTI) are amongst the most common bacterial infections occurring in human beings during their lifetime[1]. The usual organisms responsible for UTI belong to the family *Enterobacteriaceae* and gram-positive bacteria like *Staphylococcus* and *Enterococcus*[2]. UTI caused by non-fermenters (NF) is being increasingly reported especially in the nosocomial settings, with *Pseudomonas and Acinetobacter spp.* being the most common agents. However, UTI due to other NFs like *Alcaligenes, Flavobacterium, Oligella, Flavimonas, Agrobacter, Weeksiella* are also on the rise[3]. Routine laboratory identification of NF is difficult and labour-intensive, which often misclassifies or misidentifies these agents and thereby may mask the exact clinical significance of these isolates. Nowadays, the identification of these NF has become easy by the advent of matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF-MS). We recently encountered a case of UTI caused by rare multidrug resistant non-fermenter *E. miricola*, which was identified by MALDI-TOF.

CASE REPORT

A 25-year-old female presented with complaints of increased bowel frequency, oliguria, fever and abdominal pain since one month. Detailed history revealed that the patient had difficulty in micturition for past two weeks. The routine laboratory investigations revealed a haemoglobin of 7.8 gm/dL, total leucocytes count 3200 cells/mm^3, platelet count of 70000 cells/mm^3. Renal function tests revealed normal sodium concentration (139 mEq/L), hyperkalemia (8.2 mEq/L), hyperuricemia (74 mg/dL) and elevated creatinine levels (7.5 mg/dL). Coagulation profile was normal. Ultrasonography (USG) revealed bilateral hydroureteronephrosis with normal renal parenchyma and features of vesicoureteric reflux. The midstream urine sample was subjected to microbiological testing. The wet mount microscopic examination showed 1-2 RBCs, numerous pus cells and bacteria per high-power field[4]. The semi-quantitative culture done on the cysteine lysine electrolyte deficient agar showed significant bacterial growth (colony count > 10^5 CFU/mL). The colonies were non-lactose fermenting, translucent, greenish blue, smooth having entire edges and became mucoid on prolonged incubation. Subculture on MacConkey agar showed pale, translucent, glistening colonies with entire edges (Figure 1). Gram staining showed 0.5 μm × 2 μm gram-negative bacilli, with no spores and no capsule. The isolate was also subjected to conventional identification using a battery of biochemical tests. The isolate was catalase positive, oxidase positive, produced indole, was non-nitrate reducing, mannitol fermenting, esculin and gelatinase hydrolysis positive. Urease was produced and this test helped to distinguish it from *E. meningoseptica*. The isolate was confirmed as *Elizabethkingia miricola* (*E. miricola*) (identification score of 2.29) by using MALDI-TOF-MS (BrukerDaltonics, Bremen, Germany). The antimicrobial susceptibility was carried out using Kirby-Bauer disc diffusion method and the antibiotics tested were chosen from the available literature as there are no CLSI guidelines available till now[5,6]. The isolate was sensitive to gentamicin, ceftriaxone, aztreonam, piperacillin-tazobactam and imipenem, and resistant to ampicillin, ciprofloxacin, levofloxacin, vancomycin and colistin. The patient was started on piperacillin-tazobactam and responded well to the treatment. The patient improved clinically and the follow-up urine culture after two weeks of therapy was sterile.

DISCUSSION

E. miricola was first isolated from Mir space station, Russia and hence named as *E. miricola*[7]. Previously, it was classified into genus *Chryseobacterium* but later in 2005, the genus was changed to *Elizabethkingia* on the basis of the comparative analytical studies involving DNA hybridization and sequencing of the 16S rRNA region[8]. *E. miricola* is a gram-negative (0.5 μm × 1-2.5 μm), non-motile, non-spore-forming bacterium. It grows well on blood and MacConkey agar producing non-fermenting sticky colonies. Biochemical reactions show indole positive, citrate positive, produce acid from D-glucose, D-fructose, D-lactose, trehalose, D-mannitol, D-maltose, but not from D-xylose, L-arabinose, D-cellobiose, sucrose and raffinose. It can be differentiated from *Chryseobacterium* because of the absence of yellow pigment in culture. Urease production is the test used to differentiate *E. miricola* from *E. meningoseptica*[8]. Till date, *E. miricola* has been isolated from blood and sputum and has been found to be responsible for sepsis. The first case of *E. miricola* was reported in 2008 in an adult with mantle cell carcinoma, who underwent stem cell transplant[5]. In this case, *E. miricola* was isolated from sputum and blood and the identification was confirmed using 16S rRNA sequencing. Later on, *E. miricola* was isolated from the blood sample of a young female with alcoholic pancreatitis[6]. More recently, *E. miricola* has been isolated from a patient with severe sepsis and pulmonary abscess[9]. In both the above cases, the isolate was identified by MALDI-TOF. In the present case, *E. miricola* was isolated from the urine sample of a young female with clinical features of UTI and bilateral hydroureteronephrosis. The clinical presentation pointed towards differential diagnosis like pyelonephritis, renal abscess, renal infarction, venous obstruction or ATN. However, the USG findings of bilateral hydroureteronephrosis and sterile blood culture pointed

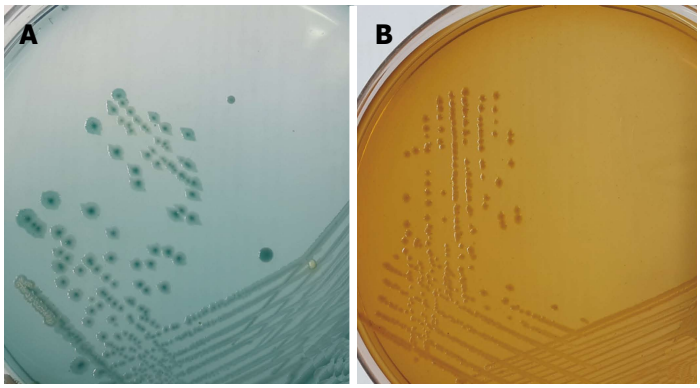

Figure 1 Culture plates showing the growth of *Elizabethkingia miricola* on (A) cystein-lactose-electrolyte-deficient medium agar and (B) MacConkey agar.

towards localised urinary tract infection.

E. miricola has been found to be multidrug resistant similar to *E. meningoseptica* which is known to harbor β-lactamases showing resistant to β-lactams and carbapenems[10]. The *E. miricola* isolates have been found to be resistant to many antibiotics. Previous studies have shown resistance to ampicillin, ceftazidime, imipenem, gentamicin, cotrimoxazole, colistin and with variable susceptibility to ciprofloxacin, vancomycin and rifampicin[5,6,11]. It is interesting to note that, *E. miricola* isolates in previous studies were sensitive to levofloxacin, but in our case, the isolate was resistant to both ciprofloxacin and levofloxacin. Limited clinical reports, varied susceptibility profiles, lack of antimicrobial susceptibility breakpoint and no defined consensus for the empiric treatment regimen makes it difficult to treat such rare organisms.

We present the first case report of human UTI caused by rare multidrug resistant *E. miricola*. The present case emphasizes the clinical importance of rare non-fermenters like *E. miricola* in human infections especially in case of UTI. The knowledge of newer species and their antimicrobial susceptibility profile will help in formulating appropriate antibiotic treatment regimens to tackle such rarely encountered bacteria.

COMMENTS

Case characteristics

A 25-year-old female complaining of difficulty in micturition, oliguria fever with abdominal pain.

Clinical diagnosis

Urinary tract infections (UTI) with bilateral hydroureteronephrosis.

Differential diagnosis

Chronic pyelonephritis.

Laboratory diagnosis

The routine laboratory investigations revealed anemia, leucopenia, hyperkalemia, hyperuricaemia and elevated creatinine levels. Urine culture had significant bacterial growth (colony count >10^5 CFU/mL) of *Elizabethkingia miricola* (*E. miricola*).

Imaging diagnosis

Bilateral hydroureteronephrosis.

Pathological diagnosis

Bilateral hydroureteronephrosis with urinary tract infection.

Treatment

Piperacillin-tazobactam.

Related reports

E. miricola has been reported to cause sepsis and pulmonary infection.

Experiences and lessons

Rare non-fermenters can cause UTI and prompt identification is required to guide proper antimicrobial therapy. CLSI/EUCAST guidelines need to be developed.

Peer-review

Interesting case of unusual bacterial cause of UTI with a severe clinical scenario.

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MINIREVIEWS

Complementary examinations other than neuroimaging and neurosonology in acute stroke

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Abstract

The etiologic diagnosis of cerebrovascular diseases requires non-routine complementary examinations to be performed. Thus, in specific cases, after neuroimaging (computed tomography/magnetic resonance imaging cerebral scan sequences) and neurosonology (Doppler test of the supra-aortic trunks, transcranial echography and echocardiography), which academically allow us to classify the patients according to their etiologic stroke subtype, further examinations must be used to make a correct etiologic diagnostic. The present review aims to update knowledge about the usefulness of the different tests of blood and urine, plain chest radiography, X-ray of the spine, skull and abdomen, lumbar puncture, electroencephalography, evoked potentials, polysomnography, and pathologic examination after biopsy of the artery, skin, muscles, nerves, meninges, and brain, in the management of patients who have suffered an acute stroke.

Key words: Complementary examinations; Cerebrovascular disorders; Acute stroke; Diagnostic techniques; Blood biochemistry; Polysomnography

Core tip: In selected cases of acute stroke, some complementary examinations (different from neuroimaging, neurosonology and cardiac tests) are needed for the adequate etiological diagnosis. For example, the polysomnographic study allows for the diagnosis of respiratory sleep disorders; urinalysis may rule out the presence of toxins related to stroke; the analysis of the cerebrospinal fluid eliminates the possibility of an infection or an inflammatory process of the central nervous system and the artery biopsy lets you diagnose inflammatory arteritis. The knowledge of the diagnostic performance of these complementary examinations, which are sometimes true diagnostic tests, is very useful in the daily clinical practice of stroke patients.

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INTRODUCTION

In patients presenting with acute stroke, a thorough medical history and complete neurological and physical examination should be performed, in order to initiate the diagnostic process. This diagnostic work includes syndromic diagnosis, nosological, etiological and pathophysiological background, and differential diagnosis.

Complementary examinations are all those explorations requested by the clinician or specialist providing care for the stroke patient. These examinations, rarely performed by the clinician, require more or less sophisticated tools which in turn demand highly specialization in their use or interpretation.

The prescription of a complementary examination in the management of acute stroke must comply, on the part of the clinician requesting it, a series of conditions: (1) know what possible information about diagnostic or therapy will provide us, and therefore, which are its indications. This information is fundamental because complementary examinations should only be requested when their results had the possibility to modify the diagnostic or therapeutic attitude towards the patient; (2) know the sensitivity and specificity of the requested examination. Sensitivity or positive predictive value is the probability of obtaining a positive result in a person with the disease under study. The specificity or negative predictive value is the probability of obtaining a negative result in a person who does not have the disease under study; (3) know the right time to order; (4) know the possible contraindications; and (5) inform the patient about the exploration and why it is necessary, obtaining the informed consent.

In this review we will examine the following complementary explorations: (1) blood biochemistry: general, toxicology, endocrinological study, immunological study; (2) microbiology and serology; (3) genetic study; (4) urine test; (5) lumbar puncture: cerebrospinal fluid; (6) plain radiography: thorax, spine, skull, abdomen; (7) electroencephalogram; (8) evoked potentials; (9) polysomnography; (10) neuropsychological study; and (11) pathological study: Biopsies: Artery, skin, muscular, nerve, meningeal, and cerebral.

Neuroimaging, neurosonology and hematological explorations are not analyzed in this review.

BLOOD BIOCHEMISTRY

Blood electrolytes: Sodium, potassium, calcium and phosphorus[1-5]

These tests are useful in patient requiring intravenous fluid therapy. They are also necessary to diagnose hypokalemia secondary to diuretic therapy. Hyponatremia may cause fluctuating focal neurological deficits, and simulate stroke or transient ischemic attacks. The cause of these neurological deficits is unclear, but it has been suggested that such metabolic disorders could unmask previously existing areas of clinically silent cerebral ischemia. In a recent clinical study hyponatremia occurred in 43% of stroke patients, 6% had hypernatremia, and 4% had both. Cerebral salt wasting was the most common cause of hyponatremia in stroke patients. Exceptionally, hypoparathyroidism and hyperparathyroidism, by variations of calcemia, can cause focal neurological deficits similar to those of stroke. True cerebral infarcts due to hypercalcemia secondary to persistent arterial vasospasm have also been described.

Glucose tests[6-9]

Glucose and glycosylated hemoglobin levels are the primary indicators of effective metabolic control of those patients diagnosed with diabetes. An analysis of glucose is required for the diagnosis of diabetes mellitus, one of the most common cerebrovascular risk factors in all types of stroke, but especially in lacunar and atherothrombotic infarctions.

Hyperglycemia in the onset of cerebrovascular diseases may cause larger lesions and a worse prognosis due to its harmful effect on the area of ischemic penumbra. Irrespective of other adverse prognostic factors - including advanced age, type and severity of stroke, and irreversible neurological deficit, hyperglycemia above 8 mmol/L is associated with an increased mortality and morbidity after acute stroke. Hyperglycemia may also be the answer to a serious brain injury. Decompensated hyperglycemic hyperosmolarity may cause a reduced cerebral flow, leading to focal epilepsy and even cerebral ischemia.

Likewise, in 2.4% of cases hypoglycemia may produce diverse clinical features, ranging from hemiparesis to coma, mimicking and, exceptionally, leading to cerebral infarction. The underlying pathophysiological mechanism is not well known, but has been ascribed to a selective neuronal vulnerability, to cerebral arterial spasms, or to a clinically silent cerebrovascular disease exposed by the hypoglycemia itself. Therefore, hypoglycemic hemiplegia is exceptional, although it should be borne in mind in diabetic patients with cerebral infarction treated with either insulin or oral hypoglycemic agents. In addition, hypoglycemia and hypoglycemic hemiplegia can result in insulinoma. Hypoglycemia may also result in permanent neurological damage if prolonged, caused by hypoglycemic necrosis usually affecting caudate nucleus, putamen, hippocampus and periventricular level. Finally, hypoglycemia is also a rare cause of non-valvular atrial fibrillation which is self-limited and reverts to sinus rhythm when managing this metabolic disorder.

Creatinine[10-12]

It's a valuable screening test in evaluating kidney function. Normal serum creatinine levels allow us ruling out renal failure while, on the other hand, increased levels act as a marker for generalized vascular disease. In patients with cerebral infarction, the presence of renal dysfunction is usually indicative of the repercussion of arteriosclerotic vascular disease on this target organ, or even acts a marker of the severity or duration of arterial hypertension, the main cerebrovascular risk factor.

Cholesterol and triglycerides[13,14]

Hypercholesterolemia is a risk factor for cerebral infarction, and may be a manifestation of thyroid disease, hepatic or pancreatic dysfunction, diabetes, and nephrotic syndrome. Hypertriglyceridemia (levels greater than 150 mg/dL or 1.7 mmol/L) is also a risk factor for coronary heart disease. Hyperlipidemias may be graded according to the Fredrickson classification, which is based on the pattern of lipoproteins on electrophoresis. Cholesterol associated with high-density lipoprotein (HDL-cholesterol) plays a protective role in atherosclerosis. In contrast, cholesterol linked to low density lipoproteins (LDL-cholesterol) favors the atherogenic process. The risk of cerebral infarction is greater in patients with low levels of HDL and elevated levels of LDL-cholesterol: A decreased HDL/LDL or HDL ratio per 100/total cholesterol.

Recent studies have demonstrated the protective effect of statins, specifically on atherosclerotic plaques regression, and its role as secondary prevention of cerebral infarction in patients with ischemic heart disease regardless of cholesterol figures. It is recommended to maintain the following levels of cholesterol: LDL < 50 mg/dL (2.59 mmol/L), HDL > 35 mg/dL (0.91 mmol/L), total cholesterol < 200 mg/dL and triglycerides < 200 mg/dL (2.26 mmol/L).

Total protein and proteinogram[15-18]

A protein alteration may suggest the presence of a hyperviscosity syndrome and guide physicians in the diagnosis of systemic diseases causing cerebrovascular pathology, such as collagen diseases, multiple myeloma, and Waldenstrom's macroglobulinemia.

For its part, malnutrition is associated to increased risk for medical complications and mortality, mainly related to a high risk of hospital acquired infections (respiratory and urinary), decubitus ulcers, and longer hospital stay; all this is possibly due to an alteration in the immune function.

Furthermore, it has recently been reported that serum albumin levels below 4.2 g/dL are associated with increased mortality in patients with cerebral infarction.

Uric acid[7,19]

The role of hyperuricemia and its possible association with coronary, peripheral, and cerebral arteriosclerosis is uncertain. Therefore, its relation to the pathogenesis of cerebral vascular disease is controversial. However, a recent study showed that intravenous administration of uric acid may have a protective effect on cerebral infarction since it appears to be effective in improving the clinical prognosis of patients, possibly because of its antioxidant properties.

Arterial blood gas test and pH[1,7]

They may be helpful in the differential diagnosis between a metabolic coma and a coma secondary to acute cerebral vascular disease, and also in the therapeutic management of patients with severe stroke and renal, pulmonary or cardiac complications.

Toxicological study[15,20,21]

A toxicological study may be necessary in the diagnostic evaluation of the unconscious patient. It may assist in atypical intracranial hemorrhages, in subarachnoid hemorrhages, and in identifying intoxicated patients with amphetamines, sympathomimetics or cocaine, which can cause hemorrhagic and ischemic strokes.

Thyroid hormones[1,7,22]

The determination of T3, T4 and TSH may be helpful in young patients with non-valvular atrial fibrillation and cardioembolic cerebral infarction, as well as in all patients with suspected hyperfunction or hypofunction of the thyroid gland.

Immunology[7,23,24]

Immunological studies (complement consumption, ANA, ENA, anti-DNA antibodies, rheumatoid factor, LE cells, cryoglobulins, circulating immune complexes, ANCA, mainly) should be performed in selected patients when regular diagnostic tests do not confirm the diagnosis of stroke subtype.

Most autoimmune or connective diseases, as systemic lupus erythematosus or vasculitis, may lead to TIA or stroke, in both arterial or venous thrombosis as well as subarachnoid or intracerebral hemorrhage, those due to the rupture of the affected cerebral vessel. As well, in addition to inflammatory arteritis, the arterial hypertension due to renal failure or opportunistic infections caused by immunosuppressive therapy may also be the cause of stroke or hemorrhage in those patients.

Table 1 shows the major antinuclear antibodies associated with connective tissue diseases.

Other determinations[25-28]

Basal levels of lactic acid measurements are necessary if mitochondrial disease is suspected. Since recently, hyperhomocysteinemia proved to be a cerebrovascular risk factor, homocysteine testing should be requested if a patient if suspected of having hyperhomocysteinemia or in patients with essential lacunar or non-lacunar cerebral ischemia.

Table 2 shows hematological and biochemical

Table 1 Antinuclear antibodies associated with connective tissue diseases[23]

Antinuclear antibodies	
Native Anti-DNA	SLE
Anti-histone	Drug-induced SLE/SLE/RA/juvenile chronic arthritis
Anti-RNP	Mixed connective-tissue disease/SLE
Anti Sm	SLE
Anti-Ro/SS-A	Sjögren syndrome/SLE/neonatal lupus Subacute cutaneous SLE/SLE related to component deficiency
Anti-La/SS-B	Sjögren syndrome/SLE
Anti-Scl-70	Diffuse scleroderma
Anticentromere	Scleroderma (CREST syndrome)
Anti-Jo1	Polymyositis with interstitial pulmonary disease
Antinucleolar	Scleroderma

SLE: Systemic lupus erythematosus; RA: Rheumatoid arthritis; CREST: Calcinosis, Raynaud's phenomenon, Esophageal dysmotility, sclerodactyly, and telangiectasia.

laboratory parameters that contraindicate the administration of intravenous thrombolytic treatment in the acute phase of cerebral ischemia.

MICROBIOLOGY AND SEROLOGY[1,29,30]

Infections of the brain may be one of the etiologies of cerebrovascular disease. In a recent study, brain infections accounted for 15.7% of the consecutive strokes of unusual etiology admitted to a neurology department over a 10-year period. Stroke or transient ischemic attack can be caused primarily by: Infectious arteritis, chronic meningitis, acute bacterial meningitis, viruses, certain helminthiasis, cat scratch disease, carotid inflammation resulting from contiguous pharyngitis, tonsillitis or lymphadenitis, and infective endocarditis.

General serological tests and blood cultures[1,4,22,31]

Bacterial, viral, fungal infections (mainly Cryptococcus, Candida, Aspergillus or Mucor) or protozoa may affect the central nervous system and result in cerebrovascular disease, whose definitive etiological diagnosis requires special culture media.

In the Mediterranean area, cerebrovascular disease may be due to brucellosis, Mediterranean red button fever, mycoplasma infection, neuroborreliosis or herpes zoster infection, which is capable of causing periarterial inflammation with concomitant thrombosis. In some cases, bacterial meningitis, tuberculosis, leptospirosis, malaria and certain helminthiases (neurotrichinosis, cysticercosis and hydatidosis) may also cause cerebrovascular disease. In addition, stroke may be the presenting feature of the acquired immunodeficiency syndrome, and may be secondary to an opportunistic infection of the central nervous system. Cerebral embolism is the major neurological complication of infective endocarditis, and clinical examination provides a presumptive diagnosis subsequently confirmed by the identification of the germ in serial blood cultures.

Table 2 Hematologic laboratory parameters that contraindicate thrombolysis

Platelet count < 100000
Glycaemia < 50 and/or > 400 mg/dL
Severe liver failure
Oral anticoagulants with INR > 1.7
Heparin treatment and ATTP > 1.5
Analytical parameters suspicious of acute pancreatitis

Serologic diagnosis for syphilis[32-34]

The meningovascular lues should be included in the differential etiological diagnosis of acute cerebrovascular disease. Two general types are available for testing for syphilis: Reaginic and treponemal. The former detect nonspecific antibodies directed against treponemal lipid antigens, and the most used are venereal disease research laboratory (VDRL) and rapid plasma regain. Treponemal tests, for their part, detect antibodies that specifically target Treponema, and the most common are: TPI (Treponema immobilization test), FTA-ABS (test of fluorescent antibodies absorbed against Treponema) and MHA-TP (Treponema microhemagglutination). Non-specific tests can produce false positives, but not the treponemal, although they will remain positive throughout life.

Because meningovascular syphilis continues to be "the great imitator", some authors recommend the routine practice of serological tests for syphilis in all patients with acute stroke. Other authors, however, suggest restrict them to those patients with cerebrovascular disease and absence of risk factors, high risk of seropositivity or atypical clinical course. Although positivity of serological tests for syphilis in the peripheral blood indicates the presence of meningovascular lues, positive cerebrospinal fluid is essential to provide definitive etiological confirmation, thus making it a highly specific diagnostic marker for the disease.

GENETIC TESTING[1,35]

The genetic testing should be considered in those patients who present evidence of a suspected genetic condition of the cerebrovascular disease. Consideration will be given to the study of clotting disorders that can cause thrombophilia (protein S and protein deficiency, Factor V Leyden mutation and prothrombin gene mutation).

Eligible patients for genetic testing should have: (1) younger age than usual (< 50 years old); (2) family history (most especially affecting first-degree relatives and at younger ages) of ischemic heart disease, pulmonary thromboembolism/deep venous thrombosis, recurrent pregnancy loss, and peripheral arteriopathy; (3) absence of cardiovascular risk factors

Table 3 Classification for genetic disorders associated with ischemic stroke[35]

Coagulation related genes	Genetic pattern	Inheritance	Gene
Congenital deficiencies of clotting factors			
Antithrombin III	Monogenic	AD	*1q23-25*
Protein C	Monogenic	AD/AR	*2q13-14*
Protein S	Monogenic	AD	*3p11.1-q11.2*
Heparin cofactor II	Monogenic	AD	*22q11*
Factor VII	Monogenic	AR	*13q34*
Factor XII	Monogenic	AR	*5q33-ter*
Elevated factor VIII	Monogenic	?	*Xq28*
Plasminogen	Monogenic	AD	*6p26*
Plasminogen activators	Monogenic	AD	*8p12*
Polymorphism of clotting factors			
Factor V leiden (G1619A)	Polymorphism	Mutation increases risk	*1q23*
Prothrombin G20210A	Polymorphism	Mutation increases risk	*11p11q12*
Sickle-cell disease	Monogenic	AR	Mutation A→T, Glu6Val in beta chain of hemoglobin *11p15.5*
Connective tissue disorders			
Ehlers-Danlos type IV syndrome	Monogenic (genetic heterogeneity)	AD	Mutations Collagen gene type III (COL3·A1) *2q31*
Marfan syndrome	Polygenic	AD AD	Gene fibrillin-1 *15q21.1* *3p24.2-p25*
Pseudoxanthoma elasticum	Polygenic	AR & AD	*16p13.1?*
Neurofibromatosis type I	Monogenic (genetic heterogeneity)	AD	*17q11.2*
Tuberous sclerosis	Polygenic	AD AD AD	*TSC1 9q34* *TSC2 16p13* *TSC3* and *TSC4 ?*
Vasculopathies			
Fibromuscular dysplasia	Polygenic?	AD?	*?*
Moya-moya disease	Polygenic	AD/AR? AD/AR?	*3p24.2-p26* *17q25*
CADASIL	Monogenic	AD	*Notch3, 19p12*
Metabolic diseases			
Homocystinuria	Monogenic (genetic heterogeneity)	AR	More frequent Cystathionine-beta-synthase *21q22.3*
Methylenetetrahydrofolate reductase	Monogenic	AR	*1p36.3*
Fabry disease	Monogenic	X-link R	*GLA Xq21.3-22*
MELAS		mitochondrial	
Genes and diabetes mellitus, arterial hypertension, dyslipidemia	Variable (genetic heterogeneity)		
Genes and myocardiopathy, myxoma and familial arrhythmia	Variable (genetic heterogeneity)		

AD: Autosomal dominant; AR: Autosomal recessive; X-link R: Sex linked recessive; ?: Unknown.

(or risk factors unrelated to cerebrovascular disease); (4) complete cardiovascular study without evidences that can explain cerebrovascular disease; (5) concomitant neurological entities (epilepsy in MELAS syndrome, dementia and migraine in CADASIL); (6) concomitant non-neurological diseases (ischemic heart disease, pulmonary thromboembolism/deep venous thrombosis, pregnancy loss, peripheral arteriopathy); (7) atypical radiological pattern (in MELAS syndrome) or multiple silent ischemic lesions in young adult (CADASIL, Fabry disease); (8) characteristic morphologic phenotype (in Marfan syndrome, Ehlers-Danlos); (9) skin lesions (angiokeratoma in Fabry disease, telangiectasia in Rendu-Osler-Weber disease); and (10) alterations in coagulation times (in hereditary hemostatic disorders).

Table 3 shows the main genetic disorders associated with ischemic stroke and Table 4 those related to hemorrhagic strokes.

URINE TESTS

Biochemical testing of urine[1,13,36]

In patients with cerebrovascular disease is recommended to perform a biochemical analysis of urine.

Albumin: The presence of albumin may indicate nephropathy, and also Bence Jones proteinuria which may cause hyperviscosity syndrome. Albumin is usually associated with nephritic syndrome that can lead to a prothrombotic state.

Catecholamines and metabolites: Tests of catecholamines and their metabolites (free urinary catecholamines, urine metanephrines and vanillylmandelic acid) in 24-h urine may be useful in case of suspected hypertensive emergency secondary to pheochromocytoma.

Table 4 Classification for genetic disorders associated with hemorrhagic stroke[35]

Coagulation	Genetic pattern	Inheritance	Gene
Congenital deficiencies of clotting factors			
Factor VIII	Monogenic	X-link R	*Xq28*
Factor IX	Monogenic	X-link R	*Xq27.1-q27.2*
Factor XIII	Monogenic	AR	*6p25-p24*
Factor VII	Monogenic	AR	*13q34*
Factor X	Monogenic	AR	*3q34*
Factor XI	Monogenic	AR	*4q35*
Afibrinogenemia	Monogenic	AR	*4q28*
Polymorphism of clotting factors			*1q23*
Factor V Leiden (G1619A)	Polymorphism		
Factor XIII Val34Leu	Polymorphism		*6p25-p24*
Factor XIII Tyr204Phe	Polymorphism		*6p25-p24*
Factor XIII Pro564Leu	Polymorphism		*6p25-p24*
Factor VII-323Del/Ins	Polymorphism		*13q34*
PAI-I 4G/5G	Polymorphism		*7q21.3-q22*
Platelet disorders			
Thrombocytopenia-absent radius	Monogenic	AR	?
Wiskott-Aldrich syndrome	Monogenic	X-link R	*Xp11.23-p11.22*
Bernard-Soulier syndrome	Monogenic	AD	*22p11.2-17pter-p12*
Glanzmann thrombasthenia	Monogenic	AR	*17q21.32*
Storage pool deficiency	Genetic heterogeneity		
Sickle-cell disease	Monogenic	AR	Mutation A→T, Glu6Val in beta chain of hemoglobin *11p15.5*
Vascular malformations			
Multiple cavernomatosis	Polygenic		
CCM1		AD	*7q11.2-q21*
CCM2		AD	*7p15-13*
CCM3		AD	*3q25.2-27*
Arteriovenous malformations	?	?	?
Hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber)	Polygenic		
THH type 1		AD	*Endoglin gene, 9q*
THH type 2		AD	*Activin receptor-likekinase, 12q*
Von Hippel-Lindau disease	Monogenic	AD	*3p26-p25*
Bannayan-Zonana syndrome	Monogenic	AD	*10q23.3*
Familial venous malformations	Monogenic	AD	*Mutation gene Tie-2, 9p*
Cerebral aneurysms and SAH	Polygenic	?	*Ligament 5q22-q31*
			Ligament 7q11
			Ligament 14q22
Alpha-1 antitrypsin	Polymorphism		*Alleles Z and S, 14q32.1*
Endoglin gene	Polymorphism		*Intron insertion 7, 9q*
MMP-9 gene	Polymorphism		*-736 (CA)23 9q34.1*
Connective tissue disorders			
Ehlers-Danlos type IV syndrome	Monogenic (genetic heterogeneity)	AD	Mutations Collagen gene type III (COL3·A1) *2q31*
Marfan syndrome	Polygenic	AD	Gene fibrillin-1 *15q21.1*
	Polygenic	AD	*3p24.2-p25*
Polycystic kidney disease			
ADPKD 1		AD	*16p13.3*
ADPKD 2		AD	*4q13-23*
ADPKD 3		AD	*?*
ARPKD		AR	*6p21.1-p12*
Pseudoxanthoma elasticum	Polygenic	AR & AD	*16p13.1?*
Neurofibromatosis type I	Monogenic (genetic heterogeneity)	AD	*17q11.2*
Tuberous sclerosis	Polygenic	AD	*TSC1 9q34*
		AD	*TSC2 16p13*
		AD	*TSC3* and *TSC4?*
Vasculopathies			
Fibromuscular dysplasia	Polygenic?	AD?	?
Moya-moya disease	Polygenic	AD/AR?	*3p24.2-p26*
		AD/AR?	*17q25*
CADASIL	Monogenic	AD	*Notch3, 19p12*
Metabolic disorders			
Fabry disease	Monogenic	X-link R	*GLA Xq21.3-22*
MELAS		mitochondrial	
Amyloidosis related genes			
Hereditary cerebral hemorrhage with amyloidosis			

Dutch type	Monogenic (genetic heterogeneity)	AD	Mutations amyloid-beta precursos protein, *21q21*
Icelandic type	Monogenic	AD	*Substitution* Leu68 → GlnCystatin C gene, *20p11.2*
Cerebral amyloid angiopathy	?	?	*APOE, alleles E2, E4* *19q13.2*
Transtiretine gene	Monogenic	AD	*18q11.2-q12.1*
Genes and HTA	Polygenic		

MMP-9: Matrix metalloproteinase-9; AD: Autosomal dominant; AR: Autosomal recessive; SAH: Subarachnoidal hemorrhage; X-link R: Sex linked recessive; ?: Unknown.

Cyanide-nitroprusside test: It is useful to detect homocystinuria, an autosomal recessive disease due to deficiency of the cystathionine-synthase enzyme.

Toxicological study: Urine drug testing may be useful to detect the presence of drugs in the urine (cocaine, amphetamines, and sympathomimetics) and may be considered in young individuals with stroke who do not present known vascular risk factors.

Organic acids: Its determination can alert to the possibility of cerebrovascular disease related to metabolic disorders (organic acidemia of juvenile presentation, such as methylmalonic acidemia or Leigh's disease).

Urine sediment, cytology and urine culture[1,13,36]

They should be conducted in patients with vascular disease and febrile syndrome. Because urinary tract infections occur in 8%-14% of stroke patients admitted to hospital, they are the most common non-neurological medical complications. The presence of microhematuria can indicate concomitant renal infarction and guide the diagnosis of cerebral embolism of cardiac origin.

LUMBAR PUNCTURE: CEREBROSPINAL FLUID[26,37-39]

The cerebrospinal fluid (CSF) is obtained by doing a lumbar puncture (LP) to analyze its color (must be transparent, as rock water), pressure (15-20 cm H_2O), protein (15-50 mg/100 mL), glucose (2.2-4.4 mmol/L) (50-75 mg/100 mL), cells (0-5 mononuclear cells/mm^3), determination of the VDRL test, FTA-Abs test, and bacteriological study. It has been one of the most useful explorations in the diagnosis of patients with cerebrovascular disease for decades now.

LP is contraindicated by the presence of symptoms and signs suggestive of intracranial hypertension, of risk or evidence of cerebellar tonsillar herniation, of severe thrombopenia, and in the case of administration of anticoagulants.

The widespread availability of modern computed tomography (CT) and magnetic resonance imaging systems has significantly changed the diagnostic indications of LP to the extent that LP cannot be performed if there are no previous neuroimaging tests.

The current recommendations of LP in cerebrovascular pathology are the following[17,24,36-39]: (1) in case of "febrile syndrome" of unknown etiology, in order to rule out a meningeal or encephalic infectious process; (2) in patients diagnosed with or suspected of having an "infectious disease" affecting the central nervous system, such as Lyme disease, neurobrucellosis or neurocysticercosis; (3) patients with "constitutional syndrome" (asthenia, anorexia, weight loss) of unknown etiology, in order to rule out the existence of an infectious or neoplastic process; (4) positive "luetic serology", in order to perform the syphilis test (VDRL) in CSF and confirm the meningovascular syphilis; (5) in patients diagnosed with or suspected of having "autoimmune disease", such as isolated angiitis of the central nervous system, granulomatous angiitis, systemic vasculitis (polyarteritis nodosa, systemic lupus erythematosus, giant cell arteritis); and (6) clinical suspicion of "subarachnoid hemorrhage" when CT is negative or equivocal.

When a LP is performed and hematic CSF is detected, subarachnoid hemorrhage should be distinguished from traumatic LP. In order to differentiate them, a sample of CSF is collected in three consecutive tubes and, after centrifugation, examined with spectrophotometry - not visible to the naked eye - for the presence of xanthochromic supernatant. The presence of xanthochromia indicates subarachnoid hemorrhage. CSF xanthochromia may be observed within two weeks after hemorrhage.

SIMPLE X-RAY[1,7,40-43]

Chest X-ray

Chest X-ray should be performed in all patients diagnosed with or suspected of having a cerebrovascular disease. The purpose of the test is obtaining information about the presence of possible pulmonary pathology (infectious or neoplastic), and heart disease mainly in relation to cardiac size (left ventricular hypertrophy) and aortic morphology.

Skull X-ray

Plain skull X-ray may be useful in previous head-injured patients to assess the presence of fissure or fracture of the cranial bones, especially the temporal squamous bone. It can provide additional information on etiological or concurrent pathologies of the patients' neurological process, such as the dilation of the Turkish chair in pituitary tumors, and images of lysis or bone

condensation in metastases or in Paget's disease.

Cervical spine X-ray

Radiological evaluation of the cervical spine is indicated in patients who present transient ischemic attacks related to the vertebrobasilar territory, and most especially in those episodes of neurological deficit triggered by movements of rotation or cephalic extension. The goal is identify the presence of uncoarthrosis, trigger of vertebral artery compression in the intravertebral trajectory (C6-C2).

Abdominal radiograph

In patients with cerebrovascular disease and arterial hypertension or intermittent claudication, abdominal X-ray allows accurate assessment of aneurysmal dilatation or calcification of the abdominal aorta.

ELECTROENCEPHALOGRAM[44]

The electroencephalogram (EEG) is the recording of electrical activity of the brain through electrodes placed on the surface of the skull. Currently, the EEG indications in patients with cerebrovascular disease are the following: (1) assisting with diagnosis of epileptic seizures in patients with transient alterations of consciousness secondary to previous or current cerebrovascular lesions; (2) evaluation of coma or pseudocoma states (alpha coma); (3) monitoring of brain function in carotid surgery (endarterectomy); and (4) clinical diagnosis of brain death.

EVOKED POTENTIALS[45,46]

Evoked potentials (EP) are the electrical manifestations generated by the brain in response to an external stimulus. Depending on the nature of the stimulus pattern, the evoked potential can be auditory, somatosensory, or visual.

The purpose is to determine whether or not a sensory function is normal, and thus check the normality of the anatomical system that sustains the function, without specific diagnosis; furthermore, EP provide quantitative functional measures and prognostic progression of the lesion. The two main data used in the interpretation of EP are the presence or absence of the P wave, as well as its morphological characteristics, and the latency of its appearance after the application of the stimulus.

Somatosensory evoked potentials are generated by stimulation of sensory peripheral nerves; the stimulated nerve fibers reach the posterior spinal ganglion, penetrate the spinal cord and cross over to the other side ascending within the medial lemniscus to reach the thalamus, from where impulses are relayed to the frontoparietal cortex, which records and evoke the answer to the initial stimulus. They are indicated in vascular lesions of the brainstem and cerebral hemispheres, mainly in thalamic alterations, as well as the study of comatose patients and brain death.

Visual evoked potentials are generated in response to nerve stimulation through variations in light intensity using a luminous board. Each eye is analyzed separately, and the evoked responses are collected in the occipital cortex. It is particularly suitable for the study of ischemic lesions of the optic nerve, and vascular alterations in the intracranial visual pathway.

Auditory evoked potentials are activated by applying acoustic stimuli separately for each ear, which are transmitted by the cochlear nerve, stimulating the auditory nuclei of the brainstem. In cerebrovascular pathology its primary indication is the study of comatose patients and brain death.

POLYSOMNOGRAPHY[47-50]

Obstructive sleep apnea syndrome (OSAS) is a new cardiovascular risk factor that results from intermittent and repetitive complete obstruction (apnea) or partial obstruction (hypopnea) of the upper airway during sleep, which manifests by sleep fragmentation and oxygen desaturation. The most common symptoms are daytime sleepiness, snoring and sleep apnea pauses.

A recent study conducted in 161 consecutive stroke patients showed that 71.4% of patients reported an apnea-hypopnea index > 10, which is compatible with OSAS, and 28% of them reported an index > 30 (severe OSAS) during the acute phase. Central respiratory disorders such as Cheyne-Stokes syndrome (Figure 1) may also occur.

Definitive diagnosis of respiratory sleep disorders associated with stroke has to be confirmed by overnight polysomnographic recording which simultaneously measures neurophysiological and cardiorespiratory variables. This technique allows for the assessment of the impact of apneas and hypopneas on cardiorespiratory function and sleep architecture. Polysomnography measures nasal/oral airflow, abdominal and thoracic wall movements (ventilator effort), transcutaneous oxygen saturation, electrocardiogram, and body position. Currently, in selected cases, continuous positive airway pressure (CPAP) during sleep is the treatment of choice for obstructive sleep apnea. Changes in cerebral hemodynamics can be detected in obstructive sleep apnea syndrome with greater neurological deterioration in the sitting of acute cerebral ischemia.

NEUROPSYCHOLOGICAL STUDIES

Approximately 55% of patients having a first lacunar infarct have mild cognitive impairment of the executive functions at the end of the acute phase of the disease and vascular dementia reaches 32% at 3 mo after the onset of symptoms[51].

In acute stroke, the initial vascular cognitive impairment is often the prelude to the subsequent vascular dementia and its subtypes: Multi-infarct or cortical predominant dementia, the strategic infarct dementia, Alzheimer's disease with cerebrovascular disease

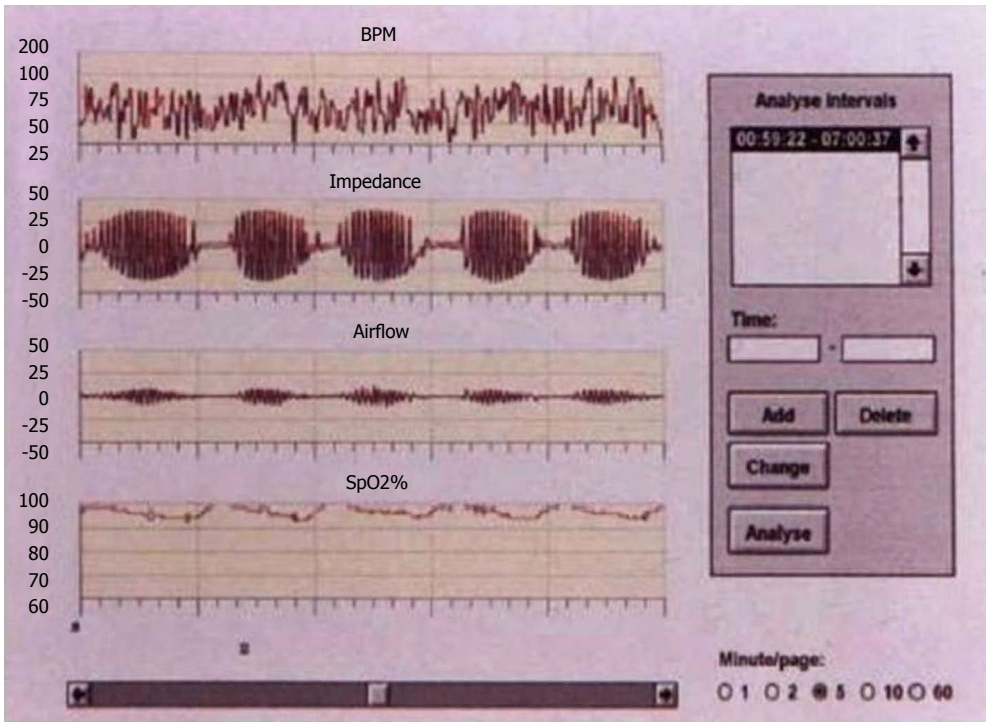

Figure 1 Cheyne-Stokes respiration in a patient with lacunar cerebral infarction[49]. BPM: Blood pressure.

and subcortical vascular dementia. Recurrent stroke is associated with an increased risk of vascular cognitive impairment, which in turn increases the risk of institutionalization and fatal outcome[52]. Antithrombotic drug therapy, statins in selected cases[53], control of stroke risk factors and non-drug therapy (physical exercise, healthy diet, avoid smoking and toxic habits) are essential for the secondary prevention of cerebral ischemia which is mandatory to prevent vascular dementia.

Recently it has been observed that asymptomatic carotid stenosis is also a risk factor for ischemic cognitive decline[54,55]. The pathophysiological mechanism whereby the carotid stenosis may cause some form of cognitive impairment can be multiple. It has been proven a decrease of approximately 25% of cerebral blood flow on the side of stenosis with respect to the contralateral side, and the long-lasting insufficient perfusion may impair energy metabolism in neurons and cause cognitive impairment[51]. In addition, cerebral magnetic resonance imaging based on weighted diffusion and gradient echo techniques suggest that either hemorrhagic and non-hemorrhagic microinfarcts or silent lacunes are far more common than clinically recognized. Beyond hypoperfusion and silent infarction, altered cerebrovascular reactivity and impaired regional functional connectivity have been associated with poorer cognitive performance in patients with asymptomatic carotid stenosis[54-56].

Conversely, neuropsychological impairments in subcortical lacunar infarcts probably result from the interruption of prefrontal-subcortical loops by lacunes and white matter lesions that result in executive dysfunction[57].

Some studies have reported conflicting results of carotid endarterectomy (CEA) and carotid artery stenting (CAS) on cognitive function. The mechanisms of CAS that can improve cognition are similar to those of CEA, including the improvement of cerebral perfusion and the reduction of the incidence of future brain infarctions[58].

The presence of brain atrophy can also play a major role in the cognitive decline associated with asymptomatic carotid disease[59]. This is an open line of research which will deserve further examination in the immediate future.

PATHOLOGICAL STUDY: BIOPSY[1,7,60-62]

Arterial biopsy

A temporal artery biopsy remains essential for the diagnosis of suspected giant cell arteritis or Horton's disease (Figure 2). Stroke may cause the onset of this disease or be a serious complication in its clinical course. In a recent study, giant cell arteritis accounted for 5.7% of strokes of unusual cause admitted consecutively during a 10-year period. The pathological study of atherosclerotic plaques and arterial segments obtained by endarterectomy is also useful to contribute to the knowledge of the natural course of ulceration and thrombosis in atherogenesis. The digital artery biopsy may also be helpful in the diagnosis of Sneddon syndrome, since pathologic findings show focal skin ulceration and chronic inflammatory infiltrates with intimal thickening and occasionally thrombosis, without vasculitis.

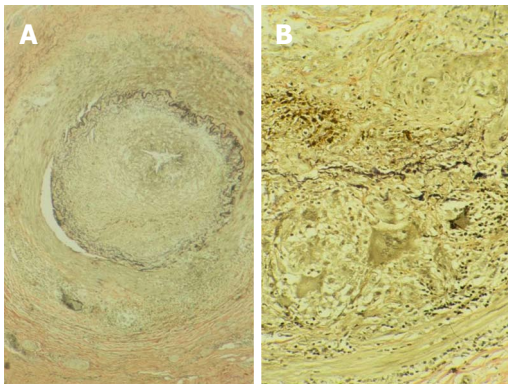

Figure 2 Temporal artery biopsy (elastin stain) in a patient (A) with Horton arteritis showing the presence of multinucleated giant cells (courtesy of Dr. Isidro Ferrer) (B).

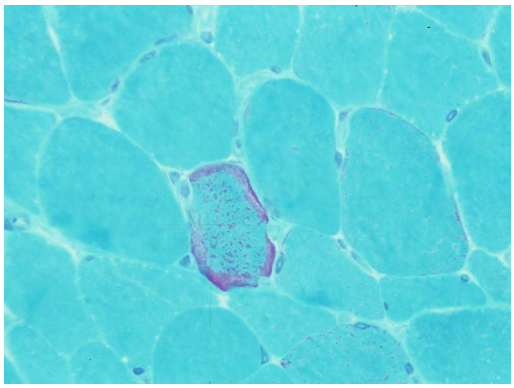

Figure 3 Ragged red fibers in muscle biopsy, stained with modified Gomori trichrome, characteristics of mitochondrial encephalomyopathy.

Skin biopsy

Skin biopsies are useful to diagnose Fabry disease, secondary to alpha-galactosidase A deficiency that leads to glycosphingolipids accumulation in vascular endothelium and in other cells. Dermal lesions like diffuse corporal angiokeratoma are observed, coexisting with polyneuropathy, renal failure, heart disease and cerebrovascular disease. Skin biopsy shows characteristic dense inclusions with "fingerprint" patterns on endothelial cells, pericytes, fibroblasts and Schwann cells, both in clinically visible capillary lesions and in apparently healthy skin.

In CADASIL Syndrome (Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy), an eosinophilic granular material deposit is observed in the leptomeningeal and perforating arterioles as well as thickening of basal lamina of the vascular smooth muscle by granular osmiophilic material seen as dense material by electron microscopy.

Muscle biopsy

Muscle biopsy is an established test to diagnose mitochondrial encephalomyopathy, mainly in MELAS syndrome (mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes). Muscle biopsy showing ragged red fibers visible under modified Gomori trichrome stain is consistent with mitochondrial myopathy. Cerebral ischemia might be related to true mitochondrial angiopathy located in the brain microcirculation (Figure 3).

Nerve biopsy

Nerve biopsy is a useful procedure in patients with suspected systemic vasculitis or connectivopathy (mainly Wegener's disease and polyarteritis nodosa).

Meningeal biopsy

Meningeal biopsies allow the visualization of the arterial vessels of the meningocortical network. The main indication is for patients with suspected isolated or granulomatous angiitis of the central nervous system. It may also be helpful in diagnosing intravascular lymphomatosis (former malignant angioendotheliosis of the central nervous system).

Brain biopsy

Intracerebral hemorrhages requiring surgical evacuation must be considered from a pathological point of view to rule out the presence of massive hemorrhage in primary or metastatic brain tumor, to detect cryptic vascular malformations causing bleeding and for the definitive diagnosis of cerebral amyloid angiopathy. Intravascular lymphomatosis and angiocentric T-cell lymphoma are two very unusual entities that involve neoplastic proliferation of lymphocytes and whose diagnosis is usually made by brain biopsy.

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MINIREVIEWS

Clinical variants of pityriasis rosea

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Abstract

Pityriasis rosea (PR) is a common erythemato-squamous dermatosis which almost always, is easily diagnosed. Mostly the disease presents in its classical form. However, clinical dermatology is all about variations and PR is not an exception. Variants of the disease in some cases may be troublesome to diagnose and confuse clinicians. Prompt diagnosis and treatment of the condition becomes necessary to avoid unnecessary investigations. We hereby review and illustrate atypical presentations of the disease, including diverse forms of location and morphology of the lesions, the course of the eruption, and its differential diagnoses.

Key words: Pityriasis; Pityriasis rosea; Pityriasis rosea of Gibert; Herald patch; Papulo-squamous dermatosis

Core tip: Pityriasis rosea (PR) is a common, self-limited disease which in its typical form should not raise diagnostic doubts. Atypical forms represent 20% of cases, with diverse variants with respect to morphology and location of lesions, and evolution of the disease. Recognition of these forms may avoid unnecessary procedures. Drug ingestion may simulate PR in some cases.

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INTRODUCTION

Pityriasis rosea (PR) is a relatively common, self-limited papulo-squamous dermatosis of unknown origin, which mainly appears in adolescents and young adults (10-35 years), slightly more common in females. It has a sudden onset, and in its typical presentation, the eruption is preceeded by a solitary patch termed "herald patch", mainly located on the trunk. Few days later, a secondary eruption appears, with little pink, oval macules, with a grayish peripheral scaling collarette around them. The secondary lesions adopt a

Table 1 Clinical classification of pityriasis rosea

Classical adult PR and pediatric PR
Based on herald patch
No herald patch
Only herald patch (absence of secondary lesions)
Multiple herald patches
Herald patch in atypical location
Based on location of lesions
Limited to scalp
Limited to trunk
Limited to limbs-girdle (pityriasis circinata et marginata of Vidal)
Limited to flexures (inverse type)
Limited to the extremities
Acral type
Along the lines of Blaschko
Unilateral
Based on morphology of lesions
Purpuric or hemorrhagic
Urticarial
Erythema multiforme-like
Papular
Follicular
Vesicular
Giant
Hypopigmented
Irritated
Based on course of the disease
Relapsing
Recurrent
Persisting
Relapsing and persisting
PR-like rashes (drug-induced)

PR: Pityriasis rosea.

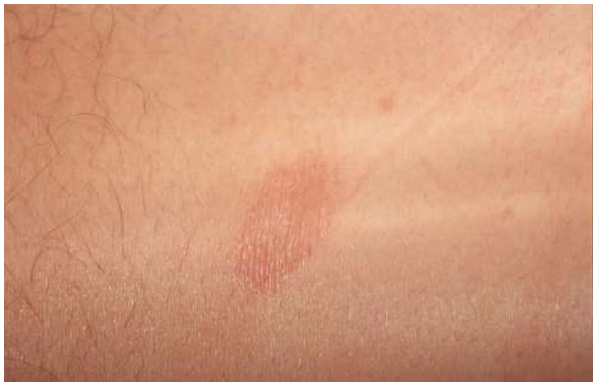

Figure 1 Herald patch. Solitary erythemato-squamous lesion, sharply defined, round or oval, mainly located on the trunk or proximal extremities.

characteristic distribution along the cleavage lines of the trunk, with a configuration of a "Christmas tree". In most cases, the eruption lasts for 6 to 8 wk. Its incidence has been estimated to be 0.68% of dermatologic patients[1], varying from 0.39%[2] to 4.8%[3].

Not so rarely (20%)[4,5], an atypical eruption may develop, concerning several aspects about the morphology or distribution of the lesions, their symptomatology and evolution.

The purpose of this article is to review and illustrate the diverse clinical presentations of PR (Table 1), which may vary in morphology, symmetry, duration, size and distribution of lesions, mucosal involvement and symptomatology.

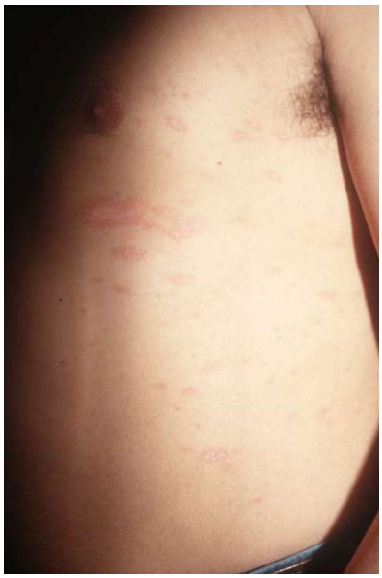

Figure 2 Classical pityriasis rosea. Exanthematous eruption with erythemato-squamous lesions following cleavage lines on the trunk.

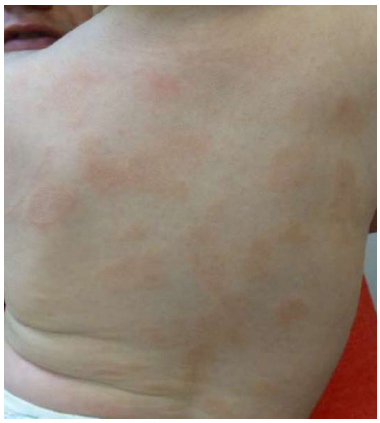

Figure 3 Pediatric pityriasis rosea. Typical lesions of PR affecting an 8-mo-old boy. PR: Pityriasis rosea.

Classical PR

A classical PR is preceeded by the herald patch, an erythematous round or oval lesion, 2-5 cm in diameter, ocassionally covered by fine scales (Figure 1). Prodromal symptoms, consisting of headache, general malaise, or flu-like symptoms are ocassionally encountered. Few days later (5-15 d), a secondary rash appears, consisting of similar, but smaller lesions, mainly located on the trunk (Figure 2). Pruritus is usually mild or absent, but can vary in intensity. The eruption lasts for 4-6 wk and fades, leaving no sequelae. Generally, it only appears once throughout life. In 75% of patients the lesions appear between the ages of 10-35 years[6].

Pediatric PR

Infrequently PR may affect children (Figure 3), with a prevalence between 8%[7] to 12%[6] below 10 years

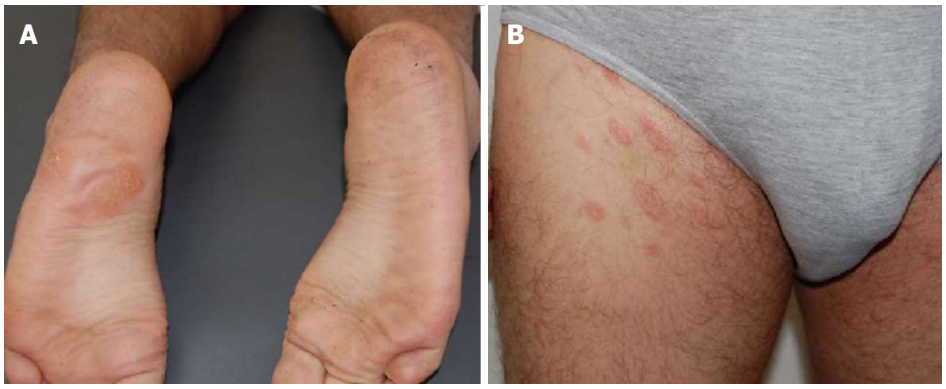

Figure 4 Herald patch in atypical location. Herald patch on a sole (A) and (B) typical PR eruption affecting trunk and proximal thighs. PR: Pityriasis rosea.

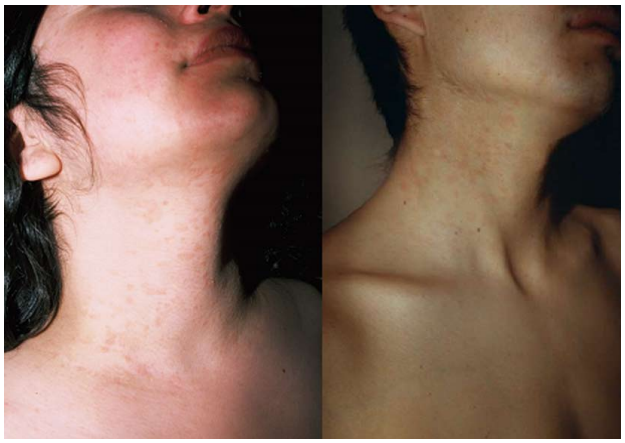

Figure 5 Inversus pityriasis rosea. Lesions distributed on face and neck in two patients; the trunk is not affected.

and 4% below 4 years of age[6] in Caucasians, whereas in dark-skinned children it increases to 26%[8]. Papular lesions prevail in them, with a short period between the herald patch and the general eruption (4 d *vs* 14 d in adults), and a shorter duration of the exanthema (16 d *vs* 45 d). The majority of cases have been described in children with ages between 3 to 9 years old, contrasting with the illustrated case of 8-mo, showing a classical variant. About half of the cases show prodromal symptoms[7].

BRIEF DESCRIPTION OF CLINICAL VARIANTS OF PR

Herald patch in atypical location

Although not mentioned in the literature, we had the opportunity to come across a patient who presented with a herald patch on a sole, and a secondary classical eruption on the trunk and proximal aspect of the extremities (Figure 4).

Circinata and marginata PR

Seen mainly in adults with few and large lesions only located on limbs-girdle, hips, shoulders, axillae or inguinal regions[9-11].

Inversus PR

The lesions are located on flexural areas (axillae, groins), face, neck (Figure 5), and acral areas (palms and soles), without affecting the trunk[12].

PR of extremities

In this variant, the lesions are confined to the extremities, with typical squamous plaques (Figure 6). The trunk is not affected.

Acral PR

The lesions are exclusively located on palms, wrists, soles[13] (Figure 7), without involvement of the flexures (axillae, groins and face), opposite to inversus PR.

Purpuric or hemorrhagic PR

Macular purpuric lesions and petechiae may appear over different locations (Figure 8) including the palate. Purpuric lesions have also appeared bilaterally on the legs in a man with a typical rash on the trunk, affecting the lines of cleavage and with collarette scaling[4].

Urticarial PR

Palpable itchy wheals-like lesions with peripheral collarette scaling (Figure 9) following the lines of skin cleavage[4,10].

Erythema multiforme-like PR

In some cases, classical lesions of PR may be accompanied by targetoid lesions resembling erythema multiforme (Figure 10). It presents with papulo-squamous lesions, admixed with few targetoid lesions distributed on the trunk, face, neck or arms[14,15]. There is no history of herpes simplex infection.

Papular PR

Multiple small papular lesions, 1-3 mm in diameter with peripheral collarette, located on the trunk and proximal extremities, along the skin cleavage lines (Figure 11). It appears predominantly in young patients[4].

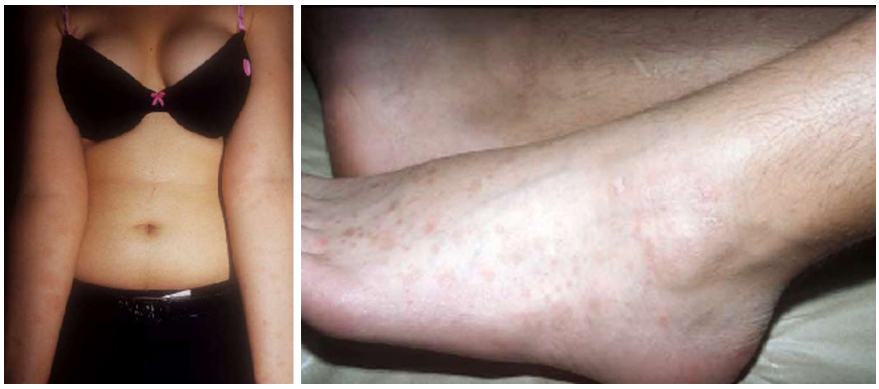

Figure 6 Pityriasis rosea of the extremities. Lesions affecting only the extremities in two different cases, without trunk involvement.

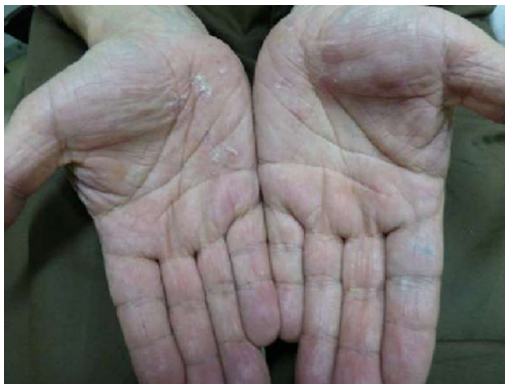

Figure 7 Acral pityriasis rosea. Desquamation affecting the palms.

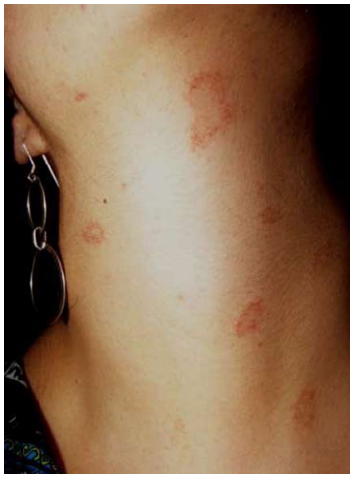

Figure 8 Purpuric pityriasis rosea. Round and oval purpuric lesions affecting the neck of a young woman.

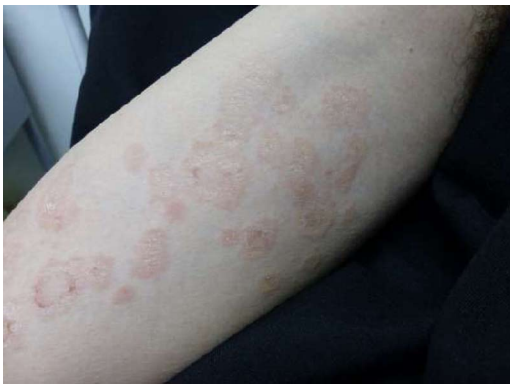

Figure 9 Urticarial pityriasis rosea. Palpable edematous, erythematous lesions with collarette scaling.

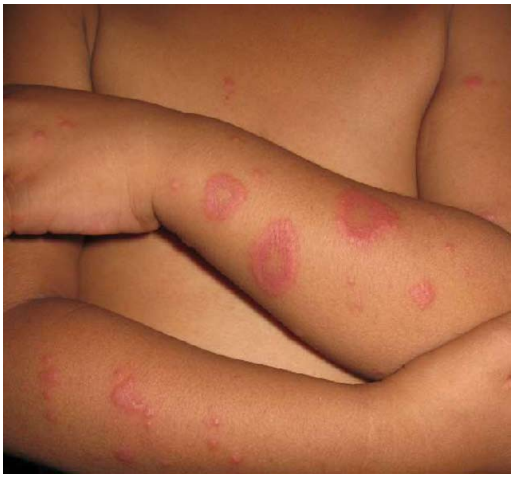

Figure 10 Erythema multiforme-like pityriasis rosea. Annular and papular lesions resembling erythema multiforme.

Follicular PR

It has been described in a 9-year-old boy with predominantly follicular scaly lesions, arranged in annular configuration[16]. The initial lesions consisted of pruritic plaques mainly located on the abdomen, thighs and groins; five days later, a striking follicular eruption - with central clearing and a peripheral collarette- developed on the posterior trunk. Prodromal symptoms included sore throat, malaise and low grade fever (Figure 12).

Vesicular PR

Generalized itchy eruption of vesicles of 2-6 mm in diameter with a rosette scaling has been described in young adults and children[17-21] (Figure 13).

Gigantea PR of darier

The dimensions of the herald patch is greater than usual, being described with the size and shape of a

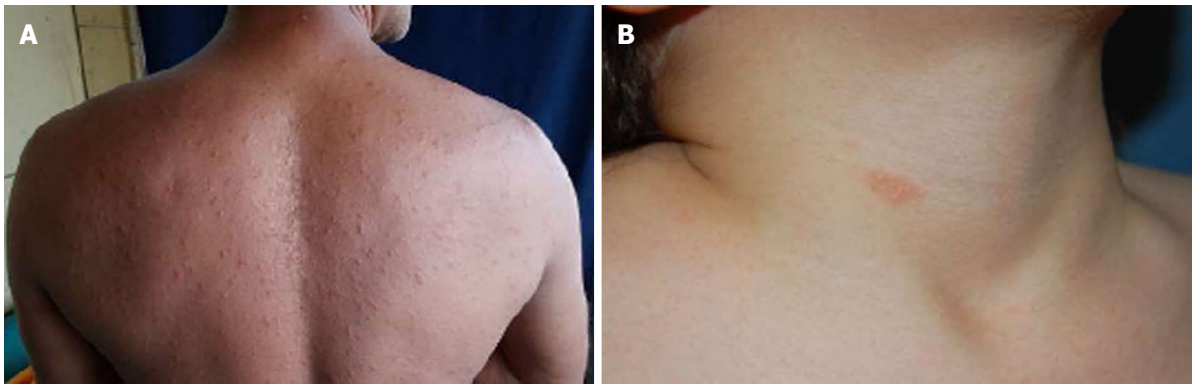

Figure 11 Papular pityriasis rosea. A: Papular lesions with peripheral collarette (Courtesy of Priyankar Misra, Junior Resident, Dermatology, Burdwan Medical College, West Bengal, India); B: Herald patch on the neck and disseminated discrete papular eruption in a girl.

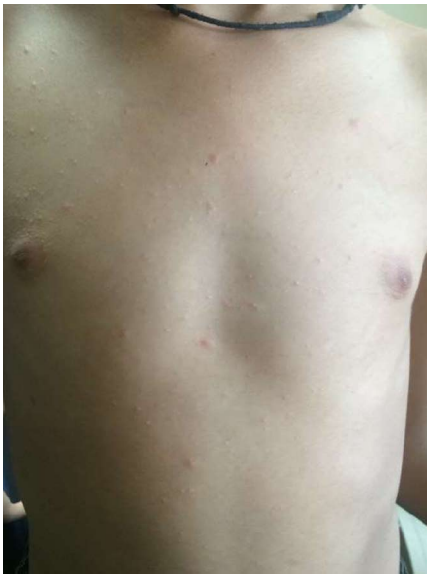

Figure 12 Follicular pityriasis rosea. Follicular lesions with scaling (Courtesy of Shankila Mittal, Junior Resident, Dermatology, Maulana Azad Medical College, New Delhi, India).

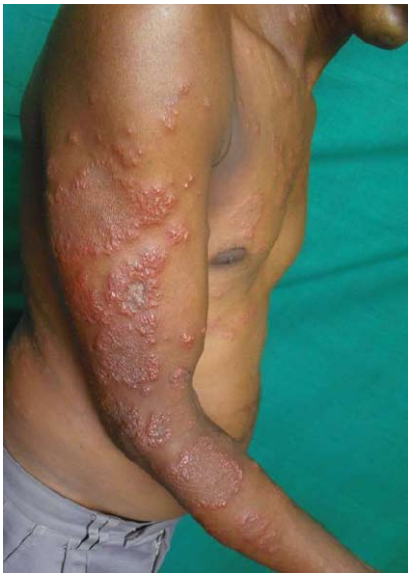

Figure 13 Vesicular pityriasis rosea. Vesicular lesions surrounding round to oval plaques (Courtesy of Dibyendu Basu, Junior Resident, Dermatology, Medical College and Hospital, Kolkata, West Bengal, India).

pear[22] (Figure 14).

Hypopigmented PR

It is essentially similar to the classic PR, with a preceding herald patch and a secondary eruption, but with hypopigmented lesions from the beginning, mainly distributed on the trunk (Figure 15). It is more frequent in dark-skinned individuals. It should not be confused with secondary hypopigmentation after a common PR.

Irritated PR

A PR with severe itch, pain and burning sensation on contact with sweat[5,23] (Figure 16).

Relapsing PR

It usually recurs within one year of the first episode, among 2.8%-3.7% of patients[8,24]. Relapses usually show absence of herald patch, and the size and number of secondary lesions are smaller. The duration of this episode is shorter and with less constitutional symptoms. Multiple relapses - though rare - have been described[25,26].

Persistent PR

By definition it lasts more than 3 mo. Its incidence in a series was 2%[1]. Most patients (75%) show a herald patch[1] and complain of systemic symptoms (most commonly fatigue, or headache, insomnia, irritability). The eruption persists for 12-24 wk. Oral lesions are common (75%), principally strawberry tongue, erythematous macules, vesicular lesions and petechiae.

Recurrent PR

Rarely, there can be multiple episodes of PR in a lifetime[25-27].

Relapsing and persisting PR

It has been described in a young man with three

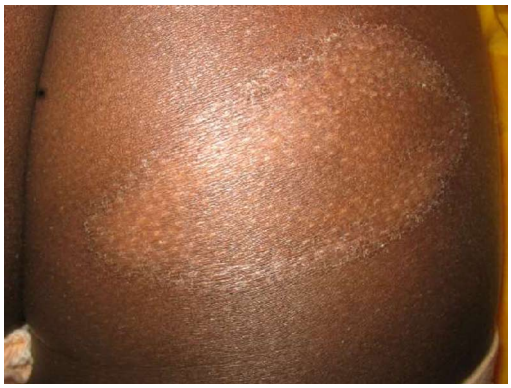

Figure 14 Giant pityriasis rosea. Large herald patch (Courtesy of Soumya Jagadeesan, Assistant Professor, Dermatology, Amrita Institute of Medical Sciences, Kochi, Kerala, India).

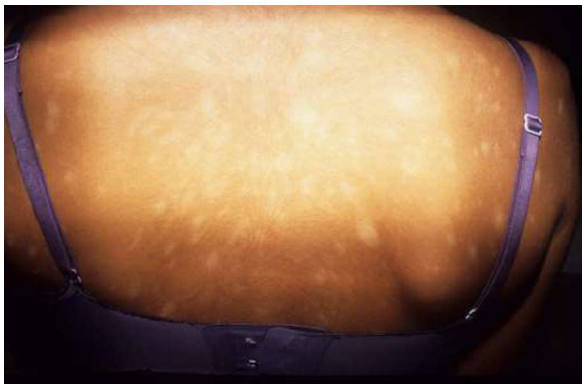

Figure 15 Hypopigmented pityriasis rosea. Round to oval hypopigmented lesions during the whole course of the eruption.

episodes of PR within one year-fulfilling the criteria for relapsing PR, and the last episode during 7 mo-consistent with persistent PR. Noteworthy, the patient presented with multiple oral ulcers[28].

Oral involvement in PR

Oral lesions in PR are more common in dark skinned people[29]. The lesions are difficult to differentiate from aphthous ulcers. Its appearance should coincide with a generalized eruption with the characteristics of PR[4]. The lesions may be punctate, erosive, bullous or hemorrhagic. They disappear concomitantly as the skin eruption fades.

PR-like rashes

They consist of exanthematous rashes which appear following the intake of several drugs: ACE inhibitors[30-32], gold[33-36], isotretinoin[37], non-steroidal anti-inflammatory agents[38,39], omeprazole[40], terbinafine[41], and tyrosine-kinase inhibitors[42]. Many of them resemble PR vaguely (Figure 17), so it may be considered as a separate condition. There is no previous herald patch and the eruption is monomorphous.

DISCUSSION

PR is a self-limited, acute inflammatory dermatosis,

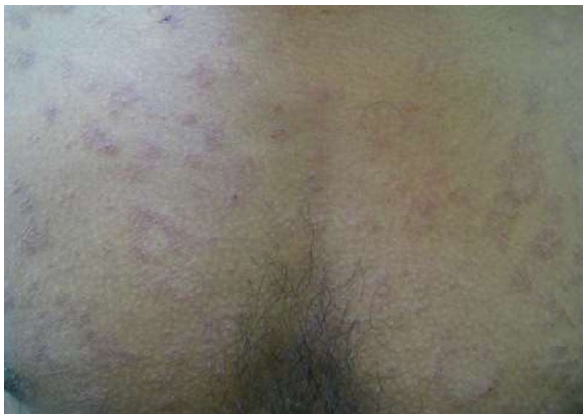

Figure 16 Irritated pityriasis rosea. Symptomatic eczematous lesions (Courtesy of Dipti Das, Consultant Dermatologist, Dr Marwah's Skin Clinic, Mumbai, Maharashtra, India).

Table 2 Diagnostic criteria of pityriasis rosea[47]

Mandatory clinical features
Discrete circular or oval lesions
Scaling within most lesions
Peripheral collarette scaling
Optional clinical features
Trunk and proximal limb distribution
Distribution along cutaneous cleavage lines
Previous herald patch

which occasionally could be persistent or recurrent. In rare situations, the symptoms or presentation may be troublesome, thus making difficulty in diagnosis or having a significant impact on the patient's quality-of-life. Its etiology has not been clearly established, but a viral origin has been suspected for years.

Recently, there are increasing evidences to suggest the role of human herpes virus (HHV) in the etiopathogenesis of PR[43,44]. Additional evidences suggest that PR is associated with reactivation of HHV 6-7[44]. Diminished levels of natural killer cells and B-cell activity in the lesions of PR has been observed. This suggests the role of a T-cell mediated immunity. Besides, increased amounts of CD4 T cells and Langerhans cells have been found in the dermis, which possibly points towards viral antigen processing and presentation. However, this matter is still debated since some individuals are infected with HHV 6-7 and do not develop the disease. PR has been also reported following vaccinations as well (B*acillus* Calmette-Guerin, influenza, H1N1, diphtheria, smallpox, hepatitis B, pneumococcus, *etc.*)[45,46].

The diagnosis of PR is essentially clinical (Table 2)[47], and in rare circumstances a biopsy may be required. Histological features are not specific and include focal parakeratosis, hypogranulosis, spongiosis, papillary dermal edema, mild perivascular lymphohistiocytic infiltrate, exocytosis and extravasated erythrocytes in the papillary dermis.

Differential diagnosis[48]

Secondary syphilis: Meticulous history taking, previous history of chancre, lymphadenopathy, positive VDRL

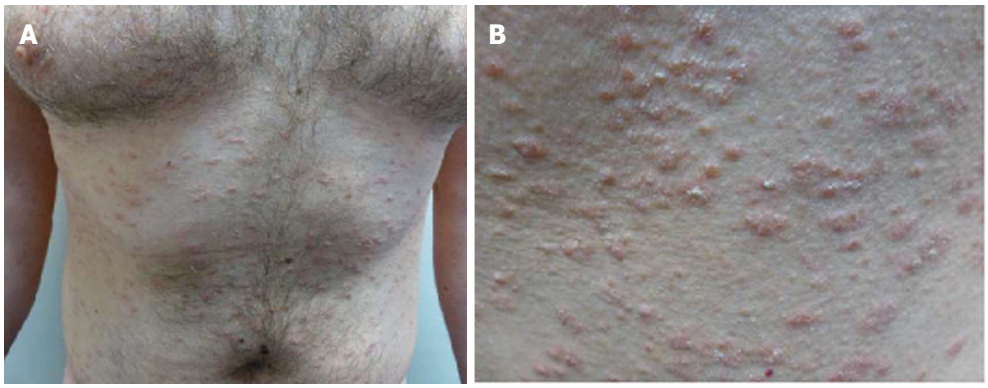

Figure 17 Pityriasis rosea-like rash. A: The eruption in this case was probably related to the ingestion of levothyroxine in a 33-year-old man, extensively affecting the trunk; B: The lesions are small and monomorphous (Courtesy of Dr. Elizabeth Rendic).

test, histology showing plasma cells and endarteritis obliterans are suggestive. Lesions of secondary syphilis are monomorphous and always asymptomatic; they almost always affect palms and soles.

Dermatophytosis: It may be troublesome to differentiate when the only lesion of PR is the herald patch. However, a mycotic lesion expands progressively and shows a clear center, whereas herald patch remains inalterable. Positive KOH mount is the pointer.

Guttate psoriasis: History of sore throat, presence of rain-drop pattern and histology are important clues. Scales are thicker and silvery-white.

Subacute cutaneous lupus erythematosus: Photosensitivity is the rule. Besides, histology shows epidermal atrophy and basal layer degeneration.

Rarely, primary HIV infection, seborrhoeic dermatitis, drug rash, erythema multiforme and cutaneous T cell lymphoma may also be confused with PR. Hypopigmented variant may be confused with pityriasis alba (lesions are mainly located on the face or arms and it is usually associated with atopic dermatitis), hypopigmented mycosis fungoides (lesions are large, persistent, and mainly distributed on buttocks and lower trunk), and progressive macular hypomelanosis of the trunk (lesions are slowly progressive, tend to coalesce, and do not show desquamation).

Therapeutic options

Many cases require no treatment at all, only reassurance directed to the patients, underlying the benign nature and self-limited duration of the disease, which do not leave sequelae and that other members of their family or friends will be not affected. Therapeutic options when needed (in the case of many or symptomatic lesions) include the use of emollients and topical corticosteroids, and antihistamines when itching.

The use of oral macrolides (erythromycin and azithromycin) have shown controversial results[49,50]. Initially, these were found to be beneficial but recent studies show that macrolides are ineffective in the management of PR.

Since the current concepts of etiopathogenesis may imply the role of HHV-7 and HHV-6 in the causation of PR, antivirals like acyclovir have been found to show good response[51-54]. The effectiveness of phototherapy is debated and further studies need to be conducted[55,56]. A statement about the management of PR has been recently raised[57]. Main conclusions include an adequate diagnosis, impact of the eruption in the quality of life since many patients do not necessitate any treatment, and use of oral acyclovir 400 mg three times daily for seven days, when not contraindicated or possible adverse effects are suspected.

CONCLUSION

The diagnosis of typical PR should not be difficult for any dermatologist. Nevertheless, its atypical presentations - as defined here - can be a challenge for the clinician. We hope the article will be helpful to the clinicians, in identifying numerous variants of this common disease.

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ORIGINAL ARTICLE

Observational Study

Vaccinations against respiratory infections in Arabian Gulf countries: Barriers and motivators

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Abstract

AIM

To study the uptake, barriers and motivators of influenza, pneumococcal, meningococcal and pertussis vaccines among members of public in Arabian Gulf countries.

METHODS

A cross-sectional survey among the Gulf Cooperation Council (GCC) countries' residents. Data collected electronically through a smartphone app. The survey variables aimed to investigate the respondents' awareness about vaccines against influenza, pneumococcal, meningococcal and pertussis infections. Collected data concerning the respondents' socio-demographic characteristics, their perception toward vaccine uptake and the factors that motivate or demotivate them from taking influenza vaccine. The data were analysed statistically using the SPSS v.23.0. Differences in the characteristics of users from different countries were quantified through bivariate analysis. Other important variables and controlling factors were studied using logistic regression.

RESULTS

A total of 1812 respondents participated in the study. Their mean age was 27 years, 82% were male and 24% had $\geqslant$ 1 chronic diseases. The overall uptake of influenza vaccine was 17% (21% among "at risk" people) and ranged from 15% in Saudi Arabia to 24% in Qatar. Doctor's advice (23%) and a perception of having low body immunity (21%) were the main cited reasons for being vaccinated, whereas unawareness about the vaccine (43%) was the main barrier. The overall uptake of pneumococcal vaccine in the preceding three years was 22% (25% among "at risk" individuals) and ranged from 0% in Bahrain to 79% in Kuwait. The overall uptake of pertussis vaccine was 16% (31% among "vulnerable" people), and ranged from 7% in Saudi Arabia to 75% in Oman. The overall uptake of meningococcal vaccine was 20% (29% among the "at risk" people) and ranged from 3% in Oman to 50% in Bahrain.

CONCLUSION

The vaccination uptake across GCC countries is suboptimal and varies widely across the countries. Further research is needed to unearth the reasons and formulate action plan.

Key words: Gulf Cooperation Council; Influenza; Meningococcal vaccine; Motivators and barriers; Pertussis vaccine; Pneumococcal vaccine; Respiratory infections

Core tip: Like many other parts of the world, the uptake of the adult vaccinations against respiratory infections in Arabian Gulf countries remains unknown. This area hosts the world's largest annual mass gathering (Hajj pilgrimage) which increases the risk of global dissemination of infectious diseases, particularly, respiratory infections. The coverage rate of the vaccinations against respiratory infections among the public in gulf cooperation council countries was low when compared to that in developed countries. Physicians could play a significant role in enhancing vaccine uptake, and their advice was the principal motivator among our participants.

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INTRODUCTION

Respiratory infections particularly influenza, pneumococcal, pertussis and meningococcal diseases are a major threat to humans and continue to take a heavy toll across the globe[1-4]. Annually, influenza causes a million deaths worldwide[5,6], and pneumonia, mostly caused by *Streptococcus pneumoniae*, is responsible for 1.6 million deaths globally[7]. The incidence of meningococcal disease ranges from one per 100000 population in developed world settings to 1000 per 100000 population in the developing countries of the "meningitis belt" during the epidemic seasons with a high rates of case fatality, and long-term sequelae[8]. In addition, there has been a resurgence of pertussis in the last several years and the disease causes about 200000 annual deaths globally[9]. Vaccinations against influenza, pertussis, and pneumococcal and meningococcal diseases are available, but the vaccination uptake against these diseases remains unknown in many parts of the world including the countries of the Gulf Cooperation Council (GCC).

The GCC comprises of six Arabian countries: Kingdom of Saudi Arabia, Kuwait, Bahrain, Qatar, United Arab Emirates (UAE) and Oman. The GCC countries share a similar social and economic background, health issues, and essentially identical health system and policy. As the host of various mass gathering events (*e.g.*, Hajj pilgrimage and international sport and business events), GCC region occupies a distinctive epidemiological position in the global map, and certain vaccines (*e.g.*, quadrivalent meningococcal vaccine) are unique requirements for some of its residents[10].

Influenza is a common disease in GCC countries[11,12], and therefore members of public especially children,

Table 1 Vaccination uptake in Gulf Cooperation Council countries in published literature

Ref.	Study year	Country	Population	Sample size	Age in years	Vaccine	Vaccine uptake % (*n*/*n*)
Abbas *et al*[39]	2004-2005	Saudi Arabia	Workers of two major industries: A food processing and a chemical plant	2400	(20-60)	Influenza	62.4 (562/900) food processing industry and 55.6 (834/1500) chemical industry
Al-Tawfiq *et al*[38]	2007	Saudi Arabia	HCWs at Saudi Aramco Medical Services Organization	244	NR	Influenza	51 in the preceding year and 71.5 in the last 5 years
Shahbic *et al*[18]	2007	Qatar	HCWs at Hamad Medical Corporation in Doha	14292	NR	Influenza	19.4 (2773/14292)
Rehmani *et al*[20]	2009	Saudi Arabia	HCWs at King Abdul-Aziz National Guard Hospital	512	Mean 35.8 (22-64)	Influenza	34.4 (176/512)
Abu-Gharbieh *et al*[64]	2009	United Arab Emirates, Kuwait and Oman	HCWs at hospitals, polyclinics and medical centres	993	(25-45)	Influenza	42.5 (442/993)
Al-Khashan *et al*[35]	2009	Saudi Arabia	Military personnel of Central Military Region in Riyadh	2230	Mean 36.3	Influenza and meningococcal	17.8 (396/2230) and 51.7 (1153/2230) respectively
AlQuliti *et al*[65]	2012	Saudi Arabia	Emergency room HCWs at 4 hospitals in Al-Madinah	321	NR	Meningococcal	84.7 (272/321)
Garcell *et al*[37]	2011-2013	Qatar	HCWs at the Cuban Hospital	209 (2011-2012), and 325 (2012-2013)	NR	Influenza	61.9 (129/209) in 2011-2012 and 71.1 (231/325) in 2012-2013
Alshammari *et al*[21]	2012-2013	Saudi Arabia	HCWs at 6 major hospitals	242	NR	Influenza	38.8 (94/242)
Alhammadi *et al*[66]	2012-2013	Qatar	HCWs at a tertiary teaching institution in Doha	223	NR	Influenza	68.3 (152/223)
Alhammadi *et al*[22]	2013	Qatar	HCWs at a paediatric unit at Hamad Medical Corporation in Doha	230	NR	Influenza	67.7 (151/230)
Fakhrawi *et al*[67]	2015	Bahrain	Sickle cell patients attending primary health care centres	230	NR	Pneumococcal	62.2 (143/230)

HCW: Health care workers; NR: Not recorded.

elderly and people with chronic diseases are specially recommended to take the vaccine[13-17]. Despite these recommendations, the vaccination rate remains low[18-20]. Studies conducted to assess the influenza vaccine uptake among health care workers (HCWs) in GCC countries reveal that the decision to receive the vaccine is influenced by an individual's type of work, gender, vaccine awareness, need to protect those around and previous vaccination encounters[18,20], whereas, lack of awareness, uncertainty of the effectiveness of the vaccine, and fear of adverse effects are the most common barriers[21,22]. Additionally, some individuals are misinformed that seasonal influenza vaccines are not necessary since they are young[21]. Similarly, for pneumococcal vaccine the barriers to the implementation of the vaccine arise from incomplete awareness of the benefit and safety of the vaccine as well as inadequate understanding of the seriousness of the disease among health professionals[23]. Meningococcal disease is uniquely important in GCC countries, especially in relation to Hajj and Umrah pilgrimages[24]; consequently, the GCC countries endeavour to ensure vaccination (with ACWY vaccine) of all pilgrims to Hajj and Umrah[14,24-26]. In GCC countries, pneumococcal vaccine is recommended for individuals with pre-existing diseases (*e.g.*, sickle cell disease) and elderly adults[27,28], and pertussis vaccine is generally advised for HCWs and pregnant women.

However, there have been limited studies assessing the coverage of influenza, pneumococcal, meningococcal and pertussis vaccines in GCC countries. Most of the available studies on the uptake of vaccines against these infections in GCC countries have been conducted among HCWs (Table 1). Essentially no study has assessed the uptake of these vaccines among the general population other than pilgrims[29,30]. In this regard, our study aims to evaluate their uptake among the members of the public in the GCC countries, explore the barriers to and facilitators of vaccination, and identify other factors that may affect uptake.

MATERIALS AND METHODS

Study design and participant recruitment

The study was a cross-sectional survey among the GCC countries' residents aged ⩾ 16 years old, as described elsewhere[31]. The survey was conducted in Arabic but the data were collated and analysed in English. The data were collected electronically (online) through the "Gulf Indicators" (GI) smartphone app which was released in Apple App store in November 2014 for the

purpose of collecting research data for cross-sectional and cohort studies. The approach was successfully tested in a few studies[32-34] and was found to be reliable and capable of collecting valid and credible data. Some of the mechanisms the app uses to ensure credibility of data include a "built-in" location verification function that verifies that users hail from the GCC countries only. In addition, the app gives each user a unique device identifier to prevent redundancy of data or rather the submission of several forms by the same user, it also promotes anonymity of the respondent. Lastly, the app does not accept submission of incomplete forms thus ensures recording of all vital information.

This survey was published on the GI platform from September to December 2015. To start with, users voluntarily registered to the GI platform. After completing the consent form, the participant could then start answering the survey. The survey variables aimed to investigate the respondents' awareness about vaccines against influenza, pneumococcal, meningococcal and pertussis infections, and collected data concerning their socio-demographic characteristics, their perception toward vaccine uptake, their understanding of the risk of exposure to viruses transmitting airborne infections, and the factors that motivate or demotivate them from taking influenza vaccine.

Sample size

If we assume that at least 50% of the public in GCC countries will have the right knowledge about airborne diseases and their vaccines, and considering an error margin of 10% to be acceptable for this survey, a minimum sample size of 480 was considered sufficient for this survey, but we aimed to recruit as many participants as possible within the survey period even after the minimum sample size was achieved.

Statistical analysis

The data collected were analysed statistically using SPSS v.23.0 (SPSS, Inc., Chicago, IL, United States). Parameters such as the response rates and users' characteristics were analysed descriptively. Differences in the characteristics of users across the countries were quantified through bivariate analysis. Other important variables and controlling factors related to the research topic such as age, gender, country, chronic medical conditions, and educational level, were studied using logistic regression, using the backward Wald method.

Ethics approval

This study was reviewed and approved by the Human Research Ethics Committee at King Saud University (Ethics Ref No: 4/2016), Riyadh, Saudi Arabia.

RESULTS

Demographics

Out of 2741 individuals who downloaded the application, 1812 (66%) completed the survey. Their mean age was 27.3 years (SD ± 8.3), 82% (1485/1812) were male and 24% (436/1812) reported having ⩾ 1 chronic diseases. Over half of participants [53% (967/1812)] were smokers and 56% (1009/1812) had up to high school level of education (Table 2).

Seasonal influenza vaccine

Overall, 17% (300/1812) received seasonal influenza vaccine during the year 2015, 74% (1345/1812) did not receive the vaccine, and 9% (167/1812) were unsure about vaccination status. The influenza vaccine uptake varied slightly across the countries ranging from 15% (163/1105) among residents of Saudi Arabia to 24% (22/93) among residents of Qatar (Table 2). The vaccine uptake among the "at risk" group (those who have chronic condition) was 21% (92/436): The uptake among people aged ⩾ 65 years with no pre-existing disease was 20% (1/5), 50% (4/8) among those with pre-existing diseases and 21% (78/423) among those aged < 65 with chronic diseases.

Physicians' advice was the most cited reason [23% (68/300)] influencing the decision for vaccine uptake, followed by the perception of having low body immunity [21% (62/300)] (the other reasons are summarised in Table 3). In contrast, not being aware of the vaccine [43% (573/1345)] was the main cited reason for non-receipt of the vaccine (the other reasons are listed in Table 3).

In multivariate analysis, light smokers (defined as smoking ⩽ 10 cigarettes per day) [adjusted odds ratio (aOR) = 2.0, 95%CI: 1.4-2.8, $P < 0.01$], medium smokers (defined as smoking between 11-20 cigarettes per day) (aOR = 2.2, 95%CI: 1.6-3.1, $P < 0.01$) and heavy smokers (smoking more than 20 cigarettes per day) (aOR = 1.8, 95%CI: 1.0-3.0, $P < 0.04$) were more likely to be vaccinated compared to not smokers. Moreover, those who had malignancy (aOR = 3.1, 95%CI: 1.3-7.2, $P = 0.01$) and those who suffered from immunosuppressive conditions (aOR = 5.1, 95%CI: 2.0-13.0, $P < 0.01$) were more likely to receive influenza vaccine compared to individuals who did not suffer from these conditions (Table 4).

Pneumococcal vaccine

Overall, 22% (397/1812) of the participants reported receiving pneumococcal vaccine in the three years prior to the survey and the remaining 78% (1415/1812) reported not receiving the vaccine. The uptake rate varied widely across the countries, ranging from 0% (0/98) in Bahrain to 79% (201/253) in Kuwait. The overall uptake rate among the "at risk" individuals was 25% (109/436), the uptake rate among participants with bronchial asthma, those with other lung diseases, heart diseases and diabetes was respectively, 35% (52/150), 52% (12/23), 32% (7/22) and 20% (31/152).

In multivariate analysis, males (aOR = 1.9, 95%CI: 1.2-2.9, $P < 0.01$), heavy smokers (smoking more than 30 cigarettes per day) (aOR = 4.6, 95%CI: 2.6-8.0, $P < 0.01$) and postgraduate degree holders (aOR = 2.1,

Table 2 Demographic characteristics of surveyed participants, and their vaccination uptake

	n (%)	Influenza vaccine *n* (%)	Pneumococcal vaccine *n* (%)	Pertussis vaccine *n* (%)	Meningococcal vaccine *n* (%)
Overall		300 (17)	397 (22)	296 (16)	363 (20)
Age (yr)					
16-36	1578 (87)	243 (15)	342 (23)	250 (16)	330 (21)
37-55	218 (12)	50 (23)	50 (23)	46 (21)	28 (13)
⩾ 56	18 (1)	7 (39)	5 (28)	0 (0)	5 (28)
Gender					
Male	1485 (82)	261 (18)	336 (23)	273 (18)	299 (20)
Female	327 (18)	39 (12)	61 (19)	23 (7)	64 (20)
Countries					
KSA	1105 (61)	163 (15)	74 (7)	82 (7)	302 (18)
Kuwait	253 (14)	42 (17)	201 (79)	87 (34)	19 (7)
UAE	203 (11)	45 (22)	43 (21)	35 (17)	76 (37)
Bahrain	98 (6)	18 (18)	0 (0)	20 (20)	49 (50)
Qatar	93 (5)	22 (24)	69 (74)	27 (29)	14 (15)
Oman	60 (3)	10 (17)	10 (17)	45 (75)	2 (3)
Education					
⩽ High school certificate	803 (44)	128 (16)	193 (24)	133 (17)	172 (21)
> High school certificate	1009 (56)	172 (17)	204 (20)	163 (16)	191 (19)
Employments statues					
No	237 (13)	23 (10)	51 (22)	26 (11)	60 (25)
Yes	1575 (87)	277 (16)	346 (22)	270 (17)	303 (19)
Government employee	530 (34)	80 (15)	114 (22)	96 (18)	110 (21)
Student	432 (27)	45 (10)	108 (25)	114 (26)	62 (14)
Private sector employee	415 (26)	104 (25)	89 (21)	44 (11)	66 (16)
Business	123 (8)	32 (26)	35 (29)	15 (12)	35 (29)
Home maker	46 (3)	12 (26)	0 (0)	0 (0)	2 (4)
Retired	29 (2)	4 (14)	0 (0)	1 (3)	28 (97)
Smoking status					
No	845 (47)	95 (11)	165 (20)	105 (12)	166 (20)
Yes/per day	967 (53)	205 (21)	232 (24)	191 (20)	197 (20)
⩽ 10 cigarettes	273 (28)	55 (20)	41 (15)	50 (18)	67 (25)
11-20 cigarettes	452 (47)	106 (24)	119 (26)	87 (19)	82 (18)
21-30 cigarettes	131 (14)	21 (16)	27 (21)	19 (15)	26 (20)
> 30 cigarettes	111 (11)	23 (21)	45 (41)	35 (32)	22 (20)
Chronic diseases					
No	1376 (76)	208 (15)	288 (21)	163 (12)	236 (17)
Yes[1]	436 (24)	92 (21)	109 (25)	133 (31)	127 (29)
Diabetes	152 (35)	32 (21)	31 (20)	42 (28)	58 (38)
Bronchial asthma	150 (34)	29 (19)	52 (35)	45 (30)	37 (25)
Hypertension	54 (12)	13 (24)	4 (7)	15 (28)	22 (41)
Hypercholesterolemia	34 (8)	6 (18)	9 (27)	10 (29)	12 (35)
Immunosuppressive	37 (8)	14 (38)	13 (35)	15 (41)	14 (38)
Malignancy	27 (6)	9 (33)	5 (16)	10 (37)	5 (19)
Other lung diseases	23 (5)	4 (17)	12 (50)	10 (44)	8 (35)
Heart diseases	22 (5)	6 (27)	7 (32)	9 (41)	10 (46)
Chronic kidney disease	10 (2)	2 (20)	3 (30)	7 (70)	2 (20)
Other	78 (18)	14 (18)	22 (28)	28 (36)	9 (12)

[1]One or more chronic conditions. KSA: Kingdom of Saudi Arabia; UAE: United Arab Emirates.

95%CI: 1.1-3.9, $P = 0.02$) were more likely to receive the vaccine. Additionally, residents of Kuwait (aOR = 20.4, 95%CI: 9.3-44.5, $P < 0.01$) and Qatar (aOR = 16.8, 95%CI: 7.1-39.5, $P < 0.01$) were more likely to take the vaccine, while Saudi Arabian residents (aOR = 0.3, 95%CI: 0.2-0.7, $P < 0.01$) were least likely to receive the vaccine (Table 4).

Pertussis vaccine

Overall, only 16% (296/1812) respondents reported receiving pertussis vaccine, the remaining 84% (1516/1812) denied taking the vaccine. The coverage varied very widely across the countries ranging from 7% (82/1105) among Saudi participants to 75% (45/60) among Omani participants. The uptake of pertussis vaccine among "at risk" people was 31% (133/436).

Multivariate analysis showed that being male (aOR = 4.8, 95%CI: 2.8-8.2, $P < 0.01$), heavy smoker (aOR = 4.5, 95%CI: 2.6-7.7, $P < 0.01$) and having a chronic disease (aOR = 4.8, 95%CI: 3.5-6.6, $P < 0.01$), especially chronic kidney disease (aOR = 6.3, 95%CI: 1.5-26.9, $P < 0.01$) significantly increased the likelihood of being vaccinated against pertussis (Table 4).

Meningococcal vaccine

Overall, only 20% (363/1812) of respondents reported

Table 3 Motivators and barriers of taking influenza vaccine among the participants

Motivators' *n* (%)[1]	Barriers' *n* (%)[1]
Doctor's advice 68 (23)	Unawareness about the vaccine 573 (38)
Perception of low body immunity 62 (21)	Relying on body immunity (healthy lifestyle) 500 (33)
Believing the vaccine to be effective in preventing influenza 61 (20)	Perception of having good immunity 299 (20)
As a workplace requirement 40 (13)	Cost of the vaccine 292 (19)
	Not worried to get flu 168 (11)
	Fear of vaccine side effects 77 (5)
	Believing that the vaccine is not effective in preventing influenza 72 (5)

[1]Some participants cited more than one reason.

receiving meningococcal vaccine while the remaining 80% (1449/1812) denied receiving it. The vaccination uptake varied greatly across the countries ranging from 3% (2/60) among Omani participants to 50% (49/98) among Bahraini participants. The uptake among "at risk" individuals was 29% (127/436). In multivariate analysis, presence of cardiovascular disease (aOR = 3.4, 95%CI: 1.3-9.0, $P < 0.01$) and diabetes (aOR = 2.7, 95%CI: 1.8-4.0, $P < 0.01$), and being a resident of Bahrain (aOR = 12.1, 95%CI: 6.5-22.4, $P < 0.01$), UAE (aOR = 8.0, 95%CI: 4.7-13.7, $P < 0.01$), and Saudi Arabia (aOR = 3.2, 95%CI: 2.0-5.1, $P < 0.01$) significantly increased the likelihood of receiving meningococcal vaccine.

DISCUSSION

To the best of our knowledge, this is the first study measuring the uptake of influenza, pertussis, pneumococcal and meningococcal vaccines among the public in the GCC countries. This study shows that the rate of vaccination against diseases that transmit via respiratory tract among people of GCC countries is suboptimal even among the high-risk individuals, and the vaccination rate varies according to the type of vaccine and the country of residence of the participants. Generally, having an "at risk" condition was associated with a higher vaccination rate among the members of public in GCC countries compared to that in normal individuals. Additionally, smokers were more likely to receive the vaccines than non-smokers.

The overall uptake of influenza vaccine was suboptimal, as we found that only 17% (300/1812) of the participants had the vaccine. Our findings are comparable to the rate (17.8%) found among Saudi military personnel in Riyadh in 2009[35], and even higher than the uptake among Saudi Arabian Hajj pilgrims (4%)[36]. However this uptake rate is much lower than the coverage rate among HCWs in GCC countries which ranges between 19% and 72%[18,20,21,37,38]. More stringent vaccination requirement for the workers applied in health care settings in some GCC countries explain higher uptake among HCWs. Similar requirement exists in other workplace settings leading to increased vaccination

Table 4 Significant predictors associated with vaccines uptake

Predictors	Adjusted OR	95%CI	*P* value
Influenza vaccine			
Smoking (< 10 sig)	1.95	1.35-2.83	< 0.01
Smoking (11-20 sig)	2.23	1.63-3.05	< 0.01
Smoking (> 20 sig)	1.75	1.04-2.96	0.04
Other respiratory disease	0.15	0.04-0.61	< 0.01
Cancer	3.05	1.29-7.21	0.01
Immune disease	5.08	1.98-13.03	< 0.01
Pneumococcal vaccine			
Male	1.90	1.23-2.93	< 0.01
Bachelor degree	0.64	0.45-0.90	0.01
Postgraduate	2.11	1.14-3.90	0.02
Smoking (> 30 sig)	4.60	2.64-7.99	< 0.01
KSA	0.31	0.15-0.66	< 0.01
Qatar	16.77	7.11-39.54	< 0.01
Kuwait	20.4	9.34-44.52	< 0.01
Meningococcal vaccine			
Postgraduate degree	2.24	1.38-3.62	< 0.01
Diabetes	2.67	1.80-3.95	< 0.01
Asthma	1.78	1.17-2.70	< 0.01
Cardiovascular disease	3.43	1.30-9.01	< 0.01
Age (16-36)	0.45	0.29-0.70	< 0.01
Age (37-55)	0.26	0.14-0.47	< 0.01
KSA	3.15	1.96-5.08	< 0.01
UAE	8.01	4.68-13.71	< 0.01
Bahrain	12.09	6.52-22.43	< 0.01
Pertussis vaccine			
Having chronic disease	4.81	3.49-6.62	< 0.01
Male	4.82	2.82-8.24	< 0.01
Smoking (11-20 sig)	1.89	1.30-2.75	< 0.01
Smoking (> 30 sig)	4.50	2.64-7.69	< 0.01
KSA	0.01	0.01-0.02	< 0.01
Qatar	0.05	0.02-0.12	< 0.01
UAE	0.02	0.01-0.05	< 0.01
Bahrain	0.03	0.01-0.07	< 0.01
Kuwait	0.08	0.04-0.16	< 0.01

KSA: Kingdom of Saudi Arabia; UAE: United Arab Emirate.

rate. For instance, Abbas *et al*[39] recorded that influenza vaccine uptake rate among the employees of two different industries in Saudi Arabia ranged from 56% to 62% in 2004-2005 (Table 1).

However, the uptake of influenza vaccine in this study was lower than what was found among adults aged ⩾ 19 years resident in the United States (43.2%)[40], France (26.4%), Germany (28.2%), and the United Kingdom (28.7%) in recent years[41]. Such a discrepancy may have stemmed from the lack of awareness about influenza vaccine which is common among the Gulf people as is evidenced by this study, and is consistent with the studies conducted in other Middle Eastern countries[42,43]. Low vaccination uptake secondary to lack of awareness has been observed even among HCWs in some GCC countries[21].

An interesting finding of this study is that other factors such as the fear of the vaccine side effects and the belief that vaccine is not effective were relatively less common among the surveyed participants (5% each), while in other studies these were common reasons for non-receipt of vaccine among HCWs in GCC countries[19,21], and among general population in some

Middle Eastern countries[43,44].

Conversely, HCWs, especially physicians, were found to play a significant role in enhancing vaccination rate among the public as physicians' advice was found to be the main motivator for vaccine uptake among our participants. In a study conducted in Australia on public perceptions towards pandemic influenza vaccine a higher rate of compliance for physician recommended vaccination was observed compared to government recommendation[45]. Furthermore, other main uptake motivators among our participants were perception of low body immunity (21%) and believing the vaccine to be effective (20%). Finally, 13% of participants received the vaccine only because it was required in their workplace which is unsurprising given the higher uptake reported by Abbas *et al*[39] among industry employees in Saudi Arabia.

This study shows that compared to other vaccines, the uptake rate of influenza vaccine varied only minimally ranging from 15% to 24%. This can be explained by the uniform recommendation regarding influenza vaccine across the GCC countries. We found that the uptake of influenza vaccine among "at risk" individuals was higher than among healthy people (21% *vs* 15%) which is consistent with the recent campaigns in the GCC countries which mostly focus on improving the uptake among "at risk" group.

An interesting finding in this study is that there was no difference in the influenza vaccine uptake between participants with varying educational levels, however, this finding was consistent with Endrich *et al*[41]'s study who demonstrated that educational level had no significant effect on the influenza vaccination coverage rate among public in most of the European countries. On the contrary, the employed people had a higher uptake of influenza vaccine: Multiple factors can explain this finding including vaccination as a workplace requirement.

Smoking is a common habit among public in GCC countries; *e.g.*, in Saudi Arabia smoking prevalence ranges between 2.4% and 52.3%[46]. Smoking is a recognised key risk factor for many respiratory infections[47], which may explain why smokers in our study were twice as likely to be vaccinated against influenza compared to non-smokers, but that was in contrast to the finding of a study conducted among United States adults, where smokers were found to be less likely to be vaccinated against influenza[48]. There might be cultural factors for this difference, which is unclear at this stage.

Pneumococcal vaccine is recommended in most of the GCC countries for adults more than 50 years of age or less than 50 with underlying health problems including smoking[23,49], despite that, except for the participants from Kuwait and Qatar, the uptake rate in this study was suboptimal. However, the coverage rate among "at risk" individuals in our study was higher than that among general population especially, among participants with bronchial asthma (35%) and smokers (24%), the group to be included in the latest recommendation by the United States Advisory Committee on Immunization Practices (ACIP)[50], these rates were higher than to what had been found in the United States a year after the implementation of this recommendation[51].

In our study, we found that the coverage rate of meningococcal vaccine was generally low but was relatively higher among "at risk" individuals compared to those who were "not at risk" (29% *vs* 17%) and that was expected as the recommendations were generally limited to certain individuals such as travellers to Hajj and Umrah pilgrimages, residents of Makkah and Madinah, and individuals with certain medical conditions. For the pertussis vaccine, the coverage rates in GCC countries varied very widely, from 7% in Saudi Arabia to 75% in Oman. A low uptake rate can be explained by not having a consistent pertussis vaccine recommendation for adults, except for certain groups in some countries such as HCWs and pregnant women. The surprisingly higher uptake reported among participants from Oman needs further research to validate, and if confirmed, to explore reasons for this better coverage. The results of studies from Australia and Canada revealed a coverage rate of pertussis vaccine among adults to be around 10%, despite the recommendation of Tdap for those who are likely to come in contact with children, and for pregnant women[52,53].

Nevertheless, unfortunately findings from other studies show that public health recommendations alone are not enough to increase the vaccination rate and that several other factors need to be addressed to achieve the target level of immunisation coverage[54,55]. One of the most important factors is physicians' recommendation in both primary health care and hospital settings, since this is a uniform finding across the studies[56,57]. In a qualitative sense, the significance of physicians' recommendations comes from two opposing directions. Firstly, it is found to be associated with increased uptake, and secondly, from the other direction, its absence represents the most important barrier[58]. Therefore, motivating the clients for vaccination should be the physicians' priority in order to achieve a satisfactory immunisation target rate. Chan *et al*[59] demonstrated that a computerised reminder system telling the physicians about any patient having an indication for preventive care such as vaccinations to be an effective technique in increasing the vaccine uptake rate but it remains to be seen if such a strategy would be effective in the context of GCC countries.

Another important factor that can improve the uptake rate is focused public educational campaigns[60], which provides the public with the knowledge of the importance of vaccination and its availability. Also, the public can be given detailed information about the disease against which the vaccine offers protection including discussions on how it can be prevented or at least its severity can be lessened by obtaining the vaccine on time as affirmed by Loubet *et al*[61].

Previously, many adult vaccination campaigns have been conducted in GCC countries particularly for influenza, pneumococcal and meningococcal vaccines but there are no published studies assessing the effectiveness of these campaigns, except for the meningococcal vaccination campaign in 1992 that followed a meningococcal outbreak in Makkah which was ultimately brought under control[62].

This study is susceptible to recall bias as data were collected through a self-reported survey. Furthermore, the use of smartphone applications is less common in elderly people who represent an important part of the "at risk" population. This impacts the generalizability of the result. Despite these limitations, this is the first study measuring the uptake rate of seasonal influenza, pneumococcal, meningococcal and pertussis vaccines among members of public in the GCC countries. Another strength is that the application used in our study was tested and validated previously in more than one setting including in GCC countries and among travellers to GCC countries (*e.g.*, Hajj pilgrims)[32-34,63]. Conversely this study does not distinguish native citizens from expatriates who may be different in having access to preventive health care.

Although GCC countries had implemented recommendations for seasonal influenza, pneumococcal and meningococcal vaccines which were very much in line with the ACIP recommendations, the uptake rates according to our study was low compared to that in developed countries. This highlights the need for further research and implementation of tailored programmes for increasing awareness about vaccine-preventable diseases among adults in GCC countries. A number of measures such as setting up of vaccination clinics in public hospitals and vaccination cards for adults, reminder systems for both the public and HCWs, and regular program evaluation may need to be considered to achieve a satisfactory vaccination rate.

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COMMENTS

Background

The Gulf Cooperation Council (GCC) countries recommend vaccinations against influenza, pertussis, pneumococcal and meningococcal diseases for their residents but there is paucity of comparative data on the uptake of these vaccines across the countries.

Research frontiers

This highlights the need for further research and implementation of tailored programmes for increasing awareness about vaccine-preventable diseases among adults in GCC countries.

Innovations and breakthroughs

There have been limited studies assessing the coverage of influenza, pneumococcal, meningococcal and pertussis vaccines in GCC countries. This study addresses those knowledge gaps.

Applications

This study demonstrates that the uptake of vaccinations against respiratory infections among residents of GCC countries was suboptimal, even among the highly susceptible people, and varied widely across the countries. These findings inform public health policy.

Terminology

GCC countries: GCC stands for Gulf Cooperation Council. It is a regional intergovernmental political and economic union consisting of six Arab states of the Arabian Gulf. The GCC countries are: Bahrain, Kuwait, Oman, Qatar, Saudi Arabia, and the United Arab Emirates; Hajj: Hajj is the Islamic pilgrimage to Mecca, Saudi Arabia which annually attracts about three million people from across the world; "At risk" group: Individuals who are aged $\geqslant$ 65 years and/or have chronic medical conditions such as diabetes, and bronchial asthma; "Not at risk" group: Individuals who do not have "at risk" conditions listed above, *i.e.*, individuals aged < 65 years and do not have pre-existing medical conditions that predispose them to certain infections.

Peer-review

This is a good and well written report regarding survey of vaccination uptake in Arabian Gulf countries. The result of this study would be good reference in this field.

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CASE REPORT

Duodenal gangliocytic paraganglioma with lymph node metastases: A case report and comparative review of 31 cases

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Author contributions: Cathcart SJ read the literature, compiled review data, wrote the first draft of the paper, and repeatedly edited the manuscript; Sasson AR was the treating surgical oncologist and participated in idea and early revisions of the paper; Kozel JA was the treating surgical pathologist and participated in the idea and early revisions of the paper, as well as provided photographs of the gross and microscopic findings; Oliveto JM assisted in reviewing remote and preoperative imaging and provided photographs of CT imaging; Ly QP repeatedly reviewed the manuscript, made surgical recommendations, and approved the final version.

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Abstract

Gangliocytic paraganglioma (GP) is a rare tumor of uncertain origin most often located in the second portion of the duodenum. It is composed of three cellular components: Epithelioid endocrine cells, spindle-like/sustentacular cells, and ganglion-like cells. While this tumor most often behaves in a benign manner, cases with metastasis are reported. We describe the case of a 62-year-old male with a periampullary GP with metastases to two regional lymph nodes who was successfully treated with pancreaticoduodenectomy. Using PubMed, EMBASE, EBSCOhost MEDLINE and CINAHL, and Google Scholar, we searched the literature for cases of GP with regional lymph node metastasis

and evaluated the varying presentations, diagnostic workup, and disease management of identified cases. Thirty-one cases of GP with metastasis were compiled (30 with at least lymph node metastases and one with only distant metastasis to bone), with age at diagnosis ranging from 16 to 74 years. Ratio of males to females was 19:12. The most common presenting symptoms were abdominal pain (55%) and gastrointestinal bleeding or sequelae (42%). Twenty-five patients underwent pancreaticoduodenectomy. Five patients were treated with local resection alone. One patient died secondary to metastatic disease, and one died secondary to perioperative decompensation. The remainder did well, with no evidence of disease at follow-up from the most recent procedure (except two in which residual disease was deliberately left behind). Of the 26 cases with sufficient histological description, 16 described a primary tumor that infiltrated deep to the submucosa, and 3 described lymphovascular invasion. Of the specific immunohistochemistry staining patterns studied, synaptophysin (SYN) stained all epithelioid endocrine cells (18/18). Neuron specific enolase (NSE) and SYN stained most ganglion-like cells (7/8 and 13/18 respectively), and S-100 stained all spindle-like/sustentacular cells (21/21). Our literature review of published cases of GP with lymph node metastasis underscores the excellent prognosis of GP regardless of specific treatment modality. We question the necessity of aggressive surgical intervention in select patients, and argue that local resection of the mass and metastasis may be adequate. We also emphasize the importance of pre-surgical assessment with imaging studies, as well as post-surgical follow-up surveillance for disease recurrence.

Key words: Gangliocytic paraganglioma; Metastases; Duodenum; Lymph node dissection; Pancreaticoduodenectomy

Core tip: Duodenal gangliocytic paragangliomas (GP) generally behave in a benign manner, but infrequently lymph node, and rarely distant, metastases occur. Even in such cases, prognosis remains excellent with only a single reported disease-related death. Here we report a patient with a duodenal GP with regional lymph node metastases and review the literature to help direct management of the rare tumor. In reviewing the literature, achieving complete resection of primary tumor and positive lymph nodes appears to be curative. As such, this should be the therapeutic goal in surgically fit patients.

Cathcart SJ, Sasson AR, Kozel JA, Oliveto JM, Ly QP. Duodenal gangliocytic paraganglioma with lymph node metastases: A case report and comparative review of 31 cases. *World J Clin Cases* 2017; 5(6): 222-233 Available from: URL: http://www.wjgnet.com/2307-8960/full/v5/i6/222.htm DOI: http://dx.doi.org/10.12998/wjcc.v5.i6.222

INTRODUCTION

Gangliocytic paraganglioma (GP) is a rare tumor most often located in the ampullary/periampullary region of the duodenum. It is composed of three cell types: Epithelioid endocrine cells, spindle-like/sustentacular cells, and ganglion-like cells. Patients frequently present with symptoms related to gastrointestinal bleeding; however, the diagnosis is occasionally made incidentally[1,2]. While this tumor typically behaves in a benign manner, there have been rare cases with metastasis, most often to regional lymph nodes. We report a case of periampullary duodenal GP with metastases to regional lymph nodes treated with pancreaticoduodenectomy. We also review published literature on other GPs demonstrating metastasis with the intention to help define the appropriate diagnostic work-up and management of this rare entity.

CASE REPORT

Our patient was a 62-year-old male with a periampullary duodenal mass discovered incidentally during a surveillance esophagogastroduodenoscopy for Barrett's esophagus. An endoscopic biopsy showed only duodenal mucosa with changes suggestive of peptic duodenitis. Subsequent endoscopic ultrasound revealed a 1.5 cm × 0.8 cm mass with a 1.2 cm × 0.8 cm periduodenal lymph node. A fine needle aspiration (FNA) biopsy and endoscopic tunneled biopsy of the duodenal mass was performed, which collectively showed features consistent with a neuroendocrine tumor. Computed tomography (CT) imaging demonstrated a well-circumscribed intraluminal duodenal mass (2.1 cm × 1.4 cm) with mild enhancement and no discernable pathologic lymphadenopathy (Figure 1). Retrospective review of CT imaging from two years prior did not show an obvious mass. The patient was asymptomatic. His past medical history was significant for Barrett's esophagus, as mentioned above, as well as hypertension, gastro-esophageal reflux disease, and hyperlipidemia. He had no smoking history and only light alcohol usage.

Two and a half months later, the patient underwent a pancreaticoduodenectomy, hepatic artery lymph node and portal lymph node excision, cholecystectomy, and partial gastrectomy (the pylorus appeared ischemic intra-operatively). The patient's course was complicated by a pancreatic leak and a pulmonary embolism. CT imaging performed at 19 mo showed no evidence of disease recurrence, and a routine healthcare check at 30 mo revealed no clinical evidence of disease recurrence.

Histopathological analysis

Cytological smear preparation (Diff-Quick and Papanicolaou stains) from the duodenal mass FNA demonstrated a cellular specimen composed of intermediate-sized, bland epithelioid cells with round to oval nuclei. Rare large ganglioid cells with eccentric nuclei and a

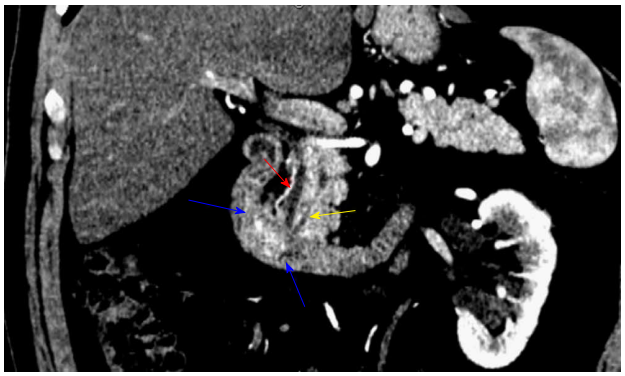

Figure 1 Preoperative computed tomography imaging. Coronal section demonstrating a 2.1 cm × 1.4 cm periampullary duodenal mass (blue arrows). Red arrow: Common bile duct; yellow arrow: Pancreatic duct.

prominent nucleolus were seen. A concurrent endoscopic tunneled biopsy contained three fragments of duodenal mucosa, one of which had a few nests of neuroendocrine tumor cells within the submucosa, which stained positively for CAM 5.2 and synaptophysin and negatively for chromogranin (Figure 2).

Grossly, the resected surgical specimen included a portion of duodenum with a 2.0 cm × 1.3 cm × 0.7 cm nodule protruding into the lumen. Overlying mucosa was intact. The lesion was 2.0 cm proximal to the ampulla of Vater. On sectioning, the mass was tan-white with focal grey-black discoloration and confined to the submucosa (Figure 3).

Microscopic examination revealed a submucosal nodule in the duodenum with three distinct cell populations. Epithelioid endocrine cells were arranged in trabeculae and nests interspersed with spindled sustentacular cells. Gangliocytic cells were scattered throughout (Figure 2). The spindle cell population stained positively for S-100, the gangliocytic cells stained positively for calretinin, and the epithelioid cells stained positively for chromogranin and synaptophysin. No mitotic figures were identified. Ki-67 immunohistochemical stain showed a proliferative index of 2% within the tumor cells. Within the primary tumor, CD117 immunohistochemical staining demonstrated up to 15 mast cells per high power field (hpf) focally, with most areas having 1 to 5 per hpf (Figure 4D). Within the lymph node metastasis, up to 7 mast cells per hpf were identified, while most areas had only 1 to 2 per hpf.

There was no intratumoral lymphovascular or perineural invasion identified, nor was there invasion into the adjacent pancreatic parenchyma. The hepatic artery lymph node and portal lymph node were also free of disease. Metastatic tumor was discovered in three of eight periduodenal lymph nodes (Figure 5). Metastases stained similarly to the primary with regard to S-100, chromogranin, and synaptophysin, but stained negatively for calretinin.

Literature search

Using PubMed, EMBASE, EBSCOhost MEDLINE and CINAHL, and Google Scholar databases, we searched for cases of GP with regional and distant metastases using variations on the key word/phrases "gangliocytic paraganglioma", "lymph nodes", "metastasis", and "distant spread". We included only cases with at least an abstract written in English or French. Four of the included cases were published as poster presentation abstracts at national and international conferences. Two poster presentation abstracts were not included due to either insufficient patient data or citation information. Finally, we excluded one case which was sited in other literature reviews, as it reported the presence of only two cellular components[3].

Results

Our literature search produced 31 cases of GP with metastatic disease (30 with at least regional lymph node involvement and one with only a single metastasis to the manubrium) (Table 1). In 28 cases, lymph node involvement/metastatic disease was present at the time of initial diagnosis (26 cases with disease spread present in initial surgical resection; 1 case with regional disease diagnosed on follow-up surgery for positive margins[2]; 1 case with regional disease diagnosis on pancreaticoduodenectomy with lymph node dissection performed after a local resection demonstrated tumor with muscularis mucosa invasion and lymphovascular space invasion[4]), while metastatic disease/lymph node involvement was diagnosed on follow-up surveillance in 2 cases[5,6]. Of the 28 cases with initial synchronous metastases/regional disease, 14 reported preoperative imaging that was suspicious for disease spread[7-19], while in 2 cases regional disease was discovered intraoperatively with frozen section confirmation, prompting a pancreaticoduodenectomy[20,21]. In 29 cases, the primary lesion occurred in the duodenum. Fourteen were in the duodenal ampulla, 6 were periampullary, and 8 were in the 2nd portion or the junction between the 2nd and 3rd portions of the duodenum, and 1 was in the 3rd portion of the duodenum. Two primary tumors occurred in the head of the pancreas[6,22]. We included only cases with histological evidence of regional spread/metastatic disease.

Clinical findings: Among the 31 patients studied, age at presentation ranged from 16-74 years, with 77% (24/31) presenting in the 5th-7th decade of life. There was a male predominance, with a male to female ratio of 19:12. The most common presenting symptoms were abdominal pain (55%) and gastrointestinal bleeding or the resultant symptomatic anemia (42%). Eight patients presented with weight loss as one of their symptoms (26%). One patient with a pancreatic primary presented with steatorrhea[22], while the other presented with jaundice[6].

Management: Twenty-five of the 31 patients with regional spread/metastatic disease underwent a pancreaticoduodenectomy, 4 of which occurred following

Table 1 Summary of patients with gangliocytic paraganglioma with metastases

Ref.	Year of publication	Age at diagnosis (yr)	Sex	Presenting symptoms	Primary location	Largest diameter, primary (mm)	Site(s) of metastasis	LNs sampled	LNs positive	Therapy	Follow-up (mo)
Büchler *et al*[7]	1985	50	M	GI bleeding	D2, ampulla	30	Peripancreatic LN	NR	1	Local resection	20, NED
Korbi *et al*[24]	1987	73	F	GI bleeding, weight loss, cardiac decompensation	D2, ampulla	90	Peripancreatic LN	NR	1	PD	0, died POD 7
Inai *et al*[4]	1989	17	M	GI bleeding	D2, ampulla	20	Peripancreatic LN	NR	1	Local resection, followed by PD with LND	32, NED
Hashimoto *et al*[20]	1992	47	M	Asymptomatic, incidental	D2, ampulla	65	Peripancreatic LN	NR	1	PD with LND	14, NED
Dookhan *et al*[5]	1993	41	M	Abdominal pain, partial duodenal obstruction	D2	25	Mesentery, mesenteric LNs	NR	2-3	Local resection (1981); resection D4, proximal jejunum, mesenteric mass (1992)	131, recurrence and metastasis
Takabayashi *et al*[33]	1993	63	F	Abdominal pain	D3	32	Regional LN	NR	1	PPPD	24, NED
Tomic *et al*[22]	1996	74	M	Anemia, steatorrhea, abdominal pain, weight loss	Pancreas, head	40	Peripancreatic LN	NR	1	PD	19, NED
Henry *et al*[6]	2003	50	M	Jaundice	Pancreas, head	30	Manubrium	NR	0	FNA[1], followed by PD, followed by manubrium resection	21, NED
Sundararajan *et al*[1]	2003	67	F	Asymptomatic, incidental	D2	50	Regional LNs	NR	2	PD with LND	9, NED
Wong *et al*[23]	2005	49	F	GI bleeding, abdominal pain	D2, periampullary	14	Periduodenal and Peripancreatic LNs	7	6	PPPD with LND, radiotherapy	12, NED
Witkiewicz *et al*[2]	2007	38	F	Abdominal pain	D2, periampullary	15	Regional LNs	7	2	Local resection, followed by PPPD	NR
Mann *et al*[8]	2009	17	F	Duodenal obstruction, weight loss, abdominal pain	D2/D3 junction		Regional LNs	11	4	PD	7, NED
Okubo *et al*[9]	2010	61	M	GI bleeding, abdominal pain	D2, ampulla	30	Regional LNs	NR	1	PPPD with LND	6, NED
Saito *et al*[10]	2010	28	M	GI bleeding	D2, ampulla	17	Regional LNs	N/A	2	Local resection, followed by PD	N/A
Uchida *et al*[11]	2010	67	F	Anemia	D2	N/A	LN	N/A	N/A	PD	N/A
Ogata *et al*[27]	2011	16	M	GI bleeding	D2, ampulla	35	Peripancreatic LNs	NR	4	PPPD with LND	36, NED
Barret *et al*[12]	2012	51	F	GI bleeding	D2, ampulla	25	Peripancreatic LNs	NR	2	FNA, followed by PD	96, NED
Rowsell *et al*[13]	2011	52	F	Asymptomatic, incidental	D2, periampullary	10	Regional LNs, liver nodule	23	2	PD, post-op octreotide injections	27, No change in residual liver metastases
Dustin *et al*[14]	2011	56	F	Abdominal pain, weight loss	D2, periampullary	18	Retroperitoneal LN, later resection Peripancreatic LNs	10	3	Local resection of retroperitoneal mass, followed by duodenal mass FNA, followed by PPPD with LND and cholecystectomy	NR

Fiscaletti *et al*[25]	2011	61	M	Abdominal pain, weight loss	D2, minor papilla (discovered incidentally)	15	Peripancreatic LN	7	1	FNA[2], followed by PPPD	12, NED
Amin *et al*[15]	2013	57	M	Abdominal pain, vomiting	D2, ampulla	30	Portal hepatic LNs, Liver	NR	NR	Resection of duodenal mass, retropancreatic mass, part of hepatic lesion, enlarged portal lymph nodes	8, Residual liver lesion slowly enlarging
Choi *et al*[21] (poster)	2014	41	M	GI bleeding	D2	25	Periduodenal LN	11	1	PD	NR
Li *et al*[16]	2014	47	M	Abdominal pain	D2, periampullary	30	Regional LNs, pelvic cavity, liver	16	7	PD, radiotherapy, chemotherapy	13, died secondary to liver and pelvic metastases
Micev *et al*[30] (poster)	2014	57	M	Abdominal pain, back pain, intermittent jaundice	D2, ampulla	35	Regional LNs	NR	2	NR	NR
Shi *et al*[17]	2014	47	M	Abdominal pain, weight loss	D2, ampulla	40	Regional LNs	20	8	PD with LND	24, NED
Dowden *et al*[32]	2015	59	F	Abdominal pain, weight loss	D2, ampulla	28	Regional LNs	22	2	FNA, followed by PPPD	5, NED
Lei *et al*[19]	2015	45	M	GI bleeding, weight loss, vomiting and diarrhea, abdominal cramps (functional tumor)	D2	15	Periduodenal LN	NR	1	FNA, followed by ampullectomy with periduodenal and retropancreatic LND	3, functional symptoms and CT showing lympha-denopathy, lost to follow-up
Sun *et al*[26] (poster)	2015	40	F	Abdominal pain	D2, ampulla	20	Peripancreatic LN	NR	1[3]	FNA, followed by PD	12, NED
Wang *et al*[18]	2015	49	M	Abdominal pain	D2	33	Regional LNs	9	3	PD with LND, chemotherapy	36, NED
Hu *et al*[31]	2016	65	M	GI bleeding	D2	30	LN	NR	1	Local resection	2, NED
Current case	2016	62	M	Asymptomatic, incidental	D2, periampullary	20	Regional LNs	8	3	FNA, PD	30, NED

[1]Suggestive of ductal adenocarcinoma; [2]Fibroinflammatory changes consistent with pancreatitis; [3]Involved by direct extension and replacement. GI: Gastrointestinal; D2: Duodenum 2nd portion; D3: Duodenum 3rd portion; LN: Lymph node; LND: Lymph node dissection; PD: Pancreaticoduodenectomy; PPPD: Pylorus-preserving pancreaticoduodenectomy; NED: No evidence of disease; N/A: Not available; NR: Not reported; LtFU: Lost to follow-up.

local resection. In one case, massive hematemesis prompted an exploratory laparotomy and local resection of tumor, which was found to have muscularis mucosa invasion and lymphovascular space invasion[4]. In another case, pancreaticoduodenectomy was performed after local resection demonstrated positive margins[2]. In the third case, pancreaticoduodenectomy followed resection of an 11 cm multiloculated retroperitoneal mass, which was determined to be a lymph node containing metastatic PG. Further workup revealed a 2 cm periampullary submucosal mass in the duodenum[14]. In the fourth case, regional lymph node involvement was found in the initial local resection, as well as in the secondary resection[10].

Four of the 31 patients were treated with local resection only, one of which underwent initial local resection of the primary tumor and lymph node metastasis with no signs of recurrence over a 20-mo follow-up period[7]. The second patient presented with gastrointestinal complaints and was found to have a partially calcified mass in the liver and abdomen, which was initially diagnosed as metastatic neuroendocrine carcinoma. Later testing revealed a duodenal lesion extending posteriorly to the pancreas with lymph node and liver involvement. Subsequently, the patient underwent resection of the duodenal lesion, retropancreatic mass, part of the hepatic lesions, and all enlarged portal lymph nodes. CT at 8 mo follow-up revealed a slowly enlarging residual liver lesion[15].

One remarkable patient with innumerable liver metastases in addition to her lymph node metastases was treated with adjuvant octreotide injections for residual disease left behind in her liver. At 27 mo follow-up, she had no significant change in residual disease[13]. One patient with metastases to 6 of 7 sampled lymph nodes received adjuvant external beam radiotherapy and was disease-free at 12 mo[23], while another patient with metastases in 3 of 9 sampled lymph nodes received 5 cycles of adjuvant chemotherapy (regimen not specified) with no evidence of disease at 36 mo[18].

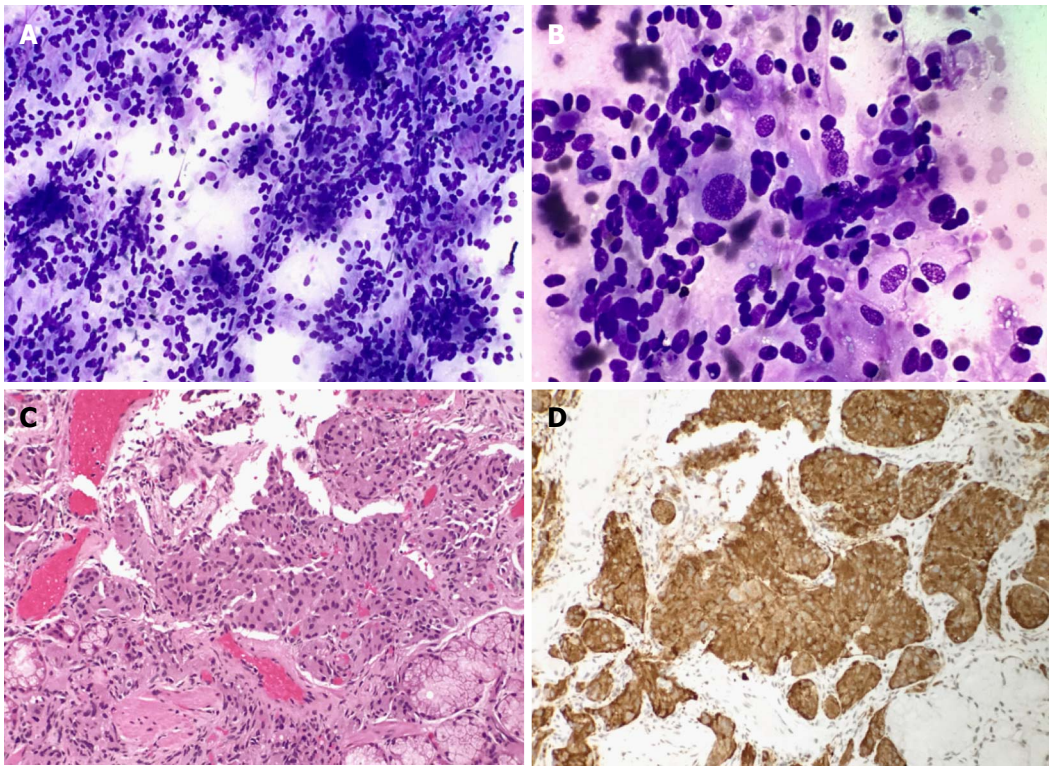

Figure 2 Fine needle aspiration biopsy and endoscopic tunneled biopsy of duodenal mass. A: Cellular specimen with predominantly bland epithelioid cells with round to oval nuclei, Diff-Quick stain, × 20; B: Rare large ganglion-like cells with eccentric nuclei and prominent nucleoli, Diff-Quick stain, × 40; C: Epithelioid tumor cells within the duodenal lamina propria/submucosa, endoscopic tunnel biopsy, H&E stain, × 20; D: Tumor cells with positive reactivity for synaptophysin, endoscopic tunnel biopsy, × 20.

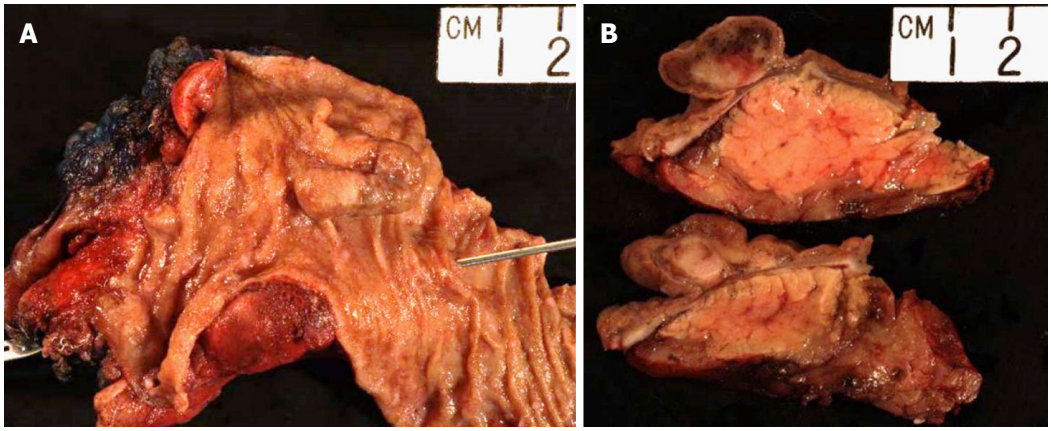

Figure 3 The tumor protruded into the duodenal lumen, 2.0 cm proximal to the ampulla (A, probed). The mass was restricted to the duodenal submucosa, and did not invade into the adjacent pancreas (B).

Finally, one patient expired secondary to metastatic disease burden. On initial pancreaticoduodenectomy, the patient was diagnosed with a periampullary GP metastatic to 7 of 16 regional lymph nodes. A follow-up CT at 4 mo revealed liver and pelvic cavity metastases, and radiotherapy (total dose of 5040 cGy) was performed with no improvement, followed by chemotherapy (combination of cyclophosphamide, vincristine, and dacarbazine) with no improvement. Nine months after the initial surgery, he underwent partial resection of the pelvic mass. His liver mass continued to enlarge, and he developed persistent ascites and fever and passed away 13 mo following his initial operation[16]. This is the only case, to our knowledge, to follow a lethal course directly resultant from disease burden.

Follow-up: Of the 25 cases with available follow-up (including the case presented here), follow-up ranged from 0 (perioperative demise) to 131 mo after the initial surgical intervention. In most cases, patients remained without evidence of recurrent disease. Exceptions include the two with residual liver disease and the one

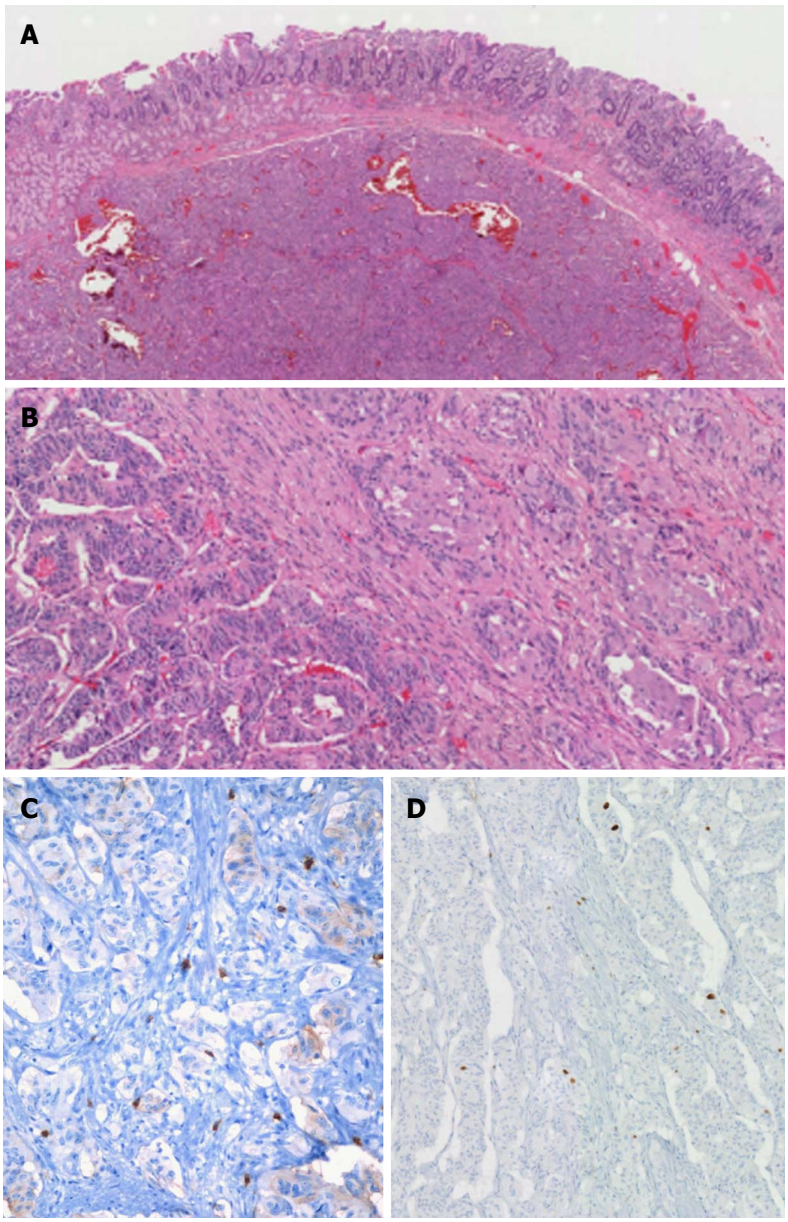

Figure 4 Primary tumor. A: Tumor with overlying mucosa, H&E × 100; B: Tumor with epithelioid (left) and gangliocytic (right) components, H&E × 200; C: Ki-67 immunostaining proliferative index, × 100; D: CD-117 immunostaining for mast cells, × 200.

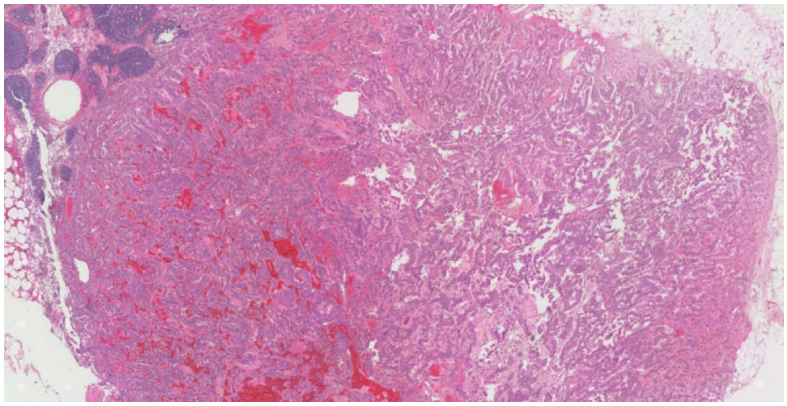

Figure 5 Lymph node metastasis, × 200. Inset, positive immunostaining for synaptophysin, × 100.

Table 2 Pathologic features of gangliocytic paragangliomas found to have metastases

General	Rare tumor of uncertain origin and low malignant potential, composed of epithelioid cells, spindle cells, and ganglion-like cells
Clinical features	Most often 5th-7th decade of life Most often abdominal pain or gastrointestinal bleeding
Gross findings	90% occurring in second portion of duodenum 10-90 cm in greatest dimension (average 30 cm)
Cytologic findings	Typically cellular specimen Epithelioid cells predominate All three components may be present
Histologic findings	Epithelioid cells, spindle-like/sustentactular cells, and ganglion-like cells Submucosal Unencapsulated Necrosis absent No to rare mitoses Frequent extension beyond submucosa and/or lymphovascular invasion Metastases: 75% of those reported demonstrated all three cellular components; 25% predominantly epithelioid

with death secondary to metastatic disease as detailed above, as well as a patient whose 3-mo follow-up revealed a return of functional symptoms (elevated serum chromogranin A and serotonin at the time of initial diagnosis) and a CT demonstrating lymphadenopathy. This last patient was unfortunately lost to follow-up[19]. In one case, the patient died from anuria and cardiorespiratory decompensation one week after initial surgery[24]. The minority of case reports that discussed methods of surveillance described using CT scans, endoscopy, and physical examination.

Histopathological findings: Pathologic findings are briefly summarized in Table 2. All cases included describe three cellular components in the primary tumor: Epithelioid/endocrine-like, spindle-like, and ganglion-like. Of those, immunohistochemical staining of each cell type was described for 19[1,2,4-7,9,12-20,22,24-26]. Bucher *et al*[3] describe a case of an ampullary "alveolar paraganglioma" with lymph node metastases, which has been included in other GP literature reviews. We have elected to omit this case from our comparative review, maintaining strict inclusion of only cases with the three separate components described[3]. Twenty-one cases described histology of the metastatic disease, of which 15 reported all three components to be present.

Most frequently, mitotic figures were not found among tumor cells. When present, they consisted of no more than two per ten hpf. Necrosis was absent from the primary tumor site in all cases that included a histologic description. No cases were described as having a tumor capsule. Seventeen cases specified extent of primary tumor invasion and/or the presence of lymphovascular space invasion. Thirteen described invasion into at least the muscularis propria, and one invaded into the pancreas[17]. Three cases reported lymphovascular space invasion[4,20,27].

Of the cases describing immunohistochemical staining, those most commonly employed were S-100, chromogranin (CG), synaptophysin (SYN), somatostatin (SS), cytokeratin (CK), neuron-specific enolase (NSE), neurofilament (NF), and pancreatic polypeptide (PP). Nineteen cases described specific staining patterns among the three cell populations. Of note, SYN stained all epithelioid endocrine cells studied (18/18), NSE and SYN stained most ganglion-like cells studied (7/8 and 12/18 respectively), and S-100 stained all spindle-like/sustentacular cells studied (21/21).

DISCUSSION

While most GPs are restricted to the duodenal submucosa, a small but significant proportion demonstrates regional spread/metastasis, thus defining the malignant potential of this lesion. The rarity of this tumor has made it difficult to determine a standard of care and thus optimum treatment parameters are undefined. Until recently, no reported deaths had been directly related to underlying disease process. While one patient experienced tumor progression refractory to adjuvant radiation and chemotherapy with subsequent death, the overwhelming trend is that of low malignant potential and indolent behavior, despite nodal metastasis. Even with distant metastatic disease, patients seem to generally have a good prognosis. Our aim was to help further characterize the behavior of this rare tumor to help guide diagnosis and management.

In 2011, Okubo *et al*[28] reported a rate of lymph node metastasis at 6.9% (12/173 cases). In their survey, they also reported no significant difference in gender among patients with and without lymph node metastasis. They did, however, find a significant difference for the rate of lymph node metastasis among patients with GP extending beyond the submucosal layer versus those with GP confined to the submucosa[28]. Though our study population is small and does not include cases without metastasis, our findings appear to be consistent. Of those that reported depth of invasion, primary tumor invaded into the muscularis propria and/or demonstrated lymphovascular invasion in 86% (18/21) of cases. Okubo *et al*[28] showed a rate of 92% (11/12) of cases with lymph node metastasis when the primary tumor invaded beyond the submucosal layer. As mentioned above, they further clarified that there was a significant difference among those that did not exhibit metastasis. They concluded that tumor penetrating through the submucosal layer may be a risk factor for disease progression[28]. In the circumstance of local resection with tumor extension beyond the submucosa, it may be prudent to consider more frequent follow-up with imaging surveillance for possible recurrence.

Researchers have attempted to elucidate tumor characteristics, such as Bcl-2 and p53 biomarkers, proliferative index with Ki-67 immunolabeling, mitotic index, and necrosis that may serve as prognostic factors. Aside

from primary tumor extent, as detailed above, these have not demonstrated an association with metastatic potential[9,18,28]. Concordantly, even in the single case of rapidly progressive metastatic GP with a lethal course, authors report a Ki-67 labeling index of less than 1% in both the primary and metastatic tumor[16]. One case of appendiceal GP, while not found to have nodal or distant metastases, did present with microscopically aggressive features, including infiltrative margins with extension to the visceral peritoneum, tumor cell necrosis, and a mitotic rate of 3 per 10 high power fields. Tumor cells still did not demonstrate reactivity for Bcl-2 or p53[29]. In a recent case report and literature review by Wang *et al*[18], they offer increased mast cell accumulation in tumor stroma as a potential marker for aggressive behavior. They describe two cases of GP, one with metastatic disease and one without, in which increased mast cells were identified in the case with metastatic disease[18]. As a follow-up, we have performed CD117 immunohistochemistry on the current case presented, which showed a mild mast cell infiltration within the tumor stroma (focally up to 15 per hpf, with most of the tumor < 5 per hpf). While ours is only one case, we are unable to corroborate mast cells as a marker of aggressive behavior.

In 2011, Barret *et al*[12] suggested a treatment algorithm based on size of the primary tumor and lymph node status. They suggested local resection for tumors < 2 cm without evidence of lymph node involvement on CT scan. For larger tumors, suspicious lymph nodes, infiltrative margins upon local resection, nuclear pleomorphism, or high mitotic activity, they suggested pancreaticoduodenectomy with lymph node dissection[12]. While we do not dispute these suggestions, we believe that aggressive lymph node dissection beyond what is typically removed during a Whipple procedure is likely unnecessary. Depending on tumor location, some patients may be better served by local resection of the mass and individual grossly metastatic lymph nodes.

In our survey, only 5 (surgical procedure not reported in Micev *et al*[30] abstract) of the 31 patients were not treated with pancreaticoduodenectomy. One patient underwent excision of the duodenal tumor, ampulla, and peripancreatic lymph node. The pancreatic duct was then sutured to the duodenum. The patient remained disease-free at 20 mo[7]. The second patient, discussed earlier, underwent resection of a duodenal mass, retropancreatic mass, enlarged portal lymph nodes, and part of a hepatic lesion. At eight months, his disease was restricted to the residual hepatic tumor[15]. The third patient had an initial local resection for tumor located in the 2nd portion of the duodenum and was found to have recurrent disease 11 years later in the mesentery, which was treated with resection of the 4th portion of the duodenum, proximal jejunum, and a mesenteric mass[5]. The fourth patient presented with functional tumor as discussed above, underwent initial FNA revealing histology consistent with a GP, then subsequently underwent ampullectomy with a periduodenal and retropancreatic lymph node dissection. Unfortunately, he had return of symptoms and lymphadenopathy at 3 mo, but was lost to follow-up[19]. Finally, the fifth patient was reported simply to have undergone local resection without detail of the surgical approach[31]. Though we report on a very small population of patients, we are encouraged by the nearly uniformly favorable outcomes, regardless of the surgical approach taken, and emphasize the necessity for close follow-up.

Some authors have questioned the necessity for aggressive therapy, even in the case of metastatic disease. Rowsell *et al*[13] report a case of GP with two lymph node metastases as well as enumerable liver metastases. The primary and lymph node lesions were removed, while the liver lesions were treated conservatively with octreotide injections, and the patient exhibited stable disease at 27 mo. Authors offer that these lesions may be better described as tumors of "uncertain malignant potential[13]". Another author describes a patient with metastatic disease in four lymph nodes as having "lymph node invasion of uncertain significance[8]". Considering that patients tend to do well regardless of disease extent, one could conclude that surgical treatment in the case of asymptomatic disease may be too aggressive, particularly for patients who are poor surgical candidates. Conversely, for medically fit patients, surgical resection appears to be curative. It would require long periods of surveillance to answer this question, however.

Correct diagnosis is of great importance when planning surgical treatment and follow-up, as GPs seem to behave in a very indolent fashion and generally carry an excellent prognosis. Diagnosis depends on the presence of three cellular components: Epithelioid endocrine cells, ganglion-like cells, and spindle-like sustentacular cells. In addition to assessing cellular morphology with routine hematoxylin and eosin staining, a wide variety of immunohistochemical stains have been used. The stains used most commonly were S-100, CG, SYN, SS, CK, NSE, NF, and PP. The staining patterns found in our survey are consistent with those of Okubo *et al*[28]. In their 2011 literature survey, they include a table summarizing immunohistochemical findings from 173 duodenal gangliocytic paragangliomas[28]. As their study population is much larger than ours, we would defer to their findings for more accurate estimates of antibody sensitivities and specificities. While immunohistochemical stains can be performed to aid in recognizing the three cellular components, the histomorphologic features are typically sufficient for diagnosis.

Several reported cases have employed the use of cytology in the initial diagnostic evaluation. Of the 31 cases detailed here, 8 patients underwent fine needle aspiration (FNA) at some point. In one case, FNA of a pancreatic head mass was suggestive of pancreatic ductal adenocarcinoma, prompting a pancreaticoduodenectomy[6]. In another patient found to have segmental groove pancreatitis secondary to a

Table 3 Treatment recommendations for a duodenal gangliocytic paraganglioma

Ampullary/ periampullary mass	EUS with FNA to rule out pancreatic adenocarcinoma, followed by pancreaticoduodenectomy with resection of suspicious lymph nodes
Duodenal mass, away from pancreas	CT to evaluate disease extent +/- FNA with local resection of primary tumor and suspicious lymph nodes if tumor location permits
Complete resection unattainable and/or surgically unfit candidate	Imaging modality + FNA/biopsy to establish diagnosis, octreotide scan, and trial of medical management with somatostatin analogues
	Tumor debulking should be attempted if surgically fit

EUS: Endoscopic ultrasound; CT: Computed tomography; FNA: Fine needle aspiration.

compressive ampullary GP, the initial FNA of a cystic mass-like lesion in the head of the pancreas was determined to be consistent with pancreatitis. FNA of the actual tumor was not performed[25]. In the remaining six cases, FNA was either diagnostic of a GP or carcinoid/ neuroendocrine tumor[12,14,19,26,32]. While the epithelioid cellular population seems to predominate, all three cell types have been observed on cytology, and thus may be very helpful in making a pre-surgical diagnosis of GP. Dustin *et al*[14] and Lei *et al*[19] offer more complete cytological descriptions of the lesion, and Dustin *et al*[14] advocates the utility of cytology in initial assessment. They also discuss the use of immunohistochemistry performed on an adequate cell block to help distinguish GP from other lesions in the differential diagnosis, such as gastrointestinal stromal tumor, paraganglioma, leiomyoma, and schwannoma[14,19].

In a 2007 literature review by Witkiewicz *et al*[2], they point out that the incidence of malignant cases of GP may be underestimated, as most cases have been treated by simple local resection[2]. We summarize our management recommendations in Table 3. Briefly, upon discovery of a periampullary duodenal mass, we recommend endoscopic ultrasound (EUS) or CT imaging to assess extent of disease before proceeding with surgical treatment. While not specifically described in the cases herein, EUS may also be helpful in evaluating for an infiltrative border, raising suspicion for tumor extent beyond the submucosa (the only reliable association with lymph node involvement). We also advocate the use of cytology when clinically appropriate. Though diagnostic confidence will vary depending on cellular yield and composition, it has repeatedly resulted in either a positive diagnosis or a narrowed differential. Most importantly, in the event of a tumor arising near the pancreas, FNA biopsy may help rule out pancreatic adenocarcinoma, and thus the need for neoadjuvant therapy. Based on our literature review, achieving a surgical resection without residual disease seems to be curative. As such, we believe a strong argument can be made for an aggressive surgical approach to eradicate all tumor in patients who are good surgical candidates. There are very few reports of patients treated with chemotherapy or radiation. From these limited examples, this low-grade tumor seems to be poorly-responsive, highlighting the importance of primary surgical eradication. In the event that a complete surgical resection cannot be achieved or attempted (due to extensive metastatic disease or poor surgical candidacy), medical management with a somatostatin analogue should be trialed.

In conclusion, we describe a case of duodenal gangliocytic paraganglioma with metastasis to three regional lymph nodes that was effectively treated with pancreaticoduodenectomy. We also summarize other reported cases of GP with metastasis to further aid in diagnosis and management of this rare disease. While management guidelines are undefined, we emphasize the importance of pre-surgical assessment with imaging studies and FNA to rule out pancreatic adenocarcinoma in the case of peripancreatic lesions, as well as post-surgical follow-up surveillance for disease recurrence. In medically fit candidates, we strongly advocate surgical management to remove all primary and metastatic disease, as achievement of a complete surgical resection appears to be curative.

COMMENTS

Case characteristics

A 62-year-old man was found to have an asymptomatic duodenal mass on routine esophagogastroduodenoscopy for Barrett's esophagus.

Clinical diagnosis

A submucosal periampullary duodenal mass without ulceration protruded into the intestinal lumen.

Differential diagnosis

Pancreatic adenocarcinoma, lipoma, neuroendocrine tumor, paraganglioma, gangliocytic paraganglioma, gastrointestinal stromal tumor, leiomyoma, schwannoma, Brunner's gland adenoma, fibroma.

Laboratory diagnosis

Preoperative complete blood count and metabolic panel were unremarkable.

Imaging diagnosis

Computed tomography showed a well-circumscribed, intraluminal 2.1 cm × 1.4 cm duodenal mass with mild enhancement and no discernable pathologic lymphadenopathy.

Pathological diagnosis

Fine needle aspiration demonstrated a neuroendocrine tumor, and the final diagnosis of gangliocytic paraganglioma (GP) with lymph node metastases was made on the pancreaticoduodenectomy specimen.

Treatment

Complete surgical resection with pancreaticoduodenectomy.

Related reports

The authors report 30 additional cases of duodenal/head of pancreas GP with metastases, which generally have an excellent prognosis regardless of disease extent at the time of diagnosis, with only a single case of disease-related mortality.

Term explanation

Duodenal GP is a rare tumor of low-malignant potential most often arising in the second portion of the duodenum. It is defined by the presence of three histological components: Epithelioid cells, ganglion-like cells, and spindle-like sustentacular cells.

Experiences and lessons

Aggressive surgical management for this lesion is recommended, as achieving a complete resection of the primary tumor and metastases seems to be curative. If a complete resection cannot be attained (due to either extensive disease or poor surgical candidacy) tumor debulking and/or medical management with somatostatin analogues should be considered.

Peer-review

This is an interesting case report and collective review of previous case reports on paraganglionoma with lymph node metastasis. The manuscript describes well the characterictics, clinical and pathological picture, and also the therapy of a rare duodenal tumor.

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CASE REPORT

Bilateral renal cortical necrosis associated with smoking synthetic cannabinoids

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Abstract

Synthetic cannabinoids have become a common drug of abuse in recent years and their toxicities have come to light as well. They are known to be notorious for the kidneys, with acute tubular necrosis, acute interstitial nephritis and rhabdomyolysis induced renal injury being the frequent nephrotoxic outcomes in users. We report a case of bilateral renal cortical necrosis, leading to irreversible renal damage and lifelong dialysis dependency.

Key words: Synthetic cannabinoids; Renal cortical necrosis; Dialysis

Core tip: Renal cortical necrosis is a debilitating condition and has a number of causes, in our case a 47 years old female suffered from this condition after smoking synthetic cannabinoids (SCBs) which are a new form of synthetic illicit designer drugs. The patient presented with nausea for 5 d along with anuria for past 24 h before presentation. On laboratory findings the patient had thrombocytopenia while clinically the patient had thrombotic microangiopathy which leads to bilateral renal cortical necrosis. Patient was placed permanently on hemodialysis. Thus awareness needs to be dispersed about potential effects of SCBs.

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cortical necrosis associated with smoking synthetic cannabinoids. *World J Clin Cases* 2017; 5(6): 234-237 Available from: URL: http://www.wjgnet.com/2307-8960/full/v5/i6/234.htm DOI: http://dx.doi.org/10.12998/wjcc.v5.i6.234

INTRODUCTION

Synthetic cannabinoids (SCBs) are classified as new psychoactive substances (NPS). There are various types of SCBs available, K2, and Spice being the most popular products. They have gained popularity among peddlers and users because not all are listed as controlled substances, they are freely available, they are relatively inexpensive and most importantly they are not detectable by routine drug screening methods[1].

SBCs have a wide array of adverse effects and toxicities, ranging from nausea to agitation, seizures, stroke and multi-organ failure. These adverse effects led 28531 patients to the emergency departments in the United States in 2011[2]. We report a case of bilateral cortical necrosis associated with the use of SCBs.

CASE REPORT

A 47-year-old Caucasian female presented to the emergency department with complaints of nausea and vomiting for 5 d along with hallucinations, abdominal pain and severe back pain with hematuria which progressed to anuria over the next 24 h. She admitted to smoking marijuana and stated that she had recently switched to a new dealer and smoked SCB 5 d ago. Past medical history included thyroid cancer status post thyroidectomy followed by radioactive iodine therapy 10 years ago, interosseous lipoma, hyperlipidemia, history of poly-substance abuse, tobacco abuse and history of bipolar disorder.

On physical exam she was ill appearing, hypotensive with a blood pressure of 71/48 mmHg. Pupils were 2 mm in size and sluggish. Lung exam noted diminished breath sounds in the left lower lobe along with bilateral costo-vertebral angle tenderness.

The patient was admitted to the intensive care unit, intravenous fluid bolus was initiated and nephrology service was consulted. Blood cultures were obtained to rule out sepsis, serum toxicology was positive for benzodiazepines and tetrahydrocannabinol. Laboratory results showed WBC 33.4 × 10^9/L, Platelets 84 × 10^9/L, Creatinine 6.13 mg/dL, BUN 49 mg/dL, Total CK 3603 U/L, ALT 1016 U/L, AST 716 U/L, D-dimer 25.95 mcg/mL, Fibrinogen 493.5 mg/dL, LDH 1983 U/L, Hepatitis viral serology was negative as well as antinuclear antibody, complements, antineutrophil cytoplasmic antibody, anticardiolipin antibody and blood cultures. For the first 24 h the patient remained hypotensive and anuric. Abdominal cat scan showed a striated appearance of both kidneys. Hemodialysis was initiated on day three.

Computed tomography (CT) guided kidney biopsy was obtained on day ten. The biopsy contained adequate amount of renal cortex with 19 glomeruli. Except for the corticomedullary junction, the entire cortex was necrotic (Figure 1A and B). At the corticomedullary junction, an arcuate artery had severely obliterating mucoid to fibrous intimal thickening (Figure 1C). Occasional arterioles at the corticomedullary junctions were obliterated by amorphous material, most likely platelet and fibrin thrombi (Figure 1D). Some interstitial inflammation was evident at the corticomedullary junction (Figure 1A and D). The renal medulla was viable. The tissue for immunofluorescence and electron microscopy represented a completely necrotic renal cortex (pictures not shown). The biopsy findings were consistent with a severe form of thrombotic microangiopathy (TMA) causing renal cortical necrosis.

DISCUSSION

This case illustrates the extent of toxicity of SCBs with recreational use. Use of SCBs has been reported to be associated with devastating renal outcomes and multi-organ failure in patients. Most of these reports suggested prerenal azotemia and rhabdomyolysis as the cause of acute tubular necrosis[1].

In 2013 the center for disease control reported a case series of 16 patients who developed acute kidney injury while using SCBs[3]. Majority (93.8%) of the patients presented with nausea and vomiting, 12 (75%) patients had either abdominal pain or flank pain and only 1 patient had anuria.

Physiological effects of SCB's are similar but more intense than cannabinoids. This is related to the greater binding affinity to cannabinoid receptors centrally and peripherally as well as their active metabolites that contribute to the intensity of their effects[4]. Similar to cannabinoids and following a brief pressor phase, SCB's can cause longstanding hypotension and bradycardia as a result of a decrease in the sympathetic tone[5]. Non-neural sites of the cannabinoids action on the vascular smooth muscle and endothelial cells can also add to the degree of systemic hypotension[6]. Animal studies in canines and rodents using different vascular beds suggested a direct effect of cannabinoids on smooth muscle cells mediated through the modulation of calcium and potassium cellular transport resulting in hyperpolarization and relaxation[7,8]. Cannabinoids also have endothelial-dependent effects on the vascular beds. This can be initiated by binding to CB1 receptors on the surface of the endothelial cell and to a different type of receptor that might not be specific to the class of cannabinoids[6].

Taken all together, it is reasonable to state that SCB is a more potent drug than the natural cannabinoids can potentially result in major vascular compromise followed by stasis secondary to vascular paralysis. This state can result in anoxic endothelial cell damage that leads to thrombotic microangipathy. In our patient, this

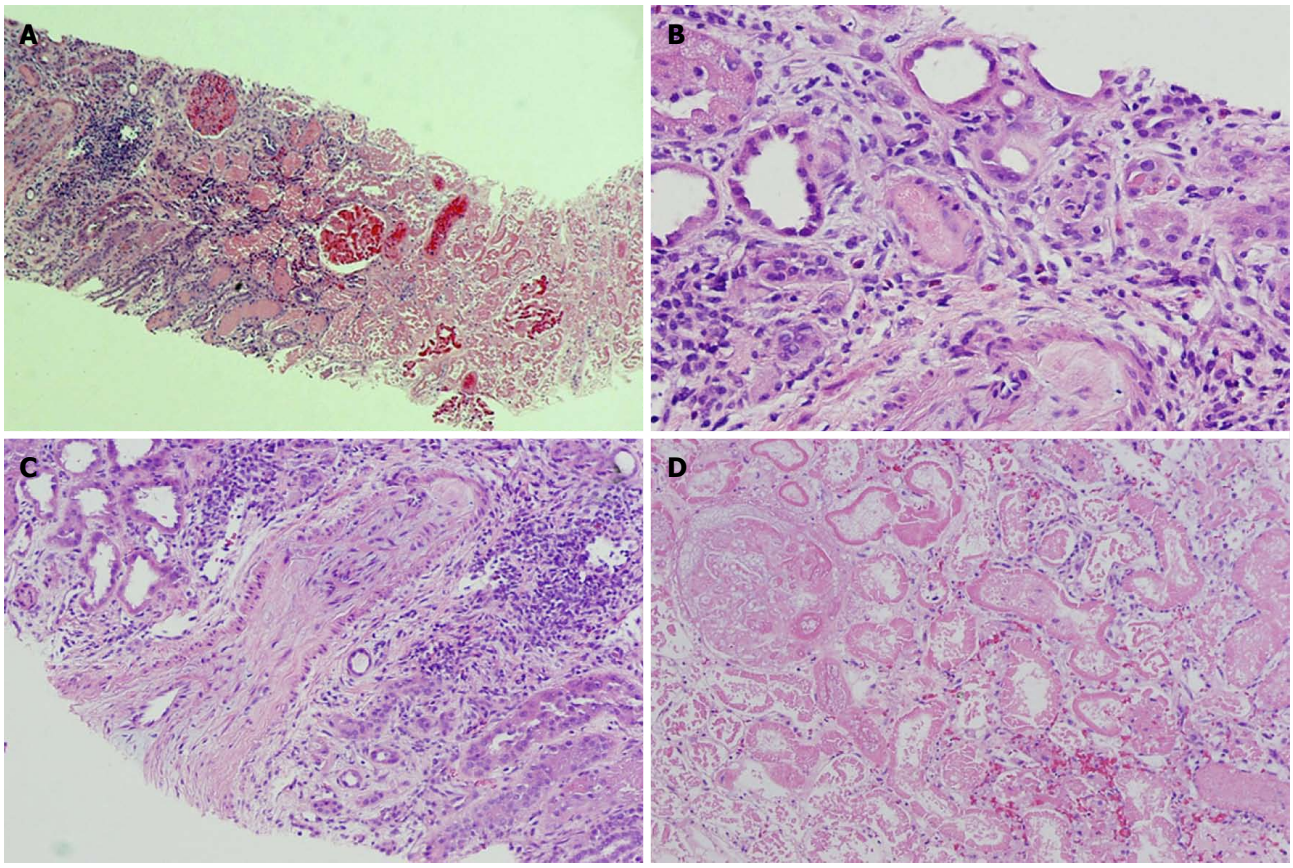

Figure 1 Renal pathology. Pathological findings: A: Corticomedullary junction. The right side is necrotic renal cortex. On the left side of the image there is still viable corticomedullary junction. H and E, × 40; B: An arteriole obliterated with amorphous material (platelet and fibrin thrombus). H and E, × 200; C: An arcuate artery with almost completely obliterated lumen by severe fibrous to mucoid intimal thickening at the corticomedullary junction. H and E, × 100; D: Necrotic renal cortex without nuclear staining in the cells. H and E, × 200.

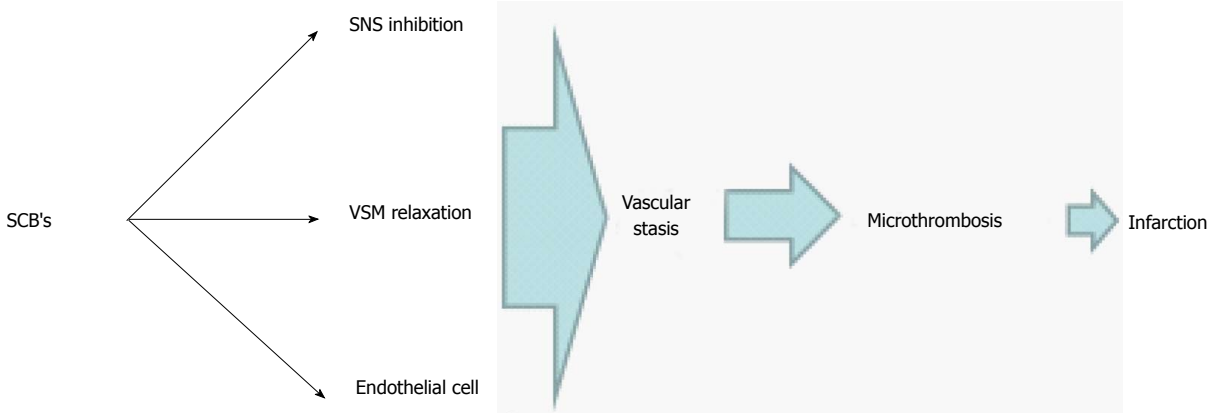

Figure 2 Proposed mechanism of synthetic cannabinoids-induced thrombotic microangiopathy. Prolonged hypotension secondary to the inhibitory effect of the SCBs on the sympathetic tone and vascular smooth muscle cells along with endothelial release of nitric oxide can lead to stasis followed by endothelial ischemia and microthrombosis leading to renal cortical necrosis. SCBs: Synthetic cannabinoids; SNS: Sympathetic nervous system; VSM: Vascular smooth muscle.

is suggested by laboratory markers of compromised organ perfusion along with thrombocytopenia. Figure 2 illustrates the mechanism of TMA in this patient.

Alternative etiologies of TMA were either ruled out or were unlikely in this patient with a temporal relationship between the exposure and the onset of clinical manifestations. An underlying tendency or inherited alternative complement pathway abnormalities as in hemolytic uremic syndrome is also unlikely, as the systemic presentation was suggestive of multi-organ intense hypoperfusion rather than primary renal involvement. Moreover, the normal complement levels, although a nonspecific finding, add to this argument. To our knowledge, this is the first case that shows biopsy proven cortical necrosis due to SCB use. Three years later, our patient is still dialysis dependent.

COMMENTS

Case characteristics

A 47-year-old Caucasian female presented to the emergency department with complaints of nausea and vomiting for 5 d along with hallucinations, abdominal pain and severe back pain with hematuria which progressed to anuria after smoking synthetic cannabinoids (SCBs).

Clinical diagnosis

Ill appearing, hypotensive patient with bilateral costo-vertebral angle tenderness.

Differential diagnosis

Acute renal failure, acute tubular necrosis, renal cortical necrosis.

Laboratory diagnosis

Laboratory investigations showed thrombocytopenia, acute renal failure, while serologies for autoimmune diseases were negative.

Imaging diagnosis

Abdominal computed tomography showed bilateral striated kidneys.

Pathological diagnosis

Cortical necrosis.

Treatment

Hemodialysis and supportive treatment.

Related reports

Thrombotic microangiopathy occurs because of endothelial injury to the capillaries and arterioles. It is has numerous causes but it has rarely been attributed to have been caused by Marijuana use.

Term explanation

SCBs are new and potent synthetic illicit designer drugs.

Experiences and lessons

This condition presented with signs of hypotension and acute renal failure, even after the conventional treatment, there was no response or improvement in the symptoms of the patient. Thus, patients suspected of marijuana or synthetic cannabinoid use should be probed for a pertinent history which will be vital for diagnosis and timely treatment. More awareness needs to be created about SCBs and their potential side effects.

Peer-review

The manuscript is interesting.

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CASE REPORT

Effect of double platinum agents, combination of miriplatin-transarterial oily chemoembolization and cisplatin-hepatic arterial infusion chemotherapy, in patients with hepatocellular carcinoma: Report of two cases

Kohei Ogawa, Kenya Kamimura, Yukari Watanabe, Yosuke Motai, Daisuke Kumaki, Ryoya Seki, Akira Sakamaki, Satoshi Abe, Hirokazu Kawai, Takeshi Suda, Satoshi Yamagiwa, Shuji Terai

Kohei Ogawa, Kenya Kamimura, Yukari Watanabe, Yosuke Motai, Daisuke Kumaki, Ryoya Seki, Akira Sakamaki, Satoshi Abe, Hirokazu Kawai, Satoshi Yamagiwa, Shuji Terai, Division of Gastroenterology and Hepatology, Graduate School of Medical and Dental Sciences, Niigata University, Niigata 951-8510, Japan

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Author contributions: Ogawa K, Kamimura K, Watanabe Y, Motai Y, Kumaki D, Seki R, Sakamaki A and Abe S performed procedure; Kawai H, Suda T, Yamagiwa S and Terai S confirmed the therapeutic effects; Kamimura K analyzed data and prepared the manuscript.

Institutional review board statement: The study was reviewed and approved by the Institutional Review Board of Niigata University.

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Abstract

Hepatocellular carcinoma (HCC) is one of the most common cancers and the third highest cause of cancer-associated mortality worldwide. The treatment of HCC is complicated by its variable biological behavior and the frequent coexistence of chronic liver disease, particularly cirrhosis. To date, multiple treatment modalities have been developed according to the stage of the tumor and the hepatic functional reserve, including transarterial treatments such as transarterial chemoembolization, transarterial oily chemoembolization (TOCE), and hepatic arterial infusion chemotherapy (HAIC). We conducted a phase I and II study of the combination therapy with double platinum agents, miriplatin and cisplatin, and confirmed its safety and efficacy. Here, we describe two cases of unresectable HCC who were successfully treated by miriplatin-TOCE/cisplatin-HAIC combination therapy, resulting in complete responses with no significant adverse events. This report will provide that the combination therapy can be the

therapeutic option for HCC patients in the advanced stage.

Key words: Hepatocellular carcinoma; Double platinum; Transarterial oily chemoembolization; Hepatic arterial infusion chemotherapy; Combination

Core tip: To date, multiple treatment modalities of hepatocellular carcinoma (HCC) exist; however, only liver transplantation or surgical resection is curative. Hepatic resection remains the most frequently performed treatment modality, but curative resection cases are limited. Therefore, palliative treatment options are necessary, including transarterial chemoembolization, transarterial oily chemoembolization (TOCE), and hepatic arterial infusion chemotherapy (HAIC). We conducted a clinical trial of combination therapy with miriplatin-TOCE and cisplatin-HAIC and demonstrated its safety and efficacy for patients with unresectable HCC. Here, we presented two cases who showed good response after the several sessions of the combination therapy.

Ogawa K, Kamimura K, Watanabe Y, Motai Y, Kumaki D, Seki R, Sakamaki A, Abe S, Kawai H, Suda T, Yamagiwa S, Terai S. Effect of double platinum agents, combination of miriplatin-transarterial oily chemoembolization and cisplatin-hepatic arterial infusion chemotherapy, in patients with hepatocellular carcinoma: Report of two cases. *World J Clin Cases* 2017; 5(6): 238-246 Available from: URL: http://www.wjgnet.com/2307-8960/full/v5/i6/238.htm DOI: http://dx.doi.org/10.12998/wjcc.v5.i6.238

INTRODUCTION

Hepatocellular carcinoma (HCC) is the sixth most common cancer and the third highest cause of cancer-associated mortality worldwide[1,2]. The treatment of HCC is complicated by its variable biological behavior and the frequent coexistence of chronic liver disease, particularly cirrhosis. To date, multiple treatment modalities exist; however, only liver transplantation or surgical resection is curative. Hepatic resection remains the most frequently performed treatment modality, but curative resection cases are limited[3,4]. Another curative treatment is ablation therapy, including radiofrequency ablation (RFA). These treatments have been adopted for patients who are in Child-Pugh A or B cirrhosis states and have fewer than three tumors, all of which are less than 3 cm in diameter[5]. For many patients whose diagnosis does not fit these criteria, palliative treatment options are necessary, including transarterial treatments such as transarterial chemoembolization (TACE), transarterial oily chemoembolization (TOCE), and hepatic arterial infusion chemotherapy (HAIC).

Among these therapeutic options, TOCE showed equivalent therapeutic effect to TACE for many HCC patients with low hepatic reserve in a randomized phase Ⅲ trial using zinostatin stimalamer dissolved in lipiodol[6]. Additionally, miriplatin, a third-generation platinum agent that forms a stable suspension with lipiodol[7], was developed for TOCE in HCC and approved for clinical use in Japan as a novel chemotherapeutic agent[8-14]. On the other hand, HAIC can affect larger areas of the liver without reducing hepatic arterial flow[15]. As the chemotherapeutic agent used in HAIC, a multicenter phase Ⅱ study in patients with unresectable HCC using cisplatin (CDDP), a first-generation platinum agent, revealed that the response rate with CDDP powder (DDP-H, IA-call®; Nippon Kayaku, Tokyo, Japan) was better than that with other chemotherapeutic agents, such as epirubicin[16] and mitomycin C[17]. Based on these results, we decided to combine TOCE using miriplatin with HAIC using CDDP to improve the efficacy and decrease the risk of hepatic failure. We conducted a phase Ⅰ study of the combination therapy and determined that both miriplatin and DDP-H can be administered up to the maximum tolerated dose of each drug without additional adverse effects[18]. Along with these results, we conducted a phase Ⅱ study and confirmed the efficacy and safety of the combination therapy in cases with multiple HCC[19]. Here, we report two cases of patients with unresectable HCC who were successfully treated by miriplatin-TOCE/DDP-H-HAIC combination therapy, resulting in complete responses with no significant adverse events.

Table 1 Results of laboratory investigation of case 1 on the day of the admission

Hematology		Bio-chemistry			
WBC	5100/μL	TP	7.3 g/dL	Na	142 mEq/L
RBC	399×10^4/μL	Alb	4.5 g/dL	K	2.9 mEq/L
Hb	14.1 g/dL	BUN	7 mg/dL	Cl	101 mEq/L
Ht	41.80%	Cre	0.44 mg/dL	CRP	0.50 mg/dL
PLT	7.4×10^4/μL	T-Bil	0.8 mg/dL	AFP	7 ng/mL
Coagulation		D-Bil	0.1 mg/dL	AFP-L3	< 0.5%
PT	85%	AST	28 IU/L	DCP	24 mAU/mL
		ALT	20 IU/L	CEA	5.8 ng/mL
		ChE	211 IU/L	CA 19-9	68 U/mL
		LDH	181 IU/L		
		γ-GTP	256 IU/L		

WBC: White blood cell; RBC: Red blood cell; PLT: Platelet; PT: Prothrombin time; TP: Total protein; BUN: Blood urea nitrogen; AST: Aspartate aminotransferase; ALT: Alanine transaminase; LDH: Lactate dehydrogenase; γ-GTP: γ-glutamyltransferase; CRP: C-reactive protein; AFP: Alpha-fetoprotein; DCP: des-γ-carboxy prothrombin; CEA: Carcinoembryonic antigen.

CASE REPORT

Case presentation

Case 1: A 37-year-old Japanese woman diagnosed with multiple liver tumors was referred to our hospital. She had been a heavy drinker for 20 years. Her physical examination revealed no remarkable changes, and laboratory analysis provided the following results (Table 1): All viral markers, including hepatitis B virus (HBV)

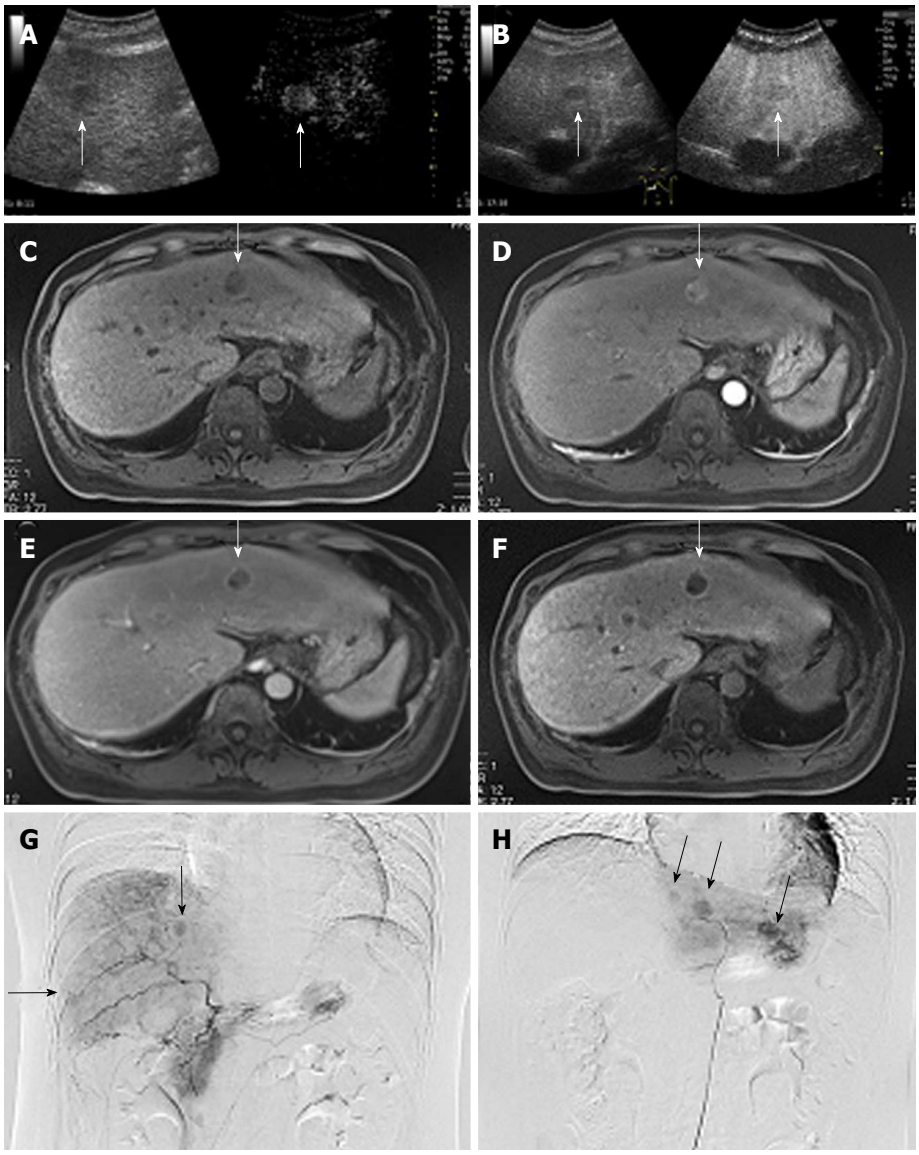

Figure 1 Images of Case 1. Contrast-enhanced ultrasonography. A: The vascular arterial phase; B: The Kupffer phase; EOB-MRI; C: T1-weighted MRI image; D: The arterial phase; E: The portal phase; F: The hepatobiliary phase; G and H: Angiography. EOB-MRI: Gd-EOB-DTPA-enhanced magnetic resonance imaging.

and hepatitis C virus (HCV), were negative (HBsAg 0.32 mIU/mL, anti-HBs 0.01 IU/mL, anti-HBc 0.04 S/CO, anti-HCV 0.03 S/CO). Platelets ($7.4 \times 10^4/\mu L$) showed a mild decrease, but serum aspartate aminotransferase (28 IU/L), alanine aminotransferase (20 IU/L), total bilirubin (0.8 mg/dL), albumin (4.5 g/dL), and prothrombin time (PT) (85%) were within normal ranges. Her Child-Pugh grade was A with a score of 5 points. There was no specific familial history of diseases.

Contrast-enhanced ultrasonography (CEUS) using a perflubutane microbubble agent (Sonazoid, Daiichi Sankyo, Tokyo, Japan), angiography, and Gd-EOB-DTPA-enhanced magnetic resonance imaging (EOB-MRI) were performed and showed multiple tumors in the both lobes of the liver (Figure 1). Ultrasonography showed multiple low echoic masses of various sizes, with the maximum diameter of 2.1 cm in the left lobe. CEUS performed for the real-time observation of tumors and hepatic blood flow showed blood flow in the vascular arterial phase in the tumorous lesions with low echoic areas in the Kupffer phase (Figure 1A and B). MRI showed T1 hypointense tumors in both lobes of the liver (Figure 1C). EOB-MRI showed hyperintense tumors with hepatic blood perfusion in the arterial phase (Figure 1D). These tumors were clearly shown to have a drainage of blood perfusion in the delayed phase (Figure 1E), and marked as typical hypointensity tumors in the hepatobiliary phase (Figure 1F). Angiography showed multiple hypervascular tumor staining by the selective hepatic angiogram through the feeding arteries (Figure 1G and H). Although the imaging studies showed typical images for HCC, to confirm the histological diagnosis, we performed a liver biopsy of the tumorous area in the left lobe and confirmed it to be HCC.

Based on these results, the patient was diagnosed with multiple HCCs with liver cirrhosis due to alcohol

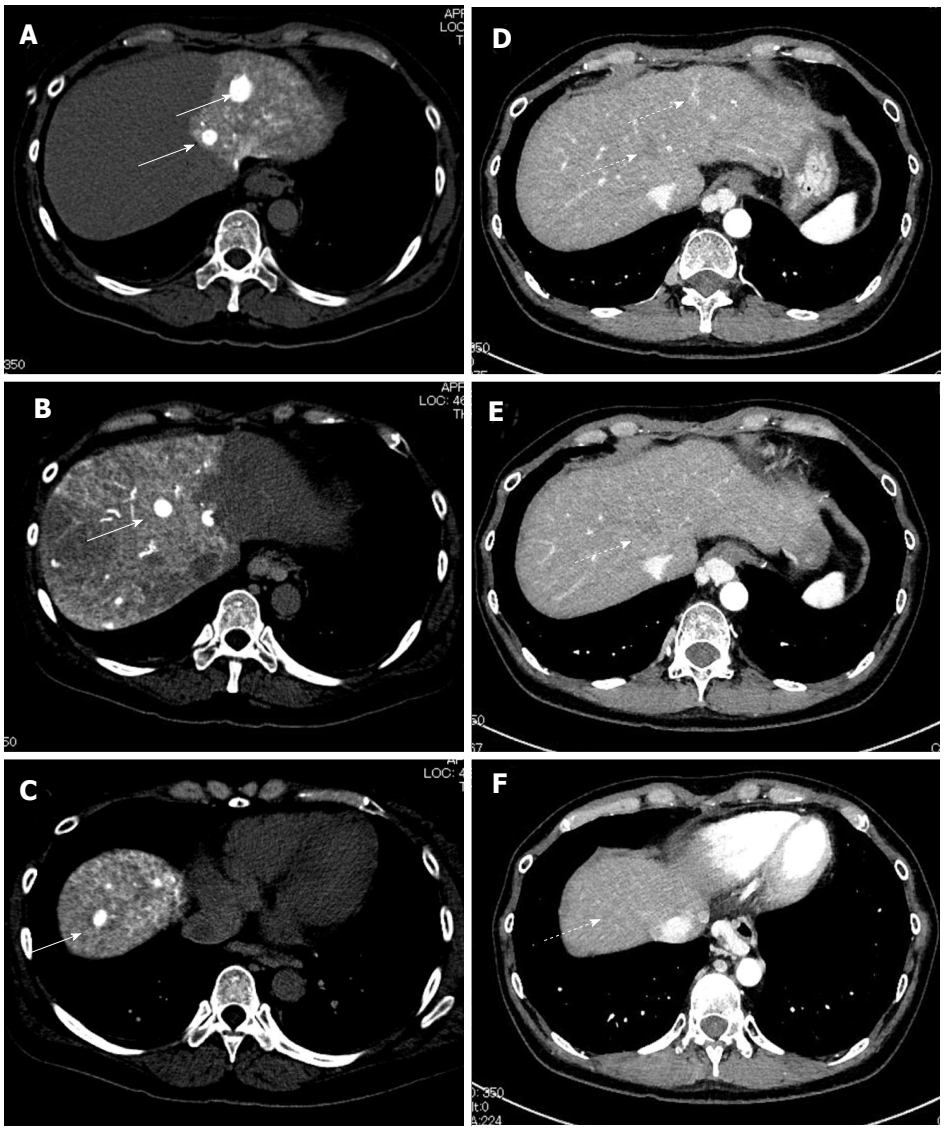

Figure 2 The representative dynamic contrast-enhanced computed tomography images of case 1 before and after eight times of combination therapy. A-C: White arrows indicate tumors before the combination therapy; D-F: White arrows with dotted line indicate the tumor disappearance after eight times of combination therapy.

abuse. Because of the bilaterality and multiplicity of the tumors, we performed transhepatic arterial chemotherapy using a combination therapy. DDP-H was administered as HAIC through the hepatic arteries covering the lobes of the liver with tumors at a concentration of 1.43 mg/mL in saline at a rate of 3 mg/min. Miriplatin was administered through the tumor feeders at a concentration of 20 mg/mL in lipiodol up to 120 mg/body. No other medication was adopted during the procedure. To date, we have performed this treatment in eight sessions without severe adverse events in any session. Dynamic contrast-enhanced CT demonstrated significant improvements in the HCCs after eight sessions of treatment (Figure 2). Based on the REIST classification, her clinical course was classified as a complete response (CR), and no recurrences were seen 2 years after the last therapy, the period of follow-up. The clinical course and time-dependent changes of serum biochemical analyses are shown in Figure 3. AFP showed decreasing whereas albumin, and PT did not change significantly during the eight sessions of combination therapy. This result suggests that this combination therapy can be performed safely and repeatedly without severe adverse events.

Case 2: A 43-year-old Japanese woman was referred to our hospital for rupture of esophageal varices. We performed endoscopic variceal ligation for the varices. CT revealed multiple tumors in bilateral lobes of the liver. CEUS and EOB-MRI showed clear enhancement in the arterial phase with detection as low echoic areas in Kupffer phase (Figure 4A and B). T1-weighted MRI revealed a hyperintense tumor with film structure (Figure 4C). EOB-MRI showed a hypointensity tumor in the hepatobiliary phase in the S5 lesion with hepatic blood perfusion in the arterial phase (Figure 4D and E). Several

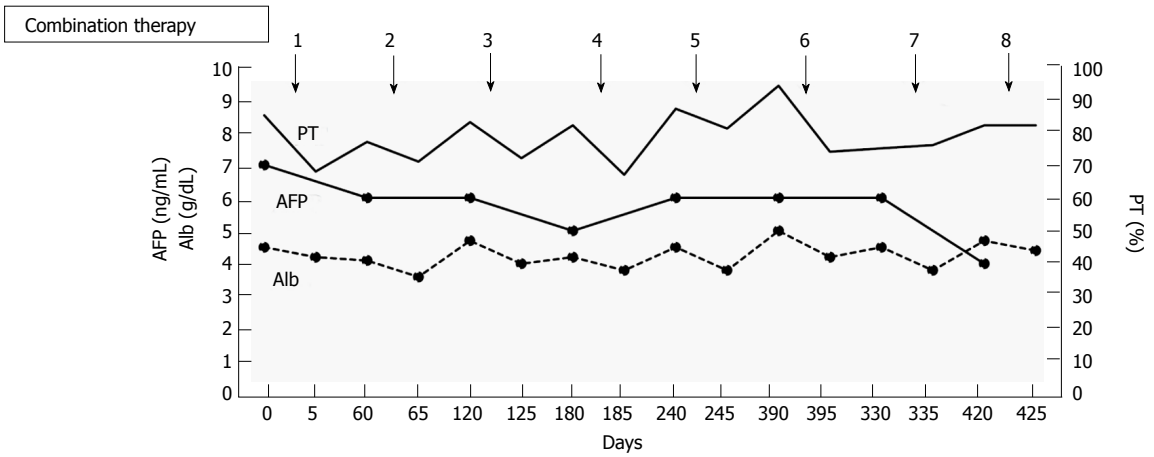

Figure 3 Changes in alpha-fetoprotein, albumin and prothrombin time after eight combination therapy. None of them did show a significant change after each session. PT: Prothrombin time; AFP: Alpha-fetoprotein.

Table 2 Results of laboratory investigation of case 2 before miriplatin- transarterial oily chemoembolization/DDP-H-hepatic arterial infusion chemotherapy combination therapy

Hematology		Bio-chemistry			
WBC	3980 /μL	TP	7.0 g/dL	Na	138 mEq/L
RBC	344 × 10^4/μL	Alb	3.1 g/dL	K	3.5 mEq/L
Hb	10.2 g/dL	BUN	11 mg/dL	Cl	106 mEq/L
Ht	30.00%	Cre	0.45 mg/dL	CRP	0.16 mg/dL
PLT	8.6 × 10^4/μL	T-Bil	0.7 mg/dL	AFP	4 ng/mL
Coagulation		D-Bil	0.1 mg/dL	AFP-L3	< 0.5%
PT	52%	AST	63 IU/L	DCP	< 15 mAU/mL
		ALT	49 IU/L	CEA	2.2 ng/mL
		ChE	124 IU/L	CA 19-9	40 U/mL
		LDH	143 IU/L		
		γ-GTP	83 IU/L		

WBC: White blood cell; RBC: Red blood cell; PLT: Platelet; PT: Prothrombin time; TP: Total protein; BUN: Blood urea nitrogen; AST: Aspartate aminotransferase; ALT: Alanine transaminase; LDH: Lactate dehydrogenase; γ-GTP: γ- glutamyltransferase; CRP: C-reactive protein; AFP: Alpha-fetoprotein; DCP: des-γ-carboxy prothrombin; CEA: Carcinoembryonic antigen.

tumorous lesions in the liver besides the S5 lesion were detected as enhanced tumors in the arterial phase of the EOB-MRI study (Figure 4F). Because tumor markers were normal, including carcinoembryonic antigen, carbohydrate antigen 19-9, alpha-fetoprotein (AFP), and des-γ-carboxy prothrombin, angiography was performed for the evaluation of these tumorous lesions which showed multiple hypervascular areas of tumor staining by the selective hepatic angiograms (Figure 4G) followed by the histological diagnosis of HCC by tumor biopsy.

Based on these findings, we diagnosed the patient with multiple HCCs. Laboratory results before the treatment of these tumors (Table 2) showed reduced levels of hemoglobin (10.2 g/dL), platelets (8.6 × 10^4/μL), cholinesterase (124 IU/L), prothrombin (52%), and albumin (3.1 g/dL) and increased aspartate aminotransferase (63 IU/L), alanine aminotransferase (49 IU/L), γ-glutamyl transpeptidase (83 IU/L), and alkaline phosphatase (471 IU/L). The physical examination showed no remarkable findings and no signs of hepatic encephalopathy or flapping tremor. Based on these results, her Child-Pugh grade was determined to be B with a score of 7 points. All viral markers, including HBV and HCV, were negative (HBs Ag 0.02 mIU/mL, anti-HBs 0.01 IU/mL, anti-HBc 0.02 S/CO, and anti-HCV 0.11 S/CO).

Based on the multiplicity of tumors and the poor hepatic reserve function, we decided to perform combination therapy with the same protocol as described for case 1. Dynamic contrast-enhanced CT demonstrated significant improvement after three sessions of treatment and because this combination therapy was successful for all other tumors, we performed an additional RFA for the tumor in S5 lesion, suspected of retaining a small part of the tumor (Figure 5). To date, the RECIST evaluation achieved CR, no recurrences were seen for 1 year, the period of follow-up, and no adverse events have been seen.

The clinical course and time-dependent changes of serum biochemical analyses are shown in Figure 6. There were no significant changes in AFP, albumin, or PT during the three sessions of combination therapy or during RFA using Cool-tip® (Medtronic, MN, United States). This result suggests that we can perform this combination therapy safely and repeatedly without adverse events, as with case 1.

DISCUSSION

In this report, we have shown two representative cases with unresectable HCC that were successfully treated by miriplatin-TOCE/DDP-H-HAIC combination therapy, resulting a CR. Because the therapeutic strategy is determined according to the stage of the tumor and the hepatic functional reserve, several therapeutic options, including surgical resection, RFA, and heavy particle radiotherapy, can be adopted as loco-regional control

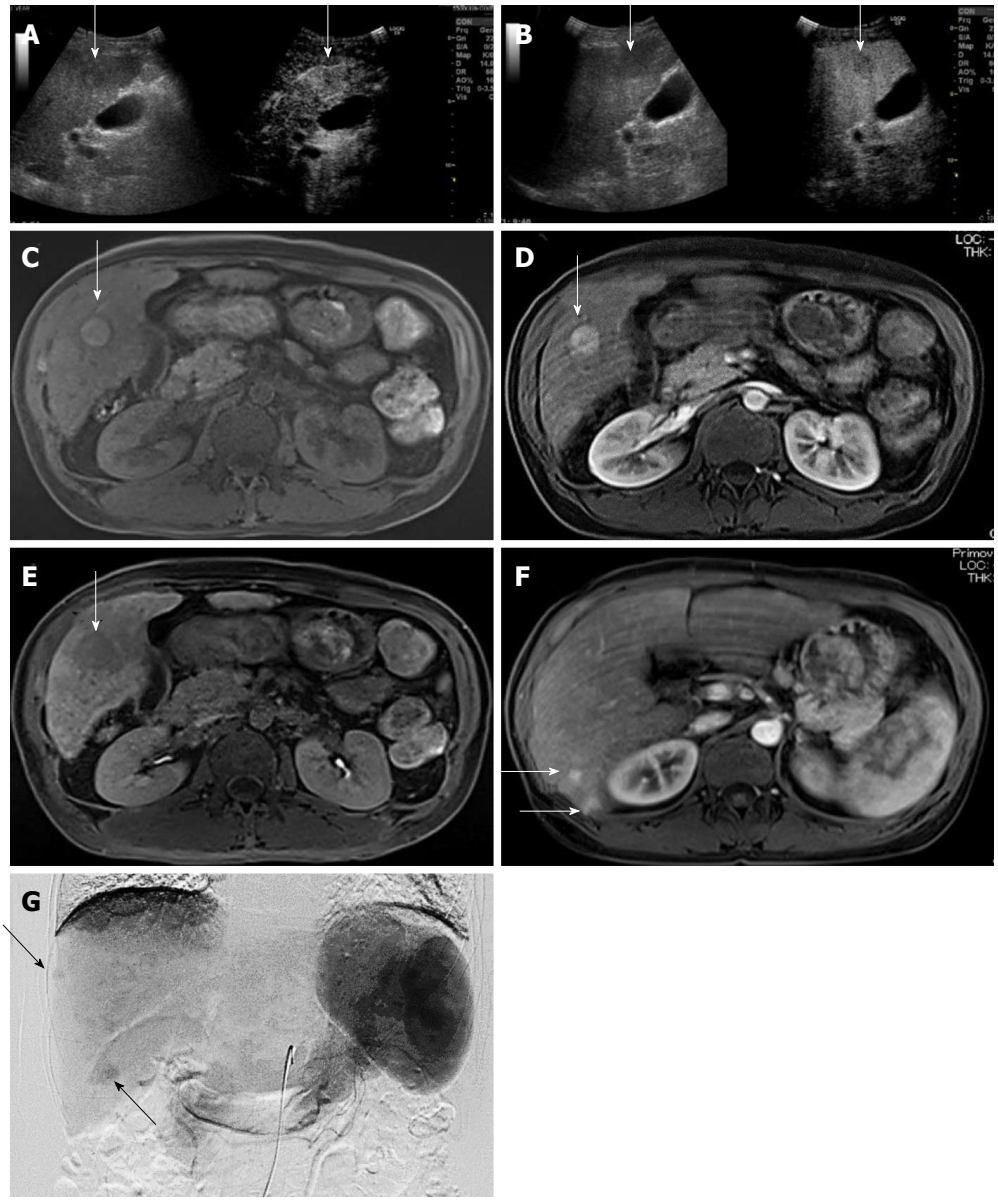

Figure 4 Images of Case 2. Contrast-enhanced ultrasonography: A: The vascular arterial phase; B: The Kupffer phase; EOB-MRI: C: T1-weighted MRI image; D: The arterial phase; E: The hepatobiliary phase of EOB-MRI; F: Several tumorous lesions in the liver besides S5 lesion in the arterial phase of EOB-MRI study; Angiography: G. EOB-MRI: Gd-EOB-DTPA-enhanced magnetic resonance imaging.

for cases of limited HCC[20,21]. The use of TACE is strictly limited because it requires a higher hepatic functional reserve[22-26]. However, in a randomized phase Ⅲ trial of zinostatin stimalamer dissolved in lipiodol, TOCE demonstrated a therapeutic effect, with no difference in the anti-tumor effect in comparison with TACE, for HCC patients with low hepatic reserve[6] TOCE has served as a therapeutic option for patients in advanced stages of HCC with poor hepatic reserve. Miriplatin was developed for TOCE in HCC because it gradually releases active derivatives *in situ*, enabling the continuous release of platinum in the tumor while avoiding systemic release and toxicity[7]. It has been used since 2010. To date, there have been some reports of the safety and efficacy of miriplatin-TOCE in patients with HCC[27]. Otsuji recently reported that the efficacy and safety of miriplatin for HCC were on the same level as the efficacy and safety of DDP-H in a randomized controlled trial[28]. Compared with TACE and TOCE, HAIC can affect larger areas of the liver without reducing hepatic arterial flow because no embolization was combined. Although various chemotherapeutic agents have been used for treating HCC[16,17], platinum agents achieved a better response rate in a multicenter phase Ⅱ study enrolling patients with unresectable HCC[29]. Based on these results and the fact that miriplatin showed no cross-resistance with different generations of platinum agents[30], we conducted a phase Ⅰ study[18] and a phase Ⅱ study[19] of combined therapy with miriplatin-TOCE and DDP-H-HAIC and demonstrated its safety and efficacy for patients with unresectable HCC. In fact, we could repeat the miriplatin-TOCE/DDP-H-HAIC combination

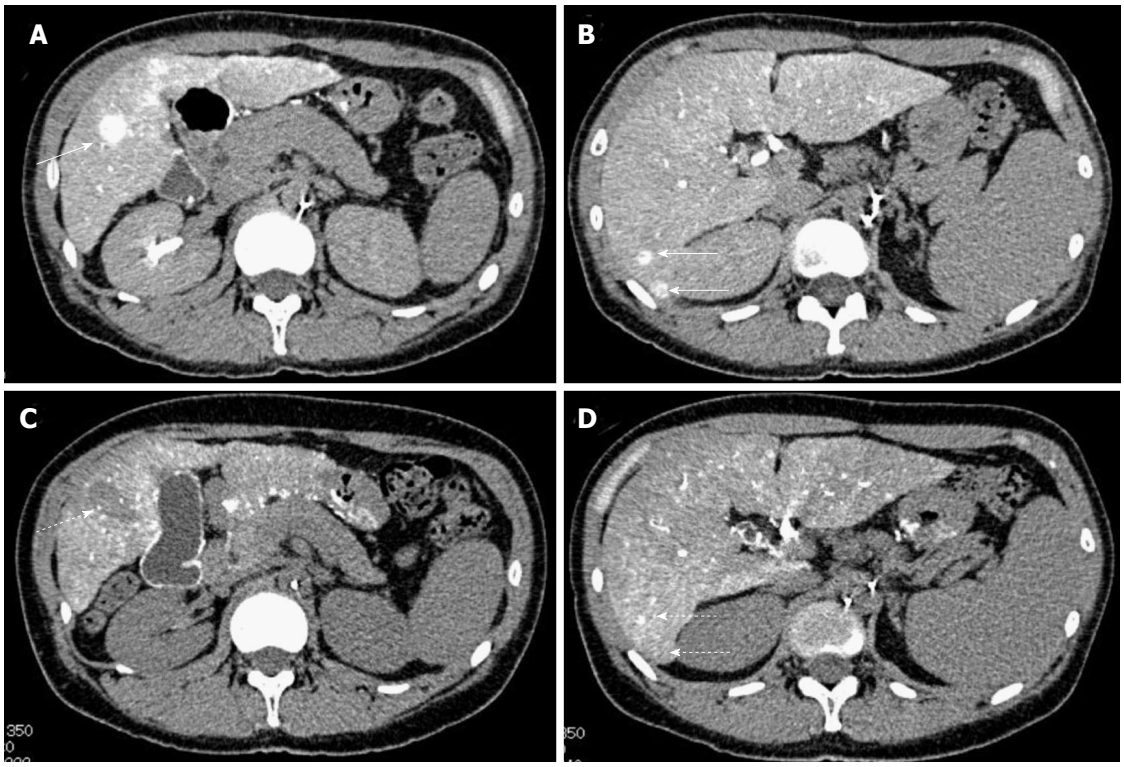

Figure 5 The representative dynamic contrast-enhanced computed tomography images of case 2 before and after three times of combination therapy and radiofrequency ablation. A and B: White arrows indicate tumors before treatment; C and D: White arrows with dotted line indicate tumors disappearance or reduction after three times of combination therapy and radiofrequency ablation.

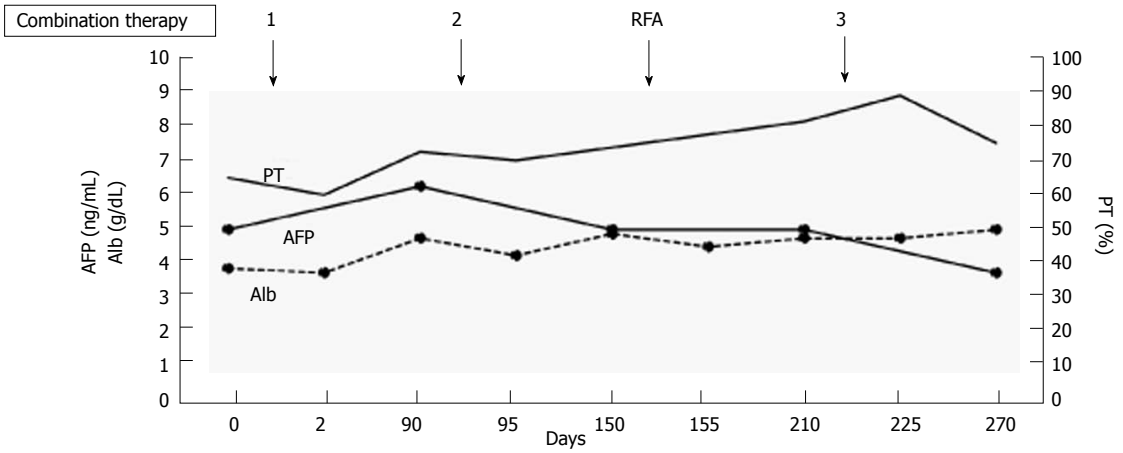

Figure 6 Changes in alpha-fetoprotein, albumin and prothrombin time after three combination therapy and radiofrequency ablation. None of them did show a significant change after each treatment. PT: Prothrombin time; AFP: Alpha-fetoprotein.

therapy for the two cases in the present study without severe adverse effects. The combination therapy may have some adverse events for specific cases with poor hepatic functional reserve. A further study should be conducted to confirm the efficacy and safety of miriplatin-TOCE/DDP-H-HAIC combination therapy for a larger number of patients with poor hepatic functional reserve.

In conclusion, we report two representative cases of patients with unresectable HCC that was successfully controlled by miriplatin-TOCE/DDP-H-HAIC combination therapy. This report suggests that the combination therapy can be performed safely and repeatedly for patients with advanced HCC.

COMMENTS

Case characteristics

Two cases with unresectable hepatocellular carcinoma (HCC).

Clinical diagnosis

HCC diagnosed with multiple imaging modalities.

Differential diagnosis

The imaging modalities clearly demonstrated the typical patterns of HCC.

Laboratory diagnosis

Mild liver injury and increase of tumor markers including alpha-fetoprotein and des-γ-carboxy prothrombin.

Imaging diagnosis

Contrast-enhanced ultrasonography showed blood flow in the vascular arterial phase in the tumorous lesions with low echoic areas in the Kupffer phase. Magnetic resonance imaging showed T1 hypointense and hyperintense with hepatic blood perfusion in the arterial phase. Hypointense in the delayed phase and marked as typical hypointensity tumors in the hepatobiliary phase.

Pathological diagnosis

HCC.

Treatment

Combination therapy of miriplatin-transarterial oily chemoembolization and cisplatin-hepatic arterial infusion chemotherapy.

Experiences and lessons

This report suggests that the combination therapy can be performed safely and repeatedly for patients with advanced HCC.

Peer-review

These cases appear to have responded which may be an important finding.

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CASE REPORT

Immunophenotypic signature of primary glioblastoma multiforme: A case of extended progression free survival

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Author contributions: Gandhi P designed the report; Khare R performed the experimental parameters, Garg N and Sorte S pooled and analyzed clinical data; Gandhi P and Khare R performed marker analysis, statistics and wrote the manuscript.

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Informed consent statement: Written informed consent as per institutional ethics committee (IEC/21/Res/11) was obtained from the subject prior to study inclusion.

Conflict-of-interest statement: The authors have no financial or any other conflict of interest to declare.

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Abstract

Glioblastoma-multiforme (GBM), the most aggressive glial tumor, has a worldwide age-adjusted incidence ranging from 0.59-3.69/100000 persons. Despite current multimodal-treatment approach, median-survival time and progression-free survival (PFS) remains short. Glioblastomas display a variety of molecular alterations, which necessitates determining which of these have a prognostic significance. This is a case of a 45-year-old patient who presented with progressive slurring of speech and features of raised intracranial pressure. Computed tomography (CT) scan revealed a large heterogeneously enhancing lesion in the left front-temporal-perisylvian region with solid, cystic areas, suggestive of malignant glioma. Partial tumor-excision was followed by concurrent chemo-radiotherapy. Histopathologically, the tumor was astrocytoma grade-IV. Patient had an extended PFS of 12 mo, with an overall survival of 26 mo. Primary-GBM was confirmed using molecular markers and the immunophenotypic signature was defined by evaluating systemic expression of human telomerase reverse transcriptase, interleukin-6, neutrophil-lymphocyte ratio, tissue inhibitor of metalloproteinases-1, human chitinase-3-like-protein-1 (YKL-40) and high mobility group-A1. Current findings suggest that this signature can identify worst outcomes, independent of clinical criteria.

Key words: Glioblastoma multiforme; Immunophenotypic signature; Progression free survival; Molecular markers; Human telomerase reverse transcriptase;

Interleukin-6; Tissue inhibitor of metalloproteinases-1; YKL-40; High mobility group-A1

Core tip: Delineating the immunophenotypic signature for glioblastoma with reference to disease progression is of clinical importance. This case report presents for the first time a panel of 6 systemic molecular markers in circulation namely; human telomerase reverse transcriptase, interleukin-6, neutrophil-lymphocyte ratio, tissue inhibitor of metalloproteinases-1, human chitinase-3-like-protein-1 and high mobility group-A1 representing the mechanistic of inflammation, proliferation and invasion of the tumor. Their expression is suggested to be linked to progression-free survival in glioblastoma-multiforme.

Gandhi P, Khare R, Garg N, Sorte S. Immunophenotypic signature of primary glioblastoma multiforme: A case of extended progression free survival. *World J Clin Cases* 2017; 5(6): 247-253 Available from: URL: http://www.wjgnet.com/2307-8960/full/v5/i6/247.htm DOI: http://dx.doi.org/10.12998/wjcc.v5.i6.247

INTRODUCTION

The most common and fatal glioma subtype in adults, glioblastoma-multiforme (GBM) has a worldwide age-adjusted incidence ranging from 0.59 to 3.69 per 100000 persons[1]. Despite the current multimodal treatment approach, the median survival time remains in the range of 15-18 mo[2]; while progression-free survival (PFS) is of 6 mo[3]. Glioblastoma display a variety of molecular alterations, which necessitates determining which of these have a diagnostic and/or prognostic significance[4]. According to the latest World Health Organization guidelines (WHO 2016), a molecular classification of tumors of the central nervous system has been established, which defines glioblastoma on the basis of IDH-*mutant* and *wild type.* In primary glioblastoma, the absence of IDH mutation, along with over-expression of p53 and epidermal growth factor receptor (EGFR) are distinct molecular signatures[5], associated with enhanced therapeutic response and longer survival[6].

The clinico-patholoical profile of GBM is not clearly defined because of the extensive variability of tumor histologies. Conventionally, a glioma is confirmed as GBM, based on positive expression of glial fibrillary acidic protein (GFAP) and Ki-67 proliferation index. At the molecular level, as per 2016 WHO guideline; screening for IDH-1, TP53 and EGFR expression is to be carried out to confirm the case as primary GBM. In lieu of this molecular scenario, delineating the molecular signature of glioblastoma with reference to progression and survival is of clinical importance.

Current research points to a strong relation between inflammatory mechanism and glioma tumor proliferation, stemness and invasion. Expression of human telomerase reverse transcriptase (hTERT) and high mobility group-A1 (HMGA1) as proliferation and stemness markers in glioma subtype has been recently established by Gandhi *et al*[7]. Similarly, human chitinase -3-like-protein-1 (YKL-40), an acute phase glycoprotein is secreted by activated macrophages and neutrophils in gliomas[8] and its involvement is documented in inflammation[9], angiogenesis[10], cell proliferation and invasion[11] of glial tumor. Longitudinal changes in plasma levels of tissue inhibitor of metalloproteinases-1 (TIMP-1) have also been seen to be associated with prognosis of GBM (grade-Ⅳ) patients[12], reflecting the role of TIMP-1 in invasive growth pattern resulting from degradation of extracellular matrix.

Neutrophils and lymphocytes too have been recently acknowledged to play an important role in uncontrolled inflammation; driving tumor proliferation[13]. There are several studies associating high pre-treatment neutrophil-lymphocyte ratio (NLR) with GBM[14,15]. Likewise, in a study by Samaras *et al*[16], IL-6 secretion levels in peripheral blood mononuclear cells of glioma patients were found to be significantly higher compared to controls indicating a role of inflammation in tumor proliferation.

Keeping in view the poor prognosis of glioblastoma, this case report undertook to define for the first time the systemic immunophenotypic molecular signature of a case of primary GBM in terms of extended PFS.

CASE REPORT

A 45-year-old patient presented with progressive slurring of speech since 2 mo and features of raised intracranial pressure since a few days. On examination, he was drowsy, obeying commands but confused; with irrelevant verbalization and irritability. Computed tomography (CT) scan revealed a large heterogeneously enhancing lesion in left front-temporal-perisylvian region with solid and cystic areas. There was significant perilesional edema surrounding the lesion in frontal and temporal lobes with mass effect (Figure 1A). Possibility of malignant glioma was considered.

Patient underwent left front-tempo-parietal decompressive craniotomy and tumor decompression, three months after initial diagnosis. Intra-operatively, tumor was soft to firm in consistency, moderately vascular with both solid and cystic areas. Partial tumor excision was done; with tumor adherent to perisylvian vessels left behind (Figure 1B). The brain was still full; hence bone flap was not repositioned but placed in the abdomen. Patient recovered well from surgery. Histo-pathological report stated sample to be glioblastoma.

Patient was administered concurrent chemo-radiotherapy and he had an extended 12 mo of PFS. After 18 mo, he developed progressive weakness of the right

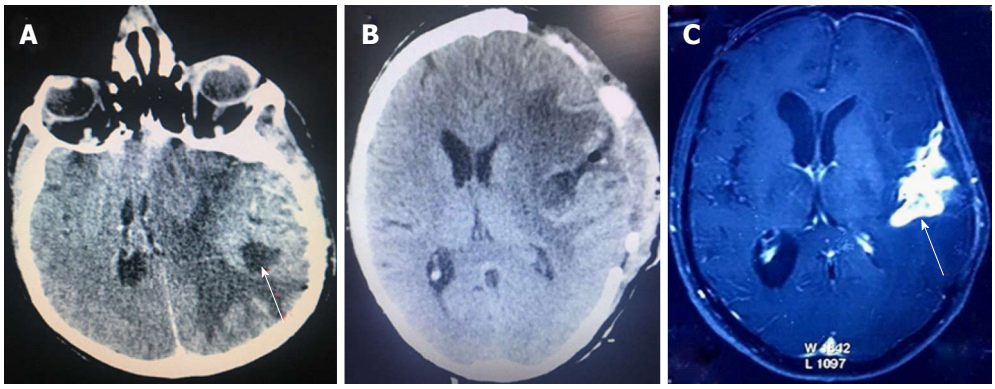

Figure 1 Showing radiological scans and findings. A: Computed tomography (CT) scan at initial diagnosis suggestive of glioma; B: Post-operative image of CT scan with adequate tumor excision and reduced mass effect; C: Magnetic resonance image after 18 mo showing the progressive recurrence of tumor.

upper and lower limbs along with seizures. Magnetic resonance imaging brain showed features of recurrence of tumor with significant edema (Figure 1C). Steroids and anti-epileptics were administered. The patient continued to have neurological deterioration and expired after few months with an overall survival (OS) of 26 mo.

Immunophenotypic signature

According to current WHO guideline, diagnosis of GBM was confirmed by tissue based expression of IDH-1, p53 and EGFR. Biomarkers hTERT and HMGA1 were quantified in formalin-fixed paraffin-embedded tissues (FFPE) in areas with the maximum proliferation. Their expression was compared with non-malignant tissues obtained from subjects serving as control, undergoing surgery for reasons other than brain tumor. Venous blood samples were collected from patient before surgery and centrifuged (Beckman Coulter, United States) at 3000 rpm, for 15 min at 4 ℃. Plasma and serum were divided into aliquots and stored at -80 ℃. This was followed by assessing levels of NLR, TIMP-1, YKL-40 in plasma as well as that of hTERT and HMGA1 in serum. Corresponding samples from 30 healthy subjects were collected to define the threshold values and statistical analysis of the panel of molecular markers mentioned above.

IDH-1, p53, EGFR, hTERT and HMGA1 by immuno-fluorescence based immuno-histochemistry: To ascertain the expression of IDH-1, p53, EGFR, hTERT and HMGA1 molecules in FFPE tissue, immunofluorescence based immuno-histochemistry (IF-IHC) was performed as per protocol discussed earlier[7]. The slides were incubated overnight at 4 ℃ with primary antibodies IDH-1 (Santa Cruz Biotechnology, United States, 1:1000 dilutions), p53 (Bethyl Laboratories, United States, 1:1000 dilutions), EGFR (Bethyl Laboratories, United States, 1:1000 dilutions), HMGA1 (Abcam, United Kingdom, 1:1000 dilutions) and hTERT (Abcam, United Kingdom, 1:1000 dilutions), followed by treatment with host specific secondary antibodies (FITC labelled, 1:300 dilutions), washed and mounted.

All images were observed with Plan-Neofluar 40 × 0.75 NA lens. With regard to protein of interest, areas with highest protein labelling were considered and approximately 1000 cells per section were captured with 40-fold magnification followed by digitalization and analysis with the Case Data Manager Expo 4.5 software (Applied Spectral Imaging, Edingen Neckarhausen, Germany). These images were exported as TIFF files and analyzed. Quantification of fluorescence signals of the identified molecular markers hTERT and HMGA1 was carried out using ImageJ software (National Institute of Health, United States).

NLR: The NLR was calculated from a pre-operative whole blood sample count stained with Leishman. The patient did not present any clinical signs of sepsis at that point of time, having been on steroids for the last 24 h.

hTERT, TIMP-1 and YKL-40 by ELISA: Plasma concentrations of TIMP-1 (ng/mL, RD Systems, MN, United States), hTERT (ng/L, MyBiosourse, CA, United States) and plasma YKL-40 (ng/mL, RD Systems, MN, United States) were determined by sandwich ELISA assay using commercially available kits as per the manufacturer's protocol. All samples were analysed in duplicate. Concentrations were measured as absorbance at 450 nm for hTERT and YKL-40 and for TIMP-1 using correction wavelength of 540 nm in ELISA Reader (Bio-Rad, United States).

HMGA-1 by Western blot: To estimate circulating HMGA1 protein in serum of the patient using minimal sample volume, 10 μL serum was subjected to protein extraction using a spin column for removing high abundance proteins, yielding ⩾ 30 μg/mL of total protein. Extracted sample was then lyophilized to 1/10th volume followed by resolution on 11.5% SDS-PAGE. Western blot analysis was performed following modified method of Ferrín *et al*[17]. Briefly, nitrocellulose membrane was probed with primary polyclonal HMGA1 antibody (rabbit anti-human HMGA1 antibody, Abcam, United Kingdom; 1:1000 dilution)by incubating overnight at 4 ℃; followed by compatible secondary

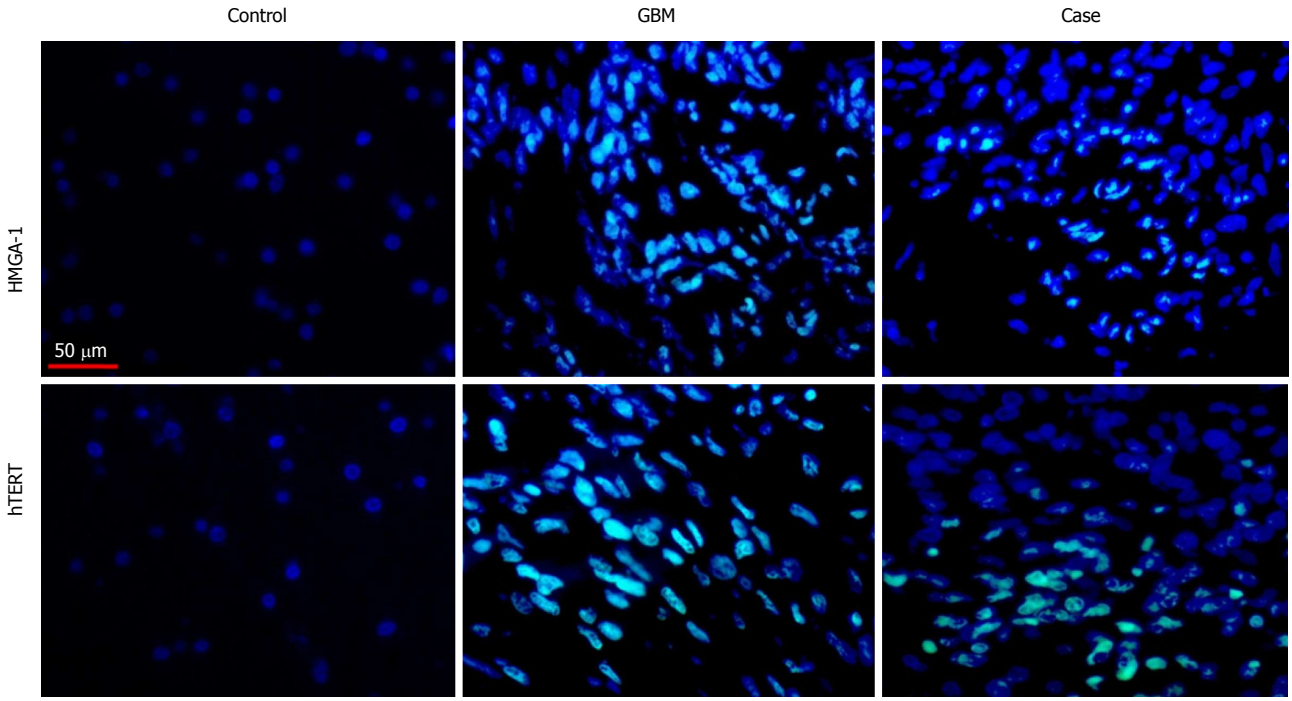

Figure 2 Immunofluorescence based immuno-histochemistry analysis and interpretation for human telomerase reverse transcriptase and high mobility group-A1: Control sample showed negative expression of both markers; intense immune-reactivity of high mobility group-A1 and human telomerase reverse transcriptase in Glioblastoma-multiforme and moderate expression in our case.

Table 1 Evaluated parameters in formalin-fixed paraffin-embedded tissue

No.	Case/groups	HMGA1 (%)	hTERT (%)	Ki-67 (%)
1	Case	2.6	11.5	45
2	controls (n = 15, median with range)	0.0 (0-0)	0.0 (0.0-0.05)	0.0 (0-0)
3	GBM (n = 30, median with range)	14.55 (2.3-23.9)	25.76 (10.5-44.75)	28 (6.5-80)

HMGA1: High mobility group-A1; hTERT: Human telomerase reverse transcriptase; GBM: Glioblastoma-multiforme.

alkaline phosphatase-conjugated antibody (Santa Cruz Biotechnology, United States; 1:5000 dilution) for two hours at room temperature.

According to the institutional ethics committee sanction reference (IEC/21/Res/11), a written informed consent was taken from the patient. Data regarding histo-pathological grade, GFAP, Ki-67 score and IL-6 were obtained from medical records and re-analysed by an independent pathologist.

IF-IHC: Negative expression of IDH-1 and over-expression of p53 and EGFR confirmed the case as primary GBM at the molecular level. Amplified expression of markers hTERT and HMGA1 in tissue was concurrent with GBM grade-Ⅳ and Ki-67 proliferation index (Figure 2, Table 1) and also correlated with the OS (Supplementary Table S1). However the values of hTERT and HMGA1 markers in FFPE tissue of the subject in question were found to be lower than the threshold values of these markers established for GBM group (n = 30) in our study (Supplementary Table S2).

Following this, the five molecular markers identified for systemic immmunophenotypic signature were quantified.

NLR: The pre-operative NLR value of patient was 3.9 while that of the GBM group was 5.58 (Table 2).

ELISA: The inflammatory and proliferation markers hTERT, IL-6, YKL-40 and TIMP-1 for this GBM patient were analyzed (Table 2) and showed significantly higher levels than control samples. But this patient's values were lower than the median values of the GBM reference group.

Western Blot: The 12 kDa band of HMGA1 was identified and quantified using Image J software. The level of HMGA1 in circulation was found to be lower than the reference GBM group studied (Figure 3, Table 1).

DISCUSSION

Glioblastomas have extensive and divergent alterations of molecular pathways but morphological differences are insignificant, making conventional histochemical diagnosis unreliable. The immuno-molecular characterization of GBM is therefore, a prerequisite to decision-making regarding diagnosis and prognosis. Herein, a case-based approach is presented to illustrate

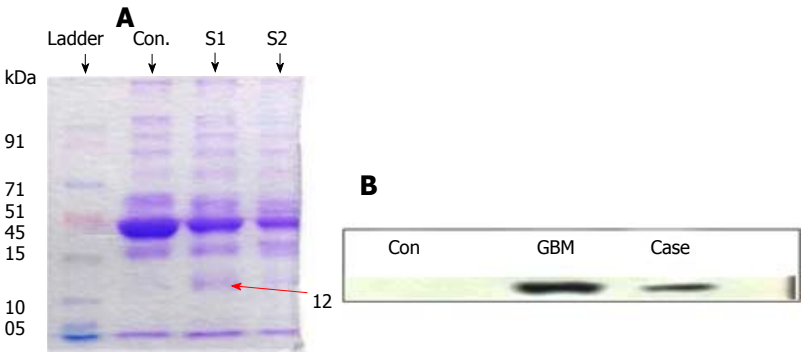

Figure 3 High mobility group-A1. A: SDS-PAGE protein profile of serum samples; B: Western blot expression for high mobility group-A1 antibody in control serum sample (Con), GBM and present case. GBM: Glioblastoma-multiforme.

Table 2 Parameters evaluated in circulation (serum/plasma)

No.	Case/group	NLR	hTERT	YKL-40	TIMP-1	[1]IL-6	[2]HMGA1
1	Case	3.9	6.125	71.47	80	645.207	16.8
2	Control (n = 15)	1.6 (0.87-28)	1.14 (0.22-1.585)	18.3 (1.12-66.7)	23.7 (10.3-88.4)	48.9 (6.71-72.8)	-
3	GBM (n = 30)	5.58 (3.1-18)	2.18 (0.565-8.84)	101.2 (21.2-198.8)	93.8 (37.2-185.1)	197.6 (59.2-803.7)	30.613

[1]n = 15; hTERT, TIMP-1 and YKL-40, IL-6 quantified in ng/L, ng/mL and pg/mL respectively; [2]HMGA1 quantified in terms of protein band density. NLR: Neutrophil lymphocyte ratio; HMGA1: High mobility group-A1; hTERT: Human telomerase reverse transcriptase; IL-6: Interleukin-6; TIMP-1: Tissue inhibitor of metalloproteinases-1; YKL-40: Human chitinase-3-like-protein-1.

the prognostic significance of circulating molecular biomarkers: hTERT, HMGA1, IL-6, NLR, YKL-40, and TIMP-1 in a primary GBM with extended PFS of 12 mo.

On reviewing various recent studies on GBM, expression of these markers was seen to be linked to inflammation, increased cell proliferation and invasion, parameters that are directly associated with survival in this grade Ⅳ tumor. Molecular basis of cell proliferation is crucial for prognosis when dealing with this malignancy. Our results indicate that increased expression of hTERT in tissue and serum corresponds with GBM status, but are lower in the presented case than the threshold value of this maker in tissue and blood of reference GBM group (Supplementary Table S2) and thus may have contributed to the extended PFS seen in this case.

Experimental findings of a group working with prognosticators in GBM suggest that IL-6 expression is regulated by TERT status[18]. A parallel increase in values of IL-6 with that of hTERT (P = 0.0286) as evident from the reference GBM group, indicates that this inflammatory marker plays a key role in tumor progression and prognosis of GBM. The level of circulating IL-6 being less for our patient than the cut off value set for GBM, positively predicts a longer time to progression (Table 2, Supplementary Table S2). In accordance is a recent study by Hori and Sasayama[19] which correlates levels of IL-6 in cerebro-spinal fluid with PFS in glioblastoma.

The value of NLR (3.9) in this patient positively correlated with extended PFS. In agreement are studies on grade Ⅳ patients (glioblastoma) describing NLR ($\leqslant$ 4.73) to be significantly correlated with longer PFS[20,21].

Blood based studies determining the unfavourable prognostic markers in GBM point towards a positive correlation of lower levels YKL-40 with slow progression of the disease, but are limited in number. The plasma level of YKL-40 in this case was 71.47 ng/mL and TIMP1 plasma level corresponded to 80 ng/mL, values, which were within the range of the control group. In line with this observation, is the study of Hormigo *et al*[22], which also suggests that GBM patients with persistently normal values of YKL-40 have a longer overall survival as well as disease-free survival. However, no studies correlating levels of TIMP-1 with PFS are available in literature.

It can be inferred from the medical history of the case that tumor re-growth was initiated probably due to the stem cells that were left behind in the tumor mass during surgical intervention. At the molecular level, analysis is suggestive of tumor recurrence due to increased expression of HMGA1, a stemness marker. This can be distinctly linked to recurrence, as evident from IF based quantitative analysis and levels of expression of this protein in patient's serum (Tables 1 and 2). The results are corroborated by earlier studies, one, which showed a differential IHC expression of HMGA1 in patients with primary and recurrent GBM[23] and also with our previous study, which correlates HMGA1 expression to recurrence and survival [7].

In the present case, the level of all systemic molecular markers was lower than the median values of the GBM reference group which is concomitant with an extended PFS of this patient, than documented for GBM in literature. Establishing optimal cut off for threshold values of this blood-based marker panel with enhanced sensitivity and specificity (Supplementary Table S2,

Supplementary Figure S1) indicated that these markers were significantly associated with median survival (Supplementary Table S3, Supplementary Figure S2) in GBM. The current investigation thus provides experimental data-based evidence of the clinical utility of circulating plasma YKL-40, TIMP-1, IL-6 and NLR and serum hTERT and HMGA1 for monitoring primary GBM patients.

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COMMENTS

Case characteristics

A 45-year-old male presenting with features of progressive raised intracranial pressure and focal neurological deficits.

Clinical diagnosis

Intracranial space occupying lesion presenting with features of raised intracranial pressure and focal neurological deficits.

Differential diagnosis

Malignant glioma, metastasis.

Laboratory diagnosis

All labs were within normal limits.

Imaging diagnosis

Magnetic resonance imaging revealed heterogeneously enhancing variegated intensity lesion suggestive of malignant glioma.

Pathological diagnosis

Haematoxylin and eosin stained sections showed fragments of necrotic tissue and small fragments of neoplastic astrocytes moderate nuclear pleomorphism, high endothelial vessel proliferation, at places forming glomeruloid bodies. Peroxidase-immuno-histochemistry (IHC) was used to assess Ki-67, glial fibrillary acidic protein and immunofluorescence based IHC was used to evaluate IDH-1, p53, epidermal growth factor receptor, human telomerase reverse transcriptase (hTERT) and high mobility group-A1 (HMGA1).

Treatment

Near/sub-total excision of the tumor was done at initial resection. Concomitant chemo-radiotherapy followed.

Related reports

Predicting progression-free survival in glioblastoma-multiforme (GBM) based on histological findings has limitations and necessitates defining the GBM sub-type based on molecular markers, followed by systemic immunophenotypic signature for monitoring outcome in terms of survival.

Term explanation

hTERT is a ribonucleoprotein polymerase that maintains telomere ends with reverse transcriptase activity, its expression correlates with grade of malignancy. HMGA1 protein is an architectural transcription factor widely expressed during embryonic development and tumor progression. Neutrophil-lymphocyte ratio (NLR) is a marker of subclinical inflammation and a factor of poor prognosis in glioma. Human chitinase-3-like-protein-1 (YKL-40), an acute phase glycoprotein is secreted by activated macrophages and neutrophils in various cancers. Tissue inhibitor of metalloproteinases-1 (TIMP-1) glycoprotein is a natural inhibitor of the matrix metalloproteinases, a group of peptidases involved in degradation of the extracellular matrix. Interleukin 6 (IL-6) is an interleukin that is characterized as a regulator of immune and inflammatory responses and capable of crossing the blood-brain barrier.

Experiences and lessons

The current investigation provides experimental data-based evidence for systemic monitoring of disease progression in GBM in terms of the delineated immunophenotypic signature. Systemic expression of, plasma YKL-40, TIMP-1, IL-6 and NLR and serum hTERT, HMGA1; has clinical utility for predicting progression-free survival.

Peer-review

The case presented by Gandhi *et al*, is interesting, thoroughly studied and well documented.

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CASE REPORT

Ileocolic intussusception caused by a lipoma in an adult

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Author contributions: All authors were involved in the preparation of this manuscript; Lee DE was a major contributor in writing the manuscript; both authors read and approved the final manuscript; all authors read and approved this article.

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Informed consent statement: The patient involved in this study gave her verbal informed consent authorizing use and disclosure of her protected health information.

Conflict-of-interest statement: All the authors have no conflicts of interest to declare.

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Abstract

Intussusception is rarely observed in adults. Adult cases account for only 5% of all cases of intussusceptions and almost 1%-5% of bowel obstruction cases. The etiology, presentation and management of intussusception in adults are different from those in children. The clinical presentation in adults often includes nonspecific signs and symptoms, thereby complicating differential diagnosis from other causes of abdominal pain. We report a 29-year-old Asian woman who visited our emergency department with complaints of fever associated with epigastric pain since one day. Abdominal computed tomography demonstrated ileocolic intussusception, and laparoscopic small bowel luminal mass resection was performed. Histopathology report confirmed a 3.5 cm × 2.7 cm submucosal lipoma in the terminal ileum. Sufficient vigilance and appropriate investigations are important for prompt diagnosis and surgical referral of patients to enable favorable outcomes. A computed tomography scan can be a helpful modality in establishing a diagnosis.

Key words: Adult intussusception; ILeocolic; Laparoscopic surgery; Lipoma; Computed tomography

Core tip: Intussusception is rarely observed in adult patients. Adult clinical presentation is non-specific. A 29-year-old Asian female patient presented with a fever and abdominal pain. Abdominal computed tomography demonstrated ileocolic intussusception. A computed tomography scan can help diagnose ileocolic intussusception. Ileocolic intussusception should be considered as an infrequent cause of acute abdominal pain in adults.

Lee DE, Choe JY. Ileocolic intussusception caused by a lipoma in an adult. *World J Clin Cases* 2017; 5(6): 254-257 Available from: URL: http://www.wjgnet.com/2307-8960/full/v5/i6/254.htm DOI: http://dx.doi.org/10.12998/wjcc.v5.i6.254

INTRODUCTION

Intussusception of the bowel is defined as a condition in which a proximal bowel segment (intussusceptum) invaginates into an adjacent distal segment (intussuscipiens), thereby causing bowel obstruction[1]. Intussusception is a rare cause of abdominal pain in the adult population, accounting for only 1%-5% of all cases of intestinal obstructions and 5% of all cases of intussusception[2-4]. The clinical presentation in adults often includes nonspecific signs and symptoms, thereby complicating the differential diagnosis from other causes of abdominal pain. With early diagnosis, appropriate treatment including surgery can be performed. This has resulted in the mortality rate from intussusception being less than 1%[5]. We present a case of a 29-year-old Asian woman with ileocolic intussusception caused by a lipoma and resected by laparoscopy-assisted surgery.

CASE REPORT

A 29-year-old Asian woman was admitted to our emergency department (ED) with complaints of epigastric pain, nausea, fever and a chill that persisted for one day. One day previously, she presented to a regional emergency center with nausea, fever and a chill. She was diagnosed with viral enterocolitis and treated by intravenous hydration and antipyretics. Her symptoms progressively worsened despite consuming analgesics and she was admitted to our ED. She denied any history of diarrhea, melena, hematochezia, weight gain or loss and bowel habit change.

Her past medical history included gastric polypectomy in the previous year and a 3-cm lipoma in the colon, which was incidentally detected using colonoscopy. She was a non-smoker and denied alcohol use. In the ED, her blood pressure was 115/76 mmHg, her heart rate was 109 beats/min and her axillary temperature was 36.9 ℃. A physical examination revealed diffuse tenderness upon palpation, particularly in the epigastric area and right lower quadrant and normoactive bowel sounds. The other examination results were normal.

Initial laboratory data were significant for a white cell count of 11.34 × 10^9/L, with 93.7% neutrophils. The C-reactive protein (CRP) level was elevated at 8.21 mg/L (ref. < 0.5 mg/dL). The results of other blood tests and urine analysis were within normal ranges.

Plain abdominal radiography was performed and did not show signs of obstruction or perforation. A contrast-enhanced abdomen and pelvis computed tomography (CT) scan was performed, which revealed diffuse edematous wall thickening of the ascending and transverse colon, and the entrance of the ileal segment of the small intestines into the colon, thereby indicating ileocolic intussusception (Figure 1). The leading structure was a 27-mm fatty dense structure within the bowel lumen that was separate from the mesentery (Figure 2). The general surgery team was consulted and the patient underwent laparoscopic small bowel luminal mass resection on the third day following admission, which revealed intussusception for the ileum to the colon (Figure 3). The mass was located in the proximal 5 cm of the ileocecal valve and the surgeon found it on palpation during surgery. The histopathology report confirmed a 3.5 cm × 2.7 cm submucosal lipoma in the terminal ileum. The patient was discharged on the fifth postoperative day without complications. One week later, she visited the outpatient department and didn't complain any symptoms.

DISCUSSION

Intussusception is common in children and mainly in those under the age of three. Overall, the male-to-female ratio is approximately 3:1. With advancing age, the sexual difference becomes marked. In patients older than four years, the male-to-female ratio is 8:1[6,7]. The etiology, presentation and management of intussusception in adults are different from those of children. In children, intussusception is usually idiopathic or secondary to a viral illness. Furthermore, the ileocecal valve may be functioning as the lead point in ileocecal intussusception[8]. In the adult population, primary or idiopathic intussusception accounts for about 8%-20% of cases[9,10]. Secondary intussusception, which is more common in the adult population, is associated with a pathological lesion involving a lead point, which can be a benign polyp, enlarged mesenteric lymph node, lipoma, appendix, Meckel's diverticulum, or malignant tumors, such as lymphoma, gastrointestinal stromal tumor, primary or metastatic adenocarcinoma[4,10,11]. Lipomas may occur throughout the intestinal tract, but occur most frequently in the colon. Intussusception can be classified into four types depending on its location: (1) entero-enteric, or involving the small intestine; (2) colo-colic, or involving the large intestine; (3) ileo-colic, or involving the terminal ileum and ascending colon; and (4) ileo-cecal, or involving the ileo-cecal valve as the lead point[4,12].

Early diagnosis of adult intussusception is difficult because most cases present with non-specific signs and symptoms as well as have a chronic, sub-acute or acute course. The classic triad of intermittent abdominal pain, currant jelly stools, and a palpable tender mass seen in children is rarely present in adults. However, in adults, nausea, vomiting, gastrointestinal bleeding, changes in bowel habits and abdominal distension are more common[9,11]. Adult intussusceptions are detected using plain abdominal film, barium studies, colonoscopy, abdominal sonography, abdominal CT, angiography and magnetic resonance imaging[11,13,14]. Although there are

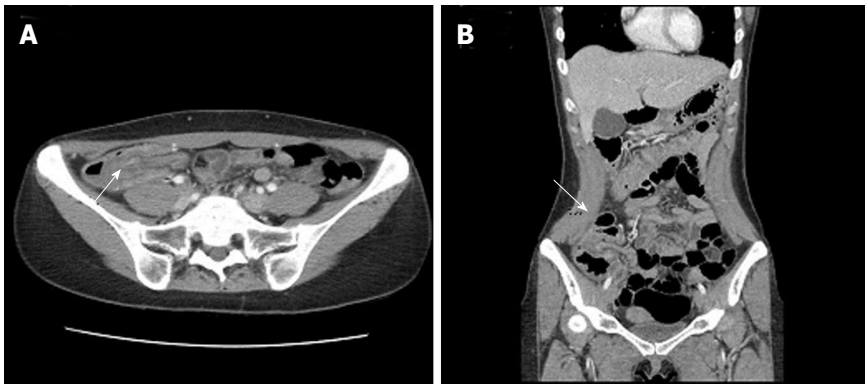

Figure 1 Axial (A) and coronal (B) view of abdominal computed tomography scans demonstrated an ileocolic intussusception with diffuse wall thickening of the ascending and transverse colon. The entrance of the ileal segment into the colon is shown (arrow).

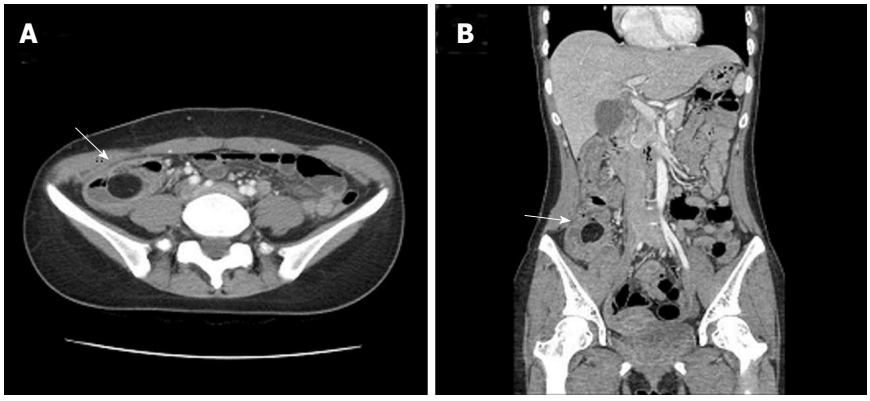

Figure 2 Axial (A) and coronal (B) plain abdominal computed tomography scans demonstrate a well-circumscribed, intraluminal hypodense mass with fat attenuation in the terminal ileum (arrow).

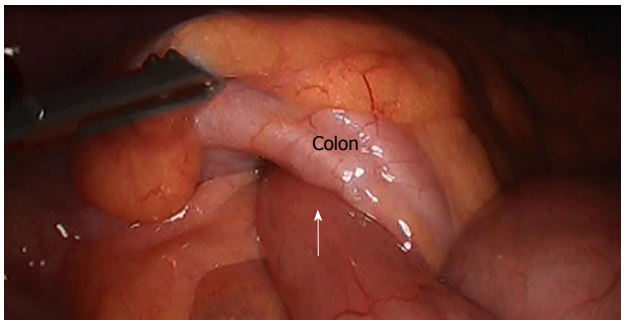

Figure 3 Laparoscopic view. The ileum was invaginated at the colon (arrow).

several diagnostic imaging techniques, as mentioned above, an abdominal CT scan is the most commonly used and accurate diagnostic modality[9,13-15]. CT shows "target" or "sausage"-shaped lesions, while also defining the location, nature and relationship of the lesion to surrounding tissues with an accuracy that ranges from 60% to 100%[3,9,13,15]. Abdominal ultrasonography has also been successful in diagnosing intussusception, especially if a palpable mass is found[16].

Adult intussusception is associated with a pathological lesion involving a lead point. Therefore, surgical intervention is mandatory. Most surgeons accept that adult intussusception requires surgical intervention because of the large proportion of structural anomalies and the high incidence of occurring malignancy[4].

Endoscopic resection has been reported, but it can result in unfavorable complications, including perforation or hemorrhage. Surgical resection is commonly recommended to remove the lead point, such as lipomas that are larger than 2-cm in diameter[17].

Emergency physicians and clinicians frequently face a patient complaining of abdominal pain. Ileocolic intussusception is a rare cause of abdominal pain in adults that can often be elusive due to the frequent lack of peritoneal irritation signs and specific symptoms. Complications associated with intussusception, which rarely occur when the diagnosis is prompt, include perforation during non-operative reduction, wound infection, sepsis from undetected peritonitis (which is a major complication that occurs following a missed diagnosis), necrosis and bowel perforation and recurrence. While intussusception itself has good prognosis, the main prognostic factor affecting the course of the disease is the nature of the causative lesion. Mortality for adult intussusception increases from 8.7% of cases with benign lesions to 52.4% of cases with malignant lesions[9].

A sufficient level of vigilance and appropriate investigations are important for a prompt diagnosis and

surgical referral of patients for a favorable outcome. In this case, we illustrate the importance of a thorough evaluation in patients with acute abdominal pain. In doing so, we highlight the diagnostic values of CT scanning and performing a complete ileocolonoscopy.

COMMENTS

Case characteristics

A 29-year-old Asian female presented to the authors' emergency department with complaints of epigastric pain, nausea, fever and a chill that persisted for one day.

Clinical diagnosis

Ileocolic intussusception.

Differential diagnosis

Acute enteritis, colitis, diverticulitis.

Laboratory diagnosis

Laboratory data were significant for a white cell count of 11.34 × 10^9/L, with 93.7% neutrophils and the C-reactive protein of 8.21 mg/L, respectively.

Imaging diagnosis

Computed tomography demonstrated ileocolic intussusception and a 27-mm fatty dense mass.

Pathological diagnosis

The histopathology report confirmed a 3.5 cm × 2.7 cm submucosal lipoma in the terminal ileum.

Treatment

Laparoscopic small bowel luminal mass resection was performed.

Related reports

There have been various case reports of intussusception in adult on this rare disease entity.

Experiences and lessons

Sufficient vigilance and appropriate investigations are important for prompt diagnosis and surgical referral of patients to enable favorable outcomes.

Peer-review

The case the authors reported was interesting.

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MINIREVIEWS

New device to implement the adenoma detection rate

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Abstract

It is well-known that colonoscopy is considered the gold standard for colon cancer prevention. Although performed by experienced endoscopists, the matter remains of polyps missed during this examination. The reasons may include the size, shape and location of the lesions. Many colorectal cancer screening programs have been proposed to increase the adenoma detection rate. The substantial difference between these methods is whether the improvement in vision, particularly the detection of irregularities of the mucosa, is inside the endoscope electronic components (magnification, wide-angle vision, narrow band imaging, flexible spectral imaging colour enhancement, i-Scan) or outside the same, by the use of specific caps (EndoCuff, EndoVision, EndoRings). Endocuff is a plastic device mounted at the end of the scope with a constant vision field of the entire colon. The aim of this study is to explore the potential clinical and technical benefits of Endocuff.

Key words: Adenoma detection rate; Cap-assisted colonoscopy; Colorectal cancer; Endocuff-assisted colonoscopy; Standard colonoscopies

Core tip: One of the main goals of colonoscopy screening is to identify polypoid lesions, which are precursors of colorectal cancer. Once identified, the polypoid lesions need to be removed whenever possible. Throughout the years, many prototypes of colonoscopes, magnification techniques, and different devices such as caps have been developed for colonoscopy screening. Endocuff is a new device used to improve adenoma detection rates during colonoscopy. Based on the findings of many studies, Endocuff seems to be of great help in increasing the detection of colonic polyps, with no significant complications associated with its use.

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ment the adenoma detection rate. *World J Clin Cases* 2017; 5(7): 258-263 Available from: URL: http://www.wjgnet.com/2307-8960/full/v5/i7/258.htm DOI: http://dx.doi.org/10.12998/wjcc.v5.i7.258

INTRODUCTION

Colorectal cancer (CRC) is one of the most frequently observed cancers, and screening programs, including the adenoma detection rate (ADR), play an important role in reducing its incidence. There are many screening methods such as withdrawal time and technique, second evaluation of the right colon, patient positional changes, gastrointestinal assistant participation during colonoscopy, water-aided technique, optimisation of bowel preparation, and antispasmodic administration[1].

Colonoscopy is globally recognised as the gold standard for CRC screening. A widely used indicator to emphasise "good colonoscopy" is the ADR, which refers to the number of patients out of every 100 undergoing first-time colonoscopy who have at least one adenoma removed[2]. Several studies showed that the prevalence of adenomas in asymptomatic adults vary from 25% to 40%[3-6]. Based on these findings, in 2014, a joint task force of the American College of Gastroenterology and the American Society of Gastrointestinal Endoscopy recommended an ADR benchmark of 25% for all patients (30% for men and 20% for women)[7]. ADR has been considered as the major quality measure predicting subsequent CRC incidence and mortality[8].

Over the years, several accessories have been developed in order to obtain a more accurate visualisation of the colon, facilitating and increasing the identification of polypoid lesions. Recently, one such new device called Endocuff has been developed.

The aim of this review is to identify the studies comparing Endocuff-assisted colonoscopy to standard colonoscopy considering the ADR as the end-point by searching through MEDLINE/PubMed and abstracts presented at international meetings, from January 2014 until January 2017. In particular, the following key-words were searched: "adenoma detection rate", "Endocuff" and "Endocuff-assisted colonoscopy".

TECHNICAL CHARACTERISTICS, METHODS OF USE AND INDICATIONS

The Endocuff™ Vision (ARC Medical Design and Norgine) is a new device created with the intent to improve the endoscopic view. It is a soft plastic cap of 2 cm in length, consisting of a cylindrical core in propylene endowed with small flexible finger-like projections made of a thermoplastic elastomer fixed to the core[9,10]. The first version of Endocuff™, dated in 2012 with the Food and Drug Administration approval, presented one proximal and one distal row of finger-like projections. On the contrary, the latest version, named Endocuff Vision™, has only one proximal row of more rounded finger-like projections in order to eliminate mucosal lacerations that were observed in the first model[11] (Figure 1). This device presents different colour-coded sizes (blue, green, purple, and orange) depending on the various colonoscopy compatible, both for paediatric than for adults instruments.

The device is for single use and is not recyclable. The usage is very simple, as it uses the distal end of the endoscope (Figure 2), which virtually coincides with the end of the tip of the colonoscope. Here, lubricants are not used due to their high risk of displacement from the scope during the procedure.

There are two principal indications for use: (1) keeping the suitable depth of endoscope's view field; and (2) helping the endoscope with being inserted into the gastrointestinal tract. During colon intubation, this accessory is practically invisible, and the projections do not interfere with the introduction. On the contrary, during the tool retraction, this device flattens folds, in particular of the sigmoid colon, and flexures of bowels (Figure 3).

Pioche *et al*[12] conducted a simulated pilot study which included an animal colorectal model used for learning and 32 endoscopists as follows, 16 Japanese and 16 visitors, in order to verify the Endocuoff's effectiveness in identifying the polypoid lesions. The model was specifically designed with the "packaging" of 13 polyps located in various locations, including those behind the folds. Endoscopists had a different degree of experience and worked randomly, either by performing standard colonoscopies (SC) or Endocuff-assisted colonoscopy (EAC). Their results showed that EAC detected more polyps compared to SC (mean lesions: 9.9 *vs* 7.5, $P = 0.03$) and that the use of this device was independent of the various endoscopic medical expertise levels[12].

CONTRAINDICATIONS

Reported contraindications in the usage of Endocuff Vision™ are: (1) known colonic strictures; and (2) active inflammatory disorders (acute infective colitis, colonic Crohn's disease, ulcerative colitis, and acute diverticulitis)[11]. Moreover, this device was not designed with the objective of deep ileal intubation, and it is strongly discouraged for complex sub-mucosal dissection (such as ESD, Endoscopic Submucosal resection).

ANALYSIS OF STUDIES AVAILABLE IN THE LITERATURE

The first report on the use of this accessory was

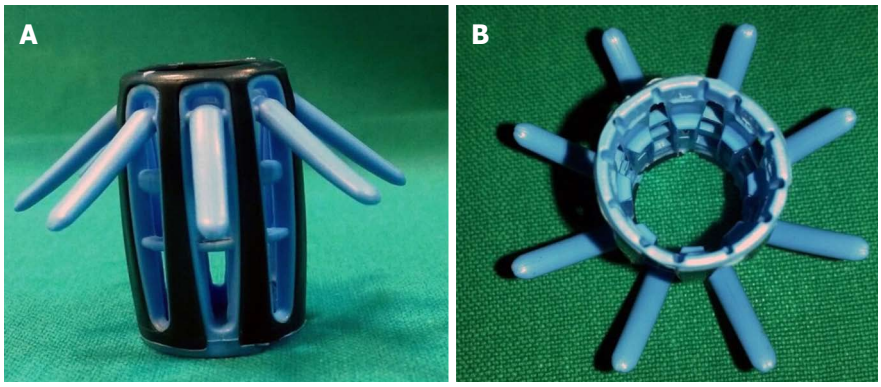

Figure 1 Endocuff's view: (A) lateral; (B) from above.

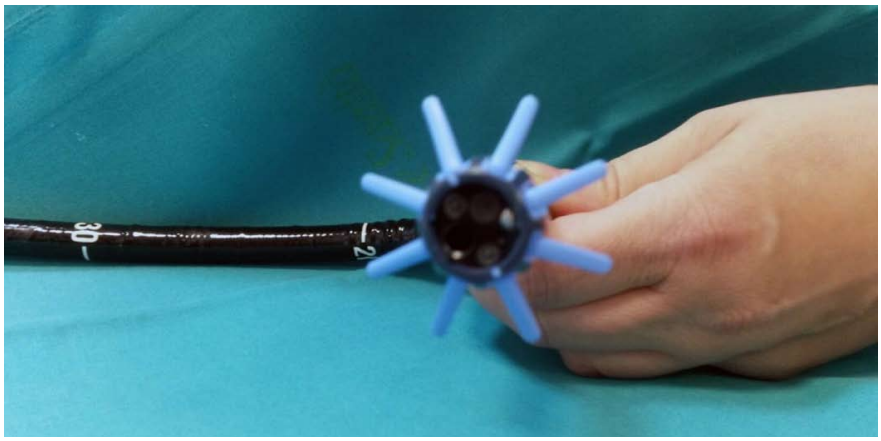

Figure 2 Endocuff Vision™ mounted at the tip of the colonoscope.

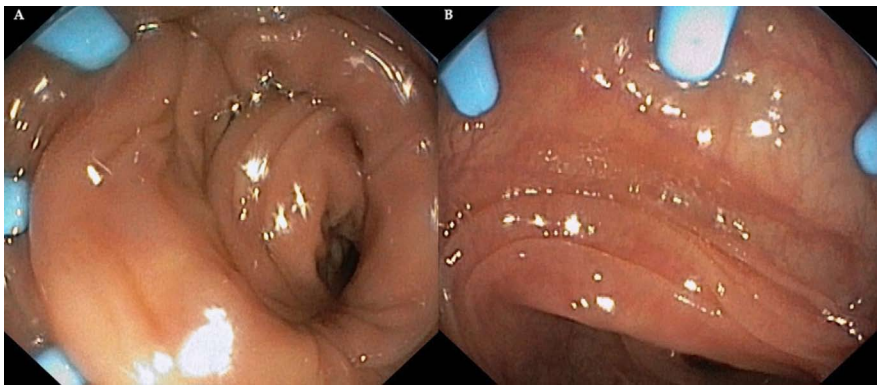

Figure 3 Endoscopic view of colonoscope retraction in which it's possible to note the flatting folds.

published in 2012 by Sanders and Tsiamoulos *et al*[9] of St Mark's Hospital in London. This was a single-centre, retrospective study with a small number of cases. The authors reported their experience with endoscopic cuff-assisted endoscopic mucosal resection (EMR) (5 patients) and control post scars-EMR (7 patients) for large flat/sessile sigmoid colon polyps. All the lesions were located in the sigmoid sigma, and no adverse events were seen.

Reviewed available studies focusing on EndoCuff-assisted colonoscopy are reported in Table 1. It was excluded from the analysis of the data, an ongoing study, promoted by Bevan *et al*[11]. It is a is a prospective, multicenter, randomised controlled trial comparing the ADR in patients undergoing EAC with SC. This study will be held at seven hospitals and will include the enrolment of 1772 patients[11].

REPORTED COMPLICATIONS

As observed in a recent meta-analysis[13], four studies[10,14,17,20] reported complication rates in the EC groups. The most frequent complication was superficial mucosal injury of negligible clinical significance that was found in 27 patients. Patient discomfort resulted in the removal of the cap in 23 cases, following which it was possible to complete the procedure. Another common complication was the loss of the device during the examination of 6 patients. In all these cases, the accessory was removed, and the study was complete. No perforations were reported[13]. Tsiamoulos *et al*[17] described elective removal in 4 cases due to sigmoid diverticulitis and 1 due to anal discomfort. Cattau *et al*[21] signalled one loss of the cap and one incomplete examination due to advanced diverticulosis. De Palma

Table 1 Studies focusing on EndoCuff-assisted colonoscopy

Ref.	Year	No. of patients (EAC)	No.of patients (SC)	Adenoma detection rate (%) (EAC)	Adenoma detection rate (%) (SC)	ADR significance
Floer *et al*[14]	2014	238	229	35.4	20.7	$P < 0.0001$
Lenze *et al*[15]	2014	50	//	34	//	//
Marsano *et al*[16]	2014	165	153	46.6	30	$P = 0.002$
Tsiamoulos *et al*[17]	2014	133	133 (pre-cuff period) 133 (post-cuff period)	68.98	55.13 61.74	//
Sawatzki *et al*[18]	2015	104	//	47	//	//
Chin *et al*[19]	2015	93	193	44.1	27.3	$P = 0.01$
Van Doorn *et al*[20]	2015	530	533	52	52	$P = 0.92$
Biecker *et al*[10]	2015	245	253	56	42	$P = 0.001$
Cattau *et al*[21]	2015	329	329	49.7	46.4	$P = 0.392$
Shah-Ghassemzadeh *et al*[22]	2015	219	230	62.1	49.13	$P = 0.0057$
Bhattacharyya *et al*[23]	2016	266	265	63	60.9	NS
Cavallaro *et al*[24]	2016	445	403	53	46	$P < 0.05$
De Palma *et al*[25]	2017	137	137	26.9	26.3	$P = 0.002$

EAC: Endocuff-assisted colonoscopy; SC: Standard colonoscopy; NS: Not significant; ADR: Adenoma detection rate.

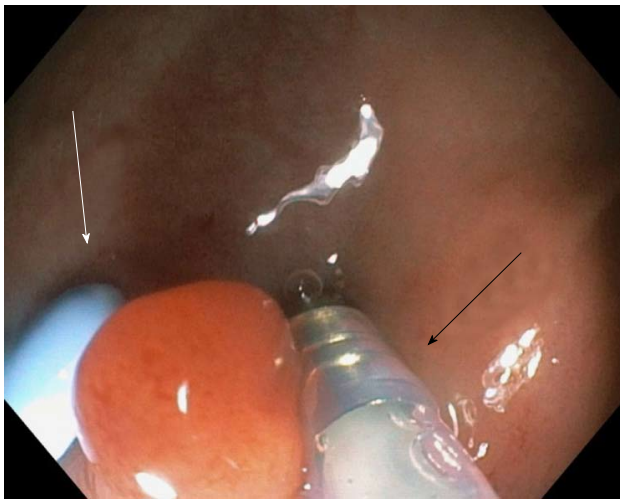

Figure 4 Endoscopic removal of a sessile polyp of the sigmoid colon, in which it's possible to see the Endocuff's flat (white arrow) and injection needle (22 G, Micro-Tech, Nanjing Co, Ltd) (black arrow).

et al[25] reported nine complications: 2 cases of device loss during the withdrawal and 7 cases of mucosal erosions, of which in 1 case was necessary sclerosis with adrenaline.

OUR INITIAL EXPERIENCE

The regional program for the CRC screening is operating at our Hospital. After the adhesion of the population to faecal occult blood test (FOBT), colonoscopy is mandatory. Colonoscopies, all conducted until the cecum, were performed using Endocuff Vision™ by expert operators with conventional colonoscopes (CF-Q165L, CF-H1285L, Olympus Optical, Hamburg, Germany). The bowel preparations used were the standard large-volume polyethylene glycol electrolyte solutions prepared the previous day or the split-dose regimens, depending on the time of the examination. Thirty patients (F 18, M 12) with a mean age of 67 years (range: 50-75 years), who underwent first-time screening colonoscopy, were studied. A total of 45 polyps were removed, 36 sessile (80%) and 9 pedunculated (20%). The sigma was involved in nearly half of the cases (45.7%). During our initial experience, we found polypoid lesions localised especially in the sigmoid colon that could be easily removed (Figure 4). No major adverse events were recorded, except for two cases of superficial "scratch-like" mucosal lesions of no clinical significance that occurred in the case of rigid colon due to inflammation (mild diverticulitis).

CONCLUSION

Prompt diagnosis of precancerous polyps during colonoscopy is extremely important in order to reduce CRC rate, especially in asymptomatic patients. During colonoscopy, the rate of colonic polyps missed varies from 6% to 27%[26]. It is known that the most effective way to estimate the adenoma miss rate, and consequently improve the ADR, is represented by the "back-to-back colonoscopy" technique performed in two consecutive same-day procedures in the same patient[27]. However, we cannot ignore this may double the potential complications, such as the risk of perforation.

The first study of this method using EndoCuff has been conducted by De Palma *et al*[25] in a single-centre randomised back-to-back-study. The participants underwent two colonoscopies, with and without the use of the device. The authors concluded that these kinds of examinations allow finding lesions missed by other procedures, but on the other hand, a limitation raised being the endoscopists not blinded for the presence of Endocuff[25]. From these studies emerge that the use of transparent plastic caps attached to the tip of the colonoscope can increase the ADR, with a mechanical mechanism of flattening the folds and the consequent increase of the visual field. This technique is known as cap-assisted colonoscopy (CAC). However,

several works show conflicting results with respect to improvement in adenoma detection by CAC. In particular, the ADR was not significantly improved in 6 studies analysed in a meta-analysis including 16 RCTs that compared CAC to standard colonoscopy[28].

As for the CAP, our results were not in agreement in defining the EAC superiority over SC. In fact, in three studies, there was no statistical significance between the two groups (EAC *vs* SC)[20,21,23]. As the Table 1 shows, this device can enhance the ADR.

The most frequently observed complication was the removal of Endocuff's due to the discomfort of the patient (24 times), followed by the loss of the device during the examination (9 times). No major complications were reported.

In Italy, CRC is one of the most frequently found cancers. At our local hospital, we started regional screening program for this kind of tumor from January 2012 onwards. In our country, the device has been registered in the database of medical devices of the Ministry of Health on January 29, 2016[29].

Our early experiences with EAC on a small population show that Endocuff can identify and facilitate polypectomy, especially in floppy folds of sigma, allowing better stabilization of endoscope in front of the polyp. Among 30 patients, we found 2 cases (6.6%) of insignificant superficial mucosal lacerations, probably related to the lack of experience with this accessory.

Some major limitations are represented by special circumstances such as sub-colonic strictures and acute inflammation of the mucosa (diverticulitis and inflammatory bowel diseases).

Unfortunately, when a person is subjected to colonoscopy for the first time, it is impossible to know any underlying diseases. Therefore, in some cases, it becomes necessary to remove the device in order to complete the procedure safely.

In conclusion, the results of EAC are still evolving. This accessory appears safe and useful in increasing the detection of the number of polyps and subsequently, the detection rate of adenomas. We recommend that Endocuff should be further investigated in other larger trials.

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MINIREVIEWS

Screening of celiac disease in Down syndrome - Old and new dilemmas

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Abstract

Celiac disease (CD) is a common and well defined autoimmune disorder caused by gliadin and related proteins of wheat, rye, and barley. Epidemiologic studies confirmed that CD is highly associated with other autoimmune diseases and with Down syndrome (DS). The symptomatic form of CD in patients with DS is more frequent than asymptomatic forms. However, growth impairment, anemia, intermittent diarrhea, and constipation are symptoms and signs typically of children with DS without CD. Late identification of the disease can lead to various complications, sometimes even very severe. Therefore, systematic screening for CD is essential in the management of children and adolescents with DS. Many medical organizations recommend screening in this group of patients. However, current policy statements vary in their recommendations for screening and there is still a need for establishing uniform diagnostic criteria.

Key words: Down syndrome; Celiac disease; Children; Screening; Practice guideline

Core tip: Celiac disease (CD) is more common in children with Down syndrome (DS) than in general population. Recommendations for screening for DS and CD remain controversial and we still lack standard evidence-based guidelines. This review, based on existing reports, indicates the need for establishing uniform and immediately applicable diagnostic criteria.

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INTRODUCTION

Down syndrome (DS) is a chromosomal disorder caused by trisomy and other aberrations of chromosome 21[1]. This syndrome was first described by Langdon

Down[2] in 1886, while in 1959, French pediatrician and geneticist. Lejeune published a paper in which he identified trisomy 21 as its genetic cause[3]. It occurs with a prevalence of 1:733, therefore representing the most common chromosomal disorder and one of the leading causes of mental retardation[4]. DS is characterized by many typical somatic and visceral malformations. People with this syndrome are prone to autoimmune and other diseases, such as hearing and vision problems, immune dysfunction, obstructive sleep apnea, Alzheimer disease-like dementia, megakaryoblastic leukemia, hypothyroidism, diabetes mellitus (DM), and celiac disease (CD)[1,4].

CD is an autoimmune disorder induced by gluten-containing food from seeds of wheat, rye, and barley[5]. It can develop at any age as a result of an inherited (polygenic) disposition and exposure to gluten. Research carried out during the last two decades has shown that a central role in the occurrence of the disease is played by MHC class Ⅱ HLA antigens: HLA-DQ2 and HLA-DQ8[6]. The absence of HLA-DQ2 and HLA-DQ8 has a strong negative predictive value for CD[7]. Therefore, the question remains, why only a small percent of patients develops CD while approximately 40% of the population carries HLA-DQ2/DQ8 alleles and is exposed to gluten without developing a disease.

Even though enteropathy is the primary characteristic of the disease, CD may involve other extraintestinal organs[8]. Based on clinical, serological and histological variations, CD may be classified into two basic types: symptomatic and asymptomatic. Within symptomatic form of the disease, there are forms with classical and atypical clinical picture[9]. Classical form of CD occurs in infants and toddlers (9-36 mo) and it is characterized by gradual, rarely sudden onset of the disease. It is presented with a chronic diarrheal disorder, anorexia, vomiting, abdominal distension and pain, and in the most severe cases, with celiac crisis[10]. In the past two decades, the classical clinical manifestations in patients became less common, and we can see the emergence of a growing number of cases with the atypical form of CD (1:8 in general population)[11]. Among adolescents and adults, disease presents in atypical form, with absent or mild gastrointestinal symptoms, and with more common extraintestinal manifestations, such as sideropenic anemia resistant to oral therapy with iron, delay in longitudinal growth, marked thinness, chronic fatigue, osteopenia and osteoporosis, enamel hypoplasia, arthralgia, myalgia, epilepsy, ataxia, polyneuropathy, vitiligo, alopecia, dermatitis herpetiformis, *etc*[12].

Autoimmune diseases are ten times more common in patients with CD compared to general population. Such diseases include type 1 DM, autoimmune thyroid disease, Sjögren's syndrome, Addison's disease, chronic active hepatitis (elevated transaminases), primary biliary cirrhosis, IgA nephropathy, and juvenile chronic arthritis. Almost the same prevalence of the disease is also found in some chromosomal aberration disorders, such as Turner syndrome, Williams syndrome, and DS[13,14].

Diagnosis of CD is based on histological analysis of duodenal biopsies, HLA testing for HLA-DQ2 and HLA-DQ8, and detection of specific autoantibodies (mostly immunoglobulin A tissue transglutaminase - anti-TG2 and/or anti-endomysial antibodies - EMA). Gliadin antibody test and IgG class anti-TG2 antibody does not have the same specificity and clinical relevance. Use of a gluten-free diet is an effective treatment for CD as it has been shown to decrease the severity of clinical symptoms and reduce the risk of complications[6-8,15].

CD AND DS

Association between CD and DS was first described in 1975, by Bentley *et al*[16]. Since then, many papers were published in Europe, reporting the prevalence of CD in DS patients to be from 0-18.6%[17-28] (Figure 1), which is far more prevalent than CD in general population (1% in Western countries)[29].

Similar prevalence of CD among DS patients were found in the United States - 3.8% and 10.3%[30,31], Australia 3.9%[32], Argentina - 3.6%[33], and Brazil - 5.6%[34]. The reported rates are probably overestimated because most of the authors did not perform small bowel biopsy in all DS patients with positive serology[20,23,25-27,31-34]. Variability in prevalence may have been caused by differences in type of antibody used for screening, different cohort sizes (25-1453), variable age stratification and applied criteria for CD diagnosis. Most of the studies were conducted on patients receiving care from local medical centers, and only a few studies were conducted at the level of the region or a country[18,20,24,32]. Furthermore, in the majority of children, the authors did not perform testing for HLA-DQ2 and HLA-DQ8 recommended by European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) criteria[15].

In their study, Pavlovic *et al*[17] did not find CD in any of 82 children with DS. This can be explained by age of children (8 mo to 8.6 years), but further serological monitoring of these children would probably show the presence of the disease in this group of patients. Higher prevalence was found only in two previous smaller series from Sweden; Jansson and Johansson[23] screened 65 DS patients and they found CD prevalence of 16.9% while Carlsson *et al*[24] reported the similar prevalence of 18.6% (8/43). These regional differences raise the question about the relationship of environmental factors and ethnic influence.

Compared to the general population, the symptomatic form of CD is more frequent in DS children than asymptomatic form[35]. However, about one-third of DS patients with CD have no gastrointestinal symptoms[20]. In children with DS and symptomatic form of CD, growth failure, anemia, intermittent diarrhea, vomiting, and constipation are described as the most common manifestations of the disease[36]. Their significance

Figure 1 Prevalence of celiac disease in children with Down syndrome in Europe.

in clinical practice is not entirely obvious, bearing in mind the occurrence of the same symptoms and signs in children with DS, but without CD. Because of intellectual disability, DS patients may also be unable to accurately describe their symptoms. Growth failure as the manifestation of CD has little significance in children with DS, considering that the associated malformations, such as congenital heart defects and hypothyroidism, may also have the same effect[37]. Late identification or missed diagnosis of CD in DS patients can lead to failure to thrive, anemia, osteoporosis, and lymphoma[14,15].

WHEN AND HOW SHOULD WE SCREEN?

The screening is planned on the basis of prevalence of the disease, sensitivity and specificity of tests, complications or comorbidities of the disease, effectiveness of the therapy (gluten-free diet), and costs. Swigonski *et al*[38] believe that the consistent use of serological screening for CD might not be entirely justified, primarily for economic reasons. Kolek *et al*[19] suggest CD screening only in patients with symptoms (loose stool, constipation, abdominal discomfort), but not in patients without symptoms. Mackey *et al*[39] suggested routine follow-up testing at least every 3 years for all children with DS, and yearly CD screening for patients who are serology positive and biopsy-negative.

Despite some common diseases associated with DS have clear screening guidelines, *e.g.*, thyroid function, screening for CD remains controversial still lacking standard evidence-based guidelines (Table 1).

The healthcare guidelines for patients with DS developed by the American Academy of Pediatrics (AAP)[40] published in 2001 and Down's Syndrome Medical Interest Group United Kingdom and Ireland[41] did not made any recommendations for CD screening, even though they advised thyroid screening tests annually (risk of thyroid disease is 15%). Ten years later, AAP changed its position and advised screening for CD in the presence of symptoms, such as protracted constipation, slow growth, unexplained failure to thrive and anemia[42]. American Gastroenterological Association suggested that antibodies testing for CD is justified in patients with symptoms, but not those without symptoms and that HLA testing is appropriate only when the diagnosis based on other tests is not clear[44]. The recent recommendations by National Institute for Health and Care Excellence consider serological testing for CD in DS patients with IgA anti-TG2 as the first line of screening, and IgA EMA only if IgA anti-TG2 is weakly positive[45]. These recommendations do not imply HLA testing in the initial diagnosis of CD. The European Down Syndrome Association recommends blood tests for anemia, thyroid disease, CD and autoim-

Table 1 Health care guidelines for people with Down syndrome

Association	Screening for other diseases	CD screening	CD antibodies	Further CD antibodies testing	HLA testing
United Kingdom Down's Syndrome Medical Interest Group[41]	Thyroid function	No	No	No	No
American Academy of Pediatrics[42]	Thyroid function, anemia	Symptomatic patients	IgA, IgA anti-TG2	No	No
American Family Physician[43]	Thyroid function, diabetes mellitus	Not for adult	No	No	No
American Gastroenterological Association[44]		Symptomatic patients	IgA anti-TG2, IgA EMA	No	If other tests is not clear
National Institute for Health and Care Excellence[45]		In all patients	IgA anti-TG2	No	No
European Down Syndrome Association[46]	Thyroid function, anemia, immunological defects	In all patients	IgG, IgA AGA, IgA anti-TG2, IgA EMA	Annually	No
Down's Syndrome Medical Interest Group[47]	Thyroid function	At 2-3 yr in all patients	IgA EMA	No	No
North American Society for Pediatric Gastroenterology, Hepatology and Nutrition[48]		After 3 yr in all patients	IgA, IgA anti-TG2	Some years	If IgA anti-TG2 negative
European Society for Pediatric Gastroenterology, Hepatology and Nutrition[15]		After 2 yr in all patients	IgA anti-TG2 if HLA positive	Every 2 to 3 yr in DQ2 or DQ8 positive children	Yes

CD: Celiac disease; EMA: Antiendomisium antibodies; AGA: Antigliadin antibodies; anti-TG2: Tissue transglutaminase antibodies; IgA: Immunoglobulin A; IgG: Immunoglobulin G.

mune disorders at 12 mo, and yearly thereafter, until old age in all patients[46]. The Down's Syndrome Medical Interest group[47] recommends lifetime annual thyroid screening, and one-time screening for CD between ages 2 and 3, although North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) reports that the youngest child with both DS and CD diagnosed through screening was 3.2 years old. On the other hand, NASPGHAN has suggested that CD screening of children with DS once in a lifetime is not enough and that periodic screening should be done[48]. Finally, according to the latest recommendations of the ESPGHAN from 2012, human leukocyte antigen HLA-DQ2 and HLA-DQ8 typing should be the first line of screening[15]. In patients who are HLA-DQ2 and HLA-DQ8 negative, further serological testing is unnecessary. If the patient is DQ8 and/or DQ2 positive, then an anti-TG2 IgA test and total IgA determination should be performed. If antibodies are negative, repeated testing for CD-specific antibodies is recommended every 2 to 3 years. Although HLA typing is relatively expensive and not always feasible, finally, it likely seems to be a cost-effective procedure because the significant proportion of patients can be excluded from further antibodies testing.

CONCLUSION

DS patients have increased the risk of congenital malformations and a higher incidence of CD. Current evidence has important implications to support obligatory screening for CD in DS patients. Currently, many policy statements vary in their recommendations, and there is a need for further harmonization. The strategy should aim at early diagnosis and treatment of the condition in order to prevent the development of osteoporosis and lymphoma, as the most severe complication of this disease.

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MINIREVIEWS

Practical approach to the patient with acute neuromuscular weakness

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Abstract

Acute neuromuscular paralysis (ANMP) is a clinical syndrome characterized by rapid onset muscle weakness progressing to maximum severity within several days to weeks (less than 4 wk). Bulbar and respiratory muscle weakness may or may not be present. It is a common neurological emergency which requires immediate and careful investigations to determine the etiology because accurate diagnosis has significant impact on therapy and prognosis. Respiratory failure caused by neuromuscular weakness is considered as more critical than lung disease because its development may be insidious or subtle until sudden decompensation leads to life threatening hypoxia. Also, the arterial blood gas finding of severe hypoxemia, hypercapnia, and acidosis may not be apparent until respiratory failure is profound. Hence, the requirement for respiratory assistance should also be intensively and promptly investigated in all patients with neuromuscular disease. The disorder is classified based on the site of defect in motor unit pathway, *i.e.*, anterior horn cells, nerve root, peripheral nerve, neuromuscular junction or muscle. Identification of the cause is primarily based on a good medical history and detailed clinical examination supplemented with neurophysiologic investigations and sometimes few specific laboratory tests. Medical history and neurological examination should be focused on the onset, progression, pattern and severity of muscle weakness as well as cranial nerves testing and tests for autonomic dysfunction. Associated non neurological features like fever, rash or other skin lesions etc. should also be noted. Globally, Guillain-Barré syndrome is the most frequent cause of ANMP and accounts for the majority of cases of respiratory muscles weakness associated with neuromuscular disorders. Newly acquired neuromuscular weakness in intensive care unit patients consist of critical illness polyneuropathy, critical illness myopathy and drug induced neuromuscular weakness which may arise as a consequence of sepsis, multi-organ failure, and exposure to certain medications like intravenous corticosteroids and neuromuscular blocking agents.

Key words: Neuromuscular weakness; Paralysis; Approach; Nerve; Muscle

Core tip: Acute neuromuscular paralysis is a clinical syndrome characterized by rapid onset muscle weakness progressing to maximum severity within several days to weeks. It is a neurological emergency which requires immediate and careful investigations to determine the etiology because accurate diagnosis has significant impact on therapy and prognosis. Disorder is classified based on the site of defect in motor unit pathway, *i.e.*, anterior horn cells, nerve root, peripheral nerve, neuromuscular junction or muscle. Identification of the cause is primarily based on a good medical history and detailed clinical examination supplemented with neurophysiologic investigations and sometimes few specific laboratory tests. Medical history and neurological examination should be focused on the onset, progression, pattern and severity of muscle weakness as well as cranial nerves testing and tests for autonomic dysfunction.

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INTRODUCTION

Acute neuromuscular paralysis (ANMP) is a common neurological emergency and can be defined as a clinical syndrome characterized by rapid onset muscle weakness progressing to maximum severity within several days to weeks (less than 4 wk)[1,2]. ANMP carries high mortality when it leads to bulbar palsy, respiratory muscle weakness or autonomic dysfunction. The disorder is caused by defect somewhere in the pathway of motor unit (MU), *i.e.*, anterior horn cells, nerve root, peripheral nerve, neuromuscular junction or muscle (Figure 1). Immediate and careful evaluation to determine the etiology is crucial as the accurate diagnosis has significant implications on management and prognosis. Identification of the cause is primarily based on a good medical history and detailed clinical examination supplemented with neurophysiologic investigations and sometimes few specific laboratory tests.

The requirement for respiratory assistance should also be intensively and promptly investigated in patients with neuromuscular disease. Respiratory failure caused by neuromuscular weakness is considered as more critical than lung disease because its development may be insidious or subtle until sudden decompensation leads to life threatening hypoxia[2,3]. Also, the arterial blood gas finding of severe hypoxemia, hypercapnia, and acidosis may not be apparent until respiratory failure is profound[2,3].

Globally, Guillain-Barré syndrome (GBS) is the most frequent cause of ANMP and accounts for the majority of cases of respiratory muscles weakness associated with neuromuscular disorders[3-5]. Newly acquired neuromuscular weakness in intensive care unit (ICU) patients consist of critical illness polyneuropathy (CIP), critical illness myopathy and drug induced neuromuscular weakness which may arise as a consequence of sepsis, multi-organ failure, and exposure to certain medications like intravenous corticosteroids and neuromuscular blocking agents[1,2,6]. The disorders under the spectrum of ANMP are wide and based on the site of MU affection, ANMP can be classified as anterior horn cell disorder, polyradiculoneuropathy, peripheral neuropathy, disorders of myoneural junction and primary muscle diseases (Table 1).

Table 1 Differential diagnosis of acute neuromuscular paralysis

Anterior horn cell disorders
Poliomyelitis
West Nile virus
Peripheral neuropathy/polyradiculopathy
GBS
Porphyria
Diptheria
CMV polyradiculopathy
Lyme neuroborreliosis
Toxins (heavy metals, *e.g.*, arsenic, mercury, hexacarbon, drug intoxication, organophosphate, Buckthorn)
Critical illness polyneuropathy
Tick paralysis
Vasculitic neuropathy
Neuromuscular junction disorder
MG
Lambert-Eaton syndrome
Neuroparalytic envenomation (*e.g.*, tick and snake bites)
Botulism
Organophosphate and carbamate
Hypermagnesemia
Prolonged neuromuscular blockade
Overdose of anticholinesterases
Muscle disease
Periodic paralysis (hypokalemic: Hereditary and secondary, hyperkalemic)
Hypophosphatemia
Critical illness myopathy
Polymyositis, dermatomyositis, infectious myositis (*e.g.*, dengue myositis)
Acute rhabdomyolysis

Adapted from Maramattom *et al*[2]. GBS: Guillain-Barré syndrome; CMV: Cytomegalovirus; MG: Myasthenia gravis.

ANTERIOR HORN CELL DISORDER

Polio virus and West Nile virus (WNV) infections are two important causes of infection-associated acute muscular paralysis that primarily affect anterior horn cells. Poliovirus poliomyelitis is no longer prevalent nowadays. Afghanistan and Pakistan are two polio endemic countries[7-9]. WNV introduced to the United States in 1999 and has become endemic in North America and emerged as the commonest cause of epidemic meningoencephalitis. Presently, WNV is the leading cause of arboviral encephalitis in the United States[10].

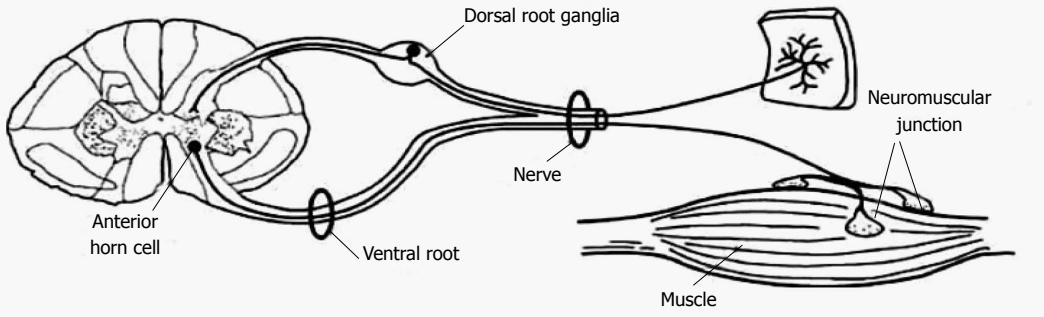

Figure 1 Schematic diagram showing the motor unit pathway.

Polio virus poliomyelitis

Poliomyelitis is a highly infectious disease caused by a virus belonging to the Picornaviridae family[9]. The clinical manifestations are varied, ranging from mild cases of respiratory symptoms, gastroenteritis, and malaise to severe forms of paralysis. These have been categorized into asymptomatic cases (90%-95%), mild illness or abortive poliomyelitis (4%-8%), aseptic meningitis (1%-5%), and paralytic poliomyelitis (0.1%-2%)[9]. Paralytic poliomyelitis is the most severe form presents as excruciating episodes of pain in back and limbs followed by motor weakness[9]. Weakness is rapid or gradual, asymmetric, predominantly proximal, and most commonly involves legs followed by the arms, abdominal, thoracic or even bulbar muscles. Respiratory failure may ensue in some patients either due to medullary involvement or phrenic or intercostal nerve paralysis[10]. Recovery may be complete in some patients but if the motor weakness persists beyond one year, lifelong disability occurs.

WNV associated paralysis

Acute, flaccid, and asymmetric motor weakness mimicking poliovirus may occur due to WNV[10]. Approximately 80% of WNV infections are asymptomatic, and 20% result in a self-limited disease referred to as West Nile fever. Less than 1% of patients develop neuroinvasive disease including meningitis, encephalitis, and acute flaccid paralysis or poliomyelitis[10]. As in poliovirus poliomyelitis, bulbar and respiratory muscles involvement may occur. Although anterior horn cells are primarily get affected, inflammatory changes may also involve muscles, peripheral nerves, spinal roots, spinal sympathetic neurons and ganglia. Rarely, WNV has been associated with demyelinating polyneuropathy similar to GBS.

The occurrence of meningoencephalitis, asymmetric pattern of weakness, normal sensory examination, lymphocytic pleocytosis in the cerebrospinal fluid (CSF) and reduced or absent compound muscle action potentials (CMAPs), preserved sensory nerve action potentials (SNAPs), and neurogenic electromyography (EMG) in a segmental pattern are core features that distinguish poliovirus or WNV paralysis from GBS[9]. Diagnosis is confirmed by detection of WNV-specific IgM antibody in CSF and serum nucleic acid amplification test is required in immunocompromised patients when antibody development is delayed or absent[9]. There is no specific treatment available for poliovirus and WNV poliomyelitis and management is primarily supportive care[10].

PERIPHERAL NEUROPATHY AND POLYRADICULONEUROPATHY

GBS

GBS is the most common and potentially life-threatening acute paralytic neuropathy worldwide with the reported annual incidence rate of 1-2 cases per 100000[11]. It is an acute-onset, rapidly progressive, immune-mediated symmetrical polyneuropathy with or without respiratory muscle involvement that often follows an antecedent infection. Two thirds of cases are usually preceded by systemic infection like upper respiratory tract infection or diarrhea[12]. *Campylobacter jejuni* is the most frequent antecedent infectious agent associated with subsequent development of the Guillain-Barré syndrome[13]. Epstein Barr virus, Cytomegalovirus (CMV), Mycoplasma, Human immunodeficiency virus are other common infectious agents that have been linked to GBS[13,14]. Studies have also documented the occurrence of GBS shortly after vaccinations or surgical procedures. Molecular mimicry between infectious antigen and surface components of peripheral nerve leads to activation of humoral and complement activation with membrane attack complex formation and nerve damage is the most accepted pathogenesis of disorder[15].

Any patient developing rapidly progressive, symmetrical limb weakness with/without sensory disturbances, hyporeflexia or areflexia and albuminocytological dissociation in CSF should first raise the diagnostic possibility of GBS. Neurological examination demonstrates proximal and often distal muscle involvement or sometimes limb weakness is global-both proximal and distal. Numbness, paresthesia and pain in the limbs are usual initial symptoms of GBS. The weakness progresses over a period of 12 h to 28 d before a plateau is reached and 80%-90% of patients with GBS become non-ambulatory during the

Table 2 Diagnostic criteria for Guillain-Barré syndrome

Features required for diagnosis
Progressive weakness in both arms and legs
Areflexia or hyporeflexia
Features that strongly support the diagnosis
Progressive motor weakness up to 4 wk
Relative symmetry of symptoms
Mild sensory involvement
Cranial nerve involvement, especially bilateral facial Weakness
Autonomic dysfunction
Pain
Albuminocytological dissociation in CSF
Electrodiagnostic features of demyelination
Features that should raise doubt about the diagnosis
Respiratory failure with limited weakness of limbs at onset
Severe sensory signs at onset
Bladder or bowel dysfunction at onset and persistence of dysfunction in the disease course
Fever at onset
Sharp sensory level
Slow progression with limited weakness without Respiratory involvement
Persistent asymmetry of motor weakness
Mono/polymorphonuclear leukocytosis in CSF

Adapted from Asbury *et al*[14]. CSF: Cerebrospinal fluid.

Table 3 Guillain-Barré syndrome Disability score[17]

0 Healthy state
1 Minor symptoms and capable of running
2 Able to walk 10 m or more without assistance but unable to run
3 Able to walk 10 m across an open space with help
4 Bedridden or chair bound
5 Requiring assisted ventilation for at least part of the day
6 Dead

illness[16]. Patients then have slow recovery phase that varies from weeks to months. Diagnostic criteria for the diagnosis of GBS as suggested by Asbury *et al*[14] and GBS Disability score are provided in Tables 2 and 3 respectively[14,17].

Respiratory insufficiency occurs in 25% of patients, and major complications, including pneumonia, sepsis, pulmonary embolism, and gastrointestinal bleeding, autonomic dysfunctions develop in 60% of mechanically ventilated patients[18]. Among the cranial nerves, the facial nerves are most commonly affected followed by bulbar and ocular motor nerves. Despite the appropriate treatment, mortality occurs in 4%-15% of cases and about 20% of severely-affected patients remain non-ambulatory after 6 mo of symptoms onset[18].

Based on the electrophysiological and pathological studies, GBS is classified into axonal and demyelinating subtypes[16,18]. Acute inflammatory demyelinating polyneuropathy is the most common GBS subtype, which is characterized pathologically by demyelination, lymphocytic infiltration, and macrophage-mediated clearance of myelin. The two axonal variant of GBS are acute motor axonal neuropathy (AMAN), characterized by pure motor neurological deficit, and acute motor sensory axonal neuropathy in which sensory fibers are also involved. However, detailed studies have suggested that mild sensory changes may occur in some patients with AMAN. The Miller Fisher syndrome is the least common type of GBS and appears to be more common among peoples who live in eastern Asia. It is characterized by a triad of ophthalmoplegia, ataxia, and areflexia. Facial and lower cranial nerve involvement, limb weakness, respiratory failure, and mild sensory involvement may occur in various combinations[16,18].

CSF examination in GBS typically reveals increased protein with normal CSF leukocyte count and termed as albumino-cytological dissociation. The protein concentrations are often normal in the first week, but increased in more than 90% of the patients at the end of the second week[16,18]. Increased CSF leukocyte count should raise the possibility of illness like leptomeningeal malignancy, Lyme's disease, WNV infection, HIV-related GBS, or poliomyelitis[18,19]. Electrophysiological studies have an important role in disease confirmation, subtype classification, and prognostication. Nerve conduction study of at least 4 motor nerves, at least 3 sensory nerves, F waves, and H reflexes provide sufficient electrodiagnostic information for the diagnosis of GBS[16,18]. Nerve conduction studies often reveal evidence of patchy demyelination, manifested as conduction block, slowed motor conduction velocities, prolonged distal latencies, and temporal dispersion of CMAPs (Figure 2). Similar to CSF analysis, electrodiagnostic testing may be entirely normal in the early phase of GBS. Inconsistent or absent F wave, prolonged F wave and distal motor latencies, reduced nerve conduction velocities, absent H response and abnormal upper extremity SNAP combined with a normal sural SNAP are the characteristic electrophysiological findings in early GBS[16,18].

Immunological treatment along with meticulous supportive care to prevent or manage complications is required[19-21]. Frequent monitoring of respiratory function by measurement of vital capacity, cardiac and hemodynamic monitoring, prophylaxis for deep vein thrombosis, management of bladder and bowel dysfunction, early initiation of physiotherapy, and pain management should be done. Intravenous immunoglobulin (IVIg) and plasma exchange (PE) are effective immunotherapies if given during the initial phase of disease. PE or IVIg is indicated in severely-affected patients with inability to walk unaided or GBS disability score $\geqslant$ 3. Immunotherapy should be started as soon as possible in these patients before irreversible nerve damage has taken place. Although equally effective, IVIg is preferred over PE because of its ease of administration and fewer side effects. It is unclear whether IVIg is effective in mildly-affected patients (GBS disability score $\leqslant$ 2) or in Miller Fisher syndrome. The recommended dose of IVIg is 0.4 g/kg

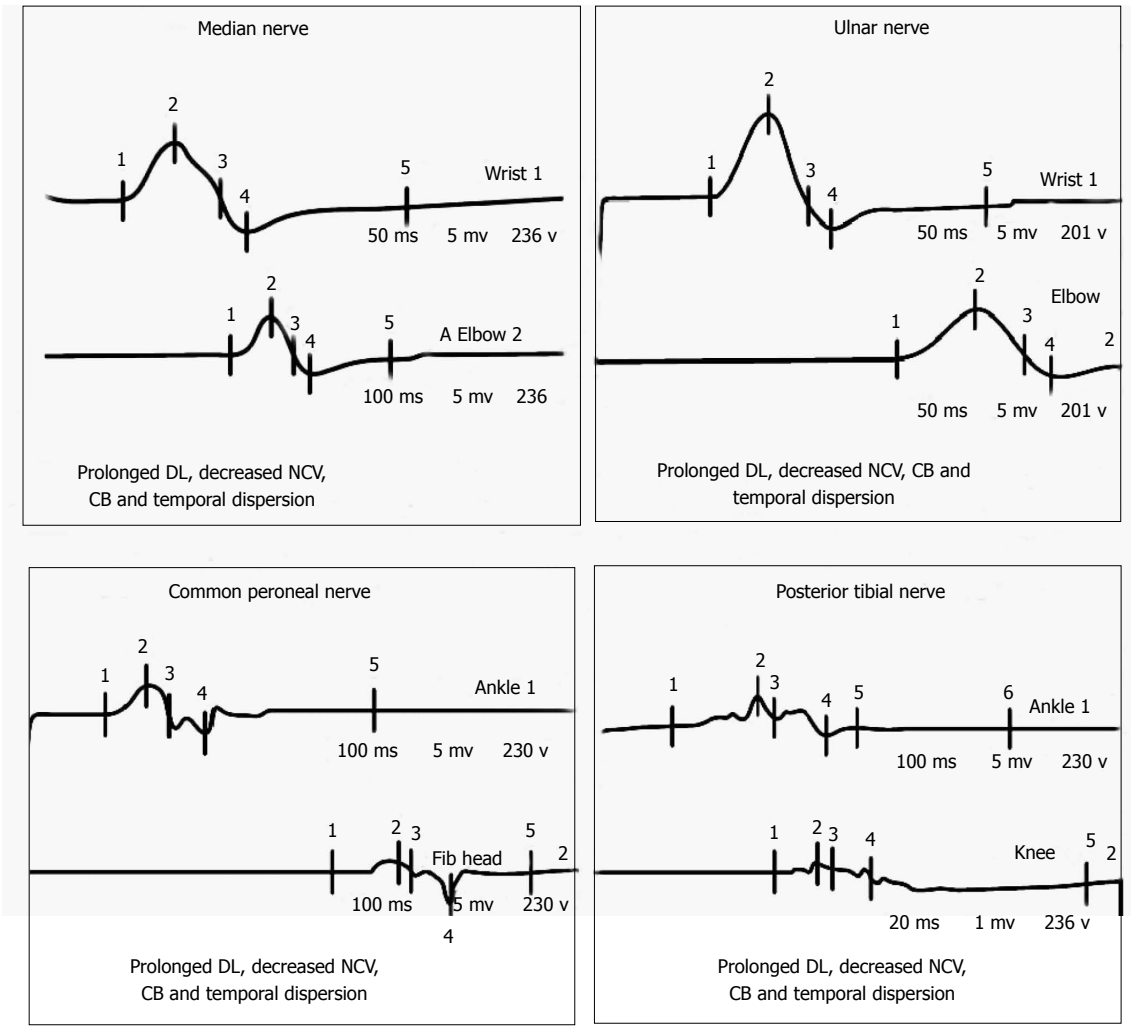

Figure 2 Motor nerve conduction study of a 24-year male patient presented with acute onset flaccid quadriparesis without sensory involvement. Nerve conduction study performed on day 2 shows typical findings of acquired demyelinating polyneuropathy. DL: Distal latency; NCV: Nerve conduction velocity; CB: Conduction block.

for 5 d and the usual regimen of PE is 5 times during 2 wk, with a total exchange of about 5 plasma volumes. In mildly-affected patients only 2 plasma volume may suffice and the dosage of IVIg conventionally administered (2 g/kg) may be suboptimal in some patients[18,19]. In clinical trials, no difference was found between IVIg and PE with respect to the improvement in disability grade after 4 wk, the duration of mechanical ventilation, mortality, or residual disability. The combination of PE and IVIg is not significantly better than PE or IVIg alone and oral or intravenous steroids are not beneficial[22]. About 10% of patients treated with IVIg or PE may deteriorate after initial improvement or stabilization and can be benefited by repeated treatment (2 g IVIg/kg in 2-5 d)[16-19].

Acute intermittent porphyria

Porphyrias are rare disorders of heme metabolism, characterized by a defect in an enzyme required for the synthesis of heme[23]. Acute intermittent porphyria (AIP) is an autosomal dominant disorder, results from a partial defect of porphobilinogen deaminase caused by a mutation in the hydroxymethylbilane synthase gene[23]. Neurological manifestations are characterized by acute polyneuropathy (predominantly motor), confusion, delirium, visual field defects, and seizures. Certain triggers like corticosteroids, other drugs, alcohol or fasting can precipitate an attack. The porphyric crisis typically begins with moderate to severe abdominal pain. Peripheral neuropathy is caused by axonal degeneration and predominantly affects motor nerves with minimal or no sensory involvement. Initially, weakness involves the proximal muscles of upper limbs[23]. Ankle jerk is frequently preserved. The polyneuropathy can affect cranial nerves and respiratory muscles requiring mechanical ventilation. Neuropsychiatric manifestations are common and seizures may occur in up to 20% of cases. Autonomic symptoms including tachycardia, cardiac arrhythmias, hypertension, constipation, and urinary retention are frequent and may lead to sudden death. The primary tool for diagnosis is measurement of porphyrin levels in urine, stool, and blood during an acutely symptomatic state. In an acute attack of AIP,

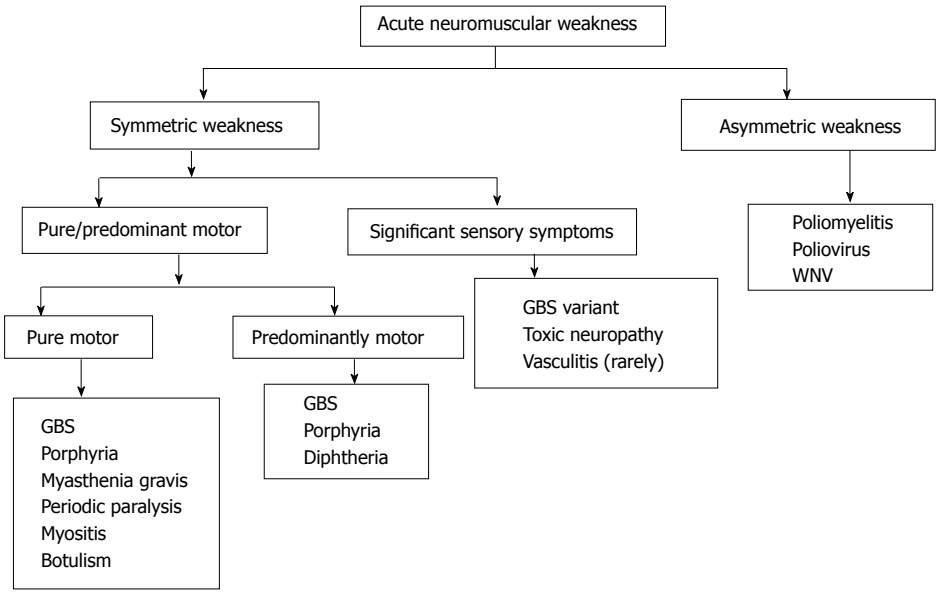

Figure 3 Althorithm: Practical approach to the patient with acute neuromuscular paralysis. GBS: Guillain-Barré syndrome; WNV: West Nile virus.

there is elevated urinary excretion of aminolevulinic acid (ALA), porphobilinogen (PBG), uroporphyrin, and coproporphyrin; erythrocyte PBG deaminase may be normal or decreased[23]. The urine turns dark when standing due to formation of porphobilin. The study of CSF is normal or may reveal slightly raised protein levels. Treatment is based on glucose supplementation, prohibition of drugs that may worsen an attack and hematin (4 mg/kg daily for 4 d) to inhibit synthesis of ALA synthetase[23]. Neuropathy begins to improve within days and may continue to improve over several days.

Diphtheria

Diphtheria is a contagious disease caused by toxin-producing strains of the bacterium *Corynebacterium diphtheriae*[24]. It is a biphasic illness with initial symptoms of fever, throat congestion, neck swelling and ipsilateral palatal weakness followed by diphtheric polyneuropathy. The latency in development of diphtheritic polyneuropathy varies from 18 to 46 d after the initial infection. It is an acute demyelinating polyneuropathy, occurs in about 20% of patients with diphtheria[24]. The classic features of include accommodation disturbances, convergence or pupillary light reflex disturbance, anisocoria, ptosis, mydriasis, malfunction of extraocular muscles and dysfunction of the other cranial nerves followed by quadriparesis[24]. Various combinations of these clinical manifestations may be seen. Respiratory muscle and diaphragmatic paresis leading to respiratory failure is a common life-threatening neurological complication. Improvement in cranial nerves occurs with evolving motor disturbance in the trunk and extremities. Autonomic dysfunction is common in diphtheritic polyneuropathy, with the incidence ranging from 36% to 100% in severe diphtheritic polyneuropathy[24]. Diphtheria antitoxin is ineffective if administered after one or two days of diphtheritic symptoms. Death from diphtheria occurs by autonomic dysfunction, cardiac arrhythmias, myocarditis, aspiration pneumonia or respiratory paralysis.

Lyme's disease and CMV related polyradiculoneuropathy

Lyme's disease is focally endemic in temperate climates of the northern hemisphere. It is the most common tick-borne disease in United States. It is a multistage and multi-system disease caused by Borrelia spirochetes, which are transmitted by ixodes ticks. It is focally endemic in temperate climates of the northern hemisphere. Early manifestations of the disease include fever, headache, fatigue, and a characteristic skin rash called erythema migrans. Weeks to months later, neurological or cardiac symptoms develop. Neurological manifestations are characterized by aseptic meningitis or fluctuating meningoencephalitis with cranial or peripheral neuropathies. Treatment is oral doxycycline or amoxicillin. Late or severe disease requires ceftriaxone or penicillin G. Single-dose doxycycline (200 mg orally) can be used as prophylaxis in selected patients. Preventive measures should be emphasized to patients to help reduce risk.

CMV polyradiculopathy is clinically characterized by lower extremity weakness, urinary retention, and sacral dysesthesias. It is an important cause of polyradiculitis in immunocompromised individuals including malignancies, organ transplant recipients and persons with acquired immunodefiency syndrome. CSF examination reveals pleocytosis. CMV polyradiculopathy is rapidly fatal without treatment. Detection of CMV in CSF is mandatory to confirm the diagnosis. Treatment with foscarnet or ganciclovir may improve or stabilize the condition.

Acute toxic polyneuropathies

Various environmental and industrial toxins including heavy metals, pesticides, organophosphates, and organic solvents can affect peripheral nerves. Although these toxins usually cause subacute or chronic neuropathy, acute polyneuropathy resembling GBS can also occur. Common toxins that can lead to acute neuropathy are described below.

Arsenic: Suicidal, homicidal or accidental ingestion of arsenic may lead to rapidly-evolving polyneuropathy 1-3 wk after acute poisoning. The neuropathy is of axonal type. Severe gastrointestinal symptoms including abdominal pain, diarrhoea, vomiting, and shock are other manifestations of acute arsenic poisoning. Urinary excretion of arsenic > 0.1 mg/L is abnormal and the levels can reach up to 1 mg/L after acute exposure. Once polyneuropathy has occurred it does not respond to chelating therapy with British anti-Lewisite agent.

Thallium: Patients with acute thallium poisoning present with abdominal pain, vomiting and diarrhea with later development of limb pain and paresthesia. Rapidly progressive muscle weakness develops soon, which is more prominent in distal muscles. Sensory impairment for pain is more markedly affected than other sensory modalities. Other neurological manifestations like cranial neuropathies, nystagmus, and optic neuritis may occur. Alopecia is another important clinical finding of thallium poisoning.

Organophosphate poisoning: Organophosphate compounds are widely used as pesticides and insecticides in agriculture and household. Organophosphorus poisoning may result from occupational, accidental or intentional exposure. Tri-ortho-cresyl phosphate is a common organophosphate compound leading to neurological disorders. Three typical patterns of neurological manifestations usually occur following organophosphates poisoning. Type 1 paralysis or acute cholinergic crisis occurs because of excessive muscarinic receptor stimulation by acetylcholine. Type 2 paralysis or intermediate syndrome usually appears 24-96 h after the apparent recovery from acute cholinergic phase. Dysfunction of neuromuscular junction caused by downregulation of presynaptic and postsynaptic nicotinic receptors is the proposed hypothesis in the pathogenesis of intermediate syndrome. The clinical features consist of proximal muscles weakness, neck flexors weakness, and respiratory paralysis. As the clinical manifestations occurred after the acute cholinergic phase but before organophosphate-induced delayed polyneuropathy, it is called "intermediate syndrome". Organophosphate-induced delayed neuropathy is a distal symmetric sensory motor (predominantly motor) axonal neuropathy, which occurs 2-5 wk after exposure. Cramping muscle pain in the lower limbs and paraesthesia occur, followed by progressive muscle weakness and diminished deep tendon reflexes.

Buckthorn poisoning: Buckthorn shrub is found mainly in Texas and Mexico. Ingestion of the green or ripe fruit of the buckthorn or tullidora shrub can cause a rapidly progressive, symmetric, progressive and severe axonal type neuropathy. Facial and pharyngeal weakness may also occur and neurological picture resembles GBS or other polyradiculoneuropathies.

Vasculitic neuropathy: Although, vasculitic neuropathies usually present in a subacute or chronic manner, sometimes aggressive vasculitic neuropathy may manifest acutely and resembles GBS[25]. Pseudo-conduction block in vasculitic neuropathy may be mistaken for conduction block typically seen in GBS. Presence of fever, history of multifocal involvement that very rapidly became confluent and pain accompanying focal weakness are important clinical features suggestive of vasculitic neuropathy. Nerve conduction studies in vasculitic neuropathy usually show only conduction block but no other features of demyelination. Also, conduction block disappears subsequently because axonal degeneration follows as a consequence of nerve infarct[25].

CIP

CIP is an acute reversible neuropathy that develops during the treatment of critically-ill patients and has an important impact on the outcome of patients in the ICU[26-28]. Difficulty in weaning from the mechanical ventilator in the absence of cardiopulmonary compromise and generalized muscle weakness in critically-ill patient should always lead to suspicion of CIP. It has been reported to occur in 70% of patients with sepsis and multiorgan failure[6,26]. Other causes of acute onset flaccid paralysis and areflexia in critically-ill patients needs to be ruled out before diagnosis of CIP is made. The severity of weakness ranges from moderate paresis to complete quadriplegia. The muscle weakness is predominantly distal and involves the lower limbs. The cranial nerves are usually spared, although facial weakness has been occasionally reported. Hyporeflexia or areflexia is common, although deep tendon reflexes may be normal in about one-third of the patients. The course of CIP is monophasic and self-limiting and shows significant recovery if the patient survives the underlying critical illness[26-28]. Sepsis, multi-organ dysfunction syndrome, multi-organ failure, female sex, use of corticosteroids, severe asthma, ionic abnormalities, malnutrition and immobility are frequently reported risk factors of CIP. Electrophysiological studies shows diminished compound motor and sensory nerve action potential amplitudes with normal conduction velocities suggesting axonal neuropathy. Needle EMG shows fibrillation potentials and positive sharp waves

suggesting denervation. Abnormal phrenic nerve conduction (bilateral reduced or absent diaphragmatic CMAP) is reported in about 50%-80% of patients. There is no specific treatment for CIP and management is primarily supportive[6,26,27].

DISORDERS OF NEUROMUSCULAR JUNCTION

Myasthenia gravis

Myasthenia gravis (MG) is the most common neuromuscular junction disorder featured by fluctuating motor weakness that has a predilection for the ocular and bulbar musculature. Incidence of MG has been reported to be 0.25-2 patients per 100000 populations[29]. It is an immune mediated disorder due to circulating antibodies directed against the postsynaptic acetylcholine receptors. Most common clinical manifestations include fatigue, diplopia, ptosis, dysphagia, difficulty in mastication, dysarthria, proximal and neck muscle weakness[29]. Involvement of respiratory muscles may lead to acute respiratory insufficiency. Although the subacute and chronic presentation is more common, a subset of patients with MG can present with ANMP. Diagnosis is essentially based on a positive edrophonium test, decremental response on repetitive nerve stimulation, and presence of serum acetylcholine receptor antibodies. About 85% of patients with generalized MG are seropositive for acetylcholine receptor antibodies. Patients with MG typically require admission to the ICU for myasthenic crisis or cholinergic crisis. The term myasthenic crisis refers to respiratory weakness in patients with acquired, autoimmune form of MG. The life-time risk of myasthenic crisis in patients with MG is about 20%-30% and it usually occurs during the course of first symptomatic presentation in the young and later in the course of the illness in elderly[29]. Two-thirds to 90% of patients with myasthenic crisis require intubation and mechanical ventilation. Most patients need immunosuppression, in addition to symptomatic therapy with acetylcholinesterase inhibitors. The most commonly used symptomatic drug in MG is pyridostigmine and also the faster acting neostigmine. Prednisolone and azathioprine are the first choice among immunosuppressants. Several second choice drugs like cyclosporine and mycophenolate mofetil are methotrexate may also be used. Thymectomy should be performed in MG with thymoma and in generalized, early-onset MG. For MG crisis and other acute exacerbations, IVIg and PE are equally effective and safe treatments. Whenever difficult to differentiate between myasthenic and cholinergic crisis, acetylcholinesterase inhibitors should be stopped and the patient should be observed in the ICU.

Botulism

Botulism is a food-borne illness caused by the exotoxin of *Clostridium botulinum,* which acts by blocking the presynaptic release of acetylcholine. The clinical manifestations usually begins 12-36 h after consumption of the tained food with bulbar symptoms, nasal intonation, blurred vision, ophthalmoplegia, fixed dilated pupils, and autonomic dysfunction including dry mouth, constipation, and urinary retention. The severity of muscle weakness is variable and may present with progressive descending flaccid paralysis and sometimes respiratory involvement. Deep tendon reflexes and gag reflex may be preserved except in cases of severe generalised weakness. Sensory symptoms are absent. The diagnosis should be suspected based on history of ingestion of improperly sterilized home-canned foods followed by the development of the clinical manifestations described above. It is confirmed by detection of toxin in serum, feces or contaminated food scraps and is supported by electrophysiological studies, which show small amplitude motor responses that increase in amplitude at high rates of repetitive nerve stimulation. Treatment involves administration of trivalent antitoxin to neutralize circulating neurotoxin in the serum. Mechanical ventilation may be required in severely-affected patients.

Snake bite and other neuroparalytic envenomation

Snake bite is common in the rural parts of developing countries and carries high mortality if not adequately managed. The venom of elapid snakes, cobra and krait are predominantly neurotoxic, causing a selective neuromuscular block. Post-synaptic neurotoxins in snake venom such as bungarotoxin and cobrotoxin bind to acetylcholine receptors at motor end plates, while presynaptic neurotoxins such as bungarotoxin, crotoxin, and taipoxin interferes the release of acetylcholine at the neuromuscular junction. The nerve conduction study plays an important role in supplementing the diagnosis of snake bite and may also help to differentiate it from other causes of neuromuscular paralysis. Cobra and krait venom affect mainly the ocular, bulbar, and respiratory muscles leading to respiratory failure. Early morning neuroparalytic syndrome or pseudomyasthenic syndrome commonly seen among farmers and slum dwellers is a presentation of the krait bite as their bites are generally painless. Timely administration of anti-snake venom serum and institution of supportive treatment is associated with good outcome.

The neurotoxin produced by the Rocky Mountain wood tick, Dermacentor andersoni causes rapidly progressive ascending paralysis that can lead to respiratory failure and death. Weakness usually starts after about 5-6 d after the insect has embedded itself into the skin. The toxin acts by inhibiting the release of acetylcholine from the presynaptic nerve terminal.

Drug-induced neuromuscular junction disorders

Several groups of drug including aminoglycosides, quinolones, polymyxin antibiotics, calcium-channel blockers, beta-blockers, quinidine, procainamide, and

neuromuscular blocking agents have been reported to produce or potentiate neuromuscular weakness[30]. Patients treated with high doses of nondepolarizing neuromuscular blocking agents such as vecuronium and pancuronium may have persistent weakness and difficult weaning from the ventilator even after drug has been stopped. At high doses, acetylcholinesterase inhibitors given to myasthenic patients can produce neuromuscular blockade and cause respiratory weakness. This overdose reaction is termed as cholinergic crisis and is characterized by nausea, diarrhea, miosis, bradycardia, muscle fasciculations, and hypersalivation[30].

MUSCLE DISORDERS

Periodic paralysis

Hypokalemic periodic paralysis is the classical and most common form of periodic paralysis. It is a calcium channel disorder manifests with acute muscle weakness that closely mimics GBS. Attacks usually begin in adolescence and are precipitated by exercise followed by rest, high carbohydrate and sodium content meals or sudden changes in temperature. The weakness evolves rapidly over minutes to several hours. Limbs are affected more than trunk and weakness is predominantly proximal. Deep tendon reflexes may be normal, decreased or absent. Ankle reflex is usually preserved even at the peak of weakness. Facial, ocular, bulbar, and respiratory muscles are rarely involved. Serum potassium levels are low. Hypokalemic periodic paralysis can be primary/hereditary (transmitted in an autosomal dominant pattern) or secondary caused by conditions such as thyrotoxicosis, barium poisoning, aldosteronism, and renal tubular acidosis. Treatment consists of large doses of oral potassium (0.25 mEq potassium chloride/kg) or potassium chloride intravenous solution in refractory cases and prevention with diet rich in potassium and low in carbohydrates and sodium. Acetazolamide can be used to prevent attacks. Hyperkalemic periodic paralysis is an autosomal dominant, inherited sodium channelopathy. It begins during childhood or the second decade of life and presents with crises of varying severity after exercise, cold, and fasting that usually last 1-2 h. The serum potassium level is high or borderline.

Polymyositis and dermatomyositis

Both polymyositis and dermatomyositis are inflammatory muscle disease which manifest in a subacute or chronic manner, although acute presentation can occur in rare cases[31]. In contrast to MG, extraocular muscles are never affected. Facial, bulbar, and respiratory muscles involvement is rare[31]. The clinical diagnosis of polymyositis and dermatomyositis is confirmed by elevated serum muscle enzyme concentrations, EMG, and muscle biopsy. In dermatomyositis, the inflammation is predominantly perivascular or in the interfascicular septae and around rather than within the fascicles; whereas in polymyositis, multifocal lymphocytic infiltrates surround and invade healthy muscle fibers. Prednisolone is the first-line drug and the addition of another immunosuppressive drug may be necessary in subjects who do not show improvement even after 3 mo of adequate dose of corticosteroids. In the first double-blind trial conducted for dermatomyositis, IVIg was reported to be effective in improving muscle strength and resolving the underlying immunopathology[32]. No controlled studies have been undertaken in polymyositis, but IVIg seems to be effective in about 70% of patients. Plasmapheresis was not found to be helpful in a double-blind, placebo-controlled study[33].

Several viruses (coxsackieviruses, infl uenza, parvoviruses, paramyxoviruses, CMV, Epstein-Barr virus, dengue) and bacteria (Borrelia burgdorferi, streptococci) have also been reported to be associated with acute myositis and muscle paralysis. Rhabdomyolysis trauma, sepsis, alcohol abuse, certain viral infections like influenza, dengue, *etc*. and various medications can lead to acute rhabdomyolysis. Rapid-onset muscle pain, swelling, tenderness, predominant proximal or generalized weakness, acute renal failure, myoglobinuria, and markedly raised serum ceatinine kinase are the core features. Sometimes weakness is severe enough to cause respiratory failure. Electromyography shows myopathic changes and spontaneous fibrillations. A muscle biopsy is confirmatory and shows massive muscle fiber necrosis and often numerous regenerating fibers with minimal inflammatory changes[33,34].

CONCLUSION

ANMP is a common neurological emergency and should be promptly investigated and treated. Sometimes, neurological examination in the emergency department or in ICU can be difficult. Combined clinical and electrophysiological assessment helps to locate the site of MU affection, *i.e.*, anterior horn cell, radical, nerve, muscle, and neuromuscular junction disorders. Algorithmic approach to a patient with acute neuromuscular weakness is shown in the Figure 3. Complications of critical illness, including critical illness neuropathy, critical illness myopathy and prolonged neuromuscular blockade, are now considered as the principal cause of new onset weakness in the seriously ill patients. These disorders should to be differentiated from other neurological conditions that may develop after admission to the ICU. A proper protocol based clinical and investigational approach is essential in every emergency department to manage such cases.

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ORIGINAL ARTICLE

Retrospective Study

Feasibility of initial endoscopic common bile duct stone removal in patients with acute cholangitis

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Author contributions: Kitamura K designed this study as well as collected and analyzed the data; Yamamiya A analyzed the data and drafted the manuscript; Kitamura K checked the manuscript and approved the final version; Yamamiya A, Kitamura K, Ishii Y, Mitsui Y, Nomoto T and Yoshida H participated in this study as either endoscopic operators or assistants.

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Abstract

AIM

To investigate the feasibility of initial endoscopic common bile duct (CBD) stone removal in patients with acute cholangitis (AC).

METHODS

A single-center, retrospective study was conducted between April 2013 and December 2014 and was approved by the Medical Ethics Committee at our institution. Written informed consent was obtained from each patient prior to the procedure. The cohort comprised 31 AC patients with CBD stones who underwent endoscopic biliary drainage (EBD) for naïve papilla within 48 h after AC onset. We retrospectively divided the participants into two groups: 19 patients with initial endoscopic CBD stone removal (initial group) and 12 patients with delayed endoscopic CBD stone removal (delayed group). We evaluated the feasibility of initial endoscopic CBD stone removal in patients with AC.

RESULTS

We observed no significant differences between the groups regarding patient characteristics. According to the assessments based on the Tokyo Guidelines, the AC severity of patients with initial endoscopic CBD stone removal was mild to moderate. The use of antithrombotic agents before EBD was less frequent in the initial group than in the delayed group (11% *vs* 58%, respectively; P = 0.004). All the patients underwent successful endoscopic CBD stone removal

and adverse events did not differ significantly between the groups. The number of endoscopic retrograde cholangiopancreatography procedures was significantly lower in the initial group than in the delayed group [median (interquartile range) 1 (1-1) *vs* 2 (2-2), respectively; $P < 0.001$]. The length of hospital stay was significantly shorter for the initial group than for the delayed group [10 (9-15) *vs* 17 (14-20), respectively; $P = 0.010$].

CONCLUSION

Initial endoscopic CBD stone removal in patients with AC may be feasible when AC severity and the use of antithrombotic agents are carefully considered.

Key words: Acute cholangitis; Common bile duct stone; Feasibility; Initial endoscopic common bile stone removal; Endoscopic retrograde cholangiopancreatography

Core tip: Initial endoscopic common bile duct stone removal in patients with acute cholangitis (AC) may be feasible when AC severity and the use of antithrombotic agents are carefully considered.

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INTRODUCTION

Acute cholangitis (AC) is an acute inflammatory condition caused by a rise in bile duct pressure and biliary infection secondary to biliary obstruction[1]. Clinical findings include fever, abdominal pain and jaundice (Charcot's triad). Patients with severe AC present with septic shock and altered consciousness in addition to the classical signs of Charcot's triad (Reynolds' pentad).

First published in 2007, the Tokyo Guidelines for the management of AC (TG07)[2] were modified in 2013 to the updated version (TG13)[1]. The basic treatment for AC is conservative medical therapy with antimicrobial agents and biliary tract drainage.

According to the TG07, an additional endoscopic sphincterotomy (EST) is not necessary during initial biliary drainage. However, in the TG13, based on the clinical condition of the patient, initial common bile duct (CBD) stone removal with an additional EST may be performed. Furthermore, no consensus exists for when CBD stones should be removed in patients with AC. The aim of this study was to evaluate the feasibility of initial endoscopic CBD stone removal in patients with AC.

MATERIALS AND METHODS

This retrospective study was conducted at Showa University Hospital and was approved by the Medical Ethics Committee of our institution. The study was registered at the University Hospital Medical Information Network (UMIN) Clinical Trials Registry (registry number: 000020770). Informed written consent was obtained from each patient prior to the procedure.

Patients

Seven hundred thirty-seven patients underwent an endoscopic retrograde cholangiopancreatography (ERCP)-related procedure at our institution between April 2013 and December 2014. Among them, 164 patients underwent an emergency ERCP procedure. Following the exclusion of acute biliary pancreatitis ($n = 13$), altered gastrointestinal anatomy ($n = 9$), and other entities ($n = 111$), we analyzed the remaining 31 AC patients with CBD stones who underwent endoscopic biliary drainage (EBD) for naïve papilla within 48 h after AC onset.

We retrospectively divided the participants into two groups: 19 patients who underwent initial endoscopic CBD stone removal (initial group) and 12 patients who underwent delayed endoscopic CBD stone removal (delayed group) (Figure 1).

The delayed group was defined as patients who received EBD without CBD stone removal at first ERCP and underwent endoscopic CBD stone removal later.

Devices

ERCP was performed using a duodenoscope (JF-260V; Olympus Medical Systems Corp., Tokyo, Japan). The following devices were employed during the procedure: A sphincterotome with a tip length of 7 mm and a cutting wire length of 20 mm (Autotome RX44; Boston Scientific, Natick, MA, United States), a 0.035-inch guidewire (Jagwire; Boston Scientific), a balloon catheter for CBD stone removal (Multi-3V Plus; Olympus Medical Systems Corp., Tokyo, Japan), a biliary dilation balloon catheter designed to produce three distinct diameters at three separate pressures (CRE™ wire-guided biliary dilation balloon catheter; Boston Scientific), and a 5-Fr pigtail nasobiliary catheter (Create Medic Co. LTD., Tokyo, Japan) or a 7-Fr 10-cm Double Pigtail Stent delivery system Through Pass (Gadelius Medical K.K., Tokyo, Japan) as a drainage catheter and stent.

Endoscopic CBD stone removal

All ERCP procedures were performed by expert endoscopists. All patients provided written consent to undergo ERCP and were informed of the risks and benefits of the procedure. The patients who exhibited no evidence of altered consciousness or septic shock

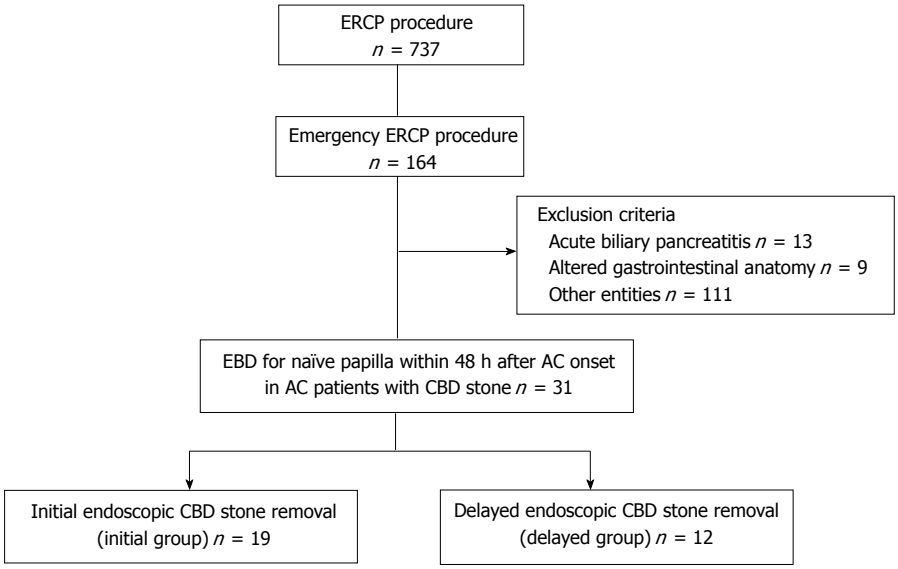

Figure 1 Flow diagram of patient selection process. ERCP: Endoscopic retrograde cholangiopancreatography; EBD: Endoscopic biliary drainage; AC: Acute cholangitis; CBD: Common bile duct.

received ERCP under sedation with benzodiazepines or pentazocine as analgesics. Wire-guided cannulation for selective bile duct cannulation and EST with a small or medium-sized incision of the papilla of Vater were primarily performed to remove the CBD stone. An Erbotom ICC200 (ERBE Elektromedizin GmbH, Tubingen, Germany) was used for the EST using the Endocut mode. The effect 3 current was set at an output limit of 120 W and the forced coagulation current was set at an output limit of 30 W. Patients with large CBD stones (*i.e.*, diameter of 13 mm or more) received endoscopic papillary large balloon dilation (EPLBD) with EST. A balloon catheter was used to remove the CBD stone. All patients received intravenous infusions of a protease inhibitor (gabexate mesilate - 600 mg or nafamostat mesilate - 60 mg) for approximately 12 h (beginning immediately after the ERCP procedures). All patients were administered antibiotics before the ERCP procedure, and antimicrobial therapy was continued until the cholangitis symptoms improved. The off-period for antithrombotic agents was based on the Japanese guidelines for gastroenterological endoscopy in patients undergoing antithrombotic treatment[3]. Based on the judgment of the endoscopist, either a 5-Fr drainage catheter or a 7-Fr 10-cm double pigtail stent was inserted for EBD.

Outcome measures

The primary outcome of this study was the success rate of initial endoscopic CBD stone removal in patients with AC. The secondary outcomes were the number of ERCP procedures, the incidence of adverse events, the duration of antibiotic administration, the length of hospital stay and hospital costs.

Post-ERCP pancreatitis was defined as the presence of abdominal pain lasting for more than 24 h after ERCP with serum amylase levels 3 times the upper limit of normal or higher and graded by CT when necessary[4]. Bleeding complications were classified as follows: Mild, with hemoglobin drop < 3 g without a need for transfusion; moderate, with transfusion (4 units or less) with no angiographic intervention or surgery; and severe, with transfusion (5 units or more) or additional intervention[4].

Statistical analysis

Continuous variables are expressed as the median with interquartile range (IQR). Statistical analyses were performed using JMP version 12 (SAS Institute Inc., Cary, NC, United States). Data were analyzed using the Mann-Whitney *U* and χ^2 tests. Differences of $P < 0.05$ were considered significant.

RESULTS

Patient characteristics

Patient characteristics are presented in Table 1. No significant differences between the groups were observed regarding age, sex, AC severity, CBD diameter, number of CBD stones, diameter of CBD stones, periampullary diverticulum, period until EBD, blood CRP level before EBD or positive blood cultures. The use of antithrombotic agents before EBD was less frequent in the initial group than in the delayed group (11% *vs* 58%, respectively; $P = 0.004$).

Success rate of endoscopic CBD stone removal

There was no significant difference between the groups regarding procedures involving the ampulla, such as EST or EPLBD, to remove CBD stones. All patients underwent successful endoscopic CBD stone removal using a balloon catheter (Table 2).

Table 1 Patient characteristics *n* (%)

	Initial group (*n* = 19)	Delayed group (*n* = 12)	*P* value
Age, median (IQR), yr	71 (62-80)	80 (74-84)	0.064[1]
Sex, male/female, *n*	11/8	6/6	0.667[2]
AC severity[3], mild/moderate/severe, *n*	11/8/0	5/4/3	0.072[2]
CBD diameter, median (IQR), mm	9 (8-10)	11 (8-13)	0.169[1]
Number of CBD stones, single/multiple, *n*	9/10	6/6	0.886[2]
Diameter of CBD stone, < 10 mm/≥ 10 mm, *n*	15/4	9/3	0.798[2]
Periampullary diverticulum	9 (47)	4 (33)	0.441[2]
Use of antithrombotic agents before EBD	2 (11)	7 (58)	0.004[2]
Period until EBD from AC onset, < 24 h/24-48 h, *n*	11/8	8/4	0.648[2]
Blood CRP level before EBD, median (IQR), mg/dL	3.9 (1.4-6.7)	5 (1.6-12.2)	0.429[1]
Positive blood culture, *n*/total	6/14 (43)	5/7 (71)	0.217[2]

[1]Mann-Whitney *U* test; [2]χ^2 test; [3]Tokyo Guidelines for the management of acute cholangitis (TG13). IQR: Interquartile range; AC: Acute cholangitis; CBD: Common bile duct; EBD: Endoscopic biliary drainage; CRP: C-reactive protein.

Table 2 Clinical outcomes *n* (%)

	Initial group (*n* = 19)	Delayed group (*n* = 12)	*P* value
Procedures for ampulla, EST/EPLBD with EST, *n*	18/1	10/2	0.296[1]
Use of balloon catheter for stone removal	19 (100)	12 (100)	
Successful CBD stone removal	19 (100)	12 (100)	
Number of ERCP procedures, median (IQR)	1 (1-1)	2 (2-2)	< 0.001[2]
Adverse events, pancreatitis/bleeding/perforation, *n*	0/0/0	0/1/0	0.201[1]
Duration of antibiotic administration, median (IQR), d	7 (5-8)	6 (5-7)	0.059[2]
Hospital stay, median (IQR), d	10 (9-15)	17 (14-20)	0.010[2]
Hospital costs, median (IQR), $	726 (579-1028)	988 (868-1033)	0.224[2]

[1]χ^2 test; [2]Mann-Whitney *U* test. EST: Endoscopic sphincterotomy; EPLBD: Endoscopic papillary large balloon dilation; CBD: Common bile duct; ERCP: Endoscopic retrograde cholangiopancreatography; IQR: Interquartile range.

Number of ERCP procedures

The number of the ERCP procedures performed was significantly lower in the initial group than in the delayed group [1 (1-1) *vs* 2 (2-2) for the initial and delayed groups, respectively; $P < 0.001$] (Table 2).

Adverse events

Adverse events did not differ significantly between the two groups. Post-ERCP pancreatitis or perforation did not occur in either group. Mild bleeding 4 d after ERCP occurred in 1 patient in the delayed group (Table 2).

Antibiotic administration

The duration of antibiotic administration did not differ significantly between the groups [7 (5-8) d *vs* 6 (5-7) d for the initial and delayed groups, respectively, $P = 0.059$] (Table 2).

Hospital stay

The length of hospital stay was significantly shorter for the initial group than that for the delayed group [10 (9-15) d *vs* 17 (14-20) d for the initial and delayed groups, respectively; $P = 0.010$] (Table 2).

Hospital costs

There was no significant difference in hospital cost between the groups [$726 (579-1028) *vs* $988 (868-1033) for the initial and delayed groups, respectively, $P = 0.224$] (Table 2).

DISCUSSION

This study suggested that emergency initial endoscopic CBD stone removal in patients with AC may be feasible when AC severity and the use of antithrombotic agents are carefully considered.

In 2013, the TG07 was modified to the updated version, TG13[1]. AC results from causes such as CBD stones, benign biliary tract strictures, biliary anastomotic strictures and malignant biliary tract strictures. Though a CBD stone is the most frequent etiology of AC, the incidences of AC due to malignant biliary tract stricture and sclerosing cholangitis have been increasing recently[5,6].

The major changes reflected in the TG13 were a rearrangement of the diagnostic items and the exclusion of abdominal pain from the diagnostic list. Cholangitis severity was categorized as grade Ⅰ (mild), grade Ⅱ (moderate) and grade Ⅲ (severe). Kiriyama *et al*[7] investigated the accuracy of the TG13. The sensitivity for AC severity is 91.8%, and the specificity for AC is 77.7%.

According to the TG13, appropriate treatment during the acute phase of AC is important because the mortality associated with AC is 2.7%-10%. Among 60842 AC cases extracted from the Japanese admini-

strative database according to the Diagnosis Procedure Combination system of Japan, the mortality was 2.7%[8]. The primary cause of death among patients with AC is multiple organ failure associated with irreversible shock[9].

The TG13 further recommends treatment based on AC severity. The initial treatment, which includes a full dose of antimicrobial agents, is provided for all patients with AC. For non-responders with mild and moderate AC, biliary drainage should be performed immediately. For patients with severe AC, appropriate organ support is required, and biliary drainage should be performed after hemodynamic stabilization has been achieved[10]. Biliary drainage includes percutaneous transhepatic biliary drainage, surgical biliary drainage, EBD and endoscopic ultrasonography-guided biliary drainage. EBD is recommended as the first choice because it is considered a minimally invasive biliary drainage technique[11-13].

There are several differences in EST between the TG07 and TG13. In the TG07, an additional EST is not necessary because EST is associated with serious complications, such as hemorrhage. AC alone is a risk factor for post-EST hemorrhage[14]. In particular, EST should be avoided in patients with severe AC because they often have blood-coagulation disorders. According to the TG13, EST may be indicated for the initial endoscopic CBD stone removal in patients with AC[1]. These recommendations suggest that the choice of performing an additional EST should be based on the patient's clinical condition[15].

Recently, studies evaluating initial endoscopic CBD stone removal in patients with AC have emerged in the literature. Eto *et al*[16] reported that the improvement rate of cholangitis was 90% and that the rate of complications was 10% (post-ERCP pancreatitis, hemorrhage, cholecystitis, or pneumonia). Notably, hemorrhage occurred in 2% of patients[16].

At our institution, patients with moderate and severe AC undergo emergency EBD. We also perform emergency EBD in patients with mild AC and high fever (> 38 ℃) or severe abdominal pain. When AC patients with CBD stones are administered antithrombotic agents, we consider the off-period of these drugs and perform additional EST according to the Japanese guidelines for gastroenterological endoscopy in patients undergoing antithrombotic treatment[3]. In this guideline, EST is classified in the high bleeding risk group. We have performed additional EST and CBD stone removal in patients with mild and moderate AC. Based on the guideline, we do not perform additional EST for the following patients: Those taking antithrombotic agents that require an off-period of more than 5-7 d; those taking more than 2 types of antithrombotic agents; and those with evidence of septic shock. Therefore, these patients received only EBD. In this study, the use of antithrombotic agents before EBD was less frequent in the initial group than in the delayed group (P = 0.004). Hemorrhage occurred in 1 patient from the delayed group, an older adult with underlying disease who was taking more than 2 types of antithrombotic agents. After the EBD and antithrombotic agent off-period, the patient underwent successful delayed CBD stone removal with EST. However, this patient developed a mild hemorrhage 4 d after the procedure.

In this study, emergency initial endoscopic CBD stone removal was feasible for patients with mild or moderate AC when the guidelines in the TG13 and the recommendations for the use of antithrombotic agents were strictly followed. The number of ERCP procedures was significantly less in the initial group than in the delayed group (P < 0.001) because the delayed group underwent ERCP for CBD stone removal after the severe AC had subsided or during the antithrombotic agent off-period. The length of hospital stay was significantly shorter for the initial group than for the delayed group (P = 0.010) with no significant differences regarding the number of adverse events observed between the two groups. Thus, initial endoscopic CBD stone removal in patients with AC may reduce the treatment-associated patient burden.

The limitations of this study are the single-center focus, the retrospective design and the small number of patients. Additional multicenter, randomized controlled trials are necessary to confirm the feasibility of emergency initial endoscopic CBD stone removal in patients with AC.

Emergency initial endoscopic CBD stone removal in patients with AC may be feasible when AC severity and the use of antithrombotic agents are carefully considered.

COMMENTS

Background

Initial endoscopic common bile duct (CBD) stone removal in patients with acute cholangitis (AC) may reduce the number of endoscopic retrograde cholangiopancreatography (ERCP) procedures performed and the length of hospital stay. However, there is no consensus on when CBD stones should be removed in patients with AC. The aim of this study was to investigate the feasibility of initial endoscopic CBD stone removal in patients with AC.

Research frontiers

The current standard for treating AC patients with CBD stones is a conservative medical approach with antimicrobial agents and biliary drainage. However, few studies have evaluated the timing of CBD stone removal in patients with AC.

Innovations and breakthroughs

The authors compared the clinical outcomes among patients with AC who underwent either initial endoscopic CBD stone removal or delayed endoscopic CBD stone removal. The number of ERCP procedures and the length of hospital stay were significantly reduced in the initial group compared to that in the delayed group.

Applications

Emergency initial endoscopic CBD stone removal in patients with AC may reduce subsequent patient burden associated with the treatment. However, multicenter, randomized, controlled trials are needed to confirm these findings.

Terminology

Endoscopic CBD stone removal is a stone removal method that utilizes the ERCP-related procedure with a duodenoscope.

Peer-review

Although this is a small study, it was well written.

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SYSTEMATIC REVIEWS

Diagnostic performance of high resolution computed tomography in otosclerosis

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Data sharing statement: Technical appendix, statistical code, and dataset available from the corresponding author at Dryad repository, who will provide a permanent, citable and open-access home for the dataset.

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Abstract

AIM

To determine the sensitivity and specificity of high resolution computed tomography (HRCT) in the diagnosis of otosclerosis.

METHODS

A systematic literature review was undertaken to include Level I-III studies (Oxford Centre for Evidenced based Medicine) that utilised HRCT to detect histology confirmed otosclerosis. Quantitative synthesis was then performed.

RESULTS

Based on available level III literature, HRCT has a relatively low sensitivity of 58% (95%CI: 49.4-66.9), a high specificity, 95% (95%CI: 89.9-98.0) and a positive predictive value of 92% (95%CI: 84.1-95.8). HRCT is better at diagnosing the more prevalent fenestral form of otosclerosis but remains vulnerable to inframillimetre, retrofenestral and dense sclerotic lesions, despite the advent of more advanced CT scanners with improved collimation.

CONCLUSION

Whilst the diagnosis of otosclerosis remains largely clinical, HRCT remains the gold standard imaging of choice for the middle ear and serves as a useful adjunct to the clinician, helping to delineate extent of disease and exclude other causes.

Key words: Otosclerosis; High resolution computed tomography; Otospongiosis; Retrofenestral; Sensitivity; Specificity; Fenestral; Computed tomography

Core tip: Diagnosis of otosclerosis remains clinical and

high resolution computed tomography (HRCT) can be a useful adjunct when assessing the extent of disease and excluding other causes. HRCT of the temporal bones has a high specificity and low sensitivity and is particularly vulnerable to inframillimetre lesions.

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INTRODUCTION

Otosclerosis is focal osseous dyscrasia of unknown aetiology which predominantly affects only the endochondral bone of the otic capsule in humans[1]. In the Caucasian population the estimated prevalence is between 0.3% and 0.4% but this is thought to be less in the Asian population[2,3]. However, there is a dearth of high level studies evaluating the incidence and prevalence of otosclerosis in the non-Caucasian population. Histopathologically normal endochondral bone of the otic capsule is replaced by disorganised foci of Haversian bone which ultimately becomes sclerotic and dense. Otospongiosis, the early or active phase of otosclerosis, is characterized by the presence of spongy irregular vascular foci of demineralised bone. This is followed by an otosclerotic or inactive phase where these diseased foci become less vascular, forming dense bone[4].

Otosclerosis can be divided into 2 types: Fenestral and retrofenestral, depending on the topography of the lesions. Fenestral lesions are in the lateral wall of the otic capsule, *i.e.*, the regions of the round and oval windows, promontory, and tympanic segment of the fallopian canal. The retrofenesteral type affects the labyrinthine capsule, including the pericochlear region, the semicircular canals, internal acoustic meatus, vestibule, and cochlear and vestibular aqueducts[5,6].

Diagnosis is based on a combination of medical history, physical examination, audiological testing and imaging. The clinical findings include conductive, mixed, or rarely, pure sensorineural hearing loss and vertiginous symptoms in the absence of middle ear inflammation[2,7,8]. Surgical or histological confirmation is important in correlating clinical findings.

High resolution computed tomography (HRCT) is the gold standard imaging modality in the diagnosis of otosclerosis; it detects pathologic bone lesions in and around the stapes footplate, cochlea, and labyrinth[9-11]. In active otospongiosis, disease foci are visualised on CT as areas of reduced bone density and appear as increased bony radiolucency in the otic capsule, typically at the fissula ante fenestram, just anterior to the oval window in the fenestral type of the disease. HRCT can also demonstrate disease within the peri-labyrinthine bone and the cochlea in the retrofenestral subgroup. CT highlights differences in the density of the capsule's outline, the so called double ring sign, which is a low density demineralised endochondral defect outlining the cochlea[7,9]. The density of disease foci increases in otosclerosis giving an appearance resembling normal otic capsule bone thereby complicating diagnosis and increasing the false negative rates[1,2,8].

HRCT may also be useful in distinguishing between otosclerosis and other pathological conditions such as tympanosclerosis, cholesteatoma, ossicular fixation and congenital malformations[9-11]. Its use in the preoperative stage for otosclerosis surgery remains debatable[12]. The aim of this study is to evaluate the sensitivity and specificity of HRCT in the diagnosis of otosclerosis using the best available evidence.

MATERIALS AND METHODS

A contemporary literature review regarding the use of HRCT imaging in the diagnosis of otosclerosis was undertaken. A PubMed, MEDLINE and Google Scholar database search using terms "high resolution computed tomography", "HRCT", "CT", "otosclerosis", "diagnosis", "sensitivity", "specificity" in all combinations was completed. Abstracts were reviewed independently by two authors and relevant articles were then evaluated. Inclusion criteria were Level Ⅰ-Ⅲ studies where a diagnostic work up consisting of history and otolaryngology examination; speech/pure tone audiometry; tympanometry; and imaging in the form of HCRT had been carried out. We also included other studies where a CT diagnosis of otosclerosis was confirmed histologically in the absence of clinical information. Exclusion criteria were level Ⅳ-Ⅴ evidence, studies where HRCT was used postoperatively and studies prior to 2000.

Level of evidence was assigned in accordance with the Oxford Centre for Evidence-based Medicine guidance, in a hierarchy of evidence strength from randomised controlled trials (level Ⅰ), cohort studies (level Ⅱ), case-control studies (level Ⅲ), case series (level Ⅳ) to expert opinion and, case reports (level Ⅴ) with suffixes "a" and "b" denoting a systematic review and an individual study respectively[13].

Statistical analysis

Statistical analysis was performed using MedCalc (Ostend, Belgium).

RESULTS

Figure 1 summarises the PRISMA systematic review flow diagram; the checklist is available as a supplementary file.

The 5 level Ⅲ studies (Table 1) had a combined pool of 206 ears and 130 patients. A HRCT bone protocol was utilised in all studies. Axial and coronal

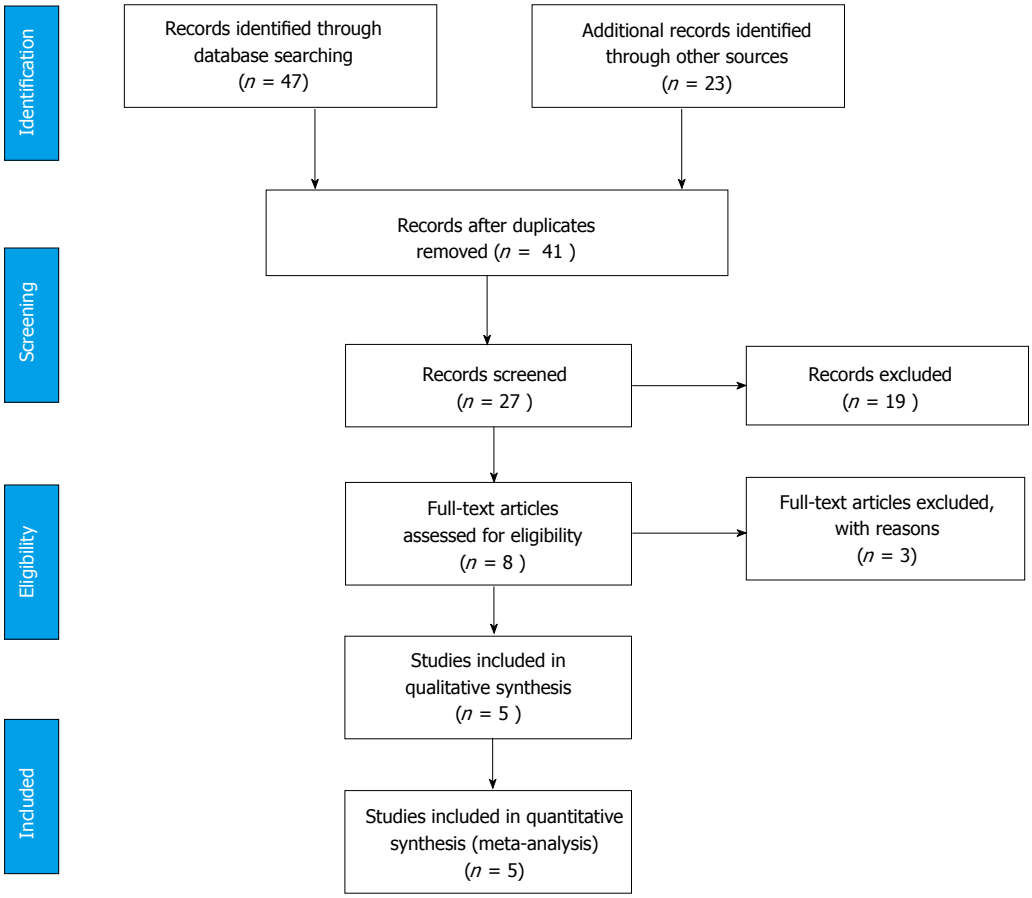

Figure 1 PRISMA flow diagram.

Table 1 Studies included in analysis

Ref.	Year	Level of evidence	No. of patients	Control group (*n*)	Sensitivity	Specificity
Grayeli *et al*[15]	2004	IIIb	10	33	70%	100%
Vicente *et al*[8]	2006	IIIb	54	22	87%	82%
Lee *et al*[2]	2009	IIIb	22	15	46%	100%
Zhu *et al*[14]	2010	IIIb	34	33	12%	100%
Quesnel *et al*[1]	2013	IIIb	10	36	80%	92%

reconstruction of the HRCT images with a slice thickness ranging from 0.6-2 mm were reviewed on a computerised picture archiving system and analysed in a blinded fashion by a radiologist, otologist or both. Otosclerotic foci were defined as hypodense lesions in the otic capsule or thickening/obliteration of the round and oval windows.

All analysed studies used control groups. The age and sex of the control group was not always included in the studies. There was a clear definition of control groups and we judged the risk of bias to be low, given that these included confirmed otosclerosis negative groups, vestibular schwannoma patients and contralateral ears in facial palsy patients.

Quantitative synthesis analysis demonstrated low sensitivity of 58% (95%CI: 49.4-66.9), a high specificity of 95% (95%CI: 89.9-98.0) and a positive predictive value of 92% (95%CI: 84.1-95.8). Negative predictive value was 71% (95%CI: 66.1-74.7) (Figure 2). The majority of the otosclerotic foci identified on CT were in the fenestral region and a combination of fenestral and retrofenestral foci was second most common.

Quesnel *et al*[1]'s study demonstrated an excellent correlation between CT imaging on a series of temporal bones with otosclerosis and corresponding histology slides of the same. The same study also concluded that CT can diagnose endosteal margin involvement (63% sensitivity) but cannot be relied upon to exclude it[1].

Lee *et al*[2]'s study specifically focused on a specific ethnic group (Taiwanese) with the ultimate objective of elucidating the tomographic findings of otosclerosis in that group.

In Zhu *et al*[14]'s study all positive results had a double ring sign on HRCT. This study was the outlier

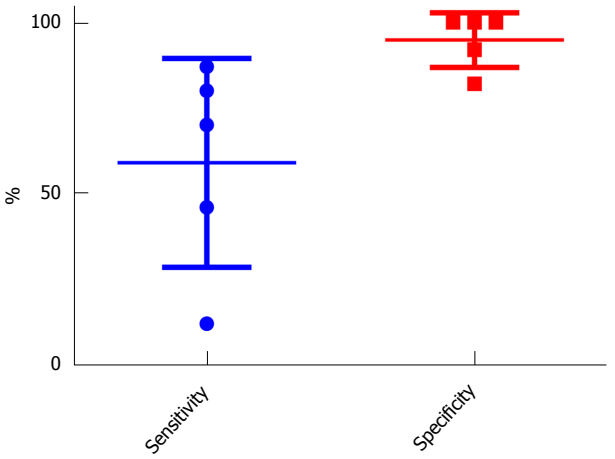

Figure 2 Box and Whisper Plot highlighting range of sensitivity and specificity.

by some distance and markedly affected the overall sensitivity of the pooled analysis. It is questionable that such a low diagnostic performance (4 of 34) should be possible and it is notable that some data was extrapolated as the primary aim of this study, like Zhu *et al*[14], was to assess the role of automated bone densitometry to diagnose otosclerosis. However, the study was retained within the analysis.

Quesnel *et al*[1] demonstrated a false positive rate of 8% (3/36) in their control group. These false positive cases which had appeared as hypodense lesions like otospongiotic foci were shown to be areas of increased connective tissue and vessels on histology. In another study a hypodense area in the anterior vestibule of 1 temporal bone in the control group was identified and judged to be a silent otosclerotic foci even though the subject was asymptomatic[8]. This was purely speculative and was not confirmed surgically.

A longer duration of disease was linked to multiple lesions in the otic capsule, false negative rates and larger preoperative air-bone gap (Vicente *et al*[8], 2006 and Lee *et al*[2], 2009).

DISCUSSION

In this review, we sought to elucidate the diagnostic performance of HRCT in otosclerosis using current level I-III studies. Numerous level IV and V papers have reported a wide-ranging sensitivity between 34% and 95%, with more recent studies suggesting values above 90%[10]. HRCT scans in otosclerosis are typically acquired using a bone algorithm with a slice thickness of 1 mm or less; slice thickness greater than 1 mm leads to increased false negative rates. Various studies have demonstrated that the sensitivity of HRCT is limited by inframillimetre and superficial foci, inactive disease, and density variations of less than 200 hounsfield units which are imperceptible to the naked eye[7,10].

The advent of improved CT scanning machines with improved collimation is thought to have raised the quality of the images available for analysis[1,2]. This, allied to the use of computerised workstations such as PACS for image analysis, has led to a higher diagnostic yield. Computerised workstations afford the ability to zoom in and scroll through images leading to a better appreciation of subtle abnormalities[16].

Overall, the analysed studies demonstrated a low sensitivity, high specificity and a high positive predictive value. However, there were wide confidence intervals particularly in the sensitivity, largely due to Zhu *et al*[14] study (12%). This study has limitations and has a particularly poor sensitivity in comparison to all other studies, possibly in part due to their primary aim being a densitometry study alongside with possible differing expertise levels. Other considerations include the disparate characteristics of the tested populations and the possible differences in the stages of the disease when the scans were performed. For instance, Lee *et al*[2]'s study (46% sensitivity) focused exclusively on a Taiwanese study group. With previous reports[17,18] suggesting a low sensitivity and incidence in other Asian ethnic groups it is impossible to ascertain whether the relatively low sensitivity in Lee *et al*[2]'s study is due to ethnic differences per se or is a manifestation of other factors such as patients presenting late in the otosclerotic phase. The rarity of the disease in Asians and the dearth of otologists with expertise in stapes surgery has led to a preference for non-surgical treatment amongst the greater proportion of patients with otosclerosis within the Taiwanese subgroup[2]. These factors are inevitably linked to the late presentation and arguably the low sensitivity on HRCT. Wider application of these findings is limited by the unique characteristics of the subgroup.

Quesnel *et al*[1] provide some useful insight into the relationship between HRCT and the size of disease foci. By matching presumed foci of otosclerosis identified on axial imaging with corresponding histology slides they demonstrate a sensitivity of 80%. The false negative results were due to the presence of an inframillimetres lesion which interestingly had not become clinically apparent. By correlating HRCT findings and histology, Quesnel *et al*[1] provide good evidence for the utility of HRCT in otosclerosis given that clinical/histopathological diagnosis is the gold standard in confirming pathology. Unfortunately their study is limited by a small sample size (18 ears) and the fact that the conditions under which the study was carried out are not easily reproducible clinically.

Our review shows that HRCT is better at identifying fenestral otospongiosis, thus confirming findings from previous studies. Identifying retrofenestral and endosteal margin involvement remains challenging notwithstanding that retrofenesteral otosclerosis is less common than fenesteral disease[8,10,14]. Studies have reported the limitations of HRCT in diagnosing retrofenestral otosclerosis with Dudau *et al*[19] sug-

gesting a sensitivity of 58%. The main areas of interest in retrofenesteral otosclerosis are the cochlear, pericochlear, and the areas anterior to the round window niche[1,15]. Clinically, the presence of cochlear disease has implications for planning treatment and counselling patients because of the risk of developing sensorineural hearing loss. This makes preoperative diagnosis useful.

Unfortunately, CT diagnosis remains problematic particularly where otospongiotic foci are small and where other conditions that demineralise the otic capsule such as osteogenesis imperfecta, Paget's disease or syphilis are considered[2,8]. These limitations are highlighted in Quesnel *et al*[1]'s study where CT had a sensitivity of 63% in identifying endosteal margin involvement.[1]The false negatives where due to inframillimetre disease. This illustrates that while HRCT can identify endosteal lesions it cannot be relied upon to conclusively rule it out.

Quesnel *et al*[1] and Vicente *et al*[8]'s studies identified abnormalities on HRCT in their respective control groups. Having dismissed findings of mild pericochlear lucency as a non-specific sign and therefore not necessarily suggestive of otosclerosis, Vicente *et al*[8] concluded that a hypodense focus anterior to the wall of the vestibule in one of the control ears was suggestive of silent otosclerosis. This taken in context with Quesnel *et al*[1]'s study where presumed area of otosclerotic foci on HRCT were shown to be areas of connective tissue and vessels on histology highlights the limitations of HRCT in diagnosing otosclerosis: Normal variants and other disease processes can appear as otosclerosis on HRCT[1,8]. Diagnosis of otosclerosis remains clinical and HRCT can play an ancillary role.

Study limitations

The studies included in our review used small sample sizes which makes them vulnerable to some of the limitations associated with such studies, *i.e.*, underpowered, with large confidence intervals and heterogeneity. In addition, we have pooled data from disparate groups which adds to the limitations of using small samples. This, however, must be taken in the context of an overall dearth in studies that are level Ⅲ or above whose primary aim is to investigate the utility of HRCT in diagnosing otosclerosis. Also, 2 of the 5 studies reviewed are retrospective and therefore prone to the shortcomings of such studies. Furthermore, because we have relied upon authors reporting of methodology and results for quality assessment and data extraction we cannot eliminate all bias.

The sensitivity and specificity of HRCT in diagnosing otosclerosis were not always the primary objective of all the studies included; in some studies, this was an indirect measure. For instance, in studies examining the utility of HRCT bone densitometry in otosclerosis (Grayeli *et al*[15] 2004 and Zhu *et al*[14] 2010). Zhu's study in particular demonstrates an outlying sensitivity that had to be extrapolated from their study. Had this study been excluded the sensitivity of this pooled dataset would be 71%. It is unusual to have such a low diagnostic performance and this may reflect patient factors, disease factors (*i.e.*, advanced disease) or local expertise factors. This demonstrates the inherent difficulty in pooling data from differing authors and studies and serves as a significant limiting factor in this analysis.

In conclusion, Based on current level Ⅲ evidence HRCT has a high specificity and positive predictive value and a relatively low sensitivity in diagnosing otosclerosis. HRCT has a high sensitivity in identifying the more prevalent fenestral subtype of otosclerosis, particularly lesions in the fissula ante fenestram.

Inframillimetres lesions, retrofenestral lesions and dense sclerotic lesions present a diagnostic challenge despite the advent of more advanced CT scanners and better understanding of otosclerosis as a disease process. Diagnosis of otosclerosis remains clinical and HRCT can be a useful adjunct especially when assessing the extent of disease and when excluding other causes.

COMMENTS

Background

Otosclerosis is focal bone dyscrasia of unknown aetiology which predominantly affects only the endochondral bone of the otic capsule in humans. Patients typically present with conductive hearing loss. The diagnosis of otosclerosis is based on a combination of medical history, physical examination, audiological testing and imaging.

Research frontiers

High resolution computed tomography (HRCT) of the temporal bones is the current imaging modality of choice in the investigation of otosclerosis. However, as demonstrated in this study and others, it has variable sensitivity and specificity.

Innovations and breakthroughs

This study highlights the value and limitations of HRCT in the diagnosis of Otosclerosis. Some studies in the literature are exploring the utility of cone beam computed tomography (CBCT) as an alternative to HRCT in the investigation of otosclerosis. However, these are in their infancy and time will tell whether CBCT supersedes HRCT as the modality of choice in imaging the middle ear.

Applications

HRCT is the gold standard imaging technique in investigating the middle ear. It may be useful in distinguishing between otosclerosis and other pathological conditions of the middle ear such as tympanosclerosis, cholesteatoma, ossicular fixation and congenital malformations

Peer-review

Otosclerosis is a bony dyscrasia of the inner ear otic capsule. HRCT has a significant role in imaging the labyrinthine and bony capsule of the temporal bone. The extent of otosclerosis into the cochlear capsule can be quantitatively evaluated using densitometric measurements. In this manuscript, the authors focused on the sensitivity and specificity of HRCT in the diagnosis of otosclerosis. This systematic review indicates that HRCT is a useful imaging method in diagnosis of otosclerosis [HRCT has a high specificity (98%) and low sensitivity (63%) in diagnosing otosclerosis], supported by level Ⅲ evidence. This review has some significance for clinicians and researchers working.

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CASE REPORT

Post traumatic dural sinus thrombosis following epidural hematoma: Literature review and case report

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Institutional review board statement: This case report was exempt from the Institutional Review Board standards at Sapienza University of Rome.

Informed consent statement: The patient gave his written informed consent authorizing use and disclosure of his protected health information.

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Abstract

Dural sinus thrombosis following a head trauma is a rare condition, described in literature along with the lack of consensus regarding diagnosis and management. We present a case of a fifty-year-old man with a head injury and combined supratentorial-subtentorial epidural hematoma who was treated conservatively through the administration of low molecular weight heparin. The diagnosis and management of this condition are discussed based on a literature review. The early diagnosis may prevent potentially treatable poor outcomes.

Key words: Dural sinus thrombosis; Epidural hematoma; Low molecular weight heparin

Core tip: Dural sinus thrombosis (DST) is a rare although serious clinicopathological entity that causes approximately 0.5% of all stroke cases. Head trauma may be identified as a possible cause of DST. The lack of consensus regarding the most appropriate therapeutic strategy prompted us to describe this unusual case of transverse sinus thrombosis caused by a combined supra-subtentorial haematoma. The absence of symptoms of the patient convinced us to assume a conservative behaviour which consisted in the administration of low molecular weight heparin after the computed tomography scan had

documented the stability of the extradural collection. Our strategy leads to the recanalization of the sinus.

Pescatori L, Tropeano MP, Mancarella C, Prizio E, Santoro G, Domenicucci M. Post traumatic dural sinus thrombosis following epidural hematoma: Literature review and case report. *World J Clin Cases* 2017; 5(7): 292-298 Available from: URL: http://www.wjgnet.com/2307-8960/full/v5/i7/292.htm DOI: http://dx.doi.org/10.12998/wjcc.v5.i7.292

INTRODUCTION

Dural sinus thrombosis (DST) is a rare although serious clinicopathological entity that causes approximately 0.5% of all stroke cases[1]. Superior sagittal sinus as well as transverse sinus are more affected than other dural sinuses[1]. Head trauma may be identified as a possible cause of DST. In particular, depressed skull fractures occurring at the site of the dural sinuses as well as epidural or subdural hematoma have been found to be associated with DST[2-6]. Here we describe the case of a man who reported the occlusion of the transverse sinus as the consequence of the development of a combined supratentorial-subtentorial epidural hematoma. The patient was treated conservatively through the administration of low molecular weight heparin (LMWH). We discuss the physiopathologycal hypothesis, the clinic-radiological aspects as well as the management options reviewing the literature.

CASE REPORT

This is the case of a fifty-year-old man who was hospitalized after being involved in a car accident in which he reported a concussive head trauma. Except for the trauma he did not have a significant history of illness. The patient was subjected to a brain computed tomography (CT) scan which showed the presence of a combined right supra-subtentorial hematoma (Figure 1). Clinical evaluation of the patient did not reveal any neurological signs except for a mild headache. Because of the site of the hematoma, an involvement of the transverse sinus was suspected. As a consequence a brain magnetic resonance imaging (MRI) with arterial and venous reconstruction was performed. The MRI confirmed the presence of the hematoma involving the supratentorial and the subtentorial compartment. Furthermore the venous study did not show any appreciable signal of blood flow within the right transverse sinus. This radiological finding was likely to be due to the occlusion of the sinus (Figures 2 and 3). Because of the absence of neurological signs as well as the patency of the contralateral dural sinuses system, a conservative management was adopted. A CT scan performed 48 h after the accident showed a slight increase in the size of the hematoma (Figure 4). As a consequence, administration of LMWH was delayed. By the 10th post-traumatic day two more brain CT scan had been performed which had shown the progressive decrease in the size of the hematoma (Figure 5). This reduction encouraged us to begin the administration of LMWH. On 15th post-traumatic day the patient was discharged at home. During the subsequent 23 d the patient did not experience any symptoms related to the trauma. On 24th post-traumatic day, he began to complain of mild headache, vertigo and nausea. Since the symptoms were not responsive to oral analgesics and antiemetic drugs, the patient came back to the Emergency Department of our Hospital. A new brain CT scan was performed. It showed a further reduction of the size of both hematomas. Given the clinical history, a new brain MRIs can with venous angiographic reconstruction was performed. The new MRI confirmed the further decrease in the size of the epidural hematomas. Angiographic reconstructions of the dural sinuses showed that, although characterized by a less intensity in comparison with the contralateral sinus, the blood flow signal within the previously occluded transverse sinus was now visible. These radiological findings were likely to be due to the partial recanalization of the sinus (Figure 6). Symptoms progressively disappeared and after a brief period of hospitalization the patient was discharged at home.

DISCUSSION

DST is a rare although serious clinicopathological entity that causes approximately 0.5% of all stroke cases. The signs and symptoms are extremely varied and non specific. Cerebral sinus thrombus formation due to head injury has been postulated to be caused by a sinus endothelial injury, thrombus extension from scalp abrasions, or damage to the emissary veins[7]. Sinus thrombosis can often occur with thrombosis of the cerebral veins, leading to cytotoxic and vasogenic edema[8]. The sinus thrombi lead directly to the decreased absorption of cerebrospinal fluid because of the increased sinus venous pressure, resulting in intracranial hypertension. Patients with cerebral sinus thrombosis most often present with severe headache that can be gradual or acute in nature. Patients can also have symptoms of increased intracranial pressure, including nausea and vomiting. Some patients have seizures. In 1946, Ecker described the first case of head injury associated with DST. Since then, other trauma-induced DSTs have been reported in cases of head injuries[5,9,10]. Ochagavia announced that the incidence of DST was 4% after penetrating head trauma[10]. However, Stiefel *et al*[11] reported that he found DST with an incidence of 6.8% in the pediatric age group. There are two series on post traumatic DST in children but sporadic case reports in adults and in

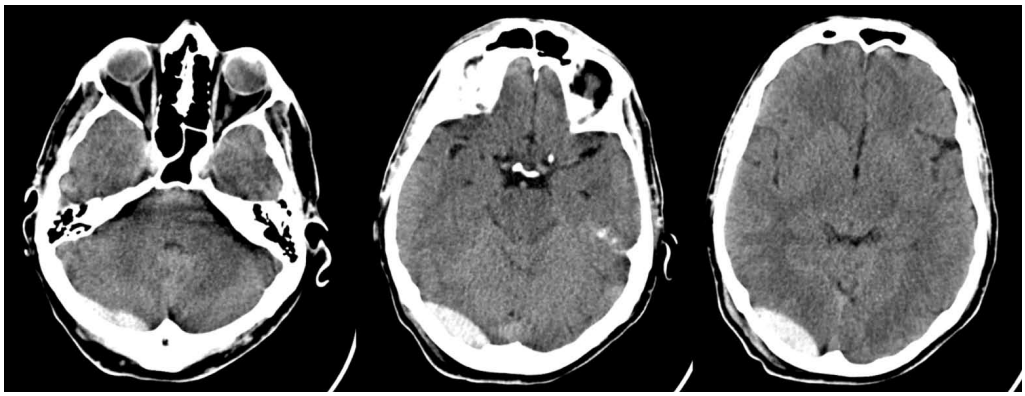

Figure 1 First computed tomography scan performed after the trauma. It shows the presence of a combined supra-subtentorial epidural hematoma.

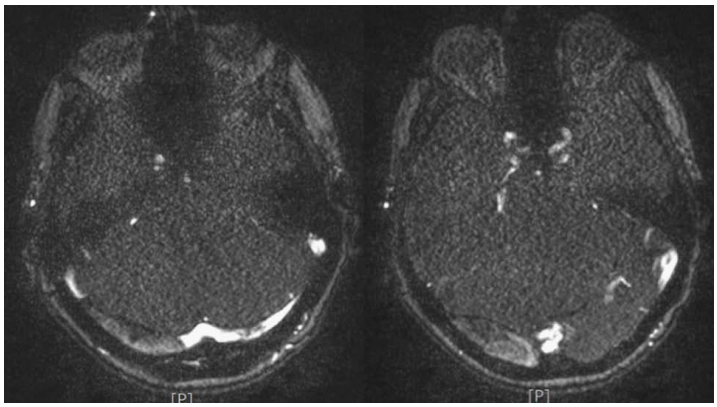

Figure 2 Angio-magnetic resonance imaging documenting the absence of the blood signal within the sinus as well as the epidural hematoma compressing the cerebellum and the sinus wall.

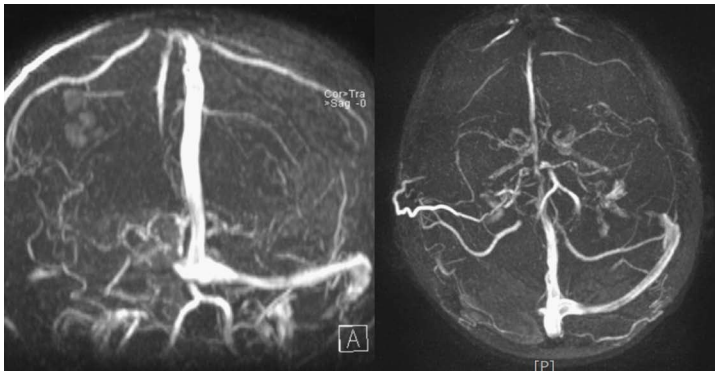

Figure 3 Angio-magnetic resonance imaging three dimensional reconstruction of the dural sinus system. It is not possible to appreciate any signal within the right transverse sinus as it happens for dural sinus occlusion. Notice the patency of the contralateral dural sinus complex.

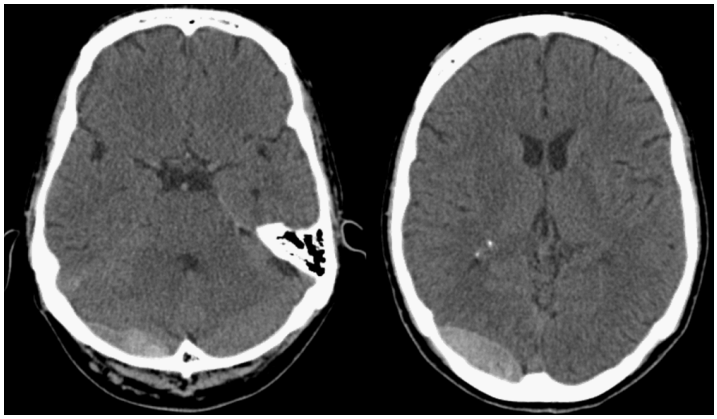

Figure 4 Computed tomography scan performed 48 h after the trauma. An increase of the size of the ematoma was identified by the radiologist. As a consequence we decided to postpone the administration of low molecular weight heparin.

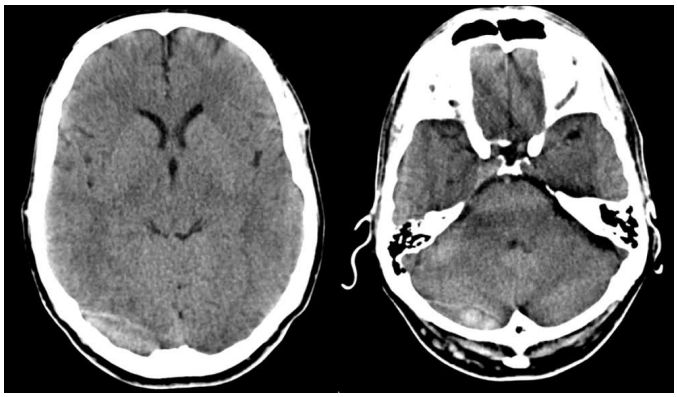

Figure 5 By the 10th post-traumatic day two more brain computed tomography scan had been performed showing the partial reabsorption of the hematoma. From this moment the administration of low molecular weight heparin heparin began.

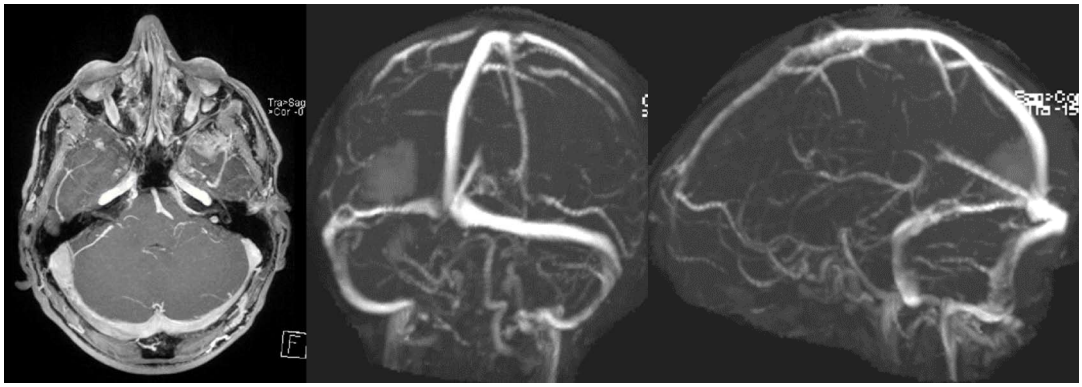

Figure 6 Brain magnetic resonance imaging with angiographic reconstruction of the venous system performed on 24th post-traumatic day after the onset of posterior cranial fossa symptoms. Magnetic resonance imaging shows the partial recanalization of the right transverse sinus as well as the almost complete reabsorption of the epidural hematoma.

Table 1 Summary of reported cases with cerebral sinus thrombosis due to head injury in the last 30 years

Ref.	Age, sex	Symptom	Skull fracture	Intracranial lesion	Treatment	Follow-up
Hesselbrock *et al*[8]	44, M	IICPS, seizure	?	Contusion	Supportive	Unknown
Taha *et al*[22]	5 (3M/2F) children	Various	3 cases	Contusion	Supportive	4 RC 1 no RC
Ochagavia *et al*[10]	27, M	Herniation due to IICPS	-	Edema	-	dead
Ferrera *et al*[17]	24, M	IICPS	+	Venous infarct	Surgery	Unknown
Stiefel *et al*[11]	8 (5F/3M) children	IICPS	All cases	-	-	6 RC 1 no RC 1 dead
Meena *et al*[9]	40, M	IICPS, seizure, hemiparesi	-	-	AC	Unknown
Satoh *et al*[21]	2, F	IICPS	-	-	Supportive	RC
Brors *et al*[13]	32, M	Cranial nerve palsy	+	Contusion	AC	RC
Erdogan *et al*[16]	1, M	IICPS	-	Venous infarct, SH	Supportive	Unknown
Owler *et al*[4]	18, M	IICPS, hemiparesi	-	Venous infarct	Supportive, surgery	Unknown
Sousa *et al*[19]	7, F	IICPS	-	-	supportive	Unknown
Muthukumar *et al*[25]	7, F	IICPS	+	-	AC	Unknown
Saad *et al*[20]	10, F	IICPS	-	-	AC	Unknown
Yuen *et al*[23]	4, F	IICPS	+	-	Supportive	RC
Dalgiç *et al*[15]	35, M	IICPS	-	-	AC	RC
	25, M	Facial palsy	+	EH	AC	No RC
Caplan *et al*[14]	27, M	IICPS, paraesthesias	+	Contusion	AC	Unknown
Bakar *et al*[12]	18, M	IICPS	+	Edema	Surgery	Unknown
Beer-Furlan *et al*[26]	3, M	IICPS	+	EH	Surgery	Dead
Lebowitz *et al*[18]	6, M	IICPS	-	SH	AC	No RC
Yun *et al*[24]	10, M	IICPS	+	EH	Supportive	RC
Our case	50, M	IICPS	-	EH	Supportive, AC	RC

M: Male; F: Female; IICPS: Increased intracranial pressure; EH: Epidural hematoma; RC: Recanalization; SH: Subdural hematoma; AC: Anticoagulation.

children have been published[4,6,12-25]. Overall, there are 32 cases including 22 children and 10 adults (Table 1). The higher number of children can be explained by the fact that the venous collateral system is not completely mature in their cerebrum. In only 3 cases (1 adult and 2 children) there was an epidural hematoma (EH). It was always associated with skull fracture. Our case is the first case reported, to our knowledge, in which the epidural hematoma was not associated to skull fracture and had a supra and subtentorial localization. In our case, although it is difficult to establish if the occlusion of the sinus was owed to the extrinsic compression of the hematoma on the sinus wall or to the development of a thrombus within the sinus, it is possible that both the phenomenon contributed to the occlusion through a cause-effect process. The extrinsic compression of the hematoma probably caused a deceleration of the blood flow within the sinus. As a consequence, according to the principles of blood stasis, modifications of the vascular wall and blood rheology enunciated by Virchow, it is likely that a thrombus within the transverse sinus developed. The initial imaging study in the evaluation of patients with possible DST is usually a brain CT scan. Magnetic resonance imaging, as well as MR angiography and venography, provide us with the most sensitive tools for detecting DST. The combination of these imaging modalities constitutes the study of choice in the diagnosis of DST. In fact the images shown by our MRI are compatible with an occlusion of the transverse sinus. There is no consensus on the overall treatment concerning surgical, radiosurgical, endovascular or conservative treatment. Identification and treatment of the underlying causes should represent the first step in the treatment of dural sinus occlusion. In case of extrinsic compression such as depressed skull fractures as well as epidural or subdural hematoma surgical removal of the identified source of compression has been advocated by several authors[12,14], even if only 1 case of post-traumatic DST related to EH, reported in literature, was underwent to surgical treatment[26]. In our case, despite the presence of the epidural hematoma without mass effect as well as the occlusion of the sinus, the complete absence of neurological symptoms encouraged us to adopt a conservative behaviour. Despite the role of antithrombotic therapy has been widely examined and several studies have been published in this sense, its use in post-traumatic DST still remain controversial, because of increased risk for venous hemorrhagic infarction[26]. A meta-analysis conducted by Coutinho *et al*[27] which included 2 randomized controlled studies investigating the role of unfractionated heparin as well as LMWH, concluded that the anticoagulant treatment can be considered safe and is associated with a better overall outcome in patients affected with DST. The EFNS guideline on the treatment of cerebral venous and sinus thrombosis in adult patients conducted by Einhäupl *et al*[28] in 2010 concludes that patients with cerebral sinus thrombosis without contraindications for anticoagulant should be treated either with body weight-adjusted subcutaneous LMWH or with dose adjusted intravenous heparin. In addition the study concluded that the use of LMWH should be considered safe despite the presence of intracranial haemorrhage. Although conscious of current literature, we decided to postpone the administration of subcutaneous LMWH because of the growth of the epidural hematoma that had been shown by a control CT scan performed 48 h after trauma. Once seriated CT scan demonstrated the progressive reduction in the size of the hematoma subcutaneous LMWH heparin was administered and continued after discharge. LMWH pharmacologically doesn't possess thrombolytic action; given this the main purpose of their administration is to prevent recurrent thrombosis and appositional thrombus growth. Data collected from different studies confirm that DST patients display a high spontaneous and intrinsic thrombolytic potential, with recanalization rates of 60% during the first 20 d as happened in our case. Thereafter, recanalization rates increase insignificantly[26]. The second MRI with angiographic and venous reconstruction performed during the second hospitalization showed that the blood flow within the transverse sinus had reappeared. The administration of LMWH as well as the progressive reabsorption of the epidural hematoma are related to the recanalization of the transverse sinus. The consequent reorganization of the venous blood flow within the dural sinus system was may explain the physiopathology of the posterior cranial fossa symptoms characterized by vertigo and headache.

DST is a rare although serious condition described in literature along with a lack of consensus regarding diagnosis and management. Most reports show good outcome and recovery, but DST might be related to a poor recovery and even lead to death. DST may be caused by post-traumatic depressed skull fractures or intracerebral hematomas compressing the sinus wall and altering the blood flow within the sinus until thrombosis, so additional diagnostic investigations should be performed in terms of DST in head trauma cases that have other risk factors. The administration of anticoagulant therapy still remains controversial but in association with the progressive reabsorption of the hematoma it could allow the recanalization of the dural sinus.

COMMENTS

Case characteristics

A fifty-year-old man was hospitalized after being involved in a car accident in which he reported a concussive head trauma.

Clinical diagnosis

Except for a mild headache, the patient didn't show neurological signs.

Differential diagnosis

Haemorrhage, concussion injury, cerebral contusion.

Laboratory diagnosis
All labs were within normal limits.

Imaging diagnosis
Computed tomography (CT) scan showed the presence of a combined right supra-subtentorial hematoma, while the magnetic resonance imaging scan showed the occlusion of the transverse sinus.

Treatment
Once seriated CT scan demonstrated the progressive reduction in the size of the hematoma subcutaneous heparin or low molecular weight heparin was administered and continued after discharge.

Related reports
Dural sinus thrombosis (DST) following a head trauma is a rare condition, described in literature along with the lack of consensus regarding diagnosis and management.

Term explanation
Dural venous sinus thrombosis is a subset of cerebral venous thrombosis. It is the presence of a blood clot in the dural venous sinuses that causes approximately 0.5% of all stroke cases. The symptoms depend mainly on which sinus is involved.

Experience and lessons
In case of head trauma the DST should always be considered. This entity is often underestimated. Recognizing this condition can prevent misdiagnosis and suggest the best treatment option. The administration of anticoagulant therapy could allow the recanalization of the dural sinus.

Peer-review
This is a rare and interesting case, which could highlight a differential diagnosis for clinical doctors.

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CASE REPORT

Rare case of cryptogenic brain abscess caused by *Raoultella ornithinolityca*

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Abstract

Cerebral abscess is a potentially fatal neurosurgical condition, despite improvements in technology, new antimicrobial agents and modern neurosurgical instruments and techniques. I report the case of a 64-year-old woman, affected by a right frontobasal brain abscess, compressing the homolateral frontal horn of lateral ventricle, with a second mass partially occupying the right orbital cavity. She presented also with inflammatory sinusopathy involving the right maxillary, ethmoid and frontal sinuses. After 14 d of clinical observation and antimicrobial therapy, the patient received a computed tomography scan, which showed growth of the cerebral mass, with a ring of peripheral contrast enhancement and surrounding edema. She promptly underwent neurosurgical treatment and recovered well, except for the sight in her right eye, which remained compromised, as before the operation. This is believed to be the first case of cryptogenic cerebral abscess caused by *Raoultella ornithinolityca* isolated from the brain, with more than 1-year follow-up.

Key words: Brain abscess; Headache; *Raoultella ornithinolityca*; Visual loss

Core tip: Brain abscess is a focal intracranial infection that evolves in a collection of pus. It could have cryptogenic origin in 10%-35% of cases. I present a 64-year-old woman affected by a frontal brain abscess that was surgically treated, from which *Raoultella ornithinolytica* (*R. ornithinolytica*) was isolated. The patient, after > 1 year, is doing well, except for her right eye that had already lost its visual power before surgery. This is believed to be the first case of cryptogenic cerebral abscess caused by *R. ornithinolytica*.

Luongo M. Rare case of cryptogenic brain abscess caused by *Raoultella ornithinolityca*. *World J Clin Cases* 2017; 5(7): 299-302 Available from: URL: http://www.wjgnet.com/2307-8960/full/v5/i7/299.htm DOI: http://dx.doi.org/10.12998/wjcc.v5.i7.299

INTRODUCTION

Brain abscess is a focal intracranial infection characterized as an area of cerebritis that evolves in a collection of pus surrounded by a vascularized capsule. Organisms can reach the central nervous system by spreading from a contiguous source of infection, hematogenous dissemination, or trauma, but there are cryptogenic brain abscesses in 10%-35% of cases. The frontal lobe is the predominant site of cerebral abscess in patients with paranasal sinusitis. *Raoultella ornithinolytica* (*R. ornithinolytica*) is an encapsulated Gram-negative bacterium and member of the Enterobacteriaceae. Human infections caused by *Raoultella* are rare. I describe a case of cryptogenic cerebral abscess caused by *R. ornithinolytica*, with good recovery after > 1 year after surgery.

CASE REPORT

A 64-year-old woman was admitted to our hospital for fever and headache. She was hospitalized in the Infectious Disease Department for observation and study. Chest X-ray and abdominal ultrasound examination were normal. Magnetic resonance imaging (MRI) with gadolinium revealed a right frontobasal brain abscess, compressing the homolateral frontal horn of the lateral ventricle, with a second mass partially occupying the right orbital cavity (Figure 1A). She presented also with inflammatory sinusopathy involving the right frontal, ethmoid and maxillary sinuses. After 14 d of clinical observation and intravenous broad-spectrum antibiotic therapy, nasal culture was performed on day 14 of hospitalization, which showed evidence of low levels of *Candida albicans*. Ophthalmological consultation revealed visual loss from her right eye, and contrast computed tomography (CT) showed an increase in abscess size, so the patient underwent prompt surgery with right frontobasal craniotomy (Figure 1B). Thanks to neuronavigation and under operative microscopy, the abscessual capsule was opened widely, in order to drain its content, and it was coagulated to avoid damage to nervous structures, given that the cerebral parenchyma in the right orbit appeared to be involved in an inflammatory reaction. Some of the mass content was sent for microbiological examination in Bactec broth and, 8 d after surgery, *R. ornithinolytica* was isolated by conventional microbiological tests. On the basis of an antibiogram, determined according to the European Committee on Antimicrobial Susceptibility Testing, and after consulting an infectious diseases specialist, the patient started intravenous therapy with metronidazole and ceftriaxone, four times and twice daily, respectively (Table 1). She received a basal CT scan that showed no residual or recurrent brain abscess.

Her general clinical conditions were improved but, on day 30 in hospital (approximately 2 wk after surgery) she developed right-side pneumonia with pleural effusion, caused by *Klebsiella pneumoniae*, which was treated by intravenous ceftriaxone and ciprofloxacin twice daily, together with amphotericin B and amikacin once daily (Table 1). During the last month she was free from antimicrobial therapy, without infectious problems, but it was necessary to correct persistent hypokalemia, presented by the patient from the first time. The patient was discharged after approximately 3 mo of hospitalization and she is currently well.

DISCUSSION

R. ornithinolytica is an encapsulated, aerobic, non-motile, blood-borne Gram-negative bacterium belonging to the Enterobacteriaceae, which is frequently misidentified as *Klebsiella* spp. It was first described by Sakazaki *et al*[1] in 1989 and it can be isolated from aquatic environments, insects, fish and brackish water. It can cause fish poisoning because of its capacity to produce histamine and it can cause headache, flushing, abdominal cramps, pruritus, and rarely, bradycardia, bronchospasm and hypotension. Over the years, *R. ornithinolytica* has emerged as an infrequent cause of human infections, with about 10 cases reported linking the bacterium to bacteremia, sepsis, and soft tissue and other infections, as described by Nakasone *et al*[2] in their article about a case of community-acquired urinary infection.

An important study on clinical characteristics of *R. ornithinolytica* bacteremia focused on its unfavorable outcomes, compared to bacteremia caused by other *Raoultella* spp. The study analyzed 16 patients (11 male and 5 female) over 10 years, with a mean age of 55.7 years; all but one had an underlying malignant condition and seven had infections associated with the biliary tract. They found that the overall mortality of *R. ornithinolytica* bacteremia could be compared to that of *Klebsiella* spp., and it was reported to be 20%-25%. In addition, suggested an increased risk of *R. ornithinolytica* bacteremia in patients affected by underlying malignant conditions extending to the biliary tract[3]. Even though some cases of biliary tract infection, urinary infection and bacteremia have been reported, there is not much information about clinical features and outcomes of *R. ornithinolytica*. A recent review by Seng and colleagues discusses the largest series reported to date of 86 cases from four French universities over 12 years (with half of cases in 2015), and emphasizes different important characteristics such as a high rate of hospital-acquired infection (49%). Besides comorbidity and risk factors previously reported such as solid tumor, post-urethra trauma, and post invasive procedures, Seng *et al*[4] found that half of the patients had diabetes or immunodeficiency, and they described infections not previously reported, including pleural effusion, meningitis and cerebral

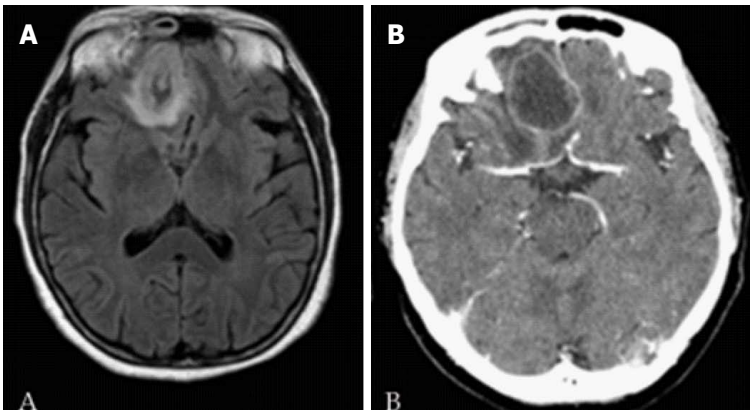

Figure 1 Preoperative images. A: Magnetic resonance imaging with gadolium showing right frontobasal brain abscess and a second mass occupying the right orbit; B: Contrast-enhanced computed tomography scan.

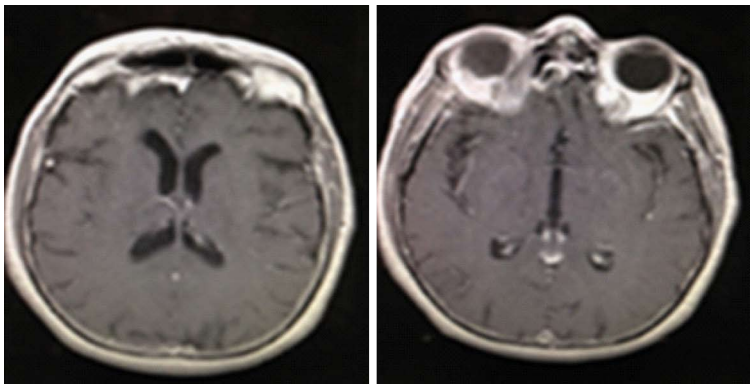

Figure 2 Magnetic resonance imaging performed 14 mo after surgery.

Table 1 Scheme summarizing the antimicrobial drugs assumed by the patient during the hospitalization

Drug	Dosage	Administration route	Duration of therapy, d	Frequency of administration, d
Ceftriaxone	2 g	Intravenous	50	2
Amphotericin b	50 mg	Intravenous	20	1
Amikacin	500 mg	Intravenous	12	1
Ciprofloxacin	200 mg	Intravenous	11	2

abscess. The cerebral abscess described by Seng *et al*[4] was secondary to a craniotomy for head trauma and not spontaneous as in the present case[4].

The frontal lobe is the predominant site in patients with brain abscess secondary to paranasal sinusitis, so I thought that the cerebral abscess in my patient was secondary to sinusopathy, but nasal culture only isolated a low number of *C. albicans*. The patient has diabetes and experienced pleural effusion caused by *K. pneumoniae* during hospitalization, > 2 wk after surgery, so this case was not related to any condition previously described.

In summary this is the report of a rare case of brain abscess caused by *R. ornithinolytica* that was successfully treated by intravenous antibiotics and prompt surgical intervention. This is believed to be the first cryptogenic brain abscess caused by *R. ornithinolytica*, with MRI showing complete surgical removal and no recurrence after > 1 year (Figure 2). It could be important to focus attention on this bacterium in order to understand better and eventually prevent occurrence of this potentially fatal condition.

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COMMENTS

Case characteristics

A 64-year-old woman with inflammatory sinosupathy and, a few days later, visual loss in the right eye.

Clinical diagnosis

Fever and headache with visual disturbance.

Differential diagnosis

Central nervous system inflammatory conditions, cerebral abscess, meningitis, and brain tumor.

Laboratory diagnosis

Nasal culture and microbiological examination of the surgically removed cerebral

mass.

Imaging diagnosis
Magnetic resonance imaging with gadolinium revealing the presence of a right frontobasal brain abscess and a second mass partially occupying the right orbital cavity.

Pathological diagnosis
Some of the mass content was sent for microbiological examination and *Raoultella ornithinolytica* was isolated by conventional microbiological tests.

Treatment
Right frontobasal craniotomy was performed and the abscessual capsule was opened widely and coagulated. On the basis of an antibiogram and after consulting an infectious diseases specialist, the patient started intravenous therapy with antibiotics.

Related reports
R. ornithinolytica is a Gram-negative bacterium belonging to the family Enterobacteriaceae that is frequently misidentified as *Klebsiella* spp.. It has potent virulence and is rare in clinical situations but results in a high risk of bacteremia in patients affected by underlying malignant conditions extending to the biliary tract.

Term explanation
R. ornithinolytica brain abscess is a rare condition because, over the years, the bacterium has mainly been responsible for infrequent but important human urinary tract infections.

Experience and lessons
Brain abscess caused by *R. ornithinolytica* is a rare condition to be aware of in daily clinical practice in order to understand, prevent and treat it, through a combination of prompt surgical intervention and intravenous antibiotics.

Peer-review
This is a very interesting presentation about a rare etiology for brain abscess. It is a case that reminds us to be aware of this condition in the daily practice. The paper is well structured and written.

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CASE REPORT

Is dengue emerging as important cause of acute liver failure in endemic regions?

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Abstract

Dengue virus infection continues to be major public health problem in large part of world. The epidemiology of dengue viral infection is becoming increasingly complex and has substantially changed over almost past six decades not only in terms of prevalent strains and geographical locations but also in terms of disease severity and atypical presentations. Though liver is the most common organ affected but is generally asymptomatic. We present a case of infant with severe dengue who died of fulminant hepatic failure and showed pan lobular necrosis on post mortem liver biopsy. The case is being presented to highlight life threatening complication of dengue in young children, and dengue viral infection as a cause of acute liver failure in endemic areas. Thus dengue fever should also be considered as one of the differential diagnosis in children presenting with fever and fulminant hepatic failure in endemic regions.

Key words: Dengue viral infection; Acute liver failure; Panlobular hepatic necrosis; Hepatomegaly; Transaminitis

Core tip: Dengue infection has more severe manifestation in young children and it should be considered as a cause of acute liver failure in children residing in endemic area.

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INTRODUCTION

Dengue virus (DENV) infections continue to be a major public health problem in large parts of the world[1]. It is one of the most important causes of febrile illness in endemic regions. DENV affects various organs during the period of viremia including liver and brain. Liver is the most common organ affected but is generally asymptomatic. Liver involvement ranges from derangement of liver enzymes, increased bilirubin to clinical jaundice and acute liver failure rarely. DENV is known to cause severe manifestation in infants. Virus virulence factor and detrimental host response are responsible for severe manifestations of dengue.

We present a case of infant with severe dengue who died of fulminant hepatic failure and showed pan lobular necrosis on post mortem liver biopsy. The case is again a reminder of life threatening complication of dengue in young children, and DENV as a cause of acute liver failure in endemic areas.

CASE REPORT

A 3-mo-old male, presented, with jaundice and frank bleeding from multiple sites (gastrointestinal, nasal, skin). Child was relatively asymptomatic 1 wk back then developed high grade fever with running nose. On 3rd day of illness, child had one episode of seizure followed by altered sensorium which persisted beyond postictal period. He was documented to be afebrile for 2 d before developing frank bleeding, abdominal distension and worsening of sensorium. On examination, child was sick looking with pallor, deep icterus and rapid pulse. Abdominal examination revealed hepatomegaly with liver 8 cm below the costal margin with sharp border and mild tenderness.

The differential diagnosis of acute infective viral hepatitis, complicated malaria, leptospirosis, severe dengue was kept and investigations ordered. Baseline investigations are shown in Table 1.

Child met the criteria for acute liver failure defined by the Pediatric Acute Liver Failure study group as there was no past history of chronic liver disease, his coagulopathy was not corrected after giving vitamin K and he was in hepatic encephalopathy with deranged PT/INR. Child was managed with supportive care (vitamin K, fresh frozen plasma infusion for coagulopathy), broad spectrum antibiotic, monitoring for electrolyte abnormality and hypoglycaemia and management of raised intracranial pressure. Despite these measures, there was progressive deterioration in clinical condition with requirement for mechanical ventilation. Child succumbed to the illness, 12 h after admission due to massive bleed and refractory shock, in the setting of fulminant hepatic failure.

The post-mortem liver biopsy showed multilobular and pan lobular hepatic necrosis with predominant involvement of centrilobular and midzonal regions with relative sparing of zone 1 (Figure 1). Thus, final diagnosis of severe dengue fever[1] with acute liver failure was made.

DISCUSSION

Dengue has recently emerged as the most rapidly spreading arboviral disease with an estimated 390 million dengue infections annually[2]. The pattern of dengue fever in Indian subcontinent has changed substantially in the last 60 years shifting from sporadic epidemic disease to an endemic one. With the endemicity, the disease severity has changed and atypical presentations like acute liver failure, myositis, hemophagocytic syndrome myositis are increasingly being reported[3].

Dengue fever has a spectrum of clinical manifestations ranging from self-limited illness to fulminant course resulting in death. Younger age is a risk factor for severe manifestation of dengue. Virus virulence factor and detrimental host response are responsible for severe manifestations of dengue. Pathogenesis of the different manifestations of dengue virus infections in humans is still an area of research. The spectrum of clinical manifestation of dengue involves relatively benign subclinical infection or dengue fever to life-threatening dengue haemorrhagic fever, and dengue shock syndrome (DSS). Differential targeting of specific vascular beds may cause localized vascular hyperpermeability seen in DSS. Hepatic involvement is usually subclinical but dengue virus is known to have hepatotoxic effect. Derangement of liver enzymes and jaundice may be seen and rarely it may cause acute liver failure. In presence of detrimental host response like young age as in our case, the rare manifestations of dengue are increasingly being recognized in endemic areas.

With considerable decrease in the prevalence of hepatitis B due to universal immunization and hepatitis A due to improved sanitation dengue has emerged as an important cause of acute liver failure in children especially during epidemics[4].

Hepatic involvement in dengue fever presents with liver enlargement and elevated transaminases[5,6]. In most of the studies, elevation in AST is more than ALT. The increased AST/ALT ratio seen in dengue fever is rarely observed in Hepatitis A, B or C viruses induced acute hepatitis[7]. The mortality rate is reported to be 50% to 66% in childhood dengue infection associated ALF[8].

The pathogenesis of hepatic injury in dengue infection remains elusive however it is believed to be multi factorial and various factors implicated include direct viral injury, dysregulated immune response and hypoxic/ischemic injury. The frequent use of acetamino-

Table 1 Baseline investigation of the infant with acute liver failure caused by Dengue infection

Investigation	Result	Reference range
Hb	8.4 g/dL (haematocrit 25.9%)	10.0-13.2 g/dL
Total leukocyte count	14000/mm^3	6-17.2 × 10^3/uL
Differential count	Neutrophil (N) 68, Lymphocyte (L) 25	N 15-45, L-47-77
Platelet	98 × 10^3 cells/mm^3	1.5-4.5
Peripheral smear	No malarial parasite, no atypical cell, microcytic hypochromic picture	
ALT	3853 IU	13-45 IU/L
AST	20861 IU	9-80 IU/L
Total bilirubin	8.28 mg/dL	< 1.2 mg/dL
Direct bilirubin	4.59 mg/dL	< 0.2 mg/dL
Total protein	4.02 g/dL	
Alkaline phosphatase	171 IU	80-280 IU
Prothrombin time	56.4 s	11.5-15.3
Control	12.4 s	
CRP	90 mg/L	0-5 mg/L
Renal function test	Urea 121.6 mg/dL	7-20 mg/dL
	Creatinine -0.3	0.2-0.4 mg/dL
Infective etiology work up	LDH antigen for malarial parasite - negative	
	Chikungunya PCR - negative	
	Hepatitis A IgM, anti hepatitis E IgM - negative	
	Hepatitis B surface antigen - negative	
	Hepatitis C IgM - negative	
	Dengue NS-1 antigen and IgM antibody - positive	
	(serum capture enzyme linked immunosorbent assay)	
	Leptospira IgM - negative	

ALT: Alanine transaminase; AST: Aspartate transaminase.

Table 2 Differential diagnosis in cases presenting with fever and acute hepatic failure[12]

	Acute viral hepatitis	Complicated malaria	Leptospirosis	Dengue associated ALF
High grade fever	Absent	Present	Present	Present
Haematocrit	Normal	Normal	Falls	Raised
Platelet	Normal	Decreased	Normal	Decreased
SGOT	Raised	Normal	Normal	Raised
SGPT	Raised	Normal	Normal	Raised
SGOT/SGPT	Raised	Normal	Normal	Markedly raised
Hypoalbuminemia	Not seen in acute viral hepatitis may be seen in acute on chronic cases	Absent	Absent	Present especially in DHF due to plasma leakage[11]
Renal function test	Deranged	Normal	Normal	Deranged in DHF and DSS due to hypotension
Plasma leak	Absent	Rare	absent	Present
Peripheral smear	-	Malaria Parasite	-	-

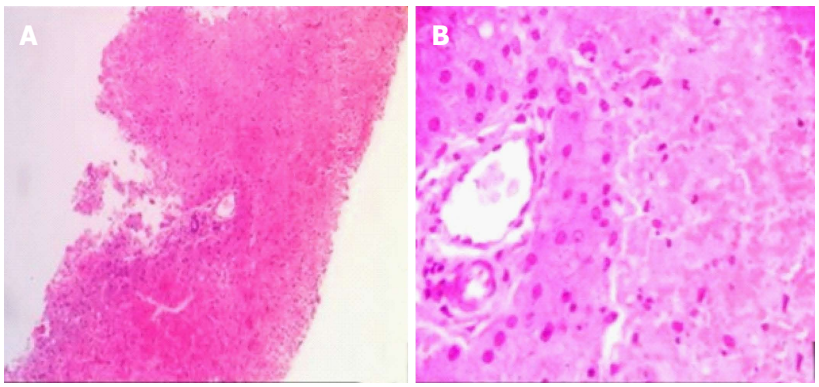

Figure 1 Liver biopsy showing multilobular and pan-lobular hepatic necrosis (A, HE × 200); Higher magnification shows relative sparing of zone 1 hepato-cytes (B, HE × 400).

phen in dengue may add to liver injury in susceptible individual[9].

Liver biopsy in fatal cases of dengue points to Hepatocytes and Kupffer cells as prime targets for dengue virus infection[10].

Several hepatic histological changes have been reported in dengue infection[9]. This includes fatty change (micro vesicular), Kupffer cells hyperplasia, and destruction, hepatic necrosis, Councilman bodies and infiltrates at the portal tract consisting of mainly

mononuclear cells. The midzonal area is most commonly involved followed by the centrilobular area. This may be due to higher susceptibility of the hepatocytes in midzonal area to anoxia but preferential targeting of the midzonal hepatocytes by dengue virus may also be a possibility.

The magnitude of liver involvement in acute phase of dengue may be missed as DENV hepatic involvement and its manifestations peaks around day 6-7 of illness[11].

The possible pointers to hepatic involvement in early phase include extreme nausea and vomiting with laboratory tests showing very high levels of AST with rise in serum bilirubin and alkaline phosphatase. Such presentation should raise the suspicion of impending liver failure (Table 2).

Primary dengue infection may lead to pan lobular hepatic necrosis. In dengue, endemic regions, dengue fever should be one of the differential for fever with fulminant hepatic failure in children.

COMMENTS

Case characteristics

A three-month-old child with fulminant hepatic failure.

Clinical diagnosis

Child was clinically diagnosed as dengue induced acute liver failure with evidence of coagulopathy and encephalopathy.

Differential diagnosis

The differential of acute liver failure in such young infant will be infective or metabolic causes. For the indexed patient infective causes were considered as the first possibility. Malaria, chikungunya, leptospirosis, hepatitis A and E were ruled out.

Laboratory diagnosis

Dengue NS1 Ag and IgM were positive by serum capture enzyme linked immunosorbent assay.

Pathological diagnosis

Panlobular hepatic necrosis caused by dengue virus infection.

Treatment

Child received vitamin K, fresh frozen plasma, broad spectrum antibiotic and 3% NaCl for raised intracranial pressure.

Related reports

Please provide other contents related to the case report to help readers better understand the present case.

Experiences and lessons

Dengue may have fulminant course in young children. The prognosis will be worse in presence of pan lobular necrosis.

Peer-review

The main highlight of the case is presence of dengue induced pan lobular necrosis in such a young infant. The main limitation of the report is inability to explain reasons behind such fatal complication of dengue virus in such patients.

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EDITORIAL

Adjuvants to local anesthetics: Current understanding and future trends

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Abstract

Although beneficial in acute and chronic pain management, the use of local anaesthetics is limited by its duration of action and the dose dependent adverse effects on the cardiac and central nervous system. Adjuvants or additives are often used with local anaesthetics for its synergistic effect by prolonging the duration of sensory-motor block and limiting the cumulative dose requirement of local anaesthetics. The armamentarium of local anesthetic adjuvants have evolved over time from classical opioids to a wide array of drugs spanning several groups and varying mechanisms of action. A large array of opioids ranging from morphine, fentanyl and sufentanyl to hydromorphone, buprenorphine and tramadol has been used with varying success. However, their use has been limited by their adverse effect like respiratory depression, nausea, vomiting and pruritus, especially with its neuraxial use. Epinephrine potentiates the local anesthetics by its antinociceptive properties mediated by alpha-2 adrenoreceptor activation along with its vasoconstrictive properties limiting the systemic absorption of local anesthetics. Alpha 2 adrenoreceptor antagonists like clonidine and dexmedetomidine are one of the most widely used class of local anesthetic adjuvants. Other drugs like steroids (dexamethasone), anti-inflammatory agents (parecoxib and lornoxicam), midazolam, ketamine, magnesium sulfate and neostigmine have also been used with mixed success. The concern regarding the safety profile of these adjuvants is due to its potential neurotoxicity and neurological complications which necessitate further research in this direction. Current research is directed towards a search for agents and techniques which would prolong local anaesthetic action without its deleterious effects. This includes novel approaches like use of charged molecules to produce local anaesthetic action (tonicaine and n butyl tetracaine), new age delivery mechanisms for prolonged bioavailability (liposomal, microspheres and cyclodextrin systems) and further studies with other drugs (adenosine, neuromuscular blockers, dextrans).

Key words: Local anesthetics; Adjuvants; Neurotoxicity; Opioids; Ketamine; Midazolam; Alpha-2 adrenoreceptor antagonists

Core tip: The use of local anaesthetics in acute and chronic pain is limited by its duration of action and the dose dependent adverse effects. Adjuvants or additives are often used with local anaesthetics for its synergistic effect by prolonging the duration of sensory-motor block and limiting its cumulative dose requirement. Various drugs like opioids, epinephrine, alpha-2 adrenergic antagonists, steroids, anti-inflammatory drugs, midazolam, ketamine, magnesium sulfate and neostigmine have been used to potentiate the effect of local anesthetics. Due its potential adverse effects, current research is exploring newer drugs and delivery mechanisms to prolong the duration of action of local anesthetics.

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INTRODUCTION

From time immemorial, alleviation of acute and chronic pain has continued to perplex medical professionals. The early success of pharmacologic endeavors in pain mitigation involved extensive use of opioids. Although reasonably successful, it was often associated with systemic complications like nausea, vomiting, respiratory depression, sedation, delayed recovery of bowel functions and hyperalgesia. In an effort to reduce the need and adverse effects of systemic opioids, the perineural (intrathecal, epidural or peripheral nerve blocks) use of local anesthetics have gradually evolved over time.

Although beneficial in acute and chronic pain management, local anaesthetics do have the potential to produce deleterious effects like cardiac arrhythmias, central nervous system depression, seizures, respiratory depression, hypertension and allergic reactions[1-4]. By prolonging the duration of sensory-motor block and limiting the cumulative dose requirement of local anaesthetics, co-administration of adjuvants has the potential to improve efficacy of perineural blocks and decrease local anaesthetic toxicity. The terms, local anaesthetic "adjuvants" or "additives", have often been used interchangeably. They contribute in their own special manner to potentiate the analgesic effect of the local anaesthetics[5]. The armamentarium of local anesthetic adjuvants have evolved over time from classical opioids to a wide array of drugs spanning several groups and varying mechanisms of action.

The aim of this editorial is to have a comprehensive look at the various local anesthetic adjuvants which have been studied till date, ascertain the evidence for their safety and efficacy in perineural use, discuss various novel approaches in local anesthetic usage and highlight the present lacuna in knowledge for directing future research on the subject.

DISCUSSION

Opioid

Opioids are the most frequently used local anesthetic adjuvants and their use in neuraxial blocks have evolved over the last 50 years[6]. The opioids potentiate antinociception of local anesthetics by G protein coupled receptor mechanisms by causing hyperpolarisation of the afferent sensory neurons[7]. The dose, site of injection, lipophilicity and the acid-base milieu of the site of drug deposition determine the extent of efficacy of the block[8,9].

Morphine: Use of preservative free morphine with or without local anesthetics has been used extensively in neuraxial blocks across all age groups[10,11]. Intrathecal Morphine in the dose range of 100-200 μg has exhibited good analgesic efficacy, especially in obstetric and orthopedic subsets[12,13]. Similarly epidural morphine has also been used over a wide dose range (1-5 mg) and has exhibited efficacy in diverse population subsets[14-17]. The hydrophilic nature of neuraxial Morphine results in cephalad spread, thereby increasing the area of analgesia. However the adverse effect of its use in neuraxial blocks includes respiratory depression (early and late), nausea, vomiting, pruritus and urinary retention. Specifically, there is evidence to suggest that intrathecal morphine administration of doses lower than 100 μg results in lesser adverse effects in elderly patients[13]. The use of Morphine in peripheral nerve blocks is presently not recommended as studies have failed to show any advantage over intravenous (Ⅳ) and intramuscular (IM) routes. Their adverse effects persist irrespective of the route of administration[18-22].

Fentanyl: Intrathecal fentanyl in the dose range of 10-25 μg has also been shown to prolong the duration and extent of sensory block with a favorable adverse effect profile in comparison to morphine[23-25]. However, epidural fentanyl does not necessarily follow the same pattern and a higher incidence of adverse effects have been observed with its use[26]. The addition of epinephrine 2 μg/mL to neuraxial local anesthetic-fentanyl mixtures has also been investigated. However, it was demonstrated that thoracic neuraxial instillation resulted in lesser nausea but its lumbar neuraxial administration didn't reduce any opioid related adverse effects[27-29]. Numerous studies have however failed

to conclusively prove the efficacy of fentanyl as an adjuvant in peripheral nerve blocks[30-35].

Sufentanyl: Intrathecal sufentanyl in the dose of 5 μg as an adjuvant to local anesthetics has shown good efficacy, however, for lesser adverse effects, the dose range needs to be lower (around 1.5 μg)[36,37]. The epidural dose of sufentanyl is 0.75-1 μg/mL and has been shown to be strikingly effective in ameliorating pain in various patient subsets[38-40].

Other opioids: Hydromorphone and Buprenorphine: Hydromorphone has been shown be an efficacious adjuvant in both intrathecal and epidural routes at the dosages of 100 μg and 500-600 μg respectively[41,42]. It is preferred in patients with renal insufficiency and had a better adverse effect profile when compared to morphine[43,44].

Buprenorphine has also been used in intrathecal (75-150 μg) and epidural routes (150-300 μg) with reasonable efficacy[5,45]. Additionally, it has also shown good efficacy when used in a dose of 0.3 mg as an adjuvant to peripheral nerve blocks[46-48].

Tramadol: Tramadol is a weak opioid agonist having sodium and potassium channel blocking actions as well as ancillary actions such as blockage of uptake of norepinephrine and serotonin[49-51]. Intrathecal tramadol in doses ranging from 10-50 mg has been in used different subsets with varying success[52-57].

Epidural tramadol in doses of 1-2 mg/kg presented itself as an attractive alternative to morphine for postoperative analgesia without any respiratory depressant effect[58]. Epidural tramadol has given good results for amelioration of pain in various patient subsets ranging from obstetric patients and abdominal surgeries to pediatric patients for lower abdominal procedures[59-63].

The incidence of nausea and vomiting remains a concern. However, incidence was less with lower doses. Other adverse effects like itching and sedation are less frequent[58,62]. Tramadol when used as an adjuvant in peripheral nerve blocks has shown conflicting and contradictory results with an unknown safety profile[64-67]. A couple of studies have shown Tramadol to increase the analgesic efficacy[64,66]. However, there have been other studies which have shown limited or no benefit of Tramadol when used as an adjuvant to local anesthetics for peripheral nerve blocks[65,68-72]. Hence, except for postoperative epidural infusions, present day anesthesia practice does not recommend routine use of Tramadol as a local anesthetic adjuvant.

Adverse effects of neuraxial opioids: The troublesome adverse effects of neuraxial opioids include pruritus, nausea, vomiting and respiratory failure, especially in elderly patients. This has prompted studies to determine the upper safe limit of administration of these drugs. The effects are more profound when the drug is deposited in the intrathecal space resulting in recommendations to reduce intrathecal dosage to avoid respiratory depression[73]. The pruritus produced by neuraxial opioids is dose dependent and responds well to Naloxone 200 μg and Ondansetron 4-8 mg[24,37,74].

Epinephrine

Epinephrine is one of the oldest additives to local anesthetic solutions with a recommended dosing of 0.5-1.0 μg/kg in a concentration of 5-10 μg/mL[75,76]. In addition to its vasoconstrictive actions, it also seems to have intrinsic antinociceptive properties mediated by alpha-2 adrenoreceptor activation[77]. A matter of concern with the use of continuous infusion of neuraxial epinephrine has been the association of severe neurologic complications as well as evidence of intrinsic neurotoxicity attributed to epinephrine[78-82]. Its use in neuraxial anesthesia is limited to being used as an additive to caudal Bupivacaine administration and for the detection of inadvertent intra vascular placement of epidural and other perineural catheters[83,84]. In peripheral nerve blocks, Epinephrine has shown certain analgesic benefits with short and intermediate acting local anesthetic such as lidocaine, but similar effects have not been observed with long acting local anesthetic such as Bupivacaine and Ropivacaine[85,86]. The effect of Epinephrine in peripheral blocks seems to be largely dependent on its vasoconstrictive action as perineural Epinephrine alone doesn't seem to cause any sensory or motor block[82,87,88].

Epinephrine has however had a significant role in preventing inadvertent intravascular administration of local anesthetic solutions; however the recent surge in routine use of ultrasonography in nerve blocks has made such use largely redundant. There is significant evidence indicating potential neurotoxicity with the perineural use of Epinephrine, especially in patients with diabetes mellitus, hypertension and in smokers[80,87]. Current recommendations allow use of epinephrine in peripheral blocks only when ultrasonography is not available or where needle tip and local anesthetic spread are not visualized[85].

Alpha 2 adrenoreceptor antagonists

Alpha 2 adrenoreceptor antagonists (Clonidine, Dexmedetomidine) are one of the most widely used class of local anesthetic adjuvants which give satisfactory effect in neuraxial and peripheral blocks.

Clonidine: Clonidine is an imidazole derivative with selective partial agonist properties which inhibits nociceptive impulses by activation of postjunctional alpha-2 adrenoreceptor in the dorsal horn of spinal cord[89]. In neuraxial blocks, it has a local effect on blockage of sympathetic outflow while in peripheral nerve blocks it prolongs duration of analgesia by

hyperpolarisation of cyclic nucleotide gated cation channels[87,90].

Clonidine was first used in 1984 in epidural blocks[91]. Epidural clonidine in doses of 25-50 μg/h has been found to have beneficial effects in various study populations like spine instrumentation and orthopedic procedures[92-96]. Caudal administration of clonidine in pediatric age groups has also exhibited significant prolongation of the duration of analgesia with minimal cardiorespiratory perturbations[97-99]. Intrathecal administration of clonidine has evolved in terms of dosing from the initial phases of higher doses (150 μg) to routine use of lesser doses (15-40 μg) in present day practice to avoid its cardiovascular adverse effects. Intrathecal Clonidine supplementation of local anesthetic solutions result in increased segmental spread of sensory block, delayed regression of such blocks and decrease the failure rate and analgesic supplementation required in various surgical subsets[100-103]. It has also peculiarly shown benefits in alcoholics undergoing surgery by preventing postoperative alcohol withdrawal symptoms[104]. Use of clonidine in neuraxial blocks had been plagued by the adverse effects like sedation, bradycardia and hypotension, thus necessitating a gradual evolution to present day recommendations of lower dosages[93,105,106].

There have been a plethora of studies investigating efficacy of Clonidine as a local anesthetic adjuvant and results have shown varying outcomes[107-112]. A meta analysis by Pöpping *et al*[113] demonstrated prolongation of peripheral nerve block duration by 2 h when clonidine was used as an adjuvant. McCartney *et al*[114] analyzed 27 well designed studies (15 positive, 12 negative) and found that clonidine prolonged peripheral nerve blockade best in amalgamation with intermediate acting local anesthetics such as mepivacaine and lidocaine. Lesser potentiation was observed with bupivacaine and levobupivacaine while ropivacaine produced the most disappointing results. Interestingly upper extremity blocks fared better in comparison to the lower extremity blocks when clonidine was used as an adjuvant[114]. The extensive studies by McCartney and Pöpping presented convincing evidence suggesting significant association of increased doses with hemodynamic manifestations such as hypotension and bradycardia. Hence a dose of 0.5 μg/kg with a maximum of 150 μg is the recommended maximum dose of clonidine for use as an adjuvant in peripheral blocks[113,114]. Subsequently there has been evidence suggesting that clonidine as an adjuvant is beneficial in popliteal sciatic block and in specific circumstances such as axillary blocks in patients with chronic renal failure and patients undergoing paronychia surgery (analgesia in infected tissue)[115,116]. The heterogeneity of results, especially in routine brachial plexus blocks, suggest that until further well directed research shows unequivocal evidence to advocate the use of Clonidine as an adjuvant to local anesthetic, it cannot be routinely recommended for perineural use[117-120].

Dexmedetomidine: Dexmedetomidine is a 7 times more selective alpha-2 receptor agonist in comparison to clonidine and has a similar mechanism of blocking hyperpolarisation activated cation channels[121,122].

Intrathecal (5-10 μg) and epidural dexmedetomidine (1 μg/kg) as an adjuvant to isobaric bupivacaine or in combination with commonly used local anaesthetics (like ropivacaine) have been investigated for its analgesic efficacy in various patient subsets[123-129]. A meta-analysis on intrathecal dexmedetomidine has shown that its use has been associated with prolonged duration of block and improved post-operative analgesia without any associated hypotension or other adverse events, especially when used at doses less than 5 μg[130]. A qualitative review and meta-analysis on the role of dexmedetomidine in neuraxial blocks had concluded that it is a favorable local anesthetic adjuvant providing prolonged anesthesia and analgesia and decrease the need for rescue analgesics; however, it is often associated with a higher incidence of bradycardia[131]. Comparative evaluation of dexmedetomidine and clonidine has revealed the superiority of dexmedetomidine when used as an adjuvant for epidural or intrathecal administration[132,133].

Since 2004, when it was first used as a local anaesthetic adjuvant in Ⅳ regional anaesthesia, the use of dexmedetomidine in peripheral nerve blocks have evolved with burgeoning evidence of considerable utility in such situations[134]. There have been multiple studies claiming increased effectiveness of use of dexmedetomidine and this has been consolidated in a meta-analysis examining the effectiveness of dexmedetomidine as a peripheral nerve block adjuvant[135].

The meta-analysis examined primarily brachial plexus blocks at doses of 0.75 μg/kg, 1.0 μg/kg, 30 μg and 100 μg and found significant prolongation of motor block and reduced requirement of rescue analgesics[135]. The studies in this review did not reveal any increase in the incidence of hypotension as a significant adverse effect. However, reversible bradycardia was observed in less than 10% of the patients. Sensory block prolongation was not statistically significant[135].

Subsequently, there have been studies in supraclavicular, interscalene, cervical plexus and ulnar nerve blocks where dexmedetomidine has been shown to increase quality and duration of analgesia of commonly used local anaesthetics like ropivacaine and bupivacaine[136-141]. An interesting study found that dexmedetomidine fared significantly better than clonidine when used as a adjuvant in supraclavicular blocks[142]. Neuro-toxicity of dexmedetomidine, especially when used in perineural spaces is a valid

concern. Surprisingly, preliminary evidence seems to suggest that dexmedetomidine has potential for neuroprotection, especially when compared with lidocaine and bupivacaine[143,144].

Hence current evidence seems to suggest that dexmedetomidine is effective when used as an adjuvant in peripheral nerve blocks in doses of 1 μg/kg. The adverse affect profile seems to be acceptable with known complications such as hypotension and bradycardia which are responsive to conventional therapies[145].

Steroids

Dexamethasone: Dexamethasone is a potent anti-inflammatory agent which has been investigated in the last decade for its role as an adjuvant to local anaesthetics in neuraxial as well as peripheral nerve blocks.

The mechanisms by which steroids potentiate the analgesic effects seem to be different from its intrinsic anti-inflammatory mechanism[146,147]. There is also evidence to show that the local action on nerve fibres and systemic effects, both potentiate dexamethasone's analgesic properties[148,149].

A study examined the effect of intrathecal dexamethasone in a dose of 8 mg (preservative free) with standard doses of hyperbaric bupivacaine 0.5% in orthopedic surgeries. It was shown to significantly prolong the duration of sensory block in spinal anaesthesia without any significant adverse effects[150].

Epidural dexamethasone in dose range of 4-8 mg has also been investigated for its analgesic efficacy and a recent meta-analysis has looked at its effectiveness[151]. The meta-analysis showed the advantages of the use of dexamethasone as an adjuvant to epidural local anaesthetics. However, it also highlighted the need of further well powered studies to establish its safety in terms of neurological complications[151].

Dexamethasone in a dose range of 1, 2, 4 and 8 mg has largely shown to be efficacious as a local anaesthetic adjuvant in a variety of blocks such as supraclavicular and inter-scalene brachial plexus block, ankle block and TAP block[152-155]. In fact, a meta-analysis exploring the use of dexamethasone as an adjuvant in brachial plexus block has found it to significantly prolong the duration of block of conventional local anaesthetic solutions[156]. A recent study by Liu *et al*[157] demonstrated that perineural dexamethasone (1, 2 and 4 mg) prolonged the duration of analgesia and motor blockade of bupivacaine in patients receiving supraclavicular brachial plexus nerve block for ambulatory shoulder surgery. This effect was despite the fact that most patients in the study population as well as control group received intravenous dexamethasone as well, hence refuting the assumption that perineural dexamethasone produced analgesia because of systemic absorption[157]. However, in some studies the use of perineural dexamethasone has not produced desirable results and it continues to be debated whether the analgesia produced by dexamethasone is related to its systemic effects[158-160].

Other anti-inflammatory agents

Other than dexamethasone, there have been very few studies on anti-inflammatory agents as perineural local anesthetic adjuvants. Neurotoxicity of neuraxial or perineural non-steroidal anti-inflammatory drugs (NSAIDs) as adjuvants has been a major concern. Although there are studies showing prolongation of the effect of local anaesthetics with epidural instillation of Parecoxib and Lornoxicam[161,162], the use of epidural Lornoxicam has also shown "histopathological signs of neurotoxicity". There is very little research evidence available on the use of anti-inflammatory medications in peripheral nerve blocks and further studies are warranted. Until new evidence comes up, their use cannot be recommended for neuraxial and peripheral nerve blocks.

Other drugs

Midazolam: Neuraxial midazolam acts on the benzodiazepine receptors on the gray matter of the spinal cord, the highest concentration of which is found on the lamina Ⅱ of the dorsal horn. The analgesic effect of neuraxial midazolam is caused by the spinal suppression of sensory functions and its anti-nociceptive effect mediated by GABAergic and opioid receptor mechanisms[163-168].

Intrathecal midazolam in a dose of 1-2.5 mg has been shown to be effective in providing prolonged post-operative analgesia without significant adverse effects in adults undergoing orthopedic, urological and lower abdominal surgeries, parturients undergoing caesarean sections and children undergoing urologic procedures[169-178]. Prochazka reported the safe use of intrathecal midazolam as a useful adjuvant for prolongation of analgesia in 775 patients over a period of 10 years[179].

Studies have found that epidural midazolam in doses of 50 μg/kg potentiates the effect of bupivacaine in patients undergoing upper abdominal surgery[180]. Similarly, it has also been found to potentiate the effect of caudal epidural bupivacaine by increasing the time to first analgesic requirement and decreasing the need for post-operative analgesia in children undergoing inguinal herniotomy[181].

Neurotoxicity of intrathecal and epidural midazolam in animal models has been a concern[182-184]. However, its use in a cohort study in 1100 patients by Tucker *et al*[185] conclusively proved that neuraxial midazolam is not associated with any adverse neurological or bladder-bowel symptoms in conventional therapeutic doses. Midazolam is not currently recommended for use in peripheral nerve blocks[145].

Neostigmine: Intrathecal neostigmine has been found

to cause analgesia by muscarinic receptor mediated mechanisms[186-188]. Studies have reported its usage in the dose of 5-10 μg to as high as 50-150 μg in the intrathecal route with increased doses showing greater association with nausea and vomiting, bradycardia, agitation and restlessness[189-196].

Epidural neostigmine in the doses of 1 μg, 2 μg and 4 μg have also been investigated and have been found to be efficacious local anaesthetic adjuvants[197,198]. Studies on the use of neostigmine as a peripheral nerve block adjuvant have been very few and have exhibited very little clinical prolongation of anaesthesia and have shown to be associated with troublesome gastrointestinal adverse effects. Currently its use in peripheral nerve blocks is not recommended[199].

Neurotoxicity of perineural neostigmine remains a concern, especially because animal studies have shown mixed results and human studies have essentially found the adverse effect to be related to its dose, with doses less than 50 μg not being associated with any adverse effects[200-203].

Ketamine: Ketamine, a NMDA receptor antagonist has been explored for its local anesthetic properties[204]. Preservative free forms of ketamine are recommended for neuraxial use because of the evidence of neurotoxicity due to its preservative[205]. Ketamine has been shown to exert analgesic effects by epidural, caudal and spinal routes by a multitude of mechanisms involving N-methyl-D-aspartate (NMDA), Cholinergic, adrenergic and 5-hydroxytryptamine receptors or 5-HT receptors[206-213].

Intrathecal and epidural ketamine has been studied most commonly in patients undergoing caesarean section, prostate surgeries and orthopedic procedures. It has been found to potentiate the effect of local anaesthetics by shortening the onset of sensory and motor block, but simultaneously decreasing the duration and extent of motor block[214-219]. This effect profile of intrathecal ketamine (early onset and decreased duration of action) has led to its use in day care surgeries wherein the early return of full motor power could be advantageous[220].

Caudal ketamine in a dose of 0.5 mg/kg has been studied in children undergoing lower abdominal surgeries and has prolonged the duration of analgesia without significant adverse effects[221]. A systematic review of caudal ketamine use concluded that though efficacious, there are uncertainties related to its neurotoxicity[222]. The association of neuraxial ketamine use with troublesome adverse effects which seems to be a dose dependant phenomenon with lower doses associated with lesser systemic effects[219,223].

Use of ketamine in peripheral nerve blocks has shown it to be associated with unacceptably high incidence of adverse affects such as psychotomimetic sequelae (hallucinations, drowsiness, nausea) without any increase of block duration. Currently, ketamine is not recommended for use in peripheral nerve blocks[224].

Magnesium sulfate: Magnesium sulfate is an NMDA receptor antagonist and inhibitor of voltage gated calcium channel. It had been investigated for its analgesic properties in a variety of clinical scenarios and routes of administration[225]. It had been shown to reduce the postoperative analgesic requirements in a variety of cases.

Intrathecal administration of magnesium sulfate has been shown to suppress nociceptive impulses in neuropathic pain and potentiates opioid anti-nociception in animal studies[226,227]. In humans, profound motor and sensory block for up to 3-27 h was reported in orthopedic, general surgery and gynecological procedures[228]. The duration of spinal opioid analgesia in patients requesting analgesia for labor was significantly prolonged by co-administration of magnesium sulfate with no effect on motor block, sensory block or the incidence of adverse effects like pruritus[229]. Magnesium sulfate has been used in doses of 25-100 mg along with opioids (fentanyl/sufentanyl) with or without local anaesthetic agents (lidocaine, bupivacaine, levobupivacaine and ropivacaine)[225].

A rapid onset of sensory block has been reported with epidural administration of magnesium sulfate as an adjuvant to local anaesthetic agents in thoracic and orthopedic surgeries with a lower incidence of post-operative shivering, nausea and vomiting[230-232]. A faster onset of action, longer duration of actions and reduced breakthrough pain with no change in adverse effects or fetal outcome was observed when magnesium sulfate was used as an adjuvant in labor analgesia[233].

Magnesium sulfate has been used as an adjuvant to local anaesthetics in interscalene and supraclavicular brachial plexus block, axillary block, femoral nerve block and popliteal nerve block. It has shown to increase the duration of analgesia without any adverse effects[234-237].

The adverse effects of neuraxial use of magnesium sulfate has been reported in isolated cases and are restricted to bradycardia, hypotension, sedation, headache, disorientation or periumbilical burning pain[238,239].

Animal studies were the first to report neurological complications and pain at injection site in a dose dependant manner, especially at dose more than 2-3 mg/kg[240]. Although neurodegenerative changes on intrathecal administration of magnesium sulfate into the rat spine have been reported[241], histological evidence of direct neuronal injury is lacking in canine models, thus suggesting that the neurological injury associated with the use of magnesium sulfate in neuraxial blocks may be species specific[242,243]. The

lack of well defined neurotoxicity studies for the use of magnesium sulfate precludes any recommendation for its use as an adjuvant to local anaesthetic agents[145].

FUTURE TRENDS

There has been an ongoing search for agents and techniques which would prolong local anaesthetic action without its deleterious effects, primarily systemic toxicity and neurotoxicity. Butyl-amino-benzoate is an ester local anaesthetic agent, which though not strictly an adjuvant, has shown to provide pain relief for up-to 14 wk by novel mechanisms such as blockade of sodium and potassium channels[244-247].

Another novel approach has been to use charged molecules to produce local anaesthetic action, as with tonicaine and n butyl tetracaine[248-251]. Although onset is slow because of the time required to penetrate neuronal membranes, the duration of action is prolonged because of charge properties. However, more human trials are required before these novel local anesthetics can be used in routine clinical practice.

Recent advancement in the world of perineural local anaesthetic use has been the progress in new age delivery mechanisms such as liposomal, microspheres and cyclodextrin systems. Liposomes are microscopic lipid vesicles ranging in size from 0.02-40 μm which have the advantage of acting as a reservoir of drug with low bioavailability resulting in prolonged analgesic effects without systemic toxicity[252-254]. Liposomal local anesthetics have been used in multiple routes[255,256] and had shown prolonged analgesia with less motor block in various populations[257-259]. However there are concerns about their potential toxicity because of the compounds, their metabolites and breakdown of the liposomal core[260]. Microspheres and cyclodextrins are also alternatives drug delivery systems which have shown initial promises in animal models[149,261-264].

Among other adjuvants, adenosine showed initial promise because of its analgesia mediated at the spinal adenosine receptors and inherent anti-inflammatory actions without any neurotoxicity in initial animal studies[265-267]. However human studies using intrathecal adenosine (0.5-1.0 mg) as well as its use as an adjuvant to local anaesthetic solutions in peripheral nerve blocks have shown no additional benefit[268-270]. Dextrans, a complex branched polysaccharides derived from sucrose, had been hypothesized to form water soluble complexes with local anesthetics and thereby prolonging the duration of analgesia by sustained action at the store of its deposition, as well as by altering the local pH favorably[271,272]. Human studies on the use of dextrans as a local anaesthetic adjuvant have been mixed, some showing advantage and others being inconclusive and there remains a need for further high powered studies[273-276].

Neuromuscular blocking drugs have also been explored as local anaesthetic adjuncts and have shown promising results in peri-bulbar blocks and intravenous regional anaesthesia with good results[277-281]. However there have been concerns of such use being associated with local anesthetic toxicity and prolonged motor blockade[282].

A summary of commonly used local anaesthetic adjuvants is given in Table 1.

CONCLUSION

Adjuvant to local anesthetics is an evolving and exciting field of anesthesia practice with new technology promising to improve patient satisfaction and safety. While opioids continue to be the most commonly used local anesthetic adjuvant in clinical practice, alpha-2 receptor antagonists, especially dexmedetomidine, has been shown to potentiate the effect of local anaesthetics with an acceptable safety profile. Use of adjuvants to local anesthetic should take into consideration the available evidence and the advocated safe dose ranges, its effective routes of administration, the adverse effect profile of use of such adjuncts as well as preparedness to manage life threatening complications such as Local Anesthesia Systemic Toxicity (LAST). Its users should be aware of its neurotoxicity potential following perineural use and watch for its clinical implications. Search for newer molecules and techniques allowing for lesser perineural doses of local anesthetic, enhanced analgesic effect and improved safety profile are expected to guide further studies in future to fill up the present lacuna in evidence about the use of adjuvant for local anaesthetics.

Table 1 Summary of the commonly used local anaesthetic adjuvants

Name of drug	Routes and dosages	Adverse effects	Recommendations for use	Mechanism of action
Morphine[12,22]	Intrathecal: 100-200 μg Epidural: 1-5 mg Peripheral nerve block: 75-100 μg/kg	Pruritus Nausea vomiting Respiratory failure	Useful in neuraxial blocks Not recommended for peripheral nerve blocks	
Fentanyl[23-26,30-35]	Intrathecal: 10-25 μg Epidural: 2-4 μg/mL Peripheral nerve block	Same adverse effects as morphine Adverse effect profile slightly favourable in neuraxial use Increased sedation, bradycardia and hypotension	Useful in neuraxial blocks Not recommended in neuraxial blocks due to inconsistent results	Spinal opioid receptor
Sufentanyl[36-40]	Intrathecal: 1.5-5 μg Epidural: 0.75-1.0 μg/mL Not used in peripheral nerve blocks		Efficacious in neuraxial blocks	Local action in peripheral nerve blocks
Hydromorphone[41-44]	Intrathecal: 100 μg Epidural: 500-600 μg Not used in peripheral nerve blocks	Better adverse effect profile than Morphine	Useful in neuraxial blocks	
Buprenorphine[5,45-48]	Intrathecal: 75-150 μg Epidural: 150-300 μg Peripheral nerve block: 300 μg		Good efficacy in neuraxial and peripheral nerve block routes	
Tramadol[49-72]	Intrathecal: 10-50 mg Epidural: 1-2 mg/kg Peripheral nerve block: 1-5 mg/kg	Nausea and vomiting	Present evidence supports use in epidural infusions Poor evidence in peripheral nerve block studies	Weak opioid agonist actions Sodium/potassium channel blocking actions Blockade of norepinephrine and serotonin uptake
Clonidine[89-121]	Intrathecal: 15-40 μg Epidural: 25-50 μg Peripheral nerve block: 0.5-5 μg/kg (150 μg is the maximum allowed dose in PNB)	Sedation Bradycardia Hypertension Adverse effects show association with dose	Good quality evidence to support use in neuraxial blocks especially at lower dosages In PNB prolongs block with Bupivacaine but poor efficacy with Ropivacaine and levobupivacaine Additional benefit in Alcohol withdrawal	Activation of post junctional alpha-2 receptors in dorsal horn of spinal cord
Dexmeditomidine[122-147]	Intrathecal: 5-10 μg Epidural: 1 μg/kg Peripheral nerve block: 20-150 μg	Sedation Bradycardia Hypertension Adverse effects show association with dose	Prolongation of neuraxial and peripheral nerve blocks with good efficacy of use	Mechanism similar to Clonidine
Dexamethasone[148-161]	Intrathecal: 8 mg Epidural: 4-8 mg Peripheral nerve block: 1-8 mg	Adverse effects minimal Advantageous to prevent ponv Troublesome paresthesias with PNB use	Efficacious in neuraxial blocks, however better studies required Prolongs nerve blockade in PNB	Local action on nerve fibers
Midazolam[164-184]	Intrathecal: 1-2.5 mg Epidural: 50 μg/kg diluted in 10 mL of saline	Sedation Respiratory depression	Neurotoxicity is a major concern in neuraxial and peripheral nerve routes Not recommended for routine neuraxial and PNB use	GABAergic and opioid receptor mechanisms
Neostigmine[185-202]	Intrathecal: 5-10 μg to 50-150 μg Epidural: 1, 2 and 4 μg Peripheral nerve block-not investigated	Neuraxial use associated with bradycardia, restlessness PNB use associated with gastrointestinal adverse effects	Lower dosages recommended for neuraxial use Not recommended for PNB use (neurotoxicity in animal models)	Enhancement of endogenous acetylcholine at nerve terminal

Ketamine[203-223]		Neuraxial use associated with nausea, vomiting and hallucinations	Neuraxial use-shortens onset and duration of anesthesia	NMDA receptor antagonists shown to have local anesthetic properties
		PNB use associated with psychomimetic sequelae	Not recommended for PNB use	Cholinergic, adrenergic and 5HT mechanisms
Magnesium[224-238]	Intrathecal: 25-100 mg	Headache	Prolongs analgesia and quality of block by all perineural routes	NMDA receptor antagonism
	Epidural: 50-100 mg	Cardiovascular disturbances	However more studies required to determine minimal effective doses	Voltage gated calcium channel blockade
		Nausea vomiting	Not recommended for routine use	

PNB: Peripheral nerve block; NMDA: N-methyl-D-aspartate; 5HT: % hydroxyl-tryptamine.

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MINIREVIEWS

Treatment of sepsis: What is the antibiotic choice in bacteremia due to carbapenem resistant *Enterobacteriaceae*?

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Abstract

Sepsis is one of the major challenges of today. Although gram-positive bacteria related infections are more prevalent in hospital setting, the highest mortality rate is associated with gram-negative microorganisms especially *Enterobacteriaceae*. *Enterobacteriaceae*, including *Escherichia coli*, *Klebsiella* spp., *Proteus* spp., *Enterobacter* spp. and *Serratia* spp. Resistance to β-lactams in *Enterobacteriaceae* is primarily attributed to the production of B-lactamase enzymes with subsequent antibiotic hydrolysis and to a lesser extent by alteration of efflux pump or porins expression. Carbapenem resistant *Enterobacteriaceae* (CRE) and *Acinetobacter baumannii* are the most notorious pathogens due to the high incidence of morbidity and mortality especially in the immunocompromised patients in the intensive care unit. The most appropriate antimicrobial therapy to treat CRE is still controversial. Combination therapy is preferred over monotherapy due to its broad-spectrum coverage of micro-organisms, due to its synergetic effect and to prevent development of further resistance. Current suggested therapies for CRE resistance as well as promising antibiotics that are currently under investigation for winning the war against the emerging CRE resistance are reviewed and discussed.

Key words: Carbapenem resistant *Enterobacteriaceae*; Sepsis; Bacteraemia; Bacteremia; Treatment; Antibiotics

Core tip: Carbapenem resistant *Enterobacteriaceae* (CRE) is the most notorious pathogens contributing to a significant morbidity and mortality rate in septic patients especially in the intensive care unit. The most appropriate antimicrobial therapy to treat CRE is still controversial. This review is conducted to discuss the

effectiveness of available therapies at this moment and to elaborate on different promising drugs that are still under investigation in order to win the combat on rising antimicrobial resistance.

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INTRODUCTION

Sepsis is a global healthcare problem and one of the major challenges that health care practitioners face worldwide[1]. It has become one of the major causes of death and its incidence is continuing to rise making it a huge burden in terms of increased morbidity and mortality, prolonged hospital stay, increased risk of having antimicrobial resistance and increasing hospital cost. It was estimated that the incidence of septic cases increased 13.7% each year over a period of 22 years[2-4]. Sepsis is newly re-defined as a life-threatening organ dysfunction due to a dysregulated host response to infection. Septic shock is defined as a subset of sepsis in which particularly profound circulatory, cellular and metabolic abnormalities substantially increase mortality[5].

Sepsis is a medical emergency; hence, antimicrobial treatment should be started as soon as sepsis is suspected. To prevent development of further complications and progression of the patient into septic shock and multi organ failure, profound knowledge of the causative pathogens is needed to select the proper antibiotic treatment. To reduce sepsis associated mortality, it has been widely advocated to start empirical antibiotic therapy from the first hour following sepsis identification. This strategy leads to a reduction in mortality of 13.7%[6-8]. The most common primary site involved in sepsis is the respiratory tract, mainly pneumonia, followed by genitourinary tract infections. Other sites involved are the abdomen, wound and soft tissue infections, the central nervous system (CNS) and the cardiovascular system. In some cases, the source origin is unknown (Table 1)[6,9,10]. However, the most commonly isolated pathogens depend on the infection site. In wound infections *Staphylococcus aureus* and coagulase negative staphylococci was found to be the most causative organism of both meningitis and pneumonia, while *Escherichia coli* is the most prevalent cause of urinary tract infections (UTI) related sepsis[11,12]. Regarding blood stream infection (BSI), coagulase negative staphylococci *and E. coli* are the notable organisms isolated[10].

In the intensive care unit (ICU) setting, the most common isolated pathogens causing severe sepsis are *S. aureus* followed by Pseudomonas infection, Enterobacteriaceae and fungal infection, respectively. Acinetobacter baumannii was involved in 9% of all infections[10]. But in general, gram negative pathogens are the most commonly found in sepsis patients[2,4,11,13].

Although gram-positive bacteria related infections (especially *Staphylococcus*) are more prevalent in the hospital setting (62.2%), the highest mortality rate is associated with gram-negative micro-organisms. *Enterobacteriaceae* are the most common microorganisms in gram-negative sepsis[14].

EPIDEMIOLOGY OF *ENTEROBACTERIACEAE*

Enterobacteriaceae, a family of Gram negative pathogens, includes E. coli, Klebsiella spp., Proteus spp., Enterobacter spp. and Serratia spp. These organisms account for half of the bacteremia's that are usually caused by overspill of bacteria from their primary sites[14]. *E. coli* and *K. pneumoniae*, in particular, are the major community and hospital acquired pathogens that usually cause intra-abdominal infections, urinary tract infections and primary bacteremia[15]. The emergence of multi-drug resistant microorganisms has become one of the most important hazards that health care is facing worldwide. Development of such resistance can be attributed to many risk factors including previous ICU admission, presence of a central venous catheter especially in hemato-oncology patients who are receiving chemotherapy, presence of an indwelling catheter insertion, prolonged use of antibiotics, prolonged hospital stay, hospitalization in an area endemic for multidrug resistance (MDR) and a history of previous colonization or infection with these microorganisms[16,17]. Resistance to β-lactams in *Enterobacteriaceae* is primarily attributed to the production of B-lactamase enzymes with subsequent antibiotic hydrolysis and to a lesser extent by alteration of efflux pump or porins expression[18]. One of the main causes of *Enterobacteriaceae* resistance is extended spectrum beta-lactamases (ESBL) production. ESBLs are plasmid encoded enzymes that are able to hydrolyze penicillins, broad-spectrum cephalosporins with an oxyiminoside chain, *e.g.*, cefotaxime, ceftazidime and ceftriaxone as well as oxyimino-monobactams such as azetreonam. However, they are ineffective against cephamycins or carbapenems and their antimicrobial activity is inhibited by clavulanic acid[19,20]. The main problem concerning ESBL-producing bacteria is that they usually acquire multiple antimicrobial resistance mechanisms causing not only resistance to cephalosporins but also to aminoglycosides and fluoroquinolones, which further narrows the choices of finding an effective therapeutic agent[21].

Regrettably, these organisms belonging to the β-lactamases producing *Enterobacteriaceae* have acquired new genetic mutations and became resistant to

Table 1 The most common sites of infection and mortality rates in sepsis

Site of infection	Mortality (%)
Blood stream infection	34.2
Respiratory	22
Genitourinary	8.2
Wound and soft tissue infection	10.55
Abdomen	10.25
CNS	17.4
Device related	9.5
Endocarditis	25.95
Others	7.05

Table was modified from the ref. [9]. CNS: Central nervous system.

Table 2 Resistance mechanisms of carbapenemase producing *Enterobacteriaceae*

Class	Genetic mutation	Clavulanic acid inhibition
Class A	Chromosomal encoded (NmcA, Sme, IMI-1, SFC-1) Plasmid encoded (IMI-2, GES, KPC)	Partially inhibited
Class B	Metallo-β-lactamase (IMP, VIM and NDM-1, SIM, GIM, SPM)	Resistant to clavulanic acid
Class D	Plasmid encoded oxa-48	Resistant to clavulanic aci

KPC: *K. pneumoniae* carbapenemases; OXA: Oxacillin-hydrolising; NDM: New Delhi metallo-beta-lactamase. Table was modified from the ref. [22].

carbapenem antimicrobial therapy.

These carbapenemase producing *Enterobacteriaceae* are classified into group A, B and D. β-lactamases micro-organisms based on the type of gene mutation (Table 2). Class A and D have a serine based hydrolytic mechanism, but class B consists of metallo- β-lactamase[22-24].

Carbapenem resistant *Enterobacteriaceae* (CRE) and *A. baumannii* are the most notorious pathogens due to the high incidence of morbidity and mortality especially in the immunocompromised patients in the ICU. The incidence of CRE was reported in various countries worldwide including East Asia, India, USA and many European countries. A multicenter study, conducted in Shanghai, China, revealed a high proportion of ESBL type *E. coli* as a cause of bloodstream infections. In addition, it was noted that the most common involved gene was CTX-M (CTX-M-15 CTX-M-14 and CTX-M-55, respectively). No carbapenemases producing *Entero-bacteriaceae* were reported[25]. On the contrary, in Turkey a retrospective study evaluating ICU patients over ten years, showed that antibiotic resistance most dramatically increased due to carbapenem resistant *A. baumannii* followed by *Pseudomonas* spp, *E. coli* and *K. pneumoniae,* respectively. In addition, a reduction in methicillin resistant *S. aureus* (MRSA) prevalence from 96% to 54% was noticed[26]. In the United States, it was reported in CRE outbreaks that resistance, especially to *K. pneumoniae* and to a lesser extent other *Enterobacteriaceae*, were important in CRE resistance[27].

A case control study in New York showed that the majority of deaths due to bacteremia in neutropenic oncology patients were caused by CRE infections in 53%, of which gram negative *Enterobacteriaceae* was found in 13%-18% of the patients. Independent risk factors for increased CRE susceptibility were: Previous use of β -lactam antibiotics (*e.g.*, 3rd or 4th generation cephalosporins or carbapenems) within the last 30 d; receiving trimethoprim-sulfamethoxazole or glucocorticoids at the time of onset of blood stream infection and having previous CRE infection isolate[27]. In order to avoid development of more resistance, it is crucial to be selective in the choice of antibiotics. Choosing the proper antibiotic regimen should be based on clinical findings supported by rapid diagnosis[22].

Goodman *et al*[16] tried to develop a clinical decision tree to predict whether a patient with bacteremia was infected with an ESBL-producing pathogen. They retrospectively studied a cohort of patients with bacteremia in Johns Hopkins hospital to identify clinical criteria to diagnose those patients with ESBL bacteremia, especially gram negative *Enterobacteriaceae*, to avoid misuse of antibiotics in the future. The clinical criteria were: A history of ESBL colonization or infection in the last 6 mo with chronic usage of indwelling venous catheter or dialysis, patient age ⩾ 43 years, recent hospitalization in an ESBL high-burden area and a history antibiotic use for ⩾ 6 d in the previous 6 mo. They made a clinical decision based on these five yes-or-no questions. When the patient had a history of ESBL colonization or infection in the last 6 mo with chronic usage of indwelling venous catheter or dialysis they had a 92% chance of being ESBL positive. With these criteria, positive predictive value was 90.8% and negative predictive value was 91.9%. In addition, they found that 43% of patients with an ESBL positive culture had received chemotherapy in the recent history.

Another score has been developed to identify patients with high suspicion of CRE or ESBL-BSI so antibiotic therapy might be started on time to reduce mortality (Table 3). Risk factors were chemotherapy in the last 3 mo, foreign invasive device, absence of peripheral vascular disease, reduced level of consciousness, hospitalization of > 3 d and age < 65 years old. With a total score ⩾ 32 patients were considered as high risk for CRE BSI infections and required antimicrobial therapy targeted for CRE BSI infections. Although this test showed a lower sensitivity and specificity, its negative predictive value might prevent needless use of toxic antibiotics[28].

The Carba NP test is such a rapid diagnostic with a very high sensitivity and specificity that can differentiate between class A, B and C CRE. In addition, other promising tests such as PCR assay and matrix assisted laser desorption ionization might facilitate CRE diagnosis. In addition, fast gram-negative blood culture assays and film array blood culture can help

Table 3 Bed side risk score for carbapenem resistant *Enterobacteriaceae*

Risk factor	Score (points)
History of chemotherapy in the last 3 mo	19
Invasive devices	10
Absence of peripheral vascular disease	10
Impairment of level of consciousness at the time of illness	9
Hospitalization for 3 or more days before development of BSI	7
Age < 65 years old	6

Table was modified from the ref. [28]. BSI: Blood stream infection.

in identifying carbapenemase genes within two hours[29,30]. However, deciding on the most appropriate antibiotic choice in bacteremia due to CRE can be very challenging.

TREATMENT OF CRE

The most appropriate antimicrobial therapy to treat CRE is still controversial. No consensus has been reached regarding the optimal choice of antibiotic therapy. As a consequence of the evolving broad spectrum antibiotic resistance, the old fashioned antibiotics, previously discarded because of their side effects, *e.g*., polymyxin E (colistin), polymyxin B, aminoglycosides and fosfomycin, have reappeared, because of effectiveness to some extent[31,32]. Despite the numerous publications on the subject, no consensus has been reached even on the preference of monotherapy or combination therapy[33].

Monotherapy vs combination therapy for treatment of sepsis

In a study conducted in a mice sepsis model, no significant difference was shown between colistin monotherapy and tigecycline monotherapy in treating carbapenem-resistant *K. pneumoniae*. In addition, combination of both colistin and tigecycline did not show superiority over monotherapy[34]. However, several studies suggested that combination therapy might be superior to monotherapy in terms of mortality rates. A review conducted by Falagas *et al*[35] described a cohort of 692 patients in which majority had confirmed *Klebsiella pneumoniae* carbapenemase producing *K. Pneumoniae* (KPC-KP) isolates and most of them related to bacteraemia. Mortality rate among those who received combination antimicrobial therapy ranged from 50% to 67% with the lowest rate associated with combination of tigecycline and gentamicin and highest rate with colistin and carbapenem (50% mortality rate in combination of tigecylcine with gentamicin, 64% in tigecycline-colistin and 67% for carbapenem-colistin combination). Patients who received colistin monotherapy had a mortality rate of 57% and patients who received tigecycline monotherapy 80%. The superiority of using combination therapy was shown in only three studies. No hard conclusions can be drawn from this review to decide on the use of single agent or combined therapy. Except in the critically ill patients, it is preferable to use combination therapy with superiority of tigecycline and gentamicin as a first choice, but randomized clinical trials need to confirm this statement.

But even with combination therapy, mortality rate remains high in patients with CRE related bacteremia. The underlying illness of the patient remains the most important risk factor for mortality. Tumbarello *et al*[36] showed the lowest mortality rate in patients with KPC-KP related sepsis using combined antimicrobial regimens especially those containing meropenem (when MIC $\leqslant$ 8 mg/L).

In a retrospective cohort study by Tumbarello *et al*[36] it was shown that combined therapy was superior to monotherapy in treating KPC-KP infection. Survival in patients with blood stream infection (mainly septic patients) with KPC-KP receiving monotherapy had a mortality rate of 54.3% while those receiving a combination therapy had a mortality rate of 34.1%. The same study demonstrated that a combination of tigecycline or colistin with meropenem had a better outcome compared to other combination therapies (12.5% mortality rate compared to 16.6% for tigecyclin, gentamicin with meropenem, 57% for colistin-gentamicin, 50% for tigecyclin-gentamicin and 30.4% tigecycline and colistin combination therapy).

Interestingly, in a prospective study by de Maio Carrilho *et al*[37] in patients with infections caused by KPC-KP (but also *Enterobacteriaceae* and *E. coli*) regimens of three or more antibiotics did not show any improved survival in comparison to regimens with two antibiotics. Moreover, monotherapy was just as effective as combination therapy in patients with UTI. Other independent risk factors such as dialysis, older age and septic shock seem to influence patient outcome more than monotherapy *vs* combination therapy.

Nevertheless, taken all current evidence into account, combination therapy can have a significant association with a lower mortality rate and increase the cure rate compared to monotherapy in the septic patient since each drug has its own mechanism of action, which can create a synergistic environment while combating resistant bacterial strains. The limited number of antimicrobial agents currently available to treat CRE will be further discussed in this review.

Colistin

Colistin is one of polymyxin antibiotics with bactericidal activity against Gram-negative bacterial infection[38]. Although the usage of this antibiotic was banned for many years due to its nephrotoxicity and neurotoxicity effect, it was reintroduced again due to emergence of MDR microorganisms. However, the use of colistin in treating CRE infection is still controversial[39].

Qureshi *et al*[40] retrospectively evaluated a cohort of 41 patients admitted to the ICU from two different

hospitals in the United States with almost similar clinical and demographic variables. Of the 41 patients who developed bacteremia with a KPC-producing *K. pneumoniae*, seven patients died before initiating treatment. Among those who received combination therapy with carbapenem/tigecycline or carbapenem/colistin 28 d survival was significantly higher than in those on monotherapy (2 out of 15 patients receiving combination therapy died compared to 11 out of 19 patients receiving monotherapy).

Regarding the optimal dose for colistin, Gibson *et al*[41] showed that use of high dose colistin (> 4.4 mg/kg per day) in patients with CRE bacteremia was associated with a better clinical outcome, *i.e*., reduction of leucocyte < 12000 cells/mm^3, no fever for 48 h and hemodynamically stable without any vasopressor. Also a better microbiological outcome was demonstrated, *i.e.,* eradication of CRE on day 7 after starting colistin.

Unfortunately, although still rare, colistin resistant CRE species are emerging in China, United States and different European countries. It is most often observed in *Enterobacteriaceae* harboring the *mcr-1* gene along with carbapenemase resistant gene[42-44].

Despite the fact that some investigators showed that development of colistin resistant CRE did not correlate with an increased mortality compared to patients without colistin resistant CRE[37], others have found that having colistin resistant KP is an independent risk factor of death especially in those with bacteremia[36,43].

Colistin seems to be a good alternative in vulnerable patients (without any evidence of renal impairment) especially when combined with other antibiotics such as carbapenems. However, it is very important to pay extra-attention for colistin resistant strains.

Carbapenems

Despite the fact of developing resistance to carbapenems anti-microbial therapy, they still can be of use especially in combination with other antimicrobial agents in colistin resistant *Enterobacteriaceae*. In a review by Bassetti *et al*[45], it was recommended that patients with KPC-KP and a MIC of isolate between 8 mg/L-16 mg/L or < 8 mg/L should receive a high dose of carbapenem containing therapy with a prolonged infusion together with colistin, tigecycline or an aminoglycoside. The underlying reason was prevention of developing new resistance to the rest of CRE antimicrobial therapy

In a case report on ertapenem and meropenem combination therapy, it was reported that an elderly patient with KPC-producing *E. coli* isolated from surgical site and nosocomial pneumonia with a contra-indication to colistin use due to a recent renal transplantation was started on combination therapy with ertapenem and meropenem showing good response. Unfortunately, the patient died later due to hemorrhagic shock[46].

In order to have a better outcome in colistin resistant *Enterobacteriaceae*, double carbapenem treatment was introduced. In two patients with carbapenemase-producing K. pneumoniae who were also colistin resistant, a combination of meropenem 2 g every 8 h and ertapenem 1 g every 24 h were given. In a third patient, dosages were adjusted for renal function. Both patients showed clinical improvement and also *in vitro* bactericidal activity was maintained up to 24 h. In conclusion, in such select cases like resistance to colistin, where options to treat CRE related sepsis are limited, a combination of two carbapenem antibiotics could be beneficial[47].

In a trial performed by Cprek *et al*[48] ertapenem/carbapenem double therapy (consisting of one gift of 1 g ertapenem given daily 1 h before administration of meropenem 2 g or doripenem 500 mg and the rest of the daily doses of meropenem or doripenem given normally) a favorable outcome was observed with maximum benefit in patients with CRKP bacteremia (43%) followed by pneumonia, intraabdominal, UTI and skin associated CRE infections.

Taking these observations into account, a combination of two carbapenems can be effective and even superior to other combination regimens in bacteremia patients due to its synergistic effect.

Tigecycline and other tetracyclines

Tetracyclines are a group of antibiotics that exhibit bacteriostatic activity by reversible binding to 30S ribosomes that interfere with protein synthesis. It is widely used due to its coverage of both gram-positive and gram-negative bacteria as well as some anaerobes and parasites[49]. Tigecycline is a glycylcycline, which is a tetracycline derivative and exhibits broad spectrum activity covering many organisms including MDR pathogens[50]. Many studies were conducted to evaluate the efficacy of tetracyclines mainly tigecycline in treating CRE related sepsis. A systematic review demonstrated that tigecycline did not significantly improve sepsis related mortality[51]. However, combination therapy containing tigecycline did significantly improve survival. In addition, it was found that administration of high dose regimen was associated with better outcome compared to standard dose tigecycline in combination therapy.

Administration of tigecycline monotherapy was associated with a high mortality rate[52]. Tigecycline might have a role in the treatment of CRE if it is used as a part of combination therapy particularly with aminoglycoside group or colistin[52]. Other tetracyclines, minocycline and eravacycline, are also studied in the treatment of CRE. Although high dose intravenous minocycline (200 mg twice daily) can be effective in carbapenem resistant *A. baumannii* up to 74%, its efficacy is less when dealing with CRE with only 12% of the CRE susceptible to minocycline[53]. Another promising agent is eravacycline, belonging to the fluorocyclines. *In vitro* it showed a potent effectiveness to MDR organisms[54]. An ongoing phase 3 clinical trial with eravacycline (GNITE4) might give us more data on its effectiveness[55]. The preliminary results suggest

that there is no place for the use of tetracyclines in the treatment of CRE related sepsis; however the definitive results have not been published until now.

Aminoglycosides

The antibiotic group of aminoglycosides consists of gentamicin, amikacin, streptomycin, paromomycin, streptomycin and plazomicin, the last one still under clinical research. This group covers mainly gram negative and to some extent gram-positive pathogens and Mycobacteria[56]. It is usually used in combination with other antimicrobial agents in serious infections due to its synergistic effect[57]. The major side effects are ototoxicity and nephrotoxicity together with its narrow therapeutic window it can limit its use[58]. Aminoglycosides (especially gentamicin and amikacin) have shown their efficacy in treating carbapenem resistant KP UTI compared to other carbapenem resistant antimicrobial treatment (88% clearance compared to tigecycline and colistin), but its role in carbapenem resistant bacteremia as monotherapy is still uncertain[58]. A retrospective cohort study demonstrated that administration of gentamicin is an independent factor, which can improve 30 d mortality mainly in cases of KPC-KP related sepsis.

Especially in patients with both Carbapenem and colistin resistant KP, it decreased the mortality rate to 20.7% in comparison to 61.9% in patients treated with non-gentamicin containing therapy[59].

In conclusion, the role of aminoglycosides, mainly gentamicin, was studied previously particularly in combination with tigecycline with promising results. Now, it can be considered as a good option in the CRE patient with sepsis. Regarding the rest of aminoglycoside group antibiotics, further prospective studies are recommended.

Fosfomycin

The same might be applied for fosfomycin which has shown only its effectiveness in the treatment of patients with CRE UTI, but up until now no sufficient data exists supporting the use of fosfomycin either as a monotherapy or as part of a combination therapy in treating sepsis[58]. In a study by Bowers *et al*[60], 68 patients were treated with intravenous fosfomycin either in combination with colistin or with tigecycline. Effectiveness was demonstrated in 54.2% of patients at day 14. Mortality rate was 37.5% at day 28, with the highest mortality in having bacteremia; ventilator associated pneumonia and CRE KP isolates or *P. aeruginosa* isolates. Interestingly, three patients developed fosfomycin resistance shortly after treatment.

PROMISING NEW TREATMENTS

Alternative combination regimens can be considered in the future as curative agents in CRE related sepsis, but further clinical trials and prospective studies are required to assess its effectiveness. Fortunately, many new promising drugs might win the current battle against the current CRE resistance. One of them is plazomicin that belongs to the group of aminoglycosides. Recently, a phase 3 clinical trial was published showing efficacy of plazomicin. It was demonstrated that plazomicin significantly reduced mortality rate and reduced complications in patients with severe infection including CRE bacteremia, ventilation associated pneumonia and hospital acquired pneumonia related to CRE compared to colistin (28 d mortality rate was 11.4% in the plazmicin group compared to 40% in the colistin group). It also showed that plazomicin has the same efficacy of ertapenem in treating UTI[61], therefore it might play an important role in ceftazidime-avibactam combination therapy. In a recent study by Wu *et al*[62], three patients with CRE bacteremia (one patient with septic shock and one patient with suspected endocarditis) were successfully treated with ceftazidime-avibactam combination therapy. Combination of ceftazidime-avibactam is effective against oxa-48 and KP CRE[63].

Another option in the battle of CRE might be the addition of vabobactam to meropenem. Vabobactam is a boronic acid beta-lactamase inhibitor, which acts mainly on the serine carbapenamase and it has shown its efficacy in treating complicated UTI including those caused by CRE in phase 1 and 2 trials. A phase 3 trial is still ongoing now. In addition, its role in treating bacteremia needs further investigation[64].

In addition, combination of relebactam with imipenem and cilastatin is a promising option. Relebactam belongs to same group of vabobactam antibiotics. A phase 3 trial is designed to compare this combination with piperacillin/tazobactam in the treatment of complicated UTI. Its role in treatment of bacteraemia has not been investigated up until now[65].

One of the promising discoveries that can help in reducing the rate of CRE resistance is the peptide-conjugated phosphorodiamidate morpholino oligomer. It is a neutral DNA analogue which can inhibit gene expression of carbapenemases. It has been demonstrated that PRMO can target NDM1 (class B carbapenemases). It was shown that in combination with meropenem, it improved patient survival up to 92% because it re-established meropenem function[66].

CONCLUSION

The most appropriate antibiotics to treat CRE related sepsis is still debatable. Combination therapy is preferred over monotherapy in most of the studies due to its broad-spectrum coverage of organisms, its synergetic effect and to prevent development of further resistance.

In severely ill patients with co morbidities, a combination of two or more antibiotics is preferred. One of the best treatments up until now has been a combination of meropenem, tigecycline and colistin. A second option might be the combination therapy with

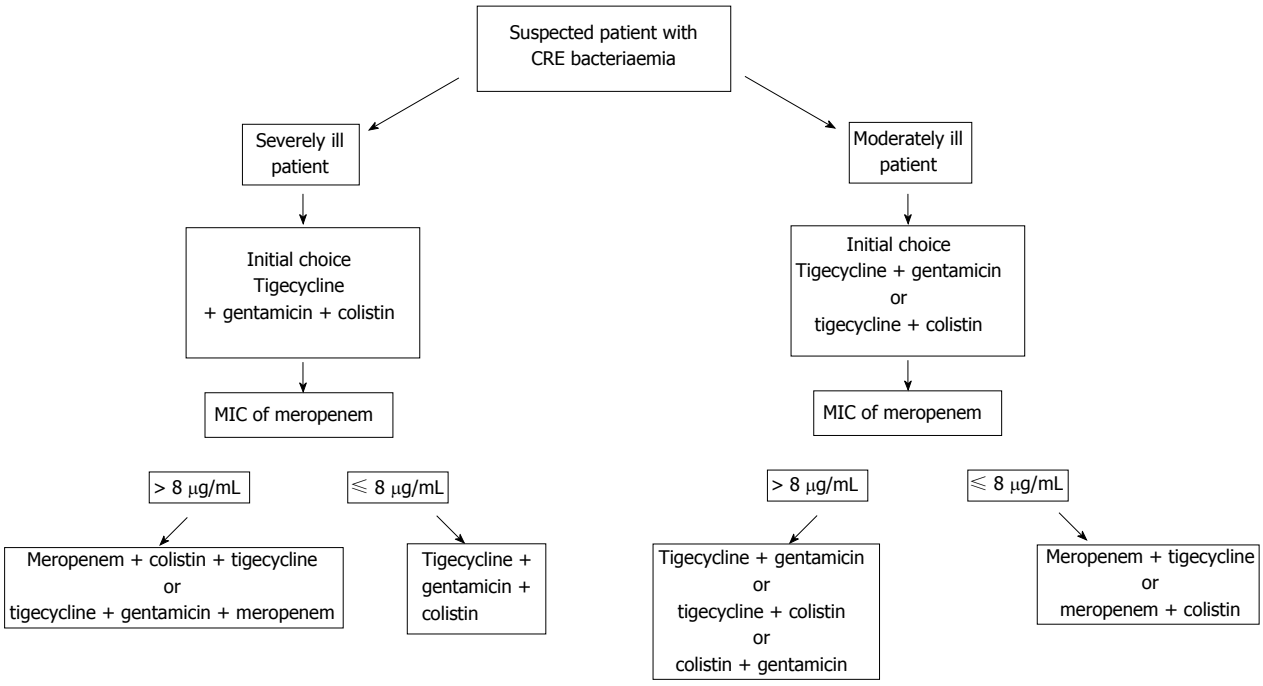

Figure 1 Suggested algorithm for antibiotic choice in patient with bacteriaemia of carbapenem resistant *Enterobacteriaceae*[1]. [1]The algorithm is based on the following references: [35,36,40,45,51,59]. CRE: Carbapenem resistant *Enterobacteriaceae*.

tigecycline, gentamicin and meropenem. In moderately ill patients, it is recommended to administer the combination of tigecycline and gentamicin. If the MIC is less than 8 μg/mL, it is advisable to switch to a carbapenem containing therapy. In case of colistin resistance, a combination of two carbapenems can be used (*e.g.*, ertapenem with meropenem or ertapenem with doripenem) besides the combinations shown in the algorithm (Figure 1). Many promising antibiotics are currently under investigation. The most optimal treatment still needs to be determined to win the battle against the emerging CRE resistance.

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CASE REPORT

Vertebroplasty and delayed subdural cauda equina hematoma: Review of literature and case report

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Abstract

Vertebroplasy is considered an alternative and effective treatment of painful oncologic spine disease. Major complications are very rare, but with high morbidity and occur in less than 1% of patients who undergo vertebroplasty. Spinal subdural hematoma (SDH) is an extremely rare complication, usual developing within 12 h to 24 h after the procedure. We report the case of a tardive SDH in an oncologic patient who underwent VP for Myxoid Liposarcoma metastasis. Trying to explain the pathogenesis, we support the hypothesis that both venous congestion of the vertebral venous plexus of the vertebral body and venous congestion due to a traumatic injury can provoke SDH. To our best knowledge, only 4 cases of spinal subdural hematoma following a transpedicular vertebroplasty have been previously described in International literature and only one of them occurred two weeks after that surgical procedures. Percutaneous verteboplasty is a well-known treatment of pain oncologic spine disease, used to provide pain relief and improvement of quality life and is considered a simple surgical procedure, involving a low risk of complications, but related to high morbidity, such as SDH. Therefore it has to be performed by experienced and skilled surgeons, that should also recognize possible risk factors, making SDH more risky.

Key words: Subdural hematoma; Liposarcoma; Surgery; Radiotherapy; Vertebroplasty

Core tip: This is an original paper about a rare complication of vertebroplasty: A subdural hematoma. In literature there are only 4 cases described. To our knowledge thid is the first case in which this complication occur after 20 d. In this work we try to explain the pathogenesis and the importance of a correct and rapid diagnosis, and, if needed, an emergency treatment.

Tropeano MP, La Pira B, Pescatori L, Piccirilli M. Vertebroplasty and delayed subdural cauda equina hematoma: Review of literature and case report. *World J Clin Cases* 2017; 5(8): 333-339 Available from: URL: http://www.wjgnet.com/2307-8960/full/v5/i8/333.htm DOI: http://dx.doi.org/10.12998/wjcc.v5.i8.333

INTRODUCTION

Myxoid liposarcoma is the most common subtype of liposarcoma, accounting for 10% of all adult tissue sarcomas[1]. The frequency of bone metastasis arising from liposarcoma has been reported to be 14% and 17%[2]. In one of the largest series, which analyze specifically the development of bone metastases, the incidence of spinal metastases was 83%[2]. Treatment options included: Surgical excision, chemotherapy, adjuvant radiotherapy, surgical decompression of spinal metastasis after having their surgery elsewhere.

The first percutaneous vertebroplasty in an oncological patient, was performed at the University Hospital of Amiens, France, to fill a vertebral void after the removal of a benign spinal tumor, then it was quickly adopted also for use in metastatic vertebral lesions and hematologic malignancies such as multiple myeloma and lymphoma. Clinical studies documented the effectiveness of VP as an alternative treatment of painful oncologic spine disease[3].

The first vertebroplasty was performed by Galibert in 1987 for a C2 hemangioma[4]. The first series was reported in 1997 and since[5], it has become a very common surgical technique for the symptomatic treatment of painful osteoporotic vertebral fractures, wedge-compression fractures, vertebral malignancies and painful vertebral angiomas.

The goal is to provide pain relief and bone strengthening, injecting cement or calcium phosphate bone cement into the vertebral body, *via* a transpedicular or an extrapedicular approach under fluoroscopic guidance. There is strong evidence of pain relief and improvement in the patient's quality life. Percutaneous vertebroplasty is usually performed in the thoracic and lumbar vertebrae and rarely in the cervical vertebrae and cervico-thoracic junction. Absolute contraindications are: Unstable fractures with posterior element involvement, bleeding disorders, active local infections and sepsis[6]. Relative contraindications are: clinical conditions not allowing to lie prone, neurological signs and symptoms due to vertebral body collapse or tumor extension[7].

Major complications are very rare, but with high morbidity and occur in less than 1% of patients who undergo vertebroplasty. The most common are anaphylaxis and hypotension due to an adverse reaction to the cement, pneumothorax, pulmonary embolism due to cement leakage, spinal cord compression following the cement leakage, epidural or subdural hematoma, vertebral injury, infections and death[8,9]. Most often, complications occur during surgery or immediately following surgery. Late-developing complications are infection, adjacent vertebral body fractures and recurrent fracture; they appear within days to weeks following surgical procedure. Spinal subdural hematoma (SDH) is an extremely rare complication, usual developing within 12 h to 24 h after the procedure. To our knowledge, to date, only 4 cases have been previously reported in International literature[10,11], where only one of them occurred two weeks following transpedicular vertebroplasty[12]. We report the case of a tardive SDH in an oncologic patient who underwent VP for Myxoid Liposarcoma metastasis.

CASE REPORT

We report the case of a 63-year-old man who presented to our emergency department with bilateral inferior limb numbness and weakness, mainly to the left leg and complaining of bladder retention. Neurological assessment revealed a 1/5 monoparesis of the left inferior limb and 3/5 monoparesis of the right, as well hypoesthesia and dysesthesia in the same region. Perineal reflexes were absent. The patient was on anticoagulants.

Three weeks prior to the onset of neurological symptoms, the patient underwent percutaneous VP of L1 and L3 vertebrae, in an oncology institute, for pathological compression fractures, due to secondary localization of a retroperitoneal myxoid liposarcoma, removed several years before. VP was indicated by an oncologist and performed at the above-mentioned institute of oncology. Pathological anamnesis revealed that the patient underwent surgery several times for the removal of a retroperitoneal liposarcoma. In 1997 the patient underwent the first surgical procedure for the removal of the lesion located in the upper left quadrant of the retroperitoneal space. During the same procedure, the left colon was also removed. In 2004 a second surgical procedure was performed for the removal of a local relapse of the lesion as well as for the removal of the spleen. In February 2005 a follow up abdominal magnetic resonance imaging (MRI) showed the presence of another local relapse of the pathology. In consequence, another surgical excision of the lesion was performed, including excision of the pancreatic tail. The procedure was proceeded by the administration of a chemotherapeutic protocol consisting of Antracicline and Ifosfamide. In November 2011 another surgical excision was performed. It included the left part of the diaphragm as well as a portion of the small intestine and the left half of the transverse colon. Furthermore, on November 2013 the patient underwent cyberknife radiotherapy.

Upon admittance at our emergency department for paraparesis, an emergency spinal MRI with gadolinium was obtained. Results showed the presence of a high signal lesion in the intradural extramedullary space, at the conus medullaris (Figure 1). Furthermore,

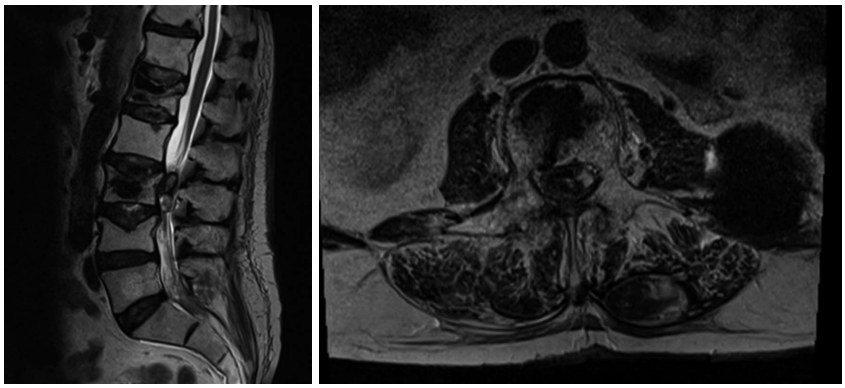

Figure 1 T2 weighed magnetic resonance imaging of the lumbar tract of the spinal column on sagittal and axial planes. The images reveal the presence of a lesion located within the spinal channel at L2-L3. It is not possible to establish if it is located within the intradural or extradural space by the mere observation of the MRI. Note the needle trajectory inside the spinal channel at L1 on the right side.

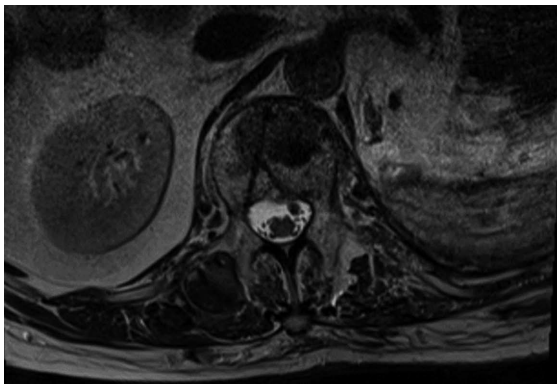

Figure 2 T2 weighed magnetic resonance imaging of the L1 vertebra on axial plane. As the image show, the trajectory of the needle used to perform the vertebroplasty passes within the spinal channel on the left side.

the trajectory of the needle used to perform the vertebroplasty was detected at L1 and L3 levels and it suggested that the needle had passed through the dura into the subarachnoid space and then into the vertebral body (Figure 2). An emergency decompressive bilateral laminectomy of L2 and L3 vertebrae was performed. No epidural bleeding was observed. A longitudinal durotomy revealed a blood clot, tightly adherent to the cauda equina rootlets (Figure 3). The hemorrhagic lesion was completely removed with the assistance of a surgical microscope (Figure 4). After the procedure, neurological symptoms progressively disappeared and 5 d later, the patient completely recovered both motor and sensory deficits, as well as bladder functions. Postoperative MRI documented adequate surgical decompression and removal of the intradural lesion (Figure 5). Histological examination confirmed the haemorrhagic origin of the lesion, constituted by clots and fibrin, with no evidence of tumor.

DISCUSSION

Liposarcoma is a common malignant soft tissue tumor, accounting for 10% to 16% of all sarcomas[1]. It typically affects patients between the fifth and seventh decade of life and usually develops in the extremities or retroperitoneum[13]. It can be classified into five distinct histological subtypes (WHO 1994): Well-differentiated, dedifferentiated, mixed, round cell and pleomorphic. Myxoid liposarcoma (MLS) is the second most common subtype, accounting for 10% of all adult soft tissue sarcoma, occurring more frequently during the fourth and fifth decades of life[14]. It is considered as a clinicopathologically and genetically distinct type, characterized by its common occurrence in young patient, its location in the thigh and the presence of at translocation[12,15,16]. Specifically, it is common associated with TLS-CHOP fusion transcript. Differently from other soft-tissue sarcomas, that show a tendency for metastasis to the lung, MLS has a propensity to spread to extrapulmonary sites, including bone. The frequency of bone metastasis is reported at 14%[2] and 17%[16]. Furthermore, MLS presents often as a multifocal disease, either synchronous or metachronous. The degree to which MLS spreads to bone has not been specifically studied and it is still unclear if skeletal metastasis represents the usual pattern of spread in MLS, or if it is the mark of specific molecular subset. In a large series, including 40 patients who developed skeletal metastasis, 33 (83%) were diagnosed with spine metastasis[2]. The spine metastases demonstrated the typical MRI findings of MLP. T1 weight images were heterogenous with areas go high signal intensity corresponding to the lipid component and low signal to the mixed component, as T2 images as well. The treatment of metastasis is individualized to each patient. Surgical excision is the treatment of choice; chemotherapy and radiotherapy are also utilized. Percutaneous verteboplasty (VP) is a well-known treatment of pain oncologic spine disease, used to provide pain relief and improvement of quality life. It was introduced for the first time to fill a vertebral void after a the removal of a benign spinal tumor, since then it was introduced as a treatment option also for primary and metastatic spinal tumor[17]. During the last few decades, improvement in surgical

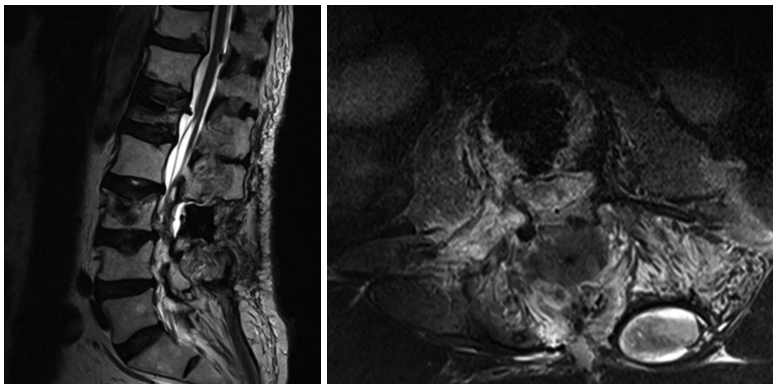

Figure 3 Postoperative T2 weighed magnetic resonance imaging on sagittal and axial plane showing the proper execution of the bilateral laminectomy at L2 L3 as well as the removal of the intradural lesion.

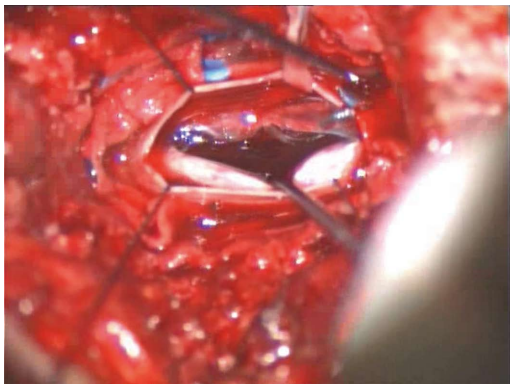

Figure 4 Intraoperative image by microscope, showing the dura mater opened and the hematoma between the radiculae.

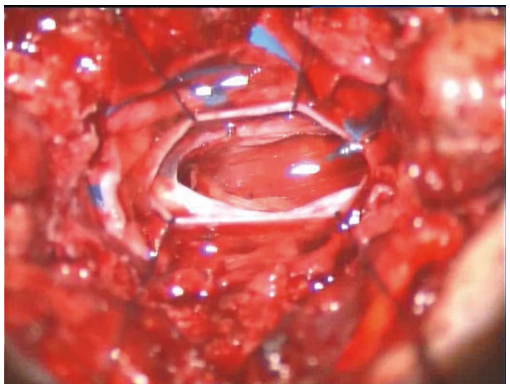

Figure 5 Intraoperative image by microscope, showing the complete removal of the hematoma.

strategies and technologies, have increased disease-free survival rates, in patient with a wide variety of malignant tumors that were once considered inoperable. Despite these advances, many patients present with widespread tumor and minimal life expectancy and surgical or any other aggressive treatment cannot be medically or ethically considered[18]. Palliative strategies are recommended in this cases, such methods include medical management, pain management, vertebroplasty, radiotherapy. Vertebroplasty and Kyphoplasty are usually indicated for the treatment of metastatic spinal tumors without epidural compression, to improve the anterior column stably of the spine in conjunction with medical and radiation therapies and to obtain pain relief[19]. In particular, these conservative procedures are recommended in elderly patients, at high anesthetic risk, because less operating time under anesthesia and minimal blood loss. Randomized, multi centered and controlled trials, demonstrated that the use of VP, specifically for spinal metastasis, had an improvement in pain (among 73% to 100% of patients), mobility and vertebral height restoration[20,21]. To our knowledge, Yang *et al*[22] conduct- ed the largest vertebroplasty study in patients with metastatic spinal disease. A total of 196 patients were treated during the study and a 98.5% improvement in pain was seen, as well as statistically significant improvements in vertebral body height[22].

Percutaneous vertebroplasty is a therapeutic strategy, that gained increasing popularity among the neurosurgical community for the treatment of refractory axial mechanical pain due to osteoporotic fractures, malignancy fractures and painful hemangiomas. With time, the indications for vertebroplasty were extended to include acute traumatic vertebral compression fractures[23]. The therapeutic mechanism of action consists of injecting polymethyl methacrylate into the fractured vertebral body. There is evidence of the ability of vertebroplasty to provide pain relief and improvement of patient's quality of life. Although it is a safe procedure, the rate of major complications is from 0.5% to 1%, when it is conducted by experienced spinal surgeons. Complications reported in literature are often related to the cement extravasation into the epidural space[24] (some series reported up to 20% extravasation rates, occasionally requiring surgical decompression) causing spinal cord compression, or related to the cement migration through the epidural veins to the venous system leading to pulmonary embolism[25]. To our knowledge only 5 cases of SDH, including our own, have been reported in literature (Table 1). Cosar *et al*[10] reported two cases: An 18-year-old man with an acute compression fracture of the L2 and L4 vertebrae (AO Type A1.1), in whom both levels were treated with

Table 1 Cases of spinal subdural hematoma following a transpedicular vertebroplasty reported in literature

Case	Age, gender	Fracture level	Fracture cause	SDH symptoms onset	Symptoms	SDH level	Treatment	Recovery
Lee *et al*[12]	40 yr, female	T11-T12	Traumatic	2 wk	Back pain, radiating both legs	SDH T10-L5	No surgery, corticosteroid therapy	Good
Cosar *et al*[10]	75 yr, female	L1	Osteoporotic	12 h	Paraparesis, incontinence	SDH T12-L3	Laminectomy T12	Good with arachnoiditis
Cosar *et al*[10]	18 yr, male	L2-L4	Traumatic	12 h	Paraparesis	SDH T1-L2	Hemilaminectomy T1-L2	Good with arachnoiditis
Mattei *et al*[11]	49 yr, female	T8	Traumatic	Immediate	Motor deficit left leg	SDH T9-C7	Laminectomy T7-T9	Good
Our case	63 yr, male	L1-L3	Oncological fracture	2 wk	Paraparesis	SDH conus	Laminectomy L2-L3	Good

SDH: Spinal subdural hematoma.

vertebroplasty. The patient complained of severe back pain immediately after the surgical procedure and paraparesis developed in both his legs 12 h later. Postoperative MRI showed spinal SDH extending from T1 to L2, evacuated *via* cross-hemilaminectomy from T-1 to L2. The second case reports a 75-year-old woman with an osteoporotic compression fracture at L1. The patient suffered psychosomatic symptoms with paraparesis 24 h after the procedure. The Postoperative MRI revealed spinal SDH extending from T-10 to L-3, evacuated *via* T-12 laminectomy. Both patients improved after the second surgical procedure, but reported back pain after a few months, with an MRI showing spinal arachnoiditis, controlled with steroids and anti-inflammatory drug therapy. They hypothesized that the spinal SDH developed after puncture of the spinal dura mater and that venous blood began to enter the subdural space slowly after this trauma. This is reasonable, according to the time of onset of symptom presentation.

Lee *et al*[12] reported a 40-year-old female with an acute compression fracture of the T11 and T12 vertebrae, treated with successful transpedicular VP, under continuous visualization with fluoroscopic guidance. After two weeks, during which the patient's conditions were improving, she complained of acute back pain. MRI imaging showed a high signal intensity mass lesion in the intradural extra medullary space, located at the lower thoracic, lumbar and sacral area. No coagulation disturbances were detected. Open surgery was recommended but she refused. Following 10 d of intravenous therapy with dexamethasone, she improved. The authors did not give a precise explanation and concluded that pathogenesis is still unclear. Among possible theories explaining the pathogenesis of SDH after vertebroplasty, the authors hypothesize the increase in thoracic and/or abdominal pressure, due to leakage of bone cement, increasing the pressure within the intraspinal vessels, particularly the valveless radiculomedullary veins, that cross subdural and subarachnoid space (but leakage was not enough), the development after spinal puncture of dura mater, as Cosar *et al*[10] proposed and the possibility that SDH may originate directly from the subarachnoid space, dissecting through the arachnoid membrane and eventually break into the spinal subdural space.

Mattei *et al*[11] reported the case of a 49-year-old woman with a T8 compression fracture, previously treated conservatively and with a VP after 3 mo follow-up, when she complained of severe deep axial pain. After cannulation of the left T8 pedicle and the initial injection of PPMA, a small posterior extravasation of cement to the epidural veins was observed. Surgical procedure was stopped, and, after awaking, she presented diffuse numbness on the left side (both in the superior and inferior limbs) and diffuse weakness in the left leg. An emergency CT scan showed a very small posterior leakage of PMMA towards the epidural space and into the adjacent costotransverse joint and a hyperdense collection anterior to the spinal cord from T7 to the upper cervical spine. decompressive laminectomy was performed, at T8, T7, T9. Postoperative MRI confirmed the presence of SDH. The authors commented on the anatomy of spinal venous drainage and focused on the possible etiologic role of venous congestion caused by the venous obstruction.

SDHs can be divided into traumatic and spontaneous. Traumatic SDHs usually occur after minor spinal trauma, spinal anesthesia lumbar puncture and spinal surgery, especially in the presence of intraoperative dural tears[26,27]. Spontaneous (non traumatic) SDHs are much more rare, with a recent review having identified 106 cases reported in the English literature[28]. Most of them are located anteriorly to the spinal cord, differently from epidural haematomas located posteriorly, at the lower thoracic region and lumbar region. Predisposing factors are considered coagulation abnormalities, anticoagulation therapy, platelet disfunction, polycythemia vera, pregnancy, arterial wall abnormalities and spinal arteriovenous malformations[29-33], but the pathophysiology still remains unclear. The management of SDH is still controversial as well. Some authors propose emergency spinal decompression and evacuation of the hematoma, while other wait for the recovery of incomplete

neurological deficits, especially in the absence of spinal cord compression. Several theories have been proposed to explain the pathogenesis, most of them stressing the anatomy of spinal venous drainage, involving venous congestion. Although some authors have suggested that thin and delicate extra-arachnoid vessels on the inner surface of dura can give rise to SDH, it is confined to specific cases occurring in association with a subarachnoid hemorrhage of traumatic origin[34]. Alternatively, other authors have reported cases of sudden episodes of increased intra-abdominal or intra-thoracic pressure (coughing or straining) associated with SDH, suggesting the presence of a locus minoris resistentiae, that, when submitted to high pressure for venous congestion, would possibly rupture, causing extravasation of blood into the subdural space[35,36]. According to this theory, both venous congestion of the vertebral venous plexus of the vertebral body and venous congestion due to a traumatic injury can provoke SDH.

In conclusion, there are still questions that remain unclear. How can the differences in time of onset be explained? Why do certain SDH cases present immediately following intervention with neurological deficits (within 24 h), while others presented later (2 wk after)? Is it possible that there is no difference, but that the SDH already present in both cases and becomes symptomatic within 24 h or 2 wk. Can we postulate that other conditions are superimposed? Concerning our case, both theories have been proposed. The late onset of SDH at the same level of a vertebral boy previously treated by VP, without extension to the upper and lower levels, is extremely rare. It is most likely related to the wrong insertion of the needle, but also to the anticoagulants, with a delay in the onset probably due to the mechanism of venous congestion. We definitely consider VP a simple surgical procedure, involving a low risk of complications, but related to high morbidity. Therefore it has to be performed by experienced and skilled surgeons. Furthermore, surgical iatrogenic complications must be known, correctly and rapidly diagnosed and, if needed, receive emergency treatment. Experienced surgeons should also consider and evaluate possible risk factors, making SDH more risky.

COMMENTS

Case characteristics

This is the case of a 63-year-old man who presented to our emergency department with bilateral inferior limb numbness and weakness, mainly to the left leg and complaining of bladder retention. Three weeks prior to the onset of neurological symptoms, the patient underwent percutaneous vertebroplasty (VP) of L1 and L3 vertebrae, in an oncology institute, for pathological compression fractures, due to secondary localization of a retroperitoneal myxoid liposarcoma, removed several years before.

Clinical diagnosis

Neurological assessment revealed a 1/5 monoparesis of the left inferior limb and 3/5 monoparesis of the right, as well hypoesthesia and dysesthesia in the same region. Perineal reflexes were absent.

Differential diagnosis

Haemorrhage, concussion injury, spinal contusion, Guillain- Barrè Sindrome.

Laboratory diagnosis

All labs were within normal limits.

Imaging diagnosis

A magnetic resonance imaging scan showed the presence of a high signal lesion in the intradural extramedullary space, at the conus medullaris.

Treatment

An emergency decompressive bilateral laminectomy of L2 and L3 vertebrae was performed. A longitudinal durotomy revealed a blood clot, tightly adherent to the cauda equina rootlets. The hemorrhagic lesion was completely removed with the assistance of a surgical microscope.

Related reports

Spinal subdural hematoma is an extremely rare complication, usual developing within 12 to 24 h after the procedure. To our knowledge, to date, only 4 cases have been previously reported in International literature.

Term explanation

Vertebroplasty is usually indicated for the treatment of metastatic spinal tumors without epidural compression, to improve the anterior column stably of the spine in conjunction with medical and radiation therapies and to obtain pain relief.

Experience and lessons

VP a simple surgical procedure, involving a low risk of complications, but related to high morbidity. Therefore it has to be performed by experienced and skilled surgeons. Furthermore, surgical iatrogenic complications must be known, correctly and rapidly diagnosed, and, if needed, receive emergency treatment.

Peer-review

The manuscript reports a rare case and is clear, comprehensive and convincing. It is an interesting review about the complications following the percutaneous vertebroplasty, mainly about the occurrence of spinal subdural hematoma.

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CASE REPORT

Pseudotumoral acute cerebellitis associated with mumps infection in a child

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Abstract

Pseudotumoral cerebellitis in childhood is an uncommon presentation of cerebellitis mimicking a brain tumor. It often follows an inflammatory or infectious event, particularly due to varicella virus. Patients could have a wide clinical spectrum on presentation. Some patients may be asymptomatic or present at most with mild cerebellar signs, whereas others may suffer severe forms with brainstem involvement and severe intracranial hypertension mimicking tumor warranting surgical intervention. Imaging techniques especially multimodal magnetic resonance imaging represent an interesting tool to differentiate between posterior fossa tumors and acute cerebellitis. We describe a case of pseudotumoral cerebellitis in a 6-year-old girl consequent to mumps infection and review the literature on this rare association.

Key words: Acute cerebellitis; Pseudotumoral cerebellitis; Posterior fossa tumor; Children; Mumps

Core tip: Pseudotumoral cerebellitis in childhood is an uncommon presentation of cerebellitis mimicking a brain tumor. It often follows an inflammatory or infectious event, particularly due to varicella virus. Patients could have a wide clinical spectrum on presentation. Imaging techniques especially multimodal magnetic resonance imaging represent an interesting tool to differentiate between posterior fossa tumors and acute cerebellitis. We describe a case of pseudotumoral cerebellitis in a 6-year-old girl consequent to mumps infection and review the literature on this rare association.

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INTRODUCTION

Acute cerebellitis is usually a benign disease[1]. Patients could have a wide clinical spectrum on presentation. Some patients may be asymptomatic[2] or present at most with mild cerebellar signs, whereas others may suffer severe forms related to brainstem compression and severe intracranial hypertension mimicking tumor warranting surgical intervention[3]. The diagnosis and the management of these pseudotumoral forms represent a challenge for clinicians and radiologists to distinguish acute cerebellitis from posterior fossa tumors. The etiopathology of acute cerebellitis remains unknown, although an infectious or postinfectious origin is frequently advocated. Several viral infections maybe associated with cerebellitis in particular varicella virus.

We report a rare case of pseudotumoral cerebellitis secondary to mumps infection which resolved favorably after corticosteroid therapy.

CASE REPORT

A 6-year-old girl presented to the emergency department with a 2-d history of severe headache, nausea and vomiting. There was no family history of neurological disorders and her psychomotor development was normal. She had a history of a recent episode of mumps infection 10 d before presentation, with spontaneous resolution. Upon admission, the patient had an altered consciousness level and was mildly confused (Glasgow Coma Scale = E4 V4 M6). Neurological examination revealed trunk and gait ataxia with bilateral dysmetria on finger-nose tests. The body temperature was 37.5 ℃. Vital signs were initially stable with normal heart and breath rates. Few hours after her admission, she had dysautonomic troubles; her heart rate decreased unexpectedly to 55 beats/min and her arterial pressure dropped to 80/50 mmHg. Therefore, the patient was transferred to the Pediatric Intensive Care Unit for close observation. Brain computed tomography scan showed a cerebellar ill-defined hypodense lesion with mass effect on the fourth ventricle and dilation of the upper ventricular system. A multimodal magnetic resonance imaging (MRI) was performed in order to differentiate between posterior fossa tumor and acute cerebellitis. Brain MRI showed cerebellar high-intensity areas on T2-weighted and FLAIR images predominant on the right side, related to a diffuse edema with mass effect on the fourth ventricle and brainstem, tonsillar herniation and supratentorial hydrocephalus (Figure 1A and B). No bleeding on T2* sequence or diffusion restriction was noted. Gadolinium-enhanced T1-weighted sequence revealed leptomeningeal enhancement along the cerebellar folia (Figure 1C). Magnetic Resonance Spectroscopy (TE = 35 ms) showed mildly reduced level of N acetyl aspartate (NAA)/Creatine and normal Choline/Creatine ratios. Doublet of lactate-lipid peak (1.3 ppm) was also found (Figure 2). Biological investigation revealed an hemoglobin concentration of 12.7 g/dL, a white blood cell count of 14280/mm^3 (with 85% neutrophils, 9% lymphocytes and 4.8% monocytes), platelet count of. Erythrocyte sedimentation rate showed moderate increase and was 20 mm/h. C-reactive protein level was above 2 mg/L. Lumbar puncture was not performed because of the risk of cerebellar herniation. Serological tests for Epstein Barr virus, human herpes virus, human immunodeficiency virus, rubella virus, parvovirus B19, measles virus and Mycoplasma pneumoniae in serum were all negative except for the serological test for mumps virus which was positive with IgM and IgG and positive with IgG in the control serology done 10 d later. Post-infectious acute hemicerebellitis was diagnosed on the basis of the MRI features, the clinical symptoms and the biological findings. The patient was treated with mannitol and corticosteroid. She received Ⅳmethylprednisolone 30 mg/kg per day for 3 d followed by oral prednisone 1 mg/kg per day tapered within 1 mo. The evolution was rapidly favorable. Eighteen days after discharge, a brain MRI showed a partial resolution of signal alterations in the cerebellar hemispheres. Complete resolution was confirmed by brain MRI performed 3 mo later.

DISCUSSION

Acute cerebellitis often occurs as a primary infectious, post-infectious, post-vaccination disorder and it may follow a vaccine or drug administration[1]. It is associated with viral or bacterial infections in approximately 24% of the children[4]. Several infectious agents associated with cerebellitis were reported in literature: Varicella-Zoster virus, human herpes virus, Epstein-Barr virus, rubella, pertussis, diphtheria, coxsackie virus, Coxiella burnetti or Mycoplasma pneumoniae[5]. Mumps virus infection causes usually benign diseases and 30% of pediatric cases are asymptomatic[6]. It induces viremia resulting in dissemination of virus to several organ systems, including the central nervous system[7]. Mumps viruses are highly neurotropic, with evidence of central nervous system infection in more than half of all cases of infection[8]. The most common neurological complication of mumps is aseptic meningitis. Severe complications, though rare, include hearing loss in children (5/100000) and encephalitis (incidence of < 2/100000 cases, of which 1% are fatal)[6]. Our patient had an acute cerebellitis post mumps virus infection which is an unusual clinical feature. These severe complications could be explained by the neurovirulence of some mumps virus strains rather than others. This observation has been also shown by Sauder *et al*[7] through the use of different live

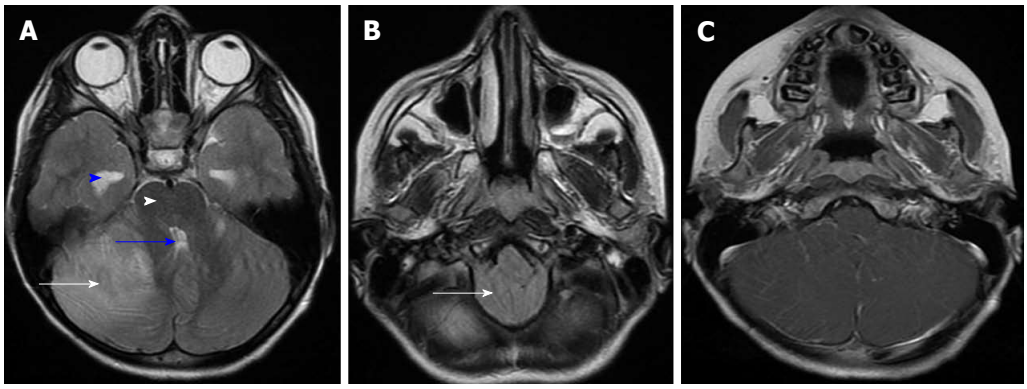

Figure 1 Magnetic resonance imaging: T2 and T1 post contrast images. A and B: Cerebellar hyperintense areas on T2-weighted images predominant on the right side (white arrow in A), related to diffuse edema and producing cerebellar mass-effect on the fourth ventricle (blue arrow) and brainstem (white head arrow), tonsillar herniation (white arrow in B) and supratentorial hydrocephalus (blue head arrow); C: Gadolinium-enhanced T1-weighted sequence revealed leptomeningeal enhancement along the cerebellar folia.

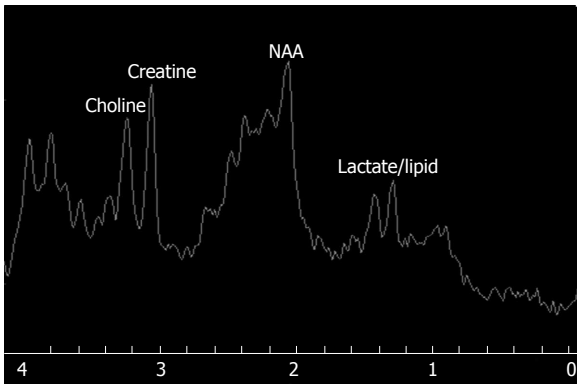

Figure 2 Magnetic resonance spectroscopy (TE = 35 ms) showed mildly reduced N actetyl aspartate/creatine and normal Choline/Creatine ratios. Doublet of lactate/lipid peak (1.3 ppm) was detected. NAA: N actetyl aspartate.

attenuated mumps viruses strains. Our observation is distinctive by its clinical and radiological presentations and by its uncommon infective etiology. It illustrates pseudotumoral feature of acute cerebellitis associated with mumps virus infection. Clinical presentation and radiological features were similar to posterior fossa tumors. The challenge in these cases is to differentiate between posterior fossa tumor and acute cerebellitis. MRI is the study of choice to demonstrate cerebellar pathology, which could be undetected on CT. It confirms acute cerebellitis and leads to a more accurate description of the lesion. Cases of cerebellitis involving only one hemisphere are rare and are more difficult to differentiate from tumors. Magnetic resonance spectroscopy is a valuable tool to exclude tumor by showing normal choline/creatine ratio. Most forms of acute cerebellitis have a good clinical outcome and have no need for specific treatment as they are benign forms. However, some cases, like in our report, could be fulminant and should be treated urgently. These severe forms require to start methylprednisolone bolus with a very close observation of clinical and imaging variables.

We report a child with acute cerebellitis secondary to post-mumps infection. This case illustrates that although mumps infection is a benign infection, it could be associated to a severe and atypical cerebellitis syndrome. Imaging techniques especially multimodal MRI represent an interesting tool to differentiate between posterior fossa tumors and acute cerebellitis. The risk of brainstem compression may be life-threatening and indicate an urgent need for treatment.

COMMENTS

Case characteristics

A 6-year-old girl presented to the emergency department with a 2-d history of severe headache, nausea and vomiting. She had a history of a recent episode of mumps infection 10 d before presentation, with spontaneous resolution.

Clinical diagnosis

Acute cerebellitis.

Differential diagnosis

A multimodal magnetic resonance imaging (MRI) was performed in order to differentiate between posterior fossa tumor and acute cerebellitis.

Laboratory diagnosis

Serological tests for Epstein-Barr virus, human herpes virus, human immunodeficiency virus, rubella virus, parvovirus B19, measles virus and Mycoplasma pneumoniae in serum were all negative except for the serological test for mumps virus which was positive with IgM and IgG and positive with IgG in the control serology done 10 d later.

Imaging diagnosis

Brain MRI showed cerebellar high-intensity areas on T2-weighted and FLAIR images predominant on the right side, related to a diffuse edema with mass effect on the fourth ventricle and brainstem, tonsillar herniation and supratentorial hydrocephalus. Gadolinium-enhanced T1-weighted sequence revealed leptomeningeal enhancement along the cerebellar folia. Magnetic resonance spectroscopy (TE = 35 ms) showed mildly reduced level of N acetyl aspartate (NAA)/Creatine and normal Choline/Creatine ratios. Doublet of lactate-lipid peak (1.3 ppm) was also found.

Pathological diagnosis

Final diagnosis: Post-infectious acute hemicerebellitis.

Treatment

The patient was treated with mannitol and corticosteroid. She received IV methylprednisolone 30 mg/kg per day for 3 d followed by oral prednisone 1 mg/kg per day tapered within 1 mo.

Related reports

Pseudotumoral cerebellitis in childhood is an uncommon presentation of cerebellitis mimicking a brain tumor. Imaging techniques especially multimodal MRI represent an interesting tool to differentiate between posterior fossa tumors and acute cerebellitis. The authors describe a case of pseudotumoral cerebellitis in a 6-year-old girl consequent to mumps infection and review the literature on this rare association.

Term explanation

Acute cerebellitis often occurs as a primary infectious, post-infectious, post-vaccination disorder and it may follow a vaccine or drug administration. It is associated with viral or bacterial infections in approximately 24% of the children.

Experiences and lessons

The authors report a child with acute cerebellitis secondary to post-mumps infection. This case illustrates that although mumps infection is a benign infection, it could be associated to a severe and atypical cerebellitis syndrome. Imaging techniques especially multimodal MRI represent an interesting tool to differentiate between posterior fossa tumors and acute cerebellitis. The risk of brainstem compression may be life-threatening and indicate an urgent need for treatment.

Peer-review

The case report is described very well and will be useful to share with the scientific community.

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CASE REPORT

Atlanto-axial langerhans cell histiocytosis in a child presented as torticollis

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Abstract

Langerhans cell histiocytosis (LCH) is a rare condition mostly seen in children and adolescents. Eosinophilic granuloma (EG) is one of its three clinical entities and is considered as a benign osteolytic lesion. Many reports of patients with spine histiocytosis are well documented in the literature but it is not the case of atlantoaxial localization. We report here a new observation of atlantoaxial LCH in a 4-year-old boy revealed by persistent torticollis. He was successfully treated with systemic chemotherapy and surgery. Inter-body fusion packed by autologous iliac bone was performed with resolution of his symptoms. It is known that conservative treatment is usually sufficient and surgery should be reserved for major neurologic defects in spine EG. In atlantoaxial lesion, surgical treatment should be frequently considered.

Key words: Langerhans cell histiocytosis; Eosinophilic granuloma; Torticollis; Cervical spine

Core tip: Langerhans cell histiocytosis (LCH) is a rare condition mostly seen in children and adolescents. Eosinophilic granuloma is one of its three clinical entities and is considered as a benign osteolytic lesion. Many reports of patients with spine histiocytosis are well documented in the literature but it is not the case of atlantoaxial localization. We report here a new observation of atlantoaxial LCH in a 4-year-old boy

revealed by persistent torticollis.

Tfifha M, Gaha M, Mama N, Yacoubi MT, Abroug S, Jemni H. Atlanto-axial langerhans cell histiocytosis in a child presented as torticollis. *World J Clin Cases* 2017; 5(8): 344-348 Available from: URL: http://www.wjgnet.com/2307-8960/full/v5/i8/344.htm DOI: http://dx.doi.org/10.12998/wjcc.v5.i8.344

INTRODUCTION

Langerhans cell histiocytosis (LCH) is an uncommon disorder characterized by an abnormal accumulation of histiocytes[1]. It includes three clinical entities namely eosinophilic granuloma (EG), Hand-Schûller-Christian syndrome and Letter-Siwe disease[2]. It consists in various clinical manifestations from a single lytic bone lesion to multisystemic lesions with organ dysfunction[3]. EG is a benign osteolytic lesion that commonly affects the skeletal system in a unifocal or multifocal form[2]. Atlantoaxial involvement by LCH is very rare[4,5], especially in a very young child[2,6,7]. The localization makes it difficult to diagnose. Neural deficit in spinal EG can be observed representing a life threatening condition[2,6]. The management is still controversial. We present, herein an unusual and rare case of atlantoaxial LCH with infiltrative mass involving the dens of C2 resulting in torticollis as the first symptom lasting for 3 wk in a 4-year-old boy. EG is discussed and the literature is reviewed.

CASE REPORT

Clinical presentation

A 4-year-old boy without significant medical history was admitted for limited neck motion for 3 wk. The physical examination showed an irreducible torticollis with analgesic attitude of cervical spine. The active and passive mobilization of the neck was painful and no motor or sensory deficit was detected. The general condition of the patient was good, the clinical examination did not show a tumoral syndrome and the neurological examination as well as skin examination and laboratory tests were normal.

Imaging features

The magnetic resonance imaging (MRI) of cerebro-spinal cord uncovered an infiltrative mass involving the dens of C2 which is hypointense on T1 sequence and hyperintense on T2 sequence, extending to the surrounding soft tissues leading to an increase in C1-C2 space, without compression of the spinal cervical cord. Complementary CT showed fragmented dens with important C1-C2 dislocation (Figure 1).

Histologic features

The odontoïd and mass biopsy was performed by endoscopic guidance. Histological features were consistent with inflammatory EG. The positivity of the immunostain by the antibody anti Ps100 and the antibody anti CD1a confirms the diagnosis of LCH (Figure 2).

Treatment and evolution

Initial treatment was started prednisolone 40 mg/m^2 per day orally, with weekly reduction starting from week 4 and intravenous Vinblastine 6 mg/m^2 per week for six weeks. An external immobilization by a cervical collar was maintained during the entire period of chemotherapy.

The evolution was marked by a decrease in pain secondary to the active mobilization of the neck with a persistent passive analgesic position. The control radiologic MRI showed a displaced horizontal fracture of the dens responsible for a posterior wall recoil reducing cervical occipital hinge without intramedullary signal abnormality. The infiltrative process had regressed in size (Figure 3).

A posterior cervical arthrodesis was performed and the spine was stabilized with a metal lacing associated with tricortical iliac crest graft interposed between the posterior arch of C1 and C2. No neuro-vascular complications have been detected.

The patient is still under treatment consisting of prednisolone 40 mg/m^2 per day orally for five days in a week every four weeks and Ⅳ Vinblastine 6 mg/m^2 bolus every four weeks for 12 mo. Repeated CT scans revealed at 5 mo a consolidation of C2 fracture with moderate stenosis of the occipital hinge (Figure 4)

DISCUSSION

Spinal LCH commonly involves vertebral bodies, thoracic spine (54%) being the most common site of involvement followed by the lumbar (35%) and cervical spine (11%)[5]. Cervical vertebral involvement is exceedingly rare[6]. More than half of the cervical LCH lesions affect the C3-C5 vertebrae[4]. Atlantoaxial involvement by LCH is very rare[7]. Less than 15 cases have been reported in the literature. To our knowledge, it was the first Tunisian case of atlantoaxial LCH with odontoid process fracture reported in a 4-year-old child.

Our case present only torticollis as the first symptom, no other neurologic deficit was detected. In fact, pain, restricted range of motion or torticollis are the most common symptoms of cervical LCH[5]. However, the spinal destructive bony lesions etiology in children is extensive. Gaucher's disease, osteogenesis imperfecta, aneurysmal bone cyst, myeloma, tuberculosis, Ewing's sarcoma, osteogenic sarcoma, metastatic lesions, posterior fossa and cervical spinal cord tumors are part of the differential diagnosis of acquired torticollis with such bony lesions[5,7].

Loss of neural function is a rare occurrence with EG. It may result from vertebral collapse and impingement or, less frequently, from extradural extension of the lesion[5]. An asymptomatic case was also reported[2].

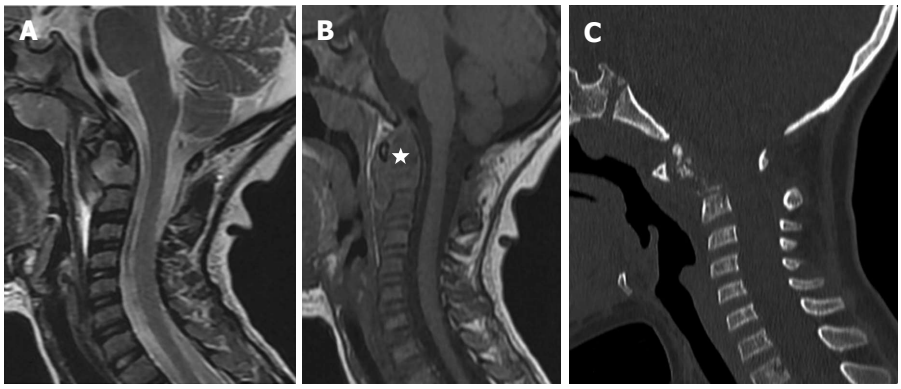

Figure 1 Initial cervical imaging: Sagittal FSET2 (A), SET1 magnetic resonance images (B) and Sagittal thin slice CT image (C). Infiltrative mass involving the dens of C2 hypointense on T1 and hyperintense on T2 sequence, extending to the surrounding soft tissues (star) leading to an increase in C1-C2 space. No compression of the spinal cervical cord. No signal abnormality nor rupture of the posterior longitudinal ligament spine. Complement CT showed fragmented dens with important C1-C2 dislocation.

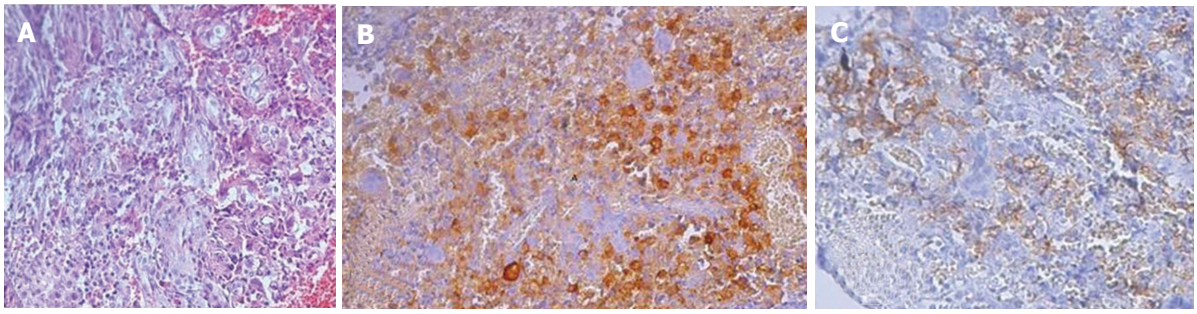

Figure 2 Langerhansien histiocytosis histology. A: Inflammatory granuloma with esinophils and histiocytes with circonvoluted nuclei; B: Positivity of the immunostain by the antibody anti Ps100; C: Positivity of the immunostain by the antibody anti CD1a.

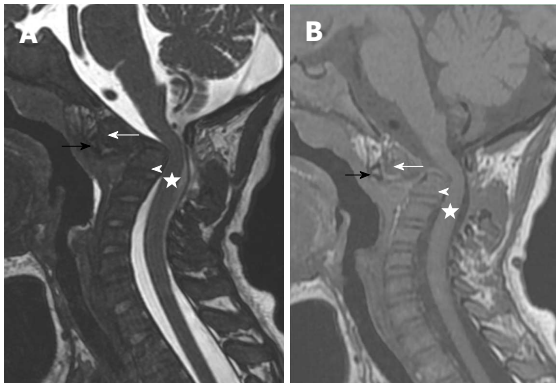

Figure 3 Six weeks follow-up after chemotherapy. Sagittal FSET2 (A), SET1 (B) magnetic resonance images: Displaced horizontal fracture of the dens responsible for a posterior wall recoil reducing cervical occipital hinge without intramedullary signal abnormality. Increase in the shrinkage of the cervical canal despite the regression of the infiltrative process. Black arrow: Anterior arch of C1; White arrow: The upper part of dens process; White arrowhead: The base of the dens; Star: Spinal cord.

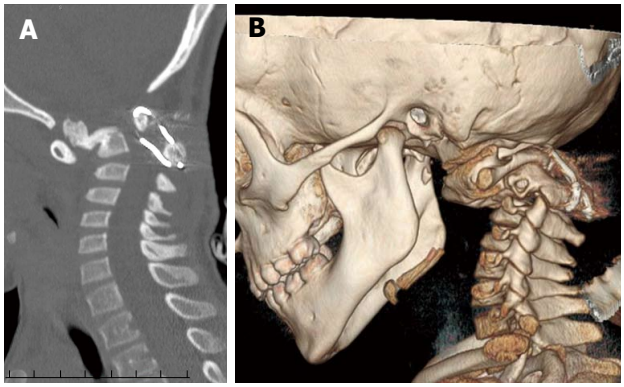

Figure 4 Five months post-operative follow-up. Sagittal thin slice CT image (A) and volume rendering CT image (B): Consolidation of C2 fracture with moderate stenosis of the occipital hing.

Since the atlantoaxial lesion was the only one detected in our case, the biopsy of the spine lesion under endoscopic guidance established the diagnosis. If there were multiple lesions, the most accessible lesion would be the appropriate for biopsy to avoid open biopsy and prevent the possible vertebral growth plate damage[6].

Our case fits into definitive diagnosis of LCH. The histological confirmation is required to establish LCH diagnosis[8]. The Writing Group of the Histiocyte Society identified three levels of confidence in the diagnosis of LCH. A definitive diagnosis, the third group, is established when histology is consistent with a diagnosis of LCH and the lesional cells are shown to express CD1a or to have intracytoplasmic Birbeck granules on electron microscopy[9]. Our patient presents a solitary spinal lesion. Spinal EG, in

the literature, is frequently associated with multiple skeletal lesion[3]. It is recommended that a technetium bone scan or a skeletal survey be performed early in the evaluation of every child with a suspected spinal lesion[3,5].

Within the adult population, displaced type 2 odontoid process fracture can be treated operatively or non-operatively, depending on the patient age, co-morbidities, fracture pattern and displacement[2]. However, the management of such fractures in the pediatric population remains unclear especially in fracture spine due to LCH[10]. With such paucity of literature on this topic, it is unknown whether operative intervention associated with chemotherapy aid fracture union and functional outcome in young child.

In the present case, treatment consisted in chemotherapy (combination of oral prednisone and intravenous vinblastine). The effectiveness of this type of combination was demonstrated by LCH-Ⅰ and LCH-Ⅱ group in systemic LCH but the situation for spine EG remained unclear[1,9]. The infiltrative process has regressed in size with this association. The patient tolerated the treatment of chemotherapy with vinblastine well and showed no serious complications. The decision to continue treatment for one year was made.

Garg *et al*[3] report a spinal LCH in a child successfully treated without any chemotherapy use. The use of chemotherapy to treat solitary EG is still controversial, but it seems safe and effective in some studies. However, localized bone lesions with spontaneous regression are described[8]. The resolution occurred at a rate unaffected by the mode of treatment[6,8].

Despite the absence of the observed neurologic deficit, the young age of the patient and radiologic assessment with displaced horizontal fracture of the dens and compromised spinal stability conducted to surgical excision followed by auto-graft fusion with satisfactory outcome in the present case. The use of surgery in such case is still controversial[1,3,6].

Jiang *et al*[6] argue that mild neurologic deficit could be immobilized under strict observation and surgery should be reserved for major neurologic defects like myelopathy or monoparesis. The authors believe some intervention should be used to prevent possible LCH progress, especially in the C2 vertebral body. In this study, a protocol for the management of suspected LCH lesion of the cervical spine was suggested, the atlantoaxial LCH lesion is not included in this protocol[6].

The radiotherapy was discussed but not applied for our patient. Some bone LCH lesions can be treated by radiotherapy alone[10,11]. However, a non successful radiotherapy performed on a 15-year-old girl presenting C1/C2 lateral LCH mass was reported[6]. Moreover, some authors support that radiotherapy might destroy the potential growth of the endochondral plates[6]. Further research on this topic is recommended.

Atlantoaxial LCH is rare. The diagnosis of the disease was made within a brief time limit with torticollis as the only clinic symptom. A delay in the diagnosis of this disease may lead to progressive neurological deterioration and increasing compression affecting largely the prognosis. Treatment modalities have changed over time depending on the clinical severity of the disease since it is quite varied. The combination of chemotherapy and surgical procedure seems to be effective in such lesion. This hypothesis needs to be improved from each other experiences.

COMMENTS

Case characteristics

A 4-year-old boy without significant medical history was admitted for limited neck motion for 3 wk.

Clinical diagnosis

The physical examination showed an irreducible torticollis with analgesic attitude of cervical spine.

Differential diagnosis

The spinal destructive bony lesions etiology in children is extensive. Gaucher's disease, osteogenesis imperfecta, aneurysmal bone cyst, myeloma, tuberculosis, Ewing's sarcoma, osteogenic sarcoma, metastatic lesions, posterior fossa and cervical spinal cord tumors are part of the differential diagnosis of acquired torticollis with such bony lesions.

Laboratory diagnosis

Laboratory tests were normal.

Imaging diagnosis

The magnetic resonance imaging of cerebro-spinal cord uncovered an infiltrative mass involving the dens of C2 which is hypointense on T1 sequence and hyperintense on T2 sequence, extending to the surrounding soft tissues leading to an increase in C1-C2 space, without compression of the spinal cervical cord. Complementary CT showed fragmented dens with important C1-C2 dislocation.

Pathological diagnosis

The odontoïd and mass biopsy was performed by endoscopic guidance. Histological features were consistent with inflammatory eosinophilic granuloma (EG). The positivity of the immunostain by the antibody anti Ps100 and the antibody anti CD1a confirms the diagnosis of langerhans cell histiocytosis (LCH).

Treatment

Initial treatment was started prednisolone 40 mg/m^2 per day orally, with weekly reduction starting from week 4 and intravenous Vinblastine 6 mg/m^2 per week for six weeks. An external immobilization by a cervical collar was maintained during the entire period of chemotherapy.

Related reports

Atlantoaxial involvement by LCH is very rare. Less than 15 cases have been reported in the literature. To our knowledge, it was the first Tunisian case of atlantoaxial LCH with odontoid process fracture reported in a 4-year-old child.

Term explanation

LCH is an uncommon disorder characterized by an abnormal accumulation of histiocytes. It includes three clinical entities namely EG, Hand-Schûller-Christian syndrome and Letter-Siwe disease. It consists in various clinical manifestations

from a single lytic bone lesion to multisystemic lesions with organ dysfunction.

Experiences and lessons

Atlantoaxial LCH is rare. A delay in the diagnosis of this disease may lead to progressive neurological deterioration and increasing compression affecting largely the prognosis. Treatment modalities have changed over time depending on the clinical severity of the disease since it is quite varied. The combination of chemotherapy and surgical procedure seems to be effective in such lesion.

Peer-review

This is an interesting case report, which seems to provide readers with useful information. The manuscript is well written.

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MINIREVIEWS

Primary prevention of cardiovascular disease in older adults in China

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Abstract

Over the past two decades, the percentage of Chinese who is 60 years or older has increased from 5.2% in 1995 to 10.5% in 2015. Approximately 16% of the population in China was 60 years old and above in 2015. Since 1990, cardiovascular disease (CVD) has been the leading cause of death in China. Cardiovascular medications of older adults are usually more complicated than younger age groups due to polypharmacy, the presence of comorbidities and more susceptible to treatment-related adverse outcomes. Therefore, effective primary prevention of CVD for older adults is important in sustaining the health of older adults and reducing the burden of the healthcare system. Proper management of CVD-related risk factors, such as hypertension, dyslipidemia, diabetes and obesity, can remarkably reduce risks of CVDs in older Chinese. These risk factors can be modified by managing blood pressure, glucose and lipids *via* lifestyle modifications or receiving medications. Smoking cessation, healthy diets, strict alcohol intake and moderate physical exercise are examples of recommended lifestyle changes for remarkably recovering health conditions of older adults who have hypertension, dyslipidemia, obesity, diabetes or complications. Treatment prescriptions of older adults, in general, are recommended to be individualized and to be initiated at a low dose. The future directions for better primary CVD prevention in older adults include establishing guidelines for primary prevention of CVD for different older adults and further research on better management strategies of CVD risks for elderly Chinese.

Key words: Cardiovascular disease; Primary prevention; Adults; China; Aged

Core tip: Cardiovascular disease (CVD) is the leading cause of death in China. More than half of the Chinese ≥ 60 years old have been exposed to at least one risk factor for CVD. This review aims to highlight the

primary CVD prevention in Chinese who are 60 years old and above. The management of common risk factors and future directions of primary CVD prevention for elderly population are described in this review.

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INTRODUCTION

Cardiovascular diseases (CVDs) have been shown to aggravate the impairment of cognitive, pulmonary, renal, gastrointestinal, and hepatic functions[1]. Since 1990, CVD has been the leading cause of death in China[2]. The percentage of the Chinese population who were 65 years old or older has gradually increased from 5.2% in 1995 to 10.5% in 2015, approximately 16% of the people in China were 60 years old and above in 2015[3]. Although studies over the past two decades have provided relevant information on CVD treatments, the prescription of medications to older adults with CVDs remains challenging to clinicians and governments because older adults usually have polypharmacy, multiple comorbidities, and are vulnerable to adverse effects of treatments[1,4]. Furthermore, the clinical evidence of CVD treatments for older adults is limited, especially adults who are ⩾ 75 years old[1,5-7]. Numerous studies have suggested that primary CVD prevention for older adults is crucial in sustaining the quality of life of older adults and in reducing the health care burden[8-10]. Therefore, there has been an increasing interest in primary CVD prevention in older adults.

A considerable amount of literature has been published on the primary prevention of CVD for older adults[1,9-11]. Since older adults across the world could vary in many aspects, such as physiological conditions, medical history, prior and concomitant medications, lifestyles and environments, the risk factors of each type of CVD and the definition of "elderly" could also differ across older adults worldwide. In China, a person who is 60 years old or above is considered older adults[5-7]. The primary CVD prevention strategies available in China are for ages, which lacks specific considerations for older adults. Older adults are in general different from younger adults regarding physiological, pharmacokinetics and pharmacodynamics, the susceptibility of adverse drugs effects, and the presence of multiple comorbidities and polypharmacy. Fortunately, there are expert consensuses for the management of common risk factors for CVD such as hypertension, dyslipidemia, and diabetes in older or very old people in China. This review highlights the current primary CVD prevention strategies by briefly describing the management of common risk factors of CVD in China and providing suggestions for future directions, for better primary CVD prevention of Chinese who are 60 years old or above.

MANAGEMENT OF COMMON RISK FACTORS OF CVDs IN CHINA

In China, hypertension, dyslipidemia, diabetes, smoking, and overweight are common high-risk factors of CVDs in older adults[1,4,12,13]. The 2011-2012 China Health and Retirement Longitudinal Study (CHARLS)[14] reported that the prevalence of hypertension, dyslipidemia, diabetes, smoking and overweight in Chinese whose age was between 65 to 74 years old were 50%, 64.2%, 19.5%, 25.9% and 30.1% respectively; in Chinese whose age was between 75 years old or above were 65.2%, 59.7%, 28.3%, 17.4% and 22.5%, respectively. Proper managements of these risk factors have been shown to reduce risks of CVDs considerably[15,16]. A recent study demonstrated that the use of blood pressure and lipids-modulating therapies on hypertension and dyslipidemia patients could potentially prevent 10 to 20 million acute myocardial infarctions[8]. In 2013, a study on Chinese population reported that managements of blood pressure, lipid and glucose have remarkably reduced risks of CVDs in diabetic patients[15].

Hypertension

Hypertension has predominantly increased the risk of ischemic heart disease, stroke, kidney failure and aortic diseases in older adults, which are the leading causes of death in older adults[17]. According to the guidelines of World Health Organization (WHO) in 1999, elderly hypertension is defined as subjects who are aged 60 years or older, systolic blood pressure continuously or 3 measurements of different days at 140 mmHg or higher and/or diastolic blood pressure of 90 mmHg or higher; isolated systolic hypertension (ISH) is defined as systolic blood pressure is at least 140 mmHg and diastolic blood pressure is less than 90 mmHg[18].

Unlike the younger age groups, the systolic blood pressure of older adults usually increases, and the diastolic blood pressure decreases as they age[19]. A China survey of 500223 adults over 10 regions in 2013 to 2014 reported that 33.3% of the older adults between 60 years old to 69 years old and 43.7% of the older adults ⩾ 70 years old had ISH[20]. Other types of blood pressure that are also common in older adults in China include high pulse pressure, high fluctuation in blood pressure, masked hypertension, susceptible to secondary hypertension or orthostatic hypotension, and unusual pattern of blood pressure change in day and night[21,22].

Target blood pressure

An expert consensus for the management of hypertension in the elderly recommended using personalize medicine and setting intermittent goals to treat elderly subjects with hypertension and other diseases such as heart, brain, and kidney functions[21]. According to the expert consensus, the target of blood pressures for older adults is recommended to begin at < 150/90 mmHg and gradually lowered to < 130/80 mmHg. For patients above 80 years old, their blood pressure is recommended to be under 140/80 mmHg.

The J-curve phenomenon of blood pressure has been increasingly recognized[23]. Although high blood pressure increases the risk of damaging target organs, excessively lowering blood pressure can influence the blood flow to target organs, which is also harmful to patients[24,25]. The degeneration of vascular elasticity and autonomic nervous system have been associated with higher risk of organ damage and stroke[1,12,21]. For older adults who had ISH and ischemic heart diseases, intense blood pressure reduction medications are not recommended to be used in lowering blood pressure[12,21,22]. Antihypertensive treatments are more effective in patients with higher baseline blood pressure level than those with lower baseline blood pressure[10,16]. Since anti-hypertensive treatments are usually much effective in reducing systolic blood pressure than in reducing diastolic blood pressure, antihypertensive medications can reduce the blood pressure of older adults with ISH[12,16,21].

The ideal blood pressure targets for older adults with high cardiovascular risks (such as elderly with coronary artery disease, diabetes, kidney disease and stroke) remain unclear. Most guidelines suggest the blood pressure targets of diabetic older patients should be under 130/80 mmHg, which lacks support from large clinical studies[5,21]. Chinese expert consensus for the management of hypertension recommended[21] the optimal blood pressure targets for patients who had kidney disease is recommended to be 130/80 mmHg; for patients who were also ⩾ 80 years old, blood pressure is recommended to be under 140/90 mmHg. In patients without contraindications, preferred treatments are ACEI or ARB because these medications can reduce proteinuria, ameliorate kidney functions, and delay the development of kidney dysfunction, decrease the risk of end-stage kidney diseases[26]. Loop diuretics are recommended for patients with severe kidney functions. Hypertension in the Very Elderly Trial (HYVET)[16] is the only large study so far that aimed to study patients who have hypertension and are 80 years old or older. That study had 3845 subjects, in which 1526 of them were Chinese patients. That study showed that reducing blood pressure < 150/80 mmHg is beneficial to reduce cardiovascular outcomes. The Chinese expert consensus for the management of hypertension in older adults[21] suggests that blood pressure can further reduce to < 140/90 mmHg if patients do not have orthostatic hypotension, fainting, angina, cardiac and cerebral vascular perfusion deficiency, or other abnormal clinical manifestation. Further studies are recommended to assess the benefit of reducing blood pressure down to 140/90 mmHg[21].

Antihypertensive therapy

The pharmacokinetics of drugs in older adults is usually different from younger adults[22,27]. Older adults with comorbidities are in general at high risk of treatment-related adverse events such as deterioration in renal function and excessive orthostatic blood pressure decline[22,27,28]. Therefore, the choice of antihypertensive medication in older adults should consider age-related physiological characteristics that are related to the pharmacokinetics of drugs and the presence of comorbidities[6,7,22,27,28]. In general, medications should be initiated at the lowest dose and be slowly titrated based on the blood pressure response of patients[21,22]. The blood pressure of older adults should be gradually reduced to below target level to prevent hypotension that usually causes older adults to have a higher risk of falling and fainting[21,22,24]. The assessment of blood pressure responses to drugs is recommended to include consideration of adherence to blood pressure medications, potential drug-drug interactions, secondary hypertension, appropriateness of drug choice and accuracy of blood pressure measurement[10,27]. Many older patients require at least two types of antihypertensive medications to reduce blood pressure[4,21,27].

The five most common classes of anti-hypertensive treatments are calcium channel blockers (CCB), diuretics, angiotensin receptor blockers (ARB), beta-blockers and angiotensin-converting-enzyme inhibitors (ACEI) are used in treating older adults with hypertension[16,22]. Diuretics and long-term calcium antagonists are recommended as preliminary treatments for older adults without symptomatic complications because these medications are effective in reducing blood pressure and have little adverse effects[21].

The recommended essential antihypertensive treatments for older adults currently are dihydropyridine (DHP) calcium channel blockers because they are reliable and effective in reducing blood pressure and can be concurrently used with other 4 classes of drugs[21]. CCB has the following characteristics[1,13]: (1) no adverse effect on metabolism, which is appropriate for older adults with diabetes and metabolic syndrome; (2) the effect of reducing blood pressure is not affected by salt intake, which is suitable for salt-sensitive hypertension; and (3) effective on older adults with low renin activity or low sympathetic activity.

The use of diuretics has been associated with the decreased number of cardiovascular events and the reduced risk of cardiovascular mortality[29]. Thiazide diuretics can be utilized with other anti-hypertensive treatments to reduce the blood pressure in older adults, including older adults with ISH, or heart failure

and edema. Long term usage of diuretics might cause electrolyte disturbance and renal blood perfusion, and increase the risk of glucose and lipid metabolic syndrome; therefore, the change of renal functions and electrolyte levels need to be carefully monitored to prevent the development of hypopotassemia and hyperuricemia[21]. The use of diuretics in older adults should start at low doses; for those older adults whom their Creatinine clearance rate < 30 mL/min per 1.73 m^2, loop diuretics such as torasemide and furosemide are recommended[21].

ACEI is effective in lowering blood pressure and protecting the renal function of older adults who have hypertension and high renin activity[27]. This drug is suitable for hypertensive older patients who also have coronary artery disease, myocardial infarction, angina pectoris, diabetes, left ventricular dysfunction, chronic kidney disease or proteinuria[22]. ACEI does not only affect glucose and lipid metabolism, heart rate and cardiac output, but it also leads to little adverse outcomes[1,13,21]. The main adverse outcomes include coughing, skin rashes; allotriogeusia, kidney function deterioration, angioneurotic edema, and fatality occur in rare cases[21].

The effect of ARB on lowering blood pressure and protecting kidney function are very similar, lead to fewer adverse outcomes such as coughing, angioneurotic[27]. This drug is particularly useful in subjects who are susceptible to ACEI-related adverse outcomes[22]. While using ACEI or ARB medications in older adults, close monitoring their blood potassium and serum creatinine levels are recommended[21].

Beta-blockers are the pre-ferred choice re-commended to hypertensive older adults with coronary artery disease, chronic kidney failure, and without contraindication[12,21]. Prescribing beta-blockers to older adults with sick sinus syndrome, second degree or higher atrioventricular block or bronchial asthma is prohibited because its long term usage will result in glucose and lipid metabolic disorder[12,21]. Since bradycardia and atrionector disorder are common in older adults, the usage and dose of beta-blockers should be determined according to their indications[12,21].

Alpha-blockers are usually not considered as the first choice for hypertensive older adults unless they have benign prostate hyperplasia[13,16,21,22]. The main adverse outcome is orthostatic hypotension. Therefore, such treatment should be initiated at low doses and eaten before sleep; the orthostatic blood pressure should be monitored to prevent orthostatic hypotension[21].

Dyslipidemia

Dyslipidemia, including hypercholesterolemia, hypertriglyceridemia, combined hyperlipidemia and low HDL-C, has been associated with increased risks of CVDs[1,6,13]. The elevation of plasma cholesterols, especially low-density lipoprotein cholesterol (LDL-C) and non-high-density lipoprotein cholesterol (non-HDL-C), are main risk factors for arteriosclerotic vascular disease (ASCVD)[30,31]. The decrease in LDL-C has been shown to improve cardiovascular health significantly[15]. Numerous guidelines, including China, have suggested that modulating LDL-C levels or non-HDL-C can considerably reduce CVD risk[6,32-34]. Therefore, the guidelines of many countries including China have selected LDL-C as the primary target of lipid-lowering therapy[32-34]. The guideline of dyslipidemia prevention for Chinese adults[34] has established target levels of LDL-C and non-HDL-C for different risk groups. Table 1 shows the target lipid levels for older Chinese (men $\geqslant$ 45 years old or women $\geqslant$ 55 years old). According to that guideline, if high LDL-C or HDL-C levels cannot be safely reduced to the target level, 50% reduction from baseline is also acceptable.

Lipid-modulating therapy

Over the past decade, a considerable amount of literature has shown that statin is effective in reducing risks of CVDs through modulating blood lipids[35,36]. For an example, Heart Outcome Prevention Evaluation-3 trial (HOPE-3)[37] found that the use of rosuvastatin (10 mg, QD) can reduce the risk of cardiovascular events in an intermediate-risk population, regardless of the baseline LDL-C levels. Open Label Study of Long Term Evaluation Against LDL-C Trial (OSLER)[38] and ODYSSEY[39] have shown that the use of Proprotein Convertase Subtilisin/Kexin type 9 (PCSK9) inhibitor in addition to statin can further reduce 50% of LDL-C level, leading to 50% reduction in risk of developing CVDs. A systematic review[40] in 2013 has demonstrated that statin, in comparison to placebo, significantly reduced the risk of myocardial infarction and stroke in elderly subjects without previous CVD by 39.4% and 23.8%, respectively. Furthermore, the HPS2-THRIVE[41] trial showed that although statin is more effective in lowering LDL-C of Chinese than in Europeans, statin-related adverse effects is also more noticeable in Chinese than in Europeans. Therefore, statin has been suggested as the first line lipid-modulating therapy[10,35,42]. Statin-related adverse events include cognitive dysfunction, myopathy, increased risk of developing diabetes and cognitive impairment[32,33]. Whether older adults are more susceptible to adverse effects of statin therapy and whether effects of statin therapy in younger population can be extrapolated to Chinese who are 80 years and above remain unclear[43]. Hence, statin therapy for older adults has been recommended to be initiated at a low dose and gradually titrated according to the response of patients, especially in Chinese who are 80 years old and above[2,3,6,27,34,35]. Non-statin therapies can be considered for older adults who cannot tolerate statin or cannot attain target LDL-C level after taken maximum tolerated statin therapy[44].

Diabetes

Type Ⅱ diabetes is the most common types of diabetes among older adults in China[4]. Postprandial hyperglycemia is more noticeable in Chinese patients

Table 1 Target lipid level across different risk groups of older Chinese (men ≥ 45 years old or women ≥ 55 years old)

Current lipid level (mmol/L)	Risk level	Target lipid level (mmol/L)
TC ≥ 7.2 or LDL-C ≥ 4.9	High	Primary target
4.1 ≤ TC < 7.2 or 2.6 ≤ LDL-C < 4.9 (hypertension + smoking or low HDL-C)		LDL-C < 2.6
3.1 ≤ TC < 7.2 or 2.6 ≤ LDL-C < 4.9 (hypertension + smoking + low-HDL-C)		Secondary target
3.1 ≤ TC < 7.2 or 1.8 ≤ LDL-C < 4.9 (diabetes)		Non-HDL-C < 3.4
5.2 ≤ TC < 7.2 or 3.4 ≤ LDL-C < 4.9 (smoking or low HDL-C)	Moderate	Primary target
4.1 ≤ TC < 7.2 or 2.6 ≤ LDL-C < 4.9 (hypertension, or smoking + low HDL-C)		LDL-C < 3.4
3.1 ≤ TC < 4.1 or 1.8 ≤ LDL-C < 2.6 (hypertension + smoking or low HDL-C)		Secondary target Non-HDL-C < 4.1
3.1 ≤ TC < 7.2 or 1.8 ≤ LDL-C < 4.9	Low	Primary target
3.1 ≤ TC<5.2 or 1.8 ≤ LDL-C < 3.4 (smoking or low HDL-C)		LDL-C < 3.4
3.1 ≤ TC < 4.1 or 1.8 ≤ LDL-C < 2.6 (hypertension or smoking + low HDL-C)		Secondary Target Non-HDL-C < 4.1

LDL-C: Low-density lipoprotein cholesterol; TC: Total cholesterol; HDL-C: High-density lipoprotein cholesterol.

with early type 2 diabetes than in other population because they have significant β-cell deterioration[45]. Chinese is at high risk of developing diabetes with BMI relatively lower than non-Asian patients[46]. Older adults with diabetes are usually complicated by other metabolism disorders such as high LDL-C, high HDL-C, and hypertriglyceridemia[7]. Moreover, older adults with diabetes usually have poor treatment adherence and tolerance, and at high risk of hypoglycemia due to the following main reasons[7,28,47]: (1) damaged autonomic nervous system and sympathetic nervous system; (2) deteriorated compensatory mechanism of blood glucose hormone; and (3) malnutrition, irregular eating habits, reduced cognitive impairment, alcohol consumption, under-reserved hepatic glycogen, polypharmacy, and declined hepatic and renal functions.

Management of diabetes

Higher risks of morbidity and mortality have been found in older adults with diabetes at both low and high glycated hemoglobin (HbA1c) levels[7]. As a consequence, the Chinese guideline for the management of diabetes[42] has recommended the control of HbA1c to effectively reducing the risk of morbidity and mortality (Table 2). The target of blood pressure and blood lipid for older adults with diabetes are shown in Table 3. Treatments that have little or no association with hypoglycemia are recommended to reduce blood glucose level of older adults[48]. Older adults are recommended to have fasting blood glucose level < 7.8 mmol/L and 2-h after fed blood glucose level < 11.1 mmol/L[48]. Treatment strategies are encouraged to avoid hypoglycemia, symptomatic hyperglycemia, orthostatic hypotension, and other drug-related complications[7,28,42,49]. Since postprandial hyperglycemia and β-cell deterioration are characteristics of Chinese patients with type 2 diabetes, considerations of anti-diabetic therapy for Chinese patients with type 2 diabetes include control of postprandial hyperglycemia and β-cell preservation. Older adults usually have lower metabolism rate, malnutrition and multiple comorbidities[7,28]; therefore, their diets are recommended to limit calorie intake and balance diet nutrition for the prevention of deteriorating other comorbidities[50]. Older adults with diabetes should avoid high-intensity exercise to prevent hypoglycemia and injury[28,42]. Intense blood-glucose-lowering therapy such as glyburide should be avoided as treatment options to prevent hypoglycemia[28,42]. Initial therapy should start at low doses, and insulin therapies must be used with caution. Older adults with diabetes and high risk of CVD are not encouraged to use glycemic agents to lower blood glucose levels[7,27,50].

In comparison to older adults who had diabetes at a younger age, older adults who developed diabetes at later age secrete more insulin resistance and insulin compensation[7,28,50]. A Chinese expert consensus for the management of diabetes in the elderly[42] has proposed an overall treatment strategy for management of diabetes in the elderly, including the four principles: (1) early prevention; (2) early diagnosis; (3) early treatment; and (4) early target attainment. Glycemic target management is encouraged to be personalized[42].

ntidiabetic therapy

The choice of type Ⅱ diabetes medications has been explicitly suggested in Expert Consensus on Diabetic Diagnosis and Treatments for Elderly[42]. In brief, first-line antidiabetic therapy includes metformin, α-glucosidase and insulin secretagogues. Metformin has been effective and safe in lowering HbA1c levels. α-glucosidase and insulin secretagogues (glinides and sulfonylurea) are alternatives for older adults who cannot tolerate metformin or who have postprandial

Table 2 Glycemic goals across different clinical conditions of older Chinese (men ≥ 45-year-old or women ≥ 55-year-old)

Clinical conditions	Glycemic goals
> 10 yr of life expectancy Good medical support High expected benefit from treatment Low hypoglycaemia risk	HbA1c < 7% Fasting plasma glucose < 7 mmol/L Postprandial blood glucose < 10.0 mmol/L Stabile blood glucose level
> 10 yr of life expectancy New diagnosed and relatively young No syndromes or complications Low risk of treatment-related hypoglycaemia Not using glycaemic-lowering medications or only use one type of non-insulin secretagogues Good treatment adherence	HbA1c = 7%
> 10 yr life expectancy Type I or type Ⅱ diabetes Mild syndromes or complications Moderate risk of treatment-related hypoglycaemia Receiving insulin secretagogues or insulin therapy	HbA1c < 7.5%
< 5 yr of life expectancy Moderate syndromes or complications Moderate risk of hypoglycaemia Receiving insulin secretagogues or primarily multiple insulin injections	HbA1c < 8%
< 5 yr of life expectancy Incapable to self-manage	HbA1c < 8.5% Avoid acute diabetic complications or refractory infections caused by severe hyperglycaemia Blood glucose < 11.1 mmol/L

Table 3 Target levels of blood pressure, low-density lipoprotein cholesterol, non-high-density lipoprotein cholesterol for older Chinese with diabetes

Risk group	Target blood pressure level (mmol/L)	Target lipid level (mmol/L)
Diabetes	< 130/80 mmHg	Primary target LDL-C < 2.6 Secondary target Non-HDL-C < 3.4
Diabetes with hypertension and another risk factor	< 130/80 mmHg	Primary target LDL-C < 1.8 Secondary target Non-HDL-C < 2.6

LDL-C: Low-density lipoprotein cholesterol; Non-HDL-C: Non-high-density lipoprotein cholesterol.

hyperglycemia at healthy weights. New diagnosed type 2 diabetic patients who have HbA1c above 9% or FPG above 11.1 mmol/L are recommended to use short-term intensive insulin therapy, including basal and prandial insulin therapy, continuous subcutaneous insulin infusion or premixed insulin for sustaining β-cell function. Chinese patients with type 2 diabetes, who usually have poor early-phase insulin secretion, are recommended to use insulin secretagogues for lowering blood glucose by stimulating the pancreatic β cell to release insulin. Although sulfonylurea is one of the first-line antidiabetic treatments in China, results of randomized controlled trials on Chinese patients are needed for a better guideline of its use in Chinese patients. Acarbose, a type of α-glucosidase inhibitor, has found to be more effective in lowering postprandial glucose and less useful in fasting plasma glucose than metformin[51].

Expert Consensus on Diabetic Diagnosis and Treatments for Elderly[42] also recommended DPP-4 inhibitor and GLP-1 receptor antagonist for treating type 2 diabetes. The effect of DPP4-inhibitors has been as efficacious as acarbose in treating drug-naïve patients with better gastrointestinal tolerability[52]. Some DPP-4 inhibitors[53,54] have been associated with improvement of β-cell function in non-Asian patients, but whether such benefit also occurs in Chinese remains unclear. In addition, long-term safety and cardiovascular outcomes of DPP-4 inhibitors in the Chinese population have not been reported[55].

LIFESTYLE INTERVENTION

Over the past two decades, the industrialization and urbanization of China have fundamentally improved the average standard of living of Chinese; on the other hand, the unhealthy eating patterns and sedentary lifestyles of Chinese have also increased as well[56]. The China Health and Nutrition Survey (CHNS) reported that the total physical activity and occupational, physical activity in men and women across nine provinces from 1991 to 2011 fell by 31% and 42%, respectively[57]. Urbanization has been associated with the decreased levels of occupational, physical activities[58]. Physical inactivity has been associated with increased risks of the five major CVDs in China, including coronary heart disease, stroke, hypertension, type 2 diabetes mellitus and cancer[59]. Over the past decade, several studies have shown that the food intake patterns of Chinese have dramatically changed as a result of urbanization; grain and vegetables consumptions are decreased, and meat and fats consumption have increased[56]. The average annual consumption of Chinese adults who were 15 years old or older has gradually increased from 2.5 L in 1978 to 6.7 L in 2010[60].

Lifestyle modifications such as no smoking, healthy diets, strict alcohol intake and regular exercise, has been suggested by experts and studies worldwide as fundamental part of risk factor management to reduce the risk of CVDs[1,10,11]. Smoking and second-hand smoking are major risk factors for chronic diseases, including CVD and diabetes[4,5,9,21,61,62]. They deteriorate the vascular elasticity, accelerate the development of atherosclerosis, and increase the risk of developing CVDs and mortality[26,63,64]. Therefore, smoking cessation is crucial in reducing the risk of CVDs for both smoking and non-smoking older adults[10,62]. Effective smoking cessation interventions include

health promotion, nicotine replacement therapy and medication[65-67].

Salt-sensitive hypertension is common in older adults in China[4,12,21]; therefore, reduction in salt intake is an essential part of hypertension management strategy[1,13]. The salt intake of subjects with hypertension is recommended to be < 5 g/d[21]. Older adults with hypertension are recommended to have high nutritional diets, which include intake of fresh vegetables, fruits, fishes, bean products, coarse grains, skim milk, other rich vitamins, high fiber and non-saturated fats food[10-12,21]. Of the total calories intake, the proportion of fats and saturated fats consumption are recommended to be less than 25% and 7%, respectively[21].

Overweight has been associated with risk of elevated blood pressure and lipid levels, and diabetes, which are high-risk factors of CVDs[68-70]. Modest weight loss has shown improvement in health conditions[71,72]. In general, the BMI of older adults are encouraged to be under than 25 kg/m^2[21] because the reduction in BMI can alleviate the insulin resistance[73,74], diabetes[48,75] and dyslipidemia[76,77]. Regular moderate exercise can control BMI and insulin resistance, improve systemic cardiovascular modulation and reduce high blood pressure[78-81]. However, weight-loss medications are in general not recommended to older adults because older adults are susceptible to adverse effects of medications[10]. Furthermore, excessively strict control of diet and salt intake in older adults often lead to malnutrition[82-84]. Food consumption is encouraged to be personalized based on individuals' clinical manifestation[1,12,21]. Rapid or extreme reduction in weight can lead to poor quality of life due to poor physical conditions or even susceptible to develop other systemic diseases[6,7,12,13,47]. Unlike the younger population, older adults should not have high-intensity exercise because that increases their risk of encountering fracture and fall[80]. These lifestyles modification factors are highly recommended for management of cardiovascular risk factors, such as obesity, hypertension, dyslipidemia, diabetes and chronic kidney disease[6,7,69,78,81].

FUTURE PERSPECTIVES

The increasing prevalence of CVD, hypertension, dyslipidemia, and diabetes are increasing in China, but clinical guidelines and expert consensuses of primary CVD prevention for older adults or very old adults are currently lacking. Unlike management of a particular risk factor (*e.g.*, hypertension, dyslipidemia) which considers treatment strategies that optimize a specific factor, primary CVD prevention strategies require treatment plans that simultaneously manage several risk factors. A systematic review in 2016 reported that many primary CVD preventions of clinical practice guidelines (CPGs) in other countries have inexplicit guidance to manage CVD risk factors of older adults[11]. Although that systematic review only reviewed English articles, some limitations that were revealed in that review also applied to Chinese clinical guidelines and expert consensuses of primary CVD prevention in older adults and very old adults: (1) limited discussion of primary prevention strategies for frail older people and older individuals with multiple comorbidities; (2) no recommendations on how to overcome problems that withhold the implementation of the CPG for older people such as treatment adherence; and (3) no specific guidance on how to prioritize treatments with consideration of multiple comorbidities, personal and family preferences, and vulnerability to adverse drug effects.

The development of CPG is recommended to be structured in ways that clearly outline primary CVD strategies for a wide variety of older Chinese. In addition, CPGs are recommended to include specific guidance to guide clinicians how to develop personalized primary CVD prevention strategies that take into consideration of clinical manifestations, tolerability, and multiple comorbidities.

In addition, with the increasing prevalence of diabetes, hypertension and dyslipidemia in Chinese elderly, better management of risk factors of CVDs for this growing population are needed. Better management of CVD risk factors includes additional research on optimizing the use of medications in the elderly and safer methods of administrating medications to avoid treatment-related adverse outcomes. Personalize, analyze, and dynamically adjust treatment plans according to responses from patients are crucial as well. The awareness and treatments of hypertension, dyslipidemia, and diabetes remain low[4,14,50,85-87]; hence, more education and training and additional social services are also encouraged in China.

Multi-center large randomized trials of primary CVD prevention on older people (with the inclusion of the frail older people with comorbidities) in China are recommended to explore optimal treatment strategies and targets of blood pressure for older adults in China. Large double-blinded randomized controlled trials on very old people (age > 80 years old) are needed to assess the lipid-lowering effect and adverse effect of statin therapies and some non-statin therapies (Omega-3 fatty acid and bile acid sequestrants) on older adults with multiple comorbidities. More studies are needed to assess the antihypertensive effect of carvedilol and nebivolol and the long-term safety of DPP-4 inhibitors on Chinese elderly. Furthermore, additional studies are needed to evaluate the benefit and harm of lowering blood pressure targets of diabetic older patients to be under 130/80 mmHg[12,21]. The implementation of these suggestions may remarkably reduce the risk of CVDs in older adults *via* more effective management of CVD-related risk factors.

CONCLUSION

In China, CVD has been the leading cause of death,

and the percentage of Chinese who are 60 years or older are increasing. Prescribing cardiovascular treatments to older adults are usually more challenging than younger adults due to polypharmacy, the presence of comorbidities and more susceptible to treatment-related adverse outcomes. Therefore, primary prevention of CVD for older adults is crucial to sustaining the health of older adults and reducing health care burden. Risks of CVDs in older adults can be remarkably reduced through appropriate management of CVD-related risk factors, such as hypertension, dyslipidemia, diabetes and obesity, by controlling blood pressure, glucose and lipids through lifestyle modifications or receiving medications. Lifestyle modifications such as smoking cessation, healthy diets, strict alcohol intake and moderate physical exercise have been recommended to effectively improve health conditions of older adults who have hypertension, dyslipidemia, obesity, diabetes or complications. Treatments for older adults, in general, are recommended to be personalized and to be initiated at low doses. The future direction for better primary CVD prevention in older adults include establishing guidelines for primary prevention of CVD across diverse older adults and further research on better management of CVD risks for elderly Chinese.

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CASE REPORT

Conservative approach to the acute management of a large mesenteric cyst

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Author contributions: Billy C Leung: Lead author and case report writer; Ruth Sankey: Literature search and content review; Matteo Fronza: Literature search and data collection (notes and radiographs); Mohamed Maatouk: Senior author, content review and guidance; all authors contributed significantly towards the completion of the case report.

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Abstract

Mesenteric cysts are rare, benign gastrointestinal cystic lesions, which are often non-troublesome and present as an incidental radiological finding. However, surgery is often performed in the acute setting to remove lesions that are symptomatic. This report highlights the case of a large, symptomatic mesenteric cyst managed successfully with initial conservative measures followed by planned elective surgery. A 44-year-old female presented with a four-day history of generalised abdominal pain associated with distension, fever, diarrhoea and vomiting. Computer tomography revealed a large (21.7 cm × 11.8 cm × 14 cm) mesenteric cyst within the left abdomen cavity. She was admitted and treated conservatively with intravenous fluids and antibiotics for four days, which lead to complete symptom resolution. Follow-up at intervals of one and three months revealed no return of symptoms. An elective laparotomy and excision of the mesenteric cyst was then scheduled and performed safely at nine months after the initial presentation. Compared to acute surgery, acute conservative management followed by planned elective resection of a symptomatic mesenteric cyst may prove safer. The withholding of an immediate operation may potentially avoid unnecessary operative risk and should be considered in patients without obstructive and peritonitic symptoms. Our case demonstrated the safe use of initial conservative management followed by planned elective surgery of a mesenteric cyst found in the acute setting, which was symptomatic but was not obstructive or causing peritonitic symptoms.

Key words: Conservative management; Acute setting; Mesenteric cysts; Elective operation

Core tip: Mesenteric cysts are often asymptomatic and

present as an incidental finding, and acute operative removal is usually performed on symptomatic cases. However for selected cases, an initial conservative approach followed by planned elective surgery can be opted for, particularly in the absence of peritonitis and bowel obstruction. A safer and planned elective procedure would reduce the risk of operative complications. Acute drainage of the cyst should also be avoided due to the high risk of recurrence and infection.

Leung BC, Sankey R, Fronza M, Maatouk M. Conservative approach to the acute management of a large mesenteric cyst. *World J Clin Cases* 2017; 5(9): 360-363 Available from: URL: http://www.wjgnet.com/2307-8960/full/v5/i9/360.htm DOI: http://dx.doi.org/10.12998/wjcc.v5.i9.360

INTRODUCTION

Mesenteric cysts are rare, benign intra-abdominal cystic lesions of the gastrointestinal mesentery, with an incidence of 1/100000 in adults and 1/20000 in children, and a female to male ratio of 2:1, which commonly present in the second decade of life[1]. Lesions are most commonly located in the small bowel (66%) and large bowel (33%), with the ascending colon being most frequently affected, and rarely found in the descending colon, sigmoid colon and rectum. They only occasionally extend to the retroperitoneum[1]. The size of a cyst can vary from a few millimetres to 30cm in diameter, containing up to 2500 mL of fluid[2]. Mesenteric cysts are often asymptomatic and discovered as an incidental finding from radiological investigations, but may present with acute or chronic abdominal pain (55%-81%), palpable mass (44%-61%), distension (17%-61%), nausea and vomiting (45%), constipation (27%) and diarrhoea (6%)[1]. In severe cases, it can lead to bowel obstruction, obstructive uropathy, volvulus, and peritonitis usually from a haemorrhagic or infective cyst[3]. Surgical excision of the mesenteric cyst, with or without resection of any neighouring visceral organs is the common management approach in the acute setting, with marsupialisation reserved for cases that may require wide resection of adjacent organs, but the recurrence rate is high[4]. Drainage is no longer advised due to infection and recurrence risks[5].

This article highlights a case of a symptomatic mesenteric cyst found in the acute setting managed successfully by conservative measures without the need for acute surgical intervention. This has not been previously reported in the literature. We postulate that the conservative approach to mesenteric cysts in the acute setting followed by planned elective surgery for selected cases may prove to be a beneficial and safe approach.

CASE REPORT

A 44-year-old female presented to our surgical assessment unit with a four-day history of generalised abdominal pain and distension, and associated fever, vomiting, diarrhoea and reduced oral intake. She did not have any symptoms of haematemesis, rectal bleeding and mucus discharge, or any urinary and gynecological symptoms. She had no significant past medical or surgical history. On examination she was haemodynamically stable with a pyrexia of 38-39 ℃. Her abdomen was distended but soft, with tenderness over the epigastrium and right-side of the abdomen, with no obvious palpable masses or shifting dullness. Normal bowel sounds were present on auscultation. Rectal examination was normal. Routine blood tests were within normal limits aside from an elevated CRP (C-reactive protein) of 120. Blood cultures, urine-dip, urine pregnancy test, electrocardiography (ECG) and chest X-ray (CXR) was unremarkable. Contrast computed tomography (CT) revealed a huge thin-walled fluid collection with no abnormal enhancement and was separated from any visceral organs, measuring 21.7 cm (craniocaudal) × 11.8 cm (transverse) × 14 cm (antero-posterior) which was occupying the left side of abdomen and upper pelvis (Figure 1). No other abnormalities were found. The lesion was reported presumably as a mesenteric cyst with a suggested element of chronicity due to the calcified nature of the cyst wall.

Initial management included intravenous fluids, analgesia, antiemetics and broad-spectrum antibiotics for symptom relief and suspected concurrent infective gastroenteritis. Explorative surgery was withheld in view of her improving clinical status and inflammatory markers when repeated hours later. She was admitted for four days and discharged with a course of oral antibiotics and no acute surgical intervention. One month after discharge, a pelvic magnetic resonance imaging scan was performed to investigate a possible retroperitoneal origin of the cyst. But the scan further confirmed the acute CT findings of a large simple left-side abdominal cyst (22 cm × 13 cm × 11.5 cm) extended superiorly to the inferior splenic margin which abutted the left kidney, it had no relation to any retroperitoneal structures, such as the ovaries or kidneys (Figure 2). Follow-up at one and three months revealed no worrying clinical features, and a subsequent decision for elective operation was made to excise the lesion. An elective laparotomy and excision of mesenteric cyst was performed at nine months after the initial presentation. There were no post-operative complications and follow-up at six weeks was unremarkable. Finally, histology of the excised lesion confirmed the diagnosis of a mesenteric cyst.

DISCUSSION

Mesenteric cysts are rare, benign intra-abdominal

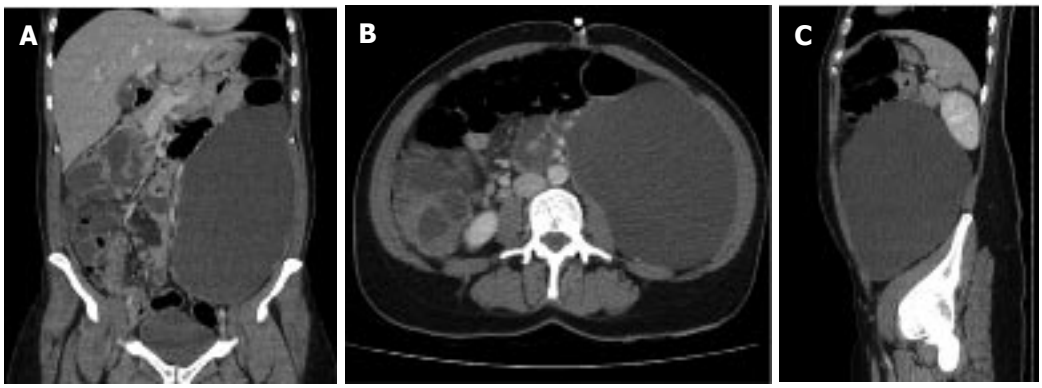

Figure 1 Computed tomography of the abdomen and pelvis showing a large-sized mesenteric cyst. A: Coronal plane-craniocadual diameter of 21.7 cm; B: Transverse plane - transverse diameter of 11.8 cm; C: Sagittal plane - antero-posterior diameter of 14 cm.

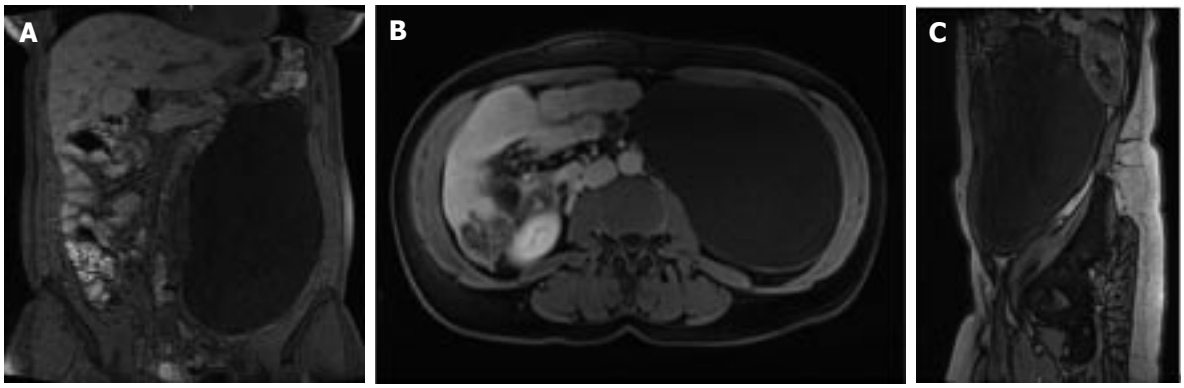

Figure 2 A pelvic magnetic resonance imaging scan confirming the intra-abdominal nature of the cyst, and ruling out a retroperitoneal origin, *i.e.*, an ovarian cyst.

lesions found in the intestinal mesentery. The aetiology is unclear, but the most accepted theory to date describes a benign proliferation of ectopic mesenteric lymphatic tissue failing to communicate with the core lymphatic system[6]. In almost all reported cases, the management approach for a symptomatic mesenteric cyst is acute surgical resection, often performed laparoscopically, or in some cases using marsupialisation to avoid extensive bowel resection. Surgical drainage is avoided due to infection and recurrence[4,5]. The use of conservative management in the acute setting followed by elective surgery had not been previously reported.

Our case demonstrated the safety of conservative management for a symptomatic cyst in the acute setting without the need for immediate surgical intervention. This avoided any potential complications associated with acute surgery. Emergency surgery yields higher risks of complications, such as damage to surrounding structures, visceral perforation, intra-abdominal sepsis, and wound infection. Furthermore, the possibility of cyst regression may fundamentally avoid the need for any operation at all, which means potentially avoiding long-term postoperative complications, such as abdominal adhesions and herniations. However, such a conservative approach should only be reserved for stable patients without symptoms of bowel obstruction, ischaemic bowel, obstructive uropathy, volvulus, and peritonitis.

However by withholding surgery, the risk of adverse sequelae such as bowel obstruction or peritonitis from cyst rupture is inherent, but with limited literature evaluating the disease course of conservatively managed mesenteric cysts, this risk is difficult to quantify currently. A literature search reveals a case-series conducted on seventeen children, which stated the importance of early diagnosis and treatment to prevent significant complications[3]. Nevertheless, we believe that the decision to operate in the acute setting should only be considered if absolutely necessary. The calcified nature of the cyst wall in our case suggests an element of chronicity and stability of the lesion, possibly a process of chronic inflammation, which supports the decision of not operating immediately. Of particular note, the clinical finding of right-sided abdominal tenderness in our participant did not correlate with the left-sided mesenteric cyst finding, which serves to highlight the often subtle nature of mesenteric cyst presentation.

The uncomplicated nature of the elective laparotomy and excision of mesenteric cyst performed nine months after the initial acute presentation highlights the advantage of a delayed planned operation. A randomised controlled trial to compare the benefit

of such an approach would be ethically challenging. Overall, the benefit of conservative management in the acute setting avoids an unplanned operation, which may have significant operative and postoperative complications.

In conclusion, This case report aims to provide future clinicians with the confidence to manage large uncomplicated mesenteric cysts conservatively in the acute setting, thus avoiding the need for an emergency operation that potentially yields a higher risk of peri and post-operative complications compared to a planned operation. The decision to manage conservatively compared to surgically in the acute setting should be considered on an individual basis. Undoubtedly, the definitive treatment is the excision of the mesenteric cyst, but a planned elective surgical approach may be significantly safer than an emergency one.

COMMENTS

Case characteristics

A 44-year-old female with no significant medical history presented with a four-day history of generalised abdominal pain associated with distension, fever, diarrhoea and vomiting.

Clinical diagnosis

Abdomen was distended but soft, with tenderness over the epigastrium and right-sided region, with no palpable mass or shifting dullness, and bowel sounds on auscultation was normal.

Differential diagnosis

Omental cyst, pancreatic or non-pancreatic pseudocyst, echinococcal cyst, enteric duplication cyst, cystic mesothelioma, and ovarian cyst, as well as ascites and lymphoma.

Laboratory diagnosis

All blood tests were within normal limits aside from a raise C-reactive protein (CRP) of 120, and blood cultures, urine-dip, pregnancy test and electrocardiography (ECG) were unremarkable.

Imaging diagnosis

Contrast computed tomography showed a huge thin-walled intra-abdominal fluid collection measuring 21.7 cm × 11.8 cm × 14 cm occupying the left side of abdomen and upper pelvis, suggestive of a mesenteric cyst.

Pathological diagnosis

Histological confirmation of mesenteric cyst after elective excision.

Treatment

Initial conservative management with fluid support in the acute setting, followed by elective surgical excision of lesion.

Related reports

Surgical excision of the mesenteric cyst, with or without resection of neighouring organs, was the most common approach in the acute setting. Marsupialisation was reserved for cases that may require wide resection of adjacent organs, but the recurrence rate is high. Drainage is no longer advised due to infection and recurrence risks.

Term explanation

Mesenteric cysts are rare, benign gastrointestinal cystic lesions, which are often non-troublesome and present as an incidental radiological finding.

Experiences and lessons

Initial conservative approach to mesenteric cysts with a planned elective surgical excision should be adopted in selected cases, such as in the absence of peritonitis and bowel obstruction.

Peer-review

This article is interesting and informative on a sensible topic, and the clinical problem is clearly presented in following parts of the article.

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CASE REPORT

Recurrent aneurysmal bone cyst of talus resulted in tibiotalocalcaneal arthrodesis

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Author contributions: Vosoughi AR and Erfani MA designed the report; Mozaffarian K collected the patient's clinical data; Vosoughi AR, Mozaffarian K and Erfani MA participated in drafting the article and they critically reviewed the manuscript and approved the final manuscript as submitted.

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Abstract

Aneurysmal bone cyst (ABC), a locally benign aggressive lytic lesion of either primary or secondary origin, seldom involves the talus. Herein, we present a 25-year-old man with recurrent ABC of the talus after curettage and bone grafting, which was managed by total resection followed by filling the defect using fibular graft and finally tibiotalocalcaneal arthrodesis due to articular surface involvement. At 18 mo postoperatively, no recurrence was detected. Arthrodesis might be a good option in cases with recurrent ABC of the talus especially with articular surface involvement.

Key words: Aneurysmal bone cyst; Tibiotalocalcaneal arthrodesis; Bone tumor; Talus

Core tip: Despite rarity of aneurysmal bone cyst (ABC) of the talus, we present a case of recurrent ABC of the talus following curettage and bone graft. The tibiotalar and subtalar joints of the patient were fused after complete resection of the tumor.

Vosoughi AR, Mozaffarian K, Erfani MA. Recurrent aneurysmal bone cyst of talus resulted in tibiotalocalcaneal arthrodesis. *World J Clin Cases* 2017; 5(9): 364-367 Available from: URL: http://www.wjgnet.com/2307-8960/full/v5/i9/364.htm DOI: http://dx.doi.org/10.12998/wjcc.v5.i9.364

INTRODUCTION

Aneurysmal bone cyst (ABC) is a benign aggressive bone lesion composed of expansible blood-filled cavities. The incidence is 0.14 per 100000 of the population per year with a slight female predominance[1]. Although all parts of human skeleton can be involved, ABC of foot bones and particularly the talus is very rare[2,3]. Several primary ABCs of the talus[2,4-6] and secondary ABCs on giant cell tumor[7] and Chondroblastoma[8] were described in the literature. Recurrence of ABC of the talus after curettage and bone grafting is extremely rare[5,6]. Surgical treatment of these lesions is essential to reduce the pain of the patient and to prevent the possibility of pathologic fracture. In the present case, we describe a case of recurrent ABC talus with articular surface involvement which resulted in tibiotalocalcaneal arthrodesis.

CASE REPORT

A 25-year-old man presented with swelling and pain in left ankle joint without any history of acute trauma. He had experienced another episode of severe swelling and pain in left ankle area without any preceding trauma about 2 years before arrival. After definite diagnosis of ABC by another surgeon in another hospital, He had undergone curettage and autologous bone grafting *via* medial ankle approach and detachment of deltoid ligament.

Eight months after previous surgery, pain and swelling had begun again and continued till the time of second operation. On examination, swelling and tenderness on medial side was clearly evident. The neurovascular status of left ankle and foot was intact. Range of motion of ankle was limited to 25 degrees in plantar flexion and 10 degrees in dorsiflexion in comparison to the right ankle. Moreover it was painful particularly in full plantar flexion. Left ankle plain radiograph showed a cystic lesion in posteromedial of left talus with invasion to the articular surface of tibiotalar and subtalar joints (Figure 1). As ankle CT scan clearly approved the size and intra-articular invasion of the lesion (Figure 2), magnetic resonance imaging was not requested.

Surgery was performed under general anesthesia in the lateral position after inflation of a thigh tourniquet using sterile conditions. Through direct lateral approach to the lateral malleolus, fibular osteotomy from 10 cm above tip of fibula was done and completely resected. The articular surfaces of tibiotalar and subtalar joints were removed. The ABC was carefully resected because of adhesions to the posteromedial structure of the ankle joint. The pathologic report confirmed recurrent ABC. After curettage, the bone graft from the excised distal fibula bone was impacted in the arthrodesis site. The correct position of tibiotalar and subtalar joints for fusion was prepared and fixed by a Steinmann wire temporarily. Finally, the fixation was achieved utilizing a compression screw and a PHILOS plate

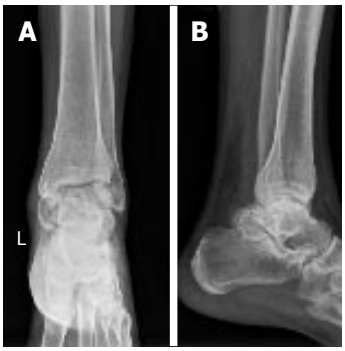

Figure 1 Anteroposterior (A) and lateral (B) radiographs of left ankle show a cystic-like lesion on posteromedial of ankle joint with destruction of articular surfaces.

on lateral side from calcaneus to the distal of tibia. Short leg cast was applied till complete union at 3 mo postoperatively.

Follow-up imaging at 18 mo after the operation showed no apparent sign of recurrence (Figure 3). The patient has a little claudication due to triceps surae weakness. He also suffers from occasional pain after long-distance walking.

DISCUSSION

ABC is a benign tumoral condition peaking at the first two decades of life[1]. Although different treatment options are available, commonly surgical treatment of ABCs including curettage with or without bone grafting in addition to different adjuvants or wide *en-bloc* resection of tumor is preferred[6,9-11]. Although the presented case was initially treated using curettage and bone grafting, recurrence was seen after 8 mo following the primary surgery. Recurrence is not uncommon and the reported rates are as high as 59%[12]. Local recurrence is particularly higher among young age male patients[13].

On the other hand, wide en-bloc excision is an excellent option with the lowest rates of recurrence (95%-100% localized control)[14]. Moreover, it leads to reduce risk of future malignant transformations. Complete resection should be limited to expandable bones like distal ulna or proximal fibula. Complete resection in the other parts is associated with high morbidity to the patient. Resection of a huge ABC with involvement of articular surfaces in the talus could result in instability and functional compromise; therefore arthrodesis might be an acceptable option to diminish the possibility of recurrence, as done in the presented case.

Tibiotalocalcaneal arthrodesis could be done utilizing retrograde hindfoot intramedullary nails or different plate and screw constructs. Although intramedullary nails are good options with higher stability and lower soft tissue damage[15], we prefer to use plate with screws because of more access to the lesion from lateral approach and surgeon experience

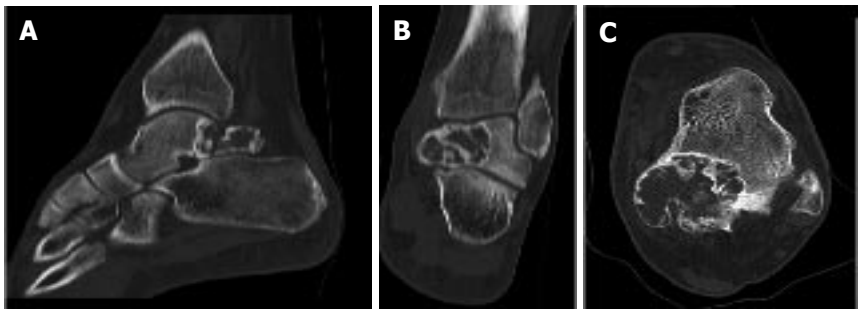

Figure 2 Sagittal (A), coronal (B), and axial (C) cuts of computed tomography scan in favor of tibiotalar and subtalar joint involvement.

Figure 3 Anteroposterior (A) and lateral (B) radiographs of left ankle shows the bone healing without any obvious recurrence at 18 mo following surgery.

for this technique.

This case approved that despite rarity of ABC in the talus, recurrence of ABC of the talus with articular surface involvement after curettage and bone grafting could be treated by en-bloc resection and consequent arthrodesis.

COMMENTS

Case characteristics

A 25-year-old male presented to the authors' outpatient clinic with swelling and pain in left ankle joint with positive history of aneurysmal bone cyst (ABC) of the talus.

Clinical diagnosis

Recurrent ABC of the talus.

Differential diagnosis

Unicameral bone cyst, bone malignancies.

Imaging diagnosis

Plain radiograph and computed tomography demonstrated a big cystic lesion in posteromedial of left talus with invasion to surrounding articular surfaces.

Pathological diagnosis

The histopathology report confirmed recurrence of ABC of the talus.

Treatment

Complete resection followed by bone grafting and tibiotalocalcaneal arthrodesis.

Related reports

There have been very rare case reports of recurrent ABC of the talus treated using arthrodesis methods.

Term explanation

PHILOS plate is an anatomical locking compression plating system for proximal humerus fracture fixation.

Experiences and lessons

Early definite treatment of massive bone cysts in hindfoot is strongly encouraged to prevent inadvertent complications like pathologic fractures.

Peer-review

This is an interesting case report.

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CASE REPORT

Anti-N-methyl-D-aspartate receptor encephalitis that aggravates after acinetobacter baumannii pneumonia: A case report

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Author contributions: Liu K designed the research, revised the paper and provided fundamental support; Wang CC searched the literature and wrote the paper; Li DJ and Xia YQ helped to search the literature and write the paper.

Institutional review board statement: This case report was exempt from the Institutional Review Board standards at West China Hospital of Sichuan University, Chengdu 610041, Sichuan Province, China.

Informed consent statement: The patient involved in this study gave his written informed consent authorizing use and disclosure of his protected health information.

Conflict-of-interest statement: The authors have declared no competing interests exist.

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Abstract

We report an atypical case of anti-N-methyl-D-aspartate receptor encephalitis (ANMDARE). A 27-year-old man diagnosed with ANMDARE received immunotherapy and had a good recovery. However, within one month, he developed severe status epilepticus and decreased level of conscience with new hyperpyrexia and dyspnea, and was admitted to the emergency intensive care unit. Acinetobacter baumanii were found in the sputum culture; and anti-NMDAR antibodies were positive (titer: 1/80) in the cerebrospinal fluid. Repeated immunotherapy was administered with antibacterial agents, and the patient recovered except for mild psychiatric sequelae. This is the first report of ANMDARE that aggravates after acinetobacter baumannii pneumonia. Awareness and knowledge of this disorder should be extended, especially in the emergency medicine community.

Key words: Anti-N-methyl-D-aspartate receptor encephalitis; Acinetobacter baumannii pneumonia; Emergency

Core tip: In this paper we presented a very rare

case of an anti-N-methyl-D-aspartate receptor encephalitis in which the patient aggravated after acinetobacter baumannii pneumonia and well responded to immunotherapy. The mechanism underlying the association needs attention.

Wang CC, Li DJ, Xia YQ, Liu K. Anti-N-methyl-D-aspartate receptor encephalitis that aggravates after acinetobacter baumannii pneumonia: A case report. *World J Clin Cases* 2017; 5(9): 368-372 Available from: URL: http://www.wjgnet.com/2307-8960/full/v5/i9/368.htm DOI: http://dx.doi.org/10.12998/wjcc.v5.i9.368

INTRODUCTION

Anti-N-methyl-D-aspartate receptor encephalitis (ANMDARE) was initially identified in young females with ovarian tumor and was classified as a new immune-mediated encephalitis, producing antibodies to the target ANMDARE[1]. Following a growing attention paid to this disease, an increasing number of reports and analyses have appeared in recent years[2-5]. Early in the disease course, ANMDARE may resemble the first presentation of viral encephalitis[2]. Compared with viral encephalitis, clinical features including psychosis, hallucinations, behavior and personality changes, seizure activity were observed more often among cases of ANMDARE[2]. This disorder is confirmed by the identification of NMDAR antibodies in cerebrospinal fluid (CSF) or serum[1,2]. It deteriorates rapidly with no or delayed treatment, but commonly improves with the application of immunotherapy or through a tumor resection, if applicable. The recovery process is slow, taking nearly 18 mo[3]. Complications in patients while receiving treatment are yet to be established. Acinetobacter baumannii pneumonia has rarely been described in patients with ANMDARE[4,6]. We here report a case of ANMDARE in a man whose clinical condition had improved after immunotherapy, but became worse in no more than one month due to acinetobacter baumannii pneumonia.

CASE REPORT

A 27-year-old man without a previous medical history, initially presenting with an acute psychiatric syndrome, including personality and behavioral change, was first evaluated by a psychiatrist and admitted to the psychiatric department in our hospital. He behaved friendly with focused attention and clear consciousness, but responded slowly to questions and manifested with emotional instability. Interruption of thinking, and thinking burst were observed in psychiatric examination with absence of hallucination, delusion and impulsive aggression. Psychotropic drugs were used, but nothing worked. Rigidity emerged in seven days after admission. On day 12, he was transferred to neurology department with suspected viral encephalitis, in consideration of neurological impairment, including abnormal movements and tachycardia. He soon progressed to status epilepticus, insomnia, confusion of consciousness, and memory deficits, but without fever.

An electroencephalogram (EEG) showed diffuse or general slowing in the patient (Figure 1). Magnetic resonance imaging (MRI) of the brain revealed no abnormal changes (Figure 2). The first evaluation of CSF in psychotropic department was analyzed with ignorance of antibody detection. It only showed mild elevations of the protein level (90 mg/dL) and karyocyte count (50 × 10^6/L), with a normal glucose level (Table 1). In the neurology department, antibody against NR1 heteromeric NMDAR was detected in the CSF (titer: 1/100), and the serum (titer: 1/10). Comprehensive tumor screening, including repeated enhanced computerized tomography (CT) and a urogenital examination for testicular tumors, was performed, with no tumors or inflammatory lesions detected. The patient was eventually diagnosed with ANMDARE without tumors, and was immediately treated with anti-epileptic drugs, corticosteroids (steroid pulse therapy of methylprednisolone 1 g/d for 5 d, followed by tapered-off oral prednisolone) as well as intravenous immunoglobulin (IVIG, 400 mg/kg daily for 5 d). After these treatments, his general condition gradually improved and he was discharged from hospital, with clear mind and normal behaviors.

However, no more than one month after the initial onset, the man typically manifested with new hyperpyrexia and dyspnea and then developed severe status epilepticus, decreased level of consciousness and convulsion of the limbs again. He was admitted to the emergency intensive care unit (EICU) where supplemental oxygen *via* a nonrebreather mask was initiated. The temperature was up to 39.0 ℃. On physical examination, perspiration and cutaneous pallor were observed. He presented mild tachypnea (35 bpm) and severe hypoxemia (SaO_2 86%). On auscultation, he had a good air entrance bilaterally with scattered to diffuse crackles and rhonchi. Serum C-reactive protein was 75 mg/L and procalcitonin (PCT) was 22 ng/mL. CT in the chest revealed acute lung inflammation (Figure 3); CSF was abnormal, and anti-NMDAR antibodies were positive (titer: 1/80) (Table 1). Herpes simplex virus (HSV) DNA polymerase chain reaction (PCR) in the CSF was negative. Acinetobacter baumanii was found in the sputum culture. A relapse of anti-NMDAR encephalitis combined with pneumonia caused by acinetobacter baumannii was diagnosed, and a cycle of steroid and IVIG pulse therapy were administered once again with antibacterial agents as well as other supportive therapies. There was no positive detection in tumor screening. The patient gradually recovered except for mild psychiatric

Table 1 Examination of cerebrospinal fluid

	First hospitalization	Post-treatment	Second hospitalization
Cerebrospinal pressure	Normal	Normal	Normal
NMDAR-Ab	1:100(+)	-	1:80(+)
CSF protein (g/L)	0.9	0.27	0.8
CSF glucose (mmol/L)	4.26	3.88	3.66
CSF chlorine (mmol/L)	12.6	128	120.1
CSF karyota count	50×10^6/L	0	60×10^6/L

CSF: Cerebrospinal fluid; NMDAR-Ab: Anti-N-methyl-D-aspartate receptor-Ab.

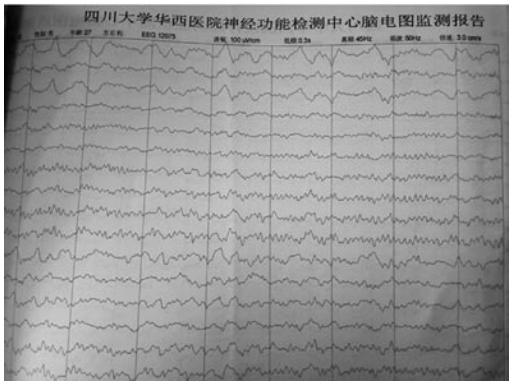

Figure 1 Electroencephalogram monitoring revealed low amplitude slow wave almost universally.

sequelae.

DISCUSSION

In our case, ANMDARE relapsed and the condition of the patient got worse following acinetobacter baumannii pneumonia, similar to that with possible mycoplasma pneumoniae infection in a previous study[2]. In recent reports[4,6], pneumonia was seen from 55% to 65% of patients with ANMDARE, more likely to accompany with status epilepticus, and was regarded as one of the risk factors influencing the outcome of this disease. The Chinese cohort study have firstly focused on and explore the causes of death of patients with ANMDARE, revealing that all the patients died with the existence of pneumonia[6]. Complications such as severe pneumonia, multiple organ dysfunction syndrome (MODS), refractory status epilepticus (RSE) and sepsis were the main causes of death of patients with ANMDARE[1,4,6]. Acinetobacter baumannii pneumonia may be a direct infectious complication of the use of immunosuppressant and may result in a fatal episode of respiratory failure or sepsis. But this has rarely been described in patients with ANMDARE. It is fairly clear that the occurrence of acinetobacter baumannii pneumonia has provoked the relapse and aggravation of ANMDARE in our case. However, the mechanism of the underlying association is not clear, and whether this connection is meaningful warrants further study. There is increasing evidence that ANMDARE might develop in the context of viral encephalitis, and in term of etiology, a viral trigger (*e.g.*, herpes simplex) might be considered in the synaptic autoimmunity[5,7]. Moreover, the frequency of ANMDARE is likely to be four times higher than HSV encephalitis in young individuals in the California Encephalitis Project[8]. Approximately 4.4% of encephalitis with unclear cause are anti-NMDAR encephalitis, followed by HSV type 1, enterovirus, varicella zoster virus, and West Nile virus[8]. The correlation between ANMDARE and viral etiology is important[5]. Whether the lung infection could be a trigger of ANMDARE and its mechanism need further studies.

Although the clinical spectrum of ANMDARE was widely reported, the disease often cannot be diagnosed earlier till the later clinical courses due to the nonspecific nature of symptoms and insufficient awareness of the disorder[9] in most departments except the neurology, especially in the emergency department. There are several challenges in managing ANMDARE: The outcome is poor among developing countries, including China, due to the knowledge gap compared with developed countries, delays in diagnosis and misdiagnosis, complications as well as economic affordability. While approximately 80% of patients have good outcome[3,10], ANMDARE carries a significant morbidity and mortality because of life-threatening illnesses such as intractable seizure, ventilator care, rhabdomyolysis or pneumonia[4,10,11]. Patients could die of MODS during hospitalization, even after immunotherapy[12]. Moreover, a minority of patients received second-line immunotherapy. It is important to make decisions regarding instance to facilitate a second-line immunotherapy and therapy timing typically based on symptoms, doctors' experience, therapeutic response, or patients' preference. Furthermore, many patients were discharged before they fully recovered due to the financial burden or ward beds shortage in hospital. While being back home or transferred to a primary care center, the condition may worse due to the progress of the disorder or complications including lung infection, urinary infection, rhabdomyolysis, venous thrombosis and hypersexuality[4,10,13]. In China, awareness and knowledge of this disorder among not only neurologists but also psychiatrists and primary care physicians, should be extended and taken into consideration in the differential diagnosis when they encounter patients with a new onset of neurologic complaints preceded by psychiatric symptoms. Meanwhile, the popularity and feasibility of test method of NMDAR-Abs are required in most hospitals in China, so that physicians can more readily identify those affected with this potentially treatable disorder, facilitating earlier treatment and good outcome.

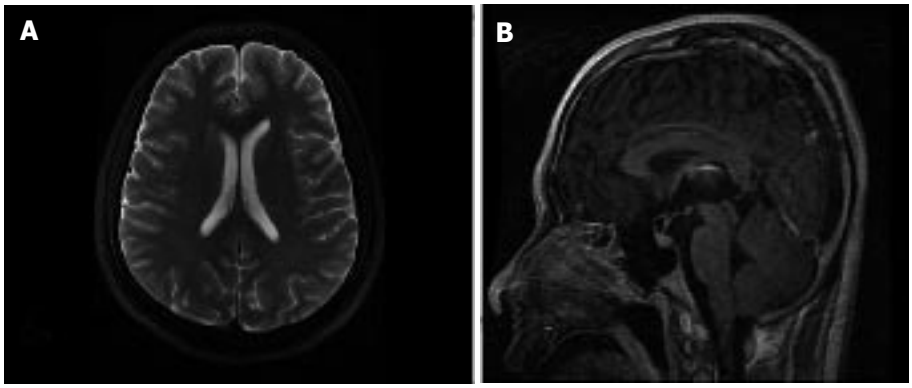

Figure 2 Transverse (A) and sagittal (B) views of magnetic resonance imaging was normal on admission.

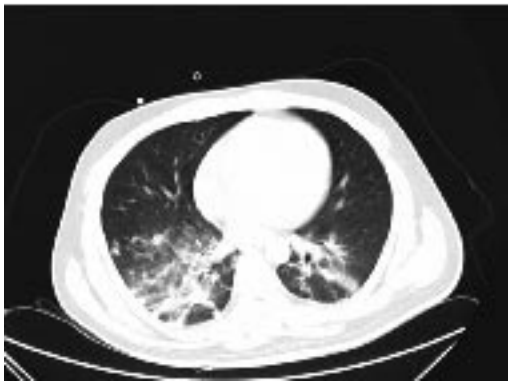

Figure 3 Computerized tomography in the chest revealed acute lung inflammation.

In conclusion, acinetobacter baumannii pneumonia can aggravate the process of ANMDARE. The mechanism underlying the association remains unknown and needs further studies. In China, awareness and knowledge of this disorder associated with lung infection should be extended, especially in the emergency medicine community.

COMMENTS

Case characteristics
A 27-year-old male with status epilepticus.

Clinical diagnosis
Anti-N-methyl-D-aspartate receptor encephalitis (ANMDARE).

Differential diagnosis
Viral encephalitis.

Laboratory diagnosis
Elevated titers of antibody against NMDAR in the cerebrospinal fluid.

Imaging diagnosis
Magnetic resonance imaging of the brain revealed no abnormal changes.

Treatment
Steroid and intravenous immunoglobulin pulse therapy.

Related reports
About 30 cases of NMDAR encephalitis after acinetobacter baumannii pneumonia.

Term explanation
ANMDARE developed multiple psychiatric and neurological features in the clinical course, including psychosis, epileptic seizures, autonomic instability, dyskinesia, decreased consciousness, and hypoventilation. It predominantly affects young adults and children with or without tumors and well responds to immunotherapy.

Experiences and lessons
This case report shows ANMDARE that aggravates after acinetobacter baumannii pneumonia. It's rarely reported.

Peer-review
This is an interesting case report.

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MINIREVIEWS

Adrenal ganglioneuroma: What you need to know

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Abstract

Adrenal ganglioneuromas (GNs) constitute rare, differentiated tumors which originate from neural crest cells. GNs are usually hormonally silent and tend to be discovered incidentally on imaging tests. Adrenalectomy is the gold standard for the treatment of primary adrenal GNs. Nevertheless, preoperative differential diagnosis of GNs remains extremely challenging, and thus histopathological examination is required in order to confirm the diagnosis of GN. Overall, prognosis after surgical resection seems to be excellent, without any recurrences or need for adjuvant therapy.

Key words: Ganglioneuroma; Neurogenic tumors; Neural crest; Adrenalectomy

Core tip: Adrenal ganglioneuromas (GNs) are uncommon, differentiated tumors which originate from neural crest cells. These lesions are usually discovered incidentally because they tend to be hormonally silent. Even though, surgery is the gold standard for the treatment of adrenal GNs, the process of preoperative differential diagnosis remains extremely challenging. Therefore, histologic examination is necessary in order to confirm this rare diagnosis. In general, there is no need for adjuvant treatment and the overall prognosis of these patients is excellent.

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INTRODUCTION

Ganglioneuromas (GNs) constitute rare, differentiated tumors which originate from neural crest cells[1]. As such, they are usually located in the retroperitoneal space (32%-52%) or in the posterior mediastinum (39%-43%). Less commonly, GNs can be seen in the cervical region (8%-9%) as well[2,3]. Interestingly enough, thoracic tumors have been found to be larger than non-thoracic ones at the time of diagnosis[4]. Adrenal GNs occur most frequently in the fourth and fifth decades of life, whereas GNs of the retroperitoneum and posterior mediastinum are usually encountered in children and younger adults. GNs seem to develop in females and males with equal rates; yet most of our data derive from case reports or small case series[5-7]. Nonetheless, a familial predisposition as well as an association with Turner syndrome and multiple endocrine neoplasia Ⅱ have also been suggested[5].

Commonly, adrenal GNs are hormonally silent and as a result can be asymptomatic; even when the lesion is of substantial size[5,8]. On the other hand, it has been reported that up to 30% of patients with GNs may have elevated plasma and urinary catecholamine levels, but without exhibiting any symptoms of catecholamine excess[4]. Additionally, it has been noted that ganglion cells can secrete vasoactive intestinal peptide (VIP), whilst pluripotent precursor cells sometimes produce steroid hormones, such as cortisol and testosterone[9,10].

IMAGING

Adrenal GNs are usually discovered incidentally due to the widespread use of computed tomography (Figure 1) and MRI (Figure 2) imaging techniques[2,11]. Particularly, GNs account for approximately 0.3%-2% of all adrenal incidentalomas[12-14]. In most cases, ultrasonography reveals a well-circumscribed, homogenous, hypo-echogenic lesion[15]. Furthermore, CT findings are usually compatible with a well-defined, lobular-shaped, solid, encapsulated mass. These tumors can been seen ranging from iso-attenuating to hypo-attenuating lesions compared to muscle signals[15]. Usually, the mass surrounds major blood vessels without imposing compression or occlusion[16]. Fine, punctate calcifications are found at a frequency ranging from 20% to 69% and are considered highly indicative of GNs[5,11]. On magnetic resonance imaging, T1-weighted images tend to have homogeneously low or intermediate signal, whereas T2-weighted images have heterogeneously intermediate or high signal[17]. Arguably, the latter is caused by the presence of the myxoid matrix along with a relatively low number of ganglion cells[18]. Furthermore, gadolinium administration can result in delayed and progressive enhancement of the lesion[8,15].

In reality, the aforementioned radiology findings are not pathognomonic of adrenal GNs[15]. Particularly the preoperative misdiagnosis rate of adrenal GNs based on CT and MRI findings has been attested to be 64.7%[5]. Also, MIBG (131-metaiodobenzylguanidine) scintigraphy produces similar results in GNs, ganglioneuroblastomas and neuroblastomas[2,15]. Recently, PET scans have been proclaimed to facilitate the diagnostic process. Particularly, Standardized Uptake Value (SUV) of 3.0 or higher has been suggested to distinguish malignant from benign adrenal lesions with 100% sensitivity and 98% specificity[19]. However, Adas *et al*[20] did report an adrenal GN with a SUV of 4.1 that was determined to be histologically benign. Taking everything into consideration, preoperative differential diagnosis of GNs remains extremely challenging and includes a variety of lesions, such as ganglioneuroblastoma, neuroblastoma, composite pheochromocytoma, adrenal cortical adenoma and adrenocortical carcinoma[2,21].

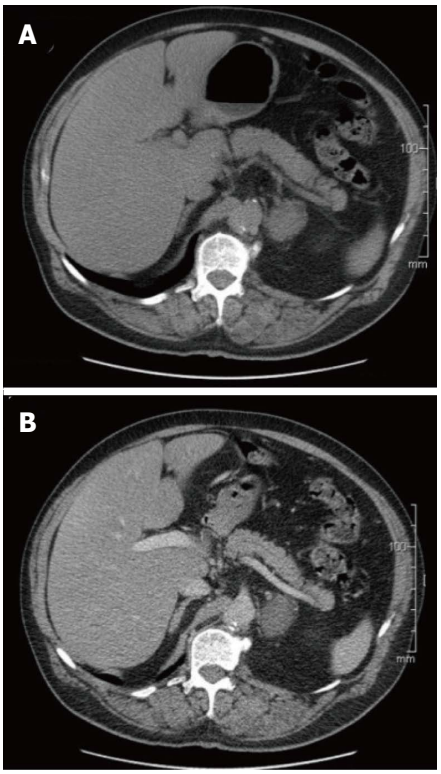

Figure 1 Axial computed tomography of left adrenal ganglioneuroma: Well-defined, solid, encapsulated mass (in *intravenous* contrast). A: Non-enhanced image; B: Enhanced image (venous phase).

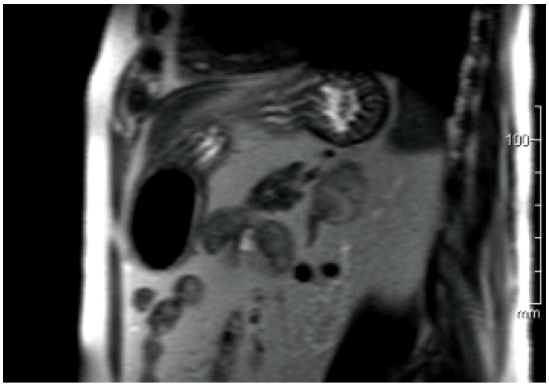

Figure 2 Coronal magnetic resonance imaging of left adrenal ganglioneuroma: A coronal T1-weighted out-of-phase image shows intracellular lipid and no signal loss within the lesion.

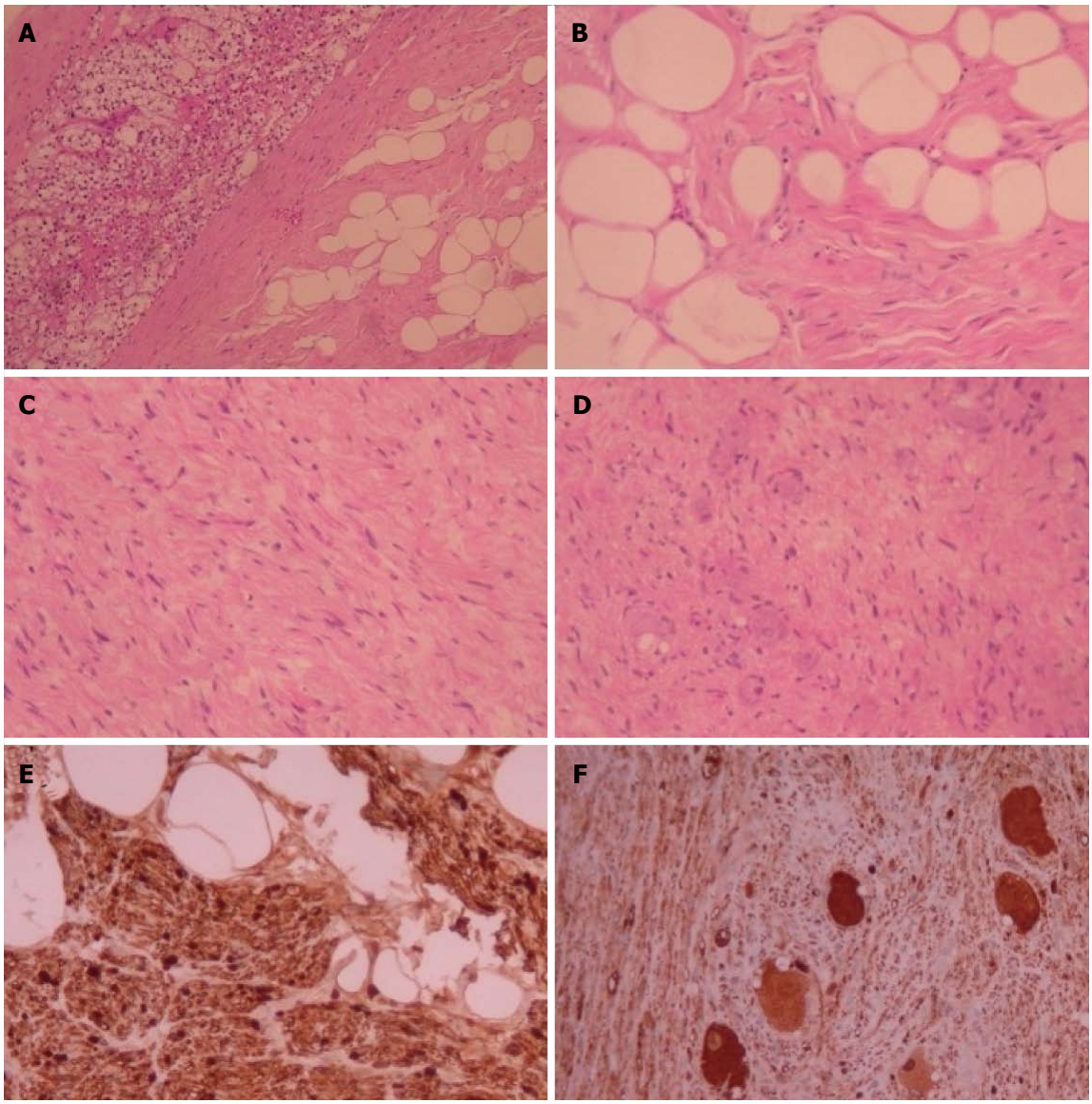

Figure 3 Histopathologic features of adrenal ganglioneuromas. A: Margin between adrenocortical parenchyma and adrenal ganglioneuroma with Schwann cells in adipose stroma (H and E × 100); B: Schwann cells in adipose stroma (H and E × 400); C: Schwann and ganglion cells in non-adipose stroma (H and E × 200); D: Schwann cells and multiple ganglion cells (H and E × 200); E: Protein S100 (+) Schwann cells (immunostaining × 400); F: Neuron-specific enolase (+) ganglion cells (immunostaining × 200). H and E: Hematoxylin and eosin.

HISTOPATHOLOGIC FEATURES

Ultimately, histopathological examination is required in order to confirm the diagnosis of GN (Figure 3). In the vast majority of cases, GNs are histologically benign lesions GNs which can be classified into two main categories[4]. Firstly, "mature type" GNs comprise of mature Schwann cells, ganglion cells and perineural cells within a fibrous stroma whilst completely lacking neuroblasts and mitotic figures[8]. Secondly, "maturing type" GNs consist of similar cellular populations with miscellaneous maturation degrees, ranging from fully mature cells to neuroblasts. Nevertheless, detection of neuroblasts is typically indicative of neuroblastomas or ganglioneuroblastomas. These types of neurogenic tumors have the potential to evolve into GNs[15]. Characteristically, GNs exhibit immunohistochemical reactivity for specific markers such as S-100, vimentin, synaptophysin and neuron-specific enolase[17].

GENETIC FEATURES

The tyrosine kinase receptor ERBB3 is one of the most commonly up-regulated genes in GNs[22]. Additionally, recent case series have found high expression of GATA3 in all of their GN tumors (100%) meaning that this may be a very reliable marker for GNs[23,24]. Lastly, the coexistence of GN with neuroblastoma has been associated with a hemizygous deletion of 11q14.1-23.3. Indeed, the predisposition to the development of neurogenic tumors may be attributed to the deletion of the *NCAM1* and *CADM1* genes which lie in 11q[25]. In contrast to neuroblastomas though, GNs do not seem to exhibit MYCN gene amplifications[4].

MANAGEMENT

Last but not least, literature is consistent with the fact that when dealing with large (> 6 cm) adrenal incidentalomas there is a 25% probability of the lesion being an adrenocortical carcinoma. Geoerger *et al*[4] described local lymph node involvement in two GN patients and one case of distant metastasis to soft tissues in their 49-patient case series. Nonetheless, malignant GNs remain extremely rare occurrences[21]. Ultimately, surgery constitutes the gold standard for the treatment of primary adrenal GNs[4,26]. Even though, laparoscopic adrenalectomy is usually the procedure of choice, a number of variables (*e.g.*, hormonal activity, tumor location, and proximity to adjacent structures) also need to be taken into account when deciding on the best approach to operate on these rare tumors[24]. Of note, wide excisions are unnecessary since adrenal GNs rarely metastasize or recur. Postoperatively, there is no need for adjuvant therapy in patients with adrenal GNs and their prognosis is excellent[4,21].

CONCLUSION

Adrenal GNs are uncommon, differentiated tumors which originate from neural crest cells. These lesions are usually discovered incidentally and tend to be hormonally silent. Even though, adrenalectomy is the gold standard for the treatment of adrenal GNs, the process of preoperative differential diagnosis remains extremely challenging. Ultimately, histologic examination is necessary in order to confirm this rare diagnosis. Postoperatively, there is no need for adjuvant treatment and the overall prognosis of these patients is excellent.

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CASE REPORT

Hydrogen peroxide ingestion with injury to upper gastrointestinal tract

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Abstract

Hydrogen peroxide is a common over-the-counter solution that has developed a growing body of literature regarding toxic ingestion. Intentional ingestion of high concentration hydrogen peroxide for health purposes has gained popularity in certain patient populations; purported benefits are due to the increased oxygen released into the blood stream. We present for evaluation one such case with associated imaging that presented to our urban medical center. A brief review of the literature was also performed noting current recommendations regarding both outcomes and indications for endoscopy as well as hyperbaric oxygen therapy following ingestion of hydrogen peroxide. Our patient was a 51-year-old white female who presented with foamy hematemesis after ingesting 10 drops of 35% hydrogen peroxide as part of a home remedy to cleanse her colon and improve blood oxygenation. In addition to hematemesis, she also reported diffuse abdominal pain with sore throat and hoarse voice. Her imaging demonstrated portal venous gas and gastric edema. She was admitted for hyperbaric oxygen therapy and underwent upper endoscopy demonstrating diffuse esophagitis and gastritis with white exudate and multiple petechiae. She was later discharged home in stable condition and was lost to follow-up.

Key words: Hydrogen peroxide; Caustic injury; Hyperbaric oxygen therapy; Ingestion of hydrogen peroxide; Arterial gas emboli

Core tip: In patients presenting with unresolving epigastric and hematemesis following ingestion of hydrogen peroxide, evaluation with endoscopy is indicated. Computed tomography and/or magnetic resonance imaging are also indicated to evaluate for formation of arterial gas emboli. Therapy is primarily supportive, ± hyperbaric oxygen therapy depending on presence of neurological symptoms, presence of gas emboli, and

availability of resources.

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INTRODUCTION

Hydrogen peroxide is a common over-the-counter solution that has developed a growing body of literature regarding toxic ingestion[1-5]. The main mechanisms for toxicity include direct lipid peroxidation, oxygen gas production, and corrosive injury[1]. Reported toxicities and fatalities tend to involve higher concentrations (> 35%) and pediatric patients[1].

Intentional ingestion of high concentration hydrogen peroxide for health purposes has gained popularity in certain patient populations; purported benefits are due to the increased oxygen released into the blood stream. We present for evaluation one such case with associated imaging.

CASE REPORT

A 51-year-old white female presented to our urban medical center with foamy hematemesis after ingesting 10 drops of 35% hydrogen peroxide as part of a home remedy to cleanse her colon and improve blood oxygenation. In addition to hematemesis, she also reported diffuse abdominal pain with sore throat and hoarse voice.

At the time of presentation, vitals were normal and stable. Her initial abdominal exam was benign and she was neurologically intact. Labs were within normal limits save for a leukocytosis of 12.6 thousand/mm^3. CT imaging obtained at admission demonstrated portal venous gas, gastric pneumatosis, and gastric edema (Figure 1). She was given a proton-pump inhibitor and admitted for hyperbaric oxygen therapy (HBT) to be followed by upper endoscopy evaluation.

Esophagogastroduodenoscopy performed the following morning revealed a small hiatal hernia, diffuse esophagitis and gastritis with white exudate and multiple petechiae, and two areas of duodenitis (Figures 2 and 3). Gastric biopsies later demonstrated only active, chronic gastritis with marked congestion and extravasated blood. Following her endoscopy and hyperbaric oxygen therapy, patient tolerated a liquid diet and was deemed stable for discharge home later that day. Patient was lost to follow-up.

DISCUSSION

Mortality associated with hydrogen peroxide ingestion

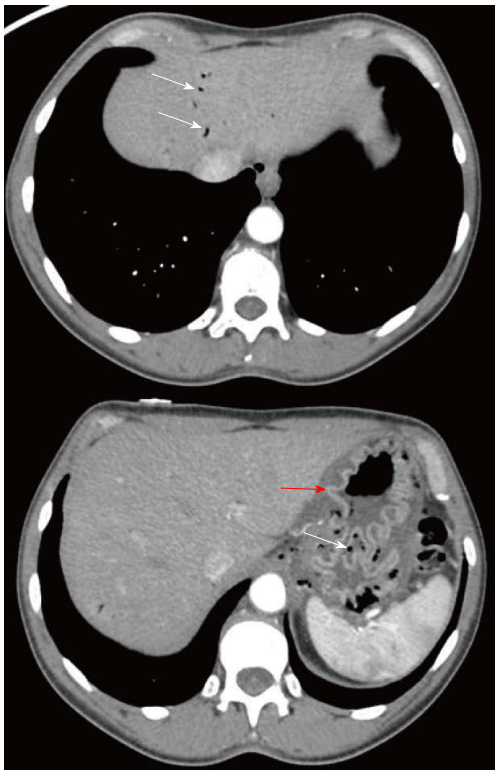

Figure 1 Computed tomography abdomen demonstrating portal venous gas as well as gastric pneumatosis and edema (portal venous gas and gastric pneumatosis noted with white arrows, gastric edema noted with red arrow).

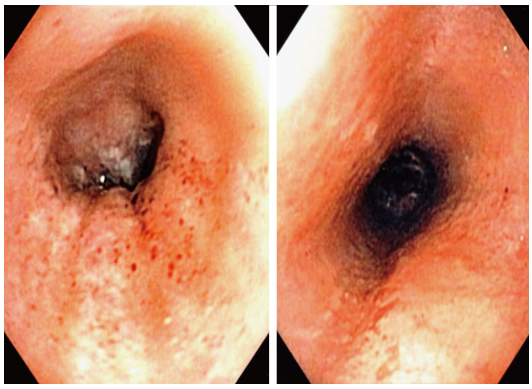

Figure 2 Esophagogastroduodenoscopy demonstrating esophagitis with multiple petechiae and white exudate.

usually involves the formation of arterial gas emboli (AGE) and the development of cerebral embolism[1-3]. Perforation may occur, but is not as commonly described as AGE. The most common injury noted on upper endoscopy following ingestion is a Grade I caustic mucosal injury which tends to resolve spontaneously without further sequelae[6]. The "snow-white" sign may be visualized, an area of mucosa that has a blanched appearance secondary to blood being driven away by rapid oxygen production; this is demonstrated on our endoscopic image (Figure 2 left panel)[1].

Management of hydrogen peroxide ingestion consists

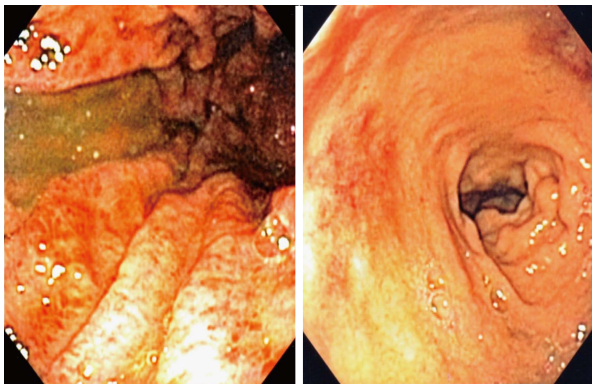

Figure 3 Esophagogastroduodenoscopy demonstrating diffuse gastritis (Left) and areas of duodenitis (Right).

mainly of supportive care and endoscopic evaluation if hematemesis or unresolving epigastric pain develops, typically in association with concentrated doses[1]. CT/MRI imaging is indicated to evaluate for formation of AGE, especially with the development of neurological symptoms. HBT has been shown to be helpful in such cases and is generally associated with complete resolution of symptoms; delayed therapy may contribute to mortality[2-4].

While neurological symptoms are definitive indications for HBT, its role in the presence of portal venous gas is still being evaluated[2,3]. Several centers with ready access to HBT have suggested that the mere presence of portal venous gas indicates need for HBT. While it would seem a prudent measure to prevent further progression of gas emboli, a case report does exist of conservatively managed portal venous gas without HBT and without subsequent negative sequelae[7].

COMMENTS

Case characteristics

The patient presented with epigastric pain, foamy hematemesis, sore throat, and hoarseness.

Clinical diagnosis

Physical exam demonstrated a benign abdomen and no neurological deficits.

Differential diagnosis

Presentation concerning for perforation of gastrointestinal tract with possible arterial gas emboli, evaluated by computed tomography and esophagogastroduodenoscopy (EGD).

Laboratory diagnosis

Electrolytes and complete blood count obtained demonstrating only leukocytosis of 12.6 thousand/mm^3.

Imaging diagnosis

Computed tomography abdomen demonstrated portal venous gas, gastric pneumatosis, and gastric edema.

Pathological diagnosis

Gastric biopsy demonstrated active, chronic gastritis with marked congestion and extravasated blood.

Treatment

Patient was kept NPO; treated with IV fluids, a proton-pump inhibitor, and hyperbaric oxygen therapy; and evaluated by EGD.

Related reports

EGD demonstrated a small hiatal hernia, diffuse esophagitis and gastritis with white exudate and multiple petechiae, and two areas of duodenitis.

Experiences and lessons

Hydrogen peroxide ingestion generally requires conservative management and may benefit from hyperbaric oxygen therapy.

Peer-review

The authors demonstrated a case of 51-year-old white female presented to our urban medical center with foamy hematemesis after ingesting 10 drops of 35% hydrogen peroxide. The present study was well investigated and will give us an important information in the field of clinical gastroenterology.

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CASE REPORT

Juvenile hemochromatosis: *HAMP* mutation and severe iron overload treated with phlebotomies and deferasirox

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Abstract

Juvenile hemochromatosis (JH) is a rare condition classified as an autosomal recessive disorder that leads to severe iron absorption. JH usually affects people under the age of 30 and presents symptoms such as chronic liver damage, hypogonadotropic hypogonadism, cardiac diseases and endocrine dysfunctions. The present case reports a 29-year-old Brazilian woman with JH condition due to *HAMP* mutation (g.47G>A), treated with phlebotomies and deferasirox. She presented symptoms such as weakness, skin hyperpigmentation, joint pain in the shoulders and hands and amenorrhea. First laboratory tests showed altered biochemical parameters [serum ferritin (SF): 5696 ng/mL, transferrin saturation (TS): 85%]. After sessions of phlebotomies (450 mL every 15 d), the patient presented partial symptomatic improvements and biochemical parameters (SF: 1000 ng/mL, Hb: 11 g/dL). One year later, deferasirox (15 mg/kg per day) was introduced to the treatment, and the patient showed total symptomatic improvement, with significant clearing of the skin, SF: 169 ng/mL, and TS: 50%. Furthermore, after the combined deferasirox-phlebotomy therapy, magnetic resonance imaging measurements revealed normalized level for liver iron (30 μmol/g; reference value < 36 μmol/g). In conclusion, combined deferasirox-phlebotomy treatment was able to normalize iron levels and improve symptoms.

Key words: Genetic disease; Juvenile hemochromatosis; *HAMP* gene; Mutation; Iron chelation

Core tip: A 29-year-old Brazilian woman, from a city in the countryside of the State of Bahia, Brazil, was referred to our service in 2015 because of a hepatomegaly clinical condition, detected by imaging exam. This case study reports a patient with juvenile hemochromatosis condition due to *HAMP* mutation (g.47G>A) treated with phlebotomies and deferasirox, which were able to normalize iron levels and improve symptoms.

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INTRODUCTION

Juvenile hemochromatosis (JH), also known as type 2 hemochromatosis, is a rare condition classified as an autosomal recessive disorder that leads to severe iron absorption. JH usually affects people under the age of 30 and presents symptoms such as chronic liver damage, hypogonadotropic hypogonadism, cardiac diseases and endocrine dysfunctions. JH is subdivided into two groups: Type 2A (associated to *HJV* - hemojuvelin gene mutation) and type 2B (associated to *HAMP* - hepcidin gene mutation). Both genes are involved in the production of hepcidin, a peptide that regulates iron homeostasis by adjusting its absorption and storage. *HJV* and *HAMP* mutations, therefore, lead to decreased hepcidin levels, and consequently to iron overload in the body[1-3].

CASE REPORT

A 29-year-old Brazilian woman, from a city in the countryside of the State of Bahia, Brazil, was referred to our service in 2015 because of a hepatomegaly clinical condition, detected by imaging exam. In the anamnesis, symptoms such as weakness, skin hyperpigmentation and joint pain in the shoulders and hands were observed. The patient had reported amenorrhea since she was 25 years old, whereas transvaginal ultrasound showed uterus and ovaries were not developed. She also reported that her father died before the age of 50 because of non-alcoholic cirrhosis and diabetes. Furthermore, one of her three brothers, who was 31 years old, died because of the same reported father diseases. The patient's other two brothers, on the other hand, are healthy.

The patient's first laboratory tests results were: Serum ferritin (SF) of 5696 ng/mL, transferrin saturation (TS) of 85%, hemoglobin (Hb) of 13.3 g/dL, international normalized ratio of 1.3, aspartate transaminase of 91 U/L, alanine transaminase of 69 U/L, alkaline phosphatase of 288 U/L, gamma-glutamyl transferase of 84 U/L, blood glucose of 72 mg/dL, creatinine of 0.7 mg/dL and albumin of 4.3 g/dL. Her echocardiogram was normal and secondary causes of iron overload (hepatitis, chronic hemolysis, oral or parenteral iron overload, metabolic syndrome and alcohol abuse) were excluded. Genetic analysis for mutations in the *HFE* gene (p.C282Y, p.H63D and p.S65C) revealed a heterozygous genotype for the p.H63D. Taking in account the patient's age and the absence of relevant genetic alteration for hereditary hemochromatosis (HH), the *HJV* (exons 1-4) and *HAMP* (exons 1-3) genes were sequenced[4], as iron overload in a young individual who presents endocrine dysfunctions is suggestive of a JH diagnosis. The *HAMP* sequencing revealed the homozygous genotype for the mutation 5'-UTR G>A at position +14 (g.47G>A), confirming the prior suspicious.

In January 2015, the patient started phlebotomies of 450 mL every 15 d. After 12 mo of treatment, there was partial improvement of weakness, skin hyperpigmentation and joint pain symptoms. In addition, the hemoglobin level was never below 11 g/dL and, despite an observed decrease in ferritin level, the values were always above 1000 ng/mL. In January 2016, deferasirox (15 mg/kg per day) was introduced to the treatment, concomitantly with the phlebotomies. No side effects were observed and the serum creatinine values remained normal. In September 2016, the patient showed total symptomatic improvement, with significant clearing of the skin, SF values of 169 ng/mL and TS of 50%. The study protocol was approved by the Ethics Committee of Hospital das Clinicas (HC) of University of Sao Paulo Medical School (FMUSP), Brazil, and consent was obtained from the participants prior to entering the study.

DISCUSSION

When compared with *HFE*-hemochromatosis, the frequency of the JH condition with *HAMP* gene mutation is considered very rare. However, some cases were reported[5,6]. Here, we report one case of a Brazilian patient with JH condition due to *HAMP* mutation (g.47G>A), first identified in a Portuguese family[7]. She presented significant improvement of symptoms through combined treatment with deferasirox and phlebotomies.

Phlebotomy is the choice treatment for hemochromatosis. However, iron chelator has been suggested as an alternative treatment option for iron overload, especially when patients have severe iron overload, did not have tolerance to phlebotomies or where it is contraindicated. The dose used in the present case report was previously evaluated in hemochromatosis patients[8]. Cançado *et al*[9] (2015) evaluated the efficacy and effectiveness of deferasirox (doses of 5-10 mg/kg per day) for treatment of hemochromatosis patients. They showed that chelation was safe and effective[9].

It is possible to estimate the quantity of liver iron removed using magnetic resonance imaging (MRI) measurements (given as mg of Fe/*g* of liver). Santos *et al*[10] (2010) performed a study that measured liver iron concentration before and after combined deferasirox-

phlebotomy treatment. They observed that approximately two-thirds (5.55 g) of the iron removed from the liver could be attributed to the action of deferasirox[10]. In the present case, however, we were not able to perform MRI measurements before and after inclusion of the deferasirox as an adjuvant. Nevertheless, we estimated that phlebotomies were able to remove approximately 8.0 *g* of liver iron (40 phlebotomies and about 200 mg Fe/phlebotomy) in 20 mo. After this period of combined therapy, the MRI showed normal value for liver iron of 30 μmol/g (reference value < 36 μmol/g).

In conclusion, combined deferasirox-phlebotomy treatment was able to promote decrease and normalization of iron levels, besides significant symptomatic improvements.

ACKNOWLEDGMENTS

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COMMENTS

Case characteristics

A 29-year-old Brazilian woman, with non-alcoholic cirrhosis and diabetes in the familiar medical history, presented symptoms such as weakness, skin hyperpigmentation, joint pain in the shoulders and hands and amenorrhea.

Clinical diagnosis

HAMP sequencing indicated juvenile hemochromatosis (JH) condition due to g.47G>A mutation.

Differential diagnosis

Patient's age (29) and absence of relevant genetic alteration for hereditary hemochromatosis (HH) led to sequencing of *HJV* (exons 1-4) and *HAMP* (exons 1-3) genes, as iron overload in a young individual who presents endocrine dysfunctions is suggestive of a JH diagnosis.

Laboratory diagnosis

Laboratory tests indicated altered iron biochemical parameters: SF = 5696 ng/mL and TS = 85%.

Treatment

Patient's treatment was performed with phlebotomies (450 mL every 15 d) for 20 mo, and the iron chelator deferasirox (15 mg/kg per day) was introduced as adjuvant in the last 8 mo of treatment.

Related reports

The dose used in the present case report was previously evaluated in hemochromatosis patients. Cançado *et al* (2015) evaluated the efficacy and effectiveness of deferasirox (doses of 5-10 mg/kg per day) for treatment of hemochromatosis patients. They showed that chelation was safe and effective. Besides that, Santos *et al* (2010) performed a study that measured liver iron concentration before and after combined deferasirox-phlebotomy treatment. They observed that approximately two-thirds (5.55 g) of the iron removed from the liver could be attributed to the action of deferasirox.

Experiences and lessons

Phlebotomy is the choice treatment for hemochromatosis. However, iron chelator has been suggested as an alternative treatment option for iron overload, especially when patients have severe iron overload, did not have tolerance to phlebotomies or where it is contraindicated.

Peer-review

In the present case, we have reported a clinical case of a patient with a very rare disorder: juvenile hemochromatosis due to *HAMP* mutation (g.47G>A). The authors presented a successful combined therapy for the iron overload and symptoms caused by the JH condition, performed with the conventional phlebotomies and the iron chelator deferasirox as an adjuvant.

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CASE REPORT

Prosthodontic management of hemimandibulectomy patients to restore form and function - A case series

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Abstract

Surgical resection of mandible owing to benign, malignant neoplasm, osteoradionecrosis is common. The resection can be total or segmental depending on the lesion. Loss of mandibular continuity causes deviation of remaining mandibular segment towards the resected side and rotation inferiorly due to muscle pull and scar contracture affecting mastication and esthetics. Surgical reconstruction may not be always possible. Prosthetic rehabilitation plays a major role in these patients. This case series describes different types of guiding flange (GF) prosthesis with modifications for three hemimandibulectomy patients at different time interval after surgery. The article details GF prosthesis combined with physiotherapy to correct deviation of mandible thereby improving mastication, esthetics and speech and thus enhancing the quality of life.

Key words: Hemimandibulectomy; Mandibular deviation; Guiding flange prosthesis; Palatal ramp

Core tip: Mandible is a significant structure in lower third of face constituting to esthetics and functions like speech, swallowing and mastication. Surgical resection owing to various reasons disrupts these functions. Both form and function should be considered in rehabilitating hemimandibulectomy patients. This article describes prosthetic rehabilitation that comprises of different types of guiding flange prosthesis with modifications for three hemimandibulectomy patients at different time interval after surgery.

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INTRODUCTION

Mandible is a significant structure in lower third of face constituting to function and esthetics. It is a single bone that creates peripheral boundaries of the floor of the mouth, facial form (lower third), speech, swallowing, mastication and respiration. Disruption of mandible due to trauma, surgical resection for benign and malignant neoplasm disrupts any of these functions. Both form and function should be considered in rehabilitating hemimandibulectomy patients. Loss of mandibular continuity causes deviation of the remaining mandibular segments towards the defect and rotation of the mandibular occlusal plane inferiorly due to muscle pull and scar contracture. Mandibulectomy with radical neck dissection increases this deviation. This results in facial disfigurement, loss of occlusal contact, in many cases, loss of lip competency for saliva control and to initiate the swallowing process[1]. Literature shows techniques to correct mandibular deviation that can vary from intermaxillary fixation with elastics, palatal or mandibular guiding flange (GF) prosthesis anchored on natural teeth or the dental flange[2]. The GF is probably the simplest and most useful in maintaining position of the remaining jaw[3]. This article describes different types of GF prosthesis with modifications for three hemimandibulectomy patients at different time interval after surgery.

CASE REPORT

Case report 1

A 36 years old male patient was referred to the hospital with the history of carcinoma left buccal mucosa for which he underwent hemimandibulectomy and modified radical neck dissection one month back and reconstructed with pectoralis major myocutaneous flap. Patient complained of difficulty in mastication and speech.

Extra oral examination revealed facial asymmetry and deviation of mandible towards the resected site and the deviation increased on opening the mouth. The mouth opening was reduced to 25 mm. Intra oral examination revealed partially edentulous mandible and loss of occlusal contact (Figure 1).The mandibular defect was classified as Cantor and Curtis Class Ⅱ that is lateral resection of the mandible distal to cuspid[4]. It was noted that mandible can be guided to centric occlusion manually but the patient could not achieve this position consistently on his own. So the treatment objective was to correct the deviation of mandible and to restore proper occlusion for mastication.

Impressions were made with modified stainless steel stock tray and irreversible hydrocolloid (Tropicalgin, IDS DENMED Pvt. Ltd.) followed by pouring cast with

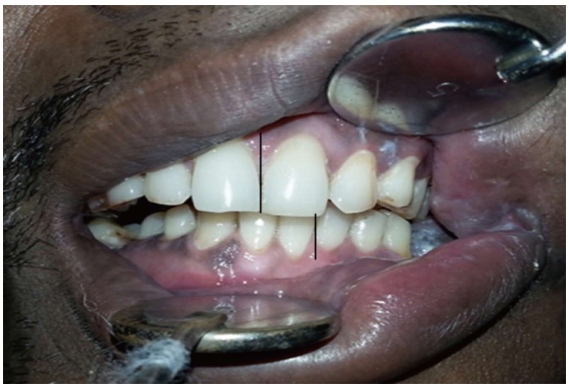

Figure 1 Midline shift and loss of occlusal contact.

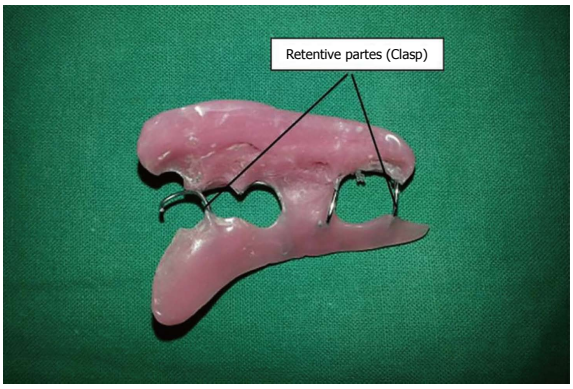

Figure 2 Mandibular guiding flange prosthesis.

Type Ⅲ Dental stone (Goldstone, mfg. by ASIAN CHEMICALS). Interocclusal record was made with modelling wax (the Hindustan dental products) by asking the patient to move the mandible away from resected site as far as possible and manually guiding the mandible to centric occlusion. This record was transferred to a mean value articulator. Three clasps were made using 21 gauge wire - "C" clasp on canine and premolar; adams clasp on molar for retention purpose. Considering the amount of deviation and reduced mouth opening, mandibular GF prosthesis was fabricated on the nondefect side using autopolymerising acrylic resin (DPI Cold Cure pink; Dental products of India). After applying sufficient separating medium, the resin was added on buccal and lingual aspect of nondefect side of mandible and on the buccal side the extension was till the maxillary buccal vestibule. The prosthesis was tried in patient mouth and checked for retention and stability. It was trimmed and adjusted so that the mandible is guided to centric occlusion without delivering excessive force to maxillary teeth. Acrylic resin was added little by little to the guide flange until there was smooth guidance of the mandible to proper occlusion without any interference. The prosthesis was finished and polished (Figure 2). After insertion of the prosthesis, midline coincided and occlusion was achieved (Figure 3). The patient was advised to use the GF throughout the day except at night and during

Figure 3 Correction of deviation after insertion of the prosthesis.

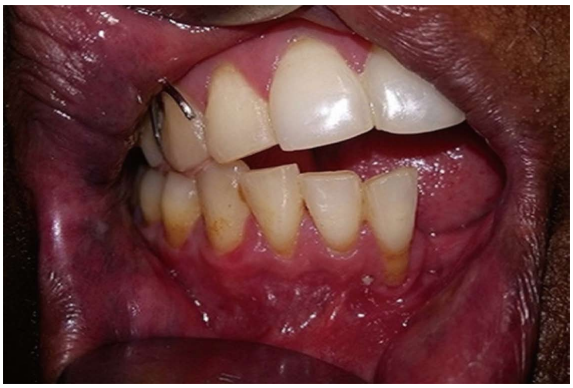

Figure 5 Occlusion contacts established with prosthesis.

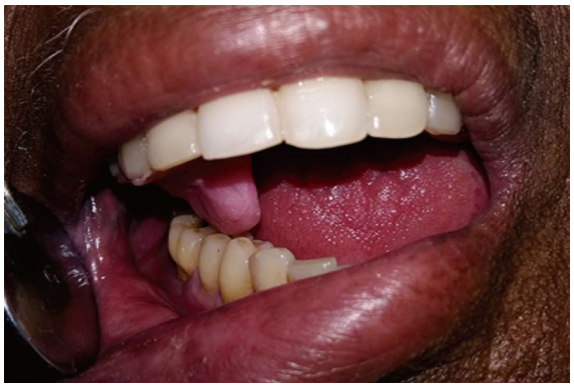

Figure 4 Palatal guiding flange prosthesis.

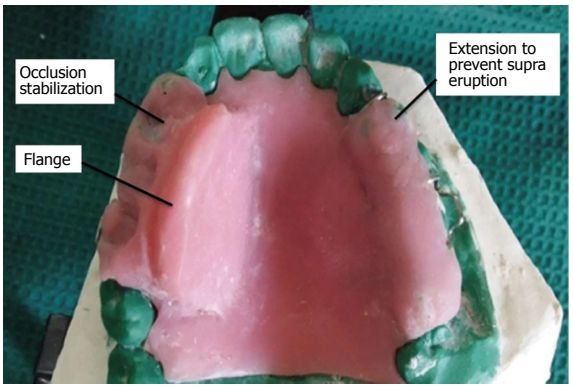

Figure 6 Palatal guiding flange prosthesis with functionally generated acrylic occlusal table on non-resected site and stabilization ramp for resected side.

meals. Physiotherapy exercises were also insisted. It included maximum mouth opening and grasping the chin to move the mandible away from surgical side. This will help in reducing trismus, minimize scar contracture and improve occlusion[1]. Review after a month, there was trivial reduction in the deviation. Hence, palatal GF prosthesis was made which wouldn't affect esthetics.

Case report 2

A 49 years old male patient presented to the hospital with the complaint of difficulty in mastication and facial disfigurement for the past three years owing to carcinoma left buccal mucosa for which he underwent composite resection of mandible and reconstructed with Pectoralis major myocutaneous flap following preoperative chemotherapy and radiotherapy. On clinical examination, there was deviation of remaining mandible towards the resected site and also downward rotation of mandible. It was noted that intermaxillary fixation was not done at the time of surgery. The mandibular defect was classified as Cantor and Curtis type Ⅲ[4]. Since it was resected till the midline the deviation and downward rotation of mandible was more due to loss of muscular support. The mouth opening was 35 mm. Intra oral examination revealed generalized attrition, supraeruption and partially edentulous mandible. Patient was able to bring remaining mandible to centric occlusion with guidance and he was not able to achieve this position consistently. Since mouth opening was normal compared to previous case, an acrylic GF on maxilla was planned as interim prosthesis.

Impression, cast, interocclusal record and articulation were made following the same procedure as in case report 1. Palatal GF prosthesis was planned for this case considering the stability of prosthesis, esthetics, occlusion and downward rotation of mandible. The guide flange extended till the lingual sulcus on the nondefect side. The prosthesis was tried in patient mouth. The inclination of the guide flange was adjusted until it guided the mandible to centric occlusion (Figure 4). But as both maxillary and mandibular teeth were attrited, functional cusps were worn out. The mandibular teeth glided beyond centric occlusion. To prevent this and to train the patient in centric occlusion, the acrylic resin was extended on the palatal cusps of maxillary teeth. A functionally generated path was recorded and an occlusal table was fabricated accordingly so as to stabilize the occlusion. The occlusal table was also extended on the maxillary teeth of defect side to prevent supraeruption as there were no opposing teeth (Figures 5 and 6). The patient was recalled after a month for review.

Case report 3

A 35 years old male patient came to the hospital with

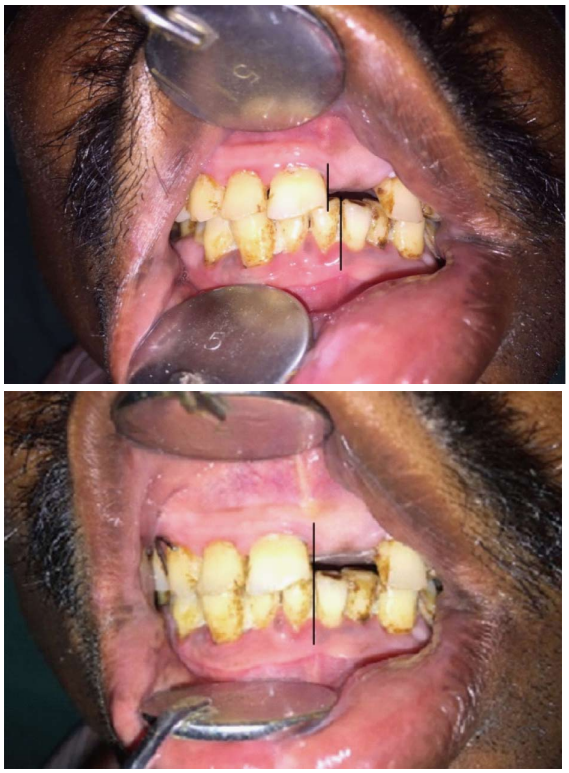

Figure 7 Note the midline before and after insertion of the prosthesis.

the history of hemimandibulectomy and left maxillary alveolectomy reconstructed with masseter flap done two weeks ago owing to carcinoma left buccal mucosa. Mouth opening was noted as 30 mm. It was noted that the deviation of mandible towards the resected side was minimum as the surgery was done only two weeks ago. If intervention with the GF was not done at this time, the deviation would worsen on healing process and scar formation. The procedure of impression making, cast, interocclusal record and articulation as in case report 1 was done. As the deviation was minimum, palatal GF prosthesis was planned for this case. As opposing teeth were present in the mandibular arch, the risk of supraeruption is nil. The prosthesis extended till the lingual sulcus on palatal non resected side. The prosthesis was tried in patient mouth and trimmed accordingly (Figure 7). The patient was able to guide the mandible into pre-existing occlusion (Figure 8). The patient was advised to wear the flange at all times except while eating and during nights and was asked to review after one week.

DISCUSSION

Segmental resection of mandible results in deviation of remaining segment towards the resected side due to uncompensated influence of contralateral musculature, particularly the internal pterygoid muscle. If this influence is uncompensated, the contraction of cicatricial tissue will fix the residual fragment in its deviated position[5]. The rotation of residual mandible in

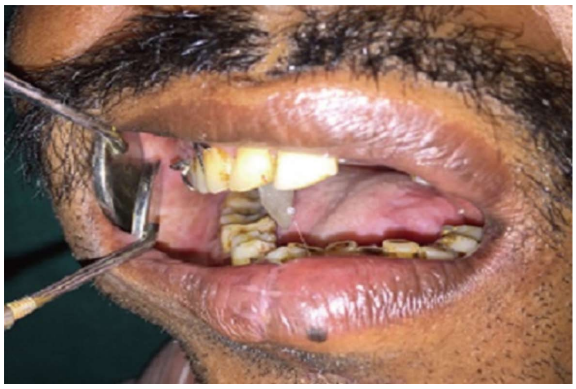

Figure 8 Mandibular first molar contacting the palatal ramp that guides the mandible to occlusion.

an inferior direction is caused by the pull of suprahyoid musculature and gravity due to loss of anchorage of elevator muscles[1]. The pathway of closure in a lateral resection of mandible starts from its medial, retruded position and closes in an upward diagonal manner into an occlusion which may or may not correspond with the patient's preoperative occlusion[6]. The amount of deviation and downward rotation depends on the extent of tissue loss. The more the mandible remaining, the better is the prosthetic prognosis. Retention of mandibular cuspids is especially beneficial[4].

The basic objective in rehabilitation is retraining the remaining mandibular muscles to provide an acceptable maxillo-mandibular relationship of the remaining portion of the mandible[7]. This would permit occlusion of remaining natural teeth or control of residual edentulous segments to provide for the reasonable placement and acceptable occlusion of the artificial teeth[7]. There are four significant factors that affect rehabilitation: The location and extent of surgery, the effect of radiation therapy, the presence or absence of teeth and the psychological aspect[6].

The time of initiation of the treatment is the key to success for restoring the form and function. The deviation after hemimandibulectomy will be difficult to correct after the healing phase of 6 to 8 wk due to scar contracture and the muscles adapting to this cicatricial tissue[1]. Patients usually have trismus following the surgery which will be a challenge for making an impression of maxilla and mandible. Hence preoperative casts should be advocated for all patients so that exact maxillo-mandibular relationship can be obtained postoperatively. Intermaxillary fixation can be advocated at time of surgery but for dressings and irrigation, it would be more advantageous to enable the patient to open and close the mouth. Temporary retainers can be made preoperatively so that it can immediately placed after surgery[8]. Robinson stated that temporary acrylic GF can be inserted on the third postoperative day[5]. In the above cases intermaxillary fixation was not done at the time of surgery and preoperative impressions were not made as they were referred only after surgery.

Table 1 Protocol for guiding flange

Based on time of referral		
1	Before surgery - 1 wk post-surgery	Intermaxillary fixation done with elastics
2	1 wk post-surgery - 1 mo	GF prosthesis and Physiotherapy
3	1 mo - 1 yr	Active physiotherapy, Counseling followed by GF prosthesis
4	> 1 yr	Surgical intervention
Based on amount of tissue resected		
1	Amount of hard and soft tissue	Directly influences success and difficulty in rehabilitation
2	Segmental resection of mandible distal to cuspid	Maxillary or Mandibular GF
2	Segmental resection of mandible that involves canine	Maxillary GF is the choice as the loss of mandibular canine results in more downward rotation of mandible and the mandibular GF might not be stable
Types of prosthesis		
1	Acrylic GF	Immediately after surgery and as training prosthesis
2	Definitive Cast metal GF	One year after training prosthesis
Modifications		
1	To prevent supraeruption	Occlusal table on Maxillary teeth on defect side
2	To stabilize occlusion	Functionally generated occlusal table on Maxillary teeth on nondefect side
	Intervention	Prognosis
1	From the time of planning and surgery	Better
2	Long time interval after surgery	Guarded

GF: Guiding flange.

Physiotherapy is recommended to reduce trismus and to loosen scar contracture. Without this, masticatory ability may decrease and lateral movement toward the nonresected side may not be possible[9]. It must be started two weeks postoperatively. Patient is asked to gently push the mandible away from the defect toward more normal position. While holding mandible in position, the patient should open the mouth as wide as possible to stretch the musculature at the resection site[1,4]. In all the three cases, physiotherapy was insisted.

Various literature shows different techniques for managing the deviation that include cast metal guidance prosthesis which is more technique sensitive, time consuming, expensive and require more number of patient visits. Acrylic GF is comparatively simple in design, cost effective, less patient visit and more importantly the ease of adjustability[10].

A common complaint without such an appliance is pain in the remaining temperomandibular joint which results from the abnormal position of the condyle[8]. Definitive treatment of these patients takes at least a year from the date of surgery as definitive treatment requires complete healing and no recurrence of cancer. Till then the acrylic GF prosthesis can be used as a training device for mandibular movements and to avoid further compilations.

In the cases presented above, acrylic GF was used as a training prosthesis. Out of three patients, one patient was referred immediately after surgery, one patient five years after surgery and other patient one month after surgery. In the first and third case report, resection was distal to canine. The amount of deviation was more in the first patient as the patient reported one month after surgery, mandibular GF was given for a period of three weeks later replaced with maxillary GF. The amount of deviation was trivial in the third patient as he reported one week following surgery, maxillary GF was given. In the second case report, the downward rotation of mandible was significant as the resection involved mandibular canine. For this case, maxillary GF was given with functionally generated occlusal table on non-defect side. For all the three patients, physiotherapy was insisted along with the insertion of GF. The patients had pain only due to scar contractures and deviation leading to pain on mandibular movements. This was addressed by correcting the deviation, and trying to maintain a stable occlusion. Guideline for GF is listed in Table 1.

Rehabilitation is an essential phase of cancer care and should be considered from the time of diagnosis in a complete and comprehensive treatment plan. The primary objective is restoration of function and appearance. GF prosthesis serves both the purpose. This article gives a comprehensive explanation about rehabilitation procedures carried out for three patients who were surgically treated for carcinoma with hemimandibulectomy and neck dissection.

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COMMENTS

Case characteristics

All three cases complained of difficulty in mastication and facial disfigurement following hemimandibulectomy reconstructed with flap.

Clinical diagnosis
All three cases showed deviation of mandible towards the resected site, los of lip competency and occlusal contact and reduced mouth opening.

Treatment
Guiding flange (GF) prosthesis to correct deviation of mandible and to stablise occlusion enhancing mastication and esthetics.

Term explanation
GF prosthesis guides the remaining mandible to proper and stable occlusion and trains the mandibular movements after hemimandibulectomy.

Experiences and lessons
The time of initiation of treatment is the key to success. A common complaint without such prosthesis is pain in temperomandibular joint. This GF prosthesis alleviates pain and can be used as training device for mandibular movements after surgery.

Peer-review
This is a well written manuscript exposing the experience of the authors in such particular field.

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CASE REPORT

Natural killer cells activity in a metastatic colorectal cancer patient with complete and long lasting response to therapy

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Abstract

Here we report a case of a 70-year-old man who received adjuvant chemotherapy with fluorouracile, folinic acid and oxaliplatin after a left hemicolectomy for a stage Ⅲb adenocarcinoma in May 2009. During follow-up he de-veloped abdominal lymphnodes metastases evidenced by positron emission tomography-computed tomography (PET-CT) scan and increase of carcinoembryonic antigen (CEA) level. Chemotherapy with capecitabine, oxaliplatin and bevacizumab was started in April 2012. Restaging showed a complete response and normalization of CEA. The patient received maintenance therapy with bevacizumab which was stopped in December 2013 for patient choice. In October 2014, a new increase in CEA was documented and PET-CT scan showed lung metastases. Analysis of RAS status revealed the absence of mutations, then the patient started a second-line chemotherapy with fluorouracile, folinic acid, irinotecan (folfiri) and panitumumab achieving, in January 2015, a complete response and normalization of CEA. Thereafter, folfiri was discontinued for toxicity; furthermore, upon the third occurrence of a grade 3 dermatologic toxicity, panitumumab was continued from June 2015 at 60% of the original dose and it was administered every three weeks. Until presentation of this case, the patient maintains a complete response, has no symptoms of disease and CEA is normal. Interestingly, this patient presented a high proportion of circulating natural killer (NK) cells (35.1%) with high cytotoxic activity against tumor cells. Study on the role of NK in patients with advanced colorectal cancer are ongoing.

Key words: Colorectal cancer; Panitumumab; Natural killers; Regulatory cells; Chemotherapy

Core tip: The case presented here shows a patients with metastatic colorectal cancer (mCRC) and long-lasting responses to different treatments including chemotherapies and targeted therapies; in particular, the patient had a long-lasting complete response to panitumumab. Additionally, he presented a high proportion of circulating natural killer (NK) cells displaying high cytotoxic activity against tumor cells in vitro. Interestingly, we previously reported that patients affected by mCRC with high NK-cell cytotoxicity showed a significantly higher response rate and a longer progression-free survival compared with patients with low NK-cell cytotoxicity. Study on the role of NK in patients with mCRC should be improved.

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INTRODUCTION

Colorectal cancer (CRC) is one of most common cancers and leading causes of mortality worldwide. Unfortunately, about twenty percent of patients with CRC have clinical evidence of metastatic disease at diagnosis and about 50% of patients will develop metastases later[1].

To date, first and second-line treat-ment of metastatic CRC (mCRC) are based on combinations of chemotherapy (fluorouracil, oxaliplatin, irinotecan) and biologic drugs (bevacizumab, cetuximab, panitumumab). Anti-EGFR agents (cetuximab and panitumumab) are reserved for RAS wild-type (RAS wt) tumors. In fact, when RAS is mutated, PI3K results in constitutive activation of its downstream signaling pathway so that tumor cells become independent of EGFR signaling inactivation by anti-EGFR drugs. Large randomized multicenter phase Ⅲ clinical trials confirmed the predictive value of KRAS for anti-EGFR therapy[2,3] and a meta-analysis of 11 studies showed that KRAS status was closely associated with the response rate ($P < 0.001$) and PFS ($P < 0.005$)[4]. KRAS mutation is a predictive marker for the efficacy of anti-EGFR agents in the treatment of mCRC as stated in guidelines from the National Comprehensive Cancer Network, European Society for Medical Oncology, and Japanese Society for Cancer of the Colon and Rectum, which recommend the use of antibodies to EGFR only for mCRC patients with WT K-RAS. In addition, N-RAS mutations have been recently included, defining the "RAS status" as the new validated marker of response to antibodies to EGFR[5].

Panitumumab is a fully humanized monoclonal antibody against EGFR approved in RAS wt mCRC as first-line therapy in association with folfox (fluorouracile, folinic acid, oxaliplatin), second-line in association with folfiri (fluorouracile, folinic acid, irinotecan) and as monotherapy following disease progression after prior treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy. The use of chemotherapy and biologic drugs in a flexible and personalized context of multidisciplinary approach (continuum of care) has improved survival of patients with mCRC which in some cases exceed two years[6].

In last years, many evidences are accumulating on the role of immune system cells in controlling tumors at different stages of disease (from the initiation to the metastatic spread and growth)[7,8]. The issue is very complex since the interactions between components of the immune system and tumor cells are largely unknown. We recently reported that polymorphisms of receptors involved in ADCC (antibody-mediated cellular cytotoxicity) as well as the NK cells activity of patients affected by mCRC were predictive and prognostic[9]. Additionally, MDSCs (myeloid-derived suppressor cells) and Tregs (regulatory T-cell) are a component of the immune system that may promote tumor progression[10] by inhibiting both innate and adaptive immune responses. In particular they are able to suppress conventional effector immune cells (T cells, NK cells, macrophages) which play an important role in anti-tumor responses.

Here we report a case of a mCRC patient responding to first and second-line chemotherapies and with a durable complete response to panitumumab single agent. NK cell activity of peripheral blood lymphocytes (PBL) was evaluated. As additional information, also MDSCs and Tregs were characterized.

Phenotypic analysis of peripheral immune cell subsets

Flow cytometry was performed on fresh venous blood (BD Biosciences), using a FACSCanto Ⅱ 6-colour flow cytometer and analyzed using BD FACSDiva™ Software version 6.2 (BD Bioscience, San Jose, CA, United States), daily calibrated with Calibrite beads (Fitc, Pe, PerCP and APC) and Compbeads (Pe-Cy7 and APC-Cy7; Becton Dickinson, San Jose, CA, United States). For identification of circulating Tregs the following fluorochrome labeled anti-human monoclonal antibodies were used: CD4, CD25, CD127, FOXP3, CD45RA, CD45R0. The classical populations were $CD4^+/CD25^+/CD127^{low}/FOXP3^{int}/CD45RA^+$ (naïve Treg cells) versus $CD4^+/CD25^+/CD127^{low}/FOXP3^{high}/CD45RA^-$ (activated Treg cells). CD39 (ENTPD1), CD152 (CTLA-4), CD184 (CXCR4), and CD279 (PD-1) were also evaluated (data not shown). For identification of

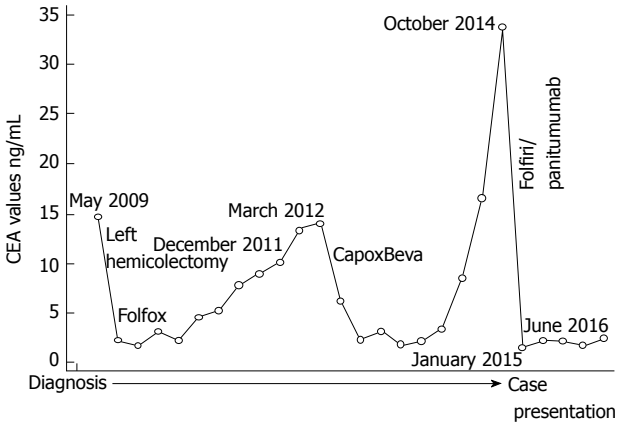

Figure 1 Time course of carcinoembryonic antigen levels during therapy and follow-up. CEA: Carcinoembryonic antigen.

circulating MDSCs: Anti-Lineage 1 antibodies (CD3, CD14, CD16, CD19, CD20, CD56), CD11b, CD33, HLA-DR, CD15 and CD14 (BD Bioscience, San Diego, CA, United States). The classical populations are shown (four types indicated as MDSC1, 2, 3, 4): 1, $CD14^+/CD124^+$; 2, $CD15^+/CD124^+$; 3, $CD33^+/SSC^+$, 4, $CD14^+/HLADR^{-/low}$. For circulating NK cells: CD3, CD16, CD56, CD158a, CD158b, CD161 and CD279 (PD-1). Monoclonal antibodies were used together with the appropriate corresponding isotype controls.

CD107a degranulation assay for NK cells cytotoxicity evaluation

NK-cell mediated cytotoxicity was evaluated using the degranulation lysosomal marker LAMP-1 or CD107a as described[11]. Blood was transferred to cell culture flasks and diluted with one volume RPMI-1640 containing 10% heat-inactivated fetal bovine serum and supplemented with 100 U/mL IL-2. Samples were incubated overnight at 37 ℃ in a humidified 5% CO_2 for 18 h. The cytotoxic activity of NK cells was tested against NK sensitive cell line K562, as previously described[12]. Briefly, 200 μL of IL-2 preactivated blood were co-cultured with 2×10^5 K562 at 5:1, 10:1 and 20:1 effector:target (e:r) ratios (only 10:1 e:r ratio experiments are shown), medium alone served as the negative control and the positive control were stimulated with phorbol-12-myristate-13-acetate (PMA) (2.5 μg/mL) and ionomycin (0.5 μg/mL) (Sigma), in presence of PE-conjugate anti-CD107a antibody (BD Bioscience, San Jose, CA, United States) at 37 ℃ in 5% CO_2. Control samples were incubated without target cells to detect spontaneous degranulation. Following a 3-h culture, cells were stained with FITC-conjugated anti-CD56, PerCP anti-CD8 and Pe-Cy7 anti CD3 (BD Bioscience, San Jose, CA, United States). NK cells were defined as $CD3^-CD56^+$ in the lymphocyte gate. CD107a expression on $CD3^-CD56^+$ NK cells and CD8 cytotoxic T cells were analyzed using a FACSCanto II 6-colour flow cytometer whit BD FACSDiva™ Software version 6.2 (BD Bioscience, San Jose, CA, United States).

CASE REPORT

No ethics approval was needed for the care of this patient as all treatments were in accordance with institutional best practice. A 70-year-old man with no relevant medical history was diagnosed in May 2009 with left-sided adenocarcinoma of the colon. He had abdominal pain and hematochezia for two weeks, then underwent colonscopy which revealed the colon cancer. CEA (CarcinoEmbryonic Antigen) was 12.3 ng/mL (Figure 1). A left hemicolectomy was performed in July 2009; pathology revealed a stage IIIb well-differentiated adenocarcinoma. He received adjuvant chemotherapy with folfox6 (oxaliplatin 85 mg/m^2 on day 1, leucovorin 200 mg/m^2 as a 2-h infusion on day 1 and 5-FU 400 mg/m^2 IV bolus on day 1 followed by a 5-FU 2.400 mg/m^2 46-h continuous infusion, repeated every 14 d) from August 2009 to November 2009 (6 cycles), stopped for his choice. During follow-up a progressive increases of CEA was registered (Figure 1). In December 2011 a CT (Computed Tomography) was completely negative, the CEA was 10.1 ng/mL. In March 2012 the CEA was 14.0 ng/mL and a PET/CT scan showed foci of abnormal uptake in abdominal nodes (SUV 3.06) and pericolic tissue (SUV 2.18). After discussion, the patient refused any surgical procedure; chemotherapy with capecitabine, oxalipltain and bevacizumab (CapOxBeva) was started in April 2012 (oxaliplatin, 130 mg/m^2 on day 1, capecitabine, 1000 mg/m^2 twice daily on days 1-14 every 3 wk, bevacizumab 7.5 mg/kg on day 1 of the 3-weekly cycle) for seven cycles; oxaliplatin was reduced at the sixth cycle and then stopped for persistent peripheral neuropathy. PET/CT scan at October 2012 showed a complete response and normalization of CEA (2.4 ng/mL). Thereafter, the patient received maintenance therapy consisting of bevacizumab (7.5 mg/kg) once every 3 wk and capecitabine (the drug was reduced for hand/foot syndrome to 750 mg/mq bis/die from day 1 to day 14 every 21 d). No adverse events were documented and the maintenance therapy was stopped in December 2013 due to patient preference.

During follow-up a new increase in tumor markers was documented (October 2014, CEA: 33.8 ng/mL) (Figure 1). PET/CT scan showed glucose uptake in lungs (lower lobe SUV: 2.8, middle lobe SUV: 2.06) (Figure 2A). Analysis of RAS status revealed the absence of KRAS mutations, thus the patient started at October 2014 a second-line chemotherapy with folfiri/panitumumab (irinotecan 180 mg/m^2 on day 1, leucovorin 200 mg/m^2 as a 2-h infusion on day 1 and 5-FU 400 mg/m^2 IV bolus on day 1 followed by a 5-FU 2.400 mg/m^2 46-h continuous infusion, panitumumab 6 mg/kg on day 1, repeated every 14 d). At January 2015 a PET/CT scan showed a complete response (Figure 2B) with normalization of CEA (1.6 ng/mL) (Figure 1) but the patient experienced neutropenia,

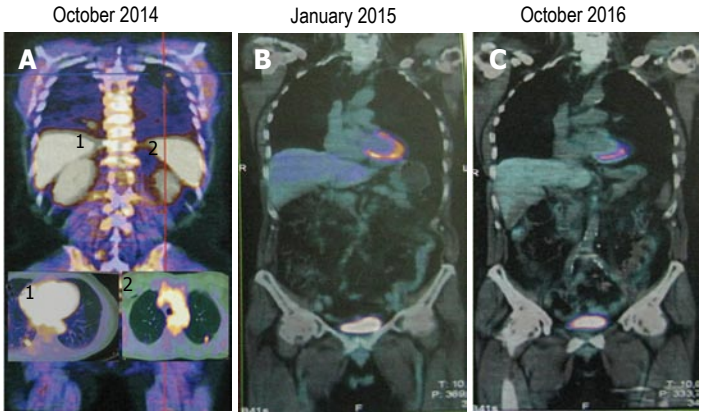

Figure 2 Positron emission tomography/computed tomography restaging after panitumumab-based therapy. A: Positron emission tomography/computed tomography scan revealing two lung metastases; B: Complete response after 6 cycles of Folfiri/Panitumumab; C: Long-lasting complete response after maintenance therapy with panitumumab single agent.

asthenia and diarrhea grade 3 according to NCI-CTC v4.0 so that folfiri was discontinued. The patient refused any rechallenge with chemotherapy. Upon the third occurrence of a grade 3 dermatologic toxicity (treated as per protocol), panitumumab was continued from June 2015 at 60% of the original dose; additionally, it was administered every three weeks as strong and explicit patient request.

Until presentation of this case (October 2016, Figure 2C) the patient maintains a complete response, has no symptoms of disease (the performance status according to ECOG is 0) and CEA is normal (Figure 1). He continues panitumumab without side effects with a very good quality of life.

At June 2016, when the complete response was confirmed with single agent panitumumab, the patient was characterized two times with respect to NK cells activity, Tregs and MSDCc cells in peripheral blood before panitumumab administration and after 10 d. The results were quite overlapping. We excluded NK cells cytotoxicity evaluation right after therapy to avoid the interference of premedication drugs (*i.e.*, corticosteroids and antihistamine). The results showed refer to a blood sample obtained just before panitumumab administration. Interestingly, the patient had 35.1% of circulating $CD3^{+}/CD56^{+}$ lymphocytes which is a high value considering the normal range (11.0%-28.0%)[13]. Furthermore, a large part of these cells where highly cytotoxic NK lymphocytes (30.4% of $CD3^{-}/CD56^{dim}$) showing high cytotoxicity activity against K562 cells (Figure 3). Furthermore, a characterization of Tregs and MDSC cells was performed and is described in Figure 4. A prospective study on the predictive and prognostic role of NK cell cytotoxicity in patients with mCRC is ongoing at the National Cancer Institute of Naples.

DISCUSSION

We report on a case of a patient with oligometastatic disease who received diagnosis of mCRC about four years ago. We studied some immunological characteristics of this patient with a descriptive and exploratory aim; high natural killer cells activity was found. Interestingly, surgery or stereotactic radiotherapy was never used for his choice; thus, the patient was exclusively treated with systemic therapy. We decided to monitor the therapeutic response with PET/CT in order to have comparable exams and to reveal early changes of tumor activity; in this case, there was high concordance between CEA values and PET/CT results.

According to RAS status, he was treated with chemotherapy and panitumumab as second-line treatment. Interestingly, a long-lasting metabolic complete response was achieved both in first and second-line therapies and it was maintained although the use of a reduced panitumumab dose density and intensity. Only recently we have extended the analysis of RAS status of this patient and no mutations of BRAF and NRAS were found.

Recently, researchers are focusing their attention to immune system and immune checkpoints in order to restore and/or potentiate cellular-mediated antitumor immunity. One of the most studied inhibitory check point is the PD-1/PD-1L pathway which suppress immune responses[14]. PD-1L is mainly expressed by B and T cells, macrophages and dendritic cells. Tumor-expressing PD-1 are able to induce an immunosuppressive status and to evade host immune surveillance by inhibiting T-cell-mediated anti-tumor activity. In advanced colorectal cancer inhibition of this pathway shows efficacy only in deficient MMR (mismatch repair) tumors (3%-6% of advanced CRC patients)[15,16]. The hypothesis is that the immune system could recognize many more somatic mutations (neoantingen load) than proficient MMR tumors. Additionally, dMMR neoplasms present prominent lymphocyte infiltrates. The PD-1/PD-L1 is not relevant to the main concept of this clinical case study and this patient did not present a deficient MMR tumor (data not shown); however, some stimulating speculations can be raised: (1) Which are the relationship between NK and T cells in tumor microenvironment? and

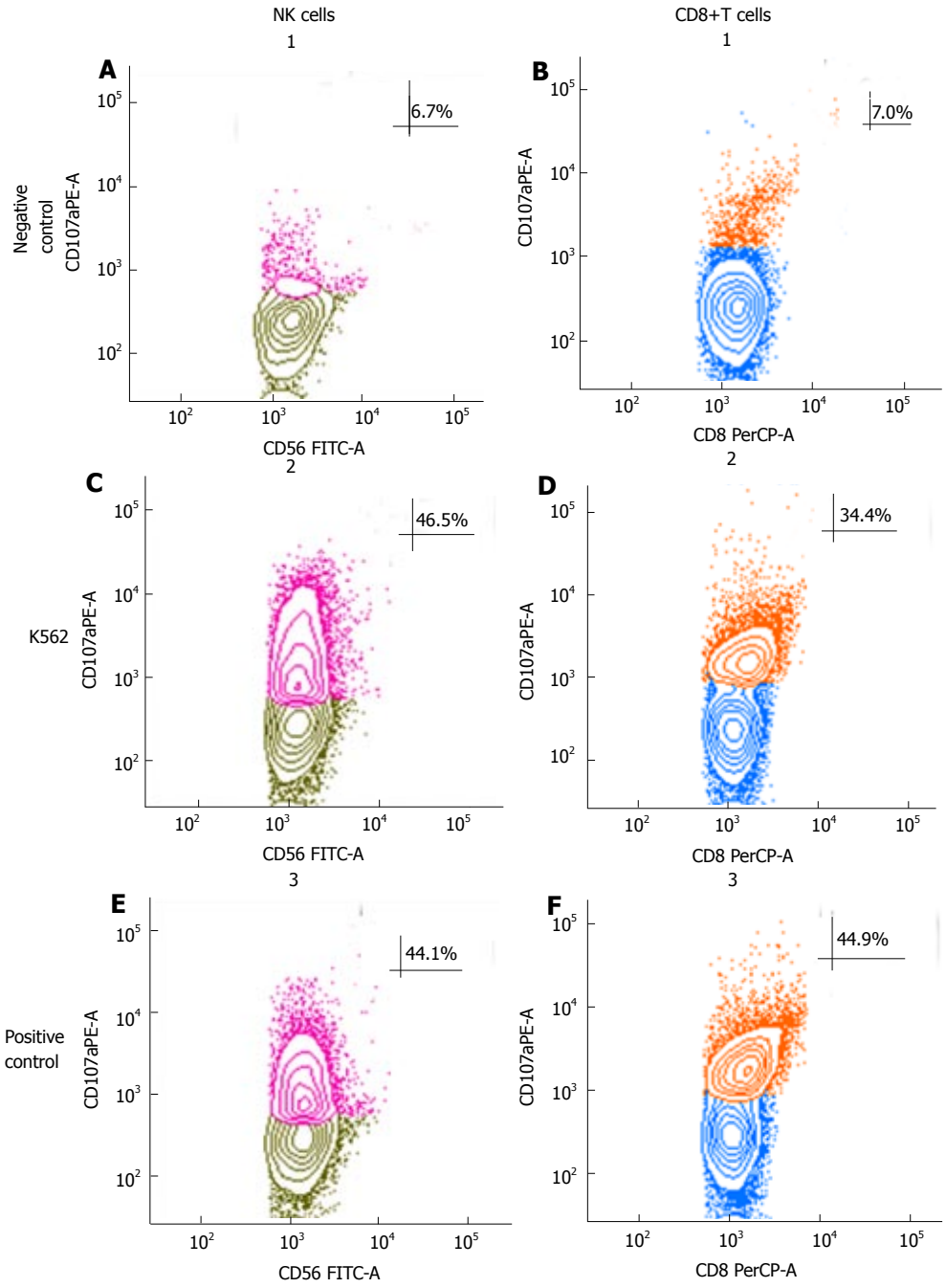

Figure 3 Cytotoxicity tests. NK-cell mediated cytotoxicity was evaluated using the degranulation lysosomal marker CD107. The cytotoxic activity of NK cells was tested against NK-sensitive cell line K562. Medium alone served as the negative control and the positive control were NK cells stimulated with phorbol-12-myristate-13-acetate (PMA) and ionomycin, in presence of PE-conjugate anti-CD107a antibody. Control samples were incubated without target cells to detect spontaneous degranulation. NK cells were defined as CD3-CD56+ in the lymphocyte gate (A, C, E). CD8 cytotoxic T cells were analyzed in B, D and F panels (see Methods for details).

(2) can other effector cells (NK cells, macrophages, regulatory cells), play a role in mCRC patients? Is there any interaction between panitumumab and NK cells?

Interestingly, we previously reported that patients affected by mCRC with high NK-cell cytotoxicity, independently from the type of therapy, showed a significantly higher response rate and a longer progression-free survival (PFS) compared with patients with low NK-cell cytotoxicity[9]. Due to the complex and dynamic nature of the immune system we are evaluating the hypothesis that decrease over time of NK cell activity could associate with progression of the tumor. Thus, we are conducting a prospective study evaluating circulating NK cells [cytotoxicity level, circulating NK $CD56^{dim}$ *vs* $CD56^{high}$, expression of KIRs (Killer-cell immunoglobulin-like receptors)] in order to evaluate their predictive and prognostic role in mCRC.

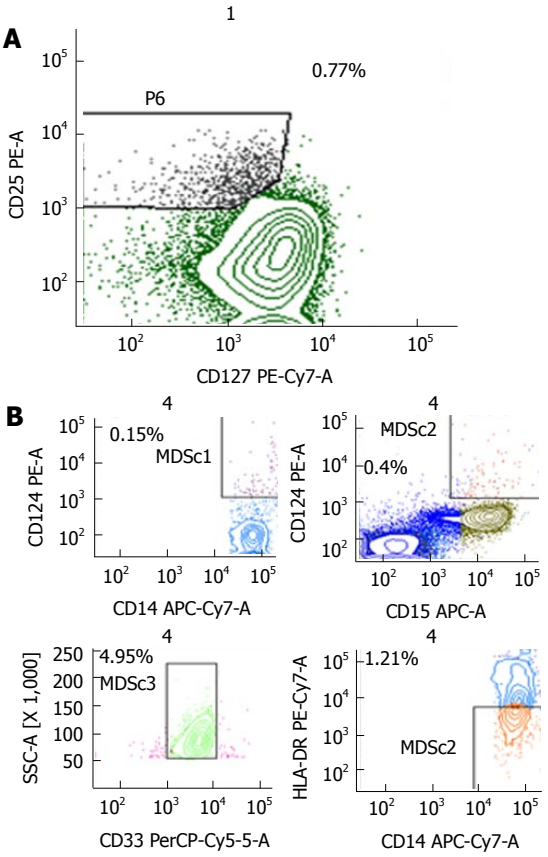

Figure 4 Characterization of regulatory cells. Flow cytometry was performed on fresh venous blood; A: Identification of circulating T regulatory cells (Treg) on CD4+ cells (gate on low CD127 and high CD25). B: Identification of four types circulating myeloid-derived suppressor cells (MDSCs1, 2, 3, 4). Percentages are relative to peripheral blood lymphocytes.

COMMENTS

Case characteristics

The patient had abdominal pain and hematochezia before undergoing surgery for colon cancer.

Clinical diagnosis

The diagnosis was done through colonscopy.

Differential diagnosis

The differential diagnosis of ulcerative colitis was excluded by colonscopy and biopsy.

Laboratory diagnosis

The diagnosis of colon cancer was definitively done through the pathological examination of biopsy and supported by carcinoembryonic antigen determination; phenotypic analysis of peripheral immune cell subsets and degranulation assay for natural killer (NK) cells were done through flow-cytometry.

Imaging diagnosis

The response to treatments as well as the evolution of the disease were studied by positron emission tomography/computed tomography.

Pathological diagnosis

Classical hematoxylin and eosin stain showed a well-differentiated adenocarcinoma of the left colon.

Treatment

The patient received the following sequence of treatments: Adjuvant chemotherapy with fluorouracile, folinic acid and oxaliplatin, first-line therapy with capecitabine, oxaliplatin and bevacizumab, maintenance therapy with bevacizumab, second-line therapy with fluorouracile, folinic acid, irinotecan and panitumumab and, finally, panitumumab monotherapy.

Related reports

The authors previously reported in Trotta *et al* (*Cancer Immunol Res* 2016; 4: 366-374) that patients affected by metastatic colorectal cancer (mCRC) with high NK-cell cytotoxicity, independently from the type of therapy, showed a significantly higher response rate and a longer progression-free survival compared with patients with low NK-cell cytotoxicity.

Term explanation

NK cells: Natural killer cells, a subset of lymphocytes with anti-tumor cytotoxic properties; CD: Cluster of differentiation, antigens used to identify molecules expressed by different leukocytes.

Experiences and lessons

NK cells might be a predictive and/or prognostic factor in patients with mCRC; comprehension of their role deserves further studies.

Peer-review

This is a well written and interesting case.

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CASE REPORT

Case of gastric neuroendocrine carcinoma showing an interesting tumorigenic pathway

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Informed consent statement: The patient and his family has provided permission to publish these features of his case, and the identity of the patient has been protected.

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Abstract

Here, we report a case of gastric neuroendocrine carcinoma showing an interesting tumorigenic pathway. A 57-year-old Japanese woman presented with epigastric tenderness, and distal gastrectomy was performed. In the surgical specimen, histologically, the tumor tissue was composed of three subtypes of tumor components showing different histological architecture and cellular atypia, diagnosed as neuroendocrine tumor (NET) G2, NET G3, and neuroendocrine carcinoma (NEC) components. Immunohistochemically, the Ki-67-positive rates of NET G2, NET G3, and NEC components were 6.5%, 99.5% and 88.1%, respectively. Although allelic imbalance (AI) on chromosomes 1p, 3p, 8q, TP53, 18q and 22q was commonly found in all components, AI of 4p was found in NET G3 and NEC components (but not in the NET G2 component). In contrast, AIs of 5q and 9p were found in only the NEC

component. Thus, we showed the progression from NET G2 to NEC, via NET G3, within the same tumor.

Key words: Stomach; Neuroendocrine tumor G2; Neuroendocrine tumor G3; Neuroendocrine carcinoma

Core tip: Gastric neuroendocrine carcninoma (NEC) is typically generated by dedifferentiation of adenocarcinoma cells to endocrine cells. However, we experienced a case of gastric NEC possibly generated from the neuroendocrine tumor (NET) component. The present case demonstrated an unconventional carcinogenic pathway in neuroendocrine tumorigenesis. In addition, we analyzed allelic imbalance in NET and NEC components and provided important insights into neuroendocrine carcinogenesis.

Uesugi N, Sugimoto R, Eizuka M, Fujita Y, Osakabe M, Koeda K, Kosaka T, Yanai S, Ishida K, Sasaki A, Matsumoto T, Sugai T. Case of gastric neuroendocrine carcinoma showing an interesting tumorigenic pathway. *World J Clin Cases* 2017; 5(11): 397-402 Available from: URL: http://www.wjgnet.com/2307-8960/full/v5/i11/397.htm DOI: http://dx.doi.org/10.12998/wjcc.v5.i11.397

INTRODUCTION

Neuroendocrine neoplasms of the digestive system are classified as neuroendocrine tumors (NETs) or neuroendocrine carcinomas (NECs) based on assessment of the pro-liferative fraction and morphological criteria in the 2010 World Health Organization (WHO) classification. Furthermore, NET can be divided into three tiers (G1, G2, and G3) based on the mitotic count and Ki-67 labeling index[1]. NEC of the stomach is composed of proliferation of poorly differentiated tumorous endocrine cells with marked cellular atypia[1]. In general, gastric NEC may be generated by dedifferentiation of adenocarcinoma cells to endocrine cells, and it is possible that gastric NETs and NECs may have different tumorigenic pathways[1,2]. Here, we report a case of gastric NEC generated from a NET component, with immunohistochemical and molecular studies.

CASE REPORT

A 57-year-old Japanese woman presented with epigastric tenderness. Gastroendoscopy showed a growing lesion (size, 16 mm × 11 mm) in the greater curvature of the upper gastric body, and the mucosa adjacent to the lesion showed atrophic gastritis. Histopathological examination of a biopsy sample revealed NEC. *Helicobactor pylori* were not detected by Giemsa staining. In addition, serum levels of chromogranin A and gastrin were not measured. The patient subsequently underwent distal gastrectomy. One year after surgery, liver metastasis was found in abdominal computed tomography examination, and chemotherapy was performed.

Pathological findings

In low-magnification images, tumor cells were distributed in two lesions. One lesion was constructed by tumor cell proliferation within the submucosal layer, and another lesion was found in the muscle layer; these two lesions were discontinuous (Figure 1A).

Microscopic examination revealed that the tumor tissue was composed of three subtypes of tumor components as follows. The first component was composed of cuboidal epithelial cells with uniform, oval nuclei showing fine nuclear chromatin and arranged in a trabecular growth pattern with focal rosettes. Tumor cells had very few mitotic figures [< 2 per 10 high-powered fields (HPF)] and no necrosis. This component corresponded to the NET G2 component (Figure 1B). The second component consisted of diffuse proliferation of tumor cells with small nuclei showing irregular, dense nuclear chromatin and high mitotic counts, corresponding to the NET G3 component (Figure 1C). The third component was composed of diffuse proliferation of tumor cells with large, irregular, coarse nuclei, high mitotic counts, and geographic necrosis, similar to the large cell NEC component (Figure 1D). Although the transition between the NET G2 component and the NET G3 component was confirmed, the submucosal lesion and intramuscular lesion were separated by the muscle layer (Figure 1A). Marked lymph vessel and venous invasion were observed in the submucosal layer, as determined by D2-40 immunohistochemical staining and EVG staining (Figure 1A, inset).

In addition, the mucosa adjacent to the tumor showed atrophic gastritis with intestinal metaplasia, but not type A gastritis. No endocrine cell micronests were found in the surrounding mucosa.

Immunohistochemical study

Immunohistochemical examination was performed using an auto-immunostaining system (Dako EnVision System, Denmark) for neuroendocrine differentiation, cell proliferation activity, p53 overexpression, and mucin phenotype (Muc2, Muc5AC, Muc6, CD10). The positive rate of Ki-67 was calculated using an APERIO virtual slide system (AT2; Leica Biosystems, United States).

All tumor components were immunopositive for chromogranin A, synaptophysin, and CD56, and decreased immunoreactivity was found in the NEC component. Differences in Ki-67-positive rates were found among NET G2, NET G3, and NEC components (NET G2, 6.5%; NET G3, 99.5%; NEC, 88.1%). Overexpression of p53 protein was not found in any component. With regard to the mucin phenotype,

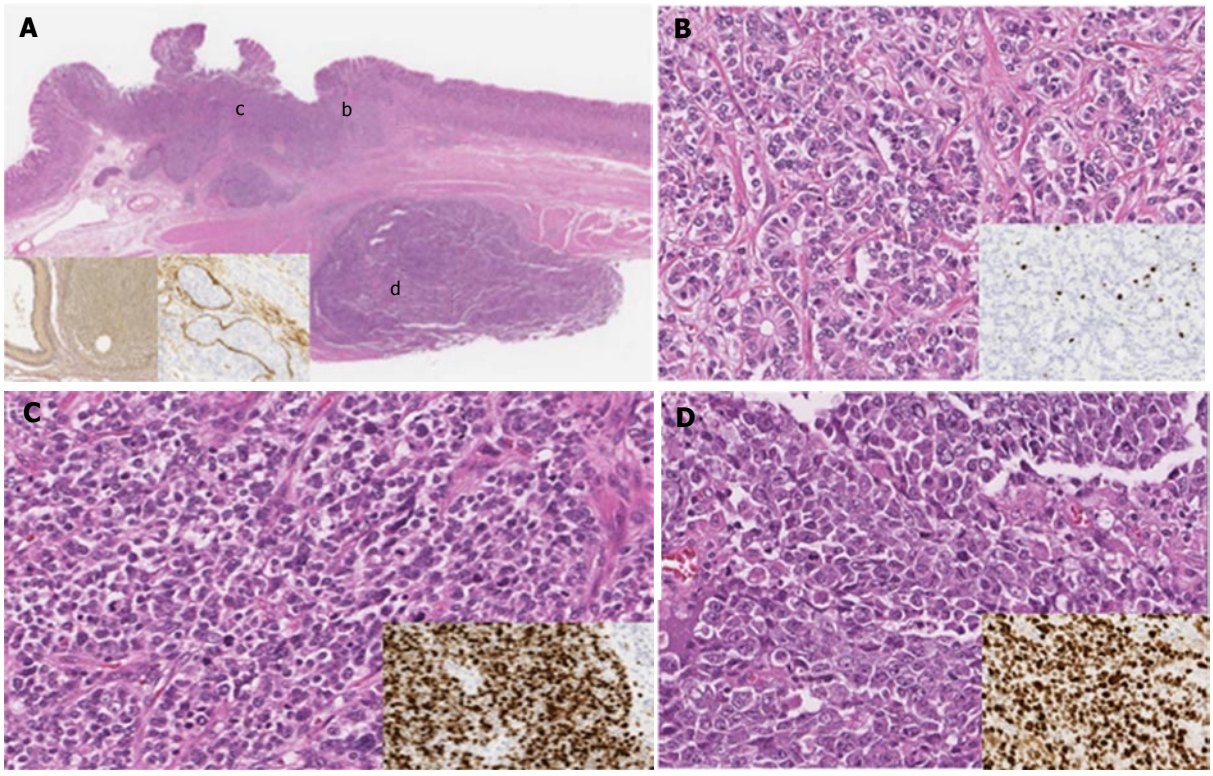

Figure 1 Histological findings of an HE-stained section of a resected specimen. A: Low-magnification image of the surgical specimen. The tumor component was composed of two lesions (a submucosal lesion and an intramucosal lesion). These two lesions were separated by muscle layer (inset: left, EVG staining; right, D2-40 immunohistochemical staining); B: NET G2 component (inset: Ki-67 positive rate, 6.5%); C: NET G3 component (inset: Ki-67 positive rate, 99.5%); D: Large cell NEC component (inset: Ki-67 positive rate, 88.1%). NEC: Neuroendocrine carcinoma; NET: Neuroendocrine tumor.

no mucin markers were expressed in any tumor component (Table 1).

Molecular findings

DNA from NET G2, NET G3, and NEC components was extracted separately. PCR-allelic imbalance (AI) analyses were performed using a thermal cycler (GeneAmp PCR System 9600; Perkin-Elmer, CA, United States) according to previously reported procedures[3]. AIs on chromosomes 1p, 3p, 4p, 5q, 8p, 9p, 13q, 17p, 18p, and 22q were examined using 22 highly pleomorphic microsatellite markers (D1S228, D1S548, D3S2402, D3S1234, D4S2639, D4S1601, D5S107, D5S346, D5S299, D5S82, D8S201, D8S513, D8S532, D9S171, D9S1118, D13S162, TP53, D18S487, D18S34, D22S274, D22S1140, and D22S1168).

In addition, PCR-MSI analysis was performed as described previously[4]. Five different loci were assessed for MSI, including all those recommended by the Bethesda panel for colon cancer (BAT25, BAT26, D5S346, D2S123, and D17S250)[4].

DNA methylation at the six specific promoters originally described by Yagi and colleagues was quantified[5]. Methylation of three markers (RUNX3, MINT31, and LOX) was analyzed, and samples with at least two methylated markers were defined as highly methylated epigenotype (HME) tumors. The remaining tumors were also screened for methylation at three other markers (NEUROG1, ELMO1, and THBD) and were defined as intermediate methylation epigenotype (IME) tumors if they had at least two methylated markers out of the three markers proposed as a second panel. Tumors not classified as HME or IME were designated as low methylation epigenotype (LME).

In the present case, DNA methylation status was LME, and MSI was not found in all tumor components. AIs at 1p, 3p, 8q, TP53, 18q and 22q were commonly found in all tumor components. Although AI of 4p was found in NET G3 and NEC components, it was not observed in the NET G2 component. In addition, AIs at 5q and 9p were found in the NEC component only (negative for NET G2 and G3 components; Figure 2).

DISCUSSION

Most cases of gastric NEC may be developed from endocrine precursor cell clones occurring in preceding adenocarcinoma components[1,2]. In the present case, histological examination revealed that the tumor tissue was composed of three subtype components. In addition, the transition between NET G2 and G3 components was confirmed. No adenocarcinoma components were found in serial sections of all specimens. Although a clear transition between the NET and NEC components was not found, we assumed that the tumor mass in the muscle layer may be an intramural metastasis because the tumor tissue

Table 1 Summary of immunohistochemical analysis

Antibody	Clone	Dilution	Source	NET G2 component	NET G3 component	NEC component
Chromogranin A	DAK-A3	1:100	DAKO, CA, Unites States	Positive	Positive	Weakly positive
Synaptophysin	SY38	1:20	DAKO, CA, Unites States	Positive	Positive	Weakly positive
NCAM	1B6	1:100	DAKO, CA, Unites States	Positive	Positive	Weakly positive
Ki-67	MIB-1	1:50	DAKO, CA, Unites States	6.50%	99.50%	88.10%
p53	DO-7	1:100	Novocastra, United Kingdom	Negative	Negative	Negative
Muc2	Ccp58	1:200	Novocastra, United Kingdom	Negative	Negative	Negative
Muc5AC	CLH2	1:100	Novocastra, United Kingdom	Negative	Negative	Negative
Muc6	CLH5	1:100	Novocastra, United Kingdom	Negative	Negative	Negative
CD10	56C6	1:50	Novocastra, United Kingdom	Negative	Negative	Negative

NEC: Neuroendocrine carcinoma.

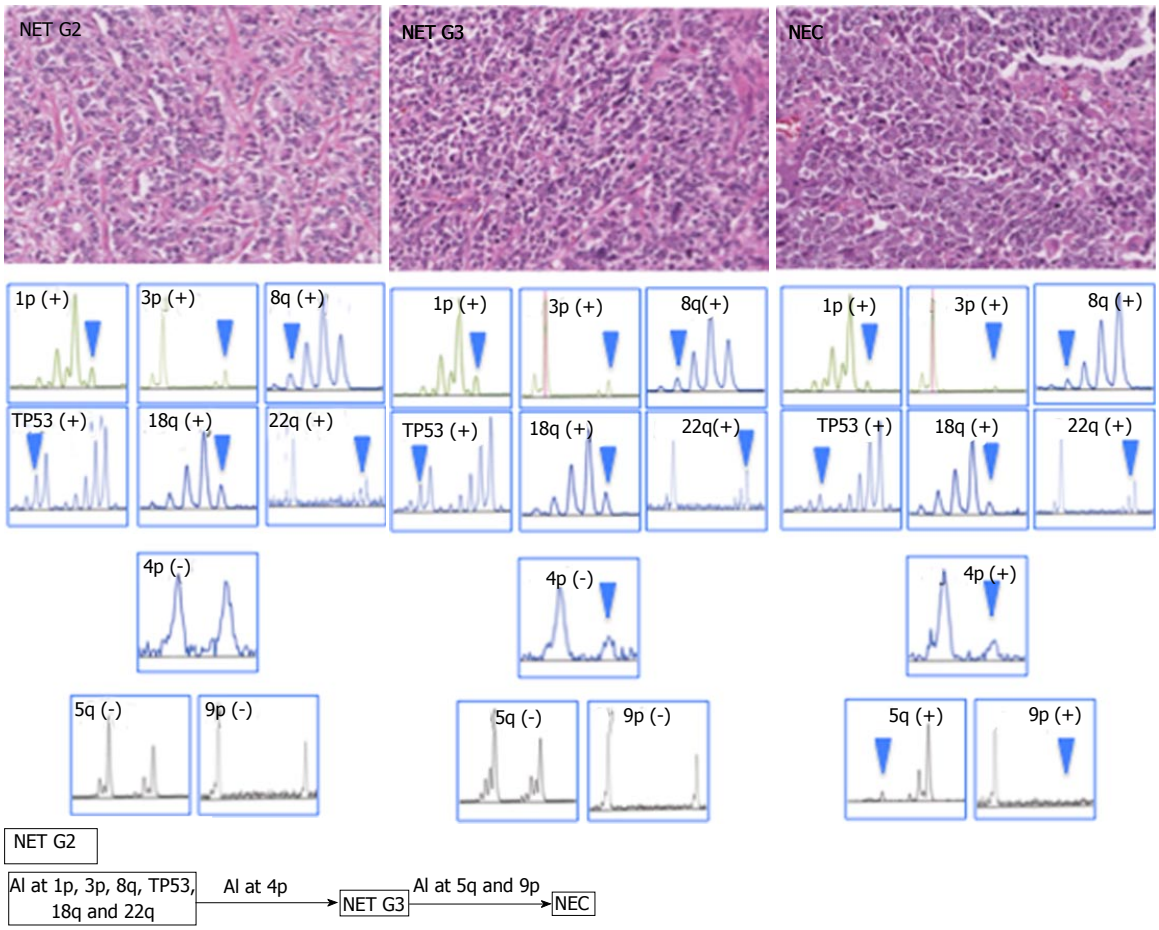

Figure 2 Accumulation of allelic imbalance through the progression from neuroendocrine tumor G2 to neuroendocrine tumor G3 to neuroendocrine carcinoma in the present case. AIs at 1p, 3p, 8q, TP53, 18q, and 22q were common in three components (NET G2, NET G3, and NEC). AI at 4p was acquired during the progression from NET G2 to G3. AIs at 5q and 8q were found during progression from NET G3 to NEC. NEC: Neuroendocrine carcinoma; NET: Neuroendocrine tumor; AI: Allelic imbalance.

showed marked vessel invasion (Figure 1A). Therefore, we speculated that the morphological change from

NET to NEC could have occurred through the process of tumor progression. Additionally, NEC may arise from the NET component, suggesting that the tumor may have developed through an unconventional pathway in neuroendocrine tumorigenesis in our case[2].

With regard to the tumorigenesis of the NET G2 component, although serum chromogranin A and gastrin had been measured, no endocrine cell micronests or findings of type A gastritis were observed in the mucosa adjacent to the tumor. Therefore, we assumed that the tumor in this case may be sporadic NET, namely non-endochromaffin-like cell tumor, defined as type 3 tumor by Rindi *et al*[1].

In previous reports, most cases of gastric NEC with an adenocarcinomatous component were found to exhibit immunopositivity of mucin markers, and the mucin phenotype of the NEC component was found to correspond with that of the adenocarcinoma component[2,6]. In our case, both the NET and NEC components showed negative immunoreactivity for all mucin markers examined. Thus, it was unlikely that the NEC component was generated from adenocarcinoma in the present case.

Fur-thermore, Nishikura *et al*[7] reported that most cases of NEC with an ad-enocarcinoma component showed p53 mutations, consistent with the adenocarcinoma component. This finding strongly supported the hypothesis that most cases of gastric NEC are developed from precursor cell clones that occur in a preceding adenocarcinoma component.

The molecular features of NET and NEC have not been clarified[8]. In the present case, AIs at 1p, 3p, 8q, TP53, 18q, and 22q were commonly found in three components (NET G2, NET G3, and NEC). These findings supported that the tumor in our case had been generated by progression from the NET G2 to NEC component. In contrast, AI at 4p was acquired during the progression from NET G2 to G3. In addition, AIs at 5q and 8q play an important role in the development from NET G3 to NEC. These findings suggested that acquisition of multiple AIs contributed to the progression from NET to NEC (Figure 2).

In conclusion, we experienced a case of gastric NEC possibly generated from the NET component. The present case demonstrated an unconventional carcinogenic pathway in neuroendocrine tumorigenesis, providing important insights into neuroendocrine carcinogenesis.

COMMENTS

Case characteristics

A 57-year-old Japanese woman presented with epigastric tenderness. Gastroendoscopy showed a growing lesion (size, 16 mm × 11 mm) in the greater curvature of the upper gastric body, and the mucosa adjacent to the lesion showed atrophic gastritis.

Clinical diagnosis

Histological examination revealed that the tumor tissue was composed of three subtype components.

Laboratory diagnosis

Serum levels of chromogranin A and gastrin were not measured by immunohistochemical study. Overexpression of p53 protein was not found in any component. With regard to the mucin phenotype, no mucin markers were expressed in any tumor component.

Imaging diagnosis

Gastroendoscopy showed a growing lesion (size, 16 mm × 11 mm) in the greater curvature of the upper gastric body, and the mucosa adjacent to the lesion showed atrophic gastritis.

Pathological diagnosis

Histopathological examination of a biopsy sample revealed neuroendocrine carcinoma (NEC). *Helicobactor pylori* were not detected by Giemsa staining.

Treatment

Distal gastrectomy.

Related reports

In previous reports, most cases of gastric NEC with an adenocarcinomatous component were found to exhibit immunopositivity of mucin markers, and the mucin phenotype of the NEC component was found to correspond with that of the adenocarcinoma component.

Experiences and lessons

The present case demonstrated an unconventional carcinogenic pathway in neuroendocrine tumorigenesis, providing important insights into neuroendocrine carcinogenesis.

Peer-review

This is an interesting case of gastric neuroendocrine carcinoma showing a tumorigenic pathway. This report presents a case of gastric NEC possibly generated from NET component by analyzing allelic imbalance and shows unconventional carcinogenic pathway in neuroendocrine tumorigenesis.

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CASE REPORT

Acid suppressive therapy improved symptoms due to circumferential cervical inlet patch with proton pumps (H^+/K^+-ATPase)

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Author contributions: Yamada T wrote the paper; Tsuji A treated the patient and performed endoscopy; Onoue S, Kaneko M, Osawa S and Saida Y contributed to the paper design and coordination; Tanioka F contributed to the pathological examination.

Institutional review board statement: This case report was exempt from the Institutional Review Board Standards at Iwata City Hospital, Iwata, Japan.

Informed consent statement: The patient has provided permission to publish this paper, and the identity of the patient has been protected.

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Abstract

Cervical inlet patch (CIP), also referred to as esophageal heterotopic gastric mucosa, is regarded as the residue of columnar epithelium of the embryonic esophagus. Narrow band imaging increases the detection rate of CIP. Herein, we present a 55-year-old man with symptomatic circumferential inlet patch. He exhibited globus and dysphagia, and esophagogastroduodenoscopy found cir-cumferential CIP, where im-munohistochemistry revealed the existence of pro-ton pumps (H^+, K^+-ATPase). His throat symptoms were relieved by acid suppressive therapy with pump inhibitors. This case indicated that CIP should be considered as a differential diagnosis for the cause of globus symptoms in rare cases.

Key words: Cervical inlet patch; Proton pump inhibitor

Core tip: Cervical inlet patch (CIP) is the esophageal heterotopic gastric mucosa in the cervical esophagus. We present a 55-year-old man exhibiting circumferential CIP with globus and dysphagia. Proton pump inhibitors relived these throat symptoms. Immunohistochemistry revealed existence of proton pumps in the CIP lesion. The throat symptoms were suggested to be related with CIP and acid secretion.

Yamada T, Tsuji A, Onoue S, Kaneko M, Tanioka F, Osawa S, Saida Y. Acid suppressive therapy improved symptoms due to circumferential cervical inlet patch with proton pumps (H^+/K^+-ATPase). *World J Clin Cases* 2017; 5(11): 403-406 Available from: URL: http://www.wjgnet.com/2307-8960/full/v5/i11/403.htm DOI: http://dx.doi.org/10.12998/wjcc.v5.i11.403

INTRODUCTION

Esophageal heterotopic gastric mucosa (HGM), also referred to as cervical inlet patch (CIP), is considered to be the residue of columnar epithelium of the embryonic esophagus[1,2]. The diagnosis rate of CIP is increasing because of the recent development and spread of image-enhanced endoscopy, including narrow band imaging (NBI)[3,4]. Patients with CIP rarely require treatment as most cases of CIP are asymptomatic. However, some reports indicated complications associated with acid secretion from CIP[5-7]. Herein, we present a patient with circumferential CIP in whom proton pump in-hibitors (PPI) were effective and proton pump existence was confirmed by immunohistochemistry.

CASE REPORT

A 55-year-old man visited the department of otolaryngology exhibiting globus and dysphagia without heartburn or epigastric pain. His past medical history only included an operation for appendicitis. Physical examination and laboratory findings were unremarkable. Laryngoscopy did not reveal the cause of the throat symptoms. He was then introduced to the department of gastroenterology and esophagogastroduodenoscopy (EGD) was performed to determine the cause. EGD revealed circular HGM in the cervical esophagus, the HGM was 19 to 21 cm from the incisor. The lesion appeared reddish by white light imaging (Figure 1A), whereas by NBI, it appeared as a dark brown lesion clearly distinguished from light green squamous epithelium (Figure 1B). There was only mild reflux esophagitis (Los Angeles grade A), but no esophageal hiatus hernia at the esophagogastric junction. His throat symptoms improved quickly by acid suppression therapy with PPI.

Endoscopic biopsy from the circumferential CIP lesion demonstrated foveolar epithelium and fundic glands (Figure 2A). Furthermore, to confirm the relationship between the throat symptoms and acid secretion from the CIP, we performed immunohistochemistry and found proton pump, H^+, K^+-ATPase alpha subunits. Immunohistochemical staining was concentrated in the glands of CIP (Figure 2B).

DISCUSSION

CIP, also referred to as cervical esophageal HGM, is generally regarded as a congenital condition that results from an incomplete replacement by squamous epithelium, and the differentiation of persistent columnar-lined mucosa into cervical HGM[1,2]. The incidence of cervical CIP was reported as 0.1% to 13.8%[3,8]. Using NBI endoscopy, there was increase in the detection of CIP[4].

Some reports demonstrated acid secretion from CIP using pH monitoring[5-7]. Here, we demonstrated the existence of proton pumps (H^+, K^+-ATPase) in CIP in a symptomatic patient by immunohistochemistry. The efficacy of PPI also supports the theory that acid secretion from proton pumps in CIP is the cause of throat symptoms. In the present case, the patient had mild esophagitis. Although there is a possibility that gastroesophageal reflux disease was one of the causes of the globus symptoms, we considered cervical CIP to be the main cause of his globus symptoms because of the existence of proton pumps in the large CIP and the previous reports of the relationship between throat symptoms and acid secretion from CIP. However, this case report did not directly show the relationship between existence of proton pumps and their acid secretion function in CIP. Further studies are needed to demonstrate the usefulness of immunohistochemistry for proton pump to predict PPI efficacy in patients with symptomatic CIP.

Recently, argon plasma coagulation and radio-frequency ablation were reported to be effective for symptomatic CIP[9-11]. However, these endoscopic ablation techniques are not available in all countries, including Japan. PPI treatment is more widely available than endoscopic ablation. PPI should be selected first in such situations. Furthermore, the detection of proton pumps by immunohistochemistry may predict the efficacy of PPI for throat symptoms in patients with CIP.

In summary, we reported a 55-year-old man with circumferential CIP where immunohistochemistry revealed proton pump existence. His throat symptoms were relieved by acid suppressive therapy with PPI. This case indicated that CIP should be considered as a differential diagnosis for the cause of globus symptoms in rare cases.

COMMENTS

Case characteristics

A 55-year-old man visited to complaint globus and dysphagia without heartburn

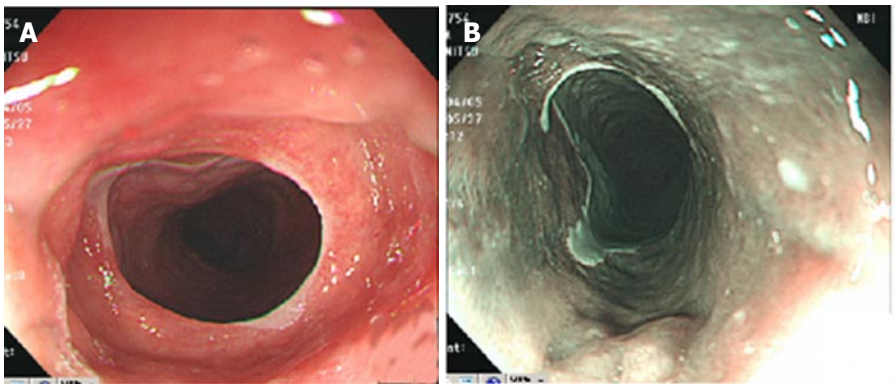

Figure 1 Endoscopic image of circumferential cervical inlet patch. A: White light image showing circular reddish cervical inlet patch (CIP) mucosa; B: On narrow band imaging, CIP is the circular dark brown area and squamous mucosa is light green. This sharp contrast of color helps to detect CIP.

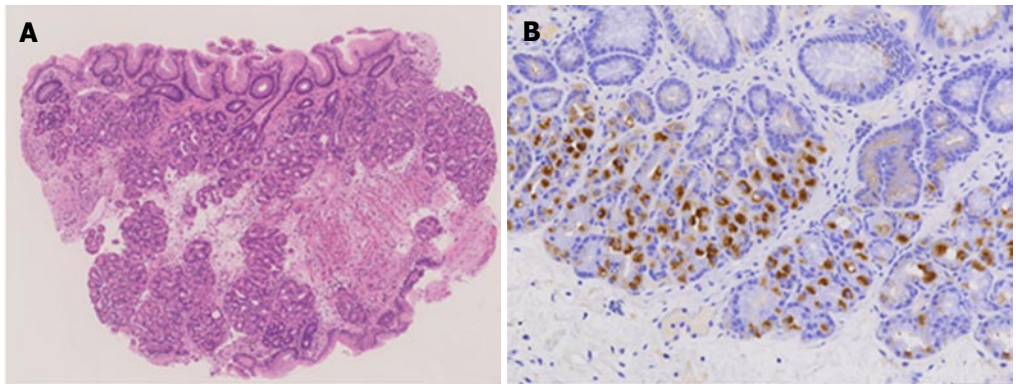

Figure 2 Histopathological findings of biopsy specimen. A: Endoscopic biopsy of cervical inlet patch (CIP) showing foveolar epithelium and fundic gland (Hematoxylin and eosin staining); B: Immunohistochemistry for proton pump alpha subunit demonstrated concentration of staining in glands of CIP (X 400).

or epigastric pain.

Clinical diagnosis
Endoscopy revealed circumferential cervical inlet patch (CIP).

Differential diagnosis
Gastroesophageal reflux and globus hystericus.

Imaging diagnosis
Esophagogastroduodenoscopy revealed circumferential CIP, where appeared reddish by white light imaging and appeared as a dark brown clearly distinguished from light green squamous epithelium by narrow band imaging.

Pathological diagnosis
Immunohistochemistry for proton pump alpha subunit demonstrated concentration of staining in glands of CIP.

Treatment
Acid suppressive therapy with proton pump inhibitors (PPI) improved globus and dysphagia in a patient with CIP.

Related reports
Although some reports demonstrated acid secretion from CIP using pH monitoring, this is the first report that demonstrated the existence of proton pumps (H^+, K^+-ATPase) in CIP in a symptomatic patient by immunohistochemistry. The relationship should be elucidated between the existence of proton pump and acid secreting function in CIP.

Term explanation
CIP is esophageal heterotopic gastric mucosa, which is considered to be the residue of columnar epithelium of the embryonic esophagus.

Experiences and lessons
CIP should be considered as a differential diagnosis for the cause of globus symptoms in rare cases.

Peer-review
This case report clearly presented a case of CIP which expressed the proton pump and was successfully treated by PPI.

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ABOUT COVER

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AIM AND SCOPE

World Journal of Clinical Cases (*World J Clin Cases*, *WJCC*, online ISSN 2307-8960, DOI: 10.12998) is a peer-reviewed open access academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

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ORIGINAL ARTICLE

Basic Study

Reliability of Sawai's classification for dental cervical abrasions: A pilot study

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Abstract

AIM

To test the reliability of the Sawai's classification for dental cervical abrasions.

METHODS

Intraoral photographs of 70 teeth from 23 patients with tooth abrasions were taken by the first examiner MS. The teeth were marked and the photos were maintained in a soft copy sequentially. Two other examiners FA and SC were trained in the use of the classification and any clarifications needed were provided at the beginning of the study. Each examiner was then given the soft copy of the complied photographs and was asked to classify the dental cervical abrasion according to their understanding of the Sawai's classification. They were given sheets to write their responses for every marked tooth. All the examiners were blinded to each other's observations which were then tested for inter-rater agreement among the three examiners.

RESULTS

The 70 teeth with tooth abrasions from 23 patients were examined by 3 investigators (MS, FA and SC) to test the reliability of the Sawai's classification system for tooth abrasion. Each examiner marked their responses in separate sheets which were blinded to each other. The kappa statistics were performed for inter-rater agreement among the three examiners. The level of agreement was evaluated according to the six-level nomenclature given by Landis and Koch. ICC and 95%CI between two examiners, *i.e.*, the inter-rater agreement among

1st examiner (MS) and 2nd examiner (FA) was 0.89. The inter-rater agreement among 1st examiner (MS) and 3rd examiner (SC) was 0.89. And the inter-rater agreement among 2nd examiner (FA) and 3rd examiner (SC) was 0.83. All the three comparisons show an almost perfect agreement between them.

CONCLUSION

There is an almost perfect agreement between multiple observers for classifying dental cervical abrasions using Sawai's classification. Hence, this classification is reliable.

Key words: Tooth abrasion; Classification; Diagnosis; Tooth wear; Dental education; Diagnostic techniques and procedures

Core tip: Currently, an ideal index for tooth abrasion is lacking. The available indices are either too time consuming or complicated. Hence, an easy and least time-consuming classification was proposed. The present study evaluates the reliability of the Sawai's classification. In this study, out of three observers, two were students of dentistry (undergoing internship). The study shows that there was almost perfect agreement amongst the observers in classifying the tooth abrasions. Also, it was noted that the classification was easy to understand and use and least time consuming. So the authors suggest that this classification can be effectively used in daily dental practice.

Sawai MA, Daing A, Adeel F, Chawla S. Reliability of Sawai's classification for dental cervical abrasions: A pilot study. *World J Clin Cases* 2017; 5(12): 407-411 Available from: URL: http://www.wjgnet.com/2307-8960/full/v5/i12/407.htm DOI: http://dx.doi.org/10.12998/wjcc.v5.i12.407

INTRODUCTION

Tooth wear is a modern day problem. It produces varying symptoms ranging from discomfort, pain and also may lead to loss of tooth vitality. As dentists, we need to diagnose and monitor tooth loss and provide adequate treatment to our patients. Though, a lot of emphasis has been given towards treatment aspect of cervical abrasions, much research is required to develop a comprehensive method to diagnose and classify cervical abrasions. Different indices have been given in the past to diagnose and grade the cervical abrasions. For example: Eccles index for dental erosion of non-industrial origin[1], Smith and Knight's Tooth Wear Index[2] and Erosion Index by Lussi[3]. Bardsley *et al*[4] pioneered a new, simplified version of tooth wear index (TWI) and Khan *et al*[5] reported cervical lesions of different morphological types. Across the world, qualitative and quantitative methods were used to measure cervical abrasion. Although these grading methods are available, they still lack objective measurements. Some methods rely on clinical descriptions and others on physical measurements. There is a lack of uniformity and hence comparison of data is difficult. An ideal index is hence needed to scientifically diagnose the disease. A classification system is necessary in order to provide a framework to scientifically study the etiology, pathogenesis and treatment of diseases in an orderly fashion. In addition, such systems give clinicians a way to organize the health care needs of their patients[6]. The already available classification systems for dental cervical abrasion have limitations as some of them are descriptive and others are time consuming. A simple classification system was proposed by Sawai in 2014[7].

The present study was conducted to test the reliability of Sawai's classification system[7] for Dental Cervical Abrasions.

MATERIALS AND METHODS

Individuals showing at least one dental cervical abrasion were recruited for the study to check the reliability of this new classification. The patients were recruited from the Out-Patient Department of Department of Periodontology, Faculty of Dentistry, Jamia Millia Islamia, NewDelhi, India and signed a written informed consent in accordance with Helsinki declaration of 1975 as revised in 2000.

Inclusion criteria including: (1) the presence of dental cervical abrasion on one or more teeth; and (2) completion of cause-related therapy when necessary. Exclusion criteria were patients who did not want to participate voluntarily.

Assessment of agreement

The subjects were recruited by the first examiner (MS) and photographs of the teeth with dental cervical abrasion were taken and teeth were marked. The photographs were sequenced and maintained in a soft copy. The other two examiners (FA and SC) were trained on the use of this classification system. All clarifications were provided before the start of the study. Each examiner was then given the soft copy of the compiled sequence of photographs and a sheet to write their responses. The examiners classified the tooth wear defect according to the Sawai's classification[7].

Each examiner used sufficient time to classify every defect. All the three examiners were blinded to the evaluation of each other. The results were then analyzed statistically to test the reliability of the classification.

Statistical analysis

Variables were reported as mean ± standard deviation (SD) for continuous variables or frequency and percentage for discreet variables unless otherwise specified. Kappa statistics were performed for 70 observations to analyze inter-rater agreement amongst the three examiners.

Table 1 MS photography based evaluation and FA photography based evaluation Crosstab

		FA photography based evaluation								Total	Measure of agreement, χ value
		Class A			Class B			Class C			
		Type Ⅰ	Type Ⅱ	Type Ⅲ	Type Ⅰ	Type Ⅱ	Type Ⅲ	Type Ⅰ	Type Ⅱ		
MS Photography based evaluation	Class A Type Ⅰ	12	0	0	0	0	0	0	0	12	0.899
	Class A Type Ⅱ	1	10	0	0	1	0	0	1	13	
	Class A Type Ⅲ	0	0	4	0	0	0	0	0	4	
	Class B Type Ⅰ	0	0	0	2	0	0	0	0	2	
	Class B Type Ⅱ	0	0	0	0	9	0	0	0	9	
	Class B Type Ⅲ	0	0	0	0	0	7	0	0	7	
	Class C Type Ⅱ	0	0	0	0	0	2	6	0	8	
	Class C Type Ⅲ	0	0	0	0	0	1	0	14	15	
Total		13	10	4	2	10	10	6	15	70	

Table 2 MS photography based evaluation and SC photography Crosstab

		SC photography								Total	Measure of agreement, χ value
		Class A			Class B			Class C			
		Type Ⅰ	Type Ⅱ	Type Ⅲ	Type Ⅰ	Type Ⅱ	Type Ⅲ	Type Ⅰ	Type Ⅱ		
MS Photography based evaluation	Class A Type Ⅰ	12	0	0	0	0	0	0	0	12	0.899
	Class A Type Ⅱ	0	11	0	0	0	0	2	0	13	
	Class A Type Ⅲ	0	0	3	0	0	0	0	1	4	
	Class B Type Ⅰ	0	0	0	2	0	0	0	0	2	
	Class B Type Ⅱ	0	0	0	0	8	0	1	0	9	
	Class B Type Ⅲ	0	0	0	0	0	6	1	0	7	
	Class C Type Ⅱ	1	0	0	0	0	0	7	0	8	
	Class C Type Ⅲ	0	0	0	0	0	0	0	15	15	
Total		13	11	3	2	8	6	11	16	70	

SPSS version 17 (SPSS, Inc., Chicago, IL, United States) was used for data analysis.

The level of agreement was evaluated according to the six-level nomenclature given by Landis and Koch[8]: (1)Poor agreement: 0.00; (2) Slight agreement: 0.00-0.20; (3) Fair agreement: 0.21-0.40; (4) Moderate agreement: 0.41-0.60; (5) Substantial agreement: 0.61-0.80; and (6) Almost perfect agreement: 0.81-1.00.

RESULTS

A total 70 observations from 23 patients were examined by 3 investigators (MS, FA and SC) to test the reliability of the Sawai's classification[7] system for tooth abrasion. The kappa statistics were performed for inter-rater agreement among the three examiners. ICC and 95%CI between two examiners, *i.e.*, the inter-rater agreement among 1st examiner (MS) and 2nd examiner (FA) was 0.89 (Table 1). The inter-rater agreement among 1st examiner (MS) and 3rd examiner (SC) was 0.89 (Table 2). And the inter-rater agreement among 2nd examiner (FA) and 3rd examiner (SC) was 0.83 (Table 3). All three comparisons show an almost perfect agreement amongst the three observers.

DISCUSSION

In dentistry, classifications are widely used to categorize defects or diseases based on their etiology, diagnosis, treatment and prognosis. A "Classification" is defined as "systematic arrangements in groups or categories according to established criteria[9]."

There are many classifications available for tooth wear. The earliest known index is by Broca[10], 1879 for tooth attrition. It was followed by index given by Restarski *et al*[11] in 1945 which evaluated the severity of erosive destruction using the 6 point grading system. But concerns were raised regarding its reproducibility.

The commonly known Eccles's index[1] was given in 1979 initially classified the lesions into early, small and advanced types. It was refined and expanded in 1982 with more descriptive criteria; grading both severity and site erosion due to non-industrial causes. It is considered as one of the cardinal indices from which others have evolved[4].

Later, Xhonga and Valdimanis[12] divided erosions into four levels by measurement with a periodontal probe: none, minor, moderate and severe. They further differentiated the types of erosion by morphological descriptions, such as wedge, saucer, groove and atypical. However, they did not address the problem of inter- or intra-examiner variability.

Other index like Smith and Knight's Tooth Wear Index (TWI)[2] was given in 1984 which was a comprehensive system and was more clinically relevant. It produced results from intra- and inter-rater reproducibility within an acceptable range. It could be used on study models and photographs also. However, it was very time consuming

Table 3 FA photography based evaluation and SC photography Cross tabulation

		SC photography								Total	Measure of agreement, χ value
		Class A			Class B			Class C			
		Type Ⅰ	Type Ⅱ	Type Ⅲ	Type Ⅰ	Type Ⅱ	Type Ⅲ	Type Ⅰ	Type Ⅱ		
MS Photography based evaluation	Class A Type Ⅰ	12	0	0	0	0	0	1	0	13	0.832
	Class A Type Ⅱ	0	9	0	0	0	0	1	0	10	
	Class A Type Ⅲ	0	0	3	0	0	0	0	1	4	
	Class B Type Ⅰ	0	0	0	2	0	0	0	0	2	
	Class B Type Ⅱ	0	1	0	0	8	0	1	0	10	
	Class B Type Ⅲ	1	0	0	0	0	6	2	1	10	
	Class C Type Ⅱ	0	0	0	0	0	0	6	0	6	
	Class C Type Ⅲ	0	1	0	0	0	0	0	14	15	
Total		13	11	3	2	8	6	11	16	70	

and always required computer assistance as the amount of data generated was very high.

Linkosalo and Markkanen[13] used a quantitative, four-scale grading system for severity relating to involvement of dentine. This index was modified by Lussi *et al*[3]. Later, Bardsley *et al*[4] carried out epidemiological studies on adolescents in North West England using a new, simplified version of TWI. It collected data from 40 surfaces from every subject. However, despite calibration and training, there were difficulties in diagnosing dentine exposure in epidemiological field.

Larsen *et al*[14] recommended a new clinical index. It was based on clinical examination, photographs and study casts. Each tooth surface was scored, with six grades of erosion severity modelled using Smith and Knight's TWI; however its criteria is complicated and time consuming.

Thus, there was a need of new classification system for tooth wear which was proposed by Sawai[7] in 2014. The present study evaluated the sensitivity of using this classification system by three observers.

An ideal classification should have following characteristics according to the criteria given by Murphy[15] in 1997: (1) Naturalness; (2) Usefulness; (3) Simplicity; (4) Exhaustiveness; (5) Disjointness; and (6) Constructability.

When this proposed classification is tested for these qualities of an "Ideal Index", it is seen that this system is simple, exhaustive, useful and clear in its classes. The distinction is based on objective criteria to avoid any confusion. It seems to be very simple for practical application as there are few subclasses. The observers reported no difficulty in using this classification system. This study conducted here tests the reliability of the use of this index, whether it can effectively communicate the findings to other colleagues, whether it creates confusion among different clinicians regarding difference in opinions in diagnosis. As the results of this study show that there was almost perfect agreement amongst the observers, it can be concluded that this proposed classification system by Sawai satisfies majority of the criteria, which are considered essential for a good classification system. This system can be used for studying dentitions from study casts and photographs as well.

The authors want to highlight that there were no observations of type Ⅳ subclass category in the present study. Hence, it is emphasized that this subclass cannot be documented using photographs or study models as one cannot identify an open pulp chamber in a photograph or study cast. However, this drawback can be defeated if this classification is used in clinical study as it is easy to identify an exposed pulp chamber.

To conclude, the Sawai's classification system is simple and practical to use in daily dental practice. The results of the study show that this classification is sensitive and reliable. The authors' recommend further clinical studies to assess the validity of this proposed classification system.

COMMENTS

Background

The authors, as dentists, always diagnose and monitor any particular oral disease. They use various indices to determine the severity and progression of a disease. For this, the authors use classifications or indices which are universally applied. Currently there is no ideal index for classification of tooth abrasion. A simple classification was proposed in 2014. This study evaluates the reliability of this index for use in practice.

Research frontiers

The currently available indices for tooth abrasion are time consuming. There is no uniformity regarding their grading. Hence there is an absolute need for a classification which is reliable for use in practice.

Innovations and breakthroughs

The available classifications for tooth abrasion lack uniformity and are either qualitative or quantitative in nature. This study proves that the classification used was easy to understand as dentistry students classify the tooth abrasions effectively. The classification is able to identify the position of the abrasion defect on the tooth surface and grade the severity as well.

Applications

The classification is reliable and can be used in daily dental practice.

Peer-review

The manuscript is interesting and with clinical relevance. It requires minor improvement in methodology. However, the conclusion that it can be used to classify cervical abrasions reliably is very important in dental clinics. Yet, it is important that the limitations regarding exposed pulp chamber are established.

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ORIGINAL ARTICLE

Observational Study

Effect of *Helicobacter pylori* eradication on elder cases: Observational study in community-based medicine

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Abstract

AIM

To examine the effect of *Helicobacter pylori* (*H. pylori*) eradication therapy on the extra-gastrointestinal factors in elderly patients by a before-after observational study in community medicine.

METHODS

Medical records (1 May 2013-31 January 2014) of 130 patients who underwent *H. pylori* eradication therapy with 2-year after-eradication observation in our institute were reviewed. Data on sex; age; body weight; body mass index (BMI); mean corpuscular volume (MCV); total protein; low-density lipoprotein cholesterol, triglyceride, haemoglobin A1c and haemoglobin levels and gastric hyperplastic polyps (GHPs) at eradication was extracted. Two-year after-eradication change in data was analysed by paired-sample *t*-test; relationship between GHPs and subclinical iron deficiency anaemia (IDA) improvement was evaluated.

RESULTS

The mean patient age (median, interquartile range) at eradication was 69.6 (71.5, 64-77) years. Paired-sample *t*-tests showed that body weight, BMI and MCV increased by 0.52 kg (P = 0.018), 0.25 kg/m^2 (P = 0.006) and 0.83 fL (P < 0.001), respectively. The nonparametric Mann-Whitney test showed no significant difference in the change rate of MCV after eradication between the groups with and without GHPs (P = 0.892).

CONCLUSION

H. pylori eradication therapy prevented weight loss and subclinical IDA in elderly individuals. GHPs were not associated with subclinical IDA.

Key words: *Helicobacter pylori*; Iron deficiency anaemia; Body weight; Elderly; Polyp

Core tip: The effect of *Helicobacter pylori* (*H. pylori*) eradication therapy on the extra-gastrointestinal factors in elderly patients was focused in this study. *H. pylori* eradication therapy prevented weight loss and subclinical iron deficiency anaemia (IDA) in elderly individuals. Gastric hyperplastic polyps were not associated with subclinical IDA. The results obtained in this study will help physician to treat elderly patients in community-based medicine.

Maruyama M, Kamimura K, Hoshiyama A, Hoshiyama K, Hoshiyama M, Hoshiyama Y, Terai S. Effect of *Helicobacter pylori* eradication on elder cases: Observational study in community-based medicine. *World J Clin Cases* 2017; 5(12): 412-418 Available from: URL: http://www.wjgnet.com/2307-8960/full/v5/i12/412.htm DOI: http://dx.doi.org/10.12998/wjcc.v5.i12.412

INTRODUCTION

Helicobacter pylori (*H. pylori*) infection affects many extra-gastrointestinal symptoms and diseases, including iron deficiency anaemia (IDA), obesity, diabetes mellitus and hyperlipidemia[1,2]. Although major population surveys and meta-analysis have revealed an increased risk for IDA in addition to a strong evidence for the efficacy of *H. pylori* eradication for the treatment of unexplained IDA, the relationship between *H. pylori* infection and prevalence of other extra-gastrointestinal tract diseases is unclear. The influence of *H. pylori* pathogenicity is currently unknown, particularly in elderly individuals[1,3-6]. In addition, the underlying mechanism of *H. pylori*-related IDA is still unclear[7,8].

H. pylori eradication therapy for patients with peptic ulcer is associated with gain of body weight[9,10]. The relationship between *H. pylori* infection and overweight is unclear, even in large-scale epidemiological studies[11-14]. However, this increase might related to the recovery of peptic ulcer and chronic inflammation. On the other hand, because of previously reported inconsistent results, the cause-and-effect relationship between *H. pylori* infection and metabolic disease is also ambiguous, and there are few reports on elderly individuals[2,15-19]. Because the development of an aging society may be upcoming event in the near future, the effect of *H. pylori* eradication therapy on the extra-gastrointestinal organs in elderly individuals should be investigated.

Therefore, the purpose of this observational study was to examine the effects of *H. pylori* eradication in elderly individuals on systemic conditions including body weight, biochemical results, and manifestations of clinical or subclinical anaemia comparing data between before-eradication and 2 years after *H. pylori* eradication. We have also compared rates of IDA improvement in chronic gastritis with and without gastric hyperplastic polyp (GHP) to investigate the relationship between GHP and *H. pylori*-related IDA.

MATERIALS AND METHODS

This was an observational before-after study in which the case group included 130 individuals who were continuously treated with medications for chronic diseases, such as essential hypertension, hyperlipidemia and/or diabetes mellitus. They were all diagnosed with *H. pylori*-infected chronic gastritis by routine esophagogastroduodenoscopy (EGD) and the rapid urease test at Kashiwazaki Central Hospital between 1 May 2013 and 31 January 2014.

The patient was considered to be eligible when fulfilled the following inclusion criteria: (1) *H. pylori* eradication therapy was successful and was followed by the urea breath test; and (2) the patient had been measured/tested for body weight; body mass index (BMI); mean corpuscular volume (MCV); total protein (TP) and low-density lipoprotein cholesterol (LDL-C), triglyceride (TG), haemoglobin (Hb) and haemoglobin A1c (HbA1c) levels at two time points: Before and 2 years after *H. pylori* eradication therapy was completed. However, we included patients with some missing measurement values and as elderly if older than 65 years old. We excluded patients with mucosal breaking lesions, such as gastric cancer or peptic ulcers, history of gastrointestinal surgery, and the other diseases might cause anemia. This study was approved by the institutional review board of Kashiwazaki Central Hospital. Written informed consent was obtained from all patients, and the study was conducted in accordance with the ethical guidance of the 1975 Declaration of Helsinki.

To identify differences in a patient between two time points, a paired-sample *t*-test was performed. When there were ⩽ 30 cases, a Wilcoxon signed test was performed. For continuous variables, two-group

Table 1 Comparison of various factors before and after *Helicobacter pylori* eradication therapy in all subjects (*n* = 130)

Variable	Subjects	Missing	Pre-eradication mean (SD)	Post-eradication mean (SD)	Mean difference	95%CI	*P* value
Body weight (kg)	124	6	57.3 (10.4)	58.2 (10.3)	0.52	0.09-0.94	0.018
BMI (kg/m^2)	121	9	23.4 (3.1)	23.7 (3.0)	0.25	0.074-0.42	0.006
Hb (g/dL)	115	15	13.8 (1.4)	13.8 (1.3)	0.018	-0.35	0.84
MCV (fL)	113	17	89.2 (4.9)	90 (4.4)	0.83	0.32-1.34	< 0.001
TP (g/dL)	90	40	7.4 (0.5)	7.5 (0.4)	0.024	-0.168	0.56
LDL-C (mg/dL)	107	23	114.3 (23.9)	116.2 (25.0)	1.20	-8.12	0.55
TG (mg/dL)	107	23	122 (70.5)	126.6 (77.1)	6.81	-22.59	0.23
HbA1c (%)	42	88	6.2 (0.81)	6.3 (0.75)	0.057	-0.305	0.45

BMI: Body mass index; Hb: Haemoglobin; MCV: Mean corpuscular volume; TP: Total protein; LDL-C: Low-density lipoprotein cholesterol; TG: Triglyceride; HbA1c: Haemoglobin A1c.

comparisons, such as Hb and MCV, were performed using the nonparametric Mann-Whitney test because assumptions of normality of the distribution were not verified. We excluded the patients with missing data in each group before analysis. The threshold for significance was $P < 0.05$. In all statistical analysis, we used EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). More precisely, it is a modified version of R commander designed to add statistical functions frequently used in biostatistics[20]. The results for changes in variable before and after *H. pylori* eradication are presented as the mean ± SD.

RESULTS

Patient characteristics

Between 1 May 2013 and 31 January 2014, 228 patients were diagnosed as having *H. pylori*-infected chronic gastritis by EGD and the rapid urease test were included. The patients who had been diagnosed as having gastric cancer ($n = 3$), gastric ulcer ($n = 16$), duodenal ulcer ($n = 20$) and gastro-duodenal ulcer ($n = 7$) who could not be followed up for 2 years after *H. pylori* eradication ($n = 52$), a total of 98 patients, were excluded from the initial 228 patients with *H. pylori*-infected chronic gastritis. Finally, a total of 130 patients [mean age, 69.6 years; median age, 71.5 (interquartile range, 64–77 years); 52 (40%) males] were analysed in the study. No patients showed re-infection of *H. pylori* after the eradication.

Effect of H. pylori eradication on various factors

The effect of *H. pylori* eradication therapy on various physiological factors was carefully examined comparing the value before and after the therapy in all 130 elderly patients with the interval of 2 years for each (Table 1). The body weight increased from a mean ± SD of 57.3 ± 10.4 kg before *H. pylori* eradication to 58.2 ± 10.3 kg 2 years after *H. pylori* eradication ($P = 0.018$). In addition, BMI increased from 23.4 ± 3.1 before *H. pylori* eradication to 23.7 ± 3.0 2 years after *H. pylori* eradication ($P = 0.006$). MCV increased from 89.2 ± 4.9 fL before *H. pylori* eradication to 90.0 ± 4.4 fL 2 years after *H. pylori* eradication ($P < 0.001$) whereas no significant changes were seen in the value of Hb ($P = 0.84$). The paired-sample *t*-test showed no significant differences in other measurements including TP, LDL-C, TG, and HbA1c, before and 2 years after *H. pylori* eradication (Table 1).

Subgroup analysis of factors in elderly patients

The patients older than 65 years old were considered to be elderly and the factors affected by the *H. pylori* eradication treatment have been carefully assessed by the subgroup analyses (Table 2). In the group of patients ⩾ 65 years ($n = 97$), BMI increased from 23.6 ± 3.0 before *H. pylori* eradication to 23.8 ± 3.1 2 years after *H. pylori* eradication ($P = 0.045$). MCV increased from 89.2 ± 5.3 fL before *H. pylori* eradication to 90.1 ± 4.7 fL 2 years after *H. pylori* eradication ($P = 0.0017$) whereas no significant changes were seen in the value of Hb ($P = 0.84$). There were no significant differences in other measurements in the group of patients ⩾ 65 years (Table 2).

These results suggest that the *H. pylori* eradication contribute to maintain the BMI avoiding the loss of body weight, and to recovery from subclinical IDA caused by the chronic inflammation in the stomach. In addition, even with the 2 years period of the study, no significant changes were seen in the various nutritional factors, indicating that the better digestion, absorption, after the eradication therapy.

Effect of eradication and the level of Hb

To determine the effect of eradication on anaemia, level of Hb was carefully assessed in the patients (Table 3). Although the patients with Hb levels < 12.5 g/dL before *H. pylori* eradication increased from 11.5 ± 0.86 g/dL to 12.3 ± 0.99 g/dL at 2 years after *H. pylori* eradication ($P = 0.017$), paired-sample t-tests showed no significant difference in Hb levels before and 2 years after *H. pylori* eradication in the group with Hb ⩾ 12.5 g/dL (Table 3). In addition, to examine whether the rates of IDA improvement in chronic gastritis is related to the existence of GHP, the level of improvement of Hb and MCV values before and after the eradication

Table 2 Subgroup analysis of various factors before and after *Helicobacter pylori* eradication therapy in the group of patients > 65 years (*n* = 97)

Variable	Subjects	Missing	Pre-eradication mean (SD)	Post-eradication mean (SD)	Mean difference	95%CI	*P* value
Body weight (kg)	92	5	57.1 (10.4)	57.8 (10.3)	0.41	-1.017	0.12
BMI (kg/m^2)	90	7	23.6 (3.0)	23.8 (3.1)	0.21	-0.4159	0.045
Hb (g/dL)	85	12	13.7 (1.5)	13.7 (1.3)	-0.02	-0.4	0.84
MCV (fL)	85	12	89.2 (5.3)	90.1 (4.7)	0.95	-1.17	0.0017
TP (g/dL)	66	31	7.5 (0.5)	7.5 (0.4)	0.011	-0.216	0.84
LDL-C (mg/dL)	77	20	111.9 (21.2)	114.2 (24.8)	1.25	-9.65	0.61
TG (mg/dL)	77	20	116.7 (56.2)	112.6 (44.8)	-1.68	-20.35	0.74
HbA1c (%)	30	67	6.4 (0.8)	6.4 (0.7)	0.013	-0.35	0.88

BMI: Body mass index; Hb: Haemoglobin; MCV: Mean corpuscular volume; TP: Total protein; LDL-C: Low-density lipoprotein cholesterol; TG: Triglyceride; HbA1c: Haemoglobin A1c.

Table 3 Differences in the eradication effect on the rate of increase in haemoglobin level between groups of patients with < haemoglobin 12.5 g/dL (*n* = 20) and patients with ⩾ haemoglobin 12.5 g/dL (*n* = 96)

Variable	Subjects	Missing	Pre-eradication mean (SD)	Post-eradication mean (SD)	Mean difference	95%CI	*P* value
Less than Hb 12.5 g/dL	19	1	11.5 (0.7)	12.3 (1.0)	0.85	0.22-1.48	0.017
More over Hb 12.5 g/dL	96	11	14.2 (1.1)	14.1 (1.2)	-0.15	-0.1592	0.064

Hb: Haemoglobin.

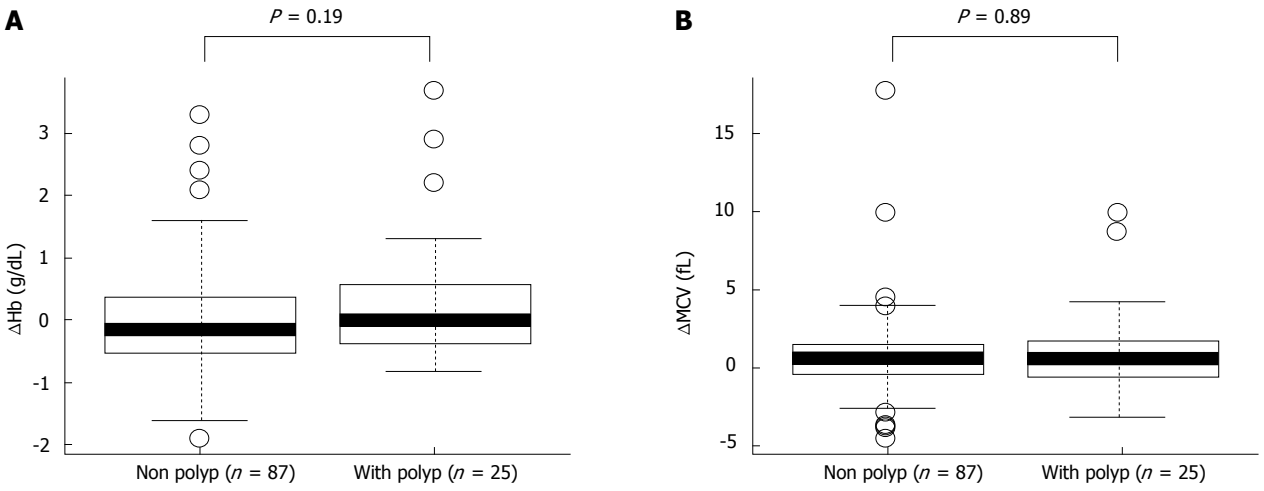

Figure 1 Comparison of haemoglobin and mean corpuscular volume levels before and after *Helicobacter pylori* eradication therapy in patients with or without gastric hyperplastic polyps. A: Change in the haemoglobin level; B: Mean corpuscular volume level. Hb: Haemoglobin; MCV: Mean corpuscular volume.

were compared (Figure 1). The nonparametric Mann-Whitney test showed no significant increase in Hb levels and MCV (P = 0.89) from before to 2 years after *H. pylori* eradication (P = 0.19) between the groups with and without GHP (Figure 1) and its size. These results indicate that the improving tendency of anaemia after *H. pylori* eradication did not correlate with the presence of GHP or its size.

DISCUSSION

Our study showed that *H. pylori* eradication therapy for elderly patients with chronic gastritis increased BMI and MCV, 2 years as a result of successful *H. pylori* eradication. The level of MCV has been considered as one of the marker of subclinical IDA and its recovery reflect the improvement of IDA[21]. Previous studies have shown similar results in patients with anaemia whose Hb significantly improved after *H. pylori* eradication[1,3-6]. There was no difference in the rate of increase in MCV (improvement in IDA) between groups with and without GHP. This finding suggests that GHP is not involved in an anaemic improvement pathway after *H. pylori* eradication.

It is known that the proportion of individuals with BMI > 30 generally increases up to the age of 60 years, and BMI tends to decrease after the age of 61 years[22]. In addition, the body weight loss in elderly individuals

is a predictive factor for death, mildly obese individuals have the lowest mortality rate[23,24]. It might be related to the recently established concept of "Frailty", a risk factor for falls, disability, hospitalization and mortality during old age. It is defined by the following criteria: Unintentional weight loss, self-reported exhaustion, weakness (grip strength), slow walking speed and low physical activity[25] and energy and protein support is recommended to treat the condition[26]. Interestingly, in our study, we found that elderly patients gained weight after *H. pylori* eradication. This result was inconsistent with the general tendency towards body weight loss in the elderly population and suggested that the effect of *H. pylori* eradication on preventing body weight loss or increase. The mechanisms might include, improvement of gastro-duodenal inflammation, ulcerative lesions, *etc*., as well as decrease of serum level of leptin which plays a crucial role to regulate food intake and energy expenditure[11,27]. Thus, we infer that *H. pylori* eradication therapy for elderly patients with *H. pylori*-infected chronic gastritis may be an effective therapy for prevention of weight loss in elderly individuals.

Our results are consistent with those of previous studies showing improvement of anaemia after *H. pylori* eradication therapy in elderly individuals[1,3-6]. Our study also showed that MCV increased after *H. pylori* eradication in the total study population as well as in the elderly patient group. However, presence of GHP was not related to the increase in the MCV rate. An important finding from previous study is that 80% of GHP disappeared after *H. pylori* eradication therapy within an average of 7.1 mo[28]. A recent report suggested that *H. pylori*-related IDA was associated with several factors in patients with GHP and nodular gastritis[29]. Bleeding from GHP is assumed to be the cause of *H. pylori*-related IDA. However, a previous study showed that even faecal occult blood-negative patients may be anaemic[30]. In addition, the mechanism might not be applicable to nodular gastritis. A recent study suggested that the cause of anaemia in patients with GHP is not bleeding from GHP but rather a decrease in iron absorption caused by a low-acid state[26]. Therefore, our results provide some support for the hypothesis that the improvement of *H. pylori*-related IDA is caused by an underlying mechanism other than GHP deletion.

One plausible reason for the finding of no significant changes in TP, TG, LDL-C and HbA1c levels is the presumed administration of statins and/or antidiabetic drugs to the patients. A previous report showed that serum total cholesterol levels did not change after *H. pylori* eradication[11]. Therefore, our results may be consistent with these previous findings.

A limitation of our study, however, is that although previous studies have shown that diabetes was exacerbated by *H. pylori* infection[17-19], our findings suggest no exacerbation or improvement of diabetes by eradication was because of strict management by a diabetologist in our hospital. In addition, the power of this study was limited because of the small number of participants and patients with subclinical IDA, of the single-centre analysis and of the retrospective-observational study design. Therefore, future larger, ad hoc, and better designed prospective studies are essential to confirm the effect of *H. pylori* eradication on systemic conditions by monitoring symptoms, medical history, and laboratory exams comparing with cases failed for the eradication.

In conclusion, our findings suggest that an increase in MCV is associated with body weight gain and improvement of subclinical IDA after *H. pylori* eradication in elderly patients with chronic gastritis. The tendency for subclinical IDA to improve after *H. pylori* eradication did not correlate with the presence of GHP. In addition, even with the 2 years period of the study, no significant changes were seen in the various nutritional factors, indicating that the better digestion, absorption, after the eradication therapy. For the future perspective, as the development of an aging society may be upcoming event in the near future, *H. pylori* eradication therapy may be a useful approach for preventing weight loss and frailty in elderly individuals to keep their quality of life and health.

ARTICLE HIGHLIGHTS

Research background

The relationship between *Helicobacter pylori* (*H. pylori*) infection and various extra-gastrointestinal symptoms, including obesity, diabetes mellitus and hyperlipidemia have been reported.

Research motivation

Although major population surveys and meta-analysis have suggested an increased risk for iron deficiency anaemia (IDA), however the relationship between *H. pylori* infection/its eradication on IDA and other extra-gastrointestinal tract diseases has not been clarified, especially in elderly patients.

Research objectives

This study was aimed to examine the effect of *H. pylori* eradication therapy on the extra-gastrointestinal factors in elderly patients by a before-after observational study in community medicine.

Research methods

Medical records (1 May 2013-31 January 2014) of 130 patients who underwent *H. pylori* eradication therapy with 2-year after-eradication observation in our institute were reviewed. Data on sex; age; body weight; body mass index (BMI); mean corpuscular volume (MCV); total protein; low-density lipoprotein cholesterol, triglyceride, haemoglobin A1c and haemoglobin levels and gastric hyperplastic polyps (GHPs) at eradication was extracted. Two-year after-eradication change in data was analysed by paired-sample *t*-test; relationship between GHPs and subclinical IDA improvement was evaluated.

Research results

The mean patient age (median, interquartile range) at eradication was 69.6 (71.5, 64-77) years. Paired-sample *t*-tests showed that body weight, BMI and MCV increased by 0.52 kg (P = 0.018), 0.25 kg/m^2 (P = 0.006) and 0.83 fL (P < 0.001), respectively. The nonparametric Mann-Whitney test showed no significant difference in the change rate of MCV after eradication between the groups with and without GHPs (P = 0.892).

Research conclusions

H. pylori eradication therapy prevented weight loss and subclinical IDA in elderly individuals, therefore, the eradication should be considered even for

those elder patients.

Research perspectives

For the future perspective, as the development of an aging society may be upcoming event in the near future, *H. pylori* eradication therapy may be a useful approach for preventing weight loss and frailty in elderly individuals to keep their quality of life and health.

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CASE REPORT

Surgical resection of rare internal jugular vein aneurysm in neurofibromatosis type 1

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Author contributions: Delvecchio K, Moghul F and Patel B examined patient and collected clinical data; Moghul F and Patel B performed surgical resection and follow up; Delvecchio K and Moghul F wrote the paper; Patel B and Seman S edited the manuscript and had final approval.

Institutional review board statement: The authors' institution does not require IRB approval to publish a single case report.

Informed consent statement: Informed written consent was obtained from the patient prior to all procedures described in the report as well as for the use of the patient's clinical information and images for published scientific works.

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Abstract

Neurofibromatosis type 1 is a congenital condition affecting neurons and connective tissue integrity including vasculature. On extremely rare occasions these patients present with venous aneurysms affecting the internal jugular vein. If they become large enough there presents a risk of rupture, thrombosis, embolization or compression of adjacent structures. In these circumstances, or when the patient becomes symptomatic, surgical exploration is warranted. We present a case of one of the largest aneurysms in the literature and one of only five associated with Neurofibromatosis type 1. A 63-year-old female who initially presented for a Hinchey Ⅲ diverticulitis requiring laparotomy developed an incidentally discovered left neck swelling prior to discharge. After nonspecific clinical exam findings, imaging identified a thrombosed internal jugular vein aneurysm. Due to the risks associated with the particularly large size of our patient's aneurysm, our patient underwent surgical exploration with ligation and excision. Although several techniques have been reported, for similar presentations, we recommend this technique.

Key words: Internal jugular; Venous aneurysm; Ligation; Neurofibromatosis 1; Excision; Resection

Core tip: Neurofibromatosis type 1 is a congenital condition occasionally affecting vascular connective tissue integrity. On extremely rare occasions these patients present with internal jugular venous aneurysms. We

present a case of the successful ligation and excision of one of the largest internal jugular vein aneurysms in the literature and one of only five associated with Neurofibromatosis type 1.

Delvecchio K, Moghul F, Patel B, Seman S. Surgical resection of rare internal jugular vein aneurysm in neurofibromatosis type 1. *World J Clin Cases* 2017; 5(12): 419-422 Available from: URL: http://www.wjgnet.com/2307-8960/full/v5/i12/419.htm DOI: http://dx.doi.org/10.12998/wjcc.v5.i12.419

INTRODUCTION

Initially described by Gruber[1] in 1875, internal jugular (IJ) aneurysms are rare entities with under 400 reported in the last 100 years in the literature. As described by Lubianca-Neto *et al*[2] these lesions have historically been described as "congenital venous cyst, venous pseudoaneurysm, venous ectasia, venous aneurysm, venous cyst, venoma, and internal jugular phlebectasia" in the literature, with an average age of under 10 and over 60% under age 40[3,4]. They most commonly occur on the right side, however may be bilateral in as many as 10% of cases[5,6]. These aneurysms classically present as unilateral, asymptomatic, soft, compressible neck swellings that enlarge with Valsalva[1-3]. Due to the relationship of the IJ abutting the vagus nerve within the carotid sheath, patients may complain of hoarseness, dysphagia or foreign body sensation[1,5,7]. Moreover, the absence of bruit or pulsation on physical exam excludes a more ominous arterial pathology[1,8].

While the underlying physiology that makes a particular patient susceptible to aneurysm formation is largely unknown, several inciting factors have been reported in the literature. These include trauma from central venous catheterization, positive-pressure ventilation, inflammation, distal obstruction from a mass, or unknown idiopathic causes[2,7,9]. Additionally, pathological analyses of resected aneurysms have described congenital thinning of the elastic and muscular layers of the venous wall, and/or elastin dysplasia[10,11]. Not surprisingly, disorders of connective tissue, including Ehlers-Danlos and Neurofibromatosis type 1 (NF1), have been linked to these anomalies[4,12-14].

NF1 aka von Recklinghausen's disease is an autosomal dominant mutation of chromosome 17 occurring in 1 in 3000 people that alters the neurofibromin protein, affecting the structural integrity of connective tissues and nerves[12,13]. Typical presentations include neurofibromas, café au lait macules, Lisch hamartomas, meningiomas, and gliomas[13,14]. Rarer manifestations involve the vasculature which can be present in up to 6.4% of patients, however it primarily involves the arterial system[12,15]. We present a case of the successful ligation and excision of one of the largest IJ vein aneurysms in the literature and one of only five associated with NF1.

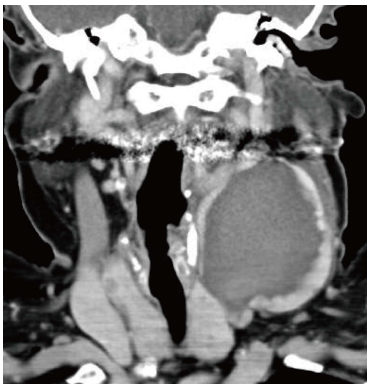

Figure 1 Coronal computed tomography of left internal jugular vein aneurysm.

CASE REPORT

A 63-year-old Caucasian female with a medical history significant for Neurofibromatosis presented to the emergency room with bilateral lower quadrant abdominal pain, diarrhea, emesis and complaints of fevers and chills for one day. She was tachycardic and peritoneal on examination and thus taken to the operating room where she underwent sigmoid resection with end colostomy and Hartmann's pouch for Hinchey Ⅲ diverticulitis. Postoperatively the patient remained intubated and was admitted to the ICU and had a left subclavian central venous catheter placed for vasopressor support. After a series of setbacks, the patient began to improve significantly around postoperative day (POD) 11 and her subclavian line was able to be removed. By POD 15 the patient was ready for discharge to rehab.

Upon preparing for departure the patient noticed in the mirror a bulge in her left neck that she did not previously feel. The nursing staff and subsequently physicians were notified. Upon examination there was no noticeable mass as the patient had significant submental ptosis. A computed tomography (CT) scan of the neck was performed which showed a 5.8 cm × 6.9 cm × 5.4 cm internal jugular collection with anterior displacement of the sternocleidomastoid (SCM) (Figures 1 and 2). The vascular surgeon was notified and a triplex ultrasound was performed showing a 6.9 cm × 3.8 cm × 6.5 cm internal jugular thrombus with minimal superior flow and a patent subclavian (Figure 3).

On POD 16 the patient was taken to the operating room where she underwent evacuation, resection and ligation of the internal jugular aneurysm *via* an anterior SCM incision. Small internal branches were ligated and the anterior vein wall was sutured closed. There was an estimated blood loss of 1 liter during dissection due to avulsion of many of these internal branches. The skin was closed and a Jackson-Pratt (JP) drain was left subcutaneously. Postoperatively the JP was removed on day 1 due to minimal output and the patient was able to be discharged home on day 2.

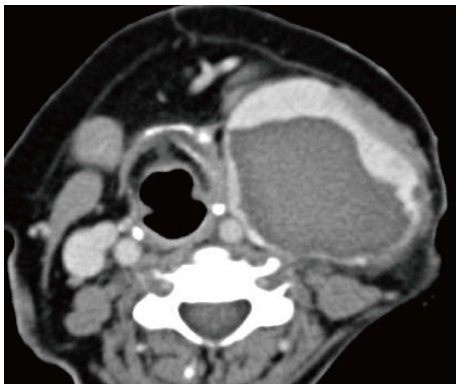

Figure 2 Transverse computed tomography of left internal jugular vein aneurysm.

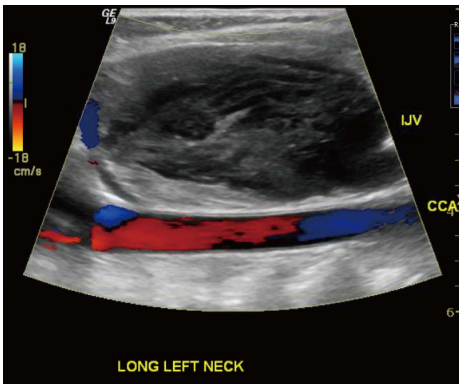

Figure 3 Color flow doppler ultrasound image depicting patent left common carotid artery and thrombosed left internal jugular vein aneurysm.

Table 1 Characteristics of Neurofibromatosis type 1-associated internal jugular aneurysms in the literature

Ref.	Age/sex	Side	Size (cm)	Treatment	Thrombosed	Confirmed NF1 in wall
Nopajaroonsri and Lurie[14] (1996)	62 M	Left	10 × 5 × 4.5	Resection	Yes	Yes
Oderich *et al*[13] (2007)	73 M	Right	"Giant"	Resection	Yes	
Belcastro *et al*[15] (2011)	60 F	Left	12 × 12 × 10	Resection	Yes	Yes
Hiraki *et al*[12] (2014)	60 M	Left	5.5 × 5 × 2	Resection	Yes	Yes
The present case	63 F	Left	6.9 × 5.8 × 5.4	Resection	Yes	

M: Male; F: Female; NF1: Neurofibromatosis type 1.

DISCUSSION

Limitations to our workup include not submitting the aneurysmal wall for pathological analysis as 3 of the 4 described aneurysms associated with NF1 in the literature describe histopathological invasion of NF1 into the wall[12,14,15]. While not necessary for the diagnosis, it could have helped substantiate a more definitive pathological explanation. Additionally, several authors have recommended that the diagnostic workup include bilateral triplex ultrasound performed with Valsalva[4-6]. The importance of a size increase with Valsalva during examinations is underscored by the fact that the majority of differential diagnoses can be ruled out if absent, leaving phlebectasias, laryngoceles and superior mediastinal cyst[4]. The most common of these, laryngocele, can be ruled out with laryngoscopy, whereas mediastinal cysts can be ruled out with CT scan[5]. Although our patient's diagnosis was easily identified with CT and confirmed with triplex ultrasound, it was not performed with these particular suggestions in mind.

Although clinical exam can provide a significant amount of information, because of the low overall rate of complications there is often adequate time for definitive imaging. As mentioned previously, triplex ultrasound is the current standard for diagnostic accuracy as it will allow for characterization of the aneurysmal size as well as visualization of directional blood flow and thrombosis[2,4,5]. Additionally, Passariello *et al*[16], described four cases in children that were successfully characterized with endovascular digital subtraction contrast fluoroscopy which has the additional benefit of simultaneous diagnosis and intervention[17].

As described above, a commonly cited etiology of IJ aneurysms is traumatic central venous catheterization[7]. A limitation with our case was the prolonged duration with which her left subclavian line was in place, possibly leading to thrombosis and propagation. It is difficult to definitively determine if the subclavian line was the inciting event, however it is likely it participated in a genetically susceptible patient.

IJ aneurysms have rarely been reported on and only a handful have been described in association with NF1 (Table 1)[12-15]. These lesions typically present much larger than other cases and ours, at 6.9 cm × 5.8 cm × 5.4 cm, is one of the largest described in the literature. Each of these aneurysms were surgically resected and each had significant blood loss[12-15].

With regard to management, because IJ aneurysms are considered to be self-limiting, operative intervention is usually reserved for cosmetic or symptomatic reasons[2,5,10,18]. Although extremely rare, if there is significant concern for thrombosis, embolization or impending rupture, resection is justified[10]. Various approaches have been described which have been largely based on size and location, including anterior SCM, transverse cervical and median sternotomy incisions[4,5,15]. Additionally Chua *et al*[17], describe a combined endovascular balloon ligation and open resection, allowing for a smaller incision. Regardless of the approach, it is important preoperatively to confirm contralateral patency for cerebral edema prevention[2] as Hu *et al*[8], reported 2 cases of unilateral ligation of bilateral lesions resulting in 3

d of cerebral swelling. While many IJ vein aneurysms have reportedly been followed successfully without intervention for up to 15 years, no studies have been performed that compare long-term outcomes of any kind[6]. This leads to the suggestion of future randomized trials featuring long-term outcomes of conservative management *vs* various surgical procedures.

COMMENTS

Case characteristics

A 63-year-old woman with neurofibromatisis type 1 who developed an incidentally discovered internal jugular vein aneurysm that was surgically resected.

Clinical diagnosis

Compressible left-sided neck swelling without dysphagia or respiratory compromise.

Differential diagnosis

Differential diagnoses include phlebectasias, laryngoceles, superior mediastinal cyst, thyroglossal duct cyst, cystic hygroma, branchial cleft cyst, pharyngocele, dermoid cyst, thyroid mass, arteriovenous malformation, carotid body tumor and squamous cell carcinoma of the neck.

Laboratory diagnosis

All labs were within normal limits.

Imaging diagnosis

Computed tomography scan showed a 5.8 cm × 6.9 cm × 5.4 cm internal jugular collection with anterior displacement of the sternocleidomastoid. A triplex ultrasound showed a 6.9 cm × 3.8 cm × 6.5 cm internal jugular thrombus with minimal superior flow and a patent subclavian.

Treatment

Surgical evacuation, resection and ligation of the aneurysm.

Related reports

Internal jugular venous aneurysms have historically gone by several names in the literature and despite very few resulting in significant morbidity with expectant management alone, they are frequently surgically resected.

Term explanation

Triplex ultrasound is an imaging method that uses color to highlight direction of vascular flow. It is the recommended diagnostic method to characterize these lesions.

Experiences and lessons

Patients with neurofibromatosis type 1 are particularly susceptible to internal jugular vein aneurysms due to vascular wall abnormalities, which should be noted when inciting etiological events occur such as central venous catheterization.

Peer-review

The information and brief literature review provided was sufficient.

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CASE REPORT

Human herpesvirus-8 positive iatrogenic Kaposi's sarcoma in the setting of refractory ulcerative colitis

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Author contributions: Duh E drafted manuscript; Fine S collected and interpreted data, proof/read manuscript.

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Abstract

Although Kaposi sarcoma (KS) has been more traditionally considered an AIDS-defining illness, it may also be seen in individuals on immunosuppresive therapy. We report a case of a patient who presented to the hospital in the setting of increasingly refractory ulcerative colitis. Computed tomography scan of the abdomen was consistent with sigmoid diverticulititis and blood cultures were positive for Klebsiella. After a course of antibiotics with resolution of infection, a colonoscopy was performed to evaluate his diverticulitis and incidentally revealed a new rectal tumor. Immunohistochemistry showed the tumor was consistent with KS, with cells staining strongly positive for human herpesvirus-8. This case not only illustrates a rare case of KS found in an HIV-negative individual, but it also highlights the importance of considering an alternative diagnosis in a patient refractory to medical treatment. We discuss the management and care of an ulcerative colitis patient diagnosed with KS on immunosuppressive therapy.

Key words: Kaposi sarcoma; Colorectal cancer; Ulcerative colitis; Inflammatory bowel disease; HIV/AIDS; Human herpesvirus-8

Core tip: Kaposi sarcoma (KS) is associated with human herpes 8 virus infection and is typically an acquired immune deficiency syndrome defining illness. However, KS may also be seen in patients who are on long-term immunosuppression. Review of the literature suggests that isolated gastrointestinal KS is a very rare complication, as there are less than 20 reported cases in the English language literature in ulcerative colitis HIV negative

host. Our findings contribute to a small body of literature illustrating the manifestation of primary gastrointestinal KS without skin manifestations in a patient with refractory colitis to medical management.

Duh E, Fine S. Human herpesvirus-8 positive iatrogenic Kaposi's sarcoma in the setting of refractory ulcerative colitis. *World J Clin Cases* 2017; 5(12): 423-427 Available from: URL: http://www.wjgnet.com/2307-8960/full/v5/i12/423.htm DOI: http://dx.doi.org/10.12998/wjcc.v5.i12.423

INTRODUCTION

Kaposi sarcoma (KS) is a vascular neoplasm caused by human herpesvirus-8 (HHV-8) infection in an immunocompromised host. There are four settings in which KS occurs: The classic form (in elderly men of Mediterranean or Eastern European background), the endemic form (in individuals of African background), the HIV-associated form, and the iatrogenic form[1]. The latter form is most commonly seen after solid organ transplantation. There are, however, several case reports of colonic KS associated with ulcerative colitis, typically in refractory cases requiring either intermittent or continuous corticosteroids. Interestingly, no association has been noted between the development of KS and duration of ulcerative colitis (UC) disease activity[2]. The relationship between KS and corticosteroid dose or duration of therapy has not been deeply explored, though there have been case-control studies that suggest oral corticosteroid use is independently associated with increased risk of classical KS[3]. Clinical manifestations may include characteristic skin lesions (not present in this case) or intraluminal vascular-appearing colonic tumors. The lack of skin lesions in primary gastrointestinal KS makes the diagnosis challenging. We report a case of a HIV-negative patient with refractory ulcerative colitis who was diagnosed with KS on histopathological examination of rectal tissue.

CASE REPORT

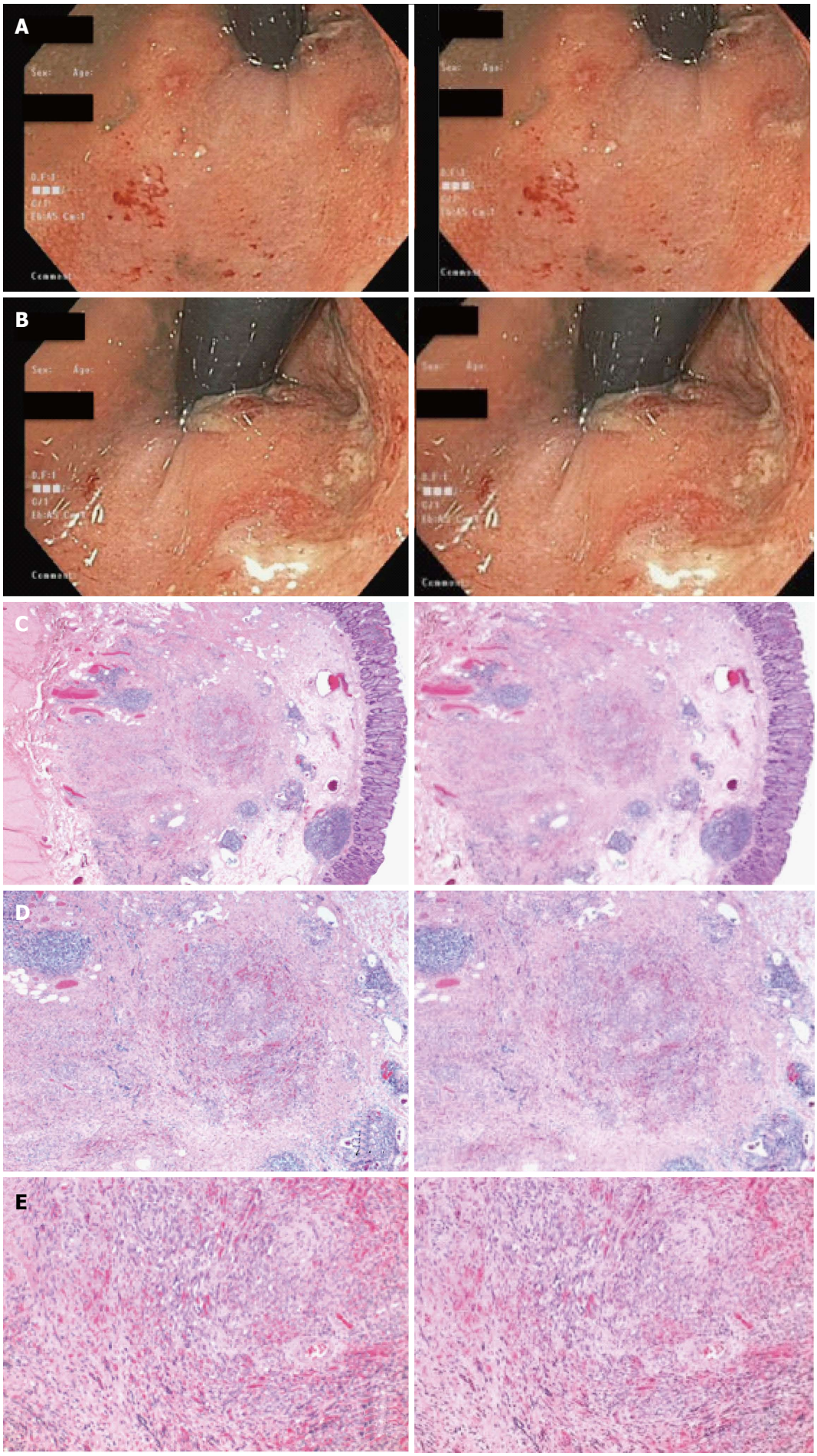
A 48-year-old man with a long-standing history of left-sided UC for 25 years presented to the hospital with fever, nausea, diarrhea and hematochezia for four days. His UC had become increasingly refractory the year prior to presentation with numerous flares that were managed with steroids. Attempts to taper and withdraw steroids had led to multiple relapses. He was started on azathioprine just eight months prior to his presentation and the remainder of his medication at the time of admission included prednisone and pantoprazole.

His exam at the time of presentation was largely unremarkable with a soft, non-tender abdomen without rebound or guarding and no evidence of skin rashes. Vital signs included a temperature of 98.6 °F, a heart rate of 62 bpm, and a blood pressure of 143/84 mmHg. Labs were notable for a hemoglobin of 12.3 g/dL (13.5-16), WBC of 10.1 × 10^9/L (3.5-11) and a negative HIV antibody. A CT scan of the abdomen showed sigmoid wall-thickening, luminal narrowing and surrounding inflammatory stranding with a small fluid collection. He was diagnosed with sigmoid diverticulitis complicated by a 3 cm abscess that was felt to not be amenable to drainage. Blood cultures were positive for Klebsiella and he was treated with a fourteen-day course of antibiotics. A colonoscopy was performed following resolution of acute diverticulitis and revealed a tumor in the rectum (Figure 1A and B). Biopsies of the distal colon revealed focal active colitis and proximal biopsies of the left colon demonstrated crypt architectural irregularities and paneth cell metaplasia consistent with quiescent colitis. Histologic sections of the rectal tumor demonstrated a cytologically bland spindle cell proliferation interspersed by irregular vascular spaces containing extravasated erythrocytes (Figures 1C-E). By immunohistochemistry, the lesional cells were strongly positive for HHV-8 (Figures 1F and G) and consistent with KS. Esophagogastroduodenoscopy and capsule endoscopy demonstrated that tumor involvement was limited to the rectum. In consultation with a sarcoma specialist, the treatment plan involved an attempt at immune reconstitution by withdrawal of steroids. Over the period of a year, attempts to taper the patient off of steroids by introducing alternative agents (including aloe vera, probiotics, phostatidylcholine and Epigallocatechin-3-gallate) were unsuccessful and led to repeated relapses. Surveillance colonoscopies completed four and seven months following diagnosis revealed persistent Kaposi rectal tumor. The patient went on to have a definitive laparoscopic assisted subtotal colectomy with end ileostomy and since has done well.

DISCUSSION

KS is a rare diagnosis and is typically diagnosed when the classic skin manifestations are present. Isolated gastrointestinal KS may occur in patients with ulcerative colitis as a result of the dysregulated immune response seen in IBD or in combination with medications causing immune suppression. Symptoms and signs of gastrointestinal KS may include diarrhea, bleeding, obstruction, and rarely perforation. A misdiagnosis of refractory ulcerative colitis may occur in part because the initial presentation may mimic a IBD flare with diarrhea and rectal bleeding and may be severe to the point requiring blood transfusions[4]. The reason KS lesions are predisposed to bleeding is that they are angioproliferative tumors. Typically, KS lesions in the intestinal tract tend to localize more to the upper intestinal tract and are less frequently encountered in the large bowel[5].

This is one of the few reported cases in the English language literature of large bowel KS associated with ulcerative colitis in an HIV-negative host with positive HHV-8 immunohistochemistry. Infection with HHV-8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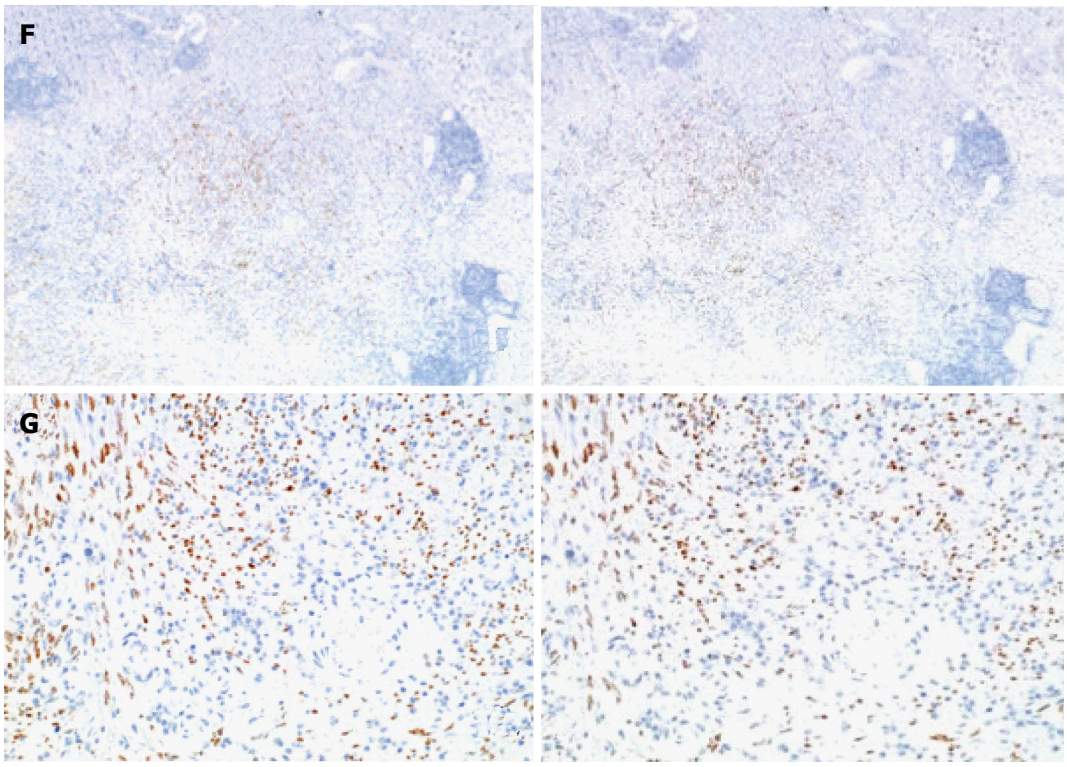

Figure 1 Colonoscopy, histologic and immunohistochemistry. A: A colonoscopy was performed following resolution of acute diverticulitis, revealing a tumor in the rectum. Biopsies of the colon revealed distal focal active colitis as well as more proximal crypt architectural irregularities and paneth cell metaplasia consistent with quiescent colitis; B: A colonoscopy was performed following resolution of acute diverticulitis, revealing a tumor in the rectum. Biopsies of the colon revealed distal focal active colitis as well as more proximal crypt architectural irregularities and paneth cell metaplasia consistent with quiescent colitis; C: Histologic sections of the rectal tumor demonstrated a cytologically bland spindle cell proliferation interspersed by irregular vascular spaces containing extravasated erythrocytes (2 ×); D: Histologic sections of the rectal tumor demonstrated a cytologically bland spindle cell proliferation interspersed by irregular vascular spaces containing extravasated erythrocytes (4 ×); E: Histologic sections of the rectal tumor demonstrated a cytologically bland spindle cell proliferation interspersed by irregular vascular spaces containing extravasated erythrocytes (10 ×); F: By immunohistochemistry, the lesional cells were strongly positive for human herpesvirus-8 and consistent with Kaposi's sarcoma (4 ×); G: By immunohistochemistry, the lesional cells were strongly positive for human herpesvirus-8 and consistent with Kaposi's sarcoma (10 ×).

is a known precedent to the development of all types of KS and has been found in over 95% of cases[5]. The literature shows that only a small proportion of HHV-8 infected people develop Kaposi Sarcoma, suggesting that additional iatrogenic causes such as immunosuppressive drugs could cause viral reactivation, and contribute to the development of KS[6].

Corticosteroid use was first implemented in the 1950's for the management of Ulcerative colitis and has played a pivotal role in decreasing mortality[7]. However, over the years evidence has demonstrated poor outcomes for patients who remain on longterm steroids, notably an increased risk for infections and mortality[8]. In the first population-based field study of classical Kaposi sarcoma, use of oral corticosteroids showed a increased risk for the development of KS (OR = 2.34, 95%CI: 1.23-4.45)[3]. KS has also been reported to be higher in illnesses that are commonly treated with corticosteroids including asthma and rheumatic diseases[9,10]. Studies have shown that glucocorticoids can induce KS and drive progression in multiple different clinical settings through interactions with the gene Transforming growth factor-β (TGF-β). This gene has several effects, one of which is inhibition of cell growth. While glucocorticoids have no effect on the actual transcription of TGF-β, the medication does decrease activation of the TGF-β gene by downregulating plasminogen activator and plasminogen activator receptor, which are known to drive the TGF-β activation pathway[13]. Thus, glucocorticoids reduce levels of plasmin, which prevents activation of TGF-β, and in turn decreases its inhibitory effects on KS cells[11].

Diagnosis of KS in the absence of characteristic skin lesions can be difficult as colonic KS development starts in the submucosa and standard biopsies may not prove diagnostic. Therefore if there is a high suspicion, "bite on bite" biopsies should be taken with large forceps, which may improve the diagnostic yield[6]. When the mucosa is involved, tumors may appear similar to pseudopolyps. Cross sectional imaging may only demonstrate colonic wall thickening. Serum PCR for HHV-8 is an available test that may be useful in the diagnosis and in guiding decision for early surgical management[12]. Treatment consists of immune reconstitution and should be pursued to prevent systemic dissemination of disease[5]. Withdrawal of immunosuppressive agents, which often requires surgical colonic resection, can lead to regression or cure of KS lesions. Lastly, involvement of a multidisciplinary treatment team is vital to coordination of care and ensuring resolution of the disease.

COMMENTS

Case characteristics
Patient's symptoms included fever, nausea, diarrhea, and hematochezia.

Clinical diagnosis
Patient was found to have a rectal tumor consistent with Kaposi sarcoma (KS) after having had surveillance colonoscopies completeded.

Differential diagnosis
Ulcerative colitis flare, vascular transformation of lymph nodes, CMV colitis, infectious colitis.

Laboratory diagnosis
Labs were notable for a hemoglobin of 12.3 g/dL (13.5-16), WBC of 10.1 × 10^9/L (3.5-11) and a negative HIV antibody.

Imaging diagnosis
Esophagogastroduodenoscopy and capsule endoscopy demonstrated that tumor involvement was limited to the rectum.

Pathological diagnosis
Histologic sections of the rectal tumor demonstrated a cytologically bland spindle cell proliferation interspersed by irregular vascular spaces containing extravasated erythrocytes, which on immunohistochemistry were positive for human herpesvirus-8 and consistent with KS.

Treatment
The patient underwent multiple failed attempts to withdraw his regimen of oral corticosteroids, and ultimately received a laparoscopic assisted subtotal colectomy with end ileostomy and since has done well.

Term explanation
Refractory: Resistant to a process or stimulus, in the context of medicine this term often refers to being resistant to treatment. Immunosuppression: Reduction of the activation or efficacy of the immune system

Experiences and lessons
This particular patient's case highlights the importance in considering the diagnosis of KS in the setting of ulcerative colitis patients, as failure to do so delay treatment.

Peer-review
This patient case illustrates the manifestation of primary gastrointestinal KS in a patient with refractory colitis to medical management.

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CASE REPORT

Sickle-cell and alpha-thalassemia traits resulting in non-atherosclerotic myocardial infarction: Beyond coincidence?

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Abstract

Alpha-thalassemia trait and sickle trait are not commonly considered risk factors of ischemic heart disease. We report the case of a non-atherosclerotic silent myocardial infarction in a 46-year-old woman, carrier of the alpha-thalassemia trait (homozygous deletion of locus -3.7) combined with sickle cell trait. While the patient was included as healthy volunteer for a metabolic study, we performed cardiac magnetic resonance imagery showing a left ventricle apicolateral myocardial infarction. Coronary computed tomography angiography showed normal coronary arteries with a coronary calcium score of 0. The patient was treated with low-dose aspirin in secondary prevention afterwards. This case allows us to discuss cardiovascular risk among patients presenting with both alpha-thalassemia trait and sickle cell trait and the indication of cardiac imagery in such patients even when considered as low-cardiovascular risk.

Key words: Alpha-thalassemia trait; Sickle-cell trait; Non-atherosclerotic myocardial infarction; Cardiovascular risk

factor; Coronary computed tomography angiography

Core tip: Alpha-thalassemia trait and sickle trait are not considered risk factors of ischemic cardiopathy. We reported the case of a non-atherosclerotic silent myocardial infarction in a 46-year-old woman, carrier of the alpha-thalassemia trait combined with sickle cell trait. While the patient was included as healthy volunteer for a metabolic study, we performed cardiac magnetic resonance imagery showing a left ventricle apicolateral myocardial infarction. Coronary computed tomography angiography showed normal coronary arteries with a null calcium score. The patient was treated with low-dose aspirin in secondary prevention afterwards. This case allows us to discuss cardiovascular risk among patients presenting with alpha-thalassemia trait and sickle cell trait.

Nguyen LS, Redheuil A, Mangin O, Salem JE. Sickle-cell and alpha-thalassemia traits resulting in non-atherosclerotic myocardial infarction: Beyond coincidence? *World J Clin Cases* 2017; 5(12): 428-431 Available from: URL: http://www.wjgnet.com/2307-8960/full/v5/i12/428.htm DOI: http://dx.doi.org/10.12998/wjcc.v5.i12.428

INTRODUCTION

Sickle-cell trait and alpha-thalassemia trait are associated in 10% of sub-Saharan population. Both are asymptomatic. The cardiovascular risk associated with both traits is unknown. We here report the case of a 46-year-old female patient, asymptomatic, who was diagnosed with both traits and a silent non-atherosclerotic myocardial infarction. This case raises the question of performing cardiac imagery in such patients and assessing their cardiovascular risk.

CASE REPORT

We report the case of a 46-year-old female patient of Erythrean origin who was included as healthy volunteer in a French observational trial on lipid metabolism during which blood analyses and cardiac magnetic resonance imaging (cMRI) were performed. Presence of myocardial silent infarction was measured using cMRI by evaluating presence and quantification of late gadolinium enhancement (LGE). In addition to LGE, cine SSFP acquisitions were acquired in the left ventricle (LV) to characterize its function and morphology. She had no known prior medical history or cardiovascular symptoms and her only cardiovascular risk factor was a light smoking habit (< 4 pack-years) with normal lipid levels (total-cholesterol = 162 mg/dL, LDL-cholesterol = 94 mg/dL, HDL-cholesterol = 53 mg/dL, triglycerides = 74 mg/dL), normal fasting glucose (4.8 mmol/L) and normal blood pressure (systolic 119 mmHg, diastolic 70 mmHg). Her Framingham risk for cardiovascular ischemic events was very low (less than 1% over 10 years). She had previously been included as a healthy volunteer in other studies and had never been diagnosed with any medical condition. Electrocardiogram (ECG) at inclusion did not show any sign of existing ischemia. Transthoracic echocardiography was considered normal, without any left ventricle wall anomaly. cMRI revealed subendocardial late gadolinium enhancement in one latero-apical segment (Figure 1) compatible with localized silent myocardial infarction. LV mass was 106.2 g (60 g/m^2), LV end diastolic and systolic volumes were respectively 168 mL (95.5 mL/m^2) and 84 mL (47.7 mL/m^2). LV ejection fraction was 50%. Subsequent computed tomography coronary angiography did not show any coronary lesions or plaques and coronary calcium score was 0 (Figure 2). Blood analysis showed normal hemoglobin (Hb) at 13.2 g/dL and Hb electrophoresis revealed a previously unknown HbS proportion of 23.8%. Further genetic analyses finally showed she carried the alpha-thalassemia trait (ATT) (homozygous deletion of locus -3.7) and sickle cell trait (heterozygous for beta-globin mutation 6 Glu-> Val), which had never been diagnosed before. She was later treated in secondary prevention by low-dose aspirin (75 mg/d) and remained asymptomatic during a 6-mo follow-up.

DISCUSSION

Etiology and demographics

Association between alpha-thalassemia and sickle cell trait is frequent with a 10% estimated prevalence, in sub-Saharan Africa from where our patient originates[1,2]. We hereafter discuss this association with cardiovascular outcomes.

Clinical and imaging findings

While alpha-thalassemia major and intermedia (= hemoglobin H disease) have been associated with an increased thrombotic risk[3], alpha-thalassemia minor (= alpha-thalassemia trait) is not considered to increase the risk of ischemic or thrombotic events. Similarly, sickle cell disease is associated with non-atherosclerotic myocardial infarction but sickle cell trait has not been shown to be associated with an increased risk of ischemic events[4].

On the other hand, sickle cell trait carriers have an increased risk of sudden death of unclear pathophysiology[5]. This risk is increased during intensive physical exercise. Hypotheses involve a lowering of pH, an increase in body temperature and concomitant dehydration, all thought to initiate intravascular sickling due to HbS polymerization. This may result in an increase of concentrations of deoxygenized HbS leading to diffuse microvascular obstruction[6].

The most prevalent cause of sudden death in this setting is fatal arrhythmia associated with ischemic

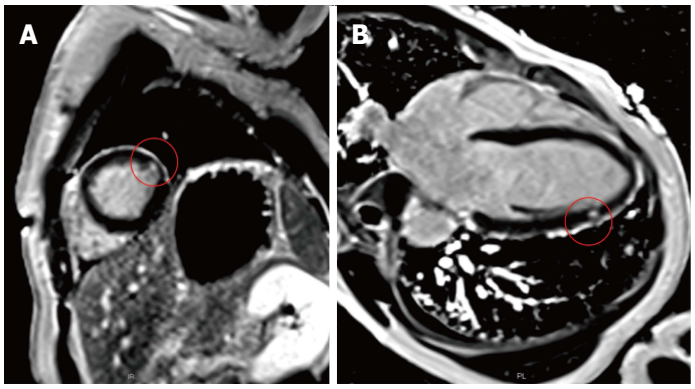

Figure 1 Forty-six-year-old woman, carrier of sickle-cell trait and alpha-thalassemia trait, presenting with silent myocardial infarction. Findings and technique Cardiac magnetic resonance imaging showing (red circle) focal subendocardial late gadolinium enhancement in one apical-lateral segment (75% transmurality). A: Short axis view of the left ventricle with late gadolinium enhancement imaging using a Phase Sensitive Inversion Recovery (PSIR) sequence, 10 min after gadolinium infusion; B: F chamber view in PSIR sequence, 10 min after gadolinium infusion.

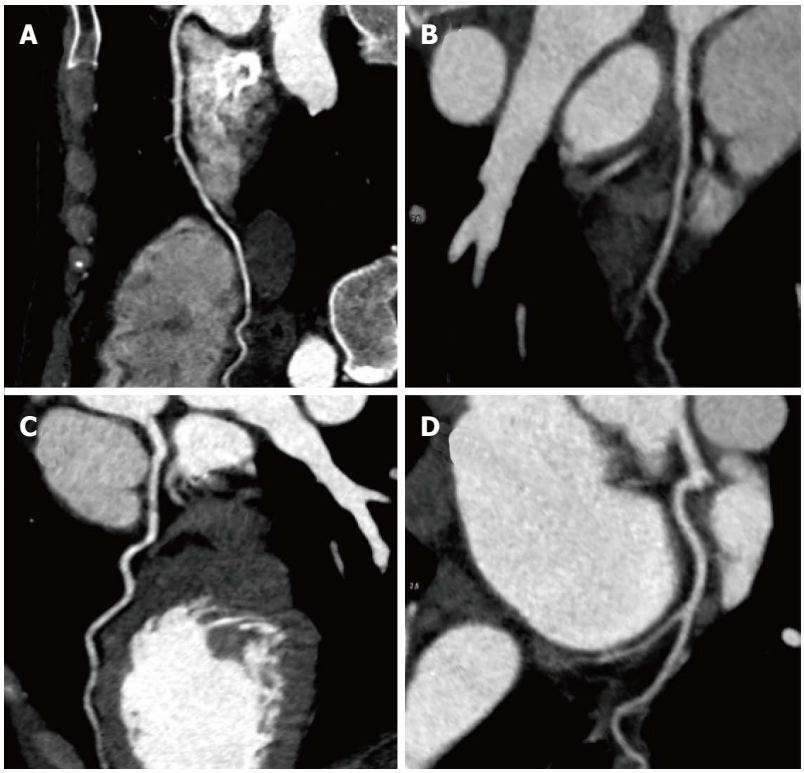

Figure 2 Forty-six-year-old woman, carrier of sickle-cell trait and alpha-thalassemia trait, presenting with silent myocardial infarction. Findings and technique Computed tomography coronary angiography showing normal coronary arteries with no plaque and a global calcium coronary score = 0. A: Right coronary artery; B: Diagonal branch; C: Left coronary artery; D: LIV: Left interventricular coronary artery.

heart disease[7]. Deriving from our case, we hereafter suggest a potential series of events, which may lead to sudden death among sickle cell trait carriers.

Cardiac MRI, a highly sensitive non-invasive myocardial imaging technique, demonstrated the presence of localized silent myocardial infarction. Mechanisms of infarction which have been suggested in the context of sickle cell trait include: (1) rheological factors of altered viscosity and membrane flexibility contributing to microcirculatory stasis; (2) lower platelet survival during sickle cell crisis; and (3) vasospasm[8].

Our patient being a mild smoker, she had an increased procoagulant state[9]. This prothrombotic, proatherogenic state may in turn have favored the formation of micro-thrombi, especially in the distal portion of the myocardial vasculature. Combining this procoagulant state with sickle cell trait may explain why the infarction remained localized without any other signs of atherosclerosis. This is a common feature of infarction among patients presenting with sickle cell disease[4].

Hence, this myocardial scar may represent a substrate for potential ventricular arrhythmia, with physical exercise increasing the risk of sudden death.

Treatment and prognosis

No guideline exists on the use of aspirin for the prophylaxis of ischemic events. A study on prevention of stroke among patients suffering from sickle cell disease is ongoing but results have yet to be published (NCT00178464).

Prognosis of silent myocardial infarction is hard to assess; as by definition, it is asymptomatic. However, with an estimated prevalence of 10% carriers of both sickle-cell and alpha-thalassemia traits in sub-Saharan Africa and a sudden death rate of 0.8/1000 person-year, the annual rate of sudden death associated with this disease would be tremendous.

Differential diagnosis

Coronary artery disease was ruled out by computed tomography coronary angiography, reference imagery in such case of a young woman not presenting with any other cardiovascular risk factor[10].

Silent myocardial infarction can of course be caused by regular cardiovascular risk factors such as smoking in this particular case. Thus, it would be relevant to conduct a large study on carriers of sickle-cell and alpha-thalassemia traits regarding ischemic cardiac disease and independent-related risk factors.

Teaching point

This case raises the importance and pertinence of performing cMRI among asymptomatic patients, and particularly those at higher cardiovascular risk. Patients presenting sickle-cell and alpha-thalassemia traits may be included in this category.

COMMENTS

Case characteristics

Patient was asymptomatic.

Clinical diagnosis

She presented an association of sickle-cell trait and alpha-thalassemia trait, resulting in a silent myocardial infarction.

Differential diagnosis

Myocardial infarction are mostly atherosclerotic, hence, coronary imagery was required.

Laboratory diagnosis

Hemoglobin electrophoresis confirmed the sickle-cell and alpha-thalassemia trait.

Imaging diagnosis

Computed tomography coronary angiography and cardiac magnetic resonance imaging (cMRI) confirmed diagnosis of myocardial infarction and ruled out atherosclerotic cause.

Treatment

Aspirin was given in secondary prevention.

Related reports

Lubega *et al*. Alpha thalassemia among sickle cell anaemia patients in Kampala, Uganda. *Afr Health Sci* 2015; 15: 682-689.

Term explanation

Alpha-thalassemia trait is also known as alpha-thalassemia minor.

Experiences and lessons

Performing cMRI among asymptomatic patients, such as alpha-thalassemia and sickle-cell trait carriers may be acceptable.

Peer-review

This study features the rare finding of myocardial infarction in a case of sickle cell and alpha-thalassemia traits.

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CASE REPORT

Taeniasis: A possible cause of ileal bleeding

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Author contributions: Settesoldi A collected and analyzed the patient's clinical data, wrote and reviewed the manuscript; Tozzi A designed the report and reviewed the manuscript; Tarantino O designed the report and reviewed the manuscript.

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Abstract

Taenia spp. are flatworms of the class Cestoda, whose definitive hosts are humans and primates. Human infestation (taeniasis) results from the ingestion of raw meat contaminated with encysted larval tapeworms and is considered relatively harmless and mostly asymptomatic. Anemia is not recognized as a possible sign of taeniasis and taeniasis-induced hemorrhage is not described in medical books. Its therapy is based on anthelmintics such praziquantel, niclosamide or albendazole. Here we describe a case of acute ileal bleeding in an Italian man affected with both *Taenia* spp. infestation resistant to albendazole and *Helicobacter pylori*-associated duodenal ulcers.

Key words: *Taenia* spp.; Intestinal bleeding; Iron-deficiency anemia; Endoscopy

Core tip: The novel contribution of our paper is to draw attention to taeniasis as a possible cause of gastrointestinal bleeding, since anemia is so far not recognized as a possible sign of taeniasis nor is taeniasis-induced hemorrhage described in medical text books. With this report we describe a case of ileal bleeding most probably caused by this kind of infestation. Our objective is to make clinicians aware of this rare but possible situation. Taeniasis should be therefore taken into account in the differential diagnosis of melena and/or hematochezia.

Settesoldi A, Tozzi A, Tarantino O. Taeniasis: A possible cause

of ileal bleeding. *World J Clin Cases* 2017; 5(12): 432-436 Available from: URL: http://www.wjgnet.com/2307-8960/full/v5/i12/432.htm DOI: http://dx.doi.org/10.12998/wjcc.v5.i12.432

INTRODUCTION

Taenia spp. are flatworms of the class Cestoda, whose definitive hosts are humans and primates. Human infestation (taeniasis) results from the ingestion of raw or undercooked meat contaminated with encysted larval tapeworms (cysticercosis), which subsequently exit the cyst and reach lengths of 3.6-7.5 m in the human gut. In Italy taeniasis incidence is 0.02%-0.04%, while cysticercosis prevalence is 0.02%-2.4%[1]. Taeniasis is relatively harmless and clinically asymptomatic. In sporadic cases it can cause loss of appetite, weight loss, abdominal pain, diarrhea or constipation, dizziness, headaches or nausea. Anemia is not recognized as a possible sign of taeniasis nor is taeniasis-induced hemorrhage described in medical text books[2]. Nevertheless there are some reports in medical literature which consider such associations possible[2-6]. Taeniasis therapy is commonly based on the use of anthelmintics like praziquantel, niclosamide or albendazole. Here we describe a case of acute ileal bleeding in an Italian man affected with both *Taenia* spp. infestation resistant to albendazole and *Helicobacter pylori* (*H. pylori*)-associated duodenal ulcers.

CASE REPORT

In March 2016 a 77-year-old Italian man attended the Emergency Room of San Giuseppe Hospital in Empoli. He was a retired farmer, who had been suffering from hematochezia together with melena for two weeks. His vital parameters were normal. In his medical history there was chronic atrial fibrillation, for which he was taking rivaroxaban 20 mg/d and digoxin 0.125 mg/d, and prior cholecystectomy. He weighed 68 kg, was 170 cm tall (body mass index 23.5). Digital rectal examination revealed the presence of melena. A nasogastric tube was inserted, with no evidence of gastric blood traces. Laboratory tests showed anemia (Hb 5.1 g/dL). The patient underwent blood transfusions and esophagogastroduodenoscopy (EGD), which showed a small hiatal hernia, bile in the stomach and a 10 mm duodenal fibrinous ulcer. We decided to suspend rivaroxaban and start low molecular weight heparin. Continuous intravenous infusion of pantoprazole was administered and the patient was admitted to the Gastroenterology Department.

In the following days he continued to bleed and required further blood transfusions. He also underwent several EGDs, which confirmed the previous findings and allowed us to get biopsies in the antrum for rapid urease test and on the ulcer margins for histology assessment. We also used argon plasma coagulation on the oozing borders of the ulcer, with consequent bleeding cessation. The rapid urease test was positive for *H. pylori* and the patient started eradication treatment. The biopsies of the ulcer margins demonstrated regenerative hyperplasia on productive inflammation.

Despite endoscopic therapy, the patient still complained of melena and hematochezia. He underwent ileocolonoscopy, which showed bright red blood in ileum and colon, without identification of the bleeding source. We performed a contrast-enhanced computed tomography (CT) scan of the abdomen and of the abdominal aorta, which showed no bleeding cause and only minor findings like parietal calcifications of blood vessels, a small hepatic cyst, diffuse moderate intra- and extrahepatic biliary ducts dilation and benign prostatic hyperplasia. We then decided to use wireless capsule endoscopy (WCE), which described two duodenal fibrinous ulcers (5 and 10 mm) without signs of recent bleeding, the presence of a tapeworm, starting from 1 h 45 min until 4 h 28 min after WCE ingestion (Figures 1 and 2) and plentiful dark red blood in the colon, lighter in the proximal regions.

The patient reported only then, that he had occasionally eaten raw beef and that he had taken mebendazole 5 mo before, because of suspected oxyuriasis. The patient received albendazole 400 mg/d for five days, since this drug was suitable for taeniasis and already available in the department.

While on albendazole, he still complained about melena and iron-deficiency anemia (IDA) (Hb 9 g/dL, Hct 27%, RDW-CV 17%, iron 27 μg/dL, ferritin 53 ng/mL), with constant need of blood transfusions. He also stated he had not discharged the head of the tapeworm yet. We performed the last EGD, which demonstrated healing of the ulcers, with no bleeding signs. The second ileocolonoscopy was comparable to the first one, hence we decided to give him a second WCE after discontinuation of albendazole, which demonstrated persistence of the tapeworm starting from jejunum to the whole ileum (last visualization at 4 h 25 min) and plentiful dark red blood in the colon, lighter in the proximal regions (Figures 1 and 2).

We consulted an infectious disease specialist for a change of therapy after albendazole failure. He advised to give the patient niclosamide 2 g in a single administration and then to initiate bowel preparation with macrogol. After niclosamide and bowel preparation we performed the last ileocolonoscopy, which displayed no blood in ileum or colon and 2 non polypoid lesions in the caecum that we removed *via* loop electrosurgical excision procedure. Histology revealed those lesions to be intestinal tubular adenomas with low grade dysplasia.

The day after niclosamide administration, the patient felt a lot better. Melena and rectal bleeding had finally stopped and after two more days he noticed the complete excretion of the tapeworm head. Since his condition was improving, we decided to dismiss him.

He was seen at follow-up visit in mid-June 2016,

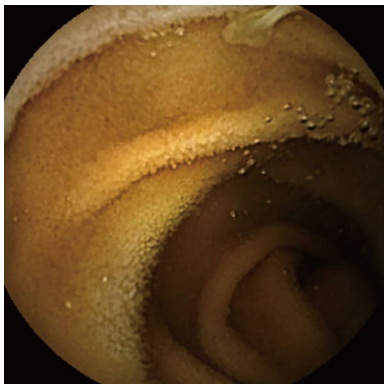

Figure 1 Head of the tapeworm attached to the jejunum at videocapsule endoscopy.

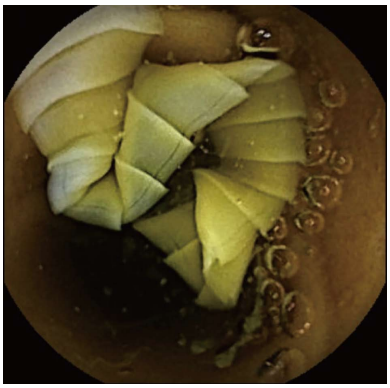

Figure 2 Body of the tapeworm in the ileum at videocapsule endoscopy.

where he stated he was feeling good and had no more rectal bleeding. He performed fecal obscure blood test and *H. pylori* stool antigen test, both showing negative results. His hemoglobin had reached 11.3 g/dL by then, with a positive trend. He underwent ova and parasite fecal exams at 2, 4 and 6 mo after dismission, none of which showed relapse of the infestation.

DISCUSSION

Among the currently accepted causes of iron-deficiency anemia, infestations with *Ascaris lumbricoides*, *Trichuris trichiura*, *Necator americanus* and *Ancylostoma duodenale* are reported, while taeniasis is not mentioned[7].

Likewise, no parasitic infection is officially listed as a cause of upper or lower gastrointestinal (GI) bleeding[8,9].

Even if not conventionally accepted, the association between anemia and/or hemorrhage and taeniasis has already been reported in a few other case reports.

In 1989 Ali *et al*[3] found anemia in 50 urban and rural Egyptians, suffering from various parasitic infestations, among which *T. saginata*.

De Simone *et al*[4] described *T. solium* as the only cause of IDA secondary to acute intestinal bleeding in a woman, who had underwent surgical enterotomy for suspected angiodysplasia.

A case of *T. saginata* infestation causing macrocytic anemia was reported by Vuylsteke *et al*[5] in 2004. The tapeworm and adjacent erosions were seen in the terminal ileum at colonoscopy and the patient recovered after therapy with niclosamide[5].

In 2007 Barnett *et al*[2] published a case of a 7-year old boy suffering from IDA, whose colonoscopy showed taeniasis after repeated normal stool examination. The tapeworm was not regarded as the cause of his anemia and 7 years later anemia recurred. Upper and lower endoscopy were negative and the boy underwent WCE, that found *Taenia* spp. in the mid jejunum, together with ulcers and areas of denuded mucosa.

A case of melena similar to ours was reported by Howell *et al*[6] in 2008. Their patient showed a pylorus ulcer and a vascular duodenal lesion at EGD, which were treated with adrenaline, electrocautery and *H. pylori* eradication, without recovery of the symptoms. A later WCE revealed taeniasis in mid-jejunum, with small erosions, without active bleeding.

In Western countries intestinal parasite infestations are rarely taken into account in the diagnostic work-up of anaemia or GI hemorrhage[4]. In our case anemia could have been attributed at first to the presence of *H. pylori*-associated duodenal ulcers, but melena and hematochezia persisted despite the healing of the ulcers, observed at repeated EGDs and at WCE. While, on the contrary, these two signs stopped after niclosamide therapy and subsequent expulsion of the tapeworm.

The mechanisms that cause digestive bleeding in taeniasis are still poorly understood and could be related to erosions of the bowel mucosa caused by the parasite[4]. Mucosal injury might be determined either directly, by the movement and feeding of the parasite or indirectly, by the host's immune response[5]. Healing of the ulcers has been described after eradication of the tapeworm[2].

Our patient had already taken mebendazole for suspected oxyuriasis 5 mo before. We can speculate that he had taeniasis rather than oxyuriasis and that he saw proglottids instead of pinworms in his feces. Mebendazole is, in fact, not indicated in taeniasis. The majority of people with taeniasis have a single tapeworm in their GI tract and *Taenia* spp. can survive up to 30 years[6].

Stool examination is not a very sensitive test for the diagnosis of taeniasis, because of the need of full maturation of the tapeworm, that can take a lot of months. Differentiation between *T. saginata* and *T. solium* can be obtained from a careful examination of fecal proglottids[6]. Unfortunately we could not perform such examination, since the tapeworm and its proglottids were never collected.

The finding of a tapeworm during an EGD is quite rare. *Taenia* spp. usually attach to the upper jejunum, because their scolex becomes evaginated under digestive enzyme stimuli in that site[10]. Most often, the diagnosis

is made during a colonoscopy or a WCE. According to international guidelines for the management of obscure GI bleeding or unexplained IDA, WCE is indicated after negative upper and lower GI endoscopy[11]. De Simone, Barnett and Howell initially used upper and/or lower endoscopy to diagnose the cause of the blood loss. These procedures didn't reveal the tapeworm. The diagnosis could only be obtained using WCE[2,4,6]. WCE allows physicians to have a look at the entire bowel, especially at those intestinal tracts that are not reachable by EGD or colonoscopy. Our case, as well, highlights the ability of WCE to diagnose taeniasis and to follow abnormalities after treatment[2].

Our patient was a retired farmer who occasionally ate raw beef. We can speculate his rural family background and poor education have led him to take this habit. In any case, we have no evidence for any specific demographics, that could include an increased number of raw meat eaters.

Treatment of taeniasis includes praziquantel (5-10 mg/kg, single-administration) or niclosamide (2 g, single-administration after a light breakfast followed after 2 h by a laxative). Treatment of human cysticercosis includes praziquantel and/or albendazole, corticosteroids and/or anti-epileptic drugs[12]. Asymptomatic cysticercosis requires no treatment. In 1991 De Kaminsky RG treated 56 individuals suffering from taeniasis with albendazole 400 mg for 3 d. All of them discharged the tapeworm and remained stool-negative after 60 and 90 d. Of the 21 *Taenia* spp. recovered, 4 were *T. saginata*, 15 were *T. solium* and 2 could not be identified. Albendazole seemed to be well-tolerated and very effective[13]. Nevertheless albendazole resistance cases have been described. Màrquez-Navarro *et al*[14] reported a case of albendazole failure in a child with 5-year long-lasting infection. Niclosamide is not absorbed by the GI tract. Therefore it has no activity against cysts and is very safe. Its efficacy is high, with cure rates of approximately 90% against *T. saginata* and *T. solium*. Unfortunately, niclosamide is not easy to find[15]. We also had to wait some days to get it, since our hospital pharmacy didn't have it.

Our case underlines the possible association between taeniasis and digestive bleeding. We recommend investigating raw meat consumption in every patients suffering from obscure anemia. In case of positive history, it is advisable to perform ova and parasite fecal tests, whose negative result should not erase the suspicion of a GI infestation. The use of WCE as diagnostic tool in obscure anemia should be supported, as its ability to reveal the presence of tapeworms, after negative EGD and colonoscopy, has been described in this and other case reports. We suggest to be aware of possible drug resistance, which could be demonstrated by the persistence of the tapeworm, and could be overcome through switching therapy. Taking into account the possible association between taeniasis and small bowel bleeding could spare hospitalization days and allow a better and faster recovery of the patients.

COMMENTS

Case characteristics

The man had been suffering of hematochezia and melena for two weeks, together with fatigue, pallor, exertional dyspnea and retrosternal pain receding with rest.

Clinical diagnosis

The patient weighed 68 kg and was 170 cm tall (body mass index 23.5), his vital parameters were good; he showed melena at the digital rectal examination but no gastric blood traces.

Differential diagnosis

Peptic ulcer, Mallory-Weiss lesion, Dieulafoy lesion, neoplasms, esophagitis, gastritis, duodenitis, polyps, inflammatory bowel disease, diverticula, infectious colitis, angiodysplasia, ischemic colitis.

Laboratory diagnosis

Laboratory tests showed anemia (Hb 5,1 g/dL), that was later defined as iron-deficiency anemia (Hb 9 g/dL, Hct 27%, RDW-CV 17%, iron 27 μg/dL, ferritin 53 ng/mL).

Imaging diagnosis

Esophagogastroduodenoscopy (EGD) showed a duodenal fibrinous ulcer, colonoscopy showed blood in ileum and colon, computed tomography scan showed only minor findings, while wireless capsule endoscopy (WCE) showed the presence of a tapeworm in the jejunum- ileum.

Pathological diagnosis

The rapid urease test was positive for *Helicobacter pylori*, the biopsies of the ulcer margins demonstrated regenerative hyperplasia on productive inflammation, the polyps of the colon turned out to be intestinal tubular adenomas with low grade dysplasia.

Treatment

The patient received albendazole 400 mg/d for five days, and then niclosamide 2 g in a single administration.

Related reports

The association between anemia and/or hemorrhage and taeniasis has already been reported in a few other case reports.

Term explanation

Taeniasis is the human infestation of *Taenia* spp., and results from the ingestion of raw or undercooked meat contaminated with encysted larval tapeworms (cysticercosis).

Experiences and lessons

This case underlines the possible association between taeniasis and acute post-hemorrhagic anemia. The authros recommend investigating raw meat consumption in every patient suffering from obscure anemia, and using WCE as a diagnostic tool in case of negative EGD and colonoscopy.

Peer-review

The authors have described a case of gastrointestinal bleeding in a man infestated with *Taenia* spp., that resolved after taeniasis treatment. The novel contribution of this paper is to draw attention to taeniasis as a possible cause of gastrointestinal bleeding that should be therefore taken into account in the differential diagnosis of melena and/or hematochezia.

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CASE REPORT

Do you want to participate in a clinical study as a healthy control? - Risk or benefit?

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Abstract

A healthy woman volunteered to participate as "healthy control" in a study. An increased level of procalcitonin (PCT) was detected and remained elevated on follow-up measurements. As calcitonin levels were elevated as well, thyroid ultrasound was performed which revealed nodes in both thyroid lobes, one of them showing metabolic activity in positron emission tomography-computed tomography scan. To exclude a malignant thyroid cancer despite the negative findings in a fine needle aspiration the patient underwent thyroidectomy and a medullary thyroid carcinoma (MTC) was detected in the right lobe. MTC is a rare endocrine tumor with a poor prognosis once having spread, therefore early detection remains a priority for the outcome. Screening parameter is serum calcitonin, in absence of infection the pro-hormone PCT can be used as a screening parameter as well with high sensitivity.

Key words: Medullary thyroid cancer; Procalcitonin; Thyroid nodes; Endocrinology; Public health; Healthy control

Core tip: A lady participating as healthy control in a study was found to suffer from a medullary thyroid cancer, a type of cancer in total surgical removal before the tumor has spread is the most important prognostic factor. The difficulty is the low diagnostic accuracy of ultrasound and procalcitonin-computed tomography scan, as well as the limitations of fine needle aspiration in a patient with several nodules. This case illustrates the consequences

of volunteering as a "healthy control" in a clinical study. While early detection of the MCT was possible in our patient it paid off for her, but abnormal test results may also cause harm to patients if being false positive and leading to invasive procedures.

Giessen H, Nebiker CA, Bruehlmeier M, Spreitzer S, Mueller B, Schuetz P. Do you want to participate in a clinical study as a healthy control? - Risk or benefit? *World J Clin Cases* 2017; 5(12): 437-439 Available from: URL: http://www.wjgnet.com/2307-8960/full/v5/i12/437.htm DOI: http://dx.doi.org/10.12998/wjcc.v5.i12.437

INTRODUCTION

In our hospital a study to validate the accuracy of a new assay of procalcitonin (PCT) was conducted and a healthy woman working in our hospital was willing to participate in this study as a healthy control.

PCT is excreted by parenchymatous organs in the presence of bacterial infection. As precursor of calcitonin it is elevated in medullary thyroid cancer (MTC) as well as calcitonin. Frozen serum calcitonin can be used as screening parameter, but several non-specialized laboratories limit the use of calcitonin in MTC[1].

CASE REPORT

A 57-year-old, previously healthy woman working in the Department of Clinical Pathology of our hospital volunteered to participate as "healthy control" in a study to validate the accuracy of a new PCT assay. She reported to be in good general health condition without signs of ongoing infection or disease. The patient did not smoke or consume large amounts of alcohol and had no signs of malignancy on physical examination or routine blood analysis. Yet, a markedly increased level of circulating PCT of 0.35 μg/L (normal range < 0.03 μg/L) was detected, which remained elevated on follow-up measurements for the next 2 mo.

Subsequently, calcitonin levels were found to be elevated as well (33 ng/L, normal range < 5 ng/L). A thyroid ultrasound revealed a goiter with small nodules in both thyroid lobes. There were two suspicious thyroid nodules, a small one lateral in the right thyroid lobe (7 mm × 5 mm × 6 mm) and a larger one (10 mm × 10 mm × 13 mm) in the left lobe. A fine needle aspiration (FNA) of the bigger node on the left side was done but neither reveal any malignant cells nor was it positive for calcitonin staining, making the existence of a MTC unlikely. To exclude a gastrointestinal neuroendocrine tumor or a small cell lung cancer, both of which have been reported to ectopically produce PCT as well, we decided to perform a ^{18}F-FDG positron emission tomography-computed tomography (PET-CT), in which the left thyroid nodule detected on ultrasound showed an increased ^{18}F-FDG uptake. There were no other suspicious lesions in the whole body PET-CT scan (Figure 1).

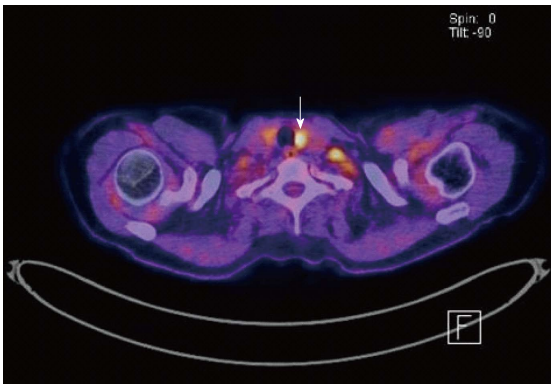

Figure 1 Positron emission tomography-computed tomography scan with ^{18}F-FDG, 2016 February. Arrow: Left thyroid lobe with metabolic active node.

A previously healthy woman willing to support a scientific study was found to have an elevated level of PCT and calcitonin, a goiter, 2 suspicious nodes in the sonography of the thyroid gland with one of them showing metabolic activity in PET-CT scan.

The case was discussed at our internal tumor board, which recommended total thyroidectomy to exclude MTC despite the negative fine needle aspiration as no other cause of elevations in calcitonin and PCT could be found (Figure 2).

The patient agreed to have surgery which went without complications. The histological evaluation of the thyroid gland showed an (incidental) 3 mm papillary microcarcinoma in the left lobe and a 6 mm medullary carcinoma in the right lobe, inconsistent with the active nodule in the left thyroid lobe in PET-CT. No further neck dissection was done due to the relatively low preoperative calcitonin levels.

Two weeks after surgery the patient came back to the endocrine office. Her PCT and calcitonin levels were now undetectable. We recommended close clinical and biochemical monitoring over the next years. Her prognosis is favorable due to the early recognition of the medullary cancer with small tumor volume, in total resection and no signs of metastasis.

DISCUSSION

This case has three key teaching points relevant for clinical care. First, MTC is a rare endocrine tumor accounting for 8% of all thyroid carcinomas[2]. With a five year mortality rate of 50%-70% it represents 14% of all thyroid gland related deaths. Early detection and in total surgical removal before the tumor has spread are the most important prognostic factors to lower mortality in this type of cancer. Due to the poor prognosis of medullary cancer once it has spread, early detection remains a priority[2]. Current guidelines are ambiguous regarding general screening for MTC with calcitonin in the work-up of thyroid nodules, whereas opponents argue it may not be cost-effective[1,3,4]. The challenge in our patient with incidental MTC is the low diagnostic accuracy of ultrasound and the PET-CT scan. In our

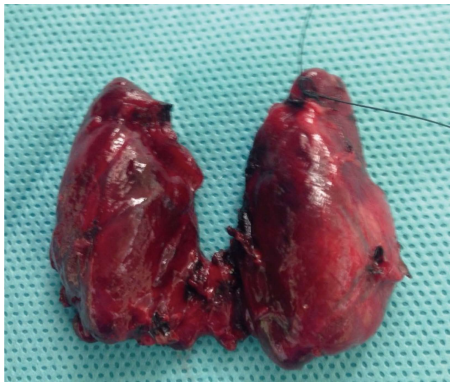

Figure 2 Total thyroidectomie (taken on Jan 17, 2017).

patient, neither test correctly identified or localized the cancer, as retrospectively the metabolically active nodule did not turn out to be malignant. Additionally, fine needle aspiration has limitations particularly sampling bias in a patient with several nodules.

Second, the precursor of calcitonin, PCT became more recently known as an ubiquitously produced biomarker of inflammation and infection. As such it can be used evidence-based in clinical routine guide to diagnosis and antibiotic therapy in respiratory infections and sepsis[5].

As an endocrine tumor marker in the absence of an infection, an elevated ratio of the procalcitonin to calcitonin indicates worse prognosis in patients suffering from MTC[6,7].

Last but not least incidental findings of clinical exams, check-ups, laboratory exams and imaging often occur during diagnostic work-up. This case illustrates possible consequences of volunteering as a "healthy control" in a clinical study. While it most certainly paid off for our patient, abnormal test results may also cause harm to patients if being false positive and leading to invasive procedures. In conclusion, it may become important to discuss risks and benefits when "simply" asking a person to volunteer for a clinical study - even if as an allegedly "healthy control".

ARTICLE HIGHLIGHTS

Case characteristics

Medullary thyroid cancer is a rare cancer that can present with an increased circumference of the throat or a change in voice but is mostly asymptomatic.

Clinical diagnosis

Most medullary carcinoma (MCT) occur sporadic, but in 20% a hereditary pattern (multiple endocrine neoplasia type 2, men 2) is present, a mutation of the RET protooncogene can be found.

Differential diagnosis

MTC is likely to spread lymphogenic to paratracheal and lateral cervical lymph nodes or hematogenous in liver, lungs and bones.

Treatment

The only curative treatment is the total thyroidectomie with removal of all affected tissue in the neck.

Related reports

Systemic chemotherapy with dacarbazine, 5-fluoruracil or doxorubicin has shown a poor response in only 10%-20%.

Experiences and lessons

Regular measurements of serum calcitonin as tumor marker is used and remission is demonstrated by undetectable serum calcitonin.

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CASE REPORT

Embryonal rhabdomyosarcoma in the maxillary sinus with orbital involvement in a pediatric patient: Case report

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Author contributions: Valença AMG, Bonan PRF and de Castro RD designed the report; da Paz AR performed the histopathological and immunohistochemical analyses; de Melo ACR and Ribeiro ILA collected the patient's clinical data; de Melo ACR, Lyra TC and Ribeiro ILA wrote the paper.

Institutional review board statement: This case report was exempt from the Institutional Review Board standards at University Federal of Paraíba.

Informed consent statement: Patient was informed about the publication.

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Abstract

This report presents a case of embryonal rhabdomyosarcoma (eRMS) located in the left maxillary sinus and invading the orbital cavity in a ten-year-old male patient who was treated at a referral hospital. The images provided from the computed tomography showed a heterogeneous mass with soft-tissue density, occupying part of the left half of the face inside the maxillary sinus, and infiltrating and destroying the bone structure of the maxillary sinus, left orbit, ethmoidal cells, nasal cavity, and sphenoid sinus. An analysis of the histological sections revealed an undifferentiated malignant neoplasm infiltrating the skeletal muscle tissue.

The immunohistochemical analysis was positive for the antigens: MyoD1, myogenin, desmin, and Ki67 (100% positivity in neoplastic cells), allowing the identification of the tumour as an eRMS. The treatment protocol included initial chemotherapy followed by radiotherapy and finally surgery. The total time of the treatment was nine months, and in 18-mo of follow-up period did not show no local recurrences and a lack of visual impairment.

Key words: Oncology; Embryonal rhabdomyosarcoma; Pediatrics; Maxillary sinus; Chemotherapy

Core tip: This case report is important because it describes the diagnosis trajectory of a rhabdomyosarcoma located in an uncommon region, presenting the steps of the exams performed and their results. The knowledge must be realized with the intention of improving the diagnosis and the clinical conduct, giving greater survival rate and better quality of life to the patient. The early diagnosis was very important in this case, due to the imaging and histopathological exams in question with the association of experienced pathologists.

de Melo ACR, Lyra TC, Ribeiro ILA, da Paz AR, Bonan PRF, de Castro RD, Valença AMG. Embryonal rhabdomyosarcoma in the maxillary sinus with orbital involvement in a pediatric patient: Case report. *World J Clin Cases* 2017; 5(12): 440-445 Available from: URL: http://www.wjgnet.com/2307-8960/full/v5/i12/440.htm DOI: http://dx.doi.org/10.12998/wjcc.v5.i12.440

INTRODUCTION

Rhabdomyosarcoma (RMS) is a malignant mesenchymal tumour of the skeletal myogenic fibres[1,2] and is considered the most common soft-tissue tumour in children and adolescents, responsible for 50% of all soft-tissue sarcomas. It is the second most common paediatric tumour of the head and neck (after lymphoma) and is most commonly located in the cervical-cephalic region or the genitourinary system[3-5].

RMS is histologically classified as embryonal (eRMS), alveolar (aRMS), pleomorphic (pRMS) and spindle cells and sclerotic type (eRMS). The first two subtypes occur in children and adolescents, with the alveolar subtype being more aggressive than the embryonal subtype, while pleomorphic RMS affects adults[5,6]. The first two subtypes (eRMS and aRMS) are diagnosed based on the expression of myogenic markers, such as transcription factors, MyoD, myogenin, myosin heavy-chain structural proteins, skeletal a-actin, and desmin. These markers connect RMS to a skeletal-muscle lineage, but the tumour may also originate from a non-myogenic cell[5,7]. Thus, although RMS usually originates from within a skeletal muscle, it can also develop in areas devoid of muscle tissue, such as the salivary glands, skull base, biliary tree, and genitourinary tract[5,7,8].

Although some eRMS cases were reported before, few cases presented a complete clinical, imaginologic and microscopic documentation, including follow up description. The present study reports a case of eRMS in the left maxillary sinus with invasion of the orbital cavity in a paediatric patient diagnosed and treated at the Hospital Napoleão Laureano in João Pessoa, PB, Brazil.

CASE REPORT

The patient (10 years old, male, mixed race) was admitted to the Hospital Napoleão Laureano, which is a referral hospital for cancer diagnosis and treatment in Paraíba State, presenting with a large swelling and exophthalmos on the left side of the face in addition to a raised and hardened area in the maxillary region that had appeared approximately 25 d prior. The patient presented no fever and reported feeling pain occasionally. The patient's visual acuity, eye structure, and ocular fundus were normal in both eyes (Figure 1).

A computed tomography (CT) scan of the paranasal sinuses was performed with and without intravenously administered contrast. The images showed a heterogeneous (DM = 32 UH) mass with soft-tissue density, measuring 1.5 cm × 6.2 cm × 5.0 cm, occupying part of the left half of the face inside the maxillary sinus, and infiltrating and destroying the bone structure of the maxillary sinus, left orbit, ethmoidal cells, nasal cavity, and sphenoid sinus. Inflammatory sinus disease was present in the left maxillary sinus and left exophthalmos due to the compression exerted on the eye (Figure 2).

Through an incisional biopsy, an oval tissue fragment of light-brown colour and firm-elastic consistency, measuring 1 cm × 0.8 cm × 0.6 cm, was collected from inside the left maxillary sinus. An analysis of the histological sections revealed an undifferentiated malignant neoplasm infiltrating the skeletal muscle tissue (Figure 3).

An immunohistochemical analysis was performed on a biopsied tumour fragment from the left maxillary sinus. The paraffin block was cut into 3-μm sections, which were analysed using an automated method (Ventana Benchmark GX, Roche Diagnostics) with a multimetric detection system (Ventana ultraView Universal DAB detection Kit, Roche Diagnostics). Positive and negative controls confirmed the reliability of the methods. The microscopic examination was positive for the following antigens: MyoD1, myogenin, desmin, and Ki67 (100% positivity in neoplastic cells) (Figure 4), allowing the identification of the tumour as an eRMS.

The treatment plan combined chemotherapy with radiation therapy; chemotherapy was initially performed for a nine-month period (Vincristine, Dactinomycin, and Cyclophosphamide), combined with 20 radiation fractions (50.4 Gy), and followed by surgical ablation of residual mass on maxillary sinus with ocular globe and

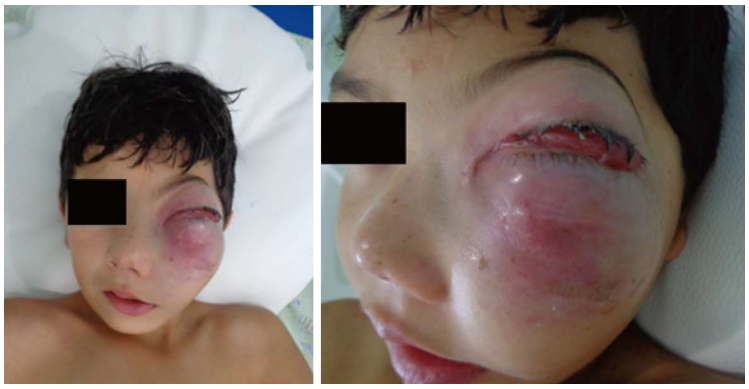

Figure 1 Initial clinical features of the lesion showing a reddish painful firm mass on left side of face with rapid evolution (25 d). This lesion was causing left visual impairment with notorious swelling on facial skin with absence of other obstructive symptoms.

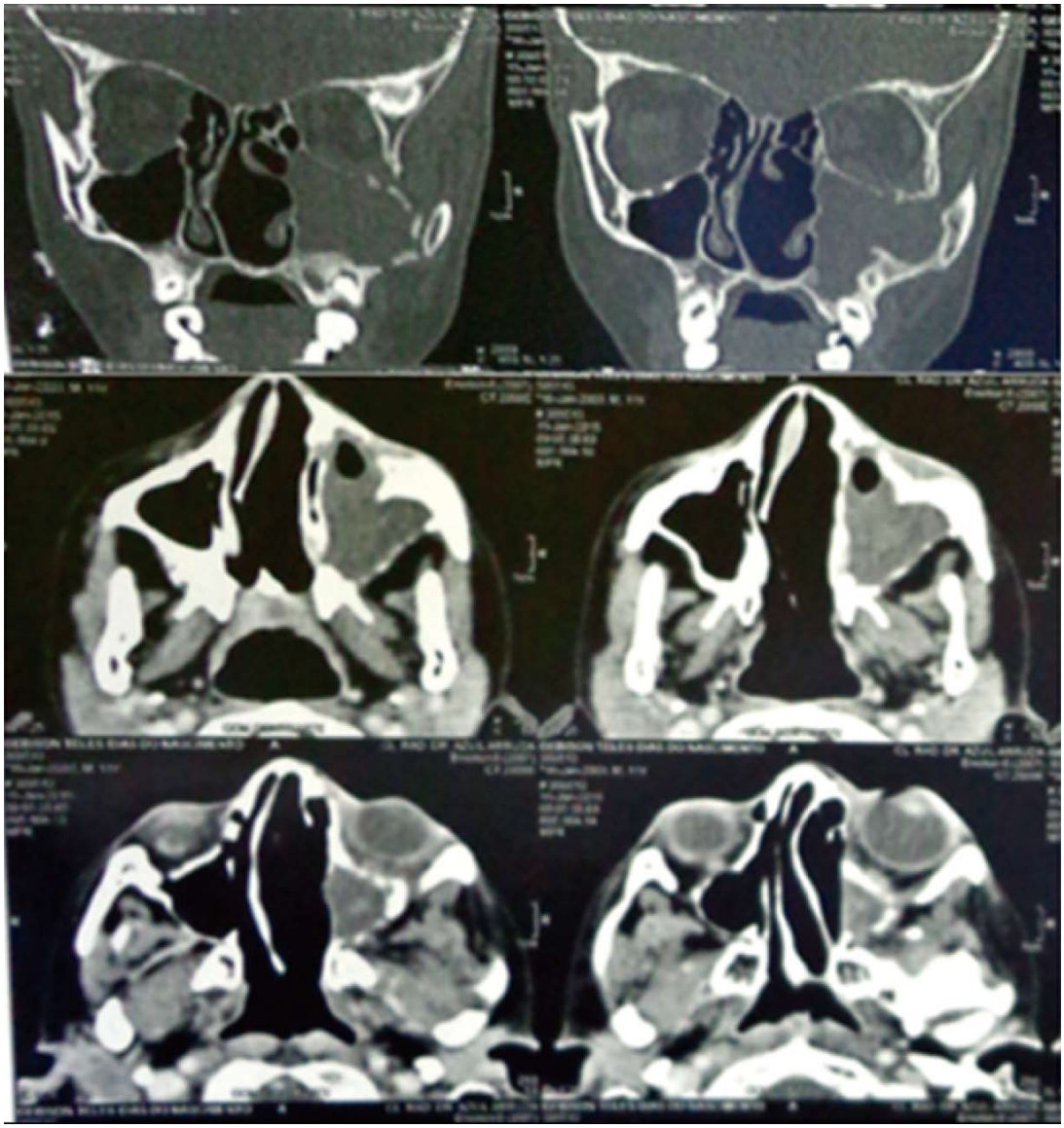

Figure 2 Computed tomography scan of the paranasal sinuses. On coronal view, a diffuse hypodense mass was dislocating lateral wall of left sinus and compressing the inferior border of left orbital structure with tumor invasion. On axial plan, tumor mass was filling the left sinus and a dislocated nasal septum was evident.

optic nerve preservation.

After 2.5 mo of chemotherapy, there was a significant reduction of the tumour mass (Figure 5A). After completion of the treatment (9 mo), the patient

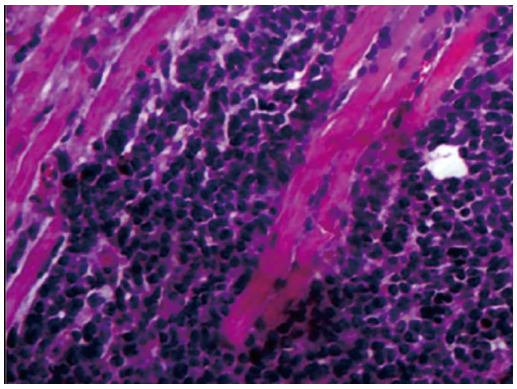

Figure 3 The microscopic slide showed an undifferentiated malignancy with hyperchromatic rounded cells with scarce and eosinophilic cytoplasma infiltrating the skeletal muscle tissue (hematoxylin-eosin, 40 ×).

progressed satisfactorily and, during the follow-up period to date (18 mo), has shown no visual impairment or tumour manifestation in any other region (Figure 5B).

DISCUSSION

The incidence of eRMS is highest in children one to four years old, lower among those 10-14 years old, and lowest among those 15-19 years old[9-11]. The head and neck region is a common site for the development of eRMS. The orbit is the most frequent site[9,12] and is also a common location for tumour extensions of the same histopathology occurring in adjacent cavities[13], such as the maxillary sinus, as reported in the present case.

The cytogenetic characterisation of eRMS is not well established; however, in ⩾ 80% of cases, aRMS is associated with chromosomal translocations between chromosomes 2 and 13 [t (2; 13) (q35; q14)] or chromosomes 1 and 13 [t (1; 13) (q36; q14)] and genetic imbalances that result in the fusion of domains of the transcription factors Pax3 and Pax7 with FOXO1a[2,5,14-16].

The final diagnosis is usually defined based on a tissue biopsy associated with a histopathological and immunohistochemical study[17]. Both aRMS and eRMS express myogenin and MyoD1 (myogenic regulatory nuclear proteins), but the alveolar subtype shows stronger and more generalised myogenin expression than eRMS. The diagnosis of RMS subtypes is important because aRMS is associated with a poorer prognosis, with a greater frequency of disseminated metastases. The immunohistochemical staining of pediatric RMS with antibodies to MyoD and myogenin provides information for a definitive diagnosis. Although almost all cases show nuclear expression of both products, staining for myogenin shows greater clinical utility due to its consistency and association with less nonspecific staining[17].

While it is desirable that pediatric tumours should be identified in their early stages to obtain the best prognosis, the reality is that early diagnosis does not occur in many cases. Additionally, the rapid growth of pediatric tumours makes medical management challenging for combating tumour growth and the complications that can arise from an advanced-stage tumour[18].

The rapid growth of tumour masses in the ocular region, whether derived from the paranasal tissues or otherwise, has been reported in other studies[19,20]. In a case reported by Magrath *et al*[19], a three-year-old male patient also showed swelling in the left eye; however, the tumour dimensions were smaller than those reported here. The growth period was also approximately four weeks; however, the growth originated within the orbit rather than arising from the maxillary sinus tissues, as in the present case. Furthermore, the initial characteristics were consistent with a framework of cellulitis, the aRMS diagnosis was obtained through immunohistochemistry, and tumour remission occurred after one month of treatment with Vincristine, Dactinomycin, and Cyclophosphamide. In a case reported by Chen *et al*[20], the patient was also male and was 13 years old. Exophthalmos of the left eye developed gradually over a two-week period until a doctor was consulted. Upon examination, the patient was diagnosed with aRMS, with destruction of the ethmoid bone, nasal cavity, and orbital cavity but without evidence of distant metastases. A combined treatment protocol consisting of chemotherapy (Vincristine + Actinomycin + Cyclophosphamide) and radiotherapy for high-risk RMS was initiated. After 44 wk of treatment, the tumour regressed completely, and no recurrence was observed at one year after the completion of treatment.

A retrospective analysis of the records of 14 patients by Fyrmpas *et al*[13] showed that the average age of patients with RMS of the sinuses was 7.5 years and that 42.8% underwent surgery before beginning chemotherapy, while 57.2% received chemotherapy and radiation. In addition, intracranial extension and ages greater than 10 years were associated with lower than average survival rates (five-year survival rates, 53.9% for all patients and 83.3% for those who underwent surgery).

The clinical differential diagnosis may be performed with others aggressive connective tissue malignant lesions as Fibrosarcoma, Ewing's sarcoma and Leiomyosarcoma. The final diagnosis is realized through microscopic tests. The prognosis of rhabdomyosarcoma is evaluated according to its clinical, anatomical, histopathological and age characteristics. Normally, the sRMS and aRMS have a good and poor prognosis, respectively. The eRMS of the present case is classified as having an intermediate prognosis lesion[21].

In general, the management of pediatric RMS requires a combination of chemotherapy, radiotherapy, and surgery. Chemotherapy is the first and most important approach to advanced-stage tumours, such as that described here. Tumours diagnosed at an early stage can be treated with a radical surgical approach because the function and cosmetic appearance can

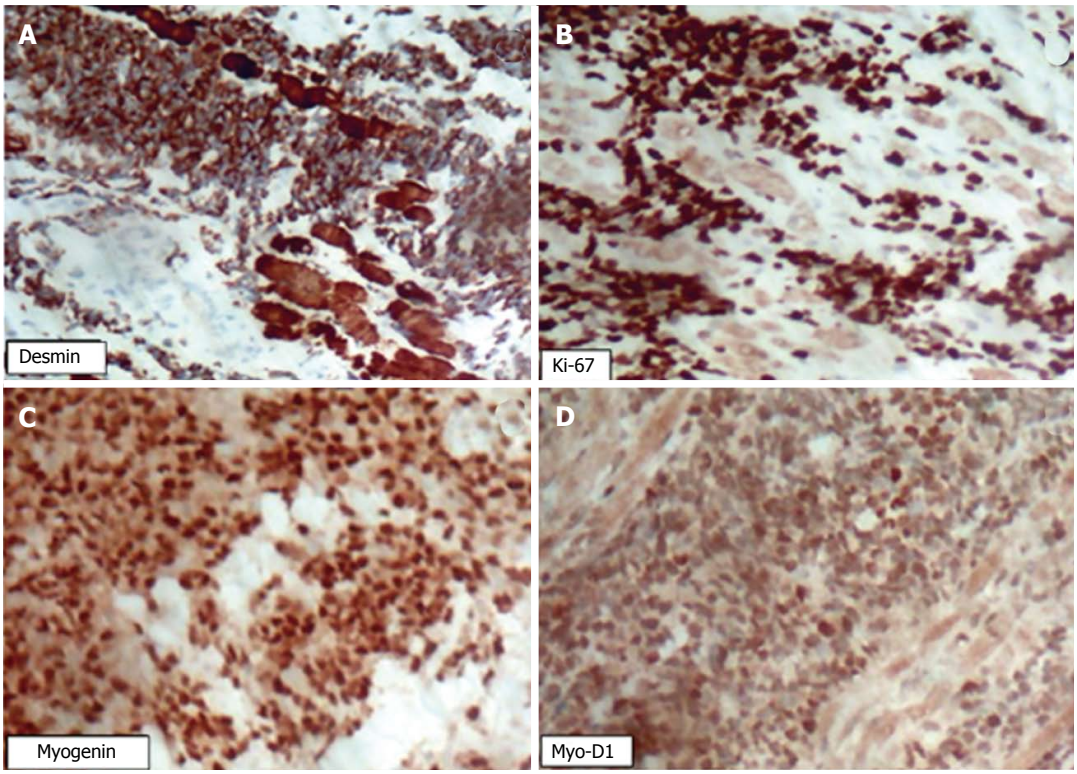

Figure 4 An immunohistochemical analysis was performed on a biopsied tumour fragment from the left maxillary sinus. A: Immunohistochemical analysis showed positiveness to anti-Desmin antibody with dual cytoplasmatic and nuclear staining; B: The same pattern was observed against anti-Ki67 (B) showing intense positiveness and high rate of cell proliferation; C and D: Anti-myogenin and MYO-D1 were positively found on nuclear staining leading to RMS lineage supposition.

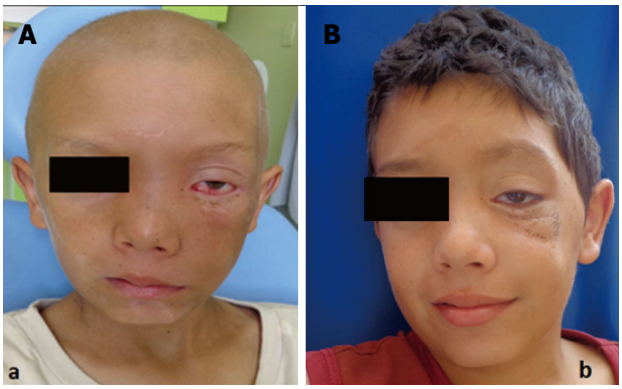

Figure 5 Monitoring of the patient after the period of 2.5 mo of chemotherapy and after completion of treatment (18 mo). A: Monitoring of the patient after the period of 2.5 mo of chemotherapy; B: Monitoring of the patient after completion of treatment (18 mo).

possibly be preserved.

This paper focused a single clinical case which could not be extrapolated to all cases of RMS on head and neck. However, due to scarcity of analogous clinical cases and needing to better comprehend this condition, this report could be useful for clinical practice, including differential diagnosis options and diagnosis by clinical or microscopic similarities. It is vital that health professionals are aware of the early signs of cancer in paediatric patients and have sufficient knowledge of efficient referral procedures to paediatric cancer diagnosis and treatment units so that children and adolescents will not suffer the consequences of late diagnosis and receive a less aggressive treatment approach.

COMMENTS

Case characteristics

The patient presented occasionally pain, large swelling and exophthalmos on the left side of the face in addition to a raised and hardened area in the maxillary region that had appeared approximately 25 d prior.

Clinical diagnosis

According to the clinical examination, the patient's visual acuity, eye structure, and ocular fundus were normal in both eyes.

Differential diagnosis

The differential diagnosis are others aggressive connective tissue malignant lesions as Fibrosarcoma, Ewing's sarcoma and Leiomyosarcoma.

Imaging diagnosis

The computed tomography showed a heterogeneous mass occupying part of the left half of the face inside the maxillary sinus, and infiltrating and destroying the bone structure of the maxillary sinus, left orbit, ethmoidal cells, nasal cavity, and sphenoid sinus.

Pathological diagnosis

An analysis of the histological sections revealed an undifferentiated malignant neoplasm infiltrating the skeletal muscle tissue.

Treatment

The treatment plan combined chemotherapy with radiation therapy and followed by surgical ablation of residual mass on maxillary sinus with ocular globe and

optic nerve preservation.

Related reports
To our knowledge, there aren't many papers about embryonal rhabdomyosarcoma (eRMS) that describes pathological, immunohistochemical and surgical findings of a clinical case in the literature.

Term explanation
Regarding the trajectory of this case, everything occurred according to the terms.

Experiences and lessons
This report helps to further understand eRMS in terms of diagnosis, clinical presentation, treatment and prognosis.

Peer-review
This is a well written case report.

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CASE REPORT

Topiramate induced peripheral neuropathy: A case report and review of literature

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Abstract

Drug-induced peripheral neuropathy had been rarely reported as an adverse effect of some antiepileptic drugs (AEDs) at high cumulative doses or even within the therapeutic drug doses or levels. We describe clinical and diagnostic features of a patient with peripheral neuropathy as an adverse effect of chronic topiramate (TPM) therapy. A 37-year-old woman was presented for the control of active epilepsy (2010). She was resistant to some AEDs as mono- or combined therapies (carbamazepine, sodium valproate, levetiracetam, oxcarbazepine and lamotrigine). She has the diagnosis of frontal lobe epilepsy with secondary generalization and has a brother, sister and son with active epilepsies. She became seizure free on TPM (2013-2017) but is complaining of persistent distal lower extremities paresthesia in a stocking distribution. Neurological examination revealed presence of diminished Achilles tendon reflexes, stocking hypesthesia and delayed distal latencies, reduced conduction velocities and amplitudes of action potentials of posterior tibial and sural nerves, indicating demyelinating and axonal peripheral neuropathy of the lower extremities. After exclusion of the possible causes of peripheral neuropathy, chronic TPM therapy is suggested as the most probable cause of patient's neuropathy. This is the first case report of topiramate induced peripheral neuropathy in the literature.

Key words: Topiramate; Peripheral neuropathy; Sodium channel blockade; Antiepileptic drugs

Core tip: Peripheral neuropathy is a rare adverse effect of short- or long-term use of antiepileptic drugs (phenytoin, phenobarbital, carbamazepine, valproate, gabapentin, levetiracetam and lacosamide). This is the first case report of topiramate induced peripheral neuropathy (TIPN). Manifestations of TIPN are distal paresthesia, areflexia, sensory deficits and reduced amplitudes and nerve

conduction velocities of motor and sensory peripheral nerves of the lower extremities indicating demyelinating and axonal neuropathies. The risk is greater with long-term therapy. The mechanisms of TIPN may involve impairment of nerve function through blocking of sodium voltage channels, enhancement of gamma amino butyric acid inhibitory neurotransmission or others.

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INTRODUCTION

Topiramate (TPM) is a broad-spectrum antiepileptic drug (AED) to treat varieties of seizures in adults and children. TPM is recommended as add-on or mono-therapy to treat patients two or more years old with generalized tonic clonic epilepsy or focal epilepsy with or without secondary generalization which are refractory to treatment with other AEDs; and for Lennox-Gastaut syndrome (LGS)[1]. TPM has been approved by the United States Food and Drug Administration (FDA) in combination with phentermine for weight loss[2] and for migraine prevention[3]. TPM has also off-label uses, *i.e.*, not mentioned in patients' leaflet and/or prescribing information] which include treatment of bipolar disorder[4]; borderline personality disorder[5]; alcoholism[6]; and antipsychotics-induced weight gain[7]; and as a mood stabilizer[8].

TPM has many adverse side effects. Some are very common (> 10% incidence) including dizziness, weight loss, paraesthesia in the face, mouth and extremities (pins and needles which occur in 12%-14% of patients), somnolence, nausea, diarrhea and fatigue. Others are common (1%-10% incidence) including disturbance in attention, memory deficits, amnesia, cognitive disorder, psychomotor slowing, abnormal coordination, tremors, sedation, vomiting, vertigo, tinnitus, dry mouth, abnormalities of taste and abdominal discomfort. However, most of these adverse effects are mild/moderate, transient and related to higher doses and/or rapid dose titration rate. Thus, these side effects can be reduced or prevented by starting TPM at low doses and gradually increasing the dosage[9]. Also, TPM has some rare and serious side effects which necessitate drug withdrawal and replacement by alternative, these include acute angle glaucoma, acute myopia, decreased sweating and increase in body temperature, confusion, speech arrest[10], manifest metabolic acidosis[11] and urolithiasis of clinical importance[12]. Most of these side effects are related to the carbonic anhydrase enzyme inhibition properties of TPM.

Review of the literature shows that AEDs therapy is rarely associated with peripheral neuropathy. Peripheral neuropathy is a rare adverse effect of phenytoin (PHT) as evidence by clinical and experimental studies[13,14]. It had been reported with short-term treatment (hours to weeks) with PHT in toxic[15-18] or non-toxic doses[19-21] and with long-term (⩾ 5 years) PHT therapy[22-25]. Peripheral neuropathy had been also reported with therapy with other AEDs as carbamazepine (CBZ)[26-28], phenobarbital (PB)[27], sodium valproate (VPA)[26,27,29,30], gabapentin (GPN)[31], levetiracetam (LEV)[32] and lacosamide (LCM)[33]. There is no previous report for peripheral neuropathy induced by TPM.

CASE REPORT

A 37-year-old well-nourished woman presented at the year 2010 with frequent attacks (two or more ictal attacks per week) of generalized tonic clonic convulsions. Clinical, electroencephalography (EEG) and magnetic resonance imaging diagnosis are consistent with idiopathic frontal lobe epilepsy with secondary generalization. The patient has a brother, sister and son with chronic active epilepsy. The patient tried different AEDs as mono- or combined therapies [CBZ and/or VPA, LEV or lamotrigine (LTG)] but with no significant improvement. TPM (100 mg BID) was started (2013) as monotherapy (associated with gradual withdrawal of the other administered AEDs) and the patient became seizure free few months after the start of TPM. The patient experienced some transient side effects which included sense of pins and needles in the face, mouth, body and limbs; myalgia, muscle spasms (cramps) and increased forgetfulness which improved spontaneously within weeks to few months. Laboratory investigations demonstrated hypocalcemia (serum Ca^{2+} = 7.6 mg/dL). Reassurance of the patient was done and muscle spasms and myalgia disappeared with vitamin D and calcium supplementations. Two years after starting TPM therapy (2015), the patient developed persistent distal numbness in the lower extremities. Neurological examination revealed presence of diminished knee and ankle tendon reflexes, diminished pain and temperature sensation of stocking distribution and decreased vibration perception in the lower limbs. Nerve conduction velocity studies of the median, ulnar, common peroneal, posterior tibial and sural nerves revealed prolonged distal latencies of the tibial nerves (right = 5.9 ms, left = 6.2 ms), reduced their motor conduction velocities (MCVs) (right = 42.7 m/s, left = 35.9 m/s) and amplitudes of their motor action potentials (MAPs) (right = 1.14, 1.25 mV, left = 1.39, 1.10 mV); prolonged distal latencies of sural nerves (right = 6.48 ms, left = 5.67 ms), reduced their sensory conduction velocities (SCVs) (right = 24.7 m/s, left = 28.2 m/s) and amplitudes of their sensory action potentials (SAPs) (right = 14.00 μV, left = 26.6 μV) (Figure 1). The diagnosis of TPM induced peripheral neuropathy was probably suggested after

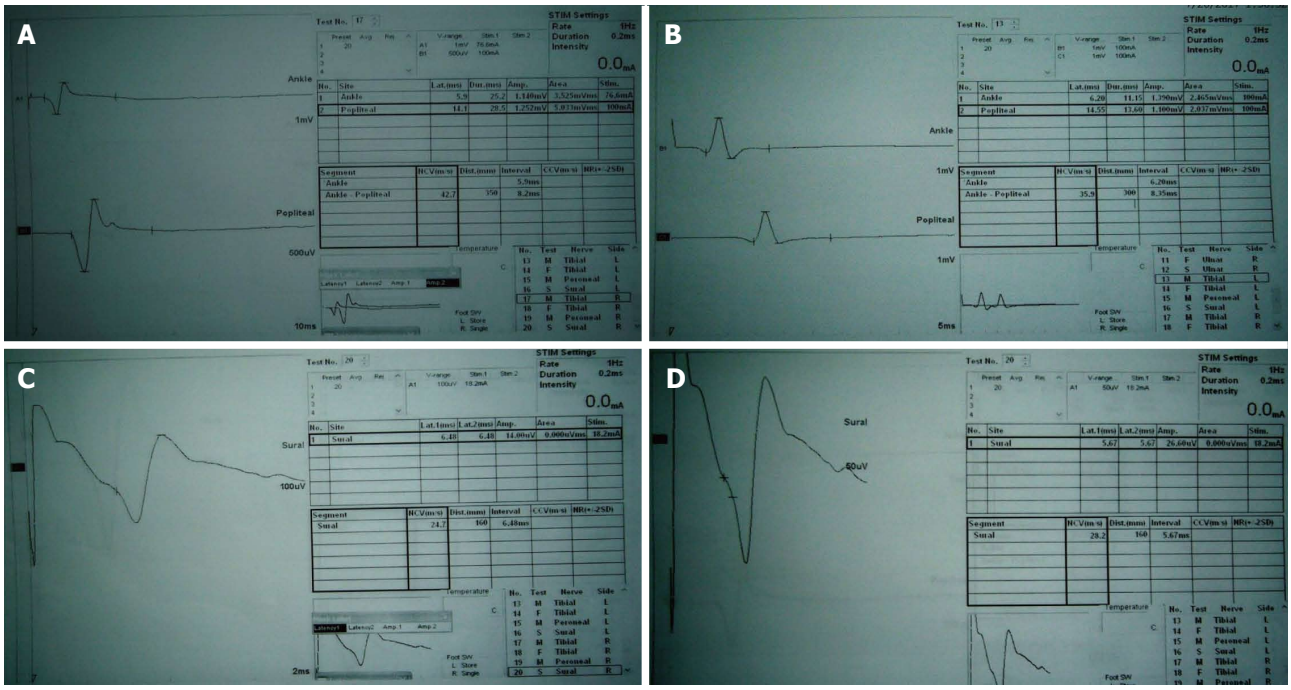

Figure 1 Nerve conduction velocity study traces of the right (A) and left tibial (B) nerves and right (C) and left sural (D) nerves show prolonged distal latencies, reduced motor and sensory conduction velocities and reduced motor and sensory action potentials (amplitudes).

exclusion of the general and common risk factors for the development of peripheral neuropathy which include diabetes, toxins, nutritional disorders (*e.g.*, B-vitamin deficiency) and infectious (*e.g.*, tuberculosis and HIV), connective tissue and metabolic diseases and according to the Naranjo adverse drug reaction (ADR) probability scale (ADR score = 7)[34]. Vitamin B supplementations (thiamine, riboflavin, pyridoxine, cyanocobalamin and folic acid) and anti-oxidants (lipoid acid, primrose oil and vitamin E) were prescribed for the patient for several weeks but no improvement was observed in peripheral neuropathy manifestations. The decision to continue on TPM was discussed with the patient because she is well-controlled (seizure free) on TPM monotherapy after failure to control seizures with other AEDs, no worsening of peripheral neuropathy with time and this side effect was well tolerated by the patient.

This study was conducted according to the principles established in Helsinki and approved by Assiut University Hospital ethics committee. Informed written consent was obtained from the patient to publish the details of her clinical history, laboratory and neurophysiological data.

DISCUSSION

Nearly 12%-14% of patients on TPM commonly experience transient parasthesia in the face, mouth and extremities early during treatment[9] which disappears spontaneously or with the use of potassium therapy[35], however, it may be severe and intolerable in some patients and resulted in discontinuation of TPM[9]. Some evidence suggests that the tendency to cause paresthesia is due to TPM effect on an enzyme called carbonic anhydrase which is an enzyme found in nerve tissue, and probably helps nerve cells talking to one another[35]. However, it seems that another cause of parasthesia may occur with chronic TPM therapy due to the effect of TPM on peripheral nerves. This is the first report of presence of peripheral neuropathy in a patient with epilepsy due to chronic therapy with TPM. Peripheral neuropathy induced by TPM is manifested by parathesia in both lower limbs, decreased ankle jerks, stocking distribution of hypesthesia and delayed distal latencies, reduced nerve conduction velocities of motor and sensory peripheral nerves and reduced amplitudes of motor and sensory action potentials of the peripheral nerves of the lower limbs, indicating demyelinating and axonal peripheral neuropathy. As the patient is seizure free on TPM after several years of ineffective other AEDs therapies, I was unable to do re-challenge testing (stopping and re-staring the treatment to be sure that it was the cause peripheral neuropathy). Only reassurance of the patient was done and no specific treatment was prescribed as the patient has mild paraesthesia and non-progressive peripheral neuropathy.

In general, AEDs are used to treat cortical hyper-excitable states which result in epilepsy and peripheral nerve hyperexcitability which both result in neuropathic pain. Regarding TPM, some experimental and clinical studies demonstrated its efficacy to treat neuropathic pain. Lopes *et al*[36] demonstrated the antinociceptive effect of oral administered doses of TPM (80 mg/kg) in the models of nociception induced by chemical (formalin) or thermal (hot plate) stimuli. Siniscalchi *et al*[37] reported complete improvement of idiopathic

glossodynia in a 65-year-old woman with 4 mo history of glossodynia with TPM after failure of CBZ or GPN. Glossodynia is a painful sensation in the mouth, throat and especially the tongue due to altered excitability in the trigeminal nociceptive pathway at peripheral and/or central nervous system levels. In another study, Siniscalchi *et al*[38] reported improvement of dysesthetic pain with TPM (150 mg/d within 8 mo) in a 42-year-old woman with 8 years history of multiple sclerosis. Erdoğan *et al*[39] observed a significant decrease in the strength duration time constant (which provides an indirect idea about the persistent, paranodal sodium channels and may indirectly reflects the peripheral nerve excitability) but did not observe significant affection of median nerve motor and sensory conduction parameters after the initiation of TPM for 4 wk, reflecting a reduction in the peripheral nerve excitability induced by TPM.

In the literature, peripheral neuropathy had been reported as a rare adverse effect with short-term treatment (hours to weeks) with PHT in toxic[15-18] or non-toxic doses[19-21] and with long-term (months to years) PHT therapy[22-25]. Acute peripheral neuropathy induced by PHT is very rare and reversible side effect[17,19-24]. Hopf *et al*[19] reported slight but significant reduction in the mean ulnar nerve conduction velocity in 13 patients after the intake of 500-600 mg PHT per day for a week which was not correlated with serum PHT levels. Lovelace and Horwitz[40] reported decrease in motor and sensory conduction velocities of the peripheral nerves without any symptoms (occult) during PHT administration among patients with epilepsy. Birket-Smith and Krogh[15] reported peripheral neuropathy with PHT level more than 20 μg/mL, however, no correlation was observed between the clinical toxicity severity and the degree of conduction velocity abnormalities. Meienberg *et al*[17] reported acute severe mainly motor polyneuropathy in the legs and cerebellar symptoms after treatment of a 34-year-old epileptic male with high doses PHT to control status epilepticus although this patient was treated for more than ten years with an average of 300 mg PHT and 200-300 mg phenobarbital (PB) daily. Fujiwara *et al*[24] reported prolonged distal latency of the tibial nerve and decreased mixed nerve action-potential amplitudes of the posterior tibial and median nerves. Wessely *et al*[20] reported an axonal polyneuropathy with minimal reduction in motor nerve conduction and a considerable extension of distal latency and diminution of compound action potential in 5 patients who were treated with long-term PHT for epilepsy. In 4 cases, the symptoms appeared following treatment of status epilepticus with additional PHT medication. All patients had acute symptomatic psychosis, diffuse slowing of the curves in the EEG and cerebellar signs and two of them additionally complained of objective polyneuropathy. Nerve biopsy in one patient showed concentric lamellar bodies coming from the axon with intact myelin sheaths. Ramirez *et al*[18] reported a 47-year-old man with clinical and electrophysiological signs of peripheral neuropathy after 30 years treatment with PHT (300 mg/d, the blood levels were 31-38 μg/mL). A sural nerve biopsy showed loss of large myelinated nerve fibers and non-random clustered distribution of segmental demyelination, remyelination and axonal shrinkage. Clinical and electrophysiological improvement was observed within 16 mo of PHT withdrawal. Yoshikawa *et al*[21] reported an 18-year-old girl who developed distal lower extremity paresthesia in a stocking distribution, motor weakness, absent Achilles tendon reflexes, slightly reduced sensory conduction velocities and mild prolongation of distal latencies in the lower extremities just few hours after the administration of PHT to control epilepsy. Discontinuation of PHT resulted in gradual disappearance of the symptoms and returning of the distal latencies and sensory conduction velocities to normal. Le Quesne *et al*[14] demonstrated acute slowing of motor nerve conduction velocity in guinea pigs after only 3-4 d of PHT administration. Furthermore long-term PHT administration can cause of peripheral neuropathy which is more frequent than acute forms. Eisen *et al*[22] reported peripheral neuropathy with the use of PHT which was correlated with PHT level. Chokroverty and Sayeed[16] reported significant reduction in the mean motor conduction velocity of posterior tibial nerves of epileptic patients treated with PHT for more than 10 years or in patients with serum PHT level above 20 μg/mL. Dobkin[23] reported dysesthesia and sensory and reflex loss in the legs in a patient treated for seizures with PHT in the therapeutic range for one year. Discontinuation of PHT resulted in resolution of peripheral neuropathy. Mochizuki *et al*[25] reported slowed motor conduction velocities of the ulnar (33.3%) and posterior tibial nerves (23.8%), followed by slowed sensory conduction velocities of the sural nerves (20%), lowered H/M ratio (14.3%), and slowed motor conduction velocities of the peroneal (14.3%) and median (14.2%) nerves in children with epilepsy. The authors observed significant correlations between the total dosage and duration of therapy with PHT and the reduction of motor conduction velocity in the posterior tibial nerve.

Peripheral neuropathy had been also reported with other AEDs therapy as CBZ[26-28], PB[27], VPA[26,29,30], GPN[31], LEV[32] and LCM[33]. A review of the literature showed that reflex sympathetic dystrophy (RSD) is precipitated by PB in 10%-30% of cases[41,42]. RSD syndrome is clinically characterized by pain and edema of one or more extremities, trophic skin changes and vasomotor instability. Swift *et al*[29] reported that 16.7% of epileptic patients may develop peripheral neuropathy with different AEDs which is characterized by stocking hypesthesia, reduced Achilles reflexes, slowing of peroneal and sural nerve conduction velocities and prolonged or absent H reflexes and F responses. Geraldini *et al*[26] reported slowing of the peroneal and median motor nerve conduction velocities and median sensory nerve conduction velocities with CBZ, PB and PHT. Significant correlation was identified

between the slowing of the conduction velocity and the daily dose of CBZ but not its serum drug level or duration of treatment. In the study done by Bono *et al*[27] on 141 adult patients treated for less than 6 mo with standard daily doses of the commonest AEDs, the authors reported that 53% of patients had one or more symptoms of polyneuropathy (paresthesias being the most common complaint). The neurologic examination was abnormal in 32%. Electrophysiologic findings in two or more separate nerves were abnormal in 77 patients (54.6%); of these, 27 (19.1%) had abnormal neurologic findings and 21 (14.9%) also had symptoms of polyneuropathy. Sensory functions were the most frequently impaired. Axonal damage with secondary myelin changes was noted in sural nerve biopsies of patients on CBZ, PB and PHT. A correlation was noted between polyneuropathy and combined therapy with two or more AEDs. Gould[31] reported a 58-year-old man who developed a painful polyneuropathy while being treated with GPN although GPN is considered an effective treatment for neuropathic pain syndromes. Kapoor *et al*[32] reported a case of polyneuropathy induced by LEV which improved with discontinuation of LEV. Boylu *et al*[28] reported mild prolongation in the distal latency of median sensory, ulnar sensory and sural nerves with diminished nerve conduction velocities with chronic CBZ therapy but not with VPA, oxcarbazepine (OXC) or TPM. Marusic *et al*[30] reported a 26-year-old man with weakness of flexion and abduction of the right arm and loss of sensation in the skin over the lateral upper right arm and reduced amplitude and prolonged latencies in the right axillary nerve because of a suicide attempt with VPA overdose (serum VPA level = 2896 μmol/L; therapeutic range = 350-690 μmol/L). In an experimental study, Zafeiridou *et al*[33] observed a differential effect for LCM, PHT and TPM on peripheral nerve excitability. The authors reported inhibition of compound action potential of the sciatic nerve of an adult rat after 48 h period of LCM exposure at concentrations higher than the therapeutic level (> 25 μg/mL). An acute and immediate increment of the latency and decrement of the amplitude of the nerve compound action potential were observed at LCM concentrations of 62.57-125.15 μg/mL. However, in contrast to LCM, PHT resulted in an acute decrement in the amplitude of the nerve compound action potential as well as an increment in the latency of the compound action potential even at sub-therapeutic levels (5 μg/mL). Reduced compound motor action potential amplitude was also observed with TPM at concentration of 33.94 μg/mL (supra-therapeutic).

The mechanism (pathogenesis) of PHT induced peripheral neuropathy is not well known. Experimental studies demonstrated a depressant effect of PHT on peripheral nerves[13] which has been attributed to the direct toxic effect of the drug on peripheral nerves and/or due to blockage of sodium channels which is its main anticonvulsant mechanism of action. Korey[43] demonstrated an inhibitory effect of PHT on the giant axon of the squid which was made hyperexcitable by low calcium and magnesium levels. Eisen *et al*[22] reported a primary axonal shrinkage and secondary demyelination with PHT. Long *et al*[44] and Hansen *et al*[45] demonstrated that peripheral neuropathy induced by PHT was related to the subnormal serum folate in association with megaloblastic anemia. We suggest that peripheral neuropathy induced by TPM may be related to its anticonvulsant mechanism of action which is multifactorial and involve blockade of voltage-dependent sodium channels (similar to PHT); inhibition of high-voltage-activated calcium channels; potentiation of GABAergic transmission through GABA-A receptors; inhibition of excitatory pathways through an action at α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) AMPA/kainate receptors sites and inhibition of carbonic anhydrase isoenzymes[1].

We report a patient with peripheral neuropathy after chronic therapeutic dose of TPM. However, this adverse effect was mild, static and tolerated by the patient and did not disappear with vitamin B supplementations. There is also a need for experimental and clinical studies to identify the effect of TPM on peripheral nerves and to identify the mechanism(s) of TPM induced peripheral neuropathy.

COMMENTS

Case characteristics

A 37-year-old woman presented with frontal lobe epilepsy with secondary generalization which was intractable to different antiepileptic medications as mono- or combined therapy. Topiramate (TPM) monotherapy significantly controlled the patient's seizures. After two years of therapy with TPM, the patient developed paresthesia, diminished Achilles tendon reflexes, stocking hypesthesia and delayed distal latencies, reduced conduction velocities and amplitudes of action potentials of posterior tibial and sural nerves.

Clinical diagnosis

Peripheral neuropathy probably induced by long-term TPM therapy.

Differential diagnosis

Other causes of peripheral neuropathy which include diabetes, toxins, nutritional disorders (*e.g.*, B-vitamin deficiency) and infectious, connective tissue and metabolic diseases.

Laboratory diagnosis

Demyelinating and axonal peripheral neuropathy of the tibial and sural nerves.

Treatment

Reassurance of the patient and continue therapy with TPM because the patient is well-controlled (seizure free) on TPM therapy, no worsening of the course of peripheral neuropathy with time and this side effect was well tolerated by the patient.

Related reports

Peripheral neuropathy has been reported as adverse side effect of some antiepileptic drugs (AEDs) including phenytoin, phenobarbital, carbamazepine, valproate, gabapentin, levetiracetam and lacosamide. Most of case reports in the literature are peripheral neuropathy induced by short-term or long-term treatment with phenytoin. There is no previous report for TPM induced peripheral neuropathy.

Term explanation

Peripheral neuropathy is a rare adverse effect of short- or long-term use of AEDs. The risks for peripheral neuropathy induced by AEDs include the high drug doses, high drug serum levels and longer duration of therapy. Some of AEDs may induce acute or severe peripheral neuropathy which necessitates drug withdrawal and use of alternative. There is no previous report of TPM induced peripheral neuropathy. This study is the first report of peripheral neuropathy which is most probably induced by long-term use of TPM.

Experiences and lessons

According to the Naranjo adverse drug reaction probability scale, it seems that chronic TPM therapy is the most probable cause of patient's neuropathy. Peripheral neuropathy induced by TPM is mild/moderate in severity, non-progressive and not bothersome to patients and may not necessitate drug discontinuation.

Peer-review

The presented case is interesting.

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