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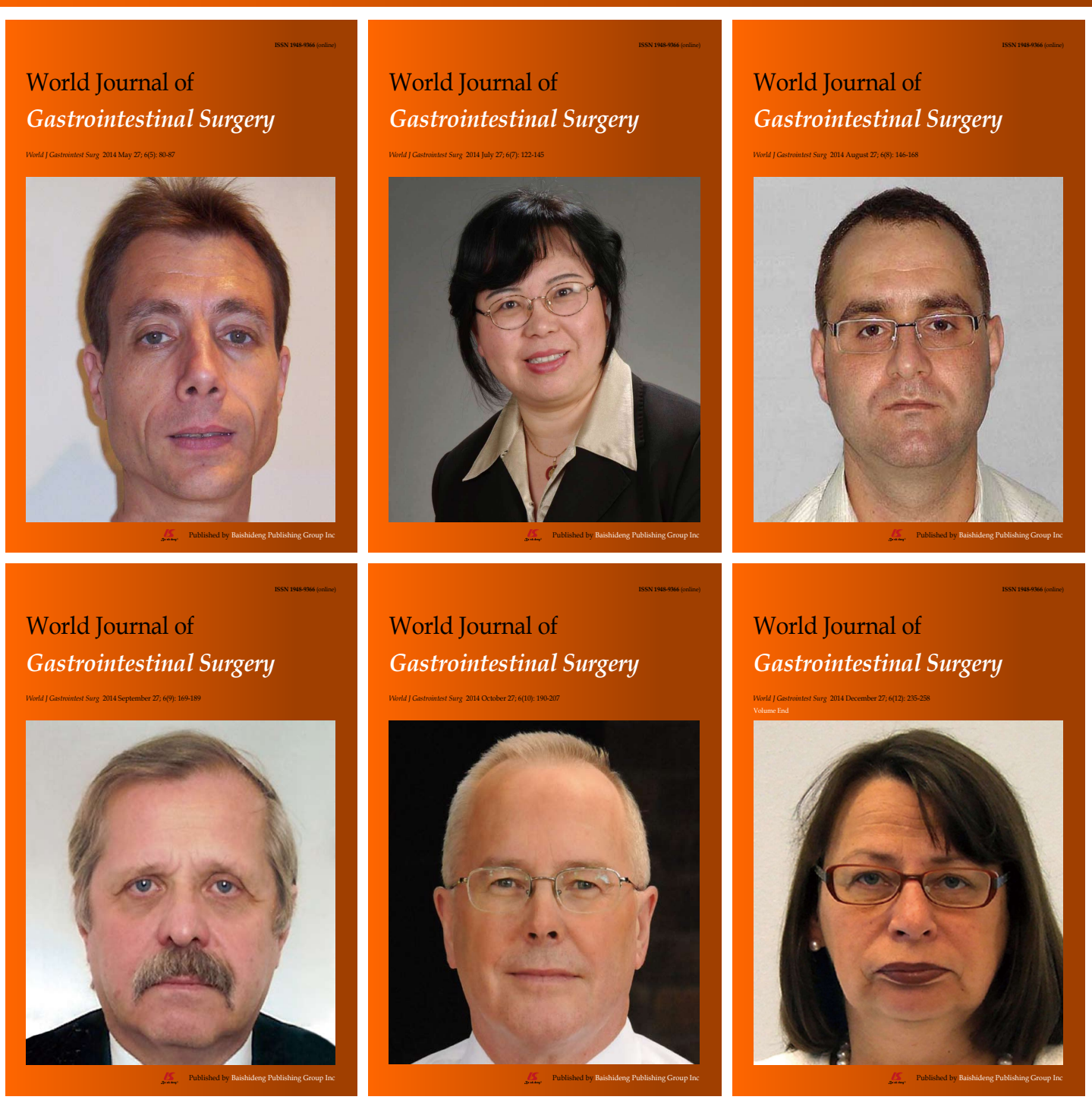

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BRIEF ARTICLE

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World Journal of Gastrointestinal Surgery (*World J Gastrointest Surg*, *WJGS*, online ISSN 1948-9366, DOI: 10.4240) 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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EDITORIAL OFFICE
Jin-Lei Wang, Director
Xiu-Xia Song, Vice Director
World Journal of Gastrointestinal Surgery
Room 903, Building D, Ocean International Center,
No. 62 Dongsihuan Zhonglu, Chaoyang District,
Beijing 100025, China
Telephone: +86-10-85381891
Fax: +86-10-85381893
E-mail: bpgoffice@wjgnet.com
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BRIEF ARTICLE

Tumor differentiation as related to sentinel lymph node status in gastric cancer

Ron Lavy, Andronik Kapiev, Yehuda Hershkovitz, Natan Poluksht, Igor Rabin, Bar Chikman, Zahar Shapira, Ilan Wasserman, Judith Sandbank, Ariel Halevy

Ron Lavy, Andronik Kapiev, Yehuda Hershkovitz, Natan Poluksht, Igor Rabin, Bar Chikman, Zahar Shapira, Ilan Wasserman, Ariel Halevy, Division of Surgery, Assaf Harofeh Medical Center, Sackler Faculty of Medicine, Tel-Aviv University, Ramat Aviv, Zerifin 70300, Israel
Igor Rabin, Department of Vascular Surgery, Assaf Harofeh Medical Center, Sackler Faculty of Medicine, Tel-Aviv University, Ramat Aviv, Zerifin 70300, Israel
Judith Sandbank, Institute of Pathology, Assaf Harofeh Medical Center, Sackler Faculty of Medicine, Tel-Aviv University, Ramat Aviv, Zerifin 70300, Israel
Author contributions: Lavy R, Kapiev A and Halevy A conceived and designed the study; Lavy R, Hershkovitz Y, Sandbank J and Halevy A analyzed and interpreted the data; Halevy A performed critical revision of the article for important intellectual content; all authors acquired the data, wrote the draft of the article and gave final approval of the version to be published.
Correspondence to: Ariel Halevy, Professor, Division of Surgery, Assaf Harofeh Medical Center, Tel-Aviv University, Weizmann 10, Ramat Aviv, Zerifin 70300,
Israel. fredricag@asaf.health.gov.il
Telephone: +972-8-9779222 Fax: +972-8-9779225
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Abstract

AIM: To investigate the influence of tumor grade on sentinel lymph node (SLN) status in patients with gastric cancer (GC).

METHODS: We retrospectively studied 71 patients with GC who underwent SLN mapping during gastric surgery to evaluate the relationship between SLN status and tumor grade.

RESULTS: Poorly differentiated tumors were detected in 50/71 patients, while the other 21 patients had moderately differentiated tumors. SLNs were identified in 58/71 patients (82%). In 41 of the 58 patients that were found to have stained nodes (70.7%), the tumor was of the poorly differentiated type (group Ⅰ), while in the remaining patients with stained nodes 17/58 (29.3%), the tumor was of the moderately differentiated type (group Ⅱ). Positive SLNs were found in 22/41 patients in group I (53.7%) and in 7/17 patients in group Ⅱ (41.2%) (P = 0.325). The rate of positivity for the SLNs in the two groups (53.7% *vs* 41.2%) was not statistically significant (P = 0.514).

CONCLUSION: Most of our patients were found to have poorly differentiated adenocarcinoma of the stomach and there was no correlation between tumor grade and SLN involvement.

Key words: Gastric cancer; Sentinel lymph nodes; Tumor differentiation; Sentinel lymph node mapping; Prognosis

Core tip: The application of sentinel lymph node (SLN) sampling in gastric cancer is limited to the early stages of the disease. The results of the sampling, which is usually not one node but rather a group of nodes, might influence the extent of lymphadenectomy to be performed. In a previous study, we clearly showed that the accuracy of SLN testing is inversely proportionate to the T stage of the tumor. In this retrospective study, we evaluated the level of tumor differentiation as related to the SLN status. Our study showed that there was no correlation between tumor differentiation and SLN status.

Lavy R, Kapiev A, Hershkovitz Y, Poluksht N, Rabin I, Chikman B, Shapira Z, Wasserman I, Sandbank J, Halevy A. Tumor differentiation as related to sentinel lymph node status in gastric

cancer. *World J Gastrointest Surg* 2014; 6(1): 1-4 Available from: URL: http://www.wjgnet.com/1948-9366/full/v6/i1/1.htm DOI: http://dx.doi.org/10.4240/wjgs.v6.i1.1

INTRODUCTION

Although first described for patients with penile cancer[1] and now used routinely in patients with malignant melanoma and breast cancer, the evaluation of sentinel lymph nodes (SLNs) has also gradually entered the field of gastrointestinal cancer[2]. SLN mapping of the gastrointestinal tract has been studied extensively, especially in patients with gastric cancer (GC) and today, SLN status plays an important role in the decision-making process regarding the extent of lymphadenectomy in selected groups of patients with early stage GC[3,4].

In a previous study, we investigated the accuracy of SLN mapping according to the T stage of the tumor and showed that in T1-2 tumors SLN mapping may be of assistance, but that in patients with T3 it will be misleading in a third of the patients and should not be attempted[5].

We used this particular group of patients to retrospectively study whether or not tumor grade also has an influence on SLN status.

MATERIALS AND METHODS

This study was performed under the authorization of the Institutional Review Board of our medical center (Assaf Harofeh Medical Center; Approval No. 82/12).

Data was retrieved from a computerized data base. Out of 80 patients, nine patients with well differentiated tumors were omitted so that only 71 patients with poorly and moderately differentiated GC entered the study. Preop evaluation included gastroscopy, intravenous contrast computed tomography (CT) and endoscopic ultrasound in a selected group of patients with a gastroesophageal junction location.

Surgery started with exploration of the abdominal cavity, disease staging and resectability assessment. Before any dissection was performed, patent blue (Guerbet Patent Blue V Sodium 2.5%; Guerbet, Roissy, France) diluted with 2 mL of normal saline was injected subserosally in four different opposing points adjacent to the tumor site. Ten minutes following dye injection, dye spread was evaluated and blue nodes were marked by a stitch. The type of D2 resection was based on tumor location and the extent of the disease.

A detailed focused pathological assessment was performed with special attention to all areas marked by patent blue. All blue-stained lymph nodes were sectioned into 0.2 cm thick slices. Two 3 μm thick sections were serially cut at 0.25 mm levels from these lymph node slices: the first was stained with hematoxylin and eosin and the second was placed on a Superfrost Plus Slide (Menzel GmbH and Co KG, Braunschweig, Germany). If the hematoxylin and eosin slides were negative for metastatic involvement, the unstained consecutive slides were stained with a pan cytokeratin antibody (CKMNF116; Dako, Carpinteria, CA, United States) to highlight micrometastases. All relevant sections were examined. The total sampling of the SLNs with systematic serial sectioning and cytokeratin immunohistochemistry enabled a relatively optimal estimation of the metastatic status of the SLNs.

The non-stained (not sentinel) lymph nodes were routinely submitted either *in toto* when less than 0.2 cm in diameter or sectioned into 0.2cm thick slices. Two levels of 3 μm thickness were performed on each of these tissue fragments, which were then stained with hematoxylin and eosin only.

All pathological slides were re-evaluated by the senior pathologist with respect to tumor grade. Tumor grade was matched to SLN status and statistically evaluated.

Statistical analysis

Statistical analysis was performed at the Department of Statistics of the Tel Aviv University using the χ^2 Test, Fisher's Exact Test and the Mann-Whitney Test.

RESULTS

Our cohort included 71 patients (30 women and 41 men) with GC with no evidence of spread (by computer tomography scan). The age range varied from 26 to 88 years (mean, 67.4 years).

The tumor was located in the lower third of the stomach in 32 patients, the middle third in 15 patients and the upper third or the gastroesophageal junction in 18 patients. Four patients had linitis plastica and two patients had gastric stump carcinoma that developed many years after a subtotal gastrectomy for benign disease.

Forty-four patients underwent distal subtotal gastrectomy, 14 patients underwent proximal gastrectomy, 11 patients underwent total gastrectomy and two patients underwent gastric stump resection, one of them with en-bloc transverse colon resection.

Poorly differentiated tumors were detected in 50/71 patients, while the other 21 patients had moderately differentiated tumors (Figure 1).

A total of 1114 regional lymph nodes were harvested in the group of patients with poorly differentiated tumors (22.7 nodes per person) with a positivity ratio of 20.3% (226/1114). In the group of patients with moderately differentiated tumors, the overall number of harvested nodes was 401 (19.1 nodes per person) with a positivity ratio of 16.5% (66/401).

SLNs were identified in 58/71 patients (82%), of which 41 (70.7%) were of the poorly differentiated type (group Ⅰ) and 17 (29.3%) were of the moderately differentiated type (group Ⅱ).

Positive SLNs were found in 22/41 patients in group Ⅰ (53.7%) and in 7/17 patients in group Ⅱ (41.2%), P = 0.325 NS (Figure 2).

The patients with poorly differentiated tumors were

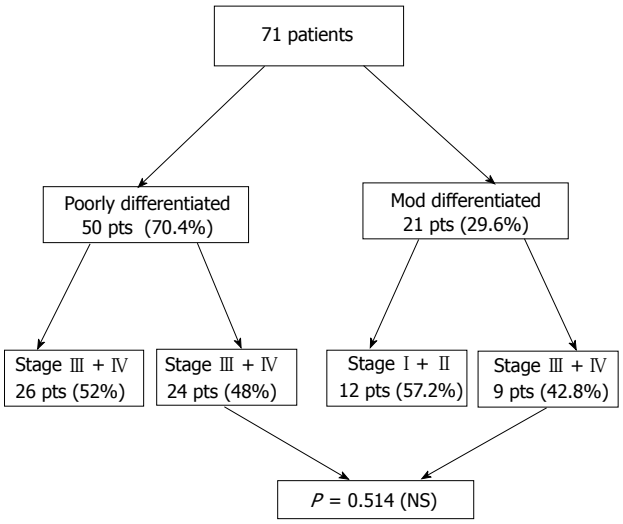

Figure 1 Distribution of the 71 patients according to tumor differentiation and state of disease. NS: No significant.

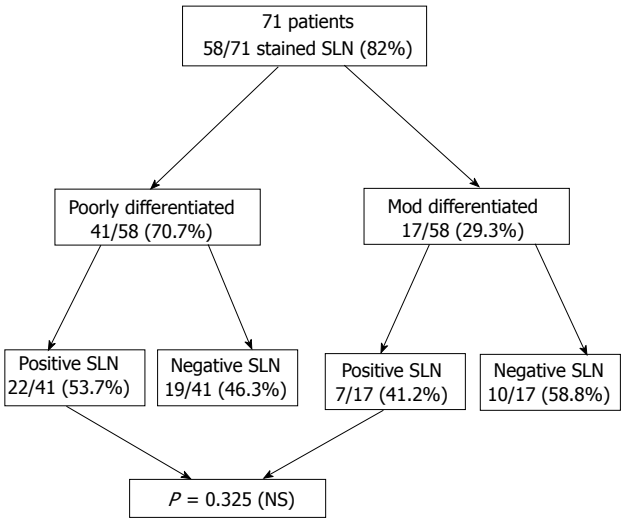

Figure 2 Distribution of sentinel lymph nodes according to tumor differentiation. SLN: Sentinel lymph node; NS: No significant.

more likely to have a higher T stage (3-4) than those with moderately differentiated tumors, 68% *vs* 47.6%.

DISCUSSION

The precise evaluation of SLN status is one of the most important factors in determining the clinical outcome when treating gastrointestinal cancer. Nodal involvement in gastric cancer is defined by two main systems: the American Joint Committee on Cancer staging system, which is based on the number of positive nodes, and the Japanese system, which is based on the location of positive nodes[6-8].

In recent years, the SLN concept has been widely investigated in different types of malignant disease as an alternative to routine lymph node dissection[9-11]. The SLN concept postulates that if the first draining node is negative for metastasis, the remaining lymph nodes in this particular nodal basin are negative for metastases. Thus one can predict the status of the nodal basin with a high degree of accuracy[12].

Numerous authors have described the successful use of SLN status in colon, rectal, gastric, esophageal and anal canal malignancies, with a high degree of accuracy when using a detailed pathological analysis of the SLNs[13].

The reported number of harvested SLNs varies according to the primary organ. For example, in patients with breast cancer, the quoted numbers vary from 1.87 to 2.14 nodes[14,15]. This number increases significantly in patients with GC and figures as high as 16 harvested SLNs have been quoted[5].

The logic of using SLN evaluation in patients with GC is related to the decision regarding the extent of the lymphadenectomy that should be performed: formal D2 lymphadenectomy in cases of positive SLNs *vs* limited lymphadenectomy for negative SLNs. The extent of gastric resection will depend on tumor location and SLN status[1,5,16].

Unfortunately, most of the patients with GC in the Western hemisphere present with advanced disease and the idea of using the SLN technique to tailor the extent of lymphadenectomy and resection to a minimum has not proven worthwhile due to the multidirectional nature of gastric lymphatic drainage[17-21].

In our previous study, we showed clearly that the SLN status depends on the T stage of the tumor. Stained nodes were detected in around 90% in T1 and T2 tumors, but in only 68.8% in T3 tumors. Based on these findings, we decided to retrospectively study the effect of tumor grade on SLN status in the same group of patients.

To the best of our knowledge (including a thorough literature search), there are no other studies dealing with this subject and we were therefore unable to compare our results with those of other reports.

In 82% of the patients (58/71), SLNs were stained (70.7% in the group of patients with poorly differentiated group compared to only 29.3% in the moderately differentiated group). There was no statistical difference in the staging based on tumor grade ($P = 0.514$). There was no statistical significance difference between positive SLNs in both groups 53.7% *vs* 41.2% ($P = 0.325$).

In conclusion, based on our previous study, we expected to see a higher rate of SLN involvement in the group of patients with poorly differentiated tumors but, despite the fact that there was a difference, this was with no statistical significance. The clinical significance of the connection between tumor grading and the SLN status was supposed to guide us how to limit the SLN procedure to a specific group of patients with gastric cancer. The results of this study failed to provide that information.

COMMENTS

Background

Sentinel lymph node (SLN) status plays an important role in the decision-making process regarding the extent of lymphadenectomy in selected groups of patients with early stage gastric cancer.

Research frontiers

This is a retrospective study on whether or not tumor grade has an influence on SLN status.

Innovations and breakthroughs

In a previous study, the authors investigated the accuracy of SLN mapping according to the T stage of the tumor and showed that in T1-2 tumors, SLN mapping may be of assistance, but in patients with T3 it will be misleading in a third of the patients and should not be attempted.

Applications

The evaluation of tumor grade may aid in predicting the outcome in patients with gastric cancer and the need for sentinel node evaluation.

Peer review

The manuscript titled "Tumor differentiation as related to sentinel lymph node status in patients with gastric cancer" by Lavy *et al*, was performed to investigate the influence of tumor grade on sentinel lymph node status in patients with gastric cancer. The paper is well written.

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BRIEF ARTICLE

Treatment of perforated giant gastric ulcer in an emergency setting

Pradeep Kumar, Hosni Mubarak Khan, Safarulla Hasanrabba

Pradeep Kumar, Hosni Mubarak Khan, Department of General Surgery, ESI-PGIMSR and Medical College, Bangalore 560010, Karnataka, India
Safarulla Hasanrabba, Department of General Surgery, Dr.B.R.Ambedkar Medical College, Bangalore 560045, Karnataka, India
Author contributions: Kumar P contributed to the concept, research, data and figures, and was the operating surgeon and attending consultant; Khan HM was the attending doctor; and Hasanrabba S contributed to the references.
Correspondence to: Dr. Pradeep Kumar, Assistant Professor, Department of General Surgery, ESI-PGIMSR and Medical College, Rajajinagar, Bangalore 560010, Karnataka, India. dr.pradeep_k20@yahoo.com
Telephone: +91-990-2349960
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Abstract

AIM: To study and assess clinical outcomes of various modes of treatment for perforated giant gastric ulcer in an emergency setting.

METHODS: From May 2010 to February 2013, 20 cases of perforated giant gastric ulcer (> 2 cm) were operated on in an emergency setting. All the patients presented with features of peritonitis and were resuscitated aggressively before taking for surgery. In the first 4 cases, primary closure was done after taking a biopsy and among these, the 3rd case also underwent partial distal gastrectomy and gastrojejunostomy and the 4th case underwent a radical subtotal gastrectomy with D2 lymphadenectomy and gastrojejunostomy for malignancy. All the remaining 16 cases underwent partial distal gastrectomy and gastrojejunostomy.

RESULTS: Among the first 4 cases, 2 had an uneventful recovery and were discharged on the 6th postoperative day. The 3rd and 4th patients developed gastric fistula, leading to prolonged hospitalization. For the 3rd patient, conservative management was tried for 1 wk, followed by partial distal gastrectomy and gastrojejunostomy, and he was discharged on the 20th day after admission, while the 4th patient underwent a radical subtotal gastrectomy with D2 lymphadenectomy and gastrojejunostomy. Postoperatively, he developed adult respiratory distress syndrome, multiorgan dysfunction syndrome and expired on the 3rd postoperative day of the second surgery. All the remaining 16 patients underwent partial distal gastrectomy and gastrojejunostomy and recovered well. Among these, 4 of them were malignant and the remaining were benign ulcers. All had an uneventful recovery. The percentage of malignancy in our series was 30% (6 out of 20 cases). In our study, 86% had an uneventful recovery, complications were seen in about 10%, and mortality was about 5%.

CONCLUSION: In giant gastric ulcer, the chances of malignancy and leak after primary closure are high. So, we feel that partial distal gastrectomy and gastrojejunostomy is better.

Key words: Giant; Gastric; Ulcer; Primary closure; Partial gastrectomy; Biopsy

Core tip: Giant gastric ulcer is considered to be more prone for perforation because of the large size and it is more likely to be malignant. Delay in seeking surgical care is to be discouraged because of the poor response to medical management. We have shown that with prompt treatment for perforated gastric ulcer, nearly 86% had uneventful recovery, complications were seen in about 10%, and mortality was about 5%. Furthermore, the chances of malignancy and leak after primary closure of giant gastric ulcer is high, so we feel partial distal gastrectomy and gastrojejunostomy is a better option, even in an emergency setting if the ex-

pertise is available.

Kumar P, Khan HM, Hasanrabba S. Treatment of perforated giant gastric ulcer in an emergency setting. *World J Gastrointest Surg* 2014; 6(1): 5-8 Available from: URL: http://www.wjgnet.com/1948-9366/full/v6/i1/5.htm DOI: http://dx.doi.org/10.4240/wjgs.v6.i1.5

INTRODUCTION

Giant gastric ulcer is defined as an ulcer greater than 2 cm in diameter[1]. It is usually found along the lesser curvature at incisura angularis. It is considered more prone for perforation because of the large size[2] and is more likely to be malignant, especially when associated with scalloped margins and loss of rugal folds around ulcer. These ulcers were traditionally treated by primary closure after taking a biopsy as it was presumed that patients would not tolerate gastrectomy in an emergency setting as the time taken is longer and prolonged anesthesia is contraindicated in compromised patients. In this paper, we have compared primary closure with partial gastrectomy and gastrojejunostomy for perforated giant gastric ulcer in an emergency setting.

MATERIALS AND METHODS

From May 2010 to February 2013, we operated on 20 cases (Table 1) of perforated giant gastric ulcer (> 2 cm, Figure 1A) in an emergency setting. All patients were > 45 years of age (Table 2), 15 males and 5 females. All patients presented with features of peritonitis with diffuse tenderness and abdominal guarding. All patients had tachycardia and 2 had hypotension. There were no significant abnormalities of the respiratory system. Plain X-ray of erect abdomen revealed gas under the diaphragm. All patients had a past history of several episodes of pain in the upper part of abdomen and were taking proton pump inhibitors. Except for leucocytosis with raised neutrophils, routine blood tests were normal. The renal parameters were slightly elevated.

All patients were resuscitated aggressively with crystalloids until the urine output was at least 30 mL per hour before being taken for surgery. In the first 4 cases, we performed primary closure after taking a biopsy as we thought that the patients would not tolerate gastrectomy in an emergency setting as the time taken is longer and prolonged anesthesia is contraindicated in compromised patients. The 3rd and 4th patients developed gastric fistula, leading to prolonged hospitalization.

In the 5th patient, when we opened the abdomen, we strongly suspected a malignant ulcer as margins were scalloped and there was a loss of rugal folds around ulcer and enlarged lymph nodes. Due to the bad experience of the previous patient, we decided to do a partial distal gastrectomy and gastrojejunostomy (Figure 1B). The patient

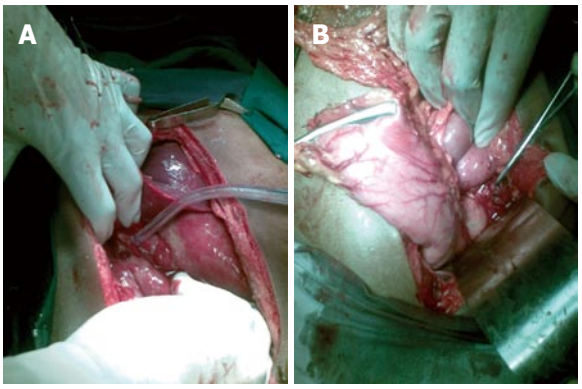

Figure 1 Photograph. A Perforated giant gastric ulcer; B: Stomach mobilized and divided at pyloroduodenal junction and duodenal stump closed by sutures.

recovered well, the biopsy report came as adenocarcinoma and chemotherapy post surgery was given.

Postprocedural management: the 3rd and 4th patients developed gastric fistula, leading to prolonged hospitalization.

For the 3rd patient, conservative management was tried for 1 wk, followed by partial distal gastrectomy and gastrojejunostomy when the oral feeds continued to come through the drain. He was discharged on the 20th day after admission.

The 4th patient underwent a radical subtotal gastrectomy with D2 lymphadenectomy and gastrojejunostomy on the 4th postoperative day when the biopsy report came back as a malignant ulcer. Postoperatively, he did not come out of anesthesia, was on ventilator, later developed adult respiratory distress syndrome (ARDS), multiorgan dysfunction syndrome (MODS) and expired on the 3rd postoperative day after the second surgery.

After this, we have done partial distal gastrectomy and gastrojejunostomy for 15 more patients, 4 of them malignant and the remaining benign ulcers, and all had an uneventful recovery. The malignant cases (6 out of 20) were also given postoperative chemotherapy.

Uneventful recovery was used to assess clinical outcome in our study.

RESULTS

Among the first 4 cases, 2 had an uneventful recovery and were discharged on 6th postoperative day (Table 1). The 3rd and 4th patients developed gastric fistula, leading to prolonged hospitalization. For the 3rd patient, conservative management was tried for 1 wk, followed by partial distal gastrectomy and gastrojejunostomy, and he was discharged on the 20th day after admission, while the 4th patient underwent a radical subtotal gastrectomy with D2 lymphadenectomy and gastrojejunostomy (Table 3). Postoperatively, he developed ARDS, MODS and expired on the 3rd postoperative day of the second surgery.

All the remaining 16 patients underwent partial distal gastrectomy and gastrojejunostomy and recovered well. Among these, 4 of them were malignant and the remain-

Table 1 Patient demography

Serial No.	Age, yr	Sex	Procedure undergone	Nature of gastric ulcer	Recovery	Discharge day post-operatively
1	47	Male	PC	BENIGN	U	6
2	54	Male	PC	BENIGN	U	6
3	52	Male	PC + DG + GJ	BENIGN	GF	17
4	77	Male	PC + SG + GJ + D2	MALIGNANT	GF + ARDS + MODS + M	-
5	63	Male	DG + GJ	MALIGNANT	U	6
6	74	Female	DG + GJ	BENIGN	U	6
7	79	Female	DG + GJ	BENIGN	U	6
8	57	Male	DG + GJ	BENIGN	U	6
9	53	Male	DG + GJ	MALIGNANT	U	8
10	46	Male	DG + GJ	BENIGN	U	
11	72	Male	DG + GJ	MALIGNANT	U	8
12	49	Female	DG + GJ	BENIGN	U	6
13	67	Male	DG + GJ	BENIGN	U	6
14	56	Male	DG + GJ	BENIGN	U	7
15	68	Female	DG + GJ	MALIGNANT	U	8
16	63	Male	DG + GJ	BENIGN	U	9
17	61	Male	DG + GJ	MALIGNANT	U	7
18	56	Female	DG + GJ	BENIGN	U	9
19	49	Male	DG + GJ	BENIGN	U	7
20	66	Male	DG + GJ	BENIGN	U	6

PC: Primary closure; DG: Distal gastrectomy; GJ: Gastrojejunostomy; SG: Subtotal gastrectomy; D2: D2 lymph node dissection for ca stomach; U: Uneventful recovery; GF: Gastric fistula; ARDS: Adult respiratory distress syndrome; M: Mortality; MODS: Multiorgan dysfunction syndrome.

Table 2 Distribution of patients according to age of the patients *n* (%)

Age group	Number of patients	
41-50	4 (20)	Mean age = 63 yr
51-60	6 (30)	
61-70	6 (30)	
71-80	4 (20)	
Total	20	

ing benign ulcers. All had an uneventful recovery (Table 4).

The percentage of malignancy in our series was 30% (6 out of 20 cases).

In our study, 86% had an uneventful recovery, complications were seen in about 10%, and mortality was about 5%.

DISCUSSION

Giant gastric ulcer is defined as an ulcer greater than 2 cm in diameter. It is usually found along the lesser curvature at incisura angularis[1,2]. It is considered more prone for perforation because of the large size and is more likely to be malignant[3-5], especially when associated with scalloped margins and loss of rugal folds around ulcer. Most giant ulcers occur beyond the middle span of life (all our patients were > 45 years of age). Indeed, the long history of most of these patients requires that they no longer be in the younger age group. The preponderance

Table 3 Distribution of patients according to the type of surgery *n* (%)

Type of surgery	Number of patients
PC	4 (18.2)
DG + GJ	17 (77.3)
SG + GJ + D2	1 (4.5)
Total	22

PC: Primary closure; DG: Distal gastrectomy; GJ: Gastrojejunostomy; SG: Subtotal gastrectomy; D2: D2 lymph node dissection for ca stomach.

Table 4 Distribution of patients according to recovery *n* (%)

Type of patient compliance	Number of patients
Uneventful recovery	18 (85.72)
Complications	2 (9.52)
Mortality	1 (4.76)
Total	21

of males is in agreement with the usual sex distribution of gastric ulcer disease. About half of the ulcers were in the antrum and half in the body. The frequency of massive bleeding and perforation indicates that giant ulcers are not immune to the usual complications of gastric ulcer disease.

The concept that giant gastric ulcers are most often benign presents the patient with an altered prognosis and makes an aggressive surgical attitude towards such a lesion even more important. Delay in seeking surgical care is to be discouraged because of the poor response to medical management[6].

Undue delay in exploration is no longer justified in a giant ulcer simply because of fear that an inoperable carcinoma will be found. On the contrary, all such patients should be subjected to exploration as soon as possible with the expectation that beneficial results may be obtained in a large percentage of these patients[7,8].

We have shown that with prompt treatment, nearly 86% had uneventful recovery, complications were seen in about 10%, and mortality was about 5%. Furthermore, the chances of malignancy and leak after primary closure of giant gastric ulcer is high, so we feel partial distal gastrectomy and gastrojejunostomy is a better option, even in an emergency setting if the expertise is available.

In conclusion, the chances of malignancy and leak after primary closure of giant gastric ulcer is high, so we feel partial distal gastrectomy and gastrojejunostomy is a better option, even in an emergency setting if the expertise is available.

ACKNOWLEDGMENTS

Written informed consent was obtained from the patients for publication of this case series and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

COMMENTS

Background

Giant gastric ulcer is considered more prone for perforation because of the large size and is more likely to be malignant. Delay in seeking surgical care is to be discouraged because of the poor response to medical management. Undue delay in exploration is no longer justified in a giant ulcer simply because of fear that an inoperable carcinoma will be found. On the contrary, all such patients should be subjected to exploration as soon as possible with the expectation that beneficial results may be obtained in a large percentage of these patients.

Research frontiers

These ulcers were traditionally treated by primary closure after taking a biopsy as it was presumed that patients would not tolerate gastrectomy in an emergency setting as the time taken is longer and prolonged anesthesia is contraindicated in compromised patients. In this paper, the authors have compared primary closure with partial gastrectomy and gastrojejunostomy for perforated giant gastric ulcer in an emergency setting.

Innovations and breakthroughs

With modern intensive care unit care, anesthesia and minimal access surgery, partial gastrectomy and gastrojejunostomy for perforated giant gastric ulcer in an emergency setting is a viable option.

Applications

The study results suggest that the chances of malignancy and leak after primary closure of giant gastric ulcer are high, so the authors feel that partial distal gastrectomy and gastrojejunostomy is a better option, even in an emergency setting if the expertise is available. In the study, after this surgery, nearly 86% had an uneventful recovery, complications were seen in about 10%, and mortality was about 5%.

Terminology

Giant gastric ulcer is defined as an ulcer greater than 2 cm in diameter. It is usually found along the lesser curvature at incisura angularis. It is considered more prone for perforation because of the large size and is more likely to be malignant. Emergency closure of perforation is essential as otherwise the acidic contents of stomach will enter the peritoneal cavity and cause peritonitis, a life threatening condition. Primary closure means simply closing the ulcer with sutures (stitches). Partial distal gastrectomy and gastrojejunostomy means removal of part of stomach along with ulcer and joining it to small intestine (jejunum) to maintain continuity of the gastrointestinal tract.

Peer review

The study is interesting. The aim of this study is to assess the clinical outcomes of various treatments for perforated giant gastric ulcer in an emergency setting.

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BRIEF ARTICLE

Implications of the presence of an aberrant right hepatic artery in patients undergoing pancreaticoduodenectomy

Ashwin Rammohan, Ravichandran Palaniappan, Anbalagan Pitchaimuthu, Kamalakannan Rajendran, Senthil Kumar Perumal, Kesavan Balaraman, Ravi Ramasamy, Jeswanth Sathyanesan, Manoharan Govindan

Ashwin Rammohan, Ravichandran Palaniappan, Anbalagan Pitchaimuthu, Kamalakannan Rajendran, Senthil Kumar Perumal, Kesavan Balaraman, Ravi Ramasamy, Jeswanth Sathyanesan, Manoharan Govindan, The Institute of Surgical Gastroenterology and Liver Transplantation, Centre for GI Bleed, Division of HPB diseases, Stanley Medical College Hospital, Chennai 600 001, India

Author contributions: Rammohan A, Palaniappan R, Pitchaimuthu A, Rajendran K and Perumal SK contributed to the conception and design, acquisition, analysis and interpretation of data; Rammohan A, Balaraman K, Ramasamy R and Sathyanesan J drafted the article and revised it critically for important intellectual content; Sathyanesan J, Palaniappan R and Govindan M gave the final approval of the version to be published.

Correspondence to: Dr. Ashwin Rammohan, The Institute of Surgical Gastroenterology and Liver Transplantation, Centre for GI Bleed, Division of HPB diseases, Stanley Medical College Hospital, Old Jail Road, Chennai 600 001, India. ashwinrammohan@gmail.com

Telephone: +91-988-4173583 Fax: +91-44-25289595

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Abstract

AIM: To analyze the differences in outcomes and the clinical impact following pancreatoduodenectomy (PD) in patients with and without aberrant right hepatic artery (aRHA).

METHODS: All patients undergoing PD between January 2008 and December 2012 were divided into two groups, one with aRHA and the other without. These groups were compared to identify differences in the intraoperative variables, the oncological clearance and the postoperative morbidity, mortality and hospital stay.

RESULTS: A total of 225 patients underwent PD, of which 43 (19.1%) patients were found to have either accessory or replaced right hepatic arteries (aRHA group). The aRHA was preserved in 79% of the patients. There was no significant difference in the intraoperative blood loss but operative time was prolonged, reflecting the complexity of the procedure [420 ± 44 (240-540) min *vs* 480 ± 45 (300-600) min, $P < 0.05$)]. There were no differences in the incidence of postoperative complications (pancreatic leak, pancreatic fistula, delayed gastric emptying and mortality) and hospital stay. Oncological clearance in the form of positive resection margins [13 (7.1%) *vs* 3 (6.9%)] and lymph node yield were also similar in the two groups.

CONCLUSION: An aRHA is found in approximately one fifth of patients undergoing PD. Preservation is technically possible in most patients and can increase the operative complexity but does not negatively affect the safety or oncological outcomes of the procedure.

Key words: Pancreatoduodenectomy; Aberrant right hepatic artery; Arterial anomalies; Outcomes

Core tip: Appreciation and study of hepatic arterial anatomical variability is essential to the successful performance of complex pancreaticobiliary procedures. An aberrant right hepatic artery (aRHA) represents the vascular anomaly encountered most frequently during pancreatoduodenectomy (PD) and, because of its course, is most susceptible to intraoperative damage and tumor involvement. When an aRHA is present, the challenge in peripancreatic malignant disease is to balance its preservation and the need to achieve oncological clearance. In this study, we analyzed the incidence of aRHA and its relationship with the operative complexity, occurrence of complications and oncological clearance in a large cohort of patients undergoing PD.

Rammohan A, Palaniappan R, Pitchaimuthu A, Rajendran K, Perumal SK, Balaraman K, Ramasamy R, Sathyanesan J, Govindan M. Implications of the presence of an aberrant right hepatic artery in patients undergoing pancreaticoduodenectomy. *World J Gastrointest Surg* 2014; 6(1): 9-13 Available from: URL: http://www.wjgnet.com/1948-9366/full/v6/i1/9.htm DOI: http://dx.doi.org/10.4240/wjgs.v6.i1.9

INTRODUCTION

Even although well described in the literature, the surgical anatomy of the hepatic arteries is notoriously variable. Appreciation and study of hepatic arterial anatomical variability is essential to the successful performance of complex pancreaticobiliary procedures, such as the pancreaticoduodenectomy (PD). Although anatomically interesting, the presence of aberrant hepatic arterial anatomy raises the surgical complexity and increases the potential risk of injury to the hepatic arterial supply during a PD[1]. The two most widely accepted classifications of hepatic arterial variations are those by Michels[2], based on 200 autopsies, and Hiatt, based on 1000 donor livers[2,3]. In both series, the most commonly reported vascular anomaly is an aberrant right hepatic artery (aRHA)[2,3].

An aRHA represents the vascular anomaly encountered most frequently during PD. It may have a suprapancreatic, intrapancreatic or rarely transpancreatic course, and, because of its course, it is most susceptible to intraoperative damage and tumor involvement[4,5]. The incidence of an aRHA identified in patients undergoing PD varies from 11%-26.5%[1,6]. When an aRHA is present, the challenge in peripancreatic malignant disease is to balance between its preservation and the need to achieve oncological clearance, which represents the only chance for prolonged survival[1,5,7]. The presence of an aRHA leads not only to an alteration in the surgical approach, but may also adversely affect the outcomes of the surgical procedure[5,8]. In this study, we analyzed the incidence of aRHA and its relationship with the operative complexity, occurrence of complications and oncological clearance in a large cohort of patients undergoing PD.

MATERIALS AND METHODS

The study was conducted over a five year period (2008-2012) which included all patients who underwent a PD by a single surgical team in a tertiary care center. Detailed information regarding their demography, characteristics, imaging, intraoperative findings and operative details were maintained on a prospective database. Demography and patient characteristics were carefully recorded. The details of the arterial anatomy, variations and the operative complexities, including duration of surgery and blood loss, were noted. In the specimen, the arterial margin was inked in addition to the resection margins. Postoperative course was recorded, with death during the same hospital stay or within 30 d of surgery being considered as operative mortality. Histopathology, along with resection margin status and lymph nodal yield, was also documented.

Table 1 Patient demography *n* (%)

Patient characteristics	No arterial anomaly *n* = 182	Arterial anomaly *n* = 43	*P* value
Age	52.1 ± 10.9	52.4 ± 11.2	NS
Males/females	135/53	32/11	NS
ASA			
Ⅰ	45 (24.7)	11 (25.6)	NS
Ⅱ	115 (63.2)	27 (62.7)	NS
Ⅲ/Ⅳ	22 (12.1)	5 (11.6)	NS

ASA: American Society of Anesthesiologists.

Definitions

Normal anatomy was defined as when the celiac axis trifurcated into the left gastric artery, the splenic artery and the common hepatic artery, with the common hepatic artery continuing as a hepatic artery proper after the branching off of the gastroduodenal artery, finally bifurcating into the right and left hepatic arteries. The term anomalous or aberrant encompassed both the "accessory" and the "replaced" vessels. An extra right hepatic artery that supplied the liver, which also received blood supply from a normally located right hepatic artery, was termed an accessory right hepatic artery. If the liver received its primary blood supply from the aberrant right hepatic artery, it was called a replaced hepatic artery.

Statistical analysis

Data are reported as frequencies or mean ± SD and ranges. SPSS version 20.0 (SPSS, Inc., Chicago, IL, United States) software was used for data analysis. The Student *t* test was used to test significance for continuous variables and the Fisher's exact test was used for categorical variables. *P* values less than 0.05 were considered significant.

RESULTS

Between January 2008 and December 2012, two hundred and twenty-five consecutive patients who underwent PD were included in the study. No significant differences were noted in terms of age, gender, American Society of Anesthesiologists class and indication for pancreaticoduodenectomy (Tables 1 and 2). The most common indication for surgery was ampullary adenocarcinoma, followed by distal cholangiocarcinoma. There were 43 (19.1%) arterial anomalies detected during the procedure. The spectrum of arterial anomalies is shown in Table 3. Replaced RHA from superior mesenteric artery (SMA) was the most common anomaly noted. The artery could be preserved in 79% of the cases (Table 4). In eight patients (6%) with aRHA, the aberrant vessel was sacrificed for oncological ($n = 6$) or technical ($n = 2$) reasons. While in 6, the aberrant artery was found to be accessory and was ligated. In two patients, there was an inadvertent

Table 2 Underlying disease in patients with and without arterial anomaly *n* (%)

Indication	No arterial anomaly *n* = 182	Arterial anomaly *n* = 43	*P* value
Ampullary adenocarcinoma	99 (54.4)	23 (53.5)	NS
Distal cholangiocarcinoma	43 (23.6)	10 (23.2)	NS
Pancreatic adenocarcinoma	25 (13.7)	6 (13.9)	NS
Duodenal carcinoma	15 (8.2)	3 (7.0)	NS
GIST	0	1 (2.3)	-

GIST: Gastrointestinal stromal tumor.

Table 3 Hepatic arterial variations observed during pancreaticoduodenectomy *n* (%)

Arterial variations	*n* = 43
Replaced RHA from SMA	31 (72.1)
Accessory RHA from SMA	10 (23.2)
Replaced CHA from SMA	1 (2.3)
Accessory RHA from GDA	1 (2.3)

RHA: Right hepatic artery; SMA: Superior mesenteric artery; GDA: Gateway design automation.

Table 4 Intraoperative management of aberrant artery *n* (%)

Management	*n* = 43
Dissection and preservation	34 (79)
Ligation	8 (18.6)
Dissection and primary anastomosis	1 (2.3)

Table 5 Intraoperative and postoperative comparison in patients with or without arterial anomalies *n* (%)

Variables	No arterial anomaly *n* = 182	Arterial anomaly *n* = 43	*P* value
Duration of surgery (min)	420 ± 44 (240-540)	480 ± 45 (300-600)	< 0.05
Blood loss (mL)	360 ± 52 (200-630)	390 ± 45 (300-650)	NS
Postpancreatectomy hemorrhage	4 (2.1)	1 (2.3)	NS
Postpancreatectomy fistula	9 (4.9)	2 (4.65)	NS
Delayed gastric emptying	98 (53.8)	23 (53.4)	NS
Length of hospital stay	13.6 ± 6.0	13.1 ± 5.1	NS
Mortality	3 (1.7)	1 (2.3)	NS
Positive margin	13 (7.1)	3 (6.9)	NS
Lymph node yield	12 ± 4	12 ± 5	NS

ligation which did not result in any ischemia of the liver; following an intraoperative Doppler confirmation, no reconstruction was undertaken. In one patient, the replaced right hepatic artery was resected for oncological reasons and a primary anastomosis was performed. Apart from an increase in operating time by approximately an hour, there were no other significant differences in intraoperative variables between the two groups (Table 5). There were also no differences in the overall rates of postpancreatectomy hemorrhage, postpancreatectomy fistula, delayed gastric emptying, positive resection margin, length of hospital stay and mortality between the two groups (Table 5). Seven point one percent of the patients undergoing PD had positive resection margins, 10 of them with their SMA margin positive for tumor. None of the arterial margins were positive for tumor (Table 5).

DISCUSSION

The significance of the aberrant arterial anatomy is enormous during surgery, especially PD. The artery could necessitate altering the surgical approach by interfering with the resection and/or lymphadenectomy. These anomalous vessels may interfere with reconstruction of the pancreatic remnant, precluding safe pancreatic stump drainage. Aberrant anatomy increases the risk of injury to the hepatic arterial supply, leading to unexpected bleeding (intra- or postoperative) and ischemia[1,5,7,9-11]. The extrahepatic biliary tree receives a substantial portion of its blood supply from the RHA. Any ischemia secondary to hepatic artery injury will lead to ischemia of the biliary anastomosis, resulting in a biliary anastomotic leak. Ischemic liver dysfunction may also manifest in the form of elevations in hepatic enzymes[1,5,7,9,10]. During dissection of these arteries, excessive handling of the vessel should be avoided as it may damage the vessel adventitia, thereby increasing the chances of pseudoaneurysm. This can lead to catastrophic complications in the event of pancreatic anastomotic leak[1,5,7,10,11].

A precise knowledge of normal hepatic arterial anatomy is necessary to appreciate abnormal anatomy. Preoperative imaging can detect up to 60%-80% of all arterial anomalies. If the anomaly is detected preoperatively, embolization of the vessel can be performed with microcoils[12-14]. It also helps to forewarn the surgeon, thereby preventing inadvertent injury to the RHA[1,7]. Multidetector row computed tomography (CT) (MDCT) scan shows enhanced delineation of the pancreatic lesion and vascular structures along with the benefit of CT angiography in preoperative delineation of the arterial anatomy[4,15]. A visceral angiography is recommended only when very rare or complex visceral arterial anomalies are encountered on noninvasive imaging[15,16]. Although advance planning is ideal, extemporaneous decisions may be required intraoperatively[1,7,10,11]. In our series, imaging picked up the anomalies preoperatively in 58% of the cases. Interestingly, Perwaiz *et al*[11] have shown that the duration of the surgery did not differ significantly between those patients whose arterial anomalies were detected preoperatively compared to those detected intraoperatively. A recent study from The Netherlands has shown that preservation of an aRHA is technically possible in most patients and does not negatively impact on outcomes in patients undergoing PD. Surgical morbidity is also not higher in patients with an aRHA[6]. Another study, a series from India, has shown that while oncological outcomes and safety of the procedure are not compromised, there is an increased operative complexity[11]. This is in concurrence with our study results. A report by Jah *et al*[17] showed a trend towards prolonged operative

times and blood loss but these did not reach statistical significance. This is mirrored in a study by Yang *et al*[18], whose incidence of postoperative complications, operating time and blood loss is similar to ours.

Prevention of the injury is the best policy. Hence, an early step in every PD should be a conscious attempt to define the vascular anatomy. After a complete kocherisation and opening of the pars flaccida, the porta hepatis should be palpated to determine the location of the arterial pulsation[1,5,7,10,11,19-24]. Any variation in the normal location of the proper hepatic artery pulsations should raise the suspicion of an aberrant artery. Performing intraoperative liver Doppler ultrasonography is recommended to ensure the results of the arterial sacrifice or reconstruction and to prevent postoperative complications[1,5,7,10,11,25,26]. Surgical expertise is a key factor in reducing morbidity so these patients should be managed in high volume centers where arterial reconstructions are routinely performed[19,27].

An all-important factor in the management of vascular anomalies is its recognition. There are multiple approaches to deal with an anomalous vessel interfering with the pancreatic resection. These include avoidance, ligation, dissection and traction away from the site of dissection, and division and anastomosis. Preservation is technically possible in most patients; this increases the operative complexity but does not negatively affect the safety or oncological outcomes of the procedure. A high index of suspicion in every patient along with an awareness of the normal and aberrant anatomy is a sine qua non to the performance of a safe pancreaticoduodenectomy.

COMMENTS

Background

An aberrant right hepatic artery (aRHA) is the most frequently encountered vascular anomaly during pancreatoduodenectomy (PD) which necessitates control of various arcades of the upper gastrointestinal tract. When an aRHA is present, the challenge in peripancreatic malignant disease is to balance its preservation and the need to achieve oncological clearance which represents the only chance for prolonged survival. The presence of an aRHA leads not only to an alteration in the surgical approach, but may also adversely affect the outcomes of the surgical procedure. This study was performed to analyze the differences in outcomes and the clinical impact following PD in patients with and without aRHA.

Research frontiers

Although well described in the literature, the surgical anatomy of the hepatic arteries is notoriously variable. Appreciation and study of hepatic arterial anatomical variability is essential for the successful performance of complex pancreaticobiliary procedures, such as the PD. Although anatomically interesting, the presence of aberrant hepatic arterial anatomy raises the surgical complexity and increases the potential risk of injury to the hepatic arterial supply during a PD.

Innovations and breakthroughs

There are multiple approaches to deal with an anomalous vessel interfering with the pancreatic resection. These include avoidance, ligation, dissection and traction away from the site of dissection, and division and anastomosis. Preservation is technically possible in most patients; this increases the operative complexity in the form of operating time but does not negatively affect the safety or oncological outcomes of the procedure.

Applications

An all-important factor in the management of vascular anomalies is its recognition. A high index of suspicion in every patient along with an awareness of the normal and aberrant anatomy is a sine qua non to the performance of a safe pancreaticoduodenectomy.

Terminology

The term anomalous or aberrant artery encompasses both the "accessory" and the "replaced" vessels. An extra right hepatic artery that supplies the liver, which also receives blood supply from a normally located right hepatic artery, is termed an accessory right hepatic artery. If the liver receives its primary blood supply from the aberrant right hepatic artery, it is called a replaced hepatic artery.

Peer review

This is a brief article that analyzed 225 patients who had a pancreaticoduodenectomy during the last 5 years. The content is interesting and it implies that aberrant right hepatic artery can be handled with no adverse consequences when treated in high volume centers.

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Beijing 100025, China
Telephone: +86-10-85381892
Fax: +86-10-85381893

Representative office
USA Office
8226 Regency Drive,
Pleasanton, CA 94588-3144, United States
Telephone: +1-925-2238242
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3 **Tian D**, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

Organization as author

4 **Diabetes Prevention Program Research Group**. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. *Hypertension* 2002; **40**: 679-686 [PMID: 12411462 DOI:10.1161/01.HYP.0000035706.28494.09]

Both personal authors and an organization as author

5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

No author given

6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

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7 **Geraud G**, Spierings EL, Keywood C. Tolerability and safety of frovatriptan with short- and long-term use for treatment of migraine and in comparison with sumatriptan. *Headache* 2002; **42** Suppl 2: S93-99 [PMID: 12028325 DOI:10.1046/j.1526-4610.42.s2.7.x]

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9 Outreach: Bringing HIV-positive individuals into care. *HRSA Careaction* 2002; 1-6 [PMID: 12154804]

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10 **Sherlock S**, Dooley J. Diseases of the liver and billiary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

Chapter in a book (list all authors)

11 **Lam SK**. Academic investigator's perspectives of medical treatment for peptic ulcer. In: Swabb EA, Azabo S. Ulcer disease: investigation and basis for therapy. New York: Marcel Dekker, 1991: 431-450

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12 **Breedlove GK**, Schorfheide AM. Adolescent pregnancy. 2nd ed. Wieczorek RR, editor. White Plains (NY): March of Dimes Education Services, 2001: 20-34

Conference proceedings

13 **Harnden P**, Joffe JK, Jones WG, editors. Germ cell tumours V. Proceedings of the 5th Germ cell tumours Conference; 2001 Sep 13-15; Leeds, UK. New York: Springer, 2002: 30-56

Conference paper

14 **Christensen S**, Oppacher F. An analysis of Koza's computa-

tional effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer, 2002: 182-191

Electronic journal (list all authors)

15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

Patent (list all authors)

16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

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REVIEW

Prediction and diagnosis of colorectal anastomotic leakage: A systematic review of literature

Freek Daams, Zhouqiao Wu, Max Jef Lahaye, Johannus Jeekel, Johan Frederik Lange

Freek Daams, Department of Surgery, Catharina Ziekenhuis, Postbus 1350, 5602 ZA Eindhoven, The Netherlands
Freek Daams, Zhouqiao Wu, Johan Frederik Lange, Department of Surgery, Erasmus Medical Center, Postbus 2040, 3000 CA Rotterdam, The Netherlands
Max Jef Lahaye, Department of Radiology, Maastricht University Medical Centre, Postbus 5800, 6202 AZ Maastricht, The Netherlands
Johan Frederik Lange, Department of Neuroscience, Erasmus Medical Center, Postbus 2040, 3000 CA Rotterdam, The Netherlands
Author contributions: Daams F, Wu Z, Jeekel J and Lange JF designed the paper; Daams F and Wu Z performed data acquisition; Daams F, Wu Z, Lahaye MJ, Jeekel J and Lange JF analysed and interpreted the data; Daams F, Wu Z, Lahaye MJ, Jeekel J and Lange JF drafted the article; Daams F, Wu Z and Lahaye MJ wrote the paper; Jeekel J and Lange JF approved of the paper.
Correspondence to: Freek Daams, MD, Department of Surgery, Erasmus Medical Center, Secretariaat Chirurgie, Erasmus-MC, Postbus 2040, 3000 CA Rotterdam,
The Netherlands. freek.daams@cze.nl
Telephone: +31-10-7043683 Fax: +31-10-7044746
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Abstract

Although many studies have focused on the preoperative risk factors of anastomotic leakage after colorectal surgery (CAL), postoperative delay in diagnosis is common and harmful. This review provides a systematic overview of all available literature on diagnostic tools used for CAL. A systematic search of literature was undertaken using Medline, Embase, Cochrane and Web-of-Science libraries. Articles were selected when a diagnostic or prediction tool for CAL was described and tested. Two reviewers separately assessed the eligibility and level of evidence of the papers. Sixty-nine articles were selected (clinical methods: 11, laboratory tests: 12, drain fluid analysis: 12, intraoperative techniques: 22, radiology: 16). Clinical scoring leads to early awareness of probability of CAL and reduces delay of diagnosis. C-reactive protein measurement at postoperative day 3-4 is helpful. CAL patients are characterized by elevated cytokine levels in drain fluid in the very early postoperative phase in CAL patients. Intraoperative testing using the air leak test allows intraoperative repair of the anastomosis. Routine contrast enema is not recommended. If CAL is clinically suspected, rectal contrast-computer tomography is recommended by a few studies. In many studies a "no-test" control group was lacking, furthermore no golden standard for CAL is available. These two factors contributed to a relatively low level of evidence in the majority of the papers. This paper provides a systematic overview of literature on the available tools for diagnosing CAL. The study shows that colorectal surgery patients could benefit from some diagnostic interventions that can easily be performed in daily postoperative care.

Key words: Colorectal; Anastomosis; Leakage; Diagnosis; Prediction

Core tip: Postoperative delay in diagnosis of colorectal anastomotic leakage is common and harmful. This paper provides a systematic overview of literature on the available tools for diagnosing colorectal surgery. The study shows that colorectal surgery patients could benefit from some diagnostic interventions that can easily be performed in daily postoperative care.

Daams F, Wu Z, Lahaye MJ, Jeekel J, Lange JF. Prediction and diagnosis of colorectal anastomotic leakage: A systematic review of literature. *World J Gastrointest Surg* 2014; 6(2): 14-26 Available from: URL: http://www.wjgnet.com/1948-9366/full/v6/i2/14.htm DOI: http://dx.doi.org/10.4240/wjgs.v6.i2.14

INTRODUCTION

Anastomotic leakage is the most frequent major adverse event after colorectal surgery and remains a large burden for patients and surgeons[1]. Despite evolutions in stapling techniques and operation modalities, incidence of anastomotic leakage after colorectal surgery (CAL) has not decreased over the last decade[1,2]. In the abundant literature on CAL, figures on incidence vary widely, most probably because many studies did not apply the unequivocal definition of CAL that has been available since 2010[3,4]. Clinical signs of CAL before the fifth postoperative day (POD) are uncommon, and most studies described a mean POD of 8 d for CAL to become clinically apparent. However, some studies even show that CAL is diagnosed at mean POD 12[5,6]. Short-term morbidity and mortality, as well as detrimental long-term effects, such as permanent stoma, might be reduced if CAL is detected and treated in an early phase[7]. Many studies have focused on preoperative risk factors, such as age, sex, neoadjuvant therapy, emergency surgery and distance to the anal verge, and should enable an estimation of risk of postoperative CAL[8-11]. Despite this caution, delay in diagnosis is common and has been described to be caused by false negative radiological investigation and intervening weekends[12]. This study was designed to provide colorectal surgeons with a systematic review of the predictive value of the diagnostic techniques for detection of CAL that are currently described in literature.

METHODS OF STUDY

Search methods

A systematic search of literature was undertaken using Medline, Embase, Cochrane and Web-of-Science libraries. No limitations for year of publication were applied. Search terms were: anastomosis, leakage, dehiscence, colorectal, rectum, resection, anterior resection, diagnosis, sensitivity, specificity, prediction, forecasting, monitoring. The search was restricted to publications in English and French. Full search syntax is shown in Addendum and was carried out lastly on 15 October, 2012. All references in eligible articles were screened for additional publications. Articles were retrieved according to the Preferred Items for Reporting of Systematic Reviews and Meta-Analyses guidelines (Figure 1).

Study selection

Articles were selected if a diagnostic tool or prediction model for CAL was described and tested, preferably using a reference. Furthermore, definition of CAL was required. If an article described more than one diagnostic tool, it was included for all the tools that were addressed, with the exception of the technique serving as reference/golden standard.

Studies were excluded if they reported on risk prediction of other complications than CAL. The included anastomosis were ileo-colic, colo-colic, colorectal and colo-anal. Total coloproctectomy with ileal pouch anal anastomosis was excluded since etiology, diagnosis and treatment are very different from the types of anastomosis mentioned before. Moreover, studies on risk factors for CAL and randomized trials studying treatment modalities were excluded, as were presentations, experimental studies, narrative reviews and letters to the editor.

Data extraction

For all eligible studies, a standard data extraction form was filled in and the following data were extracted: study design, number of patients, percentage of clinically important CAL, diagnostic tool and main results. If published, sensitivity, specificity, positive predictive value and negative predictive value were noted, or, if possible, calculated. If stated, the POD of CAL diagnosis was recorded. Furthermore, two authors (Daams, Wu) separately determined the level of evidence for validation studies according to the Levels of Evidence 2011 from the Centre for Evidence Based Medicine. In case of inconsistencies, agreement was accomplished by discussion.

RESULTS OF STUDY

The abstracts of a total of 859 articles were screened separately by 2 authors (Daams, Wu) for eligibility. Of these article, 771 were excluded, either for being written in a different language than French and English (n = 25), or for description of preoperative risk factors for CAL (n = 90), or due to irrelevance (n = 308), or because they described a patient cohort or randomized trial or experimental studies, or for other reasons than early detection of CAL (n = 348). This resulted in 88 articles, 18 of which were excluded after full text examination, either for being a narrative review (n = 3), or abstract (n = 11), or due to irrelevance (n = 4).

The remaining 70 articles were included and subdivided into 5 groups, according to type of method used. Two studies were included in two different groups, some studies related to more than one diagnostic tool from one category. (1) Clinical methods: Eleven articles focused on clinical methods, such as the value of physical examination (n = 1), the correlation between clinical symptoms and CAL (n = 5), the application of CAL risk scores (n = 2) or the direct postoperative prediction of the risk of CAL by the surgeon (n = 3); (2) laboratory tests: Twelve articles related to the correlation between CAL and postoperative levels of cytokines (n = 1), C-reactive protein (CRP, n = 10) or coagulation parameters (n = 1); (3) drain fluid analysis: Twelve articles related to diagnosis of CAL by analysing peritoneal drain fluid, in one case using two different methods in one study. The articles focussed on macroscopic findings of drain production (n = 2) or on drain fluid analysis of cytokine levels (n = 6), lipopolysaccharides levels (n = 1) or lysozym levels (n = 1). One article addressed the topic of intramucosal pH-measurement, and two articles focused on microdialysis of the peritoneal cavity; (4) intra-operative techniques: Twenty-three articles investigated the correlation between preop-

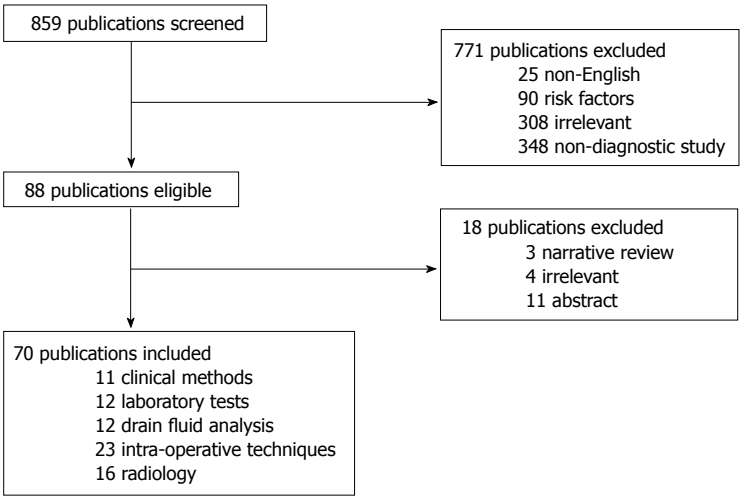

Figure 1 Preferred items for reporting of systematic reviews and meta-analyses-chart for included articles. Two articles could be included in two subgroups.

erative assessment of the anastomosis and CAL, using one or more of the following techniques: air/methylene blue leak test (ALT, n = 13), intraoperative endoscopy (IOE, n = 4), Doppler ultrasound (n = 2), tissue oxygen tension measurement (n = 1), intraoperative inspection of marginal artery bleeding (n = 1), laser fluorescence angiography (LFA, n = 1) and near infra-red/visible light spectroscopy (n = 2); and (5) radiology: Sixteen studies evaluated the accuracy of one or more of the following radiological techniques in detecting CAL: computer tomography (CT, n = 7), water-soluble contrast enema (WSCE, n = 10) and plain X-ray (n = 2).

Clinical methods

Table 1 gives an overview of the main results of the eleven included studies. Three studies described direct postoperative CAL risk prediction by the surgeon. Two studies described direct postoperative assessment by the surgeon as valuable[13,14]. Karliczek *et al*[15] prospectively studied subjective assessment of the risk of CAL by the surgeon directly after surgery. Low predictive values were found, with a sensitivity of 62% and a specificity of 52% for low rectal anastomosis.

Five studies analysed the postoperative clinical course of patients with CAL in comparison to patients with an uncomplicated course. Two retrospective studies noted that occurrence of respiratory and neurological disorders often precede CAL after colonic surgery (OR = 2.8 and 5.3 respectively)[16,17]. One prospective study noted that cardiac disorders preceded CAL in 40% of 22 patients with CAL[18]. A small study reported no differences in heart rate variability between patients with and without CAL[19]. In a prospective study by Nesbakken *et al*[20], the postoperative assessment of the patient by the surgeon was reported to have high specificity and low sensitivity (91% and 50% respectively). Tang *et al*[21] investigated the value of digital rectal examination in assessing CAL before stoma closure, and found a sensitivity of 98.4%.

Two Dutch authors developed and applied leakage scores for the detection of CAL. One risk score prospectively combined preoperative and intraoperative items and yielded a twofold higher score in patients with CAL than in patients without CAL[22]. For postoperative clinical course assessment, a standardized leakage score was developed by den Dulk *et al*[23] attributing points to certain clinical factors, nutritional status and biochemic findings, thus identifying high risk patients. It facilitated the diagnosis of CAL at POD 6, as opposed to POD 8 in a historical control group.

Laboratory tests

Ten studies investigated the correlation between postoperative levels of CRP and CAL as shown in Table 2[24-28]. Five of them were included in a meta-analysis of 1832 patients by Warschkow *et al*[24], which did not focus solely on CAL but on all postoperative infectious complications. In all studies, CRP-levels were elevated several days before the diagnosis of CAL was established. Slotwinski and colleagues reported higher levels of soluble-tumour necrosis factor (TNF)-receptor at POD 1 in patients who developed CAL after colorectal surgery[29]. Iversen *et al*[30] studied levels of markers of coagulation and fibrinolysis in patients with CAL showed elevated levels 5-6 PODs before clinical onset of CAL compared to patients without leakage.

Drain fluid analysis

Table 3 shows twelve studies on drain fluid analysis. Six out of twelve studies investigated cytokine levels after colorectal surgery, mainly focussing on interleukin (IL)-6, IL-10 and TNF-α. In 4 of these studies, patients after colorectal surgery who developed CAL at POD 5-20 had elevated cytokine levels from POD 1 onwards[31-34]. One study reported the same phenomenon, but the onset of increased cytokine levels was POD 3[35]. Another study did not find a relation between CAL and levels of IL-6 and TNF-α[36]. In two studies describing the technique of microdialysis, local signs of ischemia were measured before CAL became clinically apparent in some patients, although both studies also describe patients with CAL who showed no preceding abnormal microdialysis values[33,37]. Macroscopic changes in drain production were

Table 1 Clinical methods

Author	Type of study	Loe	*n* (CAL/non-CAL)	Colorectal/rectum	Stapled/handsewn anastomosis	Study subject/tool		Se	Sp	PPV	NPV	ROC	Main outcome
Dekker *et al*[22]	Pro	3b	10/121	Colorectal	?	Leakage score		-	-	-	-	0.95	OR = 1.74 for leakage score predictive of CAL
den Dulk *et al*[23]	Pro	2b	21/223	Colorectal	Both	Leakage score		-	-	-	-	-	Delay of treatment reduced from 4 d to 1.5 d
Sutton *et al*[18]	Pro	3b	22/398	Colorectal	?	Clinical symptoms		0.33	0.97	0.59	0.93		Over 40% of patients with cardiac event has CAL
Haase *et al*[19]	Pro	4	3/40	Colorectal	?	Clinical symptoms		-	-	-	-	-	No difference in heart rate variability between CAL and non-CAL
Ghariani *et al*[17]	Retro	3b	23/314	Colon	?	Clinical symptoms		-	-	-	-	-	Respiratory, neurological disorders and bloating precipitate CAL
Bellows *et al*[16]	Retro	3b	25/311	Colorectal	?	Clinical symptoms	Respiratory symptoms	0.52	0.84	0.22	0.95	-	Respiratory, neurological disorders and abdominal pain and distension precipitate CAL
							Neurology symptoms	0.24	0.97	0.4	0.94	-	
							Abdominal pain and distension	0.52	0.83	0.21	0.95	-	
Nesbakken *et al*[20]	Pro	3b	5/56	Rectum	?	Clinical symptoms	Daily assessment by surgeon	0.50	0.89	0.5	0.89	-	50% of CAL is silent
Tang *et al*[21]	Pro	3b	10/195	Rectum	Both	Digital rectal examination		0.98	-	-	-	-	As valuable as WSCE before stoma closure
Pettigrew *et al*[13]	Pro	3b	28/113	Colorectal and general	?	Risk prediction by surgeon		0.38	0.91	0.56	0.82		Highest predictive value for postop surg assessment
Makela *et al*[14]	Retro	3b	44/88	Rectum	Both	Risk prediction by surgeon		-	-	-	-	-	In 86% of pts with > 3 risk factors CAL occurs
Karliczek *et al*[15]	Pro	3b	26/191	Colorectal	?	Risk prediction by surgeon	High anastomosis	0.38	0.46	-	-	-	Low predictive value for prediction of CAL by surgeon
							Low anastomosis	0.62	0.52	-	-	-	

Pro: Prospective; Retro: Retrospective; Loe: Level of evidence; CAL: Colorectal anastomotic leakage; Se: Sensitivity; Sp: Specificity; PPV: Positive predictive value; NPV: Negative predictive value; ROC: Receiver-operating characteristic curve; WSCE: Water soluble contrast enema.

examined by Tsujinaka *et al*[38]. Of 21 patients with CAL, 15 had previous changes in drain content, while other clinical signs were not obvious. Likewise, Eckmann *et al*[39] found that 80% patients that developed CAL after rectum resection had changes in drain fluid aspect. By measuring intramucosal pH, Millan *et al*[40] found that the risk of CAL was 22 times higher when juxta-anastomotic intramucosal pH was below 7.28. In a small study, intraperitoneal levels of lipopolysaccharides were elevated from POD 3 in patients with CAL, while CAL was only clinically evident at mean POD 6, 7[41]. By contrast, lysozyme activity was not correlated with clinical CAL in another small study[42].

Intra-operative techniques

Table 4 demonstrates the studies on intraoperative techniques to detect CAL. Thirteen studies on peroperative leak tests were evaluated[43-55]. Although these tests facilitate intraoperative repair of the anastomosis or creation of faecal diversion in case of air leakage or methylene blue leakage, postoperative leakage rates were not reduced to 0%. A study by Beard, reported on 18 intraoperative anastomotic corrections, leading to CAL in 3 patients in the "test"-group, compared to 10 patients with CAL in the "no test"-group[43]. As with the air leak test, colonoscopy, performed in 4 studies, led to intraoperative correction of the anastomosis for reasons of leakage and bleeding[52,56-58]. All studies reported low incidences of CAL, although no study compared intraoperative colonoscopy to no intraoperative control. Two studies comparing routine intraoperative colonoscopy to selective use of this technique showed no benefit of routine application of this technique[57,58]. For assessing local anastomotic blood flow, multiple techniques have been described. Ambrosetti *et al*[59] studied the use of Doppler intraoperatively at the site of the anastomosis, enabling correction of the anastomosis in 10 of 200 patients, leading to CAL in 2 (1%). Vignali *et al*[60] found

Table 2 Laboratory tests

Author	Type of study	Loe	*n* (CAL/non-CAL)	Colorectal/rectum	Stapled/handsewn anastomosis	Study subject/tool	Cut-off value	Se	Sp	PPV	NPV	ROC	Main outcome	Onset CAL (POD)
Slotwinksi *et al*[29]	Pro	3b	2/16	Colorectal	?	sTNF-R1, IL-1RA/-6/-8/-10, CRP	-	-	-	-	-	-	TNF higher at POD 1 in CAL	?
Iversen *et al*[30]	Pro	3b	17/34[1]	Colorectal	Both	s-Fibrin, TAT-complex, PT-f1/-2	-	-	-	-	-	-	PT-f1/-2, TAT-complex, s-Fibrin higher at POD 1/2 in CAL	7
Woeste *et al*[25]	Retro	3b	26/342	Colorectal	Both	CRP	-	-	-	-	-	-	CRP higher from POD 3 to POD 7 in CAL	8,7
Warschkow *et al*[24]	Meta	3a	?/1832	Colorectal	Both	CRP	135 mg/L at POD 4	0.680	0.830	0.560	0.89	-	CRP < 135 mg/L at POD 4 discharge is safe	?
Kornerin *et al*[24]	Retro	3b[3]	18/231	Colorectal	Both	CRP	190 mg/L at POD 3	0.820	0.730	-	-	0.820	Persisting elevation of CRP is indicative for CAL	8
Mackay[in] *et al*[24]	Pro	3b[3]	5/160	Colorectal	?	CRP	145 mg/L at POD 4	0.850	0.860	0.610	0.96	-	CRP > 145 mg/L at POD 4 is highly predictive for CAL	?
Ortega[in] *et al*[24]	Pro	3b[3]	21/133	Colorectal	Both	CRP	125 mg/L at POD 4	0.820	0.960	-	-	-	CRP > 125 mg/L at POD 4 discharge is not safe	6
Welsch[in] *et al*[24]	Pro	3b[3]	22/96[1]	Rectum	Staples	CRP	140 mg/L at POD 3	0.80[2]	0.81[2]	0.86[2]	-	-	Persisting elevation of CRP is indicative for CAL	8
Warschkow[in] *et al*[24]	Retro	3b[3]	89/1115	Colorectal	?	CRP	143 mg/L at POD 4	0.750	0.710	0.190	0.97	-	Use CRP as screening at POD 4	9
Platt *et al*[26]	Pro	3b	26/454	Colorectal	Both	CRP	190 mg/L at POD 3	0.772	0.80[2]	-	-	0.89[2]	CRP at POD 3 is useful for predicting CAL	6-8
Matthiessen *et al*[27]	Pro	3b	9/33	Rectum	?	CRP	-	-	-	-	-	-	CRP higher from POD 2 in CAL	8
Almeida *et al*[28]	Retro	3b	24/149	Colorectal	?	CRP	140 mg/L at POD 3	0.780	0.860	-	-	-	CRP sign higher from POD 2 in CAL	7

[1]Selected groups; [2]All complications; [3]Included in meta-analysis. Pro: Prospective; Retro: Retrospective; Meta: Meta-analysis; Loe: Level of evidence; CAL: Colorectal anastomotic leakage; TNF: Tumour necrosis factor; IL: Interleukin; CRP: C-reactive protein; TAT: Thrombin-antithrombin complexes; PT: Prothrombin; POD: Postoperative day; Se: Sensitivity; Sp: Specificity; PPV: Positive predictive value; NPV: Negative predictive value; ROC: Receiver-operating characteristic curve.

that reduced microperfusion at the rectal stump, during creation of a colorectal anastomosis, measured by laser Doppler increased the risk of CAL. In a study by Kudszus *et al*[61] intraoperative LFA led to 28 intraoperative corrections, an absolute reintervention rate of 4% and reduced hospital stay. Hirano *et al*[62] studied the application of near infrared spectroscopy of the anastomosis. In their small study, perianastomotic StO_2 < 60 mmHg was measured in patients who developed CAL. In a similar study by Karliczek *et al*[63], using visible light spectroscopy, changes in perianastomotic pO_2 before and after creation of the anastomosis had a significant correlation with CAL. One study showed that reduced pO_2 in perianastomotic tissue was predictive for CAL, although cut-off values for routine clinical application were lacking[64,65].

Radiology

Table 5 demonstrates sixteen studies evaluated several imaging modalities for the detection of CAL. Seven studies in this review used computed tomography (CT) for the detection of CAL[20,66-78]. A prospective study by Nesbakken *et al*[20] reported a 94% accuracy for 5 patients with CAL out of 56 patients who had received rectum resection. Similarly, Eckman *et al*[77] concluded that CT detected 29 of 30 leaks in a group of 305 patients after stapled rectum resection, although no data were presented on the specificity of the technique. Gouya *et al*[75]

Table 3 Drain fluid analysis

Aauthor	Type of study	Loe	*n* (CAL /non-CAL)	Colorectal/ rectum	Stapled/ handsewn anastomosis	Study subject/tool	Main outcome	Onset CAL (POD)
Bertram *et al*[36]	Pro	4	3/28	Colorectal	?	Cytokines	No correlation between IL-6, TNF-alpha and CAL	5.3
Herwig *et al*[34]	Pro	3b	12/24	Colorectal	?	Cytokines	IL-6 and TNF-alpha elevated from POD 1 in CAL	5.8
Yamamoto *et al*[35]	Pro	3b	7/90	Colorectal	Stapled	Cytokines	IL-1beta, IL-6, TNF-alpha elevated from POD 3 in CAL	5-8
Ugras *et al*[32]	Pro	3b	4/34	Colorectal	Both	Cytokines	IL-6, IL-10, TNF-alpha elevated from POD 1 in CAL	6
Fouda *et al*[31]	Pro	3b	8/56	Rectum	Both	Cytokines	IL-6, IL-10 elevated from POD 1 in CAL, TNF-alpha elevated from POD 2 in CAL	6
Mattiessen *et al*[33]	Pro	3b	7/23	Rectum	?	Microdialysis, cytokines	L/P-ratio elevated at POD 5/6 in CAL; IL-6, IL-10, TNF-alpha elevated from POD 1 in CAL	Early CAL: 6 Late CAL: 20
Ellebaek *et al*[37]	Pro	3b	4/50	Colorectal	?	Microdialysis	Mean L/P-ratio higher in CAL,	Early CAL: 5-10 Late CAL: 20
Tsujinaka *et al*[38]	Pro	3b	21/196	Rectum	Both	Drainproduction	15/21 Patients with CAL had changes in drain content	7
Eckmann *et al*[39]	Retro	3b	30/306	Rectum	Stapled	Drainproduction	80% of leakages were indicated by drain, 40% of which prior to clinical symptoms	?
Millan *et al*[40]	Pro	3b	6/90	Colorectal	Stapled	Intramucosal pH	Intramucosal pH < 7.28 on POD1 increases risk of CAL 22 fold	?
Junger *et al*[41]	Pro	3b	3/22	Colorectal	Both, biodegradable ring	LPS	Excretion of LPS and LPS concentration is higher at POD 3 in CAL	6,7
Miller *et al*[42]	Pro	2b	2/42	Rectum	Stapled	Lysozym activity	No correlation between lysozyme activity and CAL	?

Pro: Prospective; Retro: Retrospective; Loe: Level of evidence; CAL: Colorectal anastomotic leakage; LPS: Lipopolysaccharides; IL: Interleukin; TNF: Tumour necrosis factor; POD: Postoperative day.

even reported an excellent 100% sensitivity and specificity. However CT will only show leakage of intraluminal contrast at the site of the CAL in 10% of the patients[67]. Improved results are achieved with the detection of associated features such like pericolic/pelvic fluid collections[78]. Presacral abnormalities, commonly described as caused by leakage, were found in 70% of the patients without clinical anastomotic leakage[68].

Ten studies investigated the value of the water-soluble contrast enema in determining CAL, mostly after rectum resection, both in the postoperative phase and before closure of deviating ileostomy[20,66,67,69-75]. All studies described a high degree, in one case even up to 41%[72], of asymptomatic radiological leakage that resolved without therapeutic intervention. In addition, no study performed contrast enemas in the very early postoperative phase (< POD 5) due to the potential risk of complications so that, when performed at POD 7, 8, a clinical leakage concurred with radiological leakage. For these reasons, most studies concluded that routine application of WSCE at POD 7, 8 did not contribute to clinical decision-making or to early detection. In the presence of clinical signs suggestive for CAL, a study by Nesbakken *et al*[20] described an accuracy of 93% for WSCE in the detection of CAL. Doeksen *et al*[67] reported a high specificity and positive predictive value of 94% and 91% respectively, with an interobserver variability of 14%.

Two studies investigated the value of plain X-ray. One of these studies reported that increase of subdiafragmatical free air after POD5 increased the likelihood of CAL[76]. The other study, by Williams *et al*[79], reported that the finding of staple line disruption on plain X-ray was suggestive for CAL.

In this paper, all available evidence on the diagnostic tools for detection of CAL was systematically reviewed, according to the guidelines of the Oxford Centre of evidence based medicine. Diagnostic techniques were appraised for their ability to predict or detect clinically relevant CAL, since this is relevant in daily care for patients directly after colorectal surgery. Early intervention in abdominal sepsis is essential as is shown by the Surviving Sepsis Campaign, emphasizing on source identification and surgical control when possible[80].

Many studies report data on asymptomatic or radiological CAL. However, these data were not included in this review, since asymptomatic CAL, if detected, will be left untreated as a rule. Furthermore, it has a poor correlation with clinically relevant CAL. Theoretically, asymptomatic CAL might prove to be important if the oncologic outcome is studied, since equivocal literature is available showing a higher percentage of local recurrence after CAL[81-83]. To this date, however, the role of asymp-

Table 4 Intra-operative techniques

Author	Type of study	Loe	*n* (CAL/non-CAL	Colorectal/rectum	Stapled/handsewn anastomosis	Test	Test performed	Test +	Intra-operative correction	CAL test +	Test -	CAL test -	Test not performed	CAL test not performed	Main outcome
Beard *et al*[43]	Pro	1b	13/145	Colorectal	Both	ALT	73	18	18	3	55	0	70	10	ALT and preoperative repair reduce risk of AL
Davies *et al*[44]	Pro	3b	4/33	Rectum	?	ALT	33	6	6	1	27	3	-	-	LT helpful to reduce leakage rate
Dixon *et al*[45]	Retro	3b	2/202	Rectum	Both	ALT	119	5	5	0	114	0	-	-	Leaks were avoided
Gilbert *et al*[46]	Retro	3b	1/21	Colorectal	Handsewn	ALT	21	5	5	1	16	0	-	-	ALT facilitates IOR
Lazorthes *et al*[47]	Pro	3b	3/82	Colorectal	Stapled, doughnut complete 68	ALT	68	0	0	0	68	3	-	-	High NPV for ALT
					Stapled, doughnut incomplete 14		14	4	4	0	10	0	-	-	
Ricciardi *et al*[48]	Retro	3b	48/998	Colorectal	Both	ALT	825	65	65	5	760	29	173	14	ALT for leftsided anastomosis
Schmidt *et al*[49]	Pro	3b	68/933	Rectum	Both	ALT	260	47	42	5	213	22	36	4	Risk of AL is unrelated to ALT
Wheeler *et al*[50]	Pro	4	7/102	Colorectal	?	ALT	99	21	21	2	85	2	-	-	LT facilitates IOR
Yalin *et al*[51]	Po	3b	1/23	Colo-rectal	Stapled	ALT	21	5	5	1	16	0	-	-	LT facilitates IOR
Griffith *et al*[54]	Pro	4	2/60	Colorectal	Stapled	ALT	60	11	11	0	49	2	-	-	ALT facilitates IOR
Sakanoue *et al*[55]	Pro	3b	4/70	Rectum	?	ALT	35	2	2	0	33	0	35	4	Useful for intraoperative decision making
Smith *et al*[53]	Pro	4	7/229	Colon	Both	ALT	229	16	16	0	213	7	-	-	After IOR no CAL occurred
Lanthaler *et al*[56]	Pro	3b	6/122	Colorectal	Stapled	IOE	73	5	5	0	68	4	49	2	ALT prevents early leak
Li *et al*[57]	Pro	3b	2/244	Rectum	Stapled	IOE	107	11	11	0	96	0	137, 30 IOC[1]	2/137, 1/30	Routine IOE and selective IOE equal results
Shamiyeh *et al*[58]	Pro	3b	7/253	Rectum	Stapled	IOE	85	2	2	0	83	1	253	4	Routine IOE does not reduce CAL
Ishihara *et al*[52]	Pro	4	1/73	Rectum	Stapled	IOE and ALT	73	4	4	0	69	1	-	-	ALT recommended
Ambrosetti *et al*[59]	Pro	4	2/200	Colorectal	Both	Doppler ultra-sound									Doppler facilitates IOR
Vignali *et al*[60]	Pro	3b	8/55	Colorectal	Stapled	Laser doppler	-	-	-	-	-	-	-	-	Reduction in microperfusion increases risk of CAL
Kudszus *et al*[61]	Retro	3b	22/402	Colorectal	Both	LFA	201	28	28	8	-	-	201	15	LFA reduces reoperation rate for AL, most prominent in handsewn
Hirano *et al*[62]	Pro	4	1/20	Colorectal	?	Near infrared spectro-scopy									StO_2 < 60% in CAL

Novell *et al*[64]	Pro	3b	275	Colorectal	Both	Obser-vation of marginal artery bleeding					Pulsatile flow: lower incidence CAL
Sheridan *et al*[65]	Pro	3b	5/50	Colon	?	Tissue pO_2 measurement					Reduced anastomotic pO_2 predictive CAL
Karliczek *et al*[63]	Pro	3b	14/77	Colorectal	?	Visible light spectro-scopy					pO_2 could predict CAL

[1]Indicated by the surgeon. Pro: Prospective; Retro: Retrospective; Exp: Experimental (model); Loe: Level of evidence; CAL: Colorectal anastomotic leakage; ALT: Air or methylene blue leak test; IOC: Intra-operative endoscopy; LFA: Laser fluorescence angiography; IOR: Intra-operative repair; NPV: Negative predictive value.

Table 5 Radiology

Author	Type of study	Loe	*n* (CAL/ non-CAL)	Colorectal/ rectum	Stapled/ handsewn anastomosis	Study tool	Se	Sp	PPV	NPV	Main outcome
Eckmann *et al*[77]	Retro	3b	30/306	Rectum	Stapled	CT	-	-	-	-	29 of 30 CAL detected by CT
Power *et al*[78]	Retro	3b	17/50	Colorectal	?	CT	0.30	0.90	0.58	0.74	Peri-anastomotic located fluid containing air found in CAL
Gouya *et al*[75]	Retro	3b	10/195	Rectum	?	CT	-	-	1.00	1.00	CT has role in predicting CAL
DuBrow *et al*[68]	Retro	3b	35/75	Rectum	?	CT	-	-	-	-	30% of pts with CAL have presacral abnormalities
Nicksa *et al*[73]	Retro	4	36 CAL	Rectum	?	CT	0.12	-	-	-	Low percentage true positives
Doeksen *et al*[67]	Retro	3b	68/429	Colorectal	?	CT	0.54	0.78	0.68	0.66	Interobserver variability 10%
Nesbakken *et al*[20]	Pro	3b	5/56	Rectum	?	CT	0.57	1.00	-	-	94% accuracy of CT for detection of CAL
Severini *et al*[74]	Retro	3b	12/175	Rectum	?	WSCE	-	-	-	-	2 CAL out of 78 positive WSCE, low predictive value
Hoffmann *et al*[70]	Retro	3b	5/51	Colorectal	Both	WSCE	0.20	0.85	0.13	0.91	WSCE not recommended for routine use
Markham *et al*[72]	Retro	3b	1/136	Rectum	Handsewn	WSCE	1.00	0.57	0.02	1.00	WSCE no contribution to surgical management
Kalady *et al*[71]	Retro	3b	8/211	Rectum	?	WSCE	0.88	1.00	1.00	0.99	WSCE does not provide additional information
Akyol *et al*[66]	Pro	3b	12/233	Colorectal	Both	WSCE	0.52	0.87	0.30	0.94	WSCE provides little useful clinical information
Haynes *et al*[69]	Retro	3b	14/117	Colorectal	Both	WSCE	0.71	0.86	0.42	0.96	WSCE not recommended for routine use
Gouya *et al*[75]	Retro	3b	10/195	Rectum	?	WSCE	-	-	1.00	0,98	WSCE is recommended for routine use
Nicksa *et al*[73]	Retro	4	36 CAL	Rectum	?	WSCE	0.88	-	-	-	WSCE superior to CT
Doeksen *et al*[67]	Retro	3b	68/429	Colorectal	?	WSCE	0.68	0.94	0.91	0.76	Interobserver variability 13%
Nesbakken *et al*[20]	Pro	3b	5/56	Rectum	?	WSCE	0.60	1.00	-	-	93% accuracy of WSCE for detection of CAL
Williams *et al*[76]	Retro	4	10/31	Rectum	Stapled	X-ray	0.90	1.00	1.00	0.95	Staple line dehiscence in 9/10 patients with CAL
Tang *et al*[79]	Pro	4	2/64	Colorectal	?	X-ray	-	-	-	-	Increase free air after POD 5 higher chance CAL

Pro: Prospective; Retro: Retrospective; Meta: Meta-analysis; Leo: Level of evidence; CAL: Colorectal anastomotic leakage; CT: Computer tomography; WSCE: Water-soluble contrast enema; Se: Sensitivity; Sp: Specificity; PPV: Positive predictive value; NPV: Negative predictive value; POD: Postoperative day.

tomatic CAL in local recurrence is unknown.

Two investigators separately evaluated all eligible studies and a level of evidence was assigned to each of them. Overall, the level of evidence was considered low. This was due to factors that coincide with the problem of CAL. First, in the field of the diagnosis of CAL, no definition of CAL is available, nor is a golden standard[3]. Such a golden standard cannot even be found in relaparotomy during which faecal discharge at the site of the anastomosis is established, since many patients are treated for CAL without direct visualization of the anastomosis during reoperation. Secondly, a major cause of the low level of evidence is the fact that many studies lack a non-test group. Finally, guidelines to determine the level of evidence differ between diagnostic studies and their therapeutic counterparts. Publication bias and reporting bias in particular were estimated to be low, since the primary search yielded many studies with negative results and small numbers of subjects.

Much research has been done on the early detection of leakage after ileoanal pouch reconstruction following total colectomy for inflammatory bowel disease. These studies were excluded from this review, since they comprise more extensive surgery, different types of leakage, other types of pouch failure and different therapy modalities.

Clinical methods

Clinical factors are objective and easily available for risk prediction. A few problems, however, occur if surgeons rely solely on clinical factors. First, the influence of individual factors is not exactly known. Secondly, by the time signs of septicaemia occur; patients will be in a worse clinical state at the onset of an often prolonged and onerous therapeutic course. Subjective prognosis of leakage at the moment of finishing the anastomosis was proven to have a limited prognostic value[15]. Objective measurements might be of greater prognostic value, as shown by the Colon Leakage Score, in which the presence of objective risk factors leads to a higher score representing a higher chance of CAL[22]. This leakage score was based on previously identified risk factors and to our knowledge is the first to translate all available literature on risk factors for CAL into an instrument that can easily be implemented in daily practice. In a cohort of 233 patients, using a historical control group of 1066 patients, den Dulk *et al*[23] developed a similar score system for postoperative clinical evaluation of the colorectal patient. When a high score is found, computer tomography using rectal contrast is warranted. Although this promising method has shown to reduce delay in diagnosis, no information was provided on the prognostic value of this risk score, nor did the study mention the number of CT-scans and concomitant negative results In a study on tracking of surgical site infections (SSI), van Ramshorst *et al*[84] found that protocolled tracking yields a higher reported incidence of SSI than self-reported detection. We believe that this finding could be applied to the protocolled detection of CAL as described above, as it contributes to increased awareness and early detection. Little is known about the value of physical examination in relation to CAL, except that digital rectal examination has at least the same prognostic value for low anastomosis as contrast enema prior to stoma reversal.

Laboratory tests

Many investigators have studied the behaviour of CRP during the subclinical phase of CAL. CRP has the capacity to rise quickly after the onset of an inflammatory stimulus, reaching its highest serum level within 48 h. Since it has a short halftime of around 19 h, a drop in CRP corresponds well with the removal of the stimulus. Most studies investigating CRP used cut-off values of around 120-190 mg/L at POD 3, 4, and all studies in this review showed a reasonable predictive value of CRP for CAL. Drawbacks of all studies described in this review is that the number of included patients per study is rather small and that none of these studies provide a protocol that structurally describes the postoperative clinical examination, the clinical state of the patients during postoperative follow-up and the type of CAL (*i.e.*, faecal peritonitis, juxta-anastomotic abscess, rectovaginal fistula). Despite these drawbacks, we believe that these studies have indeed shown that measurement of CRP is of great importance in detecting CAL in the preclinical phase.

Other laboratory tests like coagulation factors and cytokines show a correlation with occurrence of CAL, but they have been studied sparsely. Since no parameters for their predictive value can be calculated from the available data, there is no basis for incorporating them in the standard postoperative lab tests.

Drain fluid analysis

In this review, the results for cytokine levels in peritoneal drain fluid, as biomarkers for local infection, seem promising. In most studies cytokine levels were elevated from POD 1 in patients with CAL compared to patients without CAL. This finding suggests an early onset of local infection in patients with CAL, or at least a more prominent postoperative reaction in this group. It is hypothesised that cytokines are directly elevated postoperatively and will normalise unless infectious complications occur. Most frequently investigated cytokines are IL-1, IL-6, IL-10 and TNF-α.

Although routine drainage after colorectal surgery does not seem to prevent CAL and is omitted in enhanced recovery programs, two studies showed that changes of drain production occur frequently and before clinical symptoms. These interesting findings might justify the routine placement of a drain for the first postoperative days as an indicator for CAL.

Two studies on intraperitoneal microdialysis show, by retrospectively analysing of peritoneal microdialysis samples, that CAL was preceded by changes in local lactate/pyruvate ratio. Although these findings are promising, patient numbers were too low to compute predictive values and cut-off values. Future research should elucidate if prospective, real-time analysis actually leads to early detection and determine whether this technique is cost effective.

For intramucosal pH monitoring, as a measure for mucosal hypoperfusion and subsequent hypoxia, data are limited but promising. The same holds for measurement of lipopolysaccharides, integral components of normal gut flora, and measurements of lysozym in drain fluid, since the studies investigating these biomarkers did neither lead neither to confirmation of these techniques nor to a re-evaluation.

Intra-operative techniques

Except for one, all studies evaluating the ALT confirm the importance of this simple intervention. Although not completely eliminating the occurrence of CAL, ALT allows intraoperative revision of the anastomosis, is easy to perform and has a high negative predictive value. Understandably, no studies have been performed that relate a positive ALT without intraoperative repair to CAL. All valuable studies, those that use a no-test control group, show a lower percentage of CAL in the group in which ALT was performed; in two out of four papers this difference was significant.

IOE can, apart from direct visualisation of CAL, be of diagnostic and therapeutical importance if the location of the tumour or of additional lesions is unknown

or if anastomotic bleeding occurs. More recently, the routine application of IOE has been studied in comparison to selective IOE. No favourable results in occurrence of CAL were described for routinely performed IOE compared to selective IOE. Apart from the mentioned benefits of IOE, no data are available on the superiority of IOE compared to ALT for intraoperative diagnosis of anastomotic dehiscence. Thus, ALT seems to be favourable to IOE since it is faster, easier and cheaper.

Some authors have attempted to relate anastomotic perfusion parameters to anastomotic leakage. Except for one, all studies are case controlled without reference and have not been repeated. It has not led to clear cut-off values for any of these techniques that seem not very practical in daily current practice. At least one cohort study with a good reference is needed before clinical implementation.

Radiology

As far as CT with rectal contrast is concerned, only 7 studies could be included. These studies showed large differences in methodology and lacked generally applied definitions. These differences between several studies, especially in CT criteria for CAL, resulted in equivocal results. Intestinal contrast leakage is not regularly depicted with CT in patients with CAL. However CT can accurately depict the associated features of anastomotic leakage such like pericolic/pelvic fluid collections and free air. When these additional criteria were used the accuracy improved dramatically with accuracies varying from 80%-100%.

All six studies that were performed on the subject of WSCE over the last two decades concluded that there is no place for routine application of WSCE. In these studies, WSCE did not have a consistently high positive predictive value, and other techniques, such as digital rectal examination in low rectal anastomosis, appeared to provide at least equal results. Furthermore due to the potential risk of complications no study performed contrast enemas in the very early postoperative phase. This means that, when performed at POD 7-8, clinical CAL concurred with radiological leakage. In addition, radiologic signs of CAL do not correlate with clinical CAL and frequently do not require any form of treatment. Another drawback of WSCE is that the rectally administered contrast has been diluted and there may be not enough remaining pressure to induce contrast leakage in more proximal anastomoses.

Two older studies describe how plain X-rays can be used in assessment of intra-abdominal free air and staple line integrity in the diagnosis of CAL. Although sometimes helpful, modern techniques offer the surgeon much more detailed information on the extend of CAL compared to plain X-rays.

CONCLUSION

Many studies have been performed in the field of diagnosis of CAL. Many lack a no-test control group and reference; therefore the general level of evidence is relatively low. The air leak test is recommended for intraoperative assessment of CAL. When a leakage score system is used intraoperatively, preoperative preventive measures can be taken. When using a clinical algorithm postoperatively, delay in diagnosis of CAL might be reduced. CRP measurement should be part of postoperative laboratory routine at least at POD 3 and 4, since due to a high negative predictive value patients with an uncomplicated course can be identified. Cytokine measurement among other measurements of peritoneal drain fluid is promising and could justify the routine placement of a juxta-anastomotic drain, while peritoneal microdialysis might develop as minimally invasive peritoneal "smart"-drain. When clinical signs are present, CT with rectal contrast is recommended. CT cannot only to detect CAL but also can be used as a therapeutic instrument for percutaneous drainage of a pericolic/pelvic abscess. We believe that this review reaffirms the importance of early detection of colorectal anastomotic leakage and that it offers colorectal surgeons an overview on easily applicable diagnostic tools to improve early detection.

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BRIEF ARTICLE

Transversus abdominis plane infiltration for laparoscopic gastric banding: A pilot study

Gildasio S De Oliveira Jr, Paul Fitzgerald, Shireen Ahmad, John Kim, Rohit Rahangdale, Robert McCarthy

Gildasio S De Oliveira Jr, Paul Fitzgerald, Shireen Ahmad, Rohit Rahangdale, Robert McCarthy, Department of Anesthesiology, Feinberg School of Medicine, Northwestern University, Chicago, IL 60611, United States
John Kim, Department of Surgery, Northwestern University, Chicago, IL 60611, United States
Author contributions: De Oliveira Jr GS and McCarthy R analysed data; De Oliveira Jr GS and Fitzgerald P contributed to conduct of the study; De Oliveira Jr GS, Ahmad S, Rahangdale R and McCarthy R participated in study design and manuscript preparation; Kim J amd Fitzgerald P participated in manuscript preparation.
Supported by Department of Anesthesiology, Northwestern University
Correspondence to: Gildasio S De Oliveira Jr, MD, MSCI, Associate Chair for Research, Department of Anesthesiology, Feinberg School of Medicine, Northwestern University, 241 East Huron, St F5-704, Chicago, IL 60611,
United States. g-jr@northwestern.edu
Telephone: +1-312-4733573 Fax: +1-312-4733573
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Abstract

AIM: To estimate an effect size for the transversus abdominis plane (TAP) infiltration on quality of recovery in patients undergoing laparoscopic gastric band surgery.

METHODS: The pilot study was a randomized, double blinded, placebo controlled trial. Patients undergoing laparoscopic gastric band surgery were randomized to receive a bilateral TAP infiltration with 20 mL of 0.5% ropivacaine or saline. The evaluated outcomes included quality of recovery-40 (QoR-40) at 24 h, postoperative opioid consumption and pain. Data was examined using the Mann-Whitney *U* test.

RESULTS: Nineteen subjects were recruited. There was a positive trend favoring the TAP infiltration group in global QoR-40 scores at 24 h after surgery, median [interquartile range (IQR)] of 175.5 (170-189) compared to 170 (160-175) in the control group (P = 0.06). There also a positive trend toward a lower cumulative opioid consumption in the TAP infiltration group, median (IQR) of 7.5 (2.5-11.5) mg *iv* morphine equivalents compared to 13 (7-21.5) in the control group (P = 0.07). Correlation analysis (Spearman's Rho) demonstrated an inverse relationship between 24 h cumulative opioid consumption and global QoR-40 scores, -0.49 (P = 0.03).

CONCLUSION: The use of multimodal analgesic techniques to reduce opioid related side effects is particularly desirable in morbidly obese patients undergoing gastric reduction surgery. The TAP infiltration seems to have a clinically important effect in reducing postoperative opioid consumption and improve quality of recovery after laparoscopic gastric band surgery in morbid obese patients. Future studies to confirm the beneficial effects of the TAP infiltration in these patients are warranted.

Key words: Transversus abdominis plane; Infiltration; Gastric band; Pain; Recovery

Core tip: In this current randomized, double blinded, placebo controlled pilot study we estimated the effect of a transversus abdominis plane block on postoperative quality of recovery in morbidly obese patients undergoing laparoscopic gastric band surgery. Postoperative opioid consumption was inversely correlated to quality of recovery in this surgical population. The transversus abdominis plane block seems to be an effective strategy to improve quality of recovery in those patients.

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INTRODUCTION

Pain after surgery is undertreated and fails to be managed optimally despite compelling data regarding the consequence of poorly managed analgesia[1-3]. In addition to patient suffering, postoperative pain can also affect quality of recovery after surgical procedures[4-6]. It is likely, therefore, that strategies that improve postoperative pain can also ameliorate postsurgical recovery[7-9]. The improvement of postsurgical recovery is particularly important for patients having ambulatory surgery, since those patients do not benefit from structured hospital support for recover after surgery[10-12].

Laparoscopic gastric band surgery can be performed in the outpatient setting when optimal postsurgical pain control is achived[13]. Interventions to minimize pain and reduce opioid consumption in those patients are particularly desirable in order to avoid opioids related side effect such as nausea and vomiting[14,15]. The transversus abdominis plane (TAP) Infiltration has been used to minimize pain in a diverse range of surgical procedures but its effect on obese patients undergoing laparoscopic gastric band surgery has it to be investigated[16-19]. More importantly, it is currently unknown if the analgesic benefits of the TAP infiltration can translate to a better recovery for patients undergoing laparoscopic gastric band procedures.

The main objective of the current pilot study was to estimate an effect size for TAP analgesia on postsurgical quality of recovery in patients having laparoscopic gastric band surgery. We hypothesized that patients receiving a TAP infiltration with ropivacaine would have a better quality of postsurgical recovery than patients having a TAP infiltration with saline. We also sought to estimate an effect of the TAP infiltration on postoperative analgesia.

MATERIALS AND METHODS

This pilot study was a prospective, randomized, double-blinded placebo controlled trial. Clinical trial registration for this study can be found at ClinicalTrial.gov (http://www.clinicaltrials.gov); registration identified: NCT01075087. Eligible subjects were patients undergoing laparoscopic gastric band surgery to reduce morbid obesity. Patients with a history of allergy to local anesthetics, chronic use of an opioid analgesic, corticosteroid and/or pregnant subjects were not enrolled. Reason for exclusion from the study following study drug administration was conversion from a laparoscopic to an open incision or patient request. Subjects were randomized using a computer generated table of random numbers into two groups to receive 20 mL of a bilateral ultrasound guided TAP infiltration using: saline or ropivacaine 0.5% (Naropin, APP Pharmaceuticals, Schaumburg, IL, United States). Group assignments were sealed in sequentially numbered opaque envelopes that were opened by a research nurse not involved with the patient care or data collection after the subject provided written informed consent. The same nurse prepared syringes labeled with study drug to blind subjects enrolled in the study, anesthesia providers and investigators collecting the data.

After anesthesia induction a bilateral TAP infiltration was performed in all subjects using ultrasound guidance with a portable ultrasound device (SonoSite, Bothell, WA, United States) and a linear 6-13 Mega Hertz ultrasound transducer. The technique used to performed the TAP infiltrations was the posterior approach as previously described by Hebbard *et al*[20]. Once the external oblique abdominal, the internal oblique abdominal and the transversus abdominal muscles were visualized using the ultrasound probe at the level of the anterior axillary line between the 12th rib and the iliac crest, the puncture area was prepared in a sterile manner. The injection of the study drug was performed using a 21 gauge 90 mm StimuQuik needle (Arrow International, Reading, PA, United States) by a single investigator with extensive experience in performing the TAP block (Gildasio S De Oliveira Jr). Once the tip of the needle was placed in the space between the internal oblique abdominal muscle and the transversus abdominal muscle, and after negative aspiration of blood, 20 mL of the study drug was administered and distribution of the solution in the TAP was confirmed using ultrasonography observation. A contralateral infiltration was performed in the same fashion.

All subjects were premedicated with 0.04 mg/kg *iv* midazolam. Propofol 1-2 mg/kg was administered for anesthesia induction, a remifentanil 0.05 mcg/kg per minute *iv* infusion was begun and succinylcholine 1-2 mg/kg was administered to induce muscle paralysis. All the medications in the study protocol were dosed based on the dosing body weight [ideal body weight (IBW) + [0.4 × (actual body weight - IBW)][21]. Tracheal intubation was initially attempted by an anesthesia resident physician or a certified registered nurse anesthetist under supervision of an attending anesthesiologist. Anesthesia maintenance was achieved using remifentanil, titrated to maintain the mean arterial pressure within 20% of baseline, desflurane titrated to a bispectral index (Aspect Medical System Inc., Norwood, MA, United States) between 40 and 60 and rocuronium. At the end of the procedure at removal of the laparoscopic instruments the remifentanil infusion was discontinued and the subjects received intravenous ketorolac 30 mg and ondansetron 4 mg. The laparoscopic insufflation pressure was kept at 15 mmHg for the procedure. Five trocars were used for the surgery (two below the xyphoid, one in the right upper quadrant, one in the left upper quadrant and the last one on the left anterior axillary line below the costal margin).

In the post anesthesia care unit (PACU) subjects were asked to rate their pain at rest upon arrival and at regular (30 min) intervals on a 0-10 pain numeric rating scale (NRS), where 0 means no pain and 10 is the worst pain

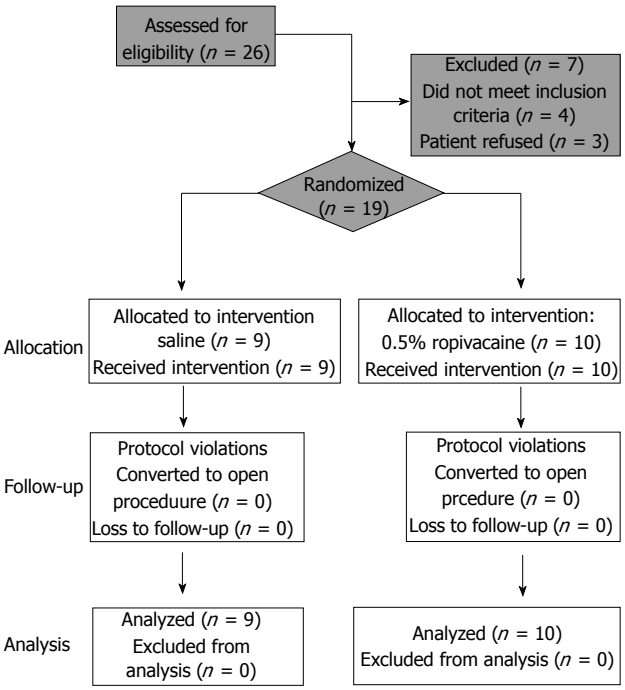

Figure 1 Flow chart describing subjects allocation.

imaginable. The area under the NRS pain scale *vs* time curve was calculated using the trapezoidal method as an indicator of pain burden during early recovery (Graph Pad Prism ver 5.03, Graph Pad Software, Inc., La Jola, CA, United States). Hydromorphone 0.4 mg *iv* was administered every 5 min to maintain a NRS pain score less than 4 out of 10. In cases of postoperative nausea or vomiting, subjects received 10 mg *iv* metoclopramide. When subjects were able to tolerate oral medications, a combination of hydrocodone 10 mg plus acetaminophen 325 mg were used for pain greater than 4 of 10. Postoperative opioid consumption (24 h) was converted to equivalent dose of oral morphine[22].

Subjects were followed up at 24 h after the procedure by an investigator unaware of group allocation and were questioned regarding analgesic consumption, pain score and the QoR-40 questionnaire was administered[23]. The questionnaire consists of 40 questions that examine 5 domains of patient recovery using a 5 point Likert scale: none of the time, some of the time, usually, most of the time and all of the time. The five domains include physical comfort, pain, physical independence, psychological support and emotional state. Individualized items of the questionnaire have been previously presented by our group[24]. Other perioperative data collected included subject's age, height, weight, American Society of Anesthesiologist physical status, surgical duration, intraoperative remifentanil use, total intravenous fluids and total amount of hydromorphone in PACU and time to hospital discharge.

Ethics

This work has been carried out in accordance with the declaration of Helsinki (2000) of the World Medical Association. Study approval was obtained from the Northwestern University Institutional Review Board (STU00023482), and written informed consent was obtained from all the study participants.

Statistical analysis

A sample size of 23 subjects per group was estimated to achieve 80% power to detect a 10 point difference in the aggregated QoR-40 score for the 2 study groups to be compared assuming an overall standard deviation of 12 points similar what was observed in a previous investigation[25]. To account for drop-outs 50 subjects were planned to be recruited and randomized. However, due to changes in the case profiles in our hospital (increased number of gastric sleeve surgery and decreased number of laparoscopic gastric band surgery, nineteen patients were recruited). The sample size calculation was made using PASS version 8.0.15 release date January 14, 2010 (NCSS, LLC, Kaysville, UT).

The Shapiro-Wilk and Kolmogorov-Smirnov tests were used to test the hypothesis of normal distribution. Normally distributed interval data are reported as mean (SD) and were evaluated with Student's *t* test for equal variances. Non-normally distributed interval and ordinal data are reported as median [range or interquartile range (IQR)] and compared among groups using the Mann-Whitney *U* test. A correlation analysis (Spearman's Rho) was performed to examine a relationship between opioids consumption and global quality of recovery score. All reported *P* values are two-tailed. To avoid the chance of a type I error, the criterion for rejection of the null hypothesis was a two-tailed $P < 0.05$ for comparisons.

Statistical analysis was performed using NCSS 8 8.0.15, release date 5/15/2013 (NCSS, LLC, Kaysville, UT) and R version 3.0.1, release date 5/16/2013 (The R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

The details of the conduct of the study are shown in Figure 1. Nineteen subjects were randomized and nineteen completed the study. Patients were enrolled consecutively from 3/2010 through 7/2012. Patients' baseline characteristics and surgical factors were not different between groups (Table 1).

There was a positive trend favoring the TAP infiltration group in global QoR-40 scores at 24 h after surgery, median (IQR) of 175.5 (170-189) compared to 170 (160-175) in the control group ($P = 0.06$). There was also a positive trend towards a reduction of postoperative pain in the post-anesthesia care unit for the TAP infiltration group, median (IQR) of 195 (135-300) (score × min) compared to 315 (195-420) (score × min) in the control group ($P = 0.09$). Other postoperative variables are presented in Table 2.

Another positive trend was identified toward a lower cumulative opioid consumption in the TAP infiltration group, median (IQR) of 7.5 (2.5-11.5) mg *iv* morphine equivalents compared to 13 (7-21.5) mg *iv* morphine

Table 1 Baseline patient and surgical characteristics

	TAP infiltration (n = 10)	Saline (n = 9)	P value
Age (yr)	47 (39-53)	50 (36-54)	0.90
Gender			1.00
Male	2	2	
Female	8	7	
BMI (kg/m^2)	44.2 (39.0-45.7)	40.1(38.5-44.3)	0.46
ASA class			0.37
Ⅱ	3	5	
Ⅲ	7	4	
Surgical duration (min)	76.5 (51-106)	92 (61-120)	0.53
Remifentanil (mcg)	620 (500-750)	850 (600-1100)	0.23
Intravenous fluids (mL)	1050 (585-1600)	1300 (1200-1500)	0.43

Data are expressed as median [interquartile range (IQR)]. TAP: Transversus abdominis plane; ASA: American society of anesthesiologists; BMI: Body mass index.

Table 2 Postoperative data

	TAP infiltration (n = 10)	Saline (n = 9)	P value
Nausea in PACU			0.33
Yes	1	3	
No	9	6	
Vomiting/Retching in PACU			0.47
Yes	0	1	
No	10	8	
Time to discharge from PACU (min)	60 (60-75)	75 (60-90)	0.41
Time to discharge from the hospital (h)	32.1 (13.9-52.6)	22.5 (19-26)	0.47

TAP: Transversus abdominis plane; PACU: Post anesthesia care unit.

equivalents in the control group (P = 0.07)

Correlation analysis (Spearman's Rho) demonstrated an inverse relationship between 24 h cumulative opioid consumption and global QoR-40 scores, ρ = -0.49 (P = 0.03).

DISCUSSION

The most important finding of the current study was a probable benefit of the TAP infiltration to improve postoperative quality of recovery after laparoscopic gastric band surgery in morbidly obese patients. In addition, a similar trend toward a reduction in pain burden and opioid consumption was also detected in the TAP infiltration group compared to saline. The inverse relationship between postoperative opioid consumption and quality of recovery in the subjects in this study support our previous findings of reduced opioid use and improved postoperative recovery[16,23,25]. Our results suggest that the TAP infiltration may be a clinically significant multimodal strategy to reduce pain and improve quality of postsurgical recovery in patients undergoing laparoscopic gastric band surgery.

Our results are particularly important since the development of opioid related side effects such as vomiting in gastric reduction surgery can lead to surgical complications[26]. In addition greater opioid consumption in obese patients with obstructive sleep apnea can also result in postoperative hypoxemic events[27-29]. It remains to be determined if the opioid reduction due to the TAP infiltration can minimize opioid related side effects in morbid obese patients undergoing gastric reduction surgery.

Despite a possible benefit on postoperative analgesia, we did not observe a parallel reduction in hospital stay in our study population. Hospital stay, in the inpatient population, has been criticized as a reliable outcome due to the innumerous potential confounders that can alter that outcome[30-32]. Even established analgesic interventions, often fail to demonstrate a beneficial effect on duration of hospital stay[33,34]. Nevertheless, the optimal postoperative pain control in patients undergoing laparoscopic gastric band surgery may help the performance of this surgery as an outpatient procedure[35,36].

It is important to note that the transversus abdominis block successfully treats parietal pain but visceral pain is not treated by a TAP block. This is likely the reason why even patients in the TAP block group required the use of systemic opioids. Nevertheless, it seems that the reduction in the parietal pain is an important step to improve quality of recovery in patients undergoing laparoscopic gastric bending.

The TAP infiltration has been previously evaluated in morbidly obese patients undergoing different surgical procedures than the one presented in the current investigation. Sinha *et al*[37] detected a large effect on analgesic outcomes of the TAP infiltration in patients undergoing laparoscopic gastric bypass. The authors' results were interesting since laparoscopic gastric bypass surgery requires a more extensive procedure which can result in greater visceral pain and a potential lower benefit of the TAP infiltration. In contrast, a retrospective evaluation of obese patients undergoing abdominal plastic surgery did not detect a benefit of the TAP infiltration compared to control for postoperative pain[38]. The effect of the TAP infiltration on postoperative pain outcomes in obese patients may, therefore, be dependent on the type of surgical procedure.

Our current study should only be interpreted according to its limitations. We were unable to complete recruitment and we were underpowered to achieve statistically significant results in our main outcomes. Based on the differences observed in the current study, group sample sizes of 24 per group would have been needed to show a difference in opioid consumption between groups if the actual difference was 5.5 as observed in the current study. Nevertheless, we believe that our current results are clinically important and will stimulate future studies involving regional and local anesthesia techniques in the morbidly obese patient population.

In summary, we report an important beneficial clinical effect of TAP infiltration on quality of recovery in morbidly obese patients after laparoscopic gastric band surgery. It seems that the reduction in postoperative opioids by the TAP infiltration resulted in a better recovery in that patient population. Future studies are warranted to

confirm the beneficial effect of the TAP infiltration on postoperative recovery and analgesia in the same patient population.

COMMENTS

Background

Opioids are commonly used to treat postoperative pain in patients undergoing laparoscopic gastric banding. The transversus abdominis plane block has been used successfully to improve recovery in other patient populations but it is unknown if it can also improve recovery for obese patients undergoing laparoscopic gastric banding.

Research frontiers

The transversus abdominis plane (TAP) block seems to improve quality of recovery in patients undergoing laparoscopic gastric banding through a reduction in the consumption of opioids.

Innovations and breakthroughs

This is the first study to demonstrate a possible benefit of the TAP block on obese patients undergoing laparoscopic gastric banding

Applications

Patients undergoing laparoscopic gastric banding may have better quality of postsurgical recovery if they receive a TAP block before the surgical procedure

Terminology

Transversus abdominis block is the application of local anesthetics in the abdominal wall using ultrasound.

Peer review

This manuscript is described as a pilot study but realistically is an underpowered study that if recruitment had been successfully would have realised significant results.

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CASE REPORT

Rare diaphragmatic tumor mimicking liver mass

Shalini Thapar, Arvind Ahuja, Archana Rastogi

Shalini Thapar, Department of Radiodiagnosis, Institute of Liver and Biliary Sciences, New Delhi 110070, India
Arvind Ahuja, Archana Rastogi, Department of Hepatopathology, Institute of Liver and Biliary Sciences, New Delhi 110070, India
Author contributions: Thapar S made substantial contributions to the conception and design, acquisition, analysis and interpretation of data, and drafted the article and helped in final approval of the version to be published; Ahuja A and Rastogi A helped in critically revising the article for important intellectual content and contributed to the conception, design, acquisition, analysis and interpretation of data; and Ahuja A helped in drafting the article.
Correspondence to: Shalini Thapar, Associate Professor, Department of Radiodiagnosis, Institute of Liver and Biliary Sciences, Sector D-1 Vasant Kunj, New Delhi 110070, India. thaparshalini@gmail.com
Telephone: +91-981-0757973 Fax: +91-981-0757973
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Abstract

Primary tumors of the diaphragm are quite rare. About 150 cases have been reported in the literature. Fibrosarcomas are the commonest malignant neoplasms of the diaphragm; however, only a few (less than 20) cases have been reported to date. We present the case of an extremely rare tumor of the diaphragm mimicking a liver mass. The patient, a young 28-year-old woman, presented with an 8-month-history of mildly progressive upper abdominal pain and early fullness after meals. Computed tomography scan of the abdomen revealed a mass located in the region of the left lobe of the liver with non visualized left lobe and partial vascular supply of the mass from the left hepatic artery. The tumor was also seen to draw its vascularity from bilateral internal mammary arteries. Surgical excision and hepatectomy was planned, keeping in mind the diagnosis of an atypical left hepatic mass. Laparotomy revealed a left diaphragmatic tumor growing caudally into the upper abdomen, compressing and splaying the liver along the left medial surface where the tumor was virtually adherent to it. Successful excision of the mass and subsequent histopathological and immunochemistry examination of the specimen revealed low grade fibromyxoid sarcoma of the diaphragm. This case highlights the unusual presentation of a diaphragmatic mesenchymal tumor and how it can be mistaken as an atypical liver mass. It also emphasizes the tumoral vascular supply as an indicator of its organ of origin.

Key words: Diaphragmatic tumor; Low grade; Fibromyxoid sarcoma; Liver mass; Atypical liver mass; Computed tomography

Core tip: In this paper, a patient with low grade fibromyxoid sarcoma of the diaphragm which mimicked a liver mass on preoperative imaging is reported. Particular attention is paid to retrospective analysis of the vascularity of the mass on computed tomography angiography to differentiate it as an extrahepatic mass. The histopathological analysis of this case, as well as a collective review, is also presented in this report.

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INTRODUCTION

Primary tumors of the diaphragm have a rare incidence and prevalence. Only about 150 cases have been reported in literature to date[1-5]. Most primary tumors of the diaphragm are benign. Of the malignant subgroup, fibrosarcoma appears to be the commonest. Low grade fibromyxoid sarcoma (LGFMS) is a unique sub entity in the group of fibrosarcomas. These tumors are unique in their reappearance as metastases after significant time in-

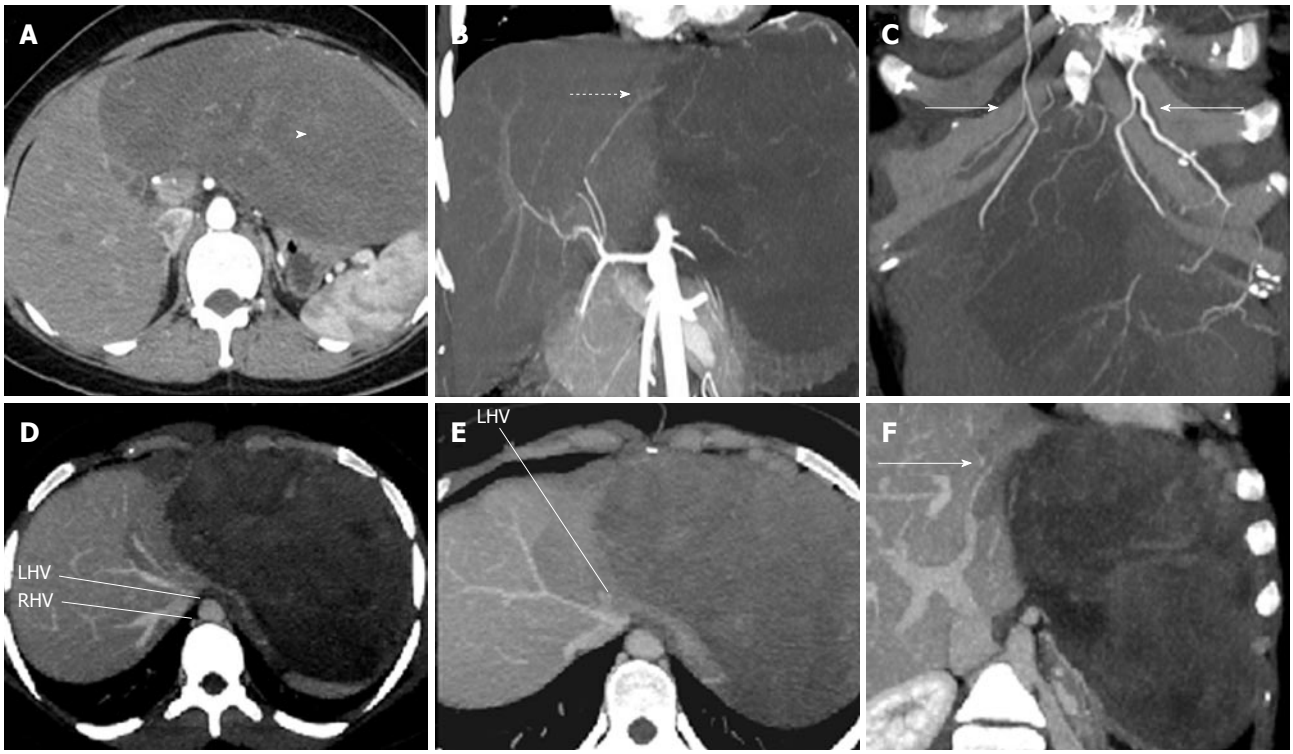

Figure 1 A 28-year-old lady with low grade fibromyxoid sarcoma on dynamic computed tomography. A: Soft tissue homogenously enhancing mildly hypodense mass (arrowhead) in the region of left lobe of liver is seen on the arterial phase of the dynamic triple phase computed tomography scan; B: The mass shows small arterial feeders from the left hepatic artery (dotted arrow); C: Large feeders from bilateral internal mammary arteries (solid arrows) to the mass are seen; D: Middle hepatic vein and right hepatic vein show normal patency and course; E: Left hepatic vein is only seen at the ostium, appears compressed by the mass and is not seen beyond the ostium; F: Left portal vein (solid arrow) is also splayed and partially attenuated by the tumor.

tervals. Around 20 cases of the same have been reported in the English literature so far, to the best of our knowledge[1-7]. LGFMS shows characteristic histopathological and immunochemistry features. In the last decade, sporadic cases of fibromyxoid sarcoma have been reported in the literature. Even after recent major advances in imaging technology, such as the advent of multidetector, multi slice computed tomography (CT) and 3Tesla magnetic resonance imaging (MRI), diaphragmatic tumors still present as a diagnostic dilemna and are difficult to diagnose preoperatively or without a pathological diagnosis. They are known to mimic other large masses arising from the mediastinum in the majority of cases. In this paper, a patient with low grade fibromyxoid sarcoma of the diaphragm which mimicked a liver mass on preoperative imaging is reported. Particular attention is paid to retrospective analysis of the vascularity of the mass on CT angiography to differentiate it as an extrahepatic mass. The histopathological analysis of this case, as well as a collective review, is also presented in this report.

CASE REPORT

A 28-year-old lady presented to the hospital with an 8 mo progressive history of nagging upper abdominal pain and a feeling of early satiety. The pain was localized without associated vomiting, aggravating or relieving factors. The patient complained of feeling a gradually increasing lump in the upper abdomen for 6 mo. However, she had no definite history of cough, hiccups or difficulty in breathing. The lady had loss of appetite with significant weight loss of 5 kg over 6 mo. On general examination, the lady was well preserved. Local palpation revealed a firm lump in the epigastrium and left hypochondrium with a perceptible lower border. Palpating fingers could not be insinuated between the lump and the upper border, as well as the costal margin. Laboratory tests showed normal serum alpha fetoprotein and carcinoembryonic antigen levels (1.16 U) and (1.8 mg/L) respectively. All other tests, such as hemogram, kidney function tests and liver function tests, were within the normal reference ranges.

A dynamic triple phase CT scan of the upper abdomen was performed and showed a homogenous soft tissue mass lesion measuring approximately 25 cm × 20 cm × 13.5 cm in the left upper hypochondrium, almost entirely replacing the left lobe of the liver (Figure 1A). The left hepatic vein and portal vein were only partially visualized and were grossly attenuated by the mass (Figure 1E-G). Enlarged left supra-diaphragmatic nodes were present (Figure 2A). The sections of bilateral lower lobes of chest did not show evidence of basal atelectasis or pleural effusion (Figure 2B). The tumor showed arterial feeders from the left hepatic artery which was splayed but showed normal patency (Figure 1B). The major chunk of tumor vascularity appeared to be from bilateral internal mammary arteries (Figure 1C). The tumor appearance was thought to be of an atypical hepatic mass and a decision for surgical laparotomy with surgical excision of the

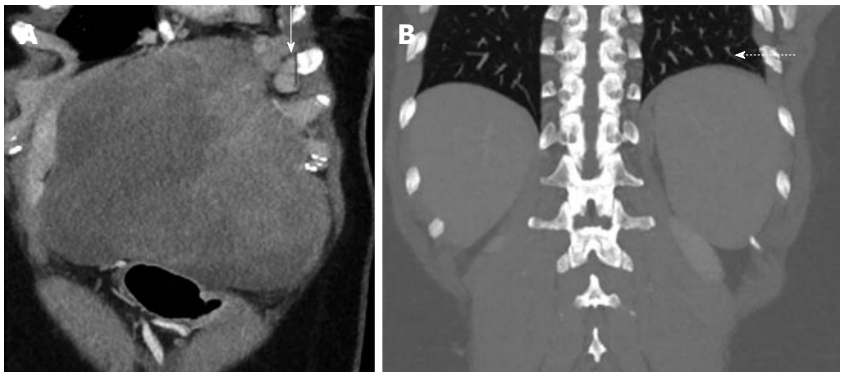

Figure 2 Sagittal and coronal multiplanar reformats of a 28-year-old lady with low grade fibromyxoid sarcoma on dynamic computed tomography. A: Sagittal reconstruction of the abdomen shows supra-diaphragmatic enlarged lymph nodes (solid arrow); B: Coronal reconstruction images shows normal basal lung fields (dotted arrow).

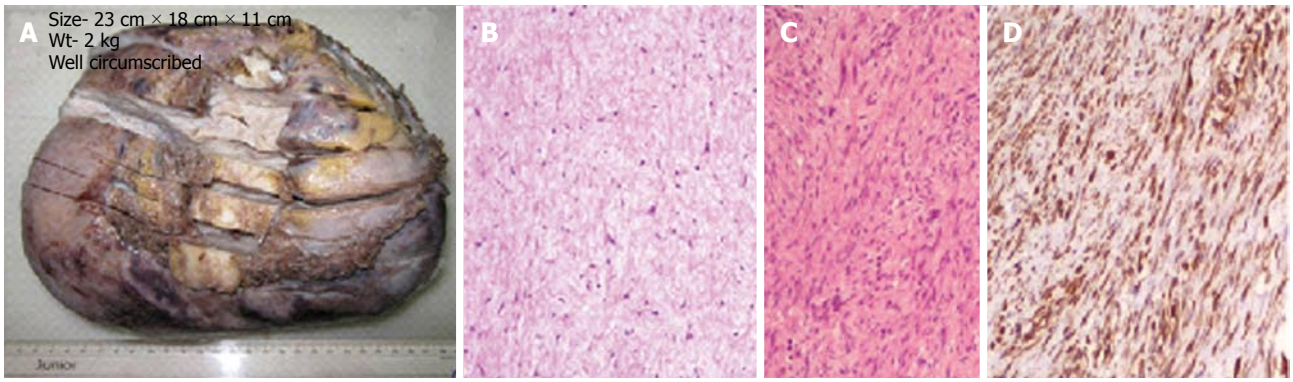

Figure 3 Gross, histopathological and immunochemistry slides of 28-year-old lady with low grade fibromyxoid sarcoma. A: Gross specimen of the resected tumor mass along with the left lower 3 ribs; B: Histopathology at (× 100, HE stain) showing low cellularity with bland appearing spindle and stellate cells and minimal nuclear atypia; C: Histopathology (× 100, HE) shows low grade fibromyxoid sarcoma with focal areas of storiform and fascicular arrangement of spindle cells; D: Spindle cells show strong positive immunostaining with vimentin (× 200, Vimentin, LSAB immunohistochemistry method).

tumor was made.

On laparotomy, a solid, rounded, grey tumor was found arising from the left diaphragm, compressing and splaying the entire left lobe of liver which was adherent to the tumor medially. The upper border of the mass was attached to the inferior surface of the left diaphragm. The entire mass was excised along with the left lower 3 ribs from which it was inseparable. The superficial structures of the left chest wall were not involved. Local left supra-diaphragmatic lymph nodes were also excised.

The tumor was well encapsulated, firm, weighed approximately 2 kg and measured 23 cm × 18 cm × 11 cm (Figure 3A). Microscopy revealed a bland appearing spindle cell tumor of low cellularity. The tumor showed contrasting fibrous and myxoid areas (Figure 3B). The spindle cells demonstrated a focal swirling or whorled pattern. On high power, the tumor cells showed minimal pleomorphism without any mitosis. Focally, tumor cells appeared stellate shaped. Few areas showed curvilinear or capillary sized blood vessels with spindle cells encasing around them (Figure 3C). Immunohistochemistry revealed strong positive immunostaining of the spindle cells with vimentin and focally for Bcl-2 (Figure 3D), but negative for S100, smooth muscle antigen, desmin, epithelial membrane antigen and CD34. Based on characteristic histomorphological features and immunohistochemistry results, a diagnosis of low grade fibromyxoid sarcoma was made.

The patient was offered radiation therapy, which she refused. At the 1 year follow up, she is symptom free, with no evidence of disease spread.

DISCUSSION

Primary tumors of the diaphragm are very rare. The first diaphragmatic tumor was reported in 1868 by Grancher[8]. About 150 cases have been reported in the English literature since then[9]. The majority of diaphragmatic tumors are benign. Most malignant tumors of the diaphragm are sarcomas of fibrous or muscular origin[7].

They include leiomyosarcoma, germ cell tumors, hemangiopericytoma, pheochromocytoma, fibrosarcoma and malignant fibrous histiocytoma. On imaging, most diaphragmatic tumors present as homogenous masses which appear as mediastinal or thoracic masses with contour abnormality of the diaphragmatic leaves, suggesting herniation or eventration. Although multiplanar imaging with CT and MRI are almost first line modes of investigation in the present era, large tumors may sometimes pose a diagnostic difficulty. A differential diagnosis of lung, mediastinal, pleural, vertebral or upper abdominal masses has to be considered in such situations. All of the above tumors may sometimes grow to large proportions without any specific clinical symptoms. Secondary involvement of the diaphragm from adjacent structures may also be present. Symptoms are usually produced due to esophageal, stomach or mediastinal compression and

not due to the tumor bulk.

The patient in our study also reported vague symptoms, which did not raise any suspicion about the extent of the mass. Imaging provided the only clue to the large size and extent of the tumor, which was solely limited to the upper abdomen. The initial suspicion of a liver mass was compounded by the vascular supply of the mass from the left hepatic artery. However, in retrospect, the majority of the tumor blood supply from bilateral internal mammary arteries was indicative of the extrahepatic origin of the tumor. The sharp interface of the mass with the liver parenchyma despite the lack of a proper cleavage plane was also a soft indicator of the extrahepatic origin.

Low-grade fibromyxoid sarcomas are distinctive, indolent soft-tissue sarcomas, first described by Evans in 1987. Low grade fibromyxoid sarcoma of the diaphragm is extremely rare. From 1868 to 1982, only 11 cases of low grade fibrosarcoma were reported[4]. Less than 20 cases have been reported in literature to date, to the best of our knowledge[1-3,6,7]. The sites described in literature so far have been commonly in the shoulder, neck or thigh[1]. On histopathology, low-grade fibromyxoid sarcomas demonstrate contrasting fibrous and myxoid areas, a swirling, whorled growth pattern and bland benign-appearing fibroblastic spindle cells. Cellularity is low to moderate, mitotic figures are uncommon, and nuclear pleomorphism is usually absent or slight. In addition, LFGMS shows a specific genetic transcript fused in sarcoma-cAMP responsive element binding protein 3 (FUS-CREB3)L2 and FUS-CREB3L1 in up to 95%-100% of cases[10]. The common differentials of low grade fibromyxoid sarcoma include myxoid neurofibroma, malignant peripheral nerve sheath tumor of low grade, myxofibrosarcoma and spindle cell liposarcoma. Myxoid neurofibroma and low grade malignant peripheral nerve sheath tumor show slender and wavy nuclei which are positive for S100. Myxofibrosarcoma is mostly a subcutaneous tumor of the elderly and shows a greater degree of nuclear pleomorphism, hyperchromasia and brisk mitosis. Spindle cell liposarcoma is cellular and shows more nuclear atypia. It always contains an atypical adipocytic component which includes the presence of lipoblasts and shows positivity for S100.

Primary diaphragmatic fibromyxoid sarcomas, especially low grade like in this case, have a good prognosis. One of the reports has shown survival even up to 10 years[7]. Treatment options include surgery followed by radiotherapy and, in some cases, chemotherapy to shrink tumor bulk, followed by resection. These tumors are usually resistant to chemotherapy and radiotherapy with surgical resection being the treatment of choice[11].

In conclusion, this case highlights that an extrahepatic vascular supply may act as an indicator of the extrahepatic origin of a tumor showing indistinct fat planes from the liver. Also, although rare, diaphragmatic mesenchymal tumors should also be included in the differential of atypical appearing hepatic or extrahepatic masses in the upper abdomen. In a recent study at a dedicated sarcoma centre in Denmark where 14 patients of LGFMS were studied for the disease and metastases treatment strategies, multi-agent chemotherapy was found useful, especially in the setting of metastases. The best possible response to chemotherapy was only a short term disease non progression with the use of trabectedin[12].

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COMMENTS

Case characteristics

The patient, a young-28-year old woman, presented with an 8-mo-history of mildly progressive upper abdominal pain and early fullness after meals.

Clinical diagnosis

The patient complained of feeling a gradually increasing lump in the upper abdomen for 6 mo.

Laboratory diagnosis

Laboratory tests showed normal serum alpha fetoprotein and carcinoembryonic antigen levels (1.16 U) and (1.8 mg/L) respectively.

Imaging diagnosis

Computed tomography scan of the abdomen revealed a mass located in the region of left lobe of liver with non visualized left lobe and partial vascular supply of the mass from the left hepatic artery.

Pathological diagnosis

Immunohistochemistry revealed strong positive immunostaining of the spindle cells with vimentin and focally for Bcl-2, but negative for S100, smooth muscle antigen, desmin, epithelial membrane antigen and CD34.

Treatment

Surgical excision and hepatectomy was planned, keeping in mind the diagnosis of an atypical left hepatic mass.

Experiences and lessons

This case highlights that extrahepatic vascular supply may act as an indicator of the extrahepatic origin of a tumor showing indistinct fat planes from the liver.

Peer review

The authors need to discuss pathological findings in more detail to substantiate the diagnosis of Low grade fibromyxoid sarcoma at this relatively uncommon location.

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MINIREVIEWS

Role of stenting in the palliation of gastroesophageal junction cancer: A brief review

Theodoros E Pavlidis, Efstathios T Pavlidis

Theodoros E Pavlidis, Efstathios T Pavlidis, Second Surgical Propedeutic Department, Medical School, Aristotle University of Thessaloniki, Hippocration Hospital, 54642 Thessaloniki, Greece

Author contributions: Pavlidis TE designed the research and wrote the paper; Pavlidis ET performed the research and analyzed the data.

Correspondence to: Theodoros E Pavlidis, MD, PhD, Professor, Second Surgical Propedeutic Department, Medical School, Aristotle University of Thessaloniki, Hippocration Hospital, Konstantinoupoleos 49, A Samothraki 23, 54642 Thessaloniki, Greece. pavlidth@med.auth.gr
Telephone: +30-2310-992861 Fax: +30-2310-992932
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Abstract

Gastroesophageal junction cancer has an increasing incidence in western countries. It is inoperable when first manifested in more than 50% of cases. So, palliation is the only therapeutic option for the advanced disease to relieve dysphagia and its consequences in weakened patients with an estimated mean survival under 6 mo. This article has tried to identify trends focusing on current information about the best palliative treatment, with an emphasis on the role of stenting. Self-expanding stent placement, either metal or plastic, is the main management option. However, this anatomical location creates some particular problems for stent safety and effectiveness which may be overcome by properly designed novel stents. The stents ensure a good quality of life and must be preferred over other alternative methods of loco-regional modalities, *i.e.*, external radiation, laser thermal or photodynamic therapy. Although stent placement is generally a simple, safe and effective method, there are sometimes complications, increasing the morbidity and mortality rate. Bypass operative procedures have now been abandoned as a first choice. The stomach instead of the colon must be used for a bypass operation when it is needed. Chemotherapy, despite the toxicity, and intraluminal radiation (brachytherapy) have a well-defined role.

Key words: Gastroesophageal junction cancer; Palliative therapy; Stent placement; Dysphagia relief; Esophageal carcinoma; Gastric carcinoma

Core tip: The topic is interesting and this manuscript contains the most recent data briefly highlighting it. More than half of the patients with gastroesophageal junction cancer present with inoperable disease at the time of diagnosis so they need palliative treatment to relieve dysphagia and its consequences. Stent placement ensures good quality of life during the short survival time but it has some additional specific problems in this particular location.

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INTRODUCTION

Cancer of the gastroesophageal junction has had an increasing incidence over the past thirty years in western countries and is now the eighth most common malignancy. However, the exact incidence cannot be precisely assessed because it can be allocated as either gastric or esophageal cancer. This confusion is not of particular importance since in both cases the management is the same. Its prognosis is not good, with a 5 year survival less than 20% and even less in younger patients under 35

years old[1,2].

More than half of these patients present with inoperable disease at the time of diagnosis. Hence, they need palliative treatment in order to alleviate dysphagia and its further consequences for the life expectancy, given that the average survival time does not exceed 6 mo[1-4]. Although the kind of palliation must be individualized, generally stent placement is the first choice. There are also other alternatives, such as bypass operation, external radiation, intraluminal radiation (brachytherapy), chemotherapy, laser ablation (thermal Nd: YAG or photodynamic), dilatations, chemical substance injection, mainly ethanol, as well as nutritional support *via* a nasoenteric feeding tube or percutaneous endoscopic gastrostomy[1,4].

STENT PLACEMENT

Endoscopic self-expanding metal stent (SEMS) placement provides a rapid relief of dysphagia and it is currently the most frequently chosen method[3,5,6]. However, according to the relevant researchers, the recurrence of dysphagia varies between 22%-50%. This recurrence may occur due to various reasons, such as tissue growth in the stent space, stent migration or its obstruction by bolus. The incidence of cancerous tissue overgrowth *via* the stent is 26%-36%, while the non-cancerous granulomatous tissue overgrowth is 20%. The former has been estimated to occur after 18 wk and the latter after 22 wk following the stent placement. This tissue overgrowth can be managed either by thermal ablation or the recently introduced self-expanding plastic stent (SEPS) placement, with the advantage of lower cost[3].

The placement of SEMS has also been proposed for relieving dysphagia due to local recurrence after esophagogastrectomy, in which the mean survival time has been limited to 4-6 mo or even less[7].

The application of SEMSs does not require dilatation of the stricture before placement; they are also flexible and ensure a diameter of patent lumen from 16 to 24 mm.

Dysphagia is staged in 5 grades: (0) Ability to swallow normal diet; (1) Ability to swallow part of solid diet; (2) Ability to swallow part of semi-solid diet; (3) Ability to swallow only liquids; and (4) Complete obstruction. The indication for stent placement includes grade 3 and 4 or the presence of tracheobronchial fistula irrespective of the grade[5].

In a recent meta-analysis on published reports including 1027 patients in 16 randomized controlled trials, it was concluded that endoscopic placement of self-expanding stents is the most widely used method for the management of dysphagia in comparison to other alternative methods of loco-regional modalities, *i.e.*, radiation, laser thermal or photodynamic therapy. Despite its high cost, it is a simple and effective method (with minimal invasiveness and discomfort) to ameliorate dysphagia in the vast majority of patients with a mean survival of no more than six months. In addition, its superiority is mainly associated with the fact that, unlike what is commonly observed in alternative methods, there is no need for re-interventions. However, in patients with one year survival, a loco-regional palliation seems better despite the need for further re-intervention. Furthermore, their higher life expectancy is possibly associated with the application of loco-regional treatment[4]. According to the aforementioned meta-analysis, the choice of conventional self-expanding stents *vs* modern anti-reflux stents has been found to be equally effective in relieving reflux since there was no difference between them. There are minimal differences among the various types of stents with regards to the outcome[4].

COMPLICATIONS OF STENTS

Significant differences have been noted between endoscopic and radiographic stent placements regarding the short-term complications. They encompass hemorrhage, pneumonia, exhaustion, heart abnormalities, perforation and sepsis. The morbidity and mortality rate exceeds 45% and 9%, respectively[6].

Due to the high frequency of the manifestation of long-term complications, *i.e.*, stent migration, hemorrhage and protrusion of gastroesophageal junction mucosa, opposition to the use of metal stents has been recently expressed and the individualized design of nitinol stents in special anatomical conditions has been proposed[8]. The placement of SEMSs for palliative management of obstruction due to gastroesophageal junction cancer has often been related to stent migration, as well as with symptoms of gastroesophageal reflux. The stent placement in this particular location has some additional specific problems compared to proximal esophageal cancer and therefore it implies less palliation and a higher rate of complications. Stent migration is more frequent due to the fact that the distal end of the stent protruding freely into the stomach fundus cannot be fixed to the wall. Hemorrhage is even more frequent in such cases. Firstly, the distal end of the stent may corrode the posterior wall of the stomach resulting in ulceration and subsequent bleeding. Secondly, the stent *via* the gastroesophageal junction cannot remain straight due to the angle of his, resulting in high pressure and ulceration with subsequent bleeding. The stent angulations are mainly responsible for the lack of significant improvement in the swallow quality. Moreover, gastroesophageal reflux is particularly common. Novel stents with specific design have certain advantages in overcoming those difficulties of the gastroesophageal junction.

TYPES OF STENTS

Thus, such stents have been designed, including the anti-reflux Z mechanism[9]. There are different types available: (1) Z-stent with the Korean modification (Choo stent) composed of nitinol or the European version of stainless steel, both covered by polyethylene; and (2) Flamingo Wallstent (available only in Europe) composed of cobalt mixture covered by polyurethane specifically designed for gastroesophageal junction with diameter of either 30

mm (distal 20 mm) or 24 mm (distal 16 mm). Some other stent types include Ultraflex composed of a plexus of nitinol wire covered by polyurethane with a diameter of 28 mm (distal 23 mm) or 23 mm (distal 18 mm), Wallstent Ⅱ composed of cobalt mixture covered by silicone with a diameter of 28 mm in both ends (20 mm in the middle) and the latest nitinol stents double layer composition (inner of polyurethane and outer of uncovered nitinol wire preventing stent migration). Reflux is prevented by a glove of polyurethane extended into the stomach[9] or a membrane into the lower end functioning as a valve[10]. Additionally, there are available novel SEPSs (Polyflex) consisting of polyester covered by silicone which have been used with satisfactory results[11].

OTHER MODALITIES

The combination of stricture dilatation by balloon, chemotherapy and/or radiation, with additional metal stent placement has been proposed in some cases[12].

Radiation and intraluminal high dose brachytherapy is indicated in advanced cancer, offering palliation by relieving dysphagia and improving the quality of life[13-17]. Despite the toxicity and its complications, chemotherapy has a place in such condemned patients[18-20].

The cooperation of various medical specialities is mandatory since the use of all available current diagnostic and therapeutic tools improves the outcome[21,22]. Nowadays, in western countries, adenocarcinoma represents two thirds of esophageal cancer. The current modalities of palliative treatment are equally effective in both adenocarcinoma and squamous cell carcinoma, contributing to a satisfactory quality of life[23].

BYPASS OPERATION

With the introduction of modern, safe and effective non-operative alternative interventional methods for the management of dysphagia, the palliative bypass operation has been applied even less, mainly due to its high morbidity and mortality rates. On the other hand, the average survival time of these patients is limited to about 6 mo. The stomach has been preferred to be used for a bypass procedure and when the stomach cannot be used, we use the colon, which historically was first used[24-26]. The gastric conduit was introduced first by Kirschner in 1920 and so the operation was established using his name. However, it should be mentioned that this operation is now considered an obsolete planned procedure although it remains a reasonable choice in cases when unexpected findings appear that exclude any radical operation during the operative exploration[25].

CONCLUSION

In conclusion, palliative treatment of inoperable gastroesophageal junction cancer aims at managing dysphagia. It can now mainly be achieved by interventional stent placement, ensuring good quality of life during the short survival time. The bypass operation must be avoided as a first choice in these severely affected patients. The gastric conduit is preferred instead of colon interposition.

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CASE REPORT

Giant mucinous cystic adenoma with pancreatic atrophy mimicking dorsal agenesis of the pancreas

Johan Gagnière, Aurélien Dupré, David Da Ines, Lucie Tixier, Denis Pezet, Emmanuel Buc

Johan Gagnière, Aurélien Dupré, Denis Pezet, Emmanuel Buc, Department of Digestive and Hepatobiliary Surgery, Centre Hospitalier Universitaire Estaing, 63003 Clermont-Ferrand, France
David Da Ines, Lucie Tixier, Department of Radiology, Centre Hospitalier Universitaire Estaing, 63003 Clermont-Ferrand, France
Author contributions: Gagnière J and Dupré A contributed equally to this work; Gagnière J, Dupré A and Buc E designed the research; Gagniere J, Dupré A, Da Ines D and Tixier L performed the research; Da Ines D and Tixier L supervised the iconography and Gagnière J, Dupré A, Pezet D and Buc E wrote the paper.
Correspondence to: Emmanuel Buc, PhD, Department of Digestive and Hepatobiliary Surgery, Centre Hospitalier Universitaire Estaing, place Lucie et Raymond Aubrac, 63003 Clermont-Ferrand, France. ebuc@chu-clermontferrand.fr
Telephone: +33-473-750494 Fax: + 33-473-750459
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Abstract

Mucinous cystic adenoma (MCA) of the pancreas is a rare benign cystic tumor with ovarian-like stroma and lack of communication with the pancreatic ductal system. The ovarian tissue is incorporated from the left gonad within the dorsal pancreas during embryogenesis. Consequently, congenital dorsal agenesis of the pancreas (DAP) cannot be associated with MCA. We report the case of a giant MCA associated with atrophy of the dorsal pancreas mimicking complete DAP. Pancreato-magnetic resonance imaging failed to identify the dorsal pancreas but the absence of diabetes mellitus and compression of the splenic vein with major tributaries rectified the diagnosis of secondary atrophy of the distal pancreas. Unusual proximal location of the cyst in the pancreas may have induced chronic obstruction of both the dorsal pancreatic duct and the splenic vein, with secondary atrophy of the distal pancreas.

Key words: Dorsal agenesis; Pancreas; Cystic tumor; Diabetes; Surgery

Core tip: Mucinous cystic adenoma (MCA) of the pancreas is a benign tumor with ovarian-like tissue located in the body or the tail of the pancreas. We report the first case of atrophy of the distal pancreas secondary to compression by a giant MCA. We raise the question of underlying dorsal agenesis of the pancreas (DAP) but as ovarian-like tissue of MCA comes from the close migration of the left gonad and the dorsal pancreas during embryogenesis MCA can not be associated with true DAP. Finally, the absence of diabetes mellitus, and thrombosis of the splenic vein confirmed the secondary atrophy caused by a mechanism of compression.

Gagnière J, Dupré A, Da Ines D, Tixier L, Pezet D, Buc E. Giant mucinous cystic adenoma with pancreatic atrophy mimicking dorsal agenesis of the pancreas. *World J Gastrointest Surg* 2014; 6(3): 42-46 Available from: URL: http://www.wjgnet.com/1948-9366/full/v6/i3/42.htm DOI: http://dx.doi.org/10.4240/wjgs.v6.i3.42

INTRODUCTION

Dorsal agenesis of the pancreas (DAP) is a rare disease that is frequently asymptomatic except when associated with polysplenia syndrome. Etiology remains unclear, but dysgenesis of the dorsal bud during embryogenesis seems to be the most plausible explanation. Confounding diagnoses include pseudo-agenesis of the dorsal pancreas following acute pancreatitis or compression by a tumor[1,2]. In such cases, the mechanism involves pancreatic duct obstruction with atrophy of pancreatic acini replaced by

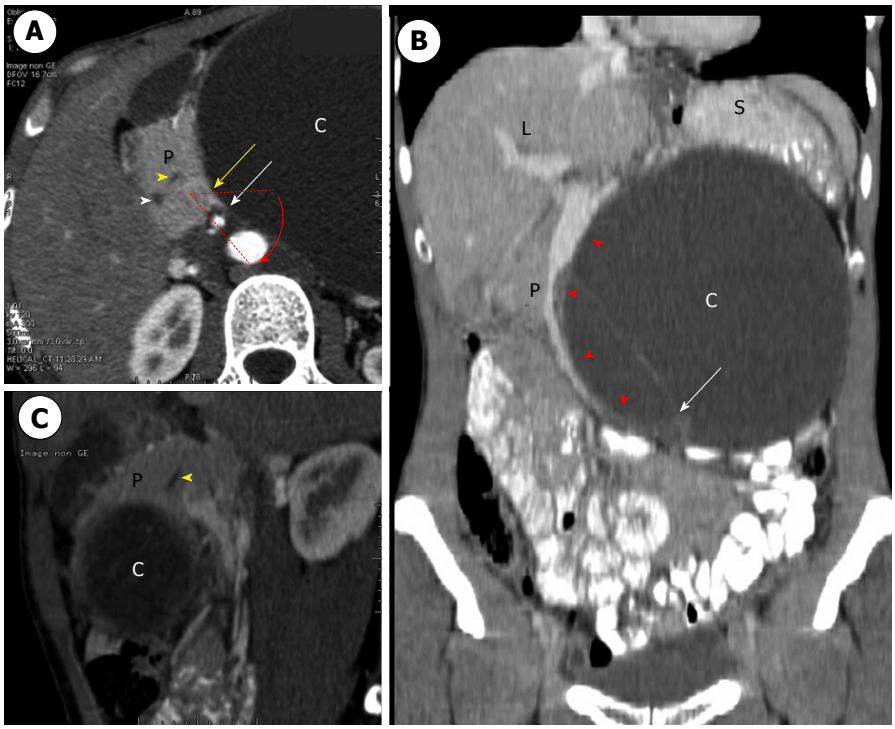

Figure 1 Preoperative contrast-enhanced computed tomography showing a huge cyst with septa developed close to the head of the pancreas, exophytic development to the left and downward, and rotation of the mesenteric axis. A: Axial view showing the head of the P with the intrapancreatic main bile duct (white arrowhead) and ventral pancreatic duct (yellow arrowhead). There is rotation of the mesenteric axis, as shown by the oblique plane made by the superior mesenteric artery (white arrow) and the superior mesenteric vein (yellow arrow); B: Coronal view showing thin septa within the macrocyst (white arrow) and deviation without thrombosis of the mesenterico-portal axis (red arrowhead); C: Sagittal view showing anterior development of the cyst, close to the head of the pancreas (P) and the ventral pancreatic duct (yellow arrowhead). L: Liver; S: Spleen; P: Pancreas; C: Cyst.

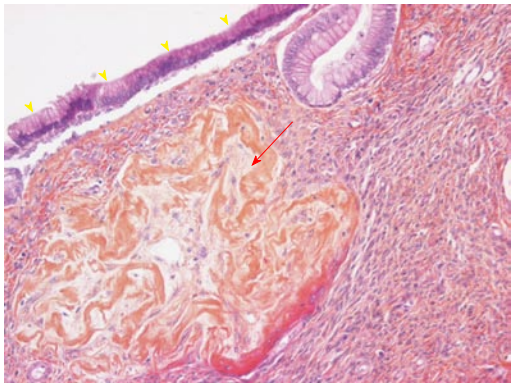

Figure 2 Histologic examination (× 20) showing the cyst lined by tall columnar epithelial cell (yellow arrowheads) with underlying ovarian-type stroma composed of densely packed spindle cells (red arrow).

fat. However, endocrine cells generally still persist and prevent the occurrence of diabetes mellitus. Benign cystic or non-cystic tumors cannot usually induce pancreatic atrophy since invasive contingents are missing. We herein present the first documented case of a giant mucinous cystic adenoma (MCA) of the pancreas responsible for secondary atrophy of the dorsal pancreas and mimicking a complete DAP.

CASE REPORT

A 36-year-old female was referred to a first institution for exploration of an asymptomatic abdominal mass. She had no previous medical or surgical history. Physical examination showed a large painless epigastric mass. Ultrasound (US) showed a well-limited cyst in the epigastric area 15 cm × 10 cm in size with a thick wall, heterogeneous content and peripheral calcifications. Laboratory test results including amylase, lipase and serum glucose levels were within the normal range. The serum tumor markers carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) were normal. Contrast-enhanced computed tomography (CT) scan confirmed a well-defined, low-density, 17 cm × 11 cm, unilocular cystic tumor (Figure 1). It seemed to originate from the proximal part of the distal pancreas but the rotation to the left of both the head of the pancreas and the superior mesenteric vessels rendered the exact location of the cyst inconclusive (Figure 1). Thin septa, contrast enhancement and calcifications were also observed. Magnetic resonance imaging (MRI) and endoscopic US-guided fine needle aspiration (EUS-FNA) of the cyst were not performed preoperatively as giant benign MCA was suspected. The patient underwent surgical enucleation of an exophytic 14 cm × 10 cm cystic tumor of the pancreas. In his operative report, the surgeon noted a difficult procedure with accidental intraoperative rupture of the cyst. The postoperative period was uneventful and the patient was discharged on postoperative day 7. The pathological report confirmed a multilocular, thick-walled, 14 cm × 10 cm cyst with intracystic hemorrhage and disruption. Microscopically, the cyst was lined by tall columnar, mucin-containing epithelial cells, surrounded by an ovarian-like stroma (Figure 2). The epithelium was benign and positive for cytokeratins 7 and 19, which is consistent with the diagnosis of pancreatic MCA. Enucleation was complete and conservative as pancreatic parenchyma was absent on the specimen.

An abdominal CT-scan was performed 6 mo after surgery for exploration of abdominal tenderness and showed four low-density homogenous cystic lesions with contrast-enhanced wall in the previous pancreatic

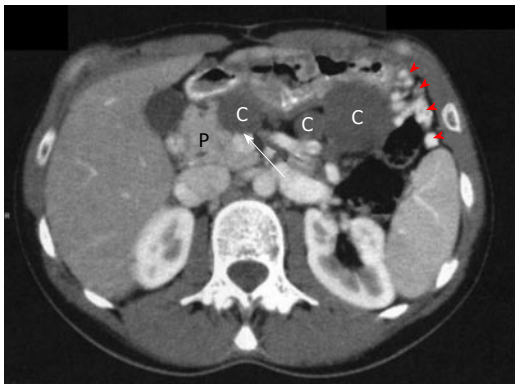

Figure 3 Post-operative contrast-enhanced computed tomography showing three low-density homogenous cystic lesions suggesting secondary dissemination of the resected cyst. Major tributaries were also present around the stomach (red arrowheads). The P has a total distal atrophy as shown by lack of pancreatic tissue behind the mesenterico-portal axis (white arrow). P: Pancreas; C: Cyst.

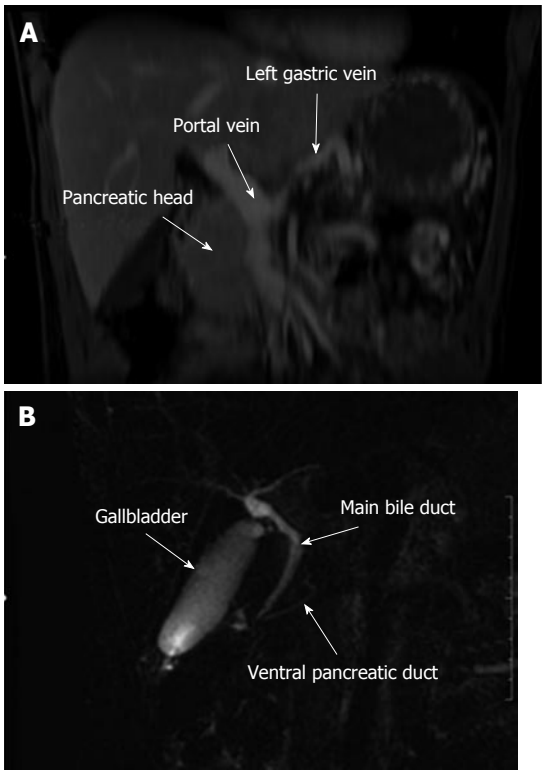

Figure 4 Coronal magnetic resonance imagery showing lack of the body and tail of the pancreas and of the splenic vein (A), magnetic resonance cholangiopancreatography showing the common bile duct joining the ventral pancreatic duct at the posterior part of the head of the pancreas (B). The dorsal pancreatic duct is not visible.

enucleation area (Figure 3). The body and tail of the pancreas were not visible on CT nor on the upper part of the head of the pancreas, suggesting complete DAP. Magnetic resonance cholangiopancreatography (MRCP) showed absence of the body and tail of the pancreas with no accessory pancreatic duct that would confirm the diagnosis of DAP (Figure 4). There was no other pancreatic anomaly and no polysplenia. The patient was then referred to our institution. A second interpretation of the scan pictures showed splenic vein obstruction with major tributaries around the stomach, suggesting segmental portal hypertension (Figure 3). These features were also present on the initial CT. The serum levels of glucose, amylase and lipase were still normal. The suspected diagnoses were either recurrence of the MCA following difficult and incomplete primary resection, as suggested by intraoperative rupture, or multiple pseudocysts due to a latent post-operative pancreatic leak. A second-look laparoscopy was advocated because of abdominal tenderness, risk of recurrence of the MCA and because EUS-FNA failed to distinguish MCA from pancreatic pseudocysts. Laparoscopic exploration showed extra-pancreatic multiple cysts close to the first duodenum at the anterior part of the head of the pancreas, without pancreatic leak. The body and tail of the pancreas were also absent. Intraoperative pathology examination of the cysts confirmed pseudocysts with fat necrosis. Postoperative course was uneventful and the patient was discharged on postoperative day 3. One year after initial resection the patient had no diabetes mellitus, and routine blood parameters, in particular serum glucose level, were normal.

DISCUSSION

To the best of our knowledge, there are no documented reports of pancreatic cyst-including benign MCA-associated with congenital or secondary atrophy of the distal pancreas. MCA is a rare benign cystic tumor characterized by an ovarian stroma underlying the epithelium of the cyst. Differential diagnosis includes other benign cystic lesions such as serous cystic neoplasm, intraductal papillary mucinous neoplasm and post-pancreatitis pseudocysts[3]. Clinical presentation (female sex, location in the distal pancreas and no history of pancreatitis) and paraclinical investigations (MRI and EUS-FNA showing no pancreatic duct communication, wall calcifications and high level of intra-cystic CA19-9 and CEA) are suggestive of MCA[4]. Prophylactic resection is warranted as malignant transformation can occur in 6%-27% of cases[5,6]. The origin of ovarian stroma remains unclear. It has been suggested to derive from ectopic tissue within the pancreas incorporated throughout close migration of the left primordial gonad and dorsal pancreatic bud during embryogenesis[7-9], which would explain the predilection of MCA for the body-tail region of the pancreas. Consequently, the association of complete DAP with MCA is theoretically not possible.

DAP is a congenital agenesis of the pancreas that can be partial or complete. It is a rare event since only 54 cases have been reported in the literature[10]. The pancreas develops from ventral and dorsal endodermal buds during embryogenesis. The ventral bud gives rise to the major part of the head and uncinate process, which drains through the duct of Wirsung (*i.e.*, the main pancreatic duct). The dorsal bud forms the upper part of the head, body and tail of the pancreas and drains through the duct of Santorini (*i.e.*, the accessory pancreatic duct). Each

bud develops a tree-like ductal system and, during growth and rotation of the gut in the seventh week of gestation, the two buds fuse and form the main pancreatic gland. Exocrine secretion is consistent in both dorsal and ventral pancreas, whereas insulin-secreting cells of the islets of Langerhans are located predominantly in the dorsal pancreas[11]. Rarely, DAP is complete with lack of structures originating from the dorsal pancreas - such as minor papilla, accessory pancreatic duct, body and tail[12]. When DAP is partial, which is most frequently the case, the minor papilla with a remnant accessory pancreatic duct and the body of the pancreas usually persist[13]. Confounding diagnosis is secondary atrophy of the distal pancreas due to chronic obstruction of the pancreatic duct. In this case, atrophy involves predominantly the exocrine tissue while endocrine cells are still present and prevent the occurrence of diabetes mellitus[1,2].

In our patient, despite arguments for congenital DAP, compression of the main pancreatic duct by the giant cyst with secondary atrophy of the distal pancreas was the most probable hypothesis. As discussed above, the association of complete DAP with MCA is not possible. Although there was no accessory pancreatic duct on MR-CP, the unusual proximal location within the dorsal pancreas of the MCA could have induced atrophy of the distal pancreas with no or undetectable remnant accessory pancreatic duct. This is consistent with atrophy of the splenic vein and collateral vascularization developed from the gastric veins, usually absent in congenital DAP[10,13]. Atrophy may have been worsened by intraoperative injury in what was described as a difficult procedure, as shown by the presence of a postoperative pseudocyst close to the head of the pancreas (Figure 3). Another argument for secondary atrophy is the absence of diabetes mellitus, since congenital DAP involves both endocrine and exocrine secretions with diabetes mellitus in around 40% of cases[2].

To the best of our knowledge, there is no published report of the effects of MCA on the distal pancreas. There are at least two reasons for this[14,15]. First, observations usually focus on the size, symptoms and management of the MCA, with little or no information about the distal pancreas. Second, MCAs are located in the distal position and usually spare the proximal pancreatic parenchyma. The pathological report usually insists on the features of the MCA, but not in the distal pancreas, and whether it is atrophied or absent. There have been reports of DAP associated with non-invasive tumors[16,17]. In these cases, the diagnosis of DAP was based on atrophy of the distal pancreas but in no instance it was possible to differentiate congenital agenesis from secondary atrophy. The unusual occurrence of congenital DAP makes the association with tumor very unlikely and we suggest that, as in our case, most DAPs associated with huge tumors are the result of secondary atrophy. Furthermore, tumors located within the dorsal pancreas cannot be associated with DAP given that complete agenesis of an organ cannot lead to the development of a tumor because neoplastic transformation can not occur from cells that do not exist.

Our observation is a reminder that the management of huge benign tumors is problematic. Preoperative imaging must be rigorous to detect congenital or acquired anomalies of the pancreas, and to describe pancreatic ductal anatomy. Resection must be conservative as often as possible, to avoid injury of the ductal system and secondary occurrence of pancreatic fistula or pseudocysts. Non-visualization of distal pancreas can be the consequence of long term compression of the main pancreatic duct. However, islets cells may still be present and accidental resection of the atrophic pancreas can lead to secondary diabetes mellitus. Thus, we recommend addressing these patients to tertiary centers for adequate preoperative evaluation and surgical management.

COMMENTS

Case characteristics

A 36-year-old female presented with asymptomatic abdominal mass.

Clinical diagnosis

Painless huge epigastric mass with no digestive repercussion.

Differential diagnosis

Gastric tumor, liver tumor, liver cyst, pancreatic tumor.

Laboratory diagnosis

WBC 9.80 k/μL, HGB 14.0 mg/dL, glucose 7 mmol/L, lipase 80 U/L, CRP 2.9 mg/L. Carbohydrate antigen 19-9 and carcinoembryonic antigen were within normal limits.

Imaging diagnosis

Computed tomography showed a huge mucinous cystic adenoma (MCA) that originated from the head or the body of the pancreas, with thrombosis of the splenic vein and complete atrophy of the pancreas distal to the cyst mimicking dorsal agenesis of the pancreas (DAP).

Pathological diagnosis

Specimen showed a cyst lined by tall columnar epithelial cells surrounded by an ovarian-like stroma, positive for cytokeratins 7 and 19, consistent with the diagnosis of MCA.

Treatment

The patient was treated by enucleation of the cyst, but recurrence of multiple cysts six months later led to second-look laparoscopy, which showed pseudocysts resulting from the initial surgery.

Related reports

Atrophy of the dorsal pancreas is usually observed in invasive tumors or in chronic pancreatitis but not in non-invasive benign tumors.

Term explanation

DAP is defined as embryological agency of the dorsal pancreatic bud resulting in lack of development of the superior part of the head, body and tail of the pancreas.

Experiences and lessons

Right-sided pancreatic MCA can lead to atrophy of the distal pancreas but can not be associated with DAP as MCAs usually originate from the dorsal pancreas.

Peer review

Splenic vein thrombosis and absence of diabetes mellitus are good markers of secondary atrophy of the pancreas.

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CASE REPORT

Giant Meckel's diverticulum: An exceptional cause of intestinal obstruction

Sami Akbulut, Yusuf Yagmur

Sami Akbulut, Yusuf Yagmur, Department of Surgery, Diyarbakir Education and Research Hospital, Diyarbakir 21400, Turkey
Author contributions: Akbulut S and Yagmur Y designed, organized and wrote the report, and were attending doctors for the patients; Akbulut S performed surgical operation.
Correspondence to: Sami Akbulut, MD, FICS, FACS, Department of Surgery, Diyarbakir Education and Research Hospital, Uckuyular Mevki, Kayapinar, Diyarbakir 21400, Turkey. akbulutsami@gmail.com
Telephone: +90-412-2580075 Fax: +90-412-2580070
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Abstract

Meckel's diverticulum (MD) results from incomplete involution of the proximal portion of the vitelline (also known as the omphalomesenteric) duct during weeks 5-7 of foetal development. Although MD is the most commonly diagnosed congenital gastrointestinal anomaly, it is estimated to affect only 2% of the population worldwide. Most cases are asymptomatic, and diagnosis is often made following investigation of unexplained gastrointestinal bleeding, perforation, inflammation or obstruction that prompt clinic presentation. While MD range in size from 1-10 cm, cases of giant MD (≥ 5 cm) are relatively rare and associated with more severe forms of the complications, especially for obstruction. Herein, we report a case of giant MD with secondary small bowel obstruction in an adult male that was successfully managed by surgical resection and anastomosis created with endoscopic stapler device (80 mm, endo-GIA stapler). Patient was discharged on postoperative day 6 without any complications. Histopathologic examination indicated Meckel's diverticulitis without gastric or pancreatic metaplasia.

Key words: Meckel's diverticulum; Giant Meckel's diverticulum; Intestinal obstruction; Small bowel

Core tip: The most commonly diagnosed congenital anomaly of the gastrointestinal tract is Meckel's diverticulum (MD), which occurs upon failure of the omphalomesenteric duct to regress and involute. MD can remain asymptomatic, and cases are generally diagnosed incidentally or upon investigation of unexplained gastrointestinal bleeding, perforation, inflammation, or obstruction for both paediatric and adult cases. It is estimated that as little as 4% of cases manifest complications, and obstruction is the most common presenting symptom in adults. In this case study, we report a case of giant MD with secondary small bowel obstruction in an adult male that was successfully managed by surgical resection and anastomosis created with endoscopic stapler.

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INTRODUCTION

The most commonly diagnosed congenital anomaly of the gastrointestinal tract is Meckel's diverticulum (MD), which occurs upon failure of the vitelline (also known as the omphalomesenteric) duct to regress and involute[1-3]. Accumulated experience with surgical treatment of MD (using both open and laparoscopic procedures) has led to the clinical "rule of 2" for symptomatic cases, whereby the anatomical deformity (with estimated prevalence in 2% of the population) is most frequently located 2 feet from the ileocaecal junction and is 2 inches long[2]. MD can remain asymptomatic, and cases are generally diag-

nosed incidentally or upon investigation of unexplained gastrointestinal bleeding, perforation, inflammation, or obstruction for both paediatric and adult cases[1].

It is estimated that as little as 4% of cases manifest complications, and obstruction is the most common presenting symptom in adults[1]. There is evidence that severity of symptoms correlates with MD size. Ninety percent of the reported MDs are between 1 and 10 cm, the average size being 3 cm. MDs ⩾ 5 cm are classified as giant MD, are relatively rare, and may be more prone to complications[1]. Here, we report a case of giant MD which was diagnosed in an adult male with small bowel obstruction and successfully managed by resection.

CASE REPORT

A 23-year-old male patient presented at the Emergency Department with a complaint of abdominal pain, nausea, and vomiting that had persisted for 5 d and increased in severity over the last 24 h. The patient reported no faecal or gas discharge during the previous 48 h. History taking upon admission revealed that the patient had visited hospitals frequently for many years with similar gastrointestinal complaints as well as bloating. The patient's abdomen was remarkably distended and initial clinical assessment indicated hypovolemia. Physical examination revealed significant bowel sounds and substantial abdominal rebound pain, both more robust in the periumbilical area. Laboratory testing showed increased white blood cell count ($11.8 \times 10^3/\mu L$; normal range: 4.1×10^3-11.2×10^3), haemoglobin (17.0 g/dL; 12.5-16.0), haematocrit (49.6%; 37.0-47.0) and creatinine (1.4 mg/dL; 0.4-1.2), but normal blood urea nitrogen (27 mg/dL; 10-50). Abdominal X-ray indicated remarkably high air-fluid levels (Figure 1).

An emergency laparotomy was performed and revealed oedema throughout the entire small bowel, dilation of small bowel segments, and a giant MD (27 cm long and 6 cm wide) on the antimesenteric border of the small bowel at 80 cm proximal to the ileocaecal valve (Figure 2). The diverticulum's tip was strongly adhered to the parietal peritoneum of the abdominal wall at the site of the pelvis, having been pushed up against this site due to the MD's excessively large size and high-volume intestinal content. No other obstruction was observed in the gastrointestinal tract. Resection of the small bowel was performed with a linear stapler and an ileoileal anastomosis was generated using a 80 mm endo-GIA stapler (Figure 3). The resection was completed without incident, and the patient was discharged on post-operative day 6 without any complications. Pathology findings indicated diverticulitis without gastric or pancreatic metaplasia.

DISCUSSION

MD is a true diverticulum, comprising all three layers of the small intestine. Compared to the overall incidence of 0.14%-4.50% (estimated by autopsy findings and retrospective studies)[4], giant MD are rare[5]. The largest giant

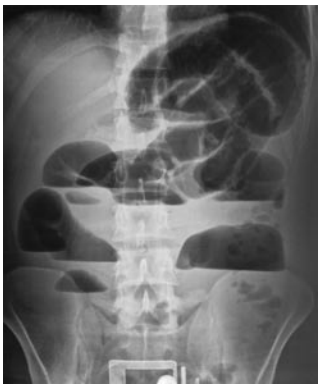

Figure 1 Abdominal X-ray radiography showing air-fluid levels representative of intestinal obstruction.

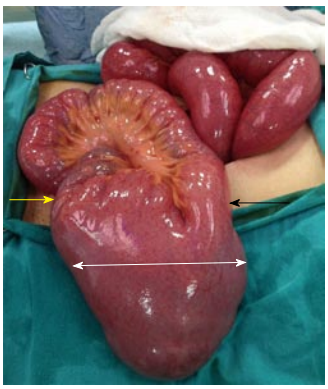

Figure 2 Giant Meckel's diverticulum causing gastrointestinal obstruction. White arrow: Diameter of Meckel's diverticulum; Black arrow: Proximal ileal segment; Yellow arrow: Distal ileal segment.

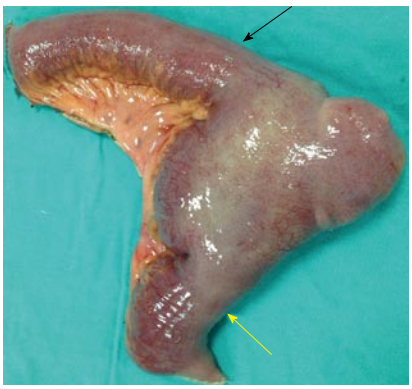

Figure 3 Giant Meckel's diverticulum view after resection. Black arrow: Proximal ileal segment; Yellow arrow: Distal ileal segment.

MDs reported have been > 100 cm long[6], 96 cm long[7], 85 cm long[8], and 66 cm long[9,10].

In adult cases of MD, obstruction is the most frequently reporting presenting symptom[11-14] and can be caused by either the diverticulum's attachment to the umbilicus, abdominal wall or other viscera by a fibrous band or by interference due to the mobility of an unattached diverticulum[11]. Though first hypothesized in 1902[13], these potential reasons for MD-caused intestinal obstruc-

tion remain the features by which MD cases are classified. The obstructions associated with a free or unattached diverticulum, or having only one attachment to the intestine, represent first MD type, and obstructions associated with an attached diverticulum, including through its terminal ligament, to the abdominal wall or intestinal viscus, represent the second type. Between these two types, the former is much rarer.

When the congenital malformation occurs, the free diverticulum forms a volvulus with a loop, twisting the gut structure. Adhesions commonly form between the two arms of the twist, making an obstruction. Subsequent inflammation of the diverticulum further promotes constriction of the bowel. Furthermore, an unattached, distended diverticulum may cause movement of the looped intestine so that a kink forms in the intestine at the attachment point of the diverticulum; this event could lead to an obstruction without any concomitant structural changes in the intestinal wall. Persistence of such kinking may ultimately cause necrosis of the involved and proximal gut tissues. Other potential aetiologies of MD-related intestinal obstructions exist. For example, the obstruction may be caused by twisting of the bowel along its long axis at the point of the diverticulum's origin, by chronic inflammation of the diverticulum and its adjacent bowel, or by inversion of the mucous membrane alone, or of the entire diverticulum, with or without invagination.

Several case reports of MD-related obstructions have described strangulation caused by an adherent diverticulum. Many causes of such an event have been proposed. First, the adherent diverticulum itself may act as a constricting band, such as an adventitious band or a peritoneal adhesion. Second, the adherent diverticulum may have resulted from looping and twisting of the gut in upon itself, forming a volvulus. Third, a volvulus of the attached diverticulum may itself represent a physical obstruction of the intestine. Finally, the diverticular band may become tensely drawn under certain conditions[13].

In a review of 402 patients with MD, 16.9% of the patients were found to have demonstrated symptoms that are considered clinical references for diverticulum[14], with obstruction of the small intestine, and inflammation and bleeding of the lower gastrointestinal tract accounting for 90% of those presenting symptoms. In another study of 34 MD cases, the most common complications were intestinal obstruction (37%), intussusception (14%), inflammation, and rectal bleeding (12%); interestingly, intussusception and volvulus were associated with those patients having intestinal obstruction[15].

For the current case of giant MD, the diverticulum was large in diameter, long in length, and adherent (causing a small bowel obstruction). The structural features of a MD provide clues to the type of complications it may cause. For example, diverticulitis and torsion are common complications observed with long MDs that have a narrow base, while short MDs that have a stumpy base are more often associated with intussusception[16]. Thus, an elongated variant with a narrow neck is more likely to result in torsion, whereas a short, wide-base diverticula may promote foreign body entrapment.

Cullen *et al*[17] studied the outcomes of diverticulectomy surgical management of MD-related complications and determined that the operative mortality and morbidity rates were 2% and 12%, respectively, and that the cumulative risk of long-term post-operative complications was 7%; in contrast, analysis of patients receiving incidental diverticulectomy showed that the operative mortality, morbidity, and risk of long-term post-operative complications were lower (1%, 2%, and 2%, respectively). It is generally recommended that MD discovered incidentally during operation should be removed, regardless of the patient's age.

In conclusion, this report describes a very rare form of acute small bowel obstruction secondary to giant MD encircling the terminal ileum, providing novel insights into this condition and describing its successful management by surgical resection.

COMMENTS

Case characteristics

Clinical symptoms include abdominal pain, nausea, vomiting, and no faecal or gas discharge.

Clinical diagnosis

Acute abdomen, mechanical small bowel obstructions.

Differential diagnosis

Intestinal malrotation, congenital anomalous bands, tumor obstruction.

Laboratory diagnosis

Laboratory tests showed a leukocytosis (11800/μL; 4100-11200), haemoglobin (17.0 g/dL; 12.5-16.0), haematocrit (49.6%; 37.0-47.0) and creatinine (1.4 mg/dL; 0.4-1.2).

Imaging diagnosis

An abdominal X-ray radiography indicated remarkably high air-fluid levels.

Pathological diagnosis

Pathology findings indicated Meckel's diverticulitis without gastric or pancreatic metaplasia.

Treatment

Limited ileal resection and end-to-end anastomosis created with stapler device.

Term explanation

Meckel's diverticulum (MD), a remnant of the vitelline duct that normally disappears at the end of the seventh week of gestation, is the most common congenital abnormality of the small intestine. It arises from the antimesenteric border of the terminal ileum as a true diverticulum that contains all layers of the intestinal wall.

Peer review

This is a well written case report on a farly common subject. It is well know that MD can couse intestinal obstruction and can reach fairly large dimensions, depending on the duration of the sub-occlusive symptoms.

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CASE REPORT

Coexistence of abdominal cocoon, intestinal perforation and incarcerated Meckel's diverticulum in an inguinal hernia: A troublesome condition

Sami Akbulut, Yusuf Yagmur, Mehmet Babur

Sami Akbulut, Yusuf Yagmur, Mehmet Babur, Department of Surgery, Diyarbakir Education and Research Hospital, Uckuyular Mevki, Diyarbakir 21400, Turkey
Author contributions: Akbulut S and Yagmur Y designed the report, were the attending doctors for the patient, and wrote the manuscript; Akbulut S and Babur M performed the surgical operation.
Correspondence to: Sami Akbulut, MD, FICS, FACS, Department of Surgery, Diyarbakir Education and Research Hospital, Uckuyular Mevki, Kayapinar, Diyarbakir 21400, Turkey. akbulutsami@gmail.com
Telephone: +90-412- 2580075 Fax: +90-412-2580070
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Abstract

Sclerosing encapsulating peritonitis (SEP) is a rare disease entity, in which the small intestine becomes encased and mechanically obstructed by a dense, fibrotic membrane. The disorder is characterized as either primary (idiopathic) or secondary to other causes. The idiopathic cases of SEP, which lack any identifiable etiology according to clinical, radiological and histopathological findings, are also reported under the designation of abdominal cocoon syndrome. The most frequent presenting symptoms of all SEP cases are nausea, vomiting, abdominal distention and inability to defecate, all of which are associated with the underlying intestinal obstruction. Persistent untreated SEP may advance to intestinal perforation, representing a life-threatening condition. However, preoperative diagnosis remains a particular clinical challenge, and most diagnoses are confirmed only when the typical fibrous membrane encasing the small intestine is discovered by laparotomy. Here, we report the clinical presentation of an 87-year-old male with signs of intestinal obstruction and the ultimate diagnosis of concurrent abdominal cocoon, right incarcerated Meckel's diverticulum, and gastrointestinal perforation in laparotomy.

Key words: Sclerosing encapsulating peritonitis; Cocoon syndrome; Perforation; Meckel's diverticulum

Core tip: Abdominal cocoon syndrome, also known as idiopathic sclerosing encapsulating peritonitis, is a rare disease entity, in which the small intestine becomes encased and mechanically obstructed by a dense, fibrotic membrane. While some patients with cocoon syndrome remain asymptomatic, the majority experience gastrointestinal symptoms, including recurrent attacks of acute, sub-acute or chronic gastrointestinal obstruction, weight loss, loss of appetite, and development of a palpable abdominal mass. Herein, we describe an elderly patient who presented with signs of intestinal obstruction and who was diagnosed with concurrent abdominal cocoon, right incarcerated Meckel's diverticulum, and gastrointestinal perforation by exploratory laparotomy.

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INTRODUCTION

Sclerosing encapsulating peritonitis (SEP) is a rare structural abnormality whereby the small intestine becomes encased (or cocooned) by a dense fibrocollagenous

membrane that causes intestinal obstruction[1,2]. First described in 1907 as "peritonitis chronica fibrosa incapsula" by Owtschinnikow[1,3-7], subsequent case reports have described the disease condition as primary (idiopathic) or secondary, depending on the underlying etiological causes. The idiopathic form is also reported under the alternative descriptive name of "abdominal cocoon syndrome"[1,3,4,8,9].

The most common clinical signs and symptoms of SEP include nausea, vomiting, abdominal distention and inability to defecate, all of which are indicative of gastrointestinal obstruction. Rare cases of SEP manifest the severe complication of perforation. The relatively nonspecific nature of the common symptomology makes preoperative diagnosis a clinical challenge, and many cases are only diagnosed during laparotomy[3,6]. In this case report, we describe an elderly patient who presented with signs of intestinal obstruction and who was diagnosed with concurrent abdominal cocoon, right incarcerated Meckel's diverticulum, and gastrointestinal perforation by exploratory laparotomy.

CASE REPORT

An 87-year-old male patient presented to our emergency department upon referral from an outside center for management of severe abdominal pain, nausea, vomiting and inability to defecate for 3 d. The patient's medical history was generally unremarkable, with hypertension and bronchial asthma the only major afflictions. Physical examination findings were distended abdomen, sunken eyes, dry mucosa, and vital signs consistent with hypovolemia and sepsis (blood pressure: 100/60 mmHg; pulse: 90 beats per minute; body temperature: 38.1 ℃). In addition, severe rebound tenderness was observed in all abdominal quadrants, with the most severe being in the right lower quadrant. Findings from laboratory tests were white blood cell count of 13900/μL (neutrophils: 83.2%), hemoglobin level of 11.4 g/dL, blood urea nitrogen level of 60 mg/dL, and creatinine level of 1.5 mg/dL. Abdominal imaging examination revealed diffuse air-fluid levels (by X-ray; Figure 1) and free fluid in the pelvis and right lower quadrant, as well as dilatation and edema in all intestinal segments (by ultrasonography, United States). Exploratory laparotomy was performed according to the initial diagnosis of perforation, mechanical bowel obstruction due to tumor, and mesenteric vascular disease. All intestinal segments from 60 cm distal to the Treitz ligament to the ileocecal valve were found to be dilated and encapsulated (Figure 2). Meckel's diverticulum, at the 60 cm proximal to ileocecal valve, was incarcerated into the right inguinal canal. This clinicopathologic condition is also referred to as Littre hernia (Figure 3). Some intestinal segments at 100 cm proximal to the ileocecal valve were conglomerated and adhered to the retroperitoneum. In addition, a 1 cm perforation immediately proximal to the conglomerated segment and an abscess located posterior to the conglomerated segment were detected. The

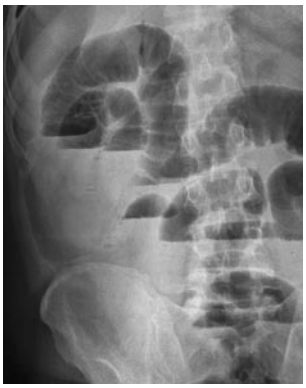

Figure 1 X-ray plain abdominal imaging (posteroanterior) revealed intestinal obstruction with marked small bowel air-fluid levels.

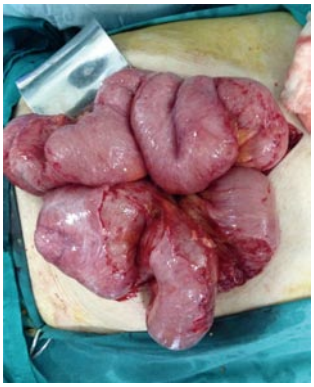

Figure 2 Intraoperative photographs taken along the midline incision and showing the encapsulated small bowel segments with a dense fibrous layer.

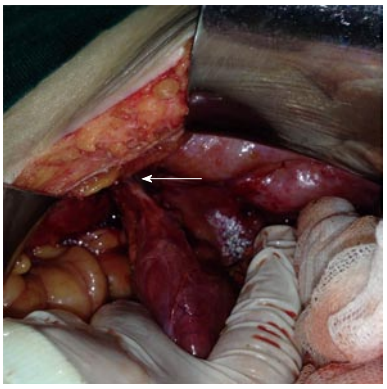

Figure 3 Intraoperative photographs showing the Meckel's diverticulum incarcerated within the right inguinal canal (arrow).

intra-operative management was initiated by performing decapsulation and adhesiolysis of all encapsulated segments, and followed by freeing of the incarcerated intestinal segments and closing of the mouth of the hernia sac. Then, the conglomerated and perforated ileal segment was resected and the abdominal cavity was irrigated. A side-to-side ileoileal anastomosis was constructed using an Endo-GIA stapler (Covidien, Dublin, Ireland), and a loop ileostomy was constructed at 40 cm proximal

to the anastomosis site. Post-operative recovery was uncomplicated and the patient was discharged to home at 12 d after the surgery. The histopathologic examination of the excised peritoneal capsule showed proliferation of the fibroconnective tissue with signs of a non-specific inflammatory reaction. Diagnosis of SEP was established based on the intraoperative view, results from histopathologic examination, and findings from other clinical and biochemical analyses.

DISCUSSION

SEP is a disease entity characterized by partial or complete encasement of small intestine by a thick fibrotic membrane[1,5]. This fibrocollagenous membrane may extend to encase other proximal organs as well, such as stomach, liver and large intestine; in some forms of the disease, this extension of the encasing membrane can cause segregation of the intraperitoneal organs (as if they were extraperitoneal)[8]. Although epidemiological studies of SEP have not fully elucidated the precise etiologic profile of primary/idiopathic or secondary SEP[4], they have revealed a trend in incidence involving young females living in temperate geographic zones. It has been speculated that infections of the Fallopian tubes or retrograde menstruation may be related to disease onset and progression[7]. In addition, incidence of SEP is not infrequent in patients with ambulatory peritoneal dialysis, suggesting that this condition may represent an etiology of secondary SEP[6,10]. Other cases of SEP have been reported in patients with abdominal tuberculosis, sarcoidosis, gastrointestinal malignancies, systemic lupus erythematosus, familial Mediterranean fever, with fibrogenic foreign materials, undergoing beta-blocker (practolol) therapy[4,7,9-12], fitted with ventriculoperitoneal and peritoneovenous shunts, recipients of orthotopic liver transplantation, and suffering from recurrent peritonitis attacks[6]. The current patient, described herein, had no chronic disease history and normal test results from biochemical (erythrocyte sedimentation rate) and microbiological (blood and peritoneal fluid culture, and PPD skin test) assays. Therefore, we considered that this case was likely primary SEP.

While some SEP patients remain asymptomatic, the majority experience gastrointestinal symptoms, including recurrent attacks of acute, sub-acute or chronic gastrointestinal obstruction, weight loss, loss of appetite, and a palpable abdominal mass[1,3,6,8]. Additionally, some of the SEP patients with severe abdominal distention also have ascites[3]. Gastrointestinal perforation is a relatively rare complication of SEP. To our knowledge only one case of SEP-related perforation has been reported, and the etiology was evidenced as tuberculosis[12]. The current case herein also had an ileal perforation, but the absence of any clear etiologic factor (primary SEP) makes this case unique in the literature.

SEP is suspected according to the gastrointestinal clinical signs coupled with suggestive findings from physical examination, biochemical testing, and radiological analyses [*i.e.,* X-ray, barium studies, United States, computed tomography (CT)]. Unfortunately, preoperative diagnosis of SEP remains a challenge and intraoperative findings and histopathological data are required for a definitive diagnosis[9]. Malignancy (particularly colorectal tumor) is the first differential diagnosis considered for individuals with advanced age, unremarkable medical history, physical symptoms of intestinal obstruction, and abdominal X-ray detection of air-fluid levels[1,2,6]. Furthermore, ulcerative perforation, septic peritonitis, and tuberculotic peritonitis encapsulans should be considered in the differential diagnosis.

Barium-enhanced imaging is not always possible in patients with marked intestinal obstruction. Abdominal US can demonstrate a dilated intestinal segment, free fluid accumulation, and the status of the peritoneal membrane (when sufficiently thickened)[4]. Abdominal United States examination of the current case showed free fluid in the pelvis and right lower quadrant, as well as dilatation and edema in all intestinal segments. Nonetheless, CT is considered the best imaging modality for diagnostic purposes, as it can show thickened peritoneum and mesentery as well as capsulated intestinal loops[13]. The typical CT finding for SEP is intestinal loops conglomerated at the midline and encased by a dense mantle without contrast uptake[5,6,13]. Since an urgent laparotomy had to be performed on our patient to address the severe distention, we did not have the opportunity to carry out a CT scan.

The typical finding of SEP is a bobbin-like appearance of the intestine, which results from the partial or whole encasement of intestinal segments by the thick, dense membrane[9]. Upon histopathological examination, the encapsulating membrane appears as a thickened and inflamed vascular fibrocollagenous tissue, with infiltrating lymphocytes and plasma cells[5]. The efficacy and safety of surgical treatment for cases that have a surgical indication and are confirmed by laparotomy remain unknown. Review of the literature suggests that many surgeons favor a minimally invasive approach to treating SEP[6], possibly because the sclerotic membranes on intestinal surfaces (and also between segments) can be easily removed in mild cases without marked intestinal obstruction. However, it is almost impossible to remove the sclerotic membrane successfully in patients with complete intestinal obstruction.

Clinical suspicion and early diagnosis of SEP are crucial to disease and treatment outcome[7]; overly aggressive surgical intervention in SEP cases with severe adhesions may cause multiple perforations. In summary, the basic approach of surgical treatment should include freeing of adhesions, total excision of the membrane, or partial intestinal resection when necessary[9]. It has been reported that the morbidity and mortality rates are higher in patients undergoing intestinal resection[9].

Entirely by coincidence, several clinical conditions were present simultaneously in the case presented herein. The clinical picture of this patient was made even worse

by the collective presence of intestinal perforation, a focus of interloop abscess extending to retroperitoneum, and a Meckel's diverticulum incarcerated into the right inguinal canal. Fortunately, the patient experienced an uncomplicated recovery following the surgical treatment, at least partially due to the well-managed clinical care that was given.

In conclusion, SEP is a rare disease entity causing intestinal obstruction. Preoperative diagnosis is considerably difficult to make, and the majority of previously reported cases have been diagnosed incidentally during laparotomy[11]. Some imaging methods may help clinicians to make the diagnosis of suspected cases. Surgery is an important treatment modality for SEP, but the dissections must be made carefully to free the small intestine and resect the affected tissues and to allow a complete cure[3,6].

COMMENTS

Case characteristics

Clinical symptoms included severe abdominal pain, nausea, vomiting and inability to defecate.

Clinical diagnosis

Mechanical small bowel obstruction.

Differential diagnosis

Gastrointestinal malignancy, perforation, herniation, and mesenteric vascular disease.

Laboratory diagnosis

Laboratory analysis showed leukocytosis (neutrophils: 83.2%) and elevated levels of renal function markers.

Imaging diagnosis

Abdominal X-ray examination showed diffuse air-fluid levels and abdominal ultrasonography revealed free fluid in the lower right quadrant and pelvis, as well as dilatation and edema in all intestinal segments.

Pathological diagnosis

Histopathologic examination of the excised peritoneal capsule showed proliferation of fibroconnective tissue with signs of a non-specific inflammatory reaction. The diagnosis of abdominal cocoon syndrome was established according to the intraoperative view and by ruling-out any other causes.

Treatment

The operative treatment included decapsulation, adhesiolysis, partial small bowel resection, side-to-side ileoileal anastomosis (using an endoscopic stapler), and a loop ileostomy (opened at 40 cm proximal to the anastomosis site).

Related reports

Early diagnosis of abdominal cocoon syndrome is crucial to disease and treatment outcome; overly aggressive surgical intervention in cocoon cases may cause severe adhesions. The basic approach of surgical treatment should include freeing of adhesions, total excision of the membrane, or partial intestinal resection when necessary, as in our case.

Term explanation

Sclerosing encapsulating peritonitis, also known abdominal cocoon syndrome, is a rare structural abnormality whereby the small intestine becomes encased (or cocooned) by a dense fibrocollagenous membrane that causes intestinal obstruction.

Peer review

This paper demonstrates coexistence of abdominal cocoon, intestinal perforation and incarcerated Meckel's diverticulum in an inguinal hernia, and considered to be well written.

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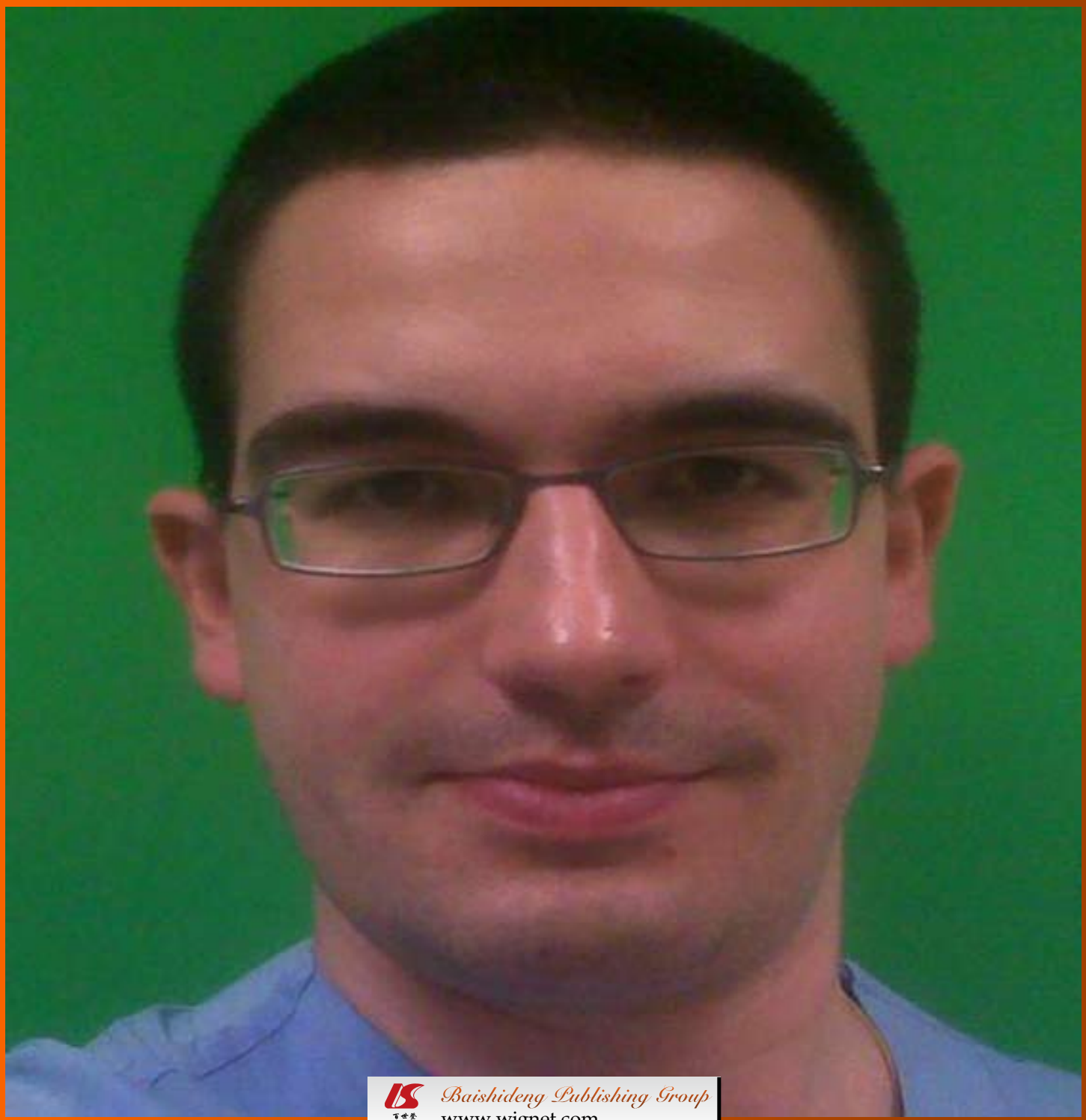

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No. 62 Dongsihuan Zhonglu, Chaoyang District,
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MINIREVIEWS

Multimodal treatment of gastric cancer

Ilaria Proserpio, Stefano Rausei, Sabrina Barzaghi, Francesco Frattini, Federica Galli, Domenico Iovino, Francesca Rovera, Luigi Boni, Gianlorenzo Dionigi, Graziella Pinotti

Ilaria Proserpio, Sabrina Barzaghi, Graziella Pinotti, Department of Oncology, Ospedale di Circolo and University of Insubria, 21100 Varese, Italy
Stefano Rausei, Francesco Frattini, Federica Galli, Domenico Iovino, Francesca Rovera, Luigi Boni, Gianlorenzo Dionigi, Department of Surgery, Ospedale di Circolo and University of Insubria, 21100 Varese, Italy
Author contributions: Proserpio I and Rausei S contributed to the design and conceptualization of the study and editing of the manuscript; Barzaghi S and Frattini F contributed to the drafting of the manuscript; Galli F and Iovino D contributed to the paper collection and analysis; Rovera F and Boni L contributed to the revision of the manuscript; Dionigi G and Pinotti G gave final approval of the manuscript.
Correspondence to: Stefano Rausei, MD, PhD, Department of Surgery, University of Insubria, Viale Borri 57, 21100 Varese, Italy. s.rausei@libero.it
Telephone: +39-332-278577 Fax: +39-332-260260
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Abstract

Gastric cancer is the second leading cause of death from malignant disease worldwide. Although complete surgical resection remains the only curative modality for early stage gastric cancer, surgery alone only provides long-term survival in 20% of patients with advanced-stage disease. To improve current results, it is necessary to consider multimodality treatment, including chemotherapy, radiotherapy and surgery. Recent clinical trials have shown survival benefit of combining different neoadjuvant or adjuvant protocols compared with surgery with curative intent. Furthermore, the implementation of chemotherapy with novel targeted agents could play an important role in the multimodal management of advanced gastric cancer. In this paper, we focus on a multidisciplinary approach in the treatment of gastric cancer and discuss future strategies to improve the outcome for these patients.

Key words: Gastric cancer; Gastrectomy; Lymphadenectomy; Multimodal treatment; Adjuvant therapy; Neoadjuvant therapy; Chemotherapy; Radiotherapy; Targeted therapy

Core tip: It is necessary to consider multimodality treatment, including chemotherapy, radiotherapy and surgery, to improve current results of gastric cancer treatment. Recent clinical trials have shown survival benefit combining different neoadjuvant or adjuvant protocols compared with curative surgery. Furthermore, the implementation of chemotherapy with novel targeted agents could play an important role in the multimodal management of advanced gastric cancer. In this paper, we focus on a multidisciplinary approach in the treatment of gastric cancer and discuss future strategies to improve the outcome for these patients.

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INTRODUCTION

Gastric cancer is one of the most common cancers worldwide and the second leading cause of death from malignant disease. This mortality data is explained by a late diagnosis. The incidence justifies screening programs only in Asia; in other parts of the world, gastric cancer remains a healthcare dilemma. In fact, in Japan and South Korea, the diffusion of endoscopy for gastric cancer resulted in 50% of patients with early disease (*i.e.*, T1 tumors). Conversely, in Europe and the United States, more

than two thirds of gastric cancers are found in advanced stages and most of these patients have a locally advanced resectable disease. Surgery with D2 nodal dissection is the primary treatment for patients with resectable cancer, with only a-5-year survival rate of 25.7% in locally advanced disease in these countries. To improve survival multimodal treatment has been used as an adjunct to surgery in recent years. In this review, we present a short analysis of high evidence level contributions published in the literature (phase-Ⅲ randomized controlled trials) on this topic.

POSTOPERATIVE THERAPY: CHEMORADIOTHERAPY

The role of adjuvant chemoradiotherapy (CRT) was established by the SWOG 9008/INT-0116 trial[1]. In this study, patients with completely resected gastric and esophagogastric junction (EGJ) adenocarcinoma were randomized to receive surgery alone or surgery plus postoperative chemoradiation [bolus 5-fluorouracil (5-FU) and leucovorin before and after chemoradiation with the same combination]. Overall survival was 27 mo in the group that received surgery alone and 36 mo in the group that received adjuvant CRT. After ten years follow-up, overall survival advantage is confirmed in favor of adjuvant CRT[2]. This trial has been criticized because the surgical procedure was considered inadequate since only 10% of patients had the recommended extended lymph node dissection (D2) and the combined modality arm reported a high rate of acute toxicity, probably due to the large field of irradiation and to the RTX technique used.

In the CALGB 80101 trial[3], postoperative CRT with epirubicin, cisplatin and 5fluorouracil (ECF) before and after CRT with concurrent infusional fluorouracil did not improve survival compared to bolus 5-FU-LV before and after 5-FU-RT (INT regimen).

More recently, the role of adjuvant CRT has not been confirmed. In the ARTIST trial[4], the authors investigated the role of postoperative CRT in addition to chemotherapy (cisplatin, capecitabine) in patients with curatively resected gastric cancer with D2 lymph node dissection. In this study, CTR did not significantly reduce recurrence compared to chemotherapy alone. Stratified analysis showed that the 3 year disease free survival rate was better in the CRT group in patients with positive lymph nodes.

Pending the results of ongoing clinical trials, we can conclude that while postoperative CRT is considered a standard therapy in the United States, in Europe it remains an effective and preferred treatment after D0 or D1 dissection and R1 resection, but not after D2 dissection[5], when the role of adjuvant chemotherapy is demonstrated.

POSTOPERATIVE THERAPY: CHEMOTHERAPY

The role of adjuvant therapy in GC has been studied during the past three decades in an attempt to improve the prognosis of patients who have undergone curative surgery. A recent meta-analysis[6] suggested a survival benefit with adjuvant chemotherapy based on fluorouracil regimens (HR = 0.82, 95%CI: 0.75-0.9, $P < 0.001$).

These results were recently confirmed by the CLASSIC and the ACTC-GC trial. The ACTS-GC study conducted in Japan demonstrated that adjuvant chemotherapy with 1 year treatment of S-1, an oral fluoropyrimidine, showed a significant benefit for gastric cancer with stage II and III who underwent gastrectomy with extended (D2) lymph node dissection, with a 3-year-overall survival (OS) for S-1 group of 80.1% compared with 70.1% for controls. The study was prematurely stopped by the Data and Safety Monitoring Committee because active treatment exceeded the efficacy threshold. The comparison of this study with those done in Western countries is difficult because of differences in survival rates, early detection rates and surgical techniques between Western and Asian countries.

Furthermore, S-1 remains an investigational agent in North America due to biological differences of how the drug is metabolized between patient populations[7].

In the CLASSIC trial[8] conducted in South Korea, China and Taiwan, patients with stage Ⅱ-ⅢB gastric cancer who underwent curative gastrectomy (D2 dissection) were randomized to surgery alone or postoperative chemotherapy with capecitabine and oxaliplatin (XELOX). The primary endpoint of the 3 year disease free survival (DSF) rate was 74% in the XELOX group and 59% in the surgery only group (HR = 0.56); stratified analysis revealed a significant difference between the two groups in stage Ⅲ disease.

However, there is no currently recognized standard regimen, particularly in countries where D2 dissection is a routine procedure.

The ITACA-S trial[9] was published during the last year in which the authors assessed whether a more intensive postoperative chemotherapy than fluoropyrimidine improves effectiveness. Patients radically resected for gastric or GEJ (≥ D1 node dissection) pN0 with pT > 2b or pN+ were randomized to receive CPT-11, LV, 5-FU for 4 cycles (FOLFIRI regimen) followed by docetaxel, cisplatin for 3 cycles or to LV, 5-FU (De-Gramont regimen) for 9 cycles. With a median follow-up of 49 mo, the use of an intensive treatment did not result in a significant prolongation of DFS and OS when compared to the De-Gramont regimen.

In conclusion, adjuvant chemotherapy with fluoropyrimidine is associated with improvement in overall survival and is recommended after complete resection in patients with stage ≥ I B who have not received perioperative treatment. The data seem to also confirm this benefit in patients treated with extended lymph node dissection.

PERIOPERATIVE THERAPY: NEOADJUVANT CHEMOTHERAPY

Neo-adjuvant chemotherapy (CHT) has been shown to

increase the rate of complete tumor resection, to reduce the incidence of systemic metastases and, probably, to prolong survival. Overall, the data indicate that neo-adjuvant CHT is feasible, does not increase post-operative morbidity and mortality, and is able to increase the rate of R0 resection.

The MAGIC trial[10] evaluated the efficacy of a perioperative CHT. Five hundred and three patients with potentially resectable GC were randomly assigned to both preoperative and postoperative cisplatin, epirubicin and 5-FU (ECF) CHT versus surgery alone. The results evidenced a statistically significant improvement of the ECF arm in progression free survival (PFS) (HR = 0.66; 95%CI 0.53-0.81) and OS (HR = 0.75; 95%CI: 0.60-0.93; 5 year OS 36% *vs* 23%). The resected tumors were significantly smaller and less advanced in the perioperative CHT group.

The two groups had a similar incidence of postoperative complications and mortality rates and, additionally, the completion rate of 3 course preoperative CHT was 86%, while only 42% of the patients completed postoperative ECF therapy.

Recently, in the FNCLCC/FFCD TRIAL[11], 224 patients with resectable adenocarcinoma of the lower esophagus, GEJ or stomach were randomized to either perioperative chemotherapy with cisplatin and 5fluorouracil continuous intravenous infusion plus surgery or surgery alone. The multimodal treatment significantly increased the curative resection (84% *vs* 74%; $P = 0.04$), disease free (5 year rate: 34% *vs* 19%; $P = 0.003$) and overall survival (5 year rate: 38% *vs* 24%; $P = 0.02$) rates.

We are awaiting the results of the ongoing CRITICS trial that compares three cycles of preoperative polychemotherapy followed by surgery and then randomised between adjuvant chemotherapy and CRT.

In our institution, we are involved in the multicentric randomized phase Ⅲ study ITACA-S-2 that compares the efficacy of a perioperative versus a postoperative CHT treatment in patients with operable gastric cancer and assesses the benefit of a postoperative CRT.

According to published data, perioperative chemotherapy is considered the preferred option in most of Europe and the United Kingdom, but we believe that each patient should be assessed within a multidisciplinary team, waiting the pending data of ongoing trials.

MOLECULAR TARGETED AGENTS

Recently, new elements have emerged which have shown the benefit of molecular targeted agents (MTA) in the treatment of advanced gastric cancer. human epidermal growth factor receptor 2 (HER2) overexpression has been reported in 13%-20% of gastric cancer specimens and is associated with a poor prognosis. Trastuzumab is a humanized monoclonal antibody that selectively blinds to the human epidermal growth factor receptor type 2. Based on results obtained in the treatment of HER2 positive breast cancer, the role of trastuzumab has also been studied in gastric cancer. The ToGA trial[12] randomised 594 patients with HER2 positive locally advanced, recurrent and metastatic gastric and EGJ cancer to receive trastuzumab, plus chemotherapy (cisplatin and fluorouracil or capecitabine) or CHT alone. Overall survival was 11.1 mo in patients who received chemotherapy alone and 13.8 mo in patients who received chemotherapy plus trastuzumab. This result established trastuzumab in combination with chemotherapy as the standard of care for first line treatment of HER2 positive advanced gastric cancer. According to the results obtained in metastatic settings, further clinical trials should be undertaken to evaluate the role of MTA in the perioperative setting.

Conversely, anti epidermal growth factor receptor and vascular endothelial growth factor antibodies that are widely used in advanced colon cancer have failed to improve overall survival of patients in association with chemotherapy.

CONCLUSION

The management of gastric cancer has been evolving during the last years. Clinical data demonstrated that a multimodal approach is mandatory to achieve maximum clinical benefit; therefore, it is desirable that each center has a multidisciplinary team which should include a surgeon, gastroenterologist, medical and radiation oncologist and pathologist. An adequate selection of the patients is mandatory to optimize clinical results. To obtain this endpoint, it is critical to make an accurate and strict patient selection by a correct staging of the disease, which has to take laparoscopy into account.

We recognize that increasing numbers of patients in controlled clinical trials is essential to improve our knowledge about the best clinical practice.

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RETROSPECTIVE STUDY

Short-term efficacy of laparoscopy-assisted *vs* open radical gastrectomy in gastric cancer

Hong-Tao Li, Xiao-Peng Han, Lin Su, Wan-Kun Zhu, Wei Xu, Kun Li, Qing-Chuan Zhao, Hua Yang, Hong-Bin Liu

Hong-Tao Li, Xiao-Peng Han, Lin Su, Wan-Kun Zhu, Wei Xu, Kun Li, Hong-Bin Liu, Department of General Surgery, General Hospital of Lanzhou Military Region, Lanzhou 730050, Gansu Province, China
Qing-Chuan Zhao, Xijing Hospital of Digestive Disease, The Fourth Military Medical University, Xi'an 710032, Shaanxi Province, China
Hua Yang, Xinqiao Hospital, The Third Military Medical University, Chongqing 400037, China
Author contributions: Li HT and Liu HB designed the study and wrote the manuscript; Han XP, Su L, Zhu WK, Xu W, Li K performed the majority of the experiments; Zhao QC, Yang H were also involved in editing the manuscript.
Correspondence to: Hong-Bin Liu, Professor, Department of General Surgery, General Hospital of Lanzhou Military Region, #333 Binhe South Road, Lanzhou 730050, Gansu Province, China. liuhongbin999@163.com
Telephone: +86-931-8994364 Fax: +86-931-8994002
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Abstract

AIM: To investigate the short-term benefits of laparoscopic radical gastrectomy (LARG) and open radical gastrectomy (ORG) in patients with gastric cancer.

METHODS: A total of 400 patients with gastric cancer aged ⩽ 65 years who were treated at General Hospital of Lanzhou Military Region were enrolled. Among these, 200 patients underwent LARG between October 2008 and August 2012 (LARG group); and 200 patients underwent ORG between March 2000 and September 2008 (ORG group). The short-term therapeutic benefits between the two groups were analyzed.

RESULTS: The LARG procedure offered significantly better benefits to the patients compared to the ORG procedure, including less intraoperative blood loss (103.1 ± 19.5 mL *vs* 163.0 ± 32.9 mL, $P < 0.0001$), shorter postoperative hospital stay (6.8 ± 1.2 d *vs* 9.5 ± 1.6 d, $P < 0.0001$), less frequent occurrence of postoperative complications (6.5% *vs* 13.5%, $P = 0.02$), shorter time to mobilization (1.0 ± 0.3 *vs* 3.3 ± 0.4 d, $P < 0.0001$), shorter time to bowel opening (3.3 ± 0.7 d *vs* 4.5 ± 0.7 d, $P < 0.0001$), and shorter time to normal diet (3.0 ± 0.4 *vs* d 3.8 ± 0.5 d, $P < 0.0001$). However, LARG required a longer time to complete than the ORG procedure (192.3 ± 20.9 min *vs* 180.0 ± 26.9 min, $P < 0.0001$).

CONCLUSION: Compared to ORG, LARG is safer, more effective, and less invasive for treating gastric cancer, with better short-term efficacy.

Key words: Laparoscopic surgery; Gastric cancer; Short-term efficacy; Open surgery

Core tip: We compared patients who underwent laparoscopic-assisted radical gastrectomy (LARG) with those who underwent open radical surgery (ORG) in terms of intra- and postoperative benefits. LARG was successfully completed without needing to convert to laparotomy in all patients, and no residual cancerous tissues were noted in the surgical margins. LARG offered the patients several better short-term benefits compared to the ORG procedure, such as less intraoperative blood loss, shorter hospitalization time, shorter time to mobilization, and shorter time to bowel opening. Additionally, LARG was also associated with fewer postoperative complications.

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INTRODUCTION

Gastric cancer is one of the most common malignant tumors worldwide, with a yearly incidence of about 900000. In China, > 400000 cases of gastric cancer are diagnosed annually, and the mortality rate is estimated to be 25.2/100000, which accounts for 23.3% of cancer-related mortality[1]. The 5-year survival rate is about 95% for early gastric cancer but, in patients with advanced gastric carcinoma, the 5-year survival falls to < 50%[2]. In China, > 90% of gastric cancer patients are diagnosed at an advanced stage when they first present[1].

At the present time, radical surgery is the only effective treatment for early gastric cancer with a potential to cure the disease[3]. Since its seminal application in patients with advanced gastric cancer in 1991 by a group of Japanese surgeons[4], laparoscopic radical gastrectomy (LARG) has been increasingly used as a promising approach for the management of gastric cancer because of its minimal invasiveness and its potential to treat successfully patients with lymph node metastasis[5,6]. However, LARG is technically demanding and requires a long learning curve[4,7].

Although LARG and laparoscopic D2 gastrectomy have now been widely used in the treatment of gastric cancer, including advanced gastric carcinoma, the short- and long-term benefits are unclear. The short-term outcomes of LARG have recently been reported, although these studies were based on small samples.

In the current study, we compared the short-term outcomes between LARG and open radical gastrectomy (ORG) in patients with gastric cancer in our department.

MATERIALS AND METHODS

Patient selection criteria

A total of 200 patients with gastric cancer who were treated with LARG after 2008 were randomly selected (LARG group). Tumors were located in the antrum (n = 95), cardia-fundus (n = 56), and corpus (n = 49) of the stomach. Pathological diagnosis of gastric cancer was confirmed in all patients using gastroscopic biopsy specimens. These samples included adenocarcinoma (n = 156), signet ring cell carcinoma (n = 15), adenosquamous carcinoma (n = 6), squamous cell carcinoma (n = 8), carcinoid (n = 4), and undifferentiated carcinoma (n = 11). The pathological classification was based on the 2010 World Health Organization (WHO) classification[8].

We also randomly selected 200 patients with gastric cancer who were treated with ORG between 2000 and 2008 (ORG group). Within this group, tumors were located in the antrum (n = 91), cardia-fundus (n = 58), and corpus (n = 51) of the stomach. Pathological diagnosis was confirmed in all patients using gastroscopic biopsy specimens, including adenocarcinoma (n = 162), signet ring cell carcinoma (n = 10), adenosquamous carcinoma (n = 7), squamous cell carcinoma (n = 6), carcinoid (n = 7), and undifferentiated carcinoma (n = 8), based on the 2010 WHO classification[8].

Surgical procedures

Patients fasted for 24 h prior to surgery. Following general anesthesia and endotracheal intubation, patients were placed in the supine position with their legs apart. A small subumbilical arc incision of 1 cm was made, and a pneumascos needle was inserted to generate CO_2 pneumoperitoneum, which was maintained at 12-14 mmHg during surgery. A 10-mm trocar was inserted into the same incision, and laparoscopy-assisted examination was performed to assess visually the extension, diameter, and location of the lesion. Tumor metastasis, serous layer invasion, adhesion to adjacent tissues, and organs were also carefully examined to determine the best angle of approach. A 12-mm trocar was inserted at the junction of the left lower costal margin and anterior axillary line to conduct the operation. Three 5-mm trocars were inserted through the abdominal wall; one at the level of the umbilicus at the left midclavicular line; one at the junction of the right lower costal margin and right midclavicular line; and one at the junction of the right lower costal margin and anterior axillary line. The operator was standing on the left side of the patient, while one assistant was standing on the right side, and another assistant who was holding the laparoscope was standing between the patient's legs. Blocking glue was used at the serous layer of the tumor to prevent implantation metastasis, and biological glue was used to seal the anastomosis after the tumor was removed completely to prevent the formation of anastomotic leakage or stump fistula.

Radical distal subtotal gastrectomy

The greater omentum was resected off the transverse colon using an ultrasonic knife along the border of the transverse colon. The dissection was continued to the left toward the splenic flexure, and to the right toward the origin of right gastroepiploic artery. The anterior lobe of the transverse mesocolon and pancreatic capsule were also resected, and lymph nodes along the middle colic artery were removed. The right gastroepiploic artery and the right gastro-omental vein were isolated and resected after ligation using titanium clips, and lymph nodes (Group 6) were removed. The greater omentum was pulled to the front of the stomach, and the stomach was gently picked up. The common hepatic artery, splenic artery, and left gastric artery were dissected, and the lymph nodes of Groups 8, 11, 7 and 9 were removed. The left gastric artery was ligated by two titanium clips and resected. The hepatogastric ligament and right gastric artery were resected along the lesser curvature, and the lymph nodes of Groups 5, 12, 3, 1 and 4 were removed. A longitudinal incision of 5 cm was made in the center of the upper abdomen. After an incision protective layer

Table 1 Patients characteristics *n* (%)

	LARG	ORG	*P* value
Sex (male/female)	109/91	112/88	0.84
Age (yr)	58.3 ± 6.5	58.6 ± 6.3	
Pathological type			
Well-differentiated adenocarcinoma	49 (24.5)	38 (19.0)	0.32[1]
Moderately-differentiated adenocarcinoma	23 (11.5)	31 (15.5)	
Poorly-differentiated adenocarcinoma	115 (57.5)	122 (61.0)	
Signet ring cell carcinoma	13 (6.5)	9 (4.5)	
Classification (T)			
T1	18 (9.0)	15 (7.5)	0.86[2]
T2	89 (44.5)	91 (45.5)	
T3	93 (46.5)	94 (47.0)	
Lymph node metastasis			
N0	13 (6.5)	11 (5.5)	0.90[3]
N1	88 (44.0)	91 (45.5)	
N2	99 (49.5)	98 (49.0)	
Clinical stage			
Ⅰ + Ⅱ	91 (45.5)	89 (44.5)	0.92
Ⅲ + Ⅳ	109 (54.5%)	111 (55.5)	

[1]Well-differentiated adenocarcinoma group of LARG and ORG; [2]T1 group of LARG and ORG; [3] Ⅰ + Ⅱ group of LARG and ORG. LARG: Laparoscopic radical gastrectomy; ORG: Open radical gastrectomy.

was placed, the stomach was pulled out of the abdominal cavity, and the distal part of the stomach was resected. A Billroth Ⅰ or Ⅱ reconstruction was then performed. The abdominal cavity was perfused with low-permeability, warm sterilized distilled water for 30 min. The distilled water was discarded, and the peritoneal cavity was perfused with 1 g Tegafur and 0.3 g leucovorin in 250 mL saline. The abdomen was closed after drainage tubes were placed.

Radical proximal subtotal gastrectomy

The greater omentum, anterior lobe of the transverse mesocolon, and pancreatic capsule were isolated along the border of the transverse colon to the splenic flexure, and the right gastroepiploic hemal arch was kept intact at the distal greater curvature. The lymph nodes of Groups 6 and 4 were removed. The splenic flexure was isolated, and the left gastroepiploic artery and vein were dissected. The short gastric vessel was resected at the origin. The splenic artery was isolated and the lymph nodes of Groups 11 and 10 were removed. The stomach was isolated from the gastric fundus and posterior stomach, and the lymph nodes of Groups 8, 9 and 7 were removed. The lesser omentum was isolated along the inferior border of the liver, 5 cm of the esophagus was exposed, and the cardia was dissected. The anterior and posterior vagal trunks were resected, and the lymph nodes of Groups 1-3 were removed. A longitudinal incision of 5 cm was made in the center of the subcostal area. The same procedures to protect the incision were performed as for radical distal subtotal gastrectomy as described above, and the stomach was pulled out of the abdominal cavity. After the proximal part of the stomach was resected, the anterior wall of the residual stomach was resected, and staples were placed. The esophagus and residual stomach were anastomosed, and the anterior wall of the stomach was stitched. The abdominal cavity was perfused with low-permeability, warm sterilized distilled water for 30 min. The distilled water was discarded, and peritoneal perfusion with chemotherapy drugs was performed. The abdomen was closed after drainage tubes were placed.

Radical total gastrectomy

The veins and lymph nodes were isolated and removed in the same way as in subtotal gastrectomy. A longitudinal incision of 5-7 cm was made in the center of the upper abdomen. The same procedures were performed to protect the incision as in radical distal subtotal gastrectomy, and the stomach was pulled out of the abdominal cavity. The cardia was then resected, and the whole stomach and lymph nodes around the omentum were removed. Roux-en-Y reconstruction was performed. The abdominal cavity was perfused with low-permeability, warm sterilized distilled water for 30 min. The distilled water was discarded, and peritoneal cavity was perfused as described above. The abdomen was closed after drainage tubes were placed.

ORG

The operation was carried out under general anesthesia with endotracheal intubation. Patients were placed in the supine position. An incision of 15-20 cm was made in the center of the upper abdomen. Radical gastrectomy was performed as described above.

Outcomes

The readout outcomes selected to assess the therapeutic efficacy were: operation time, number of lymph nodes dissected, intraoperative blood loss, length of hospital stay, time to mobilization, time to bowel opening, and time to normal diet.

Statistical analysis

Statistical analysis was performed using SPSS 18.0 (SPSS Inc., Chicago, IL, United States). Continuous data are presented as mean ± SD, and were analyzed using Student's *t* test. Categorical data are presented as proportions, and were analyzed using the χ^2 test. $P < 0.05$ was considered statistically significant.

RESULTS

Patient characteristics

A total of 200 patients, including 109 men and 91 women with a mean age of 56.1 years (range: 23-63 years) were included in the LARG group. In the ORG group, there were 112 men and 88 women with a mean age of 56.3 years (range: 21-65 years). No significant differences were observed between the two groups in terms of age, sex, pathological type of tumor, depth of tissue invasion, lymph node metastasis, and clinical stage (Table 1).

Table 2 Comparison of surgical outcomes between laparoscopic radical gastrectomy and open radical gastrectomy groups

Outcomes	LARG	ORG	*P* value
Operation time (min)	192.3 ± 20.9	180.0 ± 26.9	< 0.0001
No. of lymph nodes removed	28.5 ± 4.5	28.3 ± 3.4	0.62
Intraoperative blood loss (mL)	103.1 ± 19.5	163.0 ± 32.9	< 0.0001
Bedbound time (d)	1.0 ± 0.3	3.3 ± 0.4	< 0.0001
Time to bowel opening (d)	3.3 ± 0.7	4.5 ± 0.7	< 0.0001
Length of incision (cm)	5.2 ± 0.7	17.8 ± 1.0	< 0.0001
Time to normal diet (d)	3.0 ± 0.4	3.8 ± 0.5	< 0.0001
Total hospital stay (d)	6.8 ± 1.2	9.5 ± 1.6	< 0.0001

LARG: Laparoscopic radical gastrectomy; ORG: Open radical gastrectomy.

Table 3 Comparison of postoperative complications between the two groups *n* (%)

Postoperative complications	LARG	ORG	*P* value
Decreased gastrointestinal motility	3 (1.5)	7 (3.5)	0.2
Anastomotic leakage/stump fistula	7 (3.5)	15 (7.5)	0.08
Poor incision healing	5 (2.5)	16 (8.0)	0.01
Pulmonary infection	4 (2.0)	19 (9.5)	0.001
Acute liver/kidney failure	1 (0.5)	4 (2.0)	0.18
Total	13[1] (6.5)	27[1] (13.5)	0.02

[1]Some patients had two or more concomitant complications. LARG: Laparoscopic radical gastrectomy; ORG: Open radical gastrectomy.

Major intraoperative characteristics and outcomes

LARG was successfully performed in the 200 patients without conversion to laparotomy. ORG was also successfully performed in 200 patients. No malignant tissues were found at the lower or upper resection margin in any of the patients.

Table 2 shows the treatment characteristics between the two groups. Longer time was needed for LARG than for ORG (192.3 ± 20.9 min *vs* 180.0 ± 26.9 min, respectively, $P < 0.0001$). A similar number of lymph nodes was removed by both approaches ($P = 0.62$). The LARG procedure was superior to ORG for several outcomes, including: less intraoperative blood loss (103.1 ± 19.5 mL *vs* 163.0 ± 32.9 mL, $P < 0.0001$); less bedbound time (1.0 ± 0.3 d *vs* 3.3 ± 0.4 d, $P < 0.0001$); less time to bowel opening (3.3 ± 0.7 d *vs* 4.5 ± 0.7 d, $P < 0.0001$); less time to normal diet (3.0 ± 0.4 d *vs* 3.8 ± 0.5 d, $P < 0.0001$); and shorter hospital stay (6.8 ± 1.2 d *vs* 9.5 ± 1.6 d, $P < 0.0001$). In addition, the incision length was shorter in the LARG group than in the ORG group (5.2 ± 0.7 *vs* 17.8 ± 1.0 cm, $P < 0.0001$), and fewer patients required special pain control in the LARG group than in the ORG group (39.5% *vs* 56.5%, $P = 0.0007$).

Postoperative complications

As shown in Table 3, significantly fewer patients in the LARG group suffered from poor incision healing (2.5% *vs* 8.0%, $P = 0.01$) and pulmonary infection (2.0% *vs* 9.5%, $P = 0.001$). Fewer patients experienced anastomotic leakage or stump fistula in the LARG group than ORG group, although the difference was not significant (3.5% *vs* 7.5%, $P = 0.08$). No difference was observed in the incidence of decreased gastrointestinal motility and acute organ (liver or kidney) failure between the LARG and ORG groups ($P > 0.05$). Overall, the LARG group was associated with less frequent complications than the ORG group was (13% *vs* 27%, $P = 0.02$).

DISCUSSION

We compared 200 patients who underwent LARG and 200 who underwent ORG in terms of their intra- and postoperative benefits. The laparoscopic procedures were successfully completed without needing to convert to laparotomy in all patients in the LARG group, and no residual cancerous tissues were noted in the surgical margins. Despite a significantly longer operation time with LARG, this approach offered the patients several better short-term benefits compared to the ORG procedure, such as less intraoperative blood loss, shorter hospitalization time, shorter time to mobilization, shorter time to bowel opening, and shorter time to normal dietary intake. Additionally, LARG was also associated with fewer postoperative complications.

Well-exposed surgical fields could help reduce blood vessel damage and reduce intraoperative blood loss. A satisfactory surgical field can be obtained using laparoscopy with the assistance of an ultrasonic knife and titanium clips, and this could greatly reduce intraoperative blood loss. Currently, the same surgical processes used in traditional radical gastrectomy are still used in LARG, including blood vessel ligation at the origin, excessive margin resection, and removal of perigastric lymphoid tissues. However, because LARG is performed with laparoscopic instruments inside the abdominal cavity, mechanic organ damage by direct contact with the stomach during surgery can be minimized.

The indications for LARG in the treatment of patients with gastric cancer vary among different centers. For example, Kitano *et al*[9] have suggested that LARG could be indicated for patients with advanced-stage gastric carcinoma with an invasion depth lower than T2[9,10], whereas Huscher *et al*[11] have suggested that LARG is the best choice for patients with advanced gastric carcinoma in whom tumor invasion has reached T3[11]. Based on our study, we believe that LARG is a safe, effective, and minimally invasive approach for treatment of gastric cancer, as previously reported[7,12,13]. The long-term efficacy of LARG in patients with gastric cancer has also been reported[10]. In this long-term follow-up study, no significant difference in the 5-year survival rate was observed between 136 patients with gastric cancer who underwent LARG and 120 who underwent ORG.

Currently, CO_2 pneumoperitoneum is widely used in LARG procedures. However, the use of CO_2 pneumoperitoneum could result in inhibition of the immune response in the abdominal cavity. In an animal experiment[14], a significant decrease in the number of CD4/CD8 cells was observed after the induction of CO_2 pneu-

moperitoneum. CO_2 pneumoperitoneum was also shown to inhibit macrophage activation in the abdominal cavity, and thus inhibit the release of tumor necrosis factor (TNF)-α and interleukin-1 by macrophages. Both macrophages and TNF-α play a potent role in the antitumor activity in the abdominal cavity[15].

During the treatment of malignant tumors using laparoscopy-assisted approaches, potential tumor implantation induced by the operation has been a major concern. Based on our study, the possible impact of CO_2 pneumoperitoneum on immune disturbance and possible implantation metastasis could not be determined. However, previous studies have reported no significant increase in metastasis implantation after LARG, and the rate of incision metastasis did not differ between patients who underwent and those who did not undergo CO_2 pneumoperitoneum during surgery[16]. Similarly, no implantation metastasis was found in patients treated with LARG in our study. We believe that gentle surgical maneuver without squeezing the tumor tissues, and withdrawal of the laparoscopic instruments only after the intra-abdominal gas is completely removed, are important.

In conclusion, LARG is a safe, effective, and minimally invasive approach for the treatment of gastric cancer. LARG may offer better short-term benefits to patients than ORG offers. Further studies are needed to investigate the long-term efficacy of the LARG approach.

COMMENTS

Background

Gastric cancer is one of the most common malignant tumors worldwide, with a yearly incidence of about 900000. Laparoscopic radical gastrectomy (LARG) has been increasingly used as a promising approach for the management of gastric cancer because of its minimal invasiveness and a potential to treat successfully patients with lymph node metastasis. Although LARG and laparoscopic D2 gastrectomy have now been widely used in the treatment of gastric cancer, including advanced gastric carcinoma, the short- and long-term benefits are unclear. The short-term outcomes of LARG have recently been reported, although these studies were based on small samples. In the current study, authors compared the short-term outcomes between LARG and open radical gastrectomy (ORG) performed in patients with gastric cancer in our department.

Research frontiers

LARG and laparoscopic D2 gastrectomy have now been widely used in the treatment of gastric cancer, including advanced gastric carcinoma. The research hotspot is how to investigate the short-term benefits of LARG and ORG in patients with gastric cancer.

Innovations and breakthroughs

Based on this study, authors believe that LARG is a safe, effective, and minimally invasive approach for the treatment of gastric cancer, as previously reported. The long-term efficacy of LARG in patients with gastric cancer has also been reported. In this long-term follow-up study, no significant difference in the 5-year survival rate was observed between 136 patients with gastric cancer who underwent LARG and 120 patients who underwent ORG. Well-exposed surgical fields could help reduce blood vessel damage and reduce intraoperative blood loss. A satisfactory surgical field can be obtained using laparoscopy with the assistance of an ultrasonic knife and titanium clips, and this could greatly reduce intraoperative blood loss. Currently, the same surgical processes used in traditional radical gastrectomy are still used in LARG, including blood vessel ligation at the origin, excessive margin resection, and removal of perigastric lymphoid tissues. However, because LARG is performed with laparoscopic instruments inside the abdominal cavity, mechanical organ damage by direct contact with the stomach during surgery can be minimized.

Applications

The results suggest that LARG is a safer, more effective, and less-invasive approach for treating gastric cancer with a better short-term efficacy.

Terminology

LARG: LARG is a novel minimally invasive surgical technique. It is associated with such advantages as less injury, reduced postoperative pain, lower impact on immune function, rapid recovery of gastrointestinal function, and short hospital study.

Peer review

The authors have performed a well-designed study and submitted a full detailed manuscript. The overall body of the article is fine and they have presented the results and discussion well.

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CASE REPORT

Pancreatic recurrence of intrahepatic cholangiocarcinoma: Case report and review of the literature

Ismaïl Labgaa, Gonzalo Carrasco-Avino, Maria Isabel Fiel, Myron Eliot Schwartz

Ismaïl Labgaa, Myron Eliot Schwartz, Department of Surgery, Mount Sinai School of Medicine, NewYork, NY 10029, United States
Gonzalo Carrasco-Avino, Maria Isabel Fiel, Department of Pathology, Mount Sinai School of Medicine, New York, NY 10029, United States
Author contributions: Labgaa I and Schwartz ME designed the report; Schwartz ME was the attending doctor for the patient; Schwartz ME performed the surgical operations; Fiel MI and Carrasco-Avino G performed the pathological examinations; Labgaa I wrote the paper.
Correspondence to: Myron Eliot Schwartz, MD, Department of Surgery, Mount Sinai School of Medicine, RMTI Liver Surgery Program, 5 East 98th Street, 12th Floor, Box 1104 New York, NY 10029, United States. myron.schwartz@mountsinai.org
Telephone: +1-212-6598084 Fax: +1-646-5379238
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Abstract

Intrahepatic cholangiocarcinomas (ICC) are malignant tumors arising from the intrahepatic bile ducts that frequently recur after resection. The main sites of recurrence are the remnant liver, lymph nodes and lungs. Metastasis to the pancreas has never been reported. This case describes a 24-year-old woman who underwent a hepatic lobectomy in 2008 for an ICC. Almost 4 years after her surgery she presented with a pancreatic mass and lung nodules. An endoscopic ultrasound guided fine needle aspiration of the pancreatic mass and a video-assisted thoracoscopic surgery resection for the lung nodules were performed for diagnostic purposes. Pathological analyses of specimens revealed recurrence of her primary ICC in both pancreas and lungs. Subsequently, the patient received systemic chemotherapy. The patient is currently off chemotherapy and remains well. Moreover, she is pregnant. This is the first report of an ICC with pancreatic metastasis.

Key words: Intrahepatic cholangiocarcinoma; Recurrence; Liver resection; Pancreatic metastasis; Pulmonary metastasis

Core tip: Intrahepatic cholangiocarcinoma (ICC) is characterized by its high potential to metastasize. Most frequent sites for metastases are the remnant liver, lymph nodes and lungs. Metastasis to the pancreas has never been described. Although this may happen exceedingly rarely, hepatobiliary surgeons should be made aware that ICC can also metastasize to the pancreas.

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INTRODUCTION

Cholangiocarcinomas are malignant tumors arising from the biliary tree. They account for about 3% of all digestive cancers and are the second most common primary liver tumors following hepatocellular carcinoma. In the United States approximately 5000 new cases are diagnosed each year[1] but the frequency considerably varies worldwide[2,3]. There are well-established risk factors as well as controversial ones. The former include primary sclerosing cholangitis, parasitic infections and biliary anomalies whereas the latter include inflammatory bowel diseases, obesity, diabetes, smoking and liver inflammatory conditions such as cirrhosis, hepatitis C and hepatitis B (HBV)[2-4]. Cholangiocarcinomas are divided into three different types according to their anatomic location along the biliary tree: intrahepatic cholangiocarcinomas (ICC),

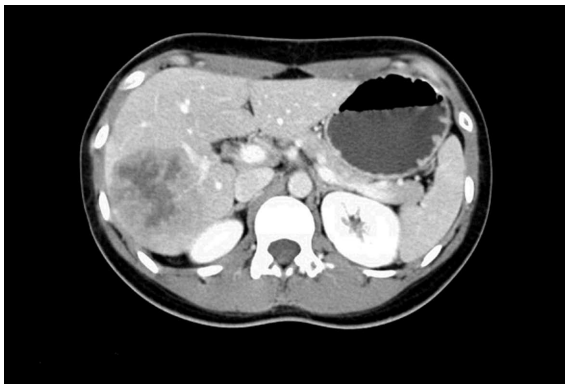

Figure 1 A computed tomography scan with nonionic contrast confirmed a mass located in the posterior right lobe within segments VI-VII and measuring 7.2 cm × 6.0 cm. The lesion demonstrated peripheral enhancement with central necrosis but no evidence for portal vein invasion. The hepatic veins were patent and no biliary dilatation was observed. No pulmonary lesion was highlighted.

perihilar or Klatskin tumor (PCC) and distal extrahepatic cholangiocarcinoma[5]. Tumor features and behavior seem to vary according to its type, thus, the importance of a precise classification that will influence the management and eventual outcomes. ICC are located above the second-order bile duct that represents the segregation point from PCC. They account for approximately 10%-20% of all primary liver cancers)[2-4] and their incidence has been reported to increase disturbingly, especially within Western countries[6-8]. It is also characterized by its poor prognosis despite liver resection although surgery is considered as the only curative treatment. Studies have reported a 3-year survival rate of 22%-55% after extended surgery[9-13] whereas survival rate without surgical treatment was much poorer at 7%-21%[8,9,12]. The reason for this could be that ICC are longer clinically silent being often diagnosed at an advanced stage but also their strong tendency to recur. Postoperative recurrences were mainly located in the remnant liver whereas extrahepatic recurrences especially involved lymph nodes, lungs and peritoneum[9,14]. To our knowledge there is no case of pancreatic metastasis from ICC being reported in the literature. Thus, this case report is the first to address this interesting issue.

CASE REPORT

In May 2008 a healthy 24-year-old Chinese woman longtime immigrant was referred to our Division for the investigation of a liver mass revealed by an ultrasound at an outside hospital, as part of her regular follow up for chronic hepatitis B. A computed tomography (CT) scan with nonionic contrast confirmed a mass within segments VI-VII measuring 7.2 cm × 6.0 cm. No lesion was observed in the lungs and her pancreas appeared normal (Figure 1). The patient had no health issue beside HBV, received no medication and had not undergone any surgery so far. Her brother also had HBV but her family history for liver cancer was negative. She presented without symptoms and was not icteric. Abdominal palpation was

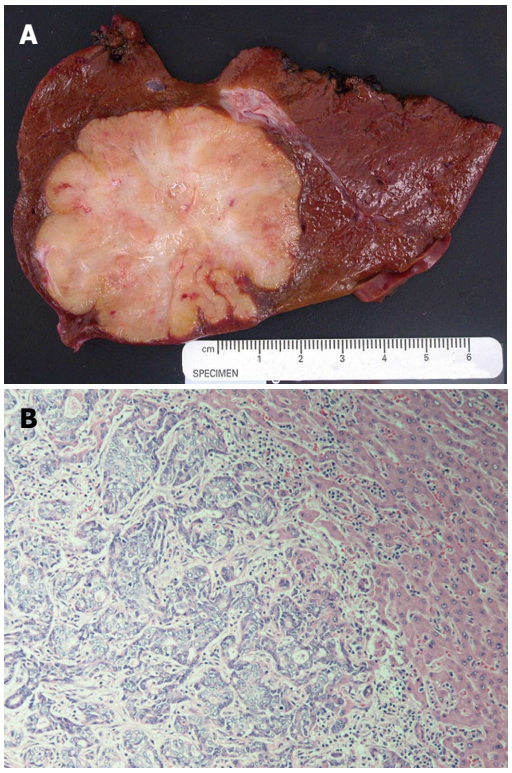

Figure 2 Photograph. A: Right lobe liver resection specimen showing a 6.0 cm × 5.5 cm × 5 cm well-circumscribed tumor with a firm, heterogeneous, yellow tan and white cut surface with areas of fibrosis. The surrounding liver is unremarkable; B: Representative photomicrograph of the tumor shows anastomosing glandular structures composed of highly pleomorphic epithelial cells in a desmoplastic stroma. The findings are consistent with intrahepatic cholangiocarcinoma (HE, original magnification × 200).

unremarkable with a negative Murphy's sign. Laboratory tests were performed and reported normal white cell count and hemoglobin. Kidney function and liver function were unremarkable. Tumors markers AFP and CA 19-9 were normal, 1.9 ng/mL and 8.4 U/mL, respectively. Based on the imaging studies, the pre-operative diagnosis was hepatocellular carcinoma. The patient underwent a right hepatic lobectomy and cholecystectomy. At surgery, the uninvolved liver appeared normal and there was no evidence of extrahepatic disease in the lymph nodes or anywhere else in the abdomen.

Pathology: A right liver lobe resection specimen was received and revealed a 6 cm × 5.5 cm × 5 cm white tan well-circumscribed firm mass with scalloped borders (Figure 2A). The tumor was 2 cm from the closest resection margin. Microscopically, the tumor consisted of moderately-differentiated intrahepatic cholangiocarcinoma characterized by anastomosing cords and glands with marked cytological atypical and embedded in dense stroma (Figure 2B). No lymphovascular invasion was noted. The bile duct margin was negative; no lymph nodes were identified from the hilar soft tissue that was entirely submitted. Carcinoma-*in-situ* and dysplastic changes involving adjacent bile ducts were seen. The uninvolved liver showed portal fibrosis but no portal inflammation. Rare ground-glass hepatocytes were idenfied. Immunohisto-

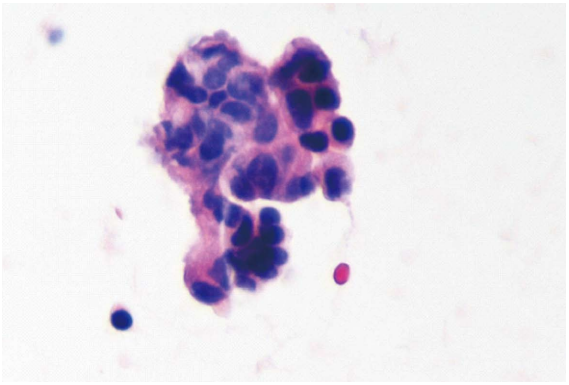

Figure 3 Endoscopic ultrasound-guided fine needle aspiration biopsy of pancreatic tail mass. Cytospin material showing a loose three-dimensional cluster of cells with high nuclear to cytoplasmic ratio, hyperchromasia, and eosinophilic cytoplasm. Several other clusters similar to these were found on the slide. The findings are consistent with adenocarcinoma compatible with metastatic cholangiocarcinoma.

chemical stain for hepatitis B surface antigen showed scattered hepatocytes with positive cytoplasmic staining, whereas hepatitis B core antigen was negative, findings that confirm hepatitis B infection.

The patient recovered with no complication and was discharged 5 d after surgery. She was then routinely followed-up with CT of the chest and abdomen, tumor markers and complete lab tests on an outpatient mode. In January 2012, approximately 2 mo after delivering her baby and almost 4 years after her prior surgery, a CT-scan of the abdomen performed in an outside hospital highlighted a pancreatic ductal dilatation, suspicious to be secondary to a mass in the tail of the pancreas and nine nodules on both sides of the chest; each lesion was then confirmed by a positron emission tomography-computed tomography. In order to determine the nature of the pancreatic lesion, an endoscopic ultrasound (EUS)-Fine needle aspiration (FNA) was performed. In order to clarify the nature of the lung nodules the patient underwent a left video-assisted thoracoscopic surgery wedge resection. The specimen revealed a white firm well-circumscribed lesion measuring 1 cm × 1 cm with free margins. The findings supported metastatic cholangiocarcinoma (Figure 3). Surgery having no role in systemic cholangiocarcinoma, our plan was to introduce chemotherapy with Gemcitabine/Cisplatin for 3 mo followed by restaging.

Currently, the patient is off chemotherapy and remains very well. She is pregnant G2P1, due to have a baby in March 2014.

DISCUSSION

Intrahepatic cholangiocarcinomas are malignant neoplasms arising from the biliary tree, beyond the second order[5]. They represent approximately 10%-20% of all primary liver cancers[2-4]. ICC include different growth types: mass-forming, periductal-infiltrating and intraductal-growth[5]. Furthermore, they display a very malignant potential leading to a high risk of recurrence and a poor prognosis. Surgery, *via* liver transplant and hepatic resection, is considered as the only curative treatment for ICC[15]. Notwithstanding long-term outcomes are still far from reaching the expectancy. Most patients with ICC present recurrence within 2 years after surgery[9,10,12,14]. Not surprisingly survival rates are low. Despite an aggressive approach Konstadoulakis *et al*[13] reported 1-year, 3-year and 5-year survival rates of 80%, 49% and 25%, respectively[13]. Many potential predictor factors have been suggested. Concerning the well-established ones, several studies demonstrated the negative impact of positive margins[8,12,13,16-18]. Lymph nodes metastasis has also been identified as negative predictive factor although the benefit of lymphadenectomy is still debatable[8,10,11,14,16,17]. Intrahepatic cholangiocarcinomas have the potential to invade Glissonean sheath[16] leading to hematogenous, lymphatic or direct extension, causing dissemination of the disease. The absence of other lesion or peri-pancreatic adenopathy supports the hypothesis of hematogenous spreading although the dissemination pattern remains unclear in this case.

Concerning the liver lesion, as above mentioned, "carcinoma-in-situ and dysplastic changes involving adjacent bile ducts were seen". This finding supports the diagnosis of primary cholangiocarcinoma, rather than metastatic tumor. This finding, associated with cytological features: (high N/C ratios, pleomorphism and high mitotic rates), permit to confidently rule-out the differential diagnosis of cholangiolocellular carcinoma[19,20].

Considering the pancreatic lesion, its morphology has been compared with the hepatic one; they were considered similar. Unfortunately, no tissue from the pancreatic FNA specimen is available for immunohistochemical studies. If tissue was available we may have add breast cancer markers to rule out metastatic breast cancer that could be considered in a young female patient.

The metastatic lesion in the pancreas could be explained as hematogenous spread from lesions in the lungs.

In term of risk factors the patient was HBV carrier. The role of HBV in ICC needs to be clarified. Although several studies considered it as a risk factor[2-4], a recent study suggested HBV could be a favorable prognostic factor after resection[21]. Liver fluke infestation was not tested. The patient did not present any other major risk factor but her recent history of pregnancy should be addressed although its role remains uncertain. Little is known in this field but clinical courses of ICC worsened by gravid state have been reported[22,23]. Indeed the high concentration of estrogen and the suppression of the immune system arising from pregnancy could potentially promote recurrence of ICC like it can aggravate preexisting liver lesion[24]. Chemotherapy is considered as the standard care for extrahepatic recurrences while surgery is not the gold standard in these cases[15]. Nevertheless data are strongly limited in this field and further studies are needed, especially to assess to role of combining therapies that may play an increasing role in the future.

Considering the absence of reported pancreatic metastases from ICC, achieving an EUS-FNA in order to get a diagnosis was probably the correct strategy. Regarding the lungs nodules we decided to perform a video-assisted thoracoscopic surgery resection although they were highlighted on the PET/CT. Many other causes could explain lung nodules in a young Chinese patient. Therefore we needed a precise diagnosis of the lesion to decide whether the patient could be candidate to surgery or to systemic therapy. Yoon *et al*[25] reported a case of cholangiocarcinoma that metastasized to the pancreas, however they did not reported whether it was an intrahepatic, hilar or extrahepatic one[25].

In conclusion, the present case report describes a recurrence of intrahepatic cholangiocarcinoma in lungs and pancreas in a patient who underwent liver resection approximately 4 years previously. This is the first report of pancreatic metastasis from ICC.

ACKNOWLEDGMENTS

This case report was showed at the Swiss Congress of Surgery (Bern, June 2013) and the French Congress of Surgery (Paris, October 2013).

COMMENTS

Case characteristics

A 24-year-old woman was referred for a liver mass.

Clinical diagnosis

No symptom, no jaundice. Abdominal palpation was unremarkable with a negative Murphy's sign.

Differential diagnosis

Hepatocellular carcinoma.

Laboratory diagnosis

Laboratory tests were perfectly unremarkable.

Imaging diagnosis

A computed tomography scan with nonionic contrast confirmed a mass within segments VI-VII measuring 7.2 cm × 6.0 cm. No lesion was observed in the lungs and her pancreas appeared normal.

Pathological diagnosis

The tumor consisted of moderately-differentiated intrahepatic cholangiocarcinoma.

Treatment

Chemotherapy with Gemcitabine/Cisplatin.

Related reports

Intrahepatic cholangiocarcinomas (ICC) are malignant tumors arising from the intrahepatic bile ducts that frequently recur after resection.

Experiences and lessons

The present case report describes a recurrence of intrahepatic cholangiocarcinoma in lungs and pancreas in a patient who underwent liver resection approximately 4 years previously. This is the first report of pancreatic metastasis from ICC.

Peer review

This article shows the risk for intrahepatic cholangiocarcinoma to metastasize to the pancreas.

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CASE REPORT

Retroperitoneal paragangliomas: Report of 4 cases

Helmi Kallel, Hassen Hentati, Amine Baklouti, Ali Gassara, Ahmed Saadaoui, Ghassen Halek, Sana Landolsi, MA El Ouaer, Wajdi Chaieb, Fethia Maamouri, Saber Mannaï

Helmi Kallel, Hassen Hentati, Amine Baklouti, Ali Gassara, Ahmed Saadaoui, Ghassen Halek, Sana Landolsi, MA El Ouaer, Wajdi Chaieb, Saber Mannaï, Department of Visceral Surgery, Hospital of Jendouba, Faculty of Medicine of Tunis, University of Tunis El Manar, 2083 Ariana, Tunis
Fethia Maamouri, Department of Histopathology, Hospital of Jendouba, Faculty of Medicine of Tunis, University of Tunis El Manar, 2083 Ariana, Tunis
Author contributions: All the authors contributed to this manuscript.
Correspondence to: Dr. Kallel Helmi, Department of Visceral Surgery, Hospital of Jendouba, Faculty of Medicine of Tunis, University of Tunis El Manar, Residence Omrane 6, App A8, Cité el Ghazela, 2083 Ariana, Tunis. helmi.kallel@gmail.com
Telephone: +216-98-670457 Fax: +216-70-681281
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Abstract

We reviewed the data of all patients managed for retroperitoneal paragangliomas (PGLs) between June 2010 and June 2011 to present our experience concerning this uncommon entity to highlight diagnostic and therapeutic challenges of retroperitoneal PGLs. All patients were admitted to the department of general and hepatobiliary surgery in the regional hospital of Jendouba, Tunisia. The size of the tumor was taken at its largest dimension, as determined in a computed tomography (CT) scan and pathological reports. There were 4 patients (all women) with a median age of 48 years (range 46-56 years). Abdominal pain was the commonest presentation. CT showed and localized the tumors which were all retroperitoneal. All patients had successful surgical resection of the tumors under invasive arterial blood pressure monitoring. One patient underwent surgery for a presumed tumor of the pancreatic head. The fresh-mount microscopic study of the peroperative biopsy yielded inflammatory tissue without malignancy and no resection was performed. Final histological examination of the biopsy concluded PGL. A second laparotomy was performed and the tumor was entirely resected. The diagnosis was made after surgery by histology in all patients. The control of the blood pressure was improved after surgery in 3 patients. Paragangliomas are rare tumors. The retroperitoneal localization is uncommon. Complete surgical resection remains the only curative treatment but it is often challenging as these tumors are located near multiple vital blood vessels.

Key words: Paraganglioma; Extra adrenal pheochromocytoma, Retroperitoneal; Surgery; Histology

Core tip: Retroperitoneal paragangliomas are uncommon tumors causing considerable difficulty in both diagnosis and treatment. Its complete surgical removal is often challenging as these tumors are located near multiple vital blood vessels. Any surgeon could face such a rare tumor.

Kallel H, Hentati H, Baklouti A, Gassara A, Saadaoui A, Halek G, Landolsi S, El Ouaer MA, Chaieb W, Maamouri F, Mannaï S. Retroperitoneal paragangliomas: Report of 4 cases. *World J Gastrointest Surg* 2014; 6(4): 70-73 Available from: URL: http://www.wjgnet.com/1948-9366/full/v6/i4/70.htm DOI: http://dx.doi.org/10.4240/wjgs.v6.i4.70

INTRODUCTION

Paragangliomas (PGLs), or extra-adrenal phaeochromocytomas, are tumors arising from chromaffin tissues. Abdominal localizations are less frequent than head and neck. Retroperitoneal PGLs are more uncommon, causing considerable difficulty in diagnosis and treatment. In this article, we present our experience concerning this uncommon entity to highlight diagnostic and therapeutic

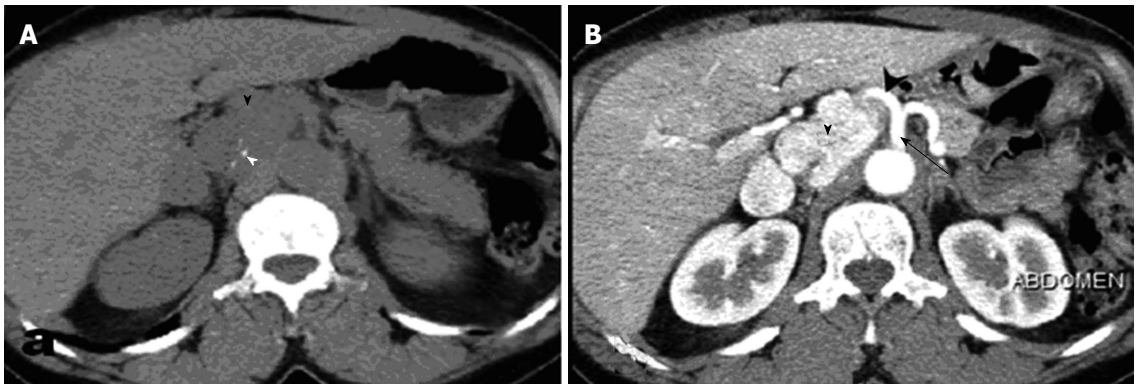

Figure 1 Abdominal computed tomography without (A) and after (B) contrast material administration, showing the tumor (arrowhead) with calcifications (white arrowhead) and precocious enhancement. Note the close tumoral relationship to the celiac trunk (black arrow) and hepatic artery (black arrowhead).

Table 1 Clinical features of the patients with paragangliomas

Patient	Age (yr)/sex	Abdominal pain	Hypertension	Palpitation	Headache	Sweating	Location	Size (cm)
1	54/F	Y	N	Y	N	Y	Celiac region	6
2	46/F	Y	Y	N	Y	N	Right para-aortic	4
3	56/F	Y	Y	Y	N	N	Retrocaval	5
4	48/F	Y	Y	N	Y	N	Near right adrenal Near pancreatic head	5

F: Female; Y: Yes; N: No.

challenges of retroperitoneal PGLs.

CASE REPORT

We reviewed the data of all patients managed for retroperitoneal PGLs between June 2010 and June 2011. All patients were admitted to the department of general and hepatobiliary surgery in the regional hospital of Jendouba, Tunisia. The size of the tumor was taken at its largest dimension, as determined in a computed tomography (CT) scan and pathological reports.

There were 4 patients (all women) with a median age of 48 years (range 46-56 years). The clinical features are shown in Table 1. Abdominal pain was the commonest presentation, followed by hypertension in 3 cases, headache and palpitation in 2 cases and sweating in 1 case. No abdominal mass was detected on palpation in any patient. Abdominal CT showed and localized the tumor in all patients. The tumor measured from 4 to 6 cm in diameter and showed obvious intensification after contrast material administration (Figure 1). All tumors were retroperitoneal. The diagnosis was evoked preoperatively by the CT data for the 3 first patients. Patient 4 underwent surgery for a presumed tumor of the pancreatic head. Surgical exploration revealed a soft mass of the pancreatic head without dilatation of the common bile duct. The fresh-mount microscopic study of the peroperative biopsy yielded inflammatory tissue without malignancy. No resection was performed. Final histological examination of the biopsy concluded PGL. A second laparotomy was performed. The tumor was adherent to the pancreatic parenchyma and the inferior vena cava. It was carefully dissected and entirely resected. Final histological examination of the specimen confirmed the diagnosis of PGL. All patients had successful surgical resection of the tumors under invasive arterial blood pressure monitoring. Complete surgical removal was difficult because the tumors were located near multiple vital blood vessels: celiac region for patient 1 (Figure 2A), right para aortic for patient 2, retrocaval for patient 3 (Figure 2B) and near the pancreatic head for patient 4. There was no evidence of malignancy, as judged by local infiltration or the presence of metastasis. The diagnosis was made after surgery by histology in all cases because of the unavailability of measurements of urinary and plasma adrenaline, noradrenaline and metanephrine concentrations in our hospital. Histology revealed a tumor composed of spindle to polygonal cells with abundant basophilic granular cytoplasm and moderate pleomorphism. The cell architecture was trabecular and nested, pathognomonic of paraganglioma (Figure 3). Low mitotic activity was observed and there was no capsular invasion. The tumor was encapsulated and demarcated from the surrounding effaced pancreatic parenchyma in patient 4. Tumor cells stained positively for synaptophysin, chromogranin and S100 in all cases (Figure 4). The morphological and immunohistochemical profile was consistent with extra-adrenal PGL. The control of the blood pressure was improved after surgery in 3 patients.

DISCUSSION

Retroperitoneal PGL is a rare pathological entity that occurs most often in young adults[1]. PGLs are often unique; multiple tumors are observed in only 10% of the

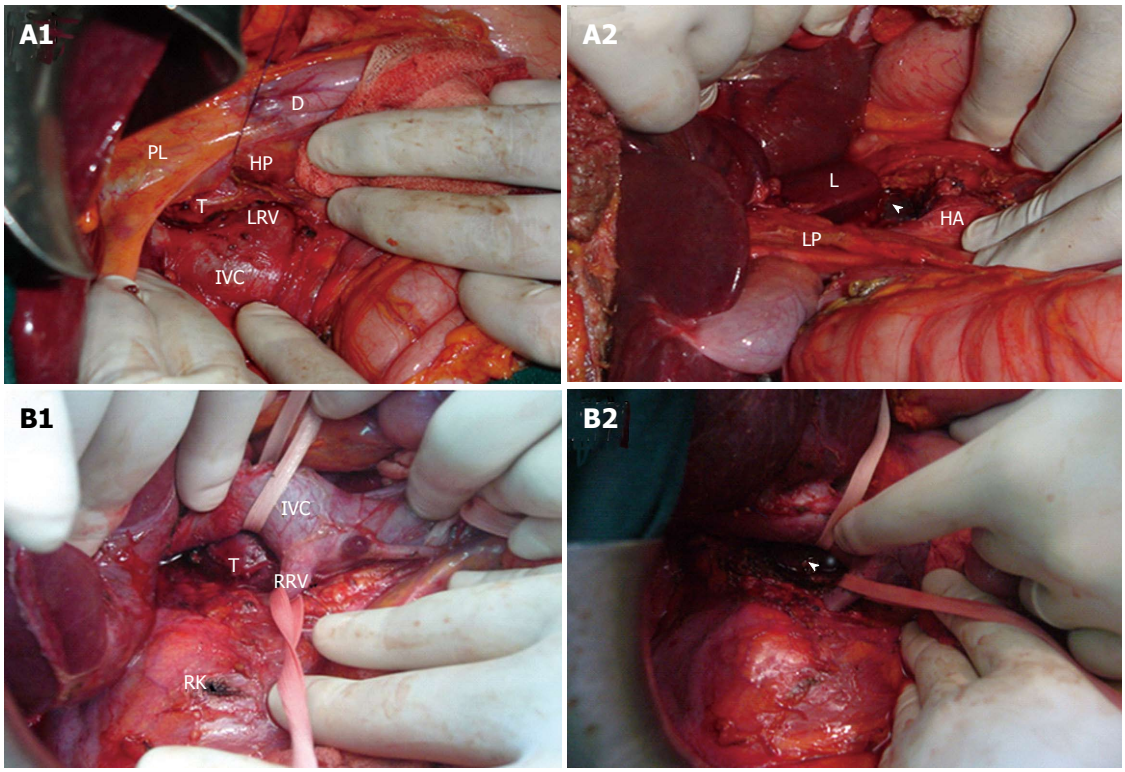

Figure 2 Operative view. A: Patient 1. A1: Separation of the tumor (T) from the anterior aspect of the inferior vena cava (IVC); A2: Surgical site after tumor resection (arrowhead); B: Patient 3. B1: Separation of the tumor (T) from the posterior wall of the IVC; B2: Surgical site after tumor resection (arrowhead). LRV: Left renal vein; D: Duodenum; HP: Head of the pancreas; PL: Liver pedicle; RRV: Right renal vein; RK: Right kidney; HA: Hepatic artery; LP: Liver pedicle; L: Liver (Lobe of Spiegel).

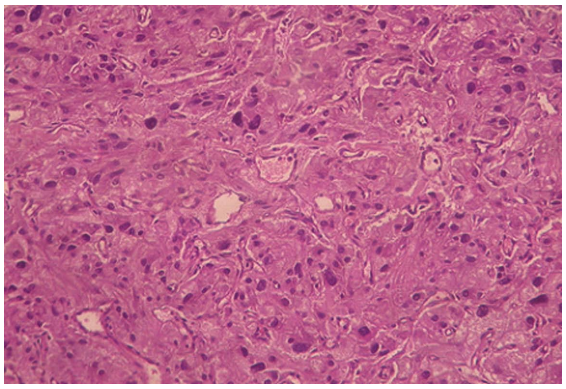

Figure 3 Microscopic view of paraganglioma. Large polygonal cells with granular cytoplasm arranged in nests (hematoxylin and eosin).

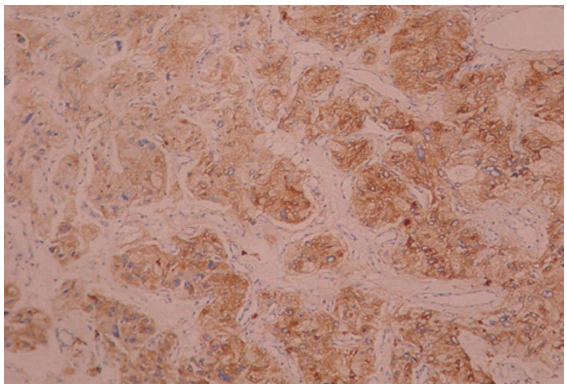

Figure 4 Immunohistochemistry. Tumoral cells strongly express anti-chromogranin antibody.

cases. Signs and symptoms are variable and frequently paroxysmal due to the variable and disorderly release of catecholamines by the tumor. The typical presentation is a combination of variable hypertension with paroxysmal symptoms, either occurring spontaneously or provoked by high abdominal pressure during anteflexion, urination or defecation[2]. The diagnosis of catecholamine-secreting tumors should be based on the determination of plasma or urinary metanephrine concentration[2]. Preoperative imaging tests are used to locate the tumor, to determine whether it is single or multiple, adrenal or ectopic, benign or malignant and isolated or present with other neoplasms in the context of familial syndromes. Magnetic resonance imaging is similar to CT in the diagnosis of PG, but it is preferred in children and pregnant women[2]. Some authors propose ^{123}I-MIBG scintigraphy to diagnose secreting PGLs, with a sensitivity and specificity of 90% and 99% respectively[1]. Complete surgical removal provides a 5 year survival of 75%. It is then considered as the only curative treatment of PGLs[1] but it is often challenging as these highly vascular tumors are located near multiple vital blood vessels. Preoperative pharmacological preparation is necessary. It has an important role in achieving the safest and most successful outcome[3]. Given the hypervascular aspect of the tumor, some authors propose pre-operative embolization. Laparoscopic

resection of PGL has been reported in the literature, with all the known advantages of the mini-invasive surgery. In our patients, we performed open surgery because of the localization of the tumor in contact with important vessels. PGLs also have potential to be malignant. It has been reported in the literature that around 20% of PGLs could be malignant with poor survival[4]. While histopathological findings are not very useful to differentiate between benign and malignant PGLs, extensive local invasion and distant metastasis have been used as indicators for malignancy[5-7]. Recurrences and malignancy are more frequent in cases with large or extra-adrenal tumors. Patients should be followed up indefinitely, particularly if they have inherited or extra-adrenal tumors.

In conclusion, paragangliomas are rare tumors with a limited number of cases reported. The localization in the retroperitoneal region is uncommon and is a challenge for surgical resection. Complete surgical resection remains the only curative treatment. Lifetime follow-up is necessary to detect recurrences.

COMMENTS

Case characteristics

There were 4 patients (all women) with a median age of 48 years (range 46-56 years). Abdominal pain was the commonest presentation. Computed tomography showed and localized the tumors which were all retroperitoneal.

Clinical diagnosis

One patient underwent surgery for a presumed tumor of the pancreatic head. The fresh-mount microscopic study of a preoperative biopsy yielded inflammatory tissue without malignancy and no resection was performed. Final histological examination of the biopsy concluded paragangliomas. A second laparotomy was performed and the tumor was entirely resected.

Differential diagnosis

The diagnosis was made after surgery by histology in all patients.

Experiences and lessons

The retroperitoneal localization is uncommon. Complete surgical resection remains the only curative treatment but it is often challenging as these tumors are located near multiple vital blood vessels.

Peer review

The authors report on a relatively uncommon condition. It would be worth detailing the histopathology and defining how this differs from other retroperitoneal neoplastic lesions.

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CASE REPORT

Recurrence of gastric cancer in the jejunal stump after radical total gastrectomy

Jong Han Yoo, Sang Hyuk Seo, Min Sung An, Tae Kwun Ha, Kwang Hee Kim, Ki Beom Bae, Chang Soo Choi, Sang Hun Oh, Young Kil Choi

Jong Han Yoo, Sang Hyuk Seo, Min Sung An, Tae Kwun Ha, Kwang Hee Kim, Ki Beom Bae, Chang Soo Choi, Sang Hun Oh, Young Kil Choi, Department of Surgery, Busan Paik Hospital, Inje University College of Medicine, Busan 614-735, South Korea

Author contributions: Yoo JH and Kim KH designed the report; Kim KH, Choi CS and Choi YK were the attending doctors for the patient; Kim KH and Choi YK performed the surgical operation; An MS, Ha TK and Bae KB organized the report; and Yoo JH and Seo SH wrote the paper; Oh SH organized the report.

Correspondence to: Kwang Hee Kim, MD, Department of Surgery, Busan Paik Hospital, Inje University College of Medicine, Gaegum 2-dong, Busanjingu, Busan 614-735, South Korea. inwoodog@naver.com

Telephone: +82-51-8906352 Fax: +82-51-8989427

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Key words: Gastric cancer; Recurrence; Jejunal stump

Core tip: In our study, there was a case of recurrence of gastric cancer in the jejunal stump after radical total gastrectomy with Roux-en-Y reconstruction. The patient underwent jejunal pouch resection, distal pancreatectomy and splenectomy. On histopathologic examinations, the patient was diagnosed with gastric cancer.

Yoo JH, Seo SH, An MS, Ha TK, Kim KH, Bae KB, Choi CS, Oh SH, Choi YK. Recurrence of gastric cancer in the jejunal stump after radical total gastrectomy. *World J Gastrointest Surg* 2014; 6(4): 74-76 Available from: URL: http://www.wjgnet.com/1948-9366/full/v6/i4/74.htm DOI: http://dx.doi.org/10.4240/wjgs.v6.i4.74

Abstract

This is a very rare case of the recurrence of gastric cancer in the jejunal stump after radical total gastrectomy with Roux-en-Y reconstruction. In January 2008, a 65-year-old man underwent radical total gastrectomy with Roux-en-Y reconstruction for stage I B gastric cancer of the upper body. At a follow-up in December 2011, the patient had a recurrence of gastric cancer on gastroduodenal fibroscopy. The gastroduodenal fibroscopic biopsy specimens show a well-differentiated tubular adenocarcinoma. Computed tomography showed no lymphadenopathy or hepatic metastases. At laparotomy, there was a tumor in the jejunal stump involving the pancreatic tail and spleen. Therefore, the patient underwent jejunal pouch resection, distal pancreatectomy and splenectomy. The patient was diagnosed with gastric cancer on histopathological examination.

INTRODUCTION

Gastric cancer is a highly prevalent cancer that occurs the most commonly in Korea. It shows a very good prognosis when detected earlier in a regular medical check-up. In advanced cancer, however, a poor prognosis has been well documented. There are many recurrent cases of gastric cancer despite radical surgery. Its recurrence occurs through hematogenous, peritoneal dissemination or via the lymph nodes. We report a case of recurrence of gastric cancer in the jejunal stump after radical total gastrectomy with Roux-en-Y reconstruction.

CASE REPORT

A 65-year-old man presented with a recurrence on gastroduodenal fibroscopy (Figure 1) at a follow-up after gastric cancer surgery. He underwent radical total gastrectomy with Roux-en-Y reconstruction (end to side esophagojejunostomy with circular stapler), for gastric cancer detected on gastroduodenal fibroscopy in January 2008. The

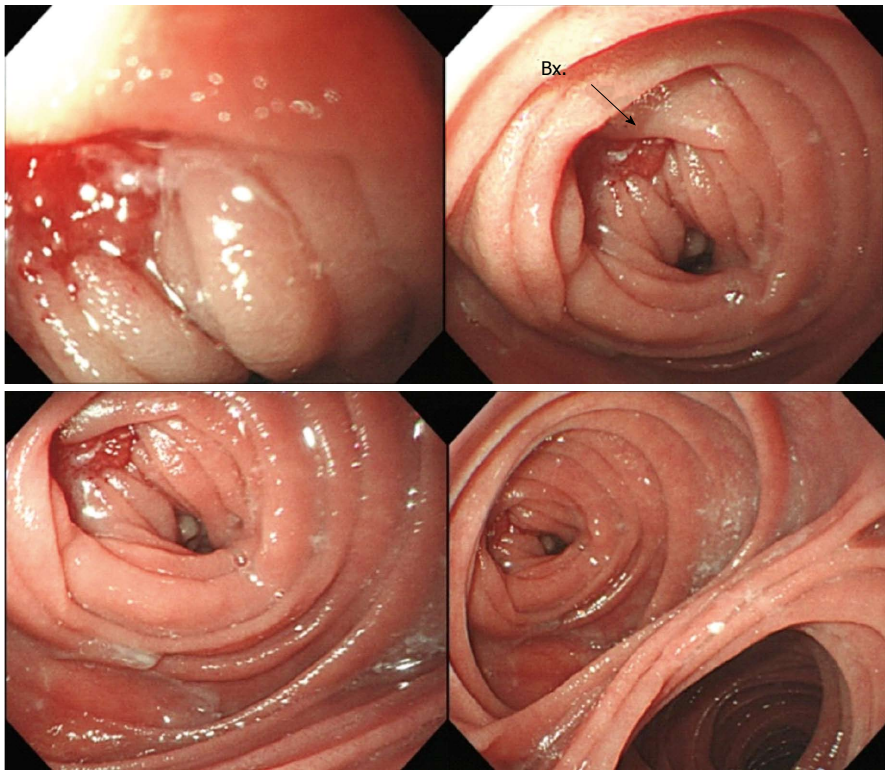

Figure 1 Endoscopic findings. There was a medium-sized single small polypoid infiltrative ill-defined mass, with nodular overlying mucosa without bleeding evidence at jejunal pouch (1.2 cm in diameter). Tubular adenocarcinoma, well differentiated.

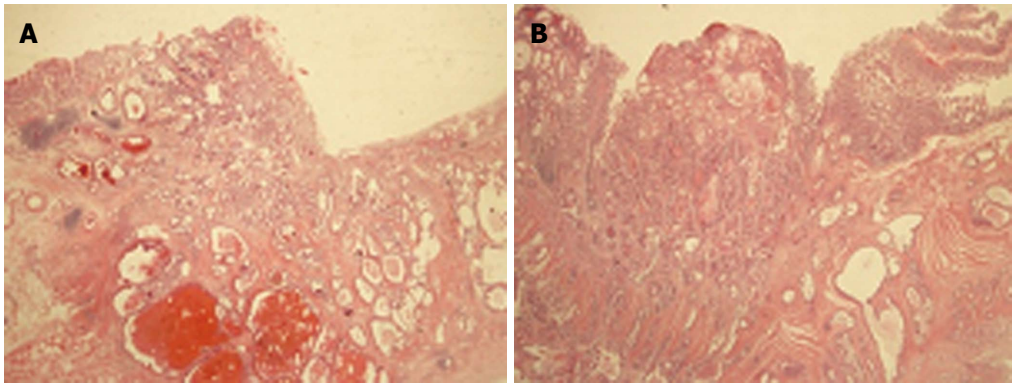

Figure 2 Pathological findings. A: January 2008, slide of gastric cancer lesion (primary lesion); B: December 2011, slide of jejunal stump lesion (recurrent lesion).

gastric cancer had a tumor node metastasis stage of IB (T2N0M0), which had lesions of 2.5 cm × 2.0 cm in size on the posterior wall of the upper part of the gastric fundus. Based on histopathology, findings were suggestive of well-differentiated tubular adenocarcinoma. There was no lymph node metastasis or metastasis to other organs in the abdomen (Figure 2). Postoperatively, the patient underwent an uneventful course without notable episodes and achieved a recovery. The patient had been taking oral chemotherapeutic drugs (5-fluorouracil) during a period ranging from January 2008 to December 2009. Following this, the patient had no recurrence and had an outpatient follow-up. Meanwhile, in December 2011, the patient had a single small polypoid infiltrative ill-defined mass of approximately 1.2 cm in size at the site approximately 3 cm from the distal part of the esophagojejunal junction to the blind loop (the posterior wall of the jejunal stump) on gastroduodenal fibroscopy (Figure 1). The patient therefore underwent histopathological examinations, presenting with findings suggestive of well-differentiated tubular adenocarcinoma. Therefore, the patient was admitted for further evaluation and treatment. At the time of admission, the patient had a good systemic and nutritional status with stable vital signs. On examination, the patient had no palpable left supraclavicular lymph nodes. On abdominal examination, the patient had no tenderness, shifting dullness or palpable abdominal masses. In addition, the patient also had no positive findings on rectal examination. The patient underwent clinical laboratory tests for hemoglobin, white blood cell counts, platelet

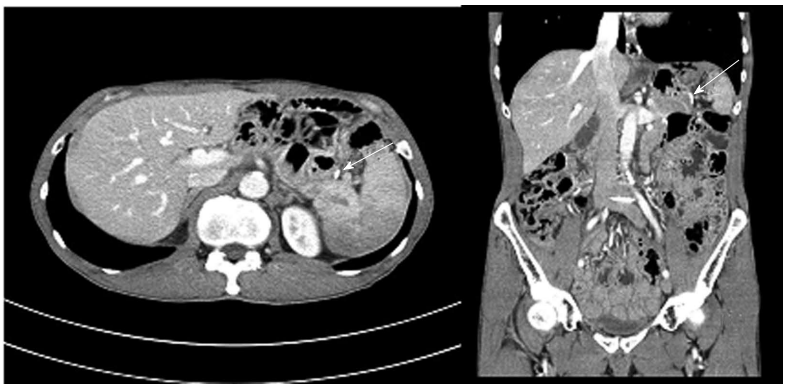

Figure 3 Pre-operation computed tomography findings. No evidence of local tumor recurrence or distant metastasis. Arrow: Distal jejunal stump stapling line (recurrence site).

counts, serum electrolytes, serum biochemistry, urinalysis, serological tests and blood coagulation tests, all of which were normal. Serum levels of carcinoembryonic antigen, a tumor marker, were 4.95 ng/mL. Abdominal computed tomography (CT) showed no recurrence and metastasis, which is also consistent with previous abdominal CT scans (Figure 3). Under general anesthesia, the patient underwent surgery for jejunal stump resection, distal pancreatectomy with splenectomy in January 2012. Intraoperatively, the patient presented with a tumor in the jejunum and invasion to the pancreatic tail and the spleen, with no evidence of hepatic or peritoneal recurrence, for which the patient underwent dissection of the jejunal stump, the pancreatic tail and the spleen. The postoperative course was uneventful. On histopathological examination, there was a recurrence of the gastric cancer in the jejunal pouch, the pancreatic tail and the spleen. Currently, the patient is receiving an injection of chemotherapy regimens (FOLFOX chemotherapy).

DISCUSSION

The local recurrence of gastric cancer after total gastrectomy mostly occurs in the proximal region from the esophagojejunal junction. Anastomotic or suture-line recurrence after gastrectomy is reported to be 3%-10%[1]. Recurrence in the distal jejunal stump is a rare entity. The main theory of the cause and mechanisms of recurrence includes submucosal or subserosal lymphatic spread of cancer, the remainder of the stump and the implantation of exfoliated cancer cells[1-3]. In this case, histological study revealed no lymph node metastasis and no vessel permeation. Both resection margins were also negative for cancer cells. For this reason, the theory of lymphatic spread of cancer and the remainder of the stump can be rejected. The implantation of exfoliated cancer cells may be the reason for recurrence but it is unclear. The recurrence of the anastomosis or suture-line is rare and its mechanism is unclear but local recurrence can be treated by surgery. So, an early diagnosis of local recurrence can improve the prognosis. Gastroduodenal fibroscopy can be useful to detect an intraluminal recurrence. CT or positron emission tomography (PET) can detect gastric bed or regional lymph nodes. We recommend that routine outpatient follow-up includes gastroduodenal fibroscopy, CT and PET.

COMMENTS

Case characteristics

A 65-year-old man presented with gastric cancer recurrence, as shown on gastroduodenal fibroscopy.

Clinical diagnosis

Histopathological examination revealed a diagnosis of gastric cancer.

Imaging diagnosis

Gastroduodenal fibroscopy, computed tomography and positron emission tomography.

Peer review

Yoo JH *et al* described a rare case of recurrence of gastric cancer in the jejunal pouch after radical total gastrectomy with Roux-en-Y reconstruction. This is an interesting case.

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CASE REPORT

Neuroendocrine carcinoma of the stomach: A case report

Sang Hyun Kang, Kwang Hee Kim, Sang Hyuk Seo, Min Sung An, Tae Kwun Ha, Ha Kyung Park, Ki Beom Bae, Chang Soo Choi, Sang Hun Oh, Young Kil Choi

Sang Hyun Kang, Kwang Hee Kim, Sang Hyuk Seo, Min Sung An, Tae Kwun Ha, Ha Kyung Park, Ki Beom Bae, Chang Soo Choi, Sang Hun Oh, Young Kil Choi, Department of Surgery, Busan Paik Hospital, Inje University College of Medicine, Busan 614-735, South Korea

Author contributions: Kang SH and Kim KH designed the report; Kim KH, Oh SH and Park HK were the attending doctors for the patient; Kang SH and Kim KH performed the surgical operation; An MS, Ha TK, Bae KB and Choi CS organized the report; and Kang SH, Seo SH and Choi YK wrote the paper.

Correspondence to: Kwang Hee Kim, MD, Department of Surgery, Busan Paik Hospital, Inje University College of Medicine, Gaegum 2-dong, Busanjingu, Busan 614-735, South Korea. inwoodog@naver.com

Telephone: +82-51-8906352 Fax: +82-51-8989427
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Abstract

Neuroendocrine carcinoma (NEC) is a rare tumor, comprising < 1% of stomach cancers. A 55-year-old woman was referred to our hospital with biopsy-proven gastric cancer. A shallow ulcerative lesion was detected in the lesser curvature of the lower body. It was suspected to be early gastric cancer ⅡA + ⅡC type. Thus, endoscopic submucosal dissection was performed. She was subsequently diagnosed with NEC, which is aggressive and carries a poor prognosis. We conducted a radical resection and a laparoscopic-assisted distal gastrectomy. The tumor had infiltrated the subserosal layer and 6/42 lymph nodes were involved. The mitotic index was 16/10 high power fields and the Ki-67 labeling index was 26%-50%. The final diagnosis of NEC was made according to the World Health Organization 2010 criteria. She was suspected of having jumping metastasis to the proximal margin. The patient was treated with an oral anticancer drug (5-flurouracil based drug) for 2 years. The patient has been followed up for 3 years without recurrence.

Key words: Neuroendocrine carcinoma; Mitosis; Ki-67; Gastrectomy; Prognosis

Core tip: Some studies argue that neuroendocrine carcinoma (NEC) can be removed by endoscopic resection. However, in this case, we found that NEC can have jumping metastasis. Thus, NEC must be removed by radical surgical resection.

Kang SH, Kim KH, Seo SH, An MS, Ha TK, Park HK, Bae KB, Choi CS, Oh SH, Choi YK. Neuroendocrine carcinoma of the stomach: A case report. *World J Gastrointest Surg* 2014; 6(4): 77-79 Available from: URL: http://www.wjgnet.com/1948-9366/full/v6/i4/77.htm DOI: http://dx.doi.org/10.4240/wjgs.v6.i4.77

INTRODUCTION

Neuroendocrine carcinoma (NEC) is rare tumor that includes < 1% of stomach cancers. It is aggressive and has a poor prognosis[1-3]. NEC is classified as neuroendocrine carcinoma G3 according to The World Health Organization (WHO) classification of tumors of the digestive system, 2010[4].

In this report, we describe a patient with NEC who underwent endoscopic submucosal dissection (ESD) and laparoscopic assisted distal gastrectomy (LADG) for removal of a tumor.

CASE REPORT

A 55-year-old woman with acid reflux underwent an esophagogastroduodenoscopy (EGD) for a checkup. A shallow ulcerative lesion was detected in the lesser curvature of the lower body (Figure 1). It was suspected to be early gastric

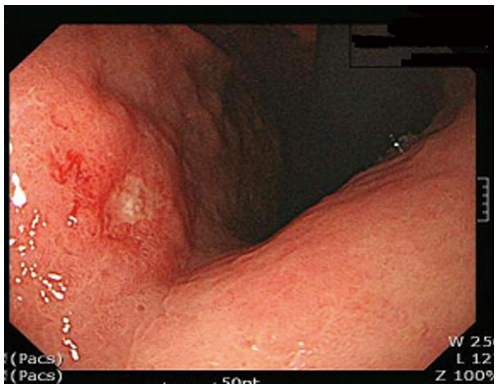

Figure 1 Endoscopic findings. Ulcerative lesion in the lesser curvature of the lower body.

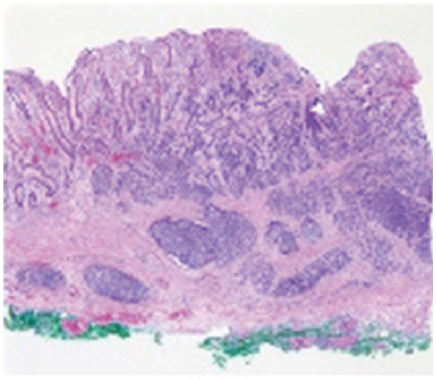

Figure 2 Endoscopic submucosal dissection specimen. A hypercellular lesion was detected in the mucosa and submucosal layers.

cancer ⅡA + ⅡC type. A biopsy was done and it was diagnosed as a well differentiated adenocarcinoma. She was transferred to the digestive department of our hospital.

On July 13, she underwent ESD. The specimen was 6.3 cm × 3.8 cm and a pathological examination revealed a 1.2 cm × 1.4 cm NEC that had invaded the submucosal layer. The tumor cells exhibited mitosis in 16/10 high power fields (HPF). The resection margin was clear (Figure 2) and no lymphatic, vascular or neural invasion was observed. She was advised to undergo an operation due to possible neural invasion by the NEC. On July 24, she vomited blood from an ulcer because of the weakened mucosa after ESD. The bleeding was stopped under emergency EGD. She underwent conservative treatment with a proton-pump inhibitor and no oral intake.

On August 9, she underwent LADG with a D2 lymphadenectomy. A Billroth type I anastomosis was done. A frozen biopsy revealed that the proximal and distal resection margins were clear of lesions. The mass was 2.2 cm × 1.3 cm in size and limited to the subserosa (Figure 3). The proximal resection margin was very close to the lesion but the distal resection margin was clear. Neural and lymphatic invasion was observed with 6 of 42 metastatic lymph nodes harvested. The tumor cells were positive for synaptophysin, chromogranin and CD56. The Ki-67 labeling index was 2+ (26%-50%). These findings led to the diagnosis of NEC, according to the 2010 WHO criteria[4]. The proximal margin was clear but the final pathology showed that some cancer cells were found between the mucosa and submucosa.

Minor bleeding was detected through the drain during the first 3 d. After an antihemorrhagic treatment and a transfusion, the blood tests were stable and the drain color changed to clear. She was discharged after the drain was removed.

She was treated with an oral anticancer drug [5-flurouracil (5-FU) based drug] for 2 years. No recurrence at the anastomosis or other site in the stomach was observed 3 years later.

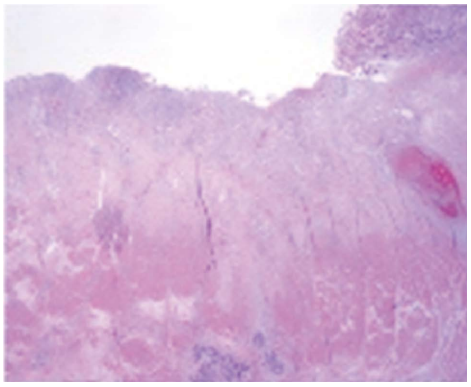

Figure 3 Laparoscopic assisted distal gastrectomy specimen. The ulcerative lesion due to mucosal detachment after endoscopic submucosal dissection is distinguished from normal mucosa (right side). Fibrosis was observed in the submucosal layer and a hypercellular lesion that was the same as the endoscopic submucosal dissection specimen in the muscle and subserosa layers.

DISCUSSION

Neuroendocrine neoplasm (NEN) is an epithelial neoplasm with predominant neuroendocrine differentiation and is an uncommon tumor with multiple sites of occurrence[5].

NENs are commonly divided by origin as located in the foregut (lung, bronchus, stomach or duodenum), midgut (jejunum, ileum, appendix or proximal colon) and hindgut (distal colon or rectum). The percentage of foregut cases is 34%, midgut 30% and hindgut 36%[6].

Gastric NEN is classified into neuroendocrine tumor (NET), neuroendocrine carcinoma (NEC), mixed adenoneuroendocrine carcinoma, enterochromaffin cells, serotonin-producing NETs and gastrin-producing NETs. NETs include NET G1 (carcinoid) and NET G2 (well-differentiated neuroendocrine tumor/carcinoma). NECs include NEC G3 (poorly differentiated neuroendocrine carcinoma small cell type/large cell type)[4]. NEN is positive for synaptophysin and chromogranin A[7].

NEN is classified based on the level of cellular proliferation, including the mitotic and Ki-67 indices[4]. In our case, the mitotic index was 16/10 HPF and the Ki-67 labeling index was 26%-50%. Thus, she was diagnosed with NEC. We suspected jumping metastasis from the main lesion to the proximal margin.

Gastric NEN has different prognoses and treatments depending on type. The prognosis of NET G1 is good and the 5 year survival rate is high. NET G2 has a favorable prognosis but is aggressive. NEC has the highest malignant potential but the 5 year survival rate is 75%-80%; however, the prognosis is poor. NET can be removed by endoscopic resection, whereas NEC requires surgical resection and lymph node dissection[8]. The best choice adjuvant chemotherapy for NEC is cisplatinum-based chemotherapy[9]. However, in this case we used a 5-FU oral agent because of the patient's financial status and compliance.

In conclusion, a neuroendocrine tumor can be removed by endoscopic resection but it must be a radical surgical resection in accordance with a malignant tumor, due to its aggressive tendency and high malignant potential.

COMMENTS

Case characteristics

This case reports a neuroendocrine carcinoma with jumping metastasis.

Pathological diagnosis

Neuroendocrine neoplasm can be diagnosed using a mitotic count and the Ki-67 index.

Treatment

Neuroendocrine tumors can be removed by endoscopic resection but a neuroendocrine carcinoma must be excised by radical surgical resection.

Peer review

In this case, the authors used 5-flurouracil chemotherapy, but a common choice for neuroendocrine carcinoma is cisplatinum-based chemotherapy.

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EDITOR-IN-CHIEF
Timothy M Pawlik, MD, MPH, FACS, Associate Professor of Surgery and Oncology, Hepatobiliary Surgery Program Director, Director, Johns Hopkins Medicine Liver Tumor Center Multi-Disciplinary Clinic, Co-Director of Center for Surgical Trials and Outcomes Research, Johns Hopkins Hospital, 600 N. Wolfe Street, Harvey 611, Baltimore, MD 21287, United States

EDITORIAL OFFICE
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Xiu-Xia Song, Vice Director
World Journal of Gastrointestinal Surgery
Room 903, Building D, Ocean International Center,
No. 62 Dongsihuan Zhonglu, Chaoyang District,
Beijing 100025, China
Telephone: +86-10-85381891
Fax: +86-10-85381893
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CASE REPORT

Rare cause of abdominal incidentaloma: Hepatoduodenal ligament teratoma

Vagner Birk Jeismann, Rodrigo Blanco Dumarco, Celso di Loreto, Ricardo Correa Barbuti, José Jukemura

Vagner Birk Jeismann, Rodrigo Blanco Dumarco, Ricardo Correa Barbuti, José Jukemura, Department of Gastroenterology, School of Medicine, University of São Paulo, São Paulo, SP 05403-900, Brazil
Celso di Loreto, CICAP Pathology Laboratory, Oswaldo Cruz German Hospital, Sao Paulo, SP 01323-903, Brazil
Celso di Loreto, The Adolfo Lutz Institute, Sao Paulo, SP 01246-902, Brazil
Author contributions: Jeismann VB, Dumarco RB and Jukemura J performed the procedure; Jeismann VB and Dumarco RB reviewed the literature; di Loreto C, Barbuti RC and Jukemura J analyzed and reviewed the paper; Jeismann VB and Jukemura J wrote the paper.
Correspondence to: Vagner Birk Jeismann, MD, Department of Gastroenterology, School of Medicine, University of São Paulo, Avenida Doutor Enéas de Carvalho Aguiar, 255 Central Institute, Room 9074, São Paulo, SP 05403-900, Brazil. vjeismann@gmail.com
Telephone: +55-11-26617560 Fax: +55-11-26617560
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Abstract

The occurrence of a hepatoduodenal ligament teratoma is extremely rare, with only a few cases reported in the literature. This case report describes the discovery of a hepatoduodenal ligament lesion revealed during abdominal ultrasonography for cholelithiasis-related abdominal pain in a 27-year-old female. Cross-sectional imaging identified a 5 cm × 4 cm heterogeneous mass of fat tissue with irregular calcification located in the posterior-superior aspect of the head of the pancreas. An encapsulated lesion showing no invasion to the common bile duct or adjacent organs and vessels was exposed during laparotomy and resected. Intraoperative cholangiography during the cholecystectomy showed no abnormalities. The postoperative course was uneventful. Pathological analysis of the resected mass indicated hepatoduodenal ligament teratoma. This case report demonstrates that cross-sectional imaging, such as computed tomography, can reveal suspected incidences of this rare type of teratoma, which can then be confirmed after pathologic analysis of the specimen. The prognosis after complete surgical resection of lesions presenting with benign pathological features is excellent.

Key words: Abdominal incidentaloma; Teratoma; Hepatoduodenal ligament; Surgery; Hepatobiliary surgery

Core tip: The 10th reported case of hepatoduodenal ligament teratoma is presented in a patient who underwent cross-sectional imaging for the evaluation of an abdominal mass. As incidences of hepatoduodenal ligament teratoma are extremely rare, this report may help physicians to suspect this disorder in an emergent group of patients with abdominal incidentaloma.

Jeismann VB, Dumarco RB, di Loreto C, Barbuti RC, Jukemura J. Rare cause of abdominal incidentaloma: Hepatoduodenal ligament teratoma. *World J Gastrointest Surg* 2014; 6(5): 80-83 Available from: URL: http://www.wjgnet.com/1948-9366/full/v6/i5/80.htm DOI: http://dx.doi.org/10.4240/wjgs.v6.i5.80

INTRODUCTION

Teratomas are neoplasms comprised of mixed dermal elements derived from the three germ cell layers. Although the majority of teratomas are congenitally present in the gonads of men and women, they have been identified in extra-gonadal sites, such as the anterior mediastinum, retroperitoneum and sacrococcygeal regions[1]. Teratomas in the hepatoduodenal ligament are extremely rare, with only nine cases described in the literature[2-10] (Table 1). We report a case of hepatoduodenal ligament teratoma

Table 1 Reported cases of hepatoduodenal ligament teratoma (adapted and expanded with permission from Ukiyama *et al*[8])

Patient	1	2	3	4	5	6	7	8	9	10
Year reported	1986	1989	1993	2004	2004	2005	2008	2008	2012	2013
Ref.	Frexes *et al*[2]	Akimov *et al*[3]	Kim *et al*[4]	Demircan *et al*[5]	Wang *et al*[6]	Sasaki *et al*[7]	Ukiyama *et al*[8]	Souftas *et al*[9]	Bagga *et al*[10]	Our case
Age	Neonate	6 yr	5 yr	4 mo	29 yr	38 yr	20 mo	26 yr	11 yr	27 yr
Sex	NA	NA	Male	Female	Female	Male	Male	Female	Female	Female
Origin	Extrahepatic bile duct	HL	CBD	Anomalous CBD	HL	HL	HL	HL	HL and fistulization with the CBD	HL
Signs and symptoms	Jaundice	Portal hypertension	Jaundice	Jaundice, abdominal distension	Portal hypertension	Abdominal mass	Abdominal mass	Abdominal pain	Jaundice, abdominal mass	Asymptomatic
Size	Small mass	NA	NA	Cystic mass 15 cm	Solid mass 7 cm × 6 cm × 6 cm	Cystic mass 8 cm	Solid mass 9 cm × 6 cm × 6 cm	Cystic mass 11 cm	Cystic mass 9 cm × 9 cm	5 cm × 4 cm
Pathology	Teratoma	NA	Endodermal sinus tumor associated with teratoma	Benign cystic teratoma	Benign teratoma	Benign cystic teratoma	Benign teratoma	Dermoid cyst	Benign cystic teratoma	Benign teratoma
Treatment	Local excision, recurrence, re-excision with chemotherapy	NA	Whipple's operation with chemotherapy	Extirpation with CBD	Extirpation	Extirpation with CBD, Roux-en-Y, Choledocho-jejunostomy	Extirpation	Excision of the tumor	Extirpation leaving the outer cyst wall in situ (Lilly technique), hepatico-duodenostomy	Extirpation
Prognosis	Asymptomatic after 5 yr	Death	Death	Asymptomatic after 4 yr	Asymptomatic after 2 yr	NA	Asymptomatic after 5 yr	Asymptomatic after 33 mo	Asymptomatic after 2 yr	Asymptomatic after 6 mo

CBD: Common bile duct; HL: Hepatoduodenal ligament; NA: Not available.

in an adult female patient examined for cholelithiasis-related abdominal pain.

CASE REPORT

A 27-year-old female presented with cholelithiasis-related pain. There was no history of jaundice, and the past medical history was unremarkable. Physical examination failed to detect the presence of an abdominal mass, and routine laboratory tests were normal. Abdominal ultrasonography revealed cholelithiasis and a mass adjacent to the hepatic hilum. Computed tomography (CT) and magnetic resonance imaging revealed a heterogeneous mass of 5 cm × 4 cm comprised of fat tissue and irregular calcifications located in the hepatoduodenal ligament at the posterior-superior aspect of the head of the pancreas (Figure 1).

Following patient consent, a laparotomy was performed. A Kocher maneuver with extensive mobilization of the duodenum exposed an encapsulated lesion. It was dissected and resected, and the multiple small vessels from the hepatic pedicle to the lesion were divided. There was no invasion of adjacent organs, vessels or the common bile duct (Figures 2 and 3). A cholecystectomy was performed and the intraoperative cholangiogram did not show abnormalities. The postoperative course was uneventful, and the patient was discharged after four days. The patient remains asymptomatic after six months. Histopathology confirmed that the mass was a mature teratoma. Microscopic examination revealed the presence of a cystic wall with cutaneous annexes and a mature neural area with glial fibrillary acidic protein immunoreactivity (Figure 4).

DISCUSSION

Teratomas are composed of structures derived from the three germ layers, namely the ectoderm, mesoderm and endoderm. Most mature teratomas are benign, but can undergo a malignant change in one of their elements[6]. Although plain abdominal radiographs show calcification in most (60%) extra-gonadal teratomas, either in the wall of the cyst

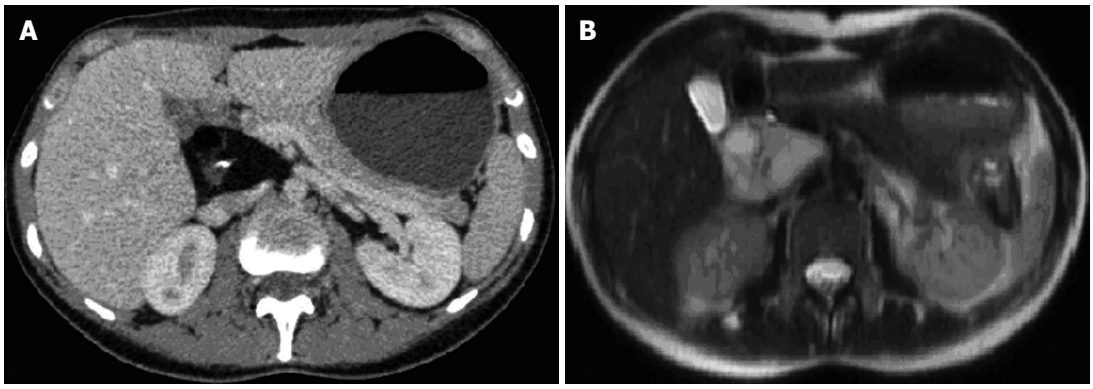

Figure 1 Cross-sectional imaging. A hepatoduodenal heterogeneous mass was revealed by A: Computed tomography; B: Magnetic resonance imaging.

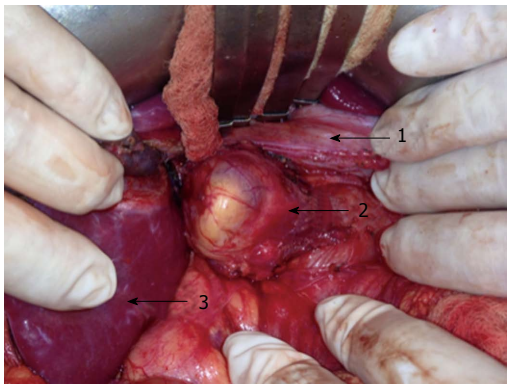

Figure 2 Operative finding. A laparotomy revealed an encapsulated lesion without invasion to adjacent organs or vessels (1: Common bile duct; 2: Teratoma; 3: Right lobe of the liver).

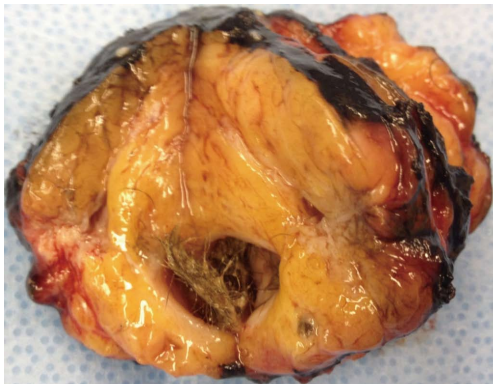

Figure 3 Tumor appearance. The resected heterogeneous lesion was composed of fat tissue, calcifications and hair.

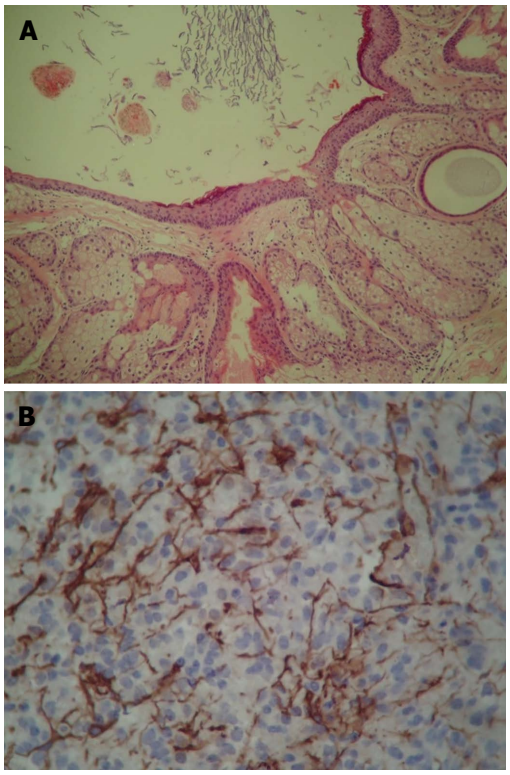

Figure 4 Histopathology of the tumor. Microscopic examination of the specimen revealed A: A cystic wall with cutaneous annexes; B: Glial fibrillary acidic protein immunoreactivity.

or in structures such as teeth or bones, CT is generally the most helpful imaging modality for diagnosis[7].

An extensive review of the literature identified nine reported cases of hepatoduodenal teratoma[2-10]. Six of the described cases were in children[2-5,8,10], and the oldest patient identified was 38 years old at the time of diagnosis[7]. A small gender difference is evident, as the lesions were more often described in women[5,6,9,10]. Clinical manifestations were variable, including jaundice[2,4,10], portal hypertension[3,6] and a palpable abdominal mass[7,8,10]. Some patients demonstrated elevated levels of serum alpha-fetoprotein, carcinoembryonic antigen and carbohydrate antigen 19-9, but these do not appear to be clinically useful[7]. The majority of cases reported tumors with benign pathology features, except for one case with an endodermal sinus tumor[4], and two cases that did not provide described pathology report details[2,3]. All patients underwent surgical resection, and two patients received chemotherapy[2,4], with only one incidence of recurrence[2]. Since a definitive diagnosis is only achieved following histologic examination of the cyst, surgical resection remains the primary treatment with an excellent prognosis[7]. In conclusion, this is the first reported asymptomatic case, to our knowledge, of hepatoduodenal ligament teratoma,

indicating that teratomas should not be ruled out in cases of abdominal incidentaloma.

COMMENTS

Case characteristics

The patient was asymptomatic.

Clinical diagnosis

The patient was diagnosed with abdominal incidentaloma uncovered during investigation of cholelithiasis-related abdominal pain.

Differential diagnosis

Benign and malignant abdominal tumors were alternative diagnoses.

Imaging diagnosis

A heterogeneous mass of 5 cm × 4 cm with fat tissue and irregular calcifications was located in the posterior-superior aspect of the head of the pancreas, into the hepatoduodenal ligament.

Pathological diagnosis

Analysis by microscopy revealed a mature teratoma cystic wall with cutaneous annexes and glial fibrillary acidic protein staining of a mature neural area, findings that are consistent with a teratoma.

Treatment

The patient was treated by surgical resection of the tumor.

Related reports

A hepatoduodenal teratoma is a rare occurrence and, to the best of the authors' knowledge, this is the 10th reported case and the 1st asymptomatic reported case.

Term explanation

Hepatoduodenal ligament teratoma refers to a neoplasm that is comprised of mixed dermal elements derived from the three germ cell layers and located at the portion of the lesser omentum extending between the porta hepatis of the liver and superior part of the duodenum. Computer tomography is a technology that uses computer-processed X-rays to produce cross-sectional imaging of the human body. Abdominal incidentaloma has been defined as an intraabdominal tumor found in a patient without symptoms, usually during evaluation of unrelated diseases or screening programs. Cholelithiasis is defined by the presence/formation of stones within the biliary tract, most commonly the gallbladder.

Experiences and lessons

Teratomas must be included on differential diagnosis of all abdominal incidentalomas.

Peer review

This case report provides a description of a rare disease that may be underdiagnosed due to a low index of suspicion. The pathological, radiological and surgical findings are well documented.

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CASE REPORT

Single-incision laparoscopic cecectomy for low-grade appendiceal mucinous neoplasm after laparoscopic rectectomy

Shiki Fujino, Norikatsu Miyoshi, Shingo Noura, Tatsushi Shingai, Yasuhiko Tomita, Masayuki Ohue, Masahiko Yano

Shiki Fujino, Norikatsu Miyoshi, Shingo Noura, Masayuki Ohue, Masahiko Yano, Departments of Surgery, Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka-city, 558-8585 Osaka, Japan
Tatsushi Shingai, Departments of Surgery, Saiseikai Senri Hospital, Suita-city, 590-0072 Osaka, Japan
Yasuhiko Tomita, Departments of Pathology, Osaka Medical Center for Cancer and Cardiovascular Diseases, Higashinari-Ku, Osaka-city, 558-8585 Osaka, Japan
Author contributions: Fujino S and Miyoshi N designed the report; Fujino S, Miyoshi N, Noura S, Shingai T and Ohue M were attending doctors for the patient; Tomita Y performed pathological examinations; Miyoshi N, Ohue M and Yano M organized the report; and Fujino S wrote paper.
Correspondence to: Norikatsu Miyoshi, MD, PhD, Department of Surgery, Osaka Medical Center for Cancer and Cardiovascular Diseases, 1-3-3 Nakamichi, Higashinari-Ku, Osaka-city, 558-8585 Osaka, Japan. miyosi-no@mc.pref.osaka.jp
Telephone: +81-6-60721181 Fax: +81-6-69818055
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Abstract

In this case report, we discuss single-incision laparoscopic cecectomy for low-grade appendiceal neoplasm after laparoscopic anterior resection for rectal cancer. The optimal surgical therapy for low-grade appendiceal neoplasm is controversial; currently, the options include appendectomy, cecectomy, right hemicolectomy, and open or laparoscopic surgery. Due to the risk of pseudomyxoma peritonei, complete resection without rupture is necessary. We have encountered 5 cases of low-grade appendiceal neoplasm and all 5 patients had no lymph node metastasis. We chose the appendectomy or cecectomy without lymph node dissection if preoperative imaging studies did not suspect malignancy. In the present case, we performed cecectomy without lymph node dissection by single-incision laparoscopic surgery (SILS), which is reported to be a reduced port surgery associated with decreased invasiveness and patient stress compared with conventional laparoscopic surgery. We are confident that SILS is a feasible alternative to traditional surgical procedures for borderline tumors, such as low-grade appendiceal neoplasms.

Key words: Single-incision laparoscopic surgery; Low-grade appendiceal mucinous neoplasm; Mucocele; Reduced port surgery

Core tip: The optimal surgical therapy for low-grade appendiceal neoplasm is controversial. Due to the risk of pseudomyxoma peritonei, complete resection without rupture is necessary. We performed single-incision laparoscopic surgery (SILS), which is reported to be a reduced port surgery associated with decreased invasiveness and patient stress compared with conventional laparoscopic surgery. We are confident that SILS is a feasible alternative to traditional surgical procedures for borderline tumors, such as low-grade appendiceal neoplasms.

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INTRODUCTION

Appendiceal mucocele is an uncommon pathology of the

appendix (0.08%-0.15% of all appendectomies) that is characterized by the accumulation of mucus in the appendiceal lumen[1,2]. The term mucocele, includes cystadenoma and low-grade appendiceal neoplasm, and is the same as the World Health Organization (WHO)'s classification of low-grade appendiceal neoplasm. Several optimal surgical methods are reported but are still controversial. Complete resection without rupture is definitely necessary because the dissemination of neoplastic cells and mucus in the abdominal cavity, which is often be caused by appendiceal perforation, clinically results in pseudomyxoma peritonei in 10%-15% of cases[3]. Therefore, low-grade appendiceal neoplasms are classified into carcinoma groups in the WHO's classification. In several reports, the surgical procedures used vary from simple appendectomy to right hemicolectomy[4]. Here, to identify the optimal surgical method to treat appendiceal mucocele, we report the case of a 49-year-old woman with an appendiceal lesion that was laparoscopically resected by a single incision and summarize other cases that involved surgical resections.

CASE REPORT

A 49-year-old woman underwent laparoscopic anterior resection for rectal cancer at Osaka Medical Center for Cancer and Cardiovascular Diseases in February 2009. During routine postoperative care, a mucus-filled lesion in the appendix was detected by computed tomography (CT). The patient's past medical history was not remarkable, except for the rectal cancer. Upon physical examination, there were no remarkable findings. Laboratory tests were within normal ranges. CT revealed a 55 mm × 25 mm tumor that presented as a blind-ended, tubular-shaped, fluid-filled structure in the cecum (Figure 1). Colonoscopy showed that the lesion was covered by normal colonic mucosa in the closed appendix. A colonoscopic biopsy revealed normal mucosa (Figure 2). The lesion was thought to be an appendiceal mucocele of the appendix, and single-incision laparoscopic surgery (SILS) was performed. The surgical choice was made because ultrasound examination showed a movable appendix including the surrounding intestine and no adhesion around the umbilical portion, which had an old scar from the primary operation. Under general anesthesia, the operation started with a trans-umbilical, 2.5 cm-diameter incision (SILS port). A Lap Protector (Hakko Co. Ltd., Nagano, Japan) was folded and the bottom half was inserted into the abdomen through the umbilical incision. The EZ Access (Hakko) was adjusted, and three devices were introduced through it: a flexible laparoscope (Olympus, Tokyo, Japan) and two operating forceps. The pneumoperitoneum was set at 10 mmHg. A smooth and mucus-filled lesion of the appendix was found and there were no ascites or peritoneal nodules indicating malignancy (Figure 3). To excise the tumor without rupture, we cut the peritoneum around the cecum and mobilized it without touching the tumor. After pulling the cecum with the tumor through the SILS port, a cecectomy which included the swollen appendix was performed using a linear stapler (Endo GIA universal; Covidien, Mansfield, MA, United States). The resected bowel contained the appendix (8 cm) and cecum (1 cm). The total operating time was 57 min, and the blood loss was minimal. Histological examination showed low grade epithelial dysplasia, a feature diagnostic of a low-grade appendiceal mucinous neoplasm (Figure 4). Surgical margin was negative and no lymph node metastasis was discovered. The patient recovered without any complications, and was discharged on postoperative day 6. She returned to work, and she is now doing well without any complaint postoperatively.

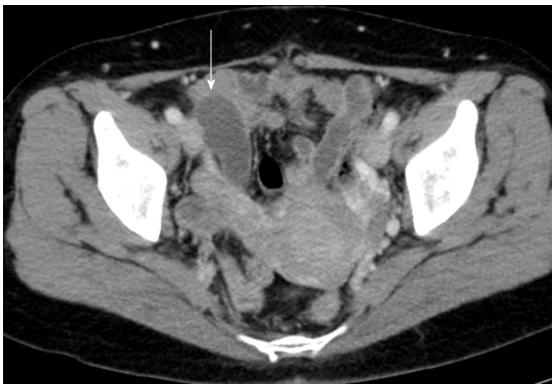

Figure 1 Computed tomography. The arrow shows a 55 mm × 25 mm, low-density and no-contrast lesion at the appendix.

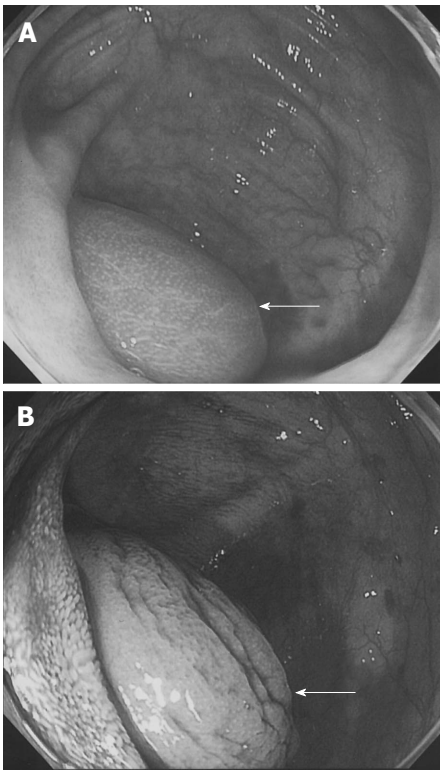

Figure 2 Colonoscopy. A: Normal image; B: Indigo carmine-stained image. There was an inflated lesion covered with normal mucosa in the appendix, suggesting a tumor under the cecal mucosa (arrows).

DISCUSSION

Appendiceal mucocele itself does not have typical clini-

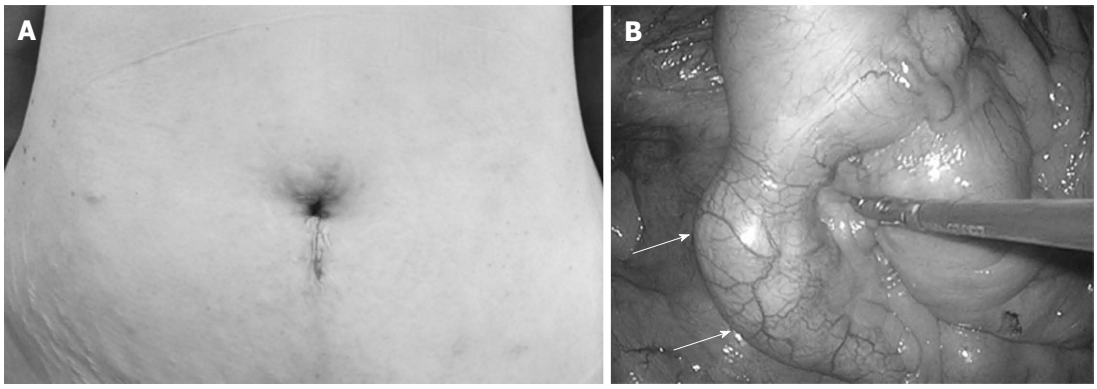

Figure 3 Photograph of the operation. A: A 2.5 cm-diameter incision was in the navel; B: The swollen appendix (arrows) and cecum were mobilized by non-touch technique.

Table 1 Six cases of mucocele of appendix in our hospital

Case	Age (yr) /sex	Chief complaint	Tumor size (mm)	Pathological findings	Operative procedures (lymph node dissection[1])	Bleeding (mL)	Operation time (min)	Time after surgery (mo)	Recurrence/ survival
1	49/F	None	55 × 25	Low-grade appendiceal mucinous neoplasm	Single incision laparoscopic cecectomy	5	57	6	None/alive
2	61/M	Right lower abdominal pain	90 × 40	Low-grade appendiceal mucinous neoplasm	Laparoscopy-assisted ileocecal resection (D3)	30	251	14	None/alive
3	61/F	None	30 × 15	Low-grade appendiceal mucinous neoplasm	Open appendectomy	70	140	25	None/alive
4	81/F	None	150 × 40	Low-grade appendiceal mucinous neoplasm	Open ileocecal resection (D3)	70	125	29	None/alive
5	69/F	None	46 × 27	Low-grade appendiceal mucinous neoplasm	Open appendectomy	50	134	32	None/alive
6	51/F	Right hypochondrial pain	30 × 30	Mucinous cystadenoma	Laparoscopy-assisted ileocecal resection (D1)	65	280	74	None/alive

[1]The defined lymph node dissection was performed according to the JSCCR guideline[12].

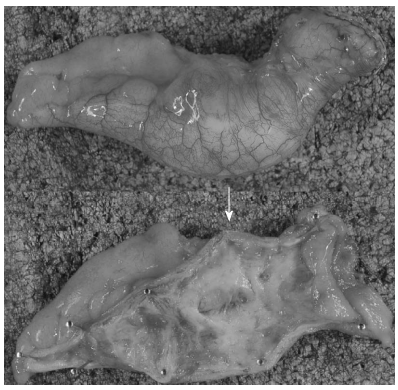

Figure 4 Macroscopic image of the removed specimen. The appendix was about 8 cm long and swollen and exhibited a fibrotic wall (arrow; the mucus in the lumen was removed).

cal features; more than two-thirds of patients have their appendiceal mucocele removed based on incidental findings, as was the case for our patient[4]. Surgical resection without rupture is necessary, and laparoscopic appendectomy is often used in accordance with the accepted treatment of mucocele[2]. Based on the tumor characteristics, including the location and size, surgical management should differ. Using either an open or a minimally invasive technique still depends on the situation and the preference and experience of the surgeon. Although an open procedure is still recommended in certain appendiceal cases, especially for those with suspected malignancy[5], the laparoscopic technique has been described and recommended as the first choice for treating this disease, rather than conventional open laparotomy. This recommendation is due to the method's ability to provide useful information regarding the entire abdominal cavity, short recovery post-surgery, and a minimized risk of seeding the tumor during laparoscopic manipulation[6]. Furthermore, SILS has been often applied in several fields, and in colectomies[7-11]. Recent reports show single incision approach through the umbilicus that is called SILS port or grove method. The narrow working space for surgical manipulation for surgical manipulation presents a technical difficulty; however, in certain cases, it is still easy and safe to convert to the conventional laparoscopic surgery with multiple ports or open laparotomy. Laparoscopic surgery has the added benefit of the laparoscope magnifying the surgical field, keeping the surgical space wide by aeroperitoneum. Additionally, in our case, the SILS operation was started but could have been changed to any operation, such as conventional laparoscopic surgery or open surgery, if we had encountered any difficulties (*e.g.,* bleeding, injury to other organs, or difficult surgical manipulation). In a case using the McBurney method, a tra-

ditional approach for treating an appendiceal locus with a minimized incision, it would be difficult to change the surgical procedure, leaving only the option of increasing the size of the incision.

We have encountered 6 cases of low-grade appendiceal neoplasm (Table 1); three cases were treated by open surgery for the reason described above, whereas the other 3 cases underwent laparoscopic surgery. In these cases, we chose the appendectomy or cecectomy without lymph node dissection if preoperative imaging studies did not suspect malignancy. In the present case, CT revealed no involvement of the mesoappendix or local lymph node metastasis. All 6 patients are doing well, without recurrence for 6-74 mo after surgery.

It is thought that minimally invasive procedures, including SILS appendectomy and cecectomy, for low-grade neoplasm, such as mucocele will be considered as the primary treatment choice in several years. The potential benefits include the superior cosmetic results, reduced postoperative pain, faster recovery, and shorter hospital stays.

COMMENTS

Case characteristics

A 49-year-old woman had no symptom and the disease was detected by computed tomography (CT) during the follow-up course of rectal cancer.

Clinical diagnosis

Physical examination shows no remarkable findings.

Differential diagnosis

Appendiceal cancer, carcinoid and cystadenoma.

Laboratory diagnosis

All laboratory tests were within normal ranges.

Imaging diagnosis

CT revealed a 55 mm × 25 mm tumor, which presented as a blind-ended, tubular-shaped, fluid-filled structure in the cecum and colonoscopy showed the lesion covered by normal colon mucosa in the closed appendix.

Pathological diagnosis

Histological examination showed low-grade epithelial dysplasia, a feature diagnostic of a low-grade appendiceal mucinous neoplasm.

Treatment

The tumor was resected by single-incision laparoscopic surgery (SILS).

Related reports

SILS has been often applied in several fields, and in colectomies.

Term explanation

SILS is used as a reduced port surgery compared to conventional laparoscopic surgery (mostly 5 ports).

Experiences and lessons

This case report shows that SILS is considered as the primary treatment choice for low-grade neoplasm, such as mucocele.

Peer review

Report is well written. This is an interesting well-described study. The review is well conducted. It addresses an interesting clinical area in an application that has not received a great deal of attention.

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World Journal of Gastrointestinal Surgery (*World J Gastrointest Surg*, *WJGS*, online ISSN 1948-9366, DOI: 10.4240) 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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World Journal of Gastrointestinal Surgery
Room 903, Building D, Ocean International Center,
No. 62 Dongsihuan Zhonglu, Chaoyang District,
Beijing 100025, China
Telephone: +86-10-85381891
Fax: +86-10-85381893
E-mail: editorialoffice@wjgnet.com
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MINIREVIEWS

Sentinel node navigation surgery in gastric cancer: Current status

Dimitrios Symeonidis, George Koukoulis, Konstantinos Tepetes

Dimitrios Symeonidis, George Koukoulis, Konstantinos Tepetes, Department of Surgery, University Hospital of Larissa, 41110 Larissa, Greece
Author contributions: Symeonidis D and Tepetes K contributed equally to this work; Symeonidis D, Koukoulis G and Tepetes K performed the literature review; Symeonidis D, Koukoulis G and Tepetes K analyzed the data; Symeonidis D and Koukoulis G drafted the article; Symeonidis D and Tepetes K critically revised the final form of the article; all authors have read and accepted the final version.
Correspondence to: Dimitrios Symeonidis, MD, PhD, General Surgeon, Department of Surgery, University Hospital of Larissa, Mezourlo, 41110 Larissa, Greece. simeonid@hotmail.com
Telephone: +30-235-1020730 Fax: +30-235-1020741
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Abstract

The theory behind using sentinel node mapping and biopsy in gastric cancer surgery, the so-called sentinel node navigation surgery, is to limit the extent of surgical tissue dissection around the affected organ and subsequently the accompanied morbidity. However, obstacles on the clinical correspondence of sentinel node navigation surgery in everyday practice have occasionally alleviated researchers' interest on the topic. Only recently with the widespread use of minimally invasive surgical techniques, *i.e.*, laparoscopic gastric cancer resections, surgical community's interest on the topic have been unavoidably reflated. Double tracer methods appear superior compared to single tracer techniques. Ongoing research is now focused on the invention of new lymph node detection methods utilizing sophisticated technology such as infrared ray endoscopy, florescence imaging and near-infrared technology. Despite its notable limitations, hematoxylin/eosin is still the mainstay staining for assessing the metastatic status of an identified lymph node. An intra-operatively verified metastatic sentinel lymph node will dictate the need for further conventional lymph node dissection. Thus, laparoscopic resection of the gastric primary tumor combined with the appropriate lymph node dissection as determined by the process of sentinel lymph node status characterization represents an option for early gastric cancer. Patients with T3 or more advanced disease should still be managed conventionally with resection plus standard lymph node dissection.

Key words: Sentinel node; Gastric cancer; Minimally invasive surgery

Core tip: Sentinel node navigation surgery can change the current surgical treatment of gastric cancer expanding the indications of minimally invasive surgical options such laparoscopic techniques. However, the complex lymphatic drainage of the stomach and the ubiquitous fear of skip metastasis make the selection of patients extremely important. Currently, laparoscopic resection of the tumor from the stomach with lymph node dissection navigated by sentinel lymph node identification represents an option only for early gastric cancer patients. Unfortunately, patients with T3 or more advanced disease should still be managed conventionally with resection plus lymph node dissection.

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INTRODUCTION

Melanoma was the first malignancy that the concept of sentinel node found application for. However, the indications and uses of this attractive procedure have been

Table 1 Lymph node stations of the stomach

Lymph node stations	Anatomic location	Group	Lymphadenectomy
1	Right cardia	N1	D1
2	Left cardia		
3	Lesser curvature		
4	Greater curvature		
4a	Short gastric vessels		
4b	Left gastroepiploic vessels		
4c	Right gastroepiploic vessels		
5	Suprapyloric		
6	Infrapyloric		
7	Left gastric artery	N2	D2
8	Common hepatic artery		(N1 + N2)
9	Celiac trunk		
10	Splenic hilus		
11	Splenic artery		
12	Hepatoduodenal ligament	N3	D3
13	Posterior surface of the head of the pancreas		(N1 + N2 + N3)
14	Root of the mesentery		
14A	Superior mesenteric artery		
14V	Superior mesenteric vein		
15	Para-aortic	N4	D4
16	Paracolic		(N1 +N2 + N3 +N4)

recently expanded in many fields of surgical oncology such as breast cancer, thyroid cancer, gynecological malignancies, colorectal and, recently, gastric cancer. Sentinel node mapping and biopsy in gastric cancer surgery, the so-called sentinel node navigation surgery, aimed to limit the extent of surgical tissue dissection around the affected organ. By convection, any unnecessary dissection, *i.e.*, dissection of virgin-tumor free areas unrelentingly increase morbidity without always respective survival benefits. Within this context, sentinel lymph node navigation surgery could, at least theoretically, facilitate precise and sufficient resections. However, in some instances, insurmountable obstacles on the clinical correspondence of the sentinel node navigation surgery concept in everyday practice have occasionally alleviated researchers' interest on the topic. Only recently with the widespread use of minimally invasive surgical techniques, *i.e.*, laparoscopic gastric cancer resections, surgical community's interest on the topic have been unavoidably reflated.

Nowadays, the following questions regarding the utility of sentinel lymph node mapping and biopsy in clinical practice need to be precisely answered: (1) which are the available techniques for sentinel lymph node mapping? (2) which is the best way to administer the tracer? (3) which is the optimal method to verify the presence of metastasis in the identified sentinel lymph node? (4) which is the gastric cancer patient subgroup suitable for sentinel node mapping and biopsy? and (5) which are the available options for primary tumor control?

LYMPH NODE STATIONS

In 1973, the Japanese Research Society for the study of gastric cancer published a manual standardizing lymph node dissections in gastric cancer by recognizing 16 distinct anatomic lymph node stations. Further grouping of these lymph node stations took place, *i.e.*, N1, N2, N3 and N4 to achieve correspondence with respective lymph node dissection extents, *i.e.*, D1, D2, D3 and D4[1] (Table 1).

LYMPHATIC STREAM IN GASTRIC CANCER

Trying to decipher the lymph route out of a malignant lesion within the stomach, a few anatomical considerations are of paramount importance. Briefly, from the anatomic viewpoint, lymph from the gastric wall is drained *via* lymphatic vessels which form a complex sub-peritoneal plexus surrounding the stomach both anteriorly and posteriorly. Depending on the location, the lymph of the upper left part of the stomach is routed to the left gastric and pericardial nodes. Lymph originated from the pylorus is filtered through the supra-pyloric and the right supra-pancreatic nodes. The region of the fundus filters lymph along the gastrosplenic ligament and splits with lymph flowing to the left supra-pancreatic nodes and the left gastroepiploic nodes via the splenic nodes. Lymph from the pyloric and the distal portion of the corpus collects in the right gastroepiploic nodes and then flows to the sub-pyloric nodes. From all regions, the lymph stream continues to the celiac nodes[1].

When dealing with malignant lesions, clarifying the lymphatic drainage pattern is crucial for performing proper lymph node dissections especially from sites "susceptible" to metastasis. However, as briefly discussed above, the lymphatic stream of the stomach appears particularly complex and multidirectional and in many occasions ill-investigated. Certainly, having even a rough idea of how lymph drains out of the stomach will render upper gastrointestinal (GI) surgeons capable of performing effective and, up to a point, targeted lymph node dissections[2]. Nevertheless, tumors at any location within the stomach have a non-negligible chance of atypical metastasis. Tumors located longitudinally or circumferentially in the lower part of the lesser curvature appear to be of higher chance for an atypical metastasis compared to other locations[3]. It becomes obvious that the efficiency of the sentinel node concept is compromised when dealing with tumors at these locations as an unacceptable increase of false-negative results should be anticipated. Studies raise the incidence of skip metastasis up to 29%[3]. Apart from the location, the degree of tumor differentiation has been inconsistently implicated as to increase skip metastasis potential[4].

Generally, the severity of gastric malignancy, *i.e.*, tumor size and depth of invasion is positively correlated with the lymph node metastasis rate[5]. In addition, studies using a retrospective methodology and including patients with sole lymph node involvement have shown that the majority of sentinel lymph nodes are located in the regional area at a close proximity to the tumor[6]. It is recommended, that if nodes are not identified in the usual locations, then No. 7, 8 and 9 lymph node stations should

be investigated as well[7].

WHICH ARE THE AVAILABLE TECHNIQUES FOR SENTINEL LYMPH NODE MAPPING?

Numerous methods in order to increase the usefulness and effectiveness of sentinel node mapping have been proposed to date[8-18]. The clinical evaluation and assessment of these modalities within studies have led to a breathtaking progress in the field rendering sentinel lymph node tracking techniques familiar to surgeons. However, the main problem is on the logistics of each technique. Identifying sentinel lymph nodes intraoperatively in a timely and effective pattern is by definition a challenging process. The tracer used should meet the minimum requirements of (1) non-toxicity; (2) easy availability; and (3) cost-effectiveness. Ideally, the tracer should accumulate within the sentinel nodes for a period of time long enough to render detection possible. Furthermore, it should be readily identifiable without the need for using sophisticated and unfamiliar to surgeons equipment. As no single tracer to date incorporates all of the above characteristics, the quest for the optimal compound seems to be ongoing.

Dye-based and radioisotope-based techniques have been the mainstay for lymph node detection so far[8-18]. Dye agents include isosulfan blue, patent blue and indocyanine green (currently, the most commonly used dye). On the other hand, technetium 99 m represents the most commonly used radioisotope. The use of infrared ray beam *via* endoscopy can, at least theoretically, facilitate the visualization of the used tracer increasing the accuracy of the detection[19,20]. Similarly, fluorescence imaging is another available adjunct which is suggested to increase the detection rates of traditional dye agents such as indocyanine green[21,22].

However, sentinel lymph node mapping of the GI tract by using available techniques is often limited by various factors. The multidirectional lymph drainage patterns and, practically, the inability to image surgical anatomy in real time in relation to the used tracer can compromise the whole process. In this direction, the use of invisible near-infrared light might have the answers. In this technique, an intraoperative near-infrared fluorescence imaging system that simultaneously displays surgical anatomy is utilized. Near-infrared fluorescence images of the surgical field are generated to illustrate intra-parenchymally injected near-infrared fluorescent quantum dots. The final result is the visualization of the draining lymphatic tree and of the nodes as well. The technique promises dissection under real time vision[23].

Generally, there is a trend for combining tracers in order to increase the detection accuracy. Double tracer techniques (dye plus isotope), almost consistently, seem to increase the rate of sentinel lymph node identification[24-30], however there are indeed studies which question this finding[31,32]. In addition, pre-clinical research is in progress for inventing the optimal tracer and visualization system. It seems pretty likely at this point that research will overcome the traditional dye-based techniques and it will open new perspectives in sentinel node mapping.

WHICH IS THE BEST WAY TO ADMINISTER THE TRACER?

Traditionally, endoscopy has been used in order to inject the tracer sub-mucosally around the primary tumor. The administration was carried out either preoperatively in case of isotopes and intra-operatively in case where a dye was the used tracer. Sub-serosal injection of dye has been tested, as well, without however notably superior results compared to the standard sub-mucosal injection[33,34].

WHICH IS THE OPTIMAL METHOD TO VERIFY THE PRESENCE OF METASTASIS IN THE IDENTIFIED SENTINEL LYMPH NODE?

The traditional practice of sentinel node biopsy for gastric cancer has been largely based on the use of hematoxylin and eosin (HE) staining for histological examination of frozen section slices. As the accuracy of intraoperative diagnosis of metastasis based on Hematoxylin/Eosin staining ranges significantly in the literature (74%-100%), the issue of whether this certain staining is efficient as a standalone modality remains controversial[35-42]. Because of this controversy, efforts have been directed towards identifying more reliable histopathological methods. Immunohistochemical staining and reverse transcription-polymerase chain reaction have been both tested in this direction yielding a significantly higher metastasis detection rate than the standard staining technique.

Having this comparative principles, Arigami *et al*[43] reported the following metastatic detection rates: 8.2% for hematoxylin/eosin, 13.1% for immunohistological staining and 36.1% for reverse transcriptase polymerase chain reaction. These major differences in the detection rates can be explained by the fact that the more sensitive and sophisticated the technique used is, the more likely the detection of micrometastasis is. As the prognostic significance of micrometastasis in gastric cancer has yet to be confirmed, the aforementioned differences require careful interpretation. However, whatever the natural history of gastric cancer micrometastasis is, the widespread use of these sophisticated techniques is quite problematic. Firstly, the penetrability of these techniques among institutions is still poor because of the unavailability of the technical equipment. Secondly, due to the logistics, obtaining a definite result in a timely manner, *i.e.*, before the end of the procedure is still mainly futile. Thus, despite its limitations hematoxylin/eosin staining remains the standard method for examining the detected sentinel

lymph nodes.

WHICH IS THE GASTRIC CANCER PATIENT SUBGROUP SUITABLE FOR SENTINEL NODE MAPPING AND BIOPSY?

Although attractive as a concept, sentinel node biopsy is indicated only for a strict subgroup of gastric cancer patients. Depending on the geographic distribution of each study's institution, eligibility ranges from 3% to 50% of all gastric cancer patient population[44-47]. Eastern studies have included clinically node-negative T1 and T2 patients[48-51]. On the other hand, studies originating from Western institutions have included T3 tumors as well[52]. The complex lymphatic drainage of the stomach and the ubiquitous fear of skip metastasis make the selection of patients extremely important. Fortunately, skip metastasis is encountered usually within the same group of nodes as the identified sentinel lymph node. An approach of removing the entire group of nodes rather than focusing on the identified represents the safest choice[28,53].

WHICH ARE THE AVAILABLE OPTIONS FOR PRIMARY TUMOR CONTROL?

The "less invasive" theory behind sentinel lymph node biopsy has its benefits based on the limitation of morbidity caused by unnecessary dissection. At least theoretically, combining the method with minimally invasive surgical procedures such as laparoscopic surgery sounds attractive. Studies have already tested the sentinel node concept for both open, laparoscopic gastrectomies and even natural orifice transluminal endoscopic surgery[54-56]. Generally, there is no consensus regarding the optimal primary tumor control during sentinel node navigation surgery[57]. Endoscopic resection may be safely applied to small mucosal cancers, but other surgical options such as minimally invasive function-preserving resection of the stomach should be employed for larger lesions, given their tendency for diffuse invasion[57].

CONCLUSION

In conclusion, sentinel node navigation surgery can change the current surgical treatment of gastric cancer. The applications and ultimately the indications of minimally invasive surgical options such as laparoscopic techniques can be significantly expanded and boosted with the generalized use of sentinel node navigation surgery. Currently, the double tracer method (indocyanine green and radio-isotope tracers) appears to be the method of choice due to its increased efficacy in detecting nodes compared with single tracer techniques. Research is focused on the invention of new lymph node detecting methods utilizing infrared ray endoscopy, florescence imaging and near-infrared technology. Despite its limitations and given that the use of more sophisticated techniques is still in a developing stage, hematoxylin/eosin remains the standard staining for assessing the metastatic status of a detected lymph node.

An intraoperatively detected metastasis of a sentinel lymph node is the factor that will determine whether a patient will proceed with conventional lymph node dissection or not. Laparoscopic resection of the tumor from the stomach with lymph node dissection navigated by sentinel lymph node identification represents an option only for early gastric cancer patients. Unfortunately, patients with T3 or more advanced disease should still be managed conventionally with resection plus lymph node dissection.

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RETROSPECTIVE STUDY

Pathological factors affecting gastric adenocarcinoma survival in a Caribbean population from 2000-2010

Patrick O Roberts, Joseph Plummer, Pierre-Anthony Leake, Shane Scott, Tamara G de Souza, Ayesha Johnson, Tracey N Gibson, Barrie Hanchard, Marvin Reid

Patrick O Roberts, Joseph Plummer, Pierre-Anthony Leake, Shane Scott, Tamara G de Souza, The Department of Surgery, Radiology, Anaesthesia and Intensive Care, The University of the West Indies, Jamaica 999172, West Indies
Ayesha Johnson, College of Public Health, University of South Florida, Tampa, FL 33620-9951, United States
Tracey N Gibson, Barrie Hanchard, The Department of Pathology, The University of the West Indies, Jamaica 999172, West Indies
Marvin Reid, Tropical Medicine Research Institute, The University of the West Indies, Jamaica 999172, West Indies
Author contributions: Roberts PO designed the study, analysed data, critically revised and approved the final version of the study; Johnson A statistically analysed data, contributed to drafting and the final approval of the study version for publication; Leake PA assisted in designing the study and critical revision; Plummer J critically revised the study; de Souza TG interpreted data, drafted, revised and approved the final manuscript; Reid M assisted in study design; Gibson TN and Hanchard B collected data and edited the final version; Scott S acquired data.
Correspondence to: Dr. Patrick O Roberts, The Department of Surgery, Radiology, Anaesthesia and Intensive Care, The University of the West Indies, Mona, Kingston 7, Jamaica, West Indies. paorro@yahoo.com
Telephone: +1-876-9271620 Fax: +1-876-9704302
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Abstract

AIM: To investigate pathological factors related to long term patient survival post surgical management of gastric adenocarcinoma in a Caribbean population.

METHODS: This is a retrospective, observational study of all patients treated surgically for gastric adenocarcinoma from January 1st 2000 to December 31st 2010 at The University Hospital of the West Indies, an urban Jamaican hospital. Pathological reports of all gastrectomy specimens post gastric cancer resection during the specified interval were accessed. Patients with a final diagnosis other than adenocarcinoma, as well as patients having undergone surgery at an external institution were excluded. The clinical records of the selected cohort were reviewed. The following variables were analysed; patient gender, patient age, the number of gastrectomies previous performed by the lead surgeon, the gross anatomical location and appearance of the tumour, the histological appearance of the tumour, infiltration of the tumour into stomach wall and surrounding structures, presence of *Helicobacter pylori* and the presence of gastritis. Patient status as dead *vs* alive was documented for the end of the interval. The effect of the aforementioned factors on patient survival were analysed using Logrank tests, Cox regression models, Ranksum tests, Kruskal-Wallis tests and Kaplan-Meier curves.

RESULTS: A total of 79 patients, 36 males and 43 females, were included. Their median age was 67 years (range 36-86 years). Median survival time from surgery was 70 mo with 40.5% of patients dying before the termination date of the study. Tumours ranged from 0.8 cm in size to encompassing the entire stomach specimen, with a median tumour size of 6 cm. The median number of nodes removed at surgery was 8 with a maximum of 28. The median number of positive lymph nodes found was 2, with a range of 0 to 22. Patients' median survival time was approximately 70 mo, with 40.5% of the patients in this cohort dying before the terminal date. An increase in the incidence of cardiac tumours was noted compared to the previous 10 year interval (7.9% to 9.1%). Patients who had serosal involvement of the tumour did have a significantly shorter survival than those who did not (P = 0.017). A significant increase in the hazard ratio (HR), 2.424, for patients with circumferential tumours was found (P = 0.044). *Via* Kaplan-Meier estimates, the presence of venous infiltration as well as involvement of the circumferential resection margin were found to be poor prog-

nostic markers, decreasing survival at 50 mo by 46.2% and 36.3% respectively. The increased HR for venous infiltration, 2.424, trended toward significant (P = 0.055) Age, size of tumour, number of positive nodes found and total number of lymph nodes removed were not useful predictors of survival. It is noted that the results were mostly negative, that is many tumour characteristics did not indicate any evidence of affecting patient survival. The current sample, with 30 observed events (deaths), would have about 30% power to detect a HR of 2.5.

CONCLUSION: This study mirrors pathological factors used for gastric cancer prognostication in other populations. As evaluation continues, a larger cohort will strengthen the significance of observed trends.

Key words: Gastric adenocarcinoma; Caribbean; Jamaica; Pathologic; Survival; Gastrectomy; Gastritis; *Helicobacter pylori*; Cardia; Circumferential resection margin

Core tip: This ten year retrospective analysis of pathologic factors affecting the survival of gastric cancer patients is the first ever to be done in a Caribbean population. Significant findings meriting publication include increasing incidence of proximal tumours and decreased survival with involvement of the circumferential resection margin. Among other factors also examined, are the impact of surgeon and pathologist training on patient survival. By describing the current state of gastric cancer management in this population, this study aspires to lay the foundation for further work enhancing gastric cancer care in this region.

Roberts PO, Plummer J, Leake PA, Scott S, de Souza TG, Johnson A, Gibson TN, Hanchard B, Reid M. Pathological factors affecting gastric adenocarcinoma survival in a Caribbean population from 2000-2010. *World J Gastrointest Surg* 2014; 6(6): 94-100 Available from: URL: http://www.wjgnet.com/1948-9366/full/v6/i6/94.htm DOI: http://dx.doi.org/10.4240/wjgs.v6.i6.94

INTRODUCTION

Gastric cancer is the fourth most common malignancy in men, and the fifth commonest in women diagnosed worldwide[1]. In Jamaica it is the seventh commonest cancer in men and the ninth most common in women[2]. Worldwide, gastric cancer is the third most frequent cause of cancer death in men and the fifth most common in women[1]. In Jamaica it is the fourth leading cause of cancer related death[3].

These figures prompt scrutiny and characterization of the Jamaican gastric cancer patient population. Accordingly, Plummer *et al*[4] had previously outlined age and sex related incidence, histological appearance, as well as tumour location in a surgically treated cohort of gastric adenocarcinoma patients in Jamaica from 1993-2002, and found that the antrum of the stomach was most often involved, with a trend toward increased incidence of more proximal tumours in the latter 5 years studied, and that lymph node metastases were common[4].

It was our aim to build on this base of information and to explore prognostication in this patient demographic. Our study seeks, for the first time in the Jamaican population, to describe the post-surgical survival rate of gastric adenocarcinoma patients and to elucidate related pathological factors.

MATERIALS AND METHODS

This retrospective, observational study summarizes the analyses conducted on patients diagnosed with gastric adenocarcinoma at the University Hospital of the West Indies (UHWI) from 2000 to 2010. Analysis was conducted using STATA 9. Approval was granted from the Ethics Committee of the hospital (file number ECP334, 12/13). This study was carried out in accordance with the Second International Helsinki Declaration[5].

All patients who were diagnosed with gastric cancer at UHWI during the period January 1st 2000 to December 31st 2010 were enrolled *via* review of pathology reports. UHWI is a type A teaching hospital and a referral centre, accepting the management of patients exceeding the resource capability of several smaller hospitals throughout Jamaica. These patients had all been seen at the General Surgery outpatient clinic, and subsequently undergone upper gastrointestinal endoscopy with biopsy proving gastric cancer. Other forms of gastric cancer besides adenocarcinoma were excluded. Patients with a final diagnosis of gastric adenocarcinoma, but who had undergone surgery at other institutions were excluded. This exclusion came as a matter of access to the clinical records of those patients. Demographically, the patients receiving definitive management at external institutions are not anticipated to greatly differ from the patient population investigated in this study. Of note, the population of Jamaica is predominantly Afro-Caribbean.

Survival data was analysed with the event being death and the time to death being defined as the time in months from surgery until the patient's death. Persons who did not die were censored at the date of their last visit or if confirmed to be alive, they were censored at December 31, 2011.

Logrank tests were conducted to determine whether the survival rate was different across various groupings within variables. Cox regression models were built to determine whether various pathological characteristics would be able to predict a person's risk of death. Rank-sum tests as well as Kruskal-Wallis tests of association were done to determine whether the relationships between clinicopathological factors and survival were different for persons who were dead as opposed to confirmed alive or censored prior to the end of the studied interval[6,7].

Table 1 Clinical characteristics

Characteristic		*n* (%)
Gender	Male	36 (45.6)
	Female	43 (54.4)
Number of previous gastrectomies	< 10	30 (38.0)
by surgeon	> 10	49 (62.0)
Patient status	Alive	7 (8.9)
	Censored	40 (50.6)
	Dead	32 (40.5)

RESULTS

The surgical notes and pathological reports of the 79 patients meeting the criteria of histologically identified gastric adenocarcinoma, and having had D1 gastrectomy at UHWI were reviewed. There were more females (54.4%) than males (Table 1). The median age of the patients was 67 years with a range of 36 to 86 years. Tumours ranged from 0.8 cm in size to encompassing the entire stomach specimen, with a median tumour size of 6 cm. The median number of nodes removed at surgery was 8 with a maximum of 28. Four specimens included 15 or more lymph nodes. Seventy-seven specimens were found to have nodal metastasis. The median number of positive lymph nodes found was 2, with a range of 0 to 22. Patients' median survival time was approximately 70 mo, with 40.5% of the patients in this cohort dying before the terminal date (Table 1). A total of 47 patients were censored, with 7 of those being censored at the end of the study, *i.e.*, confirmed to be still living as at December 31, 2011.

In this series, thirty-eight percent of the surgeries were performed by doctors who had performed less than 10 gastrectomies, while the other 62% were performed by surgeons who had performed 10 or more (Table 1) . Approximately a quarter (24.7%) of patients had tumours situated on the lesser curvature of the stomach while about half that number (11.7%) had tumours involving the greater curvature. The most common anatomical location was the antrum (54%), followed by the pylorus (37.7%). Fifteen point six percent of patients had tumours located on the anterior wall of the stomach, 24.7% on the posterior wall, and 16.9% were circumferential (Table 2).

Histologically, less than half of the patients had tumours that were diffuse, while a little more than half (57.4%) were intestinal. Most (43.2%) patients had low grade tumours compared to 32.4% having tumours of moderate grade and the remainder of high grade. More than half of the patients had ulcerative lesions. Few (5.7%) had tumours that were well differentiated, while the majority (50.9%) of patients had tumours that were moderately differentiated. Ninety-six percent of tumours were advanced with involvement of muscularis propria, subserosa and serosa. Forty-eight percent of the patients had venous infiltration by the adenocarcinoma, while 60% had tumours that exhibited perineural invasion. Approximately 20% of patient specimens had *Helicobacter pylori*. While few (3.8%) patients were found to have chronic active gastritis, about 40% of them had chronic gastritis and about 30% had chronic multifocal atrophic gastritis (Table 3).

Table 2 Tumour location *n* (%)

Location of tumour		*n* = 79
Lesser curvature	Uninvolved	60 (75.3)
	Involved	19 (24.7)
Greater curvature	Uninvolved	70 (88.3)
	Involved	9 (11.7)
Antrum	Uninvolved	35 (45.5)
	Involved	34 (54.5)
Pylorus	Uninvolved	49 (62.3)
	Involved	50 (37.7)
Body	Uninvolved	62 (79.2)
	Involved	17 (20.8)
Cardia	Uninvolved	71 (90.9)
	Involved	8 (9.1)
Fundus	Uninvolved	73 (92.2)
	Involved	6 (7.8)
Anterior wall	Uninvolved	66 (84.4)
	Involved	13 (15.6)
Posterior wall	Uninvolved	59 (75.3)
	Involved	20 (24.7)
Circumferential	Uninvolved	66 (83.1)
	Involved	13 (16.9)

There was a trend toward significance ($P = 0.0577$) in the lower survivorship of patients who had tumours of the gastric cardia *vs* those who did not. Patients who had a circumferential tumour had significantly worse survival times from those who did not have a circumferential tumour ($P = 0.0370$). There was also a near significant difference between patients with subserosal involvement *vs* those without ($P = 0.0731$). Patients who had serosal involvement of tumour did have a shorter survival than those who did not ($P = 0.017$) (Table 4). Patients who had venous infiltration also had shorter survival ($P = 0.055$) (Table 5). Differences for subserosal and serosal involvement could not be quantified as there were no deaths among patients who were negative. Differences in HRs were estimated for tumours of the gastric cardia, circumferential lesions and those with venous infiltration. Figure 1 show the survival curves for the aforementioned variables.

DISCUSSION

The Kaplan-Meier estimated 10-year survival rate of this cohort is 42.1%, with a 95% confidence interval of 24.4%-58.7%. This Kaplan-Meier estimate accounts for the varying risks within the population with respect to their clinicopathological factors. This is appropriate as we have noted statistically significant impact of certain parameters on patient survival. If it were assumed that each patient was at an equivalent risk for mortality following surgery the incidental survival rate would be 35%. The median survival time was about 70 mo. These statistics reflect patients' median follow up time and not a true median survival. Patients were followed for a total of

Table 3 Pathological characteristics

Gross appearance		Percentage
Configuration	Ulcerative	56.00
	Infiltrative	22.70
	Exophytic	21.30
	n	75
Gross location		
Proximal	Uninvolved	88.20
	Involved	11.80
	n	76
Distal	Uninvolved	84.20
	Involved	15.80
	n	76
Histological appearance		
Intestinal	No	42.60
	Yes	57.40
	n	68
Differentiation	Poor	43.40
	Moderate	50.90
	Well	5.70
	n	53
Grade	Low	43.20
	Moderate	32.40
	High	24.30
Maximum extent of invasion through stomach wall		
Mucosa	Involved	100.00
	n	78
Muscularis propria	Uninvolved	3.80
	Involved	96.20
	n	78
Sub–Serosa	Uninvolved	9.00
	Involved	91.00
	n	78
Serosa	Uninvolved	13.30
	Involved	86.70
Histological appearance		
Venous infiltration	Absent	51.90
	Present	48.10
	n	52
Perineural infiltration	Absent	40.00
	Present	60.00
	n	35
H. Pylori	Absent	80.50
	Present	19.50
	n	77
Chronic active gastritis	Absent	96.20
	Present	3.80
	n	78
Chronic gastritis	Absent	59.00
	Present	41.00
	n	78
Chronic multifocal Atrophic gastritis	Absent	70.50
	Present	29.50
	n	78

Table 4 Logrank test of survival functions

Variable	*P* value
Gender	0.9688
Number of gastrectomies previously performed	0.6725
Lesser curvature	0.9716
Greater curvature	0.7928
Antrum	0.2613
Pylorus	0.2486
Body	0.2581
Cardia	0.0577
Fundus	0.9704
Anterior wall	0.3977
Posterior wall	0.9507
Circumferential	0.0370
Diffuse	0.9389
Intestinal	0.6020
Grade	0.2436
Configuration	0.2598
Differentiation	0.2416

1912.115 person months during which time there were 30 deaths. This yields an estimated death rate of 0.0157 deaths per person-month, or 18.8% per person-year (95%CI: 0.132-0.269). This means that if we observed 100 persons with the disease for 1 year we would expect approximately 19 of them to die.

It is noted that the results were mostly negative, that is many tumour characteristics did not indicate any evidence of affecting patient survival. Table 3 shows the results of a power analysis to determine the power of our study to detect varying hazard rates. We see that, at best, the current sample with 30 observed events (deaths) would have about 30% power to detect a HR of 2.5. It is likely that the ability of this study to demonstrate pathological prognosticators already commonly accepted in the literature was limited by this relatively low power. We see that we could detect a hazard rate of 2 with power 80%, if we observed 202 deaths. As the examined cohort continues to grow yearly we can expect more robust statistics in future analyses. Furthermore, this study included all cause mortality. As the cohort continues to grow, exact causes of death can be better examined and adjusted for according to their likely direct relation to gastric cancer and therapeutic intervention for this disease process.

Age, size of tumour, number of positive nodes found and total number of lymph nodes removed were not useful predictors of survival. However, it was noted that patients who had a circumferential tumour were almost two and a half times more likely to die than those without. There was a similar increase in the likelihood of death for patients with tumours of the cardia, as well as in those with venous infiltration (Table 3).

In a previous clinicopathological audit of gastric carcinomas at this institution between 1993-2002, the majority of tumours (56%) were of the antrum. The cardia was the third most involved site at 7.9%[4]. The current study, 2000-2010, noted 9.1% of cases to involve the gastric cardia and 54.5% involving the antrum. While the majority of gastric cancers in our population continue to be found in the antrum, it is worth noting the increased incidence of cancers of the cardia. This early trend parallels the 29.0% to 52.2% increase in incidence of adenocarcinomas of the gastric cardia noted in the United Kingdom from 1984 to 1993[8]. Similarly the incidence of cardiac lesions increased from 29% to 52%, in the United States of America, between 1984-1993[9]. McLoughlin purports a generally poorer prognosis associated with cancers of the gastric cardia as opposed to other anatomical sites[10].

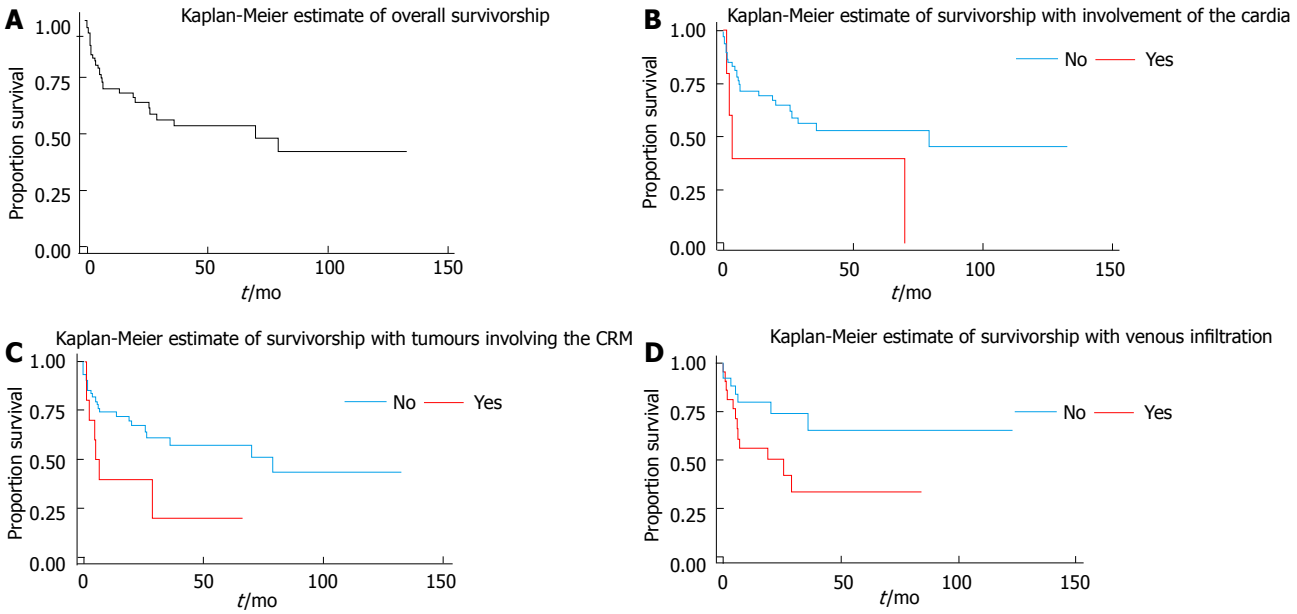

Figure 1 Kaplan-Meier survival. A: Estimate of gastric cancer (2000–2010); B: Estimate of patients with involvement of the Cardia; C: Estimate of patients with tumour involving the circumferential resection margin; D: Estimate of patients with venous infiltration. CRM: Circumferential resection margin.

Table 5 Single predictor cox regression models

Predictor	HR	*P* value	95%CI	
Cardia				
Involved *vs* uninvolved	2.685	0.069	0.927	7.779
Circumferential				
Involved *vs* uninvolved	2.424	0.044	1.025	5.732
Venous infiltration				
Present *vs* absent	2.502	0.055	0.98	6.384
Age	1.007	0.643	0.978	1.037
Size	0.992	0.897	0.877	1.122
Positive lymph nodes	1.059	0.118	0.986	1.137
Total lymph nodes removed	0.981	0.603	0.911	1.055
Type of surgery				
Total gastrectomy *vs* subtotal gastrectomy	1.45	0.417	0.591	3.553
Presence of *Helicobacter pylori*	0.456	0.198	0.138	1.508

This prognosis is likely a consequence of more extensive lymphatic drainage of the region, and later diagnosis[10,11]. In this study a HR of 2.685 (P = 0.069) reflected, although not significantly, this increased risk of mortality. Kaplan-Meier curves demonstrate the decreased survivorship of cardiac gastric cancers in this Jamaican cohort. Finally, the Logrank test trended toward significance with a P value of 0.0577.

This study made evident a significant HR of 2.424 (P = 0.044) for patients with circumferential resection margin (CRM) involvement post-gastrectomy. Logrank survival tests reflect this decreased survivorship with a P value of 0.0370. This applies to cancers of the cardia with extension into the distal oesophagus. CRM involvement has been shown to be an important prognostication factor for oesophageal cancer. Several studies have shown a poor prognosis in patients with potentially resectable malignancies of the distal 5 cm of the oesophagus and Siewert I adenocarcinomas of the gastro-oesophageal junction[12,13]. It would appear that the findings of our study reflect such trends.

As, both globally and locally, more proximal gastric tumour sites become increasingly prevalent, it is important to note the relatively poor outcomes of such cases post gastrectomy. As alluded to above, lymphatic drainage is thought to be a key contributor to such poor outcomes. Accordingly it is prudent to examine the approach to lymph node dissection and excision employed locally, as well as the correlation between lymph node positivity and survivorship. Our study did not demonstrate any significant influence of either lymph node positivity or total number of nodes resected on survivorship. However, Shimada *et al*[14] (2001) with a much larger cohort (982) concluded that the involvement of three or more metastatic lymph nodes is an independent prognostic factor with a sharp decrease in 5-year survivorship of patients with greater than two nodes. An Italian randomised trial involving 615 gastric cancer patients demonstrated significant decrease in all-cause mortality varying proportionately with number of lymph nodes removed up to 25. The authors suggest a minimum of 25 nodes be removed for better long term survivorship[15]. Our study saw an average of only 8 nodes being removed. During this time at our institution the standard procedure performed was that of D1 gastrectomy. This was due to lack of personnel trained in D2 gastrectomy technique. The American Joint Committee on Cancer recommends a minimum of 15 lymph nodes be examined for accurate staging of gastric cancer as retrieved by D2 lymphadenectomy[16]. Only 4 of the 79 specimens reviewed met this recommendation, as D1 gastrectomies were performed. Interestingly, Schoenleber *et al*[17] suggest that the single most influential factor in optimising the number of lymph nodes retrieved, and consequently the number of positive lymph

nodes identified from a gastric specimen, is the technique of the pathology technician in trimming the gross specimen. Thus, the relatively low yield of lymph nodes from the surgical specimens in this study may be a function of either surgeon skill or the technical ability of the pathologist trimming the specimen.

It is important to note that meta-analyses of D1 *vs* D2 lymphadenectomy for gastric cancer have failed to demonstrate any survival benefit of extended resection[18]. The reason for this may be the increased surgical morbidity and mortality that is expected when less experienced staff perform the more technically complex D2 resection classically inclusive of splenectomy and pancreatectomy. At our institution 38% of the reviewed cases had been done by a surgeon who had previously performed less than 10 gastrectomies. No significant change in survivorship was attributable to surgeon experience. The ideal answer to balancing the risk of increased operative morbidity, against the need for oncological clearance of involved nodes, would be to identify involved nodes preoperatively. Currently, algorithms utilising prognostic factors such as age, sex, Borrmann classification and histology are being developed to do just that. The Maruyama computer program was used retrospectively to predict lymph node involvement by level and the results compared to actual pathological specimen findings. The prediction rate was highly accurate (82%-96%)[19]. This high predictive accuracy has been reproduced[20].

This study has also demonstrated an almost significant HR of 2.5 with regard to the survivorship of patients with tumours featuring venous infiltration (P = 0.055). A retrospective analysis, done in China, of 487 gastric cancer patients showed that lymphatic or blood vessel invasion in the presence of metastatic lymph node disease significantly decreased survivorship post gastrectomy[21]. In our study, all but two of the histological specimens had positive nodes, therefore a similar overall trend was observed. Additionally, a study, done in South Korea, of 280 node negative patients demonstrated significant worsened prognosis for patients with blood vessel invasion[22].

Given that there is sufficient evidence in the literature that some of these characteristics are clear indicators of survival, we could conclude that our study lacked the power to sufficiently detect the results. Specifically, a hazard rate of 2 with power of 80 would require 202 deaths to be observed and this would take about 30 years at our institution. This type of study would provide useful information for the Caribbean. We believe that it would be prudent to continue following this cohort of persons as well as enrolling new patients who are diagnosed with gastric cancer in order to better understand factors affecting survival in our population.

Of note, in this retrospective study we did not investigate the effect of chemotherapeutic interventions on survivorship. Numerous clinical trials have demonstrated the positive effect of such treatment on postoperative survival times of gastric cancer patients *vs* having just surgery[23].

Finally, modification of not only surgical but pathology staff practices may improve survivorship. Alteration of D2 gastrectomy to preserve pancreas and spleen has been shown to increase survival of stage three gastric cancer patients without any added risk of mortality or morbidity compared to D1 gastrectomy[24]. As previously mentioned, level of training of the pathology staff significantly affects the rate of retrieval of lymph nodes from surgical specimens. Education of relevant staff should be of benefit in that regard. Also, implementation of a surgical protocol ensuring AJCC recommendations, such as appropriate lymph node dissection, are followed, may improve specimen yield and thus diagnostic relevance. Epidemiological mapping of gastric cancer in the Afro-Caribbean population is of worldwide significance as, interestingly, relative rates of gastric cancer by ethnicity in England have been shown to be higher in black persons of Caribbean heritage[25].

COMMENTS

Background

Gastric adenocarcinoma is the most common type of cancer occurring the stomach. Despite robust clinical research, predominantly out of Japan, it remains a leading cause of cancer death both worldwide and in Jamaica. Before therapeutic strategies can be devised to reduce this burden in Jamaica, it is important to thoroughly describe both the pathological patterns seen here and the efficaciousness of current surgical management.

Research frontiers

D2 gastrectomy, especially as performed by well practiced experts, has been shown to improve patient survivorship. The role of adjuvant chemotherapy is gaining international acceptance as beneficial to survival following the MAGIC trial. The use of software, such as the Maruyama computer program, has shown reproducible and accurate retrospective prediction of lymph node involvement by level. This is a potential means of minimising perioperative morbidity and mortality, by obviating unnecessarily extensive lymph node dissection during gastrectomy.

Innovations and breakthroughs

In Asia, Europe and North America clinicopathological factors such as tumour size, lymph node metastases, vascular and serosal invasion have been demonstrated as significant factors affecting patient prognosis. In addition a trend has been noted of increased incidence of more proximal anatomic location of these tumours in the stomach. This study sought to see whether these findings were similar in a Caribbean population.

Applications

The findings of this study will be used to refine and standardise lymphadenectomy technique at the institution and in the region. This is the first study of its kind from the Caribbean region which differs significantly in racial composition, dietary practice and resource availability from the regions of origin of most published data.

Terminology

D1 gastrectomy–surgical resection of the stomach plus dissection of all group one or perigastric lymph nodes (left cardia, right cardia, lesser curve, greater curve, suprapyloric, infrapyloric); D2 gastrectomy–surgical resection of the stomach plus dissection of all perigastric lymph nodes plus those about the hepatic, left gastric, celiac, and splenic arteries, as well as those in the splenic hilum.

Peer review

It has been well written and presents the valid issues regarding association of various factors with the survival of gastric cancer patients.

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CLINICAL TRIALS STUDY

Laparoscopic re-sleeve gastrectomy as a treatment of weight regain after sleeve gastrectomy

Giovanni Cesana, Matteo Uccelli, Francesca Ciccarese, Domenico Carrieri, Giorgio Castello, Stefano Olmi

Giovanni Cesana, Matteo Uccelli, Francesca Ciccarese, Domenico Carrieri, Giorgio Castello, Stefano Olmi, Department of General and Oncologic Surgery, Centre of Laparoscopic and Bariatric Surgery, Istituti Ospedalieri Bergamaschi-Policlinico San Marco, 24040 Zingonia-Osio Sotto, Italy

Author contributions: Cesana G, Ciccarese F and Olmi S performed the interventions; Uccelli M, Carrieri D and Castello G provided the collection and the analysis of the data; Cesana G designed the study and wrote the manuscript; Olmi S edited the manuscript.

Correspondence to: Dr. Giovanni Cesana, Department of General and Oncologic Surgery, Centre of Laparoscopic and Bariatric Surgery, Istituti Ospedalieri Bergamaschi-Policlinico San Marco, Corso Europa 7, 24040 Zingonia-Osio Sotto, Italy. giovanni.cesana@gmail.com
Telephone: +39-331-6526615 Fax: +39-35-885789
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Abstract

AIM: To evaluate laparoscopic re-sleeve gastrectomy as a treatment of weight regain after Sleeve.

METHODS: Laparoscopic sleeve gastrectomy is a common bariatric procedure. Weight regain after long-term follow-up is reported. Patients were considered for laparoscopic re-sleeve gastrectomy when we observed progressive weight regain and persistence of comorbidities associated with evidence of dilated gastric fundus and/or antrum on upper gastro-intestinal series. Follow-up visits were scheduled at 1, 3, 6 and 12 mo after surgery and every 6 mo thereafter. Measures of change from baseline at different times were analyzed with the paired samples *t* test.

RESULTS: We observed progressive weight regain after sleeve in 11 of the 201 patients (5.4%) who had a mean follow-up of 21.1 ± 9.7 mo (range 6-57 mo). Three patients started to regain weight after 6 mo following Sleeve, 5 patients after 12 mo, 3 patients after 18 m. Re-sleeve gastrectomy was always performed by laparoscopy. The mean time of intervention was 55.8 ± 29.1 min. In all cases, neither intra-operative nor post-operative complications occurred. After 1 year follow-up we observed a significant ($P < 0.05$) mean body mass index reduction (-6.6 ± 2.7 kg/m^2) and mean % excess weight loss (%EWL) increase (+31.0% ± 15.8%). An important reduction of antihypertensive drugs and hypoglycemic agents was observed after re-sleeve in those patients affected by hypertension and diabetes. Joint problems and sleep apnea syndrome improved in all 11 patients.

CONCLUSION: Laparoscopic re-sleeve gastrectomy is a feasible and effective intervention to correct weight regain after sleeve.

Key words: Obesity; Bariatric surgery; Laparoscopic surgery; Stomach stapling; Gastrectomy; Surgery; Repeat

Core tip: Laparoscopic sleeve gastrectomy is gaining an important role in bariatric surgery because it may have similar results to gastric by-pass and duodenal switch, without problems of malabsorption and digestive anastomosis. However, weight regain after a long-term follow-up is reported. In this paper we show that re-sleeve gastrectomy is a valid and effective intervention to correct weight regain after sleeve.

Cesana G, Uccelli M, Ciccarese F, Carrieri D, Castello G, Olmi S. Laparoscopic re-sleeve gastrectomy as a treatment of weight regain after sleeve gastrectomy. *World J Gastrointest Surg* 2014; 6(6): 101-106 Available from: URL: http://www.wjgnet.com/1948-9366/full/v6/i6/101.htm DOI: http://dx.doi.org/10.4240/wjgs.v6.i6.101

INTRODUCTION

Laparoscopic sleeve gastrectomy (LSG) is a bariatric procedure that may allow similar results to Roux-en-Y gastric bypass (RYGB) and duodenal switch (DS), without problem of malabsorption[1-4]. Several studies, reporting large series, show that LSG is safe and effective in terms of weight loss[5-8] and improvement of comorbidities[9-11] in the first post-operative years. For these reasons and for the fact that it does not imply any digestive anastomosis, LSG has become very popular among surgeons. It appears that there are less complications after LSG compared to those seen after RYGB[7,12-14]. The most worrisome complication of LSG is a leak of the long suture line, reported in 1%-7% of patients[6]. Despite its wide diffusion, LSG's long-term weight loss data are not uniform. Some authors report a regain of weight after LSG[15-17]. This data could be in line with the fact that weight regain has been found after all bariatric operations[18,19]. One of the main advantages of LSG is that it may also work as a bridge procedure before a laparoscopic DS[20-22] or a laparoscopic RYGB[23], in case of insufficient weight loss or progressive weight regain. Recently, some authors suggested treating the inadequate weight loss, resulting from a large stomach or neofundus after LSG, with laparoscopic re-sleeve gastrectomy (LRSG)[24-27]. In this paper we present our series of 11 LRSG procedures with 1 year follow up.

MATERIALS AND METHODS

Patient characteristics

All patients who underwent LSG in our institution from December 2007 to September 2011 were considered for LRSG when we observed progressive weight regain and persistence of comorbidities, associated with evidence of persistence of gastric fundus and/or antrum on upper gastro-intestinal series (Figure 1B). No patients were considered for RYGB or DS after failed LSG because, in accordance with patients, we wanted to maintain the advantages of Sleeve in terms of avoiding post-operative malabsorption and in terms of preserving the possibility to easily explore the gastro-intestinal tract in the necessity of diagnostic or operative endoscopy. Institutional Review Board approval was obtained for the present study and all patients gave their informed consent prior to surgery. The presence of comorbidities, such as joint problems, was quantified according to anamnesis and use of specific medications before and after surgery. The presence of Diabetes was quantified by pre and post-operative fasting blood glucose (FBG) and glycosylated hemoglobin (HbA_{1c}). The presence of blood hypertension was quantified by systolic and diastolic pressure before and after surgery. The presence of sleep apnea was quantified by sleep studies before surgery and post-operative resolution by discontinuation of the use of CPAP (Continuous Positive Airway Pressure) mask.

Surgical technique

Surgery was performed according to our usual technique for laparoscopic Sleeve Gastrectomy. A Veress needle was used to accomplish pneumoperitoneum. The first trocar (12 mm, Endopath XCEL, Ethicon Endo-surgery, Cincinnati, OH, United States) was placed in the left subcostal space. The second and the third trocars (5 mm, Endopath XCEL, Ethicon Endo-surgery, Cincinnati, OH, United States) were placed in the subxiphoid space and in the right flank respectively. The last trocar (15 mm, Endopath XCEL, Ethicon Endo-surgery, Cincinnati, OH, United States) was placed above the umbilicus. The stomach was separated from the gastrocolic ligament and gastrosplenic ligament by Harmonic ACE 5 mm (Ethicon Endo-Surgery, Cincinnati, OH, United States). The left diaphragmatic crus was freed. The excessive part of the stomach was cut over a 12.7 mm (38 Fr) Gastric Calibration Tube (Ethicon Endo-Surgery, Cincinnati, OH, United States) starting from 6 cm proximal to the pylorus and proceeding up toward the diaphragmatic left crus. An articulating endoscopic linear cutter (Echelon Flex 60, Ethicon Endo-Surgery, Cincinnati, OHIO, United States) with 4.1 mm (Green) and 3.8 mm (Gold), 6 row cartridges (Endoscopic Linear Cutter Reloads, Ethicon Endosurgery, Cincinnati, OH, United States), was used to staple the stomach. In LRSG we rarely used 3.5 mm (Blue) cartridges because of the tissue's density after the prior stapling. Running suture with PDS 3/0 (MIC55E, PDS* Ⅱ, Ethicon Endo-Clip Suture, Cincinnati, OH, United States) was used to reinforce the stapled line. Surgical technique was the same in LSG and LRSG. The same calibration tube was used for all the patients in LSG and LRSG.

Post-operative management

Patients were started on an oral fluid diet on post-operative day 3 after upper gastro-intestinal series had shown no leak. Patients were discharged on day 5 if no post-operative complications occurred. Follow-up visits were scheduled at 1, 3, 6 and 12 mo after surgery and every 6 mo thereafter. Data were entered into a prospectively held database including age, gender, body mass index (BMI), excess of weight (EW), % of excess weight loss (%EWL), comorbidities before and after surgery, post-operative complications.

Statistical analysis

Data were obtained by review of the prospectively maintained database. Quantitative variables were reported as mean and standard deviation (SD); qualitative variables were described as number and percentages. Measures of change from baseline at 3, 6, 12 mo after surgery were analyzed with the paired *t* test. Statistical significance was set at $P \leqslant 0.05$. All statistical analyses were performed with the Statistical Product and Service Solutions (SPSS) software package (version 19, SPSS-IBM, Chicago, IL, United States).

RESULTS

Patients characteristics

From December 2007 to September 2011, 201 patients

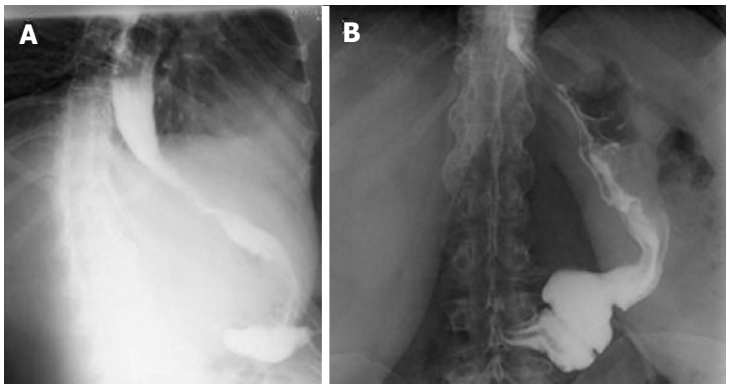

Figure 1 Comparison of upper gastro-intestinal series in the same patient on post-operative day 2 after sleeve gastrectomy (A) and one year later (B). After one year we see a dilated stomach (B) that allows weight regain.

Table 1 Pre-operative patients' characteristics *n* (%)

Characteristics	Value, mean ± SD *n* = 11
Age (yr)	40.6 ± 10.2
Height (m)	1.60 ± 0.1
Ideal body weight (kg)	57.4 ± 8.9
Excess body weight (kg)	59.3 ± 16
Excess body weight (%)	104.2 ± 25.5
Body mass index (kg/m^2)	45.2 ± 5.6
Gender	
Male	3 (27.3)
Female	8 (72.7)
Comorbidities	
At least 1 comorbidity	4 (36.4)
Blood hypertension	3 (27.3)
Type 2 diabetes mellitus	2 (18.2)
Sleep apnea syndrome	1 (9.1)
Joint problems	3 (27.3)

underwent LSG at our Institution. We observed progressive weight regain in 11 patients (5.4%). Three patients started to regain weight after 6 mo post-LSG, 5 patients after 12 mo, 3 patients after 18 mo. An upper gastro-intestinal series showed gastric dilatation in all 11 patients. Three patients (27.3%) had another bariatric surgery prior to LSG: 2 patients had an adjustable gastric band (AGB) already removed before LSG and one patient underwent surgical intervention of laparoscopic Band removal and LSG at the same time. The AGB was removed because of dysfunction associated with weight regain.

Four patients (45.5%) were affected by at least 1 comorbidity (Table 1). Two of them (a female with BMI = 54.1 kg/m^2 and a male with BMI = 48.5 kg/m^2) were affected by blood hypertension, type II diabetes and joint problems. A third patient, a female with BMI = 52.7 kg/m^2, was affected by blood hypertension and joint problems. A fourth patient, a male with BMI = 43.3 kg/m^2, was affected by sleep apnea syndrome. In all patients, pre-operative blood hypertension was well controlled by drugs (mean systolic 123.3 ± 2.9 mmHg and mean diastolic 78.3 ± 2.9 mmHg). Two patients were in therapy with combination diuretics and ACE inhibitors; one patients with ACE inhibitors alone. Regarding the treatment of diabetes, the two patients affected used oral hypoglycemic agents. The average FBG before surgery was 147.5 ± 3.5 mg/dL and HbA$_{1c}$ averaged 6.9% ± 0.1%. The mean age of the patients (3 males and 8 females) was 40.6 ± 10.2 years (Table 1).

Findings after LSG

Before LSG, mean absolute weight was 116.4 ± 21.5 kg, mean EW was 59.3 ± 16 kg and mean BMI was 45.2 ± 5.6 kg/m^2 (Table 1). One patient developed a high gastric leak after LSG and underwent a second operation six days later. She was a female with BMI = 41 kg/m^2 and no comorbidities. She had surgical revision of the gastric staple line without resewing it. A perigastric abscess was drained and a drain tube was left in place. The leak resolved in 15 d and the patient was discharged on day 18. BMI and %EWL variations after LSG are collected in Figure 2. After an initial decrease, mean BMI start to increase after 6 mo.

After LSG, systolic and diastolic pressure values did not differ significantly to prior LSG; however a reduction in requirement of antihypertensive drugs was observed. One patient suspended therapy and the others 2 reduced therapy. After LSG, FBG and HbA$_{1c}$ showed an important decrease (respectively 105.5 ± 28.9 mg/dL and 6.2% ± 0.5%). One of two patients (50%) suspended oral hypoglycemic agents. Joint problems and sleep apnea syndrome improved in all (100%).

Findings after LRSG

LRSG was performed at a mean interval of 21.1 ± 9.7 mo after LSG. The mean BMI before LRSG was 38.9 ± 3.8 kg/m^2 and the mean %EWL was 25.3% ± 14.2% (Figure 2). LRSG was completed laparoscopically in all cases and no intra-operative or post-operative complications occurred. The mean time of intervention was 55.8 ± 29.1 min. The mean operative time for LSG in the same patients was longer: 65.4 ± 17.4 min. This finding could be related to the fact that when we perform LRSG the stomach is already dissected and prepared. We only cut off the exceeding part of the stomach over the boogie. No significative blood loss occurred either in LSG or in LRSG. No patient showed leakage from the stapled line at upper gastro-intestinal series scheduled on day 2. All patients resumed an oral liquid diet on day 3 and they were discharged from the hospital on day 5 after LRSG. At 1, 6, 12 mo after LRSG the BMI progressively decreased and %EWL increased in each patient. As shown

Table 2 Weight loss at 12 mo after laparoscopic re-sleeve gastrectomy

	Value (n = 11) before LRSG mean ± SD	After LRSG mean ± SD	Mean change (SD)	95%CI	P value
Absolute weight (kg)	100.3 ± 17.5	82.9 ± 14.7	-17.4 (± 7.8)	-12.0--22.6	< 0.001
BMI (kg/m^2)	38.9 ± 3.8	32.2 ± 3.9	-6.6 (± 2.7)	-4.8--8.5	< 0.001
Excess weight (kg)	43.2 ± 10.1	25.8 ± 9.5	-17.4 (± 7.8)	-12.0--22.6	< 0.001
Excess weight (%)	75.4 ± 11.6	45.4 ± 16.5	-29.2 (± 12.4)	-20.8--37.6	< 0.001
Excess weight loss (%)	25.3 ± 14.2	56.8 ± 12.4	+31.0 (± 15.8)	41.6-20.4	< 0.001

P value is calculated with paired t test assessing change from LRSG. BMI: Body mass index; LRSG: Laparoscopic re-sleeve gastrectomy.

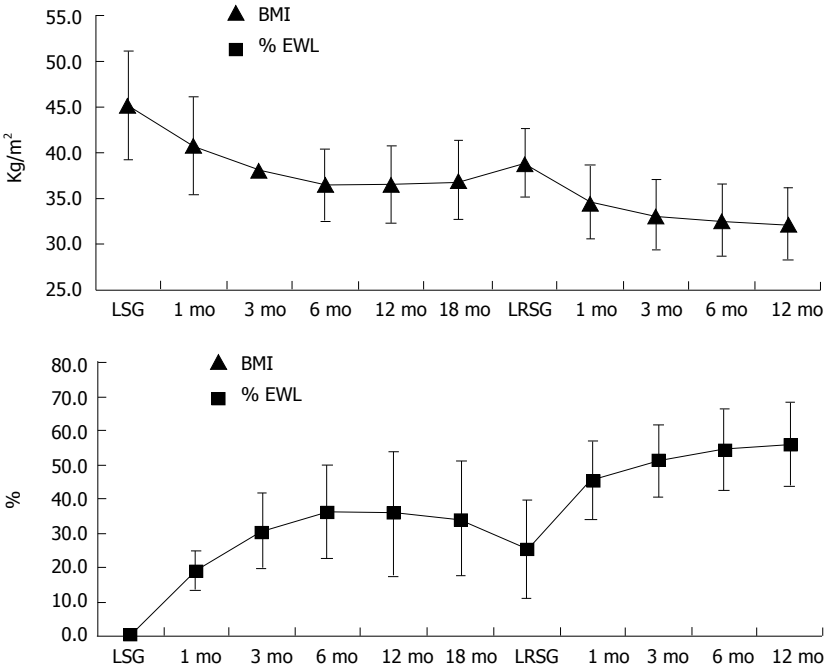

Figure 2 Body mass index and % of excess weight loss before and after laparoscopic sleeve gastrectomy and laparoscopic re-sleeve gastrectomy. Data are expressed as means and standard deviations. BMI decrease and %EWL increases for few months (mo) after LSG, then patients start to regain weight. After LRSG, BMI decreases and %EWL increases again. BMI: Body mass index; %EWL: % of excess weight loss; LSG: Laparoscopic sleeve gastrectomy; LRSG: Laparoscopic re-sleeve gastrectomy.

in Table 2, after 1 year of follow-up the mean BMI significantly decreased from 38.9 ± 3.4 kg/m^2 to 32.2 ± 3.9 kg/m^2 (P < 0.05) and the %EWL significantly increased from 25.3 ± 14.2 to 56.3 ± 12.4 (P < 0.05).

After LRSG only 1 of 3 patients continued to use antihypertensive drugs and only 1 of 2 continued to use oral hypoglycemic agents. Mean systolic pressure was 121.6 ± 1.5 mmHg and mean diastolic was 78 ± 2 mmHg. Mean FBG was 98.5 ± 16.2 mg/dL and mean HbA_{1c} was 6.1 ± 0.6 %. Neither joint problems nor sleep apnea were noted after LRSG.

DISCUSSION

LSG is gaining an important role in bariatric surgery because it may have similar results to RYGB and DS, without malabsorbitive problems and digestive anastomosis[1-3]. Moreover, after LSG there are no problems exploring the upper gastro-intestinal tract. Some authors have noted a weight regain after LSG[15-17]. In our series we observed weight regain in 11 out of 201 patients (5.4%), who had a mean follow-up of 21.1 ± 9.7 mo (range 6-57 mo). Three patients started to regain weight after 6 mo post-LSG, 5 patients after 12 mo, 3 patients after 18 mo. An upper gastro-intestinal series was performed and showed a dilatation of the antrum and/or gastric fundus in all the 11 patients (Figure 1). The causes of gastric dilatation are not clear[27]. It could be related to a technical problem or to a natural process of stomach tissue dilatation. The main technical cause for a dilated antrum might be a dissection started farther than 6 cm from the pylorus. In these cases the patients will regain weight after a few months. The main cause for a dilated fundus might be a dissection farther than 1 cm to the left of the esophagus. A complete dissection of the gastric fundus is difficult when the patient underwent prior AGB placement or removal. Other causes of stomach tissue dilatation after LSG, besides technical problems, could be related to patient's psychological problems or negligence in following the post-surgical diet recommendations. We believe that these factors, technical and not, are often both involved in the process of weight regain after LSG. For example, an incomplete section of the gastric fundus will not decrease the secretion of ghrelin[27], which can explain the incapacity of the patient to follow diet recommendations, therefore permitting stomach dilatation and weight regain.

In order to resume weight loss in patients for which LSG failed, there are few surgical options. LSG can be converted to RYGB or DS[20-23], or a LRSG can be performed[24-27]. In our series, no patients underwent RYGB

or DS because we wanted to maintain the advantages of LSG in terms of avoiding malabsorption or gastro-intestinal anastomosis, and of preserving the possibility to easily explore the gastro-intestinal tract in the necessity of diagnostic or operative endoscopy. Our patients underwent LRSG over the same calibration tube of LSG: 12.7 cm boogie (38 Fr). After LSG, the gastric tissue around the stapled line is denser because of the scar' s healing and remodeling. For this reason, we used only Green (4.1 mm) and Gold (3.8 mm) cartridges to dissect the stomach in the LRSG. An oversewing suture of the stapled line was always performed.

LRSG was feasible in all patients in our series. Although we had neither intra-operative nor post-operative complications, the main post-operative problem after LRSG may be the same of LSG: leakage from the long stapled line. LRSG was effective for weight loss in all patients (Table 2). After one year follow-up we noted a significant decrease in mean BMI from 38.9 ± 3.4 kg/m^2 to 32.2 ± 3.9 kg/m^2 ($P < 0.05$) and a significant increase in mean %EWL from 25.3 ± 14.2 to 56.3 ± 12.4 ($P < 0.05$) (Figure 2). Although median BMI was > 30 kg/m^2 after one year, we noted a significative trend in decreasing weight after LRSG. We need a longer follow-up to determine if the treatment is really effective, but these preliminary data are encouraging in not substituting LSG with a malabsorbitive intervention, loosing the advantages of LSG, especially in terms of quality of life. If weight regain will still occur after a longer follow-up post-LRSG, patients will undergo upper gastro-intestinal series. If the series will show a dilatation of the stomach, the patient will undergo another LRSG. If patients will regain weight without signs of stomach dilatation, he will be led to a malabsorbitive intervention.

Comorbidities improved: sleep apneas and joint problems disappeared completely 12 mo after LSG. Blood hypertension values did not differ significantly before surgery, after LSG and after LRSG, but a significant reduction in the requirement of antihypertensive drugs was observed. FBG and HbA_{1c} gradually decreased after LSG and LRSG. One of two patient suspended oral hypoglycemic agents.

In conclusion, like the other major bariatric interventions[18,19] LSG can result in weight regain. Other bariatric procedures can be performed to correct it[20-27]. In our series of patients who regained weight after LSG, LRSG was performed. The result was a safe procedure which allowed a significant weight loss in each patient. LRSG appears to be a valid correction for post-LSG weight regain. Our study is limited by the fact that it is retrospective, involves few patients and has a limited follow-up (12 mo after LRSG). We believe that these preliminary data can be a promising start for further studies, which are needed to confirm the initial results.

COMMENTS

Background

Obesity is an increasing problem in modern western society. In the past few years, different types of surgery have been developed to resolve this problem when it could not be treated by diets or drugs. Sleeve gastrectomy is an intervention that allows for good results in term of weight loss without problems of malabsorption. Sleeve became very popular among surgeons. Despite its wide diffusion, sleeve's long-term weight loss data are not uniform. Some authors report a regain of weight after Sleeve.

Research frontiers

To show that it is feasible and effective to correct weight regain after sleeve through a re-sleeve gastrectomy.

Innovations and breakthroughs

Re-sleeve gastrectomy can correct weight regain after sleeve. It avoids converting sleeve in a malabsorbitive intervention, loosing the advantages of sleeve. They describe the surgical technique, which is valid and without major complications.

Applications

Sleeve gastrectomy has advantages in terms of quality of life for obese patients, avoiding problems of malabsorption and allowing weight lost. The possibility of managing weight regain with a re-sleeve, without converting it in a malabsorbitive intervention, can allow surgeons to choose this type of surgery in the cure of obesity.

Terminology

Sleeve gastrectomy is a vertical resection of stomach. Re-sleeve gastrectomy is the resection of those parts of stomach that underwent dilatation after sleeve.

Peer review

This is a case series of laparoscopic re-sleeve gastrectomy in obese patients who showed weight regain after laparoscopic sleeve gastrectomy. The present study is important because there are few data on this type of bariatric surgery.

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CASE REPORT

Downstaging and resection after neoadjuvant therapy for fibrolamellar hepatocellular carcinoma

Gilton Marques Fonseca, Antonio Drauzio Varella, Fabricio Ferreira Coelho, Emerson Shigueaki Abe, Rodrigo Blanco Dumarco, Paulo Herman

Gilton Marques Fonseca, Fabricio Ferreira Coelho, Emerson Shigueaki Abe, Rodrigo Blanco Dumarco, Paulo Herman, Digestive Surgery Division, Department of Gastroenterology, University of São Paulo School of Medicine, Avenida Doutor Enéas de Carvalho Aguiar 255, Instituto Central, 05403-900, São Paulo, Brazil

Antonio Drauzio Varella, Clinical Oncologist, Hospital Sírio-Libanês, 01308-050, São Paulo, Brazil

Author contributions: Fonseca GM and Herman P designed the study and wrote the manuscript; Fonseca GM, Coelho FF, Abe ES and Dumarco RB performed revision research; Coelho FF, Abe ES, Dumarco RB and Varella AD reviewed the manuscript.

Correspondence to: Gilton Marques Fonseca, MD, Digestive Surgery Division, Department of Gastroenterology, University of São Paulo School of Medicine, Avenida Doutor Enéas de Carvalho Aguiar, 255, Instituto Central, 9° Andar, Sala 9074, 05403-900, São Paulo, Brazil. medgilton@yahoo.com.br
Telephone: +55-11-26617560 Fax: +55-11-26617560

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Abstract

Fibrolamellar hepatocellular carcinoma (FLHCC) is a rare malignant liver neoplasm, commonly observed in adolescents and young adults of both genders. The disease is more common in Caucasians and in patients without a prior history of liver disease. The best treatment option is a surgical resection associated with liver hilum lymph node dissection. However, there is no established systemic drug treatment for patients with locally advanced or metastatic disease. We report on a patient with advanced FLHCC, initially considered unresectable due to invasion of the right and the middle hepatic veins and circumferential involvement of the left hepatic vein. Following the treatment with gemcitabine-oxaliplatin systemic chemotherapy, the patient exhibited a significant tumor reduction. As a result, a complete resection was performed with an extended right hepatectomy associated with a partial resection of the inferior vena cava, a wedge resection in segment 2, and lymphadenectomy of the hepatic hilum. The case was unusual due to the significant tumor downstaging with gemcitabine-oxaliplatin, potentially enabling curative resection. More studies are needed to confirm the efficacy of the systemic drug treatment for FLHCC.

Key words: Chemotherapy; Gemcitabine; Oxaliplatin; Hepatectomy; Hepatic veins; Fibrolamellar hepatocellular carcinoma

Core tip: Fibrolamellar hepatocellular carcinoma (FLHCC) is a rare malignant liver neoplasm. The best treatment option is a surgical resection with liver hilum lymph node dissection. Currently there is no established systemic drug treatment for patients with locally advanced or metastatic disease. In this report, a patient with advanced FLHCC, initially considered unresectable due to vascular invasion, exhibited a significant tumor reduction following systemic chemotherapy with gemcitabine-oxaliplatin, allowing resection. This was an unusual case where gemcitabine-oxaliplatin treatment led to a significant tumor downstaging enabling curative resection. Additional studies are needed to confirm the efficacy of the systemic drug treatment for FLHCC.

Fonseca GM, Varella AD, Coelho FF, Abe ES, Dumarco RB, Herman P. Downstaging and resection after neoadjuvant therapy for fibrolamellar hepatocellular carcinoma. *World J Gastrointest Surg* 2014; 6(6): 107-111 Available from: URL: http://www.wjgnet.com/1948-9366/full/v6/i6/107.htm DOI: http://dx.doi.org/10.4240/wjgs.v6.i6.107

INTRODUCTION

Fibrolamellar hepatocellular carcinoma (FLHCC) is

an uncommon primary liver neoplasm, representing 0.6%-8.6% of all hepatocellular carcinomas (HCC)[1]. It was first described in 1956 by Edmonson as a rare distinctive form of HCC[2]. In general, it is a vascular tumor with prominent fibrosis. Microscopically, FLHCC appears as a well-differentiated tumor comprised of large polygonal cells with large nuclei and nucleoli, as well as an abundant eosinophilic cytoplasm, arranged in lamellar bands of collagen fibers[3]. FLHCC most often affects adolescents and young adults of both genders, often Caucasian, and without a prior history of liver disease[1,4]. Liver function tests are typically normal or only mildly elevated. Commonly used HCC markers, such as alpha-fetoprotein, are of little help in diagnosing and monitoring disease progression in the majority of patients, as only a small proportion of patients (7%-11%) show elevation in alpha-fetoprotein levels[5,6].

FLHCC is believed to more commonly metastasize to regional lymph nodes. The cornerstone for FLHCC treatment is a surgical resection associated with lymph node dissection[3,4]. Patients with advanced FLHCC represent a population in need of novel and effective treatments. Due to the lack of data on effective systemic drug treatments as well as the FLHCC patients' paucity, it is difficult to conduct clinical trials[1]. The authors report an unusual case of a young patient, initially with an unresectable FLHCC, treated with gemcitabine-oxaliplatin (GEMOX), resulting in an excellent response and complete resection of the tumor.

CASE REPORT

A previously healthy 35-year-old Caucasian female complaining of abdominal pain, 3 kg weight loss, weakness, back pain, and a palpable mass in the right upper quadrant, was referred for evaluation. Physical examination disclosed a palpable hard mass 20 cm below the right costal margin. There were no signs of liver disease or other relevant findings. A computed tomography scan (Figure 1) showed a suggestive FLHCC mass (17 cm × 15 cm) affecting the right liver lobe. In addition, the mass affected segment 4b by obstructing the right portal branch, invading both the right and middle hepatic veins, circumferentially wrapping the left hepatic vein, and compressing the inferior vena cava. A lesion (ø 6.5 cm) in segment 2 displayed the same characteristics, as well as lymphadenopathy at the liver hilum up to 2.7 cm in size. Laboratory tests revealed elevated levels of alkaline phosphatase, gamma-glutamyl transpeptidase, and alpha-fetoprotein (44.395 ng/mL). Both hepatitis B and C serologies were negative. Colonoscopy and endoscopy results were normal. Percutaneous biopsy of the tumor confirmed FLHCC. The lesion was considered unresectable because of the extensive vascular involvement, especially of the hepatic veins; therefore, the patient was referred to an oncologist for a systemic drug treatment. Transplantation was eliminated due to the presence of the hilar lymph nodes (extra hepatic disease).

The patient received 100 mg of oxaliplatin and 1400 mg of gemcitabine (20 mg/kg) every two weeks during an 11-mo treatment period, with good tolerance. The staging intervals, scheduled every four months, included either a computed tomography scan or magnetic resonance imaging. After one year of treatment, magnetic resonance imaging showed significant tumor size reduction (the larger lesion size was 8.5 cm and the smaller 2.2 cm), decrease in contact with the left hepatic vein and inferior vena cava, disappearance of the lymphadenopathy, and hypertrophy of the left lateral segment of the liver (38% of total liver volume) (Figure 1). In addition, there was a significant decrease in alpha-fetoprotein levels to 45 ng/mL.

The patient was submitted to an extended right hepatectomy with partial resection of the inferior vena cava associated with a wedge resection in segment 2 and lymphadenectomy of the hepatic hilum. The procedure lasted 450 min with the patient receiving two units of packed red blood cells and staying in the intensive care unit for two days. The patient developed a postoperative biliary fistula, which was treated conservatively, with spontaneous closure after 28 d. Our patient was discharged on the 17th postoperative day in a good clinical condition.

Histology examination confirmed FLHCC with microscopically free margins (R0 resection). The hepatic hilum lymph nodes were free of the disease. At discharge, the level of alpha-fetoprotein was within normal limits (4.7 ng/mL). The patient had no signs of the disease recurrence at the 14-mo follow-up.

DISCUSSION

The best treatment option for FLHCC is a resection with adequate lymph node dissection[3,5]. However, a resection is not always possible due to locally advanced disease. The best therapy for these patients has not been well established[1]. Several chemotherapy agents have been used for FLHCC treatment, including fluoropyrimidines, doxorubicin, cisplatin, oxaliplatin, gemcitabine, and irinotecan, as well as interferon, bevacizumab, and sorafenib in either combination regimens or separately[1,5]. Locoregional therapies, such as transarterial chemoembolization, radiofrequency ablation, external beam radiation, percutaneous ethanol injection, and hepatic arterial infusion of cisplatin, had disappointing results[1,5]. A study from the Fibrolamellar Carcinoma Consortium, which contained 99 patients diagnosed with FLHCC, showed that from the 73 patients who underwent surgery, 13% (10/73) received preoperative chemotherapy, external beam radiation, and/or transarterial chemoembolization. Twenty one percent (20/99) were considered to have unresectable disease and 13 of them were treated with various combinations of systemic drug therapy with or without locoregional therapies. Chemotherapy agents used in the study included fluoropyrimidines, doxorubicin, cisplatin, oxaliplatin, gemcitabine, and irinotecan. However, a multivariate analysis showed a lack of surgery to be an independently poor overall survival predictor[1]. Kaseb *et al*[7] studied 94 FLHCC patients and found tumor resection

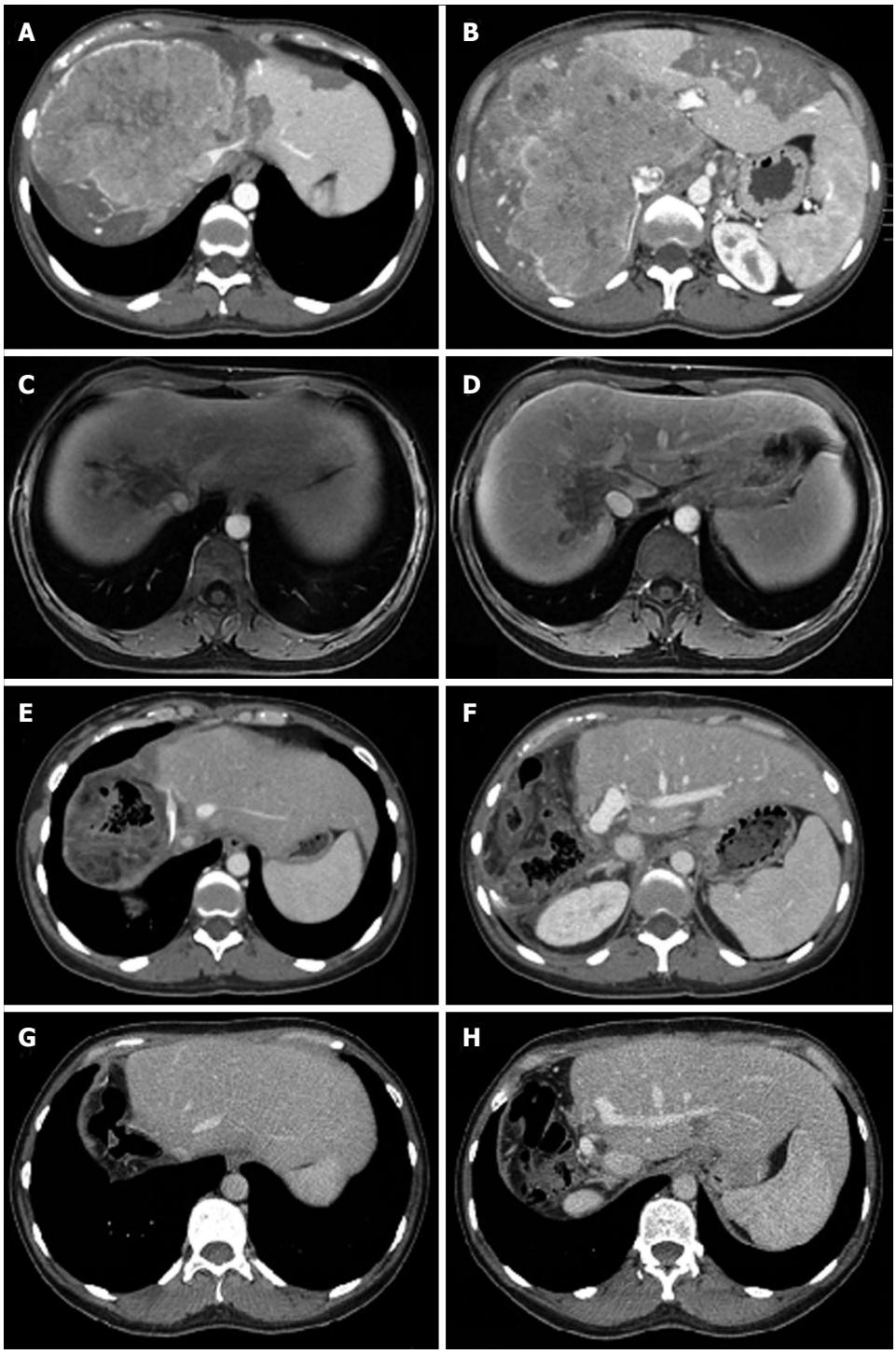

Figure 1 Abdominal computed tomography and magnetic resonance imaging of a 35-year-old Caucasian female, with no previous history of liver disease, showing a large mass in the upper right quadrant. A, B: Abdominal computed tomography (CT) before chemotherapy showing a large mass invading (17 cm × 15 cm) the right and the middle hepatic veins, and surrounding the left hepatic vein; C, D: Abdominal magnetic resonance imaging after gemcitabine-oxaliplatin chemotherapy showing significant reduction of the tumor size; E, F: Abdominal CT two weeks after surgery with hypertrophy of the left lateral segment of liver (liver remnant), and free and patent left branch of the portal vein and left hepatic vein; G, H: Late follow-up after 14 mo.

to be a factor positively associated with longer overall survival; 5-fluorouracil-interferon combination was the most frequently used systemic therapy.

HCC markers, such as alpha-fetoprotein, are of little help in diagnosing and monitoring disease progression in the majority of patients. This is mostly due to a small proportion of patients (7%-11%) showing elevated alpha-fetoprotein levels[5,6]. Our patient probably belongs to this peculiar group since her initial levels of alpha-fetoprotein were high, and were lowered to normal levels following surgery.

Sorafenib is currently the standard treatment for advanced HCC[8,9]. However, no systemic drug therapy had convincingly improved survival among patients with

advanced HCC. There have been attempts to evaluate the efficacy of new drugs or combination treatments in clinical trials. Some of the examples of these trials include: (1) doxorubicin alone and/or with gemcitabine; (2) combination of cisplatin, doxorubicin, 5-fluorouracil, and alpha-interferon; and (3) combination of irinotecan, taxanes, gemcitabine, topotecan, and thymidilate synthase inhibitors[10]. The GEMOX regimen appeared to be the most promising, based on a lack of renal and hepatic toxicity in cirrhotic patients, promising efficacy in the phase II trials for advanced HCC, and with possible extended benefit for Child B cirrhosis[10-13]. Louafi *et al*[12], studying 32 patients treated for advanced HCC, had two patients that underwent HCC curative resection after partial response to GEMOX. In a retrospective multicenter study, Zaanan *et al*[10] observed tumor responses in 204 patients with advanced HCC treated with GEMOX. In 10 patients, tumor response either permitted secondary surgical resection of residual tumors or orthotopic liver transplantation. Radiofrequency ablation was performed in one patient, transcatheter arterial chemoembolization in three patients, cyberknife treatment in one patient, and radioembolization in two patients. There was also a case report on a patient with metastatic HCC without liver disease with a complete response after 12 cycles of GEMOX[14].

There has been only one reported case of FLHCC with a complete response after GEMOX treatment. In this case, a young woman had a histologically proven metastatic lymph node relapse after resection of the primary tumor. GEMOX regimen lead to a complete response without relapse five years after chemotherapy discontinuation[15].

HCC patients have poor tolerance to systemic chemotherapy, mostly due to cirrhotic liver[15]. In most cases FLHCC patients do not have a prior history of liver disease[4]. This may explain the better tolerance to chemotherapy, hence leading to a better response, as is the case in our patient. In the present case, the chemotherapy regimen with GEMOX promoted FLHCC downstaging, potentially allowing for a curative treatment. However, more studies are needed to confirm GEMOX efficacy.

COMMENTS

Case characteristics

A previously healthy 35-year-old Caucasian female complained of abdominal pain, 3 kg weight loss, weakness, back pain, and a palpable mass in the right upper quadrant.

Clinical diagnosis

A palpable hard mass was found to be located 20 cm below the right costal margin with no signs of liver disease.

Differential diagnosis

Hepatocellular carcinoma, cholangiocarcinoma, liver metastasis.

Laboratory diagnosis

The patient had elevated levels of alkaline phosphatase, gamma-glutamyl transpeptidase, and alpha-fetoprotein, and negative serologies for both hepatitis B and C.

Imaging diagnosis

A computed tomography scan showed a suggestive fibrolamellar hepatocellular carcinoma (FLHCC) mass (17 cm × 15 cm) affecting the right liver lobe and segment 4b, obstructing the right portal branch, invading the right and middle hepatic veins, circumferentially wrapping the left hepatic vein, and compressing the inferior vena cava; the second lesion (6.5 cm) in segment 2 had the same characteristics and lymphadenopathy at the liver hilum (up to 2.7 cm), with colonoscopy and endoscopy results being normal.

Pathological diagnosis

FLHCC was confirmed by percutaneous biopsy of the tumor.

Treatment

The patient received 1400 mg of gemcitabine (20 mg/kg) and 100 mg of oxaliplatin (GEMOX) every 2 wk over 11 mo, with a significant tumor reduction, allowing for resection.

Related reports

The best treatment option for FLHCC is resection with adequate lymph node dissection. However, resection is not always possible due to local disease advancement. There has not been well-established disease therapy for these patients.

Term explanation

FLHCC is an uncommon primary liver neoplasm. In general, it is a vascular tumor with prominent fibrosis. Microscopically, FLHCC appears as a well-differentiated tumor comprised of large polygonal cells with large nuclei and nucleoli, as well as an abundant eosinophilic cytoplasm, arranged in lamellar bands of collagen fibers.

Experiences and lessons

In the present case, the chemotherapy regimen with GEMOX promoted FLHCC downstaging, potentially allowing for curative treatment and suggesting GEMOX as a possible chemotherapy treatment for patients with advanced FLHCC; however, more studies are needed to confirm GEMOX efficacy.

Peer review

This is an interesting case of a young female with an initially considered unresectable FLHCC. Significant tumor downstaging with GEMOX allowed surgical resection.

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CASE REPORT

Intra-abdominal esophageal duplication cyst: A case report and review of the literature

Petrus Sebastianus Simon Castelijns, Karlijn Woensdregt, Brigiet Hoevenaars, Gelde Arie Pieter Nieuwenhuijzen

Petrus Sebastianus Simon Castelijns, Karlijn Woensdregt, Gelde Arie Pieter Nieuwenhuijzen, Department of Surgery, Catharina Hospital Eindhoven, 5623 EJ, Eindhoven, The Netherlands
Brigiet Hoevenaars, Department of Pathology, Catharina Hospital Eindhoven, 5623 EJ, Eindhoven, The Netherlands
Author contributions: Nieuwenhuijzen GAP performed the surgical operation and revised the paper; Hoevenaars B performed pathological examinations; Castelijns PSS and Woensdregt K wrote the paper.
Correspondence to: Karlijn Woensdregt, MD, Department of Surgery, Catharina Hospital Eindhoven, Michelangelolaan 2, 5623 EJ, Eindhoven,
The Netherlands. karlijn.woensdregt@catharinaziekenhuis.nl
Telephone: +31-40-2399111 Fax: +31-40-2443370
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Abstract

Intra-abdominal esophageal duplications are rare entities in adults. They are mostly asymptomatic, but since they can lead to complications surgical excision is advised for all duplication cysts. We present a case of a 20-year-old male with colic-like abdominal pain, mimicking symptoms of cholecystolithiasis. However after cholecystectomy the symptoms were still present. A computed tomography-scan of the abdomen and an endoscopic ultrasound revealed a cyst of the esophagus of 3.0 cm × 2.3 cm in size. Diagnostic laparoscopy was planned, during which we observed a para-esophageal cyst at the gastro-esophageal junction. Laparoscopic excision of this cyst was performed. Pathophysiological examination revealed an esophageal duplication cyst. We report a rare case of a symptomatic intra-abdominal esophageal duplication cyst in an adult. One must consider this diagnosis when more common diagnoses to account for the patient's symptoms are excluded. Removal of duplication cysts can be done laparoscopically.

Key words: Esophageal duplication cyst; Intra-abdominal; Symptomatic; Laparoscopy

Core tip: Intra-abdominal esophageal duplication cysts are rare entities in adults, especially when they are symptomatic. Since these anomalies can lead to complications surgical excision is advised for all of them. We present a case of a 20-year-old male with colic-like abdominal pain, mimicking symptoms of cholecystolithiasis, but caused by an intra-abdominal duplication cyst of the esophagus. The cyst was excised laparoscopically. The procedure was uneventful and the patient was free of symptoms. This case shows that one must consider the diagnosis of a symptomatic intra-abdominal esophageal duplication cyst when more common diagnoses to account for the patient's symptoms are excluded.

Castelijns PSS, Woensdregt K, Hoevenaars B, Nieuwenhuijzen GAP. Intra-abdominal esophageal duplication cyst: A case report and review of the literature. *World J Gastrointest Surg* 2014; 6(6): 112-116 Available from: URL: http://www.wjgnet.com/1948-9366/full/v6/i6/112.htm DOI: http://dx.doi.org/10.4240/wjgs.v6.i6.112

INTRODUCTION

Gastroenteric duplication cysts are congenital malformations that may affect the gastro-intestinal tract from mouth to anus. They are usually attached to the gastrointestinal tract, have smooth muscle cells in the wall of the cyst and are lined with gastrointestinal epithelium. Most of them are found in the small intestine (44%), the esophagus (20%) or in the large intestine (15%)[1]. Esophageal duplication cysts mostly arise in the mediastinum.

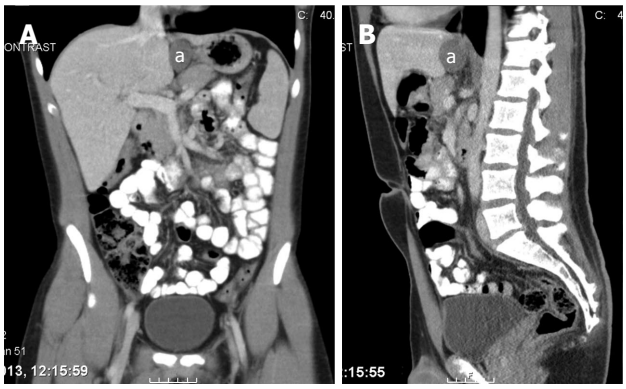

Figure 1 Computed tomography images of the esophageal duplication cyst (a). A: Frontal view; B: Sagittal view.

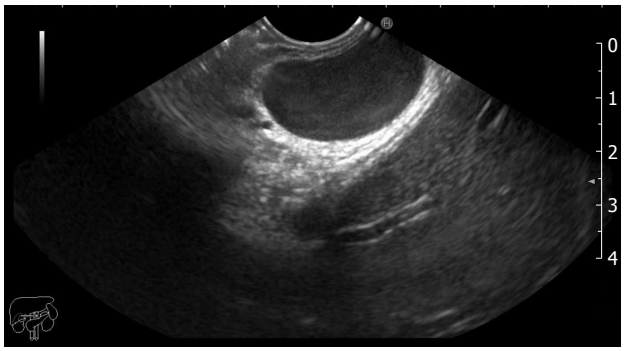

Figure 2 Endoscopic ultrasound image of the cyst.

There are only a few case reports that describe intra-abdominal esophageal duplication.

Duplication cysts may be symptomatic, but even then definitive pre-operative diagnosis can be difficult because of non-specific clinical symptoms. Also, symptoms might be mistaken for other more common abdominal conditions. Because of potential complications such as bleeding, infection or conversion to a malignancy, currently the most common treatment of these anomalies is surgical excision, even if they are not symptomatic.

CASE REPORT

We present a 20-year-old male with no medical or surgical history who was evaluated because of nausea and recurrent colic pain in the right upper abdomen radiating towards his back, but no vomiting or fever. Ultrasound of the upper abdomen was performed, which showed gallstones but no other abnormalities. Initially, symptomatic cholecystolithiasis was considered as the primary diagnosis and subsequently our patient underwent a laparoscopic cholecystectomy. The procedure was performed without complications and the patient was initially free from symptoms.

However, one year later he presented again with the same symptoms as before. Physical examination and laboratory testing did not reveal any abnormalities. The differential diagnosis at this point was choledocholithiasis or urolithiasis. Ultrasound of the abdomen showed no dilatation of intra- or extrahepatic bile ducts or choledocholithiasis. A computed tomography (CT)-scan of the abdomen revealed no urolithiasis, but it did show a mass at the gastro-esophageal junction that was further evaluated with endoscopic ultrasonography (EUS). EUS identified a 3.2 cm × 2.8 cm sized smooth lined lesion (Figure 1) in the distal esophagus just below the diaphragm (Figure 2) We could not differentiate between a gastrointestinal cyst or a leiomyoma, necessitating further analysis.

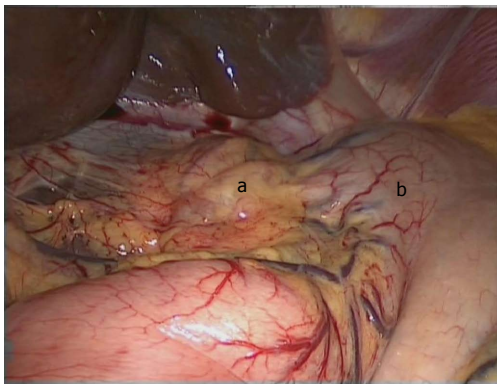

Figure 3 Preoperative image with the cyst (a) medial to the esophagus and stomach (b).

Endoscopic fine needle aspiration revealed mucinous material without any signs of malignant cells on histopathological examination. Gastro-intestinal duplication cyst was considered as one of the possible diagnoses and diagnostic laparoscopy was planned. During laparoscopic exploration we observed a 3 cm × 3 cm sized paraesophageal cystic lesion at the gastro-esophageal junction, 2-3 cm above the Z-line (Figure 3). The cyst was dissected free and the connection with the oesophagus was excised with an endoGIA© after which the staple line was oversewn with a V-loc© suture. The procedure went uneventful.

Histopathological analysis of the specimen revealed a 30 mm × 30 mm × 25 mm sized cyst filled with clear fluid. The wall had a thickness of 3 mm and consisted of two muscular layers lined by respiratory columnar epithelium without any signs of cartilage tissue found in the cyst (typical for bronchogenic cysts) and therefore the final diagnosis of esophageal duplication cyst was suggested (Figure 4).

The postoperative course was uncomplicated and the patient could be discharged on day two postoperatively. At follow up 5 mo later the patient did not display any of the earlier experienced abdominal symptoms.

DISCUSSION

Gastrointestinal duplication cysts are very rare abnormalities. Autopsy studies have shown a prevalence of approximately 1:4500 and esophageal duplications occur even less frequently, 1:8200[2,3]. Only a few cases are described in which the cyst is connected to the intra-abdominal part of the esophagus. Only ten percent of the esophageal cysts communicate with the lumen of the esophagus[4].

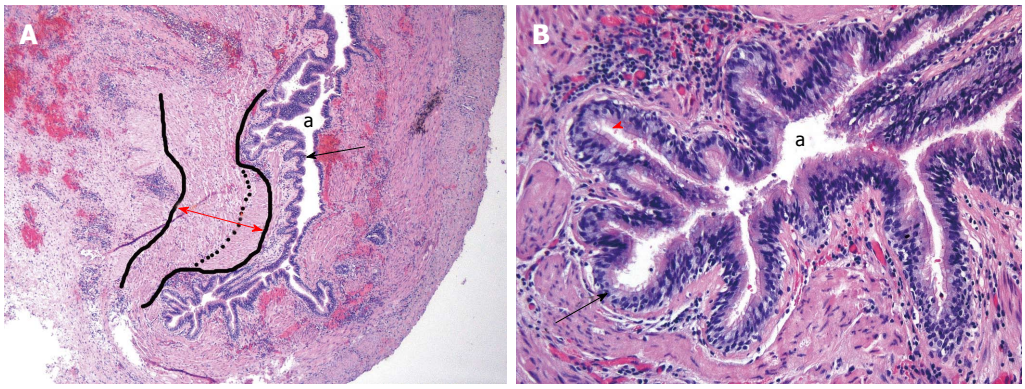

Figure 4 Histological findings of the cyst (hematoxylin/eosin staining). A: Magnification × 20; B: Magnification × 40. Indicated are the lining of respiratory epithelium (black arrows) with a muscularis propia consisting of two muscular layers (red arrow), the lumen of the cyst (a) and the ciliated pseudo stratified columnar epithelium (red arrowhead).

Table 1 Overview of published case reports of intra-abdominal esophageal duplication cysts

Ref.	Year	Patients age	Sex	Symptoms	Location of cyst	Size (cm)	Treatment
Pujar *et al*[1]	2013	13	F	Pain in epigastric region	Gastroesophageal junction, adjacent to left liver lobe	4.0 × 5.0	Laparoscopic resection
Bhamidipati *et al*[7]	2013	69	M	Weight loss, incidental at CT for diverticulitis	Gastroesophageal junction	4.4 × 3.7 × 3.9	Laparoscopic resection
Gümüş *et al*[8]	2011	18	F	At CT for dyspeptic complaints	Lower end of the esophagus, adjecent to liver	4.2 × 3.6	Open resection
Aldrink *et al*[2]	2011	2	M	No symptoms. Incidental at fundoplication	Gastroesophageal junction	3.0	Laparoscopic resection, with fundoplication
Martin *et al*[5]	2007	60	M	Gastric outlet obstruction	Retro-duodenal	10.0 × 10.0	Open resection
Martin *et al*[5]	2007	50	F	Left flank pain	Inferior to pancreatic tail	6.5 × 5.5 × 4.2	Open resection
Kin *et al*[9]	2003	51	F	No symptoms: incidental at staging CT for breastcancer	Diafragmatic crura	4.5 × 4.0 × 3.5	Laparoscopic resection with intra-operative esophagoscopy
Noguchi *et al*[10]	2003	26	F	Anal bleeding: incidental at ultrasound	Anterior wall of distal esophagus	4.0 × 3.0 × 3.0	Laparoscopic resection with esophageal repair(nissen)
Vijayaragh *et al*[11]	2002	70	F	Retching, rigidness and headache, incidental at ultrasound	Midline between stomach and liver	7.5	Open resection, combined with cholecystectomie
Nelms *et al*[4]	2002	44	M	Low back pain: incidental at CT	Diaphragmatic crura	7.0	Laparoscopic resection
Rathaus *et al*[12]	2000	5	F	Epigastric pain, ultrasound	Distal esophagus, between liver and cardia	1.0	Open resection
Janssen *et al*[13]	1998	56	F	Incidental at staging CT for rectal cancer	Superior to left kidney	8.0 × 6.0 × 4.5	Open resection
Karahasanoglu *et al*[14]	1997	51	M	Epigastric pain, dysphagia	Sub-diaphragmatic	11.0 × 9.0 × 8.0	Esophagogastrectomy
Harvell *et al*[15]	1996	57	F	Epigastric pain	Superior border of pancreas	2.2 × 1.7 × 1.5	Laparoscopic resection
Ruffin *et al*[16]	1989	38	F	Epigastric pain, nausea	Distal esophagus	4.0	Resection with esophageal repair

M: Male; F: Female; CT: Computed tomography.

Table 1 shows an overview of the abdominal cases that have been published so far. This overview shows that most cysts were asymptomatic and found incidental. In case of symptoms the most common complaint was epigastrical pain. In all cases the cyst was surgically removed, of which nearly 50% by means of laparoscopy. Four cases appeared in minors, 11 cases in adults. The median age at diagnosis was 50 years.

Besides the location of the cyst, a differentiation between the origin of the cyst can be made. Although it might not have clinical relevance in case of an asymptomatic cyst, the origin can be bronchogenic, esophageal, gastroenteric, neurenteric or pericardial. The latter three are histologically easy to differentiate. Gastroenteric and neurenteric cysts are lined with gastric mucosa and pericardial cysts are lined with flattened mesothelium. The difference between a bronchogenic and esophageal cyst is more difficult since both derive from the foregut and

contain ciliated epithelium. To differentiate bronchogenic from esophageal duplication cysts, Palmer's pathologic criteria are useful. These criteria include: (1) attachment to the esophageal wall; (2) presence of gastrointestinal tract epithelium; and (3) presence of two layers of muscularis propria[5]. Duplication cysts of bronchogenic origin do not have these two layers of smooth muscle, instead they contain cartilage, bronchogenic glands or both.

In intra-abdominal esophageal duplication cysts Palmer's criteria are not always applicable[4]. For example, in 2007 Martin *et al*[5] presented two cases of isolated intra-abdominal esophageal duplication cyst with no connection to any luminal organ.

The majority (80%) of esophageal duplication cysts becomes symptomatic during childhood and will be removed for that reason[1]. As a consequence these types of cysts are rarely seen in adults. If they are found during adulthood, they are mostly asymptomatic and most case reports are therefore based on an incidental finding during some kind of routine radiological investigation. However cysts can become symptomatic, like in our patient, causing abdominal pain, vomiting, dysphagia or reflux[1,2]. The growing cyst may also cause some mechanical problems of the passage of solid food and fluids because of compression of the esophagus[2]. Finally these cysts can perforate, they can cause an upper gastrointestinal bleeding or can get infected. Although a causal relationship is difficult to define, one case report has described a patient with a duplication cyst with an associated intracystic malignancy[6]. Because of these complications it is recommended to excise the cyst, whether it is symptomatic or not.

In our patient, symptoms of colic-like abdominal pain were initially addressed to symptomatic cholecystolithiasis, but eventually an esophageal duplication cyst appeared to be the actual cause of his symptoms. Although these cysts are very rare and mostly asymptomatic, they can mimic symptoms of common gastro-intestinal conditions. Therefore, one should consider these anomalies as a possible diagnosis if more obvious causes are excluded.

COMMENTS

Case characteristics

A 20-year-old male with a history of a cholecystectomy presents with colic like symptoms mimicking a cholecystolithiasis.

Clinical diagnosis

No abnormalities were found during physical examination, especially no pain during palpation of the right upper region of the abdomen.

Differential diagnosis

Choledocholithiasis, urolithiasis, esophageal duplication cyst

Laboratory diagnosis

Lab results showed no abnormalities in particular no signs of inflammation nor infection.

Imaging diagnosis

Computed tomography-scan and endoscopic ultrasonography (EUS) showed a 3.2 cm × 2.8 cm sized smooth lined lesion in the distal esophagus just below the diaphragm.

Pathological diagnosis

Histopathological analysis of the specimen revealed a 30 mm × 30 mm × 25 mm esophageal duplication cyst filled with clear fluid and a double muscular layer lined with respiratory columnar epithelium without any signs of cartilage.

Treatment

Laparoscopic excision of this cyst was performed.

Related reports

An esophageal duplication cyst is a rare diagnosis and is often asymptomatic.

Term explanation

An EUS is an endoscopic ultrasonography, which is an ultrasound made through the esophagus.

Experiences and lessons

Although these cysts are very rare and mostly asymptomatic, they can mimic symptoms of common gastro-intestinal conditions. Therefore, one should consider these anomalies as a possible diagnosis if more obvious causes are excluded.

Peer review

The paper describes a rare case of a symptomatic intra-abdominal esophageal duplication cyst and gives a complete overview of published cases until now. This case is very interesting for gastrointestinal surgeons. The paper is well written and concise.

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CASE REPORT

Repair of an aberrant subclavian arterioesophageal fistula following esophageal stent placement

Maen Aboul Hosn, Fady Haddad, Fadi El-Merhi, Bassem Safadi, Ali Hallal

Maen Aboul Hosn, Bassem Safadi, Ali Hallal, Division of General Surgery, Department of Surgery, American University of Beirut, Riad El-Solh, Beirut 1107 2020, Lebanon
Fady Haddad, Division of Vascular Surgery, Department of Surgery, American University of Beirut, Riad El-Solh, Beirut 1107 2020, Lebanon
Fadi El-Merhi, Department of Diagnostic Radiology, American University of Beirut, Riad El-Solh, Beirut 1107 2020, Lebanon
Author contributions: All authors actively participated in the design, drafting, revision and final approval of the manuscript prior to submission; Hosn MA and Safadi B did most of the literature review; Haddad F and El-Merhi F were involved in writing the manuscript and evaluating the relevance of the sources obtained; Hallal A did the manuscript editing and critical appraisal.
Correspondence to: Maen Aboul Hosn, Chief Resident, Division of General Surgery, Department of Surgery, American University of Beirut, P.O.Box 11-0236, Riad El-Solh, Beirut 1107 2020, Lebanon. ma198@aub.edu.lb
Telephone: +961-3-079863 Fax: +961-1-363291
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Abstract

A fistula formation between the esophagus and an aberrant right subclavian artery is a rare but fatal complication that has been mostly described in the setting of prolonged nasogastric intubation and foreign body erosion. We report a case of a young morbidly obese patient who underwent sleeve gastrectomy that was complicated by a postoperative leak at the level of the gastroesophageal junction. A covered esophageal stent was placed endoscopically to treat the leak. The patient developed massive upper gastrointestinal bleeding secondary to the erosion of the stent into an aberrant retroesophageal right subclavian artery twelve days after stent placement. She was ultimately treated by endovascular stenting of the aberrant right subclavian artery followed by thoracotomy and esophageal repair over a T-tube. This case report highlights the multidisciplinary approach needed to diagnose and manage such a devastating complication. It also emphasizes the need for imaging studies prior to stent deployment to delineate the vascular anatomy and rule out the possibility of such an anomaly in view of the growing popularity of esophageal stents, especially in the setting of a leak.

Key words: Aberrant subclavian artery; Arterioesophageal fistula; Esophageal stent; Esophageal repair; Angioplasty; Sleeve gastrectomy; Leak

Core tip: The use of esophageal covered stents to treat leaks following sleeve gastrectomy has increased significantly over the past years. However, their possible complications have not yet been fully explored. As demonstrated by our case report, the presence of an aberrant retroesophageal Subclavian artery can predispose to the formation of a fistula with the esophagus secondary to stent erosion, thereby leading to catastrophic hemorrhage and death. Our approach in this case was to start with stent angioplasty of the Subclavian artery followed by thoracotomy and esophageal repair over a T-tube and this approach proved successful in saving the patient's life.

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INTRODUCTION

Aorto-esophageal and arterial-esophageal fistulae have both been described in the literature. These usually arise in the setting of arterial aneurysms and esophageal malignancy. An aberrant subclavian arterioesophageal fistula,

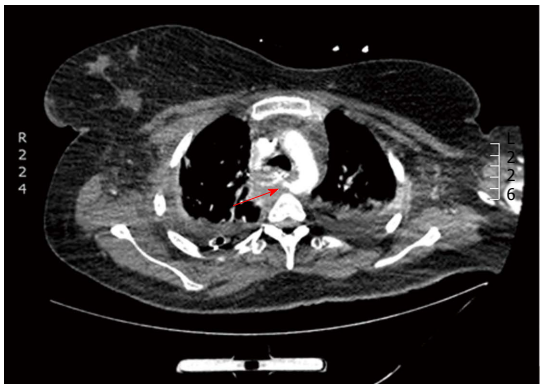

Figure 1 Computed tomography angiography showing a retroesophageal right suclavian artery with a pseudoaneurysm (arrow) around 1cm from its takeoff.

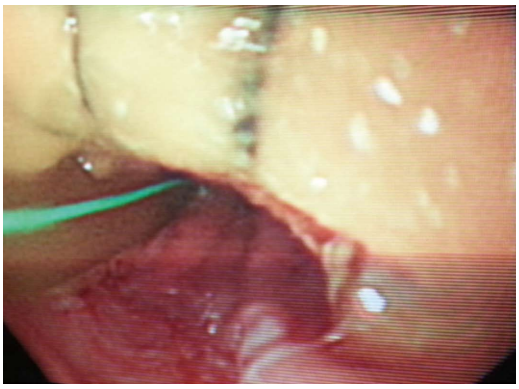

Figure 2 Upper endoscopy showing a 2 cm × 3 cm Teflon patch 22 cm from the incisor.

on the other hand, is an exceedingly rare occurrence and has been mostly reported in association with prolonged nasogastric intubation and erosion of esophageal instrumentation into the retroesophageal vessel. The mortality rate in such cases is extremely high as the bleeding is usually massive and sudden and ultimately leads to hemorrhagic shock and death. There are only a handful of reported cases of successful management of such a fistula. This paper describes the case of a young female who developed this devastating complication following the placement esophageal covered stent to treat a leak after sleeve gastrectomy. It also highlights the multidisciplinary approach used to diagnose and treat this complication.

CASE REPORT

A 29-year-old morbidly obese female developed a leak at the gastroesophageal junction following laparoscopic sleeve gastrectomy and underwent jejunostomy feeding tube insertion to allow spontaneous closure of the fistula. A gastrografin swallow performed a month later showed persistence of the leak. The patient then underwent an uneventful endoscopic stenting to exclude the leak and was discharged home on the same day. Twelve days later, she developed massive hematemesis and was taken to a district general hospital in a state of shock, where she was intubated and resuscitated. She underwent endoscopic removal of the stent followed by right thoracotomy, esophageal exploration and suturing of the fistula opening from the esophageal mucosal side thus obliterating and controlling the bleeding, followed by primary repair of the esophagus. Twelve hours later, the patient had a second episode of massive upper gastrointestinal (GI) bleeding and was in shock. She was taken back to the operating room where she was re-explored through a right thoracotomy. The esophagus was opened again and the bleeding site at the posterior wall of the esophagus was overrun and buttressed with a Teflon patch. She received a total of 29 units of packed red blood cells and 15 units of fresh frozen plasma. She was transferred to the intensive care unit at our medical center in critical condition. Computed tomography (CT) angiography revealed the presence of an esophageal perforation and a large pseudoaneurysm involving a right aberrant subclavian artery but there was no evidence of active bleeding at that point in time (Figure 1). Upper endoscopy revealed the presence of a Teflon patch within the lumen of the esophagus. The Teflon patch measured 2 cm × 3 cm and was placed at 22 cm from the incisors (Figure 2). After stabilizing the patient, she was taken to the interventional radiology suite for endovascular stenting and exclusion of the subclavian pseudoaneurysm to be followed by definitive surgical repair of the esophagus. Thoracic aorta angiography was performed and it revealed the presence of a right aberrant subclavian artery and a diverticulum of Kommerell as well as a 7 mm pseudoaneurysm approximately 1 cm from the origin of the right aberrant subclavian artery (Figure 3A). A right brachial artery cut down was then performed and a 6F sheath was used to deploy an 8 mm × 38 mm ATRIUM covered stent over the targeted area. Sequential balloon dilatation of the stent was then performed using 12 mm × 2 mm and 12 mm × 3 mm balloons and completion angiography demonstrated total occlusion of the pseudoaneurysm (Figure 3B). Following angioplasty, a right posterolateral thoracotomy with esophageal exploration was performed. The esophagotomy site was located above the division of the azygous vein. It was opened longitudinally and the Teflon patch was released from the posterior wall of the esophagus on the mucosal side (Figure 4). There was no evidence of bleeding through the surgically obliterated fistulous opening. The esophagus and its mucosa looked healthy and therefore primary closure over a 19F T-tube was performed. The esophagotomy was closed as a single layer using interrupted Polydioxanone sutures and was then buttressed with a fourth intercostal muscle flap.

The patient had a complicated postoperative course as she developed Acute Respiratory Distress Syndrome and was kept on mechanical ventilation for 10 d. She was fed through the previously inserted jejunostomy feeding tube. A gastrografin swallow performed two weeks after her surgery showed no evidence of contrast leak at the level of the esophageal repair (Figure 5). She was discharged home 33 d after her last operation. Twelve weeks later, the T tube was removed and she was started

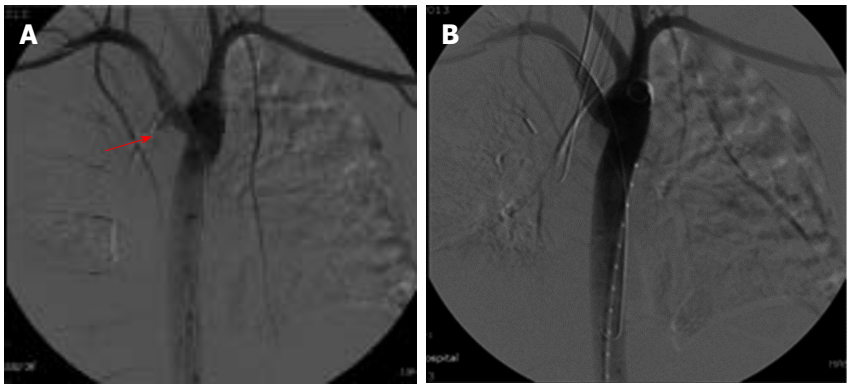

Figure 3 Thoracic aortic angiography. A: Showing the pseudoaneurysm (arrow); B: Angiography after stent deployment.

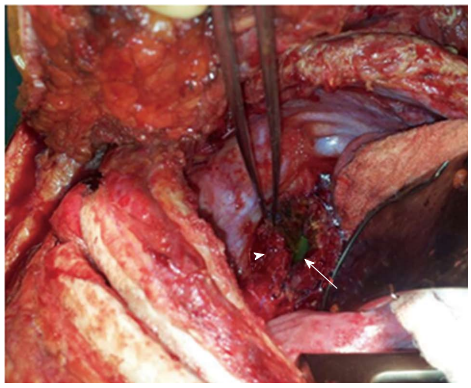

Figure 4 Thoracotomy with the Teflon patch (arrowhead) and nasogastric tube (arrow) visible through the esophagotomy.

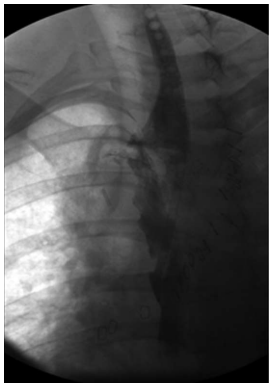

Figure 5 Gastrografin swallow performed postoperatively showing no evidence of a contrast leak at the site of the esophageal repair.

on regular oral feeding after a CT scan with oral contrast revealed no evidence of contrast extravasation (Figure 6).

DISCUSSION

An aberrant retroesophageal subclavian artery, also known as arteria lusoria, is the most common aortic arch anomaly. It has an incidence of 0.2% to 2% in the general population and is even more prevalent in patients with Down syndrome[1]. The persistence of the right dorsal aorta (known as Kommerell's diveritculum) and involution of the right 4th embryologic arch causes the advent of an aberrant right subclavian artery (ARSA)[2]. It is usually asymptomatic but may cause dysphagia (dysphagia lusoria) and may demonstrate symptomatic atherosclerotic and aneurysmal degeneration[3].

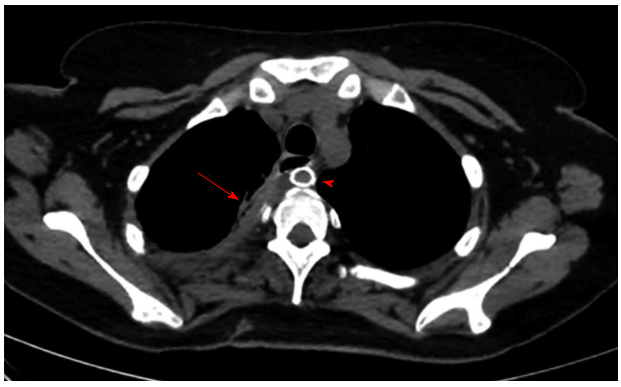

Figure 6 Computed tomography scan with oral contrast done after removal of the T-Tube with both the remnant tract of the T-tube (arrow) and the subclavian artery stent (arrowhead) seen.

Aorto-esophageal, arterial-esophageal, and aorto-enteric fistulae have all been described in the literature mainly in the setting aortic aneurysms, aortitis, atherosclerosis, and gastrointestinal malignancies[4]. Such fistulae have also been described in otherwise healthy people secondary to sharp trauma to the esophagus after swallowing animal bones, dentures, coins and other sharp objects[5]. A fistula between the esophagus and an ARSA, however, remains an exceptional event that has mostly been described in association with prolonged NG intubation[6]. The abnormal anatomic proximity to the esophagus or trachea likely renders the aberrant subclavian artery vulnerable to extrinsic compression and pressure necrosis by indwelling NG or endotracheal (ET) tubes[7]. The sequence of events may involve occlusion and thrombosis of the vasa vasorum, leading to vessel wall infarction and eventual wall dissolution. Moreover, ischemia and bacterial invasion of the vessel wall have also been suggested as important etiologic factors[8]. Unlike aorto-esophageal fistulae which present with sentinel bleeding in around 63% of cases, ARSA-esophageal fistulae present with

massive upper GI bleeding with an associated mortality approaching 100%[5]. As such, early diagnosis is of paramount importance.

In our literature review, we were able to find 17 reported cases of ARSA-esophageal fistulae out of which, only 4 patients survived the acute event[9-12]. In all reported cases, bleeding was sudden, unheralded by prior symptoms, and massive. In the surviving patients, the upper GI bleeding was controlled by a multidisciplinary approach consisting of endoscopic balloon compression or angiographic control or both, and the definitive therapy was provided by urgent surgery. Described successful surgical interventions include ligation of the subclavian artery after angiographic or endoscopic control followed mostly by subclavian artery bypass. Left thoracotomy has been advocated for satisfactory control of the aorta and ligation of the origin of the ARSA, but other recommendations include right thoracotomy for optimal exposure for both the arterial resection and the esophageal repair[10]. Miller *et al*[9] described the first successful repair of such a fistula in a young girl who developed massive hematemesis two weeks after insertion of an Endotracheal (ET) and NG tubes. She underwent left thoracotomy with esophagotomy and intraesophageal balloon tamponade by positioning a 30F Foley catheter at the bleeding point to control the hemorrhage and allow the patient to be stabilized hemodynamically. Following that, aortic arch arteriography through a right femoral approach was performed demonstrating an aberrant right subclavian artery as well as contrast extravasation consistent with a fistula between the anomalous vessel and the esophagus. The involved segment of the aberrant vessel was then ligated and resected via right thoracotomy, and the esophagus was repaired primarily. No revascularization of the right upper extremity was performed and the patient was reported to be symptom free. A similar successful repair was reported by Feugier *et al*[10] in which a 24-year-old male with prolonged Intensive Care Unit stay following polytrauma developed massive upper GI bleeding 31 d after insertion of ET and NG tubes. Urgent CT angiography revealed an ARSA in direct contact with the NG tube. Angiography was then performed through the right brachial artery confirming contrast extravasation and the bleeding was controlled by inflating a 7 mm × 20 mm balloon. The patient then underwent left anterolatral thoracotomy with ligation of the subclavian origin and carotid to subclavian bypass.

Embolization of the bleeding vessel has been described but it may not always be successful in stopping the bleeding and may even create further complications. This was demonstrated by Vanden Eynden *et al*[11] in a patient with an esophageal stent that was placed to manage an esophageal stricture and eroded into a retroesophageal subclavian artery. Attempted endovascular coil embolization failed to control the bleeding vessel and the patient underwent urgent exploration with ligation of the artery at its takeoff while the endoesophageal prosthesis was left in place followed by construction of an aorto-axillary bypass using an 8-mm polytetrafluoroethylene graft constructed between the lateral aspect of the ascending aorta and the axillary artery. Postoperative endoscopy revealed erosion of the deployed endovascular coils into the lumen of the esophagus.

Complete endovascular repair with covered stents without dividing the fistulous tract theoretically carries a risk of graft infection and should be reserved to extremely critical patients when a rapid and minimally invasive procedure could positively affect patient's outcome. Magagna *et al*[12] reported the placement of a 14 mm endovascular prosthesis in an ARSA to cover a fistula between the artery and the oesophagus in an elderly female with a tracheostomy and history of laryngectomy and radiotherapy who presented with massive upper GI bleeding. The procedure was performed after the bleeding was controlled by positioning a Sengstaken-Blakemore tube and the patient was stabilized.

The surgical rationale followed in our case which included stenting of the artery followed by thoracotomy and primary esophageal repair over T tube and buttressing with an intercostal muscle flap has never been attempted in the literature but appears to be an equally effective and successful option. Although our patient' s initial operation to control her bleeding stabilized her enough to allow for endovascular stenting of the pseudoaneurysm, it also necessitated another esophageal exploration for removal of the prosthetic patch and definitive esophageal repair. As the patient had two previous thoracotomies, it was of paramount importance to make sure that the esophageal repair is solid and to rule out a communication between the posterior wall of the esophagus and the stent that was placed in the subclavian artery. The Teflon patch that was previously placed in the lumen of the esophagus prevented us from assessing the posterior lumen of the esophagus and the integrity of the esophageal wall. It is also important to point to the fact that our patient had a sleeve gastrectomy, which precluded the option of using the stomach as conduit in the future should the esophageal repair fail. It was therefore extremely important to preserve the esophagus and as such, exploration and repair over a T-tube rather than a diverting cervical esphagostomy seemed the only treatment option.

ARSA-esophageal fistula is a rare but devastating complication of prolonged esophageal stenting and intubation and should be included in the differential diagnosis when investigating upper GI bleeding in patients with prolonged NG and ET intubation. It requires a multidisciplinary approach of different specialties including general and cardiothoracic surgery, interventional radiology, vascular surgery and intensive care. Angiography is an essential diagnostic and therapeutic tool as endoluminal balloons and stent grafts can be used as temporizing measures when feasible. Thoracotomy with ligation of the bleeding vessel and repair of the esophagotomy followed by revascularization of the right arm appears to be the most successful approach described in the literature. However, as demonstrated in our case, endovascular stenting of the fistulous tract followed by esophageal re-

pair offers an alternate effective treatment modality. Taking into account the poor survival after massive bleeding caused by an esophageal stent erosion into a major mediastinal vessels, and given the fact that esophageal stenting is gaining ground in the management of esophageal and gastroesophageal junction leaks post bariatric surgery[13], we recommend CT angiography of the chest to rule out the presence of the not uncommon ARSA in patients considered for prolonged esophageal stent placement.

COMMENTS

Case characteristics

Twenty-nine years old obese female with history of leak following sleeve gastrectomy underwent esophageal stent placement.

Clinical diagnosis

Massive upper gastrointestinal bleeding with hemorrhagic shock 12 d after stent placement.

Differential diagnosis

Bleeding gastric ulcer, esophageal bleeding, erosion of the stent into a major vessel.

Laboratory diagnosis

White blood cells 10.1 k/μL; HGB 6 mg/dL; hematocrit 18%; the electrolytes and metabolic panel were within normal limits.

Imaging diagnosis

Computed tomography angiography showed a communication between the esophagus and an aberrant retroesophageal right subclavian artery around 1 cm from the takeoff of the artery.

Pathological diagnosis

The esophageal covered stent eroded through the layers of the esophagus posteriorly reaching the aberrant Subclavian artery.

Treatment

Endovascular stenting of the Subclavian artery was first performed followed by thoracotomy and repair of the esophageal perforation over a T tube with intercostal muscle flap coverage.

Related reports

Aberrant right Subclavian rterioesophageal fistulas have been reported in the setting of prolonged nasogastric and endotracheal intubation causing erosion of the tube through the esophageal wall into the adjacent vessel with a high associated mortality rate.

Term explanation

An aberrant right Subclavian artery describes an anatomic variant in which the right Subclavian artery arises distal to the left Subclavian artery and courses behind the esophagus.

Experiences and lessons

This case report is the fifth reported case in literature of successful treatment of an aberrant subclavian arterioesophageal fistula. This was achieved by adopting a multidisciplinary approach spanning over different medical and surgical specialties. To prevent such a devastating complication, computed tomography angiography should be done to rule out the presence of an aberrant retroesophageal artery when contemplating the use of an esophageal stent for a prolonged period of time.

Peer review

The case is very interesting and the subject clinically relevant. The manuscript is well written and the images are nice. The subject is nicely reviewed in the discussion.

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Beijing 100025, China
Telephone: +86-10-85381891
Fax: +86-10-85381893
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REVIEW

Mechanisms of hepatic ischemia-reperfusion injury and protective effects of nitric oxide

Lian-Yue Guan, Pei-Yao Fu, Pei-Dong Li, Zhuo-Nan Li, Hong-Yu Liu, Min-Gang Xin, Wei Li

Lian-Yue Guan, Pei-Yao Fu, Pei-Dong Li, Zhuo-Nan Li, Hong-Yu Liu, Wei Li, Department of Hepatobiliary-Pancreatic Surgery, Third Hospital (China-Japan Union Hospital) of Jilin University, Changchun 130033, Jilin Province, China
Min-Gang Xin, Departments of Anesthesiology, Third Hospital (China-Japan Union Hospital) of Jilin University, Changchun 130033, Jilin Province, China
Author contributions: Guan LY and Fu PY contributed equally to the paper; Guan LY primarily drafted the article; Fu PY performed the intensive revision and drew the two figures; Li PD drafted the nitric oxide portion of the manuscript; Li ZN, Liu HY and Xin MG conducted the data collection and interpretation, selected the references, and drafted the discussion; Li W contributed to the concept design, critical revision and finalization of the manuscript.
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Correspondence to: Wei Li, MD, PhD, Department of Hepatobiliary-Pancreatic Surgery, Third Hospital (China-Japan Union Hospital) of Jilin University, 126 Xiantai Street, Changchun 130033, Jilin Province, China. weili888@hotmail.com
Telephone: +86-431-89876816 Fax: +86-431-84641026
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Abstract

Hepatic ischemia-reperfusion injury (IRI) is a pathophysiological event post liver surgery or transplantation and significantly influences the prognosis of liver function. The mechanisms of IRI remain unclear, and effective methods are lacking for the prevention and therapy of IRI. Several factors/pathways have been implicated in the hepatic IRI process, including anaerobic metabolism, mitochondria, oxidative stress, intracellular calcium overload, liver Kupffer cells and neutrophils, and cytokines and chemokines. The role of nitric oxide (NO) in protecting against liver IRI has recently been reported. NO has been found to attenuate liver IRI through various mechanisms including reducing hepatocellular apoptosis, decreasing oxidative stress and leukocyte adhesion, increasing microcirculatory flow, and enhancing mitochondrial function. The purpose of this review is to provide insights into the mechanisms of liver IRI, indicating the potential protective factors/pathways that may help to improve therapeutic regimens for controlling hepatic IRI during liver surgery, and the potential therapeutic role of NO in liver IRI.

Key words: Liver; Ischemia-reperfusion injury; Cytokine; Chemokine; Kupffer cells; Mitochondria; Nitric oxide

Core tip: This review provides insights into several key mechanisms of liver ischemia-reperfusion injury, including the effects of anaerobic metabolism and the role of mitochondria, oxidative stress, intracellular calcium overload, liver Kupffer cells and neutrophils, and cytokines and chemokines; and summarizes the protective effects of nitric oxide.

Guan LY, Fu PY, Li PD, Li ZN, Liu HY, Xin MG, Li W. Mechanisms of hepatic ischemia-reperfusion injury and protective effects of nitric oxide. *World J Gastrointest Surg* 2014; 6(7): 122-128 Available from: URL: http://www.wjgnet.com/1948-9366/full/v6/i7/122.htm DOI: http://dx.doi.org/10.4240/wjgs.v6.i7.122

INTRODUCTION

In recent years, liver resection and liver transplantation have been widely adopted in clinical practice for the treatment of liver diseases. Hepatic ischemia-reperfusion injury (IRI) occurs substantially during liver resection or

transplantation and remains a major cause of liver non-function or functional failure following liver surgery. This non-negligible injury has become a bottleneck which has restricted the use of marginal liver donors and the development of extensive liver resection. Hepatic IRI includes both warm and cold IRI - two types that share similar pathophysiological processes. The mechanisms of liver IRI have been widely investigated, but nevertheless remain largely unclear. The factors/pathways have been implicated in the hepatic IRI process include anaerobic metabolism, mitochondria, oxidative stress, intracellular calcium overload, liver Kupffer cells (KCs) and neutrophils, and cytokines and chemokines. More importantly, an effective prevention or treatment method is still lacking. Therefore, an effective method for preventing or minimizing hepatic IRI during liver surgery is urgently needed. A better understanding of the mechanisms in the development of IRI will provide insights into improving the treatment regimen for IRI. In this review, the authors comprehensively discuss the mechanisms of liver IRI and describe the role of nitric oxide (NO) in protecting the liver from IRI.

ANAEROBIC METABOLISM AND ACIDOSIS

IRI exerts wide-ranging metabolic effects on the body. During the state of hepatic ischemia, the metabolic pattern is shifted from aerobic to anaerobic, the redox process of the hepatocytes is blocked, adenosine triphosphate (ATP)-dependent cellular metabolic activities are gradually stopped, and intracellular ATP is rapidly depleted. Conversely, there is accumulation of acidic metabolites, such as lactic acid and ketone bodies, which is caused by enhanced anaerobic glycolysis. This is accompanied by hypofunction of mitochondrial oxidative phosphorylation, resulting in the decrease of pH values between tissues and cells, known as metabolic acidosis. Studies have shown that this change plays a role in protecting the liver cells[1,2]. However, the pH values restore to normal after reperfusion, and further enhance pH-dependent enzyme activation, such as activation of proteases and phospholipases, further worsening the damage of tissues and organs. This is called the pH paradox[3]. The toxicity of acidic metabolites caused by a lower ATP supply mainly impairs the cellular functions of homeostasis, signaling interactions, and sodium/potassium ATPase (Na^+/K^+-ATPase), causing mitochondrial damage and resulting in microcirculation failure and cellular destruction[4].

ROLE OF MITOCHONDRIA

IRI exerts effects not only on the body as a whole, but also at the cellular level. The mitochondria are the location where oxidative phosphorylation mainly takes place, and the mitochondria participate in multiple pathophysiological processes of IRI. A large number of reactive oxygen species (ROS) and reactive nitrogen species are generated in the mitochondria during the state of ischemia. Hypoxia undermines the process of oxidative phosphorylation in cells and obstructs the production of ATP, causing disorders of the cytoplasmic ions such as Ca^{2+}, Na^+, and H^+ in the mitochondria, and finally leads to mitochondrial membrane permeability transition (MMPT)[5]. MMPT is manifested primarily by mitochondrial swelling and the decline of membrane potential[6], which allows soluble molecules of a molecular weight less than 1500 kDa to freely pass through the inner mitochondrial membrane, the so-called "mitochondrial megachannel"[7]. Many studies have indicated that MMPT is related to the process of hepatocyte damage after IRI[5,8].

OXIDATIVE STRESS

IRI has many biochemical ramifications. It has been shown that oxidative stress plays a key role in reperfusion injury. Many highly reactive molecules, such as ROS, are induced during the period of hepatic IRI. ROS include superoxide anions, hydroxyl radicals, and peroxide hydrogen, and mainly act on proteins, enzymes, nucleic acids, cytoskeleton, and lipid peroxides, leading to mitochondrial dysfunction and lipid peroxidation[9]. ROS can also damage endothelial cells and destroy the integrity of the microvasculature. ROS can be reduced or overcome by reducing the blood flow and applying endogenous antioxidants, such as superoxide dismutase, catalase, glutathione, vitamin E, or beta-carotene[10]. On the other hand, application of recombinant adenovirus superoxide has been shown to effectively reduce hepatic IRI in mice[11].

INTRACELLULAR CALCIUM OVERLOAD

Among the biochemical factors affected by IRI, calcium has an especially important role. The electrochemical gradient of the calcium ion plays an important role in maintaining homeostasis of physical calcium (Ca^{2+}). If the calcium level is elevated when ischemia or hypoxia, oxidative stress, toxic substance release or other harmful events occur, this is called Ca^{2+} overload. Intracellular Ca^{2+} overload can activate Ca^{2+}-dependent enzymes such as calpains, protein kinase C, and phospholipase C, and ultimately leads to cell death or apoptosis. Recent studies have shown that the increased amount of intracellular Ca^{2+} is not uniform, but is a local phenomenon. Non-specific calcium channel blockers can inhibit the elevation of intracellular Ca^{2+} and reduce cellular damage, demonstrating that Ca^{2+} influx may play a major role in the IRI process[12,13].

KCS AND NEUTROPHILS

It has been demonstrated that liver KCs and neutrophils are involved in the hepatic IRI process. The KCs mainly mediate liver ischemic injury in the earlier stage of reperfusion (within 2 h) by synthesizing and releasing

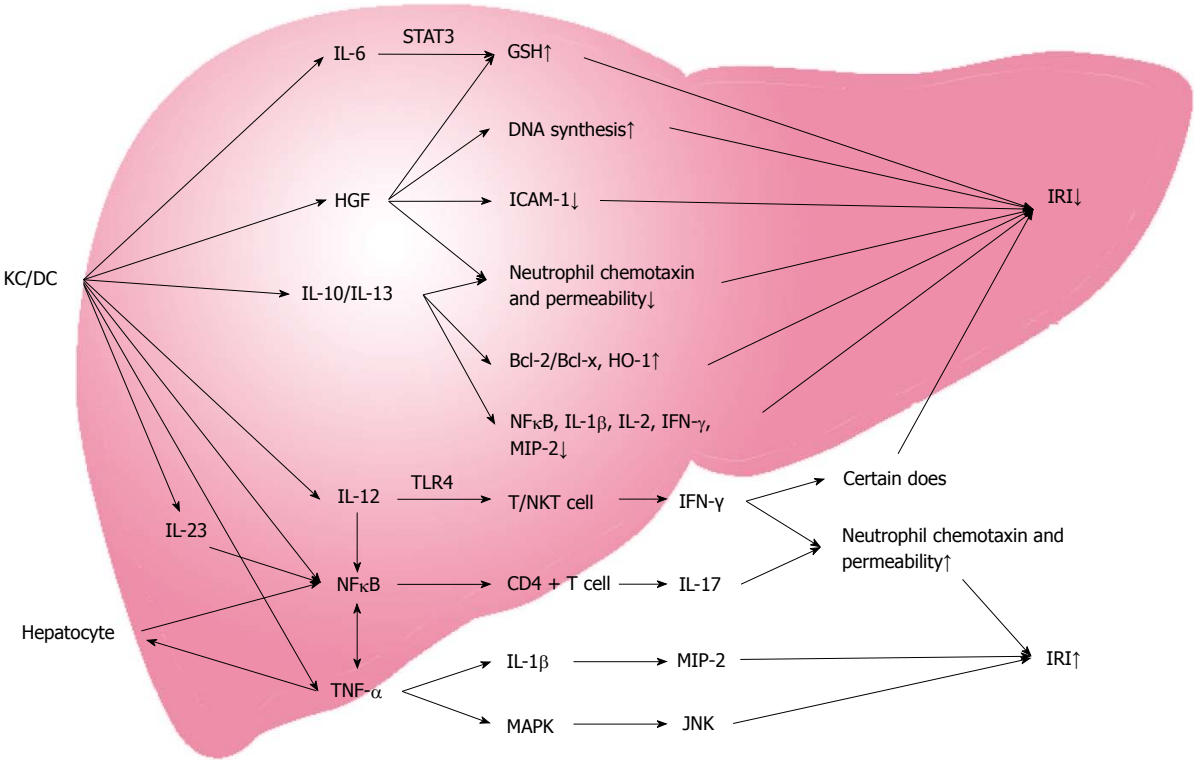

Figure 1 Cytokine network on the regulation of liver ischemia-reperfusion injury. IRI: Ischemia-reperfusion injury; IL: Interleukin; IFN-γ: Interferon-gamma; HGF: Hepatocyte growth factor; MIP: Macrophage inflammatory protein; ICAM-1: Intercellular adhesion molecule 1; NF: Nuclear factor; MAPK: Mitogen-activated protein kinase.

ROS and the pro-inflammatory cytokines tumor necrosis factor-alpha (TNF-α) and interleukin (IL)-1β to further activate liver sinusoidal endothelial cells, enhance the expression of the adhesion molecules intercellular adhesion molecule 1 (ICAM-1)/vascular cell adhesion molecule 1 (VCAM-1), further promote the adhesion, migration, and chemotaxis of neutrophils and endothelial cells, and accumulate and activate neutrophils, resulting in subsequent liver cell damage[14]. Studies have shown that endotoxins are also involved in the process of liver IRI[10,15]. Blocking KC activation by the use of gadolinium chloride or methyl palmitate can reduce acute liver cell injury significantly. Activation of neutrophils can directly damage liver cells by the release of oxidants and proteases after reperfusion. Ultimately, myeloperoxidase (halide form, such as Cl) released from neutrophils changes hydrogen peroxide (H_2O_2) into hypochlorous acid (HOCl), which is a potent oxidant. These oxidants can directly cause liver cell damage and/or induce protease-mediated injury through inactivation of the endogenous anti-protease system[15,16], suggesting that anti-oxidant or anti-protease therapy would be helpful for preventing IRI.

ROLE OF CYTOKINES AND CHEMOKINES

Cytokines play a dual role of anti-inflammatory and pro-inflammatory responses in the process of liver IRI (Figure 1). TNF-α is a key member of the group of endogenous pro-inflammatory and anti-inflammatory molecules, and is a critical factor in triggering the inflammatory cascade. It is secreted by activated KCs and impacts liver tissue and distant organs through paracrine signaling and the endocrine system[17]. TNF-α can bind to the receptors on the surface of liver cells to induce overproduction of the chemokine epithelial neutrophil activating protein-78 (ENA-78) and ROS, activate nuclear factor (NF)-κB, mitogen-activated protein kinase, and c-Jun N-terminal kinase (JNK), and cause liver injury directly[18]. In addition, TNF-α also can upregulate expression of the chemokines ICAM-1, VCAM-1 and P-selectin[19]. Moreover, JNK and ROS can directly act on liver cells to cause liver damage.

In addition to TNF-α, the other important cytokines involved in liver IRI are interferon-gamma (IFN-γ), IL-1β, IL-6, IL-12, IL-23, IL-10, IL-13, vascular endothelial growth factor (VEGF), and hepatocyte growth factor (HGF). These cytokines promote leukocyte activation in the liver after ischemia through various pathways. IFN-γ is mainly produced by T cells and natural killer T cells, and activated by toll-like receptor-4 and IL-12. IFN-γ can either aggravate liver damage or reduce liver damage through enhancing or downregulating neutrophil accumulation and activation in a dose-dependent manner[20]. IL-1β, IL-6, IL-12, and IL-23 are mainly produced by KCs and hepatocytes. IL-1β can upregulate NO synthesis through the protein kinase B (Akt), NF-κB, and inducible nitric oxide synthase (iNOS) pathways. IL-1β can further upregulate leukocyte aggregation and adhesion by activating NF-κB and macrophage inflammatory protein (MIP)-2, thus damaging the liver cells[21]. IL-12 and IL-23 can also increase TNF-α production by activating

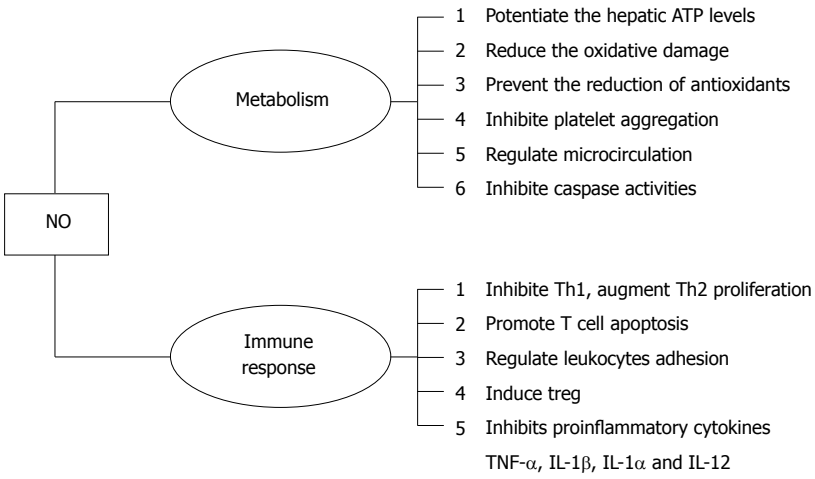

Figure 2 The protective effects of nitric oxide on liver ischemia-reperfusion injury. ATP: Adenosine triphosphate; IL: Interleukin.

NF-κB and signal transducer and activator of transcription (STAT)-4, and further stimulating CD4 T cells to produce IL-17, ensuring the accumulation of neutrophils and aggravating liver damage[22].

On the contrary, IL-6 can activate STAT-3, upregulate glutathione (GSH) expression, and downregulate oxidative stress markers, thus reducing hepatocyte damage and promoting hepatocyte proliferation[23]. IL-10 and IL-13 are mainly produced by KCs and T lymphocytes, and also play a role in alleviating liver damage and promoting liver regeneration. The protective role of IL-10 and IL-13 is mainly mediated by upregulation of heme oxygenase (HO)-1, B-cell lymphoma (Bcl)-2/bcl-x, and downregulation of NF-κB, IL-1β, IL-2, IFN-γ, MIP-2, cytokine-induced neutrophil chemotaxin, E-selectin, and neutrophil aggregation[24,25].

VEGF can be produced by many types of cells including KCs, T cells, sinusoidal endothelial cells and hepatocytes. It plays dual functions in liver IRI. IRI triggers the VEGF receptor and Src tyrosine kinase activation, and upregulates the expression of TNF-α, INF-γ, monocyte chemoattractant protein-1 and E-selectin, all of which result in the accumulation of intrahepatic T lymphocytes, macrophages and neutrophils, producing liver damage. On the other hand, exogenous administration of VEGF can upregulate iNOS production and protect the liver from IRI[26].

HGF is produced by liver non-parenchymal cells, mainly KCs. HGF can increase hepatocyte DNA synthesis, proliferation, and glutathione expression, downregulate the expression of the oxidative stress marker ICAM-1 in sinusoidal endothelial cells, and inhibit cytokine-induced neutrophil chemotaxin and neutrophil permeability, further reducing liver damage and promoting liver cell proliferation[27].

PROTECTIVE ROLE OF NITRIC OXIDE

The effects of NO in protecting the liver from IRI have been studied extensively in recent years. NO is a highly reactive free radical produced from L-arginine and oxygen by nitric oxide synthase (NOS) *in vivo*[28]. Many studies have demonstrated that NO is a versatile signaling mediator involved in a multitude of critical cellular events, such as inhibition of platelet aggregation, regulation of the microcirculation, and inhibition of caspase activities to prevent cell apoptosis[29,30]. It has been shown that both endogenously generated and exogenously administrated NO plays an important role in protecting the liver from IRI[31]. NO has been found to attenuate liver IRI through various mechanisms, including the protection of hepatocytes from apoptosis and the reduction of macrophage infiltration[32]. Complicated mechanisms and numerous molecules are involved in exerting the protective effects of NO against liver IRI, including ATP molecules, endothelin, adhesion molecules, cytokines, free radical species, and antioxidants[33] (Figure 2). NO has been shown to potentiate hepatic ATP levels, reduce oxidative damage, prevent the reduction of antioxidants such as glutathione, and reduce the adverse effects of endothelin during liver IRI[33,34]. Studies have demonstrated that NO affects cellular decisions of life and death by either turning on or shutting off apoptotic pathways, suggesting that NO can function differently depending on the dose and duration of exposure[35,36]. Large amounts of NO may in turn paradoxically damage liver tissue by forming nitrogen peroxide[37], suggesting that the therapeutic safety window of NO is limited.

NO-based therapy has been applied for many years to patients with pulmonary hypertension or cardiopulmonary disorders. The therapeutic application of NO in protecting the liver from IRI has just been emerging. A prospective randomized small group trial with liver transplant patients has demonstrated that NO inhalation in liver recipients during the perioperative period of liver transplantation significantly protects hepatocytes from apoptotic death, accelerates the restoration of liver graft function, and reduces hospital length of stay[38]. Since NO has a very short half-life *in vivo*, it is not an ideal gas

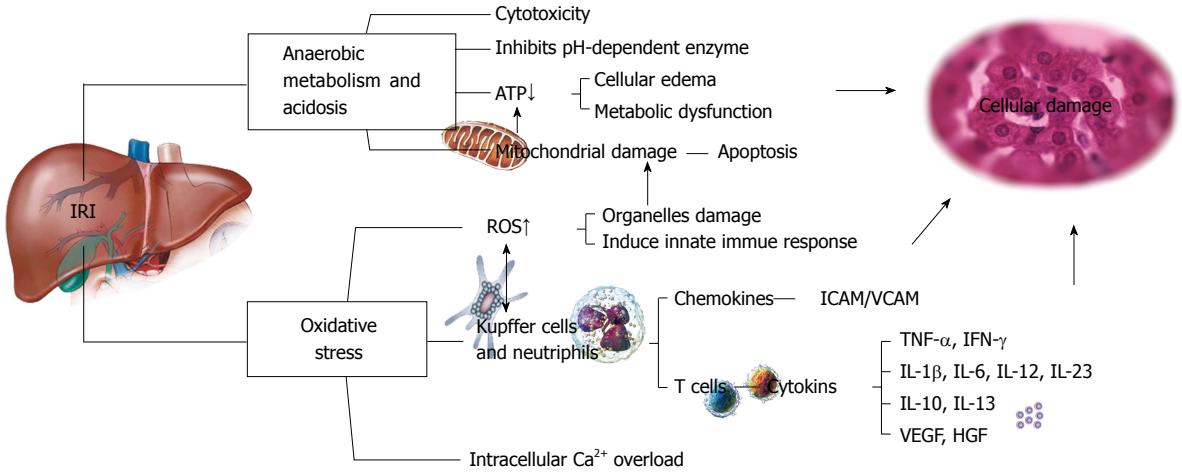

Figure 3 Mechanisms of hepatic ischemia reperfusion injury. ATP: Adenosine triphosphate; IL: Interleukin; ROS: Reactive oxygen species; IRI: Ischemia-reperfusion injury; IFN-γ: Interferon-gamma; ICAM: Intercellular adhesion molecule; VCAM: Vascular cell adhesion molecule; TNF: Tumor necrosis factor.

for the treatment of IRI. NO drugs administered to liver donors, such as organic nitrates and sodium nitroprusside, are now being explored as an alternative choice for NO delivery.

Sodium nitrite, a storage form of NO, can release NO during hypoxia and acidosis[39]. Sodium nitrite has now been identified as an important storage reservior of bioavailable NO in the blood and tissues[40]. The reduction of nitrite to NO has been demonstrated to confer cytoprotection against IRI in the heart, liver, brain, and kidney[40]. Interventions that increase NO production by the use of sodium nitrite before the occurrence of ischemia, either through intraperitoneal injection or oral administration, can mediate significant cytoprotection. This strategy has been demonstrated to potently limit acute IRI in both the heart and liver in murine warm IRI models, with the ability to decrease myocardial infarction and hepatocyte apoptosis[40-43].

NO is also an important effector molecule, produced by KCs and dendritic cells (DCs), and is involved in immune regulation and host innate and adaptive immunity[44]. NO inhibits proinflammatory cytokines, including TNF-α, IL-1β, IL-1α and IL-12, which may induce the inflammatory cascade during liver IRI [24-26,33]. It has been reported that NO exerts multiple effects on immune cells, decreasing the number of T helper (Th)1 cells and augmenting Th2 cell proliferation and their cytokine synthesis, regulating leukocyte adhesion and recruitment to the site of infection[45-47], inhibiting Th1 proliferation, and promoting T cell apoptosis[48,49]. Moreover, NO also contributes to the immunosuppressive function of induced T regulatory cells (Treg)[50]. Therefore, NO is involved in the regulation of liver IRI-associated immune responses. The underlying mechanisms are largely unknown and warrant further investigation.

CONCLUSION

Hepatic IRI is not only a pathophysiological process involving the liver itself, but also a complex systemic process affecting multiple tissues and organs. Hepatic IRI can seriously impair liver function, even producing irreversible damage, which causes a cascade of multiple organ dysfunction. Many factors, including anaerobic metabolism, mitochondrial damage, oxidative stress, intracellular Ca^{2+} overload, cytokines and chemokines produced by KCs and neutrophils, and NO, are all involved in the regulation of liver IRI processes. The most important pathways of liver IRI are initiated by oxidative stress, anaerobic metabolism and acidosis, further resulting in the cellular damage through induction of apoptosis, immune responses, and cytokine regulations (Figure 3). Inhaled NO or NO-producing drugs have shown positive effects on IRI protection in clinical practice, and may be a good choice for liver IRI therapy in the future. Therefore, further exploration of the mechanisms of IRI on animal models focusing on the regulatory pathway of IRI development, with concomitant development of a more effective method of controlling IRI, will help overcome the challenges in the prevention of IRI and therapeutic strategies.

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MINIREVIEWS

Chronic pancreatitis: A surgical disease? Role of the Frey procedure

Alexandra Roch, Jérome Teyssedou, Didier Mutter, Jacques Marescaux, Patrick Pessaux

Alexandra Roch, Jérome Teyssedou, Didier Mutter, Jacques Marescaux, Patrick Pessaux, Digestive and Endocrine Surgery, Nouvel Hôpital Civil, University of Strasbourg, 67000 Strabourg, France
Alexandra Roch, Jérome Teyssedou, Didier Mutter, Jacques Marescaux, Patrick Pessaux, Institut de recherche en cancérologie de l'appareil digestif (IRCAD), 67000 Strasbourg, France
Alexandra Roch, Jérome Teyssedou, Didier Mutter, Jacques Marescaux, Patrick Pessaux, IHU-Strasbourg, Minimally-Invasive Image-Guided Surgical Institute, University of Strasbourg, 67000 Strabourg, France
Author contributions: All the authors contributed to this paper.
Correspondence to: Patrick Pessaux, MD, PhD, Professor, Head of the Hepatobiliary and Pancreatic Surgical Unit, Digestive and Endocrine Surgery, Nouvel Hôpital Civil, University of Strasbourg, 1 place de l'hopital, 67000 Strasbourg, France. patrick.pessaux@chru-strasbourg.fr
Telephone: +33-3-69551563
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Abstract

Although medical treatment and endoscopic interventions are primarily offered to patients with chronic pancreatitis, approximately 40% to 75% will ultimately require surgery during the course of their disease. Although pancreaticoduodenectomy has been considered the standard surgical procedure because of its favorable results on pain control, its high postoperative complication and pancreatic exocrine or/and endocrine dysfunction rates have led to a growing enthusiasm for duodenal preserving pancreatic head resection. The aim of this review is to better understand the rationale underlying of the Frey procedure in chronic pancreatitis and to analyze its outcome. Because of its hybrid nature, combining both resection and drainage, the Frey procedure has been conceptualized based on the pathophysiology of chronic pancreatitis. The short and long-term outcome, especially pain relief and quality of life, are better after the Frey procedure than after any other surgical procedure performed for chronic pancreatitis.

Key words: Chronic pancreatitis; Frey procedure; Surgery; Complication; Outcome

Core tip: The management and the treatment of chronic pancreatitis are challenging. Many surgical procedures were described with 2 different types of concepts: resection *vs* drainage. The Frey procedure is an association of these 2 concepts. This manuscript contains the most recent data about the technique, the short and long-term outcomes of this technique. In addition, there is a review of the literature of series comparing this technique with the other surgical procedures.

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INTRODUCTION

Chronic pancreatitis is a progressive inflammatory disease characterized by debilitating pain and pancreatic insufficiency (nutritional deficiency and glucose deregulation)[1,2]. The enormous personal and socioeconomic impact comprises impairment of quality of life, inability to work and even shortening in life expectancy[3]. Although medical treatment and endoscopic interventions are primarily offered to patients with chronic pancreatitis[4,5], approximately 40% to 75% will ultimately require surgery during the course of their disease[6,7].

Although pancreaticoduodenectomy has been considered the standard surgical procedure for patients with chronic pancreatitis because of its favorable results

on pain control, its high postoperative complication and pancreatic exocrine or/and endocrine dysfunction rates[8,9] have led to a growing enthusiasm for duodenal preserving pancreatic head resection[10,11]. When in 1987 Frey *et al*[12] described a novel hybrid procedure combining local resection of the head of the pancreas and longitudinal pancreatico-jejunostomy, surgeons favorably welcomed it because of its technical feasibility and low surgical risk. Since 1987, numerous studies have analyzed the short and long-term outcome following the Frey procedure and have compared it to other surgical procedures commonly performed for chronic pancreatitis. The aim of this review is to better understand the rationale underlying of the Frey procedure in chronic pancreatitis and to analyze its outcome.

WHY CAN CHRONIC PANCREATITIS BE CONSIDERED A SURGICAL DISEASE?

Mechanisms of pain in chronic pancreatitis

Although pain is the most common symptom (85% of patients)[2] in chronic pancreatitis, its mechanism remains unclear and debated[13-15]. Several concepts have been hypothesized and pain probably results from a combination of them. The intraductal and interstitial hypertension theory is similar to a compartment syndrome[16,17]. Increased ductal pressure related to duct stricture or calculi and intraparenchymal hypertension as a result of fibrosis and edema can activate intrapancreatic nociceptors. The neurogenic theory focuses on intrapancreatic neural damage[18]. Inflammatory mediators from infiltrating lymphocytes are responsible for increased signals along the axons of pain-sensitive neurons, which ultimately can result in a "centrally sensitized" pain state[19]. Traditionally, the head of the pancreas is called the "pacemaker" of pain in chronic pancreatitis. It is often enlarged and can be replaced by an inflammatory mass that can lead to common bile duct or duodenal stenosis[20]. Another explanation to this pain is the compression of adjacent organs by a pseudocyst.

Indications for surgery

Surgical management is usually offered to patients after medical treatment and endoscopic intervention have failed[4,5], and is considered the last option of this step-up approach[21]. Medical treatment for pain related to chronic pancreatitis usually fails, as narcotic dependency occurs in most patients[11]. Longitudinal studies have shown that 40% to 75% of all patients with chronic pancreatitis will require surgery in the course of the disease[7]. The main indications for surgery are intractable pain, non-resolving common bile duct or duodenal stenosis and suspicion of malignancy. The objective of surgery is to relieve intractable pain while preserving pancreatic endocrine and exocrine functions.

Rationale for surgery in chronic pancreatitis

First, surgery has been proved superior to endoscopic treatment in 2 main randomized controlled trials[22,23]. Moreover, several studies have suggested that surgery early in the course of chronic pancreatitis is beneficial in terms of pain control and pancreatic function[21,24]. One experimental and three clinical observational cohort studies have concluded that surgery, especially drainage procedures, can delay the natural course and progressive loss of pancreatic function in chronic pancreatitis. In an experimental model of early *vs* late surgical drainage in pigs, early surgery resulted in less pathological cell damage and better exocrine function[25]. When Nealon *et al*[26] compared the outcomes of conservative treatment *vs* surgery, they reported a delay in pancreatic function impairment after surgical treatment. They concluded that early operative drainage should be performed before the pancreas shows morphological and functional irreversible damage. Ihse *et al*[27] also have recommended surgical treatment to be performed before nutritional or metabolic disorders develop.

Prolonged periods of pain can be associated with peripheral and central nerve sensitization, leading to a permanent state of pain impossible to reverse[19]. A recent observational study suggests that longstanding disease is associated with poor pain control after surgical intervention[28]. In 266 consecutive patients undergoing surgery for chronic pancreatitis, surgery after 3 years of onset of symptoms was independently associated with impaired pain relief and increased rate of endocrine pancreatic insufficiency. A small pilot trial randomized 32 patients with early stage chronic pancreatitis and dilated pancreatic duct between upfront surgical drainage and conservative approach[29]. Significant pain relief was observed in 94% patients in the surgical group compared to 13% patients in the conservative group. New onset pancreatic insufficiency was significantly less frequently observed in the early surgical group compared conservative group. Despite the evidence suggesting a benefit of early surgery, most patients are still managed by a conservative step-up approach. To evaluate the benefits, risks and costs of early surgical intervention, the Dutch Pancreatitis Study Group is currently conducting a multicentric randomized controlled trial (the Early Surgery *vs* Optimal Current Step-up Practice for Chronic Pancreatitis trial) [21].

The role of chronic pancreatitis as a risk factor for pancreatic carcinogenesis has been supported by numerous studies since 1993[30-32]. Lowenfels *et al*[30] published an international cohort study of 2015 patients that reported a cumulative risk of pancreatic cancer in subjects with chronic pancreatitis of 1.8% after 10 years and 4%, after 20 years with a standardized incidence ratio of 14.4. A recent multicentric Japanese study[33] of 506 patients found that the incidence of pancreatic cancer was significantly lower in patients who underwent surgery for chronic pancreatitis than in patients who had a conservative treatment (0.7% *vs* 5.1%, $P = 0.03$, HR = 0.11). Although this study shows a protective effect of surgery in the development of pancreatic cancer from chronic pancreatitis, the exact mechanism remains unclear probably through reduction in pancreatic inflammation.

FREY PROCEDURE: SURGICAL TECHNIQUE

Rationale for the Frey procedure

Based on the pathophysiological mechanisms described above[13-19], two main surgical procedure types have been described in patients with chronic pancreatitis: drainage and resection procedures[11,34,35]. Until the late 80s, pancreaticoduodenectomy was the resection procedure of choice for "head-dominant" disease[11]. The Frey procedure was first described in 1987 by Frey *et al*[12] and combines partial resection of the head of the pancreas (resection) with lateral pancreatico-jejunostomy (drainage). The rationale for this hybrid procedure[12, 36-38] is that it improves the overall pancreatic ductal drainage by decompressing both the duct of Santorini and ducts in the uncinate process. It also allows removal of calculi. Moreover, the partial pancreatic head resection removes what is thought to be the "epicenter" of chronic pain and can relieve symptoms related to ductal stricture.

The Frey procedure was originally applied to patients with an enlarged fibrotic head of the pancreas and an associated dilated main pancreatic duct. It has since then been described in various indications, including patients who have had prior lateral pancreatico-jejunostomy (Puestow or Partington and Rochelle procedures) with no relief of symptoms[38].

Surgical technique

Through a bilateral subcostal incision and after exposure of the pancreas (Kocher maneuver), the main pancreatic duct is located using a syringe aiming toward the tail of the pancreas[12,36-40]. The pancreatic duct is then opened longitudinally (the incision in the tail of the pancreas is extended to within 1-2 cm of the distal portion of the gland and the incision in the head to within 1 cm of the inner aspect of the duodenum). When the main pancreatic duct is exposed, it can be inspected and all calculi removed. The head of the pancreas is partially cored-out while preserving a rim of pancreatic tissue along the inner aspect of the duodenum (to allow blood supply to the duodenum from superior and inferior pancreaticoduodenal arteries), along the pancreatic medial margin (to avoid injuring the superior mesenteric/portal vein) and posteriorly (between the head excavation and the uncinate process and vena cava). During the local excision of the head of the pancreas, the intrapancreatic portion of the common bile duct is freed from inflamed and fibrotic periodical tissue. In about 70% of cases, resection of the fibrotic pancreatic parenchyma is sufficient to relieve a common bile duct stricture. If the obstruction cannot be relieved, a choledocho-duodenostomy or a choledocho-jejunostomy can be performed. The cored-out head of the pancreas and the open main duct are drained into Roux-en-Y limb of jejunum. The Roux-en-Y limb is passed through the transverse mesocolon to lie over the pancreas. A two-layer pancreatico-jejunostomy is performed. The gastrointestinal tract continuity is restored by and end-to-side jejuno-jejunostomy. Owing to the increased risk of pancreatic cancer in patients with chronic pancreatitis, the cored tissue from the pancreatic head is routinely sent for pathological analysis.

Technical key points

Compared to other surgical procedures (especially pancreaticoduodenectomy and Beger procedure), the Frey procedure is easier to perform by avoiding the transsection of the pancreas neck over the superior mesenteric/portal vein.

Although Frey *et al*[37-39] analyzed the relation between weight of the cored pancreatic head tissue and pain relief, this amount of tissue depends on the size of the head of the pancreas, which is highly variable. Some studies suggested that a mean volume percent of head mass resected between 60% and 65% allowed better pain relief. Extensive pancreatic head excision should not be performed as it may lead to increased parenchymal loss and ultimately pancreatic exocrine insufficiency.

Current data suggest that the Frey procedure in small duct chronic pancreatitis is associated with a significantly increased operative time[41]. Difficulty in locating the main pancreatic duct contributes to the delay and intra operative ultrasound in those cases proves useful[42].

Because the Frey procedure can be technically challenging due to major chronic inflammation, it is traditionally performed as an open surgery. Surgeons from John Hopkins recently published a case report describing a total laparoscopic Frey procedure for chronic pancreatitis caused by recurrent pancreatic ductal stones[43]. The laparoscopic approach confers the benefits of magnified visualization while reducing the rate of postoperative wound infection, incisional hernia, bowel obstruction and pain[44]. As laparoscopic Frey procedure is very demanding, the selection of patients that can benefit from it is very important. This approach will less likely be offered to obese patients, as visualization can be impaired by retroperitoneal fat. Similarly, this approach does not fit patients with a highly vascular head of the pancreas because of the increased risk of bleeding.

RESULTS OF THE FREY PROCEDURE

Complications

The Frey procedure can be performed with low mortality (< 2%). The published complication rates range from 7% to 42%[45-50]. The most common complications include hemorrhage, pancreatic fistula and intra-abdominal abscess. Arterial bleeding is the major life-threatening complication (2%-3%). It can occur several days from surgery after erosion of per pancreatic vessels by pancreatic fluid from an anastomotic leakage, or due to the rupture of a pseudoaneurysm[41,49]. Late complications rate after the Frey procedure is high, probably because of comorbidities (alcohol, smoking) in most patients with chronic pancreatitis. The main medical complication is pulmonary infection and/or insufficiency[50]. In 2006, Pessaux *et al*[49]

recommended preoperative respiratory physiotherapy for all patients before the Frey procedure to avoid postoperative respiratory complications.

Short and long-term outcome

Exocrine insufficiency has been described in up to 79% of patients following the Frey procedure, whereas de novo diabetes occurs in only 8% to 34% of patients[45-50].

Keck *et al*[47] showed that 62% of patients were completely pain free 5 years after the Frey procedure. Similarly, Negi *et al*[51] showed that the Frey procedure led to significant and sustained complete or partial pain relief in 75% over a median follow-up of 6 years. This study suggests that the Frey procedure significantly decreases the severity of recurrent exacerbations and also the number of acute episodes requiring hospital readmission. Falconi *et al*[52] reported up to 90% of partially or completely pain-free patients after the Frey procedure. Hildebrand *et al*[53] showed that the indices for global quality of life and for physical and emotional status increased after the Frey procedure.

Factors predicting outcome

Ten to 20% of patients demonstrate persistent pain after the Frey procedure[44-50]. Several risk factors for poor pain relief have been described in the literature, with controversial results[54]. In 1999, Frey and Amikura[38] found that chronic narcotic use, multiple abdominal interventions before pancreatic surgery were associated with poor outcome, whereas Riediger *et al*[55] found that preoperative exocrine insufficiency and postoperative surgical complications were the strongest predictors of poor pain relief. In an Indian study[41], preoperative use of opiates, continuous pattern of pain and postoperative complications were significant predictive factors of failure to achieve complete pain relief after surgery. However, even patients who used opiate medication preoperatively benefited from surgery (significant reduction in pain score, number of pain exacerbation and hospital readmissions). These results suggest that preoperative narcotic use should not be considered a contraindication to the Frey procedure although patients should be referred for surgery early in the course of chronic pancreatitis before drug addiction becomes an issue.

The correlation between main pancreatic duct diameter and pain relief after the Frey procedure remains debated[38,56,57]. A recent study from John Hopkins showed that the degree of pancreatic fibrosis correlated with the resolution of pain in a series of 35 patients treated with the Frey procedure[58]. Their results suggest that pain in patients with extensive pancreatic fibrosis is significantly better relieved by the Frey procedure than in patients with mild or minimal fibrosis. They implied that patients with mild or minimal fibrosis may respond more favorably to other procedures such as total pancreatectomy with islet auto-transplantation. Determination of pancreatic fibrosis extent preoperatively, thanks to improving imaging technologies, might be an important variable to choose the surgical procedure more likely to achieve pain relief. They also found an association between ductal dilation $\geqslant$ 4 mm and better pain relief. However, they believe that the influence of main pancreatic duct diameter on outcome following the Frey procedure may be biased, as ductal dilation is usually the consequence of progressive fibrosis. In these cases, an alternative could be an extended drainage by "V-shaped excision" advocated by Izbicki *et al*[59] and Yekebas *et al*[60] with a partial head resection. This technique seems to be a secure and effective approach for small duct chronic pancreatitis achieving significant improvement in quality of life and pain relief.

Comparison Frey vs other surgical procedures for chronic pancreatitis

Frey procedure *vs* pancreaticoduodenectomy: Operation time is shorter with the Frey procedure, with lower intraoperative blood loss and perioperative transfusion requirements[61]. Chiang *et al*[62], in a prospective study comparing the Frey procedure to pancreaticoduodenectomy found no difference in mortality, morbidity, pain relief or improvement in pancreatic function 3 and 6 mo after surgery. One randomized controlled trial including 61 patients compared the outcome of pancreaticoduodenectomy and Frey procedure[63]. In this trial (follow-up of 2 years), Izbicki *et al*[63] found better results after Frey procedure regarding quality of life, although pain relief was similar after both procedures. Additionally, the rate of complications after the Frey procedure was significantly lower than after pancreaticoduodenectomy (19% *vs* 53%). Farkas *et al*[64] supported those results concluded that the Frey procedure led to better long-term quality of life. In the long-term follow-up study (mean of 7 years) published by Strate *et al*[65], there was no difference between Frey and pancreaticoduodenectomy regarding late mortality, survival rate, exocrine and endocrine insufficiency (although the rates of new onset diabetes after both procedures were twice higher than preoperatively) and need for reintervention. The initial favorable results of quality of life and pain after Frey procedure still existed but were not statistically significant. Interestingly, Aspelund *et al*[66] found however a significantly lower incidence of new onset diabetes after the Frey procedure (8%) than after pancreaticoduodenectomy (25%). A recent randomized controlled trial presented at the European Surgical Association in 2013 reported the 15-year follow-up of the Frey procedure *vs* pancreaticoduodenectomy for chronic pancreatitis[67]. They concluded that long-term pain relief was comparable after both surgical procedures but the quality of life was better after the Frey procedure. Moreover, mean survival was significantly shorter after pancreaticoduodenectomy because of a higher delayed and long-term mortality rate. Regarding weight gain and work rehabilitation, the Frey procedure also showed better outcome than pancreaticoduodenectomy[53] (Table 1).

Frey procedure *vs* Beger procedure: A randomized controlled trial comparing the Frey procedure with Be-

Table 1 Main studies comparing surgical procedures for chronic pancreatitis

Ref.	Year	Study design	Comparison	Median follow-up (in months)
Izbicki *et al*[63]	1998	Retrospective	Frey *vs* PPPD	24
Aspelund *et al*[66]	2005	Retrospective	Frey *vs* PD	36
Hildebrand *et al*[53]	2010	Retrospective	Frey *vs* PD	50
Farkas *et al*[64]	2006	Prospective	Frey *vs* PPPD	24
Chiang *et al*[62]	2007	Prospective	Frey *vs* PD	6
Strate *et al*[65]	2008	Prospective	Frey *vs* PPPD	84
Bachmann *et al*[67]	2013	Prospective	Frey *vs* PD	180
Izbicki *et al*[46]	1995	Prospective	Frey *vs* Beger	18
Strate *et al*[68]	2005	Prospective	Frey *vs* Beger	104
Keck *et al*[47]	2010	Retrospective	Frey *vs* Beger	20.6

PPPD: Pylorus-preserving pancreaticoduodenectomy; PD: Pancreaticoduodenectomy.

ger procedure[46] found that the Frey procedure was associated with a lower complication rate (9% *vs* 15%). In the 8-year follow-up study published by Strate *et al*[68] in 2005, both procedures showed equivalent mortality, pain relief, exocrine/endocrine insufficiency, rate of reintervention and quality of life. Similarly, a study by Keck *et al*[47] including 92 patients showed a trend toward better pain control but similar pancreatic insufficiency rates and weight gain after the Frey procedure when compared to the Beger procedure.

In conclusion, because of its hybrid nature, combining both resection and drainage, the Frey procedure has been conceptualized based on the pathophysiology of chronic pancreatitis. The short and long-term outcome, especially pain relief and quality of life, are better after the Frey procedure than after any other surgical procedure performed for chronic pancreatitis.

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ORIGINAL ARTICLE

Lymphoepithelial cysts and cystic lymphangiomas: Under-recognized benign cystic lesions of the pancreas

Ioannis T Konstantinidis, Avinash Kambadakone, Onofrio A Catalano, Dushyant V Sahani, Vikram Deshpande, David G Forcione, Jennifer A Wargo, Carlos Fernandez-del Castillo, Keith D Lillemoe, Andrew L Warshaw, Cristina R Ferrone

Ioannis T Konstantinidis, Jennifer A Wargo, Carlos Fernandez-del Castillo, Keith D Lillemoe, Andrew L Warshaw, Cristina R Ferrone, Departments of Surgery, Massachusetts General Hospital, Boston, MA 02114, United States
Ioannis T Konstantinidis, Department of Surgery, University of Arizona, Tucson, AZ 85724, United States
Vikram Deshpande, Departments of Pathology, Massachusetts General Hospital, Boston, MA 02114, United States
Avinash Kambadakone, Onofrio A Catalano, Dushyant V Sahani, Departments of Radiology, Massachusetts General Hospital, Boston, MA 02114, United States
Onofrio A Catalano, Department of Radiology, University of Napoli, 80138 Napoli, Italy
David G Forcione, Departments of Gastroenterology, Massachusetts General Hospital, Boston, MA 02114, United States
Author contributions: All the authors contributed to this work.
Correspondence to: Cristina R Ferrone, MD, Assistant Professor, Departments of Surgery, Massachusetts General Hospital, Wang Ambulatory Care Center 460, 15 Parkman Street, Boston, MA 02114, United States. cferrone@partners.org
Telephone: +1-617-6436189 Fax: +1-617-6436116
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Abstract

AIM: To identify their diagnostic and prognostic clinical characteristics in a large series.

METHODS: Retrospective review of clinicopathologic and imaging characteristics of patients diagnosed with lymphoepithelial cysts and cystic lymphangiomas of the pancreas at Massachusetts General Hospital.

RESULTS: Twelve patients were identified between 1/1/1997 and 8/1/2007. Their median age was 55.5 years (range 19-78 years), and 6 were females. The lesion was incidentally discovered in half of the patients. Contrast enhanced computed tomography demonstrated that the cysts had thin walls, without calcifications, pancreatic duct dilation or pancreatic parenchyma invasion. Endoscopic ultrasound with fine needle aspiration (EUS/FNA) confirmed the diagnosis of a lymphoepithelial cyst in 3 patients, one of whom was spared an operation and continues to do well after 6 years. Eleven patients had a resection: 3 pancreaticoduodenectomies, 7 distal pancreatectomies, and 1 enucleation. The median size of the cysts was 3 cm (range 2-20 cm). At a median follow-up of 57 mo no recurrences or other pancreas-related conditions occurred.

CONCLUSION: Lymphoepithelial cysts and cystic lymphangiomas of the pancreas can be diagnosed with a combination of contrast-enhanced computed tomography scans and EUS/FNA. If the lesion is asymptomatic, an operation might be avoided.

Key words: Lymphoepithelial cysts; Cystic lymphangiomas; Pancreas; Asymptomatic cysts; Benign cystic lesions of the pancreas

Core tip: Lymphoepithelial cysts and cystic lymphangiomas of the pancreas represent rare, benign cystic lesions. The experience with their diagnosis and treatment is limited mostly to case reports. This report describes our experience with twelve lymphoepithelial cysts and cystic lymhangiomas of the pancreas, analyzing their clinicopathologic characteristics, the role of contrast enhanced computed tomography and endoscopic ultrasound with fine needle aspiration for their diagnosis with an emphasis on non-surgical management when a correct diagnosis can be established in an asymptomatic patient.

Konstantinidis IT, Kambadakone A, Catalano OA, Sahani DV, Deshpande V, Forcione DG, Wargo JA, Fernandez-del Castillo C, Lillemoe KD, Warshaw AL, Ferrone CR. Lymphoepithelial cysts and cystic lymphangiomas: Under-recognized benign cystic lesions of the pancreas. *World J Gastrointest Surg* 2014; 6(7): 136-141 Available from: URL: http://www.wjgnet.com/1948-9366/full/v6/i7/136.htm DOI: http://dx.doi.org/10.4240/wjgs.v6.i7.136

INTRODUCTION

The differential diagnosis of cystic lesions of the pancreas includes a variety of inflammatory and neoplastic lesions, some of which have malignant potential, any of which may be symptomatic or not[1].

Among the least known pancreatic cystic lesions are the lymphoepithelial cysts and the cystic lymphangiomas[2]. Their natural history is unknown, but asymptomatic cysts might be left alone if diagnosed accurately. A diagnosis may be possible with a combination of imaging and endoscopic ultrasound with fine needle aspiration (EUS/FNA).

In this study we report our experience with twelve patients diagnosed with lymphoepithelial cysts or cystic lymphangiomas over a period of more than 10 years, focusing on diagnostic evaluation and surgical treatment and exploring the potential of avoiding an operation on asymptomatic patients.

MATERIALS AND METHODS

Study design

Review of a pathology database was performed to identify patients diagnosed with lymphoepithelial cysts and cystic lymphangiomas between 1/1/1997-8/1/2007. A prospectively maintained surgical database since 1/2001 was used to identify the relative frequency of the lymphoepithelial cysts and cystic lymphangiomas among the pancreatic cysts who underwent surgical resection.

Clinical data evaluated included gender, age, presenting symptoms, past medical history, laboratory values, operative procedures and pathology reports. The available computed tomography (CT) scans and endoscopic ultrasound studies performed at the Massachusetts General Hospital were re-reviewed. Pancreatic fistula was defined according to the international study group definition[3]. Operative mortality was defined as death within 30 d of the operation.

Ethics

This study was approved by the institutional review board (IRB) of the Massachusetts General Hospital.

Statistical analysis

Statistical analysis was conducted using SPSS software (version 20.0; SPSS, Chicago, Ill). Continuous variables are shown as median and range. Categorical or dichotomous data are presented in frequencies and percentage (%) as appropriate. This study was approved by the IRB of the Massachusetts General Hospital (MGH).

Table 1 Clinicopathologic characteristics of 12 patients *n* (%)

Factors	LECP (*n* = 8)	Lymphangioma (*n* = 4)
Median age, yr (range)	60.5 (24-78)	37.5 (19-69)
Females	2 (25)	4 (100)
Symptomatic	4 (50)	2 (50)
Abdominal pain	2 (25)	2 (50)
Other (nausea, fever)	2 (25)	0
Operation	7 (87.5)	4 (100)
Distal pancreatectomy	4 (50)	3 (75)
Pancreaticoduodenectomy	2 (25)	1 (25)
Enucleation	1 (12.5)	0
Pathology		
Median size, cm (range)	2 (2-7.6)	10.5 (2.5-20)

LECP: Lymphoepithelial cyst of the pancreas.

Table 2 Diagnostic studies *n* (%)

Factors	LECP (*n* = 8)	Lymphangioma (*n* = 4)
Median CA 19-9, U/mL (range)	35 (3-79)	10 (9-36)
CT characteristics		
Mean size, cm (range)	2.3 (1.5-2.9)	9.2 (2.3-16.5)
Loculations	1 (25)	0
Microcystic	1 (25)	0
Central scar	0	0
Septations	3 (75)	2 (50)
Calcifications	0	0
Mural nodules	0	1 (25)
Thin cyst wall	4 (100)	4 (100)
Pancreatic Duct Dilatation	0	0
Other (vascular invasion, lymphadenopathy)	0	0
FNA	(*n* = 6)	(*n* = 1)
Sufficient	4 (67)	1 (100)
Diagnostic	3 (50)	0

LECP: Lymphoepithelial cyst of the pancreas; FNA: Fine needle aspiration; CT: Computed tomography.

RESULTS

Between 1997 and 2007, 12 patients with cystic lymphangiomas or lymphoepithelial cysts were identified, representing approximately 2% of the pancreatic cystic lesions resected during this period. Median age for these 12 patients was 55.5 years (range 19-78) and 6 (50%) were females. The clinicopathologic data of these patients are shown in Table 1. Half of the patients were asymptomatic. Of the 6 symptomatic patients, 4 presented with abdominal pain (two patients presented with severe, abrupt, abdominal pain and the other two with episodes of right lower and left upper quadrant abdominal pain), 1 with fever, and 1 with nausea. One patient had previously undergone resection of ruptured lymphangiomas at an outside hospital 5 and 10 mo prior to presentation. He underwent a distal pancreatectomy for a second recurrence of a retroperitoneal lymphangioma.

Diagnostic evaluation

The results of the diagnostic evaluation of these patients are shown in Table 2. All of the patients had normal

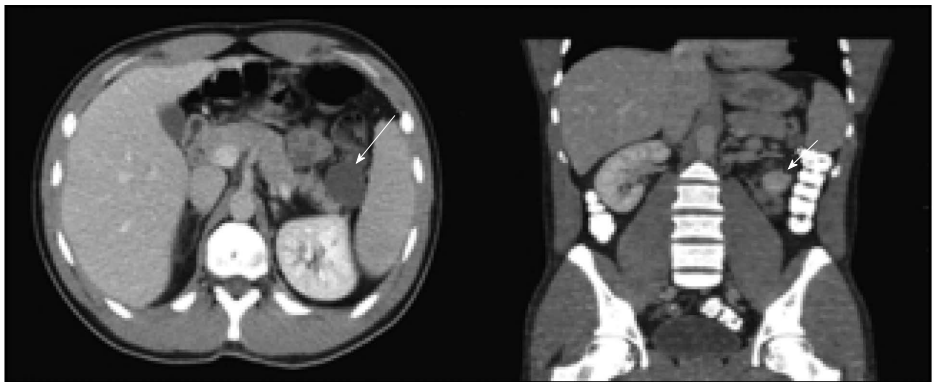

Figure 1 The usual appearance of lymphoepithelial cysts and lymphangiomas on contrast enhanced computerized tomography is that of simple cysts (arrows).

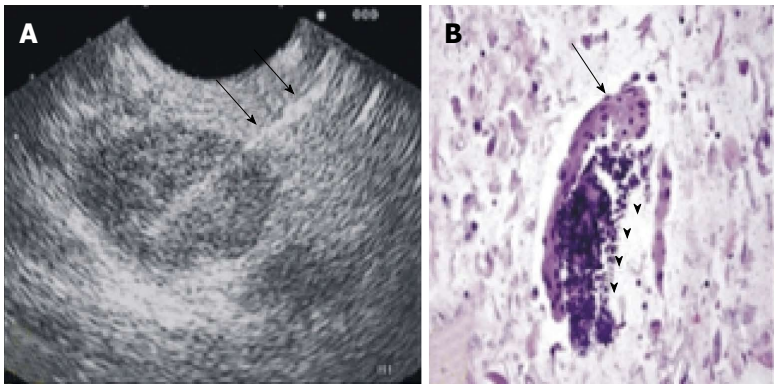

Figure 2 Endoscopic ultrasound guided fine needle aspiration (A) of the cyst with a 22G needle (black arrows) can aid in the correct diagnosis by demonstrating cellular elements characteristic of a lymphoepithelial cyst of the pancreas (B), including squamous (black arrow) and lymphoid subsets (black arrowheads) (HE stain, cell block preparation).

biochemical studies including serum CA 19-9 levels. Abdominal contrast-enhanced computerized tomography (CECT) scans were available for review in 8 (67%) patients. On CT evaluation, lymphoepithelial cysts/lymphangiomas were seen as low attenuation lesions with thin walls without evidence of calcifications, pancreatic duct dilatation, vascular invasion or enlarged lymph nodes (Figure 1). Cyst septa were evident in most of the cysts (62.5%), and there was a mural nodule in one cystic lymphangioma.

Seven patients (58.3%) underwent an endoscopic ultrasound and fine needle aspiration of the cyst (EUS/FNA). Samples were sufficient for cytology evaluation in 71.4% of patients and led to the diagnosis of a lymphoepithelial cyst in 50% of patients who harbored lymphoepithelial cysts based on demonstration of anucleated squamous cells and a lymphoid component (Figure 2). Based on the EUS/FNA results and stable imaging over the course of 6 years one patient was spared an operation. Two other patients were initially spared an operation with the presumptive diagnosis of a benign cyst but both patients eventually underwent a resection due to an increase in cyst size or the suspicion of nodules on subsequent imaging (Figure 3). Histological examination confirmed a lymphoepithelial cyst and a lymphangioma in these cases.

Surgical treatment and outcome

The operations performed included 3 pancreaticoduodenectomies, 7 distal pancreatectomies and 1 enucleation. There was no operative mortality. Pancreatic fistulas developed in two patients after Whipple operations for lymphoepithelial cysts (1 grade A and 1 grade B fistula). At a median follow up of 56.6 mo (range 1-148 mo) no recurrences or other pancreas-related conditions occurred in any of the eleven patients; all of them remain asymptomatic.

Pathologic assessment of the resected specimens confirmed seven lymphoepithelial cysts and four cystic lymphangiomas (Figure 4). The macroscopic appearance of lymphoepithelial cysts demonstrated a cyst filled with characteristic keratinaceous, cheesy material (Figure 5). Cystic lymphangiomas were filled with chylous fluid consistent with lymph. Median size of the cysts at pathologic review was 2 cm, with a range of 1.5 to 7.6 cm for the lymphoepithelial cysts and 10.5 cm for the cystic lymphangiomas (range: 2.5-20 cm). One patient had two lymphoepithelial cyst measuring 1.5 cm and 2 cm in size.

DISCUSSION

The widespread use of abdominal imaging has led to the increasing identification of asymptomatic pancreatic

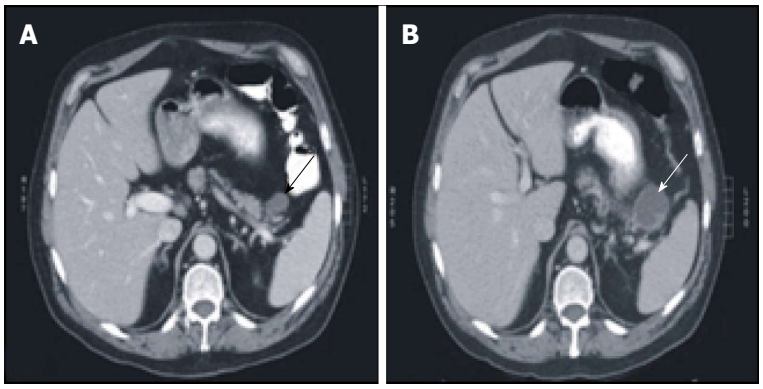

Figure 3 Lymphoepithelial cyst of the pancreas may increase in size during observation. Contrast enhanced computed tomography images demonstrate that the cyst increased from 2.6 cm (A, black arrow) to 4.2 cm (B, white arrow) over a two-month period.

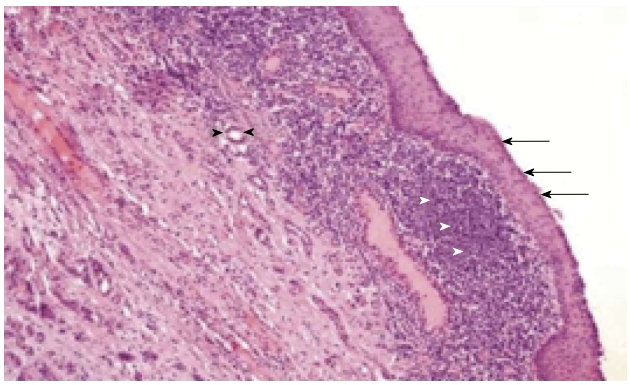

Figure 4 Lymphoepithelial cyst of the pancreas lined by squamous epithelium (black arrows), underlying lymphoid tissue (white arrowheads). Pancreatic ductules are also identified (black arrowheads) (HE stain).

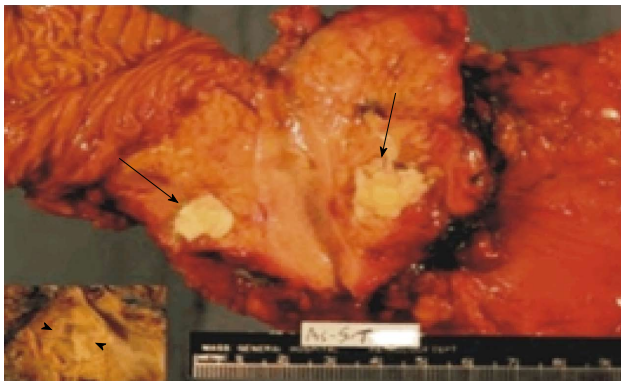

Figure 5 Photo of a transected lymphoepithelial cyst. The characteristic keratinaceous cheesy material is shown (arrows). Inset: the multilocular cyst (arrowheads).

cystic lesions. Seventy-one percent of cysts in a recent report from our institution were serendipitous imaging findings[4]. It becomes likely that uncommon lymphoepithelial cysts and cystic lymphangiomas will increasingly be found incidentally. Although an accurate preoperative diagnosis of pancreatic cysts is not always feasible, criteria associated with an increased risk of malignancy have been established by expert consensus[5] and subsequently validated[6,7] and updated[8]. Establishing a correct diagnosis in a benign asymptomatic cyst can spare the patient a pancreatectomy, which even in specialized tertiary centers carries significant morbidity[9].

This report, representing one of the largest case series describing the clinicopathologic characteristics of lymphoepithelial cysts and cystic lymphangiomas, provides insights into their correct management and spotlights establishment of an accurate diagnosis to avoid an operation in asymptomatic patients. In 3 (50%) of our asymptomatic patients a non-surgical approach was initially chosen on the basis of the probability of a benign lesion in an asymptomatic patient. Two of those eventually underwent resection because of new suspicious imaging findings, but the third continues to do well without intervention during follow-up of 6 years.

Lymphoepithelial cysts of the pancreas are most often found in men in their fifth and six decades of life; 75% of our patients were males who had a median age of 60.5 years. Their characteristic pathologic features are a squamous epithelial lining and surrounding lymphoid tissue, which can be identified on EUS/FNA[1].

Cystic lymphangiomas are benign multicystic lesions that are believed to result from blockage of the lymphatic system and, for unknown reasons, are more common in young females. They can be very large in size and they are frequently located in the peripancreatic tissues in close association with the pancreas. They harbor an endothelial cell lining[10]. In our series four patients were female and had median age of 37.5 years. The largest lesion was 16.5 cm.

The preoperative diagnostic evaluation of the patients in our study included a combination of biochemical and tumor markers, CECT scans of the abdomen and EUS/FNA. Although elevations of serum CA 19-9[11], cyst fluid CA 19-9[12] and persistence of elevated CA 19-9 post-resection[13] have been described in lymphoepithelial cysts, none of our patients had such abnormal levels. Thus, we believe that this marker has no utility in the clinical assessment of these cystic lesions[14]. Consistent with published reports[15], CECT scans in our patients demonstrated cysts with thin walls, without evidence of calcifi-

cations, pancreatic duct dilation or local invasion. Cystic lymphangiomas additionally contain septa, appear multiloculated, and may have papillary projections[16]. A mural nodule (which proved to be an organizing hematoma) was seen in one of our patients who had a lymphangioma. On EUS/FNA lymphoepithelial cysts demonstrate anucleated squamous cells on cytology while their pathology is consistent with a keratinized squamous lining with a lymphocytic infiltrate in the cyst wall[1]. This characteristic, identifiable in 75% of the fine needle aspirations in our study, helps the differentiation from other squamous epithelium-lined cysts (dermoid cysts, splenic epidermoid cysts, squamous cell cancer, primary or metastatic)[12,17-20]. The cyst aspirates may be thick, milky, gray or frothy[2]. Cystic lymphangiomas characteristically contain chylous, milky fluid with a very high triglyceride level, commonly > 3000-5000 mg/dL, consistent with lymph. Cytologic features are consistent with lymphoid tissue[21-23]. They are lined by endothelium with immunohistochemical markers including factor VIII-R Ag, CD 31 and CD 34[10].

Our experience with these uncommon benign pancreatic cysts demonstrates that accurate diagnosis may be feasible through a combination of a contrast-enhanced abdominal CT scan and cyst fluid analyses acquired *via* endoscopic ultrasound and fine needle aspiration. These results can direct the appropriate management strategy, and asymptomatic patients can be spared an operation.

ACKNOWLEDGMENTS

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COMMENTS

Background

The treatment of pancreatic cysts is a continuously evolving field. Amongst the least well studied pancreatic cystic lesions are lymphoepithelial cysts and cystic lymphangiomas of the pancreas. Familiarity with their correct diagnosis is crucial as they can be followed non-operatively in asymptomatic patients.

Research frontiers

The existing literature on lymphoepithelial cysts and cystic lymphangiomas of the pancreas is limited to case reports. In this report the authors demonstrate our experience with twelve patients, one of the largest single institution experience reported, emphasizing on their correct diagnosis and treatment.

Innovations and breakthroughs

Lymphoepithelial cysts and cystic lymphangiomas of the pancreas can be diagnosed with a combination of contrast-enhanced computed tomography scans and endoscopic ultrasound with fine needle aspiration. Conservative management avoiding a major surgery can be followed as long as the lesions remain asymptomatic.

Applications

The description of the experience with the diagnosis and treatment of these rare pancreatic cystic lesions will aid in their safe management.

Terminology

Lymphoepithelial cysts and cystic lymphangiomas of the pancreas represent rare, benign cystic lesions. Their lining is being characterized by squamous epithelial lining with surrounding lymphoid tissue and endothelial cells respectively.

Peer review

This is a retrospective study regarding lymphoepithelial cysts or cystic lymphangiomas in 12 patients. This is a very uncommon pancreatic pathology and the paper carries a significant number of patients.

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CASE REPORT

Isotretinoin and ulcerative colitis: A case report and review of the literature

Ioannis Papaconstantinou, Anastasios Stefanopoulos, Aspasia Papailia, Christos Zeglinas, Ioannis Georgopoulos, Spyridon Michopoulos

Ioannis Papaconstantinou, Anastasios Stefanopoulos, Aspasia Papailia, Ioannis Georgopoulos, Second Department of Surgery, Aretaieion Hospital, Athens 11528, Greece
Christos Zeglinas, Department of Gastroenterology, Tzaneio General Hospital, Piraeus 18536, Greece
Spyridon Michopoulos, Department of Gastrenterology, General Hospital of Athens "Aleksandra", Athens 11528, Greece
Author contributions: Papaconstantinou I, Stefanopoulos A, Papailia A, Zeglinas C, Georgopoulos I and Michopoulos S designed research; Papaconstantinou I, Stefanopoulos A, Papailia A and Georgopoulos I performed research; Papaconstantinou I, Stefanopoulos A, Papailia A and Zeglinas C analyzed data and wrote the paper.
Correspondence to: Ioannis Georgopoulos, General Surgeon, Second Department of Surgery, Aretaieion Hospital, Vas. Sofias Ave. 76, Athens 11528,
Greece. georgopoulos.ioannis@yahoo.gr
Telephone: +30-210-7286193 Fax: +30-210-7286128
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Abstract

This case report describes a case of ulcerative colitis the onset of which occurred after the use of isotretinoin for acne treatment. Our patient, a healthy male young adult, after several months of isotretinoin use, developed gastrointestinal disorders and after thorough medical workup was diagnosed with ulcerative colitis. The literature regarding a possible correlation between isotretinoin use and ulcerative colitis is scarce. Nevertheless, recent epidemiological studies have shed more light on this possible association.

Key words: Ulcerative colitis; Isotretinoin; Acne; Inflammatory bowel disease; Heroin addiction

Core tip: Case reports suggest that isotretinoin administration may trigger inflammatory bowel diseases. This hypothesis has raised great scientific interest and numerous propositions addressing the pathophysiology of this potent association have been made. However, demographic data do not support a correlation between isotretinoin and inflammatory bowel disease. The current case describes a patient who developed ulcerative colitis while on isotretinoin administration. We hope that this case report may contribute to future epidemiological studies with scope to clarify the association between isotretinoin and inflammatory bowel diseases and more specifically ulcerative colitis.

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INTRODUCTION

Ulcerative colitis (UC) is an idiopathic inflammatory bowel disease affecting mostly young adults[1]. Acne is a skin disease that occurs commonly in adolescents and young adults[2]. Isotretinoin is a synthetic analogue of vitamin A and it is approved as treatment of severe acne that is resistant to standard therapy[3]. It has been prescribed to many patients worldwide since its introduction in 1982. Isotretinoin use has some known and well described severe adverse effects. Therefore the onset of ulcerative colitis after isotretinoin use had been reported only in case reports and therefore the risk had not been assessed[4]. Although the association of isotretinoin with

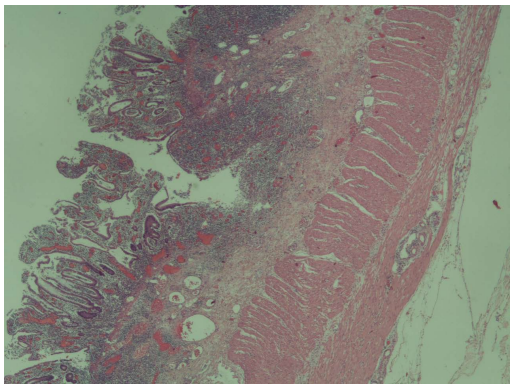

Figure 1 Biopsy from colonoscopy which revealed mucosal inflammation, compatible with ulcerative colitis.

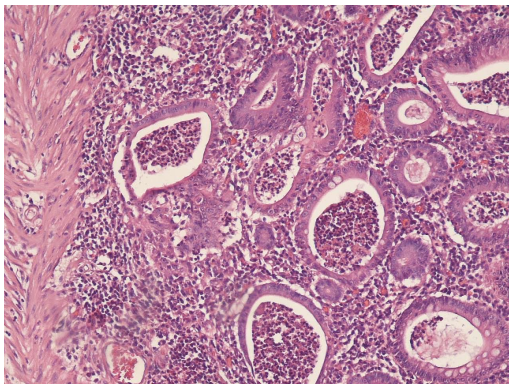

Figure 2 Histopathological image from the excised colon, typical of ulcerative colitis. This image demonstrates marked lymphocytic infiltration (blue/purple) of the intestinal mucosa and architectural distortion of the crypts (right side of the image). The inflammation is shallow and affects only the mucosa sparing the muscularis mucosal (left side).

Table 1 Laboratory findings

Test	Result	Normal lab values
WBC	21.300 per mcL	4-9 × 1000 per mcL
NEU	95%	43%-75%
LYM	1%	11%-49%
CRP	5.9 mg/dL	0.0-0.5 mg/dL
RBC	3.17 × 10^6/UL	3.8-5.3 × 10^6/UL
Hb	9.6 g/dL	13.5-17.0 g/dL
ESR	47 mm/h	M < 50 y.o: 0-15 mm/h
Htc	28%	40.0%-51.0%
Platelets	316 × 10^3/uL	120-380 × 10^3/uL
Alb	1.7 g/dL	3.5-5.5 g/dL
Total protein	4.6 g/dL	6.0-8.0 g/dL

WBC: White blood cells; NEU: Neutrophils; LYM: Lymphocyte; CRP: C-reactive protein; RBC: Red blood cells; ESR: Erythrocyte sedimentation rate.

ulcerative colitis has probably been answered in recent large epidemiological studies[1]. The objective of this case report is to demonstrate a case of a young male who was diagnosed with ulcerative colitis after being treated with isotretinoin for eight months and to review current literature for this association.

CASE REPORT

A 29-year-old male with past medical history of heroin addiction referred to our clinic for surgical treatment of severe ulcerative colitis resistant to conservative treatment and anti-tumor necrosis factor (TNF) therapy. Our patient was diagnosed with acne vulgares in 2007 and was treated with isotretinoin 20 mg two times daily with good results. After eight months of treatment he developed bloody diarrheas accompanied by abdominal pain. No fever or skin rashes or weight loss has been reported and had no medical or family history of gastrointestinal diseases. He was referred to a gastroenterological clinic. He admitted being addicted to heroin since 2004 but had stopped heroin use about 3 mo before this incident. Differential diagnosis on this case proposed that infectious reasons of gastroenteritis and diseases related to drug abuse should be overruled first. In that direction, stool cultures were negative for bacteria and parasites as were examinations for sexually transmitted diseases, hepatitis B, hepatitis C, human immunodeficiency virus infection and endocarditis. Abdominal X-ray was done with no specific findings. Finally colonoscopy was performed and biopsies were obtained. The endoscopic image resembled that of ulcerative colitis. The histological examination defined, from the typical histopathological findings, the diagnosis of UC (Figure 1). Isotretinoin was discontinued and he started treatment with mesalazine for six months with no significant improvement. Therefore was treated with corticosteroids at an outpatient gastroenterological clinic for several months with good clinical results. Mesalazine was used as maintenance treatment. Mild flares were reported rarely in the years that followed.

Soon after the first severe colitis episode he relapsed in his heroin addiction. Fortunately, about a year ago, he entered an anti-addiction treatment program and was treated with methadone.

However five months ago there was a severe relapse of the disease, as depicted by Truelove and Witts severity index. Laboratory findings are summarized in Table 1. The patient had more than 6 bloody diarrheas per day and reported a loss of 15 kg in the precedent two months. The patient required hospitalization for two weeks in a gastroenterological clinic. Stool cultures were negative and he was treated with corticosteroids, antibiotics and parenteral nutrition due to severe malnourishment. In addition, he was treated for his heroin-addiction. There was no clinical improvement and thus rescue therapy with anti-TNF started. The colitis did not respond to infliximab and therefore surgical treatment was proposed. He underwent subtotal colectomy with end ileostomy and mucous fistula of the remaining rectal stump, due to the risk of a vulnerable and unsafe reconstruction. The histopathological findings of the surgical specimens once more confirmed the diagnosis of ulcerative colitis (Figure 2).

During hospitalization he was also assessed by psy-

Table 2 Association between isotretinoin and ulcerative colitis in case control studies

Ref.	Population	UC [RR (95%CI)]
Bernstein *et al*[2]	Residents of Manitoba Canada	1.16 (0.56-2.20)
Crockett *et al*[8]	US health claims database	4.36 (1.97-9.66)
Etminan *et al*[7]	Women using oral contraceptives	1.10 (0.44-2.70)
Alhusayen *et al*[1]	British Columbia residents	1.31 (0.96-1.80)

UC: Ulcerative colitis.

chiatrists for his addiction. He was discharged ten days post-surgery in a significantly improved clinical status. A second restorative operation will be performed later.

DISCUSSION

This case report presented a probable adverse effect of isotretinoin that has been reported rarely by scientists. To the best of our knowledge this is the first case report of ulcerative colitis (UC) related to isotretinoin treatment in Greece. Not many cases of UC after isotretinoin exposure had been reported since its introduction for clinical use in 1982[5]. A possible mechanism is considered to be the prevention of epithelial cell growth and the activation of T-cells. Another theory is that the T-cells that are activated by isotretinoin, express the α4β7 and CCR9 receptors which are crucial to the process of the inflammation in the gastrointestinal system[6]. Several lawsuits have been filled implying correlation between isotretinoin and UC. The fact is that it is not possible to associate adequately isotretinoin isotretinoin and UC based on case reports or small case series. Moreover case reports cannot quantify the risk of UC after isotretinoin treatment[5]. The results from observational studies that followed were still confounding for a positive association. Despite all these, recent epidemiological studies and a meta-analysis suggests that isotretinoin does not increase the risk of UC[7].

Table 2 shows the pooled RR for UC from several large epidemiological studies. Bernstein *et al*[2] found no association between UC and isotretinoin. But Crockett *et al*[8] reported a strong association between them. They also demonstrated that the risk was elevated not only if the dose was increased (OR per 20 mg dose increase: 1.50 95%CI: 1.08-2.09) but also if the therapy with isotretinoin was longer than two months (OR = 5.63, 95%CI: 2.10-15.03). However the recent meta-analysis by Etminan *et al*[7] suggested that there is no correlation between UC and isotretinoin. The pooled RR from their study after the proper adjustment was 1.61 95%CI: 0.88-2.95. Another issue is that the onset of UC is about the same age as acne and UC has also extra-intestinal skin manifestations that can be misinterpreted as acne[9]. Alhusayen *et al*[1] observed that in the subgroup of 12-19 years old; there was a weak but significant association of inflammatory bowel disease and isotretinoin (RR = 1.39; 95%CI: 1.03-1.87). They did not report a separate rate ratio for UC in this subgroup. However their prime outcome was that inflammatory bowel disease was not related with isotretinoin. Moreover the studies that demonstrated a positive correlation between isotretinoin and UC did not address the possibility of previous topical treatment of acne. The main reason was that prior studies have shown that there is no association between UC and topical treatment of acne[10]. Alhusayen *et al*[1] stated that the risk of inflammatory bowel disease after topical acne medication was similar to the risk of isotretinoin. It is still unknown if acne itself is related with inflammatory bowel disease or other inflammatory diseases. Bernstein *et al*[2] concluded also that there is a smaller possibility for patients with known history of inflammatory bowel disease to use isotretinoin for acne treatment than patients from the general population. In addition there is no association from the literature between UC and heroin addiction. Our finding is similar to Papageorgiou *et al*[9] because their patient developed also UC after prolonged therapy with isotretinoin taken twice a day. It is worth of noting that in the majority of previous cases, ulcerative colitis' symptoms developed shortly after the cessation of isotretinoin therapy whereas there are only few cases[11,12], as the present one, addressing to patients who developed symptoms of UC while they were on isotretinoin treatment.

In conclusion recent data from the literature suggest that the risk for UC does not increase with isotretinoin treatment. However, in clinical practice there are significant questions that remain unanswered, such as the risks *vs* the benefits resulting from isotretinoin therapy applied to individuals with positive inflammatory bowel disease family history.

What remains to be investigated further, is the role of isotretinoin as a causative factor in ulcerative colitis or inflammatory bowel disease in general.

COMMENTS

Case characteristics

Bloody diarrheas accompanied by abdominal pain without fever or skin rashes or weight loss in a patient with personal history of heroin abuse.

Clinical diagnosis

Multiple bloody diarrheas per day accompanied by constant abdominal pain that spread in every abdominal region.

Differential diagnosis

Infectious causes of gastroenteritis, diseases related to drug abuse and inflammatory bowel diseases should be considered.

Laboratory diagnosis

Stool cultures and examinations for sexually transmitted diseases, hepatitis B, hepatitis C, human immunodeficiency virus infection and endocarditis were negative, therefore colonoscopy was performed and biopsies were obtained.

Imaging diagnosis

Abdominal X-ray, endoscopy.

Pathological diagnosis

From the endoscopic biopsy the histological findings set the diagnosis of ulcerative colitis (UC).

Treatment

The treatments that the patient underwent were firstly corticosteroids that showed good clinical results with mesalazine as maintenance treatment, thus after a severe relapse of the disease the patient was treated with corticosteroids, antibiotics and parenteral nutrition with no clinical improvement and rescue therapy with anti-tumor necrosis factor (TNF) factors (infliximab) was used, finally he underwent surgical treatment (subtotal colectomy with end ileostomy

and mucous fistula of the remaining rectal stump).

Related reports

UC is a bowel disease that in not quite sure what are its triggering factors. Though many factors are assumed to be associated to the onset of the disease. Some factors are very well studied but others need more research in order to be blamed. The use of isotretinoin, a widely used treatment for acne is associated to UC even though the case reports describing the linkage are few.

Term explanation

Isotretinoin is a medication related to vitamin A used primarily for severe cystic acne and acne that has not responded to other treatments. Anti-TNF therapy (anti-tumor necrosis factor therapy) is a new class of drugs that are approved in treating moderate-to-severe UC. The most common drug used is infliximab, that is a monoclonal antibody that binds to TNF.

Experiences and lessons

UC is a disease that is maybe associated and triggered by more drugs and factors than people already know so in the differential diagnosis of bloody diarrheas in any young patient, should always be the inflammatory bowel diseases.

Peer review

This case report is interesting and well written.

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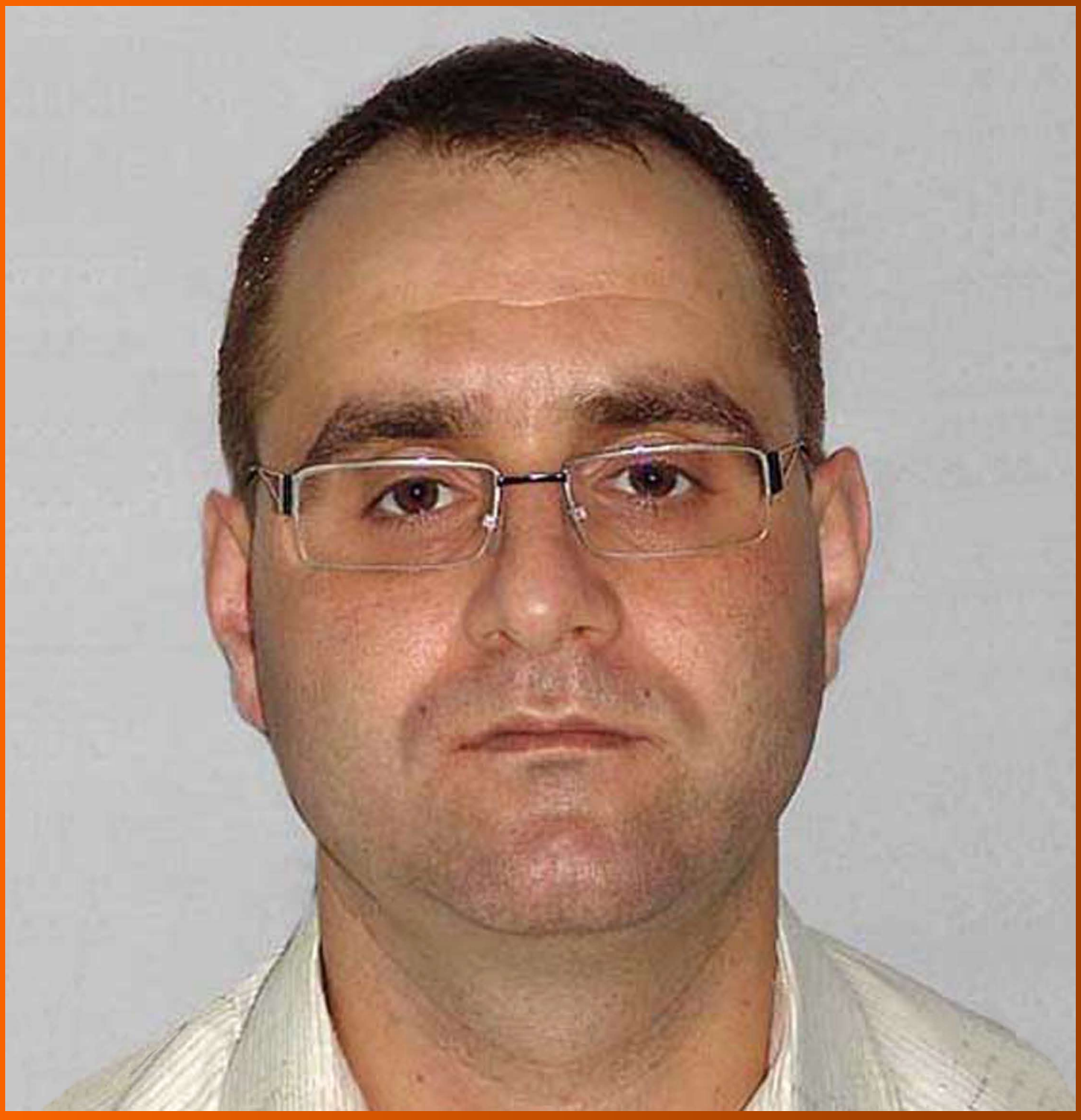

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Timothy M Pawlik, MD, MPH, FACS, Associate Professor of Surgery and Oncology, Hepatobiliary Surgery Program Director, Director, Johns Hopkins Medicine Liver Tumor Center Multi-Disciplinary Clinic, Co-Director of Center for Surgical Trials and Outcomes Research, Johns Hopkins Hospital, 600 N. Wolfe Street, Harvey 611, Baltimore, MD 21287, United States

EDITORIAL OFFICE
Jin-Lei Wang, Director

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World Journal of Gastrointestinal Surgery
Room 903, Building D, Ocean International Center,
No. 62 Dongsihuan Zhonglu, Chaoyang District,
Beijing 100025, China
Telephone: +86-10-85381891
Fax: +86-10-85381893
E-mail: editorialoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
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RETROSPECTIVE STUDY

Simultaneous operation for cardiac disease and gastrointestinal malignancy

Teruo Komokata, Mikio Fukueda, Mamoru Kaieda, Takayuki Ueno, Yoshihumi Iguro, Yutaka Imoto, Ryuzo Sakata

Teruo Komokata, Mamoru Kaieda, Takayuki Ueno, Department of Surgery, Kagoshima Medical Center, National Hospital Organization, Kagoshima 892-0853, Japan
Mikio Fukueda, Yoshihumi Iguro, Yutaka Imoto, Cardiovascular and Gastroenterological Surgery, Kagoshima University Graduate School of Medical and Dental Sciences, Kagoshima 890-8520, Japan
Ryuzo Sakata, Cardiovascular Surgery, Kyoto University Hospital, Kyoto 606-8397, Japan
Author contributions: Komokata T designed the study and provided the collection of the clinical data; Komokata T and Fukueda M wrote the manuscript; Kaieda M, Ueno T, Iguro Y, and Sakata R participated in the simultaneous surgery; Imoto Y and Sakata R were involved in editing the manuscript.
Correspondence to: Teruo Komokata, MD, PhD, Department of Surgery, Kagoshima Medical Center, National Hospital Organization, 8-1 Shiroyama, Kagoshima 892-0853, Japan. komokata@kagomc2.hosp.go.jp
Telephone: +81-99-2231151 Fax: +81-99-2269246
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Abstract

AIM: To investigate the safety of performing simultaneous cardiac surgery and a resection of a gastrointestinal malignancy.

METHODS: Among 3664 elective cardiac operations performed in adults at Kagoshima University Hospital from January 1991 to October 2009, this study reviewed the clinical records of the patients who underwent concomitant cardiac surgery and a gastrointestinal resection. Such simultaneous surgeries were performed in 15 patients between January 1991 and October 2009. The cardiac diseases included 8 cases of coronary artery disease and 7 cases with valvular heart disease. Gastrointestinal malignancies included 11 gastric and 4 colon cancers. Immediate postoperative and long-term outcomes were evaluated.

RESULTS: Postoperative complications occurred in 5 patients (33.3%), including strokes (n = 1), respiratory failure requiring re-intubation (n = 1), hemorrhage (n = 2), hyperbilirubinemia (n = 1) and aspiration pneumonia (n = 1). There was 1 hospital death caused by the development of adult respiratory distress syndrome after postoperative surgical bleeding followed aortic valve replacement plus gastrectomy. There was no cardiovascular event in the patients during the follow-up period. The cumulative survival rate for all patients was 69.2% at 5 years.

CONCLUSION: Simultaneous procedures are acceptable for the patients who require surgery for both cardiac diseases and gastrointestinal malignancy. In particular, the combination of a standard cardiac operation, such as coronary artery bypass grafting or an isolated valve replacement and simple gastrointestinal resection, such as gastrectomy or colectomy can therefore be safely performed.

Key words: Simultaneous operation; Cardiac disease; Gastrointestinal malignancy; Gastric cancer; Colon cancer

Core tip: Simultaneous surgical interventions for cardiovascular and gastrointestinal pathology have not been well adapted so far. Staged procedure, depending on the clinical priority is usually preferred. Concomitant cardiac and gastrointestinal surgery holds a bundle of advantages with some challenges. We reviewed the outcome in 15 patients who underwent simultaneous cardiovascular and gastrointestinal surgery at Kagoshima University Hospital. Postoperative complications were noted in 5 cases, with 1 death. No adverse cardiovascular events were noted during follow up. The cumulative survival rate for all patients was 69.2% at 5

years. Synchronized cardiovascular and gastrointestinal procedures can be safely performed when needed.

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INTRODUCTION

The prevalence of cardiovascular disease and malignant disease has been increasing as the proportion of elderly individuals in the general population increases in developed countries[1]. Therefore, physicians may encounter a patient with concomitant occurrence of cardiovascular disease and malignant diseases. In general, patients with both cardiovascular disease that requires surgery and a surgically resectable malignancy are treated in a staged procedure depending on the clinical priority. Simultaneous procedure are rare because the surgeon's anxiety that the incidence of complications may be higher in patients undergoing a simultaneous procedure than in those undergoing isolated cardiac surgery or gastrointestinal resection. However, a simultaneous approach would be attractive for such patients, because limiting them to a single exposure to anesthesia and one recovery period remove the potential opportunity for perioperative cardiovascular events, and moreover provide economic benefits. The recent advances in anesthesia, surgical techniques and perioperative management have allowed for combined operations to be conducted, so several studies have validated the concept that a simultaneous operation can be safely performed in a limited population of patients[2-9].

Most of them are reports concerning a combined procedure that includes a pulmonary resection and cardiac operation[2-5], and there are a few studies on the combination surgery of the heart and a gastrointestinal malignancy[6-9]. This report presents a series of 15 patients who underwent concomitant cardiac surgery and gastrointestinal resection to assess the safety of a simultaneous procedure.

MATERIALS AND METHODS

There were 3664 elective cardiac operations performed in adults at Kagoshima University Hospital from January 1991 to October 2009. This study reviewed the clinical records of the patients who underwent concomitant cardiac surgery and a gastrointestinal resection. Fifteen of these patients (0.4%) underwent a simultaneous procedure. The records of the patients were reviewed for the type of surgical procedure, complications, and the duration of the stays in the intensive care unit (ICU) and hospital. The long-term outcome was determined using hospital records and through direct contact with the patients and their family physicians. The values are expressed as the mean ± SD. Survival was estimated by the Kaplan-Meier method using the date of the combined procedure as the starting point and the date of death or last follow-up as the end-point.

RESULTS

Clinical presentation

The preoperative characteristics of the patients are summarized in Table 1. The subjects included of 11 males and 4 females with an average age of 72.3 ± 7.4 years, of whom 8 were treated for coronary artery disease (CAD) and 7 impaired valvular heart disease. CAD involved two vessels in 2 patients, three vessels in 4 patients, and the left main trunk in 2 patients. Valvular heart diseases included aortic stenosis in 4 patients, mitral stenosis accompanying with left atrial thrombus in 2 patients, and severe mitral regurgitation in one patient. The left ventricular ejection fraction assessed by ventriculography or echocardiography ranged from 36% to 81% with an average of 63.6% ± 12.1%.

Gastrointestinal malignancies included 11 patients with gastric cancer and 4 patients with colon cancer. Only one gastric cancer was located in the fundus, the other 10 lesions were in the body or antrum of the stomach. All gastric cancers were preoperatively diagnosed as early stage and no distant metastasis or multiple lymph nodes metastasis was detected radiologically. All 4 colon cancers (transverse 1, descending 1, sigmoid 1, cecum 1) were in advanced stages and one of them had multiple liver metastases preoperatively. The most common symptoms associated with the gastrointestinal malignancies were anemia, weight loss, and gastrointestinal tract bleeding. Five patients were first diagnosed as having cancer and cardiac disease was discovered during the preoperative assessment. The remaining 10 patients presented with cardiac symptoms, resulting from myocardial ischemia or valvular heart disease, classified as NYHA functional class from I to Ⅲ, and thus were found incidentally to have an asymptomatic gastrointestinal cancer.

Preoperative comorbidities included renal failure in 2 patients (1 patient required hemodialysis), diabetes controlled by oral agents in 2 patients, and chronic obstructive pulmonary disease (COPD) in one patient, in which the percentage of vital capacity was 81.1% and the forced expiratory volume at 1 s was 54.9%.

Surgical procedures

The surgical procedures carried out are listed in Table 2. All were elective procedures. The simultaneous procedures included aortic valve replacement (AVR) plus gastrectomy in 4 patients, mitral valve replacement plus gastrectomy in 3 patients, AVR plus colectomy in 1 patients, off-pump coronary artery bypass grafting (OPCAB) plus gastrectomy in 4 patients, and coronary artery bypass grafting (CABG) plus colectomy in 3 patients. The cardiac surgery was performed first in all but 1 (case

Table 1 Preoperative characteristics

No.	Age (yr)	Sex	Cardiac disease	EF (%)	Gastrointestinal cancer		Comorbidities
					Type	Stage	
1	63	F	MS + LA thrombus	69	Gastric	I B	CVD
2	73	F	MR + TR	78	Gastric	I A	-
3	78	M	CAD (LMT)	61	Colon (T)	IIIB	-
4	76	M	CAD (2)[1]	47	Colon (D)	II	DM
5	61	M	MS + LA thrombus	65	Gastric	I A	CRF (HD)
6	81	M	AS	78	Gastric	I A	-
7	66	M	CAD (3)	65	Gastric	I A	CVD
8	62	M	CAD (3)	70	Gastric	II	CVD, DM
9	85	M	AS	64	Gastric	II	COPD
10	72	F	CAD (3)	36	Gastric	I A	-
11	76	M	CAD (2)	55	Gastric	I A	-
12	73	M	CAD (LMT)	54	Gastric	I A	CRF
13	65	M	CAD (3)	60	Colon (C)	IV	Liver metastasis
14	79	F	AS	81	Gastric	I B	-
15	74	M	AS	71	Colon (S)	IIIB	-

[1]Parenthetic figure shows number of involved coronary artery. EF: Ejection fraction; CVD: Cerebrovascular disease; DM: Diabetis mellitus; CRF: Chronic renal failure; LMT: Left main trunk disease; HD: Hemodialysis; COPD: Chronic obstructive pulmonary disease; T: Transverse; D: Descending; C: Cecum; S: Sigmoid; CAD: Coronary artery disease; AS: Aortic stenosis; MS: Mitral stenosis; TR: Tricuspid regurgitation; MR: Mitral regurgitation; LA: Left atrial.

Table 2 Surgical procedures and results

No.	Cardiac procedures	Abdominal procedures	Postoperative complications	Follow-up (mo)	Results	Causes of death
1	MVR + TAP	Total gastrectomy	-	81	Dead	Cancer recurrence
2	MVR + TAP	Distal gastrectomy	-	135	Dead	Renal failure
3	CABG (2)	Right hemicolectomy	-	150	Alive	-
4	CABG (3)	Left hemicolectomy	-	53	Dead	Cancer recurrence
5	MVR	Partial gastrectomy	-	84	Dead	Suffocated
6	AVR	Distal gastrectomy	-	90	Alive	-
7	OPCAB (4)	Distal gastrectomy	-	72	Alive	-
8	OPCAB (5)	Distal gastrectomy	-	84	Alive	-
9	AVR	Distal gastrectomy	Bleeding	2	Dead	Respiratory failure
10	CABG (4)	Distal gastrectomy	Cerebral infarction	28	Alive	-
11	OPCAB (2)	Distal gastrectomy	-	25	Alive	-
12	OPCAB (3)	Distal gastrectomy	Aspiration pneumonia	21	Alive	-
13	OPCAB (3)	Ileocecal resection	-	17	Dead	Liver failure
14	AVR	Total gastrectomy	Bleeding	8	Alive	-
15	AVR	Sigmoidectomy	Hyperbilirubinmia	3	Alive	-

CABG: Coronary artery bypass grafting; AVR: Aortic valve replacement; OPCAB: Off-pump coronary artery bypass grafting; CABG: Coronary artery bypass grafting; MVR: Mitral valve replacement; TAP: Tricuspid annuloplasty.

No. 3), who underwent colectomy, followed by CABG. The gastrointestinal resections were conducted after the cardiac procedure was completed and heparin treatment was reversed to prevent excessive surgical bleeding. All gastrointestinal resections were carried out using standard techniques to accomplish complete resection of cancer and lymph node dissection, except for one case that was complicated with liver metastasis. All cardiac operation were performed through median sternotomy, and then the skin incision of median laparotomy for gastrointestinal resection was selected to avoid contact with a chest skin incision to prevent the mediastinitis.

Short-term results

The total operative time was 512.8 ± 85.4 min (range, 420 to 635 min). Ten patients were placed on cardiopulmonary bypass (CPB) for 72 to 144 min, with an average of 116.3 ± 16.0 min. The average amount of intraoperative bleeding was 1256.2 ± 1127 mL (range 330 to 4200 mL). All operations were performed without intraoperative incidents. The average ICU stay was 3.15 ± 1.98 d (range 1 to 8 d). The duration of postoperative ventilatory assistance was 35.1 ± 28.96 h (range 8 to 116 h). The mean postoperative hospital stay was 19.1 ± 2.7 d (range 8 to 51 d).

Five patients (33.3%) experienced postoperative complications. One patient had aspiration pneumonia and required re-intubation on postoperative day 4 for an additional 6 d. Cerebral infarction occurred in 1 patient, and this resolved with medical treatment. A transient increase in total bilirubin occurred in 1 patient (max value: 8 mg/dL), and the bililubin values were returned to normal by conservative therapy. Surgical bleeding complications occurred in two patients who required reoperation

for bleeding from the chest or abdomen. One was an 83-year-old man who had COPD, underwent AVR and distal gastrectomy simultaneously, and suffered massive bleeding from chest drainage tube postoperatively. He temporarily recovered after the reoperation to treat the bleeding. However, Methicillin-resistant Staphylococcus aureus pneumonitis developed shortly after the surgery and he died of respiratory failure 10 wk after undergoing the initial surgery. No clinical anastomotic leaks related to the gastrointestinal surgery and cardiovascular events were observed in the early postoperative period. In addition no mediastinitis, both wound infection and mechanical valve infection occurred. The remaining 10 patients were uneventful during postoperative course.

The surgical stage of the gastric cancers was stage I A (defined by tumor-node-metastasis classifications) in 7 patients, stage I B in 1 patient, and stage Ⅱ in 2 patients. All patients with colon cancer were in advanced stages, and thus one patient was in Stage Ⅱ, two patients were in stage ⅢB, and one patient was in stage Ⅳ. Three received postoperative chemotherapy for the treatment of colon cancer.

Long-term results

Fourteen of 15 patients were discharged, and 6 of them died during the follow-up period, which averaged 56.9 ± 47.1 mo (range, 2 to 149 mo). The patient with multiple bilobar liver metastases before the surgery died of liver failure at 17.2 mo. Two patients died of cancer recurrence at 80.8 and 53.4 mo after operation.

The causes of death of the other 2 patients were suffocation and renal failure. Six of 14 patients are currently alive without evidence of recurrence after surgery, and have experienced no cardiovascular events during the long-term follow-up. The cumulative survival rates for all patients undergoing simultaneous procedures were 69.2% at 5 years.

DISCUSSION

The treatment of patients who require surgery for both cardiac disease and gastrointestinal malignancy is still controversial. A staged procedure depending on the clinical priority is usually preferred because most surgeons assume that the prolonged operative time and extensive surgical invasiveness associated with simultaneous procedures must increase the surgical morbidity and mortality. However, there are also several unfavorable issues associated with a staged procedure. For instance, when an isolated cardiac operation is performed before gastrointestinal resection, the malignant lesion may develop massive gastrointestinal bleeding due to the heparinization required for CPB, and moreover untreated cancer may progress during the interval prior to the second operation. On the contrary, postoperative cardiovascular complication may occur during gastrointestinal resection and that could be fatal[10]. The concomitant approach, could resolve those problem. Although a simultaneous procedure is apparently attractive, it is necessary to ensure the safety so that this approach can be generally accepted. This study focused on the safety and indications of simultaneous procedures.

Most of the simultaneous procedures in the present series were performed successfully in short-term period. The hospital mortality and morbidity rate was 6.6% and 33.3%, respectively, and the outcome was quite acceptable.

One of surgeon's prime concerns about the safety of simultaneous operations is that CPB has several disadvantageous systemic effects including bleeding disorders, thrombotic complications, massive fluid shifts and immunosuppression, all associated with homeostatic disruption. Furthermore, CPB is also associated with mesenteric ischemia, which may contribute to varying degrees of organ damage[11,12].

Cerebral infarction and hyperbilirubinemia, which are the most common complications associated with CPB, occurred in one patient each, but those resolved with medical treatment. There were no postoperative gastrointestinal complications related to resection and reconstruction, such as anastomosis leakage, ileus and bleeding. Only one patient unfortunately died of respiratory failure after an early reoperation for postoperative bleeding from the chest, and he was a person of advanced age with COPD and was a high risk case. The postoperative occurrence of bleeding associated with abnormal blood coagulation following CPB and systemic heparinization, which is one of the most dreaded complications, may frequently be life-threatening for high risk patients in disrupted homeostasis. Therefore, the management of bleeding should be ensured with caution at the end of cardiac surgery. OPCAB is preferable to avoid the adverse effects of CPB, and improve the outcome of a combined operation by allowing gastrointestinal resection to be performed safely[13,14]. OPCAB was performed in all of the 4 patients in the current series, and their postoperative courses were favorable. OPCAB should be selected whenever possible in patients with severe coronary disease undergoing combined procedure.

Most cardiovascular surgeons have concern that the addition of clean-contaminated operation to cardiac operation would increase the incidence of postoperative infection; wound infection, mediastinitis and mechanical valve infection. However, there was no incidence of surgical site infection in this series, thus routine management of infection, using prophylactic antibiotics, sterilization of the surgical field, and separation of an each skin incision, was able to adequately prevent postoperative infectious complications in simultaneous operation.

This study cannot conclude that the hospital morbidity and mortality of patients undergoing simultaneous procedure are better than that of staged procedures, and cannot clarify whether simultaneous operations contribute benefits to patients over a long term period. However the current experience demonstrated that the combination of standard cardiac operations, such as CABG or single valve replacement, and uncomplicated gastrointestinal resections such as gastrectomy or colectomy was

safe and favorable excluding patients with serious comorbidities or poor cardiac function.

The result of this study suggest that, the simultaneous procedures are an acceptable alternative for selected patients, but further studies are necessary to determine the role of the two strategies for patients with cardiovascular disease and concurrent gastrointestinal malignancy.

COMMENTS

Background

Patients requiring surgical intervention for gastroenterological pathology and cardiac events mostly entail careful attention. A surgeon has to weigh the pros and cons, and decisions are sometimes cumbersome especially when simultaneous surgery has to be performed. However concomitant cardiac and gastrointestinal surgery holds some advantages at times, like limiting the patients to single exposure of anesthesia, same recovery time along with economic benefits. The aim of the study was to assess the safety and outcome of simultaneous procedure. On reviewing the outcome in 15 patients who underwent simultaneous surgical procedure, the overall outcome was found to be satisfactory.

Research frontiers

The authors retrospectively studied the outcome in the patients who underwent concomitant cardiac and gastrointestinal surgery. Same time, the authors analyzed the publish literature on concomitant surgery.

Innovations and breakthroughs

Despite advances in surgery, anesthesia, surgical skills and the high tech settings; the surgeons may find themselves reluctant to perform concomitant cardiac and gastrointestinal surgery. This study evaluated the outcome in 15 cases of simultaneous surgery. Immediate and delayed postoperative outcomes were found to be satisfactory.

Applications

The result suggests that concomitant cardiac and gastrointestinal surgery can be safely performed when required.

Terminology

Simultaneous operation, cardiac disease, gastrointestinal malignancy, gastric cancer, colon cancer.

Peer review

This is a retrospective study to assess the outcomes of concomitant surgery for gastrointestinal pathology with cardiac events. Simultaneous gastrointestinal and cardiac surgery may have an appropriate outcome and can be safely performed.

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OBSERVATIONAL STUDY

Neonatal gastric perforation: A single center experience

Jeik Byun, Hyun Young Kim, Seung Yeon Noh, Soo Hong Kim, Sung Eun Jung, Seong Cheol Lee, Kwi Won Park

Jeik Byun, Hyun Young Kim, Seung Yeon Noh, Soo Hong Kim, Sung Eun Jung, Seong Cheol Lee, Kwi Won Park, Department of Pediatric Surgery, Seoul National University Children's Hospital, Seoul 110-744, South Korea
Author contributions: All the authors contributed to this paper.
Correspondence to: Sung Eun Jung, MD, Department of Pediatric Surgery, Seoul National University Children's Hospital, 101 Daehang-ro, Yeongeon-dong, Jongro-gu, Seoul 110-744, South Korea. sejung@snu.ac.kr
Telephone: +82-02-20722478 Fax: +82-02-7405130
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Abstract

AIM: To determine the etiology and prognostic factors for neonatal gastric perforation (NGP), a rare but life-threatening disease.

METHODS: Between 1980 and 2011, nine patients underwent surgical intervention for NGP at Seoul National University Children's Hospital. The characteristics and prognosis of the patients were retrospectively analyzed.

RESULTS: Among the nine patients, three (33.3%) were preterm babies and five (55.5%) had associated anomalies, which included diaphragmatic eventration (n = 2), congenital diaphragmatic hernia, esophageal atresia with tracheoesophageal fistula, and antral web. Three (33.3%) patients were born before 1990 and three (33.3%) had a birth weight < 2500 g. Pneumoperitoneum was found on preoperative images in six (66.7%) patients, and incidentally in the other three (33.3%) patients. Surgery was performed within 24 h after the onset of symptoms in seven (77.8%) patients. The overall mortality rate was 22.2% (2/9). The time between symptoms and surgical intervention was the only prognostic factor for survival, whereas premature birth and birth weight were not.

CONCLUSION: Early detection and advances in neonatal intensive care may improve the prognosis of NGP.

Key words: Neonate; Gastric perforation; Etiology; Prognosis; Surgical intervention

Core tip: Neonatal gastric perforation (NGP) is an extremely rare condition and very few cases have been reported to date. We determined the etiology and prognostic factors for NGP in nine cases who were treated at a single center. Early detection and prompt surgical intervention are essential to improve the outcomes of NGP.

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INTRODUCTION

Neonatal gastric perforation (NGP) accounts for approximately 7% of all gastrointestinal perforations in neonates, and has a poor prognosis with a high mortality rate[1,2]. Factors associated with NGP include prematurity, asphyxia, congenital anomalies, stress at birth, vigorous respiratory resuscitative measures, increased intragastric pressure caused by distal obstruction, and anatomic abnormalities of the stomach[3-7]. Male gender, metabolic acidosis, premature birth, and low birth weight are associated with worse outcomes[8,9]. However, the etiology and prognostic factors of NGP are still widely debated. Here, we describe our experience of treating nine patients with NGP at a single center. The aim of this study was to review patients with NGP and discuss its etiology and

Table 1 Patient characteristics

Patient	Gender	Date of birth	GA (wk)	Term	BW (g)	Delivery	Symptom onset (d)	Time from symptoms to surgery (d)	pH	NG tube
A	F	1983-02-24	40^{+2}	Full term	3500	Natural	5	1	N.D.	Yes
B	F	1987-07-09	40	Full term	2950	Natural	2	2	7.13	Yes
C	M	1990-09-05	35	Preterm	2190	Natural	2	2	7.03	Yes
D	M	1993-06-03	38^{+4}	Full term	2950	C-sec	4	0	7.19	No
E	M	1999-05-13	36^{+3}	Full term	2860	Natural	2	0	7.43	No
F	F	2003-05-10	32^{+6}	Preterm	1960	C-sec	2	0	N.D.	Yes
G	M	2009-02-03	38	Full term	3620	Natural	0	1	7.086	Yes
H	M	2011-08-03	24	Preterm	730	Natural	4	1	7.058	Yes
I	F	2011-12-27	39^{+3}	Full term	4040	Natural	2	0	7.391	Yes

GA: Gestational age; BW: Birth weight; F: Female; M: Male; NG: Nasogastric; C-sec: Cesarean section.

Table 2 Preoperative conditions

Initial symptom	Diet	Ventilator	O_2 therapy	Pneumoperitoneum on X-ray	Associated anomaly	Maternal problem
High fever, vomiting, dyspnea	Yes	Yes	Yes	No	Diaphragmatic eventration	None
Vomiting dyspnea	Yes	Yes	Yes	No	Diaphragmatic eventration	None
Hematemesis	Yes	No	Yes	No		PROM
Abd. dist, vomiting, fever	Yes	No	No	Yes		None
Abd. dist	Yes	No	No	Yes		None
Abd. dist	No	No	No	Yes	TEF	None
Abd. dist	No	Yes	Yes	Yes	CDH	None
Metabolic acidosis, abd. dist,	No	Yes	Yes	Yes	Antral web	PROM
Abd. dist	Yes	No	No	Yes		None

PROM: Premature rupture of membranes.

prognosis, in order to improve patient outcomes.

MATERIALS AND METHODS

Data collection

Between 1983 and 2011, nine neonates (five males and four females) who underwent surgical treatment for NGP at a single center were identified using written and electronic medical records.

Variables

We focused on preoperative and intraoperative characteristics that are known or thought to be prognostic factors for NGP. The characteristics retrieved from medical records included gender, year of birth, gestational age, birth weight, method of delivery, maternal gestational problems, maternal age at delivery, Apgar score, initial symptoms, time from birth to initial symptoms after birth, time between symptom onset and surgery, serum pH, serum pCO_2, use of a nasogastric tube, ventilator therapy, O_2 therapy, diagnostic method, associated anomalies, site of perforation, length of perforation, type of surgical procedure, and postoperative complications.

Statistical analysis

Statistical analyses were performed using SPSS 19.0 software for Windows (IBM Inc., Armonk, NY, United States). Descriptive data are reported as percentage of patients or as mean (range). The χ^2 test was used to identify possible prognostic factors.

RESULTS

The clinical features of the nine patients are described in Table 1. There were five boys and four girls; three were born before 1990 and six after 1991. The mean gestational age was 38^{+0} wk (range, 24^{+0}-40^{+2} wk) and the mean birth weight was 2950 g (range, 730-4040 g). Three patients were preterm and six were full term. Two patients had a low birth weight (LBW; < 2500 g) and one had an extremely LBW (ELBW; < 1000 g). Seven were born *via* natural delivery and two *via* cesarean section. Two patients were born after premature rupture of the membranes, of whom one was a twin. The mean maternal age at delivery was 32 years (range, 25-32 years). In one patient, Apgar score was 1 and 4 at 1 and 5 min, respectively. In another patient, Apgar score was 2 and 7 at 1 and 5 min, respectively.

Preoperative conditions are described in Table 2. Preoperative serum pH was < 7.30 in five patients and > 7.30 in two patients, and was not determined in the other two patients. A nasogastric tube was used preoperatively in seven patients. Six were on a specialist diet, four were on ventilators, and six received supplemental O_2.

All nine patients presented with mild to severe abdominal distension. Patient A initially presented with high fever, vomiting, and dyspnea. Congenital diaphragmatic hernia was initially suspected, but the final diagnosis was diaphragmatic eventration. Gastric perforation was found during surgery. Patient B initially presented with vomiting and dyspnea. Abdominal exploration was performed because of suspected congenital diaphragmatic hernia,

Table 3 Intraoperative and postoperative outcomes

Patient	Surgical procedure	Perforated site	Length (cm)	NEC	Complications	Hospital stay (d)	Survival
A	RA	Body, LC, PW	4	Yes	Wound problem	18	Alive
B	RA	Body, PW	2.5	No	Sepsis	4	Deceased
C	Primary repair	Whole, GC	10	Yes	Sepsis	46	Deceased
D	Primary repair	Whole, GC	10	No		11	Alive
E	RA	Body, GC	5	Yes		28	Alive
F	Primary repair	LC	3	No		40	Alive
G	Primary repair	Body, GC	1	No		24	Alive
H	Primary repair	(1) LC (2) body, AW	5	No		131	Alive
I	Primary repair	Antrum, AW	0.5	No	Wound problem	11	Alive

NEC: Necrotizing enterocolitis; RA: Resection and anastomosis; LC: Lesser curvature; PW: Posterior wall; GC: Greater curvature; AW: Anterior wall.

which was ultimately diagnosed as diaphragmatic eventration. Gastric perforation was also found intraoperatively. Patient C initially presented with dyspnea and was intubated at birth. At 3 d of age, the patient exhibited hematemesis and severe abdominal distension. Paracentesis revealed bloody ascites, and explorative surgery was performed 2 d after the onset of symptoms. All of the patients, except for Patients B and C, underwent surgery within 24 h of the onset of symptoms. The mean age of symptom onset was 3 d (range, 0-5 d). Five patients had associated anomalies, which included diaphragmatic eventration, congenital diaphragmatic hernia, esophageal atresia with a tracheoesophageal fistula, and antral web.

The intraoperative and postoperative findings are summarized in Table 3. The mean size of the perforation was 4.5 cm (0.5-10 cm). The body (n = 5, 55.5%) of the stomach was the most common site of perforation. The perforation was located in the greater curvature in four patients and in the lesser curvature in three patients. Primary repair was performed in six patients, while resection and anastomosis were performed in three patients. Postoperative complications occurred in five patients (55.6%), which included wound problems in two patients and recurrence in one patient. The other four patients were discharged without any complications.

Patient H, who had recurrence, was male and was born at a gestational age of 24 wk with a birth weight of 730 g. He presented with pneumoperitoneum on infantogram and underwent surgery at 5 d old. A 5 cm long laceration on the lesser curvature and pyloric thickening were found during explorative surgery. Therefore, primary repair was done. However, the postoperative infantogram and sonogram revealed an increase in free air. Small bowel series suggested obstruction of the gastric outlet. Three days after initial surgery, the patient underwent a second operation that revealed another perforation of the upper body of the anterior wall and prepyloric antral web. Primary repair and Heineke-Mikulicz pyloroplasty were performed, and an ileostomy was formed because of enteritis of the entire small bowel. Ileostomy repair was done 3 mo after surgery.

The overall mortality rate was 22.2% (2/9). Patient B was born at a gestational age of 40 wk and the birth weight was 2950 g. The patient was diagnosed with Bochdalek hernia at another hospital and was transferred to our institute for surgery. On surgical exploration, the anterolateral portion of the diaphragm was eventrated, and a 2.5 cm long laceration was found in the posterior wall of the stomach. Diaphragm repair and primary suturing of the stomach were done. The patient died 5 d after surgery because of septic shock. Patient C was born at a gestational age of 35 wk and with a birth weight of 2190 g. Hematemesis and hematochezia were found at 3 d of age. The patient received conservative therapies, including transfusion for 24 h. Diagnostic paracentesis performed at 4 d of age revealed bloody ascites. Explorative laparotomy was done to evaluate the patient's hemoperitoneum and gastrointestinal bleeding. On exploration, a 10 cm long laceration with a necrotic margin was found on the greater curvature of the stomach, and primary repair was performed. Fifteen days later, the patient suffered from abrupt onset of abdominal distension and vomiting, and an erythematous discoloration was found on the left flank. Necrotizing enterocolitis was suspected based on infantogram, and the patient underwent surgery to repair multiple small bowel perforations. Gross fecal spillage into the abdominal cavity and multiple perforations of the small bowel were found, and approximately 20 cm of the ileum was resected. Despite intensive postoperative care, the patient's septic condition, hepatic dysfunction, and renal dysfunction resulted in death 29 d after the second surgery.

When we performed analyses to identify factors associated with survival, the time between symptoms and surgical intervention was the only prognostic factor for survival ($P < 0.05$) (Table 4). However, factors that appeared to show some association with survival included the presence of pneumoperitoneum on preoperative imaging ($P = 0.083$) and the year of birth ($P = 0.083$). Prematurity and birth weight were not associated with survival ($P = 1.000$ for both).

DISCUSSION

Since Herbut first suggested that the congenital absence of muscular structures of the stomach may result in perforation[10], multiple theories have been proposed to describe the etiology of NGP. High gastric acid produc-

Table 4 Prognostic factor analysis

	Survival (n = 7)	Deceased (n = 2)	P-value
Male	4	1	1.000
Birth before 1990	1	2	0.083
Birth before 2000	3	2	0.444
Preterm	2	1	1.000
BW < 2500 g	2	1	1.000
pH < 7.30	3	2	1.000
NG tube	5	2	1.000
Diet	4	2	0.500
Ventilator	3	1	1.000
O_2 therapy	3	2	0.464
Pneumoperitoneum	6	0	0.083
Associated anomaly	5	1	1.000
Time from symptom onset to surgery > 24 h	0	2	< 0.001
Length > 2 cm	5	2	1.000
Primary repair	5	1	1.000
NEC	2	1	1.000

BW: Body weight; NG: Nasogastric; NEC: Necrotizing enterocolitis.

tion and stress ulceration[11], abdominal trauma[12], ischemia of the stomach wall due to asphyxia[13] or vascular shunting[14], lack of intestinal pacemaker cells[15], and lack of C-KIT mast cells[16] have all been proposed as possible causes of NGP. NGP was historically thought to occur spontaneously[10,17-19] without any association with distal obstruction or other gastrointestinal conditions. However, since Shaw *et al*[20] reported perforation of the stomach after tying both ends of the stomach and insufflating it with air, mechanical pneumatic rupture has been proposed as a possible etiologic factor[6,7,14]. Gryboski[21] investigated the mechanism involved in neonatal swallowing, and reported that esophageal peristalsis was not coordinated until 3 d after birth. Jones *et al*[22] suggested that neonatal immaturity of the vomiting mechanism made it possible to increase the intragastric pressure to its limit.

Irrespective of the etiology, NGP mostly occurs between 2 and 7 d of age[23]. Indeed, all of the patients in the present series presented with symptoms by 7 d of age. Some authors have noted that premature birth is a common finding in patients with NGP[24,25]. In our study, 33.3% (3/9) of patients were preterm, which is higher than the normal rate. O_2 supplementation and hypoxic stress were also reported as etiologic factors for NGP[26], and 55.6% (5/9) received supplemental O_2 in our study and the initial symptom was dyspnea in 22.2% (2/9). None of the patients in our series had trauma, but intragastric acidity was not assessed. Leone *et al*[6] suggested that NGP is not spontaneous and most patients have accompanying anomalies, including tracheoesophageal fistula or duodenal strictures, which may lead to intestinal obstruction and increased intragastric pressure. In fact, 55.6% (5/9) of patients in our series had an associated anomaly and one patient with NGP and accompanying antral web experienced disease recurrence. This finding supports the theory that distal obstruction is a common cause of NGP. Thus, in patients with suspected NGP, the consultant should consider the likelihood of accompanying disorders, especially disorders that may increase intragastric pressure. Although the greater curvature is thought to be the most common site of perforation[6,20], the distribution of perforation sites was fairly even.

Factors predicting the survival of NGP have not been extensively examined. Lin *et al*[9] reported that the mortality rate was significantly higher in premature infants and in those with a low birth weight. Chung *et al*[8] reported that male gender and metabolic acidosis (pH < 7.3) were associated with poor prognosis. In the present patients, prematurity was not associated with survival; of three premature patients, only one died (because of septic shock) and the χ^2 test yielded a P-value of 1.000. Likewise, low birth weight was not associated with survival. There were two LBW and one ELBW patients, and only one LBW patient died. Furthermore, male gender was not associated with survival. There were five boys and four girls, and gender was not associated with survival. Five patients had preoperative metabolic acidosis, of whom two died because of postoperative septic shock. In both of these patients, the preoperative serum pH was < 7.30, but the association between preoperative pH and survival was not significant.

The time between symptoms and surgical intervention was the only prognostic factor for survival, with a P-value of < 0.05. However, because the study group was small, involving just nine patients, there is the possibility of type II error. We considered the P-value as a factor of relativity and extended its interpretation criteria. Even though several other factors were not statistically significant, they may be clinically relevant in terms of survival outcomes. The factor with the lowest P-value was the year of birth. Of note, two of three patients born before 1990 died. There is a great difference between the clinical and mechanical environments of the neonatal intensive care unit in the 1980s compared with those today. It is likely that clinical and technical developments in pre- and postoperative intensive care have improved the survival outcome of NGP patients. Another factor with a low P-value was preoperative pneumoperitoneum on plain X-ray. Notably, two of three patients who did not undergo preoperative infantography died. Had intestinal perforation been detected or suspected based on preoperative radiographs, earlier intervention may have been possible, increasing the likelihood of survival. Interestingly, all three patients who did not undergo infantography were treated before 1990. Thus, the lack of a diagnostic protocol and diagnostic tools probably contributed to the poor prognosis before 1990 in particular.

Limitations of our paper are that it was performed retrospectively and the number of patients was too small to achieve statistical significance. However, NGP is extremely rare and very few cases have been reported to date. Therefore, our findings should help clinicians and surgeons with their decisions.

In conclusion, early detection and prompt surgical intervention are essential to improve the outcomes of infants with NGP. The survival outcomes of preterm

infants or LBW infants were not inferior to those of other patients. NGP can accompany other significant anomalies. Therefore, careful examination of the patient, together with imaging studies, may lead to early detection and improve the outcomes of NGP.

COMMENTS

Background

Neonatal gastric perforation (NGP) is a very rare but life-threatening disease.

Research frontiers

Because of its rarity, the etiology and prognostic factors of NGP are debated.

Innovations and breakthroughs

The time between symptoms and surgical intervention was the only prognostic factor for survival; premature birth and birth weight were not associated with the survival of patients with NGP.

Applications

Early detection and advances in neonatal intensive care may improve the prognosis of NGP.

Terminology

NGP: Neonatal gastric perforation; LBW: Low birth weight; ELBW: Extremely low birth weight.

Peer review

This is an important case series to publish as it deals with a rare but important neonatal emergent disorder. The abstract, introduction, methods and results are all well written.

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CASE REPORT

Blind loop perforation after side-to-side ileocolonic anastomosis

Raffaele Dalla Valle, Roberto Zinicola, Maurizio Iaria

Raffaele Dalla Valle, Maurizio Iaria, Department of Surgery, Division of General Surgery and Organ Transplantation, Parma University Hospital, 43121 Parma, Italy
Roberto Zinicola, Department of Emergency, Division of Acute Care Surgery, Parma University Hospital, 43121 Parma, Italy
Author contributions: All authors contributed to this work.
Correspondence to: Maurizio Iaria, MD, PhD, Department of Surgery, Division of General Surgery and Organ Transplantation, Parma University Hospital, Via Linati, 6, 43121 Parma, Italy. miaria@ao.pr.it
Telephone: +39-05-21702006 Fax: +39-05-21704870
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Abstract

Blind loop syndrome after side-to-side ileocolonic anastomosis is a well-recognized entity even though its incidence and complication rates are not clearly defined. The inevitable dilation of the ileal cul-de-sac leads to stasis and bacterial overgrowth which eventually leads to mucosal ulceration and even full-thickness perforation. Blind loop syndrome may be an underestimated complication in the setting of digestive surgery. It should always be taken into account in cases of acute abdomen in patients who previously underwent right hemicolectomy. We herein report 3 patients who were diagnosed with perforative blind loop syndrome a few years after standard right hemicolectomy followed by a side-to-side ileocolonic anastomosis.

Key words: Blind loop syndrome; Blind loop pouch; Perforation; Ileocolonic anastomosis; Laparoscopy

Core tip: The authors suggest that we are likely to see more and more cases of blind loop syndrome in the future because more side-to-side ileocolonic anastomoses will be performed in the setting of colonic laparoscopic surgery. A blind loop perforation should immediately be investigated in a patient who presents with acute abdomen years after a right hemicolectomy. Ideally, more end-to-end anastomoses should be performed, whenever suitable, in an effort to prevent the development of a blind loop.

Dalla Valle R, Zinicola R, Iaria M. Blind loop perforation after side-to-side ileocolonic anastomosis. *World J Gastrointest Surg* 2014; 6(8): 156-159 Available from: URL: http://www.wjgnet.com/1948-9366/full/v6/i8/156.htm DOI: http://dx.doi.org/10.4240/wjgs.v6.i8.156

INTRODUCTION

In the past, digestive continuity after right hemicolectomy was often restored through either end-to-end or end-to-side ileocolonic anastomosis. Due to the extensive implementation of laparoscopy in colonic surgery, side-to-side ileocolonic anastomosis has gained popularity because of the widespread use of linear staplers in this setting. Even in open surgery, mechanical side-to-side anastomoses are easy, quick and cost-effective because these can be performed using a single linear stapling device, while an end-to-side recontruction would require both linear and circular staplers to complete the anastomosis with additional costs.

Concurrently, intracorporeal anastomoses during laparoscopic right hemicolectomies can be exclusively carried out with linear staplers (endoGIA).

Yet, in 1906, Cannon and Murphy judged side-to-side anastomoses to be far from physiological, and advocated end-to-end reconstruction instead[1]. The same recommendation was reinforced by Pearse[2], Estes *et al*[3] and Holme[4] in further studies. A key reason why side-to-side anastomoses have been questioned lies in their substan-

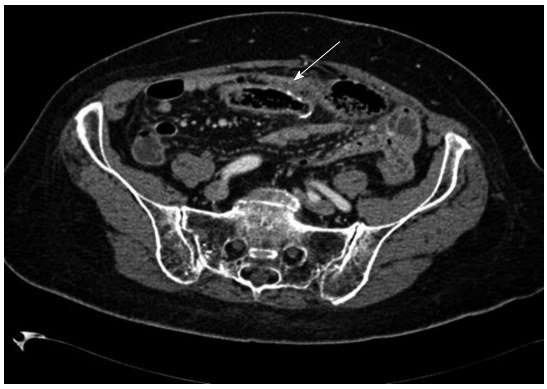

Figure 1 Computed tomography. The scan shows intraperitoneal free air with air bubbles around the ileocolonic anastomosis and a dilated blind loop with thickened bowel walls and mucosal hyperemia.

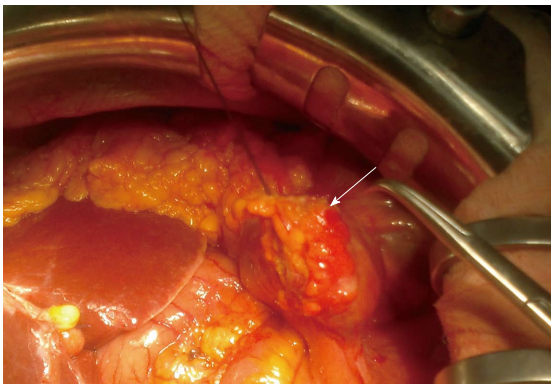

Figure 2 The image shows a long blind loop with signs of microperforation on the suture line.

tial risk of progressive dilation at the level of the cul-de-sac, which might lead to enlarged pockets prone to stasis and bacterial overgrowth. Such alterations seem to predispose to the so-called "blind loop syndrome"[5,6]. The continuous enlargement of the blind loop may eventually cause mucosal ulcerations, intestinal bleeding and/or full-thickness viscus perforation.

There are limited data in the literature about the actual incidence of blind loop syndrome and its related morbidities because, generally, studies on intestinal anastomoses are exclusively focused on short-term postoperative complications (3 mo), whereas blind loop syndrome tends to develop years after surgery. We retrospectively reviewed 3 cases of blind loop perforation which occurred during long-term follow-up after standard right hemicolectomy followed by mechanical side-to-side ileocolonic anastomosis.

CASE REPORT

Case 1

A 76-year-old woman underwent a right hemicolectomy in 2007 for a Duke's stage C adenocarcinoma of the ascending colon followed by a mechanical isoperistaltic side-to-side ileocolonic anastomosis. In September 2009, she was admitted for acute and diffuse abdominal pain, high-grade fever and leukocytosis. An abdominal X-ray series displayed free intra-peritoneal subphrenic air bilaterally. Since a computed tomography (CT) scan was not immediately available, an exploratory laparoscopy was performed followed by laparotomy. A generalized purulent peritonitis due to a pinpoint perforation of the ileocolonic blind loop was identified. The same blind loop appeared extremely enlarged, measuring about 7 cm, and was resected using a 75 mm GIA stapler (United States Surgical, Norwalk, CT, United States). The patient had an uneventful postoperative course and was discharged home 6 d after surgery. At the 12-mo outpatient clinic follow-up, the patient was asymptomatic with normal bowel function.

Case 2

An 80-year-old woman had a right hemicolectomy in 2008 for a Duke's stage B adenocarcinoma of the ileocecal junction, with a mechanical isoperistaltic side-to-side ileocolonic anastomosis. In January 2011, she was admitted with worsening generalized abdominal pain, fever and leukocytosis. Before seeking medical attention, the patient experienced loose stools and mild non-localized abdominal pain for almost 1 wk. Plain abdominal X-rays revealed free subphrenic air. A CT scan detected free air in the abdominal cavity and a slightly dilated small bowel loop. A subsequent laparoscopy identified generalized purulent peritonitis due to a tiny perforation of a 6 cm blind loop. The perforated pouch was resected with a 45 mm endoGIA stapler. She had a straightforward postoperative course and was discharged after 5 d. At a scheduled 6-mo follow-up visit, she was symptom-free except for mild sporadic diarrhea.

Case 3

A 58-year-old woman had a right hemicolectomy in 2009 for a Duke's stage B adenocarcinoma of the hepatic flexure, with a hand-sewn antiperistaltic side-to-side ileocolonic anastomosis. In November 2011, she presented with severe epigastric pain, fever and leukocytosis. Plain abdominal X-rays failed to show free air. A contrast-enhanced CT scan revealed intra-peritoneal free air localized in the lower abdomen with air bubbles near the anastomosis. The blind loop showed thick walls associated with mucosal hyperemia along with focal areas of perivisceral soft tissue fat necrosis (Figure 1). Imaging was compatible with blind loop perforation. The patient underwent laparotomy, which demonstrated generalized purulent peritonitis due to microperforation (Figure 2) of the enlarged blind ileal pouch (about 10 cm long). The blind loop was resected with a 75 mm GIA stapler. She recovered well after surgery and was discharged home in 10 d. At the 6-mo follow-up visit, she had no symptoms and regular bowel movements.

DISCUSSION

Nowadays, mechanical side-to-side anastomosis after right hemicolectomy is commonly performed either in open or laparoscopic surgery due to its simplicity and

speed. In the short-term there is no clear advantage of a specific anastomotic configuration over others. On the other hand, side-to-side anastomoses have been criticized for being theoretically anti-physiologic and for the long-term risk of a blind loop[1].

Blind loops result in abnormal peristalsis causing filling rather than emptying of the pouch. Such dismotility-related stasis predisposes to bacterial overgrowth eventually followed by mucosal and/or transmural inflammatory changes of the intestinal wall. The consequent clinical scenario is referred as blind loop syndrome and may present with a wide spectrum of morbidities such as diarrhea, vitamin B12 deficiency, iron-deficiency anemia, ulcerations, bleeding and enteroliths[5]. At times, a pinpoint perforation of the blind loop may occur[5,7,8]. Partial disruption of the muscle layer in the side-to-side anastomosis causes dysmotility, diverting intestinal content more easily unto the blind loop. The cul-de-sac dilation may occur even after an end-to-side recontruction, though it appears more likely to happen after a side-to-side anastomosis[6]. Conversely, blind loops do not develop after end-to-end anastomoses. Stellamor *et al*[9] analyzed 66 ileocolonic resections, and identified 9 blind loops (average transverse diameter between 5 and 11 cm) out of 31 side-to-side anastomoses, whereas no blind loops were observed after 12 end-to-end anastomoses.

Only a few cases have been accurately described in literature. Estes *et al*[3] reported about a 10 cm blind loop which had increased to 46 cm after only a few months. Pollock described a blind loop which started as 2 cm in length and stretched to 15 cm after 1 year[10].

We believe this critical aspect of side-to-side anastomoses will be more intensively taken into consideration in light of their expanding use in the laparoscopic era. The likelihood of enlargement and tearing appear proportional to the span of the blind loop, the bigger the pouch the higher the risk of further lengthening and stretching. It is advisable to leave the bowel stump as short as possible, even if that does not necessarily prevent the loop from enlarging in the long-term. In addition, antiperistaltic anastomoses do not seem to abolish the risk of developing a cul-de-sac, as shown in one of our cases. Some authors reported incidental findings of long blind loops discovered during either autopsy studies or surgical interventions in asymptomatic individuals[6]. Thus, the sole development of a blind loop does not cause clinical manifestations *per se*.

We found in the literature only 11 cases of blind loop perforation, some presenting with acute, generalized peritonitis due to pinpoint perforation[5,6,8]. Lack of data precludes an accurate appraisal on those factors which might cause symptomatic complications in those with a blind loop.

Usually, blind loop syndrome occurs many years after bowel surgery. In a French review, 45 out of 69 patients with a blind loop developed abdominal symptoms more than 5 years after surgery[5]. In a retrospective study based on abdominal CT examinations of 30 patients with radiological features compatible with a blind loop (eventually resected in 4 cases), the mean and median time between surgery and imaging were 49.4 and 32.2 mo, respectively[11]. In our own series, all patients presented with perforation at least 2 years after a side-to-side ileocolonic anastomosis. A CT scan seems helpful and a focally dilated loop of the small bowel adjacent to surgical clips is a recurrent finding[11]. Even so, blind loops may be mistaken for diverticula, abscesses or obstructed bowel segments. Blind loop syndrome is primarily managed through a redo anastomosis in an end-to-end fashion. We chose to resect the perforated pouch sparing a new anastomosis, deeming this limited procedure safer in the emergency setting. Our patients are free of symptoms albeit after a short clinical follow-up (6-12 mo). Blind loop syndrome along with its complications is probably underestimated and further research is needed to define the real extent of the problem. In addition, a colorectal surgeon should be aware of this potential issue before choosing the ileocolonic anastomosis reconstructive technique.

COMMENTS

Case characteristics

Three patients presented with perforation of a blind loop years after right hemicolectomy followed by side-to-side ileocolonic anastomosis.

Clinical diagnosis

They displayed peritoneal signs along with high-grade fever, one had localized epigastric pain, and the others suffered diffuse abdominal pain.

Differential diagnosis

Complicated acute diverticulitis, peptic ulcer perforation.

Laboratory diagnosis

All had leukocytosis.

Imaging diagnosis

Plain abdominal X-rays usually show peritoneal free-air. Contrast-enhanced computed tomography identified an enlarged blind loop with thick walls, mucosal hyperemia and perivisceral fat necrosis along with intra-abdominal free-air and fluid.

Pathological diagnosis

Ileal stump enlargement with full-thickness pinpoint perforation.

Treatment

Laparoscopic or laparotomic resection of the perforated blind loop with linear stapler.

Related reports

Only a few series and isolated case reports are available in the literature about the long-term complications of ileocolonic anastomoses associated with a specific anastomosis configuration. The true incidence of blind loop syndrome is probably underestimated but blind loop enlargement after side-to-side digestive anastomoses is a well-known phenomenon. Besides, only 11 cases of blind loop perforation are described in literature thus far.

Term explanation

Blind loop syndrome after right hemicolectomy develops when bacterial overgrowth occurs in the previously interrupted bowel stump, whose dysmotility tends to divert the intestinal contents away from the physiologic route. Clinically it may manifest itself with symptoms of vitamin malabsorption, malnutrition, weight loss, digestive bleeding and even viscus perforation.

Experiences and lessons

Side-to-side anastomoses are strongly related to the development of blind loop syndrome in the long-term. In open right hemicolectomy, end-to-end or end-to-side anastomoses can be used, while in the case of a full laparoscopic procedure requiring a side-to-side reconstruction, surgeons should resect the ileal stump as short as possible.

Peer review

In general the side-to-side anastomosis is a bad technique to restore intestinal

continuity but not unusual in times of laparoscopic surgery of the right colon. It leads to a progressive distention of the cul-de-sac, which produces definite pockets of stasis and infection.

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CASE REPORT

Massive surgical emphysema following transanal endoscopic microsurgery

Geert AAM Simkens, Simon W Nienhuijs, Misha DP Luyer, Ignace HJT de Hingh

Geert AAM Simkens, Simon W Nienhuijs, Misha DP Luyer, Ignace HJT de Hingh, Department of Surgical Oncology, Catharina Hospital Eindhoven, 5623 EJ Eindhoven, The Netherlands
Author contributions: Simkens GAAM, Nienhuijs SW, Luyer MDP and de Hingh IHJT contributed equally to this work.
Correspondence to: Ignace HJT de Hingh, MD, PhD, Department of Surgical Oncology, Catharina Hospital Eindhoven, Michelangelolaan 2, 5623 EJ Eindhoven, The Netherlands. ignace.d.hingh@cze.nl
Telephone: +31-40-2399111 Fax: +31-40-2455035
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Abstract

We describe an impressive and rare case of surgical emphysema after minimally invasive rectal surgery. This case reports on a patient who developed massive retroperitoneal, intraperitoneal and subcutaneous emphysema directly following a transanal endoscopic microsurgery (TEM) procedure for a rectal intramucosal carcinoma. Free intra-abdominal air after gastrointestinal surgery can be a sign of a bowel perforation or anastomotic leakage. This is a serious complication often requiring immediate surgery. In our patient an abdominal computed tomography-scan with rectal contrast showed no signs of a rectal perforation. Therefore this emphysema was caused by the insufflation of CO_2 gas in the rectum during the TEM-procedure. Conservative treatment resulted in an uneventful recovery. With the increasing usage of TEM for rectal lesions we expect this complication to occur more often. After ruling out a full thickness rectal wall perforation in patients with surgical emphysema following TEM, conservative treatment is the treatment of choice.

Key words: Transanal endoscopic microsurgery; Microsurgery; Gastrointestinal endoscopy; Colorectal neoplasms; Retropneumoperitoneum; Intraperitoneal emphysema; Subcutaneous emphysema

Core tip: Surgical emphysema after transanal endoscopic microsurgery (TEM) can be a sign of a rectal perforation. This report describes a patient with impressive retroperitoneal, intraperitoneal and subcutaneous emphysema directly following TEM without a full thickness rectal wall perforation. This is a rare complication after TEM in which conservative treatment resulted in an uneventful recovery.

Simkens GAAM, Nienhuijs SW, Luyer MDP, de Hingh IHJT. Massive surgical emphysema following transanal endoscopic microsurgery. *World J Gastrointest Surg* 2014; 6(8): 160-163 Available from: URL: http://www.wjgnet.com/1948-9366/full/v6/i8/160.htm DOI: http://dx.doi.org/10.4240/wjgs.v6.i8.160

INTRODUCTION

Transanal endoscopic microsurgery (TEM) is a minimally invasive technique developed for the resection of rectal neoplasms. This technique was first described in the early 1980's and was initially exclusively intended for benign adenomas[1]. By providing good stereoscopic views and allowing use of both hands, better exposure and more precise excision are achievable as compared to previously used techniques for local excision. With increasing experience, TEM is now considered safe and may also be offered for low-grade malignant rectal lesions without signs of lymphatic or systemic dissemination (T1-2, N0, M0)[2]. The major advantage of TEM is the significantly lower morbidity and mortality as compared to traditional treatment for malignant rectal lesions such as abdominoperineal resection and low anterior resection[2]. Furthermore, functional outcome is better since the sphincteric complex is preserved, the abdominal wall is spared and damage to autonomous pelvic nerves is

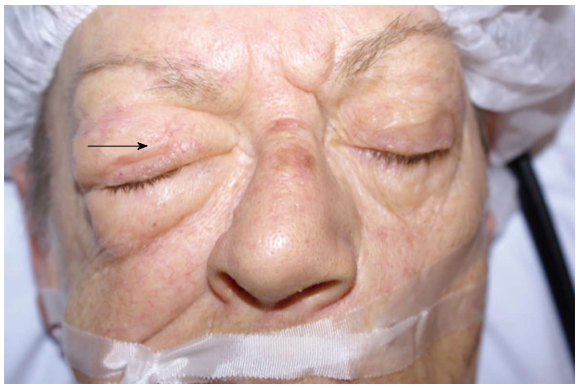

Figure 1 Right-sided peri-orbital subcutaneous emphysema directly post-operative (arrow).

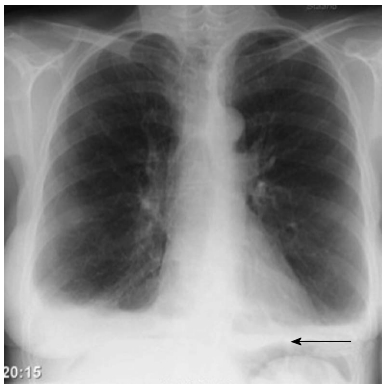

Figure 2 Thoracic X-ray suggesting free intraperitoneal air beneath the left diaphragm (arrow).

absent. Postoperative complications are rare after TEM and include postoperative bleeding (1.7%-2.7%) and pelvic sepsis due to perforation (1%-2.7%). TEM associated mortality is low (0%-2%)[3]. In this case report, a rare and impressive complication after TEM is described being the occurrence of massive retroperitoneal, intraperitoneal and subcutaneous emphysema directly following a TEM-procedure.

CASE REPORT

A 60-year-old woman was referred to our hospital with changed bowel habits including frequent defecation and soiling. Her relevant medical history includes a uterus extirpation, alcohol abuse and smoking. On a colonoscopy several sessile polyps throughout the colon were discovered which could be removed endoscopically. Pathology reports showed that these were all tubulovillous adenomas without signs of malignancy. However, in the rectum also a large villous lesion measuring 5 cm in diameter was found, located approximately 8-10 cm from the anal verge. This lesion could not be removed endoscopically due to its size and appearance. Biopsies showed at least intramucosal carcinoma but additional computed tomography (CT)-scan of the abdomen, pelvic magnetic resonance imaging and rectal endo-echography did not show signs of invasive growth, pathologic lymph nodes or systemic metastases. The tumor was therefore staged as a cT1N0M0 rectal intramucosal carcinoma and the patient was referred for a TEM-procedure.

Prior to the surgical procedure antibiotic prophylaxis was given (Cefazolin 1000 mg and Metronidazole 1500 mg both once) and the tumor was visualised on the ventral side of the rectum using rectoscopy. The patient was placed in prone position, the extended TEM-tube (TEO 15 cm, Karl Storz, Germany) was inserted and a pneumorectum was applied by insufflation of CO_2 at 6 L/min with a pressure limit of 12 mmHg using a Karl Storz insufflator. Using ultracision, the lesion was macroscopically radical removed. No rectal perforation into the peritoneal cavity was observed and the defect in the rectal wall was closed with a running suture. Duration of the procedure was 115 min. Pathological examination confirmed the diagnosis of a tubulovillous adenoma with the presence of intra-mucosal carcinoma and clear resection margins. Immediately after the procedure massive subcutaneous emphysema of the face, neck and body was noticed (Figure 1). Given the amount of emphysema in the face it was decided to keep the patient intubated and ventilated and transfer to the intensive care unit. Here, blood analysis revealed a slight leucocytosis (11.0 k/μL) and a C-reactive protein (CRP) level of < 6 mg/L. Chest X-ray showed subcutaneous emphysema of the thorax, signs of "free air" beneath the left diaphragm and a small pneumothorax of the right sinus (Figure 2). After a few hours emphysema in the face was dissolving and the patient was awake. She was then detubated and discharged from the intensive care unit. At this moment she did not experience any abdominal discomfort, systemic reaction or fever. Intravenous antibiotics (Metronidazole 500 mg, Cefuroxime 1500 mg, both 3 times daily for 3 d) were started empirically and the patient was kept hospitalized with solid diet until all subcutaneous air had resolved three days later.

One day after discharge the patient visited the emergency ward with complaints of dyspnoea. Again, no abdominal discomfort or nausea were present, the patient had no fever and solid food was tolerated. However, blood analysis now showed an elevated CRP-level of 160 mg/L and based on the thoracic X-ray an increase in the amount of "free air" in the intra-abdominal space was suspected. Given the dyspnoea, "free abdominal air" and elevated inflammatory parameters a rectal perforation with leakage was suspected and an abdominal CT-scan with rectal contrast was performed. This revealed a large amount of air in the mesorectal fascia and especially in the retroperitoneal space and only a small amount of free air in the abdomen (Figure 3A). This retroperitoneal air had erroneously suggested the presence of free air in the abdomen. No signs of leakage from the rectal wound were found. In the lower thoracic field, pleural effusion and signs of a pneumonia were revealed (Figure 3B). This eventually explained for the dyspnoea and elevated inflammatory parameters. Conservative treatment with continuation of intravenous antibiotics was installed. In the following days, the dyspnoea disappeared and also,

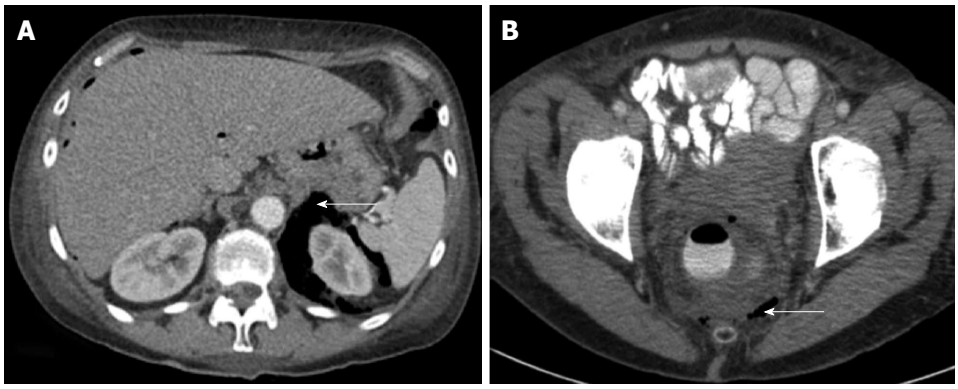

Figure 3 Computed tomography-scan. A: Abdominal computed tomography-scan showing retroperitoneal air surrounding the left kidney (arrow); B: Pelvic computed tomography-scan with rectal contrast showing free air in the mesorectum (arrow).

the retroperitoneal air disappeared on the thoracic X-ray. CRP and white blood count level normalised. On the tenth day she was discharged home in a good condition. Follow-up in our outpatient clinic did not show any abnormalities.

DISCUSSION

Free intraperitoneal air after gastro-intestinal surgery can be a sign of a bowel perforation or anastomotic leakage. These are serious and potentially life threatening complications often requiring immediate surgery and the formation of a (temporarily) diverting colostomy. Therefore, the possibility of a full-thickness defect of the rectal wall with communication to the peritoneal cavity should always be considered in patients with postoperative subcutaneous surgical emphysema and the suggestion of "free air" in the abdomen after a TEM-procedure. Close observation of body temperature, abdominal symptoms and blood infection parameters are helpful as well as an abdominal CT-scan with rectal contrast.

In the current case report subcutaneous emphysema and the suggestion of "free air" in the abdomen were suggestive of a persisting rectal wall perforation to the peritoneal cavity. However, no such defect in the rectal wall above the peritoneal fold was present and instead these features were most probably caused by insufflation of CO_2 gas during the TEM-procedure. During this procedure, CO_2 is insufflated under pressure into the rectum to create a pneumorectum. A full-thickness defect in the rectal wall is created on purpose during this procedure. Usually the mesorectal fat will seal the defect and prevent the CO_2 from entering the body but in this case CO_2 "escaped" through the loose connective tissue into the retroperitoneal cavity and eventually subcutaneously. Subsequently, due to the elevated pressure in the retroperitoneal cavity and a decreased integrity of the retroperitoneal barrier CO_2 gas was able to diffuse into the intraperitoneal cavity, as was also the case in our patient.

Surgical emphysema after a TEM-procedure has been previously described in 2 case reports describing 3 patients. Also in these patients no rectal perforation was present[4,5]. As in our case, conservative treatment in these cases resulted in an uneventful recovery. Thus, without clinical signs of a rectal perforation conservative treatment seems legitimate in patients with postoperative retroperitoneal and subcutaneous emphysema after a TEM-procedure.

In 2001 Kerr *et al*[6] described a case of a patient undergoing a TEM-procedure with intra-operative subcutaneous emphysema. Interestingly, this patient developed life-threatening hypercapnia in the early postoperative period. They hypothesize these complications were due to the insufflation of CO_2 gas into the rectum. They conclude that a patient with arterial hypercapnia or surgical emphysema after TEM should be observed for a prolonged period in the recovery room with regular arterial carbon dioxide analysis.

Postoperative complications following TEM are rare and often mild, but life-threatening complications may occur. In this case-report an impressive but self-limiting complication occurred being massive subcutaneous and retroperitoneal emphysema. With the increasing usage of TEM for rectal lesions we expect this complication to occur more frequent. After ruling out a full-thickness perforation by an abdominal CT-scan with rectal contrast a conservative treatment may be followed.

Prolonged observation in the recovery room directly postoperative may be needed, especially in elderly patients to prevent or treat severe hypercapnia.

COMMENTS

Case characteristics

A 60-year-old woman with retroperitoneal, intraperitoneal and subcutaneous emphysema directly following a transanal endoscopic microsurgery (TEM)-procedure.

Clinical diagnosis

Subcutaneous emphysema of the head, neck and body without systemic or abdominal symptoms.

Differential diagnosis

Rectal perforation or diffusion of gas during the procedure without a full thickness rectal wall defect.

Laboratory diagnosis

White blood count: 11.0 k/μL; C-reactive protein-level: < 6 mg/L.

Imaging diagnosis

Abdominal computed tomography-scan with rectal contrast showed a large

amount of air in the mesorectal fascia and especially in the retroperitoneal space and only a small amount of free air in the abdomen. No signs of leakage from the rectal wound were found.

Pathological diagnosis

cT1N0M0 rectal intramucosal carcinoma.

Treatment

Conservative treatment with intravenous antibiotics.

Related reports

Two reports previously described similar cases, with uneventful recovery after conservative treatment.

Experiences and lessons

Free intra-abdominal air after TEM can occur without a full thickness rectal wall perforation and may be treated conservative.

Peer review

Transanal endoscopic microsurgery is a minimally invasive technique developed for the resection of rectal neoplasms. This paper is very interesting case report of something observed not so rarely, even though not so evident.

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CASE REPORT

Solitary mediastinal lymph node recurrence after curative resection of colon cancer

Yasuhiro Matsuda, Masahiko Yano, Norikatsu Miyoshi, Shingo Noura, Masayuki Ohue, Keijiro Sugimura, Masaaki Motoori, Kentaro Kishi, Yoshiyuki Fujiwara, Kunihito Gotoh, Shigeru Marubashi, Hirofumi Akita, Hidenori Takahashi, Masato Sakon

Yasuhiro Matsuda, Masahiko Yano, Norikatsu Miyoshi, Shingo Noura, Masayuki Ohue, Keijiro Sugimura, Masaaki Motoori, Kentaro Kishi, Yoshiyuki Fujiwara, Kunihito Gotoh, Shigeru Marubashi, Hirofumi Akita, Hidenori Takahashi, Masato Sakon, Department of Surgery, Osaka Medical Center for Cancer and Cardiovascular Disease, Osaka 537-8511, Japan
Author contributions: Matsuda Y and Yano M designed the report; Miyoshi N, Noura S, Ohue M, Sugimura K, Motoori M and Sakon M made a decision of the treatment; Kishi K, Fujiwara Y, Gotoh K, Marubashi S, Akita H and Takahashi H collected the patient's clinical data; Matsuda Y and Yano M analyzed the data and wrote the paper.
Supported by Department of Surgery, Osaka Medical Center for Cancer and Cardiovascular Disease, Osaka 537-8511, Japan
Correspondence to: Masahiko Yano, MD, PhD, Department of Surgery, Osaka Medical Center for Cancer and Cardiovascular Disease, 1-3-3 Nakamichi, Higashinari-ku, Osaka 537-8511, Japan. yano-ma@mc.pref.osaka.jp
Telephone: +81-6-69721181 Fax: +81-6-69818055
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Abstract

We report two cases of solitary mediastinal lymph node recurrence after colon cancer resection. Both cases had para-aortic lymph node metastasis at the time of initial surgery and received adjuvant chemotherapy for 4 years in case 1 and 18 mo in case 2. The time to recurrence was more than 8 years in both cases. After resection of the recurrent tumor, the patient is doing well with no recurrence for 6 years in case 1 and 4 mo in case 2. Patients should be followed up after colon cancer surgery considering the possibility of solitary mediastinal lymph node recurrence if they had para-aortic node metastasis at the time of initial surgery.

Key words: Solitary mediastinal lymph node recurrence; Colon cance

Core tip: The first site of recurrence of colon cancer is rarely the mediastinal lymph nodes, and solitary recurrence at this site without another site of recurrence is extremely rare. The operative indication and prognostic significance of the resection of mediastinal lymph node metastasis has not been determined because such recurrence is very rare. Patients should be followed up after colon cancer surgery considering the possibility of solitary mediastinal lymph node recurrence if they had para-aortic node metastasis at the time of initial surgery.

Matsuda Y, Yano M, Miyoshi N, Noura S, Ohue M, Sugimura K, Motoori M, Kishi K, Fujiwara Y, Gotoh K, Marubashi S, Akita H, Takahashi H, Sakon M. Solitary mediastinal lymph node recurrence after curative resection of colon cancer. *World J Gastrointest Surg* 2014; 6(8): 164-168 Available from: URL: http://www.wjgnet.com/1948-9366/full/v6/i8/164.htm DOI: http://dx.doi.org/10.4240/wjgs.v6.i8.164

INTRODUCTION

Distant organ recurrence after resection of colon cancer is frequently seen in the liver, lung, bone, and brain[1]. The first site of recurrence is rarely the mediastinal lymph nodes, and solitary recurrence at this site without another site of recurrence is extremely rare[2,3]. With respect to recurrence of colon cancer in the lung and liver, surgical resection is recommended if curative resection of the recurrent tumors is possible. However, the operative indication and prognostic significance of the resection of mediastinal lymph node metastasis has not been determined

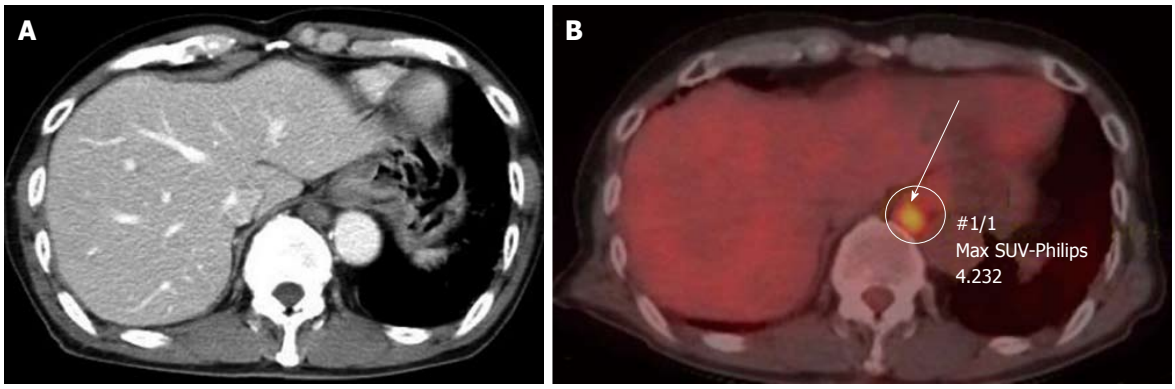

Figure 1 The tumor was 16 mm in size and located in the retrocrural space with suspicion of enlarged lymph nodes. A: Computed tomography (CT) scan showing a 16-mm tumor in the retrocrural space of the lower mediastinum; B: Positron emission tomography-CT did not reveal any other abnormal accumulation. The mediastinal mass had 4.232 of the sum of the maximum standard uptake values. SUV: Standardized uptake value.

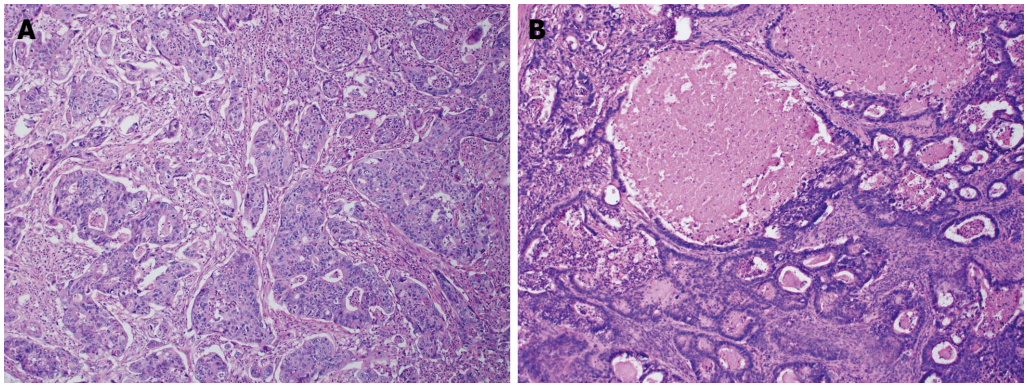

Figure 2 Histopathology revealed the widespread metastasis of moderately differentiated adenocarcinoma and necrosis. Hematoxylin and eosin stain, A: × 10, B: × 50.

because such recurrence is very rare. We report two cases of resection for isolated colon cancer metastasis to the mediastinal lymph nodes.

CASE REPORT

Case 1

A 65-year-old man visited our hospital for treatment of colon cancer in June 1998. Elevated serum carcinoembryonic antigen (CEA, 17.0 ng/dL; normal range, 0-5 ng/dL) was found at the time of diagnosis. Colonoscopy revealed a type 2 tumor in the sigmoid colon. Computed tomography (CT) showed a T3 tumor in the sigmoid colon with multiple lymph node metastases (cT3N2bM0 cStage Ⅲc). In September 1998, we performed extended left hemicolectomy (D3 dissection) and para-aortic lymph node dissection. Histological examination revealed moderately differentiated adenocarcinoma invading the muscularis propria without exposure on the serosal surface (n 2b, ly 2, v 1). Metastasis to the para-aortic lymph nodes was also found. After surgery, the patient's serum CEA level normalized. Adjuvant chemotherapy with tegafur-uracil (100 mg/m^2) was given to the patient for 4 years until 2003.

In February 2007, the patient's tumor markers were normal but CT showed a tumor in the lower mediastinum. The tumor was 16 mm in size and located in the retrocrural space with suspicion of enlarged lymph nodes (Figure 1). CT, magnetic resonance imaging (MRI), and positron emission tomography-CT (PET-CT) did not identify any other primary cancer or any other site of recurrence, such as distant organ or locoregional recurrence. We considered that the tumor was probably a solitary recurrence of the colon cancer and planned a surgical resection because the tumor had enlarged over 3 mo.

In May 2007, the patient underwent surgical resection of the tumor. We decided against a laparotomy, but performed a left thoracotomy to avoid adhesion due to the previous operation. After thoracotomy, the tumor was identified on the right-anterior surface of the descending aorta. The tumor was easily separated from neighboring organs, such as the aorta or vertebrae, but had extensively invaded the thoracic duct. Therefore, we resected the thoracic duct along with the mediastinal tumor. Histopathology revealed the widespread metastasis of moderately differentiated adenocarcinoma accompanied by necrosis, and it was diagnosed as mediastinal metastases of colon cancer (Figure 2).

The patient was given adjuvant chemotherapy with S-1 (100 mg/m^2) and irinotecan (115 mg/m^2) for 6 mo. He is doing well with no recurrence for 6 years after the surgery for the recurrent tumor.

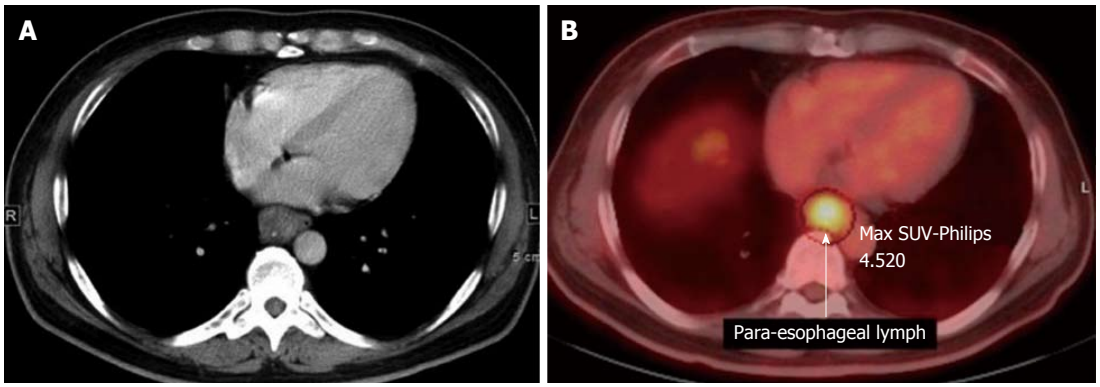

Figure 3 Computed tomography scan showing swelling of a para-esophageal lymph node (A), positron emission tomography-computed tomography did not reveal any other abnormal accumulation (B). The mediastinal mass had 4.520 of the sum of the maximum standard uptake values. SUV: Standardized uptake value.

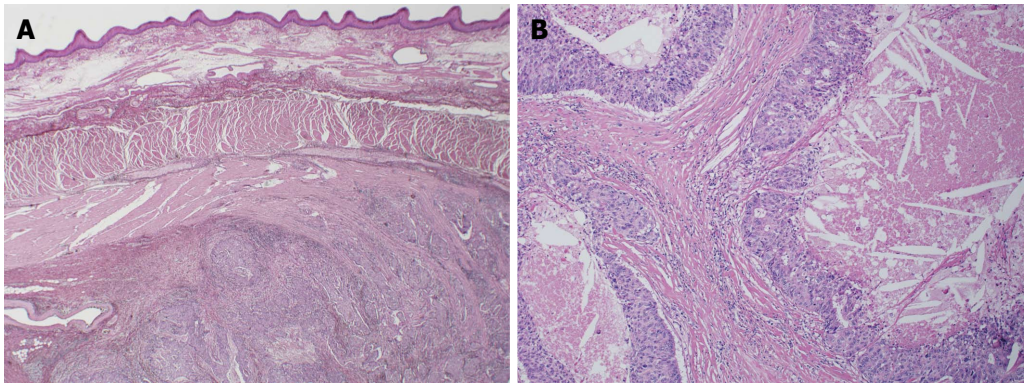

Figure 4 Histopathology showing no neoplastic change in the esophageal mucosal surface, compression from the esophageal adventitia, or infiltration of the muscularis propria. Hematoxylin and eosin stain, A: × 10, B: × 50.

Case 2

In November 2004, a 50-year-old man was admitted to our hospital for treatment of rectal cancer. Colonoscopy revealed a tumor that occupied the entire circumference of the rectum (type 2). Pre-operative CT and MRI showed a T3 tumor in the rectal colon with multiple lymph node metastasis (cT3, N2b, M0 cStage Ⅲc). In January 2005, we performed para-aortic lymph node and lateral lymph node dissection, in addition to low anterior resection (D3 dissection). Histological examination revealed moderately > poorly differentiated adenocarcinoma invading the muscularis propria without involvement of the serosa (n 2b, ly 0, v 0). Metastasis to para-aortic and lateral lymph nodes was also found. After surgery, the patient's tumor marker normalized (serum CEA 80.9 ng/dL to 3.5 ng/dL). Three regimens of adjuvant chemotherapy were carried out for 18 mo. The first regimen was irinotecan (100 mg/m^2), levofolinate (250 mg/m^2), and fluorouracil (500 mg/m^2) for 6 mo, the second was S-1 (80 mg/m^2) and irinotecan (80 mg/m^2) for 4 mo, and the last was S-1 (120 mg/m^2) for 8 mo.

In January 2013, we noted swelling of a para-esophageal lymph node on CT (Figure 3) and elevation of serum CEA (19.0 ng/dL). We performed an endoscopic ultrasound-guided fine-needle aspiration biopsy and diagnosed mediastinal metastasis of rectal cancer. No other site of distant metastasis or local recurrence was found. The patient complained of dysphagia. Therefore, we considered that the tumor was a solitary recurrence of the rectal cancer and decided to perform tumor resection.

In March 2013, using video-assisted thoracic surgery, we resected the mediastinal tumor, lower esophagus, and thoracic duct, because the tumor located in the posterior mediastinum had widely invaded the right side of the esophagus and thoracic duct, and performed reconstruction with a subtotal gastric tube. Histopathology revealed no neoplastic change in the esophageal mucosal surface, compression from the esophageal adventitia, or infiltration of the muscularis propria (Figure 4). Immunohistochemical analysis showed that the metastatic tumor was positive for cytokeratin (CK) AE1/AE3, CK20 and caudal-type homeobox transcription factor 2 (cdx-2) and negative for CK7, confirming that it was metastasis from rectal cancer.

Adjuvant chemotherapy was not given because the patient did not want it. He is doing well with no recurrence for 4 mo after the surgery for the recurrent tumor.

DISCUSSION

According to the 2010 guidelines for the treatment of colorectal cancer in Japan, the incidence of first site of

recurrence after curative resection of colon cancer is 41.2% in the liver, 27.6% in a lung, 23.1% for local recurrence, and 22.0% for others[4]. Eisenberg *et al*[1] reviewed 844 cancer-related deaths from colorectal cancer. Among the patients with evidence of recurrent metastatic diseases, the liver was the most common site (50%), followed by lung (25%), bone (10%), and brain (5%). As reported above, lymph node recurrence from colon cancer is relatively rare, especially mediastinal lymph node recurrence. We searched PubMed using keywords (colon cancer, metastasis and solitary mediastinal lymph node). To the best of our knowledge, only two cases have been reported thus far. One was a combined recurrence in an ovary and mediastinal lymph node, and another was solitary mediastinal lymph node recurrence[5,6].

Malignant intra-thoracic tumors, such as lung and esophageal cancers, often metastasize to mediastinal lymph nodes, but malignant extra-thoracic tumors are not likely to metastasize to lymph nodes. Although head and neck cancers and urogenital tumors sometimes metastasize to mediastinal lymph nodes, gastrointestinal cancers do not[7-9]. Libson *et al*[10] reported 15 cases of mediastinal lymphadenopathy among 1194 cases of gastrointestinal carcinoma. The primary tumor was colonic in nine cases, gastric in four cases, and pancreatic in two cases.

Confirmation of mediastinal lymph node metastasis is more difficult than confirmation of abdominal lymph node metastasis because more non-malignant lymph node enlargement or accumulation is present on PET-CT due to inflammation and granulation in the mediastinum[11]. Mediastinoscopy is often needed for accurate diagnosis[6]. In addition, a primary malignant tumor in the head and neck region or urological region also needs to be ruled out as a differential diagnosis.

The final pathological diagnosis of our two cases was mediastinal lymph node recurrence from colon cancer because both cases exhibited a glandular cavity formation with necrosis and histological similarity to the initial colon cancer. Furthermore, in case 2, the recurrent tumor and primary colonic tumor had the same immunostaining pattern: positive for CKAE1/AE3 CK20 and cdx-2 and negative for CK7.

There are two possible routes for mediastinal lymph node metastasis from the primary colon cancer: retrograde lymph node metastasis and hematogenous metastasis. The former occurs *via* the thoracic duct from a retroperitoneal lymph node. Thus far, several cases of gastrointestinal cancer have been reported to metastasize to mediastinal nodes *via* this route[10]. The latter occurs *via* the paravertebral venous plexus and is often seen in cases in which the patients have distant organ metastases, such as ovarian metastasis[5]. We speculated that, in our cases, the mediastinal lymph node metastasis developed *via* retrograde lymph node metastasis, as both of the cases had retroperitoneal metastasis at the time of the initial colon cancer surgery and no distant organ metastasis at the time of recurrence.

Interesting findings in our cases are that the time interval from colon cancer surgery to mediastinal lymph node recurrence was very long, more than 8 years. In addition, both of the cases received adjuvant chemotherapy for a relatively long time: 4 years in case 1 and 18 mo in case 2. Adjuvant chemotherapy over a very long time may play a role in delayed recurrence by inducing tumor dormancy or other unknown mechanism.

The prognosis of patients with lymph node recurrence after surgery for colon cancer depends on the number of organs or site of recurrence[4]. Patients with mediastinal lymph node recurrence plus lung metastasis or with multiple lymph node metastases have a poor prognosis[12,13]. Solitary lymph node metastasis without other non-curative factors has generally been reported to be a good indication for surgical treatment[14]. Min *et al*[15] investigated the outcome of 38 patients (1.3%) who developed isolated para-aortic lymph node recurrence (IPLR) from among 2916 patients who underwent curative surgery for colorectal carcinoma. The median survival time from IPLR was 34 mo, but it was 12 mo for those who did not undergo resection, suggesting the usefulness of surgical resection. Although no report has addressed the surgical indication and prognosis of patients with solitary mediastinal node recurrence, our case report indicates that surgical resection may prolong the survival of patients, considering that case 1 has survived 6 years without repeated recurrence after resection of the recurrent mediastinal node.

In conclusion, we report two very rare cases of solitary mediastinal lymph node recurrence after colon cancer surgery. Patients should be followed up after colon cancer surgery considering the possibility of mediastinal node recurrence if they had para-aortic node metastasis at the time of initial surgery.

COMMENTS

Case characteristics

A 65-year-old male and a 50-year-old male with a history of resected colon cancer had no symptoms.

Clinical diagnosis

Clinical findings were not particular.

Differential diagnosis

Esophagus cancer, metastasis of head and neck cancer or urological cancer, mediastinal tumor.

Laboratory diagnosis

Tumor markers were normal in case 1 and serum carcinoembryonic antigen elevated 19.0 ng/dL in case 2.

Imaging diagnosis

Positron emission tomography/computed tomography scan showed lower mediastinal mass (16 mm) with standardized uptake value (SUV) of 4.232 in case 1 and a para-esophageal lymph node with SUV of 4.520 in case 2.

Pathological diagnosis

Histopathology revealed the widespread metastasis of moderately differentiated adenocarcinoma in case 1 and immunohistochemical analysis showed that the metastatic tumor was positive for cytokeratin (CK), AE1/AE3, CK20 and caudal-type homeobox transcription factor 2 and negative for CK7, confirming that it was metastasis from rectal cancer in case 2.

Treatment

After surgical resection, the patient in case 1 was given adjuvant chemotherapy with S-1 (100 mg/m^2) and irinotecan (115 mg/m^2) for 6 mo and the patient in case 2 was not given adjuvant chemotherapy.

Related reports

Mediastinal lymph node recurrence is very rare and only two cases have been reported thus far. One was a combined recurrence in an ovary and mediastinal lymph node, and another was solitary mediastinal lymph node recurrence.

Term explanation

Retrograde lymph node metastasis occurs *via* the thoracic duct from a retroperitoneal lymph node. Hematogenous metastasis occurs *via* the paravertebral venous plexus.

Experiences and lessons

Patients should be followed up after colon cancer surgery considering the possibility of solitary mediastinal lymph node recurrence if they had para-aortic node metastasis at the time of initial surgery.

Peer review

This article highlights a rare entity, metastatic solitary mediastinal lymph node after resection of colon cancer in the form of two cases.

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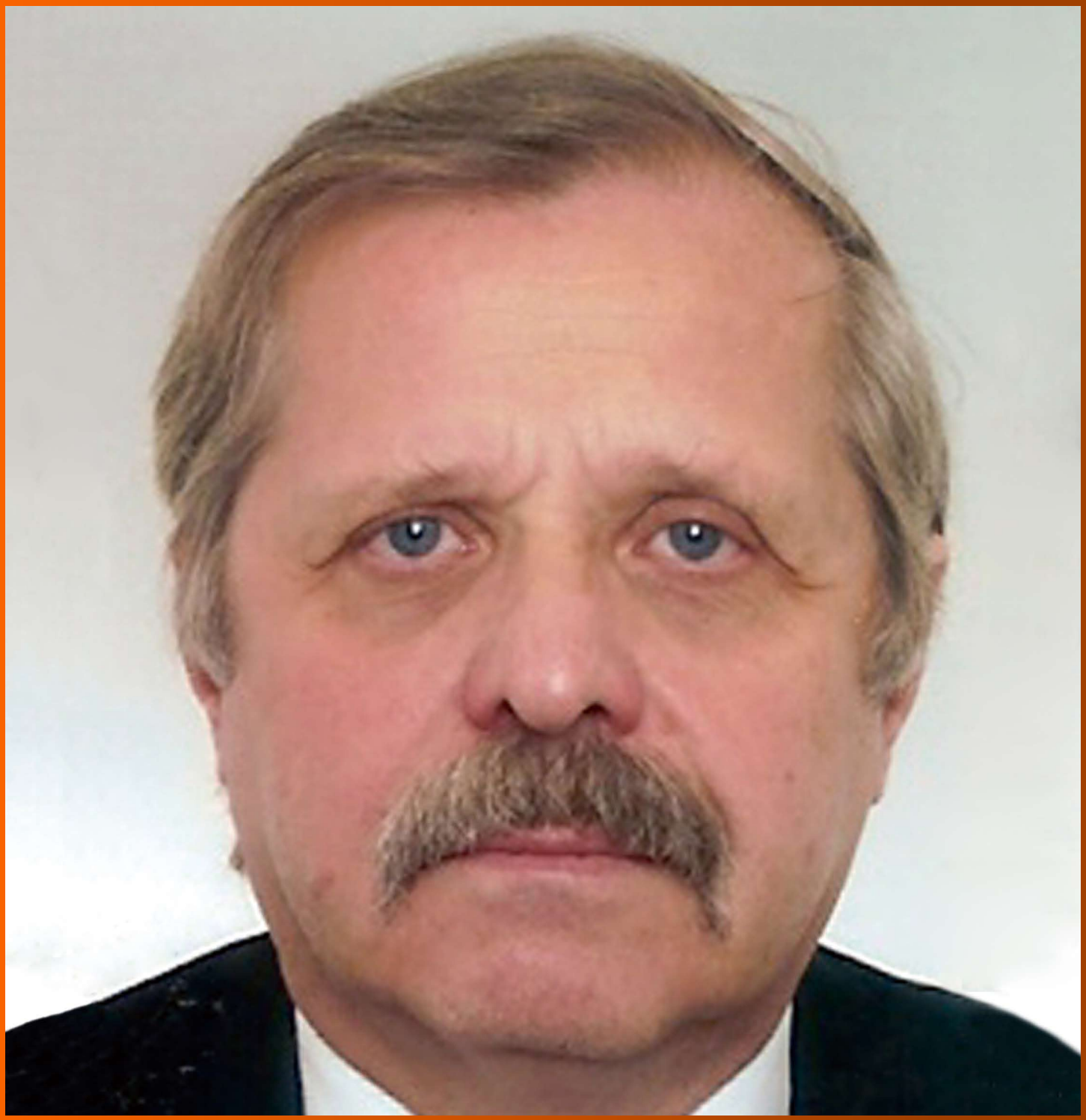

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World Journal of Gastrointestinal Surgery
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RETROSPECTIVE STUDY

Increased postoperative complications after protective ileostomy closure delay: An institutional study

Ines Rubio-Perez, Miguel Leon, Daniel Pastor, Joaquin Diaz Dominguez, Ramon Cantero

Ines Rubio-Perez, Miguel Leon, Daniel Pastor, Joaquin Diaz Dominguez, Ramon Cantero, General and Digestive Surgery Department, La Paz University Hospital, 28046 Madrid, Spain
Author contributions: Rubio-Perez I, Leon M, Diaz Dominguez J and Cantero R designed the study and performed the research; Pastor D contributed to retrieve and analyze data; Rubio-Perez I and Leon M wrote the paper; all authors critically reviewed and accepted the final version.
Correspondence to: Ines Rubio-Perez, MD, General and Digestive Surgery Department, La Paz University Hospital, Pso. Castellana 261, 28046 Madrid, Spain. dr.inesrubio@gmail.com
Telephone: +34-91-7277531 Fax: +34-91-2071064
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Abstract

AIM: To study the morbidity and complications associated to ileostomy reversal in colorectal surgery patients, and if these are related to the time of closure.

METHODS: A retrospective analysis of 93 patients, who had undergone elective ileostomy closure between 2009 and 2013 was performed. Demographic, clinical and surgical variables were reviewed for analysis. All complications were recorded, and classified according to the Clavien-Dindo Classification. Statistical univariate and multivariate analysis was performed, setting a *P* value of 0.05 for significance.

RESULTS: The patients had a mean age of 60.3 years, 58% male. The main procedure for ileostomy creation was rectal cancer (56%), and 37% had received preoperative chemo-radiotherapy. The average delay from creation to closure of the ileostomy was 10.3 mo. Postoperative complications occurred in 40% of the patients, with 1% mortality. The most frequent were ileus (13%) and wound infection (13%). Pseudomembranous colitis appeared in 4%. Increased postoperative complications were associated with delay in ileostomy closure ($P = 0.041$). Male patients had more complications ($P = 0.042$), mainly wound infections ($P = 0.007$). Pseudomembranous colitis was also associated with the delay in ileostomy closure ($P = 0.003$). End-to-end intestinal anastomosis without resection was significantly associated with postoperative ileus ($P = 0.037$).

CONCLUSION: Although closure of a protective ileostomy is a fairly common surgical procedure, it has a high rate of complications, and this must be taken into account when the indication is made. The delay in stoma closure can increase the rate of complications in general, and specifically wound infections and colitis.

Key words: Protective ileostomy; Stomas; Stoma-related complications; Surgical infections; Colorectal surgery

Core tip: Protective ileostomies are widely used by surgeons for the protection of anastomoses, but they imply a second intervention for reversal. Despite being considered a minor intervention, ileostomy reversal does not lack complications. Adjuvant treatment, complications from the first intervention, or low-priority consideration can delay the closure of the stoma. In our study, we reviewed all complications following ileostomy reversal and found they were considerably high (40%), and increased as did the time (in months) until closure ($P = 0.041$). In multivariate analysis, male patients had more complications ($P = 0.042$), mainly wound infections ($P = 0.007$). Pseudomembranous colitis was also associated with the delay in ileostomy closure ($P = 0.003$).

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INTRODUCTION

Diverting loop ileostomies are widely used by colorectal surgeons for the protection of low rectal anastomoses, as they can reduce the morbidity and rate of reintervention if an anastomotic leak occurs[1]. The use of a protective ileostomy is specially indicated in very low rectal resections, coloanal anastomosis and pouches[2,3].

However, there can be an important morbidity associated to the stoma itself, deriving in a bad quality of life for the patient. Some common problems associated to the ileostomy can be electrolytic alterations, dehydration, renal failure, infection, obstruction, prolapse, and hernias[4]. Postoperative complications of variable severity (and even mortality) have been reported in different series reviewing protective ileostomy closure, ranging from 3% to over 40%[5,6]. Surgical infection of the wound is always a relevant one. A recent systematic review on ileostomy reversal reported an overall mortality of 0.4%[7], with values ranging from 0% to 4% in different studies. The aim of our study was to review our institutional series of ileostomy reversals and identify possible risk factors for postoperative complications.

MATERIALS AND METHODS

A retrospective analysis of patients who underwent elective ileostomy reversal in our institution between 2009 and 2013 (first semester) was performed. La Paz University Hospital (Madrid, Spain) is a tertiary care university hospital, with a high-volume Colorectal Surgery Unit. Ninety-three patients were included in the study. All data from the patients were retrieved from medical records and included in a database. Analyzed variables were: demographics, comorbidities, the American Society of Anesthesiologists classification for operative risk (ASA) index, body mass index (BMI), initial surgery (when the ileostomy was created), adjuvant chemo-radiotherapy before stoma closure, time interval from stoma creation to reversal, surgical technique employed, hospital stay, surgical complications, readmissions and mortality. All patients were assessed preoperatively by a member of the Colorectal Surgery Unit, who indicated the closure of the stoma, and by an Anesthesiologist for preoperative assessment. Regarding reversal, an oval incision was performed around the stoma to release the ileal loop. The anastomotic technique employed was either a handsewn end-to-end anastomosis without resection, a handsewn end-to-end with resection, a handsewn side-to-side with resection or a stapled anastomosis. Closure of the abdominal wall was performed with absorbable sutures (PDS or Vicryl©), and skin was closed with either staples, subcuticular or interrupted sutures, at surgeon's will. All these technical data were retrieved from the surgical charts and reports in the patients' records. Thirty-day morbidity and mortality were reviewed using medical records, outpatient clinic notes and the hospital's database.

Statistical analysis was performed using SPSS 16 Software for Windows, setting statistical significance at $P < 0.05$. χ^2 or Mann-Whitney tests were used for univariate analysis (when appropriate), and a multivariate analysis of all variables was performed.

Table 1 Characteristics of the 93 patients who underwent loop ileostomy reversal

Clinical characteristics	*n* (%)
Patients included, total	93 (100)
Gender	
Male	54 (58)
Female	39 (42)
BMI	
Underweight	3 (3.1)
Normal weight	44 (47)
Overweight	31 (33.3)
Obese	15 (15.8)
ASA Index	
I	5 (5.5)
II	59 (63)
III	29 (31)
Indication for ileostomy	
Colorectal cancer	52 (56)
Anastomotic leak	16 (17.2)
IBD	6 (6.4)
Colectomy for polyposis	5 (5.3)
Endometriosis	5 (5.3)
Diverticular disease	3 (3.2)
Intestinal necrosis	1 (1.07)
Pelvi-peritonectomy	1 (1.07)
Post-endoscopy perforation	1 (1.07)
Trauma	1 (1.07)
Adjuvant therapy (in oncological patients)	
Chemotherapy	16 (17.2)
Chemo-radiotherapy	35 (37)

Demographic data, BMI, ASA Index, indications for ileostomy creation and adjuvant therapy. BMI: Body mass index; ASA: The American Society of Anesthesiologists classification for operative risk; IBD: Inflammatory bowel disease.

RESULTS

The patients had a mean age of 60.3 years (range 22-88 years), 58% male. Demographic and clinical data, including the initial indication for ileostomy, are shown in Table 1. Data related to the interval from stoma creation to reversal, and the surgical technique employed for ileostomy and skin closure are shown in Table 2. A total of 26 patients (28%) presented at least one associated major comorbidity, including liver metastases (19%), diabetes and heart disease (11.5% each), pulmonary disease, thrombotic disease, hematologic disorders, lung metastases (7.7% each), and finally arrhythmias, other malignancies and tuberculosis (1% each). Average time for reversal was 10.3 mo, ranging from 1 to 36 mo. There was an 8.6% readmission rate due to dehydration before ileostomy closure. Postoperative complications globally occurred in 38 (40%) of the patients, and some patients presented more than one complication; these are detailed in Table

Table 2 Characteristics of the ileostomy reversal procedure, including surgical technique and skin closure

Surgical variable	*n* (%)
Ileostomy closure technique	93 (100)
Stapled anastomosis	9 (9.7)
Handsewn anastomosis	84 (90.3)
Side-to-side with resection	28 (33.3)
End-to-end with resection	8 (9.5)
End-to-end without resection	48 (57.1)
Skin closure technique	70 (100)
Staples	17 (24)
Subcuticular	29 (41)
Interrupted suture	24 (34)

Table 3 Postoperative complications after loop ileostomy reversal in our study

Complications	*n* (%)
Total patients	38 (40.8)
Ileus	12 (12.9)
Wound infection	12 (12.9)
Rectal bleeding	5 (5.8)
Pseudomembranous colitis	4 (4.3)
Anemia/bleeding	3 (3.2)
Intestinal obstruction	3 (3.2)
Anastomotic leak	2 (2.15)
Urinary tract infection	2 (2.15)
Acute renal failure	2 (2.15)
Abdominal abscess	2 (2.15)
Pneumonia	1 (1)
Intestinal necrosis	1 (1)
Multiple organ failure	1 (1)
Thromboembolism	1 (1)
Sepsis	1 (1)
Evisceration	1 (1)
Clavien-Dindo classification	
Grade Ⅰ	21 (55)
Grade Ⅱ	9 (24)
Grade Ⅲ	7 (18)
Grade Ⅳ	0 (0)
Grade Ⅴ	1 (3)

Total number of patients and detailed complications classified by the Clavien-Dindo classification.

Table 4 Statistically significant conditions/complications in the multivariate analysis and their specific *P* values

Condition/complication	Statistical significance
Gender (male) and overall complications	$P = 0.042$
Gender (male) and wound infection	$P = 0.007$
Age and rectal bleeding	$P = 0.006$
Complications and time to closure (months)	$P = 0.041$
Closure > 6 mo and pseudomembranous colitis	$P = 0.003$
End-to-end intestinal anastomosis (without resection) and postoperative ileus	$P = 0.037$

3. There was a 1% mortality. The mean hospital stay was 11.5 d, ranging from 3 d to 3 mo.

Multivariate analysis was performed to identify risk factors for complications. Male patients had complications in 50% of cases (27/54) while females did in 28% (11/39). This result reached statistical significance ($P = 0.042$), so in our study male sex was a risk factor for postoperative complications. When analyzing specific complications, there was a strong association between male sex and wound infection ($P = 0.007$). Age was associated to rectal bleeding ($P = 0.006$). There was no statistically significant association between complications and ASA, BMI, or previous chemo-radiotherapy.

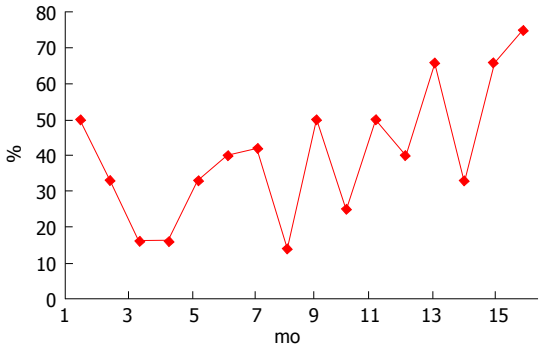

Figure 1 Percentage of postoperative complications related to ileostomy closure and time (in months) from creation to reversal.

In our series, the increased number of postoperative complications was associated with the delay in ileostomy closure ($P = 0.041$); a graphic representation of these data is shown in Figure 1. Occurrence of pseudomembranous colitis was also associated with the delay in ileostomy closure, with statistical significance ($P = 0.003$). The four cases of pseudomembranous colitis occurred in patients with ileostomy closure ranging from 9 to 15 mo.

According to the surgical technique for ileostomy reversal, only end-to-end intestinal anastomosis without resection was significantly associated with a specific complication, which was postoperative paralytic ileus ($P = 0.037$). There was no significant association between the surgical technique employed and postoperative hospitalization.

Regarding skin closure, the rate of surgical wound infection was studied in each group, when data on wound closure were available. In the staples group, infection was 5.8% (1/17 patients), in the subcuticular suture group 13% (4/29 patients) and in the interrupted suture group 20% (5/24 patients). Despite the rate of infection was highest in the interrupted suture group and lowest in the staples group these results did not reach statistical significance. All statistically significant results of the multivariate analysis are shown in Table 4.

DISCUSSION

Diverting loop ileostomies have become a common procedure when very low or high-risk rectal anastomoses are performed. Despite they can reduce morbidity and avoid reintervention if a leak occurs, their creation binds the patient to a second surgical procedure. This reversal procedure, as many published series have proven, can be associated to a high rate of morbidity, and even mortal-

ity[8]. In a recent systematic review[7], the high morbidity associated to ileostomy reversal raised concerns over the real indication of diverting stomas related to clinical outcomes, and if a better selection of patients should be made. Luglio *et al*[9], consider that if there is a > 5% risk of anastomotic leak in the primary operation, a protective stoma must be created.

In our study, the rate of postoperative morbidity was high (40%), but still among published data. The most common complications in our study were postoperative ileus and wound infections. Complications were mostly minor, classified as Clavien-Dindo Ⅰ-Ⅱ, and only 18% were considered major complications needing reoperation or invasive interventions (Clavien-Dindo Ⅲ). In a national study by Mengual-Ballester *et al*[6] data were similar to our own, with complications up to 45.9%, being ileus/obstruction the most frequent, followed by diarrhea and wound infection.

Ileus and bowel obstruction are still a concern after stoma reversal, and different studies have tried to elucidate if technical issues can reduce these complications. The surgical technique employed for the ileal anastomosis has been widely studied, and various published randomized controlled trials (RCTs) compare handsewn *vs* stapled anastomoses[10,11]. In our study, when analyzing the surgical technique and related complications, we only found statistical significance between end-to-end anastomosis without resection and postoperative paralytic ileus. This coincides with published meta-analysis[12-14] which mention a significant reduction in surgical time and a lower incidence of bowel obstruction when stapled anastomoses are performed compared to handsewn. Other complications (including infections, leak, readmission and reoperation rates) are similar.

Surgical infections after stoma reversal have been a subject of debate. Although both ileostomies and colostomies can be safe, the latter present a higher rate of infection after reversal. Therefore many authors recommend protective ileostomies for fecal diversion, if dehydration is not to be expected[15]. The rate of wound infection in our study (12.9%) was similar to other published data[16]. Wound infection is usually underestimated due to different definitions or considerations, and can be influenced by patient's characteristics and comorbidities. In some series of ileostomy closure for pouch-anal anastomoses such as that from van Westreenen *et al*[3], only a 1.4% rate of infection is reported. When analyzing patient's characteristics we realize mean age is only 49 years, most patients are ASA Ⅰ-Ⅱ, and indications for ileostomy are polyposis or inflammatory bowel disease rather than cancer. Data are therefore not comparable if the population of study is older or weaker. In our series, mean age was 60 years and patients mainly ASA Ⅱ-Ⅲ, with the main indication for ileostomy creation being colorectal cancer (56%).

Another important factor is if the 30-d infection rate is reported, or just the rate of infection during hospitalization. This can underestimate infections, as many of them occur after discharge and are managed in the outpatient clinic or by General Practitioners. This has been taken into consideration, and some recent publications already study standardized 30-d complications[17], and use classifications such as Clavien-Dindo to report results[9].

Different efforts have been made to reduce the infection rate of stoma-closure wounds. The technique employed has shown statistically significant results in various RCTs, such as that from Camacho-Mauries *et al*[18], favoring purse-string closure *vs* conventional sutures. In our study, a limitation regarding the retrospective analysis of skin closure was that data were incomplete and some surgical reports did not state the specific closure technique. From those available, interrupted, non absorbable sutures were the most frequently used, followed by subcuticular and staples. The staples group had a lower infection rate, but these data were not significant. Studies on the subject show contradictory results. In the retrospective study by Kobayashi *et al*[19], wound infection rate was as high as 23.5%, and subcuticular sutures apparently showed a protective effect. However, very recent studies and RCTs on wound closure, report purse-string sutures to achieve a 0% infection rate compared to other methods, thus not recommending linear closure of stoma wounds[20,21]. Other attempts, such as subcutaneous antibiotic implants (Gentamycin) in the wound, have not shown a relevant reduction in surgical site infections[22].

Another controversy around the subject is the best timing for stoma reversal. Some groups defend very early closure, even during the first admission, such as Alves *et al*[23], who perform reversal on the 8th postoperative day if no complications of the first intervention have occurred. Nevertheless, it is widely accepted to delay closure, and different studies report mean times of 3-6 mo, with a low medical priority given to this procedure[24].

In our study, we demonstrate that the delay in ileostomy closure (> 6 mo) is a risk factor for increased complications, and is associated with a higher incidence of pseudomembranous colitis, which was 4.3%. As can be seen in Figure 1, the incidence of complications increased with time (in months); there was an apparently 'safer' period around 3-6 mo, which could be considered optimal. From 9 mo onwards the rate of complications was > 30%.

Pseudomembranous colitis (PMC) is secondary to *Clostridium difficile* (*C.diff*) infection, and associated with substantial morbidity and mortality, increased duration of hospitalization, and a marked economic impact[25]. *C.diff* is a toxin-producing anaerobic bacterium responsible for antibiotic-associated colitis, and it is now the most common infectious cause of nosocomial diarrhea. Risk factors for PMC include advanced age, systemic antibiotic therapy, hospitalization, nursing homes or long-term care facilities, contact with active carriers, and presence of comorbidities[26]. It has been speculated that stoma closure can be another risk factor for PMC, which associates all the previous to an excluded and defunctioned bowel with altered flora, that could be more susceptible to *C.diff*

infection[27]. In a large series of 13245 United States patients undergoing ileostomy closure, Wilson *et al*[28], report a 1.6% incidence of pseudomembranous colitis. This is an important factor to be considered, especially if an earlier closure can in fact reduce the risk.

This study was a retrospective analysis of institutional patients in order to identify risk factors for postoperative complications after ileostomy reversal and improve quality of care in our Colorectal Surgery Unit. Therefore, limitations are all those of an observational retrospective study, and in some cases (as in skin closure technique) data were missing from medical records. Due to the small number of patients some data may not reach statistical significance.

Although closure of a protective ileostomy is a fairly common surgical procedure, it has a high rate of complications, and this must be taken into account when the indication is made. The delay in stoma closure can increase the rate of complications in general, and specifically wound infections and colitis.

COMMENTS

Background

The creation of a defunctioning stoma after some colorectal procedures has demonstrated to highly reduce morbidity and mortality rates if a leak occurs, and is usually widely recommended. However, a stoma can be an issue for many patients both psychologically and due of stoma-related complications. As these stomas are supposed to be temporary, a planned second operation for reversal must be performed. In some cases, due to cancer-related complications or comorbidities stomas are never reversed. In patients considered fit for surgery, the reversal of the stoma should be performed at the "safest" time possible, to reduce complications. This timing is sometimes difficult to determine, as it depends on clinical factors, oncological follow-up and treatment, surgeon's decision and institutional issues, such as "low-priority" consideration in surgical waiting lists.

Research frontiers

In the field of Colorectal Surgery, the optimization of anastomoses and methods to reinforce or protect them to avoid leaks is a matter of active research. Eventually, the creation of stomas would become obsolete if this could be achieved, improving surgical outcomes and reducing complications.

Innovations and breakthroughs

When revising the literature for the optimal timing for stoma reversal, recommendations usually suggest a 3 to 6 mo interval after the first intervention, always tailored to the specific risk factors and situation of the patient. When revising the real timing in our general practice, the authors realize there is a significant delay, and these recommendations are not followed. Complications related to prolonged bowel defunctioning (such as ileus, bleeding, diarrhea or *Clostridium difficile* colitis) and wound infections could be reduced if the time for closure is optimal. The best practice would be to guarantee an adequate healing from the first operation and close the stoma early enough to avoid the consequences of a prolonged defunctioning.

Applications

The study suggests that there is an optimal time frame to be considered when planning the ileostomy reversal that could reduce postoperative complications.

Terminology

A protective ileostomy is an opening of a loop of small bowel (usually the terminal ileum) in the abdominal wall, so that a distal anastomosis performed in the colon or rectum is protected from fecal matter and can heal properly. The ileostomy reversal is the surgical intervention performed to close the loop of small bowel and restore normal intestinal transit.

Peer review

Abstract is concise, topic is interesting, methods are appropriate, a well-structured discussion.

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Pancreatic extragastrointestinal stromal tumor: A case report and comprehensive literature review

Sami Akbulut, Rıdvan Yavuz, Emrah Otan, Sinan Hatipoglu

Sami Akbulut, Rıdvan Yavuz, Department of Surgery, Diyarbakir Education and Research Hospital, Uckuyular Mevki, Kayapinar, 21400 Diyarbakir, Turkey
Emrah Otan, Department of Surgery, Inonu University Faculty of Medicine, 44280 Malatya, Turkey
Sinan Hatipoglu, Department of Surgery, Adiyaman University Faculty of Medicine, 02040 Adiyaman, Turkey
Author contributions: Akbulut S and Hatipoglu S designed the report; Akbulut S and Yavuz R were attending doctors for the patients; Akbulut S and Yavuz R performed the surgery; Akbulut S, Otan E and Hatipoglu S organized the report and wrote the paper.
Correspondence to: Sami Akbulut, MD, FICS, FACS, Department of Surgery, Diyarbakir Education and Research Hospital, Uckuyular Mevki, Kayapinar, 21400 Diyarbakir, Turkey. akbulutsami@gmail.com
Telephone: +90-412-2580052 Fax: +90-412-2580050
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Abstract

AIM: To provide an overview of the literature on pancreatic extragastrointestinal stromal tumors (EGISTs).

METHODS: We report a case of pancreatic EGIST and review published studies on pancreatic EGIST accessed *via* the PubMed, MEDLINE, Google Scholar, and Google databases. The keywords used were "pancreas and GIST", "pancreas and extra GIST", "pancreas and gastrointestinal stromal tumor", and "pancreas and extragastrointestinal stromal tumor". Literature reviews and/or duplicate studies were excluded. The search included articles published in the English language between January 1, 2000 and May 15, 2014.

RESULTS: From our literature survey, 30 manuscripts on pancreatic EGISTs were considered, of which 27 met the search criteria and three were excluded. The studies involved 30 patients (15 men, 15 women) with a mean age of 55.3 ± 14.3 years (range 30-84 years). The mean age of the male patients was 50.8 ± 13.7 years (range 30-84 years); that of the female patients was 59.9 ± 13.3 years (range 38-81 years). Tumor dimensions were obtained for 28 cases (mean 114.4 ± 78.6 mm; range 20-350 mm). Tumors were diagnosed incidentally in 23.3% of patients; abdominal discomfort and weight loss were the major complaints in symptomatic patients. Risk of aggressive behavior according to Fletcher criteria was determined in 25 of 30 patients (68%: high risk, 28%: intermediate risk, 4%: low risk). Histopathological examination revealed the presence of spindle cells in 96.1% of cases; CD117 and CD34 were present immunohistochemically in 96.6% and 84% of patients, respectively. The most common surgical procedures were distal pancreatectomy with splenectomy (n = 9) and pancreaticoduodenectomy (n = 7). The total follow-up period for the 28 patients ranged from 3-66 mo, during which locoregional or distant metastases were diagnosed in six patients and two patients died.

CONCLUSION: Studies on EGISTs have only been published in the last decade. The lack of studies with large patient cohorts and long-term follow-up limits evidence-based commentary. In theory, each case should be assessed individually and further genetic and immunohistochemical studies are needed.

Key words: Gastrointestinal stromal tumor; Extra-gastrointestinal stromal tumor; Pancreas; Imatinib mesylate; CD117

Core tip: Gastrointestinal stromal tumors are the most common gastrointestinal (GI) tract tumors of mesenchymal origin. Stromal tumors of extragastrointestinal origin are termed extragastrointestinal stromal tumors (EGISTs) and are not associated with the walls of GI

tubular organs or the serosal walls. The pancreas is among the organs that are rarely the site of origin, and according our knowledge, about 30 cases of pancreatic EGISTs have been reported to date. In this study, we reviewed studies on pancreatic EGISTs and report a case of pancreatic head EGIST.

Akbulut S, Yavuz R, Otan E, Hatipoglu S. Pancreatic extragastrointestinal stromal tumor: A case report and comprehensive literature review. *World J Gastrointest Surg* 2014; 6(9): 175-182 Available from: URL: http://www.wjgnet.com/1948-9366/full/v6/i9/175.htm DOI: http://dx.doi.org/10.4240/wjgs.v6.i9.175

INTRODUCTION

Gastrointestinal stromal tumors (GISTs) are the most common tumors of mesenchymal origin in the gastrointestinal (GI) tract[1-3]. The disease originates from neoplastic transformation of the interstitial cells of Cajal or their precursors in the GI tract. Although GISTs can be diagnosed in all sites of the GI tract, *i.e.*, from the esophagus to the anus, they are most commonly diagnosed in the stomach and intestines[1-6]. Stromal tumors of extragastrointestinal origin are termed extragastrointestinal stromal tumors (EGISTs) and are not associated with the walls of GI tubular organs or serosal surfaces[3,7,8]. The morphological, histopathological, immunohistochemical, and molecular profiles of EGISTs are similar to those of GISTs[2,9,10]. Although EGISTS potentially originate from a variety of sites in the abdominal cavity, the majority of initial tumor progression sites include the omentum, retroperitoneum, mesentery, and the liver[1,2,11,12]. The pancreas is rarely the site of origin, and according our knowledge, 30 cases of pancreatic EGISTs have been reported to date[1-5,7-31]. We report a case of pancreatic EGIST and review the literature on pancreatic EGISTs.

MATERIALS AND METHODS

Our primary aim was to report the rare case of a 61-year-old patient who underwent surgical treatment for pancreatic head EGIST. The secondary aim was to analyze previously published articles related to pancreatic GIST. We searched for published studies on pancreatic GIST using different keyword combinations, including "pancreas and GIST", "pancreas and extra-GIST", "pancreas and gastrointestinal stromal tumor", and "pancreas and extragastrointestinal stromal tumor" in the PubMed, MEDLINE, Google Scholar, and Google databases. Studies for which full-text versions were available and that contained adequate patient details for comparison were included; literature reviews and duplicate reports were excluded. The publication language was not an exclusion criterion, and studies published before May 15, 2014 were included. Tables 1 and 2 lists the year of publication, country, patient age and sex, clinical presentation, physical examination, radiological tests, tumor size (mm), cell type (spindle, epithelioid, mixed), mitotic count [per high-power field (HPF)], immunohistochemical staining (CD117, CD34), surgical procedure, recurrence, outcome, and follow-up obtained from the studies.

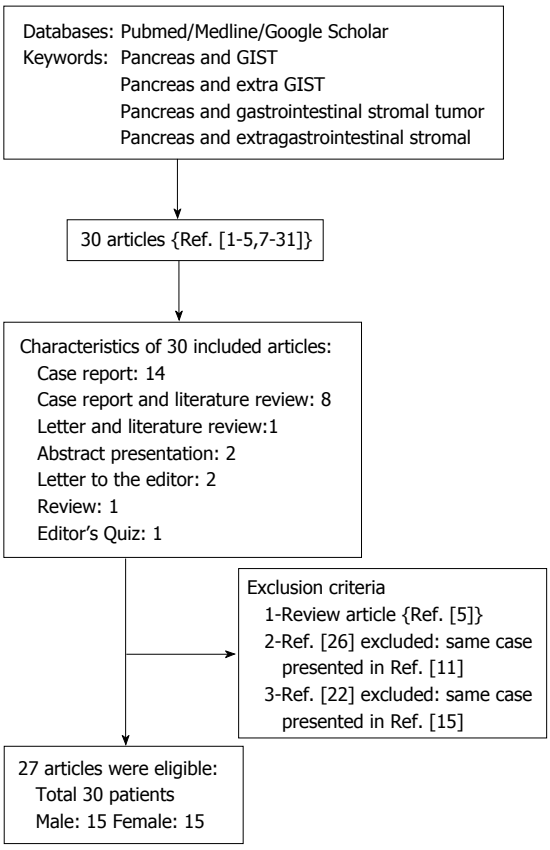

Figure 1 Flow chart of the study selection process. GIST: Gastrointestinal stromal tumor.

RESULTS

Literature review

Based on the above-mentioned search criteria, 30 manuscripts were identified[1-5,7-31]: 27 met the criteria and three were excluded[5,22,26]. The criteria are detailed in the flow chart in Figure 1. The studies involved 30 patients with pancreatic GIST: 15 were male and 15 were female; mean age was 55 ± 14.3 years (range 30-84 years). The mean ages of male and female patients were 50.8 ± 13.7 years (range 38-81 years) and 59.9 ± 13.3 years (range 38-81 years), respectively. Information regarding tumor size was obtained from 28 cases (mean 114.4 ± 78.6 mm; range 20-350 mm). The demographic and clinical data of the 30 patients are presented in Table 1. Table 2 summarizes the morphological characteristics, treatments, and outcomes of the 30 patients.

Case report

A 61-year-old woman was admitted to our clinic for a routine check-up. One year previously, she had visited another clinic complaining of loss of appetite, weight loss,

Table 1 Demographic and clinical characteristics of 30 patients with pancreatic extragastrointestinal stromal tumors identified from literature published between January 2004 and May 2014

Ref.	Year	Country	Age (yr)	Sex	Clinical presentation	Examination	Radiologic tools	Tumor location	Tumor size (cm)
Tian *et al*[4]	2014	China	61	M	Incidental finding	Abdominal mass	CT	Tail	60 × 80
			60	M	Incidental finding	NS	CT	Head	60 × 50
Paklina *et al*[11]	2013	Russia	38	F	Abdominal discomfort	NS	CT	Head	90
Serin *et al*[1]	2013	Turkey	30	M	Abdominal distension	NS	US + CT	Tail	130
Soufi *et al*[16]	2013	Morocco	39	M	Weight loss + abd pain + constipation	Distension	CT + endoscopy	Head	90 × 70 × 50
Wegge *et al*[2]	2012	USA	55	M	Haematemesis + haematochezia	Non-specific	CT + MRCP + endoscopy	Head	46 × 45 × 44
Babu *et al*[13]	2012	China	55	F	Upper abdominal pain	Non-specific	CT + US	Head	50 × 40 × 30
Kim *et al*[3]	2012	Korea	55	M	Abdominal discomfort	Non-specific	CT + MR	Tail	130 × 90 × 85
Čečka *et al*[9]	2011	Czech	74	F	Abdominal mass	Palpable mass	US + CT	Tail	110 × 80 × 40
Vij *et al*[14]	2011	India	35	M	Weight loss + abdominal discomfort	Non-specific	US + CT	Head	80 × 60
Rao *et al*[7]	2011	India	40	M	Weight loss + abdominal pain + anemia	Non-specific	US + CT	Head + Body	65 × 60
Yang *et al*[15]	2011	China	55	M	Abdominal discomfort	Abdominal mass	CT + MR	Body + Tail	178 × 196
Barros *et al*[12]	2011	Brasil	63	F	Abdominal pain + ponderal loss	NS	NS	NS	NS
			81	F	Difficult gastric emptying + ponderal loss	NS	NS	NS	100
Joshi *et al*[17]	2010	USA	84	M	Weight loss + abdominal distension	Distension	CT	Entire pancreatic tissue	340 × 240 × 270
Crisan *et al*[18]	2010	Romania	61	M	Weight loss + fever + intense sweating	Diffuse tenderness	CT X	Tail + Body	140
Saif *et al*[19]	2010	USA	31	M	Weight loss + abdominal pain + anemia	NS	CT + MR + endoscopy	Head	56 × 51 × 42
Padhi *et al*[8]	2010	India	42	F	Weight loss + abdominal pain	Palpable mass	CT + MR	Body + Tail	350 × 300 × 250
Harindhanavudhi *et al*[20]	2009	USA	63	F	Fatigue + weakness+anemia	Non-specific	CT + EUS	Body	160 × 110
Trabelsi *et al*[21]	2009	Tunisia	52	F	Epigastric pain	Palpable mass	US + CT	Head	105 × 80 × 30
Goh *et al*[10]	2009	Singapore	58	M	Incidental finding	NS	NS	Head	90
Showalter *et al*[23]	2008	USA	72	F	Incidental finding	NA	MR	Tail	70
Yan *et al*[24]	2008	USA	47	M	Nausea + vomiting + (hepatitis B)	Splenomegaly	CT + EUS	Uncinate process	24 × 21
Ganesh *et al*[25]	2008	UK	76	F	Weight loss + abdominal pain	Diffuse tenderness	CT + endoscopy	Tail + body	NS
Daum *et al*[27]	2005	Czech	70	F	Incidental finding	Palpable mass	CT	Head	100 × 80 × 60
Krska *et al*[28]	2005	Czech	38	F	Abdominal pain + fatigue	Tenderness	CT + US + EUS + CT + endoscopy	Head + Body	170 × 120
Pauser *et al*[29]	2005	USA	51	M	Incidental finding	NS	US + CT + endoscopy	Tail	30
			54	F	Abdominal discomfort	NS	US	Body	20
Neto *et al*[30]	2004	Brasil	67	F	Weight loss + abd pain + gastric bloating	NS	NS	Body + Tail	200 × 190 × 120
Yamaura *et al*[31]	2004	Japan	54	F	Incidental finding	Palpable mass	US + CT + MR + angiography	Tail	140 × 120 × 80

US: Ultasonography; CT: Computed tomography; MR: Magnetic resonance; EUS: Endoscopic ultrasound; MRCP: Magnetic resonance cholangiopancreatography; X: Partial thrombosis detected in both portal vein and inferior vena cava at the level of left renal vein; NA: Not-available; NS: Not-stated; M: Male; F: Female; UK: United Kingdom; USA: United States of America.

and jaundice. Blood tests showed elevated liver enzymes and leucocyte count. Abdominal ultrasonography (USG) revealed bile duct dilatation, multiple metastatic liver lesions, and a pancreatic head mass. Computed tomography (CT) and magnetic resonance imaging (MRI) revealed a 97 mm × 63 mm heterogeneous mass with well-defined margins in the pancreatic head, which had resulted in the bile duct dilatation. Perihilar gross lymphadenopathy was also detected. Following bile duct decompression by percutaneous transhepatic cholangiography, percutaneous biopsy samples were collected from the liver lesions and portal lymph nodes under USG guidance. The specimens were evaluated histopathologically and immunohistochemically [CD117(+); CD34(−); smooth muscle actin (SMA)(−)], and GIST was diagnosed. As the primary tumor was metastatic prior to surgery, 400 mg/d imatinib mesylate (Gleveec®, Novartis) was started and administered for four months. MRI subsequently showed a reduction in tumor size to 15 × 15 mm. CT performed during the same period showed that the tumor had shrunk to 15 × 20 mm and that the liver lesions had disappeared. Based on these findings, surgical treatment was advised, but the patient refused surgery; therefore, she was discharged and prescribed imatinib. When admitted to our clinic, she had no significant physical findings except

Table 2 Morphological characteristics, treatments, and outcomes of 30 patients with pancreatic extragastrointestinal stromal tumor identified from literature published between January 2004 and May 2014

Ref.	Cell type	Mitotic count (/50 HPF)	CD117	CD34	Surgical procedures	Recurrence (after surgery)	Outcome (follow-up)	Medical treatment
Tian *et al*[4]	Spindle	< 5 (intermediate risk)	(+)	(+)	Distal pancreatectomy + splenectomy	No	Alive (36 mo)	No
	Spindle	> 5 (high risk)	(+)	NS	Tumor resection	Yes (liver, 12 mo)	Alive (36 mo)	Gleevec + TACE
Paklina *et al*[11]	Spindle	1-2 (intermediate risk)	(+)	NS	NS	NS	NS	NS
Serin *et al*[1]	NS	NS (high risk)	(+)	NS	Distal pancreatectomy + splenectomy	No	Alive (21 mo)	No
Soufi *et al*[16]	Spindle	< 5 (intermediate risk)	(+)	(+)	Whipple + segmental colectomy	No	Alive (24 mo)	Gleevec
Wegge *et al*[2]	Spindle	6 (intermediate risk)	(+)	(+)	Whipple	No	Alive (5 mo)	Gleevec
Babu *et al*[13]	Spindle	6-8 (high risk)	(+)	(+)	Pancreatic head resection	No	Alive (11 mo)	No
Kim *et al*[3]	Spindle	7 (high risk)	(+)	(+)	Distal pancreatectomy + splenectomy	No	Alive (4 mo)	Gleevec
Čečka *et al*[9]	Spindle	5 (high risk)	(+)	(+)	Distal pancreatectomy + splenectomy	No	Alive (66 mo)	No
Vij *et al*[14]	Spindle	12-15 (high risk)	(+)	(-)	Whipple	Yes (liver, 24 mo)[a]	Alive (48 mo)	Gleevec
Rao *et al*[7]	Spindle[b]	8-10 (high risk)	(+)	(+)	Whipple	Yes (liver, 24 mo)	Alive (30 mo)	Gleevec
Yang *et al*[15]	Spindle	> 30/10 HPF (high risk)	(+)	(+)	Distal pancreatectomy + splenectomy	Yes (intraperitoneal, 24 mo)[c]	Alive (41 mo)	Gleevec
Barros *et al*[12]	NS	< 5	(+)	(+)	No	NS	Death (8 mo)	No
	NS	< 5 (intermediate risk)	(+)	(+)	Laparotomy + biopsy	Surgery not performed	Alive (12 mo)	Gleevec
Joshi *et al*[17]	Spindle	NS	(+)	(+)	None performed[d]	Surgery not performed	Death (5 d)	No
Crisan *et al*[18]	Spindle	(high risk)	(+)	(+)	Distal pancreatectomy + splenectomy + partial colectomy + duodenojejunal resection	NS	Alive (3 mo)	NS
Saif *et al*[19]	Spindle[e]	48 (high risk)	(+)	(-)	Whipple, pylorus preserving	Yes (liver, 9 mo)	Alive (NS)	Gleevec
Padhi *et al*[8]	Spindle	6-8 (high risk)	(+)	(+)	Distal pancreatectomy + splenectomy + left hemicolectomy	No	Alive (10 mo)	No
Harindhanavudhi *et al*[20]	Spindle	< 5 (high risk)	(+)	(+)	Cystojejunostomy[f]	NS	Alive (NS)	Gleevec
Trabelsi *et al*[21]	Spindle	6 (high risk)	(+)	(+)	Whipple + partial colectomy	No	Alive (10 mo)	No
Goh *et al*[10]	Spindle	> 10 (high risk)	(+)	NS	Whipple	No	Alive (58 mo)	NS
Showalter *et al*[23]	NA	3 (intermediate risk)	(+)	(-)	Distal pancreatectomy + splenectomy - laparoscopic	No	Alive (27 mo)	NS
Yan *et al*[24]	Spindle[g]	3 (low risk)	(+)	NS	NS	NS	NS	NS
Ganesh *et al*[25]	Spindle[h]	NS	(+)	(+)	No (inoperable)	Surgery no performed	Alive (30 mo)	Gleevec
Daum *et al*[27]	Spindle	2 (intermediate risk)	(+)	(-)	Whipple	No	Alive (6 mo)	Gleevec
Krska *et al*[28]	Spindle[i]	1 (high risk)	(-)	(+)	Partial pancreatectomy	No	Alive (30 mo)	NS
Pauser *et al*[29]	Spindle	NS	(+)	(+)	Resection	No	Alive (24 mo)	NS
	Spindle	NS	(+)	(+)	Resection	No	Alive (48 mo)	NS
Neto *et al*[30]	Mixed	120 (high risk)	(+)	(+)	Distal pancreatectomy	Yes (peritoneum)	Alive (NS)	Gleevec
Yamaura *et al*[31]	Spindle	Few (high risk)	(+)	(+)	Distal pancreatectomy + splenectomy + partial gastric resection	NS	Alive (30 mo)	NS

[a]Liver metastasis at postoperative month 24. Metastasectomy performed. Two years followed without recurrence; [b]Diagnosed using USG-guided fine needle aspiration (FNA); [c]Intraperitoneal recurrence at postoperative month 24. Resection performed. Imatinib treatment both before and after resection. Following second resection, followed-up without recurrence; [d]CT-guided liver biopsy diagnosed metastatic EGIST. Clinical status deteriorated prior to surgery and died five days following diagnosis; [e]Diagnosed with Endo-USG (EUS)-guided FNA. Liver lesion diagnosed with CT and PET at postoperative month 9. Biopsy diagnosis was EGIST. Gleevec treatment dose increased to 800 mg. Due to resistance to treatment, was switched to sunitinib; [f]Pancreatic mass diagnosed four years ago, patient refused surgical treatment. CT revealed 10-cm enlargement in four years. Diagnosis was made with EUS-guided FNA. Explorative laparotomy revealed pancreatic hemorrhagic cyst; cystojejunostomy performed to obtain an incisional biopsy sample diagnosed high-risk GIST. Patient refused definitive surgical treatment; [g]Diagnosis made with EUS-guided FNA; [h]Diagnosed using USG-guided FNA. Further surgical treatment aborted as the patient was inoperable, and Gleevec treatment was initiated. Clinical follow-up period of 30 mo revealed significant tumor reduction; [i]USG-guided biopsy could not provide diagnosis. CT: Computed tomography; USG: Ultrasonography; EGIST: Extragastrointestinal stromal tumor; PET: Positron emission tomography; TACE: Transcatheter arterial chemoembolization; NA: Not-available; NS: Not-stated.

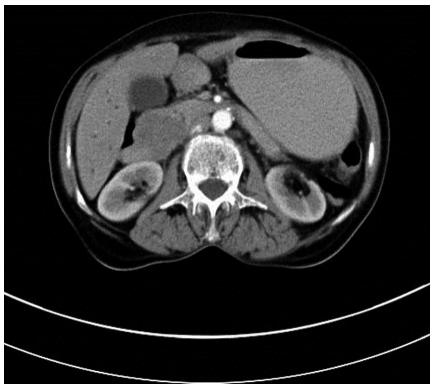

Figure 2 Contrast-enhanced abdominal computed tomography shows a well-defined solid mass of the pancreatic head.

cachexia. Laboratory test parameters, including tumor markers, were within the normal limits. Control abdominal CT scan showed that the tumor measured 45 mm × 40 mm (Figure 2). The common bile duct and major pancreatic duct diameter was 17 mm and 7 mm, respectively. No metastatic liver lesions were detected. F-18 fluorodeoxyglucose positron emission tomography-CT (PET-CT) detected a mass with increased glucose consumption at the duodenal site, consistent with a malignant lesion. Given the increased tumor size and the current complaints of the patient, surgical treatment was recommended. We detected a well-demarcated, 50 × 40 mm, semi-solid, visually heterogeneous pancreatic head mass without invasion to the surrounding tissues. Metastatic liver lesions were not observed, and lymphadenopathy was detected in the peripancreatic site and hepatoduodenal ligament. Standard pancreaticoduodenectomy with lymph node dissection was performed. The postoperative course was uneventful; she was discharged on day 13. Pathologically, the specimen contained tumor cells with low mitotic activity, severe pleomorphism, and cellularity (spindle cells); we diagnosed GIST. Postoperative imatinib mesylate was started, and there was neither locoregional nor distant metastases at the last follow-up 48 mo later.

DISCUSSION

In 1892, Cajal first observed interstitial cells of Cajal in the intestinal wall under a light microscope, which were termed "interstitial neural cells". Approximately 80 years later, Faussone-Pellegrini *et al*[32] viewed the same cells under an electron microscope and renamed them interstitial cells of Cajal[5,32]. Studies conducted during the 1970s showed that pathological changes to interstitial cells of Cajal may result in GI motility disorders and GISTs[5]. Since they were first described histologically, physiological testing has proven that interstitial cells of Cajal function as GI pacemakers[5,20,32,33].

Defined by Mazur and Clark in 1983, GISTs are the most common non-epithelial mesenchymal tumors of the GI tract[5]. Genetic studies have revealed that 90% and 5%-7% of GISTs have tyrosine kinase gene mutations in c-KIT and platelet-derived growth factor receptor alpha (PDGFRA), respectively[1,5]. The incidence of GIST varies between 10 and 20 cases per million people annually[5,9]. GISTs represent 0.1%-3% of all GI tumors and 80% of GI mesenchymal tumors, and may present at any site in the GI tract where there are interstitial cells of Cajal. The most frequently affected GI organs are the stomach (40%-70%), intestines (20%-40%), rectum and colon (< 10%), and the esophagus (rare)[5].

"EGIST" was initially used by Reith *et al*[33] in 2000 to define stromal tumors originating from outside the GI tract. EGISTs represent 5%-10% of all GISTs[1,4,5,9,12]. Although the locations from which EGISTs originate do not contain interstitial cells of Cajal, cells with the same clinical, pathological, immunohistochemical, transmission electron microscopy morphology, and biological behavior patterns as interstitial cells of Cajal have been detected[2,5,6]. Experimental and clinical studies have detected cells with biological and histopathological features similar to interstitial cells of Cajal in pancreatic tissue (interstitial Cajal-like cells = telocytes)[5,34]. The pancreas and GI tubular organs have a common embryological origin, suggesting that EGIST and GIST cells originate from multipotent mesenchymal stem cells (intestinal mesenchymal precursors)[1,5,21]. Several EGIST studies have suggested that most EGISTs are likely mural GISTs with diffuse extramural invasion resulting in loss of communication with the intestinal muscularis propria. This may occur during operative or postoperative manipulation. Furthermore, true EGISTs may be extramurally growing GISTs that lose communication with the muscularis propria after reaching this layer[2,10,16]. This is known as extensive extramural growth and requires further study.

More than 80% of EGISTs originate from EGI abdominal wall structures, including the intestinal mesentery, mesocolon, omentum, retroperitoneum, abdominal wall, liver, and pancreas[10,13]. Pancreatic EGISTs represent less than 1% of malignant pancreatic tumors, and less than 5% of EGISTs originate from the pancreas[16].

The majority of EGISTs are well demarcated and unencapsulated. Due to their slow growth rate, they may exist without any clinical signs until the majority of the abdominal cavity is invaded. Among the reported cases, tumors are 100-120 mm in diameter (range 10-400 mm)[4]. EGISTs are usually diagnosed in adults, predominantly in females[14]. Our literature review determined near equal rates of occurrence between females and males.

Pancreatic EGISTs are usually asymptomatic or minimally symptomatic and diagnosed incidentally by radiological examination[7,9]. When present, the severity of symptoms is related to tumor dimensions and location in the pancreatic tissue[2,4,7,9,16]. The most common symptoms and findings are nonspecific abdominal pain, weight loss, fatigue, abdominal mass and distention, fever of unknown origin, obstruction, GI bleeding, anemia, portal vein thrombosis, jaundice, and hepatic encephalopathy (rare)[4,16,18]. Of the cases we reviewed, 23.3% were diagnosed incidentally. The most common symptoms were

weight loss and abdominal discomfort.

The most common diagnostic studies for pancreatic masses involve biochemical [carbohydrate antigen 19-9, carcinoembryonic antigen (CEA)], radiological, histopathological, immunohistochemical, and genetic testing[3-5,21]. However, the diagnostic value of tumor markers such as CA 19-9 and CEA for pancreatic EGIST is limited, and are rarely used[4]. Abdominal CT, MRI, USG, endoscopic USG (Endo-USG), and PET-CT are the most frequently used radiological techniques, and aid in determining tumor localization, dimensions, margin irregularity, invasion of surrounding tissues, distant metastases, and resectability; however, most of them are non-diagnostic. USG and CT are often used in fine needle biopsies[5,7,17,20,24,25,28]. Endo-USG is a valuable diagnostic tool, allowing simultaneous diagnosis and biopsy of solid or cystic pancreatic masses[4,5,16,19,20,24]. PET-CT is used more frequently for both diagnosing and monitoring GIST and is very efficient in cases where CT and MRI are inconclusive[35].

Histopathologically, GISTs are classified into spindle (70%), epithelioid (20%), or mixed (< 10%) type. Most pancreatic EGISTs consist of spindle cells[4]. Therefore, leiomyoma, leiomyosarcoma, liposarcoma, rhabdomyosarcoma, schwannoma, fibromatosis, inflammatory fibroid polyps, solitary fibrous tumor, and malignant fibrous histiocytoma should be considered in the differential diagnoses[3,8,11,24,27]. Of the cases presented here, 26 had detailed histopathological data and 25 (96.1%) had spindle cells.

EGISTs have typical immunohistological staining features, among which CD117 is the most well known. KIT is a transmembrane receptor for binding tyrosine kinase enzymes, and c-KIT is a newly discovered member of this receptor family, on whose receptor CD117 is an epitope that can be stained immunohistochemically. The introduction of CD117 staining in the 1990s changed the terminology for connective tissue tumors; since then, 95% of tumors defined as GIST or EGIST stain CD117-positive. For the 5% of tumors with negative staining, another tyrosine kinase receptor family member, PDGFRA, was investigated in immunohistochemical studies, with 33.3% positive staining[5]. Additionally, GISTs stain positive for CD34 (60%-70%), heavy caldesmon (80%), SMA (30%-40%), S100 (5%), and desmin (< 5%)[2-4,8,9]. Of the 30 cases presented, 29 (96.6%) stained CD117-positive and 21 (84%) of 25 cases stained CD34-positive.

Predicting GIST clinical and biological behavior is difficult. Fletcher defined the criteria of the National Institutes of Health (Fletcher criteria) to estimate the risks of GIST aggressive behavior and metastasis (locoregional and/or distant) using tumor dimensions (cm) and mitotic counts (per 50 HPF)[2,9]. According to the criteria, GISTs are classified based on their risk of aggressive behavior: very low (< 2 cm, < 5/50 HPF), low (2-5 cm, < 5/50 HPF), intermediate (< 5 cm, 6-10/50 HPF or 5-10 cm, < 5/50 HPF), and high (> 5 cm, > 5/50 HPF or > 10 cm, any mitotic count)[3,4,9,21]. This classification aids in surgical treatment selection or neoadjuvant and/or adjuvant treatment planning. The risk of aggressive behavior according to the Fletcher criteria was determined in 25 of the 30 patients in our literature review: risk of pancreatic EGIST aggressive behavior was high in 17 cases. The remaining 8 cases were intermediate risk (n = 7; 28%) and low risk (n = 1; 4%).

The goal of surgical treatment, which is the most desirable treatment option for primary pancreatic EGISTs, is complete resection with microscopically clean (R0) margins[4,5,36]. Generally, primary surgery, surgical treatment following neoadjuvant chemotherapy, and debulking surgery for metastatic and/or advanced disease are considered in the surgical treatment of GISTs[2,5]. Surgical treatment selection depends on pancreatic EGIST localization. Standard or pylorus-preserving pancreaticoduodenectomy is the optimal treatment for pancreatic head tumors[4]. Duodenum-preserving pancreatic head resection may be performed for small tumors, low-grade tumors, or patients who cannot tolerate the Whipple procedure[4,36]. Conversely, radical surgical treatment may be the best option for preventing locoregional and/or distant metastases[13,15]. Regional lymph node metastases are rare in pancreatic EGIST cases, and routine systematic regional lymph node dissection is not indicated[4,13,16,18]. In our patient, EGIST was diagnosed after lymph node biopsy. Therefore, we suggest lymphadenectomy for cases of pathological lymphadenopathy observed during surgical exploration and for lymph node metastasis-positive cases based on intraoperative frozen section analysis. Depending on intraoperative findings and the surgeon's experience, pancreaticoduodenectomy, distal pancreatectomy with splenectomy, or partial pancreatic resection may be used for treating tumors in the pancreatic tail and corpus[13]. Nine and seven of the 30 patients underwent distal pancreatectomy with splenectomy, and the Whipple procedure, respectively.

The responses of GISTs to conventional chemotherapy and radiotherapy were very limited, being 10% and 5%, respectively[9,21]. These response rates changed when imatinib mesylate, an agent used for treating chronic myelogenous leukemia, was administered to a GIST case in the early 2000 s. Philadelphia chromosome-positive leukemia patients carry a mutation in the *BCR-ABL* gene, which is a KIT receptor family member. Additionally, the mutated *c-KIT* and *PDGFRA* genes seen in GISTs are members of the same family. Consequently, tyrosine kinase transmembrane receptors have been targeted in GIST treatment using two agents: imatinib mesylate and sunitinib malate. Imatinib was the first c-KIT tyrosine kinase inhibitor used for treating GISTs, specifically metastatic and unresectable GISTs, and was approved by the US Food and Drug Administration. Sunitinib was subsequently introduced for patients who could not tolerate imatinib or who were imatinib-resistant[2,23]. Recently, new tyrosine kinase inhibitors, such as nilotinib, sorafenib, dovitinib, and dasatinib, were introduced[5]. Despite the controversial approach of "which tyrosine kinase inhibitor, which patient and when", there is consensus for

initiating imatinib treatment in patients with high mitotic activity, gross dimensions, necrosis, and locoregional and/or distant metastasis[2,15]. Imatinib may be used as a neoadjuvant agent to downstage gross tumor volume for R0 resection and contributes to good prognosis[4]. Imatinib may be used as adjuvant treatment in cases with R1 (positive microscopic margin) or R2 (residual gross visible tumor) resection, risk of aggressive behavior, or poor prognostic features[4,5]. Similarly, imatinib treatment may be used as a primary modality in metastatic or unresectable cases to reduce tumor size, resulting in better prognosis[4]. Metastatic pancreatic EGIST cases benefit from debulking surgery, which increases the efficacy of imatinib[2]. The positive response to imatinib in patients with GISTs is 60%-70%, which can extend overall survival up to 5 years[4].

In conclusion, the term EGIST was introduced into the literature in the last decade. Debates on the similarities and differences between EGISTs and GISTs are ongoing. Despite their behavioral similarities, the initial asymptomatic period accounts for the gross tumor size of EGISTs. The lack of comprehensive case reports on EGISTs, including pancreatic EGISTs, limited our evidence-based review. Long-term follow-up studies of EGISTs are currently unavailable, limiting the amount of available information on tumor behavior. We are limited to the case reports that have been published to date and further immunohistochemical and genetic studies regarding EGIST behavior and response to treatment are needed.

COMMENTS

Background

Gastrointestinal stromal tumors (GISTs) are the most common tumors of mesenchymal origin in the gastrointestinal (GI) tract. The disease originates from neoplastic transformation of interstitial cells of Cajal or their precursors in the GI tract. Stromal tumors of extragastrointestinal origin are termed extragastrointestinal stromal tumors (EGISTs) and are not associated with the walls of GI tubular organs or serosal surfaces. The morphological, histopathological, immunohistochemical and molecular profiles of EGISTs are similar to those of GISTs.

Research frontiers

The primary aim was to report the rare case of a 61-year-old patient who underwent surgical treatment for pancreatic head EGIST. The secondary aim was to analyze previously published articles related to pancreatic GIST. To this end, the authors searched for studies on pancreatic GIST using different keyword combinations in the PubMed, MEDLINE, Google Scholar, and Google databases.

Terminology

GISTs are the most common mesenchymal tumors of the GI tract. EGISTs are defined as tumors originating from outside the GI tract. Imatinib mesylate was the first c-KIT tyrosine kinase inhibitor used to treat GISTs. The Fletcher criteria are used to estimate the risk of GIST aggressive behavior and metastasis using tumor size and mitotic counts.

Peer review

This paper comprises a case history, and a comprehensive review of the literature on pancreas GIST. The strength of the paper is that the authors have tried to collect available literature of the limited articles published on this topic.

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CASE REPORT

Gastric necrosis: A late complication of nissen fundoplication

Javier Salinas, Tihomir Georgiev, Juan Antonio González-Sánchez, Elena López-Ruiz, José Antonio Rodríguez-Montes

Javier Salinas, Tihomir Georgiev, Juan Antonio González-Sánchez, José Antonio Rodríguez-Montes, Department of General Surgery, Hospital Universitario La Paz, Madrid 28046, Spain
Elena López-Ruiz, Department of Pathology, Hospital Universitario La Paz, Madrid 28046, Spain
Author contributions: Salinas J, Georgiev T and González-Sánchez JA performed the surgery; López-Ruiz E performed the anatomopathological examination; Salinas J reviewed current literature and wrote the paper; González-Sánchez JA and Rodríguez-Montes JA coordinated the paper elaboration and revised the article.
Correspondence to: Javier Salinas, MD, Department of General Surgery, Hospital Universitario La Paz, Paseo de la Castellana, 261, Madrid 28046, Spain. jsalinas@icomen.es
Telephone: +34-91-2071667 Fax: +34-91-2071064
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Abstract

Gastric necrosis is a rare condition because of the rich blood supply and the extensive submucosal vascular network of the stomach. "Gas-bloat" syndrome is a well known Nissen fundoplication postoperative complication. It may cause severe gastric dilatation, but very rarely an ischemic compromise of the organ. Other factors, such as gastric outlet obstruction, may concur to cause an intraluminal pressure enough to blockade venous return and ultimately arterial blood supply and oxygen deliver, leading to ischaemia. We report a case of a 63-year-old women, who presented a total gastric necrosis following laparoscopic Nissen fundoplication and a pyloric phytobezoar which was the trigger event. No preexisting gastric motility disorders were present by the time of surgery, as demonstrated in the preoperative barium swallow, thus a poor mastication (patient needed no dentures) of a high fiber meal (cabbage) may have been predisposing factors for the development of a bezoar in an otherwise healthy women at the onset of old age. A total gastrectomy with esophagojejunostomy was performed and patient was discharged home after a 7-d hospital stay with no immediate complications. We also discuss some technical aspects of the procedure that might be important to reduce the incidence of this complication.

Key words: Gastric dilatation; Gastric outlet obstruction; Necrosis; Fundoplication; Nissen operation

Core tip: Gastric necrosis is a rare condition because of the rich blood supply and the extensive submucosal vascular network of the stomach. "Gas-bloat" syndrome is a Nissen fundoplication postoperative complication that causes gastric dilatation, but very rarely an ischemic compromise of the organ. We report a case of a 63-year-old women, who presented a total gastric necrosis following laparoscopic Nissen fundoplication and we discuss technical aspects of the procedure that are important to prevent this complication.

Salinas J, Georgiev T, González-Sánchez JA, López-Ruiz E, Rodríguez-Montes JA. Gastric necrosis: A late complication of nissen fundoplication. *World J Gastrointest Surg* 2014; 6(9): 183-186 Available from: URL: http://www.wjgnet.com/1948-9366/full/v6/i9/183.htm DOI: http://dx.doi.org/10.4240/wjgs.v6.i9.183

INTRODUCTION

The rich blood supply of the stomach preserves this viscera from ischemic events, even after the ligation of all the major vessels[1] (a. gastrica dextra, a. gastrica sinistra, a. gastro-omentalis dextra, a. gastro-omentalis sinistra and aa. gastricae breves). Notwithstanding this fact, acute gastric dilatation accompanied with or without gastric outlet obstruction[2-7], eating disorders[8-10] or gas-bloat syndrome are recognized causes of ischemic gastric necrosis.

The gas-bloat syndrome is defined as a variable group

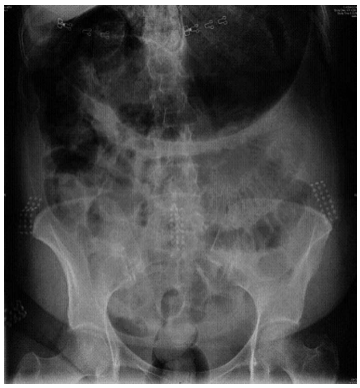

Figure 1 Plain abdominal radiography.

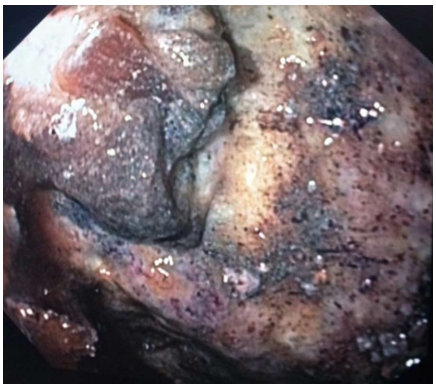

Figure 2 Gastric mucosal necrosis, endoscopic view.

of symptoms resulting from the inability to relieve gas from the stomach after fundoplication. It's incidence may vary from 1% to 85%[11]. Gastrointestinal gas may proceed either from an excessive production (carbohydrate or fat rich food, small intestinal bacterial overgrowth) or from an excess of swallowed air (disphagia secondary to orophagryngeal or esophageal motility disorders or anxiety disorders with inefficient chewing, gastroesophageal reflux disease, *etc.*). The predominant complaint is bloating, but other symptoms include abdominal distention, early satiety, nausea, upper abdominal pain, flatulence, inability to belch, and inability to vomit[11]. Antireflux surgery may contribute to the obstruction of gas blow into the esophagus by means of different mechanisms[12] (surgically altered physiology of the gastroesophageal junction, surgical injury to the vagus nerve, mechanic compression of the wrap), specially when associated to previous gastroesophageal motility disorders, such as delayed gastric emptying.

Delayed gastric emptying is a preexisting condition in many of the patients undergoing antireflux surgery. It is associated with gastroesophageal reflux disease (GERD) in up to 40% of patients, but Nissen fundoplication is known to accelerate gastric emptying and has a high rate of success controlling GERD-related symptoms[13], thus delayed gastric emptying is not a contraindication for antireflux surgery[14]. Nevertheless, a thoughtful preoperative assessment of esophagogastric motility with barium swallow is mandatory and may identify a subset of patients that will still have symptoms related to motility disorders postoperative.

Very few cases of near-total or total gastric necrosis following Nissen fundoplication have been reported. We present a case of gastric necrosis following laparoscopic Nissen fundoplication and pyloric obstruction by a phytobezoar.

CASE REPORT

A 63-year-old women was admitted to our Emergency Room with a history of sudden abdominal pain, without nausea or vomiting. No other symptoms were reported. Past medical history revealed acetylsalicylic acid intolerance, osteoporosis, supraspinatus rupture and gastroesophageal reflux disease secondary to a type I hiatal hernia, with a normal barium swallow esophagogastric motility pattern, a DeMeester of 33.1 and pathologic acid-clearance in pH-metry and a mild hypotonic lower esophageal sphincter in manometry, for which she underwent laparoscopic Nissen fundoplication 7 mo ago, with no postoperative complications and a 3-d hospital stay. The surgical record described a Rossetti-Nissen fundoplication without diversion of short gastric vessels (SGV), with a short wrap (3 cm) and suturing of the valve to the right crura. Treatment history revealed no medication that could interfere with upper digestive tract motility.

On physical examination, she was conscious, alert and oriented. Blood pressure was 123/75 mmHg with a pulse rate of 76/min. The abdomen was distended, painful to palpation with generalized peritonism and involuntary guarding in the epigastrium. Bowel sounds were diminished. Laboratory findings revealed: hemoglobin, 14.6 g/dL; hematocrit, 44.7%; white blood cell count, 18900/μL (with 15500 neutrophils); platelet count, 372000/μL; lactic dehydrogenase and amylase were elevated to 251 U/L (normal, 87-246 U/L) and 564 U/L (normal, 25-115 U/L), respectively. Arterial blood gases showed a metabolic acidosis with a blood pH of 7.23.

The patient was taken to the radiology department and plain abdominal films were performed (Figure 1). A gastroscopy was performed after X-rays, since a nasogastric tube couldn't be placed, and a wide area of mucosal necrosis was found in the posterior wall of the lesser curvature (Figure 2). In the operating room an extreme gastric dilatation was found with ischemic changes. The lesser sac was opened and dissection of the posterior gastric surface confirmed endoscopic findings. An anterior longitudinal gastrotomy was performed and trapped air was released. Suction of the gastric chamber through the gastrotomy revealed a phytobezoar in the pyloric channel. Total gastrectomy (Figure 3) with esophagojejunostomy and Roux-en-Y reconstruction was performed. The pathology (Figure 4) revealed a transmural submassive ischemic necrosis with intravascular thrombi. After a postoperative period without complications, the patient was successfully discharged home.

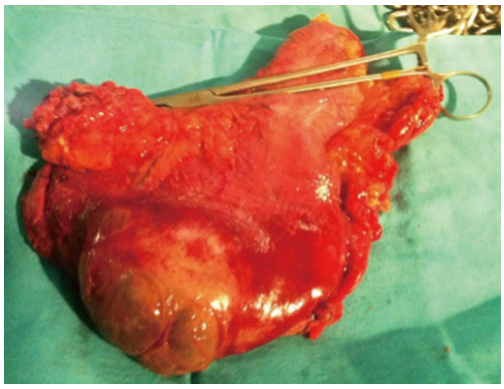

Figure 3 Transmural gastric necrosis, total gastrectomy surgical specimen.

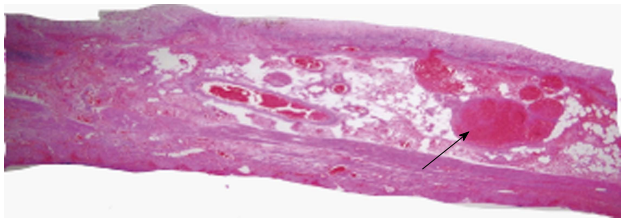

Figure 4 Submassive transmural gastric necrosis with intravascular thrombi (arrow); Hematoxilin-Eosin stain.

DISCUSSION

Gastric dilatation is a minor postoperative complication that can eventually occur after major surgery. This condition usually resolves spontaneously or with the insertion of a nasogastric tube for gastric decompression. On the contrary, ischemic necrosis following extreme gastric dilatation is a very rare phenomenon and requires urgent diagnosis and surgical treatment.

Clinical manifestations of the "gas-bloat" syndrome (abdominal pain, distension, tympanic percussion, *etc.*) are common to many other abdominal pathologies, that without a full comprehension of the surgical history, may delay the diagnosis with the increased morbidity and mortality that this entails. Early surgical consult for the evaluation of patients with abdominal pain and surgical history is vital in the emergency room context and decisive for patient outcome.

In the Nissen antireflux procedure, compression of the distal oesophagus by the gastric wrap is required to ensure the one-way valve effect that prevents gastric reflux. Expelling trapped air and belching is therefore sometimes hindered, resulting in a progressive gastric dilatation. Thanks to the anterograde propulsion, which works as an exhaust valve, this condition is intermittent. When anterograde propulsion is totally or partially blocked, gastric distension progressively tightens the periesophageal wrap, thus increasing the intragastric pressure and compromising blood flow. Some studies have shown that an intragastric pressure greater than 20-30 cm H_2O is necessary to cause the occlusion of the gastric luminal blood circulation[15]. Cases of gastric necrosis following acute small bowel obstruction based on adhesions and gastric outlet obstruction based on antral gastric cancer and trichophytobezoar after an antireflux technique[3-5] have been reported. In infants, this rare post Nissen complication has also been described[16]. In the case we present, the trigger event was a phytobezoar causing pyloric obstruction.

Since 1955, when Rudolph Nissen performed his first fundoplication, many other procedures that try to reduce the incidence of postoperative complications, including the "gas-bloat" syndrome, have been developed, without a loss of effectiveness in preventing gastroesophageal reflux disease, as demonstrated in several randomized controlled trials and long case series[17-20].

Nevertheless, due to the lack of long-term effectiveness data, it is hard to recommend one type of fundoplication over an other, and Rossetti-Nissen laparoscopic fundoplication still a valid and widespread procedure with a low rate of postoperative complications[17], when performed by trained surgeons. Some technical aspects during a Nissen fundoplication are important, specially for the novice surgeon, and should be considered to avoid surgery-related complications, including the "gas-bloat" syndrome. This may include a short wrap (typically no more than 2 cm), instead of a long one, or the systematic division of the SGV to facilitate a tension-free wrapping[21,22]. The latter is controversial and some prospective randomized trials have proven the contrary: a higher incidence of gas-bloat syndrome when the SGV are divided[23]. In the case presented, no division of the gastric short vessels was performed, but a floppy fundoplication was achieved, and the patient referred no complaints in follow-ups. So the authors do not consider that the preservation of the gastric short vessels was a contributing factor in this particular case.

An important issue to be also remarked is the importance of identifying patients with anxiety and comfort or binge eating conducts, which could have been disregarded in the preoperative consult, and that could potentially have higher risk of complications in the long term. Antidepressant medication and early psychiatric consult might be necessary.

COMMENTS

Case characteristics

The only symptom referred by the patient was sudden and intense pain in epigastrium.

Clinical diagnosis

Main clinical findings were upper abdominal distension, tympanic percussion and peritoneal irritation.

Differential diagnosis

Differential diagnosis was mainly based on past surgical history: acute gastric dilatation *vs* small bowell obstruction.

Laboratory diagnosis

Laboratory findings were congruent with an acute inflammatory process with poor splacnic perfusion: high leukocyte count and high lactic dehydrogenase and amylase.

Imaging diagnosis

Plain abdominal X-ray is more than adequate to diagnose gastric distension, but a computed tomography-scan may be also helpful to note ischemic changes

and involvement.

Pathological diagnosis

Routine Hematoxylin-Eosin stain was performed to find out ischemic tissue injuries.

Treatment

Surgery was mandatory in this case based on clinical and analytical findings, and a total gastrectomy was performed.

Experiences and lessons

Antireflux surgery, although it might not be of extreme complexity, it is not free of severe complications and common pitfalls such as long or tightened wraps should be avoided. Also, patients with antireflux surgery and anxiety symptoms or eating disorders should be recognized and properly treated with psychiatric consult if necessary.

Peer review

The case report is useful as it serves to highlight that fundoplication can have serious complications.

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CASE REPORT

Retroanastomotic hernia after Moynihan's gastroenterostomy

Kerem Karaman, Omer Yalkin, Metin Ercan, Hakan Demir, Fatih Altintoprak, Ismail Zengin

Kerem Karaman, Metin Ercan, Fatih Altintoprak, Department of General Surgery, Faculty of Medicine, Sakarya University, Serdivan 54130, Sakarya, Turkey
Omer Yalkin, Hakan Demir, Ismail Zengin, Department of General Surgery, Sakarya Teaching and Research Hospital, Serdivan 54130, Sakarya, Turkey
Author contributions: All the authors contributed equally to this work.
Correspondence to: Kerem Karaman, MD, Department of General Surgery, Faculty of Medicine, Sakarya University, No: 76 Atioglu Sitesi B Blok Kapısı Girisi Daire: 4, Serdivan 54130, Sakarya, Turkey. karaman_kerem@yahoo.com.tr
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Abstract

Retroanastomotic hernias after gastroenterostomies-either antecolic or retrocolic-are extremely rare but are associated with high mortality rates due to delayed identification which precludes immediate surgical reduction. In this report, we present a 77-year-old man with retroanastomotic herniation of the efferent loop segments that occurred 14 years after a Moynihan's gastroenterostomy.

Key words: Retroanastomotic hernia; Moynihan's gastroenterostomy; Intestinal obstruction

Core tip: Retroanastomotic hernia is a rare but fatal condition. Preoperative diagnosis by ultrasound and/or computerized tomography is difficult and sometimes confusing. Early surgery is the key to decreasing mortality. The use of a short afferent loop and closure of the retroanastomotic space would decrease the incidence of these hernias.

Karaman K, Yalkin O, Ercan M, Demir H, Altintoprak F, Zengin I. Retroanastomotic hernia after Moynihan's gastroenterostomy. *World J Gastrointest Surg* 2014; 6(9): 187-189 Available from: URL: http://www.wjgnet.com/1948-9366/full/v6/i9/187.htm
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INTRODUCTION

Retroanastomotic hernias after gastroenterostomies-either antecolic or retrocolic-are extremely rare but are associated with high mortality rates due to a delay in identification which precludes immediate surgical reduction[1]. Since Petersen[2] provided the first detailed description of a retroanastomotic hernia known as Petersen's hernia in 1900, there have been few case reports or case series in the literature referring to this entity. In this report, we present a 77-year-old man with retroanastomotic herniation of the efferent loop segments that occurred 14 years after a Moynihan's gastroenterostomy.

CASE REPORT

A 77-year-old man presented with a sudden onset of acute abdominal pain accompanied by nausea and vomiting. The physical examination revealed rebound tenderness with abdominal distention. Abdominal computed tomography showed edematous bowel wall thickening in proximal small bowel segments and dense fluid collection in the right upper quadrant which was considered an indication of visceral organ perforation (Figure 1A). The patient underwent a subtotal gastrectomy for duodenal ulcer 14 years ago. During explorative laparotomy, a retroanastomotic hernia of the efferent loop segments, passing from right to left through the orifice between the transverse colon and the antecolic, antiperistaltic gastrojejunostomy anastomosis (Moynihan type), was found (Figure 1B-D). The herniated bowel segments were reduced and the defect was closed with running sutures. Viability of the ischemic bowel segments improved after application of warm pads and the abdomen was closed without further intervention. The postoperative course was un-

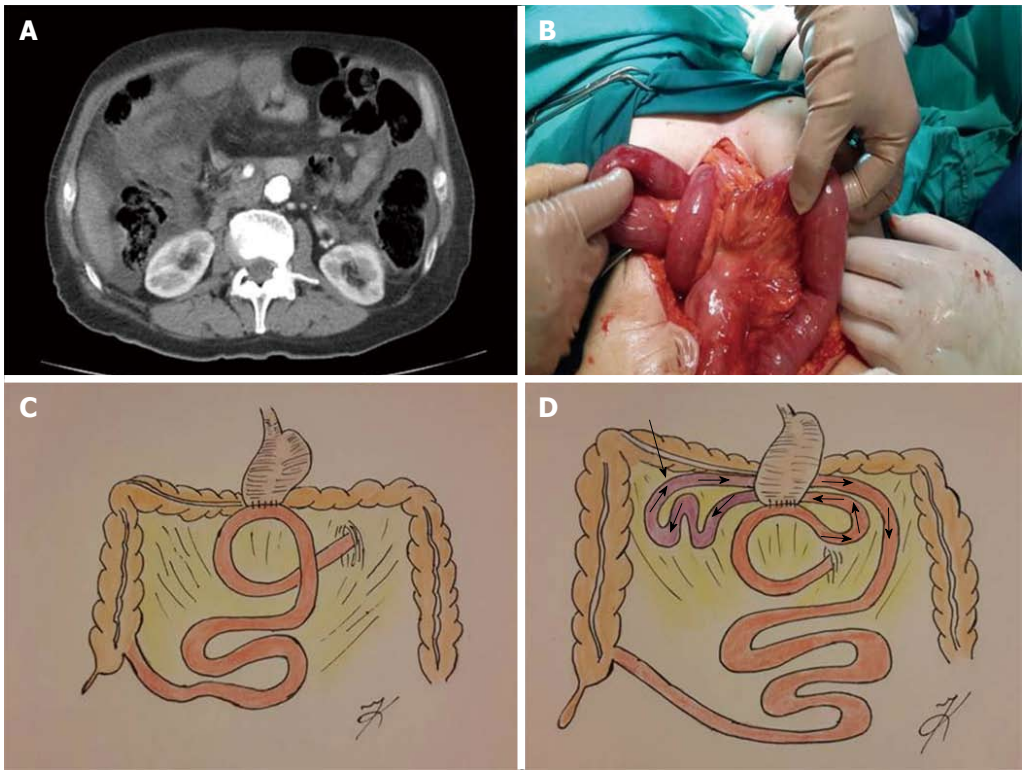

Figure 1 Illustration of diagnosis and treatment of the present case. A: Abdominal computed tomography image of the retroanastomotic hernia; B: Intraoperative image of the retroanastomotic herniation; C: Illustration of the original operation (Moynihan's gastroenterostomy); D: Illustration of the retroanastomotic herniation of the present case with a black arrow showing the incarcerated bowel segments of the efferent loop.

eventful and the patient was discharged on the fifth postoperative day.

DISCUSSION

Herniation of intestinal loops through the defect between the small bowel limbs can occur after any type of gastrojejunostomy[3,4]. Half of all retroanastomotic hernias occur within the first postoperative month; more than half of the remaining during the first year, and a small percentage even later[5]. Efferent loop hernias occur three times more than those involving the afferent loop. For afferent loop hernias, pain is localized to the epigastric region and is constantly sudden in onset. Vomiting is infrequent and bile is almost absent, if not at all. On the other hand, in efferent loop hernias, abdominal pain is more generalized and colicky, and vomiting with bile stained material is common[1]. Preoperative diagnosis by ultrasound and/or computed tomography is difficult and sometimes confusing: the most frequently detected signs are mural thickening and dilatation of the herniated bowel loops[6].

Efferent loop hernias usually occur from right to left. In the present case, however, the direction of the herniation was from left to right, which may be related to the type of gastroenterostomy (Moynihan type). Another important characteristic of the present case was the long duration of the disease without any signs.

In conclusion, retroanastomotic hernias, though rare, are a potentially fatal condition. Early surgery is the key to decreasing mortality. The use of a short afferent loop and closure of the retroanastomotic space would decrease the incidence of these hernias.

COMMENTS

Case characteristics

A 77-year-old man presented with retroanastomotic herniation of the efferent loop segments that occurred 14 years after a Moynihan's gastroenterostomy.

Clinical diagnosis

Retroanastomotic herniation of efferent loop segments after the antecolic gastrojejunostomy anastomosis.

Differential diagnosis

Acute abdomen due to visceral organ perforation.

Laboratory diagnosis

White blood cells: 16.400/mm^3; hemoglobin: 121.0 g/L. Metabolic panel and liver function test were within normal limits.

Imaging diagnosis

Computed tomography showed edematous bowel wall thickening in proximal small bowel segments and dense fluid collection in the right upper quadrant which was considered an indication of visceral organ perforation.

Treatment

Reduction of the herniated efferent loop segments and primary closure of the hernia defect.

Related reports

There have been few case reports or case series in the literature referring to this entity.

Term explanation

Retroanastomotic hernias after gastroenterostomies-either antecolic or retrocolic-are extremely rare but are associated with high mortality rates due to a delay in identification which precludes immediate surgical reduction.

Experiences and lessons

Retroanastomotic hernias, though rare, are a potentially fatal condition. Early

surgery is the key to decreasing mortality. The use of a short afferent loop and closure of the retroanastomotic space would decrease the incidence of these hernias.

Peer review

This article is referring a rare complication of gastroenterostomy anastomosis and discusses the possible causes and preventive approaches.

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ORIGINAL ARTICLE

Hydatid cyst of the pancreas: Report of an undiagnosed case of pancreatic hydatid cyst and brief literature review

Sami Akbulut, Ridvan Yavuz, Nilgun Sogutcu, Bulent Kaya, Sinan Hatipoglu, Ayhan Senol, Firat Demircan

Sami Akbulut, Ridvan Yavuz, Firat Demircan, Department of Surgery, Diyarbakir Education and Research Hospital, Diyarbakir 21400, Turkey
Nilgun Sogutcu, Department of Pathology, Diyarbakir Education and Research Hospital, Diyarbakir 21400, Turkey
Bulent Kaya, Department of Surgery, Kanuni Sultan Suleyman Education and Research Hospital, Istanbul 34303, Turkey
Sinan Hatipoglu, Department of Surgery, Adiyaman University Faculty of Medicine, Adiyaman 02040, Turkey
Ayhan Senol, Department of Radiology, Ergani State Hospital, Diyarbakir 21950, Turkey
Author contributions: Akbulut S, Kaya B and Hatipolgu S designed the report; Akbulut S and Yavuz R were the attending doctors for the patients; Akbulut S, Yavuz R and Demircan F performed the surgical operation; Akbulut S organized the report and wrote the paper; Senol A provided the radiological information; Sogutcu N provided the histopathological information.
Correspondence to: Sami Akbulut, MD, FICS, FACS, Department of Surgery, Diyarbakir Education and Research Hospital, Uckuyular Mevki, Kayapinar, Diyarbakir 21400, Turkey. akbulutsami@gmail.com
Telephone: +90-412-2580052 Fax: +90-412-2580050
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Abstract

AIM: To overview the literature on pancreatic hydatid cyst (PHC) disease, a disease frequently misdiagnosed during preoperative radiologic investigation.

METHODS: PubMed, Medline, Google Scholar, and Google databases were searched to identify articles related to PHC using the following keywords: hydatid cyst, hydatid disease, unusual location of hydatid cyst, hydatid cyst and pancreas, pancreatic hydatid cyst, and pancreatic echinococcosis. The search included letters to the editor, case reports, review articles, original articles, meeting presentations and abstracts that had been published between January 2010 and April 2014 without any restrictions on language, journal, or country. All articles identified and retrieved which contained adequate information on the study population (including patient age and sex) and disease and treatment related data (such as cyst size, cyst location, and clinical management) were included in the study; articles with insufficient demographic and clinical data were excluded. In addition, we evaluated a case of a 48-year-old female patient with PHC who was treated in our clinic.

RESULTS: A total of 58 patients, including our one new case, (age range: 4 to 70 years, mean ± SD: 31.4 ± 15.9 years) were included in the analysis. Twenty-nine of the patients were female, and 29 were male. The information about cyst location was available from studies involving 54 patients and indicated the following distribution of locations: pancreatic head (n = 21), pancreatic tail (n = 18), pancreatic body and tail (n = 8), pancreatic body (n = 5), pancreatic head and body (n = 1), and pancreatic neck (n = 1). Extra-pancreatic locations of hydatid cysts were reported in the studies involving 44 of the patients. Among these, no other focus than pancreas was detected in 32 of the patients (isolated cases) while 12 of the patients had hydatid cysts in extra-pancreatic sites (liver: n = 6, liver + spleen + peritoneum: n = 2, kidney: n = 1, liver + kidney: n = 1, kidney + peritoneum: n = 1 and liver + lung: n = 1). Serological information was available in the studies involving 40 patients, and 21 of those patients were serologically positive and 15 were serologically negative; the remaining 4 patients underwent no serological testing. Information about pancreatic cyst size was available in the studies involving 42 patients; the smallest cyst diameter reported was 26 mm and the largest cyst diameter reported was 180 mm (mean ± SD: 71.3 ± 36.1 mm). Complications were available in the studies of 16 patients and showed the following distribution: cystobiliary fistula (n = 4), cystopancreatic fistula (n = 4), pancreatitis (n = 6), and portal hypertension (n = 2). Postoperative follow-up data were available in the studies involving 48 patients and postoperative recurrence data in the studies of 51 patients; no cases of recurrence occurred in any

patient for an average follow-up duration of 22.5 ± 23.1 (range: 2-120) mo. Only two cases were reported as having died on fourth (our new case) and fifteenth days respectively.

CONCLUSION: PHC is a parasitic infestation that is rare but can cause serious pancreato-biliary complications. Its preoperative diagnosis is challenging, as its radiologic findings are often mistaken for other cystic lesions of the pancreas.

Key words: Echinococcosis; Hydatid cyst; Pancreas; Pancreaticoduodenectomy

Core tip: Hydatid disease is a zoonotic disease caused by the Echinococcus parasite, which belongs to the Taeniidae family of the Cestode class. Although hydatid cysts can be found in almost any tissue or organ of the human body, the liver, lung, spleen, and kidney are the most commonly affected. Pancreatic hydatid cyst (PHC) disease is rare, even in regions where hydatidosis is endemic. Yet, PHC disease is associated with severe complications, such as jaundice, cholangitis, and pancreatitis. These complications often develop as a result of fistulization of the cyst content into pancreato-biliary ducts or external compression of those ducts by the cyst.

Akbulut S, Yavuz R, Sogutcu N, Kaya B, Hatipoglu S, Senol A, Demircan F. Hydatid cyst of the pancreas: Report of an undiagnosed case of pancreatic hydatid cyst and brief literature review. *World J Gastrointest Surg* 2014; 6(10): 190-200 Available from: URL: http://www.wjgnet.com/1948-9366/full/v6/i10/190.htm DOI: http://dx.doi.org/10.4240/wjgs.v6.i10.190

INTRODUCTION

Hydatid disease, also known as echinococcal disease, is a zoonotic disease caused by the Echinococcus parasite belonging to the Taeniidae family of the Cestode class. Four different Echinococcus species have been defined as causative agents of hydatid disease in humans[1,2]. The most common species encountered in humans are the Echinococcus granulosus (E. granulosus), which causes cystic echinococcosis, and the Echinococcus multilocularis, which causes alveolar echinococcosis[1,2]. E. granulosus is responsible for 95% of the human hydatid cases reported. In the biological life cycle of hydatid disease, carnivores are the definitive hosts while herbivores are the intermediary hosts. Humans themselves have no role in the biological life cycle and are usually infected after inadvertent ingestion of Echinococcus eggs in canine feces[1,2]. The disease continues to be a major public health issue in many regions of the world where agriculture and stockbreeding are primary sources of income. Although hydatid cysts can localize to almost any tissue or organ of the human body, the liver (50%-77%), lung (15%-47%), spleen (0.5%-8%), and kidney (2%-4%) are the most commonly involved organs[2-5].

Pancreatic hydatid cyst (PHC) disease is rare, even in regions where hydatidosis is endemic[4-7]. While the reported incidences of PHC have varied in different studies, the rates are consistently below 1%. PHC may develop as a primary (involving the pancreas only) or secondary (with multiple organ involvement) disease[6]. Since hydatid cysts grow slowly, a considerable portion of affected patients may remain asymptomatic for years. In symptomatic patients, however, the symptoms are varied and depend on location, size, and position relative to neighboring organs[4]. The most serious complications in PHC disease are jaundice, cholangitis, and pancreatitis, all of which can develop as a result of fistulization of the cyst content into pancreato-biliary ducts or external compression of those ducts by the cyst. Clinical tools routinely used to diagnose PHC are ultrasonography (USG), computed tomography (CT), magnetic resonance cholangiopancreatography (MRCP), endoscopic ultasound (EUS), endoscopic retrograde cholangiopancreatography (ERCP), and serological testing[4]. Despite the advanced radiological imaging instruments in use, though, it is not always easy to differentiate hydatid cysts from common cystic neoplasms of the pancreas[4,8]. Thus, hydatid cyst disease should be considered in the differential diagnosis of pancreatic cystic lesions, especially in patients living in endemic areas. In this study, we review the cases of PHC in the literature and present a new PHC patient who was treated at our clinic to provide a comprehensive discussion of this disease and its features relevant to diagnosis and management.

MATERIALS AND METHODS

The primary aim of this study was to review cases of PHC published in the literature within the last 4.5 years. To this end, a literature search was made of the PubMed, Medline, Google Scholar, and Google databases using the keywords hydatid cyst, hydatid disease, unusual location of hydatid cyst, hydatid cyst and pancreas, pancreatic hydatid cyst, and pancreatic echinococcosis (alone or in different combinations). All identified abstracts, case reports, letters to the editor, review articles, original articles, and other documents were reviewed. No language filter was set and the review period was set from January 2010 to April 2014. Reference lists of the retrieved articles were also examined to identify citations that complied with our inclusion criteria. Corresponding authors of the articles were contacted by email to obtain more detailed information about the patients. Articles without an accessible full-text version or those providing insufficient information or insufficient data for comparison with other studies were excluded. A table (Table 1) was generated using the following information: publication year, country, and language; patient age, sex, and complaint; cyst

Table 1 Summary of demographic and clinic characteristics patients (*n* = 57) with pancreatic hydatid cyst published in the medical literature between January 2000 and April 2014

Ref.	Year	Country	Language	Paper type	Case count	Age (yr)	Sex	Complaint/examination findings	Cyst location	Cyst size (mm)	Serology
Trigui *et al*[4]	2013	Tunisia	English	Article	12	21	F	Epigastric mass + epigastric pain	Tail	NS	NS
						13	M	Epigastric pain + RUQ pain	Tail + Body	NS	NS
						15	M	Jaundice + RUQ pain	Head	NS	NS
						26	M	Epigastric pain	Head	NS	NS
						50	F	Epigastric pain	Head	NS	NS
						37	F	Jaundice + RUQ pain	Head	25	Negative
						8	M	Jaundice + RUQ pain	Head	83 × 76	Positive
						26	F	Pancreatitis + epigastric pain	TaİL + body	40	Positive
						61	F	Epigastric pain	Tail	NS	Positive
						11	F	Jaundice + RUQ pain	Head	NS	Negative
						16	F	Epigastric pain	Body	NS	Positive
						11	F	Jaundice + epigastric mass + RUQ pain	Head	50	NS
Yarlagadda *et al*[5]	2013	India	English	Case Report	1	43	M	Epigastric mass	Tail	180 × 170	NS
Patil *et al*[6]	2013	India	English	Case Report	1	47	M	Epigastric mass	Tail + Body	100 × 80	Positive
Kaushik *et al*[7]	2013	India	English	Case Report	1	18	F	LUQ pain	Tail	65 × 63	NS
Baghbanian *et al*[8]	2013	Iran	English	Case Report	1	46	M	Epigastric pain + fever	Tail	60 × 50	NS
Gundes *et al*[9]	2013	Turkey	Turkish	Case Report	2	24	F	Back pain	NS	70	NS
						50	F	Abdominal pain	Head	50	NS
Mandelia *et al*[10]	2012	India	English	Case Report	1	6	M	Jaundice + fever + epigastric mass	Head	54 × 41	Not-done
Kushwaha *et al*[11]	2012	India	English	Case Report	1	40	M	Epigastric mass + epigastric pain	Tail + Body	NS	Positive
Makni *et al*[12]	2012	Tunisia	English	Review	1	38	M	Abdominal pain + vomiting + nausea	Tail + Body	100 × 90	Positive
Karaman *et al*[13]	2012	Turkey	English	Case Report	1	32	M	Epigastric pain	Neck	55 × 45	Positive
Rayate *et al*[14]	2012	India	English	Case Report	1	30	F	Abdominal pain	Tail	62 × 57	Positive
Suryawanshi *et al*[15]	2011	India	English	Case Report	1	20	M	Epigastric mass + epigastric pain	Head	80 × 80	NS
Varshney *et al*[16]	2011	India	English	Case Report	1	35	M	Abdominal pain + vomiting + nausea	Tail	NS	Positive
Somani *et al*[17]	2011	India	English	Case Report	1	30	F	Epigastric mass + epigastric pain	Head	NS	NS
Masoodi *et al*[18]	2011	India	English	Case Report	1	45	M	LUQ mass	Tail	70 × 60	Positive
Makni *et al*[19]	2011	Tunisia	English	Case Report	1	30	F	Epigastric mass + discomfort	Body	80	Positive
Bhat *et al*[20]	2011	India	English	Case Report	1	4	F	Jaundice + epigastric mass	Head + Body	150 × 100	Negative
Cankorkmaz *et al*[21]	2011	Turkey	English	Case Report	1	7	F	Epigastric mass + weight loss	Tail + Body	70 × 60	Negative
Dalal *et al*[22]	2011	India	English	Case Report	1	48	M	Epigastric fullness + fever	Tail	80 × 50	Not-done
Agrawal *et al*[23]	2011	India	English	Case Report	1	5	F	Jaundice + abdominal pain	Head	120 × 100	NS
Küçükkartallar *et al*[24]	2011	Turkey	Turkish	Case Report	1	48	F	Abdominal pain	Head	28 × 25	Negative
Tavusbay *et al*[25]	2011	Turkey	English	Case Report	1	50	M	Abdominal mass	NS	NS	Positive
Derbel *et al*[26]	2010	Tunisia	English	Article	7	25	F	LUQ mass + LUQ pain	Tail	60	Negative
						19	F	Epigastric mass + RUQ pain	Tail	70	Negative
						32	F	Epigastric pain	Tail + body (two cyst)	150	Positive
						41	M	LUQ mass + LUQ pain + fever	NS	150	Negative
						38	M	Jaundice + epigastric pain	Head	50	Negative
						29	M	Jaundice + epigastric mass	Head	60	Negative
						25	F	LUQ pain + vomiting	Tail + Body	90	Positive
Bansal *et al*[27]	2010	India	English	Case Report	1	30	F	Jaundice + epigastric mass	Head	80 × 60	Not-done
Boubbou *et al*[28]	2010	Morocco	English	Case Report	1	38	M	Jaundice + epigastric pain	Head	NS	NS
Shah *et al*[29]	2010	India	English	Article	6	46	M	Epigastric pain	Tail	28	Positive
						37	F	Epigastric mass + vomiting	Body	26	Positive
						18	M	Dyspepsia	Body	33	Positive
						22	F	Epigastric pain	Tail	48	Negative
						28	M	Jaundice	Head	50	Positive
						68	M	Jaundice	Head	35	Negative
Karakas *et al*[30]	2010	Turkey	English	Letter	1	18	M	Abdominal pain + fever	Body	70 × 45	Negative
Diop *et al*[31]	2010	France	English	Case Report	1	29	M	Acute pancreatitis	Tail	35 × 25	Positive
Szanto *et al*[32]	2010	Romania	English	Case Report	1	49	F	Epigastric pain + bloating + vomiting	Tail	NS	NS
Cağlayan *et al*[33]	2010	Turkey	English	Article	1	70	M	NS	NS	NS	Positive
Orug *et al*[34]	2010	Turkey	English	Case Report	2	26	M	Abdominal pain + fatique + vomiting	Tail	115 × 95	NS
						57	F	Epigastric pain + weight loss	Tail	45 × 35	NS
Chammakhi-Jemli *et al*[35]	2010	Tunisia	French	Case Report	1	32	F	Acute pancreatitis + epigastric mass	Tail	80	Negative

Elmadi *et al*[36]	2010	Morocco	French	Case Report	1	7	M	Jaundice + fever + RUQ pain	Head	NS	Negative

RUQ: Right upper quadrant; LUQ: Left upper quadrant; NS: Not-stated.

location and size; results of serologic tests and radiologic examinations; surgical approach, intraoperative complications, postoperative medical management, recurrence, and follow-up (months). In addition, important notes from the studies were summarized in a single sentence.

We also present a case of a 48-year-old woman with PHC who was treated at our clinic and who ultimately died after follow-up. The aim of this case presentation is to emphasize the grave consequences of benign hydatid cyst disease when undiagnosed by preoperative radiological examinations or not considered by a radiologist in differential diagnosis.

RESULTS

Literature review

A literature search using the above review criteria retrieved a total of 33 articles containing 57 cases about PHC disease[4-36]. Of these, 15 articles were from India, 8 from Turkey, 5 from Tunisia, 2 from Morocco, and 1 each from Iran, France and Romania. Twenty-two cases were reported from Tunisia, 20 from India, 10 from Turkey, 2 from Morocco, and 1 each from France, Iran and Romania. Twenty-nine articles were written in English, 2 in Turkish, and 2 in French. The current analysis, therefore, included a total of 58 patients (including our one new case), represented by 29 (50%) females and 29 (50%) males, aged 4 to 70 (mean ± SD: 31.4 ± 15.9) years. The age range of the males was 6 to 70 (mean ± SD: 33.4 ± 16.2) years and that of the females was 4 to 61 (mean ± SD: 29.4 ± 15.4) years. Cyst location in pancreas was reported for 54 patients, wherein the cyst was localized to the pancreatic head in 21 (38.8%), the pancreatic tail in 18 (33.3%), the pancreatic body and tail in 8 (14.8%), the pancreatic body in 5 (9.2%), the pancreatic head and body in 1, and the pancreatic neck in 1. Extra-pancreatic location of hydatid cysts was reported for 44 patients. Among these, 32 (72.7%) had no other foci other than pancreas (isolated) while the remaining 12 patients had extra-PHC as follows: liver, n = 6; liver + spleen + peritoneum, n = 2; kidney, n = 1; liver + kidney = 1; kidney + peritoneum = 1; and liver + lung, n = 1. Serological data were available from reports of 40 patients, of which 21 (54%) were serologically positive and 15 (38%) were serologically negative; the remaining 4 patients underwent no serological testing. Information about pancreatic cyst size was available for 42 patients; the smallest cyst diameter was 26 mm and the largest cyst diameter was 180 mm (mean ± SD: 71.3 ± 36.1 mm). Postoperative follow-up information was available for 48 patients and postoperative recurrence information for 51 patients. During the average follow-up duration of 22.5 ± 23.1 (range: 2-120) mo, none of the patients developed recurrence. Only two patients (our new case) died on postoperative day 4 and 15 respectively. Tables 1 and 2 provides detailed information regarding chief demographic data of the 57 patients included in the study.

A 48-year-old woman presented to our outpatient clinic with malaise, fatigue, pruritus, yellowish discoloration of the eyes, darkening of urine color, and acholic gaita. She explained that her complaints, except for jaundice, had started 2 mo previous and the jaundice developed 15 d ago. On physical examination, her sclerae were icteric and whole body was jaundiced. Biochemical tests revealed the following results: aspartate aminotransferase (AST): 205 U/L; alanine aminotransferase (ALT): 673 U/L; total bilirubin: 11.6 mg/dL; direct bilirubin: 9.3 mg/dL; hemoglobin: 13 g/dL; platelet count: 244000/μL; white blood cell count: 5000/μL; carbohydrate antigen 19-9: 45 U/mL (normal range: 0-39). Ultrasonography showed that her gall bladder was hydropic and that the common bile duct and intrahepatic bile ducts were dilated. In addition, a 50 mm × 43 mm anechoic lesion consistent with choledococele was detected in the distal common bile duct. A MRCP was performed and showed a common bile duct diameter of 11 mm, dilated intrahepatic bile ducts, and a 4.5 cm mass in the pancreatic head, which appeared hyperintense on T2A imaging and caused stenosis in the distal tip of the common bile duct (Figure 1). An ERCP showed no intraluminal mass lesion. The consensus of a gastroenterologist and a radiologist was that this lesion could be a choledococele or duodenal diverticulum. Considering the above findings, a laparotomy was scheduled, in which the abdomen was entered *via* a midline incision followed by opening of the gastrocolic ligament and application of the Kocher maneuver. A mass lesion of 5 cm × 5 cm was observed in the pancreatic head, and appeared to be malignant. The common bile duct was markedly dilated. Based on preoperative tests and the intraoperative appearance of the pancreatic head, the mass was regarded as a malignant lesion, and a pancreaticoduodenectomy with pyloric preservation was performed without any intraoperative complications. On post-surgery day 1, the patient's liver function tests were abnormal and her blood pressure dropped. Yet, radiological tests revealed no abnormalities. Since her blood pressure and pulse continued to deteriorate substantially, the patient was taken back to the operating room. During laparotomy, it was observed that all intestinal segments were filled with abundant blood. A regional exploration revealed a pulsatile bleeding focus from a location close to the Wirsung canal in the intestinal lumen. The bleeding was stopped, and the patient was admitted to the intensive care unit. Unfortunately, the profound coagulopathy that developed in the patient could not be reverted and she died on postoperative day 4. A detailed examination of the pathology specimen demonstrated that the mass had characteristics consistent with a hydatid cyst (Figures

Table 2 Detailed information regarding chief demographic data of the 57 patients included in the study

Ref.	Radiology	Surgical approach	Complication	Medical treatment	Recurrence	Follow-up (mo)	Other hydatid cyst focuses
Trigui *et al*[4]	NS	Distal pancreatectomy	No	NS	No	24	NS
	USG + CT	Partial cystectomy + drainage	Hemorrhage	NS	No	36	Liver + spleen + peritoneum
	USG + CT	Partial cystectomy + drainage	Pancreatic fistula	NS	No	24	Liver
	USG + CT	Partial cystectomy + drainage	Cavity infection	NS	No	NS	Liver + lung
	USG + CT	Partial cystectomy + drainage	Pancreatic fistula	NS	No	5	No
	USG + CT	Pancreaticoduodenectomy	Hemorrhage	NS	No	9	NS
	USG + CT	Partial cystectomy + duodenal fistula treatment	No	NS	No	24	NS
	USG + CT	Distal pancreatectomy + splenectomy	No	NS	No	36	Liver
	USG + CT	Distal pancreatectomy + splenectomy	No	NS	No	36	NS
	USG + CT	Cysto-duodenal anastomosis	No	NS	No	NS	Liver
	USG + CT	Partial cystectomy + drainage	No	NS	No	24	NS
	USG + CT	Cysto-duodenal anastomosis	No	NS	No	NS	NS
Yarlagadda *et al*[5]	USG + CT	Distal pancreatectomy + splenectomy	No	Albendazole-6 mo	No	6	No
Patil *et al*[6]	USG + CT	Distal pancreatectomy	No	Albendazole-3 wk	No	6	No
Kaushik *et al*[7]	USG + CT	Total cystectomy + marsupialisation	No	Albendazole-3 wk	No	6	NS
[1]Baghbanian *et al*[8]	USG + CT	Distal pancreatectomy + necrozectomy + partial nephrectomy	Died (POD15)	No	Died	Died	Kidney
Gundes *et al*[9]	NS	Partial cystectomy + omentoplasty	Wound infection	Albendazole-4 mo	No	NS	NS
	CT	Partial cystectomy + omentoplasty	Wound infection	Albendazole-4 mo	No	NS	No
[2]Mandelia *et al*[10]	USG + MRCP	Enucleation + cholangiography	No	Albendazole-3 wk	No	24	No
Kushwaha *et al*[11]	USG + CT	PAIR + epigastric cyst excision	Pancreatitis	Albendazole-3 mo	No	6	Kidney + peritoneum
Makni *et al*[12]	CT	Distal pancreatectomy + splenectomy	No	Albendazole-3 mo	No	8	No
[3]Karaman *et al*[13]	USG + CT	Percutaneous drainage	No	Albendazole-2 mo	No	18	No
Rayate *et al*[14]	USG + CT	Distal pancreatectomy	No	Albendazole-2 mo	No	7	No
[4]Suryawanshi *et al*[15]	USG + CT	Cyst evacuation + omentoplasty-laparoscopic	No	Albendazole-3 mo	No	3	No
[5]Varshney *et al*[16]	CT	Distal pancreatectomy	No	Albendazole-3 wk	No	10	No
[6]Somani *et al*[17]	USG + CT + ERCP	Pancreaticoduodenectomy	No	Albendazole-6 mo	NS	6	NS
[7]Masoodi *et al*[18]	USG + CT	Distal pancreatectomy + splenectomy	Hyperglisemia?	Albendazole-1 mo	No	6	No
Makni *et al*[19]	USG	Distal pancreatectomy + splenectomy	Pancreatic fistula	Albendazole-3 mo	No	8	No
Bhat *et al*[20]	USG + CT	Partial cystectomy + drainage	No	Albendazole-3 mo	No	24	No
[8]Cankorkmaz *et al*[21]	USG + CT	Partial cystectomy + drainage	Pancreatic fistula	NS	No	24	No
[9]Dalal *et al*[22]	USG + CT	Cyst excision along with tail of the pancreas	No	Albendazole-6 mo	No	8	No
[10]Agrawal *et al*[23]	USG + MRCP	Enucleation + cholangiography + cholecystectomy + cystography	No	Albendazole-2 mo	NS	NS	NS
[11]Küçükkartallar *et al*[24]	USG + CT + MRCP	Partial cystectomy + omentoplasty	No	Albendazole-4 mo	No	10	No
[12]Tavusbay *et al*[25]	USG + CT	Partial cystectomy + omentoplasty + splenectomy + mesenteric cyst excision	Wound infection	Albendazole-6 mo	No	12	Liver + spleen + peritoneum
[13]Derbel *et al*[26]	USG + CT	Partial cystectomy	No	No	No	35	No
	USG + CT	Partial cystectomy (for all cysts)	No	Albendazole-6 mo	No	9	Liver (13 cyst)
	USG + CT	Partial cystectomy for both pancreatic cysts	No	No	No	6	No
	USG + CT	Distal pancreatectomy	No	No	No	9	No
	USG + CT	Partial cystectomy (for all cyst)	Acute pancreatitis	Albendazole-6 mo	No	14	Liver
	USG + CT + MRI	Partial cystectomy	No	No	No	16	No
	USG + CT	Distal pancreatectomy + splenectomy	No	No	No	2	No
[14]Bansal *et al*[27]	USG + MRCP + EUS	Pancreaticoduodenectomy	No	Albendazole-6 wk	No	6	No
Boubbou *et al*[28]	USG + CT	PAIR + drainage + cystogastrostomy laparoscop	No	NS	NS	NS	NS
Shah *et al*[29]	USG + CT	Distal pancreatectomy + splenectomy	No	Albendazole-6 wk	No	120	No
	USG + CT	Central pancreatectomy + reconstruction	No	Albendazole-6 mo	No	96	No

	USG + CT + MRI	Pericystectomy	No	Albendazole-6 mo	No	52	No
	USG + CT	Distal pancreatectomy + splenectomy	No	Albendazole-6 wk	No	50	No
	USG + CT + MRI	Partial cystectomy + evacuation + T-tube drainage	No	Albendazole-6 mo	No	30	Liver
	USG + CT + MRI	Partial cystectomy + evacuation + T-tube drainage	No	Albendazole-6 mo	No	4	No
[15]Karakas *et al*[30]	USG + CT + MR	Distal pancreatectomy + cystectomy	Pancreatic fistula	NS	No	4	No
[16]Diop *et al*[31]	CT + MR + EUS	Distal pancreatectomy + polar nephrectomy + partial cystectomy-Liver	No	Albendazole-18 mo	No	48	Liver + kidney
Szanto *et al*[32]	USG + CT + EUS	Distal pancreatectomy + splenectomy	Hemoperitoneum	Not-used	No	NS	NS
Cağlayan *et al*[33]	NS	NS	NS	Albendazole	NS	NS	NS
Orug *et al*[34]	USG + CT	Distal pancreatectomy + splenectomy	No	Albendazole-6 mo	No	24	No
	USG + CT	Distal pancreatectomy + splenectomy	No	Albendazole-3 mo	No	24	No
Chammakhi-Jemli *et al*[35]	USG + CT + MRI	Distal pancreatectomy + splenectomy	No	NS	NS	NS	NS
Elmadi *et al*[36]	USG + MRI	Partial cystectomy + evacuation	No	NS	NS	24	No

[1]This patient arrived at the hospital with signs of acute pancreatitis. Despite tienam therapy, he developed renal dysfunction and pancreatic necrosis that affected 50% of the organ. Due to deterioration in his overall status, the patient underwent distal pancreatectomy + necrosectomy + partial nephrectomy (for renal hydatid cyst). Unfortunately, the patient was lost on postoperative day 15; [2]This patient was admitted to physician with episodes of obstructive jaundice and elevated liver function tests. Results from MRCP and US were both consistent with a choledocal cyst. An intraoperative cholangiography revealed normal bile flow; [3]This patient underwent percutaneous drainage after 12 d treatment with albendazole. A cystogram was done, and there was no relationship between cyst and pancreatic duct. The patient received albendazole for 2 mo after the operation. The serologic test was negative during follow-up; [4]This patient was tested for abdominal pain, leukocytosis, and hyperamylasemia and diagnosed with a pancreatic head cyst that compressed the duct externally. Subsequently, the patient developed acute pancreatitis secondary to ductus compression; [5]No differential diagnosis was made on CT. Therefore, a FNAC was performed and cytologic examination revealed hooklets of parasite. The patient was administered a 21 d course of albendazole at pre-operative and post-operative periods; [6]This patient developed jaundice 1 year ago and had elevated levels of AST and ALT. Findings from US, CT, and ERCP were consistent with a choledocal cyst. Thus, a stent was placed in the common bile duct, and a laparotomy operation was performed. After intraoperative exploration, the lesion was considered a cystadenoma. Whipple operation was performed since dissection of the cystic lesion was difficult; [7]The patient was administered albendazole for 4 d preoperatively and 1 mo postoperatively. Postoperative hyperglycemia developed as a complication and was treated with insulin; [8]A pancreatic pseudocyst was considered to exist, and a US-guided drainage was attempted. However, the cyst perforated into the peritoneal cavity during the procedure, and open surgery was performed and a pancreatic fistula developed. The drain was removed 18 d later; [9]Clinical presentation and CT findings of this patient were consistent with an abscess. A US-guided aspiration was performed, and he culture result was sterile. Although the patient was sent home on medical therapy, he was admitted to the hospital again with signs of intestinal obstruction. A hydatid cyst was initially diagnosed, and a US-guided cytology confirmed hydatidosis; [10]This patient was initially diagnosed with a choledocal cyst and underwent diagnostic laparoscopy. The cystic lesion originated from the pancreatic head and the aspirated fluid sample from the cyst clear fluid rather than bile. This finding indicated hydatid cyst, and an open operation was performed. Despite findings consistent with a pancreatic fistula on MRCP, no such relationship was detected in cytography. A cholangiography was carried out, and the fluid easily passed to duodenum; [11]MRCP images of this patient were consistent with a Type-Ⅱ choledocal cyst; [12]This patient had two previous hepatic hydatid cyst surgeries. He had cysts in liver, spleen, pancreas, and the area below the incision. Albendazole treatment was begun 3 wk prior to the operation. The operation team performed splenectomy + total peritoneal cyst excision + partial cystectomy + omentoplasty for two cysts in liver; [13]The authors reported there was no relationship between hydatid cyst and common bile duct or pancreatic duct in any patient. Only 2 patients had bile duct dilatation secondary to compression of the common bile duct by hydatid cyst; [14]USG revealed dilatation in bile ducts. MRCP was consistent with a type-Ⅲ choledocal cyst. EUS showed a mass lesion originating from the pancreatic head. Since its intraoperative resembled a cystic neoplasm, a Whipple procedure was carried out. Examination of the specimen revealed the relationship between cyst and pancreatic duct; [15]This patient had elevated liver function tests and increased blood amylase levels (acute pancreatitis) in preoperative testing. Radiologically, dilation of the pancreatic duct and enlargement of the pancreatic body were apparent. The patient received preoperative albendazole treatment. A fluid collection developed at the surgical area at the postoperative period, and a US-guided drainage catheter was placed. In addition, the pancreatic duct was stented, and external drainage dramatically improved after the stenting procedure; [16]A pancreatic cyst was diagnosed in an examination performed for pancreatitis. MR and EUS localized the fistula between the pancreatic duct and cyst. USG: Ultrasonography; CT: Computed tomography; MRCP: Magnetic resonance cholangiopancreatography; ERCP: Endoscopic retrograde cholangiopancreatography; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; MRI: Magnetic resonance imaging; NS: Not-stated; FNAC: Fine needle aspiration cytology; US: Ultrasonography; EUS: Endoscopic ultrasound.

2 and 3). In addition, areas of severe fibrosis were noted in regions neighboring the cyst.

DISCUSSION

Humans have no biological role in the life cycle of hydatids, and they are inadvertently infected upon ingestion of Echinococcus eggs containing live oncospheres in canine feces. The ingested eggs first penetrate the intestinal wall, then pass to the portal system, and ultimately reside in hepatic sinusoids[3,7]. Larvae with a diameter less than 0.3 mm can escape the liver's filtering system (first Lemman's filter) and reach the lungs where they are entrapped by a second capillary filtering system (second Lemman's filter). Larvae that escape the lung may then pass to any part of the human body *via* arterial circulation[1-3]. The organization of the filtering systems explain why hydatid cysts most commonly re-

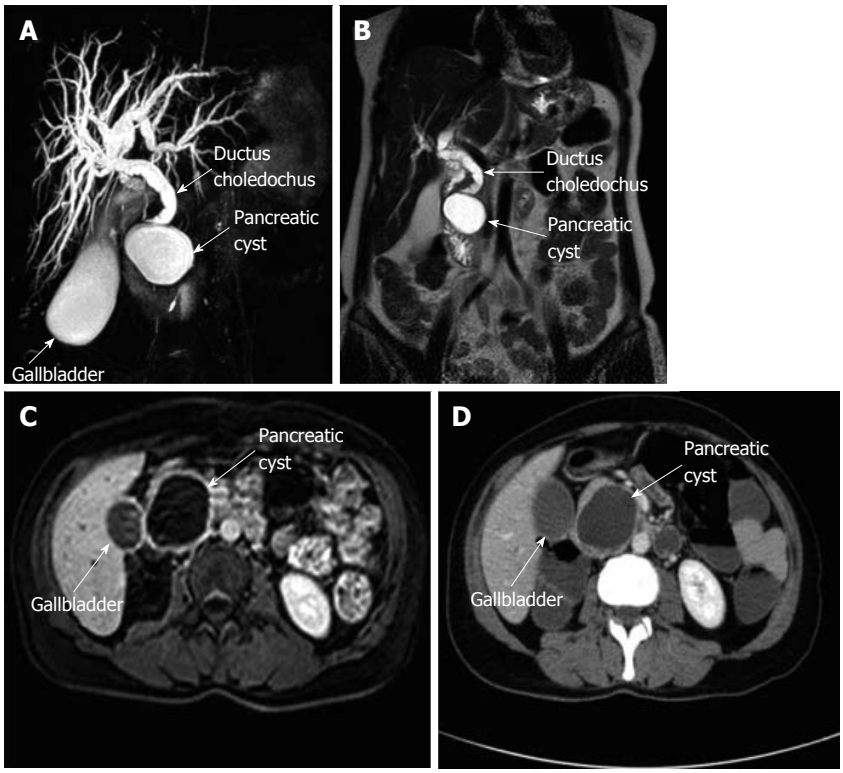

Figure 1 Magnetic resonance cholangiopancreatography shows a hydropic gall bladder and dilated intrahepatic bile ducts and common bile duct. The distal portion of the common bile duct is narrowed due to external compression. A: A pancreatic cyst compressing the lower tip of the common bile duct is also seen in this section; B: A coronal T2-weighed MR cross-section shows a pancreatic cyst and a dilated common bile duct; C: Intravenous T1-weighed axial cross-section with contrast enhancement shows a pancreatic cyst; D: An axial computerized tomography cross-section with contrast enhancement shows a pancreatic cyst with a thick wall and without central contrast uptake. MR: Magnetic resonance.

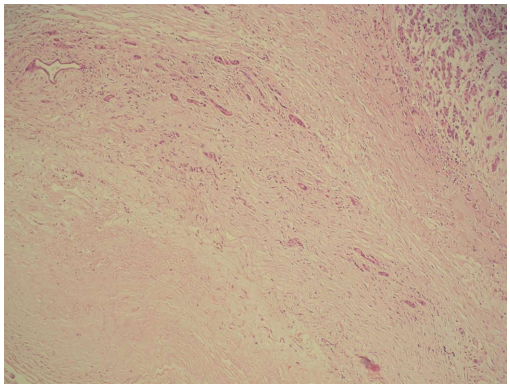

Figure 2 Patient's mass has characteristics consistent with a hydatid cyst. The cyst wall is surrounded by fibrous capsule (also called the pericyst layer). The adjacent parenchyma demonstrates pressure atrophy (hematoxylin-Eosin stain ×100).

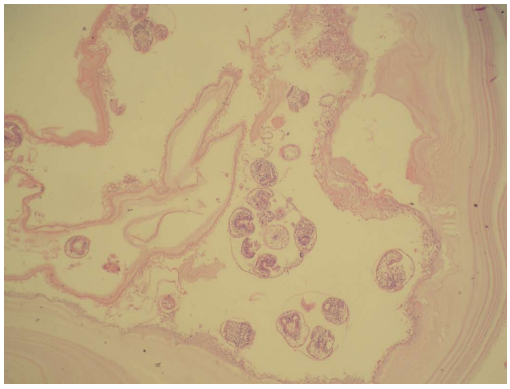

Figure 3 Cyst wall of the patient's mass consists of a laminated faintly stained chitinous membrane (outer layer). Multiple protoscolices are present within the daughter cyst (inner germinal layer, hematoxylin-Eosin stain × 100).

side in the liver, with the second most common residence being the lung.

A number of hypotheses regarding the mode of passage of E. granulosus to pancreas have been postulated, the most accepted is the hematogenous dissemination discussed above[3,8,10-12,14,27]. The second route involves passage of cystic elements into the biliary system and then to the pancreatic canal and pancreas[3,10,14,27]. The third route involves passage of cystic elements into lymphatic channels through the intestinal mucosa and then to pancreatic tissue rich in lymphatic network[3,8,10-12,14,20,27]. The fourth route is direct passage of larvae into pancreatic tissue, bypassing the liver, *via* pancreatic veins[20]. The fifth, and final, hypothesized route is retroperitoneal dissemination[27,34]. In our literature review, an isolated PHC was detected in 72% and a secondary PHC was detected in 28% of 43 cases where medical data were available.

The PHC incidence varies by region, ranging from 0.1% to 2%[5,8,9,11,13,15,16,29]. Pancreatic cysts are solitary 90%-91% of the time, and their pancreatic distribution is heterogeneous[4,19,26]. According to data from the lit-

erature, 50%-58% of PHCs are found in the pancreatic head, 24%-34% in the pancreatic body, and 16%-19% in the pancreatic tail[4,5,12,19]. The rich vascular network found in the pancreatic head suggests that larvae reach this region *via* systemic circulation[4,26]. We did not find any significant difference in location prevalence between pancreatic head (38%) and pancreatic tail (34%). Prevalence of tail localization, however, may be even higher when cysts in the pancreatic body and tail are also taken into consideration.

Pancreatic cysts grow slowly (0.3-2 cm per year)[2], and some patients remain asymptomatic for years prior to obtaining a definitive diagnosis. Such patients are often incidentally diagnosed during tests performed for other indications. In symptomatic PHC patients, clinical presentation and complications depend on the location of the cyst within the pancreas[3-5,8,12,16,19]. Almost all cases we reviewed presented with epigastric pain, 20 had a palpable abdominal mass, and 15 had intermittent/permanent jaundice. Only a small proportion of patients suffered from non-specific symptoms such as fever, nausea-vomiting, weight loss, and abdominal fullness. PHC manifested itself as an intercostal herniation in only 1 patient[6]. However, we were unable to obtain precise information regarding duration of these symptoms.

Hydatid cysts located in the pancreatic head may cause obstructive jaundice or acute pancreatitis by either exerting external compression on or fistulizing into the common bile duct[4,10,12,15,20,23,26-30,31,35,36]. Less commonly, they may lead to cholangitis, duodenal stenosis, or duodenal fistula[4,20]. On occasion, hydatid cysts in the pancreatic head may remain silent but be palpable as an epigastric mass lesion. Hydatid cysts in the pancreatic body and tail usually remain asymptomatic until they grow large enough to compress adjacent organs or anatomical structures[4,8,16,20]. Gastric compression manifests as nausea, vomiting, abdominal pain, and early satiety[4,20]. On rare occasions, splenic vein compression may lead to splenic vein thrombosis with severe complications such as left-sided portal hypertension[4,12,32,34]. A hydatid cyst may also become infected, causing an abscess, or an acute abdomen due to spontaneous intraperitoneal rupture[4,20]. Hydatid cyst may also at times erode walls of gastrointestinal luminal organs, causing a rupture into the lumen[4,20].

In this review, we found that 14 cases had bile duct dilatation due to external compression[4,10,20,23,26-30,36], while 4 had cysto-biliary fistula[4], 6 had pancreatitis due to external compression and fistulization (2 were necrotizing, and 4 were edematous)[8,12,15,30,31,35], 3 had pancreatic ductal dilatation[10,15,36], 4 had cysto-pancreatic fistula[12,27,30,31], 2 had left-sided portal hypertension[4,32], 1 had cysto-duodenal fistula[4], and 1 had splenic vein obstruction[34]. Some of these complications were detected by preoperative radiological examinations, and others were only detected at the time of surgery.

Radiological and clinical properties of the cases in this review suggest that a significant portion were characterized by cyst-induced compression of or fistulization into the pancreato-biliary system. However, the rate of this complication was far below the expected rate. Analysis of patients' blood tests showed that 8 patients had elevated bilirubin (2.9-11.7 mg/dL), 9 had elevated ALP (280-1843 U/L), 7 had elevated ALT (56-335 U/L), 7 had elevated AST (72-235 U/L), 7 had elevated amylase (610-4965 U/L), and 2 had elevated lipase (103-1390 U/L)[5,8,10,12,15,17,20,21,23,26,27,29,30,36].

The first and most important step in the diagnosis of PHC is clinical suspicion. Important clues include residence in an endemic region or a previous hydatid cyst surgery. These clues may increase diasnostic yield when assessed in conjunction with results from radiological studies and serological tests. For diagnosis of pancreatic cysts, the most commonly performed radiologic tests are, in descending order, USG, CT, and magnetic resonance imaging (MRI). Complicated cases that require further workup are examined with invasive diagnostic tools, such as EUS and ERCP[26]. USG is a noninvasive, low-cost and sensitive diagnostic instrument. Gharbi defined the typical appearance of hydatid cysts in USG[12], but application of USG to pancreatic cysts is lower than for liver cysts because of the retroperitoneal location of the pancreas and bowel gas. CT is usually successful in delineating cyst size, location, relation with pancreato-biliary system, and presence of cysts in other organs. It is also successfully used for treatment monitorization and postoperative recurrence detection[12]. MRI and MRCP are particularly useful to delineate the relationship between cysts and pancreatic and bile ducts[12,31]. However, results from these techniques may be insufficient when attempting to differentiate between cysts located at the pancreatic head and those located at the common bile duct[10,27]. In MRI, superposition of the hydatid cyst with the pancreatic duct can be misinterpreted as a fistula[23]. To demonstrate the relationship between cyst and pancreatic duct and to differentiate cysts of unknown nature, ERCP can be used. ERCP is appropriate for palliative stent applications in cases with cholangitis or pancreatitis secondary to biliary or pancreatic duct obstruction[17,26]. It is also very beneficial in non-operative management of cases that developed biliary or pancreatic fistulae[12,30]. EUS is not commonly used[31,32], but it is capable of delineating pancreato-biliary system anatomy and taking biopsy samples when necessary. It can accurately show the relationship between the cyst and pancreatic duct[12,31]. Cystography during surgery is especially helpful to demonstrate the relationship of the cyst with the pancreato-biliary ducts and gastrointestinal tract[23]. In complicated cases, the gall bladder and common bile duct can be entered with a needle and a cholangiogram can be taken[10,20,29], which may show both the anatomy of bile ducts and their relationship with cyst[12].

For diagnosis, screening, and recurrence monitoring, the following serological tests are used: enzyme-linked immunosorbent assay, indirect hemagglutination, serum immunelectrophoresis, complement fixation test, and immunofluorescence assay[17,21,28]. The seropositivity rate is

higher in hepatic hydatid cysts than cysts in other organs. We calculated a rate of 54% for PHC cases. It should be noted, however, that seronegativity does not guarantee absence of hydatid disease[26].

The differential diagnosis of PHCs include neoplastic (cystadenoma, cystadenocarcinoma, gastroenteropancreatic neuroendocrine tumors, vasculary tumors, metastatic cystic lesions) or non-neoplastic (congenital pancreatic cysts, pseudocysts) cystic lesions[16,19,27]. Diagnosis of cysts that cannot be made using noninvasive techniques can be made by taking either a biopsy from the lesion or an aspiration cytology sample from cyst fluid *via* percutaneous or endo-ultrasonographic techniques[4,18,26]. Using percutaneous fine needle aspiration cytology (FNAC) for the differential diagnosis of cystic pancreatic lesion, Varshney *et al*[16] showed hooklets of hydatid cyst cytologically. In contrast, Dalal *et al*[22] had to perform FNAC twice in order to diagnose hydatid cyst. Anaphylaxis and pouring of cyst content into the abdominal cavity are potential complications of the FNAC procedure. Hence, prophylactic antihelminthic agents should be started when FNAC is contemplated in a patient with suspected cysts; otherwise, the procedure should be avoided[4].

All patients presented in this review underwent at least one preoperative radiological or serological test. After these tests, 20 patients were diagnosed with PHC, 14 with benign/neoplastic cystic lesion of pancreas, 8 with choledocal cyst, 4 with PHC/cystic neoplasm of pancreas, 2 with hepatic hydatid cyst, and one with splenic hydatid cyst. Minimally invasive surgery was contemplated. No presumptive diagnoses were made for the remaining patients. As seen, only 40%-49% of patients were diagnosed with PHC at the preoperative period. This is true even for the most recent studies performed within the last 4.5 years. Diagnostically, the situation was even worse several decades ago, when the rate of preoperative PHC was far below 30%.

PHC can be treated with one or a combination of several therapies, including open or laparoscopic surgical approach, minimally invasive approach [puncture-aspiration-injection-reaspiration (PAIR) or direct percutaneous catheterization], and medical therapy[9]. As is the case for other organ hydatid cysts, open surgery is the gold standard for the treatment of PHC disease. Selection of the appropriate management approach is affected by many factors, such as surgeon's experience, patient age, presence of comorbid conditions, pancreatic localization of cyst(s), cyst size, and relation of cyst to adjacent structures or the pancreatic and common bile ducts[4,29,31].

Pancreatic head cysts with no communication with biliary or pancreatic ducts can be managed with partial cystectomy + external drainage, partial cystectomy + omentopexy and pericystectomy, marsupialisation, and pancreaticoduodenectomy procedures[4,29,34]. Each method has its own advantages and disadvantages. In order to avoid postoperative pancreatic fistula formation, cysts with communication with the pancreatic duct can be treated with cysto-jejunal, cysto-duodenal, or cysto-gastric anastomosis techniques[4,26]. In cysts located in the pancreatic body or tail, the most appropriate approach is a spleen-preserving distal pancreatectomy[4,26]. In cases where the spleen cannot be preserved, pneumococcal and meningococcal vaccinations should be done immediately to avert postsplenectomy complications[5]. Central pancreatectomy may be preferable when cysts are localized to the pancreatic body or neck[29]. The main advantage of this method is the preservation of pancreatic tissue and the minimization of complications, such as diabetes or exocrine pancreatic insufficiency[29]. Masoodi *et al*[18] reported in a patient that underwent a distal pancreatectomy hyperglycemia high enough to require insulin injection. For management of hydatid cysts of the pancreatic head, the role of pancreaticoduodenectomy is very limited[20]. Pancreaticoduodenectomy was performed in only 3 of 19 pancreatic head cysts[4,17,27]. A whipple procedure was applied in all three of these cases since the results of preoperative radiological examination and/or intraoperative findings were consistent with a cystic lesion of the pancreatic head. In our case, we experienced similar difficulties. While the preoperative tests, including CT, MRCP, and ERCP, were consistent with a choledocal cyst, the intraoperative appearance was totally compatible with a mass in the pancreatic head. Unfortunately, our patient was lost to a misfortunate complication. In retrospect, we realize that patient outcome may have been improved if the diagnosis was made preoperatively and simple partial cystectomy and drainage was performed intraoperatively. Hence, our main objective for writing this manuscript was to heighten awareness about this topic.

Although rarely reported in the literature, there are some studies describing percutaneous drainage of pancreatic hydatic cysts[10,13]. Percutaneous drainage can be accomplished by puncture, aspiration, injection of hypertonic saline solution, and re-aspiration of cyst content (PAIR) or direct catheterization of the cyst[13,18,28]. These procedures should be specifically carried out in Type I and Ⅱ PHCs, cysts with a diameter less than 50 mm, patients who refuse surgery, and cases with a higher anesthesia risk[1]. The main advantage of PAIR is the ability to show scoleces in the aspirated cyst fluid cytopathologically within a short period of time. Another advantage is the ability to delineate the relative location of the cyst with the pancreatic duct by contrast material administration during the procedure. However, an unconscious percutaneous drainage procedure or one that is performed without estimating the possible presence of PHC may lead to cyst perforation and surgical complications[21]. The risk associated with release of cyst contents into abdominal cavity is markedly lower with a PAIR procedure that is carried out by passing through parenchyma of solid organs like liver and spleen than it would be with pancreatic and other intraabdominal cysts[26]. In cases where minimally invasive surgical therapy has been contemplated, antihelminthic therapy should be administered before (≥ 4 d) and after (≥ 3-4 wk) the procedure in order to reduce intracystic pressure and prevent anaphylaxis[1].

Although there are numerous articles about laparoscopic excision of hydatid cysts in other organs, there are only a few case reports on the use of the laparoscopic approach for PHCs. In one report, content of a cyst located in the pancreatic head was emptied by directly inserting a 10 mm trochar into the cyst followed by omentoplasty[15]. In our opinion, in order to apply this technique to PHCs, the preoperative diagnosis should be accurately made, the cyst must have an adequate neck, and the surgeon must be experienced in laparoscopy.

Antihelminthic prophylactic therapy (albendazole, mebendazole, or praziquantel) must be administered for 2-4 wk prior to surgery (open, laparoscopic, or PAIR) in order to decrease intracystic pressure and reduce anaphylaxis and postoperative recurrence risks. With radical resections that do not open the cyst cavity, there is no need for medical therapy afterwards[32]. One of the cyclic or continuous medical therapy protocols, however, should be applied during the postoperative period to patients who underwent conservative surgery. During follow-up, these asymptomatic cysts can be followed with medical therapy alone or their size assessed at yearly intervals.

Complications of PHC surgery can be divided into short- and long-term complications. Short-term complications or early postoperative complications include pancreatic fistula, biliary fistula, biloma, intraabdominal abscess, and wound infection. The most suitable approach for treating biloma and intraabdominal abscesses is percutaneous drainage. For biliary and pancreatic fistulae, daily output guides management decisions. ERCP shows well the location of the fistula and the presence of any obstruction due to cystic elements in pancreatobiliary ducts (distal to fistula). Simultaneously, therapeutic procedures like sphincterotomy and/or stent implantation can also be performed with ERCP. Use of somatostatin analogues may hasten closure and reduce output of pancreatic fistulae[19,21]. Surgical intervention is rarely needed, and intraoperative cholangiography or cystography may be performed to avoid such complications. In addition, planning surgery in line with cyst location may avert complications. The major long-term complication of cyst surgery is hydatid cyst recurrence. Recurrence is rather common after conservative surgical operations but almost never seen after radical surgery. Recurrence rates can be minimized by applying intraoperative protective measures, which are commonly applied in hepatic hydatid cyst surgery, or by administering preoperative or postoperative medical therapy.

In conclusion, PHC is a rare parasitic infestation that can cause serious pancreato-biliary complications. Despite advances in radiological instrumentation, preoperative diagnosis of PHC remains a challenge, and it is often misdiagnosed as other cystic diseases of the pancreas and distal choledocal cysts. Conservative surgical techniques, which are preferred over radical surgical interventions, should be applied, especially in cysts located in the pancreatic head. After confirmation of the diagnosis, cystography is a suitable method to demonstrate the relationship between the cyst and pancreatic duct. While postoperative antihelminthic therapy is not necessary in surgical operations that do not open the cyst cavity, a medical therapy lasting for 3-4 wk is appropriate after more conservative surgical procedures such as partial cystectomy.

COMMENTS

Background

Pancreatic hydatid cyst disease is rare but can lead to serious pancreato-biliary complications if left untreated. Despite advances in radiological techniques, preoperative diagnosis of panceatic hydatid cyst remains challenging, and it is frequently misdiagnosed preoperatively as other cystic diseases of the pancreas and distal choledocal cysts.

Research frontiers

The authors analyzed previously published articles regarding pancreatic hydatid cyst. For this purpose, a literature search was performed in PubMed, Medline, Google Scholar, and Google databases using different keywords related to pancreatic hydatid cyst. Second, the authors presented a case of a 48-year-old female patient who underwent surgical treatment for pancreatic head hydatid cyst.

Innovations and breakthroughs

A review of the literature and personal experience suggest that pancreatic hydatid cyst disease should be considered in the differential diagnosis of pancreatic cystic lesions, especially in patients living in endemic areas.

Peer review

Echinococcosis is listed as one of World Health Organizations Neglected Zoonotic Diseases bringing a significant socioeconomic burden, mainly in impoverished and rural areas. The topic of this review is relevant although if performed in a systematic way it would have delivered a stronger evidence-based article for the medical community. Without bringing any new findings, this review stands out over previous attempts as it properly describes the methodology behind the searching and selection process of retrieving articles and represents a comprehensive source of information of reported cases in the last 4.5 years.

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CASE REPORT

Surgical management of colonic perforation due to ulcerative colitis during pregnancy: Report of a case

Douglas Overbey, Henry Govekar, Csaba Gajdos

Douglas Overbey, Henry Govekar, Csaba Gajdos, Department of Surgery, University of Colorado, Aurora, CO 80045, United States
Author contributions: All authors were involved in the case and contributed equally to writing and reviewing the manuscript.
Correspondence to: Douglas Overbey, MD, Department of Surgery, University of Colorado, 12631 E 17th Ave, Mail Stop C302, Aurora, CO 80045, United States. dmom94@gmail.com
Telephone: +1-573-2257728 Fax: +1-303-7242682
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Abstract

This report describes a young female in her second trimester of pregnancy with known ulcerative colitis on maintenance medical therapy. She was admitted for abdominal pain, and workup revealed a colonic stricture and ulceration with contained perforation. After multidisciplinary discussion she was managed with colectomy and end ileostomy. She delivered a healthy newborn 18 wk after surgery. Only a few prior reports described surgical management of inflammatory bowel disease during pregnancy, with recent results indicating low risk of adverse outcomes.

Key words: Inflammatory bowel disease; Ulcerative colitis; Colonic stricture; Colon perforation; Pregnancy

Core tip: Surgical management of inflammatory bowel disease flare during pregnancy are rare and infrequently reported in the literature. This case report summarizes the literature and describes a successful resection of a contained perforation and stricture secondary to ulcerative colitis flare.

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INTRODUCTION

Inflammatory bowel disease (IBD) encompasses Crohn's disease (CD) and Ulcerative Colitis (UC). These autoimmune conditions involve mucosal inflammation of the entire gastrointestinal tract in CD and the colon and rectum in UC. While primary management of IBD is medical, surgical indications are generally reserved for toxic colitis, perforation, bleeding, strictures, neoplasms, and failure of medical management.

Although the rate of IBD flare is similar in pregnant and nonpregnant patients (26%-34%), the primary determinant of disease outcome seems to involve quiescence *vs* active disease at the initiation of pregnancy[1]. Thus the goal in a planned pregnancy is remission before conception[1]. The optimal drug regimen is patient dependent but the aminosalicylate (mesalamine, balsalazide, sulfasalazine), thiopurine (AZA and 6-MP), and anti-TNF (INF, ADA, CZP) classes are generally considered safe in pregnancy. Active disease is a greater risk than active therapy and timing of dosages can avoid the later weeks of pregnancy to mediate placental transfer of these drugs[1,2].

Initial studies reported an association between IBD and adverse outcomes in pregnant patients, possibly mediated by the immunologic phases of pregnancy and specific interactions leading to preterm birth[3]. Surgical management of ulcerative colitis in an ongoing pregnancy is infrequently reported, with only one recent literature review published[4] and additional case reports. Results showed no mortality reported after 1974, and minimal morbidity[4,5]. Other more generalized reports of IBD relapse during pregnancy indicate a colectomy rate of up to 17%[6]. We report a case of a surgically treated compli-

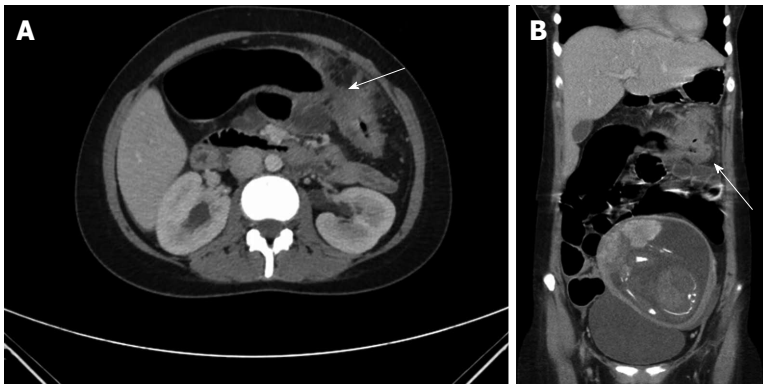

Figure 1 Computed tomography scan images revealing the strictured segment (A) and adjacent phlegmon (B).

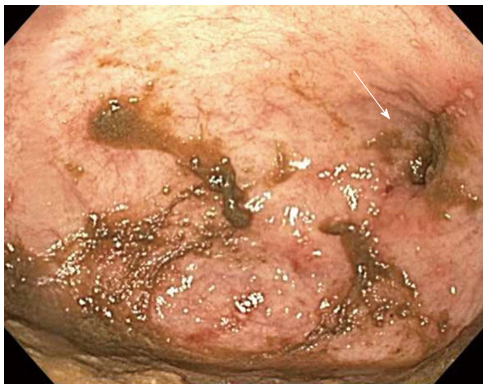

Figure 2 Colonoscopic images showing the strictured segment (arrow) and mucosal inflammation.

cated IBD during pregnancy.

CASE REPORT

Our patient is a 23-year-old female with a 13-year history of UC. She was diagnosed with IBD *via* symptoms and colonoscopic evidence of disease at ten years of age. Over the last 13 years she has been managed with mesalamine and steroid bursts. She underwent repeat colonoscopy secondary to a stricture in the transverse colon near the splenic flexure in 2012. Biopsies at that time were negative for malignancy and the lumen was viewed to be widely patent.

Patient presented to University Hospital at 21 wk of her first pregnancy in April of 2013, with worsening abdominal pain, diarrhea, nausea and intermittent emesis for two months. At the time of admission she was on mesalamine 800 mg *bid*, and prednisone 30 mg *qd*, as well as a prenatal vitamin and a proton pump inhibitor. Physical exam revealed a gravid uterus with focal tenderness in the mid epigastric region and the left upper quadrant. Laboratory analysis was significant for leukocytosis at 14.0 $\times$ 10^9/L, erythrocyte sedimentation rate of 75 mm/h and C-reactive protein of 7.0 mg/dL. She underwent a computed tomography scan showing a colonic stricture near the splenic flexure, with dilated proximal colon and a fluid collection surrounding the splenic flexure measuring up to 4.0 cm (Figure 1). She also had a colonoscopy showing a tight, inflamed and friable 8 mm stricture at 45 cm with active ulceration at 35-40 cm. The colonoscope could not be passed through the stricture. Antibiotics were continued from admission (piperacillin-tazobactam and metronidazole), with no signs of hemodynamic instability or sepsis. Multidisciplinary meetings were arranged with gastroenterology, obstetrics and surgery.

Following a week of conservative measures with total parenteral nutrition and no signs of improvement, she underwent a subtotal colectomy (cecum, ascending, transverse, descending, sigmoid colon resected), end ileostomy, and partial gastrectomy due to the colon mass being inseparable from the greater curvature of the stomach. The rectal stump was left in place and oversewn. The fetus was closely monitored.

The post-operative course was uneventful and patient was discharged home on postoperative day five, with steroid taper over the next 7 d. The follow up visit included a normal fetal ultrasound. Pathology revealed diffuse mucosal inflammation (chronic colitis) throughout the colon without skip lesions, with a normal short terminal ileum segment (Figure 2). A colonic ulcer was identified as well as the adherent abscess measuring 5.5 cm. The rest of her pregnancy was uncomplicated and she went on to deliver a healthy infant.

DISCUSSION

IBD in pregnancy presents a unique challenge. IBD flares can present with symptoms like abdominal pain, hematochezia, or varying degrees of perforation as illustrated by our case.

The goal in treating any IBD flare is to induce remission of the acute flare, and design appropriate maintenance therapy to improve quality of life. Surgical intervention in ulcerative colitis is typically reserved for failure of medical therapy, acute change such as toxic colitis, perforation, bleeding, or the development of strictures or neoplasm. Surgical intervention with a gravid uterus presents several unique challenges[7].

There were two main decision pathways in our case. First, the decision to continue medical management or

pursue surgical intervention. With patient's non-toxic state there was no urgent need for surgery, but due to the stricture and phlegmon, patient would have been unlikely to maintain adequate nutrition without repeat dilation or stenting of the strictured colonic segment. We also had concern for a developing malignancy, since UC may confer an increased risk for developing colon cancer of up to 30%[8]. Furthermore, increasing immunosuppression in the setting of a known perforation and abscess can be risky. This made surgical intervention the preferred approach.

The second decision is which operation is best suited to her case. Diversion only would allow nutritional intake and provide proximal decompression, but would leave a severely inflamed segment of colon in place thus requiring escalation of medical therapy and likely steroids throughout the rest of her pregnancy. The strictured segment of colon would ultimately require resection at a later date anyway. We elected to proceed with a subtotal colectomy. Primary anastomosis was considered too risky under the circumstances, and an end ileostomy eliminated the risk of a possible anastomotic leak. Ileostomy placement in a patient with a gravid uterus must also be given special consideration to avoid obstruction as the abdomen changes in girth[9]. A rectal stump was left in place to allow future reconstruction. Surveillance of the remaining rectal stump is recommended for malignancy concern.

A literature review in 2005 identified only five cases in 25 years at a large referral center, and 37 published cases in the literature for fulminant ulcerative colitis requiring an operation during pregnancy[4]. Although early cases noted a fetal mortality as high as 49%, more recent studies have shown subtotal colectomy and Brooke ileostomy to be safe in the pregnant population[4].

In summary, we successfully managed a case of complicated UC in pregnancy *via* extended colectomy, partial gastrectomy and end ileostomy. Patient had an uneventful recovery and delivered a healthy newborn a few weeks later. Consideration should be given to surgical resection in cases of complicated UC in pregnant women in well selected cases following multidisciplinary evaluation.

COMMENTS

Case characteristics

Twenty-three years old pregnant female with known ulcerative colitis presents with abdominal pain, nausea, emesis, and diarrhea for two months.

Clinical diagnosis

Physical exam revealed a gravid uterus with focal tenderness in the mid epigastric region and the left upper quadrant.

Differential diagnosis

Differential diagnosis included inflammatory bowel disease flare, gastroenteritis or infectious colitis, diverticulitis, and appendicitis-the next step was to discern *via* imaging and colonoscopic evaluation.

Laboratory diagnosis

Laboratory analysis was significant for leukocytosis at 14.0 × 10^9/L, erythrocyte sedimentation rate of 75 mm/h and C-reactive protein of 7.0 mg/dL.

Imaging diagnosis

Computerized tomography revealed a colonic stricture near the splenic flexure, with dilated proximal colon and a fluid collection surrounding the splenic flexure measuring up to 4.0 cm.

Pathological diagnosis

Pathology revealed diffuse mucosal inflammation limited to the colon and rectum, with a normal short terminal ileum segment. A colonic ulcer was identified as well as the adherent abscess measuring 5.5 cm.

Treatment

Treatment included antibiosis as well as surgical management including subtotal colectomy and end ileostomy.

Related reports

A literature review in 2005 identified only five cases in 25 years at a large referral center, and 37 published cases in the literature for fulminant ulcerative colitis requiring an operation during pregnancy. Although early cases noted a fetal mortality as high as 49%, more recent studies have shown subtotal colectomy and Brooke ileostomy to be safe in the pregnant population.

Experiences and lessons

An important lesson is that surgical management of complicated inflammatory bowel disease flare can be safe in pregnancy and should be considered in appropriate circumstances.

Peer review

Authors report a case of a surgically treated complicated during pregnancy. They successfully managed a case of complicated Ulcerative Colitis in pregnancy and this information is important.

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CASE REPORT

Torsion of Meckel's diverticulum as a cause of small bowel obstruction: A case report

Marko Murruste, Geidi Rajaste, Karri Kase

Marko Murruste, Geidi Rajaste, Department of General and Plastic Surgery, Surgery Clinic, Tartu University Hospital, Tartu 51014, Estonia
Karri Kase, Surgery Clinic, Tartu University Hospital, Tartu 51014, Estonia
Author contributions: Murruste M, Rajaste G and Kase K contributed to the study concept and design; Rajaste G and Kase K contributed to the acquisition and analysis of data; Murruste M and Kase K contributed to the drafting of the manuscript; Kase K critically revised the manuscript; Murruste M contributed to the study supervision; all authors have read and approved the final manuscript.
Correspondence to: Marko Murruste, MD, Department of General and Plastic Surgery, Surgery Clinic, Tartu University Hospital, Puusepa str 8, Tartu 51014, Estonia. marko.murruste@kliinikum.ee
Telephone: +372-73-18065 Fax: +372-73-18205
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Abstract

Axial torsion and necrosis of Meckel's diverticulum causing simultaneous mechanical small bowel obstruction are the rarest complications of this congenital anomaly. This kind of pathology has been reported only eleven times. Our case report presents this very unusual case of Meckel's diverticulum. A 41-year-old man presented at the emergency department with complaints of crampy abdominal pain, nausea and retention of stool and gases. Clinical diagnosis was small bowel obstruction. Because the origin of obstruction was unknown, computer tomography was indicated. Computed tomography (CT)-scan revealed dilated small bowel loops with multiple air-fluid levels; the oral contrast medium had reached the jejunum and proximal parts of the ileum but not the distal small bowel loops or the large bowel; in the right mid-abdomen there was a 11 cm × 6.4 cm × 7.8 cm fluid containing cavity with thickened wall, which was considered a dilated bowel-loop or cyst or diverticulum. Initially the patient was treated conservatively. Because of persistent abdominal pain emergency laparotomy was indicated. Abdominal exploration revealed distended small bowel loops proximal to the obstruction, and a large (12 cm × 14 cm) Meckel's diverticulum at the site of obstruction. Meckel's diverticulum was axially rotated by 720°, which caused small bowel obstruction and diverticular necrosis. About 20 cm of the small bowel with Meckel's diverticulum was resected. The postoperative course was uneventful and the patient was discharged on the fifth postoperative day. We recommend CT-scan as the most useful diagnostic tool in bowel obstruction of unknown origin. In cases of Meckel's diverticulum causing small bowel obstruction, prompt surgical treatment is indicated; delay in diagnosis and in adequate treatment may lead to bowel necrosis and peritonitis.

Key words: Meckel's diverticulum; Axial torsion; Gangrene; Bowel obstruction; Emergency surgery

Core tip: Axial torsion and necrosis of Meckel's diverticulum causing simultaneous mechanical small bowel obstruction are the rarest complications of this congenital anomaly. This kind of pathology has been reported only eleven times.

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INTRODUCTION

Although Meckel's diverticulum was first described by Fabricus Heldanus in 1650[1], and reported thereafter by Levator in 1671[2] and by Ruysch in 1730[3], it was named

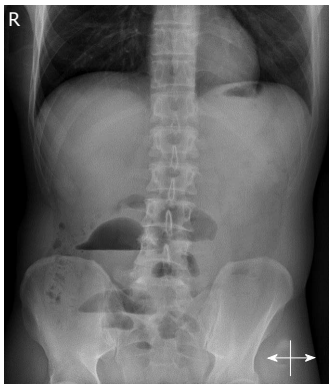

Figure 1 X-ray shows air-fluid levels in projection of the small bowel.

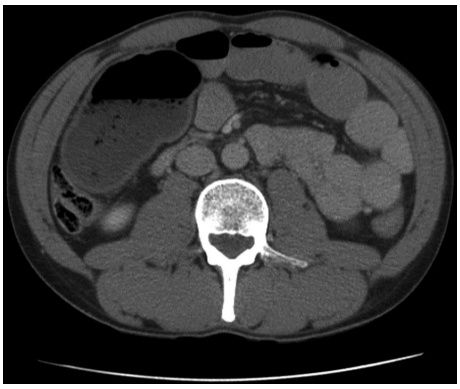

Figure 2 Computed tomography-scan shows distended small bowel loops and in the right mid-abdomen 11 cm × 6.4 cm × 7.8 cm fluid and gas containing cavity with thickened wall.

after Johann Friedrich Meckel who established its embryonic origin in 1809[4].

The characteristics of Meckel's diverticulum can be best remembered by the "rule of two": occurs in 2% of population; usually discovered before 2 years of age; 2 inches long and 2 cm in diameter; located 2 feet proximal to the ileocecal valve; 2 times more common in males; only 2% of the individuals with Meckel's diverticulum are symptomatic[5-7].

Blood supply is derived from a remnant of the primitive vitelline artery arising from the superior mesenteric artery, or less commonly from the ileocolic artery[8,9].

We present a very unusual case of Meckel's diverticulum-small bowel obstruction caused by axial torsion and gangrene of Meckel's diverticulum.

Axial torsion of Meckel's diverticulum is the rarest of complications[10]; gangrene of Meckel's diverticulum secondary to axial torsion has been reported only eleven times in adults[10-17].

Only two cases of coexistence of gangrenous Meckel's diverticulum and small bowel obstruction have been reported in the English-language literature[14,15].

CASE REPORT

A 41-year-old man presented at the emergency department with complaints of crampy and intermittent abdominal pain, nausea and retention of stool and gases. Previously the patient had been hospitalized four times with small bowel obstruction and conservative treatment had always been successful. The etiology of small bowel obstruction had remained unclear. The patient had never undergone any operations; nor had he hernias of abdominal wall. He did not have any other accompanying diseases and did not take any medications.

Physical examination revealed normal body temperature, and stable haemodynamics. The right mesogastrium was tender on palpation, peristalsis was high-sounding. On rectal examination the rectum contained no stool.

Initial laboratory tests showed haemoconcentration, the biochemical values were all normal. Initial abdominal X-ray showed air-fluid levels in projection of the small bowel (Figure 1).

Ultrasonography of the abdomen showed dilated small-bowel loops with peristalsis partially present.

Initial management of the patient included intravenous fluid resuscitation and nasogastric tube insertion. An abdominal computed tomography (CT)-scan was performed to specify the cause of small bowel obstruction. The CT-scan showed markedly dilated small-bowel loops with multiple air-fluid levels. The oral contrast medium was seen in the jejunum and proximal parts of the ileum but not in the distal small bowel loops or in the large bowel. In the right mid-abdomen there was a 11 cm × 6.4 cm × 7.8 cm fluid and gas containing cavity with thickened wall, which the radiologist considered dilated bowel-loop or cyst or diverticulum. A small amount of free fluid was present in the peritoneal cavity. The origin of small bowel obstruction remained still unclear (Figure 2).

Despite conservative treatment abdominal pain intensified. Therefore, an emergency laparotomy was opted for. Abdominal exploration revealed a small amount of haemorrhagical fluid in the peritoneal cavity and dilated small bowel loops. At approximately 50 cm from the ileocaecal junction there was a necrotic Meckel's diverticle, which was axially torsioned, with a size of 12 cm × 14 cm. The consequence of the torsion of Meckel's diverticle was small bowel obstruction.

Approximately 20 cm of the small bowel with Meckel's diverticle was resected. On a later examination, the mucosa of the diverticle was entirely necrotic, the diverticle was filled with hemorrhagic fluid (Figures 3 and 4). Postoperative recovery was uncomplicated and the patient was discharged on the fifth postoperative day.

DISCUSSION

Treatment of small bowel obstructions depends strongly on the etiology of obstruction and presence of intestinal strangulation. Therefore, quick correct diagnosis is highly important. Although Meckel's diverticulum is a rare cause of small bowel obstruction, it should never be forgotten and once it is diagnosed surgical treatment is indicated.

Suspicion of Meckel's diverticulum arises first of all in

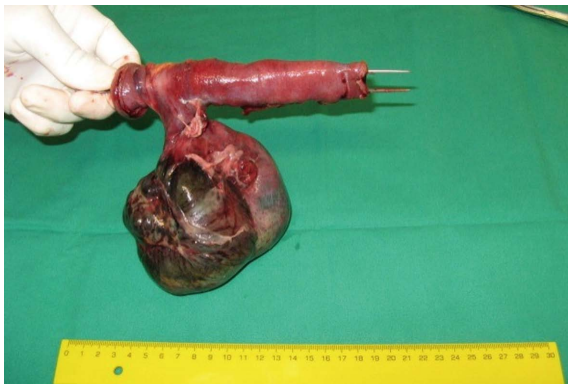

Figure 3 Torsioned necrotic Meckel´s diverticle obstructing the adjacent small bowel.

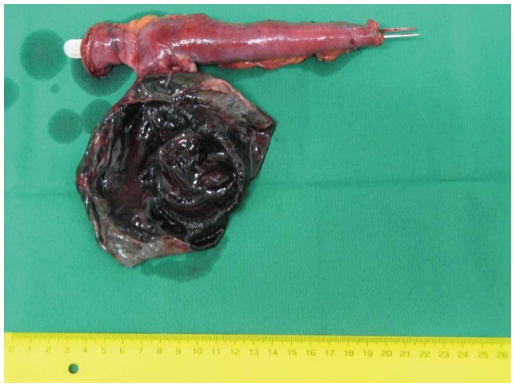

Figure 4 The mucosa of the diverticle was entirely necrotic, the diverticle was filled with hemorrhagic fluid.

patients without common causes of small bowel obstruction, *e.g.*, those without incarcerated hernias and previous abdominal surgery (low probability for adhesive obstruction). The preoperative diagnosis of almost all remaining causes of small bowel obstruction is difficult, especially with regard to complications of Meckel's diverticulum, with only about 6% of cases being diagnosed correctly[18-20]. The most useful diagnostic tool is CT-scan[21,22], as can also be seen in the present report. Once the diagnosis of Meckel's diverticulum as the cause of small bowel obstruction is made, surgical treatment is indicated. Delay in surgery carries a risk of intestinal necrosis and peritonitis.

COMMENTS

Case characteristics

A 41-year-old man with small-bowel obstruction.

Clinical diagnosis

Abdominal pain in the right mesogastrium, retention of gases, high-sounding peristalsis.

Differential diagnosis

Tumor, adhesions.

Laboratory diagnosis

Laboratory tests showed haemoconcentration, the biochemical values were all normal.

Imaging diagnosis

Abdominal computed tomography (CT)-scan showed markedly dilated small-bowel loops with multiple air-fluid levels. Oral contrast medium had reached the jejunum and the proximal ileum, but no contrast was noted distally. In the right mid-abdomen, subhepatically there was 11 cm × 6.4 cm × 7.8 cm dilated bowel-loop with a thickened wall containing fluid. A small amount of free fluid was present in the peritoneal cavity.

Pathological diagnosis

Mucosa of the diverticulum was entirely necrotic and the cavity was filled with hemorragic fluid.

Treatment

Approximately 20 cm of the small bowel with Meckel's diverticulum was resected.

Related reports

This pathology has only been reported eleven times in English-language literature and they are named in the authors references.

Experiences and lessons

In cases of small-bowel obstruction with unknown etiology, CT-scan is the most useful diagnostic tool detecting possible cause. Once the diagnosis of Meckel's diverticulum as the cause of small bowel obstruction is made, surgical treatment is indicated. Delay in surgery carries a risk of intestinal necrosis and peritonitis.

Peer review

The case report includes the description of symptoms and applied diagnostic and therapeutic procedures. The title of this paper appropriately reflects the purpose of the study.

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Room 903, Building D, Ocean International Center,
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REVIEW

Diagnosis of inflammatory bowel disease: Potential role of molecular biometrics

Amosy E M'Koma

Amosy E M'Koma, Department of Biochemistry and Cancer Biology, Meharry Medical College School of Medicine, Nashville, TN 37208-3599, United States
Amosy E M'Koma, Department of Surgery, Vanderbilt University School of Medicine, Nashville, TN 37232, United States
Author contributions: M'Koma AE contributed not only to conception and design but also participated in the acquisition of data, analysis and interpretation of data and drafting the manuscript.
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Correspondence to: Amosy E M'Koma, MD, MS, PhD, Assistant Professor of Surgery, Biochemistry and Cancer Biology, Department of Biochemistry and Cancer Biology, Meharry Medical College School of Medicine, 1005 Dr. D. B. Todd Jr. Blvd., Nashville, TN 37208-3599,
United States. amkoma@mmc.edu
Telephone: +1-615-3276796 Fax: +1-615-3276440
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Abstract

Accurate diagnosis of predominantly colonic inflammatory bowel disease (IBD) is not possible in 30% of patients. For decades, scientists have worked to find a solution to improve diagnostic accuracy for IBD, encompassing Crohn's colitis and ulcerative colitis. Evaluating protein patterns in surgical pathology colectomy specimens of colonic mucosal and submucosal compartments, individually, has potential for diagnostic medicine by identifying integrally independent, phenotype-specific cellular and molecular characteristics. Mass spectrometry (MS) and imaging (I) MS are analytical technologies that directly measure molecular species in clinical specimens, contributing to the in-depth understanding of biological molecules. The biometric-system complexity and functional diversity is well suited to proteomic and diagnostic studies. The direct analysis of cells and tissues by Matrix-Assisted-Laser Desorption/Ionization (MALDI) MS/IMS has relevant medical diagnostic potential. MALDI-MS/IMS detection generates molecular signatures obtained from specific cell types within tissue sections. Herein discussed is a perspective on the use of MALDI-MS/IMS and bioinformatics technologies for detection of molecular-biometric patterns and identification of differentiating proteins. I also discuss a perspective on the global challenge of transferring technologies to clinical laboratories dealing with IBD issues. The significance of serologic-immunometric advances is also discussed.

Key words: Inflammatory bowel disease; Diagnosis; Advances and challenges; MALDI-MS/IMS; Molecular biometrics; Immunometrics

Core tip: Pouch surgery (the restorative proctocolectomy and ileal pouch-anal anastomosis for the curative surgical treatment of ulcerative colitis and familial adenomatous polyposis) replaces the colon and rectum after proctocolectomy with a pouch constructed from the distal small bowel (ileum) and sutured to the anal canal above the dentate/pectinate line preserving the anal sphincters. The operation restores gut continuity, defecation, deferral, and discrimination, if the diagnosis is correct, which is unpredictable in 30% of the colonic-inflammatory bowel disease-patients. Mass spectrometry and imaging mass spectrometry are groundbreaking, non-invasive analytical technologies with the ability to directly measure individual molecular species in complex clinical specimens. These technologies provide quantitative and qualitative analysis of cellular systems, and allow differentiation between disease and normal molecules from the same organ. These characteristics offer diagnostic and prognostic value for clinical medicine.

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INTRODUCTION

Inflammatory bowel disease

Colonic inflammatory bowel disease (IBD) comprises Crohn's colitis (CC) and ulcerative colitis (UC), a group of diseases of the gastrointestinal (GI) tract characterized by chronic relapsing and remitting inflammation[1,2]. IBD affects as many as 1.6 million persons in the United States and 2.2 million in Europe. The incidence is increasing worldwide[1-5]. In spite of advances in IBD-therapy, IBD hospitalizations and surgery rates in the United States have increased significantly since 1990[6]. IBD is one of the five most prevalent GI disease burdens in the United States, with annual overall health care costs of more than $1.7 billion[7,8]. One to two of every 1000 people in developed countries are affected with IBD[9], and global rates seem to be increasing[1,10-12], attributable to the rapid modernization and Westernization of the population[1]. These chronic diseases result in significant morbidity and mortality, compromising quality of life and life expectancies. While there is no drug for cure for these diseases, the last three decades have seen major advances in the molecular understanding intestinal immune responses and how they relate to IBD. This, in turn, has led to the development and refinement of several new treatments. Most significant has been the development of restorative proctocolectomy (RPC) with ileal pouch-anal anastomosis (IPAA). The pelvic pouch surgery allows for the removal of the entire colon while maintaining transanal fecal continence without a permanent diverting loop ileostomy. The success of RPC (judged by the entire removal of a diseased colon while preserving gastrointestinal continuity, bowel evacuation, continence and fertility) restores physiological function and greatly improves patient health quality of life. Successful RPC also frees the healthcare system from the immense burden of current lifelong, non-curative treatments. These outcomes are dependent on a correct diagnosis and meticulous surgical techniques available at well-established IBD centers[13-15].

The etiology of IBD poorly understood. The general consensus holds that IBD is an automatic dysfunction triangle of antigen and antibody reaction against mucosal response to commensal bacteria. The fundamental question is why the immune system responds aggressively to harmless, ever-present bacteria, releasing complex mixes of cytokines, chemokines and other substances that cause inflammation. One possible explanation is that the gut immune system is compromised because of defects in the barrier function of the gut luminal epithelium[16]. Although the etiology of IBD is at present not delineated, histopathologic and clinical assessments demonstrate that CD and UC, the two major classifications of IBD, are indeed distinct entities and have different causes and discrete mechanisms of tissue damage and treatment[16-21]. UC results in inflammation and ulcerations in the mucosal and to a lesser degree submucosal linings of the colon and rectum. CD differs in that it may result in inflammation deeper within the intestinal wall (transmullary) and can occur in any parts of the digestive system (including the mouth, esophagus, stomach, duodenum, small intestine, colon and rectum). Further, Crohn's may also involve other organs outside the GI system through fistulization[22,23]. Crohn's is diagnosed in at least four patients per 100000 in the United States, and the incidence and prevalence is rising worldwide[1,10-12].

Diagnosis challenges in IBD

The current standard of care for IBD treatment is based on steroids and immunosuppressant agents, including glucocorticoids, aminosalicylates, cyclosporine, methotrexate and biologic agents such as anti-TNF-α and IL1-β. The correct IBD diagnosis is crucial for providing correct, evidence-based treatment, since treatment response and complications differ significantly among UC and CC patients[24]. The absence of specific phenotypes indicating the particular disease condition challenges pathologist interpretation and categorization of tissue morphology, subsequently leading to difficulties in diagnosis and consistent standard of care[25]. However, despite advances in our understanding of the genetic[16,26], immunologic[26,27], and environmental[1,24,28] influences that may trigger complex IBD pathologies, to date there is no single indicator sensitive enough to accurately and consistently delineate CC and UC. The available data indicate that genetic factors determine an individual's susceptibility to developing IBD, and environmental factors elicit cellular responses that drive disease progression. Histological evaluation and interpretation of tissue provides insights that directly impact care[25]. Pathologists rely mainly on microscopic visual inspection and interpretation of stained and/or dyed tissue sections to identify the disease state of a patient sample[29,30]. Inherently, these procedures possess a significant degree of subjectivity[31] and are fraught with problems[31,32]. Rigorous training in pathology subspecialties has attempted to improve the standard of care and avoid unnecessary mistakes[33]. Despite these extremely thorough standards, inevitable situations arise in which objectivity cannot be guaranteed and where significant disagreement occurs between specialists[34]. This challenge is common for IBD patient populations[13,15,35,36] To date, there is no single, absolute diagnostic test[37,38]. A diagnosis should neither be based on nor excluded by any one variable or result[39]. The consensus statement on the diagnosis, management and surveillance of both CC[40] and UC[41] recommend that "multiple" tissue biopsies from at list five sites around the colon and rectum should be collected for support of a reliable diagnosis. Of these six sites a minimum of two samples from each should be sampled[40,41]. Although the procedure is reliable, it is invasive and uncomfortable to the patients.

Table 1 Microscopic features used for the diagnosis of Crohn's colitis

Colon	
Architecture	
Crypt architectural irregularity	Focal
	Diffuse
Reduces crypt numbers/mucosal atrophy	
Irregular surface	
Chronic inflammation	
Distribution I	Focal increased in intensity
	Patchy increase
Distribution II	Diffuse increase
	Superficial
Granulomas	Transmucosal
Mucin granulomas	Basal plasma cells
Polymorph inflammation	
Lamina propria	Focal
Crypt epithelial polymorphs	Diffuse
Polymorph exudates	
Epithelial changes	
Erosion/ulceration	
Mucin	Depletion
	Preservation
Paneth cells distal to hepatic flexure	
Epithelial-associated changes	
Increased intraepithelial lymphocytes > 15	
Terminal ileum/Ileocecal /Cecum	
Architecture	Villus irregularity
	Crypt architecture
Epithelial changes	Irregularity
	Pseudopyloric gland
	Metaplasia

Reproduced by permission of the publisher from ref. [38].

Inaccurate diagnosis in IBD and consequences

When IBD predominantly involves the colon, differentiation between CC from UC is often challenging. Inaccurate diagnoses are estimated to occur in 30% of IBD patients[42,43]. In most cases the diagnostic uncertainty arises from the overlap of clinical and histologic features, making CC appear like UC[44]. This scenario is particularly relevant to young children, a population in which IBD consists of up to 80%. The differentiation between UC and CC relies on a compilation of clinical, radiologic, endoscopic, and histopathologic interpretations[40]; a compilation that is not always accurate. An estimated 15% of IBD patients are indistinguishable and are labeled as "indeterminate colitis" (IC)[45-47]. In addition, another 15% of the colonic IBD cases that undergo pouch surgery resulting from a definitive UC diagnosis (based on the pathologist's initial designation of endoscopic biopsies and colectomy specimen) will have their original UC diagnosis changed to CC based on the postoperative follow-up when clinical and histopathology changes indicate development of CC in the ileal pouch[15,35,36,48,49]. One-half of these patients will require pouch excision or diversion[49].

Because of the unpredictable nature of IBD, side effects of medications, and potential complications, some of which may end in sudden incapacitation, IBD is becoming a global health concern. Distinguishing between CC and UC is critical to therapy. The clinical experience suggests that identifying patients with CC and positive outcomes after pouch surgery is arduous. Thus, RPC should be contraindicated for CC patients, whereas IPAA is standard acceptable care for patients with UC and IC who are predicted likely to develop UC. Inevitably, pouch complications are significantly higher in patients with CC (± 64%) and IC (± 43%) *vs* patients having UC (± 22%) ($P < 0.05$)[46,47,49]. This diagnostic dilemma and the potential morbidity from a wrong diagnosis and unnecessary and/or inappropriate surgical interventions underscore the importance of research strategy focused at improving diagnosis of the colitides using molecular biometrics[42,50-52].

Clinico-histopathologic findings in Crohn's colitis

Crohn's colitis is recognized to encompass a heterogeneous group of disorders[38]. Usually CC is segmental with deep inflammation where the disease activity is transmural, with lymphoid composite extending to the sub-serosa. The Montreal classification[53] and the Paris pediatric modification[54] have brought consistency to definitions of subtypes of CC and of colitides. It is noteworthy that both the Montreal and Paris classifications rely on the location of gross disease, *i.e.*, visible lesions with more than a few aphthous ulcers. Patterns of macroscopic involvement, rather than microscopic, have been useful traditionally in predicting clinical course, as exemplified by the tendency of small bowel disease, particularly, to stricture over time. Despite the fact that microscopic involvement does not define subtypes of CC, the role of histology in the diagnosis of CC does differ according to the anatomic location of macroscopic disease[38].

Histologic features useful for the diagnosis of CC have been reviewed by Griffiths[38], (Table 1) but, according to Van Assche *et al*[40] presented at The second European evidence-based Consensus on the diagnosis and management of Crohn's colitis, there are no data available as to how many of these features must be present to allow a firm diagnosis[40]. Focal (discontinuous) chronic (lymphocytes and plasma cells) inflammation and patchy chronic inflammation, focal crypt irregularity (discontinuous crypt distortion) and granulomas (not related to crypt injury) are the generally accepted microscopic features which allow a diagnosis of CC[40]. Within one histologic section, inflammation may be immediately adjacent to an uninflamed microscopic "skip area". Mucosal changes may resemble ulcerative or infectious colitis with infiltration of the crypts by polymorphonuclear leukocytes (cryptitis or crypt abscesses), and distortion of crypt architecture. Granulomas (collections of monocytes/macrophages) in the lamina propria (not associated with crypt injury) are a corroborating feature of suspected Crohn's after exclusion of identifiable infectious etiology, but reported prevalence in mucosal biopsies at time of first diagnosis varies. The likelihood of finding granuloma is a function of the number of specimens taken, the number of sections examined,

Table 2 Classic microscopic features in untreated ulcerative colitis (comparable Crohn's colitis, hard criteria)

Feature	Ulcerative colitis	Crohn's colitis
Diffuse	Continuous disease	Segmental disease
Rectal	Involvement	Variable rectal involvement
Disease	Worse distally	Variable disease severity
Fissures	No	Fissures, sinus, fistula
Transmural aggregates	No	Transmural lymphoid aggregates
Ileal involvement	No, exception during backwash ileitis	Ileal involvement Upper gastrointestinal involvement
Granulomas	No	Granulomas

and the definition of a granuloma. Granulomas occur more commonly in the submucosa than the mucosa[55]. Hence, they are observed in 60% of surgical specimens but relevant to the question of histology for diagnosis, in only 20%-40% of mucosal biopsies[55]. Moreover, according to Griffiths[38] data indicating clinical significance or prognostic value of presence or absence of granulomata are lacking.

Clinico-histopathologic findings in ulcerative colitis

The classic microscopic features in untreated UC (and CC hard criteria) used for diagnosis, as outlined by Odze[56], and are depicted in Table 2. Clinically, the hallmark of UC is hematochezia[57,58]. Additional clinical presentations include rectal tenesmus and incontinence, abdominal pain, severe inflammation of the rectum (proctitis), leukocytosis, hospitalization for total parenteral nutrition and/or intravenous fluids correction, among others. Blood transfusion and corticosteroids are recommended when considering surgery (RPC and IPAA)[58]. As mentioned earlier, in UC, inflammation is typically confined to the mucosal layer and to the lesser degree to the submucosa. Children with UC often have evidence of chronicity, rectal frugality, and little or no architectural warping. In otherwise usual cases of UC, these conditions may lead to a confusion with CC[59-61].

Current advances in biomarker discovery to delineate the colitides

To date, there has been significant interest in attempting to identify molecular biomarkers that can accurately delineate CC and UC phenotypes. These studies have been minimally successful at identifying such biomarkers. In serum these include: placenta growth factor-1 (PLGF-1), IL-7, TGFβ1, and IL-12P40[62-67]. In biopsies obtained from the mucosa, they are Rho GD1α, desmoglein, pleckstrin, VDAC (voltage-dependent anion channel), 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG-CoA), and C10orf76[68,69]. In stool they are calprotectin, PMN-elastate, lactoferrin, and S100A12[65,70-74]. Clearly these biomarbiometrics represent an advance in the field of colitides research and have been used for clinical prognostic trials but have not been shown to delineate UC from a CC phenotype[62,64,73,74]. Thus far, the above mentioned features reflect colitides intestinal inflammation and do not discriminate UC from the CC phenotype[65].

Histology-directed proteomic advances

Histology-directed MALDI MS is the first attempt ever used to analyze and compare mined proteins of the colonic mucosal and submucosal tissue layers individually, in order to differentiate between UC and CC[42,50]. The normal *topography* of the *colon* and the layers used in mining and extraction of analytical extracts are illustrated in Figure 1. The basic steps of the methodology of histology-directed mass spectral protein profiling are outlined in Figure 2. Specialized MALDI MS offers directly the possibility of direct proteomic assessment of the tissue itself. The histologic layers of colectomy samples from patients with histologically and clinically confirmed UC and CC, with no ambiguity, are analyzed individually using MALDI MS for proteomic profiling. The results have successfully identified highly significant MALDI MS mass-to-charge ratio (m/z) signals in colonic tissue layers that appear to be phenotype-specific and are likely to help distinguish UC and CC[42,50]. Pre-sequencing and identification proteomic pattern peaks from colonic mucosal or/and submucosal tissue section are depicted in Figure 3[50]. These signatures do not correlate to tissue of origin and thus represent disease-specific markers. Some of these are found in colonic mucosa, from which endoscopic biopsies could be subjected to proteomic analysis. Other signatures come from the submucosa and could be used for proteomic studies of serum. Other protein-signatures were found in both tissue layers. Identifying proteomic patterns characteristic of one specific colitis phenotype will significantly improve our understanding of the mechanistic events associated with IBD.

It is unlikely that a single protein or small cluster of proteins will have the necessary: (1) specificity; (2) sensitivity; (3) discrimination; and (4) predictive capacity, to differentiate the heterogeneity of IBD[69]. However, if it were possible, it would require a technology that can accommodate sampling large patient cohorts, while accounting for patient variability. MS is an important profiling and identification tool for such studies[75]. As necessary as the tool is, subsequent analysis and validation methods will determine the actual success of a detection system intended for non-invasive screening and evaluating treatment efficacy. The overall goal of delineating IBD by proteomics is to illuminate the pathobiology underlying the colitides. More

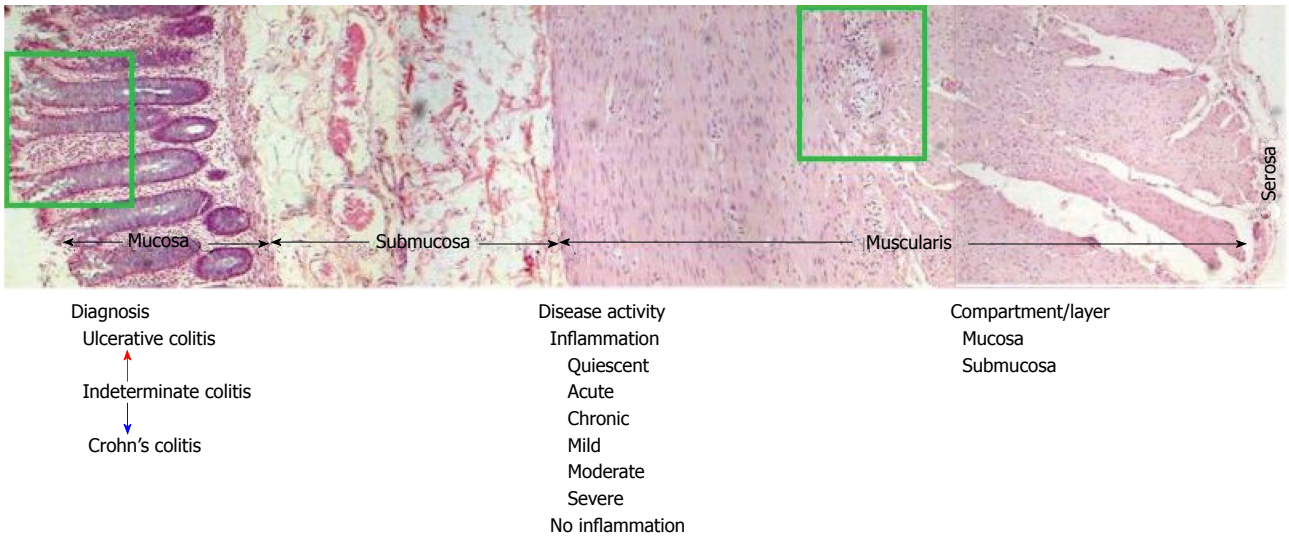

Figure 1 Human colon cross section depicts layers for mining proteomic patterns that delineates untreated ulcerative and Crohn's colitis phenotype. The colon is comprised of four distinct layers: (1) the mucosa; (2) the submucosa; (3) the muscularis (two thick bands of muscle); and (4) the serosa. Comparable proteomic patterns that are mined from these layers are analyzed, based on the diagnosis [untreated ulcerative and Crohn's colitis, (with no ambiguity)], disease activity and tissue layer.

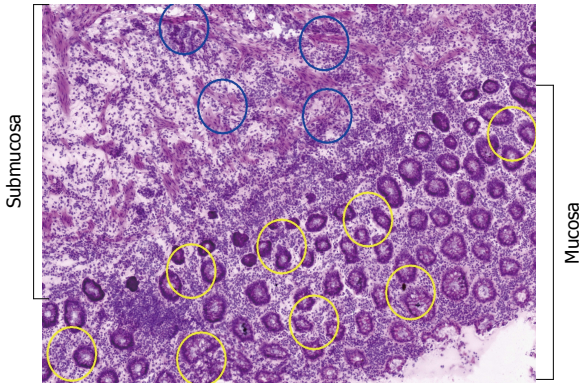

Figure 2 Histology-directed tissue layer profiling for matrix-assisted-laser desorption/ionization mass spectrometry. Digital photomicrographs acquired from histology and matrix-assisted-laser desorption/ionization sections were used to identify and designate sites of interest for profiling. Comparisons were performed in both the training and independent test set samples between inflamed mucosa Crohn's colitis (CC) *vs* ulcerative colitis (UC) and inflamed submucosa CC *vs* UC. Tissue section showing marked areas of pathological interest. Rings demonstrate matrix spots in mucosal and sub-mucosal layers (unpublished figure).

specifically, it is to identify patterns differentiating the colonic IBDs that exhibit overlapping clinical and histologic signs, but require different approaches of care. The anticipation is that this approach will eventually provide molecular biometrics of interest that can tell UC from CC through endoscopic biopsies and eventually create a serum biomarker tool assay for the identified peptide, if the protein(s) is (are) secretory and transposable. Better understandings of the bio-pathophysiologic mechanisms may allow new therapeutic and preventive avenues for maintenance or remission in IBD.

Matrix-assisted laser desorption/ionization MS

Specialized matrix-assisted laser desorption/ionization (MALDI) MS offers the possibility of direct proteomic assessment of the tissue itself[76]. The molecular specificity and sensitivity of MS can image and map biomolecules present in tissue sections. Applying complementary techniques of immunochemistry and fluorescence microscopy to MALDI MS data can improve the analysis of spatial arrangements of molecules within biological tissues. Accordingly, MALDI technology has become a popular in biology research. It combines two technologies, the MALDI "soft" ionization source and the TOF (Time of Flight) mass analyzer. The former volatilizes and ionizes molecules using a laser, a target, and an organic compound called a matrix, while the latter technology measures an ion's mass-to-charge ratio (m/z) by measuring the time it takes to reach a detector. MALDI TOF mass spectrometers come in two basic types: MALDI TOF MS and MALDI TOF/TOF MS. The latter enables tandem mass spectrometry (MS/MS) studies[69]. Thus a combination of markers may improve the chances of achieving IBD proteomics goals.

MS in combination with laser capture microdissection is another important profiling and identification tool for such studies. It allows direct tissue analysis of biomolecules and large organic molecules which are often too fragile for conventional ionization methods. These techniques may significantly enhance diagnostic accuracy and provide the basis for future bio-physiologic elucidations in IBD.

MALDI IMS

MALDI IMS stands out as a tool for imaging metabolites in the biological and medical fields, and as a new tool for pathology in the molecular age[77]. There are several advantages in IMS technology. First, IMS does not require labeling or specific probes. Second, it is a non-targeted imaging method, meaning unexpected metabolites can

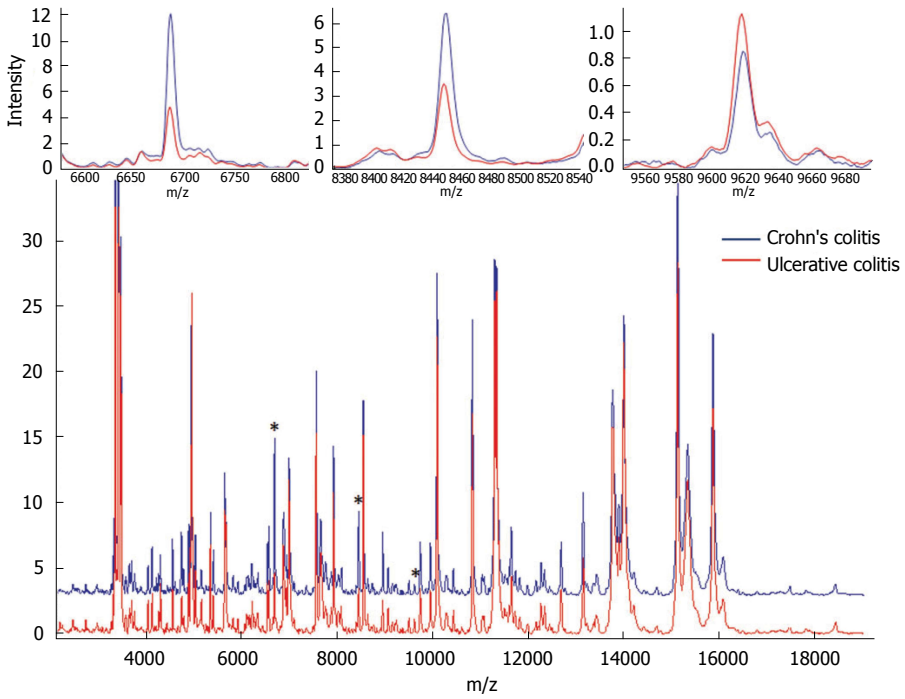

Figure 3 Show averaged mass spectrum proteomic pattern spectra from Crohn's colitis (blue) and ulcerative colitis (red). Differential distribution of three selected proteomic pattern peaks (m/z) obtained from colonic mucosal and/or submucosal tissue sections that were part of the Support Vector Machine model. They are denoted by "a" symbol in the full spectra. Reproduced with permission from the publisher: Seeley *et al*[50].

easily be imaged. Finally, several kinds of metabolites can be imaged simultaneously. The technique effectively provides a better visualization of the underlying mechanisms of biological processes of endogenous, small metabolites[78,79] and large proteins[80,81] in cells and tissues[82,83]. It can determine the distribution of hundreds of unknown compounds in a single measurement[79,84-86]. Further, IMS is capable of three-dimensional molecular images which can be combined with established imaging techniques like magnetic resonance imaging[87,88].

Due to the fact that the enormous molecular diversity of metabolite species is unknown, IMS technology is seemingly appropriate for localizing metabolites, whether they are from the molecule of interest or not[78,89,90]. The emerging technique of MALDI IMS has the capability to distinguish between parent and metabolites while maintaining spatial distribution in various tissues[91,92]. In spite of the promising advances of MALDI IMS for visual-imaging tiny metabolites, substantial concerns remain regarding its spatial resolution. The primary limitation results from the size/volume of the organic matrix crystal and analyte migration during the matrix application. There is also a lack of efficient computational techniques for constructing, processing, and visualizing large and complex 3D data which prevents experimenters from tapping its full potential[93]. In attempting to solve these important issues, researchers have devised another sophisticated method: a nanoparticle-assisted laser desorption/ionization (nano-PALDI)-based IMS, in which the matrix crystallization process is eliminated[94,95]. The use of novel nano-PALDI has enabled scientists to image compounds with spatial resolution at the cellular level (15 μmol/L; approximating the diameter of a laser spot)[96].

Serologic test advances

To date, a lack of validated information prevents recommending the use of serologic assays to screen general population patients for undiagnosed gastrointestinal symptoms in IBD-settings. As has been made clear, no unique biomarkers yet exist for the delineation between CC and UC. Serologic tests, antineutrophil cytoplasmic antibodies (ANCAs) and anti-microbial antibodies are inadequately sensitive and specific to contribute much to the diagnosis of CC or to its differentiation from UC.

ANCAs are immunoglobulin G (IgG) antibodies directed against cytoplasmic components of neutrophils[97]. The association with colitides of a subset of ANCA with a perinuclear staining pattern on immunofluorescence studies [perinuclear antineutrophil cytoplasmic autoantibodies (pANCA)] was first recognized for UC, where it was detected in 60%-70% of patients[97]. The specificity of perinuclear staining for colitides can be validated and confirmed by its disappearance after deoxyribonuclease (DNase) digestion of neutrophils. pANCA is considered a marker of the immunologic disturbance that underlies the development of chronic colonic inflammation, and should not be positive in acute self-limited, presumably infectious colitis.

Anti-*Saccharomyces cerevisiae* antibodies (ASCAs), the first anti-microbial antibodies to be described in CC, are IgG and IgA antibodies that recognize mannose sequences in the cell wall of *S. cerevisiae* strain Su1. ASCA is detected in 50%-70% of CC patients overall, 10%-15% of UC patients and in 5%-10% of controls with other

gastrointestinal disorders[97]. Newer anti-microbial antibodies (Abs), which include Abs against *Pseudomonas fluorescens*-associated sequence (anti-I2), anti-outer membrane protein C of *Escherichia coli* (anti-OmpC), anti-outer membrane protein of *Bacteroides caccae* (anti-OmpW), and anti-flagellin Abs (anti-CBir1), may result false positive and be detected in patients who otherwise have negative serology, but are nonspecific and can be detected in patients with other diseases[98,99].

Differentiation of CC from UC is clinically problematic because inflammation is only confined to the colon. pANCA is positive in up to 35% of patients with CC; ASCA is less often detected in patients with CC. Hence, the utility of combined ANCA/ASCA testing is less in the setting where it is needed most. In the one published study clearly reporting sensitivity, specificity, and predictive values of combined serologic testing, the sensitivity of ASCA+pANCA-serology for CC *vs* UC was only 32%[97]. In a long-term follow-up of patients with IC, Joossens *et al*[100] observed 26 patients who were ASCA+/pANCA- at baseline. Eight were later diagnosed with CC and 2 with UC, while the other 16 patients remained IC. The ASCA-/pANCA+ profile was even less helpful for definitive diagnosis[100].

When using upper GI biopsies, the differentiation between UC and CC is relatively straightforward in most of patients. In appropriate clinical settings, granulomatous inflammation in GI biopsies validates CC. In pediatric CC, granulomas may only be found in biopsies from the upper GI. Without routine upper endoscopy, these cases will be missed. If granulomas are not found, a diagnosis of CC or UC can be derived from endoscopic findings with histology combined with clinical and imaging determinations[101]. Determining cases of IBD as CC, UC, or IC is largely a matter of nomenclature. Supporting a determination with evidence from endoscopies, magnetic resonance enterography, or other techniques, improves clinical labelling of the condition. The colitides are a continuum between CC and UC, with a variety of inflammations between. Teasing out overlapping genetic profiles for UC and CC will be critical to applying correct treatment more accurately than using current nomenclature categories based on a current standard of histology[100]. Application and refinement of the above technologies and techniques will improve the possibility of approaching patients with individualized options reducing ineffective or unnecessary surgery. Usage of molecular biometrics to differentiate diseases of the same organ[38,102,103] is becoming ground breaking in improving diagnostic challenges in colonic IBD settings[42,50,104]. IBD has no permanent drug cure and results in significant morbidity and mortality[9,104,105]. UC is absolute colonic disease while CC can involve any part of the GI system from the mouth to the anus, which may transmurally involve partial to a full-thickness of the intestinal wall[43] and other organs through fistulization[106-108]. These diseases share several clinical biometric signatures but have different causes, mechanisms of tissue damage, and treatment options[16,109]. Therefore, accurate diagnosis is paramount for provision of correct pharmacologic therapy[110,111] and surgical care[112-114].

CONCLUSION

The term "colitides" characterizes colonic IBD and comprises ulcerative colitis and Crohn's colitis (UC and CC). The etiopathogenesis of UC and CC remains enigmatic. Diagnostic accuracy for distinguishing these two pathologies is still a significant problem in GI medicine and is hindered by a growing overlap of histopathological interpretation. Despite all efforts, many patients continue to remain undetermined as UC or CC, and are said to have indeterminate colitis. Differentiations of UC and CC are concluded from imprecise clinical, histopathologic, and other examinations. This results in speculative colitis staging and severity which cannot be conclusively differentiated in up to 30% of patients with IBD. CC and UC diagnostic features often overlap[115] even after a thorough histological assessment, the current gold-standard for distinguishing type of inflammation (for CC: lack of non-specific inflammation not confined beyond mucosa and diffused or focal granulomatous *etc*. For UC: inflammation limited to the mucosa, diffuse infiltration of acute and chronic inflammatory cells in the mucosa, continuous damage from the rectum to proximal colon, *etc*.).

Treatment options for UC and CC differ significantly. Thus appropriate individualized prognosis and treatment requires accurate diagnosis. An estimated 90% of patients with IC undergo pouch surgery (RPC and IPAA) for fulminant colitis[36,48,49,115,116] contrasting with 30% of patients in whom UC or CC was a correct diagnosis. Additionally, failure to recognize specific indicators of CC (*e.g*., granulomas and transmural inflammation) often leads to mistakes in pathological interpretation[24,36]. This results in a reciprocal misdiagnosis rate of 15% (CC as UC: UC as CC). Adding = the 15% of cases labeled as IC accounts for nearly a third of the all IBD patients. Those undergoing surgery for a presumably confirmed diagnosis of UC subsequently are diagnosed postoperatively with recurrent CC in the ileal pouch[36]. This is critical because functional failure and higher complication rates are estimated at up to 60%[35,117-123] and often require excision of the pouch with a permanent end ileostomy[35,121-124]. At this stage, patient health quality of life is significantly jeopardized for life.

There has been wide ranging interest in attempting to identify molecular biomarkers that can consistently delineate these diseases. These studies have been minimally successful at identifying quiescent or active IBD in serum[62-67], in mucosal biopsies[68,69], and in fecal matter[65,70-74]. Clearly these features represent an intriguing advance in the science of IBD for clinical disease prognostic purposes. However, these markers have not been shown to distinguish UC from CC phenotype[62,64,73,74]. A serology panel including ANCA, pANCA, anti-saccharomyces cerevisae IgG and IgA antibodies (ASCA), calgranulin (S100A12), anti-OmpC antibodies, fecal lactoferrin, calprotectin, and polymorphonuclear neutrophil

elastase (PMN-e)[65] is marketed as a promising approach to monitor disease activity and prognosis and may prove to be beneficial in the management of IBD. The specificity, sensitivity and diagnostic accuracy of these parameters with reference to clinical disease indices and/or endoscopically measured inflammation in IBD setting remain unclear. What we have learned to date is that: (1) Although not yet commercially available as tests, patients with CC are more likely than healthy control and/or IBD patients to be positive for a range of biomarkers such as S100A12 (calgranulin), ASCA, OmpC, CBir1, pseudomonas fluorescens protein, and pANCA[125,126]. Significant increases of these proteins are noted during active intestinal inflammation. The greater the number of positive serologies and the higher the titer, the more aggressive the course. These biomarkers are also seen in an active UC[127]; (2) A combination of these biomarkers and a disease-specific activity index could promote the diagnostic accuracy in clinical medicine with reference to endoscopic inflammation but at present none are superior in the ability to reflect endoscopic inflammation[70]; (3) These molecular biometrics significantly assist in predicting relapses in patients with confirmed IBD (active or quiescent)[2-5,17,21,128] but are not discriminatory between UC/CC; (4) Patients who are pANCA+ and ASCA- are more likely to have UC than CC, while in pANCA- and ASCA+ patients the reverse may be true[67]. However, these biomarkers have not demonstrated clinical utility as predictors or monitoring tools of IBD activity[67].

At the present time there is insufficient biometric information to recommend use of serologic assays in screening for IBD in patients from the general population who have undiagnosed gastrointestinal symptoms. Further, no efficacy for the delineation of CC and UC clearly exist.

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MINIREVIEWS

Medical management of patients after bariatric surgery: Principles and guidelines

Abd Elrazek Mohammad Ali Abd Elrazek, Abduh Elsayed Mohamed Elbanna, Shymaa E Bilasy

Abd Elrazek Mohammad Ali Abd Elrazek, Department of Gatsroenterology and Hepatology, Al-Azhar Faculty of Medicine, Al-Azhar University, Asiut Branch, Asuit 721572, Egypt
Abduh Elsayed Mohamed Elbanna, Department of General, Laparoscopic and Bariatric Surgery-Head of Bariatric; unit (D) - Al Husain university Hospital, Al Azhar University, Darrasa-Cairo 16789, Egypt
Shymaa E Bilasy, Department of Biochemistry, Faculty of Pharmacy, Suez Canal University, Ismailia 41522, Egypt
Author contributions: Abd Elrazek MAA wrote, drafted the manuscript and designed the figures; Elbanna AEM wrote the manuscript and designed figures; Bilasy SE wrote and critical revised the manuscript; all authors approved the final version of this review.
Correspondence to: Dr. Abd Elrazek Mohammad Ali Abd Elrazek, Department of Gatsroenterology and Hepatology, Al-Azhar Faculty of Medicine, King Faisal Area, Al-Azhar University, Asiut 721572, Egypt. ahmadrazek@gmail.com
Telephone: +2-88-2180445 Fax: +2-88-2181194
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Abstract

Obesity is a major and growing health care concern. Large epidemiologic studies that evaluated the relationship between obesity and mortality, observed that a higher body-mass index (BMI) is associated with increased rate of death from several causes, among them cardiovascular disease; which is particularly true for those with morbid obesity. Being overweight was also associated with decreased survival in several studies. Unfortunately, obese subjects are often exposed to public disapproval because of their fatness which significantly affects their psychosocial behavior. All obese patients (BMI $\geqslant$ 30 kg/m^2) should receive counseling on diet, lifestyle, exercise and goals for weight management. Individuals with BMI $\geqslant$ 40 kg/m^2 and those with BMI > 35 kg/m^2 with obesity-related comorbidities; who failed diet, exercise, and drug therapy, should be considered for bariatric surgery. In current review article, we will shed light on important medical principles that each surgeon/gastroenterologist needs to know about bariatric surgical procedure, with special concern to the early post operative period. Additionally, we will explain the common complications that usually follow bariatric surgery and elucidate medical guidelines in their management. For the first 24 h after the bariatric surgery, the postoperative priorities include pain management, leakage, nausea and vomiting, intravenous fluid management, pulmonary hygiene, and ambulation. Patients maintain a low calorie liquid diet for the first few postoperative days that is gradually changed to soft solid food diet within two or three weeks following the bariatric surgery. Later, patients should be monitored for postoperative complications. Hypertension, diabetes, dumping syndrome, gastrointestinal and psychosomatic disorders are among the most important medical conditions discussed in this review.

Key words: Obesity; Bariatric surgery; Postoperative care; Body-mass index; El banna

Core tip: Obesity is a growing health concern worldwide that impacts the life of individuals both physically and psychologically. There are several well-established health hazards associated with obesity. Additionally, obese subjects are often exposed to public disapproval because of their fatness which significantly affects their psychosocial behavior. Bariatric surgery is one of the definite solutions for obesity. In this review, we will briefly discuss the general guidelines that should be considered before bariatric surgery. Also, we discuss the protocols of patients' postoperative care and the management of medical disorders that must be considered after bariatric surgery.

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INTRODUCTION

Obesity is a chronic disease that impairs health-related quality of life in adolescents and children. In 2010, overweight and obesity were estimated to cause 3.4 million deaths, 3.9% of years of life loss, and 3.8% of disability-adjusted life-years worldwide. Obesity is increasing in prevalence, currently, the proportion of adults with a body-mass index (BMI) of 25 kg/m^2 or greater is 36.9% in men and 38.0% in women worldwide[1]. Attempts to explain the large increase in obesity in the past 30 years focused on several potential contributors including increase in caloric intake, changes in the composition of diet, decrease in the levels of physical activity and changes in the gut microbiome. More than 50% of the obese individuals in the world are located in ten countries (listed in order of number of obese individuals): United States, China, India, Russia, Brazil, Mexico, Egypt, Germany, Pakistan and Indonesia. Although age-standardized rates were lower in developing than in developed countries overall, 62% of the world's obese individuals live in developing countries. Recently, United States accounted for 13% of obese people worldwide, the prevalence of obesity was 31.7% and 33.9% among adult men and women, respectively. In Canada 21.9% of men and 20.5% of women are obese. Reported prevalence rates of obesity include: 27.5% of men and 29.8% of women in Australia, 24.5% of men and 25.4% of women in the United Kingdom, in Germany 21.9% of men and 22.5% of women, in Mexico 20.6% of men and 32.7% of women, in South Africa 13.5% of men and 42% of women, in Egypt 26.4% of men and 48.4% of women, in Saudi Arabia 30% of men and 44.4% of women and in Kuwait 43.4% of men and 58.6% of women (Table 1, Figure 1)[2]. There are several well-established health hazards associated with obesity, *e.g.,* nonalcoholic steatohepatitis (NASH), type 2 diabetes, heart disease, chronic kidney disease, gastroesophageal reflux disease, gastrointestinal motility disorders, sexual disorders, cerebrovascular stroke, certain cancers, osteoarthritis, depression and others[3-10]. The risk of development of such complications rises with the increase of adiposity, while weight loss can reduce the risk. Bariatric surgery could be the definitive clue in many situations[11-15]. Bariatric surgery is one of the fastest growing operative procedures performed worldwide, with an estimated > 340000 operations performed in 2011. While the absolute growth rate of bariatric surgery in Asia was 44.9% between 2005 and 2009, the numbers of procedures performed in the United States plateaued at approximately 200000 operations per year[16,17]. Starting in 2006, the Center for Medicare and Medicaid Services, United States, restricted the coverage of bariatric surgery to hospitals designated as "Centers of Excellence" by two major professional organizations[18]. Medical management and follow up of patients who have undergone bariatric surgery is a challenge due to post operative complications.

GENERAL GUIDELINES FOR SURGEONS/ GASTROENTEROLOGISTS

A well skilled physician or a surgeon has to consider the followings: (1) as the prevalence of obesity increases so does the prevalence of the comorbidities associated with obesity. Losing weight means overcoming illness at the present, complications in future and alleviating the economic burden in the present and future; (2) Overweight; BMI between 25 and 30, technically refers to excessive body weight, whereas "obesity" BMI $\geqslant$ 30 kg/m^2 refers excessive body fat, "Severe obesity", BMI $\geqslant$ 35 kg/m^2, or "morbid obesity" refers to individuals with obesity-related comorbidities. Furthermore, severe obesity and morbid obesity groups who failed dietary and medical regimens are candidates for bariatric surgery; (3) Children obesity; refers to children with BMI > 95th percentile for their age and sex and "overweight" refers to children with BMI between the 85th and 95th percentile for their age and sex; (4) Patients undergoing a bariatric operation should have a nutritional assessment for deficiencies in macro and micronutrients, also with no contraindication for such a major operation; (5) Most of bariatric procedures are performed in women (> 80%) and approximately half of these (> 40% of all bariatric procedures) are performed in reproductive aged women, accordingly, pregnancy planning and contraception options should be discussed in details with women who will undergo bariatric procedures. Fertility improves soon after bariatric surgery, particularly in middle-aged women, who were anovulatory. Additionally, oral contraceptives may be less effective in women who have undergone malabsorptive bariatric procedure. Therefore, it is better to delay pregnancy for 6-12 mo following bariatric surgery. Risk of preeclampsia, gestational diabetes, and macrosomia significantly decrease post bariatric surgery, but the risk of intrauterine growth restriction/small infants for their gestational age may increase. Body contouring surgery is in high demand following bariatric surgery; (6) All bariatric operations are accompanied with restrictive and/or malabsorption maneuvers; less food intake and malabsorption concepts; (7) The most common types of bariatric surgeries performed worldwide are Sleeve gastrectomy (SG): This procedure involves the longitudinal excision of the stomach and thus shaping the remaining part of the stomach into a tube or a "sleeve" like structure. SG removes almost 85% of the stomach (Figure 2); Roux-en-Y gastric bypass (RYGB): It reduces the size of the stomach to the size of a small pouch that is directly surgically attached to the lower part of the small intestine. In this procedure, most of the stomach and the duodenum are surgically stapled and therefore, bypassed (Figure 3); The laparoscopic adjustable gastric band (AGB): This is one of the least invasive procedures,

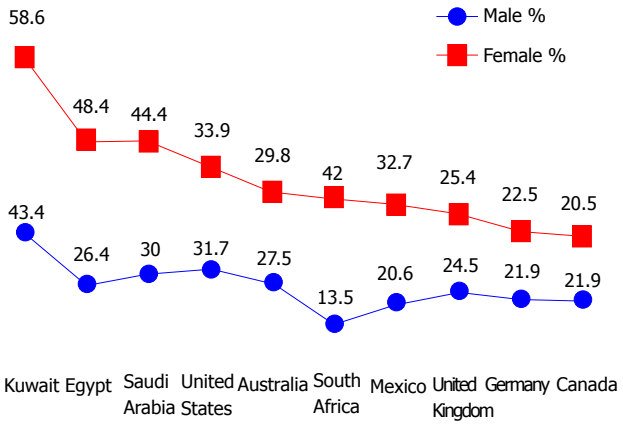

Figure 1 Male to female prevalence in different countries worldwide.

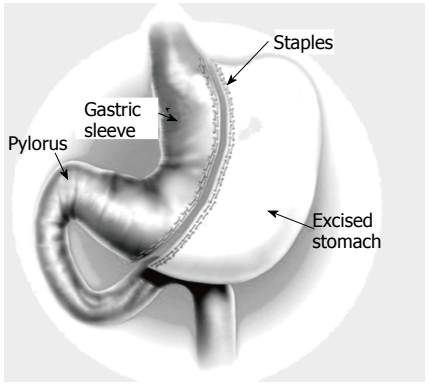

Figure 2 Schematic presentation of sleeve gastrectomy.

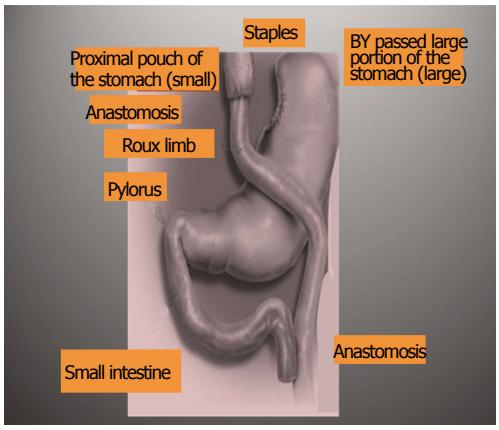

Figure 3 Schematic presentation of Roux-in Y Gastrectomy.

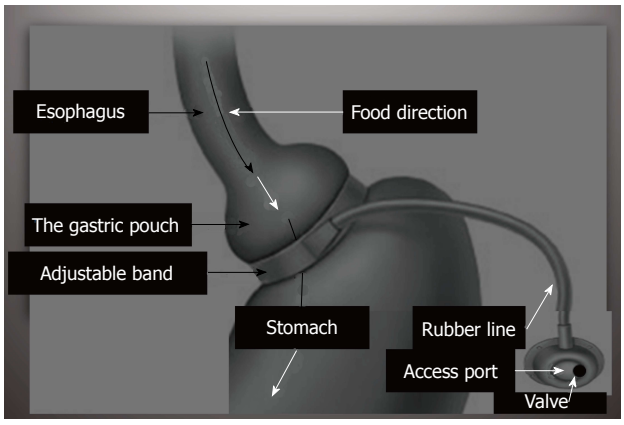

Figure 4 Schematic presentation of adjustable gastric band.

where the surgeon inserts an adjustable band around a portion of the stomach and therefore, patients feel fuller after eating smaller food portions (Figure 4). Bariatric surgical procedures, particularly RYGB, plus medical therapy, are effective interventions for treating type 2 diabetes. Improvement in metabolic control is often evident within days to weeks following RYGB; and (8) Complications reported following bariatric surgery vary based upon the procedure performed. Cholilithiasis, renal stone formation and incisional hernia could be the delayed phase complications; on the other hand, bleeding, leaking, infection and pulmonary embolism could be the early phase complications following the bariatric procedure. The overall 30-d mortality for bariatric surgical procedures worldwide is less than 1%.

POST OPERATIVE CARE AND FOLLOW UP

Early post operative period; (1-3) d post bariatric surgery

Patients undergoing a bariatric operation are admitted to the post-anesthesia care unit (PACU) immediately at the conclusion of the operation. Usually, on postoperative day (POD) one, we begin oral therapy in tablet or crushed-tablet and liquid form if there is a naso-gastric tube after the gastrografin leak test. A basic metabolic profile (*e.g.,* complete blood count, electrolytes, renal function, liver function, prothrombin time and partial thromboplastin time) should be obtained every 12 h for the successive two PODs, then every 24 h for another 3 d. Oxygen is administered by nasal cannula and weaned thereafter. The likelihood that, early specific complication, will arise for a given patient is determined by the nature of the procedure, the anesthetic techniques used, and the patient's preoperative diseases. Respiratory problems are common complication in the early postoperative period following bariatric surgery. Patients with significant comorbidities, particularly neuromuscular, pulmonary, or cardiac problems are at a higher risk for respiratory compromise, but any patient can develop hypoxemia following bariatric surgery. For prophylaxis against Deep Venous Thrombosis (DVT) following bariatric surgeries, ultrasound evaluation is recommended for all patients, D-dimer test should be applied for suspected patients with DVT, especially after long operative time, repeat ultrasound or venography may be required for those with suspected calf vein DVT and a negative initial ultrasound investigation[19,20].

Late post operative monitoring

After the PACU period, most patients are transferred to the inpatient surgical postoperative unit. For the next 24-72 h, the postoperative priorities include ruling out an

Table 1 Prevalence of obesity in different countries worldwide

Country	Male	Female
United States	31.70%	33.90%
Canada	21.90%	20.50%
United Kingdom	24.50%	25.40%
Australia	27.50%	29.80%
Germany	21.90%	22.50%
Mexico	20.60%	32.70%
South Africa	13.50%	42%
Egypt	26.40%	48.40%
Saudi Arabia	30%	44.40%
Kuwait	43.40%	58.60%

anastomotic leak following laparoscopic RYGB or laparoscopic SG. If no leak is observed, patients are allowed to start a clear liquid diet and soft drinks. The postoperative care team cares for the following: control of pain, care of the wound, continuous monitoring of blood pressure, intravenous fluid management, pulmonary hygiene, and ambulation. Post-bariatric nausea and vomiting is directly correlated with the length of the surgery; it also increases in females, non-smokers, and those patients with prior history of vomiting or motion sickness. Prophylaxis with pharmacologic treatment before the development of post operative nausea and vomiting significantly reduces its incidence after surgery[21-23].

After hospital discharge

Diet: Usually patients are discharged 4-6 d after surgery. Most patients are typically discharged from the hospital on a full liquid diet, patients should be taught to keep monitoring their hydration and urine output. Approximately two-three weeks after surgery, the diet is gradually changed to soft, solid foods. The average caloric intake ranges from (400) to (800) kcal/d for the first month, and thus the daily glycemic load is greatly reduced. We encourage patients to consume a diet consisting of salads, fruits, vegetables and soft protein daily.

To control the epigastric pain and vomiting, patients should be taught to eat slowly, to stop eating as soon as they reach satiety and not to consume food and beverages at the same time. For most patients suffering chronic vomiting, prokinetic therapy and proton-pump inhibitors (PPIs) should be considered. Patients, who underwent SG, LAGB or RYGB, benefit from a well-planned dietary advancement. Patients should understand that the surgery has changed their body but not the environment, they have to choose healthy foods, do not skip meals and to visit the dietitian regularly in the first 12 mo after surgery. However, if food intolerance develops, patients may choose a more vegetarian-based diet. Nevertheless, fresh fruits and vegetables are usually tolerated without a problem. The daily protein intake should be between 1.0 to 1.5 g/kg ideal body weight per day[24]. The biliopancreatic diversion/duodenal switch (BPD/DS) is a malabsorptive procedure for both macro- and micronutrients. Hence, we encourage higher protein intake of 1.5 g to 2.0 g of protein/kg ideal body weight per day, making the average protein requirement per day approximately 90 g/d[25,26]. Alcohol is better prevented in the first 6-12 mo after surgery[27].

Monitoring: Patients should generally have their weight and blood pressure measured weekly until the rapid weight loss phase diminishes, usually within 4-6 mo, then again at 8, 10 and 12 mo, and annually thereafter. Patients with diabetes are encouraged to check their blood glucose daily. Glycemic control typically improves rapidly following bariatric surgery. Patients maintained on antihypertensive or diabetic medications at discharge should be monitored closely for hypotension and hypoglycemia, respectively, and medications should be adjusted accordingly. We recommend that the following laboratory tests be performed at three, six, nine months and annually thereafter: (1) Complete Blood Count; (2) Electrolytes; (3) Glucose and Glucose Tolerance test; (4) Complete iron studies; (5) Vitamin B12; (6) Aminotransferases, alkaline phosphatase, bilirubin, GGT; (7) Total protein and Albumin; (8) Complete lipid profile; (9) 25-hydroxyvitamin D, parathyroid hormone; (10)Thiamine; (11) Folate; (12) Zinc; and (13) Copper.

Complications following the surgical treatment of severe obesity vary based upon the procedure performed. Secondary hyperparathyroidism, Hypocalcemia, Gastric remnant distension, Stomal stenosis/Obstruction, Marginal ulcerations, Cholilithiasis, Ventral incisional hernia, Internal hernia, Hiatus Hernia, Short bowel syndrome, Renal failure, Gastric prolapse, infection, Esophagitis, Reflux, Vomiting, Hepatic abnormalities and dumping syndrome are common late-phase complications after bariatric surgery. However, the clinician should aware of complications specific for every bariatric procedure[28,29]. Before therapy, the clinician should understand that the impact of various bariatric surgeries on drug absorption and metabolism are scarce. On the other hand, RYGB and other malabsorptive procedures that significantly exclude the proximal part of the small intestine, decrease the surface area where most drug absorption occurs and may result in a reduction in systemic bioavailability[30-32].

COMMON MEDICAL CONDITIONS FOLLOWING BARIATRIC SURGERY

Hypertension

Hypertension is not always related to obesity, and dietary interventions do not assure the normalization of blood pressure. However weight loss, whether by an intensive lifestyle medical modification program or by a bariatric operation, improves obesity-linked hypertension. Patients should be monitored weekly until the blood pressure has stabilized, and patients may need to resume antihypertensive medications, but often at adjusted doses[33].

Diabetes

Patients with diabetes should have frequent monitoring of blood glucose in the early postoperative period

and should be managed with sliding scale insulin. Many diabetic patients have a decreased need for insulin and oral hypoglycemic agents after bariatric surgery. Oral sulfonylureas and meglitinides should be discontinued postoperatively as these medications can lead to hypoglycemia after bariatric surgery. Metformin is the safest oral drug in the postoperative period, since it is not associated with dramatic fluctuations in blood glucose. RYGB is associated with durable remission of type 2 diabetes in many, but not all, severely obese diabetic adults. However those who underwent LAGB generally exhibit a slower improvement in glucose metabolism and diabetes as they lose weight in a gradual fashion[34,35].

Reflux

Medications for gastroesophageal reflux disease (GERD) may be discontinued after RYGB and Laparoscopic AGB, however, SG has been associated with an increased incidence of GERD in some procedures. Recurrent GERD symptoms after RYGB, particularly when accompanied by weight regain, should raise the possibility of a gastrogastric fistula between the gastric pouch and remnant, and should be investigated by an upper GI contrast study or CT scan and referred to the bariatric surgeon. Upper endoscopy is the best investigation to exclude other esophagogastroduodenal disorders. GERD may be associated with esophageal complications including esophagitis, peptic stricture, Barrett's metaplasia, esophageal cancer and other pulmonary complications. Failure of the PPI treatment to resolve GERD-related symptoms has become one of the most common complications of GERD after bariatric surgery. Most patients who fail PPI treatment have Non Erosive Reflux Disease and without pathological reflux on pH testing. In patients with persistent heartburn despite of medical therapy, it is reasonable to recommend avoidance of specific lifestyle activities that have been identified by patients or physicians to trigger GERD-related symptoms[36-38].

Nausea and vomiting

Nausea and vomiting can often be helped by antiemetic or prokinetic drugs, however, some patients have chronic functional nausea and/or vomiting that does not fit the pattern of cyclic vomiting syndrome or other gastrointestinal disorders, hence particular attention should be directed to potential psychosocial factors post bariatric surgery. Therefore, low dose antidepressant medications and psychotherapy should be addressed. On demand CT scan and Gastroscopy could be the gold standard investigations in chronic situations[39,40].

Marginal ulceration

Due to increased risk of ulcer formation from nonsteroidal anti-inflammatory drugs (NSAIDs), these medications should be discontinued postoperatively, especially after RYGB. NSAID use is associated with an increased risk of bleeding. If analgesic or anti-inflammatory treatment is needed, the use of acetaminophen is preferred in a dose of 1-2 g/daily[41-45]. Other factors associated with increased risk of ulcer formation are smoking, alcohol, spicy food, gastrogastric fistulas, ischemia at the site of surgical anastomosis, poor tissue perfusion due to tension, presence of foreign material, such as staples and/or Helicobacter pylori infection. Diagnosis is established by upper endoscopy. According to our strategy, all patients should undergo diagnostic upper endoscopy to exclude congenital or GI diseases prior to bariatric procedures. Medical management is usually successful and surgical intervention is rarely needed[46-48].

DUMPING SYNDROME

Dumping syndrome or rapid gastric emptying is a group of symptoms that most likely occur following bariatric bypass. It occurs when the undigested contents of the stomach move too rapidly into the small intestine. Many patients who underwent bariatric bypass experienced postprandial hypoglycemia. However, the dumping syndrome usually occurs early (within one hour) after eating and is not associated with hypoglycemia. It is presumed to be caused by contraction of the plasma volume due to fluid shifts into the gastrointestinal tract. Dumping syndrome may result in tachycardia, abdominal pain, diaphoresis, nausea, vomiting, diarrhea, and sometimes, hypoglycemia. The late dumping syndrome is a result of the hyperglycemia and the subsequent insulin response leading to hypoglycemia that occurs around 2-3 h after a meal. Dumping syndrome is a common problem that occurs in patients who have undergone RYGB and when high levels of simple carbohydrates are ingested. Accordingly, patients who have experienced postgastric bypass bariatric surgery should avoid foods that are high in simple sugar content and replace them with a diet consisting of high fiber and protein rich food. Eating vegetables and salad is encouraged; beverages and alcohol consumption are better avoided[49].

PSYCHOSOMATIC DISORDERS/ DEPRESSION

Many patients usually experience enhanced self esteem and improved situational depression following weight loss. Depression often requires continued treatment, specially that, many patients with severe obesity often use food for emotional reasons. Therefore, when those patients experience a small gastric pouch postoperatively they may grieve the loss of food. Many studies documented the relationship between eating disorder and anxiety disorder, depression or schizophrenia[50,51]. Displaced emotions can result in somatization with symptoms of depression and psychosomatic disorders. It is important that clinicians recognize the psychological aspect of food loss after bariatric surgery, and reassure patients that the symptoms are related to the small gastric pouch size. Antidepressants often help to decrease the anxiety related to grieving associated with food loss, although the

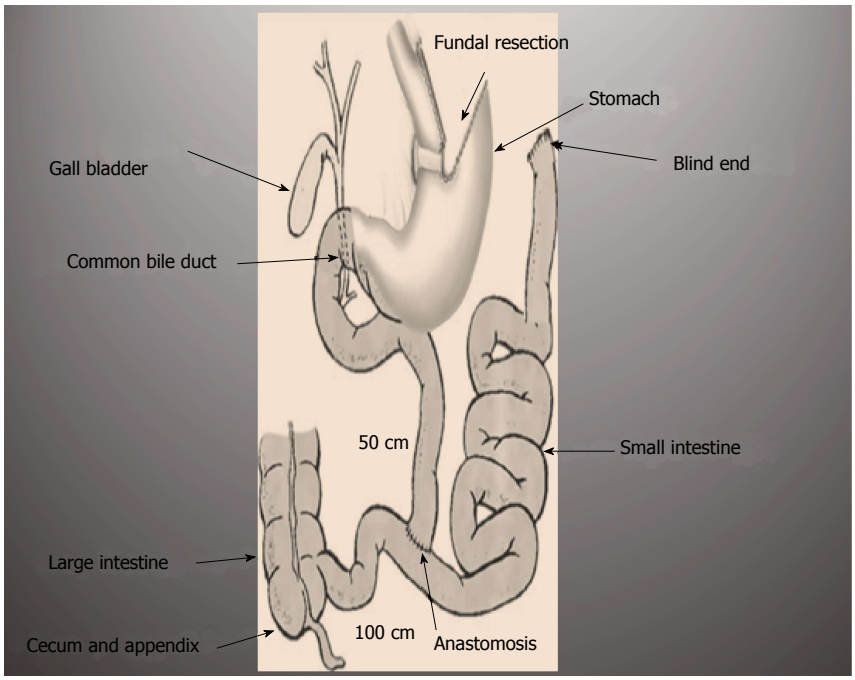

Figure 5 Novel El Banna surgical procedure.

use of antidepressants needs to be approached with an empathetic style. Behavioral and emotive therapies are reported to be very helpful[52,53].

OUTCOME

Bariatric surgery remains the only effective sustained weight loss option for morbidly obese patients. The American Society for Metabolic and Bariatric Surgery estimated that in 2008 alone, about 220000 patients in the United States underwent a weight loss operation. The optimal choice for type of bariatric procedure, *i.e.*, RYGB, SG, AGB or the selected surgical approach, *i.e.,* open versus laparoscopic depends upon each individualized goals, *i.e.*, weight loss, glycemic control, surgical skills, center experience, patient preferences, personalized risk assessment and other medical facilities. Laparoscopic sleeve gastrectomy is the most common bariatric procedure. However weight re-gain after long-term follow-up was reported[54-58]. Prospective studies and reviews report a general tendency for patients with metabolic disorders to improve or normalize after bariatric surgery. However weight loss is highly variable following each procedure. Recent studies have evaluated the potential impact of obesity on outcomes in organ-transplant recipients, for example bariatric surgery may be an important bridge to transplantation for morbidly obese patients with severe heart failure[59-63].

RECENT ADVANCES IN BARIATRIC SURGERY

A modified intestinal bypass bariatric procedure (Elbanna operation), reported a novel surgical technique designed to maintain good digestion, better satiety, and selective absorption with less medical and surgical complications (Figure 5). This procedure preserves the proximal duodenum and the terminal ileum and thus preserving the anatomical biliary drainage and enterohepatic circulation[64,65].

Recently, a novel bariatric technique dedicated; Modified Elbanna technique in childhood bariatric, showed promising success in pediatric surgeries (non published data).

CONCLUSION

The rising prevalence of overweight and obesity in several countries has been described as a global pandemic. Obesity can be considered like the driving force towards the pre-mature deaths. It increases the like hood for the development of diabetes, hypertension and NASH. The American Heart Association identified obesity as an independent risk factor for the development of coronary heart disease. In order to minimize post-surgical cardiovascular risk, surgical weight loss may become a more frequently utilized option to address obesity. Currently, bariatric surgery passes through a plateau phase, hence medical management and follow up of patients who have undergone bariatric surgery is a challenge.

FUTURE RECOMMENDATIONS

Children obesity has become one of the most important public health problems in many industrial countries. In the United States alone, 5% of children have severe obesity. It is imperative that health care providers should identify overweight and obese children so as to start early counseling and therapy. To establish a therapeutic relationship and enhance effectiveness, the communication and interventions should be supported by the entire family, society, school, public media and primary health care. Bariatric surgery could be considered in complicated cases that failed all other options.

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OBSERVATIONAL STUDY

Factors influencing the diagnostic accuracy and management in acute surgical patients

Muhammad Shafique Sajid, Thaddeus Hollingsworth, Mike McGlue, William FA Miles

Muhammad Shafique Sajid, William FA Miles, Department of General, Laparoscopic and Endoscopic Colorectal Surgery, Western Sussex Hospitals NHS Foundation Trust, Worthing Hospital, Worthing, West Sussex BN11 2DH, United Kingdom
Thaddeus Hollingsworth, Mike McGlue, The American University of the Caribbean School of Medicine, FL 33134, United States
Author contributions: All authors contributed to this manuscript.
Correspondence to: Muhammad Shafique Sajid, Surgical Specialist Registrar, Department of General, Laparoscopic and Endoscopic Colorectal Surgery, Western Sussex Hospitals NHS Foundation Trust, Worthing Hospital, Washington Suite, North Wing, Worthing, West Sussex BN11 2DH, United Kingdom. surgeon1wrh@hotmail.com
Telephone: +44-01-903205111 Fax: +44-01-903285010
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Abstract

AIM: To evaluate the diagnostic accuracy (DA) in acute surgical patients admitted to a District General Hospital.

METHODS: The case notes of all acute surgical patients admitted under the surgical team for a period of two weeks were reviewed for the data pertaining to the admission diagnoses, relevant investigations and final diagnoses confirmed by either surgery or various other diagnostic modalities. The diagnostic pathway was recorded from the source of referral [general practitioner (GP), A and E, in-patient] to the correct final diagnosis by the surgical team.

RESULTS: Forty-one patients (23 males) with acute surgical admissions during two weeks of study period were evaluated. The mean age of study group was 61.05 ± 23.24 years. There were 111 patient-doctor encounters. Final correct diagnosis was achieved in 85.4% patients. The DA was 46%, 44%, 50%, 33%, 61%, 61%, and 75% by GP, A and E, in-patient referral, surgical foundation year-1, surgical senior house officer (SHO), surgical registrar, and surgical consultant respectively. The percentage of clinical consensus diagnosis was 12%. Surgery was performed in 48.8% of patients. Sixty-seven percent of GP-referred patients, 31% of A and E-referred, and 25% of the in-patient referrals underwent surgery. Surgical SHO made the most contributions to the primary diagnostic pathway.

CONCLUSION: Approximately 85% of acute surgical patients can be diagnosed accurately along the diagnostic pathway. Patients referred by a GP are more likely to require surgery as compared to other referral sources. Surgical consultant was more likely to make correct surgical diagnosis, however it is the surgical SHO that contributes the most correct diagnoses along the diagnostic pathway.

Key words: Diagnostic accuracy; Diagnostic error; Misdiagnosis; Premature closure

Core tip: Approximately 85% of acute surgical patients can be diagnosed accurately along the diagnostic pathway. One of the strategies to reduce diagnostic error is to develop pathways for feedback. It is particularly important to develop feedback pathways for the junior doctors, as it has been shown that less experienced doctors tend to most over-estimate their diagnostic accuracy. With anonymity removed, the basic design of this study seems well suited to enable feedback to each physician involved in the care of an acute surgical patient.

Sajid MS, Hollingsworth T, McGlue M, Miles WFA. Factors influencing the diagnostic accuracy and management in acute surgical patients. *World J Gastrointest Surg* 2014; 6(11): 229-234 Available from: URL: http://www.wjgnet.com/1948-9366/full/v6/i11/229.htm DOI: http://dx.doi.org/10.4240/wjgs.v6.i11.229

INTRODUCTION

Diagnostic errors have recently begun to receive more attention as a preventable source of patient harm. Diagnostic errors are estimated to account for 80000-160000 deaths per year[1]. Misdiagnosis has been the leading cause of medical malpractice payments over the last 25 years, making up 28.6% of claims and 35.2% of total payouts[1]. Missed, incorrect, or delayed diagnoses are estimated to occur in 15% of clinical cases, accounting for 8%-20% of adverse medical events[2]. Diagnosis is the most critical of a physician's skills. Nuland previously so perfectly stated, "It is every doctor's measure of his abilities; it is the most important ingredient in his professional self image"[3], yet even with such a high regard for diagnostic accuracy, there remains an absence of ownership when it comes to quality and safety systems to reduce the diagnostic errors[4]. Most of the studies attempting to quantify the diagnostic error have either been retrospective studies examining adverse events, such as malpractice claims and autopsy reports, or have been experimental studies comparing multiple physician responses to the same diagnostically challenging scenarios, which are often not reflective of the actual clinical environment[2]. Therefore, the true prevalence of diagnostic errors and inability to make right diagnosis along the acute surgical pathway has been notoriously difficult to evaluate[2,5].

Preventable diagnostic errors can result form the system-related factors and various cognitive factors. A published article on the prevalence of diagnostic error in 100 clinical cases revealed the system-related factors result in 65% diagnostic inaccuracies and cognitive factors in 74%[6] of the diagnostic inaccuracies. While many programs have been initiated to address the system-related factors such as improved communication, enhancing the concept of an effective teamwork, and tackling the procedural problems, clear pathways to reduce the diagnostic errors contributed by the cognitive factors have been more elusive and indefinable. A wide range of suggestions have been made about how to reduce cognitive errors in making the correct diagnosis. Graber *et al*[6] have described three distinct categories of interventions as those meant to: (1) improve knowledge and experience; (2) improve clinical reasoning and decision-making skills; and (3) provide cognitive "help". Though many of these suggestions are well conceptualized and widely endorsed, a large portion remain untested or testing has been restricted to trainees in artificial settings, which does not necessarily reflect actual practice[7]. The diagnostic pathway for acute surgical patients involves GPs, Accident and Emergency, and surgeons. The need to investigate and quantify the impact of procedural and diagnostic accuracy at each level of medical contact is clear. Lack of a working diagnosis impacts patient care, outcome, and cost.

The objective of this observational study is to evaluate the diagnostic accuracy at each level of the primary diagnostic pathway in acute surgical patients admitted to a District General Hospital.

MATERIALS AND METHODS

Study conception

It was noted that ward rounds for on-call surgeons were often disorganized, with no clear roles defined, leading to inconsistent record keeping. Therefore, on call surgical team decided to address this by running ward rounds using briefing and debriefing for each ward round, rotating roles (each person present taking turns with patient presentation, record-keeping, and drug chart review), and asking each member of the team if they had anything to add before moving to the next patient. The surgical team was encouraged to clearly record 3 differential diagnoses for each doctor-patient encounter. It became apparent that the differential diagnoses listed would often change along the primary diagnostic pathway, and the idea to survey these changes emerged.

Profroma

A one-page profroma was designed and relevant variables reported in previous but similar publications were inserted on it. Because this was an observational and pilot study examining the performance of the acute surgical team without any involvement of the patients, therefore, only an informal approval of the study was taken from the local Ethics and Research Committee with verbal discussion and electronic communication. The contents of the profroma were presented in internal clinical governance meeting and few additional variables were also included based upon the recommendations of clinical governance panel. All authors and local Ethics and Research Committee approved the profroma and its contents before starting the data collection.

Inclusion criteria

To review the case notes and ward round entries of all acute surgical admissions during randomly selected two weeks.

Exclusion criteria

Patients whose notes were not available through secretaries or on the wards during data collection were excluded.

Data collection

Patient information including surname, hospital number, date of birth, and gender was collected onto a one page proforma, and each doctor/patient encounter was reviewed retrospectively to include up to 3 differential diagnoses listed in the patient notes. Doctors were anonymously recorded as general practitioner (GP), accident and emergency doctor (A and E), in-patient referrer (IP), surgical foundation year-1, surgical senior house officer (SHO), surgical registrar on-call (SROC), and the surgical consultant. Patient/doctor encounters were recorded along the primary diagnostic pathway, from GP referral, if available, up to the first surgical consultant review or definitive diagnosis by emergency surgery if that preceded consultant review. Final

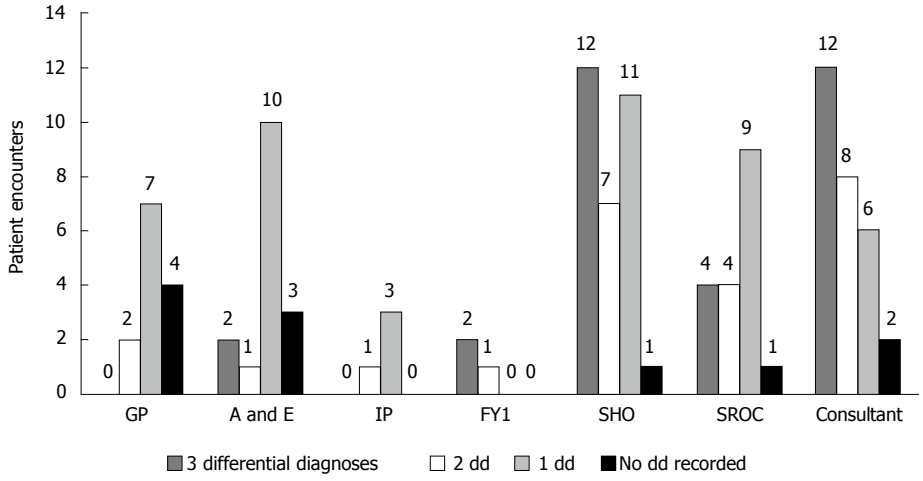

Figure 1 Number of differential diagnoses listed by each doctor grade per patient encounter. Referring physicians (GP, A and E, and IP) rarely recorded more than one differential diagnosis. Among the surgical team, three differential diagnoses were listed most frequently, with the exception of SROC. GP: General practitioner; IP: In-patient referrer; FY1: Foundation year-1; SHO: Senior house officer; SROC: Surgical registrar on-call.

diagnosis was determined by surgical findings, radiological confirmation, or clinical consensus of the rounding on call surgical team comprised of surgical F1, surgical SHO, SROC and surgical consultant as recorded in the discharge summary. All data was kept together in a ring binder and later entered into a spreadsheet for analysis. Authors collected data independently and later on the discrepancies were removed with mutual discussions. There was high and statistically satisfactory inter-observer agreement based upon the Kappa Statistic Score of 0.93.

Data analysis

Data was organized and analyzed using Microsoft Excel® spread sheet (Office 2010, Microsoft Corporation, New York, United States). Statistical analysis was performed with Review Manager 5.2. Each differential diagnosis listed in a doctor/patient encounter was compared to the final diagnosis and scored as correct or incorrect. Failure to list any differential diagnosis was regarded as incorrect.

Endpoints

Recording a differential diagnosis that corresponded with the discharge summary was accepted as an accurate diagnosis.

RESULTS

Patient demographics

Forty-one patients (23 males) with mean age of 61.05 (± 23.24) years were evaluated over 111 patient-doctor encounters. Surgery or other invasive diagnostic procedure was performed in 48.8% of patients. Correct diagnosis was achieved in 85.4% of patients along the primary diagnostic pathway.

Diagnostic outcomes

As shown in Figure 1, FY1, Consultant, and SHO recorded 3 differential diagnoses most often, (67%, 43%, and 39%, respectively) while referring physicians rarely recorded 3 differentials, *i.e.*, 0%, 12.5%, and 0% for GP, A/E, and IP respectively. Consultant was most likely to record a correct diagnosis (75%), followed by SHO (61.3%) and SROC (61.1%) (Figure 2). The accuracy of encounters with 3 differentials listed was 68.75% *vs* 63.77% for just 1-2 differentials. Among the surgical team, the use of 3 differential diagnoses did improve diagnostic accuracy by 8.1%, (65.2% to 73.3%) though significance was not reached (Figure 3). Three differentials were listed at least one time in 23 of the 41 patients. A correct diagnosis was made in 19 of these patients (82.6%). In the remaining 18 patients only 1-2 differentials were ever listed. A correct diagnosis was made in 16 of these patients (88.9%). Of the 32 times in which 3 differentials were listed, only one (3.1%) of these had the correct diagnosis as the third differential (Figure 4).

Contribution in the accurate diagnosis

It is important to identify where diagnoses were made, rather than simply repeated from a previous clinician. If a correct diagnosis had not been made previously, the clinician had the potential to contribute a correct diagnosis. As shown in Figure 5, the surgical SHO contributed the correct diagnoses most often (57.1% of potential contributions). The surgical SHO also contributed 34.3% of all correct diagnoses, the highest of any surgical personnel on call. Three differentials were used to make contributions most often by SHO, followed by Consultant and then by the SROC (66.7%, 60%, and 50% respectively).

Right-to-wrong changes

Failure to include a correct diagnosis made by a previous clinician was regarded as a right-to-wrong change. This occurred 5 times in 111 (4.5%), however 4 of these cases were due to no diagnosis being recorded after a correct

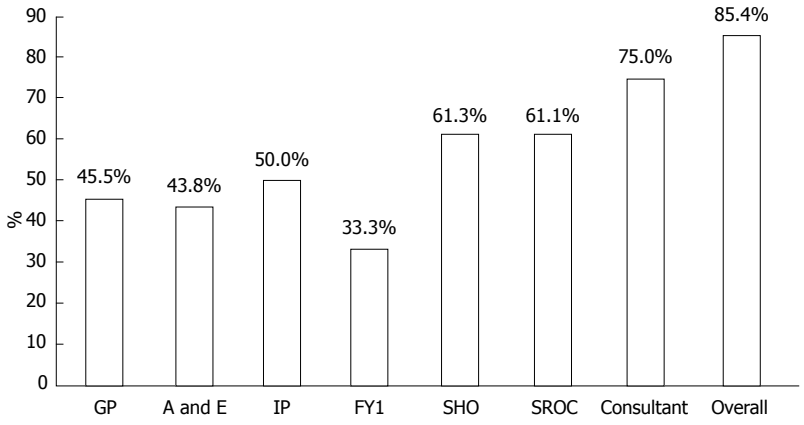

Figure 2 Percentage of patient encounters with a correct diagnosis. Consultant was most likely to record a correct diagnosis, followed by SHO and SROC. Overall 85.4% of patients received a correct diagnosis along the primary diagnostic pathway. GP: General practitioner; IP: In-patient referrer; FY1: Foundation year-1; SHO: Senior house officer; SROC: Surgical registrar on-call.

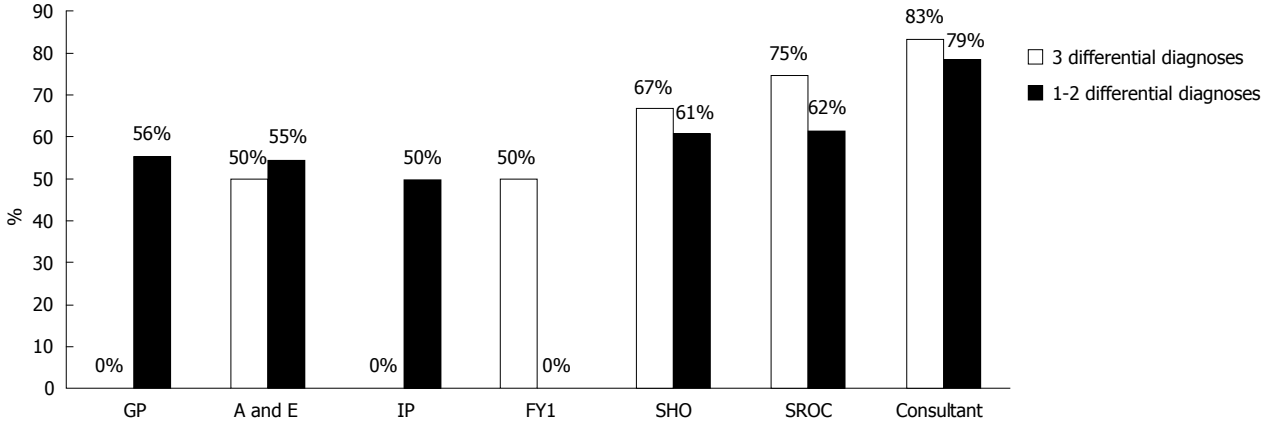

Figure 3 Percentage of correct diagnoses made with 3 differential diagnoses *vs* 1-2 differential diagnoses. The use of 3 differential diagnoses among the surgical team (FY1, SHO, SROC, and Consultant) improved diagnostic accuracy by 8.1% (73.3% *vs* 65.2%). Referring physicians did not follow this trend. GP: General practitioner; IP: In-patient referrer; FY1: Foundation year-1; SHO: Senior house officer; SROC: Surgical registrar on-call.

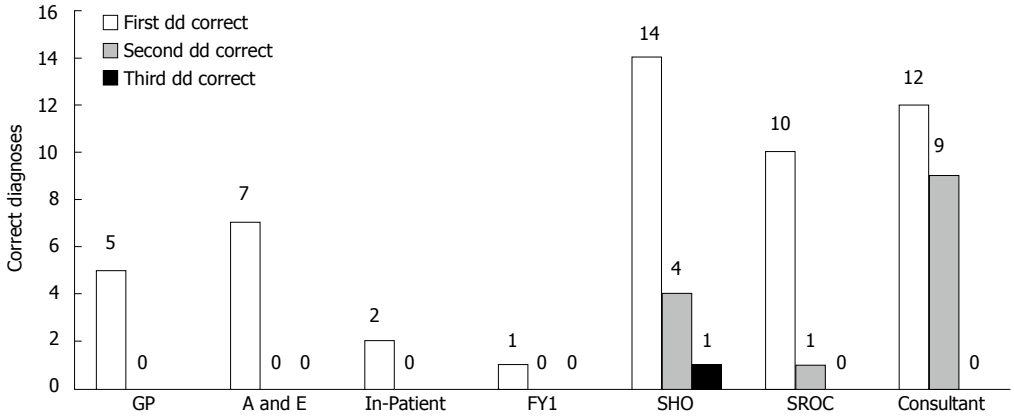

Figure 4 Differential ranking of correct diagnoses by each doctor grade. The correct diagnosis was the first differential listed in most cases for all doctors. Consultant made the correct diagnosis with the second differential diagnosis more than any other group (42.9%), followed by SHO (21.1%) and SROC (9.1%). The correct diagnosis was made with the third differential diagnosis only once, by SHO. (3.1% of 32 times three differentials were listed). GP: General practitioner; FY1: Foundation year-1; SHO: Senior house officer; SROC: Surgical registrar on-call.

diagnosis had been made previously. Only one truly right-to-wrong diagnosis was made, (0.9%) in which malignancy was removed from the list of differentials.

Surgical treatments

Patients referred by a GP were more than twice as likely to undergo surgery as patients referred from A/E. (OR 4.40, CI: 1.09-17.72, $P = 0.04$) However, due to the small size of this study, significance was not reached for GP *vs* in-patient referrals ($P = 0.15$) (Figure 6).

DISCUSSION

Approximately 85% of acute surgical patients can be di-

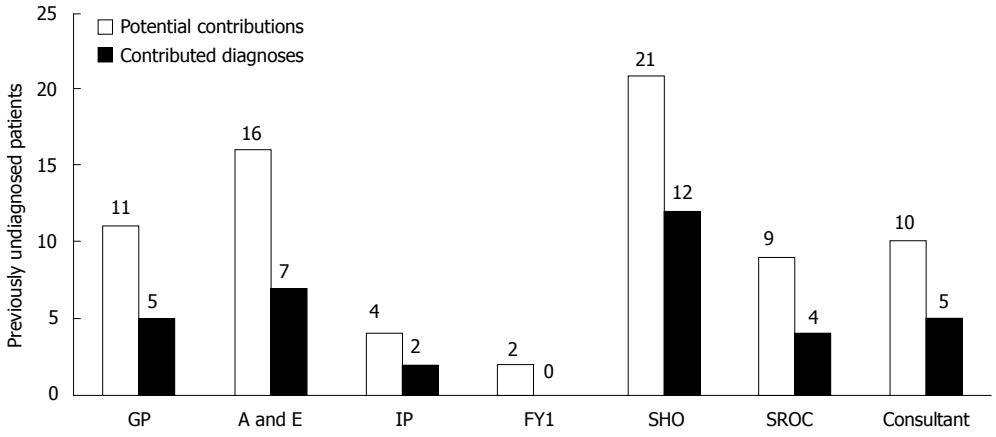

Figure 5 Potential contributions and contributed diagnoses made by each doctor grade. Potential contributions are encounters with patients that had not received a correct diagnosis from a previous physician. SHO contributed the most correct diagnoses and had the highest percent contribution (57.1%) of any group. GP: General practitioner; IP: In-patient referrer; FY1: Foundation year-1; SHO: Senior house officer; SROC: Surgical registrar on-call.

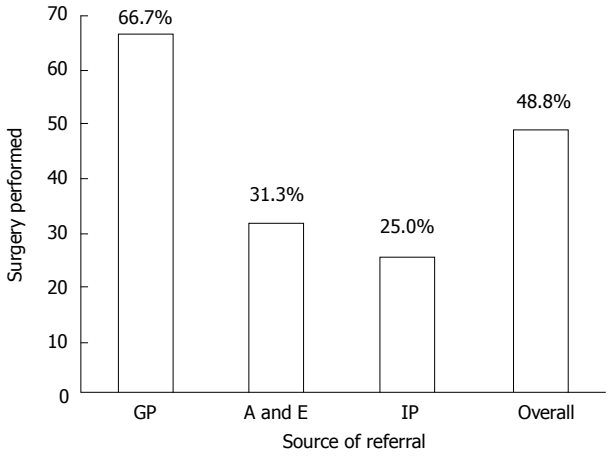

Figure 6 Percentage of patients receiving surgery or other invasive diagnostic procedure by source of referral. GP referrals were more than twice as likely to undergo surgery than patients referred from A and E (OR 4.40, CI: 1.09-17.72, $P = 0.04$). However, due to the small number of in-patient referrals, significance was not reached for GP *vs* In-Patient referrals ($P = 0.15$). IP: In-patient referrer; GP: General practitioner.

agnosed accurately along the primary diagnostic pathway during acute presentations. The surgical consultant was more likely to make a correct surgical diagnosis compared to all health personnel; however it is the surgical SHO that contributes the most correct diagnoses along the diagnostic pathway. Patients referred by a GP are more likely to require surgery as compared to other referral sources.

Premature closure, the cognitive error of failing to continue to consider reasonable alternatives after an initial diagnosis has been made, is often cited as the most common cognitive factor leading to a diagnostic error[7-11]. Much of the focus on decreasing cognitive errors has been on improving clinical reasoning and decision-making by educating physicians about how they make decisions and teaching the use of de-biasing techniques and active meta-cognitive review[12]. Some difficulties with the implementation of these strategies include time, cost, and physician interest, as well as the need to prove the efficacy of these strategies in clinical practice[13]. The potential to reduce the incidence of premature closure with a simple practice that would require no further training and could be easily tested in clinical practice would be ideal as a means to reduce dangerous and costly diagnostic errors. The authors suggest that the practice of clearly listing 3 differential diagnoses in the patient notes is a simple way to modestly decrease the cognitive error of premature closure. Listing of three differentials *vs* listing of one or two differentials seems to improve the diagnostic accuracy among the surgical team, although a larger study would be needed to reach statistical significance. For the 8.1% improvement in diagnostic accuracy seen among the surgical team to be statistically significant (95%CI, 80% power), over 547 patient records should be evaluated. Further support for the use of three differentials comes from the increased proportion of diagnoses contributed using this method. Given the impact of misdiagnosis on the healthcare system, the difficult nature of reducing cognitive errors in clinical practice, and the simplicity of the intervention described, the authors feel it is worthwhile to consider further study in this area to explore any benefit of this practice.

Limitations

The small size of this study limits the statistical significance of many of the trends seen in the data. Other limitations noted during the data collection included difficulty in locating GP referral letters in the patient notes and therefore not including those encounters, as well as missing patients that were seen by on-call surgeons in the evening and subsequently discharged before morning rounds. The use of a junior doctor scribe when patients are reviewed by a consultant or registrar may result in differential diagnoses being stated but not recorded, and therefore not counted.

Future implications

One of the strategies to reduce diagnostic error is to de-

velop pathways for feedback[2,14]. It is particularly important to develop feedback pathways for the junior doctors, as it has been shown that less experienced doctors tend to most over-estimate their diagnostic accuracy[2]. With anonymity removed, the basic design of this study seems well suited to enable feedback to each physician involved in the care of an acute surgical patient. In this way a simple score could be reported as a way to objectively evaluate diagnostic performance, with the ultimate goal of self-improvement and future decrease in diagnostic errors. This approach would allow feedback not just after a negative event, as is the case with many feedback systems in place, but would track performance in a simple, ongoing manner.

COMMENTS

Background

Accurate clinical diagnosis in acutely admitted surgical patients is of immense importance because of the necessity of timely surgical interventions such as need of laparotomy, laparoscopy and or organ resection. Inaccurate diagnosis can lead to serious consequences in terms of delayed treatment, prolonged hospital stay, increased operative morbidity or mortality putting excessive strain on the health resources. Any measure which directly or indirectly may influence the diagnostic accuracy in acute surgical patients should be investigated and implemented in a timely manner to avoid these consequences. This article highlights the value and shortcomings of a referral pathway through which acute surgical patients pass through and get accurately diagnosed for the optimum management.

Research frontier

Various studies published on this topic, although reported the diagnostic accuracy of different grades of acute surgical team with variable accuracy. This is the first study which investigates the diagnostic accuracy of all sources of referral during the course of management of acutely ill patients such as general practitioners, A/E doctors, surgical juniors, surgical middle grade doctors and eventually surgical consultant on call.

Innovations and breakthroughs

The potential to reduce the incidence of mis-diagnosis with a simple practice that would require no further training and could be easily tested in clinical practice would be ideal as a means to reduce dangerous and costly diagnostic errors. The authors suggest that the practice of clearly listing 3 differential diagnoses in the patient notes is a simple way to modestly decrease the cognitive error of premature closure. Listing of three differentials *vs* listing of one or two differentials seems to improve the diagnostic accuracy among the surgical team, although a larger study would be needed to reach statistical significance. For the 8.1% improvement in diagnostic accuracy seen among the surgical team to be statistically significant (95%CI, 80% power), over 547 patient records should be evaluated. Further support for the use of three differentials comes from the increased proportion of diagnoses contributed using this method. Given the impact of misdiagnosis on the healthcare system, the difficult nature of reducing cognitive errors in clinical practice, and the simplicity of the intervention described, the authors feel it is worthwhile to consider further study in this area to explore any benefit of this practice.

Applications

One of the strategies to reduce diagnostic error is to develop pathways for feedback. It is particularly important to develop feedback pathways for the junior doctors, as it has been shown that less experienced doctors tend to most over-estimate their diagnostic accuracy. With anonymity removed, the basic design of this study seems well suited to enable feedback to each physician involved in the care of an acute surgical patient. In this way a simple score could be reported as a way to objectively evaluate diagnostic performance, with the ultimate goal of self-improvement and future decrease in diagnostic errors. This approach would allow feedback not just after a negative event, as is the case with many feedback systems in place, but would track performance in a simple, ongoing manner.

Terminology

FY1: It stands for foundation year 1. The group of junior most surgical doctors in the United Kingdom NHS Trust health system which start clinical practice just after finishing medical school. SHO: It stands for Senior House Officer which a surgical grade after finishing two years of foundation training (FY1 and FY2). SROC: Its stands for Surgical Registrar On Call. Surgical registrar is of variable experience depending upon the step of ladder on training pathway (year 1 to year 8).

Peer review

This is an interesting article.

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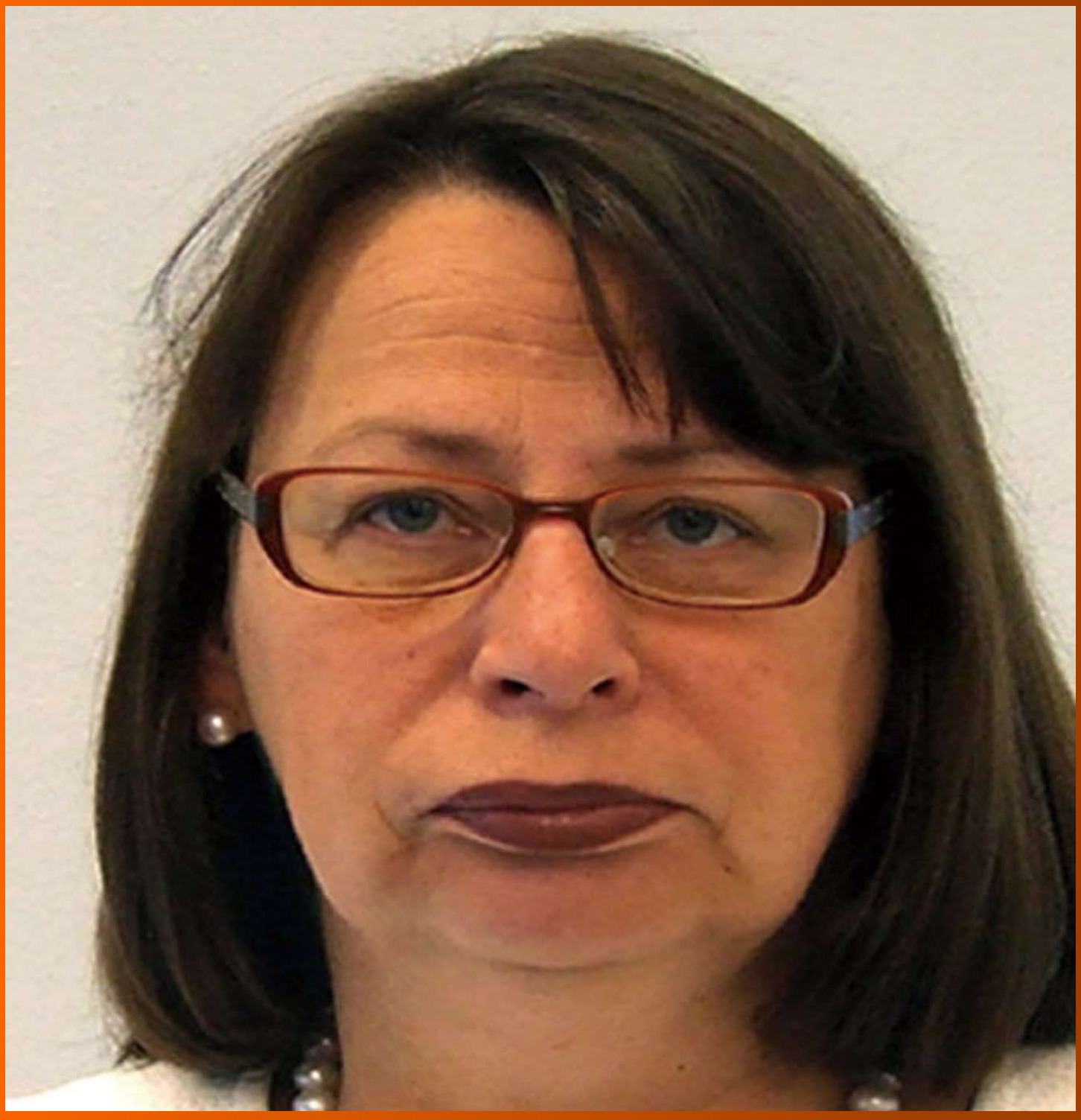

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World Journal of Gastrointestinal Surgery
Room 903, Building D, Ocean International Center,
No. 62 Dongsihuan Zhonglu, Chaoyang District,
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Fax: +86-10-85381893
E-mail: editorialoffice@wjgnet.com
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ORIGINAL ARTICLE

Intrathoracic esophagojejunostomy using OrVil™ for gastric adenocarcinoma involving the esophagus

Kazuhito Yajima, Tatsuo Kanda, Shin-ichi Kosugi, Yosuke Kano, Takashi Ishikawa, Hiroshi Ichikawa, Takaaki Hanyu, Toshifumi Wakai

Kazuhito Yajima, Tatsuo Kanda, Shin-ichi Kosugi, Yosuke Kano, Takashi Ishikawa, Hiroshi Ichikawa, Takaaki Hanyu, Toshifumi Wakai, Division of Digestive and General Surgery, Niigata University Graduate School of Medical and Dental Sciences, Niigata 951-8510, Japan

Author contributions: Yajima K performed this surgery and rote the paper; Kanda T and Kosugi S contributed assistant of this surgery; Kano Y, Ishikawa T, Ichikawa H and Hanyu T coordinated the surgery; Wakai T contributed the final coordination of this paper.

Correspondence to: Kazuhito Yajima, MD, PhD, Division of Digestive and General Surgery, Niigata University Graduate School of Medical and Dental Sciences, 1-757 Asahimachi-dori, Niigata 951-8510, Japan. yajikazu@nifty.com
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Abstract

AIM: To demonstrate a new surgical technique of lower mediastinal lymphadenectomy and intrathoracic anastomosis of esophagojejunostomy using OrVil™.

METHODS: After a total median phrenotomy, the supradiaphragmatic and lower thoracic paraesophageal lymph nodes were transhiatally dissected. The esophagus was cut off using a liner stapler and OrVil™ was inserted. Finally, end-to-side esophagojejunostomy was created by using a circular stapler. From July 2009, we adopted this surgical technique for five patients with gastric cancer involving the lower esophagus.

RESULTS: The median operation time was 314 min (range; 210-367 min), and median blood loss was 210 mL (range; 100-838 mL). The median numbers of dissected lower mediastinal nodes were 3 (range; 1-10). None of the patients had postoperative complications including anastomotic leakage and stenosis. The median hospital stay was 16 d (range: 15-20 d). The median length of esophageal involvement was 14 mm (range: 6-48 mm) and that of the resected esophagus was 40 mm (range: 35-55 mm); all resected specimens had tumor-free margins.

CONCLUSION: This surgical technique is easy and safe intrathoracic anastomosis for the patients with gastric adenocarcinoma involving the lower esophagus.

Key words: Gastric cancer; Esophageal invasion; Lower mediastinal lymphadenectomy; OrVil™; Intrathoracic anastomosis

Core tip: We report a new technique of lower intrathoracic anastomosis through the transhiatal approach using OrVil™ for five patients with gastric adenocarcinoma involving the esophagus. This surgical technique is an easy and safe method to create lower intrathoracic anastomosis.

Yajima K, Kanda T, Kosugi S, Kano Y, Ishikawa T, Ichikawa H, Hanyu T, Wakai T. Intrathoracic esophagojejunostomy using OrVil™ for gastric adenocarcinoma involving the esophagus. *World J Gastrointest Surg* 2014; 6(12): 235-240 Available from: URL: http://www.wjgnet.com/1948-9366/full/v6/i12/235.htm DOI: http://dx.doi.org/10.4240/wjgs.v6.i12.235

INTRODUCTION

Adenocarcinoma of the esophagogastric junction (EGJ) is still uncommon in Japan although the number of patients with this disease has tended to increase[1-6]. For gastric cancer surgery, ensuring safe cancer-free margins and dedicated systematic lymphadenectomy are both

Table 1 Patients' clinical background

Case	Age (yr)	Sex	Tumor location	Siewert classification	C-length (mm)	C-stage	Co-morbidity	Neoadjuvant chemotherapy
1	73	M	EU	Type Ⅰ	30	T3(SS)N0M0	DM	N
2	52	M	UME	Others	14	T3(SS)N1M0	DM	N
3	80	M	EU	Type Ⅱ	21	T3(SS)N1M0	CI	N
4	67	M	UE	Type Ⅱ	10	T1b(SM)N0M0	DM, COPD	N
5	55	M	UE	Type Ⅲ	12	T3(SS)N2M0	COPD	S-1 + CDDP

C-stage: Clinical stage; C-length: Clinical length of the esophageal involvement according to preoperative fluoroscopy; DM: Diabetes mellitus; CI: Cerebral infarction; COPD: Chronic obstructive Pulmonary disease; N: Not performed; M: Male.

important; however, it is sometimes difficult to achieve these two surgical principles in surgery for gastric adenocarcinoma involving the lower esophagus because of the anatomical complexity of the EGJ. Surgical approach for adenocarcinoma of the EGJ includes transhiatal, transthoracic, and left thoracoabdominal approach.

On the basis of the results of a randomized controlled trial by the Japan Clinical Oncology Group (JCOG 9502) comparing the transhiatal with the left thoracoabdominal approach on the prognosis of patients with Siewert type Ⅱ or Ⅲ adenocarcinoma that extended 3 cm or less to the esophagus[7], the Japan Gastric Cancer Guideline recommends the transhiatal approach for patients with this disease[8]. Resection of the long esophageal segment through the transhiatal approach is relatively easy; however, anastomosis becomes increasingly difficult as the resected esophagus is long because the remnant esophagus has shrunk and is hidden behind the heart. The conventional method using purse-string sutures is unstable in a deep and narrow working space. Insertion of an anvil into the distal esophagus is technically difficult and stressful.

Recently, a double stapling technique with a transoral anvil delivery system (EEA™ OrVil™, Covidien Japan, Tokyo, Japan) has been used for enteral anastomoses in laparoscopy-assisted gastrectomy[9-18]. With steady insertion of the anvil, the trans-oral anvil delivery system enables safe anastomosis in surgeries that permit only small working spaces.

This is a preliminary case series of five patients with gastric adenocarcinoma involving the esophagus who underwent lower intrathoracic anastomosis through the transhiatal approach using EEA™ OrVil™.

MATERIALS AND METHODS

Patients

Between July 2009 and December 2012, five consecutive patients with gastric adenocarcinoma involving the esophagus underwent esophagojejunostomy using a transoral delivery system following total gastrectomy combined with lower esophagectomy. Patients' clinical backgrounds are shown in Table 1. Preoperative staging was based on upper gastrointestinal endoscopy, fluoroscopy, and thoracic-abdominal computed tomography scans. All the patients had histologically confirmed gastric adenocarcinoma, of which esophageal involvement was clinically evaluated as 3 cm or shorter. No patients had any evidence of lymph node metastasis in the middle or upper mediastinum. Tumor details were described according to the Japanese classification of gastric carcinoma, 3rd English edition[19].

Surgical technique

All patients underwent lower mediastinal lymphadenectomy through transhiatal approach, details of which were described elsewhere[20]. After completion of lymphadenectomy, the mobilized esophagus was transected 2 cm above the tumor margin using an Endo GIA (60 mm, purple; Covidien Japan) linear stapler (Figure 1A). The OrVil™ tube was then introduced transorally into the esophagus. As the surgeon identified the OrVil tube reaching the esophageal stump, a small hole was created in the esophageal stump (Figure 1B). The tube was carefully pulled out and then the transoral anvil was positioned at the esophageal stump. Esophagojejunostomy was performed using the Roux-en-Y method. A jejunal loop was pulled-up retrocolically after dividing the jejunum approximately 20 cm from the ligament of Treitz. A circular stapler (DST Series EEA™ Stapler 25; Covidien Japan) was inserted into the jejunal stump and the anvil was connected to the circular stapler (Figure 1C). After an end-to-side anastomosis was performed using the stapler, the jejunal stump was closed with Endo GIA (60 mm, purple), completing the lower intrathoracic esophagojejunostomy. A drainage tube (Salem Sump dual lumen stomach tube, 16 Fr; Covidien Japan) was inserted from the anterior chest wall through the space between the pericardium and diaphragm and positioned in the left-side chest cavity (Figure 1D). The drainage was suctioned continuously with low pressure (12 cm H_2O) after the surgery. The schema of the figures were showed below of the Figure 1.

RESULTS

Surgical outcomes of the five patients are shown in Table 2. All patients successfully underwent this surgical technique with no intraoperative complications. The median operation time was 314 min (range: 210-367 min), and median blood loss was 210 mL (range: 100-838 mL).

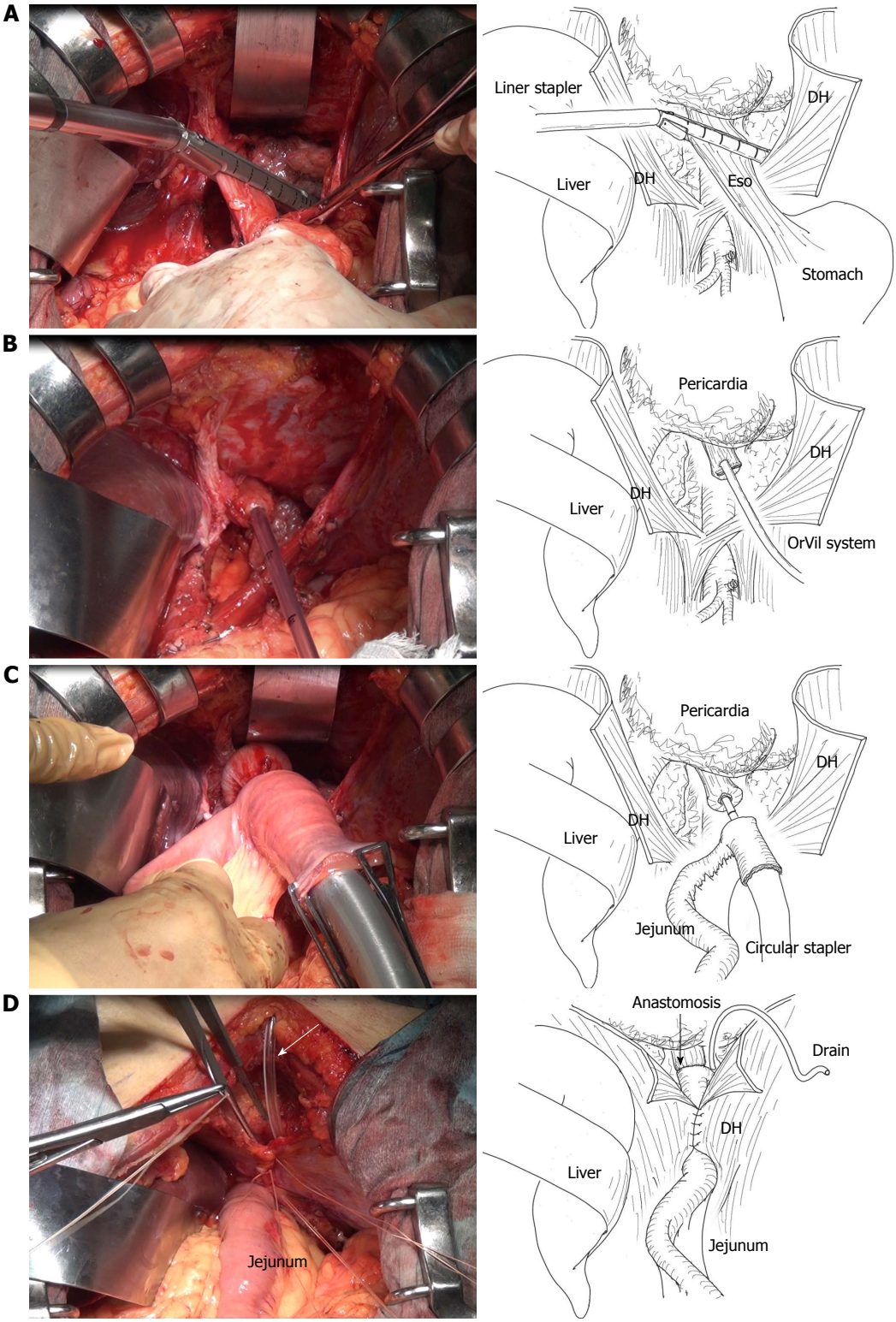

Figure 1 Intraabdominal findings of an esophagojejunostomy using a circular stapler. A: Transection of the esophagus was performed approximately 2 cm proximal to the tumor margin using an Endo GIA (60 purple; Covidien, Tokyo, Japan) linear stapler; B: The OrVil™ tube was then introduced transorally into the esophagus; C: A circular stapler (DST Series EEA Stapler 25; Covidien Japan) was inserted into the jejunal stump and the anvil was connected to the circular stapler; D: After the anastomosis, a Salem Sump Dual Lumen Stomach Tube (16 Fr; Covidien Japan) for the anastomotic site was inserted from the anterior chest wall through the space between the pericardium and diaphragm and positioned in the left-sided chest cavity (white arrow). Eso: Esophagus; DH: Diaphragm.

The median interval to water intake was 2 d (range: 1-3 d) and that to oral intake was 7 d (range: 6-10 d). None of the patients had postoperative surgical complications. Postoperative fluorography demonstrated no leakage or stenosis of the esophagojejunal anastomosis in all five patients. Figure 2 shows representative fluorography of

Table 2 Surgical outcomes

Case	Surgical procedures	Lymph-adenectomy	Residual tumor	Operation time (min)	Blood loss (mL)	Start of foods (d)	Hospital stay (d)	E-length (mm)	P-length (mm)
1	Total GR, RY	D2	R0	367	838	10	20	55	48
2	Total GR, RY	D2	R0	314	270	10	16	40	14
3	Total GR, RY	D2	R0	210	210	7	15	52	22
4	Proximal GR, JI	D1+	R0	314	100	7	18	36	6
5	Total GR, RY	D2	R0	277	140	6	15	35	10

Total GR: Total gastrectomy; Proximal GR: Proximal gastrectomy; RY: Roux-en Y reconstruction; JI: Jejunal interposition; R0: No residual tumor; E-length: Length of resected esophagus; P-length: Pathological length of esophageal involvement.

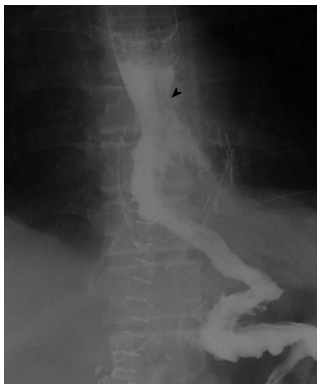

Figure 2 Postoperative fluoroscopy. Anastomosis of the esophagojejunostomy was 6.4 cm above the diaphragm (black arrowhead) with no anastomotic leakage or stenosis.

the esophagojejunal anastomosis. The median hospital stay was 16 d (range: 15-20 d).

The median length of esophageal involvement was 14 mm (range: 6-48 mm) and that of the resected esophagus was 40 mm (range: 35-55 mm); all resected specimens had tumor-free margins.

DISCUSSION

We have herein reported the use of the EEA™ OrVil™ stapler in end-to-side anastomosis for esophagojejunostomy for patients with gastric adenocarcinoma involving the esophagus. To the best of our knowledge, this is the first report of the use of a transoral anvil in lower intrathoracic esophagojejunostomy and our preliminary results showed that this technique was feasible and safe.

By literature review of PubMed database using the keywords "OrVil™", "gastric cancer", and "esophagojejunostomy", there were ten original reports describing the outcomes of esophagojejunostomy using a transoral anvil (EEA™ OrVil™) so far. However, all five reports addressed the issues of esophagojejunostomy after laparoscopic total gastrectomy for gastric cancer[9-18]. Jeong *et al*[9] reported that of the 16 patients who underwent esophagojejunostomy using OrVil™ in laparoscopy-assisted total gastrectomy, no patient had intraoperative complications or anastomotic complications, including leakage and stenosis. Liao *et al*[11] also supported the safety of esophagojejunostomy using a transoral anvil: anastomotic leakage and anastomotic stenosis occurred in one patient in their series of 21 patients undergoing laparoscopy-assisted total gastrectomy. From these reports, gastrojejunostomy using OrVil™ was acceptable in terms of fewer anastomotic complications. We successfully performed intrathoracic anastomosis with Roux-en-Y reconstruction in five patients without any anastomotic complications.

Complete resection with no residual tumor remains the only treatment that can lead to cure in gastric cancer[21]. Obtaining a safe free margin of the distal esophagus is one of the most important problems, especially in patients with junctional cancer invading the esophagus. On the other hand, the correlation between the length of esophageal resection and free surgical margin has not been well described. In the JCOG9502 trial, the median length of the resected esophagus was 4.2 cm in the transhiatal approach, with two having positive proximal margin[7]. In the present study, the median length of the resected esophagus was 40 mm and all patients had a negative proximal margin. In our technique exposing the lower mediastinum by dissection using a lower mediastinal lymphadenectomy, a wide and good view was obtained. Using this space, we could easily cut the esophagus and insert the anvil head transorally with a sufficient tumor-free margin.

Insertion of an anvil into the distal esophagus is technically difficult and stressful for the esophagojejunostomy. Kunisaki *et al*[10] and Liao *et al*[11] reported that total operation time and time of reconstruction were significantly shortened when comparing mini-laparotomy and a transorally inserted anvil in laparoscopy-assisted total gastrectomy esophagojejunostomy using OrVil™. At the same way, OrVil™ might decrease the time of reconstruction also in conventional open gastrectomy when intrathoracic anastomosis. In our series, unfortunately, the time of anastomosis was not measured, there were no trouble concerning the insertion of the OrVil and anastomosis using EEA™ during surgery. In our experience, lower intrathoracic esophagojejunostomy using OrVil™ was less stressful technique.

In conclusion, we report the surgical techniques of the EEA™ OrVil™ stapler in end-to-side anastomosis for esophagojejunostomy. We believe that this technique is especially useful for patients with lower intrathoracic anastomosis, in whom conventional anastomosis is

difficult.

COMMENTS

Background

For gastric cancer surgery, ensuring safe cancer-free margins and dedicated systematic lymphadenectomy are both important; however, it is sometimes difficult to achieve these two surgical principles in surgery for gastric adenocarcinoma involving the lower esophagus because of the anatomical complexity of the esophagogastric junction.

Research frontiers

A double stapling technique with a transoral anvil delivery system (EEA™ OrVil™, Covidien Japan, Tokyo, Japan) has been used for enteral anastomoses in laparoscopy-assisted gastrectomy. With steady insertion of the anvil, the transoral anvil delivery system enables safe anastomosis in surgeries that permit only small working spaces.

Innovations and breakthroughs

The authors demonstrate a new surgical technique of lower mediastinal lymphadenectomy and intrathoracic anastomosis of esophagojejunostomy using OrVil™. This is the first report of the use of a transoral anvil in lower intrathoracic esophagojejunostomy and our preliminary results showed that this technique was feasible and safe.

Applications

By understanding surgical procedures, this study demonstrates the photographs during the surgery and the schema of the photographs.

Terminology

A transoral anvil delivery system (EEA™ OrVil™) is one of the surgical items of anvil placement for circler stapling technique.

Peer review

The authors preliminarily demonstrated the use of the EEA™ OrVil™ stapler in end-to-side anastomosis for esophagojejunostomy and usefulness and safely in five patients. This surgical technique is easy and safe intrathoracic anastomosis for the patients with gastric adenocarcinoma involving the lower esophagus.

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Systematic review of absorbable *vs* non-absorbable sutures used for the closure of surgical incisions

Muhammad S Sajid, Malcolm R McFall, Pauline A Whitehouse, Parv S Sains

Muhammad S Sajid, Western Sussex Hospitals NHS Trust, Washington Suite, North Wing, Worthing Hospital, BN11 2DH West Sussex, United Kingdom
Muhammad S Sajid, Malcolm R McFall, Pauline A Whitehouse, Parv S Sains, Department of General, Endoscopic and Laparoscopic Colorectal Surgery, Worthing Hospital, Worthing, BN11 2DH West Sussex, United Kingdom
Author contributions: All authors contributed to this paper.
Correspondence to: Mr. Muhammad S Sajid, Western Sussex Hospitals NHS Trust, Washington Suite, North Wing, Worthing Hospital, BN11 2DH West Sussex, United Kingdom. surgeon1wrh@hotmail.com
Telephone: +44-01903-205111 Fax: +44-01903-285010
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Abstract

AIM: To report a systematic review of published randomized controlled trials (RCTs) investigating the role of absorbable suture (AS) against non-AS (NAS) used for the closure of surgical incisions.

METHODS: RCTs investigating the use of AS *vs* NAS for the closure of surgical incisions were statistically analysed based upon the principles of meta-analysis and the summated outcomes were represented as OR.

RESULTS: The systematic search of medical literature yielded 10 RCTs on 1354 patients. Prevalence of wound infection (OR = 0.97; 95%CI: 0.56, 1.69; Z = 0.11; P = 0.92) and operative morbidity (P = 0.45) was comparable in both groups. Nonetheless, the use of AS lead to lower risk of wound break-down (OR = 0.12; 95%CI: 0.04, 0.39; Z = 3.52; P < 0.0004).

CONCLUSION: This meta-analysis of 10 RCTs demonstrates that the use of AS is similar to NAS for skin closure for surgical site infection and other operative morbidities. AS do not increase the risk of skin wound dehiscence, rather lead to a reduced risk of wound dehiscence compared to NAS.

Key words: Skin closure; Surgical site infection; Wound dehiscence; Absorbable sutures; Non-absorbable suture

Core tip: Based upon the meta-analysis of 10 controlled trials, the absorbable sutures (AS) are similar to non-AS (NAS) for skin closure in cases of wound infection and other complications. AS do not increase the risk of skin wound dehiscence, rather leads to a reduced risk of wound break-down compared to NAS.

Sajid MS, McFall MR, Whitehouse PA, Sains PS. Systematic review of absorbable *vs* non-absorbable sutures used for the closure of surgical incisions. *World J Gastrointest Surg* 2014; 6(12): 241-247 Available from: URL: http://www.wjgnet.com/1948-9366/full/v6/i12/241.htm DOI: http://dx.doi.org/10.4240/wjgs.v6.i12.241

INTRODUCTION

A number of studies have been reported in search of improving the skin closure related outcome measures following various surgical procedures, and due to this fact the skin closure techniques are evolving vastly and immensely, predominantly over the last few decades. Innumerable skin closure methods reported in medical literature include continuous stitch closure, interrupted stitch closure, full thickness closure, sub-cuticular closure, primary closure, secondary closure, vacuum assisted closure, glue assisted closure, skin clips or staples closure, simple suture *vs* mattress sutures, steri-strips closure, absorbable or non-absorbable suture (NAS) closure and other innovative methods[1-13]. These manifold practices of skin approximation after surgical procedures can

jointly be classified into two groups. Group I includes the use of NAS for skin closure requiring additional clinical care due to the need of removal of stitches or metallic staples. Group Ⅱ includes the use of absorbable stitches (AS) or glue which does not require additional clinical care like the group I . The proponents of the use of NAS for skin closure claim that an increased tensile strength of NAS keep wound margins adequately coapted resulting in optimal wound and skin healing[14-16]. The supporters of AS advocate similar effectiveness in wound healing without the requirement of additional clinical care in addition to the benefits of an improved cosmetic outcome and the reduced risk of surgical site infection[17-21]. Due to significant differences in the opinion, the general consensus about the use of either absorbable AS or NAS is still lacking.

The aim of this study is to report a systematic review of published randomized controlled trials (RCTs) on the use of AS against NAS for skin closure.

MATERIALS AND METHODS

Literature search pattern

Relevant published trials for this study were retrieved from the search of MEDLINE, EMBASE, and Cochrane library for controlled trials (RCTs). The MeSH search words such as "absorbable sutures" and "non-absorbable sutures" were put in medical search engines to find studies suitable for inclusion in this systematic review. There was no linguistic, sex, trial size or country of study barrier in our search or inclusion criteria. Boolean operators (AND, OR, NOT) were entered repeatedly at different levels of literature search to achieve maximum number of studies. The published designations of the relevant articles were analysed and checked about their possibility of inclusion in this study. Furthermore, the bibliography of the potentially included studies was scrutinized to find additional studies.

Study selection

The inclusion criteria for this study was agreed which included the RCTs comparing AS and NAS, using any type of AS and NAS, investigating surgical site infection as primary end point without any limitations of age, sex on recruited patients.

Data extraction

After trial selection according to the principles of inclusion criteria, two review authors extracted the trial data from included studies. In case conflict about data, the mutual agreement was achieved by lengthy discussions among all authors. We did not use any statistical tool to calculate the inter-observer matching pattern of the data.

Statistics of the study

The statistics calculations were performed on RevMan 5.3[22,23], delivered by the Cochrane Collaboration. The OR with a 95%CI was calculated to express the

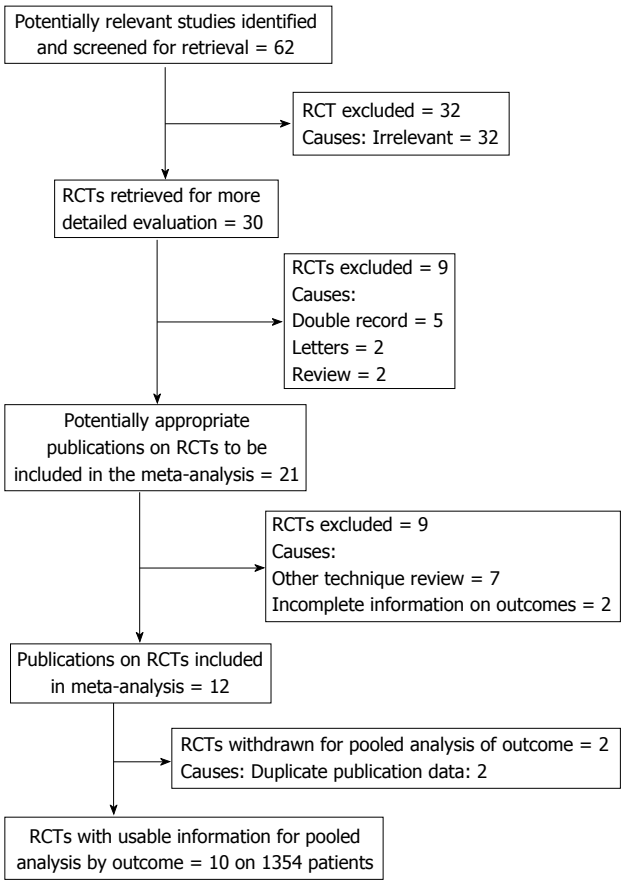

Figure 1 PRISMA flow chart showing trial selection methodology. RCT: Randomized controlled trial.

combined outcome of the dichotomous variables. The random or fixed effects model using Mantel-Haenszel method (where applicable)[24,25] were used to compute the combined results. The χ^2 test and the I^2 were used for detection and quantification of heterogeneity[26-28]. The results were displayed in the form of forest plot. The quality of included RCTs was scrutinised according to the reported recommendations by Jadad *et al*[29] and Chalmers *et al*[30]. Based on the quality of the included RCTs, the strength and summary of GRADE quality of evidence was achieved using GradePro®[28], an analytical package offered by the Cochrane Collaboration. The surgical site infection was analysed as primary outcome whereas post-operative complications and wound dehiscence was reported as secondary outcomes.

RESULTS

The PRISMA diagram flow chart explaining the trial selection approach, filtration of trials and eventual study inclusion for quantitative and qualitative analysis is shown in Figure 1. Ten RCTs[31-41] on 1354 patients were found suitable for inclusion and for final analysis. Six hundred and sixty-three were investigated in the AS arm and 691 in NAS arm of the included RCTs. Table 1 depicts the characteristics of the included RCTs. Table 2 is showing the various procedures, type of sutures, type of stiches

Table 1 Characteristics of included trials

Ref.	Year	Country	Age in years	Male:female	Duration of follow up	Operative procedure
Dørflinger *et al*[32]						
AS	1983	Denmark	64 (11-83)	27:2	6 mo	Inguinal and femoral hernia repair
NAS			64 (19-85)	21:8		
Foster *et al*[33]						
AS	1977	United Kingdom	NA	NA	1 mo	Appendicectomy
NAS						
Glough *et al*[34]						Laparotomy
AS	1975	United Kingdom	NA	Mixed groups of males and females	4 wk	Inguinal and femoral hernia repair
NAS						
Harimoto *et al*[35]						
AS	2011	Japan	68 ± 10	37:25	30 d	Hepatectomy
NAS			67 ± 12	41:22		
Kotaluoto *et al*[36]						
AS	2012	Finland	40.6 (18-88)	45:45	3 wk	Appendicectomy
NAS			40.5 (18-83)	63:32		
Lundblad *et al*[37]						
AS	1989	Norway	NA	NA	NA	Appendicectomy
NAS						Inguinal hernia repair
Pauniaho *et al*[38]						
AS	2010	Finland	12.7 (4-17)	57:43	1 wk	Appendicectomy
NAS			12.7 (4-18)	54:44		
Ralphs *et al*[39]						
AS	1982	United Kingdom	NA	NA	18 mo	Inguinal hernia repair
NAS						
Szabó *et al*[40]						
AS	2002	Hungary	64.7 (23-87)	23:2	3 mo	Inguinal hernia repair
NAS			66.3 (25-86)	21:4		
Tan *et al*[41]						
AS	2008	Malaysia	30.8 ± 7.9	0:106	4 wk	Transverse suprapubic for benign gynaecological surgery or c-section
NAS			31.6 ± 6.9	0:107		

AS: Absorbable suture; NAS: Non-absorbable suture; NA: Not available.

Table 2 Treatment protocol adopted in included trials

Ref.	Absorbable suture	Non-absorbable suture
Dørflinger *et al*[32]	Polyglycolic acid	Dacron just for aponeurotic layer
Foster *et al*[33]	Subcuticular Polyglycolic acid	Interrupted 00 nylon 1 cm apart
Glough *et al*[34]	Polyglycolic acid 3/0 straight needle	Silk 2/0 straight needle
Harimoto *et al*[35]	Polyglactin	Silk
Kotaluoto *et al*[36]	4/0 monofilament monocryl	4/0 interrupted Ethilon
Lundblad *et al*[37]	3/0 polyglycolic	4/0 monofilament nylon
Pauniaho *et al*[38]	4/0 polyglactin 910/370	4/0 braided nylon
Ralphs *et al*[39]	3/0 Dexon	5/0 nylon
Szabó *et al*[40]	Polyglactin 910/370	Monofilament nylon
Tan *et al*[41]	Monofilament poliglecaprone 25	Monofilament polypropylene

used in included RCTs.

Methodological quality of included studies

Inadequate randomization approach, improper concealment in the process of allocation, absence of power calculations, lack of utilization of single or double blinding and lastly lack of reporting of IIT were major factors responsible for scoring the majority of included RTCs of poor quality (Table 3). GRADE[31] quality of evidence is shown in Figure 2.

Surgical site infection

There was no heterogeneity [Tau^2 = 0.23, χ^2 = 12.12, γ = 8, (P = 0.15); I^2 = 34%] among RCTs that contributed to the combined calculation of this variable. In the random effects model (OR = 0.97; 95%CI: 0.56, 1.69; Z = 0.11; P = 0.92; Figure 3), the risk of surgical site infection was statistically similar in both groups. Although the AS lead to lower incidence of wound infection but it failed to reach at statistical significance.

Postoperative complications

Combined analysis showed significant statistical heterogeneity [Tau^2 = 0.61, χ^2 = 20.57, γ = 9, (P = 0.01); I^2 = 56%] among included RCTs. Therefore, in the random effects model (OR = 0.77; 95%CI: 0.39, 1.52;

Table 3 Quality assessment of included trials

Ref.	Randomisation technique	Power calculations	Blinding	Intention-to-treat analysis	Concealment
Dørflinger *et al*[32]	Consecutive patients	No	Yes	No	Inadequate
Foster *et al*[33]	Consecutive patients	No	No	No	Inadequate
Glough *et al*[34]	Consecutive patients	No	No	No	Inadequate
Harimoto *et al*[35]	Sealed envelop	Yes	No	No	Adequate
Kotaluoto *et al*[36]	Consecutive patients	Yes	No	Yes	Inadequate
Lundblad *et al*[37]	Consecutive patients	No	No	No	Inadequate
Pauniaho *et al*[38]	Consecutive patients	Yes	No	No	Inadequate
Ralphs *et al*[39]	Consecutive patients	No	No	No	Inadequate
Szabó *et al*[40]	No	No	No	No	Inadequate
Tan *et al*[41]	Consecutive patients	Yes	No	Yes	Inadequate

Absorbable compared to non-absorbable sutures for for skin closure

Patient or population: for skin closure
Settings:
Intervention: Absorbable
Comparison: non-absorbable sutures

Outcomes	Illustrative comparative risks* (95% CI) Assumed risk non-absorbable sutures	Corresponding risk Absorbable	Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
Surgical site infection Odds ratio Follow-up: 1-78 weeks	Study population		OR 0.97 (0.56 to 1.69)	1354 (10 studies)	⊕⊕⊕⊖ moderate	
	77 per 1000	75 per 1000 (44 to 123)				
	Moderate					
	63 per 1000	61 per 1000 (36 to 102)				
Postoperative complications Odds ratio Follow-up: 1-78 weeks	Study population		OR 0.77 (0.39 to 1.52)	1354 (10 studies)	⊕⊕⊕⊖ moderate	
	97 per 1000	76 per 1000 (40 to 140)				
	Moderate					
	72 per 1000	56 per 1000 (29 to 105)				
Risk of wound dehiscence Odds ratio Follow-up: 1-78 weeks	Study population		OR 0.12 (0.04 to 0.39)	737 (6 studies)	⊕⊕⊕⊖ moderate	
	63 per 1000	8 per 1000 (3 to 26)				
	Moderate					
	35 per 1000	4 per 1000 (1 to 14)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **OR:** Odds ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

Figure 2 Strength and summary of the evidence analysed on GradePro®.

Study or subgroup	Absorbable suture Events	Total	Non-absorbable suture Events	Total	Weight	Odds ratio M-H, random, 95%CI
Dorflinger 1983	0	29	0	29		Not estimable
Foster 1977	21	62	9	65	18.5%	3.19 (1.32, 7.67)
Glough 1975	7	76	8	76	15.1%	0.86 (0.30, 2.51)
Harimoto 2011	7	62	10	63	15.6%	0.67 (0.24, 1.90)
Kotaluoto 2012	3	90	7	95	10.9%	0.43 (0.11, 1.73)
Lundblad 1989	8	78	4	78	12.6%	2.11 (0.61, 7.33)
Pauniaho 2010	1	79	2	87	4.5%	0.54 (0.05, 6.13)
Ralphs 1982	1	56	3	66	5.0%	0.38 (0.04, 3.78)
Szabo 2002	1	25	1	25	3.4%	1.00 (0.06, 16.93)
Tan 2008	5	106	9	107	14.2%	0.54 (0.17, 1.67)
Total (95%CI)		663		691	100.0%	0.97 (0.56, 1.69)
Total events	54		53			

Heterogeneity: Tau^2 = 0.23, χ^2 = 12.12, *df* = 8 (*P* = 0.15); I^2 = 34%
Test for overall effect: *Z* = 0.11 (*P* = 0.92)

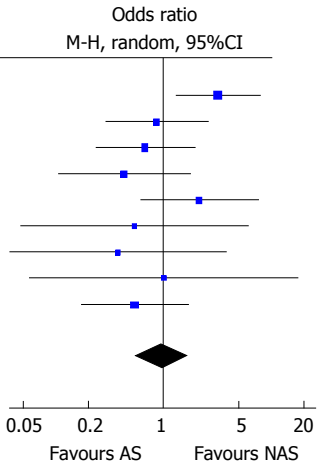

Figure 3 Forest plot for surgical site infection following the use of absorbable suture and non-absorbable suture for skin closure. Odds ratios are shown with 95%CI. AS: Absorbable stitch; NAS: Non-absorbable stitch.

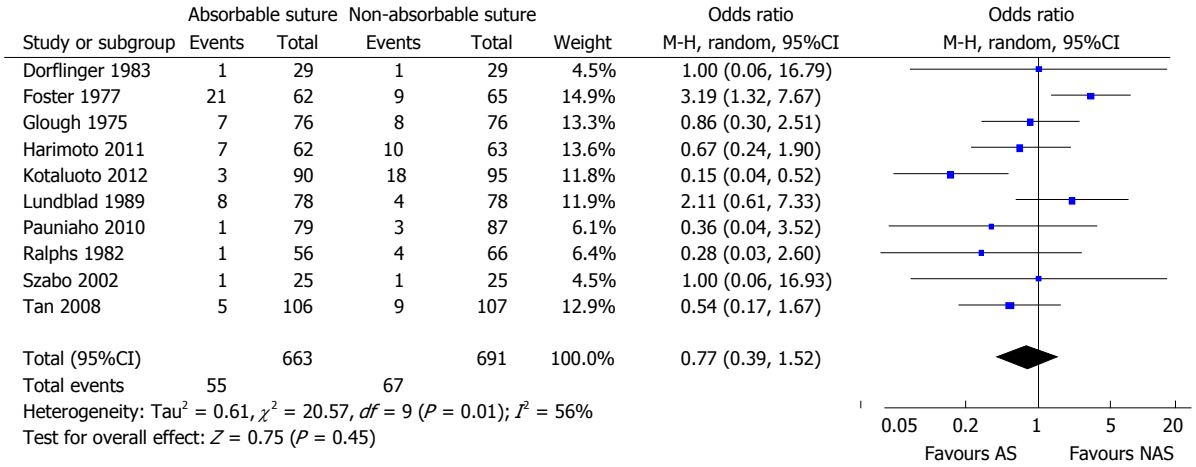

Figure 4 Forest plot for postoperative complications following the use of absorbable suture and non-absorbable suture for skin closure. Odds ratios are shown with 95%CI. AS: Absorbable stitch; NAS: Non-absorbable stitch.

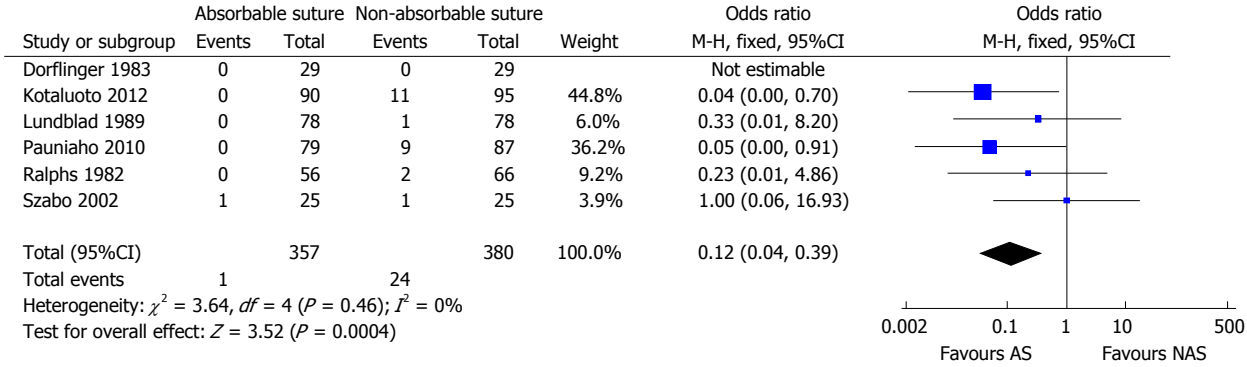

Figure 5 Forest plot for the risk of wound dehiscence following the use of absorbable suture and non-absorbable suture for skin closure. Odds ratios are shown with 95%CI. AS: Absorbable stitch; NAS: Non-absorbable stitch.

$Z = 0.75$; $P = 0.45$; Figure 4), the incidence of operative morbidity was statistically comparable in both arms of included RCTs. Although the AS was associated with the reduced risk of developing postoperative complications but statistically it was not significant.

Risk of wound dehiscence

There was no heterogeneity [$\chi^2 = 3.64$, $\gamma = 4$, ($P = 0.46$); $I^2 = 0\%$] among included RCTs. Six trials[32,36-40] contributed to the combined calculation of this variable. Therefore, in the random effects model (OR = 0.12; 95%CI: 0.04, 0.39; $Z = 3.52$; $P < 0.0004$; Figure 5), the use of AS was associated with the reduced risk of developing wound break-down.

Other variables

Authors initially planned to analyse other outcome measures such as cosmetic outcomes, stitch granulomas, health-related quality of life measurement, and outcomes comparisons between contaminated and non-contaminated skin wound closures but unfortunately there was either insufficient data reporting or these variables were not investigated.

DISCUSSION

The findings of this review article demonstrate that the use of AS is similar to NAS for skin closure for surgical site infection and other operative morbidities. AS do not increase the risk of skin wound dehiscence, rather lead to a reduced risk of wound dehiscence compared to NAS.

The conclusions of this study are consistent with the previously reported several RCTs[32,34-41] and comparative studies[32,34,35,37-41]. Majority of these studies compared the usage of AS against NAS by continuous skin closure stitches. Two trials[33,36] compared the use of AS with NAS by interrupted skin closure stiches. Their outcome was also in favour of AS as for as surgical site infection and postoperative complications are concerned. The comparison between continuous stitch *vs* interrupted stitch closure of skin by using absorbable or non-absorbable sutures could not be performed in this review due to scarcity of trials and number of patients. Therefore, it is difficult to analyse and conclude the superiority of any technique of skin closure.

Current study has many limitations. There were substantial variances in the inclusion criteria such as RCTs

on general surgical patients, plastic surgical patients and gynaecology were jointly analysed in this review which may be a potential source of bias due to diversity of patients. Further sub-classification of patients in the form of clean and contaminated wounds was not reported and therefore subgroup analysis was not possible to detect the difference in complications and wound infection following the use of AS and NAS. Varying degrees of differences also existed among included RCTs in terms of the definitions of "wound infection" and "wound dehiscence". RCTs with fewer patients may not have been sufficient power to recognise small differences in primary and secondary outcomes. Different skin closure techniques like interrupted, subcuticular and continuous suturing were reported in included trials. In addition, different types of absorbable sutures were used in the included studies and one may consider this biased. Inadequate randomization approach, improper concealment in the process of allocation, absence of power calculations, lack of utilization of single or double blinding and lastly lack of reporting of IIT were major factors responsible for scoring the majority of included RTCs of poor quality. Variables like foreign body sensation, stitch granulomas, cosmetic score, health-related quality of life measurement and cost effectiveness should have been considered too. Due to significant clinical and methodological diversity among included studies in addition to aforementioned several limitations, a major, multicentre and high quality randomized, controlled trial is required to validate these findings before recommending the routine use of AS for skin closure.

COMMENTS

Background

The conventional way of closing surgical incision wound by non-absorbable interrupted stitches have been largely replaced by the use of absorbable stitches without any conclusive and undisputable evidence in the medical literature. The aim of this article is to find relevant randomized, controlled trials and attempt to generate a guiding evidence to achieve this goal.

Research frontiers

Several study cohorts, comparative studies and randomized trials have been reported comparing absorbable stiches and non-absorbable stitches to close surgical incision wounds with outcomes reported in favour as well as against the use of either suture. Other major concern reported in the published studies was the prevalence of surgical site infection and wound dehiscence. Due to lack of consensus statement on this issue, the evidence based practice is lacking and this article is an attempt to clarify this confusion.

Innovations and breakthroughs

Based upon the meta-analysis of 10 controlled trials, the absorbable sutures are similar to non-absorbable sutures for skin closure in cases of wound infection and other complications. Absorbable sutures do not increase the risk of skin wound dehiscence, rather leads to a reduced risk of wound break-down compared to non-absorbable sutures.

Applications

To the authors' knowledge this is first systematic review reporting the comparison of both wound closure techniques and highlighting the value of the routine of absorbable stitches for the closure of surgical incision wound.

Terminology

AS: Absorbable stitch; NAS: Non-absorbable stitch; OR: Odds ration; SMD: Standardized mean difference.

Peer review

This is an important paper focusing on systematically analysis of the randomized, controlled trials comparing the use of absorbable *vs* non-absorbable suture for skin wound closure in surgical patients.

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CASE REPORT

Inflammatory pseudotumour of the spleen associated with splenic tuberculosis

Maria Isabel Prieto-Nieto, Juan Pedro Pérez-Robledo, Beatriz Díaz-San Andrés, Manuel Nistal, José Antonio Rodríguez-Montes

Maria Isabel Prieto-Nieto, Juan Pedro Pérez-Robledo, Beatriz Díaz-San Andrés, José Antonio Rodríguez-Montes, Department of General and Digestive Surgery, La Paz University Hospital, Paseo de la Castellana, 28046 Madrid, Spain
Manuel Nistal, Department of Pathology, La Paz University Hospital, Paseo de la Castellana, 28046 Madrid, Spain
Author contributions: All authors contributed to the work.
Correspondence to: Maria Isabel Prieto-Nieto, MD, PhD, FACS, Department of General and Digestive Surgery, La Paz University Hospital, Paseo de la Castellana, 261, 28046 Madrid, Spain. iprieto@intermic.com
Telephone: +34-60-6839295 Fax: +34-60-6839295
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Abstract

Inflammatory pseudotumor (IPT) of the spleen is an uncommon entity with an uncertain aetiology. Inflammatory pseudotumors present diagnostic difficulties because the clinical and radiological findings tend to suggest a malignancy. The symptoms include weight loss, fever, and abdominal pain. Most cases of splenic IPT present solitary relatively large well circumscribed masses on imaging. The diagnosis in the majority of the cases is made after histopathologic study of splenectomy specimens. The IPTs that occur in the spleen and liver are typically associated with Epstein-Barr virus. Thirty-seven percent of all new cases of active tuberculosis infection are extrapulmonary tuberculosis and tuberculous lymphadenitis the most commonly occurring form of extrapulmonary tuberculosis. We report the case of an inflammatory pseudotumor of the spleen associated with splenic tuberculous lymphadenitis in a 50-year-old female patient who was preoperatively diagnosed with a malignant spleen tumour based on her history of breast of carcinoma.

Key words: Inflammatory pseudotumour; Spleen; Splenic lymphadenitis; Splenectomy; Splenic tuberculosis

Core tip: A rare benign; lesion inflammatory pseudotumours (IPT) are infrequently found in the spleen with only sporadic case reports and short case series reported in the literature. Here we report a case of a spleen IPT associated with splenic tuberculous lymphadenitis in a 50-year-old female patient who was preoperatively diagnosed with a malignant spleen neoplasm.

Prieto-Nieto MI, Pérez-Robledo JP, Díaz-San Andrés B, Nistal M, Rodríguez-Montes JA. Inflammatory pseudotumour of the spleen associated with splenic tuberculosis. *World J Gastrointest Surg* 2014; 6(12): 248-252 Available from: URL: http://www.wjgnet.com/1948-9366/full/v6/i12/248.htm DOI: http://dx.doi.org/10.4240/wjgs.v6.i12.248

INTRODUCTION

Inflammatory pseudotumours (IPT) characterized microscopically by a proliferation of inflammatory cells, are infrequently found in the spleen and there are only sporadic case reports and short case series in the literature[1]. We report a case of a spleen IPT associated with splenic tuberculous lymphadenitis in a 50-year-old female patient who was preoperatively diagnosed with a malignant spleen neoplasm[1,2].

CASE REPORT

A 50-year-old woman had been undergone a quadrantectomy for an intraductal breast carcinoma intraductal. The sentinel ganglion was negative so the patient received radiotherapy followed by tamoxifen. Two years later her routine follow-up ultrasonography incidentally

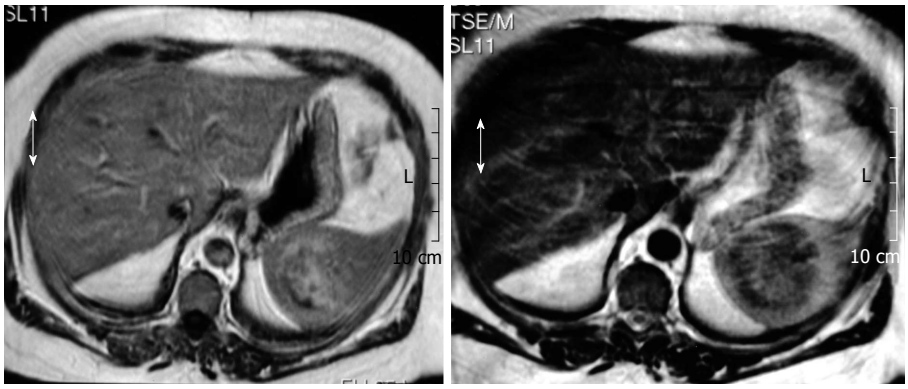

Figure 1 Magnetic resonance imaging shows a mass of 6 cm in diameter. Axial T1W image shows well circumscribed solid and heterogeneous intrasplenic mass. It might seem to have an excentric scar although calcification could also be possible. It is difficult to discern by magnetic resonance imaging.

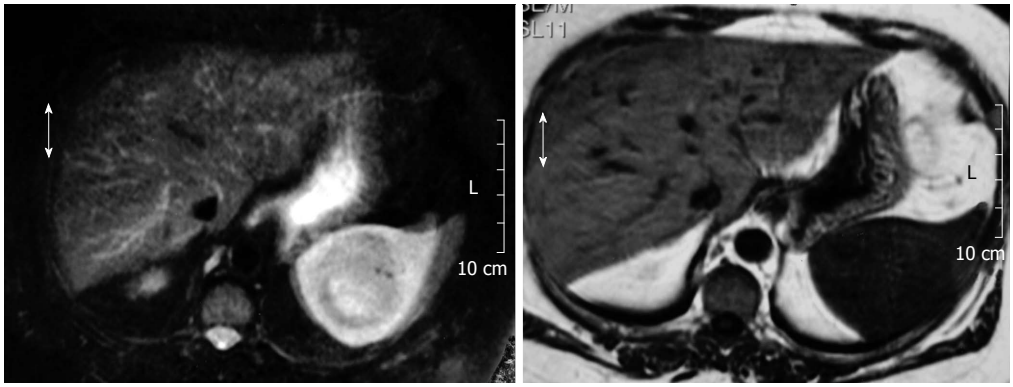

Figure 2 Axial T2W fat sat image shows a large intrasplenic mass. Notice the slightly decrease of signal intensity and the lack of a peripherical capsule.

discovered a solid mass at the inferomedial pole of the spleen. There was no history of spleen trauma. Over the previous two months, she had experienced minor weight loss and tiredness, fatigue and left flank pain. Biochemical and blood count parameters were within normal ranges. Serum α-fetoprotein, carcinoembryonic antigen, and antinuclear antibody and CA 19.9, CA 125, CA 15 levels were normal and serum echinococcus granulosis IgE and hemagglutination tests were negative. Biochemical and haematological results were all within normal ranges. Physical examination did not reveal organomegalia or lymphadenopthy. Blood antibodies for Epstein-Barr Virus (EBV), cytomegalovirus, toxoplasmosis and Human Immunodeficiency Virus (HIV) were all negative. The chest x-ray was normal. Magnetic resonance imaging (MRI) revealed a 6 cm diameter mass. T1-weighted axial imaging, showed a hypoisointense signal, while the T2-weighted axial imaging showed an isointense signal with small areas of hyperintensity (Figures 1 and 2). Post-gadolinium-DTPA T1-weighted imaging showed a heterogeneous increase in the mass[3,4]. Splenectomy was performed. The spleen measured 17 cm × 10 cm × 8 cm and weighed 415 g. The histopathological study described an inflamed spleen with an inflammatory pseudotumor (Figure 3A) showing fibroblastic and myofibroblastic proliferation (Figure 3B) that was associated with con tuberculous lymphadenitis of the spleen (Figure 3C). A six month regimen consist in two months of isoniazide 300/d (INH), rifacin 600 mg/d (RIFADIN), pyrazinamide 1.5 g/d and ethambutol 1 g/d (MYAMBUTOL), followed by four months of isoniazid and rifampin. Eighteen months after surgery the patient remains asymptomatic and there is no evidence of tumoral recurrence.

DISCUSSION

IPT are benign in nature. Slow-growing, these tumors may be located in the lung, respiratory tract, gastrointestinal tract, liver, spleen or lymph nodes,but the liver is the most common extra pulmonary site[1,2]. About one half of the lesion is discovered incidentally during revision for other malignancies after splenectomy[1].

The aetiology and pathogenesis of IPT are not yet understood. It may represent an non specific response to a bacterial or viral infection. In up to 40% of cases, granulomata, giant cells and EBV are detected in the involved tissue. EBV can be found in 66.7% of splenic and hepatic pseudotumors but it is detectable in only 20% of pseudotumors of the lymph node[3]. The frequency of EBV may vary depending on the site of the IPT[3-5]. It has been hypothesised that IPT may have an autoimmune nature. This hypothesis is supported by the fact that, in some cases, IPT are associated with thrombocytopenia

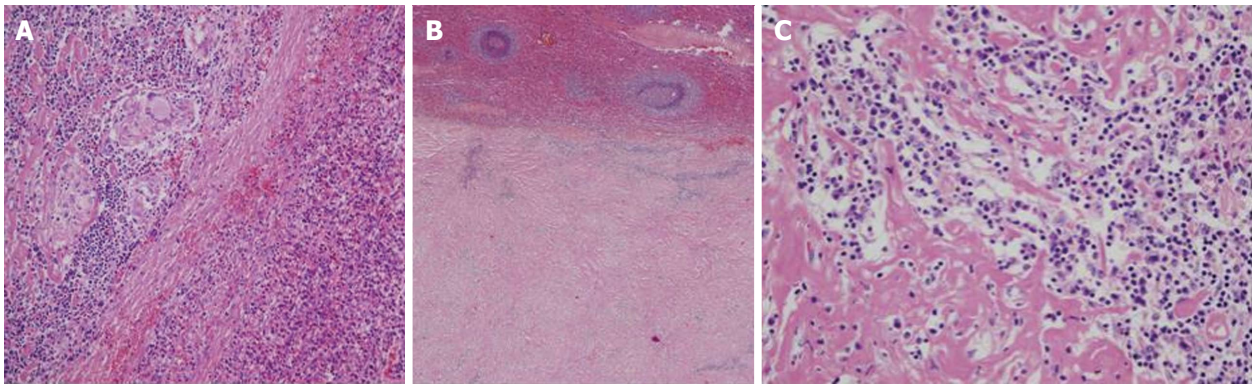

Figure 3 Histopathological study. A: Section of the spleen with a inflammatory pseudotumor (20 × HE); B: High power xamination revealed a fibroblastic and myofibroblastic proliferation with lymphocytes and plasma cells (40 × HE); C: Several tuberculoid granuloma were identified in the spleen and and in the hilar lymph node (20 × HE).

purpura[6,7]. In addition, autoimmunity is suggested by the high plasmatic cell content in histologic specimens. Infection, vascular causes and autoinmunes disorders have been hypothesised in their pathogenesis. Infection is one of the hypothesesis because of the presence of granulomas and giant cells in the masses, as occurred in our patient who had tuberculosis. Mycobacteria have been found in spindle cell pseudotumors (MSP). In most of the reported cases MSP occurs in the lymph node of inmunocompromised patients[8] and it should be noted that our patient had undergone radiotherapy so perhaps her autoinmune system had become compromised, allowing her to acquire the tuberculosis and then inflammatory pseudotumor appeared. Some 37% of all new cases of active tuberculosis infection are extrapulmonary tuberculosis[9]. Tuberculous lymphadenitis is the most commonly occurring form of extrapulmonary tuberculosis. Excisional biopsy of the lymph nodes with histology, acid fast-bacillus stain and mycobacterial culture are the diagnostic procedure of choice. A sample can be cultured in a specific medium (Lowenstein Jenssen) to diagnose the bacteria, but if there is not sufficient simple, a polymerase reaction (PCR) analysis which is highly sensitive and can distinguish tuberculosis from other mycobacteris, must be done[10,11]. Tuberculosis in the spleen is uncommon, usually associated with miliary dissemination and is most often observed in patients with immunodeficiency. Splenic tuberculoma can be micronodular or macronodular. The latter form is extremely rare and seen more often in HIV^+ individuals. However there are sporadic case reports of splenic TB in immunocompetent patients. Our patient had neither a history of TB nor showed evidence of TB in any other organ. The bacteriological findings were confirmed by histopathology and acid-fast bacillus staining as well as culture and PCR. Results with interferon gamma release assays have shown that the yield of this test is poor in patients with altered immune systems and this was done in our patient[12].

In most cases, IPT of the spleen affects patients in their fifth or sixth decade of life, with men and women being affected in the same proportion[1], although some authors report a higher incidence in women[1,2]. Patients with IPT of the spleen present with unspecific symptoms, and the diagnosis is most often the result of an incidental finding. The most usual complaint is pain located on the left upper quadrant due to either increased spleen size or compression of adjacent anatomical structures. Less frequently, fever of unknown origin, anaemia and weight loss[2], thrombocytosis, polyclonal hypergammaglobulinemia, hypercalcemia and lekocytosis all of which suggest a lymphoproliferative disorder[13,14] may be reported. Physical examination can reveal splenomegalia, but findings are most often unspecific

Preoperative diagnosis is troublesome, and can not be made by relying on laboratory findings[1] although leukocytosis and an elevated erythrocyte sedimentation rate are common. Radiological studies reveal focal necrosis, cystic calcification and myxoid changes. An abdominal radiograph can show splenomegalia and curvilinear calcifications along the inside edge of the spleen[14]. Computed tomography (CT) is not specific in differentiating between splenic IPT and other malignancies[8]. CT reveals a mass with a central hypodense area that may correspond to a necrotic zone surrounded by a hyperdense area with outlying hypodense zones[1,2,15]. MRI reveals a lesion with a minimum increase in the signal on T1, a hypersignal on T2, and gadolinium injection, a moderate enhancement in signal intensity on T1 as occurred in our patient[14,16]. The only MRI difference between a splenic tuberculoma and an inflammatory tumor of the spleen is that the image of the former changes with the evolution of the disease and may even disappear at 5-10 mo while the inflammatory pseudotumor does not change[17,18].

Radiological findings may also be indistinguishable from those of a lymphoproliferative disorder or a malignancy of the spleen. Lymphoma is the most usual misdiagnosis. The differential diagnosis should also consider hamartoma and benign tumours, including as well as vascular malformations, granulomatous infections (which most often result in systemic affectation), splenic infarct, and spleen metastases, the latter being the initial presumptive

diagnosis in our patient[13,14,19]. Surgery remains the gold stantard for definitive diagnosis.

In most cases the pseudotumor consists of a single well-circumscribed mass of 2-15 cm in diameter, composed of inflammatory cells, particularly plasmatic cells, and a fibroblastic proliferation of spindle cells, such as smooth muscle antibody (+), myofibroblasts and follicular dendritic cells (+). The spindle cells in IPT are most often myofibroblasts[5,20]. (1) IPT of the spleen is classified into three groups according to the cellular characteristics of the mass, clinical presentation and course, potential aetiology and prognosis: IPT-like follicular dendritic cell tumour. Is the kind that most frequently affects women. It is associated with a spindle cells and EBV infection; (2) The presence of myofibroblasts in a splenic IPT has led to the designation of inflammatory myofibroblastic (IMT) tumor. A considerable proportion of these tumours are EBV (+) and they have a potential for malignancy; and (3) IPT of the spleen was described by Cottelingam and Jaffe as having a predominance of spindle cells. Some 33%-48% of cases are found incidentally. This is the group which best deserves the term IPT of the spleen[5,20]. The World Health Organization classification places inflammatory myofibroblastic tumors in an intermediate category (rarely metastasizing, < 5%) between benign and malignant[14].

IPT of the spleen is a rare entity. It should be included in the differential diagnosis for splenic masses, especially when MRI discloses a single mass showing increased signal on T1 following gadolinium injection.

COMMENTS

Case characteristics

A 50-year-old woman with a inflammatory pseudotumour of the spleen that present diagnostic difficulties because the clinical and radiological findings tend to suggest a malignancy.

Clinical diagnosis

Unspecific symptoms and the diagnosis is most often the result of an incidental finding.

Differential diagnosis

Lymphoproliferative disorder or a malignancy of the spleen. Lymphoma, hamartoma, vascular malformations, splenic infarct and spleen metastases.

Laboratory diagnosis

Biochemical and blood count parameters were within normal ranges. Serum α-fetoprotein, carcinoembryonic antigen, and antinuclear antibody and CA 19.9, CA 125, CA 15 levels were normal and serum echinococcus granulosis IgE and hemagglutination tests were negative.

Imaging diagnosis

The histopathological study described an inflamed spleen with an inflammatory pseudotumor showing fibroblastic and myofibroblastic proliferation that was associated with con tuberculous lymphadenitis of the spleen.

Treatment

A six month regimen consist in two months of isoniazide 300/d (INH), rifacin 600 mg/d (RIFADIN), pyrazinamide 1.5 g/d and ethambutol 1 g/d (MYAMBUTOL), followed by four months of isoniazid and rifampin. Splenectomy was performed.

Related reports

The aetiology and pathogenesis of inflammatory pseudotumours (IPT) are not yet understood. It may represent an non specific response to a bacterial or viral infection. In up to 40% of cases, granulomata, giant cells and Epstein-Barr virus (EBV) are detected in the involved tissue. EBV can be found in 66.7% of splenic and hepatic pseudotumors but it is detectable in only 20% of pseudotumors of the lymph node.

Term explanation

Excisional biopsy of the lymph nodes with histology, acid fast-bacillus stain and mycobacterial culture are the diagnostic procedure of choice. A sample can be cultured in a specific medium (Lowenstein Jenssen) to diagnose the bacteria, but if there is not sufficient simple, a polymerase reaction analysis which is highly sensitive and can distinguish tuberculosis from other mycobacteris, must be done. Tuberculosis in the spleen is uncommon, usually associated with miliary dissemination and is most often observed in patients with immunodeficiency. Splenic tuberculoma can be micronodular or macronodular. The latter form is extremely rare and seen more often in Human Immunodeficiency Virus+ individuals.

Experiences and lessons

The frequency of EBV may vary depending on the site of the IPT. It has been hypothesised that IPT may have an autoimmune nature. This hypothesis is supported by the fact that, in some cases, IPT are associated with thrombocytopenia purpura. In addition, autoimmunity is suggested by the high plasmatic cell content in histologic specimens. Infection, vascular causes and autoinmunes disorders have been hypothesised in their pathogenesis. Infection is one of the hypothesis because of the presence of granulomas and giant cells in the masses, as occurred in their patient who had tuberculosis. Mycobacteria have been found in spindle cell pseudotumors (MSP). In most of the reported cases MSP occurs in the lymph node of inmunocompromised patients and it should be noted that their patient had undergone radiotherapy so perhaps her autoinmune system had become compromised, allowing her to acquire the tuberculosis and then inflammatory pseudotumor appeared. Tuberculous lymphadenitis is the most commonly occurring form of extrapulmonary tuberculosis.

Peer review

It is an interesting manuscript worthy of publication.

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CASE REPORT

Case of bronchoesophageal fistula with gastric perforation due to multidrug-resistant tuberculosis

Chan Sung Park, Kwang won Seo, Chang Ryul Park, Yang Won Nah, Jae Hee Suh

Chan Sung Park, Kwang won Seo, Department of Internal medicine, Ulsan University Hospital, University of Ulsan College of Medicine, Ulsan 682-714, South Korea
Chang Ryul Park, Department of Thoracic and Cardiovascular Surgery, Ulsan University Hospital, University of Ulsan College of Medicine, Ulsan 682-714, South Korea
Yang Won Nah, Department of General Surgery, Ulsan University Hospital, University of Ulsan College of Medicine, Ulsan 682-714, South Korea
Jae Hee Suh, Department of Pathology, Ulsan University Hospital, University of Ulsan College of Medicine, Ulsan 682-714, South Korea
Author contributions: Park CS, Seo KW, Park CR and Nah YW wrote the paper; Suh JH made the pathological diagnosis.
Correspondence to: Kwang Won Seo, MD, Department of Internal Medicine, Ulsan University Hospital, University of Ulsan College of Medicine, 290-3 Jeonha-dong, Dong-gu, Ulsan 682-714, South Korea. kwseo@uuh.ulsan.kr
Telephone: +82-52-2508861 Fax: +82-52-2518235
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Abstract

Gastric perforation and tuberculous bronchoesophageal fistula (TBEF) are very rare complications of extrapulmonary tuberculosis (TB). We present a case of pulmonary TB with TBEF and gastric perforation caused by a multidrug-resistant tuberculosis strain in a non-acquired immune deficiency syndrome male patient. The patient underwent total gastrectomy with Roux-en-Y end-to-side esophagojejunostomy and feeding jejunostomy during intravenous treatment with anti-TB medication, and esophageal reconstruction with colonic interposition and jejunocolostomy were performed successfully after a full course of anti-TB medication. Though recent therapies for TBEF have favored medication, patients with severe stenosis or perforation require surgery and medication with anti-TB drugs based upon adequate culture and drug susceptibility testing.

Key words: Bronchoesophageal fistula; Gastric perforation; Multidrug-resistant tuberculosis; Extrapulmonary tuberculosis; Treatment

Core tip: A case of pulmonary extrapulmonary tuberculosis (TB) with TB and gastric perforation caused by a multidrug-resistant tuberculosis strain in a non-acquired immune deficiency syndrome male patient.

Park CS, Seo KW, Park CR, Nah YW, Suh JH. Case of bronchoesophageal fistula with gastric perforation due to multidrug-resistant tuberculosis. *World J Gastrointest Surg* 2014; 6(12): 253-258 Available from: URL: http://www.wjgnet.com/1948-9366/full/v6/i12/253.htm DOI: http://dx.doi.org/10.4240/wjgs.v6.i12.253

INTRODUCTION

Tuberculous gastric perforation is a rare presentation of gastric tuberculosis (TB) with six previous cases reported in the literature[1,2]. However, to the best of our knowledge, there are no previous reports of gastric perforation due to multidrug-resistant TB (MDR-TB). Tuberculous bronchoesophageal fistula (TBEF) is also a very infrequent complication of extrapulmonary TB[3]. Although MDR-TB with TBEF has been reported in two cases, one case was in a human immunodeficiency virus (HIV) positive patient[4], and the other case was published in the Japanese language[5]. Moreover, these were cases of TBEF in patients with esophageal TB, but our case involved TBEF and gastric perforation in a patient with TB throughout the upper gastrointestinal (GI) tract. The patient with severe pulmonary TB, especially

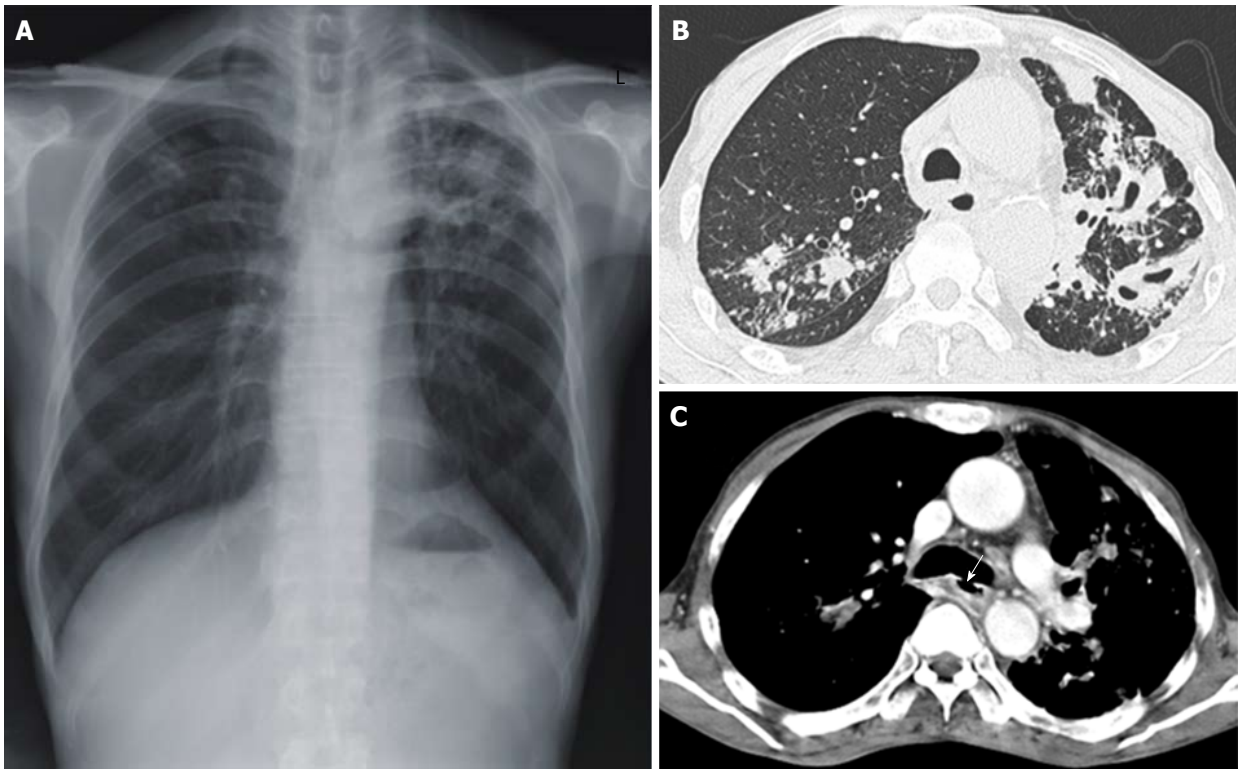

Figure 1 Chest radiograph and chest computed tomography scans are suggested reactivated pulmonary tuberculosis. A: Chest radiograph revealing combined reticulonodular densities, air space and nodular consolidation in the both upper lobe of the lung; B: Chest computed tomography showing multiple cavities with centrilobular nodules in the left upper lobe of the lung; C: A 1 cm sized bronchoesophageal fistula (white arrow) was observed in the inferior wall aspect of the left main bronchus.

combined extrapulmonary TB, can present with various complications, such as the need for surgery[6].

This report describes the first reported case of pulmonary TB with TBEF and gastric perforation caused by an MDR-TB strain in a non-acquired immune deficiency syndrome (AIDS) patient.

CASE REPORT

A 53-year-old man was referred for evaluation of dysphagia of 1 mo duration. Two weeks prior to the referral, he had been admitted to a local hospital due to general weakness with mild odynophagia. He was diagnosed with pulmonary TB by a positive acid fast bacilli (AFB) smear, and anti-TB medication (isoniazid, rifampin, ethambutol, and pyrazinamide) was started in the local hospital. However, 3 d after the initiation of anti-TB treatment, he had a sudden onset of dysphagia even for liquids. He had a history of pulmonary TB that was diagnosed 12 years prior to presentation and was cured after 6 mo of anti-TB medication. He was an active smoker with a 30 pack-year smoking history, and he was an alcoholic. He had consumed 3-5 bottles of spirits (it is called "Soju" in Korea) and several bottles of beer every day for several years. The patient was hemodynamically stable. He had lost approximately 12 kg over the course of the previous year, 5 kg of which was lost in the month prior to presentation [170 cm, 43 kg, body mass index (BMI) of 14.9 kg/m^2]. He complained of anorexia, nausea, odynodysphagia, and night sweats. On examination, he appeared cachectic, and lung auscultation revealed coarse breath sounds in the left upper lung field. There was no abdominal tenderness.

Laboratory data included the following: hemoglobin 157 (normal 140-180 g/L); white blood cell 8.5 (normal 4-10 × 10^6/L) (segmented neutrophils 73.8%, lymphocytes 16.2%); erythrocyte sedimentation rate 42 (normal < 15 mm/h); C-reactive protein 70 (normal < 0.5 mg/L); albumin 34 (normal 35-50 g/L); aspartate aminotransferase 42 (normal < 50 IU/L); alanine aminotransferase 30 (normal < 50 IU/L); alkaline phosphatase 136 (normal < 100 IU/L); amylase 203 (normal < 104 IU/L); lipase 46 (normal < 50 IU/L); and gamma-glutamyl transferase 185 (normal < 50 IU/L). HIV antibody was negative. Results of other biochemical tests were unremarkable. Staining of sputum for AFB was positive and Mycobacterium tuberculosis was cultured 1 mo later. Chest radiography at admission demonstrated combined reticulonodular densities and air space and nodular consolidation in both upper lobes, suggesting reactivated pulmonary TB (Figure 1A). Chest computed tomography (CT) revealed multiple cavitary nodules with centrilobular nodules in both upper lobes (Figure 1B), a 1 cm-sized bronchoesophageal fistula (BEF) (Figure 1C) 11 cm below the thyroid cartilage, and diffuse esophageal wall thickening at the mid to lower esophagus. Additionally, lymphadenopathy was seen in the left upper paratracheal region, aortopulmonary window, and right hilar space. Bronchoscopy revealed whitish

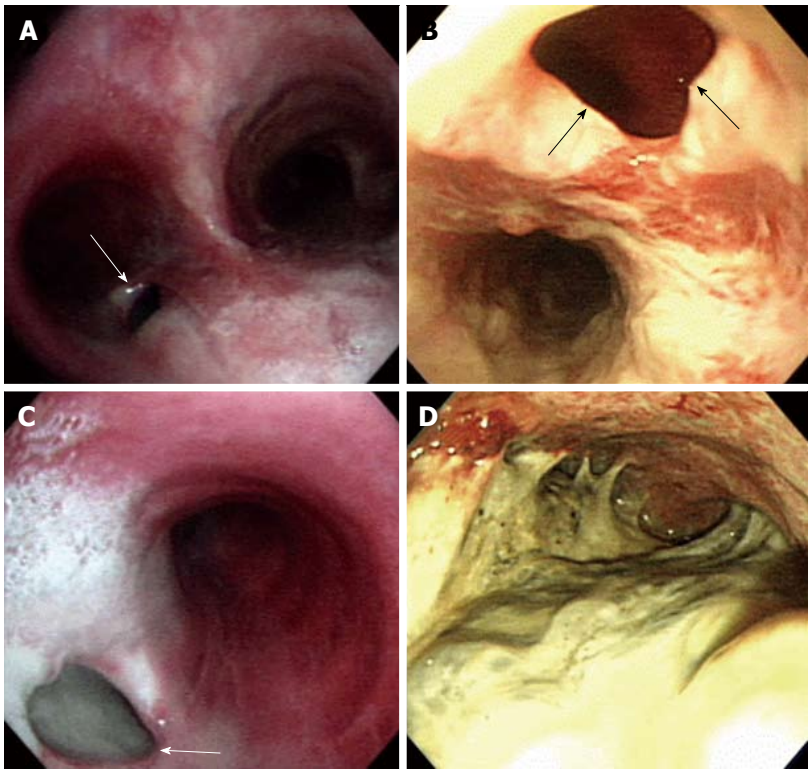

Figure 2 Bronchoscopy (A and C) and esophagogastroduodenoscopy (B and D) show tuberculous bronchoesophageal fistula and nearby lesions. A: A 1.0 cm × 1.5 cm sized hole (white arrow) was seen at the inferior wall aspect of the left main bronchus; B: Esophagogastroduodenoscopy showing a large fistula (black arrows) was noted at the level of incisor 28 cm below; C: The lumen of fistula (white arrow) was filled up with whitish exudate secretion and materials; D: Edematous and hyperemic inflammatory mucosal changes with exudate materials were observed at whole stomach.

exudates over the whole trachea and a 1.5 cm hole at the inferior aspect of the left main bronchus orifice (Figure 2A and C). Esophagogastroduodenoscopy (EGD) disclosed severe inflammation, ulceration, fibrotic scarring, easy touch bleeding throughout the entire esophagus, a fistula 28 cm from the incisors (Figure 2B), and severely inflamed gastric mucosa. The duodenum could not be observed due to pyloric deformity and exudates (Figure 2D). Polymerase chain reaction (PCR) for Mycobacterium tuberculosis with an endoscopically biopsied specimen of the stomach was positive.

After admission, because the patient could not take the pills per os and failed insertion of a nasogastric tube, four parenteral anti-TB drugs (isoniazid 300 mg, rifampin 450 mg, streptomycin 0.75 g, and moxifloxacin 400 mg) with vitamin B6 and parenteral nutrition were given intravenously. After treatment, his intermittent fever subsided and his TB was considered to be improving. Symptomatic improvement was noticed but dysphagia for liquids persisted. However, on the 20th day, the patient complained of abdominal pain. On physical examination, his temperature was 38℃ and he felt chilly. Bowel sounds were absent and his abdomen was rigid with muscle guarding. The patient was ultimately diagnosed with pan peritonitis due to spontaneous perforation of the stomach. An emergency operation was performed. Nearly the entire greater curvature of the stomach was perforated due to severe ulceration. Gelatinous dirty exudative materials, similar to cysts, were seen on the side of the perforated stomach. Total gastrectomy with Roux-en-Y end-to-side esophagojejunostomy and feeding jejunostomy were successfully performed. Because the gastroesophageal junction was severely narrowed due to fibrotic change, esophagojejunostomy was performed according to the manual without a stapling device. The surgical specimen demonstrated diffuse transmural inflammation with extensive ulceration of the stomach and duodenum (Figure 3A and B). The patient was treated with injection of anti-TB medications for 46 d, and after the operation, the patient was also treated with medication (isoniazid, rifampin, ethambutol, pyrazinamide) *via* jejunostomy for 41 d. The result of drug sensitivity testing (DST) for Mycobacterium tuberculosis showed MDR-TB (resistant to isoniazid: 1+ of 0.2 μg/mL; rifampin: 1+ of 1 μg/mL; ethambutol: 1+ for 5 μg/mL and susceptible of 10 μg/mL); therefore, the medications were changed to second line anti-TB drugs (para-aminosalicylic acid, streptomycin, and moxifloxacin) and susceptible first-line drugs (pyrazinamide and ethambutol). After 22 mo, he underwent esophageal reconstruction in our hospital with colonic interposition and jejunocolostomy using a 25-mm end-to-end anastomotic stapler. In surgical findings, we could not find the bronchoesophageal fistula, and whole esophagus had shrinkage and fibrotic changes because of severe inflammation. We think the fistula was healed by anti-TB medications and severe inflammatory changes around the esophagus. So we decided to perform a thoracic esophagectomy and colon interposition. Since

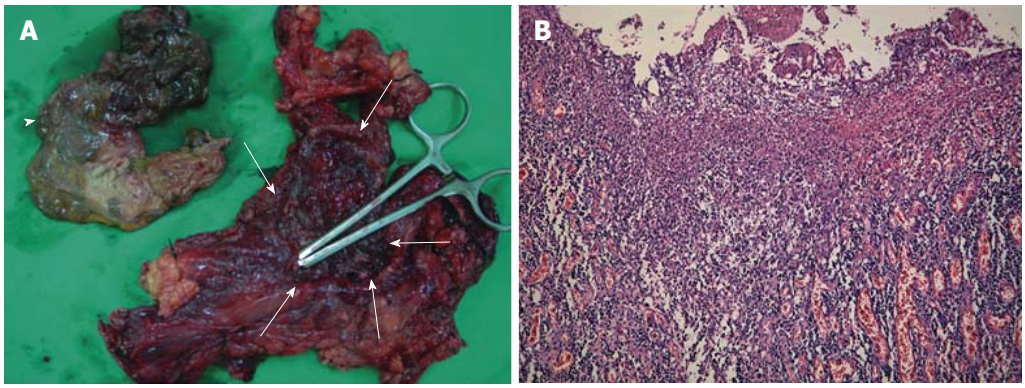

Figure 3 Gross anatomic specimen and its macroscopic histology show severe tuberculous inflammation and necrosis from the totally resected stomach and a part of duodenum. A: A huge defect (white arrows) in the gastric wall along the midbody and fundus. The dirty ragged tissue (white arrowhead) which was covering the defect was identified to be the infracted gastric wall pathologically; B: Histologic findings of the resected specimen in hematoxylin and eosin staining (original magnification × 100) showing diffuse transmural inflammation with extensive multiple ulcers on the stomach.

then, he has been able to eat through his mouth.

Although his body weight was 43 kg at the first referral time, he has gained weight up to 58 kg (BMI 20.1 kg/m^2) at that time of decision for esophageal surgery after feeding through jejunostomy and appropriate anti-TB medications. But he has complained of not being able to eat. He hoped that he could eat through his mouth after the operation. After esophageal reconstruction operation, expectedly, he suffered from dumping syndrome such as diarrhea, light-headedness and sweating after meals. But he tolerated these symptoms gradually after food intake training for preventing dumping syndrome. One month after esophageal reconstruction surgery, he was discharged with his body weight at 53.7 kg. Two months later, he was readmitted to the hospital with a three-day history of abdominal pain and nausea. Esophagography showed severe stricture at colojejunostomy. He underwent a balloon dilatation procedure using a diameter 20 mm balloon successfully. After that time, he is able to eat again and be allowed to go home. Though he lost weight, his body weight was maintained at 51 kg within 6 mo after oral food intake.

DISCUSSION

MDR-TB is defined as a strain of TB with documented resistance in vitro to at least isoniazid and rifampin. The global population weighted proportion of MDR-TB among all TB cases is 5.3% with an estimated 0.5 million cases[7]. The incidence of MDR-TB has continuously increased in Korea. According to a 2007 report[8], the prevalence of MDR-TB increased from 1.6% to 2.7% of all TB cases between 1994 and 2004. There was a particularly high increase in the 30-39 age group, with the incidence of MDR-TB in retreatment patients reaching 21.4%. Additionally, some countries are showing increases in MDR-TB with rates as high as 22.3% among new cases and 60.0% among previously treated cases[7].

Extrapulmonary TB occurs in 70% of AIDS patients compared with 20% of non-AIDS related TB cases[9]. GI TB is presently nearly the sixth most common site of extrapulmonary TB, similar to the incidence of peritoneal TB, in the United States[10]. But esophageal TB is rare among GI TB because exposure of the esophagus to the organism is limited by the rapid clearance of infected sputum by means of coordinated peristalsis combined with upright posture and an intact lower esophageal sphincter[11]. Esophageal TB may present with dysphagia and may be complicated by ulcer or stricture formation, perforation, and fistulae[12]. Upper GI endoscopy is the most useful tool in establishing the diagnosis, particularly with biopsy of the affected area[13]. In addition, chest CT may be useful in identifying the presence of enlarged mediastinal lymph nodes and fistula, as in our case. It is well established that AFB staining for Mycobacterium tuberculosis is positive in less than 25% cases[14]. Therefore, Abid *et al*[15] suggested that certain endoscopic features, such as deep and large esophageal ulcers and tracheoesophageal fistula, are strongly suggestive of TB-related lesions.

As Lado Lado *et al*[3] have reviewed, only 36 cases of TBEF were reported between 1893 and 2001. The development of TBEF could be due to the following mechanisms: rupture of caseonecrotic subcarinal lymph nodes into the esophagus and trachea; development of traction diverticula between the respiratory tree and the esophagus; or erosion of primary tracheal ulcers into the esophagus[16]. The most common symptoms of BEF are chronic and paroxysmal cough, dysphagia, fever and pneumonia[3]. Ono's sign is pathognomonic of BEF; it includes paroxysmal cough on ingestion of liquids and crepitation posteriorly over the sixth right intercostal space (cited in Alkhuja *et al*[17]). But our patient did not exhibit Ono's sign initially. He had complaints of mild odynophagia without paroxysmal cough that was simultaneous with oral ingestion of food. Three days after starting anti-TB mediation, he had the sudden onset of the inability to swallow even water.

On EGD, we found severe inflammation and easy touch bleeding from the esophageal orifice to the stomach with esophageal fistula. This sudden onset of aggravated

symptoms may represent a paradoxical response. Cheng *et al*[18] reviewed 122 episodes of paradoxical responses after anti-TB medication in non-HIV infected patients. Overall, 82.8% were associated with extrapulmonary TB and 95% of the Mycobacterium tuberculosis isolates were susceptible to first-line anti-TB therapy. Esophagography is highly helpful in visualizing the fistula[17]. However, we did not perform esophagography because the patient could not swallow. The role of bronchoscopy is diagnostic to visualize proximally located TBEF and to obtain specimens[4]. The reported overall yield of bronchoscopy in detecting TBEF is as high as 83%[19]. In addition to this diagnostic role, bronchoscopy performed in conjunction with esophagoscopy allows preoperative analysis and planning for surgical correction[20]. Though traditionally the treatment of TBEF has relied on surgery[16], recent therapies have favored medication, which has proven to be successful in anti-TB treatment[3]. However, our patient could not be treated by medication only and he ultimately underwent an esophageal reconstruction operation. Treatment for MDR-TB requires second-line drugs that are less effective. Multidrug regimens consist of a minimum of four or five drugs to which the infecting strain has documented susceptibility and the regimen should be used for a minimum of 18 to 24 mo[21]. Our patient received five drugs to which his MDT-TB was susceptible for 18 mo after DST.

The stomach is the sixth most common site in the GI tract to be affected by TB, following the ileocecal region, ascending colon, jejunum, appendix, and duodenum[22]. Possible causes for stomach sparing include high acidity, a paucity of lymphoid tissue, and rapid transit of food in the stomach[10]. Therefore, long-term therapy with H2 blockers increases the incidence of gastric TB due to decreased acidity[23]. The gross appearance of gastric TB has been described, and it is generally divided into three categories: tuberculous, ulcerative, and hypertrophic[24]. Definitive diagnosis of gastric TB requires the identification of AFB in biopsy material or microbial culture, which is not always possible. In the absence of AFB, the presence of a caseating granuloma may be considered diagnostic[22]. Our patient had severely inflamed gastric mucosa on EGD, and the PCR of the gastric biopsy specimen was positive. Gastric TB presents most commonly as an ulcer with or without associated gastric outlet obstruction. This kind of presentation is seen in approximately 80% of cases, with ulcers ranging from a few millimeters to as large as 20 cm, and manifests as non-specific chronic abdominal pain[22].

Tubercular gastric ulcers usually perforate or bleed because of their superficial location and associated endarteritis[1]. Patients with complications, such as pyloric mass, stenosis, bleeding, or perforation, require surgery[1]. Treatment with anti-TB drugs should be followed by surgical intervention[24].

In conclusion, this is the first reported case of successfully treated upper GI TB with TBEF and gastric perforation caused by an MDR-TB strain in a non-AIDS patient. Although the incidence of MDR-TB is low in the West and developed countries, some countries are showing increases of MDR-TB among new cases and particularly among previously treated cases. The various manifestations observed in patients with TBEF, gastric perforation, or both suggest a need for careful monitoring and management including surgery and anti-TB medications based on adequate culture and DST.

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