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REVIEW

Monitoring photodynamic therapy of head and neck malignancies with optical spectroscopies

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Abstract

In recent years there has been significant developments in photosensitizers (PSs), light sources and light delivery systems that have allowed decreasing the treatment time and skin phototoxicity resulting in more frequent use of photodynamic therapy (PDT) in the clinical settings. Compared to standard treatment approaches such as chemo-radiation and surgery, PDT has much reduced morbidity for head and neck malignancies and is becoming an alternative treatment option. It can be used as an adjunct therapy to other treatment modalities without any additive cumulative side effects. Surface illumination can be an option for pre-malignant and early-stage malignancies while interstitial treatment is for debulking of thick tumors in the head and neck region. PDT can achieve equivalent or greater efficacy in treating head and neck malignancies, suggesting that it may be considered as a first line therapy in the future. Despite progressive development, clinical PDT needs improvement in several topics for wider acceptance including standardization of protocols that involve the same administrated light and PS doses and establishing quantitative tools for PDT dosimetry planning and response monitoring. Quantitative measures such as optical parameters, PS concentration, tissue oxygenation and blood flow are essential for accurate PDT dosimetry as well as PDT response monitoring and assessing therapy outcome. Unlike conventional imaging modalities like magnetic resonance imaging, novel optical imaging techniques can quantify PDT-related parameters without any contrast agent administration and enable real-time assessment during PDT for providing fast feedback to clinicians. Ongoing developments in optical imaging offer the promise of optimization of PDT protocols with improved outcomes.

Key words: Head and neck cancer; Photodynamic therapy; Monitoring and predicting response; Blood flow; Oxygenation; Oxygen metabolism; Diffuse optical imaging

Core tip: Most treatment approaches including chemo-radiation and surgery can induce prolonged morbidity and functional loss resulting in severe impairment of patients' quality of life. Photodynamic therapy (PDT) is an emerging alternative treatment option without any significant accumulative side effects due to targeted light illumination and preferential accumulation of photosensitizers (PSs). However, PDT has not found widespread applications at the clinic mainly due to variable responses that originated from unstandardized treatment protocols such as different light and PS doses. Novel optical imaging techniques can quantify PDT-dosimetry related parameters such as local light and PS dose in tissue and PDT response related parameters such as tissue oxygenation and blood flow noninvasively without any contrast agent administration, thereby providing real-time feedback about the treatment efficacy for optimizing and standardizing PDT.

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INTRODUCTION

Head and neck malignancies refer to malignancies arising from the oral cavity, pharynx, nasal cavity and sinuses[1-3]. Head and neck squamous cell carcinoma (HNSCC), constituting approximately 90% of malignancies in the head and neck region, remains the fifth most common form of cancer worldwide with an incidence of approximately 800000 new cases per year[4]. Most of these tumors may be attributed to risk factors such as tobacco and alcohol consumption. HNSCC is a heterogeneous disease with different stages ranging from benign squamous hyperplasia, dysplasia, carcinoma *in situ* (CIS) to invasive carcinoma[3]. Early stage diagnosis and treatment of HNSCC increases the likelihood of successful treatment and improves patients' quality of life, lowers risk of mortality and health costs[5,6].

Substantial efforts concentrate on early detection with fair success, but still many patients present with clinically evident tumors that require effective treatment[7]. Several treatment options are available including surgery, chemotherapy, radiation therapy or combinations thereof[8]. In spite of improvements in these treatment modalities, they have their own limitations. For example, surgery may require resection of vital tissue such as part of the tongue resulting in functional loss. On the other hand, organ-preserving surgery can result in high recurrence rates. Nonsurgical management with chemo and radiation therapies to improve local-regional disease results in only modest or suboptimal improvements in survival but with significantly high cost side effects including speech and swallow function[9]. These conventional therapies may induce permanent vasculature dysfunction and necrosis, severe toxicities and irreversible injuries to non-tumor tissue such as the oral mucosa and the salivary glands, often resulting in morbidity and severe impairment of patients' quality of life. Further, normal tissue toxicity such as mucositis, bleeding and imflammation may lead to changes in applied dose quantity, and treatment re-schedule, which may affect treatment efficacy and outcome. For these reasons, an alternative treatment modality that is effective, safe, repeatable, minimally invasive and non-surgical is desired for the management of head and neck malignancies.

Photodynamic therapy (PDT) uses light to activate a photosensitizer (PS) in the presence of oxygen for local tissue destruction, has potential in these respects and is particularly attractive due to its significant level of normal tissue preservation and its repeatability without cumulative side effects[10]. It has potential impact particularly for cases with multiple lesions and wide-spread early stage head and neck diseases (*e.g.*, leukoplakia, invasive carcinoma) in the oral cavity[11]. However, PDT has not found widespread applications at the clinic mainly due to variable responses that originated from unstandardized treatment protocols such as different light and PS doses. Optical imaging can quantify local light and PS dose in tissue and monitor PDT; and therefore can provide feedback about the treatment efficacy. Thus, we expect optical imaging modalities will help in optimizing and standardizing PDT. Below we will detail PDT treatment and optical imaging for monitoring and ultimately predicting PDT response.

CLINICAL PDT

PDT is an emerging treatment option for many malignancies including head and neck. It is minimally invasive with much less side effects compared to conventional therapies. Since it does not have any significant accumulative side effects, it can be repeated many times and be applied before or after chemotherapy, radiation therapy. It can also be used as an adjuvant therapy to these therapies and surgery to eliminate residual microscopic tumor cells. PDT light can be delivered at the surface for wide and superficial malignancies and pre-malignancies such as mucosal dysplasia and CIS in the oral cavity. Interstitial light delivery is applied in treating thick and deep tumors for the aim of debulking tumors as an adjuvant to surgery.

Basics of PDT

PDT efficacy depends on three main elements: a sufficient amount of light, photosensitizing drug (also called PS) and available oxygen in tissue. The PS is activated during light illumination and the active PS reacts with molecular oxygen to produce singlet oxygen that induces direct cell killing, vascular destruction and immune response[12,13]. Most PSs are administered systematically but some can be applied topically for head and neck lesions in the oral cavity and nonmelanoma skin tumors. After a specific time, depending on the PS itself, PS accumulates specifically more in the diseased site compared to normal and surrounding periphery sites. Tumor to normal tissue contrast is generally 2-3 fold with a passive targeting mechanism, but even 10-fold contrast has been reported[14]. At the optimal time point of accumulation, a specific wavelength of light depending on the optical absorption properties of the PS is shined at a predetermined power to activate the PS to create a photodynamic reaction. Due to specific accumulation of the PS and localized light illumination, PDT is a local therapy rather than a systemic therapy like chemotherapy. The treatment volume depends on both PS and light penetration depth. For example, for the cases of Photofrin®, which is the first FDA-approved PS that was developed here at Roswell Park Cancer Institute, light illumination is at approximately 630 nm with a penetration depth of 5 mm or less. Thus, Photofrin® has been in use worldwide to treat early stage carcinomas in many organs including the head and neck.

Superficial and interstitial PDT approaches for head and neck diseases

Previous studies have shown that PDT is safe and effective in the treatment of early carcinomas of the head and neck[2,10,11,13,14-35]. PDT is an excellent choice for early-stage malignancies since local treatment and limited light

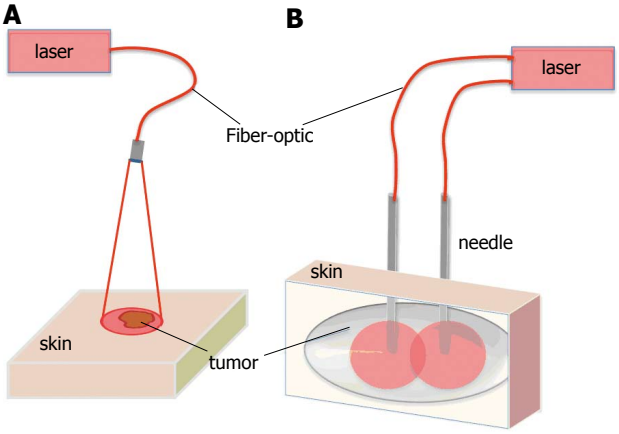

Figure 1 Representation for light delivery during surface and interstitial photodynamic therapy. A: Surface illumination photodynamic therapy (PDT) for treating superficial malignancies. Laser light is directed to tissue surface via micro-lens fiber. Tumor is located superficially; B: Interstitial PDT treatment for deeper and thicker malignancies. Individual fibers are placed inside 19-gauge needles and inserted into tissue. Number of fibers is selected according to treated volume.

penetration eliminates the side effects that can occur in the sensitive areas of the oral cavity such as soft palate. Lasers are the choice for the light sources and laser light is delivered *via* surface illumination by using a micro-lens as shown in Figure 1A. For deeper and thicker tumors, however, superficial illumination is not suitable. In this case, light is delivered by feeding laser fibers through needles placed directly into the tumor (Figure 1B). This approach is very similar to brachytherapy or interstitial radiotherapy[36,37].

CHALLENGES

One of the main challenges of PDT is treating deeper and thicker tissues. However, this is not an issue for superficial malignancies. Pain management is a frequently reported challenge[38]. Another common side effect of PDT is the long-term skin photosensitivity, especially for the cases of systemic administration of PSs such as Photofrin® (porfimer sodium). ALA-PDT is another widely used treatment option for early stage malignancies with much reduced skin photosensitization, but with the drawback of severe pain during treatment, often necessitating anesthesia. Therefore, the development of PSs that do not induce long-term photosensitivity, produce durable results and are patient friendly is of significant clinical benefit. In this respect the second generation PSs, such as Photoclor (HPPH) used in our clinical trials, have shown clinical promise with their improved efficacy, higher penetration depths and significantly less skin photosensitivity.

Variable outcomes are the main roadblock to wider use of PDT. The lack of standardized protocols with the same light and PS type and doses, as well as imprecise dosimetry drives the variable PDT responses[36,37]. There is strong evidence that variations in clinical response are a direct result of dosimetry that does not take into account individual differences[39]. In order to bring PDT to a full realization of its potential benefits, quantitative tools are likely to play an essential role. They can provide standardization of site-specific individualized protocols by assessing light and PS doses.

Another challenge for clinical PDT of the head and neck is the difficulty in predicting the responders and non-responders[36]. Quantitative optical imaging tools can play a crucial role in filling this niche. These tools are currently in primitive stages and not widely used in clinical settings for monitoring PDT mainly because optical measurements may require extra clinical time and extra fiber replacements during PDT. The techniques are limited to pre- and post-PDT measurements but with the advent of new technologies they can be adapted for monitoring during PDT, which would have three-fold benefits: (1) reduced required clinical time, (2) no interruptions of treatment light for the optical measurements, and (3) more accurate quantification of kinetics of PDT-related parameters such as photobleaching and blood flow kinetics, which have been shown to be predictors of PDT response[36,40-50].

CLINICAL OPTICAL IMAGING FOR PDT MONITORING

Tissue oxygen level is crucial for effective PDT since the PS initiates chemical reactions that result in cellular and vascular damage in targeted tissue in the presence of oxygen. Tissue oxygenation is highly affected by vascular parameters such as blood flow and blood oxygenation. During the PDT process, PS is consumed continuously. Thus, the efficacy of PDT is dependent on the vascular parameters and PS level and consumption (photobleaching)[50,51]. Vascular parameters and PS level change during PDT and these changes may be useful early markers for therapy response[36,44,52-54].

Optical imaging is a wide topic that includes many different imaging approaches. Here we will focus on a subdivision called diffuse optical spectroscopies (DOS) for probing millimeter to centimeter deep tissue[55-61]. In this context, DOS includes diffuse reflectance spectroscopy (DRS)[62-67], diffuse fluorescence spectroscopy (DFS)[40,67-70] and diffuse correlation spectroscopy (DCS)[71,72]. We have recently developed a multi-modal optical imaging technique that combines DRS, DFS and DCS in a single instrument and showed the feasibility of quantification of optical parameters (absorption and scattering), drug concentration and vascular parameters such as blood flow and oxygenation in a clinical setting[44,73].

Multi-modal optical instrument

The technical details of our multi-modal optical system can be found elsewhere[44,73], but here we briefly mention the basic working principles. The instrument performs measurements sequentially in the order of blood flow (DCS), optical parameters, blood oxygenation and volume (DRS), and fluorescence (DFS). Figure 2A and B

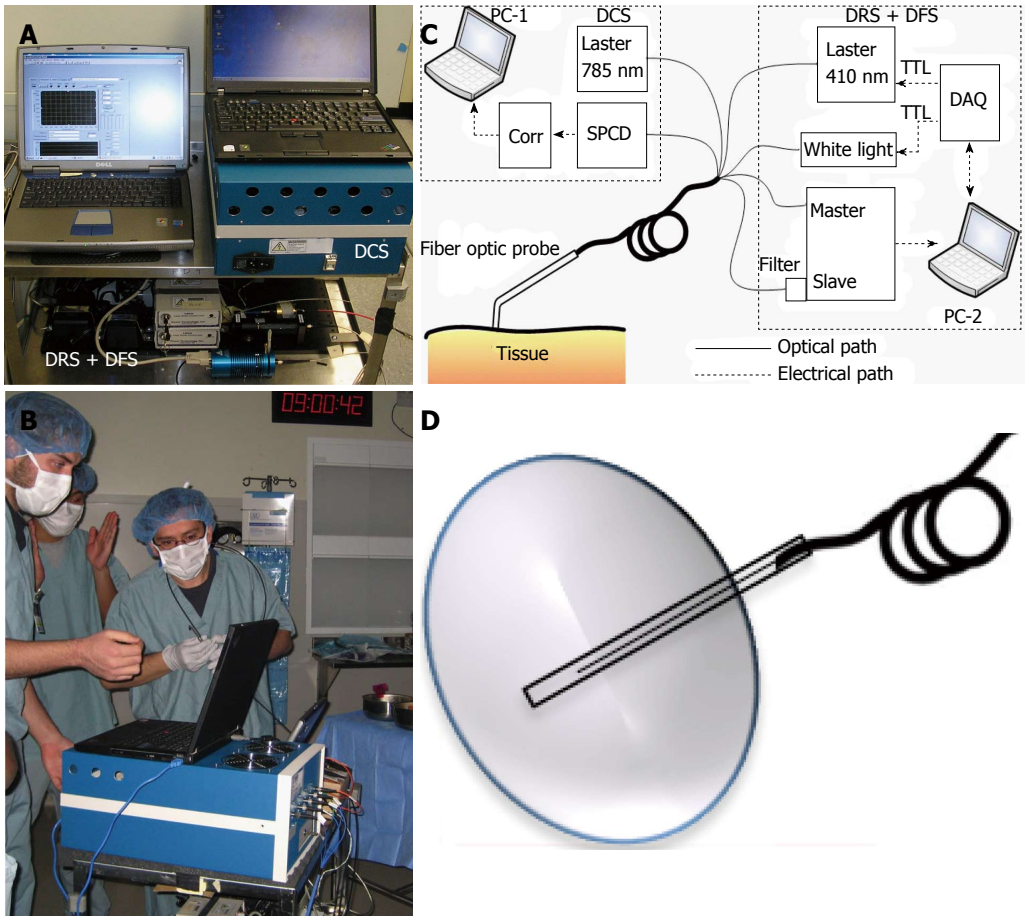

Figure 2 Clinical multi-modal optical instrument for photodynamic therapy dosimetry and response monitoring. A: Picture of multi-modal clinical optical instrument; B: During the measurements at the operating room; C: Diagram of multi-modal clinical optical instrument; D: Interstitial optical probe for measurements in deep and thick tumors. Adapted from the reference[45] with the permission.

shows the picture and schematic diagram of the instrument, respectively. The DCS instrument has a 785 nm, long coherence length laser (Crysta Laser), four single photon-counting detectors (SPCD, Perkin-Elmer), and a custom-built autocorrelator board (Correlator.com). Photodetector outputs were fed into a correlator board and intensity autocorrelation functions and photon arrival times were recorded by a computer. After blood flow measurements, the second laptop initiates fluorescence (DFS) and reflectance (DRS) data acquisition by utilizing TTL switching via a data acquisition card (DAQ, National Instruments). In absorption (DRS) mode, broadband diffuse reflectance measurements were taken by exciting the tissue with tungsten halogen lamp (Ocean Optics) and collecting the light with the Master channel of a two-channel spectrometer (Ocean Optics). In fluorescence (DFS) mode, a 410 nm laser diode (Power Technology) excites the PS in Soret band and the slave channel of the spectrometer collects the fluorescence spectra.

A hand-held "surface" probe that holds the light source and detector fibers can be used for measuring superficial malignancies by directly placing the tip of the probe on the tissue surface (Figure 2C). Although the instrument stays the same, the hand-held surface probe is ill-suited for interstitial light delivery and noninvasive measurements and the probe-tissue interface must be changed accordingly. For an "interstitial" probe, source and detector fibers are placed inside a catheter (Figure 2D).

Optical parameters and local light dose distribution by DRS

Currently the standard PDT light dosimetry at the clinics is based on the prescribed incident dose, which does not take into account reflected and scattered light in the lesion. Head and neck malignancies can exhibit a multifocal, wide-field nature of invasion and they may occur at diverse sites (*e.g.*, tongue, lip, palate, *etc.*). Therefore, they can have different optical parameters resulting in considerable inter- and intra-patient variations in the deposited local dose[11]. It has been shown that the measured effective local dose can be more than 5-fold greater than the incident administrated dose, illustrating the need for *in situ* dose monitoring on an individual basis[39]. Dosimetry systems using isotropic light detectors to measure both incident and scattered light are becoming more available in clinical systems[36,37]. Multi-channel systems that can measure light dose at multiple points of interest in real time can provide on-line feedback to clinicians during treatment planning.

Tissue absorption and tissue scattering parameters

modify light attenuation and thus affect the true light dose delivered to the whole three-dimensional tissue volume. Thus, direct light dose measurements may not be sufficient to quantify volumetric light distribution. Since malignancies can be highly heterogeneous, three dimensional optical parameter mapping can show heterogeneity of local light dose to the whole lesion volume. Several techniques are available for mapping of optical parameters (optical absorption and scattering) *in vivo*. Most of them are based on the photon diffusion equation with multi source-detector separations. Photon fluence (rate) is measured as a function of source-detector distance and measured data is fit to the diffusion model to extract optical parameters.

Local PS dose distribution by DFS and DRS

It has been demonstrated that PSs demonstrate significant inter- and intra-patient heterogeneity in distribution, leading to variations in the accumulated PDT dose and treatment failures[36,74,75]. It has been also suggested that the variation of the treatment outcome can be reduced by adjusting the light dose based on the pretreatment PS distribution so that PDT dose is uniform in the whole disease[36,75-78]. Although DRS can be used to quantify PS concentration by using the absorption peak of PSs, DFS is the preferred choice for this aim, since the fluorescence contrast is usually higher than the absorption contrast *in vivo*. However, fluorescence signal is affected by the tissue optical properties, and thus is not directly related to PS concentration. Ratiometric methods (with respect to optical attenuation and autofluorescence) may correct this signal distortion significantly[79,80]. Moreover, short source-detector separation (or single source-detector) based optical probes and empirical calibration techniques that calibrate the system with respect to reference optical phantoms may allow quantification of drug concentration. For quantifying PS concentration using DFS data, background subtracted fluorescence signal is usually normalized with the reflectance data obtained by DRS[65,66,70,81]. Fluorescence signal is assumed to be a linear combination of contributing components (*i.e.*, PS fluorescence, tissue autofluorescence, *etc.*). The normalized tissue fluorescence is fit to the modeled tissue fluorescence to extract PS concentration[44,73].

Tissue response monitoring by DRS and DCS

Tissue oxygen is crucial for effective PDT[36,82-84]. Tissue oxygen, in turn, is affected by vascular parameters such as blood oxygenation, blood volume and blood flow[50,52]. Most PSs have significant vascular disrupting effects, and can create substantial vascular changes. All these parameters are inter-dependent to each other and can change continuously during PDT[4,36]. Blood flow changes during PDT correlated strongly with tumor growth delay, and blood oxygenation and volume changes were correlated with PDT outcome[50,52,85]. Moreover, PS photobleaching has been shown to be a surrogate marker of PDT response[40,86-90]. Therefore, continuous monitoring of these parameters could be useful for providing real-time treatment feedback, and may serve as quantitative *in vivo* markers for assessing treatment response[4,36,63].

For quantifying vascular parameters such as blood oxygenation and blood volume, an analytic diffuse reflectance model can be utilized to fit the diffusion model to experimental diffuse reflectance data obtained by DRS. We assume tissue absorption is composed of a linear contribution from oxy-hemoglobin and deoxyhemoglobin in blood, and PS absorption. Blood volume is related to total hemoglobin concentration and is defined as the sum of oxy-hemoglobin and dexoy-hemoglobin concentrations, and blood oxygen saturation is defined as the ratio of oxy-hemoglobin concentration to total hemoglobin concentration. Tissue scattering is usually modeled as Mie type behavior that is related to scatterer size and concentration[91]. A multi-wavelength fitting algorithm is usually used to directly extract the hemoglobin concentrations or blood oxygen saturation and blood volume[63,92,93]. Blood oxygen saturation is related to tissue oxygen and hypoxia[52,94] and blood volume is related to microvessel density[95].

Tissue blood flow is measured using a previously described and validated DCS instrument, which measures rapid light intensity temporal fluctuations in tissue and then uses the autocorrelation functions associated with these fluctuations to extract information about the speed of moving tissue scatterers, in this case red blood cells[44,49,96-101]. The decay rate of the autocorrelation function is related to blood flow[99-101]. DCS is advantageous compared to conventional imaging modalities in that it measures directly blood cell movements and does not need any contrast agent administration and pharmacokinetic models to quantify blood flow.

A surrogate molecular marker for PDT efficacy

It is often desired to correlate noninvasive parameters with other techniques such as molecular biomarkers of a treatment response. We have shown previously in preclinical models and clinical biopsy samples that the cross-linking of the signal transducer and activator of transcription 3 (STAT3) correlates with the accumulated PDT dose and can be a quantitative biomarker of cellular killing[102,103]. The crosslinking is identified by immunoblot analysis for STAT3 protein in the extracts from tumor tissue sections calculated as homodimeric complex I relative to total STAT3 signal[102,103]. We compared our measured indices with the STAT3 crosslinking as showcased below.

A clinical case report

In our previous work we demonstrated the assessment of PDT response-related multi-parameters of blood flow, oxygenation, blood volume, PS concentration in the same clinical setting of Photoclor (HPPH)-mediated PDT in head and neck lesions in the oral cavity[44]. We reported an interesting case where two patients had lesions treated with

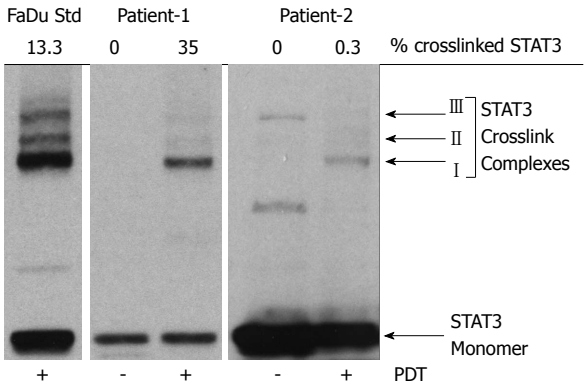

Figure 3 Signal transducer and activator of transcription 3 crosslinking as a molecular marker for local photodynamic therapy dose. Signal transducer and activator of transcription 3 (STAT3) crosslinking for Patient-1 and Patient-2 with a human hypopharyngeal carcinoma cell line (FaDu) shown as a control. Adapted from the reference[74] with the permission. PDT: Photodynamic therapy.

the same administered PS dose (HPPH, 4.0 mg/m^2) and a similar delivered light dose (approximately 125 J/cm^2), but the accumulated local doses were more than 100-fold different as determined by the STAT3 crosslinking (Table 1). The first patient had a large CIS of the hard palate on the roof of the mouth and PDT induced photoreaction with 35% STAT3 crosslinking, and the second patient had high-grade dysplasia in a papilloma of the buccal mucosa with only 0.3% STAT3 crosslinking (Figure 3). We quantified local PDT-related parameters with diffuse optical methods to investigate whether this substantial difference could be detected noninvasively since these parameters can affect accumulated local dose.

As Table 1 summarizes, PDT-induced changes in the quantified optical parameters were significantly different between these lesions. Changes in PS concentration (Δ cHPPH), blood flow index (ΔBFI) and blood volume fraction (ΔBVf) were significantly higher in Patient-1 (P1) than in Patient-2 (P2), but the changes in blood oxygen saturation were similar for both patients, though the trend was different: P1 had an increase and P2 showed a decrease trend.

We further investigated whether this difference could be observed before therapy by quantifying pre-PDT contrasts (mean ± SE) by noninvasive methods. All parameters except blood volume fraction were significantly different between the lesions (Table 2). The lesion of P1 had more favorable properties related to accumulated local PDT dose, since its PS content as well as blood flow, blood volume and blood oxygen saturation were higher than P2.

Our results indicated that parameters quantified with DOS at pre-PDT as well as PDT-induced changes may be indicative of local PDT reaction and may be *in vivo* predictors of PDT outcome. Since each parameter showed different contrast and therapy-induced changes, one parameter alone may not be a strong indicator of PDT response and multi-parameters assessed by optical methods may provide accurate measure of PDT response[44].

Table 1 Photodynamic therapy-induced changes in photodynamic therapy-related parameters for two patients

	Lesion type	STAT3	ΔBFI	ΔBVf	ΔStO2	ΔcHPPH
P1	CIS	35%	83.4%	23%	+15.2%	51.8%
P2	Dysplasia	0.3%	59.2%	7.5%	-17%	38.6%

Changes in BFI was significant for both patients while changes in cHPPH were only significant for patient-1. Adapted from the reference[74] with the permission. Δ represents changes in parameters. STAT3: Signal transducer and activator of transcription 3; cHPPH: photosensitizer concentration; BFI: Blood flow index; BVf: Blood volume fraction; StO2: Saturation; P1: Patient-1; P2: Patient-2; CIS: Carcinoma *in situ*.

Table 2 Pretreatment contrasts in photodynamic therapy-related parameters between two patients (mean ± SE)

	Lesion type	BFI (a.u.)	BVf (%)	StO2 (%)	cHPPH (μmol/L)
P1	CIS	6.7 ± 2.8	2.5 ± 0.7	74 ± 2	0.34 ± 0.02
P2	Dysplasia	1.8 ± 0.5	1.3 ± 0.2	64 ± 3	0.10 ± 0.03

All parameters except blood volume fraction showed a significant difference between two patients. Adapted from the reference[74] with the permission. cHPPH: photosensitizer concentration; BFI: Blood flow index; BVf: Blood volume fraction; StO2: Saturation; P1: Patient-1; P2: Patient-2; CIS: Carcinoma *in situ*.

CONCLUSION

In summary, PDT is regarded as an emerging treatment option for the head and neck malignancies. PDT can be applied repetitively if the previous treatment fails. With the advent of newly developed PSs, specificity and penetration depth can be improved. The simplicity of the PDT treatment and reduced cost of technology such as light sources and light delivery devices can help wide usage at the clinical settings. Moreover, there is a need for standardization of clinical protocols by using the same light and drug types and doses. Novel optical methods can provide PDT-dose related parameters such as optical parameters and PS concentration in the whole lesion, as well as can quantify blood flow, oxygenation and PS photobleaching for assessing the PDT response and providing feedback to clinicians for optimization and standardization of PDT in clinics.

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CASE REPORT

Hepatitis C treatment with triple therapy in a patient with hemophilia A

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Abstract

We report a case of successful treatment of chronic hepatitis C infection with telaprevir-based triple therapy in a patient with hemophilia A complicated by factor Ⅷ inhibitor. A twenty-two years old male with hereditary hemophilia A and high-titer factor Ⅷ inhibitor was taking maintenance doses of recombinant factor Ⅷ. He visited our clinic for treatment of his chronic hepatitis C with the newly instituted protease inhibitor based therapy. He was diagnosed with hepatitis C genotype 1a at one year of age. He was initiated on telaprevir, ribavirin and peg-interferon for treatment of hepatitis C and qualified for response-guided therapy. He completed treatment at 24 wk with minimal adverse effects. Notably, after 4 wk of hepatitis C treatment, his factor Ⅷ inhibitor screen was negative and the dose for recombinant factor Ⅷ decreased by half of the initial dosing before he was treated for hepatitis C. We suspect that suppressing hepatitis C may help decrease factor Ⅷ inhibitor level and the need for recombinant factor Ⅷ.

Key words: Hepatitis C virus; Hemophilia; Factor Ⅷ; Telaprevir; Factor Ⅷ inhibitor; Protease inhibitor

Core tip: This is a case of a patient who has Hemophilia A with factor Ⅷ inhibitor and chronic hepatitis C. After successfully treating the patient's hepatitis C with protease-inhibitor based triple therapy and achieving response-guided therapy with negative hepatitis C virus RNA after week 4, the patient's need for recombinant factor Ⅷ decreased significantly.

Singh G, Sass R, Alamiry R, Zein N, Alkhouri N. Hepatitis C treatment with triple therapy in a patient with hemophilia A. *World J Clin Cases* 2013; 1(3): 106-107 Available from: URL: http://www.wjgnet.com/2307-8960/full/v1/i3/106.htm DOI: http://dx.doi.org/10.12998/wjcc.v1.i3.106

INTRODUCTION

Chronic hepatitis C virus (HCV) infection has been a heavy burden to patients with hemophilia[1]. Patients with hemophilia A frequently receive transfusion of factor Ⅷ as part of their management which can lead to development of antibodies that can neutralize factor Ⅷ[2]. HCV infection by itself and its treatment with interferon can lead to the development of auto-antibodies including acquired factor Ⅷ inhibitor[3,4]. Therefore, treating HCV in hemophiliacs with factor Ⅷ inhibitor remains challenging.

CASE REPORT

A 22-year-old male with a history significant for hereditary hemophilia A complicated by refractory high-titer factor Ⅷ inhibitors and hepatitis C genotype 1a infection diagnosed at the age of 1 year was referred to our clinic regarding hepatitis C treatment. The patient has been treated with recombinant human factor Ⅷ 6000 IU Bid to maintain his factor level at around 20%. He was also receiving rituximab (to help decrease his factor Ⅷ auto-

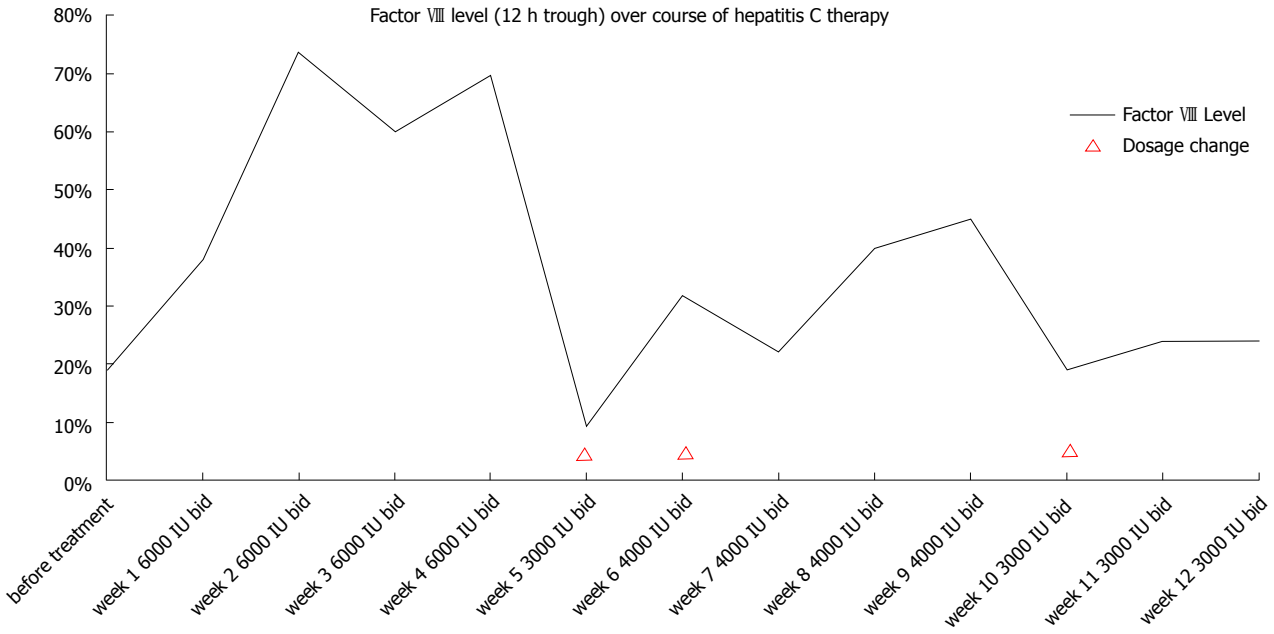

Figure 1 A graph demonstrating factor Ⅷ levels and dosage while on telaprevir-based triple therapy.

antibodies) every 4-6 mo for 3 years. Liver biopsy was not performed prior to starting HCV treatment due to concerns about bleeding and the patient was HCV treatment naive. Patient was started on hepatitis C telaprevir-based triple therapy (telaprevir 750 mg *tid*, weight based ribavirin, and peg-interferon alpha-2a) with good virologic response (HCV RNA was undetectable at treatment weeks 4, 12 and 24). He qualified for response-guided therapy and completed his treatment at 24 wk. He tolerated therapy relatively well without the need to dose reduce his ribavirin or peg-interferon alpha-2a. Interestingly, within a few days after starting telaprevir therapy his factor Ⅷ level started to increase significantly and after four wk of hepatitis C treatment, his factor Ⅷ inhibitor screen was negative and his need for recombinant factor Ⅷ decreased by 50% as shown in Figure 1. His HCV RNA remained negative at 24 wk after he completed telaprevir-based therapy and the patient achieved a sustained virologic response.

DISCUSSION

To our knowledge, this is the first case report on using telaprevir-based triple therapy in a hemophilia patient with factor Ⅷ inhibitor. Acquiring factor Ⅷ inhibitor after HCV infection has been described in previous literature[5]. In our patient, we speculate that the HCV infection itself was inducing production of a factor Ⅷ inhibitor. Consequently, the production of factor Ⅷ inhibitor was suppressed once the virus was cleared with appropriate therapy. This case demonstrates that HCV therapy was safe and that suppressing HCV may help decrease factor Ⅷ inhibitor level and the need for recombinant factor Ⅷ. We hope that our report will encourage other practicing clinicians to treat this challenging patient population.

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CASE REPORT

Paradoxical embolus straddling patent foramen ovale demonstrated by computed tomographic pulmonary angiography

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Abstract

An elderly gentleman presented to the emergency department with a recent history of dyspnoea, collapse and transient neurological symptoms. He was noted to be hypoxic with a significantly elevated D Dimer. A computer tomography pulmonary angiogram demonstrated a large embolus with a further filling defects within the left and the right atria, abutting the interatrial septum. Suspicion of a paradoxical pulmonary embolus was raised and the patient subsequently underwent echocardiography which confirmed a patent foramen ovale (PFO). He was commenced on warfarin therapy. In patients with elevated right heart pressure, a PFO can be unmasked and give rise to cerebral emboli. Clinical suspicion should be raised in patients with pulmonary emboli or deep venous thrombosis if there is a concomitant history of focal neurological symptoms.

Key words: Pulmonary embolus; Paradoxical embolus; Computer tomography pulmonary angiogram; Patent foramen ovale; Stroke

Core tip: Patent foramen ovale (PFO) are common but usually closed and asymptomatic due to the greater pressure in the left heart. They however pose a particular risk for patients with large pulmonary emboli (PE) where they can open providing a right to left shunt when the right heart pressure rises due to pulmonary arterial obstruction by PE. In these circumstances thrombus can transit the PFO paradoxically embolising systemically. We report a case of a patient with a large PE who had a cerebral embolus where thombus is imaged straddling the PFO at computer tomography pulmonary angiography.

Cormack L, Murchison JT. Paradoxical embolus straddling patent foramen ovale demonstrated by computed tomographic pulmonary angiography. *World J Clin Cases* 2013; 1(3): 108-110 Available from: URL: http://www.wjgnet.com/2307-8960/full/v1/i3/108.htm DOI: http://dx.doi.org/10.12998/wjcc.v1.i3.108

INTRODUCTION

Patent foramen ovale (PFO) is estimated to be present in approximately 27% of the population[1]. Under normal physiological conditions where left-sided heart pressure exceeds right-sided pressure, the foramen remains closed. However, in circumstances where right-sided pressure is elevated, for example in pregnancy, cor pulmonale or in the presence of pulmonary thromboembolic disease, the foramen can be opened which may result in paradoxical emboli entering the left-heart and systemic circulation. The presence of thrombo-embolic disease and a PFO thus increases the risk of stroke.

This case highlights the value of computer tomography (CT) pulmonary angiogram, for example when

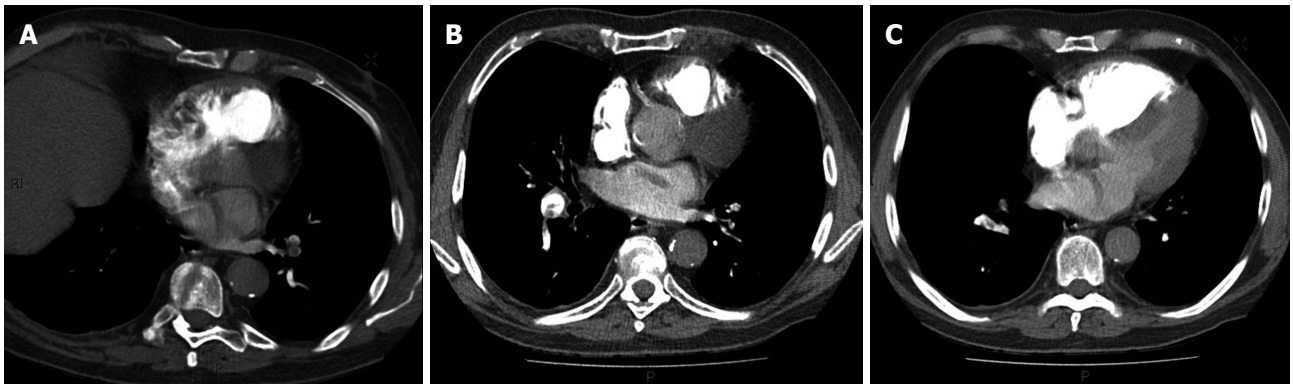

Figure 1 Findings at computed tomographic pulmonary angiography. A: Computer tomography pulmonary angiogram (CDPA) demonstrating a serpiginous low attenuation filling defect in the left atrium which extends across into the right atrium through a patent foramen ovale representing a paradoxical embolus (oblique axial view). There are also filling defects in the left lower lobe pulmonary artery due to pulmonary emboli; B: Demonstrating a filling defect in the left atrium filling defects in the right lower lobe pulmonary artery due to pulmonary emboli (axial view); C: CDPA demonstrating a filling defect in the left atrium, abutting the intra-atrial septum and bowing of the intra-ventricular septum due to raised right heart pressure (axial view).

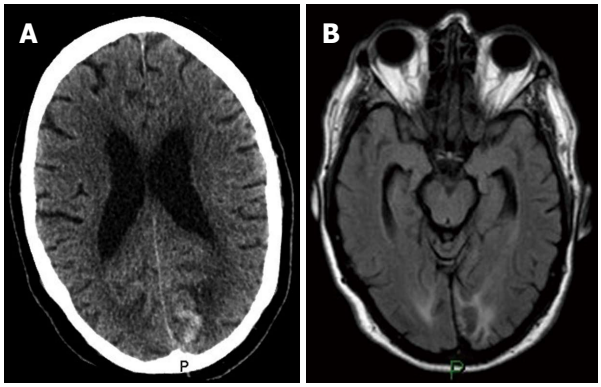

Figure 2 Neurological imaging. A: Unenhanced computer tomography brain examination (axial view) demonstrating left occipital high attenuation with surrounding low attenuation; B: Magnetic resonance imaging brain examination (axial view, FLAIR sequence) demonstrating left occipital lobe infarct with haemorrhagic transformation.

compared to perfusion scanning, in assessing right heart strain as a result of pulmonary embolus, in addition to the possibility of detecting paradoxical embolus when present.

CASE REPORT

Case presentation

An 80-year-old gentleman with history of type 2 diabetes, chronic renal impairment and hypertension presented to the emergency department with marked dyspnoea, dizziness and collapse but without loss of consciousness. There were no features to suggest underlying infection. He also described transient left-sided paraesthesia and weakness, which had largely resolved by the time he was assessed. He was noted to be hypoxic and tachycardic with a markedly raised D Dimer (34704 μg/L). CT pulmonary angiography was requested which confirmed the presence of large pulmonary emboli, but also a further filling defects within the left and right atria (see investigations below). Bubble contrast echocardiography confirmed the presence of a PFO.

Investigations

CT pulmonary angiogram: Large bilateral pulmonary artery emboli with a further serpiginous filling defect visible within the left atrium, abutting the inter-atrial septum and extending into the left atrium. Appearances represent a paradoxical embolus caught in a PFO (Figure 1).

Unenhanced CT brain examination (performed the day after computed tomographic pulmonary angiography): High attenuation within the medial aspect of the left occipital lobe, in keeping with acute haemorrhage due to haemorrhagic transformation of an infarct/embolic infarct (Figure 2A).

Magnetic resonance imaging brain examination, without contrast: Performed 19 d after CT brain examination to rule out multiple emboli to the brain in order to help decide whether to surgically close the PFO. This showed bilateral occipital increased FLAIR signal with restricted diffusion in keeping with infarction. High T1 signal in the left occipital lobe consistent with a degree of haemorrhagic transformation (Figure 2B).

Echocardiography: With bubble contrast, confirmed the presence of a PFO.

Treatment

The patient was commenced on warfarin therapy to treat pulmonary embolus. He was not considered for surgical closure of the PFO.

Outcome and follow-up

The patient made a good recovery initially. A follow-up CT brain performed because of a fall and head injury sustained at home eighteen months following initial presentation did not show any further ischaemic events.

DISCUSSION

Previous case reports of paradoxical pulmonary emboli have been able to demonstrate thrombus within a patent septal defect on echocardiography[2,3], however this finding has not been previously reported on CT pulmonary angiography. Further cases have shown a PFO only (without thrombus)[4], or have failed to demonstrate the source of the right-to-left shunt[5].

CT pulmonary angiography is the gold standard for detecting acute pulmonary embolus[6]. It has a high sensitivity (83%-100%) and specificity (89%-97%)[7,8]. An additional advantage of computed tomographic pulmonary angiography is the assessment of right ventricular/left ventricular (RV/LV) ratio as an indicator of severity in acute pulmonary embolism. Transverse RV/LV diameter ratio has been shown to be significantly higher in patients who die in hospital than amongst those who survive acute pulmonary embolus[9].

Visualisation of thrombus within the atria or ventricles is an unusual finding which should prompt further investigation of a septal defect and right-to-left shunt. Whilst the clinical history alone in this particular case may have been sufficient to provoke investigation of a PFO, the finding of thrombus within the left atrium made the presence of a PFO almost certain and may therefore have expedited echocardiography and neuro-imaging.

According to National Institute for Clinical Excellence guidelines, the optimal treatment of patients with a PFO who have had a thromboembolic event remains undefined[10]. Medical management with antiplatelet or anticoagulation therapy is frequently used to reduce the risk of further paradoxical thrombi. Closure of the PFO may be performed in patients who have further embolic events despite medical management, or in cases where anticoagulant therapy in contraindicated. Percutaneous procedures allow closure of the PFO without the need for major surgery. In this case the presence of acute haemorrhage, presumed to be haemorrhagic transformation of an embolic infarct, further complicated management, however the decision was made that it was in the patient's best interest to proceed with anticoagulation.

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CASE REPORT

Syringomyelia associated with cervical spondylosis: A rare condition

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Abstract

Spinal spondylosis is an extremely common condition that has only rarely been described as a cause of syringomyelia. We describe a case of syringomyelia associated with cervical spondylosis admitted at our division and treated by our institute. It is the case of a 66-year-old woman. At our observation she was affected by moderate-severe spastic tetraparesis. T2-weighted magnetic resonance imaging (MRI) showed an hyperintense signal within spinal cord from C3 to T1 with a more sharply defined process in the inferior cervical spinal cord. At the same level bulging discs, facets and ligamenta flava hypertrophy determined a compression towards subarachnoid space and spinal cord. Spinal cord compression was more evident in hyperextension rather than flexion. A 4-level laminectomy and subsequent posterior stabilization with intra-articular screws was executed. At 3-mo follow up there was a regression of tetraparesis but motor deficits of the lower limbs residuated. At the same follow up postoperative MRI was executed. It suggested enlargement of the syrinx. Perhaps hyperintensity within spinal cord appeared "bounded" from C3 to C7 with clearer margins. At the level of surgical decompression, subarachnoid space and spinal cord enlargement were also evident. A review of the literature was executed using PubMed database. The objective of the research was to find an etiopathological theory able to relate syringomyelia with cervical spondylosis. Only 6 articles have been found. At the origin of syringomyelia the mechanisms of compression and instability are proposed. Perhaps other studies assert the importance of subarachnoid space regard cerebrospinal fluid (CSF) dynamic. We postulate that cervical spine instability may be the cause of multiple microtrauma towards spinal cord and consequently may damage spinal cord parenchyma generating myelomalacia and consequently syrinx. Otherwise the hemorrhage within spinal cord central canal can cause an obstruction of CSF outflow, finally generating the syrinx. On the other hand in cervical spondylosis the stenotic elements can affect subarachnoid space. These elements rubbing towards spinal cord during movements of the neck can generate arachnoiditis, subarachnoid hemorrhages and arachnoid adhesions. Analyzing the literature these "complications" of cervical spondylosis are described at the origin of syringomyelia. So surgical decompression, enlarging medullary canal prevents rubbings and contacts between the bone-ligament structures of the spine towards spinal cord and subarachnoid space therefore syringomyelia. Perhaps stabilization is also necessary to prevent instability of the cervical spine at the base of central cord syndrome or syringomyelia. Finally although patients affected by central cord syndrome are usually managed conservatively we advocate, also for them, surgical treatment in cases affected by advanced state of the symptoms and MRI.

Key words: Syringomyelia; Cervical spondylosis; Syringomyelia surgery; Syringomyelia etiology; Syringomy-

elia physiopathology

Core tip: Our study assume that central cord syndrome can result in syringomyelia. We postulate that cervical spine instability may be the cause of myelomalacia and consequently syrinx. In cervical spondylosis with related central cord syndrome or syringomyelia we underline the importance of surgical decompression and stabilization. Surgical decompression prevents "complications of cervical spondylosis" at the base of syringomyelia. Stabilization is also necessary to prevent instability of the cervical spine at the base of central cord syndrome or syringomyelia. Finally we propose the surgical treatment also for patients affected by central cord syndrome showing advanced state of the symptoms and magnetic resonance imaging.

Landi A, Nigro L, Marotta N, Mancarella C, Donnarumma P, Delfini R. Syringomyelia associated with cervical spondylosis: A rare condition. *World J Clin Cases* 2013; 1(3): 111-115 Available from: URL: http://www.wjgnet.com/2307-8960/full/v1/i3/111.htm DOI: http://dx.doi.org/10.12998/wjcc.v1.i3.111

INTRODUCTION

Syringomyelia (Gr. Syrinx = tunnel) is a disease characterized by the presence of a cystic tubular cavity within the spinal cord, containing fluid that might be either cerebrospinal fluid (CSF) or indistinguishable from it. It is a very complex disorder with multiple etiologies and a variety of proposed mechanisms of cyst formation. No single theory will cover all instances[1]. It may develop by various factors. It is most commonly associated with complex hindbrain malformations, such as Chiari malformations, encephalocele and Dandy-Walker cysts. Other causes include postmeningitic and posthemorrhagic hydrocephalus, basilar invagination, spinal arachnoiditis, extramedullary compressions, tethered cord, acquired tonsillar herniation, intramedullary spinal tumours. Acute traumatic cervical spinal stenosis due to fracture or acute severe disc prolapse may result in secondary syrinx formation. Spinal spondylosis is an extremely common condition that has only rarely been described as a cause of syringomyelia[2-5]. We analyzed the pertinent literature trying to show a possible etiopathogenetic mechanism.

CASE REPORT

We describe a case of syringomyelia associated with cervical spondylosis admitted at our division and treated by our institute. Moreover a review of the literature was executed using PubMed database. Objective of the research was to find an etiopathological theory able to relate syringomyelia with cervical spondylosis. We included only case reports about syringomyelia associated with cervical spondylosis. The simultaneous presence of another etiopathological factor at the origin of syringomyelia was considered an exclusion criterion.

Table 1 Review of the literature

Author	Age (yr) and sex	Spondylosis level	Proposed mechanism
Kaar *et al*[2]	71, F	C3-C4	Instability of the spine
Kimura *et al*[3]	64, F	C4-C5, C6-C7	Intermittent spinal cord compression
Rebai *et al*[5]	70, M	Not specified	A purely extradural decompression could be sufficient to induce regression of the medullary cavitation.
Lucci *et al*[6]	56, M	C4	The bony prominence produces ischemia and thus causes the degeneration of ascending and descending nervous fibers
Butteriss *et al*[7]	70, M	C5-C6	Improvement of related symptoms after decompressive surgery
Kameyama *et al*[8]	59, M	C3-C4 at C6-C7	The symptoms of the upper limbs improved after immobilization of the neck

The table exposes case reports about syringomyelia associated with cervical spondylosis reported in literature. Author, age and sex of the patient, spondylosis level and the proposed mechanism at the base of syringomyelia are mentioned. F: Female; M: Male.

Only 6 articles have been found (Table 1). Lucci *et al*[6] reported 3 cases in their work. In all of them a relation between neurogenic osteoarthropathies of the upper limbs and intramedullary cavity at spinal computed tomography scan is described but only the third one denotes a relation between "essential" syringomyelia and cervical spondylosis. Lucci admits at the origin of syringomyelia the bony prominence that probably produces ischemia and thus causes the degeneration of the ascending and descending nervous fibers. Kimura *et al*[3] present the case of a 64-year-old woman. Dynamic magnetic resonance imaging (MRI) revealed instability at C4-C5, spondylosis at C5-C6 and the syrinx extended from C2 to T3 level. It was reduced remarkably after anterior decompression and stabilization. Towards Kimura syringomyelia was caused by intermittent spinal cord compression. Butteriss *et al*[7] report a case of a 70-year-old man with severe degenerative changes at C5/C6 with a large right paracentral disc-osteophyte complex. An unexpected cord syrinx was noted extending from C6/C7 inferiorly to T6. The patient declined decompressive surgery. Butteriss advocates surgery directed towards relieving the compressive lesion, rather than primary drainage of the syrinx. Kaar *et al*[2] describe a case of cervical spondylotic myelopathy with instability at C3/C4 and cervicothoracic syrinx at MR imaging. In Kaar's article the decompression and stabilization, without drainage of the syrinx were considered adequate surgical treatment. Rebai *et al*[5] describe a case of a 70-year-old patient whose brain and cervical MRI showed syringomyelobulbia with cervical spondylotic myelopathy. Rebai *et al*[5] proposes a decompressive surgery since extensive cervical laminectomy induced mild clinical improvement and furthermore a second MRI performed

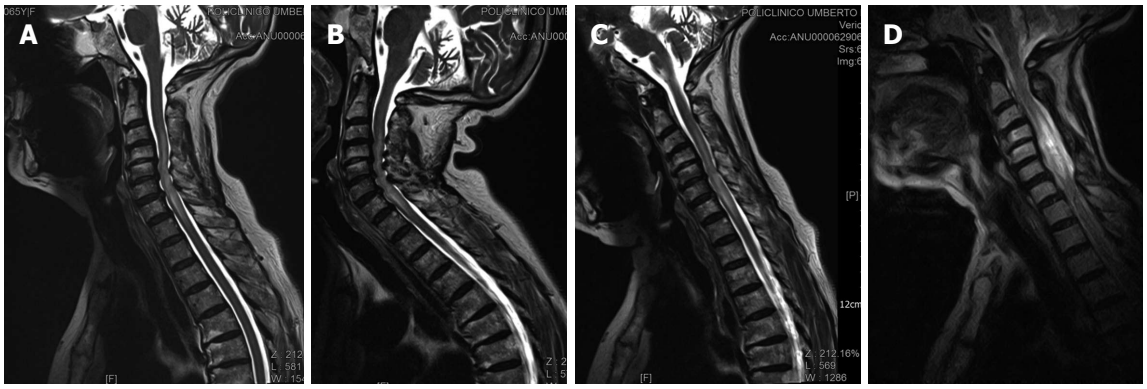

Figure 1 Preoperative magnetic resonance imaging. A: T2-weighted magnetic resonance imaging revealed hyperintensity of the central spinal cord extended from C3 to T1 without clear borders. In the inferior cervical spinal cord hyperintensity appeared more evident suggesting syrinx; B and C: At the same level cervical spinal cord compression was determined by bulging discs, facets and ligamenta flava hypertrophy, more evident in hyperextension (B) rather than flexion (C); D: It revealed enlargement of the syrinx, but decreased longitudinal extension of "central cord syndrome" bounded from C3-C4 to C7 with clearer borders. At the level of surgical decompression also spinal cord and subarachnoid space appeared expanded.

6 mo after surgery depicted a complete disappearance of the bulbo-medullar cavitation with secondary atrophy. Kameyama *et al*[8] presents the case of a 59-year-old man with spondylosis at multiple levels from C3/C4 to C6/C7, and an intramedullary high signal intensity area from the level of C1 to C3/C4.

We report the case of a 66-year-old woman, whose presenting symptoms were gait disturbances and loss of balance. These disorders appeared about 9 mo before our observation. At our observation she was affected by moderate-severe spastic tetraparesis. Cervical dynamic-MRI was executed. T2-weighted MRI showed an hyperintense signal within spinal cord from C3 to T1. This process in the central cord resembled "central cord syndrome" with a more sharply defined process in the inferior cervical spinal cord that suggested syrinx (Figure 1). In hyperextension (Figure 1B) bulging discs were evident at the levels C3-C4, C4-C5, C5-C6, C6-C7 and C7-D1. At the same level facets and ligamenta flava hypertrophy determined a compression towards subarachnoid space and spinal cord. Spinal cord compression is more evident in hyperextension rather than flexion. We decided to undergo the patient at the surgical treatment. A 4-level laminectomy and subsequent posterior stabilization with intra-articular screws was executed. In the early post-operative days the patient underwent neuromotor rehabilitazion and slight improvement of tetraparesis was evident. At 3-mo follow up there was regression of tetraparesis but motor deficits of the lower limbs residuated. At the same follow up postoperative MRI was executed. It (Figure 1D) suggested enlargement of the syrinx. Perhaps "central cord syndrome" appeared "bounded" from C3 to C7. At the level of surgical decompression, subarachnoid space and spinal cord enlargement were also evident.

DISCUSSION

Already in the 1950's some authors found a relationship between these two pathological entities. Stern *et al*[9] recognized that cervical spondylosis can present sensory and motor symptoms quite similar to the syringomyelic ones. Brain *et al*[10] found radiographic lesions of the cervical spine in about 50% of the syringomyelic cases identical to those noted in spondylosis. The possible coexistence of the two diseases was claimed by Smith[11] too. The results of the literature review revealed that compressive mechanism is the major theory at the origin of syringomyelia associated with cervical spondylosis. Al-Mefty *et al*[12] proposed that compression causes cystic necrosis (myelomalacia). In a second period as the myelomalacia progresses, the necrotic tissue is phagocytized leaving a secondary cavity (syrinx) within the atrophied spinal cord. Also Uchida *et al*[13] conducting a study on a twy/twy mouse, a unique animal that develops spontaneous spinal cord compression without any other reported genetic difference in the anatomy or physiology of the spinal cord, showed that spinal cord mechanical compression is characterized by the loss and exfoliation of anterior horn neurons with progressive spongy degeneration and demyelination in the white matter. Perhaps the extent of demyelination and Wallerian degeneration in the white matter increases proportionately with the magnitude of spinal cord compression. On the other hand, most of the apoptotic cells observed were oligodendrocyte. Though insignificant if compared to acute spinal cord injury, the longitudinally diffuse and extensive pattern of oligodendrocyte apoptosis in twy/twy mouse may be similar to the secondary damage process observed after acute trauma. In Levine's study at the origin of syringomyelia is described a subarachnoid obstruction. It may result in increasing CSF pressure above the block, compared with below generating a transmural hydrostatic effect with the collapse of vessels within the subarachnoid space above the block, and their dilatation below it. This mechanical stress on the cord parenchyma causes disruption of the blood-brain barrier, which in concert with raised intravascular pressure results in ultrafiltration of crystalloids and accumulation of fluid[14]. Goel[15] state that the fluid may dissect along planes of weakness within the cord resulting in the pathological appearance of a syrinx. It has been postulated that the development

of high fluid pressure and syrinx formation within the cord may act to counteract the local effect of the primary compressive lesion and as such may be a protective phenomenon. Several authors[16-21] observing syringomyelia in spinal arachnoiditis, stated that intramedullary cystic degeneration is caused by ischemia due to circulatory disturbance in the subarachnoid space. Also the blockage of CSF pathways around the spinal cord, contribute to formation of cystic cavities[22]. It is often believed that in syringomyelia with spinal arachnoiditis the CSF enters transmurally into the syrinx from the blocked subarachnoid space[23].

Brierley[24] first demonstrated movement of CSF tracers from the subarachnoid space into the spinal cord perivascular spaces. Then Rennels *et al*[25], Wagner *et al*[26] and Borison *et al*[27] have shown that horseradish peroxidase injected into the subarachnoid space rapidly labels the perivascular spaces of the brain and spinal cord. Rennels *et al*[25] proposed that a "paravascular" fluid circulation exists in the nervous system, with an active flow of CSF from the subarachnoid space into the perivascular spaces around arterioles and continuing through the basal lamina around capillaries. Without direct evidence, they suggested that fluid return to the basal lamina around venules or into the perivascular space of emerging veins. Milhorat *et al*[4,28,29] and Cifuentes *et al*[30] demonstrated that fluid is capable of moving from the spinal cord interstitial space into the central canal. Milhorat *et al*[4,28] suggested that this mechanism constitutes the "lymphatic" function of the spinal cord. Cho *et al*[31] reported that injection of kaolin solution into the spinal subarachnoid space enhanced the extension of intramedullary cavitations in a rabbit model of posttraumatic syringomyelia. Josephson *et al*[32] demonstrated spinal cord edema and intramedullary cyst formation after spinal thecal sac constriction in rats. Klekamp *et al*[33] produced an interstitial type of edema in the spinal cord by placement of a kaolin-soaked fibrin sponge on the posterior surface of the cat spinal cord at C1 to C2. Kimura *et al*[3] reported about a patient affected by pain in the right arm, MRI showed instability at C4-C5 and compression of the spinal cord since a central spinal cord hyperintensity was evident in hyperextension. All these characteristics can be found in "central cord syndrome". He admitted that the longstanding static and dynamic intermittent compression of the spinal cord caused by C4 instability produce disorders of CSF dynamics in the spinal subarachnoid space and associated pooling of an abnormal amount of CSF in the spinal cord parenchyma. Perhaps the sloshing effect of the pulsatile CSF pressure, could make the cavity extend into a rostral and ventral direction. Also Kaar *et al*[2] described a case of central cord syndrome since the patient was affected by dissociated sensory loss in the left upper limb, instability at C3-C4 on plains radiographs and T2-weighted MRI showing forward-bulging ligamenta flava and hyperintensity of the central spinal cord in T2-weighted MRI. He attributed the origin of the syrinx to cervical spine instability. Our case presents a more sharply defined process in the inferior cervical spinal cord. We postulate that cervical spine instability may be the cause of multiple microtrauma towards spinal cord and consequently may damage spinal cord parenchyma generating myelomalacia and consequently the syrinx. Another possible theory may supports the hemorrhage within spinal cord central canal as the cause of CSF outflow obstruction, finally generating the syrinx. On the other hand we can assert the importance of subarachnoid space regard CSF dynamic. Several studies show that syringomyelia may be caused by tethered cord, arachnoiditis, arachnoid adhesions or subarachnoid hemorrhages. In cervical spondylosis the stenotic elements can affect this space. Rubbing towards spinal cord during movements of the neck can generate these "complications". On the other hand cervical spondylosis can generate a block of CSF hydrodynamic within subarachnoid space determining a vascular occlusion of the vessels above the block and consequently a spinal cord ischemic injury. Perhaps cervical spondylosis can directly damage spinal parenchyma like acute spinal trauma. This damage may be proportionally related to the grade of stenosis. So surgical decompression, enlarging medullary canal prevents rubbings and contacts between the bone-ligament structures of the spine towards spinal cord and subarachnoid space.

In conclusion, we can assert that syringomyelia is so rarely associated with cervical spondylosis because there are many compensating mechanisms (arterial, venous, CSF ones), like that of "lymphatic" circulation, so mild and intermittent compression like that found in cervical spondylosis hardly can be associated with syringomyelia unless there are other associated conditions like arachnoid adhesions, post-traumatic arachnoiditis, subarachnoid hemorrhages, Chiari malformations that determine an alteration towards the subarachnoid space. On the other hand, cervical spine instability can generate central cord syndrome or syringomyelia. Although patients affected by central cord syndrome are usually managed conservatively we advocate, also for them, surgical treatment in cases affected by advanced state of the symptoms and MRI.

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CASE REPORT

Trans-sacral screw fixation in the treatment of high dyplastic developmental spondylolisthesis

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Author contributions: The work was carried out in collaboration between all authors; Landi A, Marotta N and Defini R defined the research theme andperformed surgery; Mancarella C contributed to acquisition of data, interpretation of results and wreote the paper; Tarantino R co-worked on interpretation of data; all authors have contributed to, seen and approved the manuscript.

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Abstract

We describe the case of a 67-year-old woman with L5-S1 ontogenetic spondylolisthesis treated with pedicle fixation associated with interbody arthrodesis performed with S1-L5 trans-sacral screwing according to the technique of Bartolozzi. The procedure was followed by a wide decompressive laminectomy. The patient had a progressive improvement of the symptoms which gradually disappeared in 12 mo. The radiograph at 6 and 12 mo showed complete fusion system. The choice of treatment in L5-S1 ontogenetic spondylolithesis is related to a correct clinical and diagnostic planning (X-ray, computer tomography magnetic resonance imaging, Measurement). In particular, the severity index and the square of unstable zone, and the standard measurements already described in the literature, are important to understand and to plane the correct surgical strategy, that require, in most of the times, fusion and interbody artrodesis.

Key words: High-dysplastic developmental spondylolisthesis; Spondylolisthesis; Trans-sacral screw; Pelvic balance; Spinopelvic imbalance

Core tip: The choice of treatment in L5-S1 ontogenetic spondylolithesis is related to a correct clinical and diagnostic planning (X-ray, computer tomography, magnetic resonance imaging, measurement). In particular, the severity index and the square of unstable zone, and the standard measurements already described in the literature, are important to understand and to plane the correct surgical strategy, that require, in most of the times, fusion and interbody artrodesis.

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INTRODUCTION

Marchetti and Bartolozzi's classification[1,2] is the most complete one regarding the prognosis and treatment of ontogenetic spondylolisthesis, including the description of the high or low dysplastic forms. Unfortunately, however, does not provide specific criteria to differentiate these two subgroups. In particular, it is accepted that the treatment of choice for both high-dysplastic developmental spondylolisthesis (HDDS) is surgical procedure, but it is unclear which is the best surgical strategy. A correct preoperative planning based on meticulous radiological examinations is crucial for the choice of the correct surgical treatment to be undertaken which is, when possible, a stabilization with interbody fusion.

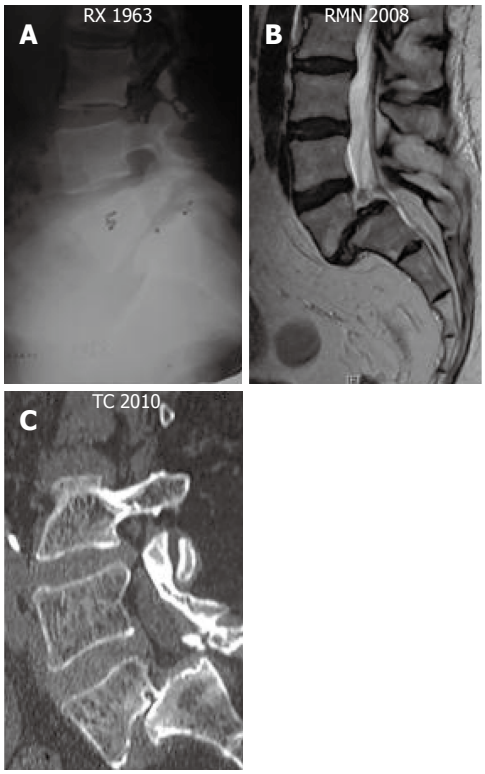

Figure 1 Seriated radiological exams showing the progression of the spondylolisthesis from grade Ⅰ in 1963, to grade Ⅲ in 2010.

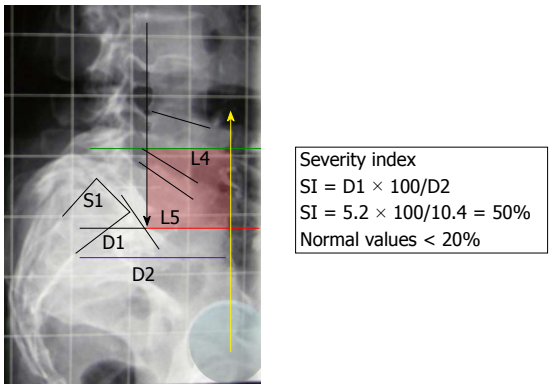

Figure 2 Analysis of the severity index and of the square of unstable zone. It's described by Lamartina[14]. SI: Severity index.

Table 1 Measurements and indexes performed for the operative planning

	Test	Our case	NR
Slipping		63%	
Sacro lumbar indexes	Lumbar index	45%	> 50%
	Pelvic incidence	86.2°	50°-60°
	Sagittal pelvic tilt index	0.52	> 0.70
Pelvic nutation indexes	Sacral slope	39.9°	32°-49°
	Pelvic tilt	40.6°	7.2°-7.9°
	Sacral inclination	45°	
Sacro-lumbar ratio	Slip angle	77.3°	
	Sacral kyphosis angle	25.8°	

CASE REPORT

We describe the case of a 67-year-old woman with L5-S1 ontogenetic spondylolisthesis known since 30 years before. The patients complained recurrence of 15-d lumbar back pain episodes that improved after medical therapy. She referred difficulty in walking and in the upright position because of the presence of low back pain and right sciatica from 2 years. The patient brought seriated radiological examinations. The first one performed 30 years earlier showing a progression of the spondylolisthesis that from Meyerding grade I currently has become Meyerding grade Ⅲ, with development of an important sacral dysmorphia giving a profile of an high dysplastic spondylolisthesis HDDS (Figure 1). Neurologically the patient presents a sacral kyphosis attitude, semi flexion of knees and hips in an upright position to compensate the pelvic imbalance, moderate weakness to the right lower limb at the dorsal flexion of the foot, sensitive disturbances in L5 territory to the right lower limb, neurogenic claudication at 100 m. According to the literature it was performed an orthostatic X-ray to visualizes the femoral heads and to calculate the dysplasia indexes in order to plan a correct surgical strategy. We have calculated: slip percentage (63%), the sacral-lumbar indexes (lumbar index 45%, pelvic incidence 86.2°, sagittal pelvic tilt index 0.52), the pelvic nutation indexes (sacral slope 39.9°, pelvic tilt 40.6°, sacral inclination 45°) and the sacro-lumbar ratio (77.3° slip angle, sacral kyphosis angle 25.8°). In relation to the measurements, the diagnosis of HDDS was confirmed (Table 1). The surgical planning requested the evaluation of the severity index and of the square of unstable zone (Figure 2)[3,4]. All the indexes suggested us the indication for L4-L5-S1 fusion and L5-S1 interbody fusion to be executed with an anterior support. It was decided to proceed with pedicle screw fixation associated with interbody fusion performed with S1-L5 trans-sacral screwing according to the Bartolozzi's technique[1,2]. The procedure was followed by a wide decompressive laminectomy (Figure 3). The patient had a progressive improvement of the symptoms which gradually disappeared in 12 mo. The radiograph at 6 and 12 mo showed a complete bone fusion (Figure 4).

DISCUSSION

The HDDS (Meyerding grade Ⅲ° and Ⅳ°), caused by isthmus lysis, are characterized by a specific aspect, the pelvic retroversion, which generates an L5 dimorphism with trapezoidal shape and a consequent S1 dysplasia and round shape of the sacral promontory. The combination of these deformities causes L5-S1 kyphosis and increases the incidence of the slipping of L5 on S1. Such deformities cause alteration of the posture of the subject; in particular the pelvic retroversion causes a compensatory flexion of the hips and knees, in an attempt to realign the sagittal balance, and the lumbosacral kyphosis causes compensatory hyperlordosis of the adjacent lumbar segment. This process cause a considerable torsional force

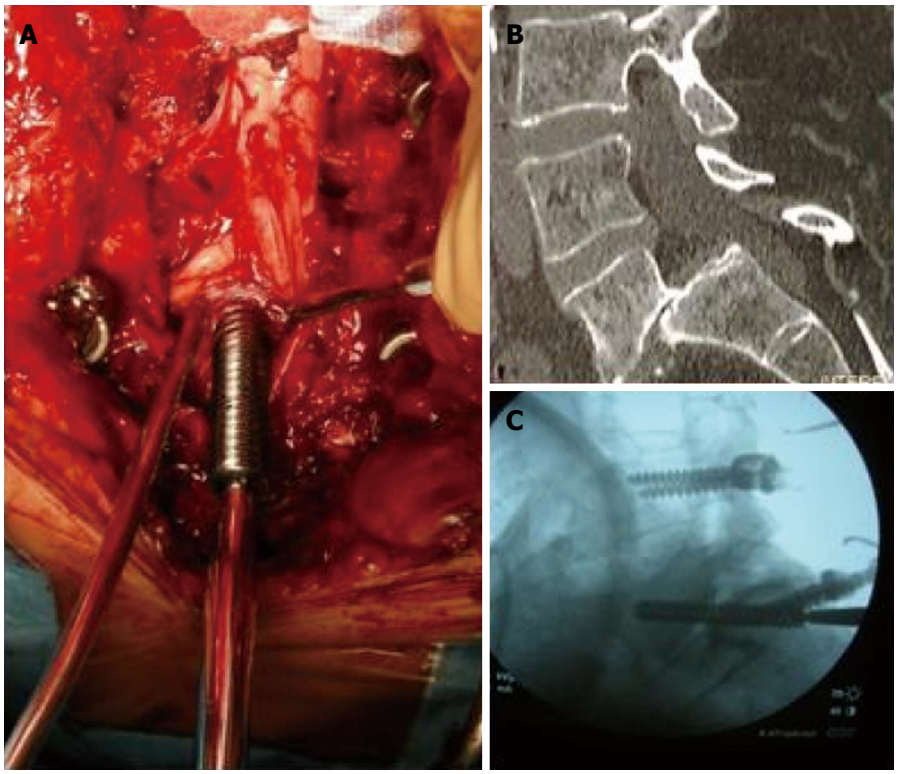

Figure 3 Intraoperative picture that showed the insertion of the trans sacral screw.

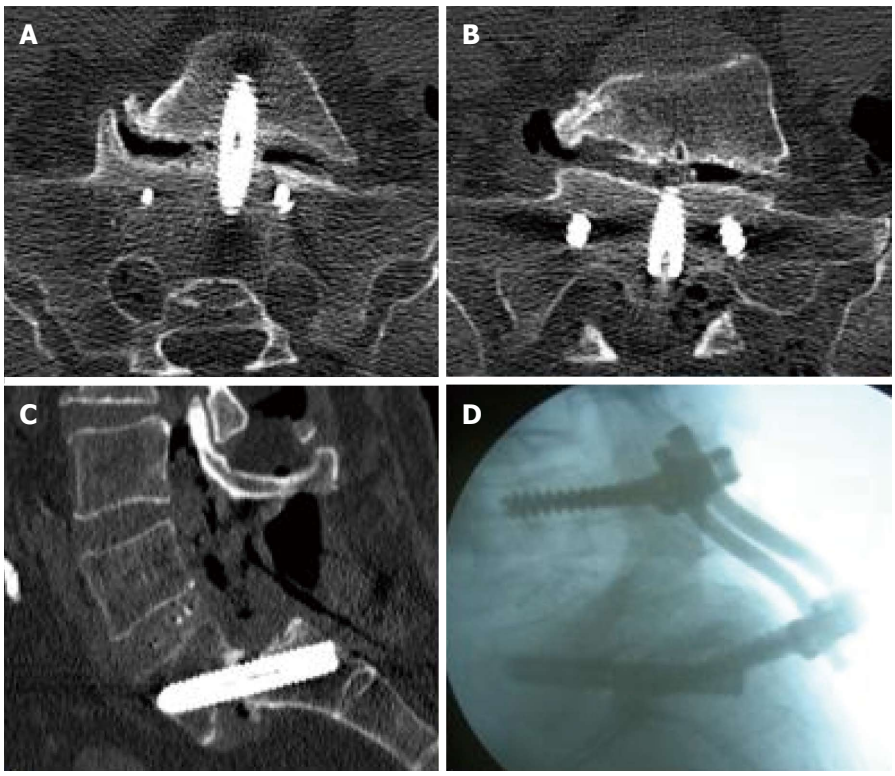

Figure 4 Computer tomography scan at 12 mo follow-up that showed the correct positioning and fusion of the system.

on the pelvis burdened by the L5-S1 disc orientation, which tends to be perpendicularly to the ground, in relation to the sacral inclination. This type of biomechanical alterations affects significantly the sagittal balance, generating shear forces that allows the vertebral body to slide ventrally causing a framework of spondyloptosis[5-11]. In

such cases, treatment of choice is surgical, and should be aimed to correct the sagittal loading, to decompress the interested tract and to fuse the mobile segment. In particular high dysplastic forms need anterior support before fusion in order to ensure a longer stability, since the only posterolateral or posterior interbody fusion (PLIF, TLIF) do not contract enough the foreword slipping of L5 on S1[1,10,12-14]. Pelvic indexes and severity index evaluation allow us to identify which HDDS have such shear forces that do not permit a L5-S1 short fixation, so that has to be involved L4 too. The extension to L4 vertebral body is essential in order to reduce the cutting forces and to avoid the breaking the system[3,4].

Low-grade HDDS (Meyerding I and Ⅱ) are treated *via* posterior approach with interbody fusion (PLIF, TLIF), or when this is not executable, with PLF, providing good results in terms of long term fusion. From a technical point of view, the interbody fusion with anterior approach is the key point for the choice of treatment; the technique of choice for anterior interbody fusion is certainly the ALIF, performed with retroperitoneal anterior approach[11]. The advantages of this approach are: the direct visualization of the L5-S1 disc, the possibility of insertion of the cage very anteriorly favoring arthrodesis, and the possibility of releasing the disc, increasing the mobility of L5 to S1 and favoring the maneuvers of reduction of the lysthesis that will be performed *via* posterior approach. The risks associated with the anterior approach are: peritoneal perforation, visceral lesions (ureters, bladder, intestines, *etc.*), vascular lesions (arteries and iliac veins), lesions of the hypogastric plexus (vaginal dryness in women and retrograde ejaculation in men) and the morbidity linked to the autologous bone graft donor site. In addition, the lack of familiarity to this approach puts the spinal surgeon in the position of having to have a general surgeon or a vascular surgeon to perform anterior approach. In the light of this, we decided to perform anterior arthrodesis with trans-sacral screw fixation described by Bartolozzi *et al*[1,2]. In our opinion, this technique has some advantages over ALIF. First of all, the risks related to the anterior approach and to the bone donor site morbidity are eliminated. The insertion of the screw is possible with the same surgical exposure of the *via* posterior approach, exposing the L5-S1 disc, the S1 back wall and the S1 lower limiting; this is achieved with a simple laminectomy. The exposure of the screw entry point is obtained by a slight pull of the dural sac medially, without any risk of neurological damage. Furthermore, as described in the literature, the possibility to insert two screws, one on the right site and one on the left site, reduces the manipulation on the dural sac. The inclination of the screw has to be almost perpendicular to the operating table, so there are no particular needs of inclination of the instrumentation. The screw are auto tapping and can be filled within autologous bone, allowing a good interbody fusion that offers excellent fusion. From a biomechanical point of view, the angle assumed by the screw respect the stabilization system, pointing from the bottom upwards, provides adequate support to L5 that in this way counteracts the forces of sliding downward arresting the progression of the slipping out of the HDDS.The choice of treatment in L5-S1 ontogenetic spondylolithesis is related to a correct clinical and diagnostic planning (X-ray, computer tomography, magnetic resonance imaging, measurement). In particular, the severity index and the square of unstable zone, and the standard measurements already described in the literature, are important to understand and to plane the correct surgical strategy that require, in most of the times, stabilization and interbody fusion. The choice of the technique depends on the surgeon and on the grade of fusion he wants to obtain: PLIF < TLIF < ALIF[11,12,14]. HDDS require anterior support (ALIF or trans-sacral fusion) since posterior fusion in long term stabilization have an high risk of failure. The choice to extend the fusion at L4-L5 cannot be left to chance, but has be carefully planned on the basis of the preoperative exams (square of unstable zone), since in cases where it is necessary, its contribution to the stability of the system is essential.

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CASE REPORT

Lymph node non-Hodgkin's lymphoma incidentally discovered during a nephrectomy for renal cell carcinoma

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Abstract

We report the case of a left laparoscopic nephroureterectomy with the incidental discovery of a non-Hodgkin's lymphoma in one of the lymph nodes of the renal hilum. A laparoscopic nephroureterectomy was decided on for a 64-year-old man. Renal cell carcinoma in the kidney and one lymph node of the renal hilum with non-Hodgkin's lymphoma was found. Chemotherapy was not started for the lymphoma discovery. There are no signs of relapse after two years of follow up. Coexistence in the same patient is an extremely rare condition. We review the literature about this issue to clarify this association.

Key words: Renal cell carcinoma; Lymphoma; Nephrectomy

Core tip: This is a case of a nephroureterectomy for a renal mass incidentally discovered by imaging techniques. One of the lymph nodes of the renal hilum was diagnosed as non-Hodgkin's lymphoma B type, the patient being asymptomatic at that moment. Chemotherapy was not started and extension studies were requested.

Fernandez-Pello S, Rodriguez Villamil L, Gonzalez Rodriguez I, Venta V, Cuervo J, Menéndez CL. Lymph node non-Hodgkin's lymphoma incidentally discovered during a nephrectomy for renal cell carcinoma. *World J Clin Cases* 2013; 1(3): 121-123 Available from: URL: http://www.wjgnet.com/2307-8960/full/v1/i3/121.htm DOI: http://dx.doi.org/10.12998/wjcc.v1.i3.121

INTRODUCTION

The association between kidney cancer and lymph node lymphoma is infrequent. The biggest series reported with the two coexisting tumors included no more than twenty patients[1,2]. Nevertheless, many authors have studied this relationship and suggest that it might be a statistical statement rather than sporadic.

We report a case of a nephroureterectomy for a renal mass incidentally discovered by imaging techniques. One of the lymph nodes of the renal hilum was diagnosed as non-Hodgkin's lymphoma B type. With the patient being asymptomatic, chemotherapy was not started and extension studies were requested.

We review the medical literature about the relationship between kidney cancer and non-Hodgkin's lymphoma.

CASE REPORT

We report a 64-year-old man with the incidental ultrasound discovery of a left kidney mass in the context of image studies for elevated blood pressure.

Medical history included ankylosing spondylitis with no other pathologies. Blood analysis showed low platelets with the rest of parameters within normal limits. One of the three urine cytologies showed urothelial atypia.

Abdominal computed tomography (CT) was requested and revealed a solid mass at the lower pole of the left kidney, in touch with the lower calyceal group, and with contrast enhancement, a permeable renal vein and one

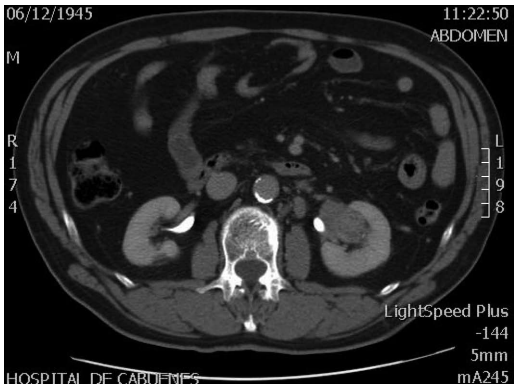

Figure 1 Abdominal contrast enhanced tomography with left kidney mass.

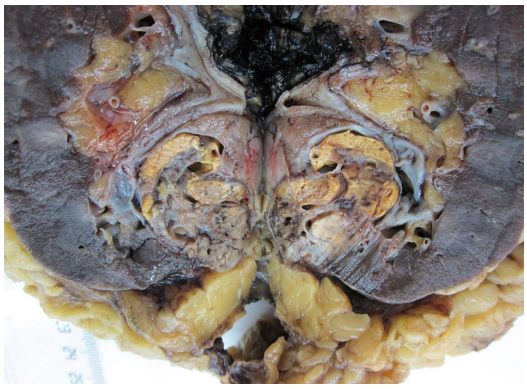

Figure 2 Yellow kidney tumor in touch with rose node, located at hilum, 4 cm in diameter.

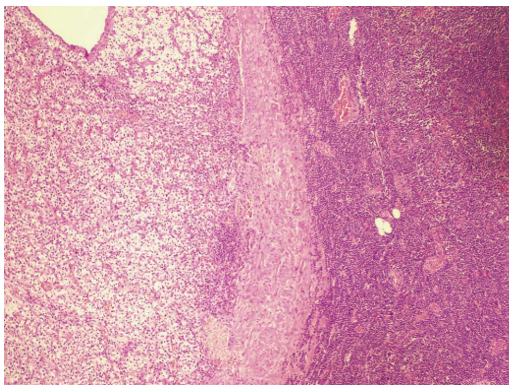

Figure 3 A microscopic view of the tumors. In the left, renal conventional clear cell carcinoma. In the right, a lymph node with small B cell lymphoma.

hilum adenopathy (Figure 1).

Exploration of the ureter with an ureterorenoscopy was performed to exclude ureteral lesions.

After discussion about the case with the contrast enhanced computed tomographic images, we performed a left laparoscopic nephrectomy and ureterectomy. We argued that the laparoscopic nephroureterectomy would not add more morbidity post surgery and it would give us information about the complete upper left urinary system (Figure 2).

The pathology report described a renal clear cell carcinoma, 3.8 cm in diameter and Ⅱ Fuhrman cell grade. Additionally, lymphoid spreading was reported at one of the lymph nodes of the left renal hilum with pathology stage pT1N0. These findings and the immunochemistry studies (which were positive for CD20, bcl-2 and bcl-6 and negative for CD10) were in concordance with follicular non-Hodgkin's lymphoma B type and cell grade 2, with extension out of the node capsule and peripheral fat (Figure 3).

The post operative course was uneventful and the patient was discharged on the fifth day.

The patient was followed up by urology and hematology. Extension studies were requested and a neck-thorax-abdominal CT showed no special radiological findings. Bone marrow biopsy was negative for lymph proliferative disease. Chemotherapy was not started and after two years of follow up, the patient is asymptomatic with no imaging signs of relapse in the control studies that were requested.

DISCUSSION

The American Cancer Society has reported that one of five Americans will develop cancer in their lifetime. For those patients who develop a tumor, the chance of developing a second tumor during their lifetime is one in three[1].

Renal cell carcinoma (RCC) and non-Hodgkin's lymphoma are relatively common neoplasms that have dramatically different natural histories and management strategies. These neoplasms are considered curable in the early stages but the ability to treat the advanced disease is much more limited in renal cell carcinoma[3].

Second malignancies reported to be associated with renal cell carcinoma include bladder[4], prostate, rectum[5], lung[6], non-Hodgkin's lymphoma and melanoma. In general, 27.4% of the cases were related previously, 44.5% were synchronous and 39.2% were subsequent. Rabbani *et al*[7] reported the specific association between non-Hodgkin's lymphoma and RCC from the whole sample of patients with RCC (763 patients) with a second primary malignancy (209 patients). They described 19 cases of non-Hodgkin's lymphoma, 8 as an antecedent, 8 synchronous and 3 metachronous[7].

Many authors have reported the association between non-Hodgkin's lymphoma and kidney cancer but there are contradictory results[8]. However, in one of the biggest series with patients affected by the two kinds of tumors (1425 patients), the standardized incidence of ratios (SIR) were used to estimate the risk of later primary cancer in patients diagnosed with renal cancer, calculated as the ratio of observed numbers (ONo) and expected numbers (ENo) of cases. The SIR for a second primary cancer in patients with RCC was significantly higher for bladder cancer, melanoma and non-Hodgkin's lymphoma. Addi-

tionally, non-Hodgkin's lymphoma was reported to occur with a much stronger rate after renal transplantation[9].

In 1996, Tihan *et al*[2] studied the coexistence of RCC and lymphoma, with 1252 renal cancer patients and 1660 non-Hodgkin's lymphoma patients reported. Two neoplasms coexisted in 15 patients, 11 females and 4 males. The average age was 62 years. The clinical presentation of patients with coexisting RCC and non-Hodgkin's lymphoma showed three patterns. In the most common pattern, patients developed lymphoma and staging work up revealed a low grade renal cancer. The second pattern was a renal mass and incidental diagnosis of low grade lymphoma located at the retroperitoneum or spleen. In the third pattern, there were 9 years between the occurrence of renal neoplasm and lymphoma. Most of the renal masses were managed by nephrectomy and the lymphoma with chemotherapy. Complete remission was reported in 50% of cases. Consequently, there was a statistical association and the possible etiology could be immune deficiencies or genetic/familiar predisposition[2].

In conclusion, we report the case of a patient that, after an intervention for a kidney tumor, a follicular non-Hodgkin's lymphoma was discovered in one of the lymph nodes of the renal hilum. The coexistence of RCC and non-Hodgkin's lymphoma is infrequent. However, many reports have investigated if this association is sporadic or statistical. In spite of the existence of papers in both directions, the most important studies with a significant number of patients suggest that the relationship between these two neoplasms is stronger than other kinds of tumors.

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CASE REPORT

Colonic lipoma covered by hyperplastic epithelium: Case report

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Abstract

Colonic lipomas are submucosal nonepithelial tumors covered by intact or eroded mucosa. In rare cases, alterations in the mucosa covering a lipoma include hyperplasia, adenoma, atrophy, ulceration, and necrosis. Here, we report a case of a colonic lipoma covered by hyperplastic epithelium in a 68-year-old woman. Based on the colonoscopy findings, a snare polypectomy was performed for a presumptive diagnosis of an epithelial lesion; however, the histological examination revealed a colonic submucosal lipoma with overlying hyperplastic epithelium.

Key words: Lipoma; Colonic lipomas; Hyperplastic; Colonoscopy

Core tip: we report a rare case of a colonic lipoma with overlying hyperplastic epithelium. Removing an asymptomatic colonic lipoma is not necessary, as it may have no clinical significance. However, treatment plans for colonic lipomas might be reconsidered as transformation of the mucosa lining of a lipoma could occur in small and asymptomatic lesions.

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INTRODUCTION

Lipomas are generally rare, but are the most common nonepithelial benign tumors of the gastrointestinal tract. Colonic lipomas are uncommon mesenchymal neoplasms, with a reported incidence of 0.2%-4.4%[1]. Colonic lipomas are usually asymptomatic and detected incidentally at colonoscopy, radiological investigation, surgery, or autopsy. The most common colonoscopic finding is a smooth, slightly yellow, spherical polyp, that is usually sessile and rarely pedunculated, with intact overlying mucosa[2]. In rare cases, the mucosa covering a lipoma shows alterations such as hyperplasia[3,4], atrophy[5], adenomatous changes[6,7], and necrosis and/or ulcerations[8-10]. We herein report a case of colonic lipoma covered with hyperplastic epithelium in a 68-year-old woman and review the literature pertaining to this condition.

CASE REPORT

A 68-year-old woman with abdominal discomfort for several weeks was referred to our department by a private internist for further investigation of a 9 mm polyp in the ascending colon that was revealed during a barium enema for the evaluation of symptom. She denied constipation,

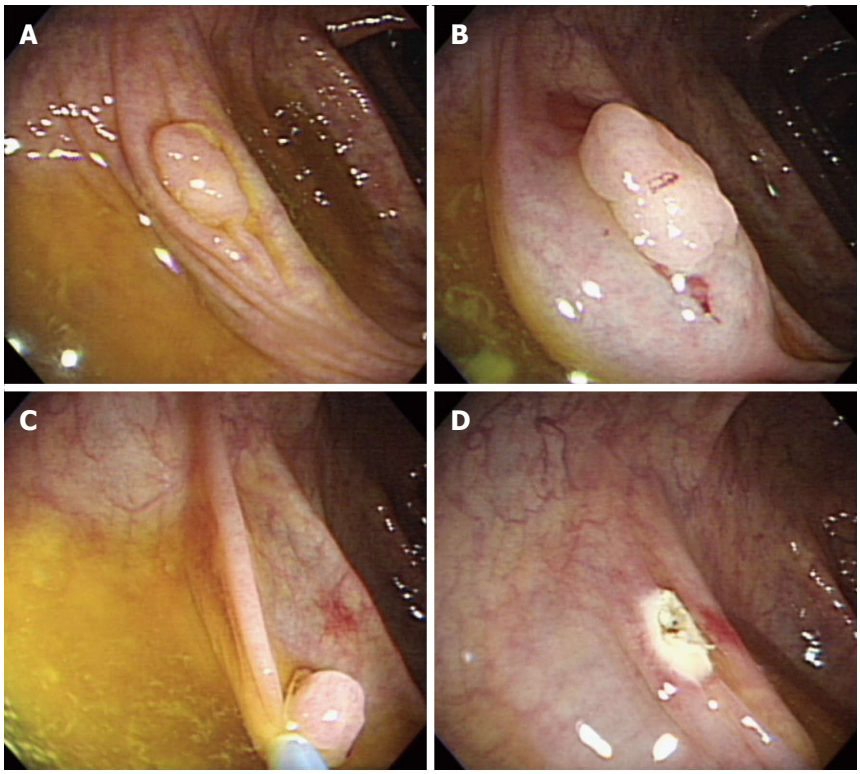

Figure 1 Colonoscopy showing a sessile polyp located in the ascending colon (A), after saline was injected (B), endoscopic mucosal resection was performed (C and D).

diarrhea, hematochezia, or melena. Her physical examination and medical history were unremarkable. All laboratory examinations, including complete peripheral blood cell counts, blood biochemistry, and carcinoembryonic antigen levels were within normal ranges. Colonoscopy revealed a sessile polyp about 9 mm in diameter in the ascending colon (Figure 1). We resected the polyp using a endoscopic mucosal resection (EMR) after a saline solution injection. No procedural-related complications were observed. A histopathological examination revealed a tumor composed of adipose tissue covered by hyperplastic and serrated epithelium consisting of columnar and goblet cells (Figure 2). The patient has been followed closely and has shown no recurrence. A follow-up colonoscopy revealed no remarkable findings 6 mo after the EMR.

DISCUSSION

Colonic lipomas are benign, slow growing tumors of mesenchymal origin that rarely cause symptoms and are usually detected incidentally[1,11]. The most common sites of colonic lipomas are the cecum, ascending colon, and sigmoid colon, in decreasing frequency. These benign tumors arise from the submucosal layer in approximately 90% of cases and from the subserosal or intermucosal layer in the remaining cases[2]. Pathologically, lipomas are composed of well-circumscribed, mature adipose tissue with varying amounts of fibrous stroma covered with intact colonic mucosa[1,2,11].

Diagnostic tools for colonic lipomas include colonoscopy, computed tomography, barium enema, and endoscopic ultrasonography. Among these, colonoscopy allows direct visualization of a colonic lipoma. Lipomas are seen as smooth, slightly yellow, rounded polyps with a thick stalk or broad-based attachment[2]. Characteristic features include the "tenting sign" (grasping the overlying mucosa), the "pillow sign" (pressing forceps against the lesion results in depression or pillowing of the mass), and the "naked fat sign" (extrusion of yellowish fat after biopsy)[1,2,11]. The current case did not show these three characteristic features of a lipoma but the morphology of an epithelial lesion such as hyperplastic polyp or sessile serrated adenoma. The resected specimen was a submucosal lipoma and the covering epithelium was hyperplastic, resembling a hyperplastic polyp. The epithelium was serrated and comprised of both columnar and goblet cells, but lacking atypia or mitotic activity. To the best of our knowledge the association of lipoma and hyperplastic polyp has been reported only once. Radhi *et al*[3] showed a large lipoma in the sigmoid colon with overlying hyperplastic epithelium that was detected during an operation in a patient with diverticulitis. It was unclear whether the co-occurrence of these entities was coincidental or correlated. Hyperplastic polyps have been considered non-neoplastic lesions without malignant potential for many years. However, recent studies have shown that some hyperplastic polyps possess molecular features similar to those of colorectal carcinomas[12,13]. Several subtypes of serrated polyps, such as sessile serrated adenomas, traditional serrated adenomas, and mixed polyps, have been proposed to be colorectal

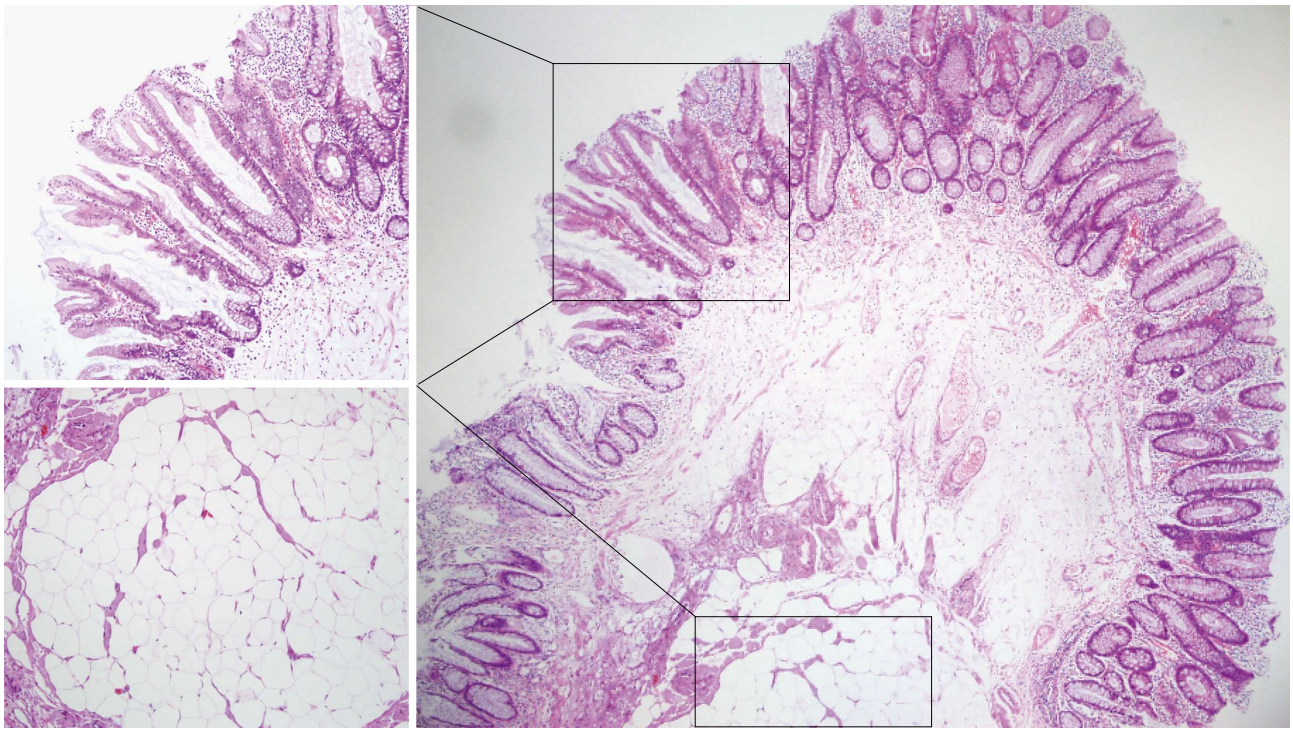

Figure 2 Microscopic image of the resected specimen showing a colonic lipoma with overlying hyperplastic epithelium in the low-magnified image (hematoxylin-eosin, × 40). The lining epithelium resembles a hyperplastic polyp and a tumor composed of adipose tissue in the high-magnified image (hematoxylin-eosin, × 100).

carcinoma precursors. In addition to hyperplastic changes of the epithelium lining in a lipoma, rare cases of adenomatous transformation have been reported[6,7]. It is speculated that chronic trauma due to the passage of stools may lead to hyperplasia and adenomatous transformation of overlying mucosa[7]. In rare cases, the colonoscopy may reveal ulcerations, a finding that may lead to a mistaken diagnosis of adenocarcinoma[8-10].

Although most lipomas require no treatment, a small subgroup requires surgical intervention, including those with suspected malignancy, symptomatic lipomas, surgical emergencies such as intussusception, and obstruction with ulceration and bleeding[1,2,11]. Colonic lipomas < 2 cm can be safely removed endoscopically, whereas larger lesions should be removed by segmental resection[1,2,14]. In the present case, the polyp was initially suspected as a small epithelial lesion based on the colonoscopic findings and was resected endoscopically.

In conclusion, we report a rare case of a colonic lipoma with overlying hyperplastic epithelium. Removing an asymptomatic colonic lipoma is not necessary, as it may have no clinical significance. However, treatment plans for colonic lipomas might be reconsidered as transformation of the mucosa lining of a lipoma could occur in small and asymptomatic lesions.

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CASE REPORT

Peripheral cemento-ossifying fibroma: A case report with review of literature

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Author contributions: Mishra AK contributed substantially to conception and design, acquisition of data, analysis and interpretation of data: diagnosis, motivation, surgical treatment follow up and data collection, final approval of the version to be published; Maru R and Dhodapkar SV contributed to first draft of the article and revision as suggested by reviewers; Jaiswal G contributed to the drafting, corrections, second revision for important intellectual content, and contributed to histopathological analysis; Kumar R and Punjabi H contributed to the drafting the article, revising it critically for important intellectual content, corrections, second revision.

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Abstract

Peripheral cemento-ossifying fibroma (PCOF) is a rare osteogenic neoplasm that ordinarily presents as an epulis-like growth. This is of a reactive rather than neoplastic nature and its pathogenesis is uncertain. PCOF predominantly affects adolescent and young adults with greatest prevalence around 28 years. We report here a rare clinical case of PCOF of the mandible, 1 cm mesiodistally and 1.5 cm occluso-gingivally in diameter, which caused difficulty in eating and speech, in a 42-year-old female patient. She was asymptomatic for 1 year and on follow-up for 6 mo post surgically showed gingival health and normal radioopacity of bone without any recurrence. Clinical, radiographic and histological characteristics are discussed and recommendations regarding differential diagnosis, treatment and follow up are provided. The controversial varied nomenclature and possible etiopathogenesis of PCOF are emphasized.

Key words: Peripheral cemento-ossifying fibroma; Gingivectomy; Granuloma

Core tip: The cemento-ossifying fibroma is a central neoplasm of bone as well as periodontium. The pathogenesis of this tumor is uncertain. Due to their clinical and histopathological similarities, some peripheral cemento ossifying fibromas (PCOFs) are believed to show fibrous maturation and subsequent calcification. The diagnosis of PCOF based only on clinical observation is difficult, hence radiographs and histopathological examination are essential for accurate diagnosis. In addition, a complete excision of the lesion is required to prevent reoccurrence.

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INTRODUCTION

Many types of localized reactive lesions may occur on the gingiva, including focal fibrous hyperplasia, pyogenic granuloma, peripheral giant cell granuloma and peripheral-cemento-ossifying fibroma[1]. These lesions may arise as a result of irritants such as trauma, microorganisms, plaque, calculus, dental restorations and dental appliances[2,3]

The 1992 World Health Organization classification groups under a single designation (cemento-ossifying fibroma) two histologic types (cementifying fibroma and ossifying fibroma) that may be clinically and radiographically indistinguishable[4].

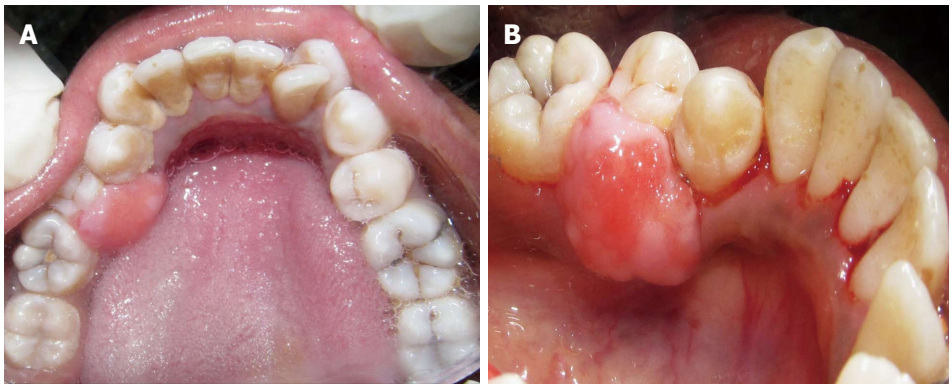

Figure 1 Lingual view of the lesion with smooth non-ulcerated surface and broad attachment base. A: The lesion with smooth non-ulcerated surface; B: Broad attachment base.

Peripheral cemento-ossifying fibroma (PCOF) is a relatively rare lesion with variable forms. It is defined as a well demarcated and occasionally encapsulated lesion consisting of fibrous tissue which contains variable amounts of mineralized material resembling bone (ossifying fibroma), cementum (cementofying fibroma) or both[5,6].

PCOF usually follows a salient clinical course, except in the case of lesions affecting gingiva which present as an enlarging mass that grows progressively, finally producing a facial deformity. The pathogenesis of this lesion is uncertain and it is thought to arise from the periosteal and periodontal membrane[7]. Because of the close proximity and similarity to the periodontal tissue, the term periodontoma sometimes is applied[8]. There is however no proof to support this connection and their occurrence in areas distant from periodontal ligament remains unexplained[9].

PCOF accounts for 3.1% of all oral tumors and 9.6% of gingival lesions[10]. It may occur at any age but exhibits a peak incidence between the second and third decades. The average age is around 28 years with females being affected more than males[11]. Female predilection has been reported to be as high as 5:112[12,13]. Clinically PCOFs are sessile or pedunculated, usually ulcerated and erythematous or exhibit a color similar to that of surrounding gingiva[14,15]. These lesions are generally < 2 cm in size although lesions larger than 10 cm are occasionally observed. About 60% of the tumors occur in the maxilla and more than 50% of all cases affect the region of the incisors and canines. A potential for tooth migration due to the presence of PCOF has been reported[15-17]. In the vast majority of cases, there is no apparent underlying bone involvement visible on roentgenograms. However on rare occasions, there appears to be superficial erosion of bone[16,17].

PCOF should be surgically excised and submitted to microscopic examination for confirmation of diagnosis. The extraction of adjacent teeth is seldom necessary or justified. Recurrences are uncommon but have been described[2]. There have, however, been few reports on this rare lesion. A case of PCOF in the mandibular gingiva of a 42-year-old female patient is described here. In this age group and in the mandibular anterior quadrant, PCOF is rare and has not previously been reported in the literature.

CASE REPORT

A 42-year-old female patient presented at the outpatient Department of Periodontics, Sri Aurobindo Institute of Dentistry and Post Graduate Institute Indore, Madhya Pradesh, India with the chief complaint of gum swelling in the lower right back tooth region (Figure 1). The swelling had been present for 1 year and had been slowly increasing in volume over that time. Occasionally bleeding occurred when the patient brushed her teeth and was associated with slight pain. She denied tobacco and alcohol use. The patient's past dental and medical histories were unremarkable.

Clinical examination

Extraoral examination showed facial symmetry and the overlying skin showed no signs of inflammation. The regional lymph nodes were palpable but were not enlarged or tender.

Intraoral examination revealed a solitary, diffuse, non-tender pinkish-red growth of approximately 1 cm × 1.5 cm, confined to the lingual gingiva in the mandibular II premolar region. The lesion was neither fluctuant nor did it blanch with digital pressure, and had firm consistency. The labial gingiva was not involved. The local irritants, plaque and calculus were abundant in the 44, 45 region.

Radiographic examination

Intraoral periapical, occlusal and ortho pantomo roentgenograms were obtained. The radiographic examination showed no signs of involvement of the alveolar ridge (Figure 2).

Blood investigations

The patient underwent complete blood investigation prior to the surgery and all readings, including hemoglobin, bleeding time, clotting time, total and differential leukocyte counts were within normal limits. The patient was negative for human immunodeficiency virus and

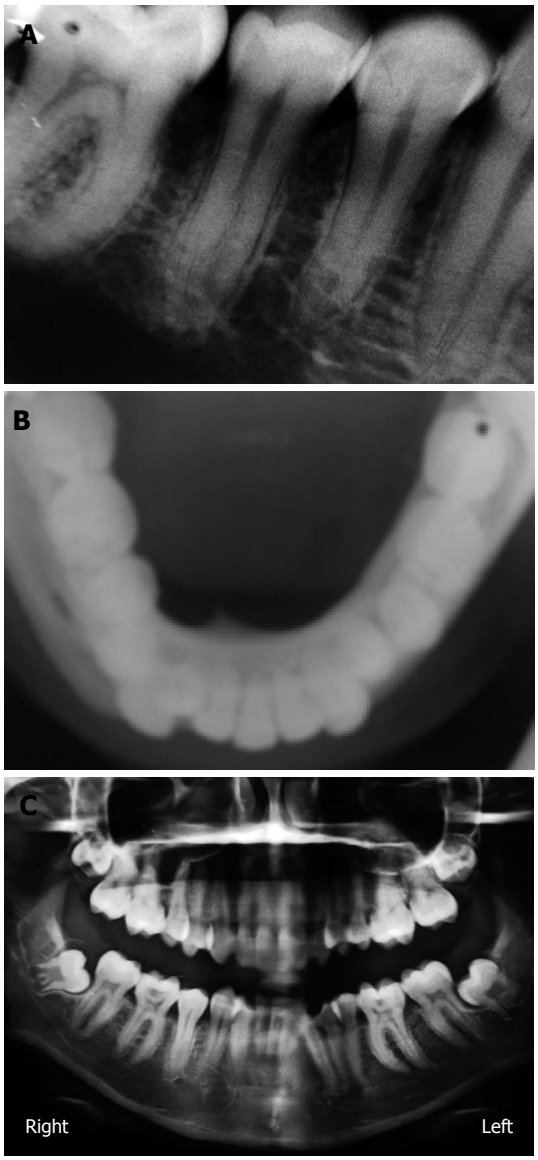

Figure 2 Non involvement of bone. A: Intra oral periapical radiograph; B: Maxillary occlusal radiograph; C: Ortho pantomo radiograph.

Australian antigen (hepatitis B surface antigen).

Diagnosis

Provisional diagnosis of PCOF was made. Clinically, the differential diagnosis included pyogenic granuloma, fibrous hyperplasia, peripheral ossifying fibroma and peripheralgiant cell granuloma.

Treatment

Since the gingival growth was diffuse, surgical removal by internal bevel gingivectomy was chosen. Under local anaesthesia containing xylocaine with adrenaline 1:80000 concentration, the initial scalloped internal bevel incision was made with a 15 No. BP blade at a point far apical to the growth. While making this incision, care was taken to preserve as much attached gingiva as possible apical to the lesion. A second crevicular incision was made with a 12 No. BP blade at the base of the pseudopocket, until it met the first internal bevel incision. To split the labial and palatal, a third interdental incision was made with a 11 No. BP blade in the adjacent interproximal areas tissue. Only the lingual mucoperiosteal flap was reflected with periosteal elevators until the apical end of internal bevel incision was visible. The three incisions completely removed the gingival growth which measured 1 cm × 1.5 cm (Figure 3). The tissue removed was submitted for histopathological examination. Adjacent teeth were scaled to remove local irritants. Underlying bone was curetted to remove periodontal ligaments and periosteum. The flap was inspected for any tissue tags and sutured with interdental interrupted non-resorbable 3-0 silk sutures (Figure 4). Non-eugenol coe-pack was applied both lingualy and labially. The patient was discharged with postoperative instructions and told to come-back after 7 d for suture removal. The patient was given cap. amoxicillin 500 mg every 8 h, beginning 1 d before the operation and continued for a 5-d postoperative period, and 500 mg of acetaminophen three times daily for 5 d along with 0.2% chlorhexidine gluconate for rinsing twice daily until proper plaque control technique could be resumed.

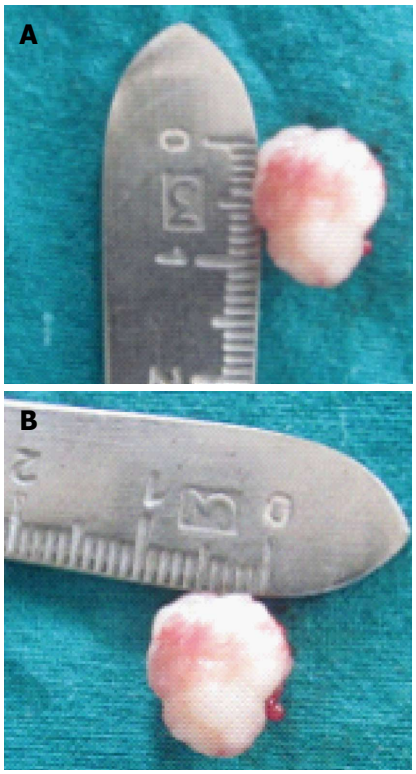

Figure 3 Excised tissue measuring 1.5 cm × 1 cm. A: Length 1.5 cm; B: Width 1 cm.

Microscopic examination

The microscopic examination of the excised tissue revealed a parakeratinized stratified squamous epithelium with long and slender rete ridges. Underlying connective tissue was fibrocellular, comprising collagen fibers. The connective tissue contained a few round to ovoid cementum-like calcified blood vessels, fibroblasts and dense in-

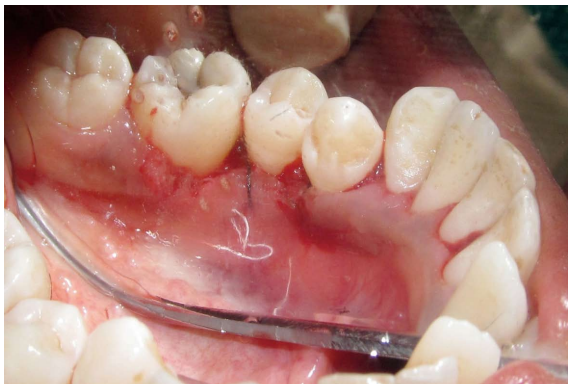

Figure 4 Interrupted sutures placed with 3-0 black braided silk.

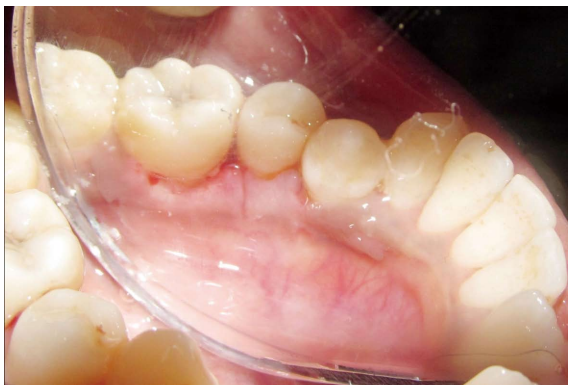

Figure 6 Post operative photograph of surgical site showing satisfactory healing 30 d after surgery.

flammatory cell infiltrate. Deeper areas showed highly cellular connective tissue comprising plump cells with oval nuclei surrounding small globular areas of calcification, resembling cementoids. In some areas bone trabeculae with osteocytes and osteoblastic rimming was also seen. The features were suggestive of "PCOF" (Figure 5).

Follow-up

The patient presented for follow-up examination 7 d post operatively. The coe-pack and the sutures were removed and the operated area was irrigated with normal saline. The surgical site appeared to be healing well and there was no need to repack the site. At one month postoperatively the surgical site had healed completely, the flap was well adapted to the underlying bone with physiologically scalloped contours and thin knife-edge margins (Figure 6). There was no evidence of recurrence of the lesion at 6 mo and the patient was asymptomatic.

DISCUSSION

PCOFs have been described in the literature since the 1940s. Many names have been given to similar lesions such as epulis[1], peripheral fibroma with calcifications[2], peripheral ossifying fibroma[2,3] calcifying fibroblastic granuloma[18], peripheral cemetifying fibroma[3], peripheral fibroma with cementogenesis[19], and peripheral cemento

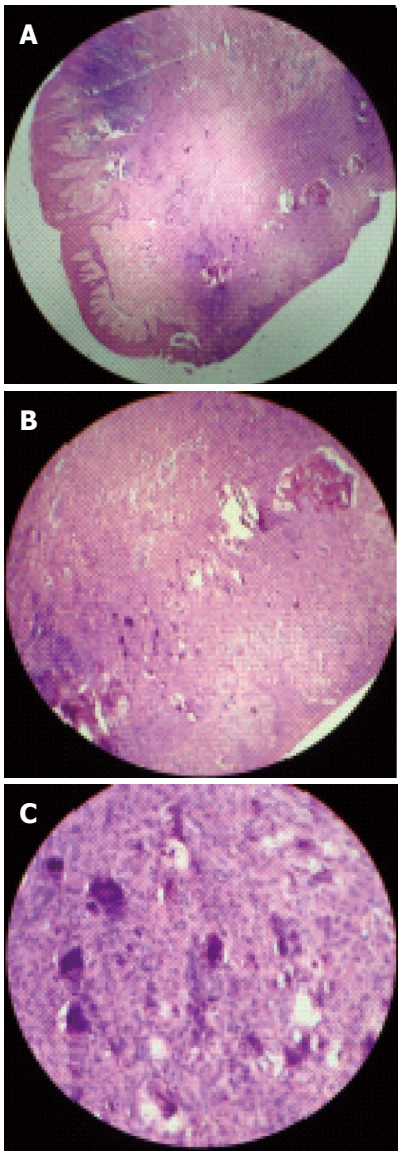

Figure 5 The features were suggestive of "peripheral cemento-ossifying fibroma". A: Histological picture showing long slender rete ridges and parakeratinized stratified squamous epithelium; B: Round to ovoid basophilic cementum-like calcifications [hematoxylin-eosin (HE) staining, × 10]; C: Basophilic globules of calcified mass along with osteoid tissue, round to ovoid basophilic cementum-like calcifications (HE staining, × 40).

ossifying firoma[20]. The sheer number of names used for fibroblastic calcifying gingival lesions indicates that there is much controversy surrounding their classification[19].

The basis of benign fibro-osseus lesions was established by Wladron[5]. They are divided into three main categories: fibrous dysplasia, reactive lesions (periapial cemento-osseus dysplasia, focal cemento-osseus dysplasia and florid cementoosseus dysplasia) and fibro-osseus neoplasms. PCOF is actually considered as a fibro-osseus dysplasia and has been included in the group of non odontogenic tumours since the 1992 WHO classification[5,6]

Alt hough the etiopathogenesis of PCOF is uncertain, an origin from cells of the periodontal ligament has been suggested[20]. The reasons for considering a periodontal origin for PCOF include the exclusive occurrence of

PCOF in the gingiva, the proximity of gingiva to the periodontal ligament and the presence of oxytalan fibers within the mineralized matrix of same lesions[19]. Excessive proliferation of mature fibrous connective tissue is a response to gingival injury, gingival irritation, subgingival calculus or a foreign body in the gingival sulcus. Chronic irritation of the periosteal and periodontal membrane causes metaplasia of the connective tissue and resultant irritation of bone formation or dystrophic calcification. It has been suggested that the lesion may be caused by fibrosis of the granulation tissue[7]. The clinical evolution of tumors is usually as follows. Initially asymptomatic, the tumor progressively grows to the point where its size causes pain as well as functional alteration and cosmetic deformities[1,6]. This was observed in our patient who presented with an enlarged mass accompanied by slight pain and cosmetic deformity. Cases of tooth migration and bone destruction have been reported, but these are not common[15,21]. In the present case the lesion was pink, firm, slightly tender on palpation with a smooth non-ulcerated surface and a broad attachment base. The dimensions were 1 cm × 1.5 cm, well within the expected range. Although the majority of lesions occur in the second decade of life[12], this female patient was 42-year-old with the lesion occurring in mandibular right premolar region[11,14,22].

Hormonal influences may play a role, given the higher incidence of PCOF among females, the increasing occurrence in the second decade and declining incidence after the third decade[16]. In an isolated case of multicentric PCOF, Kumar *et al*[19] noted the presence of a lesion at an edentulous site in a 49-year-old women which gives rise to further questions regarding the pathogenesis of this types of lesion. The same type of lesion at a dentulous site in a 50-year-old female was documented by Mishra *et al*[23].

Radiographically, PCOF may follow different patterns depending on the amount of mineralized tissue[4-6]. Radio-opaque foci of calcification have been reported to be scattered throughthe central area of the lesion but not all lesions demonstrate radiographic calcifications[7].

Underlying bone involvement is usually not visible on radiographs. In rare instances superficial erosion of bone is noted[7]. In the present case no radiographic changes were found, indicating that this could be an early stage lesion. Frequently, PCOF shows similar clinical features to other extraosseous lesions. It may be misdiagnosed as pyogenic ganuloma, fibrous dysplasia, peripheral giant cell granuloma, osteoid osteoma, osteoblastoma, low grade osteosarcoma, cementoblastoma, chronic osteomyelitis and sclerosing osteomyelitis of Garre[4-6]. In general the pyogenic granuloma presents as a red soft friable nodule that bleeds with minimal manipulation but tooth displacement and resorption of alveolar bone are not observed. Although peripheral giant cell granuloma has features similar to those of PCOF, the latter lacks the blue discoloration commonly associated with peripheral giant cell granuloma and shows flakes of calcification, radiographically as well histologically. Thus, the diagnosis of PCOF based only on clinical observations can be difficult and histopathological examination of the surgical specimen obtained by excisional biopsy is essential for an accurate diagnosis. All the classic histopathological features of PCOF were present in this case. The preferred treatment is surgical, consisting of resection of the lesion as well as curettage of its osseous floor (Periodontal ligament and Periosteum) and scaling of adjacent teeth, as was performed in this case. Recovery was uneventful and the patient has remained tumor free for 24 wk. Because this lesion is poorly vascularized and well circumscribed, it is easily removed from the surrounding bone. This is one of the main differences with fibrous dysplasia[5,6].

Prognosis is excellent and recurrence is rare if correctly managed[4,5]. The recurrence rate of PCOF is high for reactive lesions[11,16] and recurrence is probably due to incomplete removal of the lesion, repeated injury or persistence of local irritants[16]. The rate of recurrence has been reported at 8.9%[1], 9%[21], 14%[16], 16%[11] and 20%[2]. Therefore the patient is still on a regular schedule of follow up.

In conclusion, PCOF is a slowly progressive lesion generally with limited growth. Many cases will progress for long periods before the patient seeks treatment because of the lack of symptoms associated with the lesion. A slowly growing pink soft tissue nodule in the anterior maxilla of an adolescent should raise suspicion of PCOF. Since the diagnosis of PCOF based only on clinical features is very difficult, radiographs and histopathological examination are essential for accurate diagnosis.

Treatment consists of surgical excision including periodontal ligament periosteum and scaling of adjacent teeth. Close postoperative follow-up is required because of the growth potential for incompletely removed lesions and the 8%-20% recurrence rate.

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An informative, structured abstract should accompany each manuscript. Abstracts of original contributions should be structured into the following sections: AIM (no more than 20 words; Only the purpose of the study should be included. Please write the Aim in the form of "To investigate/study/…"), METHODS (no less than 140 words for Original Articles; and no less than 80 words for Brief Articles), RESULTS (no less than 150 words for Original Articles and no less than 120 words for Brief Articles; You should present *P* values where appropriate and must provide relevant data to illustrate how they were obtained, *e.g.*, 6.92 ± 3.86 *vs* 3.61 ± 1.67, $P < 0.001$), and CONCLUSION (no more than 26 words).

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Please list 5-10 key words, selected mainly from *Index Medicus*, which reflect the content of the study.

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Data that are not statistically significant should not be noted. $^{a}P < 0.05$, $^{b}P < 0.01$ should be noted ($P > 0.05$ should not be noted). If there are other series of P values, $^{c}P < 0.05$ and $^{d}P < 0.01$ are used. A third series of P values can be expressed as $^{e}P < 0.05$ and $^{f}P < 0.01$. Other notes in tables or under illustrations should be expressed as ^{1}F, ^{2}F, ^{3}F; or sometimes as other symbols with a superscript (Arabic numerals) in the upper left corner. In a multi-curve illustration, each curve should be labeled with ●, ○, ■, □, ▲, △, *etc*., in a certain sequence.

Acknowledgments

Brief acknowledgments of persons who have made genuine contributions to the manuscript and who endorse the data and conclusions should be included. Authors are responsible for obtaining written permission to use any copyrighted text and/or illustrations.

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Format

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English journal article (list all authors and include the PMID where applicable)

1 **Jung EM**, Clevert DA, Schreyer AG, Schmitt S, Rennert J, Kubale R, Feuerbach S, Jung F. Evaluation of quantitative contrast harmonic imaging to assess malignancy of liver tumors: A prospective controlled two-center study. *World J Gastroenterol* 2007; **13**: 6356-6364 [PMID: 18081224 DOI: 10.3748/wjg.13.6356]

Chinese journal article (list all authors and include the PMID where applicable)

2 **Lin GZ**, Wang XZ, Wang P, Lin J, Yang FD. Immunologic effect of Jianpi Yishen decoction in treatment of Pixu-diarrhoea. *Shijie Huaren Xiaohua Zazhi* 1999; **7**: 285-287

In press

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 PMCID:2516377 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]

Volume with supplement

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]

Issue with no volume

8 **Banit DM**, Kaufer H, Hartford JM. Intraoperative frozen section analysis in revision total joint arthroplasty. *Clin Orthop Relat Res* 2002; (**401**): 230-238 [PMID: 12151900 DOI:10.1097/00003086-200208000-00026]

No volume or issue

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

Books

Personal author(s)

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

Author(s) and editor(s)

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 computational 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

Statistical data

Write as mean ± SD or mean ± SE.

Statistical expression

Express *t* test as *t* (in italics), *F* test as *F* (in italics), chi square test as χ^2 (in Greek), related coefficient as *r* (in italics), degree of freedom as υ (in Greek), sample number as *n* (in italics), and probability as *P* (in italics).

Units

Use SI units. For example: body mass, m (B) = 78 kg; blood pressure, p (B) = 16.2/12.3 kPa; incubation time, t (incubation) = 96 h, blood glucose concentration, c (glucose) 6.4 ± 2.1 mmol/L; blood CEA mass concentration, p (CEA) = 8.6 24.5 μg/L; CO_2 volume fraction, 50 mL/L CO_2, not 5% CO_2; likewise for 40 g/L formaldehyde, not 10% formalin; and mass fraction, 8 ng/g, *etc.* Arabic numerals such as 23, 243, 641 should be read 23 243 641.

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Italics

Quantities: *t* time or temperature, *c* concentration, *A* area, *l* length, *m* mass, *V* volume.

Genotypes: *gyrA*, *arg* 1, *c myc*, *c fos*, *etc.*

Restriction enzymes: *Eco*RI, *Hin*dI, *Bam*HI, *Kbo* I, *Kpn* I, *etc.*

Biology: *H. pylori*, *E coli*, *etc.*

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