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Contents

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EDITORIAL

Isolated gastric Crohn's disease

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Abstract

Crohn's disease (CD) is a chronic idiopathic inflammatory disease of gastrointestinal tract characterized by segmental and transmural involvement of gastrointestinal tract. Ileocolonic and colonic/anorectal is a most common and account for 40% of cases and involvement of small intestine in about 30%. The stomach is rarely the sole or predominant site of CD. To date there are only a few documented case reports of adults with isolated gastric CD and no reports in the pediatric population. Isolated stomach involvement is very unusual presentation accounting for less than 0.07% of all gastrointestinal CD. The diagnosis is difficult to establish in cases of atypical presentation as in isolated gastroduodenal disease. In the absence of any other source of disease and in the presence of nonspecific upper GI endoscopy and histological findings, serological testing can play a vital role in the diagnosis of atypical CD. Recent studies have suggested that perinuclear anti-neutrophil cytoplasmic antibody and anti-*Saccharomycescervisia* antibody may be used as additional diagnostic tools. The effectiveness of infliximab in isolated gastric CD is limited to only a few case reports of adult patients and the long-term outcome is unknown.

Key words: Gastrointestinal tract; Crohn's disease; Perinuclear anti-neutrophil cytoplasmic antibody; Anti-*Saccharomycescervisia* antibody

Core tip: Crohn's disease (CD) is a chronic idiopathic inflammatory disease of gastrointestinal tract characterized by segmental and transmural involvement of gastrointestinal tract. The stomach is rarely the sole or predominant site of CD accounting for less than 0.07% of all gastrointestinal CD. Serological testing and careful histopathological examination by excluding other causes of granulomatous gastritis can play a vital role to arrive at the diagnosis of atypical CD.

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GASTRIC CROHN'S DISEASE

In common presentations, the diagnosis of Crohn's disease (CD) is usually based on a combination of typical clinical, laboratory, endoscopic and histopathological findings. However, the diagnosis is difficult to establish in cases of atypical presentation as in isolated gastric disease. In such a scenario other possible etiologies must be systematically ruled out in order to establish the correct diagnosis. These conditions may include *Helicobacter pylori* (*H. pylori*) infection, tuberculosis, non-steroidal anti-inflammatory drugs gastritis, Menetrier's disease, gastrinoma, collagen vascular disease and lymphoma. Additional diagnostic strategy in atypical cases of inflammatory bowel disease is the use of anti-*Saccharomycescervisia* antibody (ASCA). This serological marker can be a helpful adjunctive tool in the diagnostic process despite the test's limitations.

Treatment regimens for gastric CD have been poorly studied. The routine treatment of inflammatory gastritis in CD includes the concomitant use of acid-suppressive drugs and immunomodulators such as ASCA products or

steroids. In recent years infliximab [anti-tumor necrosis factor-α (TNF-α)] has become an important addition to the therapeutic options in CD. The effectiveness of infliximab in isolated gastric CD is limited to only a few case reports of adult patients and the long-term outcome isunknown[1-3].

In most cases of CD the presentation, workup and diagnosis run a familiar and substantiating course. The symptoms of gastric CD are nausea, vomiting, epigastric pain and weight loss[2,4]. These symptoms arise from peptic ulcers and or obstruction in the outlet of the stomach[5]. A clinically symptomatic disease, however, is seen in 4% of cases[6]. Sometimes, however, this disease can manifest in an entirely non-specific and unusual manner. Uncommon presentations of CD may manifest as a single symptom or sign, such as impairment of linear growth, delayed puberty, perianal disease, mouth ulcers, clubbing, chronic iron deficiency anemia or extra-intestinal manifestations preceding the gastrointestinal symptoms, mainly arthritis or arthralgia, primary sclerosing cholangitis, pyoderma gangrenosum and rarely osteoporosis. In such cases, the diagnosis is challenging and can remain elusive for some time.

The stomach is rarely the sole or predominant site of CD. To date there are only a few documented case reports of adults with isolated gastric CD and no reports in the pediatric population. Normally, the diagnosis of CD is based on clinical presentation, radiological abnormalities of the small bowel, gastroscopy and colonoscopy findings and non-specific or typical pathological features.

Radiology studies in gastroduodenal Crohn's normally demonstrate similar features to those found in more distal CD, such as thickened folds, ulcers, nodularity, stenosis and distorted anatomy. Upper gastrointestinal endoscopy in gastric CD may be grossly normal or it may reveal various combinations of edema, erythema, ulcers, nodularity and cobblestone appearance.The antrum is most frequently involved, while the proximal stomach is often spared. Gastric biopsies have poor specificity and the changes of non-specific gastritis may be seen in other conditions such as *H. pylori* infection. Discovery of granulomatous gastritis (Figure 1) might help to narrow the differential diagnosis to CD, tuberculosis, malignancy and collagen vascular disease. Interestingly, however, granulomas are only identified in 3%-24% of the biopsies and repeat biopsies do not result in higher rates of granuloma discovery[7]. However, the marked edematous, inflammed and ulcerated regions with cobblestone appearance and inflammatory pseudopolyps found mainly in the antrum on endoscopy are at least suggestive of CD.

In the absence of any other source of disease and in the presence of nonspecific upper endoscopy and histological findings, serological testing can play an important role in the diagnosis of atypical CD. Recent studies have suggested that perinuclear anti-neutrophil cytoplasmic antibody (pANCA) and ASCA may be used as additional diagnostic tools for patients with suspected inflammatory bowel disease and help to differentiate between CD and

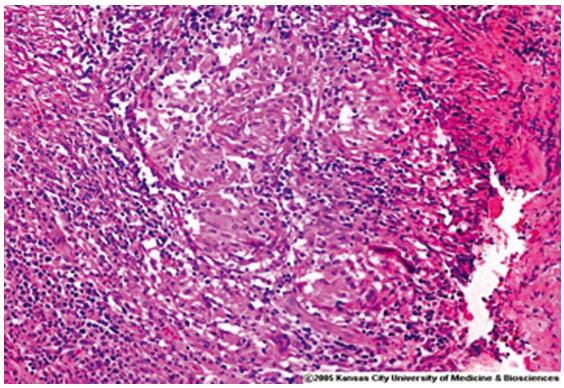

Figure 1 Section showing noncaseating granuloma (hematoxylin and eosin, × 10).

ulcerative colitis. Indeed, ASCA is detected in 55%-60% of children and adults with CD and only 5%-10% of controls with other gastrointestinal disorders. This finding pANCA highlights the relatively good specificity but poor sensitivity of ASCA as a marker for CD. pANCA on the other hand is more specific to ulcerative colitis and the combination of a positive ASCA test with a negative pANCA test has a positive predictive value of 96% and a specificity of 97% for CD. Inaddition, some *NOD2/CARD15* gene polymorphisms, particularly *L1007P* homozygosity, were found to be associated with gastroduodenal CD and with younger age at diagnosis. It is possible that these genes might also help to support the diagnosis in the atypical presentation of CD in the future.

Infliximab, a monoclonal antibody to TNF-α, is often used in cases of steroid refractory CD. The role of infliximab in treating patients with gastric CD has scarcely been studied. In one case series, infliximab was effective in healing ulcers in two patients[2], but the development of lung cancer in one and surgery in the other necessitated stopping the treatment. In another case study the symptoms in a patient with diffuse mucosal thickening and ulceration throughout the antrum and duodenum continued despite prednisone and a twice-daily dose of a proton pump inhibitor. Treatment with infliximab led to marked improvement within 1 wk[2]. Surgical therapy in CD can be indicated for ulcers not responding to medical therapy, massive bleeding, in gastric outlet obstructions for which balloon dilatation is unsuccessful, or in cases where gastric fistulas have developed[5]. Recurrence after surgical therapy is common, and re-operations are frequently required[7,8].

In summary,atypical cases with non-conclusive clinical, endoscopic and pathological findings, the ASCA test could be helpful in the diagnostic process. Infliximab may be an effective treatment in cases of severe isolated gastropathy due to CD.

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MINIREVIEW

Biological therapy for dermatological manifestations of inflammatory bowel disease

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Abstract

Ulcerative colitis and Crohn's disease are the two forms of inflammatory bowel disease (IBD). The advent of biological drugs has significantly changed the management of these conditions. Skin manifestations are not uncommon in IBD. Among the reactive lesions (immune-mediated extraintestinal manifestations), erythema nodosum (EN) and pyoderma gangrenosum (PG) are the two major cutaneous ills associated with IBD, while psoriasis is the dermatological comorbidity disease observed more often. In particular, in the last few years, anti-tumor necrosis factor (TNF)-α agents have been successfully used to treat psoriasis, especially these kinds of lesions that may occur during the treatment with biological therapies. The entity of the paradoxical manifestations has been relatively under reported as most lesions are limited and a causal relationship with the treatment is often poorly understood. The reason for this apparent side-effect of the therapy still remains unclear. Although side effects may occur, their clinical benefits are undoubted. This article reviews the therapeutic effects of the two most widely used anti-TNF-α molecules, infliximab (a fusion protein dimer of the human TNF-α receptor) and adalimumab (a fully human monoclonal antibody to TNF-α), for the treatment of the major cutaneous manifestations associated with IBD (EN, PG and psoriasis).

Key words: Biological therapies; Erythema nodosum; Inflammatory bowel disease; Psoriasis; Pyoderma gangrenosum

Core tip: Ulcerative colitis and Crohn's disease are the best known forms of inflammatory bowel disease (IBD) and are considered immune-mediated disorders of unknown etiology that primarily affect the gastrointestinal tract. In addition, other organ systems can be involved, such as skin. Erythema nodosum, pyoderma gangrenosum and psoriasis are the dermatological comorbidities often associated with it. The anti-tumor necrosis factor (TNF)-α drugs (infliximab and adalimumab) have significantly changed the management of these conditions. In this brief review, we provide an overview on the prevalence and clinical aspects of the more commonly reported skin manifestations of IBD and the role of TNF-α inhibitors in their treatment.

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INTRODUCTION

Extraintestinal manifestations (EIMs) are commonly seen in association with inflammatory bowel disease (IBD). The reported prevalence of EIMs in IBD ranges from

25% to 40%[1]. EIMs can involve any organ or system, with the musculoskeletal and the dermatological ones being the most common. Major skin involvement has been described in 2% to 34% of patients with IBD[2]. Erythema nodosum (EN) and pyoderma gangrenosum (PG) are the two major skin manifestations associated with IBD, defined as reactive lesions (immune-mediated EIMs), while psoriasis is the dermatological associated disease observed more frequently.

The advent of biological therapies [tumor necrosis factor (TNF)-α inhibitors] has changed the course of these EIMs. In particular, there are three TNF-α inhibitors commercially available: etanercept (Enbrel®, Immunex Corporation, Thousand Oaks, CA), a fusion protein dimer of the human TNF-α receptor; infliximab (Remicade®, Centocor Incorporated, Horsham, PA), a chimeric mouse-human monoclonal antibody to TNF-α; and adalimumab (Humira®, Abbott Laboratories, Abbott Park, IL), a fully human monoclonal antibody to TNF-α. All these drugs specifically bind to TNF-α, blocking its biological activity[3], with important effects on anergic regulatory T cells, restoring their capacity to inhibit cytokine production[4]. The aim of this brief review is to investigate the role of biological therapy in these kind of dermatological manifestations associated with IBD.

EN

EN is the most common cutaneous lesion. It is usually easily recognized on account of its characteristic features; in fact, a biopsy is helpful only in atypical cases. EN lesions are frequently palpable and appear as raised, tender, red or violet subcutaneous nodules 1-5 cm in diameter. EN commonly affects the extensor surfaces of the extremities, particularly the anterior tibial areas, but the arms and the trunk can also be affected. The differential diagnosis of EN includes other types of panniculitis, like cutaneous infections and subcutaneous lymphomas[5].

The prevalence of EN in IBD and Crohn's disease (CD), respectively, ranged from 4.2% to 7.5% and seems to be higher in CD than in ulcerative colitis (UC)[6-8]. The occurrence of lesions is closely related to intestinal disease activity and their treatment is based on that of the underlying IBD. In a study of 792 patients affected by IBD, every case of EN (48 patients) responded to medical treatment of the IBD[9].

Reading the literature, we have found only two cases of EN successfully treated with anti-TNF-α therapy; a case of a child with CD refractory to treatment with corticosteroids and immunomodulators had a rapid and sustained response to the anti-TNF-α antibody infliximab[10] and a case of a refractory chronic EN successfully treated with adalimumab[11]. On the other hand, a case of an EN as paradoxical occurrence has been reported after infliximab infusion given for ankylosing spondylitis in a patient without IBD[12].

PG

PG typically presents with ulcerated lesions with violaceous undetermined borders that are covered with pus or necrotic debris[13]. These ulcers can be solitary or multiple, unilateral or bilateral, and can range in size from several centimeters to an entire limb[14]. PG usually occurs on the extensor surface of the legs but can appear anywhere on the skin, like on the abdominal wall adjacent to a post-surgical stoma[15]. While EN usually correlates with IBD activity, PG correlation with IBD activity is controversial. In fact, PG does not always respond to treatment of underlying bowel disease and response to bowel resection is unpredictable[16]. In recent publications, PG is reported in 0.6%-2.1% of UC and CD patients[6,7], even though it seems more prevalent in UC.

Rapid healing of these lesions should be the therapeutic aim because PG can be a debilitating skin disorder. Usually, systemic corticosteroids and cyclosporin are the most commonly drugs used. Biological therapy is reserved only for specific cases. In fact, infliximab has been reported to be successful in treating severe or refractory lesions[5]. A multicenter retrospective study of medically refractory PG patients reports a positive response to infliximab[17]. The mechanism of action is in line with the putative involvement of immune-mediated factors in the pathogenesis of PG concerning suppression of inflammatory processes. In the study by Tan *et al*[18], two patients with refractory Crohn's fistula and PG had a rapid improvement shortly after the first infusion with infliximab. Sapienza *et al*[19] also reported a good response of PG lesions in four patients with CD treated with infliximab.

The authors supposed that the rapid response to infliximab in these patients was the result of blunted T cell activation early in the inflammatory cascade leading to a decrease in neutrophil infiltration[19]. The largest study on the treatment of PG with IFX was published by Brooklyn *et al*[20]. This was a multicenter, randomized, placebo-controlled trial of 30 patients, including 19 patients with IBD. IFX 5 mg/kg or placebo was given at week 0. At week 2 (the primary end point), significantly more patients in the IFX group had improved compared to placebo (46% *vs* 6%, $P = 0.025$); the response was based upon reduction on size, depth and degree of the lesions. At week 2, subjects in both arms were then offered an open-label for IFX. Overall, 29 patients received IFX with the majority of them showing a beneficial clinical response at week 6 (response 69%, remission 31%). The response rate was over 90% in patients with short duration of PG (< 12 wk) and less than 50% in those with disease present for more than 3 mo. In addition, there was no difference in response between PG patients with IBD and those without[20].

In the literature there is a case of a young women with CD and PG who was successfully treated with Adalimumab[21]. She was a 38-year-old woman with fistulizing CD (enterogastric fistula) that manifested as diffuse abdominal pain and bloody diarrhea, accompanied by arthralgia and PG. The patient was treated with high doses of parenteral methylprednisolone, methotrexate and IFX without any improvement. A positive response to adalimumab therapy was observed: after 2 mo of therapy, the ulcerative skin

lesion healed completely and after 5 mo the enterogastric fistula was closed[21].

On the other hand, three cases of PG as a paradoxical occurrence have been reported after infliximab infusion[22-24]. A 38-year-old woman developed severe PG while receiving treatment with infliximab and azathioprine for active lymphocytic ileitis, in whom the ulcer was finally resolved when treatment with adalimumab was initiated[22]. A 40-year-old woman with UC, developed PG following the second infusion of IFX. In this case, infliximab was discontinued and cyclosporine was initiated with remission of the skin lesion[23]. Finally, a case of a PG has been reported during infliximab infusion given for rheumatoid arthritis in a patient without IBD[24].

Psoriasis

Psoriasis is a chronic skin condition characterized by erythematous papules and plaques. Psoriasis seems to be more common in CD patients than in the general population[25]. Danese *et al*[26] found that psoriasis occurs in 7%-11% of the IBD population, compared to 1%-2% of the general population. Yates *et al*[27] in their study found that psoriasis was more prevalent in CD (11.2%) than in UC (5.7%). Psoriatic lesions have a high concentration of TNF-α, similar to lesions seen in CD, suggesting some immunological overlap. In fact, the association of IBD with psoriasis is believed to be both genetically and immunologically related[28].

Evidence in favor of infliximab and adalimumab for psoriasis has been derived from clinical studies managed by dermatologists. Gottlieb *et al*[29] analyze the efficacy and safety of infliximab as induction therapy for patients with severe plaque psoriasis. In this multicenter, double-blind, placebo-controlled trial, 249 patients with severe plaque psoriasis were randomly assigned to receive intravenous infusions of either 3 or 5 mg/kg of infliximab or placebo given at weeks 0, 2 and 6. The primary end-point was the proportion of patients who achieved at least 75% improvement in the psoriasis area and severity index score from baseline at week 10. Infliximab treatment resulted in a rapid and significant improvement in the signs and symptoms of psoriasis. At week 10, 72% of patients treated with infliximab (3 mg/kg) and 88% of patients treated with infliximab (5 mg/kg) achieved a 75% or greater improvement from baseline in the psoriasis area and severity index score compared with 6% of patients treated with placebo ($P < 0.001$)[29]. A subsequent follow-up study by Reich *et al*[30], conducted on 378 patients with moderate to severe plaque psoriasis, demonstrated that 1 year of IFX was effective in both induction and maintenance regimens[30]. In the literature, six cases of patients with plaque psoriasis unresponsive to previous therapies, including infliximab and etanercept, in whom adalimumab (given at 40 mg/wk for 20 wk) resulted in clinical improvement are also described[31].

In the last years, paradoxical cases of psoriatic lesions induced or exacerbated by anti-TNF-α therapy have been reported more frequently, an observation that does not seem to relate to the age of the patient or to the duration of treatment[32-34]. Psoriasiform eczema, eczema and xerosis were the most commonly observed type of skin paradoxical inflammation[35].

The role played by the cytokine network in psoriasis is crucial in understanding the complex mechanisms that underlie the paradox anti-TNF-α-induced psoriasis. Recently, in the pathogenesis of this condition, interferon (IFN)-γ has been called into question[36,37]. This cytokine (IFN-γ), in combination with molecules such as TGF-β, IL-15 and IL-20, can enhance the proliferation of keratinocytes and inhibit their apoptosis[38]. For these kinds of reactions topical therapy with corticosteroids, keratolytics (salicylic acid, urea), emollients, vitamin D analogues and ultraviolet (UV) therapy (UVA or narrow band UVB) are usually used. A class effect is suggested in patients with psoriatic lesions that do not improve with topical therapy and develop recurrent lesions after being switched to anti-TNF-α therapies. Uncontrolled skin lesions led to discontinuation of anti TNF agents in about 34% of patients[39].

We herein report two recent systematic reviews. Denadai *et al*[40] included thirty-four studies in their first study. Sixty-nine patients with IBD were analyzed. Most patients had CD (89.86%), were female (47.83%), had an average age of 27.11 years and no reported history of psoriasis (84.05%). The most common type of psoriatic lesion that developed was plaque-type psoriasis (40.58%). There was a complete remission of psoriatic lesions in 86.96% of IBD patients despite differences in the therapeutic approaches: cessation of infliximab therapy led to resolution in 47.83% of cases and 43.48% of patients were able to continue infliximab therapy[40].

Subsequently, in another systematic review, Denadai *et al*[41] included 47 studies (222 IBD patients). Of the 222 patients, 78.38% were diagnosed with CD and 48.20% were female. The mean patient age was 26.5 years and 70.72% of patients had no history of psoriasis. Patients developed psoriasiform lesions (55.86%) and infliximab was the anti-TNF-α therapy that caused the cutaneous reaction in most of them (69.37%). The majority of patients were managed conservatively without discontinuing anti-TNF-α therapy and complete remission of cutaneous lesions was observed in 63.96% of cases[41].

CONCLUSION

Early recognition of dermatological manifestations associated with IBD is very important for their treatment. The advent of biological response modifiers (anti-TNF-α inhibitors) represents a new and efficacious approach that is able to modify the clinical course of such patients. The diagnosis of the cutaneous manifestations of IBD generally is based on their characteristic features and biopsy is reserved only for atypical cases.

Treatment of EN is usually based on the underlying IBD (CD or UC) and is performed using systemic steroids. PG is initially treated with systemic steroids, oral

calcineurin inhibitors and then with infliximab or adalimumab.

The anti-TNF treatment can induce paradoxical inflammation of the skin which is generally considered a class-drug effect and it is usually reversible upon drug switching or discontinuation. In most cases, psoriatic lesions are the more commonly seen paradoxical inflammation of the skin. In fact, in recent years, an increasing number of cases of onset psoriasis related to anti-TNF therapy in IBD patients has been reported. Psoriasis appearing during anti-TNF-α therapy is considered a class effect of TNF-α blocking agents rather than a drug-specific adverse event[42]. Plaque psoriasis on the extremities and the trunk were the most frequent presentations. The mechanism underlying this paradoxical phenomenon is controversial but it is well known that the increased production of IFN-γ, a key element in the induction of psoriasis, after TNF-α blockage might play a major role[42]. Reading the literature, we found that actually there is no consensus as to whether to continue or discontinue the anti-TNF-α therapy in these cases. In our opinion, the decision should be individualized. Topical steroid treatment is often effective in most patients. Anti-TNF discontinuance may be reserved for patients with severe psoriasis or for the ones that do not respond to topical therapy.

In conclusion, since the introduction of the biological agents, antibodies to cytokine TNF-α, the treatment of IBD and their EIMs such as cutaneous ones has changed dramatically. Although side effects may occur, their clinical benefit remains undoubted.

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CASE REPORT

Globalised world, globalised diseases: A case report on an amoebiasis-associated colon perforation

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Abstract

In 2010 the World Health Organisation estimated the number of infections with *Entamoeba histolytica* at about 50 million cases including 100000 fatal courses. In most cases this infection is a subclinical event with few or none symptoms noticeable for the patient. Courses of this disease and incidence of this parasite in industrialised nations are not yet fully investigated. Our case reports about a 68-year-old male patient from Turkey who lives for more than 30 years in Germany and had not been abroad during the past 2 years. Resistant asymptomatic amoebic dormant bodies caused an emergency-laparoscopy and revealed the seldom complication of a colon perforation. In the age of globalisation all providers in the health care systems are urged to acquaint themselves also with non-typical syndromes for the countries they work in order to reduce preventable morbidity respectively mortality rates.

Key words: Amoebiasis; *Entamoeba histolytica*; Colon perforation; Surgical treatment

Core tip: This case shows how important it is that medicine providers expected rare diseases from other regions from the globalised world. The clinical signs of this patient have been wrongly interpreted. Itself the operation was not targeted. The histopathological examination of resected intestine had a surprising result, but not the source of the clinical signs. Only the use of the polymerase change reaction (PCR) identified the causal link between the clinical signs and the trigger. So the PCR should be the central feature in the diagnostic of unclear or undefined clinical signs.

Redaèlli M, Mahmoohdzad J, Lang R, Schencking M. Globalised world, globalised diseases: A case report on an amoebiasis-associated colon perforation. *World J Clin Cases* 2013; 1(2): 79-81 Available from: URL: http://www.wjgnet.com/2307-8960/full/v1/i2/79.htm DOI: http://dx.doi.org/10.12998/wjcc.v1.i2.79

INTRODUCTION

Infection with *Entamoeba histolytica* (*E. histolytica*) usually occurs by ingestion of contaminated water, unwashed fruits or vegetables. Faecal-oral transmission has also been described. An amoebiasis with bloody, mucousy stools with a frequency up to 40-50/d can result with intestinal pain, spasms and high fever[1].

As a resistant dormant body the amoebas can develop cysts and remain asymptomatic in the colon for years. For yet unknown reasons it can amount to a mutation of the amoebas' DNA leading to a change of the enzymatic pattern[2,3]. These enzymes may allow penetration of the amoeba into the intestinal mucous membrane sometimes with fatal outcome. A possible intestinal finding is a perfo-

ration of the colon. Furthermore dissemination of amoebas to other organ-systems is possible due to the entrance of amoebas into the bloodstream. Most frequently liver and heart as well as the central nervous system and the urinary system are affected[4,5].

Perforation of the colon as a result of an amoebic colitis is a seldom complication but typically carries a high morbidity and mortality[6-8]. On the European continent the incidence of this illness is extremely rare, yet the increasing globalisation of trade and services as well as migration result also in a globalisation of infectious diseases and therefore an increasing number of amoebic colitis in Europe.

The worldwide relevance of infections with *E. histolytica* can be evaluated by the numbers estimated by the World Health Organisation of yearly 50 million with about 100000 fatal courses.

CASE REPORT

Medical history and non-invasive diagnostic testing

A 65-year-old Turkish man presented to the emergency department with spasmodic abdominal pain that had increased over several days and was therefore hospitalized. At the time of admission his body mass index was 33.6 (height: 185 cm, weight: 115 kg). He had been living in Germany for 30 years and had not travelled to any other country during the past 2 years. The patient did not suffer from diarrhoea or fever and had no pre-existing conditions. There were no visits to the general practitioner during the past 6 mo.

Physical examination revealed the patient's general condition to be compromised with diffuse pain located throughout the abdomen and described as pressure. There were also peritoneal signs and muscular rigidity. The point of maximum tenderness was located in the right lower quadrant and midline. Peristalsis was reduced significantly; the rectal examination was without pathological findings.

The complete blood count was significant for leucocytosis (11000/L), the C-reactive protein was within the normal range with 0.7 mg/dL, and all other routine laboratory parameters were also without pathological findings.

Abdominal sonography revealed a narrow perihepatical margin of fluid. Abdominal X-rays in two planes did not show signs of free air or any typical findings of an ileus with the right colon stool-filled. Because of the clinical situation it was decided to utilize invasive diagnostics and invasive therapy if necessary.

Invasive diagnostic testing and therapeutic procedure

An emergency-laparoscopy was carried out on the day of the admission because of suspected perforated appendicitis. The intraoperative findings included a long-segment, covered perforation of the coecum and the right hemicolon accompanied by a 2 quadrant-peritonitis. Because of the seriousness of the intraoperative findings a switch to an open laparotomy became necessary.

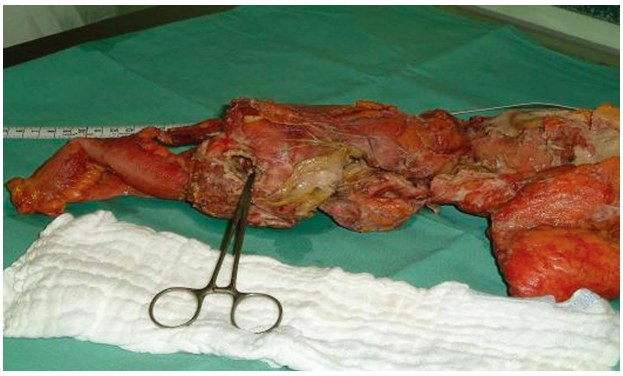

Figure 1 A right hemicolectomy with a R0-resection.

Following a median laparotomy the full extent of the patient's findings became evident: a massive necrotising inflammation of the hemicolon including perforation, plus a "wooden phlegmon" of the mesocolon reaching up to the retroperitoneum. Because of suspected sarcoma of the mesocolon, a right hemicolectomy with a R0-resection was performed accomplished after extensive mobilisation of the right colon and the colon transversum (Figure 1). This procedure was followed by an ileotransversotomy, an end-to-end anastomosis with Vicryl-single button suture seromuscular, extra mucous and in a single row.

Initial histopathological examination of formalin fixed colon dissection samples showed the characteristics of a low malignant Non-Hodgkin-lymphoma. Following further pathological examination could ascertain that the perforation was caused by a severe amoebic colitis followed by a granulomatous inflammation of the mesocolon. A diagnosis of malignant lymphoma was ruled out.

Postoperative course

The amoebic colitis was treated with metronidazole followed by paromomycin resulting in successful eradication of the amoebae. In addition methicillin resistant Staphylococcus aureus was cultured from intraoperative specimens. The patient was placed in contact isolation after the surgical intervention and provided with rehabilitation services. Repeated stool samples during the patient's stay in hospital were all negative for amoebic infection.

During the postoperative course the patient developed an infection of the laparotomy wound accompanied by symptoms of an ileus and had to undergo another laparotomy on the 5th postoperative day. This surgery revealed an abdominal wall abscess without intra-abdominal findings. The subsequent postoperative course was uncomplicated. After 63 d of stay in hospital the patient could be discharged fit and healthy.

DISCUSSION

The mechanism of infection in this case is not apparent. With amoebic infections being very uncommon in Germany one can speculate that the patient's occupation

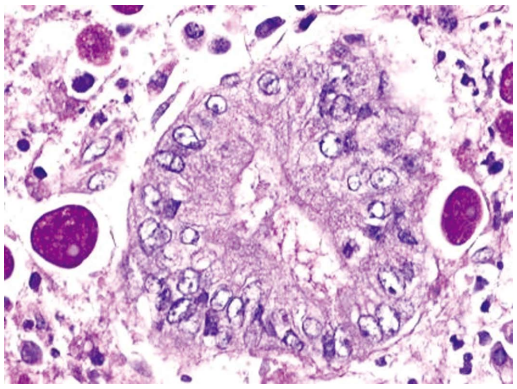

Figure 2 The intracellular phagocytosed erythrocytes, which are pathognomic for this kind of amoeba.

as a storekeeper for an airport company could have led to contact with contaminated materials or surfaces. In addition there is the possibility of this case representing a relapse. The patient could have been asymptomatically infected before his emigration to Germany or during visits to his home country (prevalence in Turkey: 15%)[9].

During laparotomy the intraoperative findings mimicked a sarcoma of the mesocolon. The diagnosis could not be assured until the final histopathological results were available: perforation because of a preexisting amoebic colitis. A granulomatous infection appearing as a "wood phlegmone" of the mesocolon has been described as a rare manifestation of infection with *E. histolytica*, which is the only pathogenic amoeba for humans. Figure 2 shows the intracellular phagocytosed erythrocytes, which are pathognomonic for this kind of amoeba.

Antibiotic therapy with metronidazole was recommended as first-line therapy in Germany at the time of hospital admission[10]. A Cochrane Review from 2009 suggests that tinidazole may be more effective[11]. If amoebas are found in the stool of asymptomatic individuals they are considered chronic carriers. Only patients, who are chronic carriers and near contact persons are considered notifiable cases in Germany.

Only a rare amount of case reports describing the *E. histolytica* induced symptoms of colitis or intestinal perforations due to wide necrosis of the intestine are existing in current scientific literature; in comparison to these cases our patient didn't suffer of fever or diarrhoea and underwent a successful inpatient treatment[1,12].

An ulcerous colitis can originate from an amoebic infection. Therefore stool samples for this pathogen should always be sent for microscopy and, in addition, if available for molecular diagnostic tests such as testing by polymerase chain reaction. Diagnostic imaging can not provide a sufficient contribution to the causality amoebic infection and colitis.

In the age of globalisation all providers in the health care systems are urged to acquaint themselves also with non-typical syndromes for the countries they work in order to reduce preventable morbidity respectively mortality rates.

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CASE REPORT

A vaginal drain of a pelvic abscess due to colonic diverticulitis

Marco Milone, Miguel Emilio Sosa Fernandez, Piero Venetucci, Paola Maietta, Loredana Maria Sosa Fernandez, Caterina Taffuri, Francesco Milone

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Abstract

Although well recognized for tubo-ovarian abscesses, we report, in our best knowledge, the first case of a vaginal drain of a pelvic abscess due to colonic diverticulitis. A 78-year-old patient presented with abdominal and pelvic pain, fever (39.3 ℃) and an elevated white blood cell count (18500/mL). After abdominopelvic computed tomography the patient was presumed to have a pelvic abscess, which developed as a complication of the sigmoid diverticulitis. Due to the numerous intervening structures that create obstacles to safe percutaneous access, we planned a trans-vaginal drain. A rapid recovery was obtained within 2 d from the procedure and, at present, the follow-up was uneventful after 18 mo. We believe that transvaginal drain of pelvic abscess could be a useful alternative, when percutaneous approach is not feasible.

Key words: Vaginal; Drain; Diverticulitis; Pelvic abscess; Echography

Core tip: Large diverticular abscesses (> 3 cm) should be treated by antibiotics and percutaneous drain. Abscess deep in the pelvis pose a unique problem because numerous intervening structures create obstacles to safe percutaneous access. Transvaginal drain of pelvic abscess could be an useful alternative, when percutaneous approach is not feasible.

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INTRODUCTION

Although well recognized for tubo-ovarian abscesses[1,2], we report, in our best knowledge, the first case of a vaginal drain of a pelvic abscess due to colonic diverticulitis.

CASE REPORT

A 78-year-old patient presented with abdominal and pelvic pain. Physical examination demonstrated fever (39.3 ℃) and mild tachycardia (120/min) with bilateral lower abdominal quadrant tenderness. Blood analysis revealed an elevated white blood cell count (18500/mL). The abdominopelvic computed tomography scan revealed a left sided collection with a prominent air-fluid level suggesting pelvic abscess, measuring 8 cm × 6 cm, close to the vagina. Multiple diverticula were identified and the sigmoid colon was lying around the collection with its borders that could not be distinguished from the abscess. The mesentery of the sigmoid colon was also found to be thickened due to inflammation (Figure 1).

The patient was presumed to have a pelvic abscess, which developed as a complication of the sigmoid di-

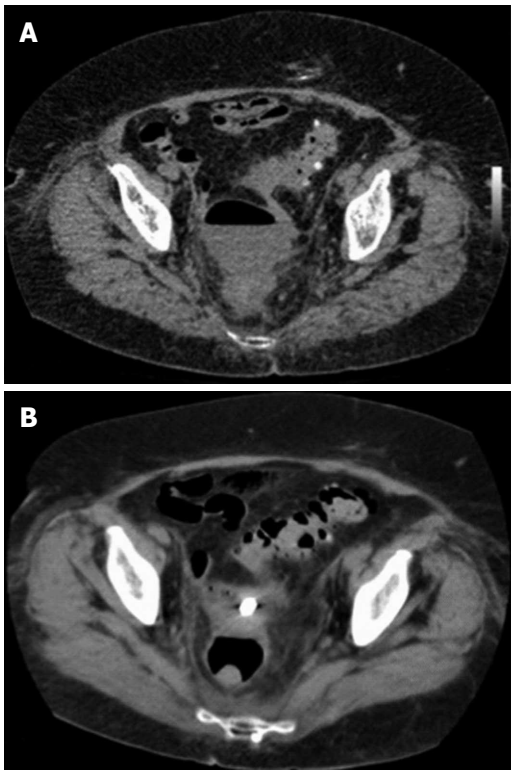

Figure 1 Abdominopelvic computed tomography. A: Before the procedure; B: After the procedure.

verticulitis, and, according to guidelines, we planned the drainage of the lesion[3]. However, due to the numerous intervening structures that create obstacles to safe percutaneous access, we planned a trans-vaginal drain.

The endovaginal ultrasound sonography (US) examination was performed using an end-fire endovaginal US probe with an attached needle guide. A puncture needle was introduced into the fluid collection under continuous US guidance and fluid from the cavity was aspirated with a syringe. A guidewire was introduced into the cavity *via* the puncture needle. Then a self-retaing pigtail catheter with a string lock was introduced over the guide wire into the cavity (Seldinger technique). The catheter was left *in situ* and irrigated three times per day.

A rapid recovery (normal temperature and leukocyte levels) was obtained within 2 d from the procedure (Figure 1). The catheter was removed after 2 wk, when the spontaneous output was clear and was less than 10 mL per day.

The short-term follow-up consisted of outpatient visits 7 to 10 d and 3 to 4 wk after operation. For long-term follow-up, a visit was scheduled and included an endovaginal US every 3 mo. At present the follow-up was uneventful after 18 mo.

DISCUSSION

Large diverticular abscesses (> 3 cm) should be treated by antibiotics and percutaneous drain. Percutaneous drain is the standard therapy in the absence of indications for immediate surgery[3]. However, abscess deep in the pelvis pose a unique problem because numerous intervening structures create obstacles for safe percutaneous access. These include pelvic bones, bowel, bladder, iliac vessels, and female reproductive organs. Alternative approaches to deep pelvic abscess include transvaginal, transrectal, transperineal and transgluteal punctures[4,5]. Transvaginal drainage has been described in several reports[1,2], but there has been no previous documentation of a vaginal drain of a pelvic abscess due to colonic diverticulitis.

In this case, rapid recovery was obtained with long-term disease-free survival, which is encouraging for its future use as an alternative drain of abscess due to diverticulitis.

Although further prospective studies evaluating the clinical usefulness of transvaginal drain of pelvic abscesses due to colonic diverticulitis are needed to give a definitive conclusion, we believe that transvaginal drain of pelvic abscess could be a useful alternative, when percutaneous approach is not feasible.

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CASE REPORT

A rare case of acute compartment syndrome after saphenectomy

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Author contributions: Milone M designed the report and wrote the paper; Venetucci P performed image diagnosis; Iervolino S, Taffuri C and Salvatore G contributed to the acquisition, analysis and interpretation of data; Milone F contributed to the final approval of the version to be published.

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Abstract

Saphenectomy is one of the most validated criteria to treat varicose veins of the lower legs. Although many complications were well described, little is known about compartment syndrome due to muscle ischemia caused by constrictive bandages applied after stripping of varicose veins. We presented a case of successful conservative treatment of compartment syndrome after saphenectomy. Rehabilitation was found effective in improving fatigue, stiffness and tenderness showing the effectiveness of the combined conservative-rehabilitative treatment. However conservative treatment could not be considered the treatment of choice in daily practice. A severity score assessment of compartment syndrome should be useful to assess to which patients is allowed to not perform fasciotomy.

Key words: Compartment; Saphenectomy; Varicose veins; Muscle ischemia; Rehabilitation

Core tip: A case of successful conservative treatment of compartment syndrome after saphenectomy. Rehabilitation was found effective in improving fatigue, stiffness and tenderness showing the effectiveness of the combined conservative-rehabilitative treatment.

Milone M, Venetucci P, Iervolino S, Taffuri C, Salvatore G, Milone F. A rare case of acute compartment syndrome after saphenectomy. *World J Clin Cases* 2013; 1(2): 84-86 Available from: URL: http://www.wjgnet.com/2307-8960/full/v1/i2/84.htm DOI: http://dx.doi.org/10.12998/wjcc.v1.i2.84

INTRODUCTION

Saphenectomy is one of the most validated criteria to treat varicose veins of the lower legs.

Although many complications were well described[1], little is known about compartment syndrome due to muscle ischemia caused by constrictive bandages applied after stripping of varicose veins[2]. We presented, in our best knowledge, the first case of a successful conservative treatment of compartment syndrome after saphenectomy.

CASE REPORT

A 51-year-old man underwent saphenectomy because of chronic varicose veins of the lower right leg. His past medical history was unremarkable. The stripping technique involved the interruption of the femoral-saphenous junction, stripping of the great saphenous vein, multiple removals of the tributary veins of the saphena and ligation of the extrafascial perforating veins. No intra-operative complications occurred.

In the immediate post-operative period (6 h from the surgery), pain and tension in the operated leg appeared. Moreover, a complete function impairment of the leg was evident. The dressing was removed when the patients started complaining of these symptoms.

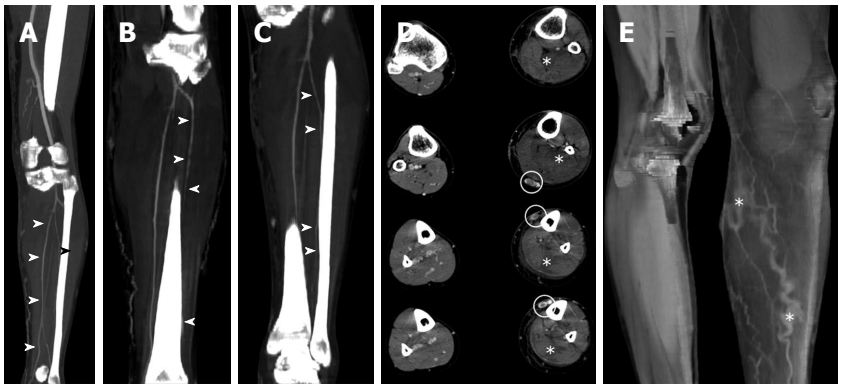

Figure 1 A computed tomography of the lower leg revealed a swollen compartment without vascular lesions and hypertension at the venous end of the capillary beds. A, B, C: The reconstruction MIP/3D that showed the viability of posterior tibial (A), anterior tibial (B) and interosseal artery (C) (marked by headarrows); D: The swollen muscle compartment (marked by *); E: The presence of hypertension at the venous end of the capillary beds (marked by *).

In the first post-operative day the physical examination demonstrated in the operated leg pain on passive stretching of the muscle, tense, swelling, sensory loss and paralysis. His blood analysis revealed a very elevated creatin kinase activity (50200 U/mL).

A computed tomography of the lower leg revealed a swollen compartment without vascular lesions and hypertension at the venous end of the capillary beds (Figure 1). The color-duplex sonography confirmed the absence of artery or vein thrombosis.

The patient was presumed to a compartment syndrome and the measurement of intracompartmental pressure was not performed for the clinical evidence according to validated criteria[3]. Decompression by fasciotomy was indicated as the primary treatment but the patient denied his consent to the procedure. Elevation of the limb was used in an attempt to reduce pressure. Two weeks later, a conservative rehabilitative treatment was started.

The patient underwent a 2 mo-lasting twice/daily comprehensive rehabilitation, defined as systematic multidisciplinary treatment given by physician, occupational therapist and exercise physiologists. The rehabilitation program included physical therapy with exercise aiming at improves aerobic fitness, muscle strength and mobility and occupational therapy. This 2-mo treatment brought to a satisfactory functional recovery. Outpatient rehabilitation program continued for 3 mo thereafter. Complete function recovery was obtained after 6 mo.

DISCUSSION

Varicose veins in the lower extremities are a sign of chronic venous disorder due to valvular incompetence of the superficial venous system. This problem has a high prevalence (a third of the population) and generates an important number of surgical interventions (one of the most frequently performed operation in the world), as shown in the Edinburgh Study[4,5]. Surgical treatment provides symptomatic relief and significant improvements in quality of life in patients with uncomplicated varicose veins. Stripping is one of the validated methods to treat varicose veins. It is a good procedure in terms of simplicity, speed safety, and because the technique is well standardized[6-9].

Although many complications were well described after stripping including the most frequently wound infection, nerve injury, vascular injury and venous thromboembolism[1], little is known about compartment syndrome due to muscle ischemia caused by constrictive bandages applied after stripping of varicose veins[2].

Acute compartment syndrome is a condition in which raised pressure within a closed fascial space reduces capillary perfusion below a level necessary for tissue viability. The initial injury leads to swelling within a compartment. This causes an increase in intracompartmental pressure with compressive closure of the thin-walled venules resulting in hypertension at the venous end of the capillary beds. Eventually arteriolar compression occurs, leading to muscle and nerve ischaemia with muscle infarction and nerve damage. Measuring intracompartmental pressure is only necessary when the clinical signs of compartment syndrome are unclear, in an unconsciousness or uncooperative patient, in a young child or when the clinical syptoms and signs are equivocal. The primary treatment should be decompression by fasciotomy as soon as possible. Elevation of the limb is sometimes used as a temporary measure in an attempt to reduce pressure[3].

Danner *et al*[2] describe four patients suffering from lower limb compartment syndromes, which were caused by constrictive bandages applied after stripping of varicose veins. The dressing was erroneously only partially removed, when the patients started complaining of severe pain and tension in the operated legs. The damages varied from extended irreversible neuromuscular defects to lesser functional handicaps. Three patients had corrective surgery. The clinical follow up over several years showed little improvement and secondary complaints were frequent.

At variance with this previous experience we have described the first case of conservative treatment without secondary complaints and a complete recovery.

Although, in our report, rehabilitation was found effective in improving fatigue, stiffness and tenderness showing the effectiveness of the combined conservative-

rehabilitative treatment, further studies are needed to evaluate the role of rehabilitation program in such disease.

However conservative treatment could not be considered the treatment of choice in daily practice. A severity score assessment of compartment syndrome should be useful to assess to which patients is allowed to not perform fasciotomy. More in details it would be important to know when a conservative treatment could be performed safely. Further more representative research are needed to assess this issue.

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CASE REPORT

Synchronous rectal and esophageal cancer treated with chemotherapy followed by two-stage resection

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Abstract

We report a case of 61-year-old male who had synchronous advanced rectal cancer involving the urinary bladder massively associated with multiple liver metastases, and esophageal cancer successfully treated by neoadjuvant chemotherapy followed by two-stage resection. Although complete resection of each of the lesions was considered possible by performing anterior pelvic exenteration, liver resection, and esophagectomy, it might be impossible for the patient to endure the stress of all of these operative procedures at once. Therefore, we planned to perform staged treatment with prioritizing consideration. First, we instituted chemotherapy with the FOLFOX (oxaliplatin + fluorouracil + leucovorin) plus cetuximab regimen, which could adequately control both rectal and esophageal cancer. After 6 cycles of chemotherapy, high anterior resection combined with cystoprostatectomy and lateral segmentectomy plus partial hepatectomy was performed followed by staged esophagectomy with three-field lymph node dissection. It was possible to use oxaliplatin and cetuximab safely as neoadjuvant therapy not only for advanced rectal cancer but for esophageal cancer, and it was effective.

Key words: Rectal cancer; Esophageal cancer; Neoadjuvant chemotherapy; Cetuximab; Oxaliplatin

Core tip: In case with synchronous multiple cancers, it is sometimes difficult to identify the origin especially when liver and/or pulmonary lesions have a possibility of metastases, or to decide on a course or priority of the treatment. FOLFOX + cetuximab (Cet) therapy could provide a favorable control of not only rectal origin accompanied by liver metastases but also esophageal cancer, which made possible to undergo two-stage curative resection. FOLFOX + Cet regimen might be a useful option for such refractory rectal and esophageal cancer.

Utsunomiya S, Uehara K, Kurimoto T, Hirose K, Fukaya M, Takahashi Y, Taguchi Y, Itatsu K, Nagino M. Synchronous rectal and esophageal cancer treated with chemotherapy followed by two-stage resection. *World J Clin Cases* 2013; 1(2): 87-91 Available from: URL: http://www.wjgnet.com/2307-8960/full/v1/i2/87.htm DOI: http://dx.doi.org/10.12998/wjcc.v1.i2.87

INTRODUCTION

In the last decade, remarkable advances have been achieved in chemotherapy for colorectal cancer as a result of the

advent of the novel anticancer drugs such as irinotecan and oxaliplatin (L-OHP), and the molecularly targeted drugs such as vascular endothelial growth factor inhibitors and epidermal growth factor receptor (EGFR) inhibitors. Cetuximab (Cet), one of the EGFR inhibitors, has a strong cytoreductive effect and survival benefit in *KRAS* wild-type colorectal cancer, and it has not only been incorporated in treatment strategies together with L-OHP as palliative therapy for unresectable metastatic colorectal cancer, but as perioperative chemotherapy for resectable advanced cancer or conversion chemotherapy for unresectable metastatic diseases[1,2].

Although, more than 50% of esophageal cancers are adenocarcinoma in Western countries, approximately 90% of esophageal cancers are squamous cell carcinoma (SCC) and the half of them are located in the mid-thoracic esophagus in Japan[3]. The gold standard of treatment for esophageal cancer in Japan is radical esophagectomy with three-field lymph node dissection, and neoadjuvant chemotherapy with a 5-fluorouracil (5-FU) plus cisplatin regimen (FP) is recommended for clinical stage Ⅱ/Ⅲ patients[4]. In Western countries, some regimens including L-OHP or Cet have been reported to be safe and effective for advanced esophageal cancer[5-8].

We report a case of synchronous advanced cancers of the rectum and the esophagus, successfully treated by neoadjuvant chemotherapy with a FOLFOX (L-OHP + 5-FU + leucovorin) plus Cet regimen followed by two-stage surgical resection.

CASE REPORT

A 61-year-old male patient was admitted for a urinary tract infection. An abdominopelvic computed tomography (CT) revealed an intrapelvic mass that had invaded the bladder and multiple hepatic lesions with weak contrast enhancement (Figure 1). On colonoscopy, a circumferential ulcerative lesion was seen in the upper rectum (Figure 2). Biopsy revealed a moderately differentiated adenocarcinoma, and *KRAS* genotyping showed that it was the wild type. On esophagogastroscopy, a depressed lesion with a little surrounding elevation was observed in the mid-thoracic esophagus, and biopsy resulted in a diagnosis of SCC (Figure 3). Based on the results of these examinations, a diagnosis of synchronous advanced cancers consisting of a rectal cancer involving the urinary bladder associated with multiple liver metastases (cT4b, cN0, cM1, Stage Ⅳ), and an esophageal cancer (cT2, cN0, cM0, Stage Ⅰ B) were made.

First, after creating a loop colostomy with the sigmoid colon in order to control the urinary tract infection, which had developed as a result of a bladder fistula, and to remove the rectal obstruction, we instituted neoadjuvant chemotherapy with the FOLFOX + Cet regimen. An abdominopelvic CT after 6 cycles of chemotherapy showed marked regression of both the primary lesion in the rectum and the liver metastases (Figure 4). Although no marked change in the size of the esophageal cancer was observed during esophagogastroscopy, flattening of the lesion was noted. Five months after diagnosis, high anterior resection combined with cystoprostatectomy, diverting ileostomy, neobladder reconstruction, and lateral segmentectomy plus partial hepatectomy were performed with 6-wk completion of chemotherapy. The operative time was 981 min, and blood loss was 1555 mL. The pathological diagnosis of the both lesions was moderately differentiated adenocarcinoma with invasion of the urinary bladder (ypT4b, ypN0, ypM1, Stage Ⅳ). There was moderate vascular invasion, but the surgical margins were negative. According to the Japanese Classification of Colorectal Carcinoma, the histological effect of the chemotherapy was Grade 1b at the primary site and Grade 2 at the site of the liver metastases. Although wound infection and urinary tract infection occurred as postoperative complications, they treated conservatively, and the patient was discharged on postoperative day 15.

Because recovery of the patient's general condition was delayed due to postoperative watery diarrhea, ileostomy closure was performed. Even though 5 mo had passed since the completion of chemotherapy, esophagogastroscopy showed no evidence of an increase in size of the esophageal cancer, and it was concluded that the disease had been adequately controlled (Figure 3B). Esophagectomy with three-field lymph node dissection and anterosternal reconstruction with gastric tube were performed 4 mo after rectal resection. The operative time was 584 min, and blood loss was 1027 mL. The pathological diagnosis was poorly differentiated SCC (ypT1b, ypN1, cM0, Stage Ⅱ B). The histological effect of chemotherapy was minimal with slight cancer cell degeneration or necrosis. Postoperatively, anastomotic leakage occurred, but it was improved by conservative management, and the patient was discharged on postoperative day 70.

Eleven months after rectal resection, pulmonary node with elevation of carcinoembryonic antigen (CEA) was pointed out and right lower lobectomy was performed. Pathological findings showed it metastasis from rectal adenocarcinoma. The patient is alive without cancer 15 mo after pulmonary resection.

DISCUSSION

In case with synchronous multiple cancers, it is sometimes difficult to identify the origin especially when liver and/or pulmonary lesions have a possibility of metastases, or to decide on a course or priority of the treatment. When the origin of liver or pulmonary lesions is unclear, there are several solution strategies. Biopsy is the most reliable method for a definite diagnosis. However, biopsy occasionally causes a future disseminated diseases, therefore it might be avoided in cases having possibility of curative resection. The increasing level of tumor markers is sometimes helps us to diagnosis. Another promising option is chemosensibility. The good response to chemotherapy is helpful to make diagnosis. In this case, if the liver tumor came from the esophageal cancer, FOLFOX and Cet

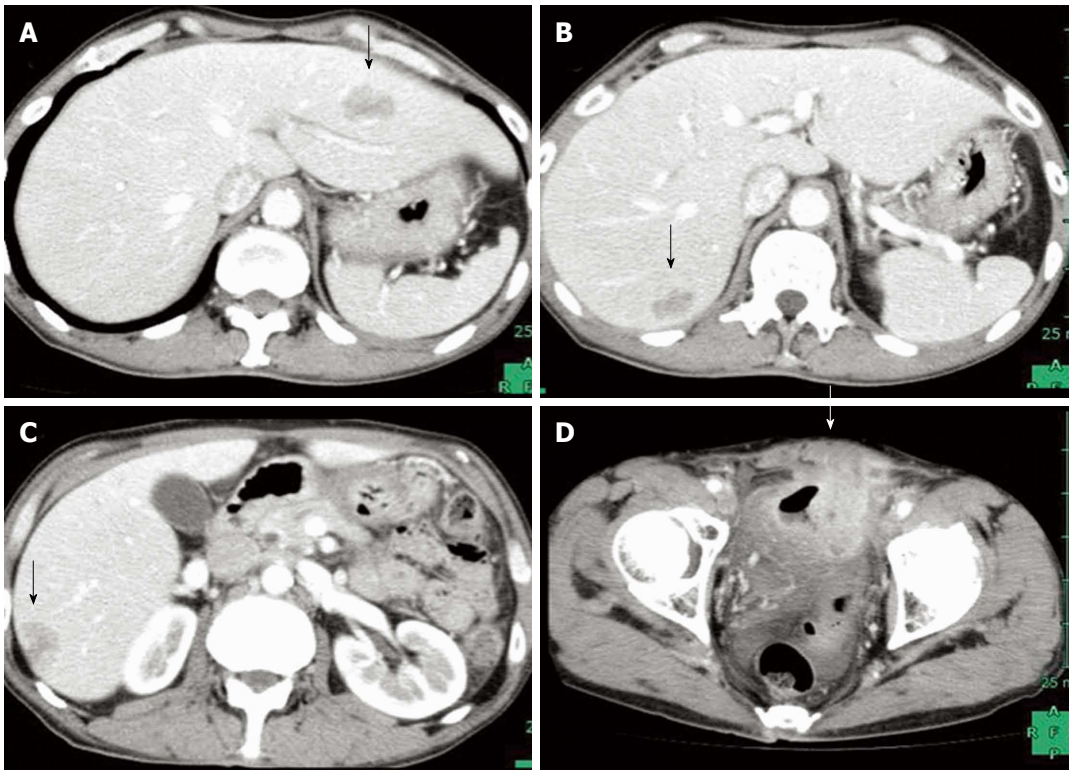

Figure 1 Computed tomography before treatment showed multiple liver metastases (arrows) and a primary upper rectal tumor that had invaded the urinary bladder. A, B: Multiple liver metastases; C, D: A primary upper rectal tumor.

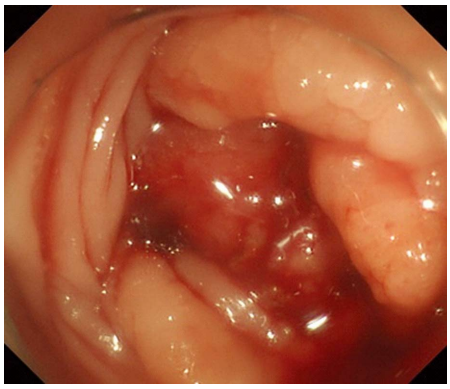

Figure 2 Colonoscopy revealed a circumferential lesion in the upper rectum and the lumen was almost completely obstructed.

might be invalid. However, in general, surgical treatment in curative intent has not indicated for the patients with liver metastases from esophageal squamous carcinoma or with colorectal liver metastases which progress in spite of aggressive chemotherapy. As a result, shrinkage of the liver tumor enabled us to perform curative resection and to confirm the origin to be the rectum. In case of progression in any tumor, palliative treatment should be one of the options. The pulmonary recurrence is also considered to come from the rectal cancer, because of increasing level of CEA. If the level of CEA was within normal range, initial chemotherapy or biopsy might be selected.

R0 resection of each of the lesions in this patient with two cancers was considered possible by performing anterior pelvic exenteration, liver resection, and esophagectomy. However, it might be impossible for the patient to endure the stress of all of these operative procedures at once. Therefore, we planned to perform staged treatment with prioritizing consideration. A 5-year overall survival (OS) rate of approximately 45% had been reported after surgical resection of liver metastases from colorectal cancer[9], as opposed to a rate of 60% after initial surgical treatment of clinical T1/2 SCC of the thoracic esophagus[10]. Additionally, the patient's complaints are another important part. In this case, the patient had repeated urinary tract infection and no esophageal obstructions. Therefore, we decided to treat the colorectal cancer and liver metastases preferentially.

The only potentially curative treatment for patients with liver metastases from colorectal cancer is surgical resection, but the postoperative recurrence rate has been reported to be approximately 75%, which is too high. To improve the survival rate or reduce the recurrence rate, new surgical strategies combined with developed systemic anticancer agents have recently been evaluated. As a result of EORTC40983 study, reported by Nordlinger *et al*[1], curative surgery combined with 6-mo perioperative chemotherapy is now generally recommended for patients with resectable liver metastasis, especially for chemotherapy naïve patients. However, the optimal chemotherapy regimen remains uncertain. A phase Ⅱ trial of the efficacy of Cet in combination with either the FOLFOX regimen or FOLFIRI regimen (CELIM study) was conducted in patients with unresectable liver metas-

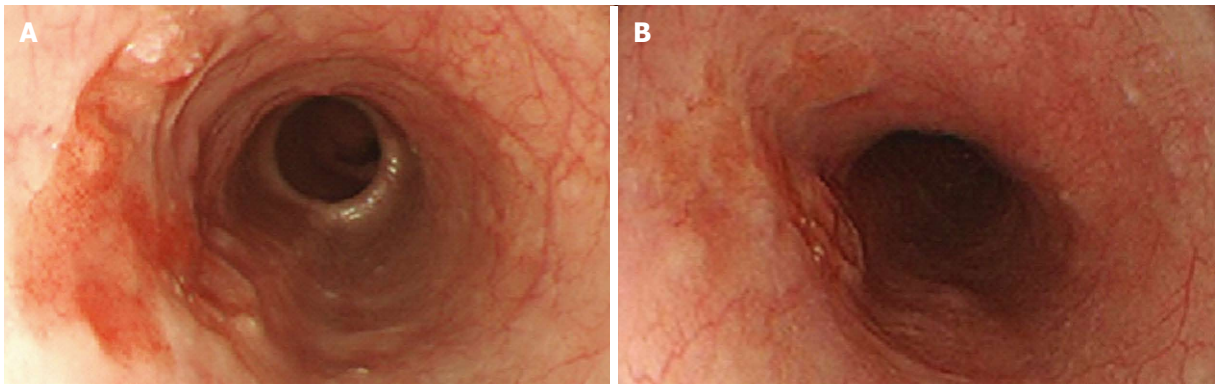

Figure 3 On esophagogastroscopy, a depressed lesion with a little surrounding elevation was observed in the mid-thoracic esophagus, and biopsy resulted in a diagnosis of squamous cell carcinoma. A: Esophagogastroscopy before treatment revealed a shallow depressed area in the middle third of the thoracic esophagus; B: After 6 cycles of chemotherapy, the esophageal lesion had flattened slightly, and there was good disease control.

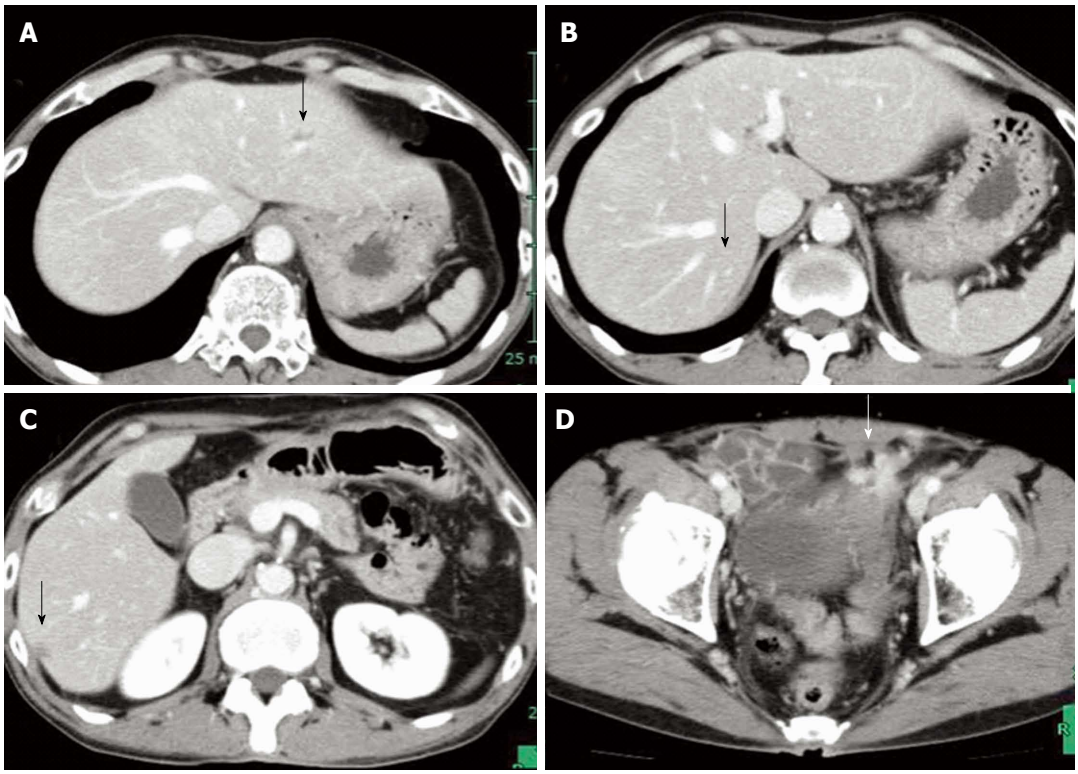

Figure 4 The computed tomography findings after 6 cycles of mFOLFOX6 plus cetuximab chemotherapy showed a good response in both the liver metastases (arrows) and primary lesion. A, B: Liver metastases; C, D: Primary lesion.

tasis. Since the overall response rate (68%) and R0 resection rate (38%) in the Cet plus FOLFOX regimen group were superior to those (57% and 30%, respectively) in the Cet plus FOLFIRI regimen group[2], we treated our patient with the mFOLFOX6 + Cet regimen in anticipation of obtaining the maximum tumor regression effect and survival benefit.

The greatest concern with this treatment strategy was rapid progression of the esophageal cancer as a result of the decreased immune capacity associated with the highly invasive operation, which consist of extended pelvic surgery and liver resection. Therefore, controlling the esophageal disease during this period for rectal cancer treatment was extremely important. A Japanese randomized phase Ⅲ trial (JCOG 9907) compared preoperative chemotherapy to postoperative chemotherapy for patients with clinical stage Ⅱ/Ⅲ SCC of the esophagus, and the results showed that the 5-year OS of the preoperative chemotherapy group was significantly superior to that in the postoperative chemotherapy group (55% *vs* 43%, $P = 0.04$)[4]. Based on the results of this trial, the standard treatment for advanced thoracic esophageal cancer has changed from surgery followed by postoperative chemotherapy to preoperative chemotherapy followed by surgery in Japan. In Western countries, modern cytotoxic agents and targeted drugs have been reported to be effec-

tive and safe in patients with advanced esophageal cancer. L-OHP is a promising antineoplastic platinum derivative with a more favorable toxicity profile than cisplatin. Response rates of to the FOLFOX regimen and CapeOx (capecitabine + LOHP) regimen have been reported to be 39%-44%, suggesting be that they might be equivalent to the current standard FP regimen[5-7]. Lorenzen *et al*[8] conducted a randomized phase Ⅱ trial that investigated the activity and safety of adding Cet to the standard FP regimen (FP + Cet). The overall response rate and disease control rate were 19% and 75%, respectively, in the FP + Cet group, and superior to the rates in the FP alone group (13% and 57%, respectively). Moreover, there was no evidence that L-OHP or Cet aggravated the known toxicities.

In our patient, objective clinical and pathological response was stable disease, which indicated FOLFOX + Cet was not necessarily effective. However, rapid progression of esophageal cancer could be avoided, although it was untreated for 6 mo between the last administration of the chemotherapy and the esophageal cancer surgery. FOLFOX + Cet might suppress the growth of esophageal cancer.

In conclusion, we have reported the case of synchronous advanced rectal cancer involving the urinary bladder massively associated with multiple liver metastases, and esophageal cancer. FOLFOX + Cet therapy could provide a favorable control of not only rectal origin accompanied by liver metastases but also esophageal cancer, which made possible to undergo two-stage curative resection. FOLFOX + Cet regimen might be a useful option for such refractory rectal and esophageal cancer.

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CASE REPORT

Squamous papilloma in the external auditory canal: A common lesion in an uncommon site

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Abstract

Squamous papillomas (SPs) are common benign neoplastic lesions, usually affecting the skin, oral mucosa, upper aerodigestive tract and genital organs. However, SPs of the external auditory canal (EAC) are rarely reported in the English literature. In this report, we present a 19-year-old female with left EAC SP. The etiology, natural course, diagnosis and management of this disease are discussed, with a brief review of the literature.

Key words: Squamous papilloma; External auditory canal; Human papilloma virus; Koilocytosis; Review

Core tip: Squamous papillomas (SPs) are common benign neoplastic lesions. However, SPs of the external auditory canal (EAC) are rarely reported in the English literature. A case of EAC SPs is presented here with a discussion and brief review of the literature.

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INTRODUCTION

Squamous papillomas (SPs) are benign neoplastic lesions usually affecting the skin, oral mucosa, upper aerodigestive tract and genital organs. It is believed that the human papilloma virus (HPV) is an etiological factor of papillomas; thus, they are also called viral warts. Cutaneous SPs are a very common skin condition; however, SPs of the external auditory canal (EAC) are rarely reported in the English literature although they commonly occur in the southern Chinese population. This indicates that SPs of EAC might be an ethnically specific disease. There are several cutaneous neoplastic lesions similar to SPs in appearance. The definitive diagnosis of SPs relies on histopathological examination. Here, we present a clinical case and briefly review the literature concerning the etiology, natural course, diagnosis and management of EAC papillomas.

CASE REPORT

The presented case is a 19-year-old young Taiwanese fe-

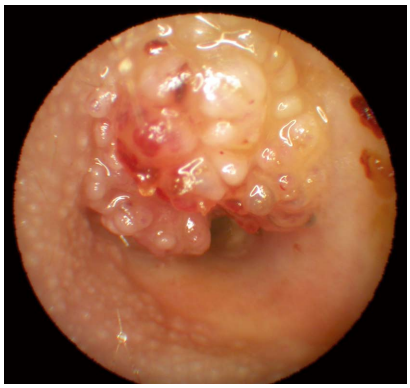

Figure 1 Pre-operative findings of the left external auditory canal. A multiple granular mulberry-like neoplastic lesion located on the superior aspect of left external auditory canal.

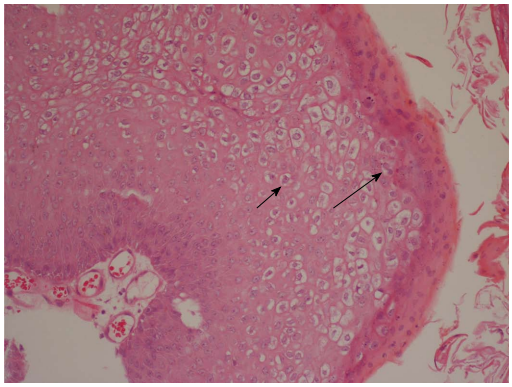

Figure 2 Histopathological findings (hematoxylin and eosin, × 200). Histopathological examinations revealed the characteristic features of hyperkeratosis, papillomatosis, parakeratosis, acanthosis and koilocytosis. Koilocytosis indicates diseased cells caused by human papilloma virus infection. Characteristic squamous cells containing peri-nuclear clearing with condensation of peripheral cytoplasm are the typical pictures of koilocytic cells. Irregular, raisin-shaped nucleus (short arrow) and bi-nuclei cells (long arrow) may be present.

male who visited our office with a history of left external ear canal blockage for several months. Surgical intervention for bilateral external ear canal tumors had been performed in another institute about 2 mo previously. Unfortunately, not long after the surgical procedure, left ear auditory canal fullness recurred and she visited our clinic for evaluation and management. She did not bring the report of the pathological examinations in the previous institute when she came to our office and merely described that they were benign lesions, as related by the previous surgeon.

Under otoscopic examination, an irregular, granular, mulberry-like neoplastic lesion was found, located at the cartilaginous part of the left EAC (Figure 1), and non-specific findings were noted in the contralateral ear. A surgical removal with ordinary instruments under microscope was arranged and performed.

The histopathological examination showed hyperkeratosis, papillomatosis, parakeratosis, acanthosis, koilocytosis and inflammatory infiltrates in the upper dermis, characteristic features of SPs (Figure 2). The wound healed well without specific complications during the post-operative follow-up (Figure 3).

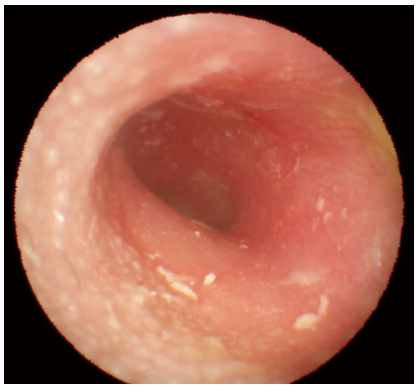

Figure 3 Post-operative follow up conditions. One month after the surgical removal was performed. The wound healed well without scar contracture or recurrence.

DISCUSSION

Etiology

SPs are very common skin lesions. There is a high prevalence of SPs in the EAC. Papillomas, accounting for up to 78.9% of benign ear tumors, have been reported, with 95.2% of ear papillomas located in the EAC[1]. However, SPs of the external ear have been reported infrequently in the English literature, although they occur commonly in the southern Chinese population. This is probably secondary to the cultural ritual of mechanical cleansing with unsterilized re-used instruments by which infectious agent inoculation may take place[1-3]. Surgical procedures of the ear may also be a route for the dissemination of SP[4]. It is generally assumed that SPs are caused by HPV infections and SP is considered to be a viral wart[5]. Cutaneous SPs are caused most frequently by HPV types 1, 2, 3, 4, 27 and 57[6,7]. However, HPV types 6 and 11 were found to be the main causative agents for SPs of the EAC[1,8]. HPV types 6 and 11 are the most common pathogens for oral papillomas, recurrent respiratory papillomatosis and anogenital warts[7]. Like the disseminations of HPV types 6 and 11 in the aerodigestive tract and genital papillomas, vertical infection of HPV from the mother at delivery might be the primary route of the virus acquisition. The hair follicles have been suggested as possible reservoirs[7]. SPs are rare in children younger than 5 years of age; however, EAC SP in a 3-year-old patient has been reported[9].

Natural course

EAC SP is a benign lesion which is generally solitary and has a low risk of bony destruction. It grows slowly and may cause a mechanical obstruction of the EAC, leading to pressure necrosis of the adjacent bone or conductive hearing impairments[10]. Involvement of the tympanic membrane is seldom reported[3,4]. Viral warts of the skin are not harmful and usually go away without any treat-

ment[6]; however, the possibility of spontaneous resolution of EAC SPs is still unclear. The common causative HPV types are quite different in skin warts (types 1, 2, 3, 4, 27 and 57) from that in EAC SPs (types 6 and 11); the behaviors may be different with distinct HPV types. Although EAC SPs are generally believed to be mainly caused by the "low-risk" HPV types 6 and 11, malignant transformation has been reported[11].

Diagnosis

Most neoplastic lesions of the EAC are benign and up to 80% of these lesions are papillomas[1]. Grossly, SPs commonly appear as a round or oval, flat papule with a broad base on the skin or mucous membranes. Histologically, they arise from stratified squamous epithelium and are characterized by the growth of multiple papillary fronds (papillomatosis), hyperkeratosis, parakeratosis, acanthosis, infrequent mitosis and rare nuclear atypia[1,11]. Squamous cells with clear cytoplasm, dense dark nuclei and occasionally bi-nuclei are called koilocytic cells, which indicate an infection of the cells by HPV[8].

Inverted papilloma (IP) in the EAC is similar to SP in gross appearance. However, IP has a distinct behavior from SP and should be carefully differentially diagnosed. IP, or Schneiderian papilloma inverted type, is an aggressive benign neoplastic lesion with a tendency for local recurrence and association with carcinoma. Microscopically, IP is characterized by the digitiform proliferation of squamous epithelium into the underlying connective tissue stroma[12]. HPV types 6, 11, 16 and 18 are the most common causative agents associated with IP and types 16 and 18 are more commonly associated with malignancy[9,12,13].

Treatments

Surgical removal of the lesion remains the most effective method in the treatment of EAC SPs. Several methods, including cryosurgery, electrodesiccation with/without curettage and carbon dioxide laser, have been described and are believed to be effective[5]. The major complication of surgical treatment is possible scarring and subsequent stenosis of the EAC. Insertion of a silastic tube in the canal as a stent and meticulous postoperative care to prevent wound infection may provide uncomplicated healing[9].

Some agents are reported to be effective in topical treatments for viral warts. Salicylic acid and cryotherapy have shown significant effects in the clearance of cutaneous warts, especially in the hand and foot areas. Dinitrochlorobenzene, 5-fluorouracil, intralesional bleomycin, intralesional interferon, photodynamic therapy and intralesional antigen have been tried in previous studies but without much evidence for their effectiveness[6]. The effects of the above topical treatments for SPs in the EAC are not clear; hence, topical methods are not recommended as primary management for EAC SPs.

Radiotherapy for SPs in the EAC was tried in an earlier report[3]. The authors reported an excellent result for the treatment of recurrent SP in the EAC, middle ear and the mastoid cavity by radiotherapy. However, radiotherapy carries potential risks for malignant transformation of the cells and other complications, such as hearing impairment, EAC stenosis and vestibular, trigeminal and facial nerve neuropathies[14,15], so it is not recommended as the primary treatment method.

There are HPV vaccinations to prevent anogenital warts and cancers[16]. These vaccines mainly protect against HPV types 6, 11, 16 and 18, the major types causing cervical cancer, anogenital wart/cancer, recurrent respiratory papillomatosis and EAC SP. These vaccines have been approved for use of prevention of genital cancers by the United States Food and Drug Administration since 2006[16,17]. The vaccines are not indicated to prevent cutaneous and oral mucosal SPs; however, along with increasing HPV vaccination rates, the decrease of SP prevalence would be expected.

SP in the EAC is a common benign neoplastic lesion located in an uncommonly reported site. It may be caused by the infection of HPV. Surgical removal remains the treatment of choice for EAC SPs.

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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]

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

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