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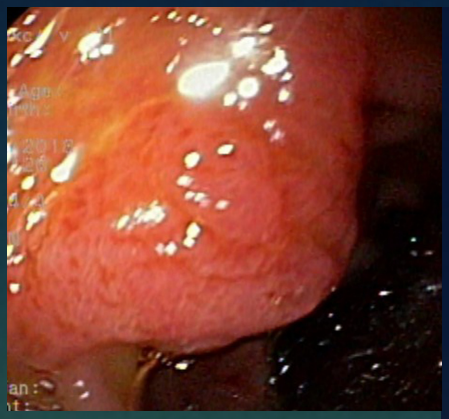

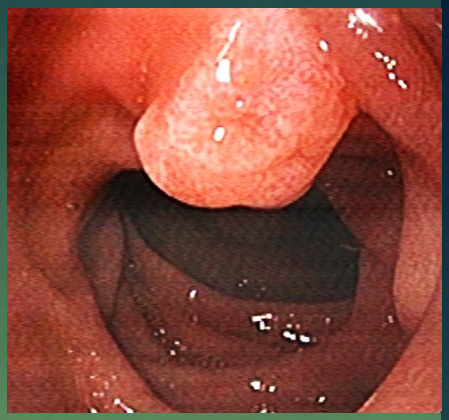

Clinical cases in gastroenterology and digestive endoscopy

A. C. G.

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Article: Endoscopic treatment of minor papilla adenomas: Report on two cases
Courtesy of the authors: Gustavo Adolfo Reyes-Medina, Germán David Carvajal-Patiño, Diana Lizcano Zea, Luis Carlos Sabbagh-Sanvicente.

Words from the editor

Diego Aponte Martín, MD[1]

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Video

Best regards from the editorial team of the Revista Colombiana de Gastroenterología, we are pleased to be able to communicate with you on a permanent basis to provide you with new information. This time, we would like to present to you this supplement, named *Clinical Cases in Gastroenterology and Digestive Endoscopy*, as a publication of the first semester of 2021 in our Journal.

One of the purposes of good practices in journal publishing is to avoid the obsolescence of the contents of articles submitted to be considered in the editorial process; thus, taking into account the large number and importance of clinical case reports submitted to our journal, we wanted them to have a timely publication in a special issue. This supplement contains 20 very interesting and entertaining clinical cases to be read, enjoyed and shared, which, hopefully, give rise to concerns and exchange of knowledge among colleagues.

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Importance of HER2 status determination in advanced gastric cancer: A case study

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Abstract

Advanced gastric cancer (AGC) is an entity that encompasses two distinct clinical situations: locally advanced unresectable gastric cancer and metastatic disease, with chemotherapy as the standard treatment. HER2 overexpression can occur in 9% to 38% of the cases with this disease and has been the first predictive biomarker used for trastuzumab-targeted therapy in patients with advanced gastric and gastroesophageal tumors. This article presents a patient with AGC and positive HER2 treated with conventional chemotherapy plus trastuzumab as targeted therapy with adequate clinical response.

Keywords

Advanced gastric cancer; Treatment; Trastuzumab; HER2.

INTRODUCTION

Gastric cancer is a public health problem. Every year there are more than 1 million new cases and about 850 000 deaths are caused by it worldwide. According to Globocan 2018, in Colombia it has been estimated that there 7419 new cases per year, being the third most frequent cancer (7.3%) and the most common cause of death from cancer in the country with 5505 deaths (13.7 %) (1). In Western countries, approximately 50 % of the patients with gastric cancer who visit the doctor for the first time are diagnosed with metastatic cancer, and in these cases, the overall survival rate at 5 years is less than 5 % (2).

There are several classifications of stomach cancer. According to one of such classifications, gastric cancer is classified as a localized cancer (stages 0, I, II and III; resectable) and as advanced and metastatic cancer (stage IV, unresectable). The latter (advanced gastric cancer) involves two clinical situations: locally advanced unresectable stomach cancer and metastatic cancer (3).

Chemotherapy based on the combination of platinum agents plus fluoropyrimidines such as 5-fluorouracil (5FU) plus cisplatin (FP) or capecitabine plus cisplatin (XP) (4) is the first-line therapy for advanced gastric cancer. These chemotherapy regimens have been shown to improve overall survival, progression-free survival, and quality of life when compared with best supportive care (3).

Human epidermal growth factor receptor 2 (HER2) is a member of the epidermal growth factor receptor (EGRF) family that has been associated with increased division, proli-

feration, differentiation, and apoptosis of tumor cells in breast and stomach cancer, as well as in other solid tumors (5).

Several studies have shown that HER2-positive breast carcinomas are more aggressive compared to HER2-negative breast carcinomas and that they are associated with an increased risk of local growth and distant metastasis (6). HER2 is also overexpressed in gastric and gastroesophageal junction carcinomas (6, 7). HER2 overexpression in gastric cancer could result in tumors with an increased proliferative and invasive capacity (6).

Several studies have evaluated the relationship between HER2 status and the prognosis of patients with gastric cancer. Some have shown that having a HER2-positive cancer is associated with a significantly worse prognosis, while others have not found any association; however, overall survival time was longer in patients with HER2-positive cancers compared to those with HER2-negative tumors. Because of this, the relationship between HER2 status and prognosis remains controversial (6).

HER2 is an important predictive biomarker in gastric and gastroesophageal junction tumors. The analysis of HER2 status through immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH) techniques using different scoring methods suggest that HER2 overexpression occurs in 7 %-34 % of gastric tumors. Furthermore, the favorable results derived from the ToGA study correlate with the level of HER2 overexpression (8, 9).

After finding out the occurrence of HER2 overexpression in patients with advanced gastric cancer, adding trastuzumab, a first-line therapy anti-HER2 antibody drug that has been shown to improve efficacy outcomes, to chemotherapy has been recommended (7, 10). Currently, result accuracy and standardization in HER2 testing is crucial to identify the target population that can be treated with this drug and benefit from it (11).

The introduction of trastuzumab has allowed the establishment of a new disease: HER2-positive gastric cancer, similar to what happened in the case of HER2-positive breast cancer (6). Currently, knowing HER2 status in patients with stomach cancer is vital to make decisions aimed at ensuring that the patient is given the best possible treatment (6). For this reason, testing HER2 status in all patients with advanced gastric or gastroesophageal junction cancer is important (6).

The objective of this paper is to report the case of a patient with HER2-positive advanced and metastatic gastric cancer treated with chemotherapy plus trastuzumab and in which favorable a clinical response and survival were obtained.

CASE PRESENTATION

This is the clinical case of a 68-year-old male from Putumayo, Colombia, who had experienced dyspepsia, a sense of stomach fullness, hyporexia, nausea, and an approximately 10 kg weight loss during four months. The patient reported having a history of smoking (he had been a heavy smoker and had stopped smoking 25 years before the time of consultation) and a family history (father) of pancreatic cancer. On physical examination an extremely thin and emaciated patient was found; no supraclavicular lymphadenopathy, abdominal masses or ascites were found. An initial esophagogastroduodenoscopy, performed in another health institution, reported a thickening of the folds in the fundus and body of the stomach with decreased distensibility and multiple superficial ulcerated lesions. The histopathology report, made in the institution where the patient was referred from, confirmed he had a 30% intestinal type poorly differentiated, infiltrating and ulcerated adenocarcinoma with mixed histologic pattern, predominantly diffuse with signet ring cells. Furthermore, a contrast-enhanced abdominal CT scan performed in the institution where he was referred from showed an abnormal neoplasm-like thickening of the stomach wall in the fundus and body regions with ulceration, as well as adenomegalies in the gastrohepatic ligament without hepatic or peritoneal involvement. A cT3N1M0 clinical staging was made.

Based on the preoperative assessment, the patient was taken to surgery with the intention of performing a gastrectomy. During the surgical procedure, a gastric lesion with wall thickening in the body and lesser curvature of the stomach and a matted lymph node in the lesser curvature and multiple metastatic-like liver nodules were found; the lesion was classified as stage IV T3N1M1 cancer. After the surgery was completed, a new computed axial tomography (CT) scan was performed and the surgical findings were confirmed, as multiple 10 mm focal hypodense lesions were observed in segments IV and VI of the liver (**Figure 1A** and **B**), with diffuse stomach wall thickening and a 31 x 17 mm matted lymph node.

Since this was an advanced metastatic stage cancer, chemotherapy with XP (cisplatin + capecitabine) chemotherapy protocol was started and after the first cycle was completed, a liver biopsy report performed in another institution was received in the treating institution informing the following findings: involvement of the liver by a HER2-positive (3+) metastatic gastric adenocarcinoma. For this reason, trastuzumab was added to the established chemotherapy regimen, a combination the patient received for 4 more cycles, when treatment was suspended due to toxicity characterized by asthenia, adynamia, hyporexia, nausea, emesis and diarrhea (up to grade 3 diarrhea). At that time, new chest and abdominal CT scans were performed, showing persistent thickening of the gastric chamber, lymphadenopathy and absence of the liver lesions with apparent complete response of the liver nodules (**Figure 1C**).

Capecitabine plus trastuzumab chemotherapy regimen was continued, but cisplatin administration was suspended. After 2 additional chemotherapy cycles, a laparoscopy was performed and no macroscopic evidence of liver metastases or peritoneal carcinomatosis was found, so the surgical board decided that surgical management with a potentially curative intent was the best treatment option.

Before undergoing the new surgical interventions, the patient was administered two trastuzumab monotherapy doses. Finally, the patient was brought to the operating room on November 27, 2017, 10 months after the initial diagnosis was reached, where a total gastrectomy with D2 lymphadenectomy was performed. The final pathology report of the surgical specimen reported a post-neoadjuvant stage (tumor regression grade 2) mixed-pattern gastric adenocarcinoma with tumor-free resection margins and 3/33 positive lymph nodes for metastasis; a HER2 positive (3+) status was also described (**Figure 2**).

After surgery, the patient was given 4 adjuvant chemotherapy cycles consisting of capecitabine, oxaliplatin and trastuzumab, and 4 more trastuzumab monotherapy cycles, for a total of 18 perioperative trastuzumab cycles.

In a new chest and abdominal CT scan performed 5 months after the surgery (April 11, 2018) the following findings were reported: liver of normal size, morphology, density and contour, without focal lesions and other tumor growth lesions (**Figure 1D**). In subsequent follow-up visits the patient was found to be asymptomatic with mild hearing loss and skin pigmentation changes resulting from chemotherapy. In addition, no tumor-like lesions were observed in a positron emission tomography (PET scan) performed on September 17, 2018 (**Figure 3**). Likewise, according to a MRI performed on October 28, 2018, there was no evidence of suspected malignant lesions at the esophagojejunal anastomosis and of lesions in the liver parenchyma. 18 months after the initial diagnosis, the

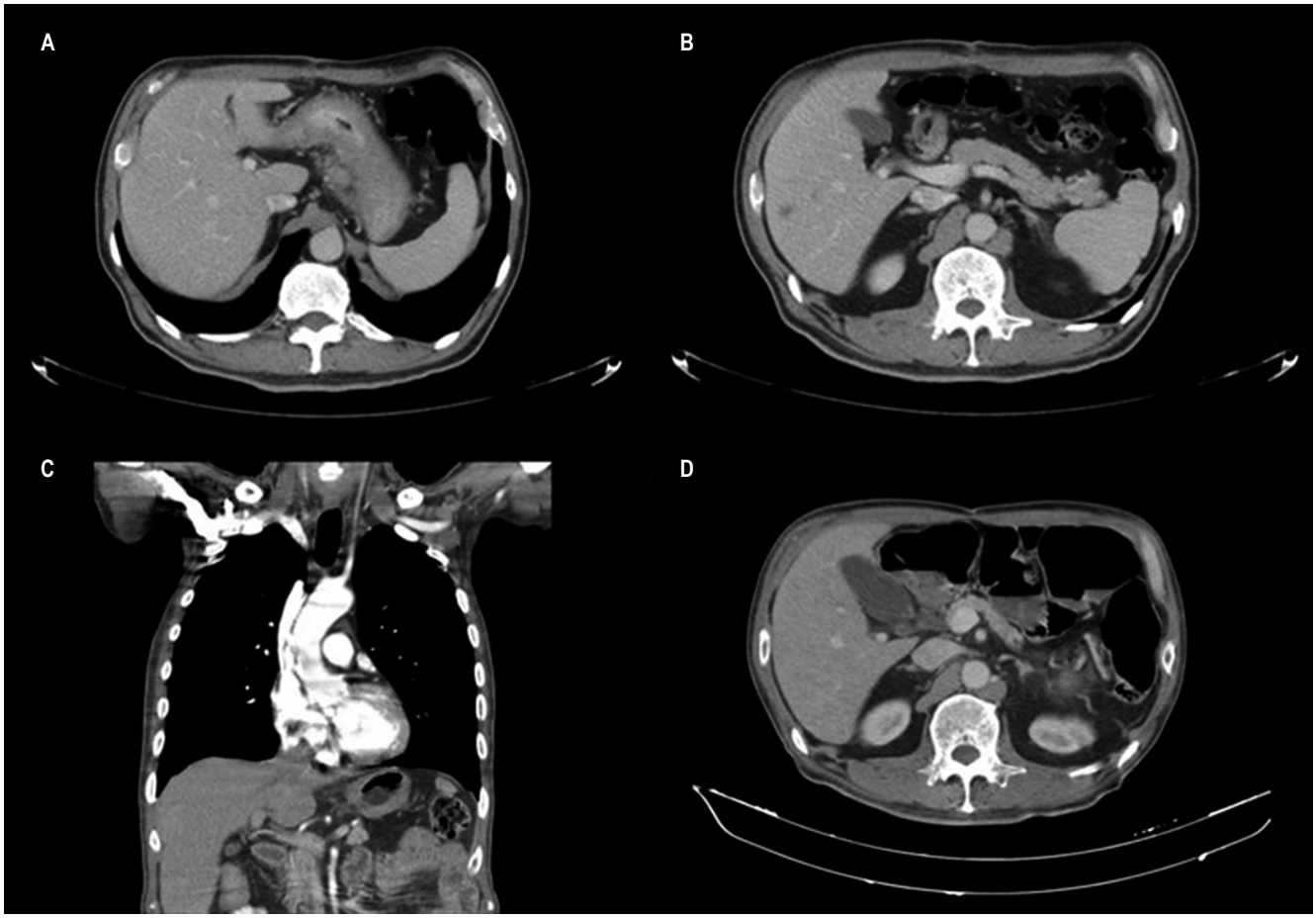


Figure 1. CT scan studies performed for tumor pathology follow-up purposes. **A.** Diffuse stomach wall thickening plus a 31 x 17 mm matted lymph node with extramural extension. **B.** Up to 10 mm focal hypodense hepatic lesions in segments IV and VI of the liver. **C.** Decreased gastric chamber thickening and adenopathies, there are no hepatic nodules or new lesions. **D.** Post gastrectomy changes, normal liver size, morphology, density and contour, without focal lesions or other tumor growth lesions.

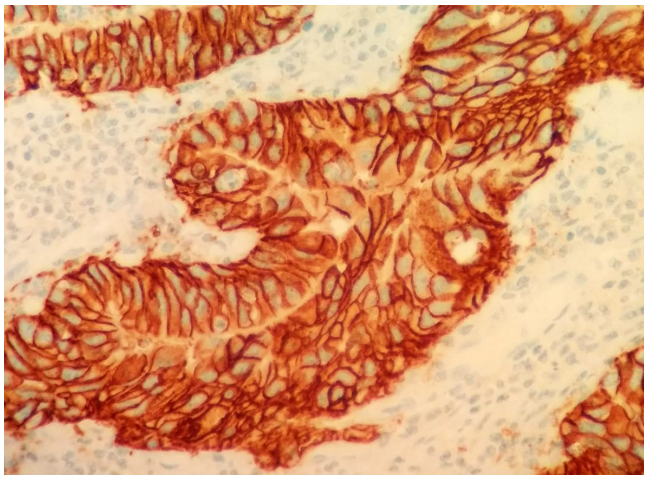


Figure 2. HER2-positive (3+) gastric adenocarcinoma. IHC 40x (in the specimen obtained from the total gastrectomy).

patient is asymptomatic and does not show signs of cancer recurrence. The aforementioned imaging studies, treatment plan and follow-up are shown in **Figure 4**.

DISCUSSION

There are several classifications systems used for gastric cancer and they are still under discussion. The classification systems proposed by the American Joint Committee on Cancer (AJCC) and the Union for International Cancer Control (UICC) are the most frequently used. These systems are based on the staging system, where the penetration of the lesion into the stomach wall (T), lymph node involvement (N) and metastasis (M) are assessed, and stomach cancer is classified as early and advanced (12). Other systems include histopathological classification, such as Lauren's classification (intestinal, diffuse and mixed type adenocarcinoma), Nakamura's classification, the classification by the World Health Organization (WHO), the endoscopic macroscopic classification of the lesion described for both early and advanced gastric cancer (Bormann), and the genomic or molecular classification (2).

On the other hand, unresectable gastric cancer is a term widely used in the clinical setting, however this a concept with highly variable clinical implications, for it does not represent the true extent of the disease.

When the treatment of stomach cancer is defined by its stage, it is classified as localized (stages 0, I, II and III resectable) and as advanced and metastatic cancer (stage IV unresectable). For this reason, the relevant literature describes gastric cancer as disease that involves two different clinical situations: locally advanced unresectable stomach cancer and metastatic cancer (3).

Patients with advanced or metastatic gastric cancer have a very poor prognosis, with a 5-year survival rate <4%. Chemotherapy is the standard treatment in these cases; however, with the emergence of targeted therapies now it is possible to choose the treatment based on the molecular characteristics of the disease (2, 8).

In 1965, Pekka Lauren, based on histopathological criteria, classified stomach cancer into 2 types: intestinal and diffuse. Before the discovery of HER2 and the introduction

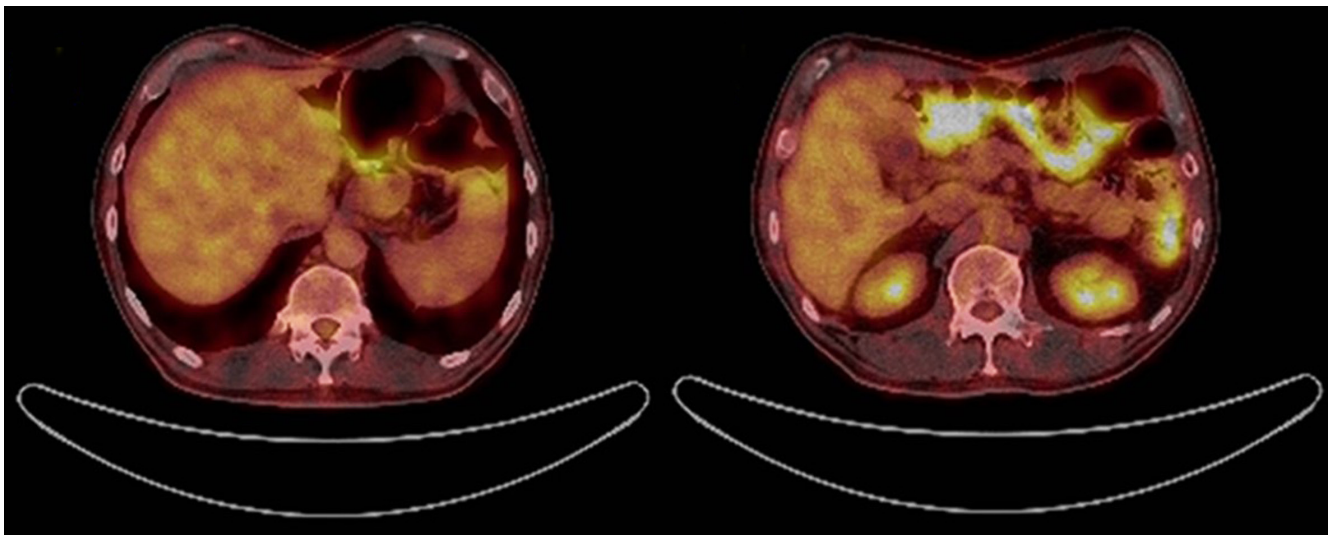
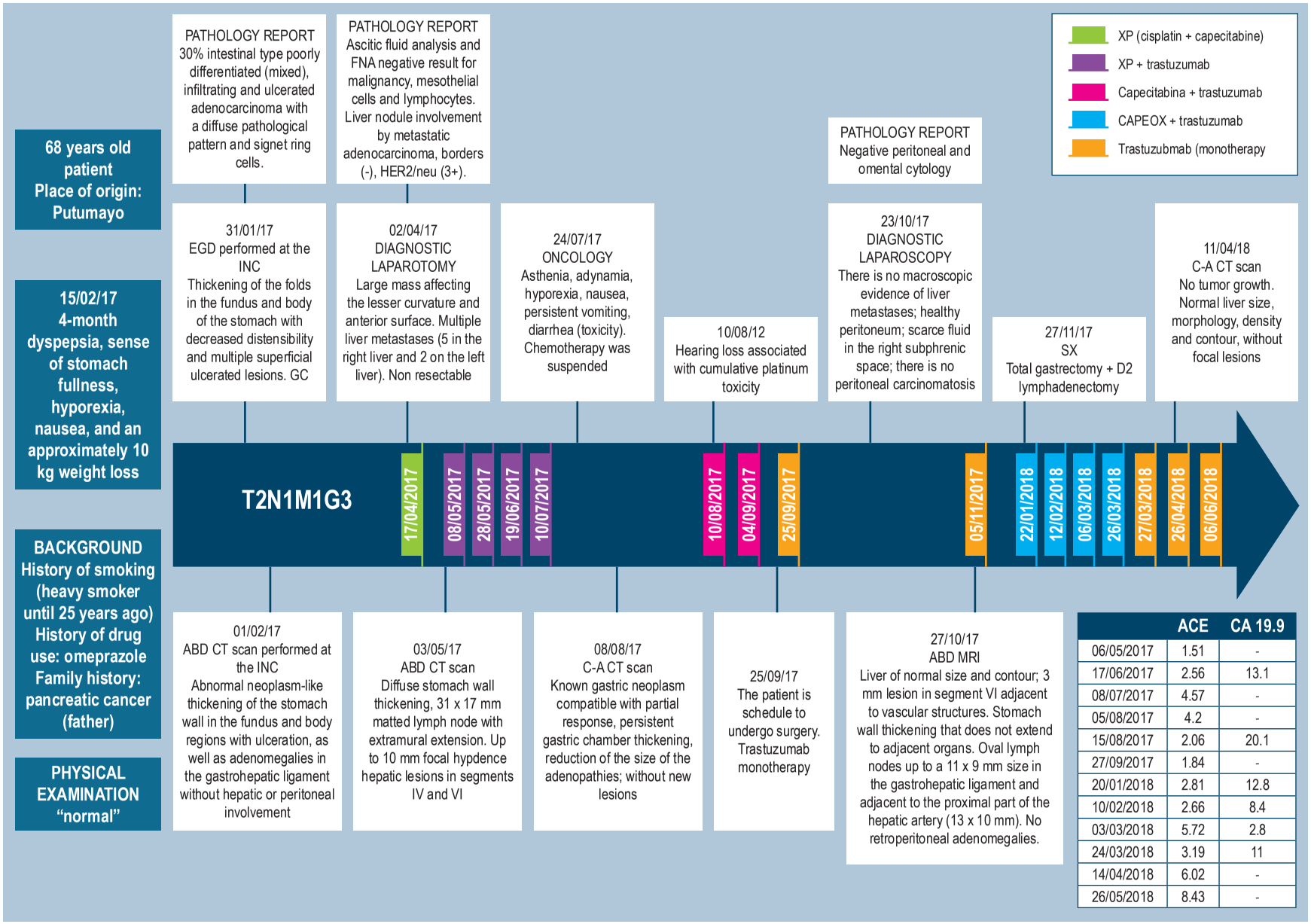


Figure 3. PET scan performed after gastrectomy and where the absence of tumor-like lesions is evidenced.



	ACE	CA 19.9
06/05/2017	1.51	-
17/06/2017	2.56	13.1
08/07/2017	4.57	-
05/08/2017	4.2	-
15/08/2017	2.06	20.1
27/09/2017	1.84	-
20/01/2018	2.81	12.8
10/02/2018	2.66	8.4
03/03/2018	5.72	2.8
24/03/2018	3.19	11
14/04/2018	6.02	-
26/05/2018	8.43	-

Figure 4. Timeline of the clinical case in which the initial management approach, the studies performed, the treatment the patient was given and follow-up of the patient are outlined. ABD: abdominal; FNA: fine needle aspiration; CEA: carcinoembryonic antigen tumor marker; CA 19-9: cancer antigen 19-9 tumor marker; SX: surgery; EGD: esophagogastroduodenoscopy or upper gastrointestinal endoscopy; GC: gastric cancer; INC: Instituto Nacional de Cancerología (National Cancer Institute of Colombia); MRI: magnetic resonance imaging; C-A: chest and abdomen.

of trastuzumab into clinical practice, there were no predictive biomarkers that allowed guiding the treatment of this type of cancer (7).

HER2 is a receptor tyrosine kinase that belongs to the EFGR family and that is encoded by the ERBB2 proto-oncogene located in chromosome 17, which plays a very important role in cell differentiation, survival, apoptosis and proliferation (6). There has been an increasing interest in this epidermal growth factor receptor 2, also known as HER2/neu, HER2, c-er-B2 and ErbB2 (13, 14).

HER2, being a co-receptor, does not have a ligand, as the other members of the EGRF family do (**Figure 5**). Homodimerization causes a conformational change of the receptor that stimulates HER2-coupled intracellular signaling pathways that occur either through the mitogen-activated protein kinase (MAPK) pathway, which is associated with tumor proliferation, migration, differentiation or angiogenesis, or through the PI3K-AKT-mTOR pathway, related to tumor survival and anti-apoptotic signaling (**Figure 5**) (13, 15).

HER2 is overexpressed in different classes of tumors that promote cell proliferation, tumor progression and metastasis. HER2 overexpression was first detected in gastric cancer by Fukushige et al. in 1986 (16). The frequency of HER2 overexpression in stomach cancer varies considerably in different studies from 6% to 30% (6). In an attempt to measure this variability, the researchers responsible for the TOGA study carried out a validation study to measure HER2 status in people with advanced gastric cancer using IHC and FISH techniques. Bearing this in mind, tissue samples from 3807 patients were collected in 24 countries and then analyzed using IHC and FISH. HER2 status was defined as positive (IHC 3+, or FISH+) based on cell membrane staining patterns or gene amplification in surgical specimens or biopsy samples, respectively (6). HER2 overexpression (HER2 positive status) was associated with being male and having well- and moderately-differentiated intestinal-type tumors (6).

The criteria for defining HER2 overexpression differ between breast and stomach cancer due to tumor biology inherent differences and to differences in the expression pattern (6, 9). Compared to breast cancer, stomach cancer exhibits different staining characteristics such as high incidence of tumor heterogeneity (defined as > 10% positive staining of

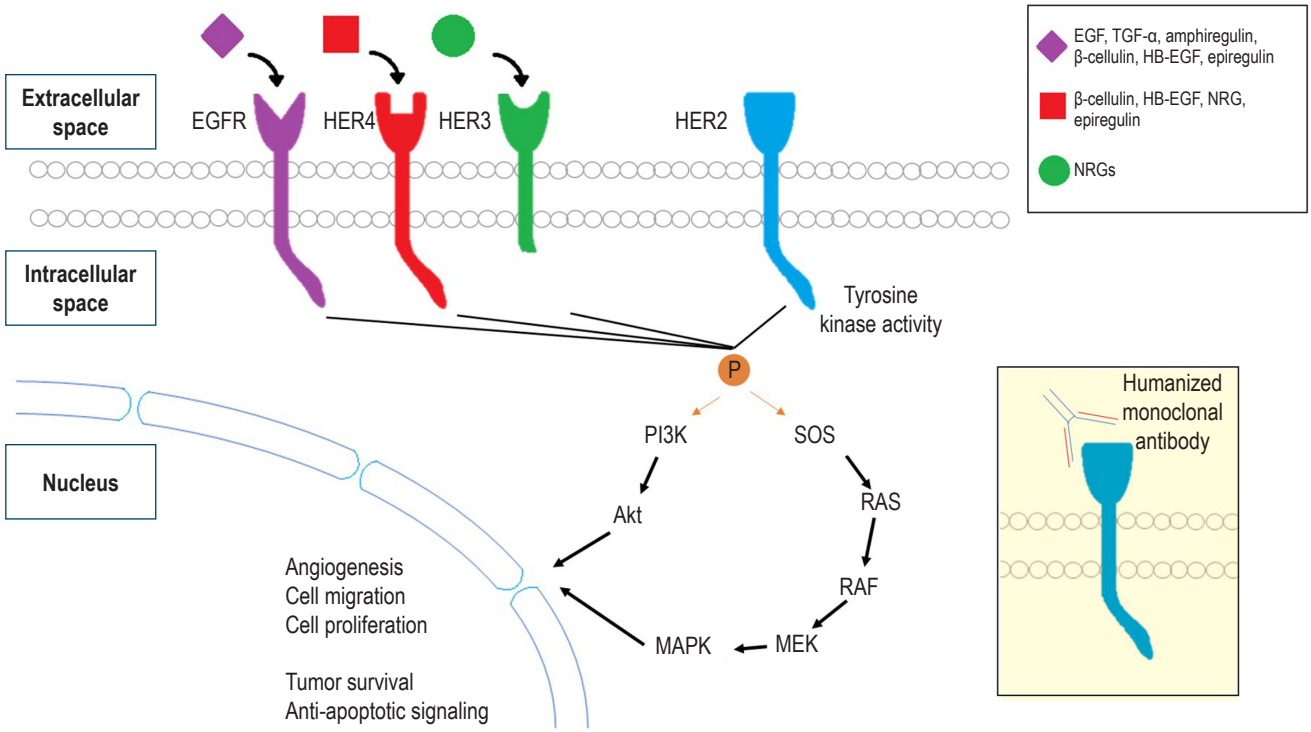


Figure 5. Interaction between receptors with tyrosine kinase activity. The different receptors are outlined and the different ligands that are related to each receptor are listed in the upper right corner. HER2 does not have specific ligands, so it must bind to the other receptors to trigger the intracellular signaling pathways that will act on tumor proliferation and survival. Trastuzumab inhibits the interaction between HER2 and the other members of the receptor family. Tka: tyrosine kinase activity; HB-EGF: heparin-binding epidermal growth factor; NRG: neuregulin; PI3K: phosphatidylinositol-3-kinase; TGF-α: transforming growth factor-alpha. Made by the authors.

cells or only focal staining of tumor cells in groups of more than 5 cells) in up to 30% of HER2-positive cases. Another key difference with breast cancer is that in HER2-positive gastric carcinomas are usually found in the intestinal-type glands and may show incomplete, basolateral or lateral staining, and all these are considered as positive results when using IHC. For this reason, specific protocols for HER2 testing in gastric cancer have been developed and standardized, and following these recommendations is imperative (2, 9).

Given these differences in terms of expression between breast and stomach cancer, an appropriate scoring system was developed exclusively for gastric tumors. This system, proposed by Hofmann et al., has been adopted and is specific for both gastric tumors and surgical specimen biopsies (2, 17).

Intratumoral heterogeneity also appears to have contradictory results regarding HER2 expression in primary tumor and metastatic lesions specimens. Previous studies have found significant differences when HER2 expression is analyzed in whole tissue sections and in small tissue samples. Thus, analyzing HER2 expression in more than one sample or in all available specimens and, if possible, in metastatic lesions specimens, is recommended. Taking this into account, surgical specimens in patients with HER2-negative biopsy results should be also analyzed in order to increase the possibility of finding HER2-positive tumors (17). Several gastric tissue biopsies must be performed, ideally between 6 and 8 fragments. In this regard, the German guidelines recommend a minimum of 8 samples (6, 18, 19). IHC test must be performed as the initial test, while molecular tests such as FISH (CISH or DISH) must be used to reevaluate 2+ or equivocal IHC test results (2, 6, 9).

Based on the results of the TOGA study, trastuzumab use was approved to treat HER2-positive gastric cancer, which is defined as IHC 3+ or FISH positive in the United States and Japan. In contrast, in Europe, HER2-positive gastric cancer is defined as IHC 3+ or as IHC 2+ plus FISH-positive (6).

The guidelines for HER2 status testing developed by the Japanese Society of Pathology recommend performing HER2 testing routinely in patients with metastatic or recurrent gastric cancer at the time of diagnosis (6, 9).

The algorithm of the test developed to determine HER2 status includes performing the IHC test first and then the FISH test in case of patients with a IHC 2+ result (**Figure 6**) (17).

Trastuzumab is a humanized monoclonal antibody that selectively binds to HER2. It is indicated for the treatment of HER2-positive breast and gastric tumors (11). In 2010 the European Medicines Agency (EMA) and the Food and Drug Administration (FDA) approved its use based on the overall survival benefit it offers to patients with metastatic gastric cancer or gastroesophageal junction cancer and in which HER2 overexpression has been determined by means of an accurate and validated measurement (9, 11).

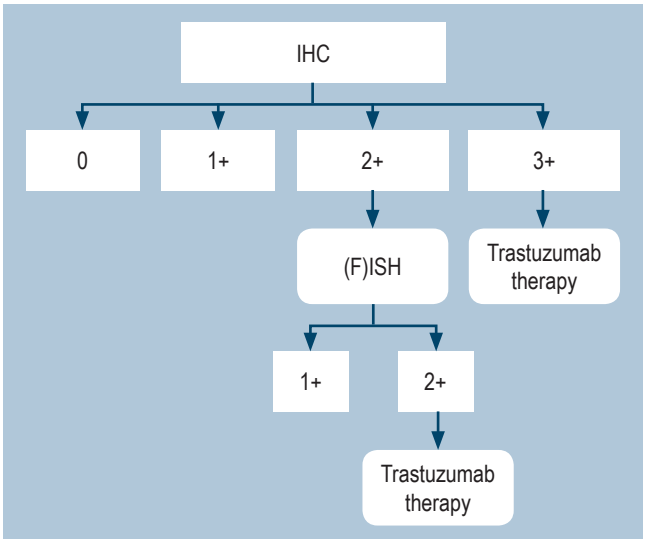


Figure 6. Histopathological algorithm to determine HER2 overexpression (18). Taken from: Lordick F et al. J Cancer Res Clin Oncol. 2017;143(5):835-841.

The TOGA study (20), published in 2010, was a prospective phase III study where patients with HER2-positive advanced gastric or gastroesophageal junction cancer were randomized into two groups: trastuzumab plus chemotherapy and chemotherapy alone. The chemotherapy regimen consisted of 6 cycles administered every 3 weeks. Trastuzumab was administered at a dose of 8 mg/kg on day 1 of the first cycle and then it was administered at a 6 mg/kg dose every 3 weeks until disease progression, unacceptable toxicity, or consented withdrawal. A total of 3803 patients were considered for being included in the study. The characteristics of both the patients allocated to the trastuzumab plus chemotherapy (n = 294) and chemotherapy alone (n = 290) groups were similar, including age, sex, chemotherapy regimens, tumor site (stomach and gastroesophageal junction). Furthermore, in both groups, 97% of patients had metastatic cancer and slightly less than half were classified as FISH + /IHC 3+ cancer (45% vs. 43%).

Overall survival, which was the primary outcome considered by the study, was significantly longer in patients in the trastuzumab plus chemotherapy group compared to those in the chemotherapy alone group, with a 2.7-month increase (13.8 months vs. 11 months). Progression-free survival was also longer in the trastuzumab plus chemotherapy group (6.7 months vs. 5.5 months). A 47% overall response rate was observed in the trastuzumab plus chemotherapy group (complete response 5%, partial response 42%). Likewise, response duration was longer in the trastuzumab plus chemotherapy group (6.9 months vs. 4.8 months) (20).

Patient subgroup analysis also showed that overall survival was longer in patients with high HER2 expression, as determined by IHC and FISH (IHC 3+ or IHC 2+ plus FISH positive) than in those with low HER2 expression (IHC 0 or 1+ plus FISH positive) (6, 20). According to these results, trastuzumab therapy is recommended for patients with IHC 3+ or IHC 2+ plus FISH positive (high HER2 expression) cancer (6).

The results of this study show that the combination of chemotherapy plus trastuzumab significantly improves overall survival in patients with HER2-positive advanced gastric or gastroesophageal junction cancer compared to chemotherapy alone, and that said improvement was particularly significant in patients with high HER2 expression. It is worth noting that trastuzumab administration did not increase the incidence of adverse events associated with chemotherapy, and that the frequency of cardiac events was low (20).

In addition, several case reports have shown favorable outcomes associated with trastuzumab when it has been used as part of perioperative chemotherapy in gastric cancer (16, 21). Some patients have experienced pathologic complete response.

In the case reported here, the patient was diagnosed with HER2-positive overexpression based on the biopsy report of the specimen taken from the liver metastatic lesion by means of laparotomy. The patient's gastric pathology report sent from the institution where he was referred from did not provide any information regarding HER2 status, and since this was an advanced stage cancer case due to gastric lesion with liver metastases, the patient was given standard chemotherapy with capecitabine plus cisplatin; however, once his HER2 status was known, trastuzumab was added to the treatment plan. This drug (trastuzumab) combined with chemotherapy (fluoropyrimidine and platinum) prolongs overall survival in patients with unresectable HER2-positive gastric cancer (2, 20).

Given the favorable response of the patient to the treatment consisting of the disappearance of the liver lesions, which was confirmed through imaging studies and a laparoscopy, a curative-intent total gastrectomy with D2 lymphadenectomy was performed. HER2 overexpression result was positive in the surgical specimen biopsy. After the surgery, the patient also received trastuzumab monotherapy and the disease was controlled for 18 months from the initial diagnosis, as a negative result was reported in the PET scan.

This allows understanding the importance of determining HER2 status in patients with advanced gastric cancer; also, the fact that the introduction of trastuzumab allowed the establishment of a new disease (HER2-positive gastric cancer), similar to the case of HER2-positive breast cancer, stands out (4, 5). Patients with advanced cancer with HER2 overexpression benefit from anti-HER2 therapy with trastuzumab (2).

In Colombia, the morbidity and mortality burden of gastric cancer is high, and more than one decade has passed since targeted therapies were developed. However, studies addressing this specific field of action in the country are scarce. One of such studies, conducted in the city of Bucaramanga and published in 2013, reported that the frequency of HER2 expression in patients with gastric adenocarcinoma was 11.2 % (22), which is higher than the frequency reported in other Latin American countries such as Brazil, Peru and Mexico (10.5 %, 9 % and 6.5 %, respectively) (23).

In conclusion, chemotherapy (FP) plus trastuzumab is the standard treatment for patients with HER2-positive metastatic advanced gastric cancer or gastroesophageal junction cancer. All of these cancers must be screened for HER2 status in paraffin blocks or biopsy specimens taken from the primary tumor or metastases at the time of initial diagnosis. Likewise, multiple gastric biopsies by endoscopy must be performed. IHC must be the initial test. Equivocal or incomplete tumors with IHC 2+ must be analyzed with FISH for confirmation. HER2 status testing and scoring must follow the specific recommendations for gastric cancer and must be performed in a laboratory experienced in doing so (2, 9). The perspectives are the evaluation of trastuzumab use for the treatment of patients with HER2-positive advanced gastric cancer in the perioperative and adjuvant setting.

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Clinical case

Leukocytoclastic vasculitis as a rare extraintestinal dermatologic manifestation of inflammatory bowel disease associated with *Clostridium difficile*: Case report

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Abstract

Leukocytoclastic vasculitis is defined as the damage and inflammation of the vascular walls. The term refers to vasculitis of the small vessels that anatomopathologically present leukocytoclasia and it can be seen as an extra-intestinal manifestation of inflammatory bowel disease. In ulcerative colitis, it occurs less frequently due to immune complexes produced in the intestinal mucosa by exposure of the submucosal lymphoid tissue to fecal antigens, which could precipitate in the walls of the small vessels. This condition can be associated with *Clostridium difficile*, which is a gram-positive, sporulated, strict anaerobic bacillus, normally found in the environment. It causes colitis that manifests as a diarrheal disease following the ingestion of antibiotics that alter the common bacterial flora of this organ. This is the case report of a 36-year-old patient with liquid diarrhea with mucus and scarce bleeding. Endoscopic and anatomopathological studies were performed, finding ulcerative colitis with positive coproparasite for *Clostridium difficile* antigen. The patient was hospitalized, and during his stay, he presented with petechiae and necrotic skin lesions on the fourth finger of the left hand. Skin biopsy showed small vessel vasculitis. This article is a practical review of the pathophysiology, histology, treatment, and diagnosis of a rare dermatologic extraintestinal manifestation, namely, leukocytoclastic vasculitis, in patients with *C. difficile*–associated ulcerative colitis.

Keywords

Leukocytoclastic vasculitis; Extraintestinal manifestations; *Clostridium difficile*; Ulcerative colitis; Inflammatory bowel disease.

INTRODUCTION

Leukocytoclastic vasculitis is defined as damage and inflammation of blood vessel walls. It consists of small-vessel vasculitides that anatomically and pathologically involve leukocytoclasia or hypersensitivity vasculitis (1). Leukocyoclastic vasculitis is an extraintestinal manifestation of inflammatory bowel disease that occurs in 15% to 20% ulcerative colitis (UC) cases, since it shares an etiopathogenic mechanism with UC, and the causal relationship of the two conditions is caused by immune complexes produced in the intestinal mucosa due to the exposure of submucosal lymphoid tissue to fecal antigens; these vasculitides could precipitate in the walls of small vessels and clinically they can be synchronous at the time of onset. At least 20 cases have been reported up to 2014 in the English literature, with 40 years being the predominant age (2, 3). The association with *Clostridium difficile* can alter the course of the disease by activating the immune response towards the pathogen causing the infection, which is nor-

mally found in the environment and causes colitis, where the patient experiences diarrhea after being administered the antibiotics, since the latter disrupt the usual microbiota of this organ (4).

CASE PRESENTATION

This is the case of a 36-year-old male with no relevant history of disease, but with a family history of colon cancer (his mother died from it) who had experienced watery diarrhea with presence of mucus and scarce bleeding for five years, and who had been treated with oral ciprofloxacin 500 mg for 7 days and probiotics on several occasions. The patient was admitted due to experiencing a worsening of his condition 20 days prior to admission consisting of colicky abdominal pain, abdominal distention, watery diarrhea with mucus and blood (4 to 6 stools per day), increased body temperature (unquantified), arthralgia without arthritis and an approximately 10 kg weight loss in 1 year. The following findings were described on the patient's physical examination: soft, non-tender abdomen with erythema, edemas on both hands and feet, and presence of aphthous ulcers on the tongue (**Figures 1** and **2**).

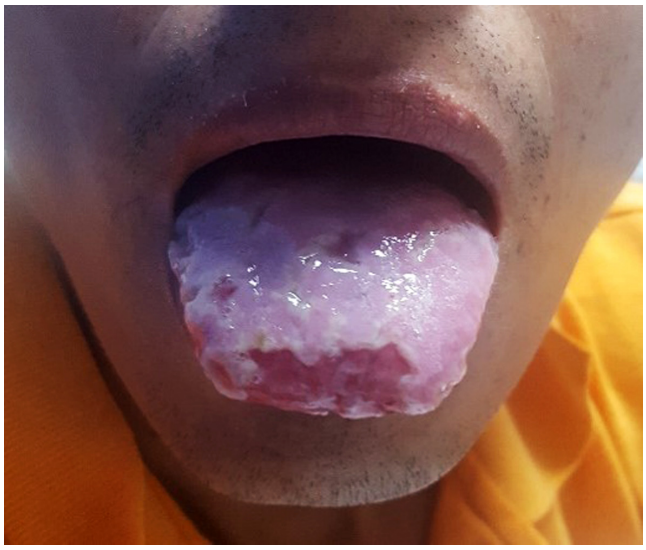

Figure 1. Oral aphthous ulcers on the tongue.

The following results were reported on the patient's admission tests: hemoglobin: 7.7 mg/dL; hematocrit: 26.5 %; leukocytes: 11 830/mm3; neutrophils 75.4 %; platelets: 544 000; CRP: 16.17 mg/dL; normal electrolytes values and kidney function; VDRL test: non-reactive; B12 vitamin > 2000; ferritin: 170.58; serum iron: 31; transferrin: 205; tumor markers within normal values; negative serology tests for cytomegalovirus, herpes virus, rubella, hepatitis B virus, hepatitis C virus and human immunodeficiency virus (HIV); positive Stool C difficile toxin test; negative stool culture; in addition, a negative result was obtained in all immunological markers tests, except for anti-neutrophil cytoplasmic antibody (c-ANCA). An upper gastrointestinal tract endoscopy allowed identifying ulcers in the distal esophagus (**Figure 3**) and performing a biopsy by removing tissue from both the edges and the center of the ulcers in order to make differential diagnoses (cytomegalovirus, herpes simplex, Crohn's disease, among others). The biopsy report described the following results: mixed inflammatory cell infiltration with nuclear polymorphs in the epithelium, positive immunohistochemistry for cytomegalovirus and negative for herpes. A thickening of the folds in the prepyloric region was also observed (**Figure 4**) and a biopsy was performed to rule out the inflammatory bowel disease with Crohn's disease differential diagnosis. In said biopsy, chronic active erosive gastritis with GIEMSA and hypodense colonization with *Helicobacter pylori* bacilli, which was associated with the incidental lesions, were

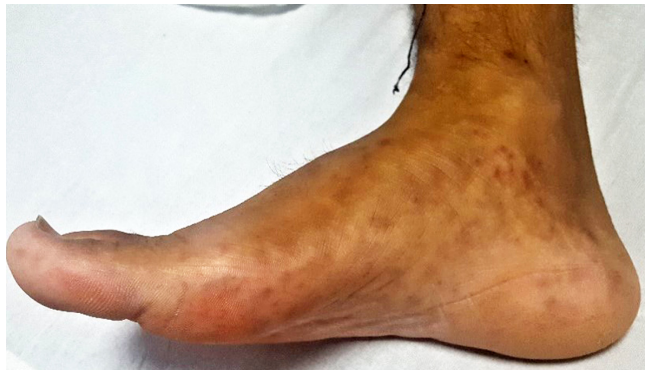

Figure 2. Erythematous lesions on the inner side of the right foot.

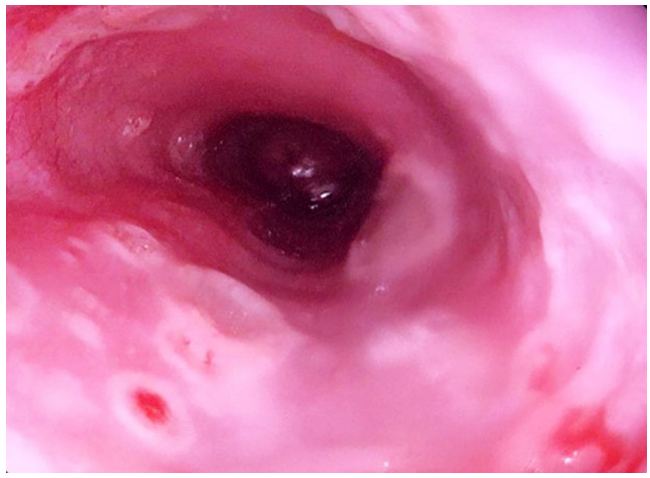

Figure 3. Upper gastrointestinal tract video endoscopy showing the presence of 5 mm ulcers with raised edges and erythematous background in the distal esophagus.

reported. In addition, a colonoscopy allowed the identification of both an altered vascular, erythematous, granular, edematous and friable pattern in the colon and a pseudopolypoid lesion in the descending colon (**Figure 5**), while UC was described in the biopsy report.

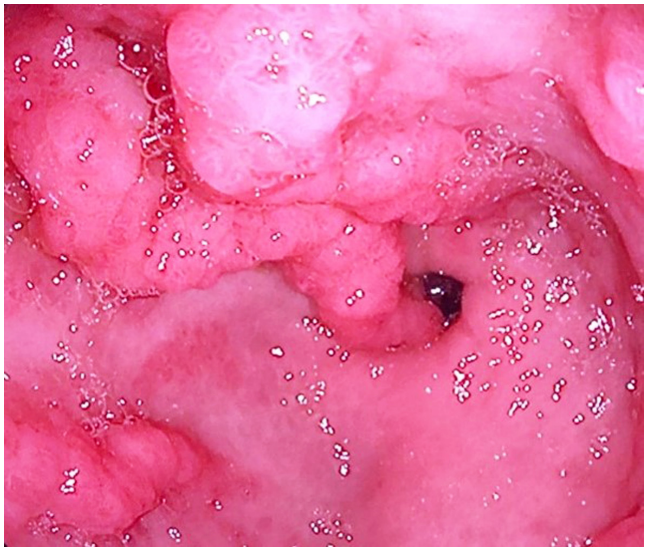

Figure 4. Upper gastrointestinal tract video endoscopy at the level of the antrum in which a thickening of the folds in the prepyloric region with erythemata and edemata are observed.

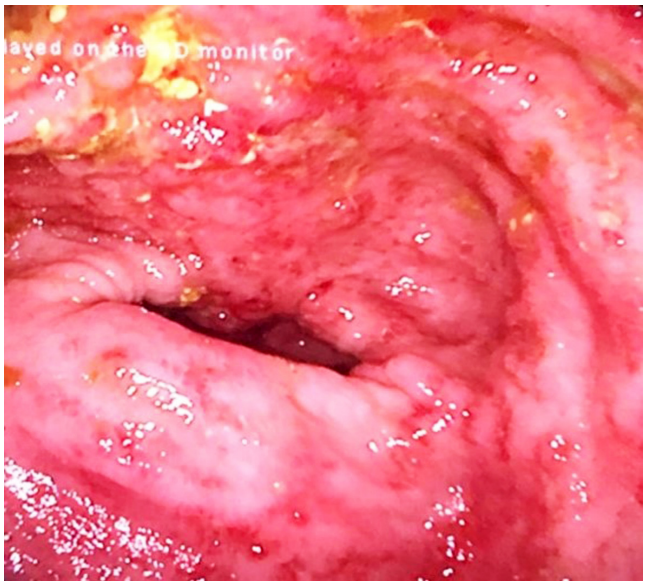

Figure 5. Colonoscopy showing an alteration of the vascular pattern, mucosa, granular erythema and friable edema and the presence of superficial ulcers in the sigmoid colon.

48 hours after the endoscopic procedure was performed, petechial and necrotic skin lesions appeared on the fourth finger of the left hand (**Figures 6** and **7**). Thus, an upper limb Doppler ultrasound that showed decreased fluids with parvus tardus waves in the palmar and dorsal digital arteries of the fourth finger of the left hand was performed (**Figure 8**). He was then assessed by the dermatology service and based on the results of a skin biopsy, a small-vessel vasculitis (septal panniculitis, perivascular inflammatory infiltration with predominance of neutrophils, fibrinoid damage and extravasated red blood cells) diagnosis was reached. The patient was then treated as follows: he was administered 3 pulses of intravenous methylprednisolone 500 mg, which was subsequently switched to oral prednisone 60 mg until corticosteroid administration was suspended; subsequently intravenous metronidazole 500 mg was administered for 14 days and oral mesalazine 3 g was prescribed, which he is currently using. At present, he is asymptomatic and does not show any sign of lesions on his hands or tongue, and UC is in clinical remission; corticosteroid therapy was suspended and the only drug he is taking is mesalazine 3 g/day; furthermore, the patient has reported he has not experienced any clinical manifestations in any of his follow-up visits in the outpatient service.

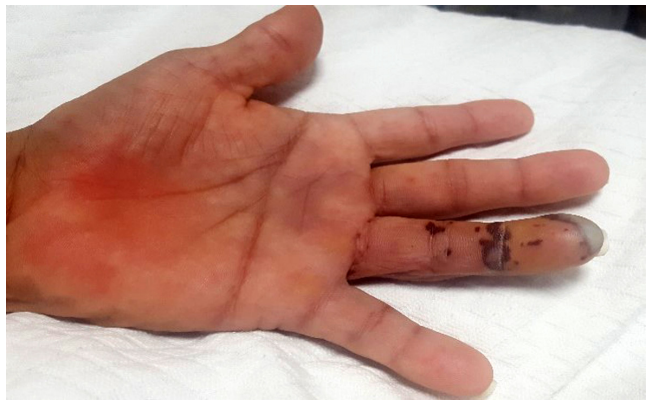

Figure 6. Petechial and necrotic skin lesions on the fourth finger of the left hand.

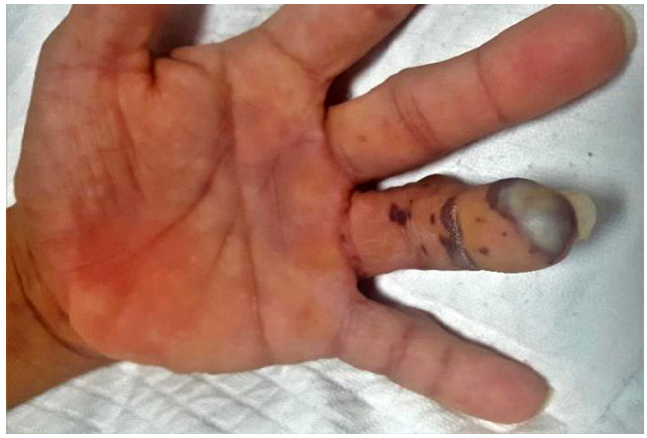

Figure 7. Whitish necrotic lesion on the distal part of the fourth finger of the left hand.

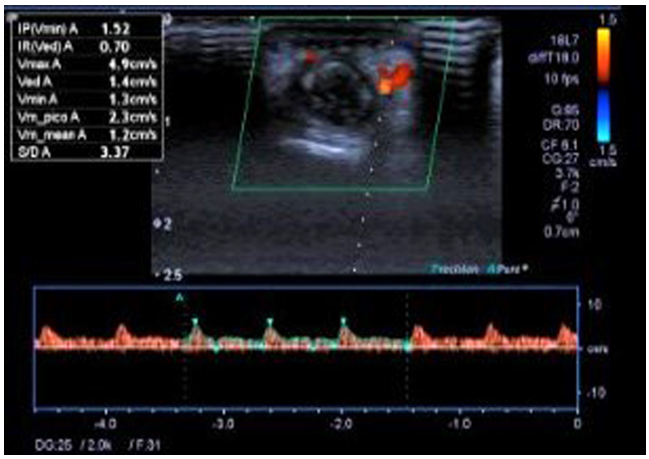

Figure 8. Upper limb Doppler ultrasound showing decreased fluids with parvus tardus waves in the palmar and dorsal digital arteries of the fourth finger of the left hand.

DISCUSSION

Inflammatory bowel disease has multiple extraintestinal manifestations. The most frequent include osteoarticular involvement (osteopenia, osteoporosis), skin (psoriasis, Sweet's syndrome, dermatitis herpetiformis, epidermolysis bullosa acquisita, necrotizing vasculitis), ophthalmologic (uveitis, dry eye, episcleritis, etc.), hepatobiliary and neurological manifestations; in addition, skin manifestations occur in 15% of cases (5, 6).

Leukocytoclastic vasculitis is a cutaneous vasculitis with varying clinical features that might include very rare systemic manifestations associated with inflammatory bowel disease (1). Histologically, these lesions show neutrophilic infiltration around the affected vessels, fibrinoid necrosis (fibrin deposition in the blood vessel wall), red blood cell extravasation, and endothelial cells damage (7). Its pathophysiology is based on the formation of antigen-antibody complexes in the vascular wall at the time the patient is exposed to the etiological factor, which triggers complement activation with subsequent occurrence of hemorrhage and ischemic thrombosis (8).

Leukocytoclastic vasculitis has an annual incidence of 30-45 cases per 1 million people. It can occur at any age and its prevalence is similar in men and women. Etiologically, it can be idiopathic in 50% of cases or it can be caused by different factors including infections (*Mycobacterium*, hepatitis B, hepatitis C, *Staphylococcus aureus, Chlamydia, Neisseria* and HIV), the use of different drugs (beta-lactams, furosemide, allopurinol, non-steroidal anti-inflammatory drugs, amiodarone, clindamycin, vancomycin, sulfonamides, metformin) and systemic or neoplastic diseases (9, 10).

Leukocytoclastic vasculitis associated with systemic autoimmune diseases accounts for 10-15% of cutaneous vasculitis cases; most frequently, it is associated with rheumatoid arthritis, systemic lupus erythematosus, phospholipid syndrome, Sjögren's syndrome and Behçet's disease; it also shares a etiopathogenic mechanism with UC and, therefore, the causal relationship of the two conditions is caused by immune complexes produced in the intestinal mucosa by exposure of the submucosal lymphoid tissue to fecal antigens; these vasculitides could precipitate in the walls of small vessels and activate proinflammatory cytokines, such as interleukin 15 (IL-15) and its receptor; likewise, they could differentiate lamina propria B cells resulting in the formation of typical lesions in patients with UC, which has been established as an extraintestinal manifestation of UC (58%) (1, 3, 10, 11).

Leukocytoclastic vasculitis clinical presentation is characterized by palpable purpura, pain and burning sensation in multiple (58%) or a single area (42%). Lesions are predominantly found in the lower limbs (83%), followed by the upper limbs (42%), the trunk (25%) and the buttocks (25%) (3, 12, 13). When leukocytoclastic vasculitis is suspected as an extraintestinal skin manifestation of UC, a skin biopsy must be performed in order to observe the histologic features of neutrophil and lymphocyte infiltration around dermal blood vessels showing leukocytoclasia, fibrin deposition in the vessels, fibrin thrombi, erythrocyte extravasation and the resultant epidermal necrosis (10, 14).

Symptoms in patients with leukocytoclastic vasculitis and UC include fever, myalgias, arthralgias, hematuria, abdominal pain, vomiting, bloody diarrhea, rectal incontinence, and tenesmus; other symptoms include anorexia, asthenia, and weight loss. Symptom onset is reported to occur approximately one week after exposure to the triggering factor (9, 15, 16). Colonic involvement in patients with leukocytoclastic vasculitis and UC is observed in 50% of cases with pancolitis, 40% with distal colitis and 10% with the development of leukocytoclastic vasculitis after total colectomy (2).

Other causes of dermatologic extraintestinal manifestations and inflammatory bowel disease must be considered as differential diagnoses and must be ruled out before a final diagnosis is reached. Dermatological causes include pyoderma gangrenosum, necrotizing vasculitis, cutaneous polyarthritis nodosa, and granulomatous vasculitis. On the other hand, infectious causes include *C. difficile, Escherichia coli, Salmonella, Shigella, Yersinia* and *Campylobacter*. Crohn's disease, pseudomembranous colitis and irritable bowel syndrome are also other differential diagnoses (9, 16, 17).

The association of *C. difficile* in patients with leukocytoclastic vasculitis and UC is due to the fact that it is a gram-positive, sporulating, strict anaerobe bacillus. It is normally found in the environment. When it causes an infection in humans, it generally produces colitis, which in turn manifests as diarrhea, fever, anorexia, leukemoid

reaction, hypoalbuminemia and bleeding after the intake of antibiotics, since the latter alter the normal bacterial flora of this organ (18). It is the most common cause of diarrhea in the hospital setting due to its etiological association with antibiotics. The risk of developing *C. difficile* infection also depends on other factors such as age, diet, and dose of the causative antibiotic, among others (19).

Diagnosis is based on clinical and laboratory criteria. These criteria must include three sudden onset diarrhea episodes in which the cause is not identified, the presence of *C. difficile* toxins A or B in the stools, or the endoscopic presence of pseudomembranes in the colon (18). In a study conducted in the United States of America, Zacharioudakis et al. assessed the factors that have been identified as triggers of *C. difficile* infection or the transition from colonization to infection in exposed patients who might require subsequent hospitalization. According to these authors, antibiotic use was associated with infection in 75% of these patients, being fluoroquinolones the most commonly prescribed class of antibiotics (20).

Most leukocytoclastic vasculitis cases are self-limited, with 90% of them occurring in weeks to months of symptom onset (10). Treatment depends on two factors: its etiology and its extent. In case of infectious causes, the underlying infection must be treated. When it occurs as part of a systemic vasculitis, treatment is based on the severity of organ involvement. Generally, it requires the use of steroids and immunosuppressants (7).

Based on the activity and severity of the disease, there are several treatment regimens to be used in patients with leukocytoclastic vasculitis and UC. Mild to moderate disease is usually treated with oral or topical aminosalicylates or with glucocorticoids. These drugs inhibit the production of cytokines and other inflammatory mediators. Glucocorticoids have shown to be effective in inducing disease remission; however, patients may experience side effects such as weight gain, hyperglycemia, acne, hirsutism, high blood pressure and bone resorption, the latter requiring the use of supplemental calcium and vitamin D. Regarding aminosalicylates, mesalazine stands out, and side effects include headache, abdominal pain, nausea, vomiting, and diarrhea, among others.

Severe disease is characterized by having more than 6 bloody stools per day, anemia and hemodynamic decompensation. Generally, it requires the patient to be hospitalized for treatment and stabilization. When glucocorticoids treatment is not effective, salvage therapy consisting of infliximab or cyclosporine use for approximately 5 to 7 days until a positive response is obtained has been reported to be effective (21).

Regarding the treatment of *C. difficile*-associated diarrhea or colitis, general measures include the suspension of medical treatments that use antiperistaltic and laxative agents, and assessing the possible suspension of antibiotic, opioids and proton pump inhibitors (PPIs) treatments (22).

The severity of *C. difficile* infection must be evaluated. In a first episode, if the infection is mild to moderate, metronidazole is administered orally for 10 days. If the infection is severe, the oral administration of vancomycin 125-500 mg 4 times per day during 14 days or fidaxomicin 200 mg 2 times a day for 10 days is required. In the case of a severe and complicated infection, the administration of vancomycin 4 times a day, either orally, using a nasoenteral tube or rectally via a retention enema, together with intravenous metronidazole, both during a period of 14 days, is indicated. On the other hand, in case of recurrent infection, the same treatment regimen used for first episode *C. difficile* infections or tapered pulsed vancomycin treatment regimens are indicated. Fecal microbiota transplantation is also indicated in cases where three or more recurrences take place (23). Fecal microbiota transplantation has shown a good clinical response in the treatment of patients with recurrent infection. In a randomized trial, symptom resolution was reported in 94% of patients who were administered vancomycin for 5 days, followed by one or two fecal microbiota transplantations (24). According to several clinical trials, the aforementioned treatments are those recommended to treat *C. difficile* infection.

From the conditions already addressed, the incidence of *C. difficile* infection has been found to be 1.8% to 5.7% in UC patients (25). In addition, this infection alters the course of UC by activating the immune response to the pathogen causing the infection (25). Both concomitant diseases are associated with a higher mortality rate (16).

CONCLUSIONS

Leukocytoclastic vasculitis and UC associated with *C. difficile* infection is uncommon. Clinically their onset is synchronous, although the occurrence of skin lesions is not always related to the activity of inflammatory bowel disease. In the case reported here, vasculitis onset coincided with the *C. difficile* infection-associated exacerbation of the undiagnosed inflammatory bowel disease. The occurrence of any dermatologic manifestations must be looked into, since reaching a diagnosis of vasculitis may have important implications for the evolution and clinical improvement of both inflammatory bowel disease and vasculitis itself.

Conflicts of interest

There are no conflicts of interest.

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Groove pancreatitis mimicking pancreatic cancer: Case report and literature review

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Abstract
Groove pancreatitis (GP) is a rare form of chronic pancreatitis located in the pancreaticoduodenal groove, hence its name. It is predominant in males with a history of alcohol intake. Making a differential diagnosis between this condition and pancreatic cancer is highly relevant given its location. Advances in diagnostic methods, such as endoscopic ultrasonography, have allowed a more accurate approach. However, no management guidelines are available and therapeutic approaches are still based on similar pathologies.

Keywords
Pancreatitis; Pancreatic cancer.

INTRODUCTION

Groove pancreatitis is a rare form of chronic pancreatitis. Its name derives from its location in the pancreaticoduodenal groove. It occurs predominantly in males with a history of alcohol consumption. Due to its location, considering pancreatic cancer as a differential diagnosis is of great importance. Currently, the advances that have been made in terms of diagnostic methods, such as endoscopic ultrasonography, have allowed a more accurate approach; however, there are no management guidelines and therapeutic interventions are still based on on those used in similar diseases.

CLINICAL CASE

This is the case of a 44-year-old man with a history of acute pancreatitis, alcohol consumption and smoking since he was 20 years old, who visited our health institution due to having experienced epigastric pain during six months, pain that worsened 4 days before admision. Elevated lipase, alkaline phosphatase and bilirubin levels (predominantly direct bilirubin) were reported in the laboratory tests results, so a cholestatic pattern was considered. A hepatobiliary ultrasound showed a 13 mm dilated common bile duct, without evidence of choledocholithiasis. In view of the patient's clinical condition, a magnetic resonance

cholangiopancreatography was performed, which showed a concentric diffuse thickening of the walls of the second part of the duodenum with a 24 x 23 x 24 mm irregular exophytic mass on the anterior wall of the duodenum, hyperintense on T1 and hypointense on T2 with restricted diffusion, which was causing the obstruction of both intra- and extrahepatic biliary ducts.

Biliopancreatic ultrasonography was then performed using linear Pentax equipment, where changes suggestive of chronic pancreatitis and dilatation of the common bile duct were found; however, in the endoscopic phase of the procedure, edema and erythema of the bulb and the second part of the duodenum were observed with an ultrasound thickening of the duodenal wall surrounding the head of the pancreas and dependent on echolayers 1 and 2, and partially on echolayer 3, i.e. the mucosa and submucosa; but the echostructure of the layers was preserved, without perilesional adenopathies. The puncture did not show any lesions suggestive of neoplasia. Then an endoscopic retrograde cholangiopancreatography (ERCP) was performed where the following findings were observed: a large edema, erythema and erosion in the second part of the duodenum, and edematous major and minor duodenal papillae with dilatation of the common bile duct, but without presence of stones (**Figure 1**). Biliary stent placement was carried out to ensure adequate drainage. In addition, biopsies were performed due to the clinical suspicion of ampullary lesion, with the following findings informed in the biopsy report: "inflammatory response without evidence of dysplasia or neoplasia". The patient's condition improved satisfactorily and currently he is under periodic clinical follow-up, undergoing oral enzymatic treatment and following nutritional recommendations, so it was considered that this was a groove pancreatitis case that mainly affected the duodenum and the two duodenal papillae and caused the obstruction of the bile and pancreatic ducts.

DISCUSSION

The duodenal pancreatic groove is a small area located between the head of the pancreas, the duodenum and the common bile duct (**Figure 2**) (1). The term groove pancreatitis refers to a type of chronic pancreatitis that mainly affects this area of the pancreas, while the rest of the organ remains intact (2, 3). It is a rare disease, probably because it is underdiagnosed (4).

Groove pancreatitis was first described in 1973 by Becker, who used the German word Rinnenpankreatitis (5). In 1982 Solte et al. translated it as groove pancreatitis (2). Subsequently, several terms have been used to refer to this disease in the literature such as dystrophy of the pancreas or duodenal dystrophy, which was reported by the French authors Potet and Duclert (6). Other terms include heterotopic cystic dystrophy, duodenal/paraduodenal wall cyst, pancreatic hamartoma of the duodenal wall, myoadenomatosis, Brunner's gland hamartoma and paraduodenal pancreatitis. These terminology differences make it difficult to find information of this condition in the literature (7).

In 1991, Becker and Mischke described two forms of groove pancreatitis: pure and segmental (8). In the pure form, infiltrative involvement or scar tissue affects only the pancreatic groove, while the parenchyma and the main pan-

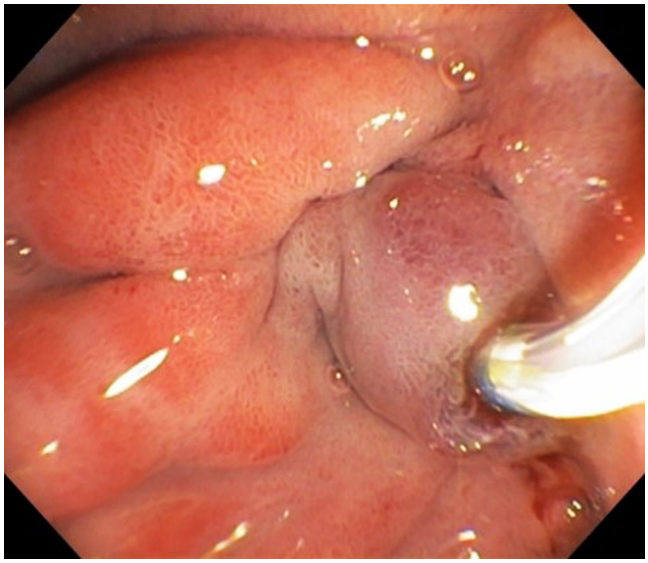

Figure 1. Edema in the papilla and peripapillary region.

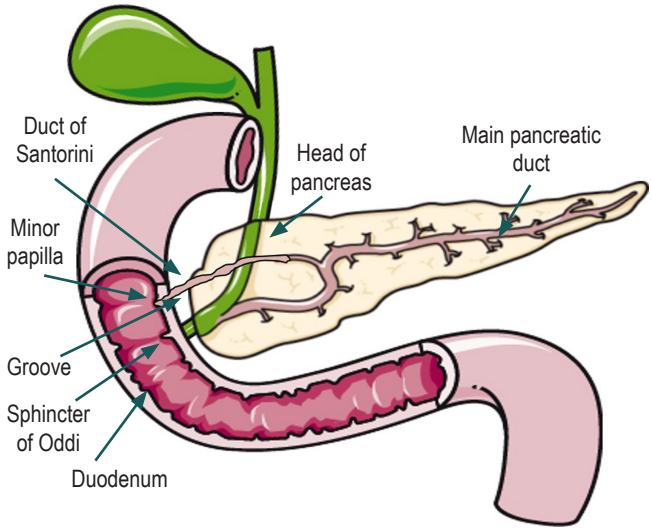

Figure 2. Anatomical relationships of the pancreatic groove.

creatic duct remain intact. In the case of segmental groove pancreatitis, scar tissue extends to the head and body of the pancreas, near the duodenal wall and the main pancreatic duct, which causes stenosis (9, 10). A clear differentiation between both is not always possible (11). Groove pancreatitis is more common in men with a history of chronic alcohol consumption and tends to occur in the fourth or fifth decade of life. Also, some case series have described smoking as a risk factor (12, 13).

The importance of groove pancreatitis is given by its capacity to imitate pancreatic carcinoma (10). In fact, there are cases of coexistence or even masking of this type of cancer (14), so it must be considered in the differential diagnosis of pancreatic masses or duodenal stenosis (15, 16).

CLINICAL PRESENTATION

The clinical presentation of groove pancreatitis consists of epigastric or mesogastric pain associated with postprandial emesis, weight loss (mainly due to altered intestinal motility) and duodenal stenosis (12, 17). The presence of jaundice is usually fluctuating, except when it occurs concomitantly with pancreatic cancer or cholangitis (18, 19). The course of the disease is chronic, and it may last years from the onset of symptoms and the time diagnosis is reached (20).

Regarding its pathophysiology, it is not clearly defined yet. It is believed that groove pancreatitis is related to the interruption of the pancreatic juice drainage through the duct of Santorini, which is located in the body of the pancreas and drains to the duct of Wirsung forming an acute angle; once there, it causes pancreatitis in the groove area due to increased pancreatic intraductal pressure (15). In addition, groove pancreatitis is caused by anatomical alterations in the minor duodenal papilla or by dysfunction of the papilla (3, 21). Tumors that occlude the minor papilla and the duct of Santorini (7), an obstructed duct of Santorini, pancreas divisum and heterotopic pancreas in the duodenal wall are among said alterations (15). Functional causes are associated with precipitating factors. Some of these include Brunner's glands hyperplasia and chronic excessive alcohol use or smoking, since they lead to dysfunction of the minor duodenal papilla and increased amounts of proteins in the pancreatic juice (3, 22). In the case reported here, alcohol consumption and smoking were considered precipitating factors of groove pancreatitis.

Macroscopic differentiation of this type of pancreatitis occurs in two scenarios: the cystic type, with 10 mm to 10 cm cysts in the duodenal mucosa beyond the ampulla of Vater region; and the solid type, characterized by the presence of <10 mm cysts associated with a significant thickening of the duodenal wall (23). Additionally, scarring causes changes in the common bile duct, leaving a smooth surface with homogeneous hyalinization changes (7). In early stages of the disease, it slightly affects the head of the pancreas and produces some scars or retractions. However, as it progresses, it produces important fibrosis that affects the head of the pancreas in its entirety (23).

Microscopically, histological findings include dilatation of the pancreatic ducts, the formation of pseudocysts in the duodenal wall, fibrosis in the duodenal submucosa that extends to the neck of the pancreas and Brunner's glands variable hyperplasia, which causes a thick layer around the smooth muscle with myofibroblast proliferation (24). Cystic changes are observed in the duodenal wall, going through the muscularis propria and superficially reaching the pancreatic parenchyma. Myofibroblastic proliferation can enclose areas of cystic changes with very thick secretions corresponding to spindle cells (13). Additionally, the dilated ducts and columnar epithelium can erode and transform into a pseudocyst-like fibrosis that constitutes the cyst type mentioned here (13, 25).

DIAGNOSIS

Groove pancreatitis diagnosis is made based on a set of biochemical tests, imaging studies and, in some cases, biopsies. Pancreatic enzyme levels (amylase and lipase) may be elevated (26). In addition, since inflammatory presentation, instead of the neoplastic one, occurs in most cases, elevated levels of tumor markers of the gastrointestinal tract (CA19-9 and carcinoembryonic antigen) are not usually found (10). Regarding imaging studies, abdominal ultrasound shows a hypoechoic lesion that thickens the duodenal wall and causes both a stenosis in the second part of the duodenum and the obstruction of the common bile duct (22). The disease can be documented by means of ultrasound in several stages: in the early stage, fibrosis predominates and it is possible to observe a hypoechoic band over the pancreatic grooves, which is associated with a thickening of the duodenal wall; on the other hand, e in the late stage, once fibrosis has been established, hyperechogenicity in the duodenal wall is observed as a result of hypertrophy of the submucosa due to Brunner's glands hyperplasia (27).

IMAGING FINDINGS

Abdominal computed axial tomography (CT) scan shows a hypodense laminar lesion between the head of the pancreas and the duodenum, close to the minor duodenal papilla; this lesion is made up of scar tissue (28, 29). In the case of contrast enhanced CT scans, there is a delay in the uptake of the groove due to a circulation alteration secondary to fibrosis (10).

In the case of segmental groove pancreatitis, a hypointense lesion can be seen in the pancreatic head, close to the duodenal wall. The main pancreatic duct may show a discrete dilatation towards the body and tail of the pancreas (30). Peripancreatic vascularization is usually preserved, without signs of thrombosis, even in the presence of extensive involvement (31). In the most advanced stages of the disease, a narrowing of the lumen in the duodenum, together with the presence of edema, erythema and polypoid mucosa can be observed in upper endoscopy. Biopsies of the duodenal mucosa usually report an inconclusive result or an active inflammatory response without any evidence of neoplastic lesions (24).

ERCP is a technically difficult procedure since the positioning of the duodenoscope in the presence of duodenal edema limits the visualization of the papilla. The distal common bile duct shows a stenosis without involvement of the main pancreatic duct. In addition, the duct of Santorini obstructed by mucus plugs or simply by the large perilesional edema (4, 32). In the case of our patient, endoscopic findings showed an edema of significant size in the duodenum and the peripapillary region (**Figure 3**).

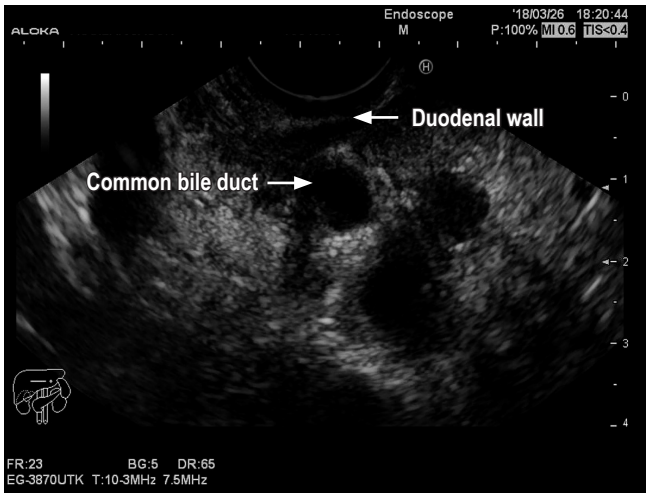

Figure 3. Endoscopic ultrasound image of edematous duodenal wall.

Endoscopic ultrasound (EUS) has been proposed as the diagnostic technique of choice due to its greater sensitivity (86%) and the added value of making it possible to take samples for histological analysis purposes (33). Imaging findings in EUS show chronic pancreatitis changes based on the Rosemont's criteria, which allow it to have a good diagnostic performance (34). As it happens in other imaging studies, a thickening of the second part of the duodenum and heterogeneity of the dorsocranial portion of the pancreatic head findings have been reported with this imaging technique. In addition, several authors have described a pathognomonic finding using EUS in advanced stages of groove pancreatitis: hyperechoic thickening of the duodenal wall in the groove area with anechoic ductal structures extending towards the head of the pancreas. This hyperechoic lesion correlates with myoadenomatous proliferation and adjacent fibrosis of the pancreas (10, 27). In our patient, a significant edema in the duodenal wall and dilatation of the common bile duct were observed in the EUS (**Figure 3**).

Magnetic resonance imaging (MRI) offers the advantage of allowing the assessment of the different pathological aspects of the disease. The characteristic lesion between the head of the pancreas and the duodenum is shown as a hypointense lesion on T1 weighted imaging sequence, while on T2 sequence it can be hypo-, iso- or hyperintense depending on the time of evolution of the disease. In acute stages it is hyperintense due to the large edema, while in chronic stages it is hypointense due to fibrosis (28, 29).

Cystic lesions in the groove or in the duodenal wall are more evident in the T2 sequence and an increased thickening or duodenal wall stenosis are frequent findings. The common bile duct may show variable stenosis. In the segmental form of the disease, the head or the entire pancreas may appear hypointense on the T1 sequence, with atrophy of the parenchyma and ductal dilatation, showing the progressive loss of glandular cells that in turn are replaced by fibrous tissue (29, 35). ERCP reports the relationship between the pancreatic duct system and cystic changes. In most cases, a widening of the space between the pancreatic ducts, the distal common bile duct and duodenal lumen, due to the space-occupying lesion located in the groove, is found, as well as a marked thickening of the duodenal wall (28). In the case reported here, dilatation of the bile duct, caused by the edema of significant size located in the peripapillary region, was evidenced on magnetic resonance cholangiopancreatography (**Figure 4**).

The anatomical location of the pancreatic groove means that any lesion in this area must be studied histologically or using imaging techniques. Differential diagnoses include pancreatic head carcinoma, periampullary cancer, neuroendocrine tumor, cystic dystrophy of the duodenum and acute pancreatitis with plastron presence in the groove. Differentiating groove pancreatitis from adenocarcinoma is particularly difficult as both conditions may have similar findings (36, 37). An important feature of groove pancreatitis is the absence of vascular involvement. In addition, it has been reported that the gastroduodenal artery is displaced to the left in this type of pancreatitis, whereas, in the case of adenocarcinoma, it is located between the lesion and the duodenum (38, 39). Also, cystic groove lesions are more common in groove pancreatitis than in adenocarcinoma cases (40). Assessment of the duodenum may also help differentiate groove pancreatitis from pancreatic

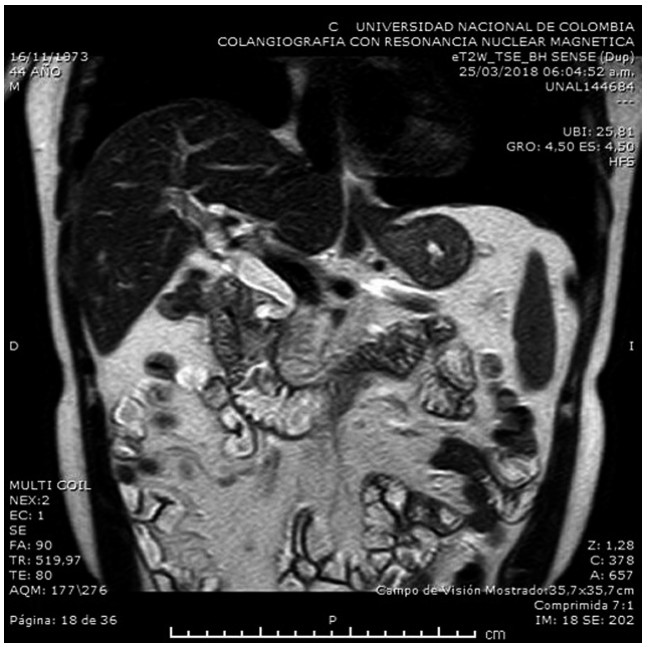

Figure 4. Magnetic resonance cholangiopancreatography showing a large edema in the second part of the duodenum.

cancer, as strictures are less common in pancreatic head tumors (35). Likewise, in groove pancreatitis, the presence of stenosis distal to the intrapancreatic portion of the bile duct is observed during magnetic resonance cholangiopancreatography, instead the abrupt and irregular stenosis seen in pancreatic adenocarcinoma patients (10). Periampullary cancer has a clinical presentation similar to that of ductal adenocarcinoma of the pancreatic head. Periampullary carcinomas typically occur in older adults, together with jaundice and weight loss; these tumors are usually sclerosing adenocarcinomas with high fibrotic tissue with low intensity on T1 and T2 sequences that cause stenosis of the common bile duct or abrupt termination at the tumor level that usually shows the shoulder sign, instead of the long and uniform narrowing seen in groove pancreatitis (41, 42). Gastrinoma is the neuroendocrine tumor most frequently located in the groove. These tumors can be differentiated from groove pancreatitis due to the hypervascularity observed in images obtained using contrast enhanced imaging studies, with enhancement of the peripheral ring after the use of gadolinium (10, 43).

Cystic dystrophy of the duodenal wall is characterized by the presence of cysts within the duodenal wall originating from ectopic pancreatic tissue. Imaging findings in cystic dystrophy are very similar to those of groove pancreatitis. So far whether groove pancreatitis and cystic duodenal dystrophy are different conditions or part of the same disease spectrum remains uncertain. Therefore, the term paraduodenal pancreatitis, which includes groove pancreatitis, cystic dystrophy of the duodenal wall, and paraduodenal wall cysts, is used in the literature (36).

CONCLUSION

Groove pancreatitis is a rare form of chronic focal pancreatitis. CT and MRI constitute the diagnostic imaging studies of choice; however, the introduction of biliopancreatic ultrasonography has allowed assessing the pancreas without exposing the patient to radiation and contrast mediums. This case report is intended to highlight the occurrence of groove pancreatitis as a differential diagnosis in acute episodes of pancreatitis that could actually be exacerbations of a chronic condition. Knowing the characteristics of groove pancreatitis favors the physician to make a correct diagnosis using less invasive diagnostic tests and reducing potential risks for the patient.

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Endoscopic treatment of minor papilla adenomas: Report on two cases

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Abstract

There are various publications on endoscopic resection of major papilla lesions, but only individual case series of resection of minor papilla lesions have been reported. This article describes the technical success and safety of endoscopic resection of two adenomatous lesions of the minor papilla.

Keywords

Minor papilla adenoma; Endoscopic papillectomy of minor papilla.

INTRODUCTION

Adenomas of the major duodenal papilla are premalignant lesions that may occur sporadically or in the context of genetic syndromes such as familial adenomatous polyposis. The endoscopic technique used to resect these lesions has been widely described (1, 2). In Colombia, several case reports and papers describing the local experience regarding endoscopic resection of adenomas of the major duodenal papilla have been published (3, 4). Adenomas of the minor duodenal papilla are much less frequent than major duodenal papilla and have been described only in case reports (5-8). So far no cases of endoscopic papillectomy of the minor papilla have been described in Colombia. This paper presents two cases of patients with adenomas of the minor duodenal papilla who were treated using endoscopic papilectomy at the Clínica Universitaria Colombia, in Bogotá.

DESCRIPTION OF THE CASES

Case 1

A 66-year-old woman underwent an esophagogastroduodenoscopy due to dyspeptic symptoms in which a 10-milli-

meter sessile polypoid lesion located in the second part of the duodenum was detected; in addition, using the side-viewing duodenoscope it was confirmed that the lesion was located in the minor duodenal papilla (**Figure 1**). A tubular adenoma with low-grade dysplasia was described in the biopsy report. Besides, a lesion, with involvement up to the muscularis mucosa, susceptible to endoscopic resection was found on endoscopic ultrasound. Normal findings were reported on total colonoscopy and magnetic resonance cholangiopancreatography; there was no evidence of pancreas divisum.

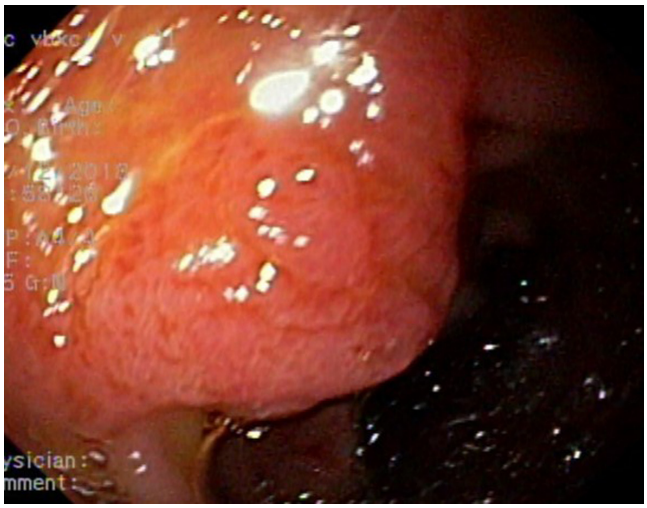

Figure 1. Endoscopic image of the adenoma of the minor duodenal papilla.

The patient underwent an ampulectomy of the minor duodenal papilla. Regarding the technique used during the procedure, the patient was under general anesthesia and was placed in a modified prone position. The second part of the duodenum was accessed using the duodenoscope and the major duodenal papilla was examined, where no abnormalities were found. An en-face view of the minor duodenal papilla was possible in the semilong axis, showing 10 millimeters of greater size adenomatous-like changes. The lesion was raised with normal saline solution + methylene blue (dilution ratio: 1:100 000) and an ampulectomy was performed using a diathermic loop. The specimen was retrieved with an endoscopic mesh basket and sent to the pathology service for analysis. There were no immediate complications. The following findings were described in the pathology report: a completely resected intestinal type tubular adenoma with low grade dysplasia (**Figures 2** and **3**).

The patient was hospitalized on the day the procedure was carried out for observation purposes, and since her condition improved satisfactorily she was discharged the following day. There was no evidence of lesion recurrence

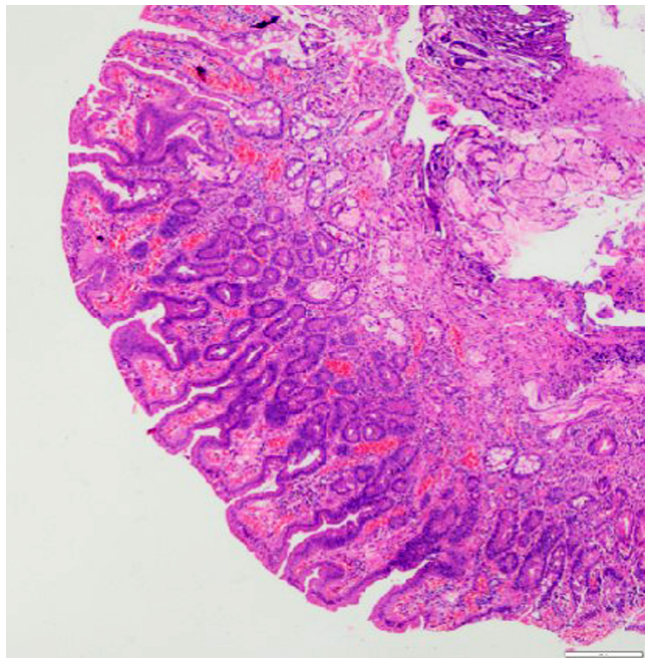

Figure 2. Histopathological image of the resected adenoma, 10x.

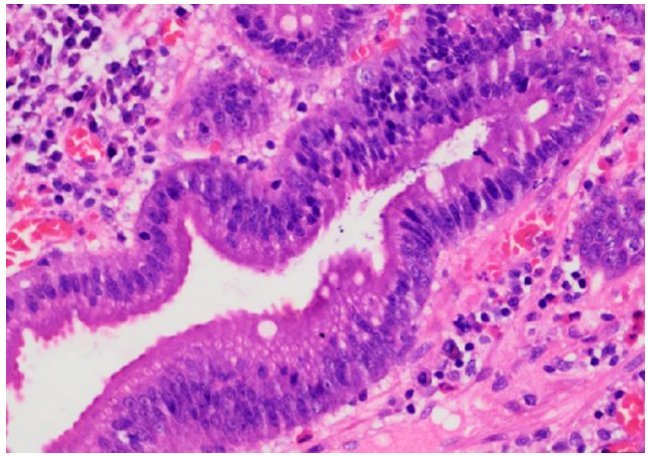

Figure 3. Histopathological image of the resected adenoma, 40x.

on follow-up duodenoscopy at 6 months, 12 months and 24 months.

Case 2

A 73-year-old male with a history of endoscopic submucosal dissection of a lesion in the rectum (high-grade dysplasia tubulovillous adenoma) underwent an esophagogastroduodenoscopy due to dyspepsia symptoms and in which an approximately 10 millimeters adenomatous-like lesion was detected; appearance was found; when assessed

with the duedonoscope the lesion was compatible with an approximately 10 millimeters adenoma of the minor duodenal papilla (**Figure 4**); there were no abnormalities in the major duodenal papilla. A tubular adenoma with low-grade dysplasia was reported in the biopsy report. No abnormal findings or evidence of pancreas divisum were reported on the magnetic resonance cholangiopancreatography. The patient underwent a papillectomy of the minor duodenal papilla; the technique used during the procedure similar to that described in case No. 1. There were no immediate complications. The following findings were described in the pathology report: a completely resected intestinal type tubular adenoma with low grade dysplasia (**Figures 5** and **6**).

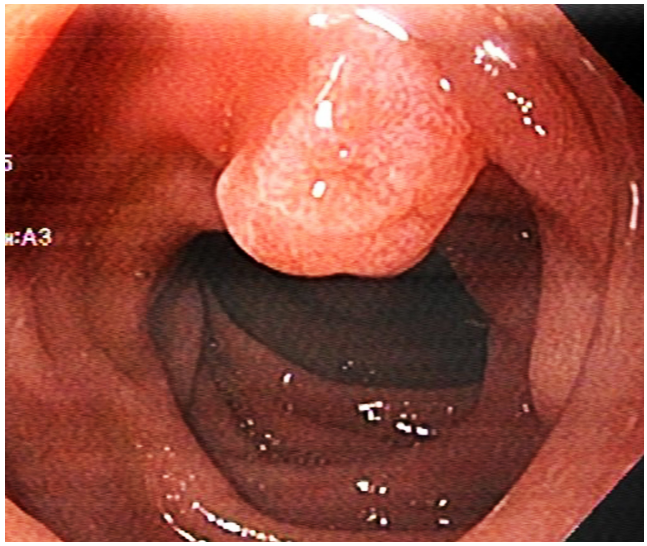

Figure 4. Endoscopic image of the adenoma of the minor duodenal papilla.

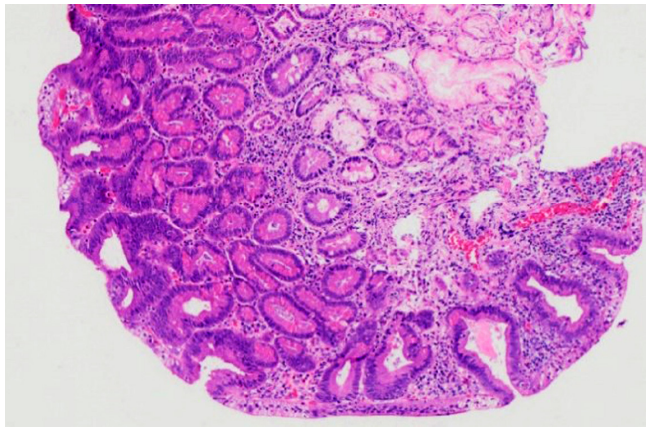

Figure 5. Histopathological image of the resected adenoma, 10x.

The patient was hospitalized on the day the procedure was carried out for observation purposes, and since his condition improved satisfactorily he was discharged the following day. There was no evidence of lesion recurrence on follow-up duodenoscopy at 4 months, 10 months and 20 months.

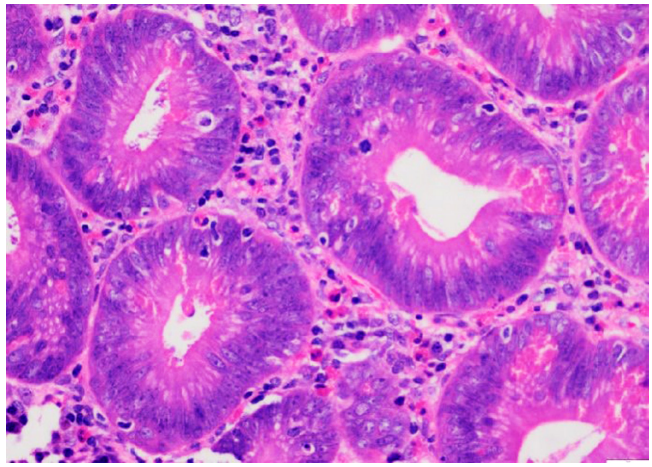

Figure 6. Histopathological image of the resected adenoma, 40x.

DISCUSSION

Lesions affecting the minor duodenal papilla are rarely described; these lesions can be benign adenomas (5-8), gangliocytic paragangliomas (9, 10) or carcinomas (11, 12). Furthermore, they can be single lesions or they can be associated with adenomas of the major duodenal papilla (8) and familial adenomatous polyposis (8).

Before performing a papilectomy it is necessary to define the anatomy of the pancreatic duct by means of endoscopic ultrasound or magnetic resonance cholangiopancreatography and rule out the adenoma involvement of the pancreatic duct. In case of concomitant pancreas divisum coexists, a pancreatic stent must be placed in the duct of Santorini after papillectomy in order to reduce the possibility of post-endoscopic retrograde cholangiopancreatography pancreatitis (5-8). Pancreas divisum was not present in none of the two patients presented here, so no pancreatic stents were placed in the duct of Santorini and neither of them developed post-resection pancreatitis. In cases in which a pancreatic stent is placed, it is recommended to remove it after 2 weeks to reduce the risk of lesions in the pancreatic duct (2).

Controversy has been raised regarding the use of submucosal infiltration to raise the lesion prior to resection. Currently, most authors do not use this measure in major duodenal papilla resection cases (1, 2). Some case series of papillectomy of the minor papilla report that this measure was not used (5), while others report its use (6). In the two cases presented here, submucosa was infiltrated with methylene blue diluted in normal saline in order to

clearly delimit the lesion and reduce the risk of perforation according to the rationale provided by the physician who performed the procedures.

The goal of papillectomy is the complete resection, in one piece, of the adenoma, which was achieved in the two cases presented here. Postresection recurrence of major duodenal papillary adenomas has been reported in 0 % to 33 % of cases (13). At the time of writing this case report, no specific data on recurrence of adenomas of the minor duodenal papilla after papillectomy were found.

Recommendations regarding endoscopic follow-up to rule out lesion recurrence vary. It must be performed using a side-viewing duodenoscope. Kandler & Neuhaus recommend performing a follow-up duedonoscopy every 3 months during the first year, then every 6 months the second year, and finally every year for 3 years (2). The American Society for Gastrointestinal Endoscopy (ASGE) guidelines recommend carrying out follow-up studies between 1 and 6 months, and then every 3 to 12 months for at least 2 years (1). These recommendations are mainly for postpapillectomy follow-up in major papilla adenomas cases. There are no specific recommendations for minor papilla adenomas postresection follow-up.

CONCLUSIONS

This paper presents two cases of patients who underwent endoscopic papillectomy of the minor duodenal papilla and in which complete resection of tubular adenomas with low-grade dysplasia was achieved without any procedure-related complication. In addition, there was no evidence of lesion recurrence at 20 and 24 months, respectively.

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Clinical case

Ileocecal tuberculosis: A case report

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Abstract

Tuberculosis is a disease of public health importance worldwide with a high incidence in Colombia. It mainly affects the lung parenchyma. However, in a large number of cases, it is diagnosed in its extrapulmonary form, with the gastrointestinal tract being one of the most frequent sites. *Mycobacterium tuberculosis* has a strong predilection for the ileocecal region and the terminal ileum. Manifestations of this rare form of the disease are abdominal pain and mass sensation mainly, as well as ulcerative lesions in the intestinal mucosa and histological findings corresponding to large caseating granulomas of confluent morphology, which distinguish it from other entities such as Crohn's disease. Invasive procedures, such as colonoscopy, and diagnostic laboratory aids, such as cultures, stains, and PCR, are used to find the disease in the gastrointestinal tract. Given the difficulty of diagnosing this type of tuberculosis, knowledge and how a patient with symptoms suggestive of the disease is approached are critical factors for establishing timely treatment. The following is an unusual case of ileocecal TB as a manifestation of prolonged febrile illness with a fatal outcome.

Keywords

Ileocecal tuberculosis; Intestinal tuberculosis; Extrapulmonary tuberculosis; PCR for *Mycobacterium tuberculosis*; Splenic infarction; Bone tuberculosis.

INTRODUCTION

Worldwide, tuberculosis is one of the major diseases with the highest social and economic burden. By 2017, a global incidence of 10 million cases was estimated, being more frequent in Southeast Asia and Africa (1), and about 1.6 million people died from it. In Latin America, an incidence of 263,000 cases and nearly 20,000 deaths were reported for the same year (1). In Colombia, tuberculosis continues to be a prevalent disease, with an incidence of 26.5 cases per 100 000 inhabitants and a total of 14 480 new cases reported in 2017 (2), where it mainly affects people older than 65 years, has a higher prevalence in males and pulmonary tuberculosis is predominant (83.3 %) (2).

Risk factors of tuberculosis can be classified into two large groups: people who have been in contact with *Mycobacterium tuberculosis* or who have had the disease (immigrants, indigents, IV drug users, health care workers) and those who are immunocompromised (the elderly, people with human immunodeficiency virus [HIV], silicosis, diabetes mellitus [DM], chronic kidney disease [CKD], malnutrition, among others) (3). Coinfection with HIV is the most important risk factor, for at least 40% of patients with the virus die from tuberculosis and in approximately half of the cases the disease is only diagnosed until an autopsy is made (4).

Although tuberculosis mainly affects the lung, the frequency of patients in which an extrapulmonary diagnosis

of the disease is made is higher, which is explained by the hematogenous or lymphatic dissemination of *M. tuberculosis* bacillus through the body and whose clinical presentation can be evidenced in later years. Risk factors of extrapulmonary tuberculosis include HIV infection, use of tumor necrosis factor (TNF) antagonists, use of corticosteroids, presence of malignancies, being female and having comorbidities such as DM or CKD (5). Its prevalence varies from 10 % to 60 % depending on the geographical location. For example, in 2016, extrapulmonary tuberculosis and the mixed presentation form had a prevalence of 20 % and 10 %, respectively, in the United States (6). In Colombia, out of the total number of new tuberculosis reported in 2017, about 17 % were extrapulmonary cases, and most of these patients had one of the abovementioned risk factors (2).

The genitourinary tract, the lymph node, the bones, and the pleura are the extrapulmonary sites most frequently affected by the disease; meanwhile, the gastrointestinal tract ranks fifth or sixth in order of frequency depending on the local epidemiology (5). Furthermore, within the gastrointestinal tract, tuberculosis is most commonly found in the ileocecal region and the terminal ileum, as it has been reported that 67% of gastrointestinal tuberculosis cases occur in these regions (7). Likewise, identifying gastrointestinal tract involvement is a diagnostic challenge given that the disease presents with a very varied and nonspecific symptomatology, which can sometimes include serious complications such as perforation, bleeding and obstruction. Secondly, it mimics other diseases like ulcerative colitis, lymphoma, amoebiasis or Crohn's disease (7). Its diagnosis requires clinical and laboratory findings, being microbiological culture and molecular analysis techniques the tests with the highest sensitivity and specificity. Finally, it can bet treated pharmacologically or surgically depending on its clinical presentation.

This is the case of a 75-year-old man with intestinal tuberculosis who had risk factors for developing this disease and in which management was complex from the time of hospitalization due to the presentation and location of the disease. Likewise, the diagnostic tools and differential diagnoses that were considered to reach the diagnosis and adequate treatment are described, as well as how, in spite of this, the patient died.

CLINICAL CASE

This is the case of a 75-year-old retired man from Bogota, who worked as a guard for more than 50 years. He also worked in the agriculture sector for 4 years in a rural area near the city. He had a history of smoking for more than 3 decades (pack-year index [PYI]= 12), exposure to wood smoke, arterial hypertension, CKD with a glomerular filtration rate (GFR) of 49 mL/min/1.73 m^2 according to the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation, prostate cancer that required him undergoing a prostatectomy and subsequent anti-androgen therapy with gonadotropin-releasing hormone (GnRH) analogues with normal prostate antigen values at 3-year follow-up. In addition, the presence of anemia was under study and iron deficiency was documented in the anemia panel tests, which was treated on an outpatient basis with erythropoietin and vitamin B12 supplementation.

The patient was admitted due to having experienced a weight loss of approximately 12 kg, night sweats, asthenia, adynamia for 9 months, as well as occasional productive cough in the last month. Additionally, he reported having experienced 4 to 5 diarrhea episodes per day, without mucus or blood, for 4 days prior to admission, which resolved with hydration and general care measures. Fever (38.3 °C), general paleness and tachycardia were documented on admission; besides, leukopenia, microcytic anemia with criteria for blood transfusion, thrombocytopenia, mild hypovolemic hypoosmolar hyponatremia, hypomagnesemia and hypoalbuminemia were reported on admission laboratory tests (**Figure 1** and **Table 1**). Findings compatible with silicoanthracosis and hypodense images in the vertebrae of unspecific nature were observed on a CT scan of the chest (**Figure 2**).

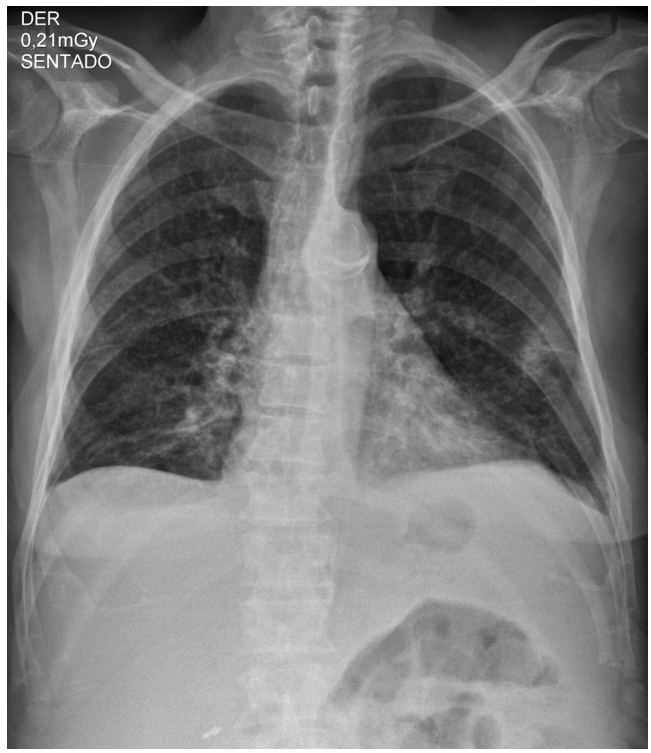

Figure 1. Anteroposterior (AP) view of chest X-ray showing thick reticular interstitial opacities in both lung fields and free costophrenic angles.

Table 1. Laboratory findings on admission and during hospitalization.

Laboratory test	On admission	At week 1	At week 2	At week 3
Total bilirubin (mg/dL)	2720	3690	2040	2530
Direct bilirubin (mg/dL)	2067	2940	1428	2049
Indirect bilirubin (mg/dL)	260	350	208	254
Albumin (g/dL)	23	28.9	23.2	24.5
Alkaline phosphatase (IU/L)	6.9	9.5	7.1	7.7
Amylase (IU/L)	78 000	92 000	58 000	50 000
AST (IU/L)	1.4	1.06	1.02	0.97
ALT (IU/L)	28.8	30.8	31.7	35.3
PT	0.52			1.06
INR	0.30			0.85
PTT	0.22			0.21
Sodium (mEq/L)	2.3			2
Potassium (mEq/L)	142			138
Chlorine (mEq/L)	24			27
Calcium (mEq/L)	31			28
Magnesium (mEq/L)	30			21
HIV	16.4			16.1
VDRL	1.06			1.04
Hepatitis C serology	33			48.5
Hepatitis B serology	126	129	135	130
Vitamin B12	4.2	3.07	5.03	4.4
Folic acid	94	99	101	99
Prostate antigen	8.1	9.2	9.3	10.3
Antigen test	1.23	1.41	2.24	1.5
Histoplasma antibodies	Negative			
Rheumatoid factor	Non-reactive			
ANA	Negative			
ENA	Negative			
Anti-Ro antibodies	> 2000			
Anti-La antibodies	19.2			
Anti-Sm antibodies	0.463			
RNP			Negative	
Anti-DNA antibodies			Negative	
Total bilirubin (mg/dL)			10.4	
Direct bilirubin (mg/dL)			Negative	
Indirect bilirubin (mg/dL)			Negative	
Albumin (g/dL)			2.9	
Alkaline phosphatase (IU/L)			3.6	
Amylase (IU/L)			12.6	
AST (IU/L)			2.0	
ALT (IU/L)			Positive 1/40	

ANA: antinuclear antibodies; ALT: alanine aminotransferase; AST: aspartate aminotransferase; BUN: blood urea nitrogen; ENA: extractable nuclear antigens; INR: international normalized ratio; RNP: ribonucleoprotein; PTT: partial thromboplastin time; PT: prothrombin time; VDRL: Venereal Disease Research Laboratory test.

Given the persistence of the fever episodes, antibiotic treatment with cefepime was started and an acid-fast bacilli smear was performed, in which negative results were obtained. Due to the altered hematological cell lines, further studies were carried out: peripheral blood smear (normal results), protein electrophoresis with a polyclonal component, flow cytometry for paroxysmal nocturnal hemoglobinuria (negative), and a bone marrow biopsy (negative for malignancy), with a hypocellularity of 10%, an expected result for a 75-year-old person. Bone marrow involvement was ruled out and intravenous iron administration was started. Regarding the febrile syndrome, the following findings were documented in additional studies: normal liver function tests, an abdominal ultrasound with evidence of hepatomegaly and splenomegaly with multiple focal lesions corresponding to prior infarcts, negative blood cultures, negative febrile antigens, negative sputum culture, normal prostate antigen and a thyroid ultrasound without any abnormal finding. A contrast-enhanced computed tomography of the abdomen was also performed, where a thickening of the ileocecal mucosa was evidenced, as well as the splenic lesions that had already been documented (**Figure 3**). Endocarditis was ruled out by means of transesophageal echocardiography.

The following findings were documented in a contrast-enhanced MRI of the whole spine: lytic lesions located in the L2, L3 and L4 vertebrae and right iliac bone with signs of bone marrow reconversion (**Figure 4**). The patient's condition worsened progressively while being clinically surveilled during the antibiotic treatment. On a colonoscopy an ulcer was evidenced in the ileocecal valve and cecum, so a biopsy was performed in order to analyze the sample using stains for detecting fungi and polymerase chain reaction (PCR) for tuberculosis. Given the worsening of the clinical condition of the patient, together with the findings evidenced in multiple organs, treatment with amphotericin B was started due to the suspicion of histoplasmosis, however such management was suspended since negative galactomannan levels were reported.

Despite the patient did not have any symptom related to autoimmunity, but he was suffering from prolonged fever, autoimmunity tests were requested, and the following findings were reported: negative rheumatoid factor, negative ENA, negative anti-dsDNA and positive ANA at a dilution of 1/40.

The patient's clinical condition deteriorated as he experienced somnolence, anasarca and the fever worsened, especially in the evenings; then he presented with ventilatory failure and multiorgan dysfunction. A positive PCR report for tuberculosis from the sample taken from the ileocecal ulcer was received, a 4-drug regime treatment for TB consisting of pyrazinamide, ethambutol, rifampicin and isoniazid was immediately started. Despite the treatment,

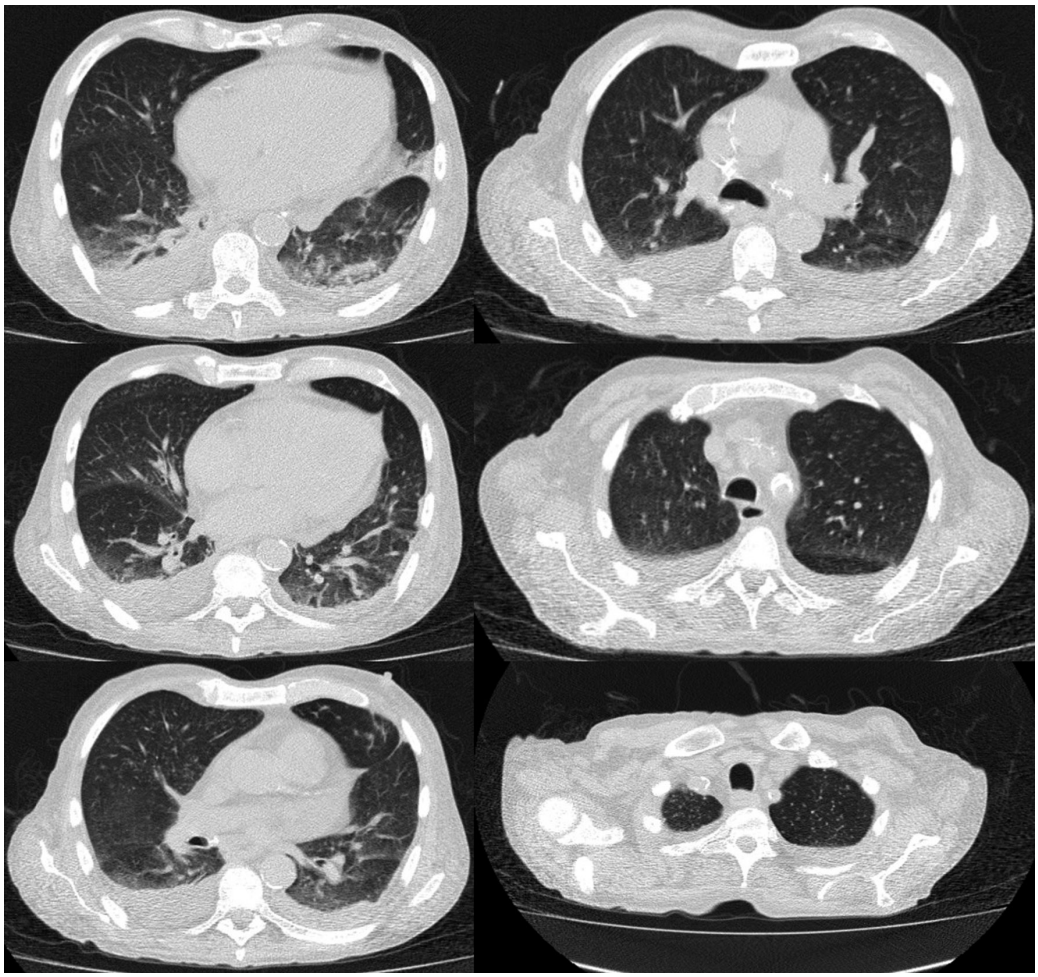

Figure 2. High-resolution computed axial tomography (HRCT) of the chest thorax in which silicoanthracosis, atelectasis of the lower lung lobes and altered density of the vertebral bodies and sternum.

the patient presented with septic and distributive shock, acute hypoxemic respiratory failure and finally died 3 days after starting the 4-drug regimen.

DISCUSSION

Extrapulmonary tuberculosis is an unusual type of tuberculosis. It accounts for 20% to 25% of TB cases (8). HIV infection, use of tumor necrosis factor (TNF) antagonists, use of corticosteroids, the presence of malignancy, DM or CKD have been described as risk factors (5). Regarding its pathophysiological mechanism, blood or lymphatic dissemination, with distribution to any region of the body, have been described; the prevalence of gastrointestinal tract (GIT) involvement in extrapulmonary tuberculosis cases ranges between 3 % and 5 %, raking sixth place in terms of frequency (9). An up to 2 % mortality rate has been reported in patients undergoing treatment for tuberculosis (10). Currently there are no local data in Colombia regarding the prevalence, morbidity and mortality of this type of extrapulmonary tuberculosis. Zoonotic tuberculosis caused by *M. bovis* represents < 1 % of the causes of GIT tuberculosis, and it is associated with the consumption of unpasteurized dairy products (11).

The pathophysiology behind infection by the bacillus can occur by the ingestion of sputum from an active focus in the lung, hematogenous or lymphatic dissemination, and direct contact from an adjacent organ. The bacillus has a predilection for the ileocecal region and the terminal ileum due to their characteristics such as stasis, abundant lymphoid tissue, increased absorption rate and direct contact of the bacillus with the mucosa (7). Additionally, in Peyer's patches, the presence of α-cells, responsible for phagocytizing foreign agents, serve as a gateway for the microorganism (11).

GIT tuberculosis has a larval, bizarre and nonspecific clinical presentation. Patel & Yagnik (12), in a study conducted in

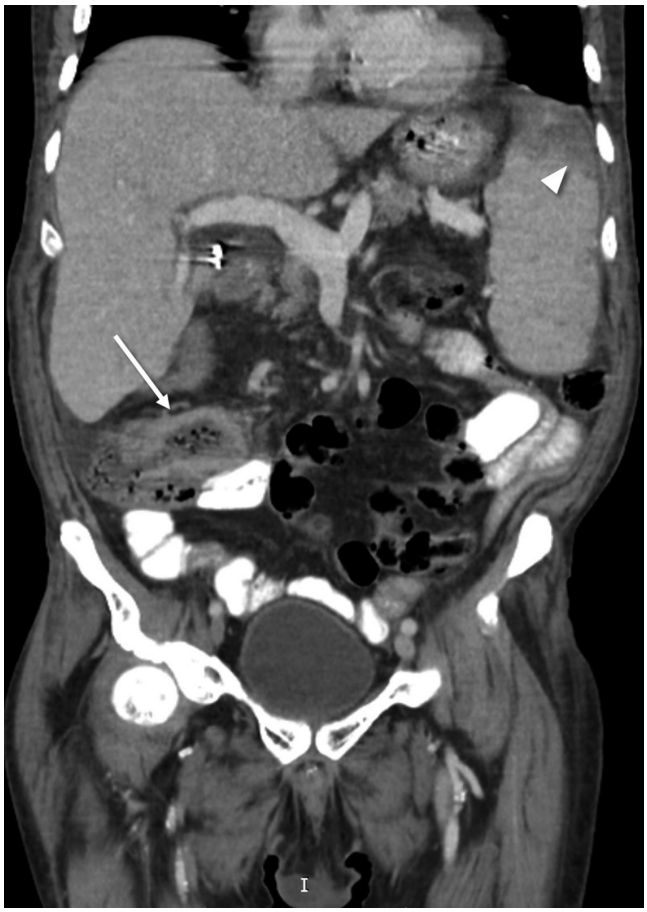

Figure 3. CT scan of the abdomen showing thickening of the distal ileum wall (white arrow) and subcapsular hypodense images corresponding to infarcts (arrowhead).

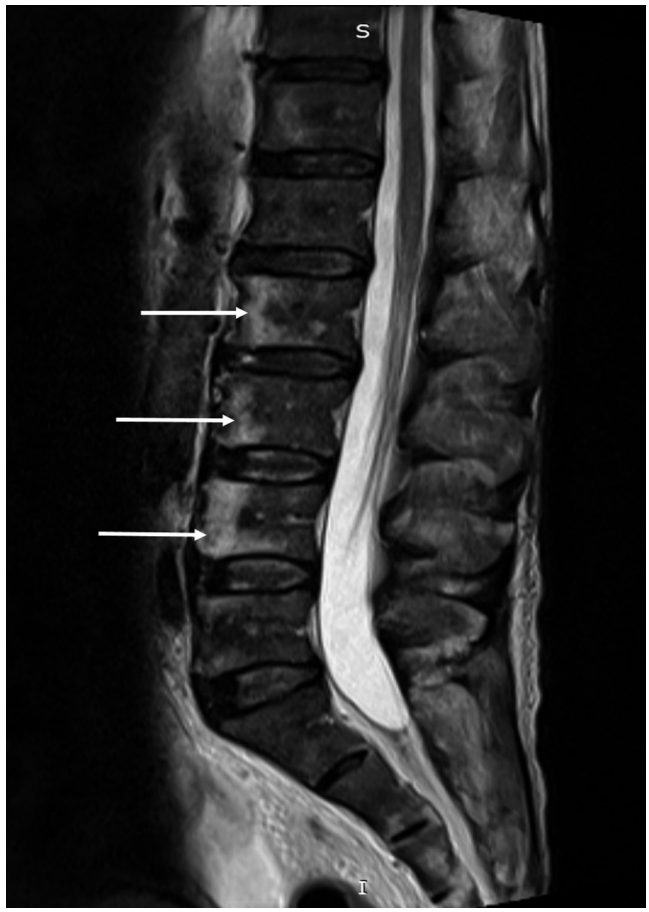

Figure 4. Magnetic resonance imaging (MRI) of the lumbar spine showing focal lytic lesions at L2, L3 and L4 (white arrows).

69 patients with GIT, 84% had ileocecal valve involvement, and the most common symptoms were abdominal pain (76%), fever (72%), weight loss (60%), chronic diarrhea (28%) and sensation of having an abdominal mass (10%). In some cases there may be complications such as intestinal perforation, fistula development, obstruction secondary to a mass (tuberculoma) or gastrointestinal tract bleeding (11, 13). Regarding macroscopic findings, transverse mucosal ulcers are the most frequent in GIT tuberculosis cases (60%), with a greater involvement of the jejunum, the ileum and the cecum; followed by hypertrophic ulcer (30%) and, finally, hypertrophic lesions (10%) with greater involvement of the ileum and the cecum (13). Histological changes include confluent caseating granulomatous inflammation, epithelioid macrophages, Langhans giant cells and lymphocytes. However, none of these findings is pathognomonic of the disease, so additional aids such as staining, culture or molecular testing are required (14).

Imaging findings are not very sensitive, with indirect signs such as obstruction, perforation or calcified mesenteric lymphoid nodules. Barium tests are useful to identify mucosal lesions, constriction, a deformed cecum or a dysfunctional and dilated ileocecal valve (13). On the other hand, findings that may observed on CT scans include an asymmetric thickening of the intestinal wall with ganglionic growth, terminal ileum stricture, para-aortic and mesenteric adenopathy with extensive areas of central hypodensity and peripheral hyperattenuation (15).

Abnormal laboratory findings are nonspecific, some of them include the presence of leukopenia, thrombocytopenia, anemia, increased erythrocyte sedimentation rate and elevated protein C levels (16). Microscopy, mycobacterial culture and PCR assay can be used to diagnose the disease or isolate the bacillus. Mycobacterial culture has a sensitivity of about 60% with a time limit of 4 weeks to obtain results. PCR is the test with the highest performance to

diagnose intestinal tuberculosis with a sensitivity and specificity of 87% and 96%, respectively, in the case of next-generation PCR assays (17). However, Kivihya-Ndugga et al. (18), in a study that compared the performance of chest X-ray, Ziehl-Neelsen staining and PCR in diagnosing tuberculosis, PCR had a specificity PCR of 84%, inferior to the 98% reported for Ziehl-Neelsen staining based microscopy. This proves that the use of PCR depends on the local prevalence of the disease and the available cost-effectiveness when tuberculosis is suspected.

Taking all of the above into account, the diagnosis of GIT tuberculosis is based on clinical suspicion and the presence of risk factors that can be confirmed in the anamnesis, supported with imaging and laboratory findings. However, the main differential diagnoses such as Crohn's disease, ulcerative colitis, lymphoma, amoebiasis, histoplasmosis, among others, must always be ruled out first (9). The treatment of tuberculosis of the GIT is similar, in terms of duration and drug regimen, to that of pulmonary tuberculosis, even 6-month treatments have a similar efficacy (11). Treatment of people with tuberculosis and HIV coinfection is based on CD4 lymphocyte levels: if they are < 100,000 cells/μL, antiretroviral treatment with HAART must be started; if they are between 100,000 and 200,000 cells/μL, the first phase of treatment for tuberculosis diseases can be implemented with subsequent initiation of HAART; finally, if they are > 200,000 cells/μL, the two phases of antituberculosis treatment can be administered before starting HAART (11). Response to treatment is usually confirmed by the disappearance of symptoms 2 weeks after starting the treatment regimen for tuberculosis and the disappearance of lesions, confirmed by means of endoscopic procedures, 3 months after starting the therapy (13).

In this paper, the case of a patient with ileocecal tuberculosis was described. This is a rare disease that, when suspected, requires ruling out other conditions more likely to be present in patients with nonspecific symptoms, persistent fever, and multiple comorbidities such as the one presented here. In addition, the unspecific symptoms and signs of our patient, together with the negative results obtained in usual diagnostic tools, made it difficult a proper management of the disease, which in turn resulted in the late initiation of treatment. We present this case as a contribution to the literature addressing GIT tuberculosis, and in our opinion, the proper understanding of this type of tuberculosis, as well as of its management, favors a proper approach of future patients with this disease.

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Conflicts of interest

None declared by the authors.

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Clinical case

Giant esophageal schwannoma, a diagnosis by exclusion: Case report

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Abstract

Introduction: Esophageal schwannomas are tumors of the perineural components of the Schwann cell nerve sheath in peripheral nerves and account for 2% of primary esophageal tumors. Its low incidence makes diagnosis challenging; however, this etiology should be considered because its clinical and imaging behavior is rapidly progressive and unusual compared to other benign esophageal tumors. **Case study:** A 38-year-old female patient with a 1-year history of dysphagia underwent upper digestive tract endoscopy and contrast chest CT showing a mass at the cervical and transmural thoracic esophagus level, obstructing the lumen and exerting a mass effect on the trachea. A biopsy revealed a spindle cell tumor with positive immunohistochemistry for the S100 marker, leading to the diagnosis of esophageal Schwannoma. The patient is currently undergoing regular check-ups and is awaiting the advice of a clinical oncologist to recommend non-surgical treatment options due to the involvement of adjacent structures. **Conclusion:** The first diagnostic impression in the case of a suspected primary esophageal tumor would be a leiomyoma based on its incidence. The present case report of an esophageal schwannoma emphasizes that this is a differential diagnosis that requires timely treatment to avoid complications and sequelae in patients.

Keywords (DeCS)

Schwannoma; Esophagus; Neurilemoma; Primary esophageal tumor; Case report.

INTRODUCTION

Esophageal schwannomas are tumors that develop from perineural components of the Schwann cell nerve sheath in peripheral nerves (1). Their incidence is rare, and in most cases they are benign. Histologically, these tumors are characterized by peripheral lymphoid nodules, benign nuclear atypia and spindle-shaped cells (2-4).

Esophageal schwannomas account for 1 in 5000 patients with esophageal tumors. They most frequently occur between the third and seventh decade of life, with a male/female ratio of 1:3 (5). Five percent of diagnosed cases can be associated with neurofibromatosis type I, which have an early presentation and the most aggressive prognosis (6). Clinically, they may be asymptomatic; however, in most cases esophageal schawannoma is diagnosed at an advanced stage, and it mainly manifests with symptoms and clinical signs such as moderate to severe dysphagia and dyspnea, associated with chest pain, epigastric pain, cough, hemoptysis, palpitations and pneumonia, depending on its location and mass effect (6).

Regarding its diagnostic approach, imaging studies (X-rays, computed tomography [CT] scans, magnetic

resonance imaging [MRI]) provide more information on the anatomical characteristics of the tumor. However, these findings do not allow differentiating a schwannoma from other submucosal tumors, for they share similar imaging characteristics (7). A correct diagnosis relies on histopathological studies and immunohistochemistry tests, being S-100 the tumor marker with the highest specificity and sensitivity for this disease, provided that in all the schwannoma case reports described in the literature this marker has been positive compared to other markers (6, 8).

CLINICAL CASE

This is the case of a 38-year-old woman who had experienced dysphagia for one year, together with occasional episodes of hematemesis; for this reason, she underwent an upper gastrointestinal endoscopy in which a 12 cm long endoluminal, friable and irregular lesion located 27 cm from the dental arch was observed and from which a sample was taken for histopathological purposes. A benign lesion compatible with leiomyoma was described in the histopathology report. In addition, a 128 mm x 66 mm x 84 mm (L x AP x T) tumor mass located in the cervical esophagus, extending to the transmural thoracic esophagus, was observed in a contrast enhanced CT scan of the chest. The lesion was exophytic, with homogeneous enhancement depending on the anterior wall, conditioned the obstruction of the light and exerted a mass effect on the trachea in approximately 70% (**Figure 1A** and **B**).

The case of the patient was taken to the medical-surgical board because of concerns regarding the histopathological findings, so performing a new biopsy of the mediastinal lesion was decided, which was achieved by means of a thoracoscopy. The following findings were informed in the biopsy report: a spindle cell tumor with immunoprofiling that favors the peripheral nerve sheath tumor without clear criteria of cellular atypia (**Figure 2**) and positive immunohistochemistry for S100 protein and negative for acute myelogenous leukemia (AML), H-Caldesmon, desmin, CD117, DOG-1, CD34, CKAE1/AE3 and STAT-6. The cell proliferation index (Ki-67) was 5%, so it was concluded that the mass was compatible with an esophageal schwannoma. A new contrast enhanced CT scan of the chest showed an increase in the size of the mass with involvement of the mediastinal pleura and the right apical pulmonary parenchyma, in direct contact with the right pulmonary artery, the aortic arch and the azygos vein arch. The case of the patient was presented again before the surgical board (thoracic, oncological and esophageal surgery services), where, after assessing the case, the tumor was deemed surgically unresectable due to its size and vascular involvement. She was referred to the clinical oncology service to consider another therapeutic option aimed at reducing the severity of her symptoms. In addition to the symptoms and clinical signs described here, the patient experienced several pneumonia episodes during the course of the disease that required inpatient antibiotic treatment and mechanical ventilation (**Figure 3**).

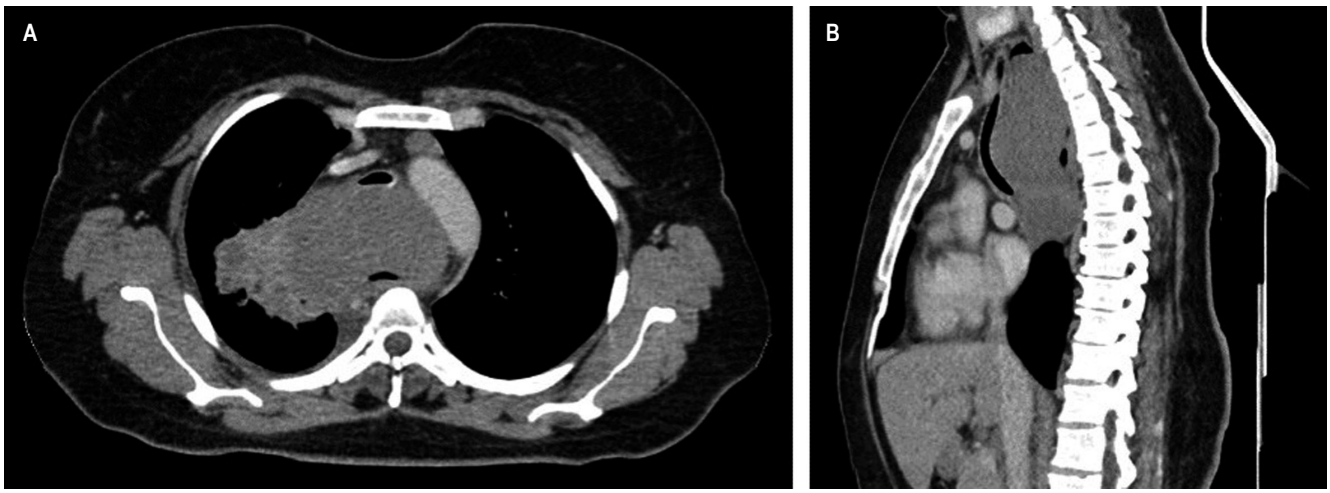

Figure 1. Contrast enhanced chest CT scan. 128 x 66 x 84 mm (L x AP x T) mass located in the middle mediastinum, without significant enhancement after the administration of the contrast medium. The mass is homogeneous, has partially defined lobulated contours, and extends from C7 to T7 with a compressive effect on the adjacent mediastinal structures, especially the trachea, that displaces the tissue in an anterior direction with a decrease in its caliber of approximately 73%; and in the esophagus, where its lumen is partially observed. Prevascular subcentimeter lymph nodes, where the largest one has a short axis of 8 mm; para-aortic lymph nodes with a short axis of 10 mm are also observed. **A.** Axial view. **B.** Sagittal reconstruction.

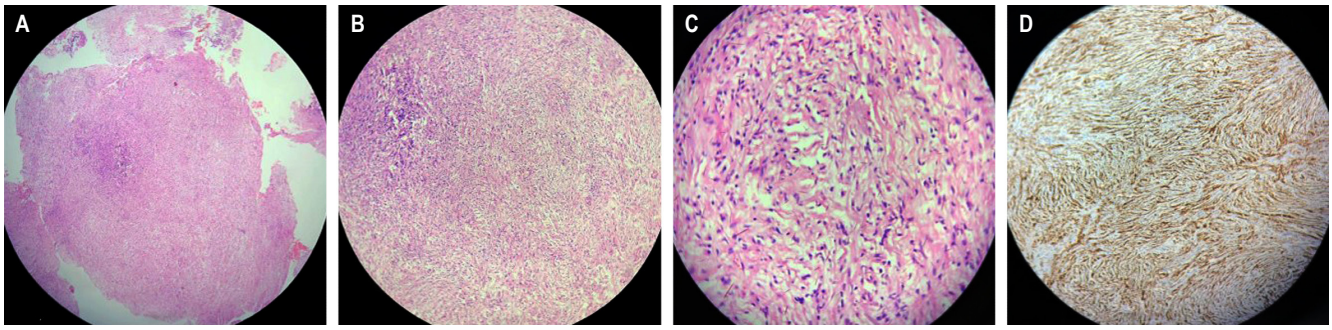

Figure 2. Microscopic study. Neoplastic lesion consisting of spindle cells and some pleomorphic cells on a fibrocollagenous stroma associated with the presence of lymphocytic inflammatory infiltrate. **A.** Hematoxylin-eosin (HE; 4X magnification) staining. **B.** HE staining (X10 magnification). **C.** HE staining (40X magnification). D. Positive immunohistochemistry for S100 protein.

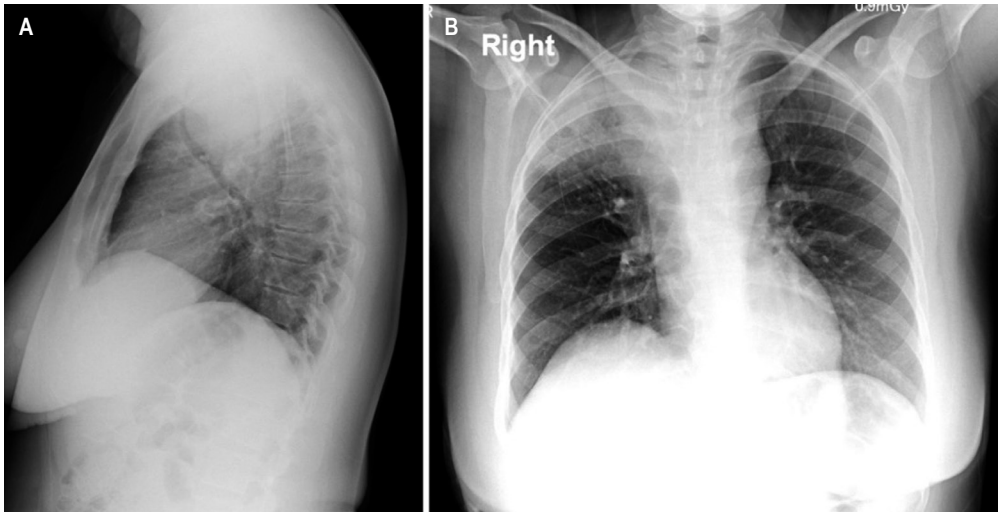

Figure 3. Chest X-ray. Mass located in the middle mediastinum with an internal air component in its upper region that does not rule out cavitation; this image communicates with adjacent consolidation of the right upper lobe, which does not rule out a fistulous tract. The mass produces an important compressive effect on adjacent structures, especially the trachea, with a decrease in its caliber of approximately 73%. Mass with involvement of the mediastinal pleura and the right apical pulmonary parenchyma, in direct contact with the right pulmonary artery, the aortic arch and the azygos vein arch without signs of infiltration. **A.** Lateral view. **B.** Posteroanterior view.

DISCUSSION

Primary esophageal tumors represent 2 % of cases; of these, 80 % are leiomyomas and only 1 %, schwannomas; the remaining percentage corresponds to other histopathological types (2, 8, 9). Esophageal schwannomas are rare and mostly benign. So far, 54 cases have been described in the literature, 6 of them being malignant; when comparing these reports it was found that our patient was in the age range between 30 and 60 years (6), but with indeterminate histological characteristics to classify the tumor as benign or malignant, since spindle cell components and some pleomorphic cells without clear criteria of atypia on a fibrocollagenous stroma associated with the presence of lymphocytic inflammatory infiltrate were found in the microscopic study, which could preliminarily suggest a benign mass, and, in the immunohistochemistry tests, a positive result was obtained for S-100 protein, the gold standard for diagnosing schwannoma, although a cell proliferation index (Ki-67) of 5% was also reported, which is higher than the average described in the literature (2%-3%) (10). From the above, an unusual development of rapid progression could be deduced, taking into account that several authors propose the presence of malignancy when there is a mass with an axis greater than 60 mm (6). In the case reported here, a mass with 66 mm

in its shortest axis was observed in the diagnostic imaging studies, which suggests malignancy.

In the literature it is common to find cases of patients with a history of masses that are first diagnosed as leiomyomas; however, if their evolution is unusual, a new biopsy, performed using another technique, is indicated when schwannoma is suspected (4, 8, 11). This diagnostic approach is necessary because most of endoscopic biopsies are superficial, so that mainly submucosal tissue is found, without really obtaining components of the peripheral nerve sheath (12). In this type of tumor, the technique used to obtain the sample for pathological and immunohistochemistry purposes is of great importance. In our case, the sample was obtained by thoracoscopy, but the initial approach was similar to what has been described in the literature, since a preliminary diagnosis of leiomyoma was made, and then, after an interdisciplinary assessment was made, a new biopsy was requested in order to confirm the schwannoma diagnosis. This could explain the underreporting of this type of tumor.

Regarding computed tomography scan findings, schwannomas share characteristics with other esophageal tumors, but they appear as rounded or oval images with defined borders, attenuation equal to or less than soft tissues, homogeneous or heterogeneous enhancement to the contrast medium depending on the presence of lipid content in the Schwann cells), trapped perineural adipose tissue and cystic spaces or small calcified areas, which are found in 5% to 10% of cases (13). The findings reported in our case are similar to those described above, but the extension of the tumor to adjacent structures such as the trachea (70% obliteration); an esophagus with a slight appreciation of its lumen and the mass effect on the aortic arch, the right pulmonary artery and the arch of the azygos vein may condition the approach to be implemented.

Esophageal schwannomas are not radiosensitive or chemosensitive, but they can be surgically resected through procedures such as right or left posterolateral thoracotomy, video-assisted thoracoscopic surgery, and robot- and video-assisted thoracic surgery plus enucleation or esophagectomy (5), depending on the tumor size, and the involvement of the esophagus and other adjacent structures. Even in the malignant schwannoma cases that have been reported, surgical treatment was implemented obtaining favorable outcomes and no evidence of recurrence was described (12). In our case, however, surgery was ruled out given the size of the tumor and the involvement of different mediastinal structures. Surgical management of leiomyoma is similar to that of schwannoma (9); in our opinion, this situation, together with the underreporting of schawannoma due to poor biopsy samples collection, facilitates said underreporting.

Currently, the patient continues to attend periodic check-up visits in order to monitor how much the functionality of her esophagus and trachea has been affected due to the mass effect exerted by the tumor. In addition, she is awaiting the concept by the clinical oncology service to evaluate possible management alternatives.

CONCLUSION

We report a case of esophageal schwannoma with a rare initial clinical presentation, S-100 marker positivity and a Ki-67 higher than what has been described in the literature; however, the patient did not show conclusive radiological or anatomopathological characteristics of malignancy, so that treatment was limited, with surgical management, the most appropriate therapeutic option, being ruled out.

Leiomyomas are the most frequent primary esophageal tumors, but obtaining a biopsy sample through an appropriate technique is of great importance, as well as achieving an anatomopathological and immunohistochemical analysis that specifies with certainty the type of histology associated with the clinical and radiological characteristics of the patient; however, in patients with a rare clinical presentation, esophageal schwannoma is a differential diagnosis in cases of primary tumors of the esophagus.

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Clinical case

Upper gastrointestinal bleeding due to atypical presentation of metastatic endometrial adenocarcinoma in the stomach. Diagnostic typing with endoscopic resources

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Abstract
Endometrial cancer is the most common gynecologic malignancy in women. Its metastatic presentation is mainly limited to neighboring organs and nearby lymph nodes, and infiltration of the upper digestive tract is uncommon. This case report depicts a patient admitted to the emergency department with upper gastrointestinal bleeding symptoms. Initially, a gastrointestinal stromal tumor (GIST) of the gastric wall was suspected, but endometrial cancer metastasis was discovered after a thorough medical examination, diagnostic imaging, and echoendoscopes.

Keywords
Endometrial cancer; gastrointestinal tract; upper gastrointestinal bleeding; metastases.

INTRODUCTION

Gastrointestinal bleeding is considered a frequent clinical condition and the main gastrointestinal emergency. Upper gastrointestinal bleeding account for 83% of cases, while lower gastrointestinal bleeding constitutes the remaining 17% (1). On the one hand, the current characteristics of patients who may develop upper gastrointestinal bleeding have changed: they are older and suffer from a highly lethal comorbidity (2). On the other, endometrial cancer is the most common malignant gynecological neoplasm in developed countries, being endometrioid adenocarcinoma its histological presentation (3). An incidence of about 60,000 new cases per year and approximately 10,000 deaths per year have been reported in the United States (4). In Colombia, by 2012, according to the GLOBOCAN (Global Observatory of Cancer) data, the age-adjusted incidence was 3.6 per 100 000 women/year (5). The occu-

rrence of endometrial cancer with metastasis in the gastrointestinal tract is rare, and the rectum is the organ most frequently affect due to local invasion (6).

We present a rare case of endometrial cancer with gastric metastasis in which the clinical presentation consisted of upper gastrointestinal bleeding of unclear origin. The patient was initially diagnosed with a GIST-type tumor (7), but later the pathology report documented the presence of endometrial tissue dependent on the fourth echolayer of the stomach wall.

CASE REPORT

This is the case of a 71-year-old woman who was admitted to the emergency department since she had experienced the following symptoms and signs during 18 hours: mesogastric pain that radiated to the lower back, together with melena; no other related symptoms were reported. Regarding any significant history of disease, she suffered from hypothyroidism, was a biological valve carrier and had a history of endometrial cancer, which was treated in July 2012 through a total hysterectomy.

The following findings were informed in the histopathology report: a uterus with a poorly differentiated endometrioid adenocarcinoma infiltrating up to 95% of the myometrial thickness, with 18 resected nodes free of metastasis and negative peritoneal fluid smear for malignant cells. At the time it was staged as a grade I tumor for a high-risk T1bN0M0, so adjuvant treatment with external radiotherapy and brachytherapy was started. The patient decided to quit the treatment after the first season and did not undergo the adjuvant brachytherapy. Provided that the patient was admitted mainly due to having upper gastrointestinal bleeding, an endoscopy was performed, where a 4 x 4 cm subepithelial ulcerated lesion located at the junction between the antrum and body of the stomach and the greater curvature. The following results were reported in the complete blood count test: absence of leukocytosis, neutrophilia, anemia, and thrombocytopenia; normal coagulation times.

Initially, it was considered that the patient had an ulcerated GIST in the distal gastric body without active bleeding and further studies were carried out to evaluate local and regional involvement, including a computed tomography (CT) scan of the abdomen and pelvis where a gastrointestinal stromal mass located in the gastrocolic space and compatible with a GIST tumor (**Figure 1**) and a retroperitoneal mass or adenomegaly located behind the head of the pancreas (**Figure 2**) were found.

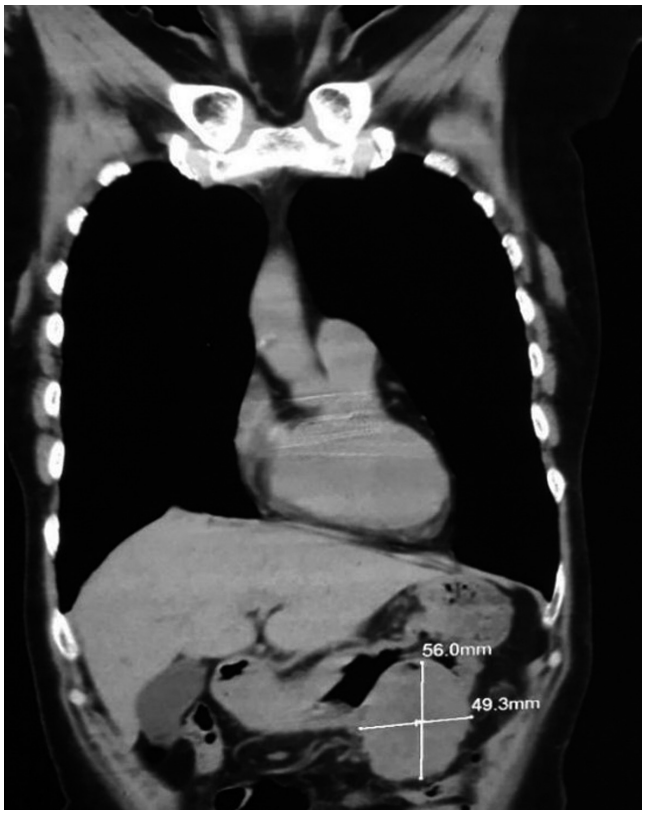

Figure 1. CT scan showing the mass in the gastric wall.

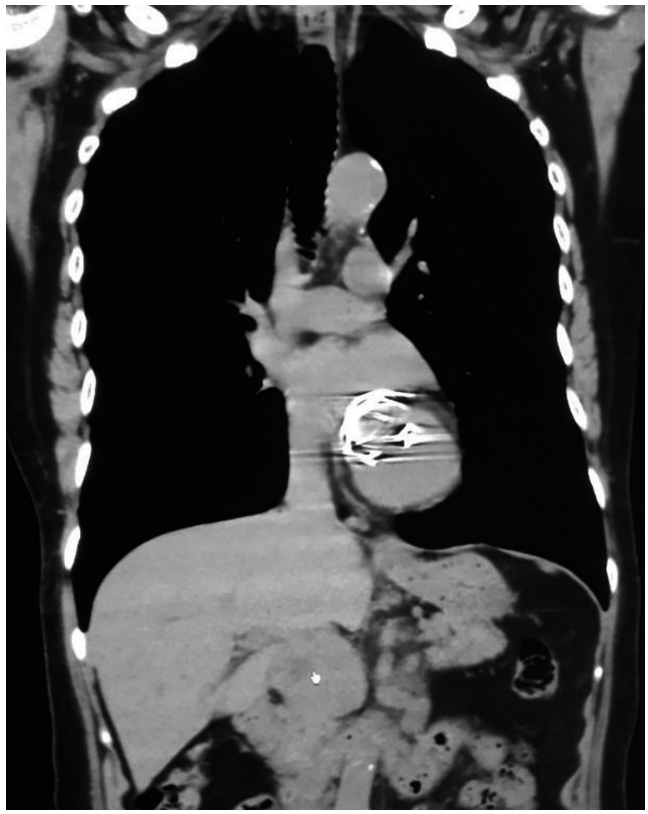

Figure 2. CT scan where the retroperitoneal mass or adenomegaly located behind the head of the pancreas can be observed.

In view of the retroperitoneal mass or adenomegaly finding, which is not a usual presentation of a GIST-type tumor, an endoscopic ultrasound (8) was performed using the Pentax-Noblux, in which a subepithelial lesion located in the greater curvature of the junction of the antrum and the body of the stomach was identified in the endoscopic view, and a 40 x 38 mm hyperechoic lesion with well-defined borders, without calcifications or necrosis, and affecting the entire wall of the stomach was observed in the ultrasound view (**Figure 3**).

Subsequently, a qualitative blue-green elastography (9) and a quantitative strain ratio of 10 and a strain histogram of 95% were performed. A 40 x 45 mm retropancreatic hyperechoic adenopathy with well-defined borders was detected in the duodenal window (**Figure 4**). Next, a blue elastography was documented when performing a qualitative elastography, a strain ratio of 10 and a strain histogram of 44% (**Figure 5**).

Once the lesion was properly characterized, the retropancreatic adenopathy was punctured using a linear echoendoscope with a 22 gauge needle (**Figure 6**). Once a sample was obtained it was sent to the pathology service for histological and immunohistochemistry analysis; likewise, another puncture was made on the subepithelial gastric lesion to

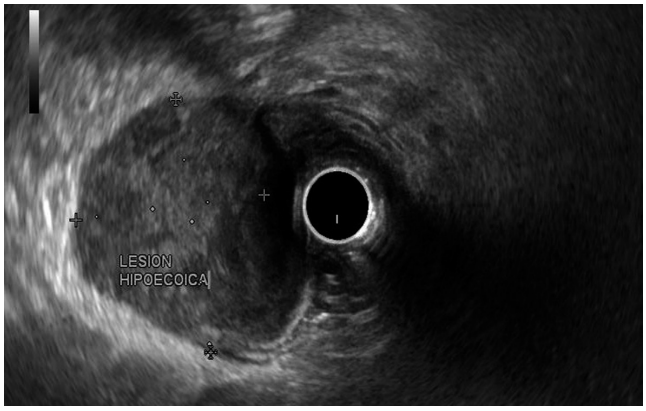

Figure 3. Gastric hyperechoic lesion.

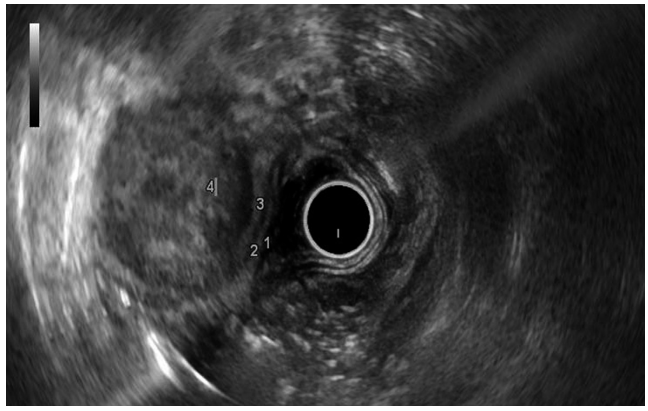

Figure 4. Retropancreatic lesion.

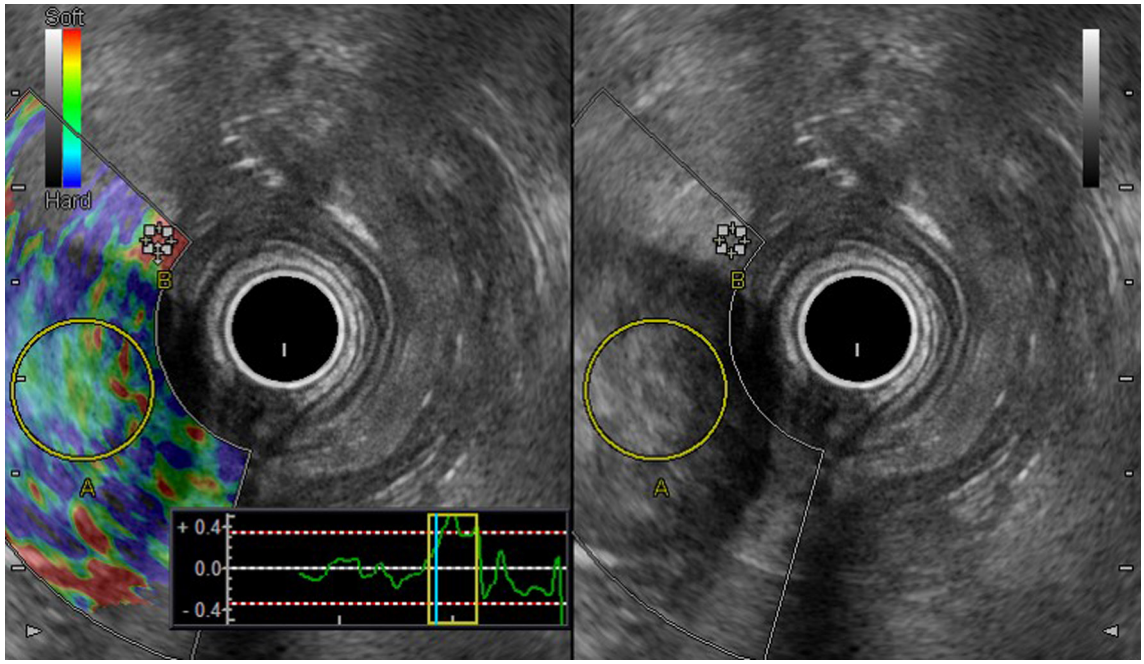

Figure 5. Qualitative elastography.

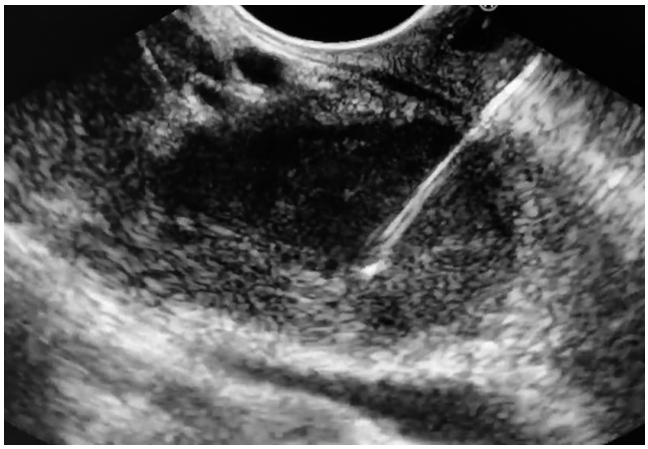

Figure 6. Puncture of the retropancreatic lesion using a 22 gauge needle.

obtain a sample, which was also sent to the pathology service to carry out histological and immunochemistry studies. The following findings were reported in the pathology reports of the stomach lesion and retropancreatic adenopathy biopsy samples: poorly differentiated carcinoma of gynecologic origin and poorly differentiated endometrioid adenocarcinoma according to immunophenotyping (**Figure 7**). Taking these findings into account, medical management was started by the oncology service, which opted for carboplatin plus paclitaxel combination therapy.

DISCUSSION

Endometrial cancer is the most common malignant gynecologic neoplasm; it accounts for 6% of all gynecologic cancers (10). In the most advanced stages of this type of cancer, metastasis most frequently occurs in nearby organs, that is, those located in the pelvis and the peritoneum, as well as the pelvic, para-aortic and intra-abdominal lymph nodes (11). Occurrence in the gastrointestinal tract is very rate, and the rectum is the part of the gastrointestinal tract most affected by this cancer (13). The importance of this case is given by its location in the stomach wall, affecting it in its entirety, and which initially led to a confusion regarding its diagnostic approach due to its clinical presentation as upper gastrointestinal bleeding and its macroscopic distribution that resembled a GIST.

Finally, thanks to an adequate anamnesis, in which the gynecologic history of the patient became clear; the performance of complementary diagnostic imaging studies such as CT scan of the abdomen and pelvis to assess tumor involvement; the proper echoendoscopic visualization of the gastric and retropancreatic lesions and the biopsies performed in both lesions, from which a satisfactory characterization of their etiology was possible based on the histopathology report, and multidisciplinary work, the therapeutic management of the lesion was completely changed from an initial surgical approach to a completely pharmacological management approach in which salvage chemotherapy was started by the oncology service.

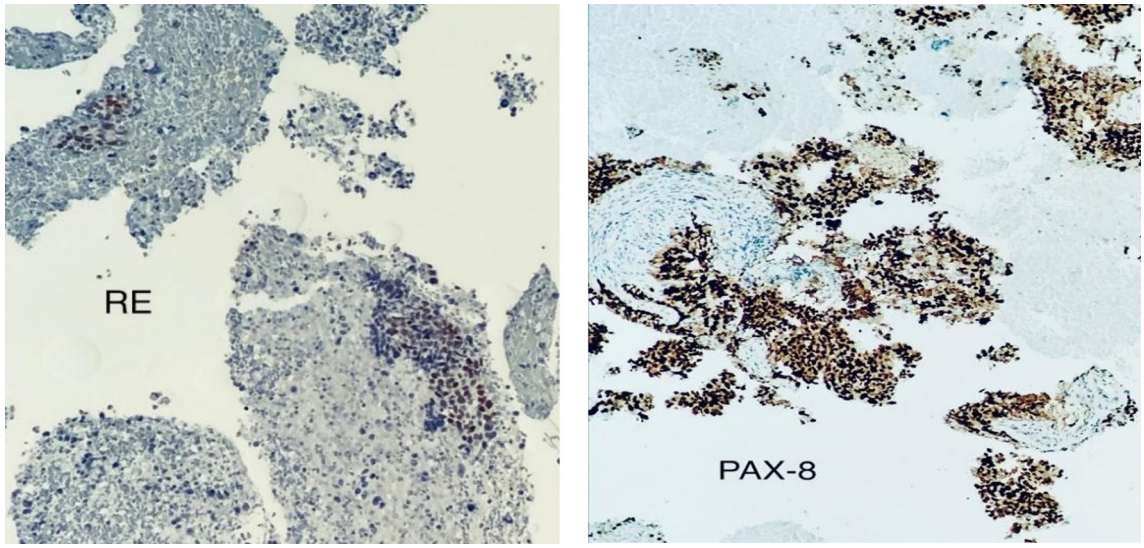

Figure 7. Pathology report images.

CONCLUSION

The importance of this case lies in raising awareness regarding one of the rare forms of metastatic endometrial cancer and showing how an upper gastrointestinal bleeding clinical presentation with the characteristics described here can mislead the initial diagnostic impression. However, thanks to the new technological advances in gastrointestinal surgery and echoendoscopy, tissue samples can be taken with high precision for proper identification of lesions, so that therapeutic approaches can be modified in order to provide patients with the best treatment option.

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Clinical case

Cystic intestinal pneumatosis in a young adult with no clinical history: Case report

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Abstract

Cystic intestinal pneumatosis refers to the presence of gas within the wall of the small or large intestine. It can be asymptomatic and life-threatening when complications occur. The causes of this entity include pulmonary, systemic, intestinal, drug, iatrogenic and traumatic factors. The following is the case of a 35-year-old man who presented with pain in his lower hemiabdomen and had no previous medical history. Imaging scans showed intestinal cystic pneumatosis and secondary pneumoperitoneum and peritonitis. The patient was taken to laparotomy, and a colonic segment was resected and sent to pathology. The diagnosis was confirmed by a biopsy. The patient was discharged after completing antibiotic treatment.

Keywords

Cystic intestinal pneumatosis.

INTRODUCTION

Cystic Intestinal pneumatosis is defined as the presence of cyst-like lesions in the intestinal wall and is divided into two categories: life-threatening intestinal pneumatosis and benign intestinal pneumatosis (1). It has a low incidence and its etiology is unclear; besides an incidence of 3 cases per 10 000 individuals has been estimated in the general population (2). The average age of onset is 45.3 ± 15.6 years, the mean course of the disease is 6 months, and a male to female ratio occurrence of 2.4: 1 have been described (3). Risk factors associated with its development include the use of certain drugs, the presence of gastrointestinal conditions such as Crohn's disease, ulcerative colitis, and other non-gastrointestinal diseases such as chronic obstructive pulmonary disease (COPD); in addition, idiopathic intestinal pneumatosis accounts for only 15% of cases (4).

As for its pathophysiology, three possibilities have been proposed as a source of gas: intraluminal gastrointestinal gas, bacterial gas production and pulmonary gas. The first theory occurs due to increased intraluminal pressure in the context of mucosal barrier injury. The second theory involves colonization of gas-producing bacteria in intramural compartments due to mucosal involvement; these bacteria produce hydrogen tensions that exceed blood nitrogen pressures, leading to a hydrogen diffusion gradient into the submucosal vessels. The last theory proposes that alveolar rupture could cause gas dissection into the vascular chan-

nels of the mediastinum, tracking caudally to the retroperitoneum and then to the mesentery of the bowel (5).

It has a nonspecific clinical presentation. Patients may be asymptomatic or present with abdominal pain, intestinal obstruction, diarrhea, hematochezia and tenesmus (1, 2). The clinical case of a 35-year-old patient with no relevant history of disease who presented with surgical acute abdomen and was taken to surgery, where a cystic intestinal pneumatosis was identified.

CLINICAL CASE

This is the case of a 35-year-old man who sought medical assistance due to having experienced a nonspecific and high intensity lower abdominal pain that radiated to the right lumbar region, without clinical signs of acute abdomen, for one month. He was initially diagnosed with urinary tract infection and was treated with levofloxacin on an outpatient basis; however, provided that his condition did not improve, he sought for medical assistance again. A contrast enhanced CT scan of the abdomen showed segmental cystic intestinal pneumatosis in the splenic flexure of the colon associated with adjacent pneumoperitonea (**Figure 1**). He was assessed by the general surgery service, where laparoscopic management was started. A plastron with omentum and pneumatosis in the splenic flexure were found during the laparoscopy, thus it was suspended and a laparotomy was then performed, where a left hemicolectomy, a partial omentectomy and a left colostomy were carried out.

The surgical specimen was sent to the pathology service, where a 15 cm serous light brown colonic segment with diameters ranging from 2 to 4 cm and fully covered by a mesentery measuring up to 4 cm was recognized. More than 80% of the mucosa had been replaced by air cystic formations, being the largest 4.5 x 4 cm and the smallest, 2 x 1 cm; with a wall measuring 0.1 cm; these lesions, although smaller in size, were also be observed in the surrounding mesentery (**Figure 2**). In addition, multiple cystic lesions located in the submucosa and the muscularis propria were observed on microscopic analysis (**Figure 3**), together with foreign body-like multinucleated giant cells and macrophages (**Figure 4**). Lesions extended into the subserosa, where reactive mesothelial cells were also observed. These findings allowed confirming the cystic intestinal pneumatosis diagnosis.

In addition, the patient received antibiotic therapy with carbapenemics for 14 days as part of the treatment of secondary peritonitis, without requiring to undergo a new surgery. There was no recurrence of digestive tract symptoms or other symptoms in the months following the surgical procedure.

DISCUSSION

Cystic intestinal pneumatosis is a rare disease characterized by the presence of cystic structures in the intestinal submucosa, the subserosa and the muscularis propria of any part of the gastrointestinal tract, most frequently in the colon (3). More than 80% of cystic intestinal pneumatosis

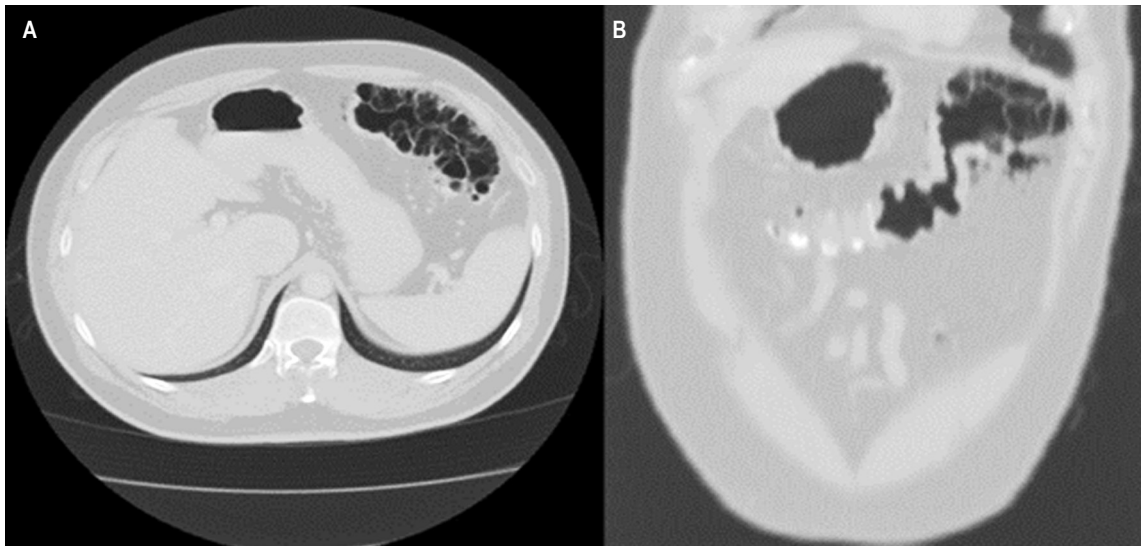

Figure 1. CT scan showing cystic intestinal pneumatosis in the splenic flexure of the colon, associated with multiple pneumoperitonea. **A.** Axial view. **B.** Coronal plane.

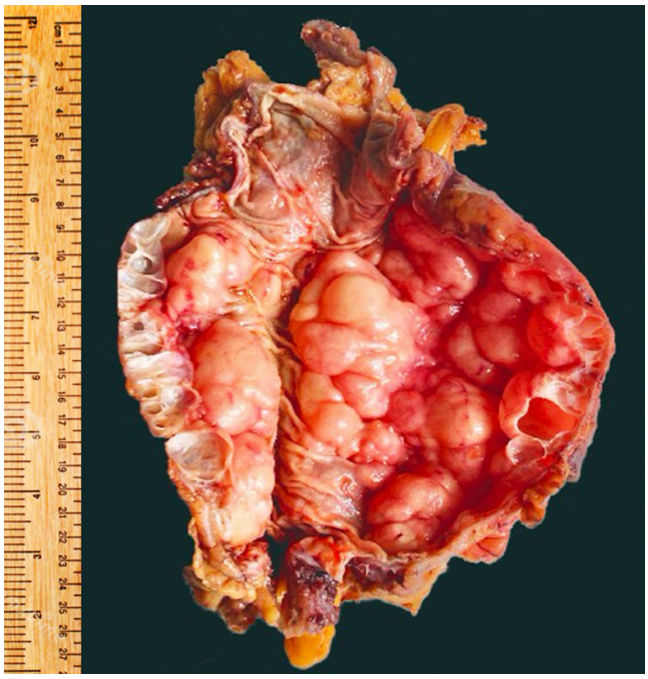

Figure 2. Macroscopic study. Segment of the colon with multiple gas-filled cystic lesions.

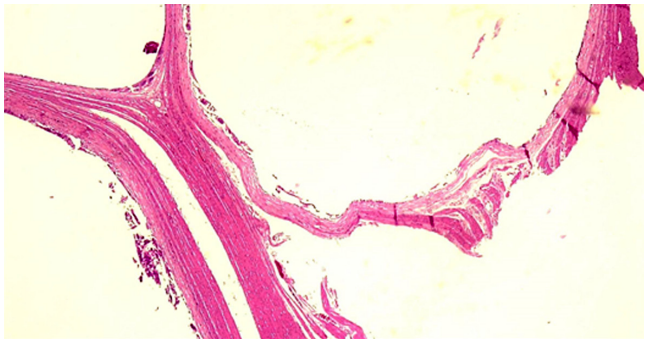

Figure 3. Cystic spaces covered by nucleated giant cells.

are considered to be iatrogenic; however, sometimes its occurrence is attributed to bacterial, metabolic or pulmonary factors, as well as to collagen tissue disorders, human immunodeficiency syndrome or the use of certain drugs such as glucocorticoids (1, 6), which causes and increased intraluminal pressure and forces the exit of gas through the altered mucosa. This in turn produces a tissue response that can be histologically evidenced by the presence of multinucleated giant cells associated with macrophages (3), whose complications may require surgical management (7).

Li-Li Wu et al. (8), in a study that included 239 cystic intestinal pneumatosis cases, reported that the patients' mean age was 45.3 ± 15.6 years, and that abdominal pain was the most common symptom (53.9 %), followed by diarrhea (53, 0 %), bloating (42.4 %), nausea and vomiting (14.3 %), rectorrhagia (12.9 %), mucous stools (12.0 %), constipation (7.8 %), and complications such as intestinal obstruction and perforation (16.3 %) (8). Life-threatening conditions were associated with mesenteric ischemia, necrosis or intestinal obstruction; these patients showed clinical signs of sepsis and symptoms of shock, presented with acute abdomen and needed surgical management (7). In conclusion, compared to asymptomatic patients, those who develop any complication have unfavorable outcomes (2). On the other hand, Greenstein et al. (9) described the following indications for surgical management: symptoms of obstruction (emesis, nausea, pain), more than 12 leukocytes per mm^3, portal venous gas visualized on CT scan, and being older than 60 years; in addition, according to these authors, patients with lactate levels > 2.0 mmol/L and a primary abdominal process have a high mortality rate.

Traditionally, intestinal pneumatosis has been associated with a high mortality rate (20%) (9). Morris et al. (10), in a study conducted in 104 patients diagnosed with intestinal pneumatosis in a 7-year period by means of CT scan

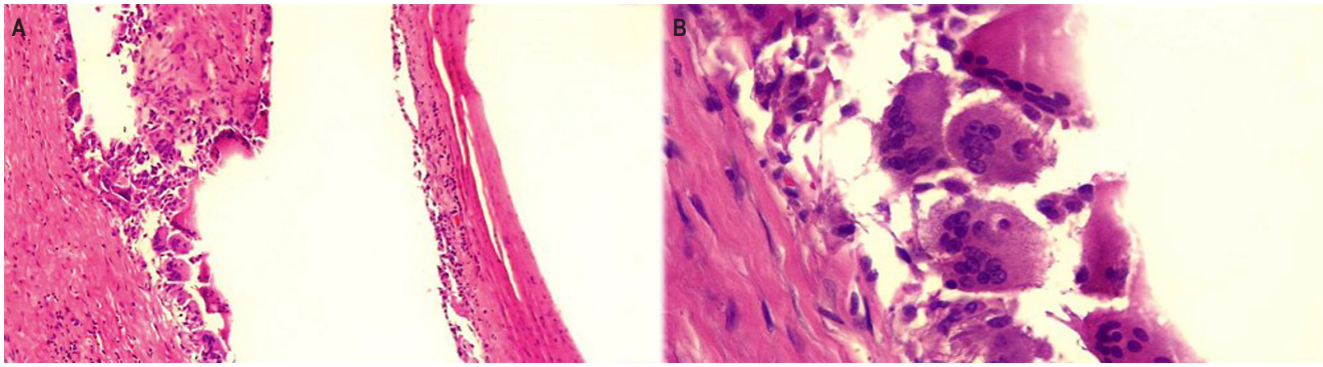

Figure 4. Histologically, cystic structures covered by foreign body-like multinucleated giant cells and mononuclear inflammatory infiltrate are evidenced. **A.** 4 X. **B.** 40 X.

findings, reported a 22% mortality rate and found that imaging findings do not correlate with the severity of intestinal ischemia. They also reported that 56% patients underwent bowel resection due to ischemia and that the colon was most frequently involved (46%), followed by the small intestine (27%) and both, the small and large intestine (7%).

Macroscopically, intestinal pneumatosis is characterized by the presence of multiple cyst-like structures in the mucosa of the intestinal wall, sometimes such structures are described as cerebriform-like. Microscopically, cyst-like formations of variable size (from millimeters to a few centimeters) are observed on the mucosa, submucosa or the muscularis propria; histologically, these cyst-like formations are covered by macrophages, foreign body-like giant multinucleated cells and mononuclear inflammatory infiltrate (3). Early cysts may be covered by endothelial cells, which can sometimes be interpreted as distension of lymphatic vessels (11).

The content of the cysts consists of a mixture of nitrogen and hydrogen with variable amounts of oxygen, carbon dioxide, butane, propane, methane, ethane and argon, which generate a foreign body type inflammatory response mediated by multinucleated giant cells that express cluster of differentiation 68 (CD68) in complementary immunohistochemistry studies (11).

In conclusion, cystic intestinal pneumatosis can be asymptomatic or life-threatening. In most cases, diagnosis is made based on imaging findings (6), in which numerous porous-like cystic air areas are evidenced within the intestinal wall (2), or based on endoscopic findings, where numerous cerebriform-like mucosal folds are visualized in the intestinal wall (8). Its treatment must be focused on the underlying disease and severe complications such as mesenteric infarction, intestinal perforation and peritonitis, which must be surgically managed (7); however, it is important to keep in mind that its prognosis varies depending on the symptoms and complications experienced by the patient. Diagnosis can often be difficult and requires an excellent clinical skill.

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Clinical case

Sphincter of Oddi dysfunction: Case report

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Abstract

Sphincter of Oddi dysfunction is a clinical syndrome caused by functional (dyskinesia) or structural (stenosis) disease. The estimated prevalence of this condition in the general population is 1%, reaching 20% in patients with persistent pain after cholecystectomy and 70% in patients with idiopathic recurrent acute pancreatitis. It is clinically characterized by the presence of abdominal pain, similar to biliary colic or pancreatic pain in the absence of organic biliary disease. It is also observed in patients with idiopathic recurrent pancreatitis, associated with elevated pancreatic or hepatic enzymes, and bile duct and/or pancreatic duct dilatation. Treatment for sphincter of Oddi dysfunction type I is based on endoscopic sphincterotomy, but there is controversy regarding the management of sphincter of Oddi dysfunction types II and III. This article presents the clinical case of a 67-year-old female patient with a history of cholecystectomy by laparotomy. After the surgical procedure, she reported abdominal pain predominantly in the right hypochondrium, colicky, associated with emesis of biliary characteristics. Cholangioresonance report revealed mild intrahepatic bile duct dilatation, and scintigraphy with HIDA scan showed sphincter of Oddi dysfunction. Endoscopic sphincterotomy was performed. The patient was asymptomatic and the sphincter of Oddi dysfunction had resolved at two-year follow-up.

Keywords

Sphincter of Oddi dyskinesia; Endoscopic sphincterotomy; Scintigraphy; Endoscopic retrograde cholangiopancreatography.

INTRODUCTION

The sphincter of Oddi, first described by Ruggero Oddi in 1887 (1), is a system of sphincters composed of connective tissue, circular and longitudinal smooth muscle fibers mostly found within the duodenal wall. The system is composed of three sphincters: the sphincter of the common bile duct, the pancreatic sphincter and a common sphincter where the muscle fibers of the other two sphincters intertwine in an 8 shape way (2).

The sphincter of Oddi is responsible for regulating the flow of bile and the exocrine secretion of the pancreas; it prevents the reflux of enteric contents from the duodenum into the pancreatic and biliary system, and it diverts bile into the gallbladder between meals, which facilitates its physiological concentration. During fasting, the sphincter of Oddi main-

tains pressures ranging from 3 mm Hg to 35 mm Hg (a pressure > 40 mm Hg is considered to be abnormal), with contractions that promote the flow into the duodenum, with an average frequency of 4 contractions per minute with an average duration of 6 seconds. Although there is a relationship with the migrating motor complex of the duodenum, most of the bile flow seems to be passive between the contractions of the sphincter of Oddi and increase due to gallbladder contraction, antral distention, the effect of cholecystokinin, and a decreased amplitude of the contractions of the sphincter in the postprandial state (3).

Sphincter of Oddi dysfunction is a clinical syndrome caused by a functional (dyskinesia) or a structural (stenosis) disease (4). It is clinically characterized by the presence of abdominal pain, similar to biliary colic or pancreatitis-like pain in the absence of an organic biliopancreatic disease. It should also be suspected in patients with recurrent idiopathic acute pancreatitis; pain and pancreatitis must be associated with elevated levels of pancreatic or hepatic enzymes, or with dilatation of the common bile duct or the pancreatic duct (5).

This syndrome occurs more frequently in women between 20 and 50-years old who have undergone a cholecystectomy. The estimated prevalence of sphincter of Oddi dysfunction in the general population is 1%, but in patients with persistent postcholecystectomy pain and in those with recurrent idiopathic acute pancreatitis it increases to 20 % and 70%, respectively. However, its true prevalence cannot be easily determined due to the lack of definitive biomarkers or diagnostic criteria (6-10).

Risk factors of sphincter of Oddi dysfunction include the presence of choledocholithiasis, cholesterosis, pancreatitis, ascaridiasis and malignancy, and the performance of endoscopic retrograde cholangiopancreatography (ERCP) or the surgical manipulation of the bile duct (5).

The Milwaukee classification for sphincter of Oddi dysfunction, which divides patients into 3 types based on its clinical presentation and altered laboratory and imaging findings, is used for its diagnosis (**Table 1**) (11-13). Somehow, the Rome IV classification, which describes 2 types of biliary sphincter of Oddi dysfunction and one third type corresponding to episodic functional abdominal pain, was published in 2016 (**Table 2**) (14).

To the best of our knowledge, to date, in Colombia there are no case reports describing a sphincter of Oddi dysfunction case; moreover, there is controversy regarding the diagnosis and treatment of this condition.

CLINICAL CASE

This is the case of a 67-year-old woman who received treatment for cholelithiasis in another health institution and who underwent a laparoscopic cholecystectomy in 2013; besides, she had a history of dyslipidemia which was being treated with atorvastatin. After the surgical procedure, she repeatedly visited the emergency department due to abdominal colicky pain predominantly located in the right hypochondrium, together with bile vomiting; however, normal liver function tests values were found in all these episodes. In December 2016, a magnetic resonance cholangiopancreatography (MRCP) showed the surgical absence of the gallbladder, a dilatation of the intrahepatic bile duct in the left lobe with an 8 mm common bile duct, and absence of choledocholithiasis (**Figure 1**). Normal

Table 1. Milwaukee classification for sphincter of Oddi dysfunction (15).

Biliary sphincter of Oddi dysfunction	Pancreatic sphincter of Oddi dysfunction
Type I: - Biliary colic-like pain - Elevated liver enzymes (AST, ALT, FA) 2 times above the normal limits and documented at least 2 times during the pain episode - Dilatation of the common bile duct (> 12 mm) or delayed biliary drainage (> 45 min)	Type I: - Recurrent pancreatitis or pain possibly associated with pancreatitis. - Elevated pancreatic enzymes (amylase, lipase) 2 times above normal limits and documented at least 2 times during the pain episode - Dilatation of the pancreatic duct (head > 6 mm and body > 5 mm) or delayed pancreatic fluid drainage (> 9 min).
Type II: - Biliary colic-like pain and at least 1 of the other 2 criteria described above	Type II: - Pain possibly associated with pancreatitis and at least 1 of the other 2 criteria described above
Type III: - Biliary colic-like pain without any other alteration	Type III: - Pain of possible pancreatic origin without any other alteration

ALT: alanine aminotransferase; AST: aspartate aminotransferase; ALP: alkaline phosphatase. Taken from: Madura JA 2nd et al. Surg Clin North Am. 2007;87(6):1417-29, ix.

Table 2. Criteria for the diagnosis of both biliary and pancreatic sphincter of Oddi dysfunction (ROMA IV classification) (14).

Biliary sphincter of Oddi dysfunction	Pancreatic sphincter of Oddi dysfunction
Diagnosis The following criteria must be met: - Biliary colic-like pain - Elevated hepatic enzymes or dilatation of the common bile duct - Absence of choledocholithiasis or other structural abnormalities. Supporting criteria: - Normal amylase and lipase levels - Abnormal sphincter of Oddi manometry - Hepatobiliary scintigraphy	**Diagnosis** The following criteria must be met: - Documented recurrent episodes of pancreatitis (typical pain with amylase or lipase levels > 3 times the upper normal limit or imaging findings of acute pancreatitis). - Exclusion of other etiologies of pancreatitis. - Negative EUS - Abnormal sphincter of Oddi manometry
Suspected biliary sphincter of Oddi dysfunction: - Biliary colic-like pain and at least 1 associated target finding.	
Episodic functional abdominal pain: - Biliary-colic pain without any other alteration.	

values were reported in both the complete blood count test and the liver function tests (**Table 3**).

Table 3. Postcholecystectomy laboratory tests results

Laboratory test	Results
Complete blood count	- Leukocytes: 10 100 x 10^3/µL - Neutrophils: 7600 x 10^3/µL - Hemoglobin: 15.5 g/dL - Hematocrit: 45.7%. - Platelets: 307 000 x 10^3/µL
Liver function tests	- AST: 19 U/L - ALT: 36 U/L - Alkaline phosphatase: 84 U/L - Total bilirubin: 0.7 mg/dL - Direct bilirubin: 0.3 mg/dL - Indirect bilirubin: 0.4 mg/dL

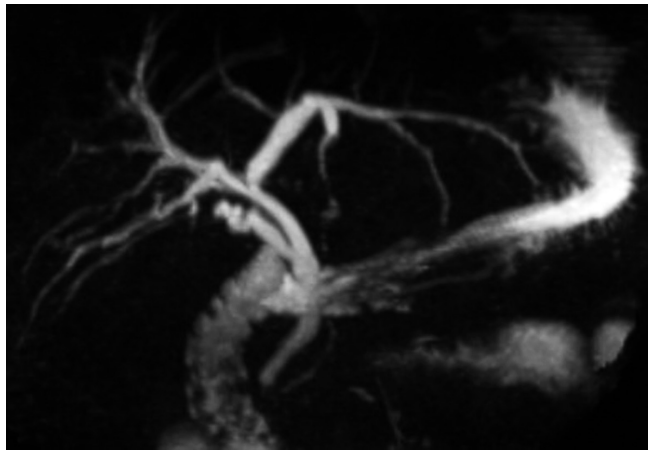

Figure 1. MRCP. Postcholecystectomy status, dilatation of the intrahepatic bile duct in the left lobe, common bile duct of 8 mm.

In October 2017, she was evaluated in a medical consultation by our service, where, due to her clinical signs and her surgical history, sphincter of Oddi dysfunction was suspected. A hepatobiliary iminodiacetic acid (HIDA) scan was then requested. The HIDA scan was performed in November 2017 and the following findings were reported: "elimination to the intrahepatic duct before 15 minutes with abundant retention in the major hepatic ducts and the common bile duct. A score of 9 points was obtained in the Sostre scale for sphincter of Oddi dysfunction (scores > 5 points are consistent)" (**Table 4, Figure 2**).

Based on these findings, a type II sphincter of Oddi dysfunction diagnosis was considered and an ERCP plus a biliary endoscopic sphincterotomy were performed in February 2018, in which a normal major papilla and dilated intra- and extrahepatic bile ducts were documented (1.3 cm). The biliary endoscopic sphincterotomy was carried out and the bile duct was explored with a basket up to the hepatic duct, obtaining a clear biliary fluid outflow.

After performing the ERCP, the patient's condition improved satisfactorily and there were no complications. In February 2020 (2 years after the ERCP), date in which the patient attended her last follow-up visit, she was asymptomatic and normal values were reported in her complete blood count test. In addition, the patient did not visit the emergency department anymore after the ERCP was performed.

Table 4. Sostre scale score.

Oddi's dysfunction. Sostre Score	Points	Patient
Common bile duct peak time		
- < 10 minutes	0	1
- > 10 minutes	1	
Biliary visualization time		
- < 15 min	0	1
- > 15 min	1	
Biliary tree prominence		
- Not prominent	0	
- Prominence of major intrahepatic ducts	1	1
- Prominence of minor intrahepatic ducts	2	
Intestinal visualization		
- < 15 minutes	0	
- 15-30 minutes	1	2
- > 30 minutes	2	
Evacuation of the common bile duct		
- > 50 %	0	
- < 50 %	1	1
- Absence of changes	2	
- Increases	3	
Common bile duct/liver ratio		
- Common bile duct 60 min < liver 60 min	0	
- Common bile duct 60 min > liver 60 < liver 15 min	1	3
- Common bile duct 60 min > liver 60 e = liver 15 min	2	
- Common bile duct 60 min > liver 60 y > liver 15 min	3	
	Total	**9**

A score of 9 points was obtained in the Sostre scale for sphincter of Oddi dysfunction (scores > 5 points are consistent).

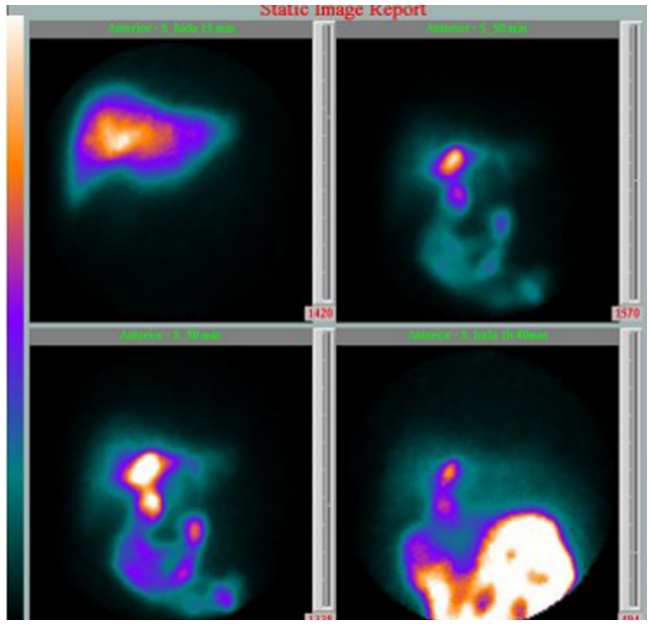

Figure 2. HIDA scan, elimination to the intrahepatic duct before 15 minutes with abundant retention in the major hepatic ducts and the common bile duct.

DISCUSSION

We present the case of a patient in which a postcholescytectomy sphincter of Oddi dysfunction diagnosis was suspected. Since diagnosis was supported by the HIDA scan findings, an ERCP was performed achieving a complete resolution of the patient's symptoms and clinical signs.

Clinically, differentiating sphincter of Oddi dysfunction from other biliopancreatic diseases, as well as from other functional digestive tract disorders is not an easy task. However, the medical record and physical examination, laboratory and imaging findings must be carefully evaluated in order to suspect its diagnosis.

The referral of patients with this condition to health centers with expertise in the treatment of biliopancreatic diseases is fundamental for their outcome, where laboratory tests (hepatic and pancreatic enzymes) and imaging studies, including abdominal ultrasound, abdominal tomography, MRCP, biliopancreatic endosonography (EUS) or isotopic techniques such as hepatobiliary scintigraphy, must be requested prior to the assessment of the patient's symptoms (10).

Regarding the analysis of the sphincter of Oddi dysfunction diagnosis, it can be noted that in patients with bile duct dilatation, diagnosis is suspected based on the symptomatology and complete blood count results; when there is a high probability of biliary disease and other causes have been ruled out based on previous imaging findings, performing an ERCP is suggested (16). On the contrary, in the case of bile duct dilatation, but low probability of biliary disease (symptomatology and complete blood count results), performing an EUS or a MRCP is suggested, since the diagnostic performance of these procedures is similar to that of ERCP, but they don't have the morbidity and mortality associated with the latter (16). Specifically, in the context of bile duct assessment, EUS has a diagnostic performance of only 53 % in patients with bile duct dilatation and abnormal complete blood count results (16), which decreases to 6% in patients with bile duct dilatation and normal complete blood count results (16). This 6% is associated with factors such as age over 65 years and having undergone a cholecystectomy (16).

The use of ERCP plus sphincter of Oddi manometry have been recommended for studying sphincter of Oddi dysfunction. In patients with clinical suspicion of the

condition and any objective alteration associated with a biliary disease (type II sphincter of Oddi dysfunction), an elevated sphincter of Oddi pressure (> 40 mm Hg) while in resting position is a diagnostic criterion for sphincter of Oddi dysfunction, as well as a good predictor of symptom resolution after undergoing a biliary endoscopic sphincterotomy. However, the probability of developing post-ERCP pancreatitis and sphincter of Oddi manometry pancreatitis can be up to 30 % (11, 17-19). In our opinion, this level of risk associated with the performance of a diagnostic study is unacceptable, not to mention the fact that the possibility of false negatives can be up to 65% (20, 21).

Research has been conducted on diagnostic and therapeutic methods including Nardi test, secretin-enhanced MRCP, cholecystokinin scintigraphy, functional luminal imaging probe, calcium channel blockers, tricyclic antidepressants, nitroglycerin, somatostatin and botulinum toxin. To date, none of the above alternatives has been shown to have relevant clinical usefulness (22-29).

Biliary endoscopic sphincterotomy is indicated in patients with type I sphincter of Oddi dysfunction; no other additional studies are required in these patients (20, 30). On the contrary, in those with type II and III sphincter of Oddi dysfunction, diagnosis and management are controversial. In our opinion, a hepatobiliary scintigraphy should be performed before ERCP in all patients with suspected type II and III sphincter of Oddi dysfunction, provided that this nuclear medicine procedure has, at least, a specificity of 90% (14, 31-34). In addition, in the evaluation of postcholecystectomy biliary colic-like pain, scintigraphy is included in the diagnostic algorithm (14).

Treatment in patients with type II sphincter of Oddi dysfunction consists of biliary endoscopic sphincterotomy, because clinical response, despite being variable, is generally favorable when the procedure is performed by an expert, with some reports describing that this treatment is successful in up to 90% of cases. We do not suggest performing a sphincter of Oddi manometry prior to the biliary endoscopic sphincterotomy because of the aforementioned risks of complications and the debatable relationship between sphincter of Oddi manometry findings and sphincter of Oddi dysfunction (12, 35-37).

Patients with type III sphincter of Oddi dysfunction are the most difficult to diagnose due to the absence of abnormal laboratory and imaging finings; in addition, there is controversy regarding their treatment. These patient do not benefit from the performance of ERCP and biliary endoscopic sphincterotomy (the severity of symptoms decrease only in approximately 20%) (38-41); on the contrary, they are exposed to the risks inherent to these procedures (42). Therefore, treatment in these patients must be symptomatic and based on medications used to treat functional gastrointestinal disorders (43).

In conclusion, we suggest suspecting sphincter of Oddi dysfunction in patients who present with symptomatology compatible with biliary colic-like pain or pain of pancreatic origin after having undergone a cholecystectomy; likewise, the diagnostic suspicion should be based on tools other than sphincter of Oddi manometry (scintigraphy) that, based on their specificity, allow making a decision regarding the performance of an ERCP plus a biliary endoscopic sphincterotomy to achieve the resolution of symptoms.

Finally, this case serves as a starting point for conducting prospective studies in other population groups.

Conflicts of interest

None declared by the authors.

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Clinical case

Subcapsular hepatic hematoma after ERCP. Case report and literature review

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Abstract

This is the case of a 68-year-old female patient, with no relevant history, who was classified as intermediate risk for choledocholithiasis due to her symptoms and lab test results. The diagnosis was confirmed by means of cholangioresonance. She was taken to ERCP on two occasions; the first failed due to intradiverticular papilla, and during the second attempt (successful with the removal of the stone), the patient had a torpid post-procedure evolution, with marked abdominal pain and anemization. An abdominal tomography with contrast was performed, which confirmed the diagnosis of subcapsular hematoma. A conservative management was implemented, achieving adequate bleeding control.

Keywords

Endoscopic retrograde cholangiopancreatography; Complication; Hematoma.

INTRODUCTION

Endoscopic retrograde cholangiopancreatography (ERCP) is a minimally invasive procedure used as a therapeutic method to treat different biliary or pancreatic diseases. It was created in 1968 to visualize the biliary tree and since 1974 it has made possible to make approaches to the ampulla of Vater, such as papillotomy (1-3). However, it is not a harmless procedure, since complications occur in 2.5% to 8% of cases, and it has a mortality rate ranging between 0.5% and 1% (1, 3). Among these complications, acute pancreatitis (1% to 7%), bacteremia (1.4%), gastrointestinal-biliary tract bleeding (1%), intestinal perforation (1%) and acute cholecystitis (0.2%) stand out in order of incidence (1, 3). Although mortality due to these complications is not very high (0.5%-1% to 3% according to some case series) (1, 3), morbidity is high and is represented by prolonged hospital stays, intensive care unit (ICU) admission requirement, among others.

Subcapsular hematoma of the liver after ERCP is a rare complication that can lead to a fatal outcome. Worldwide, most of the literature addressing this complication consists of case reports.

CASE REPORT

This is the case of a 68-year-old man with no significant history of disease who was admitted to the emergency

department since he had experienced colicky abdominal pain of high intensity in the right hypochondrium for a whole day; no other associated symptoms were reported. The following findings were described on physical examination: abdominal pain in the right hypochondrium on palpation with no signs of peritoneal irritation.

Regarding laboratory tests, altered liver function tests values (elevated AST, ALT and alkaline phosphatase) and normal range amylase levels were reported, while leukocytosis and neutrophilia were evidenced on the complete blood count test. Then a hepatobiliary ultrasound was performed in which cholelithiasis without cholecystitis, biliary mud and prominence of the extrahepatic biliary tract were documented.

With these findings, the patient was classified as having an intermediate risk of choledocholithiasis, so a magnetic resonance cholangiopancreatography (MRCP) was performed, where intra and extrahepatic bile duct dilatation secondary to choledocholithiasis, together with a 9 mm stone in the distal common bile duct were observed.

Therefore, an ERCP was performed which showed an elongated intradiverticular papilla up to the second part of the duodenum. A wire guided cannulation up to the hepatic ducts was attempted using a papillotome; however, after 3 attempts and a Needle knife infundibulotomy, accessing the biliary tract was impossible, so the ERCP was considered to be unsuccessful. Then, 5 days after the first failed procedure, a second ERCP was attempted, where metallic guidewire cannulation up to the hepatic ducts was possible; then, a large ovoid stone was extracted from the common bile duct by means of a wide papillotomy on metallic guidewire (**Figure 1**). The patient's condition improved satisfactorily after undergoing the procedure; somehow, 8 hours later he suddenly experienced abdominal pain of high intensity in the right hypochondrium, with no signs of peritoneal irritation.

In view of the deterioration of the patient's clinical condition, a complete blood count test was requested, where anemia with a hemoglobin levels of 6.8 mg/dL and amylase levels within normal limits were reported. Based on these findings and the absence of evidence of active gastrointestinal bleeding, a contrast-enhanced CT scan was performed, which allowed confirming the diagnosis of subcapsular hepatic hematoma (**Figure 2**).

After evaluating the clinical condition of the patient and in view of his hemodynamic stability, conservative management consisting of fluid replacement, transfusion of 3 units of red blood cells, intravenous administration of antibiotics and observation at the ICU was initiated.

72 hours after conservative management was started, the patient's condition improved satisfactorily, achieving hemodynamic stability. A new contrast-enhanced CT scan of the abdomen was requested, where no changes were evidenced with respect to the findings shown in the previous enhanced CT scan. Finally, given the improvement of his clinical condition, he was discharged with indications of using oral antibiotics, analgesics and attending ambulatory follow-up at the general surgery and hepatobiliary surgery service.

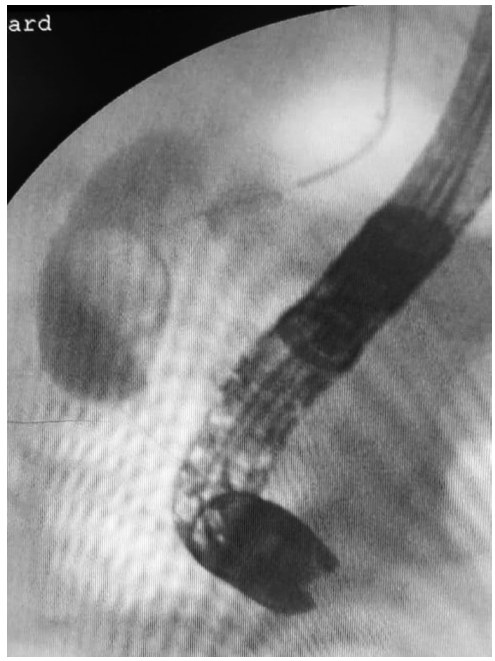

Figure 1. Intraoperative fluoroscopy - Endoscopic retrograde cholangiopancreatography, access to the biliary tract.

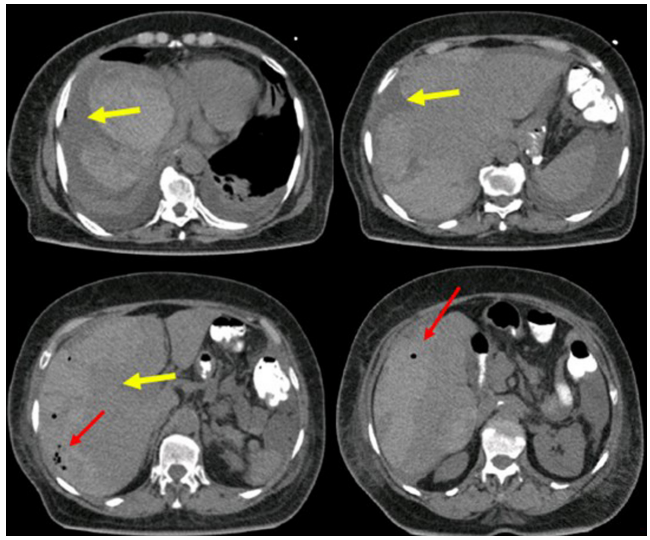

Figure 2. Contrast-enhanced CT of the abdomen. 206×150×70 subcapsular hematoma of the liver; volume: 1168 cc (yellow arrow), with free fluid in the cavity and presence of pneumobilia (red arrow).

DISCUSSION

Endoscopic approach to the bile duct (endoscopic retrograde cholangiopancreatography) is a minimally invasive procedure that, despite being safe and having low mortality rates, has a complications rate up to 7%s (2, 4, 5). These complications include gastrointestinal bleeding, which can be clinically relevant and account for 0.1% to 2% of cases (3, 5), and those that do not involve clinically relevant bleeding, which constitute 10% to 30% of cases (5). Even if ERCP is performed by an expert, its performance may be associated with the occurrence of bleeding or hematoma, conditions that can be life-threatening if they are not timely diagnosed (5, 6).

Post-ERCP subcapsular hematoma of the liver is a rare complication, with available literature consisting of case reports (1, 5). In 2001, Ortega et al. published the first case report; since then similar cases have been published (2).

According to the information we found after conducting a literature review, most patients who present with post-ERCP subcapsular hepatic hematoma are women, with a median age of 59 years; besides, in most patients, symptoms occur within the first 24 hours after undergoing the ERCP, as it happened in the case described here (7).

Abdominal pain is its most frequent clinical presentation (91%), followed by anemia (43%), hypotension (29%) and fever (20%); however, it should be noted that some patients are asymptomatic (5, 8). Computed tomography is the gold standard for confirming the diagnosis of the disease; in addition, involvement of the right lobe of the liver is reported in 95% of cases when using this imaging technique. This systematic review shows that medical treatment is the best management option. A 9% mortality rate has been reported (8).

Regarding causality, multiple theories are described, such as accidental puncture of the biliary tree leading to the rupture of the vessels of the hepatic parenchyma or the use of excessive force when extracting the stones (1-8).

To best of our knowledge, in this paper we present the case of the largest subcapsular hematoma of the liver that has been reported so far, since its size was 206 × 150 mm (being 100 × 130 mm the average size reported in the literature), and it affected both lobes of the liver (1-9).

Treatment depends on the clinical evolution and hemodynamic stability of the patient, as well as on imaging findings (4). Multidisciplinary treatment is recommended (8).

The following types of treatment can be used: conservative, surgical or interventional radiology (1, 4).

Conservative management (43.5% of cases) aims at strictly monitoring hemodynamic status (1, 5). It is indicated in patients with hemodynamic stability and in which the hepatic vein is not compressed by the hematoma (4). The use of prophylactic antibiotics is recommended due to the risk of infection of the hematoma, which has been shown to reduce mortality (8). Likewise, serial hemoglobin control tests and imaging control studies are recommended (3-5, 8) (level of recommendation: C).

Management based on interventional radiology is an alternative to surgical treatment. It consists of selective (26% of cases) or superselective embolization of the vessels or percutaneous drainage of the hematoma (17.4% of cases) (5) (level of recommendation: C).

Surgical management (13% of cases) is only indicated in the presence of deterioration of the patient's general condition, hemodynamic instability, signs of peritoneal irritation, high risk of hematoma rupture, free fluid in the abdominal cavity, contrast media extravasation, failure of conservative management, and extrinsic compression of the hepatic vein (1, 4, 8, 9) (level of recommendation: C).

If necessary, follow-up imaging studies should be also performed to evaluate is also performed to evaluate its progression (5).

Based on the literature review conducted by us and on the information described by the cases reported worldwide, we can say that the subcapsular hematoma of the liver described in this case is the largest subcapsular hematoma known to date. It is worth noting that conservative management was sufficient to control this complication and that interventional or surgical management were not required. This reflects the importance of multidisciplinary management and the impact of conservative management despite the large size of the hematoma, which must be the standard initial management approach in all subcapsular hepatic hematoma cases.

CONCLUSIONS

Post-ERCP subcapsular hematoma of the liver is a rare complication of bile duct endoscopic approach; however, it can be life-threatening if it is not timely diagnosed. Given the low number of cases reported worldwide, its true incidence remains unknown. Somehow, it is a complication that must be included as a differential diagnosis in patients who don't have a good recovery after undergoing an ERCP. Timely diagnosis is key to prevent a fatal outcome. Finally, it is worth noting that the subcapsular hepatic hematoma presented here is the largest one reported worldwide so far, and that conservative management was successful and must remain as the first-choice treatment, although it must be adjusted to each clinical situation.

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Clinical case

Cytomegalovirus-associated biliary atresia: Case report

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Abstract

Biliary atresia associated with positive cytomegalovirus IgM results is a rare condition characterized by progressive inflammatory obliteration of the intra- or extrahepatic ducts. It is caused by a perinatal autoimmune reaction against cytomegalovirus (CMV). Diagnosis is made based on positive IgM for CMV and liver biopsy with evidence of bile duct atresia. Knowledge and timely identification of this disease leads to early surgical management, considerably improving the prognosis of these patients. This is the clinical case of an 82-day-old female patient with late-onset acholia, choluria, and jaundice, associated with conjugated hyperbilirubinemia, elevated liver function tests and positive CMV IgM results. Intraoperative cholangioresonance confirmed bile duct atresia. The Kasai procedure was performed, and a liver biopsy was taken, confirming the diagnosis.

Keywords (DeCS)

Biliary atresia; Cytomegalovirus; Obstructive jaundice.

INTRODUCTION

Biliary atresia is a condition that affects the hepatobiliary system by causing a progressive inflammatory obliteration of the intra- or extrahepatic ducts. Its incidence varies from 1:3000 to 1:20 000 live births (1-3) and It occurs more frequently in females (1, 3). The onset of the disease occurs during the first weeks of life when the baby presents with progressive jaundice associated with acholia and choluria (4). Kasai biliodigestive shunt is the treatment of choice. Despite being treated, 50% of patients require a liver transplant before turning 2 years old (1).

Biliary atresia associated with positive cytomegalovirus (CMV) IgM is one type of biliary atresia (5). It accounts for 10-20% of biliary atresia cases in Europe and 50% in China (5). Its diagnosis tends to be late and is associated with a worse prognosis (1, 4).

The aim of this paper is to present the clinical case of a patient diagnosed with biliary atresia associated with positive CMV IgM, as well as discuss aspects related to this

disease, its diagnosis and the current management suggested by the relevant literature.

CLINICAL CASE

This is the case of an 82-day-old patient who was born through vaginal delivery without complications and without any significant history of disease who was referred to our health institution due to having had the following clinical signs and symptoms for two months: generalized and progressive jaundice, acholia, choluria and fever episodes. The following findings were reported on physical examination: patient in a general good condition, with jaundice, distended abdomen and painless hepatomegaly on palpation. Elevated aspartate aminotransferase (AST: 430 U/L), alanine aminotransferase (ALT: 191 U/L), alkaline phosphatase (ALP: 531 mg/dL) and total bilirubin (10.41 mg/dL) and direct bilirubin (7.28 mg/dL) levels were reported in the remission laboratory tests results. In addition, complete blood count test values and blood sugar levels were normal. Given the clinical signs of cholestasis, biliary atresia and Alagille syndrome were suspected, so a liver panel and infectious disease tests were requested, as well as diagnostic imaging studies.

Decreased total protein (5.37 mg/dL) and albumin (3.5 mg/dL) levels were reported in the liver panel; normal coagulation times were observed in the complete blood count test. Immunoglobulin G (IgG) and immunoglobulin M (IgM) antibodies were positive for CMV. In view of this, treatment with ganciclovir at a 12 mg/kg/day dose was started and further tests were performed. Viral load was positive (372 copies/mL), thus active CMV infection was confirmed. Since Alagille syndrome was also suspected, the following imaging tests were requested: abdominal, cervical, thoracic and lumbosacral spine X-rays, in which no abnormalities were evidenced. Likewise, no calcifications were observed in the cranial CT scan, but moderate right hearing loss was evidenced in auditory tests, so it was suspected that the CMV infection was probably congenital. Bearing this in mind, a liver biopsy was required for confirmation purposes.

A 2.6 mm common bile duct was observed in an abdominal ultrasound; no other relevant findings were reported. A magnetic resonance cholangiopancreatography showed a 21 mm long and 3 mm diameter collapsed gallbladder, without dilatation of the intrahepatic duct; the extrahepatic duct could not be characterized due to a technical limitation (**Figure 1**). An intraoperative cholangiography was performed, in which biliary atresia was confirmed, and a Kasai biliodigestive shunt was performed when the patient was 95 days old.

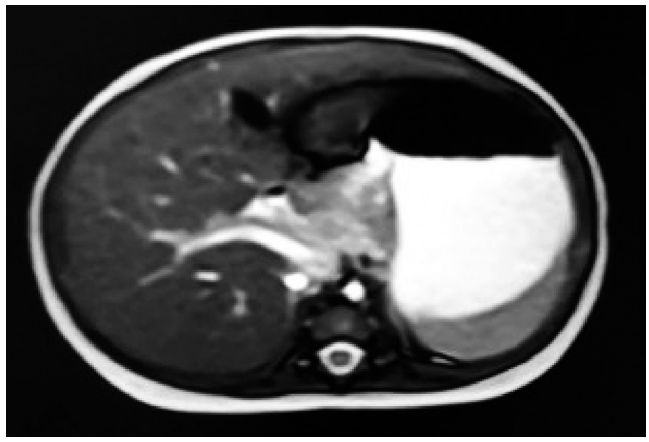

Figure 1. Magnetic resonance cholangiopancreatography.

The following intraoperative findings were evidenced: a cirrhotic and stone-like liver, with scarce bleeding on section, type III biliary atresia, without evidence of hepatic ducts or hilum dilatation, and absence of bile outflow after the section of the hepatic portal vein. Samples from the segment V were taken in order to perform a biopsy. A hepatic parenchyma with severe architectural distortion and bile ducts with mesenchyme and surrounding fibrosis showing giant cell neovascularization were described in the biopsy report. Proliferated bile ducts altered by fibrosis were seen in the portal spaces, which allowed confirming the diagnosis of biliary atresia associated with positive CMV IgM. Due to the absence of CMV deoxyribonucleic acid (DNA) samples or positive CMV IgM samples during the first 3 weeks of life, it was not possible to confirm whether the infection was neonatally acquired or congenital. After undergoing the procedure, jaundice significantly decreased and the patient was discharged. In subsequent follow-up assessments the need for liver transplant requirement was established.

DISCUSSION

Biliary atresia is a disease in which inflammatory obliteration of the intrahepatic or extrahepatic ducts is produced (1). Although its specific cause is unknown, it can be said that it is a multifactorial disease (6). Genetic, inflammatory and toxic factors have been described (6). 20% of all cases of biliary atresia are associated with other congenital malformations, in such cases it is known as biliary atresia with splenic malformation syndrome (6). The factor responsible for causing this syndrome occurs during embryogenesis. On the contrary, in the remaining 80% of the cases, where there is only hepatic involvement, it is believed that the causal factor occurs during embryogenesis. Within this group, Lakshminarayana et al. established three different

conditions with shared similarities. First, cystic biliary atresia, in which cystic changes associated with obliteration of the hepatic ducts occur; biliary atresia associated with positive CMV IgM results, the focus of this article, and finally, isolated biliary atresia, which does not share characteristics with the first two (5).

CMV is a DNA virus that belongs to the *Herpesviridae* family. It causes a common unnoticed infection in infants or adults with a prevalence of 60%-90% worldwide. It can lead to a fatal outcome in neonates (3). In the latter, its clinical manifestations vary from asymptomatic viremia to CMV syndrome or tissue-invasive CMV disease, which occurs when a specific organ is affected (pneumonitis, colitis, hepatitis) (7). Liver involvement is common in congenital and perinatal infection cases (8). Liver involvement may be mild and produce hepatomegaly or increased transaminases, or it can be moderate to severe (hepatitis, cholestatic liver disease and cirrhosis), although the latter are very rare (8).

In particular, CMV-IgM positive results have been described in patients with biliary atresia. To prove a causal relationship between the virus and biliary atresia, it has been shown that, compared to patients with biliary atresia but negative CMV IgM results, viral DNA is detected in 60% of liver biopsies in patients with biliary atresia associated with positive CMV IgM results, which is associated with a greater number of histological characteristics typical of biliary atresia (3, 9, 10). Therefore, CMV is currently considered a causative agent of biliary atresia.

It has been established that viral infection activates the immature immune system and triggers an autoimmune pattern secondary to tolerance breakdown or impaired immune regulation. It is characterized by Th1/Th2 cell differentiation imbalance and defects in the number and function of regulatory T cells leading to epithelial and ductal cell injury, fibrosis and liver cirrhosis (3, 4, 11).

The timing in which the CMV infection that leads to biliary atresia is acquired is still under study, although it is believed to occur in the third trimester of pregnancy or during the neonatal period (6). Zani et al. suggest the presence of prenatal infection if CMV DNA or positive CMV IgM are detected in the first 21 days of life. However, obtaining these laboratory results is not a usual finding (10).

Biliary atresia associated with positive CMV IgM results differs from other types of biliary atresia: its clinical manifestations have a late onset. The patient is born apparently healthy, but after the second week of life obstructive cholestasis is developed, which in turn prolongs over time (5). Given this clinical spectrum, other neonatal cholestasis etiologies must be ruled out (12). The most important complementary tests for reaching a diagnosis are liver function tests, in which elevated liver enzymes and hyperbilirubinemia resulting from elevated direct bilirubin levels, are evidenced; viral serology with CMV IgM positivity; imaging findings confirming the presence of biliary atresia, and a liver biopsy (5).

Regarding diagnostic imaging findings, a meta-analysis reported that ultrasound showed a sensitivity and a specificity of 74.9 % and 93.4 %, respectively, for the diagnosis of biliary atresia. This low sensitivity was attributed to the varying expertise of the operator (13). Magnetic resonance cholangiopancreatography has a sensitivity of 87.7% and specificity of 64.7% (13). Liver biopsy continues to be one of the most reliable methods to reach a biliary atresia diagnosis (14). Specifically, expanded portal ducts, proliferation of the bile ducts, fibrosis and marked hepatic inflammation are evidenced in cases of biliary atresia associated with positive CMV IgM results (1).

Treatment consists of Kasai biliodigestive shunt, a procedure that, when performed within the first 45 days of life, is associated with better prognosis and survival rates (15). However, in patients with biliary atresia associated with positive CMV IgM results, its late clinical presentation and late diagnosis postpones surgical management, which, according to several studies, is performed on average when the patient is 70-75 days-old (10, 16), which decreases postoperative jaundice clearance and increases the probability of requiring liver transplant in the short term (4).

Post-surgical treatment is performed using ursodeoxycholic acid, antibiotics and fat-soluble vitamins (4). So far, several studies have assessed the efficacy of antivirals in the treatment of biliary atresia associated with CMV IgM positivity (1, 17). For example, Parolini et al. showed that treatment with ganciclovir or valganciclovir improved resolution of jaundice, increased the native liver survival rate and reduced the need for liver transplant in patients who underwent Kasai biliodigestive shunt, (1, 17).

CONCLUSION

Biliary atresia associated with CMV IgM positivity has distinctive features that allow differentiating it from other causes of biliary atresia. Regarding its clinical manifestations, it has a late onset and it is diagnosed based on CMV IgM positivity and liver biopsy findings, where increased fibrosis and histologic features compatible with biliary atresia are evidenced. Treatment consists of performing a Kasai biliodigestive shunt and the postoperative administration of ursodeoxycholic acid, antibiotics and fat-soluble vitamins. At present, the effect of antivirals in the treatment of this disease is being evaluated.

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Money Bezoar: Report of atypical bezoar, its treatment, and a literature review

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Abstract

Objectives: To describe the laparoscopic management of an atypical bezoar case and present a literature review. **Materials and methods:** This is the case of a 67-year-old male patient with pyloric stenosis due to intestinal obstruction by a foreign body. **Results:** The endoscopic finding was an atypical bezoar (Money bezoar) in the prepyloric region with no possible resolution by this route, so laparoscopic treatment was considered. **Discussion:** Bezoars are defined as any object that was voluntarily or involuntarily swollen and is obstructing some part of the upper gastrointestinal tract, usually the stomach, and cannot be digested using the physiological mechanisms of the body. They are categorized based on their composition. **Conclusions:** When endoscopic treatment fails to relieve upper gastrointestinal tract obstruction caused by foreign bodies, minimally invasive surgical treatment with laparoscopic surgery is a viable and efficient option.

Keywords

Bezoars; Laparoscopy; Digestive System Endoscopy; Intestinal Obstruction.

INTRODUCTION

Bezoars are defined as any object ingested, voluntarily or involuntarily, that lodges somewhere in the upper gastrointestinal tract, most frequently the stomach, and cannot be digested by the physiological mechanisms of the body. Furthermore, they are classified according to their composition (1-4). It is an uncommon condition with a nonspecific clinical presentation (5).

Bezoars have similar characteristics such as age, anatomical location, underlying disease or excessive intake of a certain element (1-3, 5-8). There are some bezoars without these characteristics, as they are not concretions of non-digestible material or they do not fit the abovementioned sociodemographic variables, for which they could be considered atypical. However, they exhibit similar clinical signs and symptoms, and represent a high risk for patients in cases of late diagnosis, which is why their management must be optimized (1, 3).

This paper describes the use of laparoscopic management in an atypical bezoar case in which endoscopic management failed; in addition, a literature review is also presented.

CLINICAL CASE

This is the case of a 67-year-old man with diabetes, high blood pressure and cirrhosis of the liver who, after being arrested by the National Police of Colombia, was admitted to our health institution for he had experienced nausea and vomiting, associated with asthenia, adynamia and weight loss, for one month. The fact he had been on a trip outside the country for the same period of time he had been experiencing said clinical signs and symptoms stood out. In addition, he reported that before returning to Colombia he had ingested 30 capsules covered with latex and filled with cash, of which he only had expelled 20 capsules. On physical examination the patient was agitated and abdominal distension and generalized abdominal pain on palpation were evidenced; there were no signs of peritoneal irritation.

Once the ingestion of the capsule was known to us, instead of performing a diagnostic imaging test, an upper gastrointestinal endoscopy or esophagogastroduodenoscopy (EGD) was indicated as a diagnostic and management method, as shown in **Figure 1**. During the EGD, an impacted money bezoar without latex coating was found in the prepyloric region, which could not be endoscopically extracted as it was a compact mass of paper money. Laparoscopic extraction was then carried out by means of anterior gastrostomy in the antrum and body of the stomach, which was subsequently closed in 2 planes using 3-0 polydioxanone (PDS) suture with separate stitches using 3 trocars: 2 of 12 mm in the umbilical port and the right flank, and another of 3 mm in the left flank plus a liver retractor, as shown in **Figure 2**. The gastric content was extracted through the umbilical port using Endo Catch. The patient's postoperative recovery was adequate, with tolerance to the diet at 12 hours, and being discharged 18 hours after the procedure was completed. One month later, in a follow-up no complications were reported by the patient.

All procedures were performed under the supervision of the scientific and ethical committee of the institution. Besides, all protocols established by the National Police (as the competent control and surveillance body) to ensure the safekeeping of the bezoar were followed. Likewise, the National Police was in charge of carrying out the subsequent administrative procedures.

DISCUSSION

The term bezoar is believed to originate from the Arabic word *badzehr* or the Persian word *panzehr*, both of which

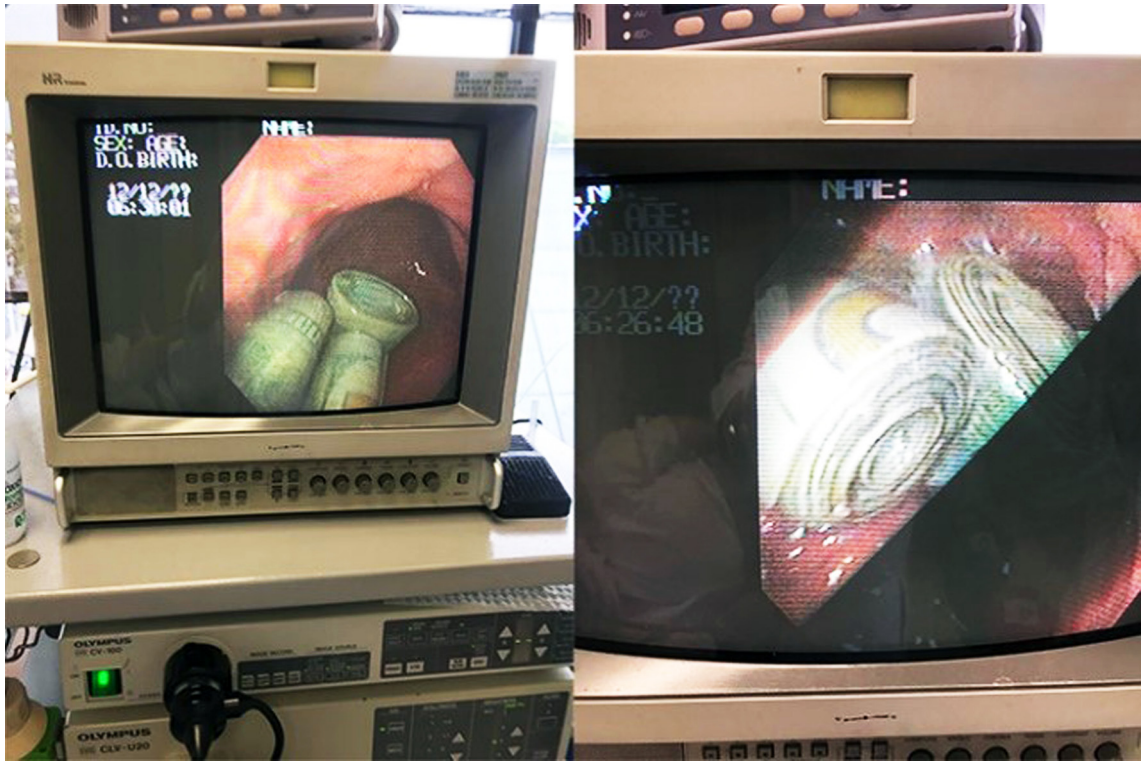

Figure 1. Money bezoar that caused a pyloric syndrome observed in the laparoscopic monitor.

Figure 2. A. Image showing the patient after the money bezoar was extracted by means of laparoscopy. **B.** Money bezoar after its extraction.

may mean "countervenom" or "antidote" (3). Generally, they are classified according to their composition. There are 4 types of typical bezoars: pharmacobezoars, lactobezoars, phytobezoars and trichobezoars, being phyto and trichobezoars the most common (1-3, 5-8). However, some literature reviews classify bezoars in 5 types, adding the foreign body bezoar type, including wood chips, resins, starch and persimmons, among others (7, 8). Risk factors for developing a bezoar are listed in **Table 1**.

This is a rare disease: it occurs in 0.06% to 4% of the population (9). The age of patients with bezoars ranges from 16 months to 79 years (1, 3); besides, 90% of patients are young adult women, mostly with psychiatric disorders (7).

Between 5 % and 12 % of patients who undergo a gastrectomy present with bezoars (6); likewise, this disease accounts for 0.4 % to 4.8 % of mechanical intestinal obstruction (IO) cases in the adult population (2, 3, 6, 9), and in 1.1 % its clinical presentation corresponds to acute abdomen that requires surgical treatment (1, 3). According to different case series of bezoars found as incidental findings during endoscopy, it has a prevalence between 0.4 % and 0.6 % (7).

Bezoars can be found in any part of the gastrointestinal tract, although most of them are located within the stomach (3, 5, 10), as it was the case of our patient, in which the bezoar was impacted in the prepyloric region. Tricobezoar is another example of intragastric bezoars; when this type of bezoar extends through the pylorus to the jejunum, ileum and sometimes colon, it is known as the Rapunzel syndrome, although it should be noted that its occurrence is very rare (1, 2). Bezoar impaction in the narrowest segment of the small intestine, 50-75 cm from the ileocecal valve, is also common (3, 6).

An atypical bezoar is a bezoar that does not match the aforementioned parameters. As shown by Masaya Iwamuro et al. (10) who reported the case of a bezoar made up of gallstones, the concept of atypia in bezoars might correspond to those with an endogenous origin (10).

Ideally, diagnosis must be early. The aim is to avoid complications associated with OI such as intestinal perforation, that may endanger the patient's life. According to the literature, bezoars diagnosis can be reached using ultrasound, CT scans or EGD (11-13). Audel Pedroza et al. (4) reported the case of a 39-year-old woman who had sought medical assistance on several episodes due to acute pancreatitis, and in which a toothbrush impacted in the duodenum was found during a biliopancreatic endoscopic ultrasound (4). As in the case of our patient, diagnosis was made endoscopically, although endoscopy was not a practical tool for

Table 1. Etiological factors for the development of bezoars (1-13)

Demographic factors	- Children with chewing deficits - Premature infants - Young women - Edentulous people - Elderly
Diet-associated factors	- Excessive persimmon intake - High fiber diet - Excessive consumption of prickly pear
Motility disorders	- Dysmotility - Diabetes - Hypothyroidism - Vagotomy - Insufficient friction surface - Myotonic dystrophy - Insufficient mucus
Gastric factors	- Decreased gastric acidity - Decreased pepsin - Presence of abnormal bacterial colonies - Delayed gastric emptying - Chronic gastritis
Intestinal factors	- Intestinal motility disorder - Intestinal stricture - Long-term constipation - Crohn's disease
Anatomical abnormalities	- Small bowel diverticula - Intestinal tumor
Neurological and psychiatric diseases	- Dementia - Trichophagia - Trichotillomania - Foreign body ingestion

extraction. Bezoars are usually asymptomatic until acute OI occurs (1). The occurrence of OI as a clinical manifestation of a bezoar will depend on its location (9). According to the literature, abdominal pain is the most common clinical sign (49%-100%), with a history of nausea and vomiting (35%-75%), bloating, constipation, epigastric pain and fever (3, 6, 5, 8); other less frequent symptoms include weight loss, anorexia, hematemesis and intussusception (5). Our patient did not experience abdominal pain, but he did suffer from nausea, vomiting and weight loss. Despite these are variable clinical signs, all these symptoms must be considered for making a bezoar diagnosis.

Bezoars are mainly removed through enzymatic methods, endoscopy and open or minimally invasive surgery (3). In the case of our patient, as well as in the case described by Audel Pedroza et al. (4), endoscopy was not an appropriate tool for extraction, because the material of the bezoar did not allow traction. For this reason, similar to our decision, Audel Pedroza et al. (4) chose to perform a laparoscopy, (4) but unlike them we used a 3-port laparoscopic approach, since there is an advanced laparoscopy expert in our institution. The choice of treatment is oriented to the case of the patient. The material, size and location of the bezoar, as well as the physiological characteristics of the patient must be taken into account (3).

Laparoscopy has been used in a small series of patients with bezoar-induced IO, with a significantly short operative time, although it often involves exploratory laparotomy, with or without enterotomy, for the subsequent extraction of the bezoar (2, 6). During surgery, a thorough exploration of the abdominal cavity must be performed to extract concomitant gastric or intestinal bezoars (6).

CONCLUSIONS

Atypical bezoars are those that deviate from the characteristics normally found in bezoars such as age, location and composition, as well as from the common characteristics of their concretion. Although they rarely occur, they can be life-threatening due to complications derived from IO, so assessing the possibility of IO is crucial at the time of diagnosis, which in turn must be based on a complete anamnesis and imaging tests, of which EGD stands out. Regarding its treatment, laparoscopic management is ideal in cases in which endoscopic intervention is not sufficient.

Informed consent

The authors of this case report declare that they have an informed consent form signed by the patient in which he authorized the use of his clinical data and images for publication purposes. Likewise, confidentiality of his personal data was preserved following the protocols of the institution.

Conflicts of interest

None declared by the authors.

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Clinical case

Villous adenoma of the esophagus in ectopic gastric mucosa: A case report

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Abstract

Introduction: Villous adenomas are lesions of the digestive tract with a high tendency to malignancy. Its location in ectopic gastric mucosa patches in the cervical esophagus is an atypical presentation of clinical and pathological interest. **Objective:** To present a case of villous adenoma in ectopic gastric mucosa of the cervical esophagus. **Methods:** A case study of a patient with a diagnosis of villous adenoma is presented, as well as a review of the current literature. **Results:** A tubulovillous adenoma with low-grade dysplasia was identified by histopathological study. Its endoscopic location was a gastric ectopic mucosa patch in the cervical esophagus. **Conclusions:** The location of villous adenomas in the cervical esophagus may predispose to the development of neoplastic lesions. Detailed evaluation of this segment using techniques, such as high-definition digital chromoendoscopy, would allow for early detection and treatment of these lesions.

Keywords

Villous adenoma; Endoscopic submucosal dissection (ESD); Endoscopic mucosectomy; Gastroesophageal reflux.

INTRODUCTION

Villous adenomas have been described as polypoid, preneoplastic lesions that account for 5 to 15 % of adenomatous polyps. They exhibit a papillary and villous architecture with a high tendency to dysplasia associated with a high mitotic activity and epithelial renewal, with malignant transformation rates up to 72 %. They are frequently found in the colon or the rectum; however, a few cases of villous adenomas occurring in the upper digestive tract, especially in the esophagus, have been described (1, 2). The finding of this type of lesions in an ectopic gastric mucosa patch in the cervical esophagus has been described in few cases; besides, these lesions are frequently underdiagnosed, since they are located in an area in which decreased endoscopic occurs due to the rapid passage of the endoscope. Furthermore, these adenomas are considered to be congenital, and therefore it is believed they have a low malignant potential (2, 3).

The case of a patient with a villous adenoma found in an ectopic gastric mucosa patch located in her cervical

esophagus is presented. Likewise, a review of the literature about this rare condition was performed (1-3).

CLINICAL CASE

This is the case of a 41-year-old man with a family history of stomach cancer (mother) and a history of hemorrhoidectomy and chronic gastritis. Two years before visiting our institution for consultation he had been treated for *Helicobacter pylori* infection. The reason for consultation was the presence of epigastric pain and intense heartburn, predominantly at night, for six months. The patient denied having experienced emesis or digestive bleeding episodes. In addition, during the consultation, he provided the treating physician with the results of an esophageal scintigraphy he had undergone and in which at least 10 episodes of gastroesophageal reflux were reported, being the most significant a 10-second episode that extended to the proximal third of the esophagus. During white light endoscopy, 2 islands of salmon-colored antral-like mucosa with well-defined borders were observed in the cervical esophagus and immediately below the upper esophageal sphincter, being the largest one about 18 x 26 mm in size. On narrow band imaging (NBI) evaluation, these 2 islands of columnar mucosa were clearly visible and, in addition, 2 small patches of adenomatous-like whitish and slightly raised mucosa were observed at the upper end of the largest island. The gastric cavity showed isolated prepyloric erosion and chronic gastropathy with multifocal atrophy (**Figure 1**).

Chronic atrophic gastritis, positive *H. pylori*, esophagitis and a lesion suggestive of villous adenoma were described in the histopathological report. First-line triple therapy for *H. pylori* infection was indicated.

Endoscopic submucosal dissection (ESD) was scheduled to resect the lesion. During the procedure, and possibly due to the scarring process secondary to the samples taken for biopsy purposes, the lesion was not successfully raised after injecting it with indigo carmine saline solution; for this reason, the resection technique was changed and complete resection was performed using the endoscopic mucosal resection (EMR) Kit Model K-009 by Olympus (injector, cap and polypectomy loop) and the ERBE VIO 200 S electrosurgical unit (endocut Q mode, level 3 effect, cut duration 1 and a cut interval 6) (**Figure 2**). Finally, the ectopic gastric mucosa patch was completely resected in 4 fragments, including the adenomatous tissue foci. No residual columnar epithelial tissue was observed and ablation of the resection borders was not performed due to the absence of bleeding and the fact that columnar mucosa itself is not a premalignant lesion (**Figure 3**).

The resected fragments were sent to the histopathology service for analysis. The larger ones were extended on a piece of cork and fixed with pins.

The following findings were informed in the histopathology report: esophageal mucosa affected by a dysplastic lesion made of tubular and villous glands, lined by a simple cylindrical epithelium, hyperchromatic nuclei without evidence of polarity loss or basement membrane involvement.

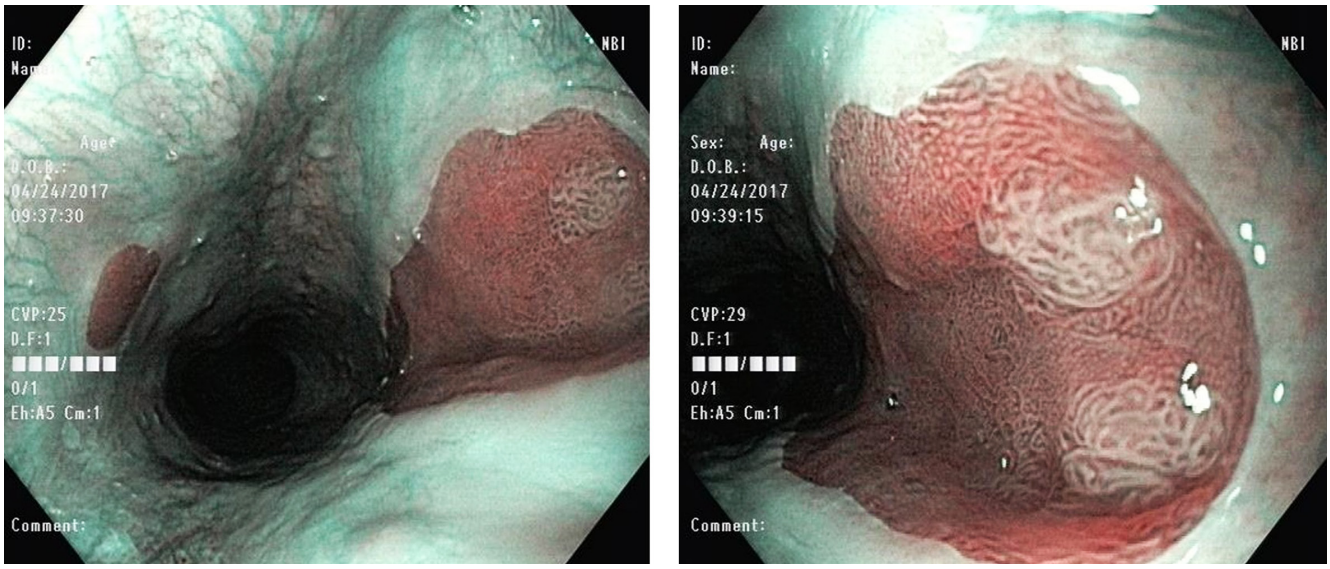

Figure 1. Ectopic gastric mucosa patch located in the cervical esophagus, with 2 islands of adenomatous-like tissue (NBI).

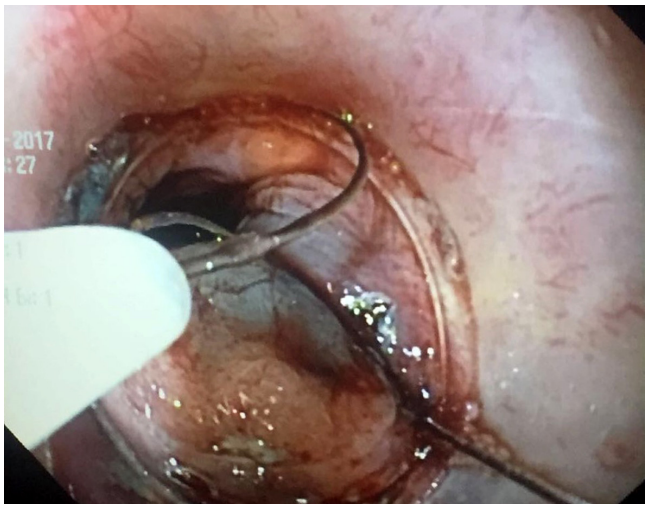

Figure 2. Mucosectomy using the EMR kit.

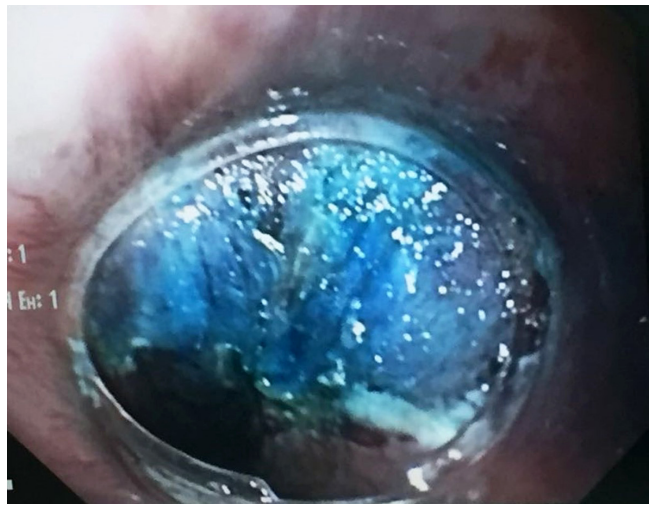

Figure 3. Post-mucosectomy endoscopic image in which a complete resection of the lesion is observed.

Scarce low grade dysplasia chronic inflammatory infiltrate compatible with villous adenoma was observed in the lamina propia (**Figures 4** and **5**).

The patient's clinical condition improved satisfactorily and he did not experience any gastrointestinal symptoms or postoperative bleeding episodes. Finally, a control endoscopic procedure carried out 6 months after the lesion was extracted evidenced the presence of a whitish tissue associated with reepithelialization in the esophagus, as well as a small central kissing scar and a small columnar mucosa island (5 mm). No other abnormal findings were described (**Figure 6**).

The patient is still being monitored by the gastrointestinal surgery group and shows an adequate clinical evolution.

DISCUSSION

Neoplastic polyps, also known as adenomas or adenomatous polyps, are premalignant lesions that can turn into adenocarcinomas. They are classified as tubular, tubulovillous and villous adenomas, being a dysplastic epithelium their histological feature. They are further subdivided into low and high grade dysplasia lesions based on the type of dysplasia, the level of nuclear agglomeration and hyperchromasia, according to their mitotic activity, cytoplasmic differentiation and distortion of cellular architecture. Tubular adenomas present between 0 % and 25 % of villous histology; tubulovillous adenomas, between 20 % and 75 %; and villous adenomas, between 75 % and 100 % (1-4).

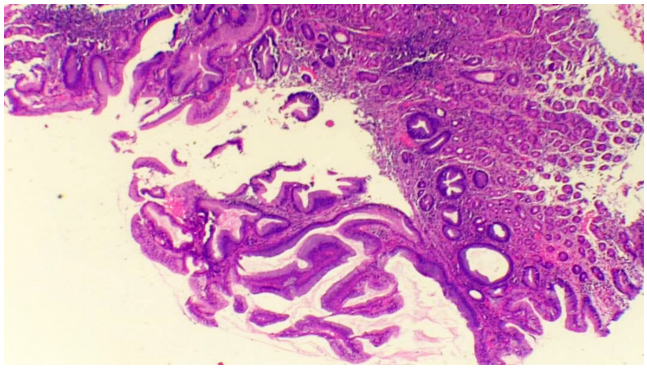

Figure 4. Microscopic image. Hematoxylin-eosin stain: 10 x magnification. Findings compatible with villous adenoma.

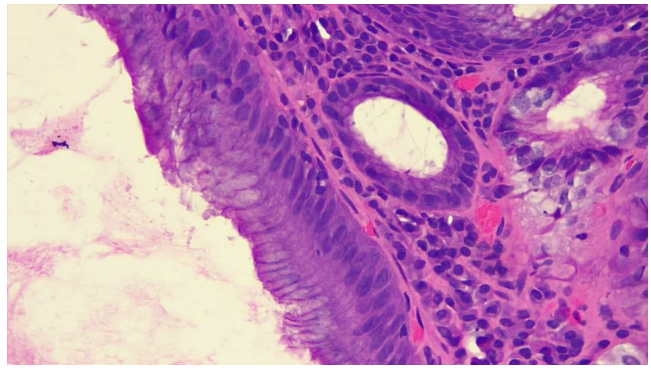

Figure 5. Microscopic image. Hematoxylin-eosin stain, 40x magnification. Findings compatible with villous adenoma.

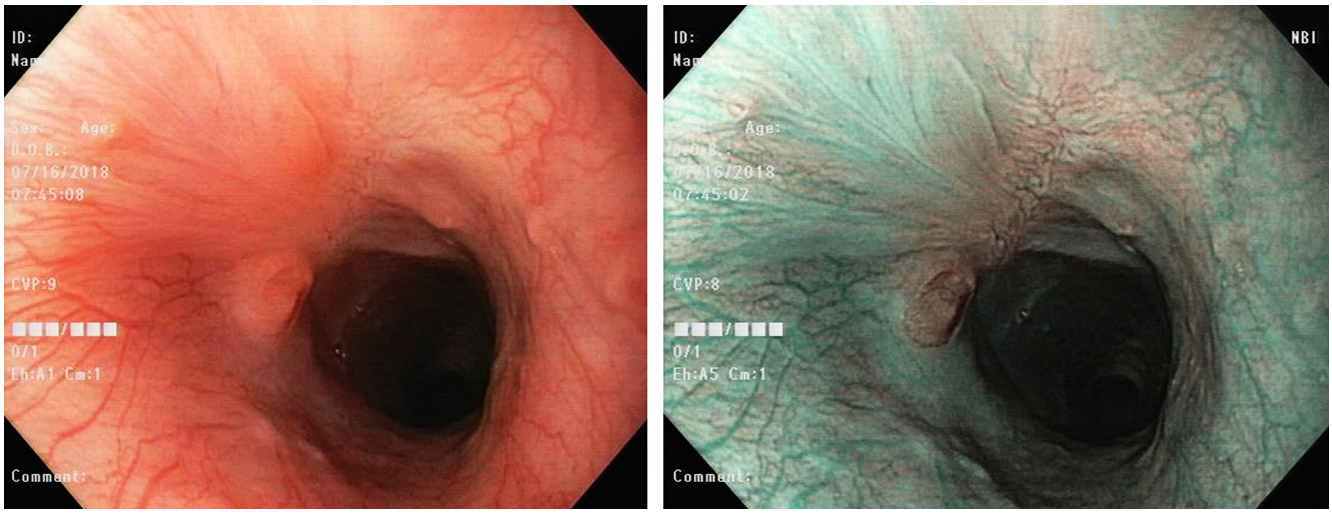

Figure 6. Follow-up endoscopy images, resection of the villous adenoma.

Villous adenomas usually have a papillary villous architecture, which has been associated more with lesions > 2 cm. This type of polyp occurs in both men and women, especially in the sixth and seventh decades of life. They are characterized by being long glandular structures extending from the surface to the center of the polyp. This subtype is associated with larger adenomas, more severe degrees of dysplasia and a greater tendency to malignancy, with malignant transformation rates of up to 72% being described (4-6). They account for 5-15% of all adenomas and occur most frequently in the rectum and the sigmoid rectum, with only a few reports of their occurrence in other parts of the digestive tract (1, 2, 4).

This condition is probably underdiagnosed and its clinical relevance is not entirely clear, since a significant proportion of patients do not report related symptoms. Although endoscopic findings may suggest a neoplastic potential, the degree of malignancy of the lesion can be only determined through histopathological analysis (1). Gastric villous adenomas are asymptomatic lesions in more than 90% of cases, but they can cause clinical manifestations such as gastrointestinal bleeding, anemia, abdominal pain or pyloric syndrome. Despite the antrum is their most frequent gastric location, case series such as those conducted by Miller et al. show that villous adenomas can also be found in the gastroesophageal junction (4, 5, 7).

In the case reported here, 2 lesions located on an ectopic gastric mucosa patch in the cervical esophagus and with endoscopic findings compatible with adenomatous neoformations were identified. These ectopic gastric mucosa patches are relatively frequent findings, but their prevalence varies greatly in the literature, with figures ranging from 0.18% to 1.6%. This discrepancy could be explained by the fact that these areas are frequently overlooked or ignored during endoscopic examinations (10, 11, 13). These islands of ectopic gastric mucosa have been associated with a congenital origin and with a low intrinsic tendency to develop malignancy. Despite this, more than 50 cases of adenocarcinomas growing from ectopic gastric mucosa patches were reported between 1950 and 2016 (8, 9, 11, 16).

Tomohiro Kadota et al. found a total of 27 cases of esophageal adenocarcinomas that formed from islands of ectopic gastric mucosa in patients aged 43-83 years, with dysphagia being the main symptom (11, 12). In 96% of cases, the neoplastic lesion was located in the cervical esophagus or the upper thoracic esophagus, the preferred location of ectopic gastric mucosa patches. The main histopathological subtypes were well-differentiated and moderately differentiated adenocarcinomas, and the presence of gastric ectopic tissue adjacent to the lesion was observed in all cases (13-16).

Ectopic gastric mucosa patches are not adaptive processes of esophageal tissue, but areas of gastric mucosa sequestered in the esophagus after a columnar epithelium is replaced by stratified squamous esophageal epithelium in an embryologic replacement process. However, the presence of intestinal metaplasia, described between 0 % and 12 % of cases, would indicate that these areas of gastric mucosa may also undergo transformation processes after being exposed to certain deleterious stimuli and represent preneoplastic conditions (8-15).

Different theories have been proposed to explain the pathophysiological changes sequence that causes an ectopic gastric mucosa island to turn into an adenocarcinoma, such

as the metaplasia-dysplasia-adenocarcinoma sequence; besides, the presence of *H. pylori* has also been associated with predisposition to malignant transformation. However, the low malignancy rates of these lesions when compared to conditions such as Barrett's esophagus have led to the conclusion that ectopic gastric mucosa islands, per se, are not premalignant lesions (8-10, 16, 17).

The case reported case, which is one of the first cases described in Colombia, helps to reflect that, although rare, there is a risk of developing potentially malignant lesions in ectopic gastric mucosa patches, which have been traditionally described as having a low tendency to malignancy.

CONCLUSIONS

In patients undergoing endoscopic studies, mainly those with gastroesophageal reflux disease, careful evaluation of the esophageal mucosa, especially in the cervical esophagus, aimed at identifying ectopic gastric mucosa patches is suggested. It is of utmost importance to remember that one of the specific quality indicators of esophagogastroduodenoscopy is the performance of a complete examination of each of the structures (esophagus, stomach and second part of the duodenum, including retroflexion of the stomach), which, in addition, must be clearly documented in the final report (18).

Ideally, this area must be evaluated using narrow band imaging (NBI), a technique based on the modification of the bandwidth of the emitted light, which allows obtaining additional information on the mucosa and the morphology of the superficial vessels. Thus, NBI is useful to identify areas of suspicious tissue of neoplasm in the squamous epithelium of the esophagus (19).

Careful endoscopic evaluation of esophageal gastric heterotopias is indicated for the assessment of findings suggestive of premalignancy. If mucosal irregularity is identified, samples must be taken for performing both a biopsy and complementary histopathological studies. The identification of adenomas in esophageal mucosa must be indicated for endoscopic resection; their percentage of villous histology will be associated with their malignant potential.

TAKE HOME POINTS

In patients scheduled for upper endoscopy and especially those presenting with any upper esophageal symptom such as dysphagia, globus pharyngeus or gastroesophageal reflux, it is suggested to perform a detailed and careful evaluation of the cervical esophageal mucosa and, if possible, to use any digital chromoendoscopy technique to facilitate the identification of ectopic gastric mucosa patches.

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Clinical case

Radioguided surgery with radiolabeled somatostatin analogues in neuroendocrine tumors: Case report

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Abstract

Introduction: The best treatment for neuroendocrine tumors is complete resection of the tumor, lymph nodes, and even distant metastases in selected cases. Sometimes, the primary tumor is small and difficult to detect before surgery, or its relapses may be difficult to locate in the fibrosis field due to previous surgeries or treatments. Although radioguided surgery allows for additional intraoperative localization, it has yet to be widely used in neuroendocrine tumors. **Case report:** A 59-year-old patient with a history of atypical resection of duodenum and pancreas due to grade 2 neuroendocrine tumor of the duodenum one year earlier. On 68Ga-DOTANOC PET/CT, a node with somatostatin receptor overexpression was found in the mesentery, with no other distant lesions. Due to the surgical history and the difficulty in visualizing the lesion on anatomical images (MRI), it was decided to perform the radioguided surgery. During the preoperative period, 15 mCi of ^{99m}Tc-HYNIC-TOC were administered verifying good uptake in the ganglion. Following the initial dissection, a gamma probe was used, detecting 5 times more activity in the ganglion than in adjacent tissues, allowing for localization and resection. The patient's progress was satisfactory, and one year later there is no evidence of relapse. **Conclusion:** Although radioguided surgery is not commonly used in the intraoperative location of neuroendocrine tumors, it is a viable option in some situations, such as the one presented here, because it allows for intraoperative detection and full resection.

Keywords

Neuroendocrine Tumors; Nuclear Medicine; Radioguided Surgery; Positron Emission Tomography.

INTRODUCTION

Neuroendocrine tumors (NETs) are a heterogeneous group of neoplasms originating from neuroendocrine cells. Most NETs overexpress somatostatin receptors, mainly types 2 and 5 (1). The European Neuroendocrine Tumor Society (ENETS) recommends, when feasible, curative surgery with removal of the primary tumor, regional lymph nodes and liver metastases (2).

However, recurrent laparotomies lead to multiple adhesions and anatomical alterations, making it difficult for surgeons to differentiate scar or inflammatory tissue from malignant tissue. The successful use of radioguided surgery (RGS) in other surgical procedures, such as sentinel node, thyroid cancer and parathyroid adenoma detection, has led to propose the use of RGS in the management of NETs (3).

Surgical intervention in patients with gastroenteropancreatic NETs can be challenging in several clinical settings.

On the one hand, some patients may have small tumors that are difficult to localize during surgical exploration (4). On the other, preoperative localization may be based only on functional imaging findings, without these tumors being localized in conventional imaging studies (computed tomography [CT], ultrasound, magnetic resonance imaging [MRI]). Localization of lesions can be difficult in sites such as the mesenteric root and the retroperitoneum (5).

However, the introduction of preoperative hybrid imaging techniques (single photon-emission computed tomography/computed tomography [SPECT/CT] or positron emission tomography/computed tomography [PET/CT]) has further improved the accuracy of CRG techniques, leading to the resection of small primary tumors, residual tumors, loco or regional relapses and distant recurrences (6).

Since this is an innovative technique, the clinical case of a patient with a NET treated at the Instituto Nacional de Cancerología (National Cancer Institute) in Bogota, Colombia, is described (**Figure 1**). Most of the CARE guidelines were followed in the description of this case report (7).

CLINICAL CASE

The following is the case of a 59-year-old patient who experienced two digestive bleeding episodes, one in June 2015 and the other in February 2017. In both episodes, an

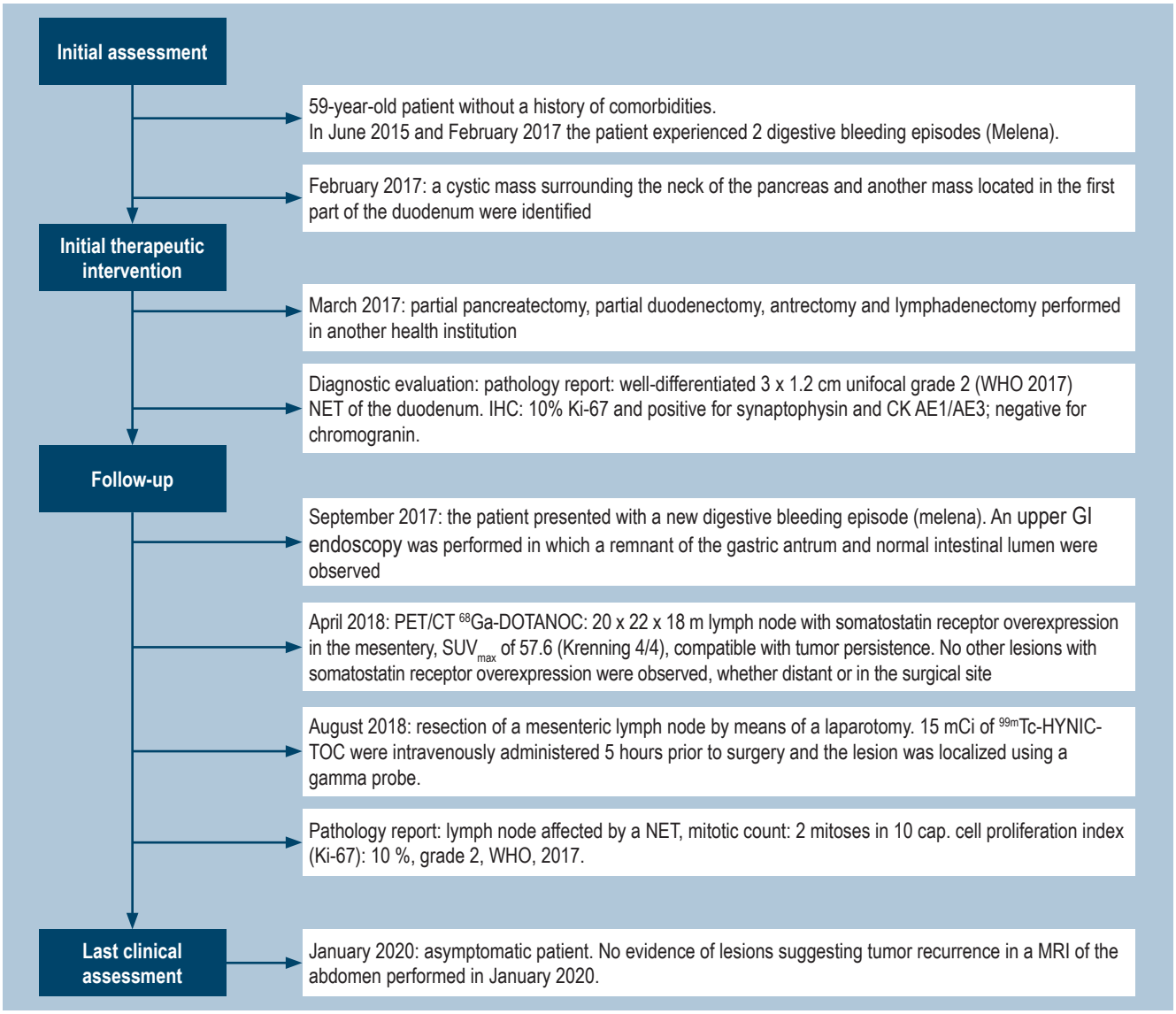

Figure 1. Flowchart of the evolution of the patient's clinical condition.

ulcer in the third part of the duodenum was observed by means of an upper gastrointestinal endoscopy; however, performing a biopsy was not possible in both procedures. In February 2017, a 44 x 32 mm cystic mass without contrast enhancement and partially surrounding the neck of the pancreas, and a 26 x 15 mass with arterial phase mild enhancement in the lumen of the first part of the duodenum were identified in an abdominal CT scan performed in another health institution. In March 2017, the patient underwent a partial pancreatectomy, a partial duodenectomy, an antrectomy and a lymphadenectomy in another health institution. The following findings were informed in the pathology report: a 3 x 1.2 cm well differentiated grade 2 (World Health Organization [WHO], 2017), unifocal duodenal NET with involvement up to the muscularis propria, without lymphovascular or perineural invasion, with a 1 x 10 cap mitotic index; negative resection margins, immunohistochemistry (IHC): Ki-67 of 10 % and positive for synaptophysin and cytokeratin (CK) AE1/AE3; negative for chromogranin.

In September 2017, the patient presented with another digestive bleeding episode (melena), so a new upper GI endoscopy was performed in which patchy erythematous mucosa in the fundus and the body of the stomach, remnant of the gastric antrum and normal intestinal lumen were observed. In October 2017, the patient underwent a somatostatin receptor scintigraphy in another health institution and in which an uptake in the right paramedian mesogastrium, Krenning 3/4, positive for somatostatin receptor overexpression, and suggestive of tumor recurrence was reported. Therefore, a ^{68}Ga-DOTANOC (3.5 mCi) PET/CT was performed (**Figure 2**) in April 2018, which allowed finding a 20 x 22 x 18 lymph node with somatostatin receptor overexpression in the mesentery, above the third part of the duodenum, and maximum standardized uptake value (SUVmax) of 57.6 (Krenning 4/4), compatible with tumor persistence. No other lesions with somatostatin receptor overexpression were observed, whether distant or in the surgical site.

Since the CT scan of the abdomen performed in September 2017 did not show the node as it was not readily visible and given the uncertainty of the postoperative anatomy or the type of digestive reconstruction the patient had, a RGS was scheduled after discussing the case with the NETs multidisciplinary board.

In August 2018, the patient underwent a laparotomy in which a mesenteric lymph node was resected. The patient was intravenously administered 15 mCi of metastable tech-

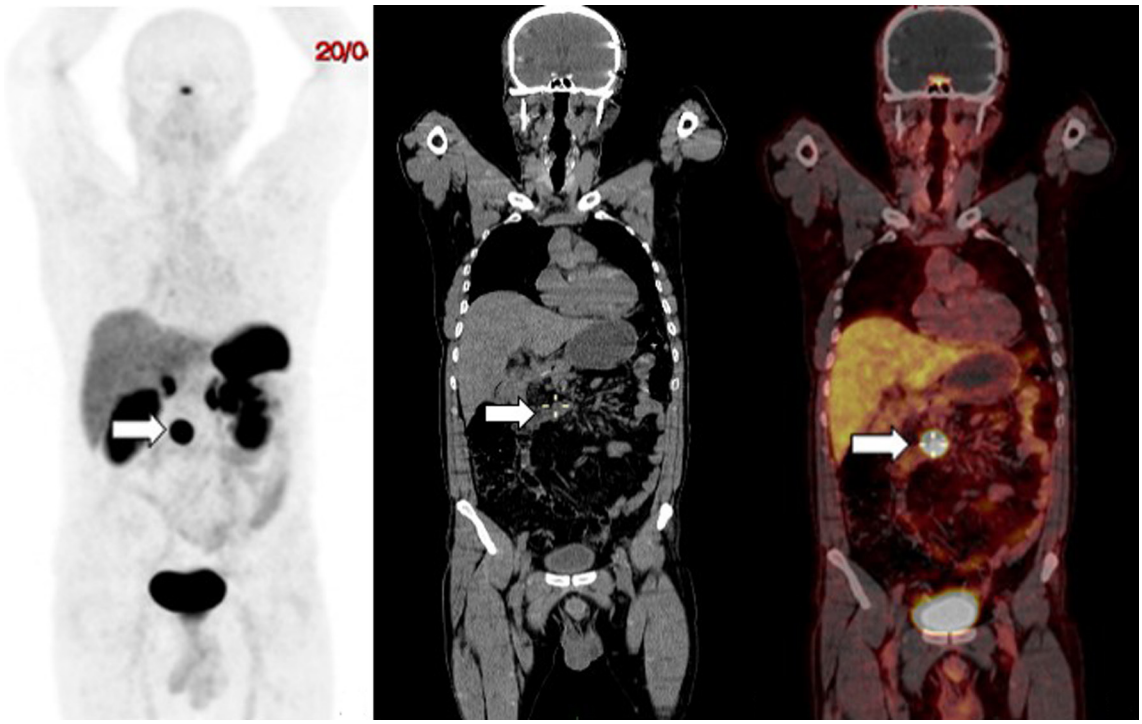

Figure 2. 59-year-old patient with a duodenal NET. The ^{68}Ga-DOTANOC PET/CT showed a 20 x 22 x 18 lymph node with somatostatin receptor overexpression located in the mesentery (arrows), above the third part of the duodenum with a SUVmax of 57.6 (Krenning 4/4). **A.** Maximal intensity image. **B.** Low-dose CT coronal view. C. PET/CT fusion image.

netium-99-hydrazinonicotinyl-Tyr3-octreotide (^{99}mTc-HYNIC-TOC) 5 hours before surgery (**Figure 3**) and the lesion was localized using a gamma probe. The following intraoperative findings were reported: a 2 cm mesenteric lymph node with an activity of 3052 counts, as recorded by the gamma probe. The activity in the tissue adjacent to the lesion was less than 700 counts (**Figure 4**). The pathology report confirmed the presence of a lymph node affected by a grade 2 (WHO, 2017) NET, mitotic count: 2 mitoses in 10 cap; cell proliferation index (Ki-67): 10%.

After the RGS, the patient continued to attend follow-up visits in the oncologic endocrinology and gastroenterology services of the institution. The patient was last assessed, at the time of writing this report, in January 2020, where no evidence of lesions suggesting tumor recurrence was observed in a MRI of the abdomen performed in the same month. Currently, the patient is asymptomatic.

DISCUSSION

The incidence of gastroenteropancreatic NETs has increased to approximately 7.8 cases per 100 000 persons each year, while a prevalence of approximately 35 cases per 100 000 persons has been described (8).

Surgical resection is the best curative treatment option for patients with early stage NETs. Complete removal of the tumor is an important prognostic factor in patients with gastroenteropancreatic NETs (9), as it improves their quality of life and reduces the incidence of metastases. For this reason, achieving R0 or R1 resection has been associated with better survival outcomes (3).

Likewise, determining both the extent of the tumor (localization and metastasis) and the location of the primary tumor is essential in the management of NETs. Certain locations, such as the small bowel, may be associated with multicentricity and special attention must be paid to ensure an adequate resection (10). Intraoperative localization can be achieved using traditional surgical, radiological and endoscopic techniques, including palpation, endoscopic marking and intraoperative ultrasound (11).

In addition, NETs can also be detected with RGS techniques using radiotracers and a gamma detection probe (11). The radiopharmaceutical is administered preoperatively or intraoperatively, and the gamma probe is used to detect the primary tumor, lymph node involvement or metastatic disease (12).

CRG has shown to be useful in the management of NETs in the detection of both occult and small tumors (1). This technique allows optimizing the identification and com-

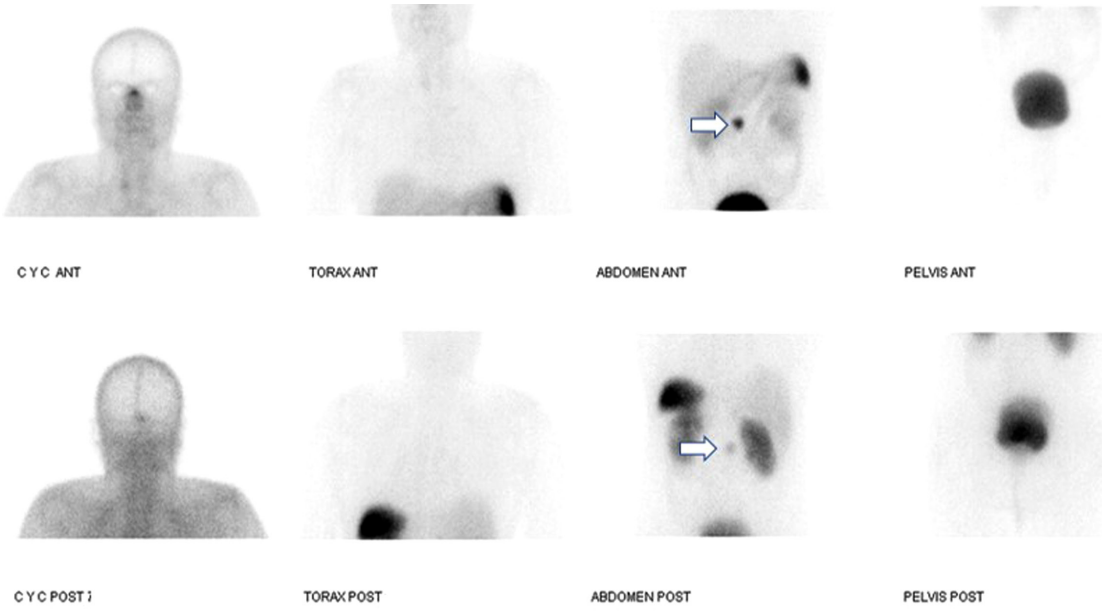

Figure 3. ^{99}mTc-HYNIC-TOC somatostatin receptor scintigraphy performed on the day of the surgery. Uptake in the mesogastrium (arrows), which corresponds to a lymph node with somatostatin receptor overexpression (Krenning 4/4) and that had already been identified in a ^{68}Ga-DOTANOC PET/CT.

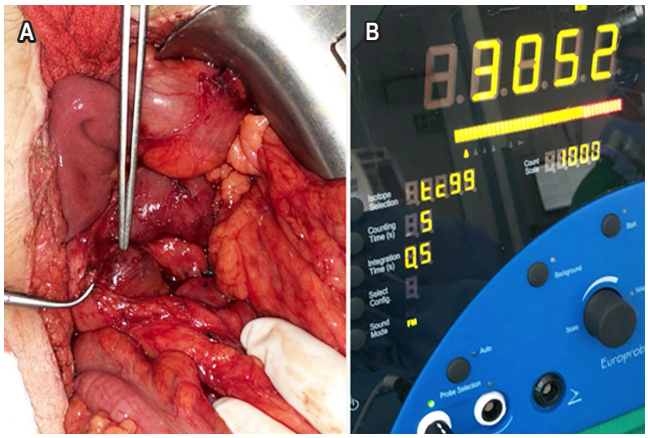

Figure 4. A. Successful radiolocalization of mesenteric adenopathy. **B.** Gamma probe that was used.

plete surgical resection of all possible areas affected by the tumor (13). In the context of tumor or lymph node relapse, cancer staging, using functional imaging with ^{68}Ga-DOTA peptide PET/CT, must be performed in all patients prior to conducting RGS, as it assesses somatostatin receptor expression, the extent of the disease, and whether it is localized or it is a case of distant metastases. Patients with small tumors or with tumors located in difficult access sites are considered to be ideal candidates for RGS resection. In the case of our patient, in which the primary tumor had already been resected and in which no involvement by other lesion was evidenced on ^{99}Tc-HYNIC-TOC scintigraphy and ^{68}Ga-DOTA peptide PET/CT scintigraphy, the affected lymph node was resected, taking into account its location in the root of the mesentery, which makes it difficult to perform a lymphadenectomy. Lymphadenectomies of peri-duodenal lymph nodes are indicated during resection of the primary tumor.

RGS, together with PET/CT, are nuclear medicine procedures that had experienced a significant growth in the last 25 years. The term RGS comprises a set of pre-, intra- and postoperative techniques, whose main feature is the injection of a radiopharmaceutical associated with the intraoperative use of a portable radioactivity counting probe (known as gamma probe) that allows surgeons to identify and remove target tissues that accumulate radioactivity (6). This gamma probe provides visual and audible feedback of the radioactivity count rate (range: 0-25 000 counts per second [cps]) as the tumor is approached by the surgeon (9).

A tumor cps/background cps ratio of at least 1.5 is required to confirm the location of the lesion using an intraoperative gamma probe (5). In our case, this ratio was 4.3, so the lymph node was successfully located.

Gamma probe scanning has identified 57% more NET lesions compared to manual scanning by the surgeon; likewise, it allows identifying lesions between 0.5 and 1 cm with high efficiency (5). Therefore, gamma probes have a high degree of specificity and they can be used to help surgeons locate small tumor lesions that are difficult to detect with the naked eye (9).

One of the largest studies, conducted in 44 patients (22 of gastrointestinal origin) and in which Gallium Ga 68-DOTATATE was used, found a sensitivity of 90 % and specificity of 25 % with a tumor/neighboring tissue ratio of 2.5, while with a ratio of 16, the sensitivity decreased to 54 %, but the specificity increased to 81 % (4).

RGS with radiolabeled somatostatin analogues is available with different radiotracers such as ^{111}In-pentetreotide, ^{99}mTc-somatostatin analogues and ^{68}Ga-somatostatin analogues (13); the latter with a higher detection rate because it has higher emission energy. The detection rate is 94% (3), which is higher compared to the other radiotracers. However, ^{68}Ga-somatostatin analogues are not yet available in our country.

^{99}mTc-HYNICTOC, a somatostatin analogue, was used in the case described here. This radiopharmaceutical was developed by Behé & Maecke (14) in 2000; it has appropriate clinical characteristics such as high and specific affinity for somatostatin receptors, good biodistribution, renal excretion, low radiation exposure, availability and cost-effectiveness. Besides high quality images, this radiotracer provides the possibility of an earlier diagnosis (images at 10 minutes-4 hours) (1). The use of this radiopharmaceutical is scarcely reported in the literature, with only 9 cases in which it was used in the small intestine (1), so it is worth noting its usefulness.

RGS radiolabeled somatostatin receptor analogs allowed for the successful resection of a mesenteric adenomegaly in our patient. However, there are other factors associated with successful resection, including appropriate preoperative diagnosis to localize tumor sites, adequate exposure of the lesion during surgery, and the performance of the gamma probe in detecting the lesion (13).

In cases where performing RGS is not possible due to is unavailability, surgeons use manual palpation or intraoperative ultrasound to identify small lesions; however, proper detection can be challenging even if skilled surgeons are in charge, due to the millimeter size of such lesions and the fact they are found in multiple locations in a single patient. Although many more studies are still required, further analysis is needed to shed light on the performance of RGS, whether it increases the number of resections or not, and how it affects the surgical procedure, as well as the survival of these patients (15).

In the future, prospective studies conducted with larger cohorts will address the efficacy of RGS in minimizing symptoms, its impact on quality of life and overall survival, as well as its intra- or perioperative risk (3). In the long term, follow-up and comparison with patients with similar characteristics and in which RGS was performed are required to determine if this therapeutic approach reduces the rate of persistent or recurrent disease in patients with NETs (4). Given the low frequency of these NET presentations, conducting a randomized clinical trial is impractical.

In patients with these diseases, multidisciplinary discussion of the cases is important to look for the best diagnostic and therapeutic options; likewise, this type of treatments must be ensured in health centers with the expertise and resources necessary for their implementation, as it is the case of our institution. In the case described here, the interaction between different services was of great importance to achieve the complete resection of the lesion.

CONCLUSION

RGS is a feasible technique that allows locating NETs; besides it can detect more lesions and of smaller size compared to preoperative imaging tests and palpation by the surgeon. ^{99}mTc-HYNICTOC is a useful radiopharmaceutical in the intraoperative localization of intestinal NETs that, despite being scarcely described in the literature, becomes a good alternative to identify the location of these tumors.

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Clinical case

Crohn's disease with extensive involvement and rare extraintestinal manifestations: A case report

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Abstract

Crohn's disease (CD) is considered an immunologically mediated entity that involves the digestive tract. It is characterized by transmural inflammation and can affect any part of the digestive tract, from the oral cavity to the anus. Although it is recognized that its severity varies, extensive and multiple organ failure is unusual. We present the case of a young patient, who initially presented with pulmonary symptoms associated with CD. Years later, digestive and bile duct symptoms appeared. Treatment was based on anti-tumor necrosis factor-alpha antibody therapy, resulting in a satisfactory clinical response. The clinical relevance of this case is its full-blown presentation, which includes extensive gastrointestinal involvement and rare extraintestinal manifestations.

Keywords

Crohn's disease; Sclerosing cholangitis; Enteritis.

INTRODUCTION

Crohn's disease (CD) can affect any segment of the digestive tract. It is characterized by segmental and transmural involvement. The most common histopathological findings in patients with CD are the presence of cryptitis, lymphoid aggregates and granulomas (1, 2). Granuloma is considered the pathognomonic finding of CD microscopic diagnosis, but it can only be detected in 40%-60% of intestinal segments resected as surgical specimens and in 15%-36% of endoscopic biopsies in 15%-36% (3).

Regarding its location, CD most commonly affects the terminal ileum (two thirds of patients), followed by the ileocolonic region (40-50%), the isolated small intestine (30-40%) and the colon (15-25 %) (4). Involvement of the upper digestive tract is less frequent (0.4 %-16 % of cases) (4); in addition, esophageal involvement occurs only in 0.2 % of patients, followed by stomach and duodenum involvement (between 1 % and 4 % of cases) (4-7). Furthermore, extraintestinal manifestations such as primary sclerosing cholangitis (PSC) and pulmonary manifestations are very rare in patients with CD (8-11).

The case of a patient with CD who first presented with pulmonary manifestations and years later experienced varied manifestations affecting the whole digestive tract, as well as the biliary tract is presented here.

CLINICAL CASE

This is the case of a 43-year-old patient with a history of recurrent aphthous ulcers in the oral cavity, general malaise, fever episodes during the night, dry cough, and involuntary and significant weight loss. On physical examination the patient was cachectic, he had fever, and abnormal breath sounds. For this reason, multiple studies were performed. A CT scan of the chest showed a 6 mm scar area with cavitation in the left upper lobe, peribronchial thickening towards the left lower lobe, a small nodular lesion in the right base and large perihilar adenopathies. Furthermore, severe nodular endobronchitis was identified by means of a fibrobronchoscopy, with biopsies showing chronic active inflammation without granulomas; Ziech-Nielsen (ZN) and methenamine silver stains were negative; bronchoalveolar lavage (BAL) cultures for bacteria, fungi and mycobacteria were negative; acid-fast bacillus test, potassium hydroxide (KOH) and polymerase chain reaction (PCR) for tuberculosis (TB) were negative. In addition, antinuclear antibodies, perinuclear staining anti- neutrophil cytoplasmic antibodies (p-ANCA) and cytoplasmic staining anti-neutrophil antibodies (c-ANCA) tests were negative; enzyme-linked immunosorbent assay (ELISA) and human immunodeficiency virus (HIV) tests were also negative. Given these negative findings, a thoracoscopic segmental lobectomy was performed, with whitish lumpy areas reminiscent of caseating granulomas being described in the macroscopic findings. According to the pathology report, none of these specimens was positive for granulomas or granulomatous infections, but acute fibrinous and organizing pneumonia with microabscesses was reported. Parenteral antibiotic treatment was started and the patient was discharged with both a diagnostic impression of granulomatosis with polyangiitis and the following indications: use of prednisolone 50 mg/day and attend outpatient evaluation in the rheumatology service.

Granulomatosis with polyangiitis diagnosis was ruled out in the outpatient visit in the rheumatology service, given that there was no vasculitis, the ANCA test was negative, and histologic findings were not compatible with this disease. The patient reported experiencing occasional headaches, so a magnetic resonance imaging (MRI) of the brain was performed, which allowed observing a small aneurysm and, based on these data, a diagnostic impression of Behçet's disease was made, so he was prescribed with methotrexate 10 mg/week and prednisolone 50 mg/day treatment was continued.

General and respiratory symptoms improved completely and the patient was asymptomatic for more than 1 year, when he began experiencing polydipsia, polyphagia and polyuria. During that year the patient did not attend any follow-up visit in the rheumatology service. Diabetes *mellitus* was diagnosed with glycosylated hemoglobin (HbA1c): 8.5%, so management with basal insulin and steroids tapering was indicated. Due to the notable improvement of the patient's clinical condition, the administration of oral steroids was gradually suspended. When they were suspended, the patient presented with diarrhea and colicky abdominal pain, so different treatment regimens consisting of metronidazole, oral antibiotics and antidiarrheals were prescribed, which allowed for the occasional control of these symptoms. Over time, the number of bowel movements frequency increased to 25-30, and sometimes there was blood or mucus in the stools, or straining and tenesmus was experienced; besides, the patient experienced a 20 kg weight loss in 6 months. Given these clinical signs and symptoms, the patient was hospitalized. The following findings were reported on the physical examination on admission to the hospital: A pale and underweight patient (weight 41 kg, vs. a usual weight of 61 kg), with tachycardia (heart rate [HR]: 122 beats per minute [bpm]) with diffuse pain on abdominal palpation, without peritoneal irritation or visceromegaly. The results of laboratory tests on admission are shown in **Table 1**.

Table 1. Laboratory tests on hospitalization admission.

Tests	Results	Reference values
Hemoglobin	8.1 g/dL	13-17 g/dL
Hematocrit	25.6%	42%-52%
Mean Corpuscular Volume	74.7 fL	78-98 fL
Leukocytes	24500 mm^3	4500-11 000 mm^3
Neutrophils	21900 mm^3, 89.4 %	1500-6000 mm^3, 50 %-70
ESR	90	Up to 20
CRP	21.79 mg/dL	0.01-0.82 mg/dL
Creatinine	0.61 mg/dL	0.60-1.10 mg/dL
ALP	202 U/L	40-150 U/L
GGT	165 U/L	12-64 U/L
ALT and AST	6 and 10 U/L	5-34 U/L
Glycemia	130 mg/dL	Up to 100 mg/dL

ALT: alanine aminotransferase; AST: aspartate aminotransferase; ALP: alkaline phosphatase; GGT: Gamma-glutamyl transferase; ESR: erythrocyte sedimentation rate.

Endoscopic studies were performed at our institution which showed lesions reminiscent of punch pouch-like pseudodiverticula in the distal esophagus (**Figure 1A**); cobblestone-like gastric mucosa of granular appearance, mainly in the distal body and the antrum; an inflammatory

ulcer in the pyloric region (**Figure 1B**), and pseudodiverticular formations of chronic inflammatory appearance in the duodenum (**Figure 1C**). Furthermore, a colonoscopy showed severe mucosal inflammation of the entire colon, with inflammatory stricture at the ileocecal valve and multiple inflammatory ulcers in the distal ileum (**Figure 1D-F**). In addition, a magnetic resonance enterography (MR enterography) showed extensive involvement of the entire small bowel by diffuse, concentric, asymmetric and irregular thickening from the stomach until the rectum (**Figure 2A**). Due to the elevated ALP and GGT levels, a magnetic resonance cholangiopancreatography was performed, which allowed detecting smooth and short stenotic segments alternating with larger caliber segments in the right and left intrahepatic bile duct associated with diffuse enhancement of the walls due to a nonspecific inflammatory phenomenon (**Figure 2B**). Colonic biopsies reported the presence of ulcerated mucosa with crypt distortion, decreased goblet cells, lymphoplasmacytic infiltrate in the lamina propria, polymorphonuclear exocytosis and microabscess formation, with negative results for ZN staining, modified ZN staining, PAS (periodic Acid-Schiff) staining and cytomegalovirus (CMV).

The clinical and radiological findings, as well as the biopsy reports were compatible with Crohn's disease with extensive involvement of the digestive tract, associated with PSC. A Crohn's Disease Activity Index (CDAI) of 623 was obtained, so treatment consisting of intravenous hydrocortisone 100 mg every 8 hours, oral mesalazine 1 gram every 8 hours and azathioprine 2 mg/kg/day was started. Infectious disease screening studies were negative, so inpatient biological therapy (infliximab) was prescribed at 10 mg/kg/dose in a shortened induction schedule (weeks 0, 1 and 4). The patient's condition started to improve from day 3 after starting this treatment, experiencing a progressive decrease in fecal output and acute phase reactants. At 1 week, intravenous steroids were replaced by oral steroids and the patient was instructed to keep using prednisolone 40 mg/day for 1 month and to gradually suspend the use of steroids. After nearly 2 weeks, the patient reported having experienced almost complete resolution of abdominal pain, improvement in stool consistency, and absence of gastrointestinal bleeding.

Four months later, in a follow-up visit in the Inflammatory Bowel Disease Clinic, the patient reported having experienced a marked improvement of symptoms: he referred

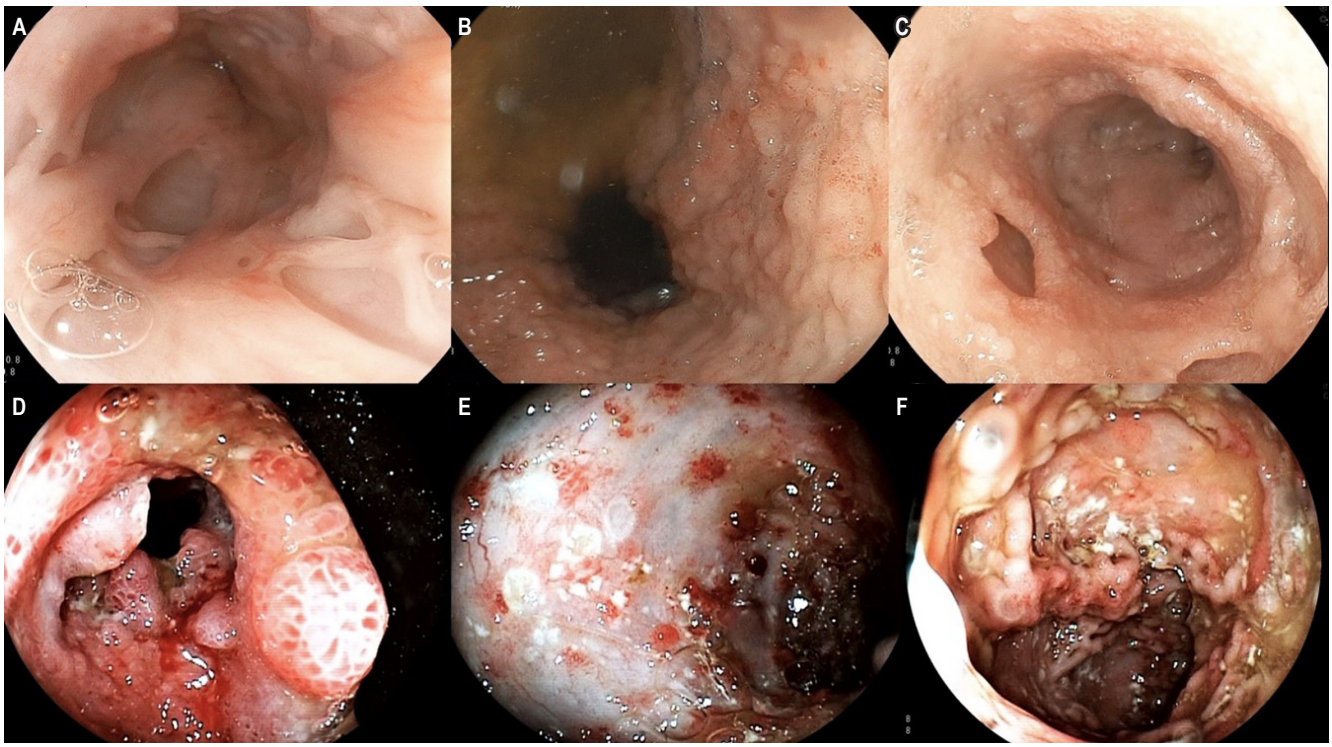

Figure 1. A. Endoscopic findings in the distal esophagus, punch pouch like pseudodiverticula. **B.** Endoscopic view of the antrum: cobblestone-like nodular mucosa. **C.** There is evidence of punch-like Kerckring's notches in the duodenum. **D.** Severe involvement of the ileocecal valve. **E** and **F.** Inflammatory changes with multiple ulcers of variable size in the colon.

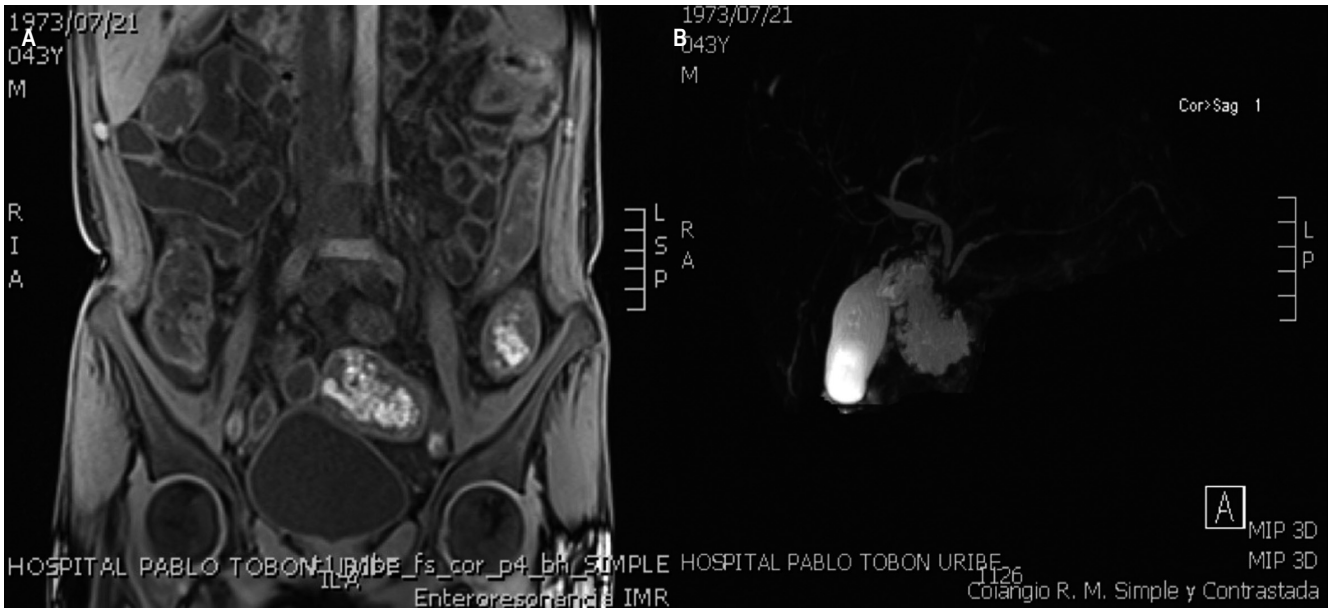

Figure 2. A. MR enterography: inflammatory changes caused by diffuse thickening throughout the digestive tract. **B.** Magnetic resonance cholangiopancreatography showing short, smooth strictures with enhancement of the intrahepatic biliary tract; findings compatible with PSC.

having three bowel movements per day, Bristol 4 consistency, and occasional non-incapacitating colicky abdominal pain that improved with antispasmodics, without rectal bleeding. Weight gain (52 kg), absence of abdominal pain or visceromegaly, and a CDAI score of 213 were reported on physical examination. Combination therapy (azathioprine 100 mg/day plus infliximab 5 mg/kg/every 2 months) was prescribed. Due to administrative issues with the patient's health insurance company, no further controls were possible.

DISCUSSION

The case of a young patient with CD who presented with respiratory manifestations long before gastrointestinal manifestations took place is reported here. In this case, multiple studies were performed, which allowed ruling out infectious diseases such as TB and deep mycosis; chronic granulomatous diseases such as sarcoidosis and granulomatosis with polyangiitis were also ruled out due to negative ANCA test results, and negative histopathology even for the surgical specimen obtained in the segmental lobectomy. Additionally, the patient had a good clinical response after undergoing a treatment consisting of steroids and immunomodulators for a long period.

IBD-related pulmonary involvement was first described in 1976 by Kraft et al (12). Pulmonary involvement by IBD is the rarest extraintestinal manifestation, but its actual prevalence is probably unknown (8-10). Pulmonary manifestations are variable and at least 4 forms of presentation have been described: small airway disease, parenchymal involvement, vascular involvement and, rarely, serosa (13). There are several hypotheses about the lung-intestine connection or axis. The lungs and intestines originate from the same embryonic cell line in the anterior region of the endoderm. These organs have in common the columnar lining cells, the goblet cells and the submucosal lymphoid tissue, so it has been proposed that the lung-intestine axis may develop similar inflammatory reactions due to these shared anatomic-histologic features (13, 14). A second hypothesis is the shared antigen theory, which states that the epithelia of the intestine and the lungs are exposed to the same antigens, and said shared exposure may induce a similar inflammatory response in both systems. Other theories adduce that, during the activation of the cellular immune response, lymphocytes have a chemokine and chemokine receptor-based homing system that allows their proper migration to the appropriate tissue. In IBD patients, this migration system may be abnormal and less specific, so that lymphocytes can invade the intestine and other organs such as the lungs (13).

The difficulty in diagnosing pulmonary manifestations of CD is likely due to the fact that pulmonary manifestations may occur before the onset of intestinal disease, and therefore the physician does not make an association between both situations (as it happened in this case), or that subclinical findings are present and the patient does not experience any symptom, and, thus, such association is not investigated by the physician (9).

Sarcoidosis and granulomatosis with polyangiitis are the conditions that represent the greatest diagnostic challenge of pulmonary involvement in CD (10). Even some cases of CD/sarcoidosis overlap have been reported. On the contrary, although granulomatosis with polyangiitis has pulmonary findings similar to those described in CD, gastrointestinal involvement is very rare (10).

PSC is a chronic inflammatory disease of the bile ducts that causes stenosis and recurrent cholangitis. It has a high correlation with IBD (especially ulcerative colitis [UC]), in which it is estimated that 50-80% of patients have concomitant IBD (11). Patients with PSC have a 2-fold increased risk of cancer and a 40-fold increased risk of primary hepatobiliary cancer (15). Provided that a large number of patients are asymptomatic, biliary manifestations associated with CD are underestimated. Individuals with concomitant IBD and PSC have a worse prognosis, in particular for they have an increased risk of colorectal cancer. The exact mechanisms are unclear, but there is clear evidence that the risk of colorectal cancer is higher in patients with IBD and PSC than in those with IBD or PSC alone (15, 16).

As for the pharmacological treatment of patients with PSC with or without IBD, treatment options do not differ much at present. Anti-TNF agents have failed to control inflammatory activity in the biliary tract, regardless of their efficacy in treating inflammation in the intestine. Currently, the use of vedolizumab, a humanized monoclonal antibody selectively targeting the a4b7 integrin, has been proposed to be included in the treatment of these patients. The safety profile of videlizumab is higher than that of the existing anti-TNF-α agents (17). The theoretical foundation of this proposal is that it has been successfully shown that intestinal adhesion molecules such as chemokine ligand 25 (CCL25) and mucosal adresin cell adhesion molecule 1 (MAdCAM-1) are abnormally expressed in the liver of patients with PSC, favoring the recruitment of gut-derived effector T cells expressing chemokine receptor 9 (CCR9) and a4b7. Although this mechanism sounds appealing, so far the clinical impact of vedolizumab on PSC has not been determined. A recent multicenter study conducted in 102 patients with PSC and IBD found that there were no significant differences in biochemical response to vedolizumab, although alkaline phosphatase level decreased by 20% or more in a subset of patients (18). Vedolizumab appears to be well tolerated and the overall IBD response was the same as the one expected in patients without PSC (18).

Although it has been described that the entire digestive tract can be affected by CD, upper digestive tract involvement is less frequent (1); however, some studies have reported data suggesting that the prognosis of the disease is usually worse when there is upper digestive tract involvement (5, 19, 20). The first and only prospective study known to date conducted in patients with CD that has actively searched for findings in the upper digestive tract was carried out in Italy. In said study, all patients underwent endoscopy in which biopsy samples were obtained for histopathological analysis and the detection of *Helicobacter pylori* at weeks 0 and 12 after receiving a treatment regimen. In this series, 119 patients with CD were recruited, and gastroduodenal involvement attributable to CD was found in 19 (16 %). Of these 19 patients, 11 were treated with anti-TNF drugs (10 with infliximab and 1 with adalimumab), and 8, with proton pump inhibitors (PPI) and other therapies (5-ASA, immunomodulators and, in one of them, steroids). According to these authors, mucosal healing was observed in 8 of the 11 patients (72.7 %) in the anti-TNF biological therapy group compared to 1 of 8 patients (12.5 %) in the PPIs and other therapies groups, with a statistically significant difference ($p < 0.001$). In addition, this study suggests that an EGD with biopsy should be performed in patients with CD in order to correctly determine the distribution of the disease (7).

Although CD is considered a disease that can affect any part of the digestive tract, extensive gastrointestinal and multiorgan involvement are very rare. Thus, there is no information in the existing literature on how the long-term follow-up and treatment of these patients should be. However, there are recent data regarding the follow-up or colon cancer screening in patients with PSC and IBD, in which performing a colonoscopy plus ileoscopy every year is recommended (15).

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Dermatomyositis and colorectal cancer: Case report and literature review

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Abstract

Patients with dermatomyositis are more likely to have an underlying malignancy, although the exact cause of this association is unknown. There are multiple possible anatomical sites, including ovaries, breasts, stomach, colorectum, blood, lungs, and prostate.

We present the case of a 58-year-old woman who during abnormal weight loss study showed severe muscle weakness and skin alterations, associated with finding of adenocarcinoma of the transverse colon.

Keywords

Dermatomyositis: Malignancy; Colorectal cancer; Paraneoplastic syndrome.

INTRODUCTION

Dermatomyositis is a widely studied collagen disease characterized by muscle weakness and associated with skin lesions. There is a higher frequency of malignancy in patients with dermatomyositis compared to the general population. Dermatomyositis frequently presents as a paraneoplastic syndrome, and the high rates of cancer detection following its diagnosis make the screening of cancer necessary taking into account the age group and clinical presentation of each patient (1-3). Additionally, dermatomyosits has been described as a paraneoplastic manifestation of gastrointestinal cancer.

The cancers most commonly associated with dermatomyositis are ovarian, pulmonary, breast, stomach, colorectal, pancreatic and non-Hodgkin's lymphoma (3-6).

CLINICAL CASE

This is the case of a 58-year-old woman without any relevant history of disease and a family history of colon cancer (her sister was diagnosed with it during the fifth decade of life) who experienced an abnormal weight loss of 6 kg during the last six months associated with scanty hematochezia and occasional diarrhea episodes. Three polyps were observed on a total colonoscopy: a 7 mm polyp in

the ascending colon (biopsy report: villous adenoma with low-grade dysplasia) (**Figure 1**), a 50 mm sessile polyp in the hepatic flexure (biopsy report: villous adenoma with low-grade dysplasia) (**Figure 2**) and a 30 mm polyp in the upper rectum (biopsy report: adenoma with low-grade dysplasia) (**Figure 3**); normal results in all 3 cell lines of the complete blood count test were reported. Endoscopic polypectomy of the rectal polyp (piecemeal resection) was performed using a hot loop, which was then classified as tubulovillous adenoma with low-grade dysplasia according to the histopathology report.

One month later, and provided that the endoscopic resection of the polyp located in the hepatic flexure was impossible, the patient underwent a right hemicolectomy and a ileotransversostomy. The following findings were described in the histopathology report of the surgical specimens resected during these procedures: 2 tubular adenomas with focal high grade dysplasia without pedicle involvement, resection margins free of lesion and absence of lymph node involvement. Two months later, in addition to postsurgical changes, a follow-up total colonoscopy allowed identifying a 40 x 20 mm sessile polyp in the transverse colon immediately distal to the anastomosis (biopsy report: villous adenoma with low-grade dysplasia) (**Figure 4**); due to this finding, a new surgery consisting of colectomy extension, an omentectomy and a new ileocolic anastomosis was carried

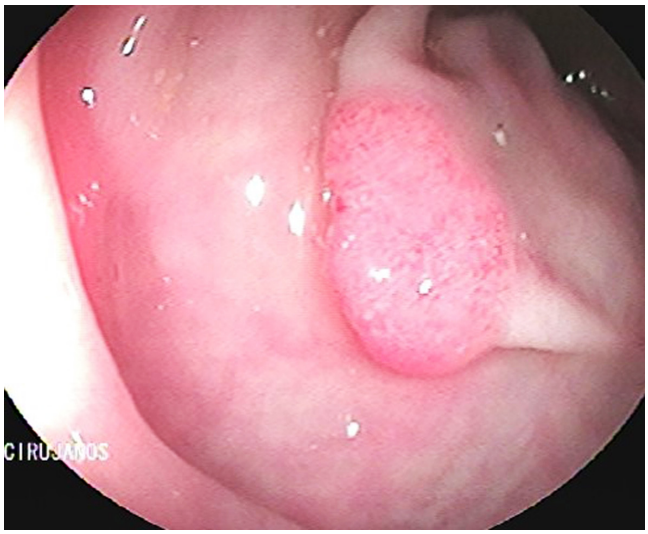

Figure 1. 7 mm sessile polyp in the ascending colon.

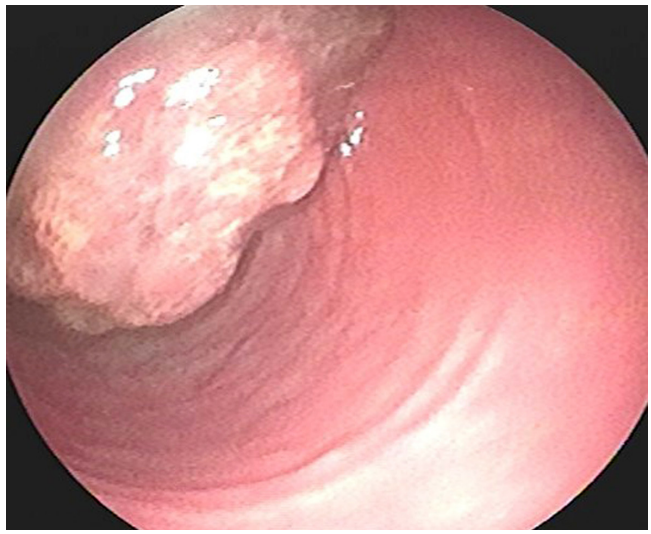

Figure 2. 50 mm sessile polyp in the hepatic flexure of the colon.

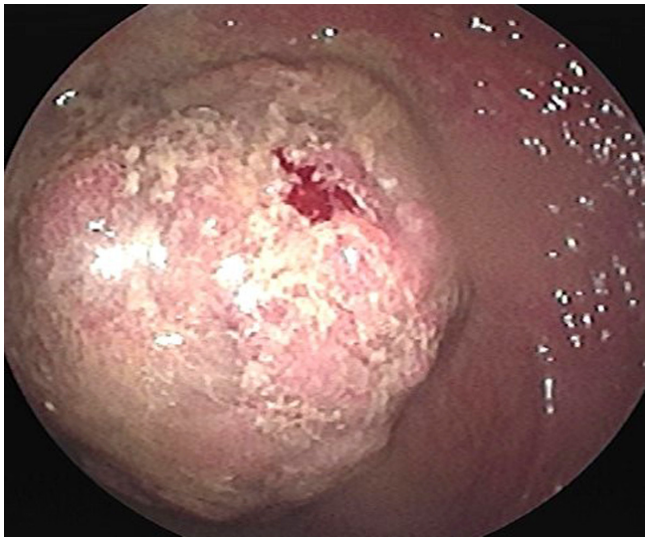

Figure 3. 30 mm polyp in the upper rectum.

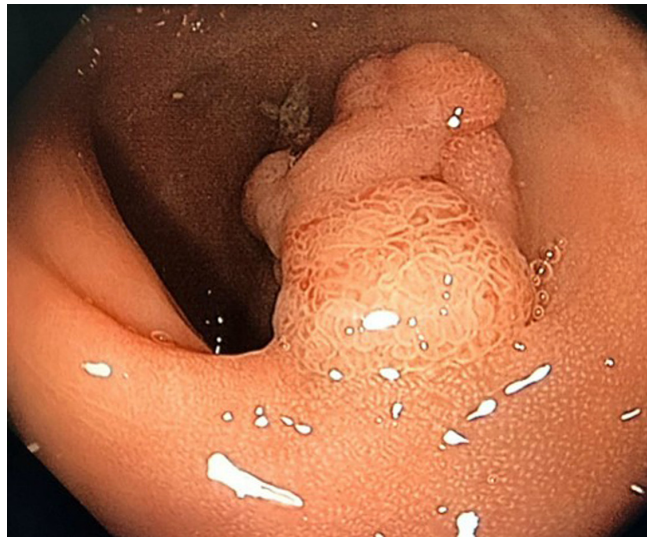

Figure 4. 40 x 20 mm sessile polyp in the transverse colon.

out (histopathology report: tubulovillous adenoma with high-grade dysplasia and *in situ* adenocarcinoma immediately distal to the previous anastomosis, with no signs of infiltration, free resection margins, and no lymph node or greater omentum involvement. Six months later, a 4 mm polyp in the upper rectum was observed in a new ileocolonoscopy, no other findings were reported; the polyp was resected using a cold loop (pathology report: tubulovillous adenoma with low-grade dysplasia) (**Figure 5**).

Four months before undergoing the first surgery, erythematous skin macules appeared on the patient's chest, which became more intense and larger and extended to the upper back, the lower back, the upper limbs and the face (**Figures 6-11**). Two months later she developed generalized muscle weakness experiencing falls while standing or walking and being unable to get up, together with edema and distal pain in the upper and lower limbs. Initial total serum creatine kinase (CK) levels were 2028 µmol/L, however after the colectomy extension, a progressive decrease to 1800 and 1028 µmol/L, together with symptomatology improvement, was evidenced. Chronic interface dermatitis with vacuolar changes compatible with dermatomyositis was reported in the skin biopsies of the right pectoral region and right arm. Based on these clinical, laboratory and histopathological findings and behaviors, it was concluded that the patient had dermatomyositis as a paraneoplastic manifestation of colon cancer. Tumor markers (Ca 19.9 and serum CEA) were normal, and no signs suggestive of second malignancy were evidenced in both a CT scan of the chest a CT scan of the abdomen and pelvis. Currently, the patient is being monitored by the rheumatology and dermatology services; also, she is undergoing systemic steroid treatment and has reported the resolution of muscular symptoms and a significant improvement of skin lesions (**Figure 12**).

DISCUSSION

Dermatomyositis belongs to a heterogeneous group of connective tissue diseases known as idiopathic inflammatory myopathy (7). Its clinical manifestations include proximal musculoskeletal weakness and inflammation, as well as skin manifestations. An incidence of 5 to 10 cases per 1 million inhabitants, being more frequent in women (3:1 ratio), has been described in the in the United States. Its peak incidence occurs between 40 and 60 years of age (8). The association of dermatomyositis and malignancy was first established in 1916 in a patient with stomach cancer. Since then, multiple retrospective case series have reported this association in approximately 24% of cases (9).

The etiology of cancer-related dermatomyositis remains unknown, although several hypotheses have been proposed, such as the release of bioactive components that generate immune reactions in muscle fibers and the skin (10). It has been found that muscle fibers affected by autoimmune diseases overexpress specific autoantigens and that this

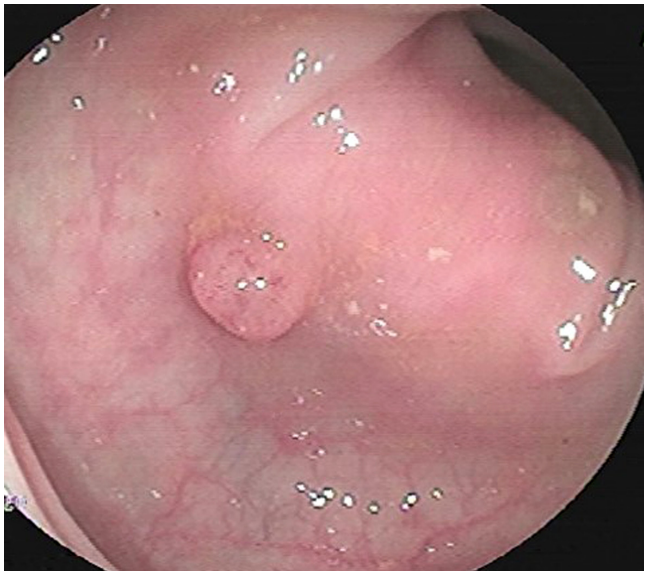

Figure 5. 4 mm polyp in the upper rectum.

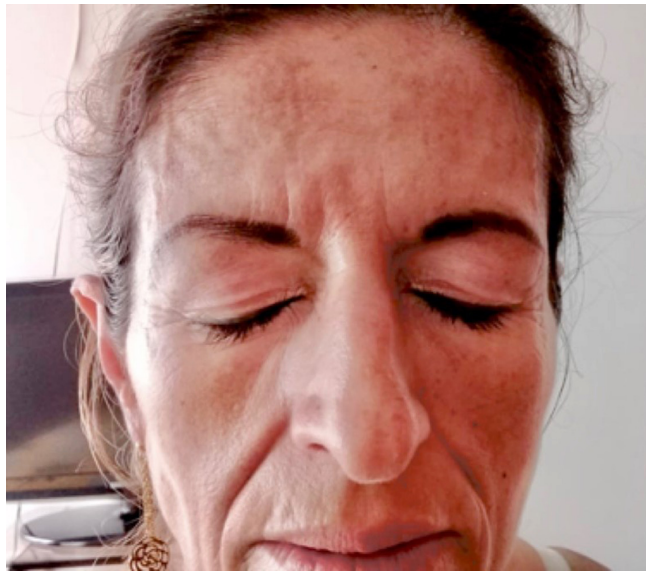

Figure 6. Bilateral eyelid erythema and facial erythema (forehead, glabella and cheeks).

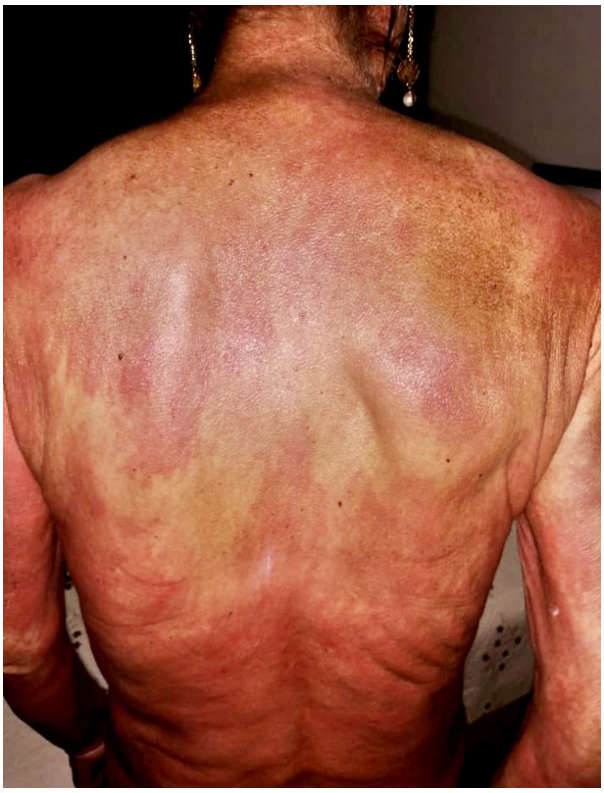

Figure 7. Erythematous plaques on the posterior cervical region, upper back and shoulders that constitute the classic "shawl sign" or capillary erythema sign.

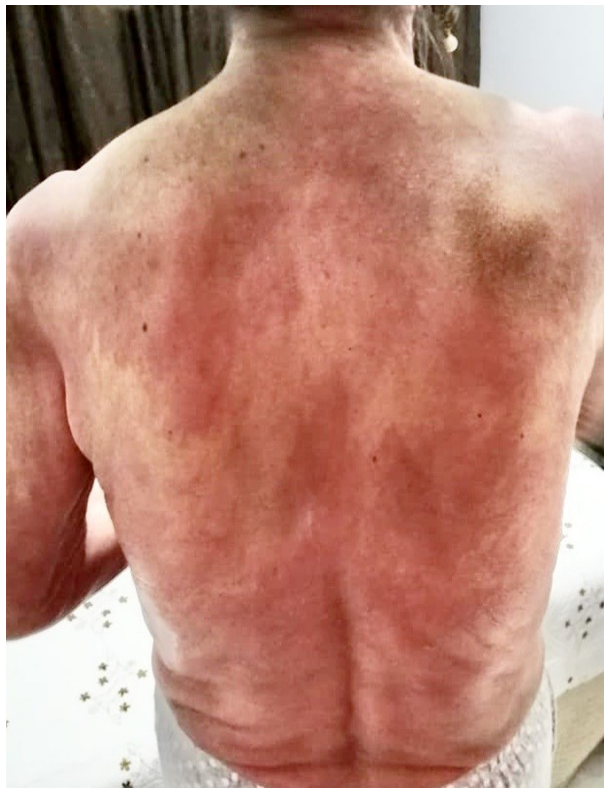

Figure 8. Erythematous plaques extending to the lower back.

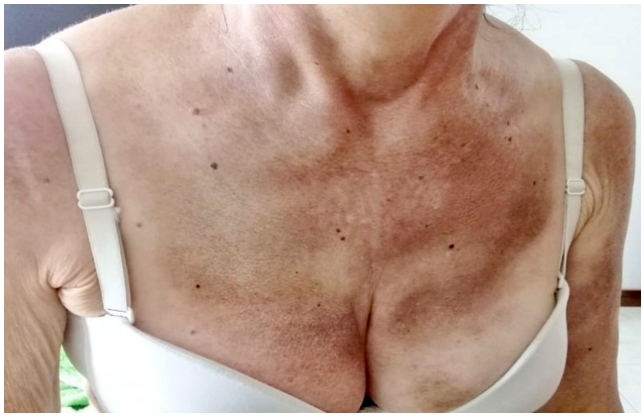

Figure 9. Violaceous erythematous plaques on the anterior triangle of the neck that extend to the chest.

overexpression is exhibited by tumor cells and regenerating myoblasts, which indicates that antigens expressed by both types of cells are similar (11). It has been proposed that there is a crossed immune response against regenerating muscle cells, which leads to the development of dematomyositis (12, 13).

In 1975, Boham & Peter (14) established the following diagnostic criteria for dermatomyositis: muscle weakness, high muscle enzymes, abnormal electromyography findings compatible with myopathy, compatible muscle or skin biopsy pathology report, and skin manifestations. Dermatomyositis diagnosis is made when the characteristic skin lesions are present and they are associated with 3 or more of the remaining criteria. In addition, when there is no muscle weakness, amyopathic dermatomyositis, which is also part of the same spectrum of paraneoplastic syndrome, is diagnosed (16, 17).

Leatham et al. (18), in a retrospective study conducted in 400 patients with dermatomyositis in the United States, reported that malignancy was found in 15.8% of cases, distributed as follows: breast cancer (24.5%), hematologic cancer (17%), colorectal cancer (9.4%) and prostate cancer (9.4%). Hill et al (4) found an association (in decreasing order of frequency) between the following types of cancer and dermatomyositis: ovarian, lung, stomach, colorectal, pancreatic and non-Hodgkin's lymphoma. Sigurgeirsson

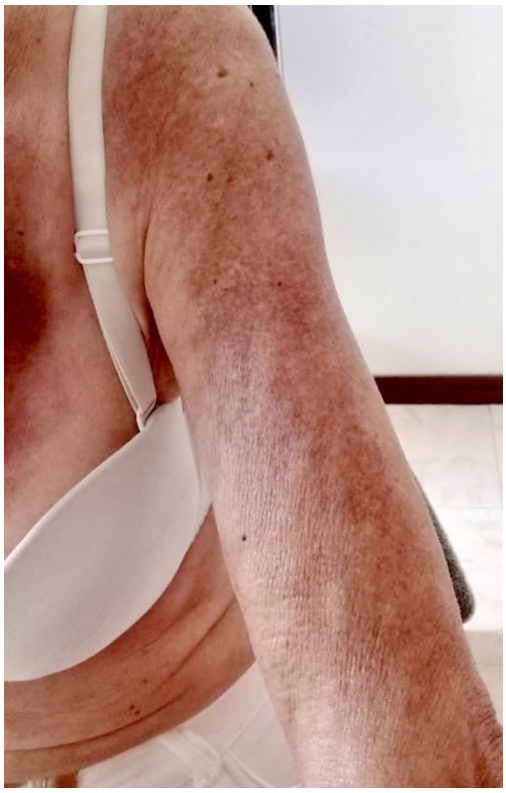

Figure 10. Violaceous erythematous plaques on the anterior aspect of the shoulder and arms.

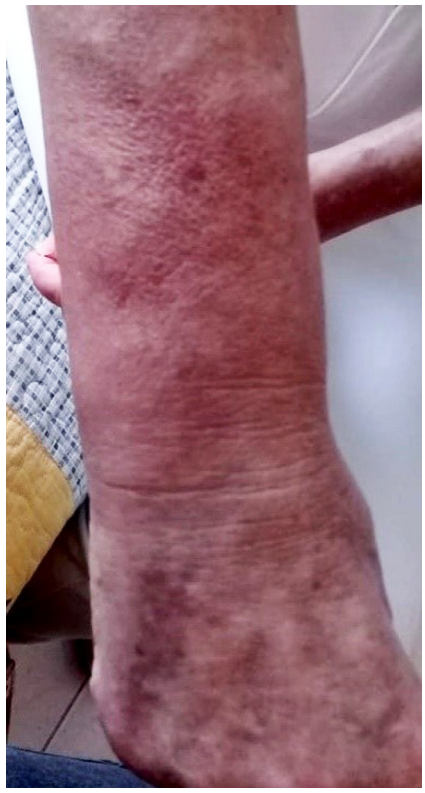

Figure 11. Distal involvement of the upper limbs caused by violaceous erythematous plaques affecting the dorsum of the hands.

et al (19), in a case series conducted in 750 patients with dermatomyositis and polymyositis, reported that the most frequent cancers were colorectal and lung cancer. In Japan, Hatada et al (20) found that gastric cancer was the most frequent malignancy in patients with dermatomyositis (25.4%). In all case series, cancers of the digestive tract are among the most frequent malignancies in patients with this condition. In addition, several studies have reported that people with dematomyositis have a higher risk of developing colorectal cancer (4, 19, 21-23).

There is ambiguity in the existing literature regarding the presence of clinical or laboratory and imaging predictors of malignancy in patients with dermatomyositis. In this sense, the presence of interstitial pneumonitis, elevated serum CK levels, skin necrosis (ulcers), poikiloderma, erythrocyte sedimentation rate (ESR) > 40 mm/h, elevated C-reactive protein (CRP) levels, hypoalbuminemia and age > 50 years have been proposed as clinical predictors (17, 24-29).

The treatment of patients with dermatomyositis and cancer is similar to that of cancer patients in general, pro-

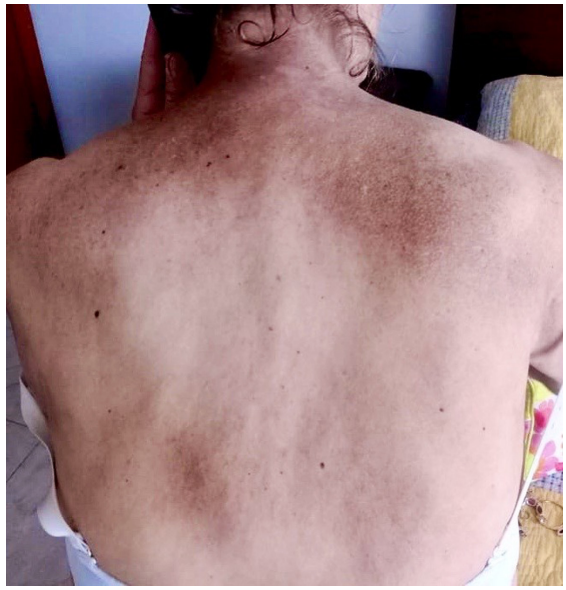

Figure 12. Improvement of lesion on the cervical region, the upper back and the lower back.

vided that the cancer-dermatomyosits association does not imply any changes in the management of dermatomyositis. However, it has been reported that patients with dermatomyositis and malignancy tend to have a worse oncologic prognosis, since advanced stages are present at diagnosis and optimal resolution is not always possible (17). Successful surgical management usually leads to complete resolution of dermatomyositis symptoms (30, 31). Early diagnosis of malignancy in these patients is paramount to achieve a better prognosis.

Most of dermatomyositis with colorectal cancer cases reported have affected women (63 %), and adenocarcinoma is the most frequent histological finding in dermatomyositis (96.3 %). In 77.7% of patients, dermatomyositis manifested before colorectal cancer with elevated CK levels. Immediate improvement of symptoms after surgery occurs in half of patients, in the remaining, improvement occurs within the first months after undergoing the surgical procedure (31, 32, 33).

In the case reported here, dermatomyositis symptoms occurred a few months before the transverse colon carcinoma was found. Resolution of muscle symptoms and significant improvement of skin lesions took place several weeks after the lesion was surgically resected.

CONCLUSIONS

The exact cause of the association between dermatomyositis and the presence of malignancy is unknown. The presence of similar autoantigens in neoplastic, musculoskeletal and cutaneous cells has been suggested. Up to a quarter of dermatomyositis cases are associated, during the course of the disease, with the presence of cancer. At the time of diagnosis, patients with associated malignancy are already developing it, and generally the latter has a slow course of disease. When a patient is diagnosed with dermatomyositis, ruling out the presence of underlying malignancy, ideally in early stages, is of utmost importance to carry out interventions that positively contribute to the achievement of a better prognosis. Generally, after successful management (complete surgical resection) of the neoplastic lesion, dermatomyositis symptoms resolve; however, in case of tumor recurrence or metastatic cancer, they usually reappear.

The digestive tract is among the main sites of potential primary tumor origin, and within the digestive tract, stomach and colorectal cancer are the neoplasms most commonly associated with dermatomyositis. Finally, the evaluation of these patients must focus on their risk factors and associated clinical manifestations.

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Peritoneal tuberculosis, a differential diagnosis for ascites in cirrhosis

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Abstract

This is the case of a patient with a history of chronic alcohol consumption, who consulted for nonspecific abdominal pain, intermittent fever, and weight loss, with subsequent increase in the abdominal perimeter. Ascites and imaging findings suggestive of cirrhosis were found. The study of ascitic fluid was non-hypertensive with a predominance of lymphocytes and elevated adenosine deaminase (ADA) levels. Ultrasound and abdominal tomography showed peritoneal thickening. Laparoscopic peritoneal biopsy was compatible with granulomatous disease, with positive PCR for *Mycobacterium tuberculosis* in a patient with no other causes of immunosuppression. This report shows the importance of keeping a high index of suspicion for TB in patients with abdominal pathology, even in those without evident inmunocompromise.

Keywords

Ascites; Hepatic cirrhosis; Peritoneum; Gastrointestinal tuberculosis.

INTRODUCTION

Peritoneal tuberculosis (TB) accounts for 1%-2% of all TB cases and 31%-58% of gastrointestinal TB cases; besides, an association with pulmonary TB has been found in 3.5% of cases (1). Its diagnosis remains a challenge due to its paucibacillary nature and the fact that its clinical findings are nonspecific; peritoneal TB poses important risks such as sepsis, intestinal obstruction and, in women, infertility, so it is considered an almost mandatory diagnosis to be ruled out in the diagnosis of ascites secondary to causes not related to portal hypertension (2).

By 2018, 10 million new TB cases were estimated worldwide, and coinfection with human immunodeficiency virus (HIV) was present in 8.6% of these cases (3). In Colombia, 14 480 cases were recorded in the Public Health Surveillance System (SIVIGILA for its acronym in Spanish), of which 11.1 % had HIV coinfection (4). Although in recent years the number of TB and HIV/AIDS coinfection cases has clearly increased, of the 1.45 million deaths registered by the World Health Organization (WHO), only 251,000 were positive for HIV, which highlights the importance of continuing to consider the presence of this condition in people who are not severely or evidently immunocompromised (3).

CLINICAL CASE

47-year-old man born in a rural area of the department of Boyacá, who lives and works as a driver in Bogotá; the patient had been drinking beer at least once a week

for about 15 years, without any other relevant history of disease, and visited our institution due to the following symptoms and signs: increased abdominal circumference (20 days), diffuse pain (4 months), occasional unquantified increases in body temperature, and a 15 kg weight loss. The patient had attended other health institutions where he was prescribed with symptomatic treatment consisting of antacids. Physical examination on admission findings: normal vital signs, body mass index (BMI) of 22, abdominal distension with signs of moderate ascites and mild diffuse pain on palpation without signs of peritoneal irritation. Admission laboratory tests results: complete blood count: mild normocytic anemia (hemoglobin 11.4 g/dL), normal white blood cell and platelet counts, elevated C-reactive protein levels and elevated erythrocyte sedimentation rate (ESR). Hyponatremia (129 mmol/L) was also evidenced; kidney function was normal, urinalysis results were normal, and no abnormal findings were evidenced on a chest X-ray.

Ascites and a liver of smaller size with lobulated contours were evidenced on an abdominal ultrasound; furthermore, esophageal and splenic varices with mild splenomegaly, and changes suggestive of portal hypertension were identified in a Doppler evaluation of the splenoportal veins and an upper GI endoscopy. Transaminases, alkaline phosphatase and bilirubin (total, direct, and indirect) levels were normal; coagulation times were prolonged (prothrombin time [PT]: 15.8 seconds; international normalized ratio [INR]: 1.44; partial thromboplastin time [PTT]: 41.8, and normal alpha-fetoprotein). Hepatitis B and C serologic tests were negative; antimitochondrial antibodies (AMA) and anti-smooth muscle antibodies tests were also negative.

Ascitic fluid cytochemistry reported a serum-ascites albumin gradient (SAAG) of 0.6, compatible with ascites secondary to causes not related to portal hypertension; leukocytes count of 2400/mm3, lymphocytes count of 100%, glucose level of 82.4 mg/dL and Gram stain negative for germs. Adenosine deaminase (ADA) levels in peritoneal fluid were 102 U/L (reference value < 36 U/L) and cytology showed lymphocytosis and was negative for malignancy. A CT scan of the chest and a CT of the abdomen were performed to rule out the presence of neoplasms as a differential diagnosis. The contrast-enhanced CT scan of the abdomen showed changes in the density of the peritoneum with thickening, multiple small nodules in the upper third part of the abdomen enhanced by the contrast medium (**Figure 1**), a small size liver, and abundant ascites; the CT scan of the chest showed scarce bilateral pleural effusion. So a laparoscopy was performed to obtain samples from the peritoneum and the liver for biopsy purposes; besides, the following findings were reported during the procedure: extensive involvement of the entire peritoneum by yellowish micronodules, presence of some inter-ascitic adhesions, abundant greenish non-purulent fluid in the peritoneal cavity, as well as a cirrhotic liver with some micronodules. The histopathological study of the peritoneum sample was compatible with granulomatous inflammation, with negative Ziehl-Neelsen (ZN) staining (**Figure 2**), but with positive polymerase chain reaction (PCR) for *Mycobacterium tuberculosis*. The enzyme-linked immunosorbent assay (ELISA) was negative for HIV.

The patient was treated for 9 months with a monitored TB treatment regimen, achieving improvement of both

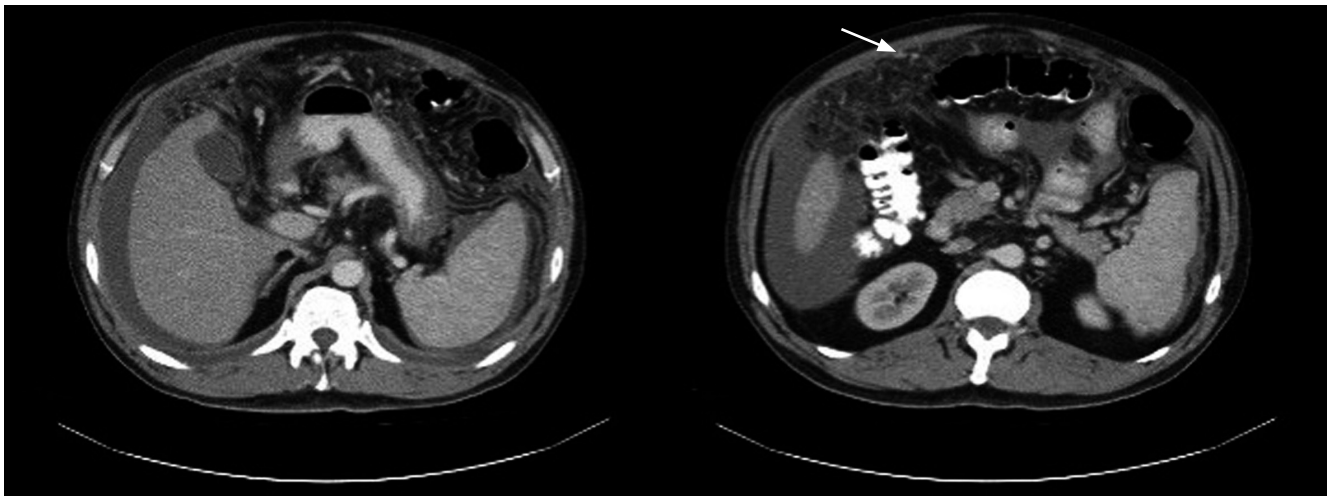

Figure 1. Contrast-enhanced CT scan of the abdomen. Small size liver, thickening and multiple small nodules in the peritoneum enhanced by the contrast medium.

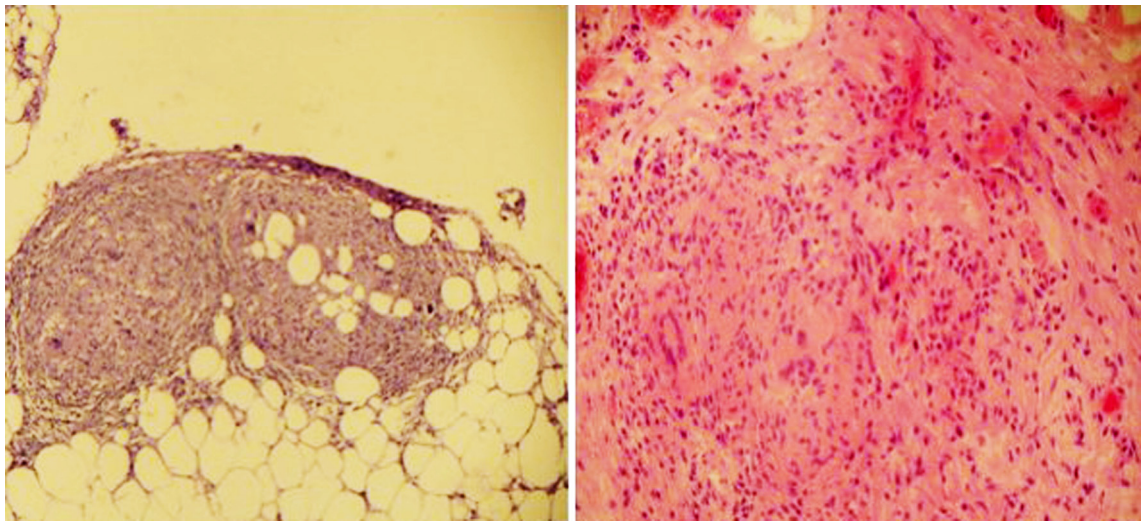

Figure 2. Histopathological study. Hematoxylin-eosin staining showing chronic granulomatous inflammation suggestive of TB. Negative ZN staining for acid-fast bacillus.

clinical signs and laboratory tests values, as evidenced in outpatient follow-up visits; likewise, normalization of body weight and complete resolution of ascites without loss of liver function were achieved after the first phase of treatment was completed. In addition, the patient keeps attending follow-up visits in the hepatology service due to the alcoholic cirrhosis (Child-Pugh score B) diagnosis.

DISCUSSION

It is well known that the clinical presentation of abdominal TB is widely variable and, therefore, it can mimic other frequent and infrequent abdominal diseases. It was first described in 1843 and it can be caused by any of the members of the *Mycobacterium Tuberculosis* complex (M. *tuberculosis, M. africanum, M. bovis, M. caprae, M. microti,* among others) known as acid-fast bacilli and is characterized by its paucibacillary nature (1, 2). It is the sixth most frequent cause of extrapulmonary TB, and peritoneal TB accounts for up to 50% of such cases (5). Some associations or possible risk factors for the development of peritoneal TB include HIV infection, peritoneal dialysis, type 2 diabetes, the use of immunosuppressive drugs such as corticosteroids and anti-tumor necrosis factor alpha (anti-TNF-α) agents, and alcoholic cirrhosis, as it happened in the case presented here (5).

The peritoneum can be infected by the bacillus through the following mechanisms: hematogenous or lymphatic route from a pulmonary focus; ingestion of infected material that reaches mesenteric and retroperitoneal lymph nodes that can rupture and disseminate the mycobacterium; direct extension from neighboring organs or direct contamination of the peritoneum in patients with chronic kidney disease (CKD) on peritoneal dialysis (1, 6). In our case, in a subsequent evaluation, the patient reported having ingested unpasteurized milk, which could be suggested as a possible pathophysiological mechanism of the infection. Clinical findings of peritoneal TB include the presence of ascites, abdominal pain, fever, weight loss, hyporexia and abdominal distension. Given the non-specific nature of its clinical manifestations, together with the subacute nature of the disease, a late diagnosis is made in up to 70% of cases, so a low threshold of clinical suspicion must be always considered (5).

In case of ascites, observing its characteristics such as a yellow-black or even hematic color is fundamental (1); usually, protein concentration is > 30 g/L and cellularity, > 400 cells/mL, of lymphocytic predominance, which constitutes an exudate with SAAG < 1.1 g/dL. However, in patients with peritoneal TB and concomitant cirrhosis, as it happened in the case described here, this index loses sensitivity with values ranging from 29% to 88%; these patients, as well as those on peritoneal dialysis, may present cellularity with neutrophilic predominance, so the possible confusion with spontaneous bacterial peritonitis must be considered (1, 5).

Cytological analysis of peritoneal fluid is necessary in the differential diagnosis of neoplasm. Measurement of lactate dehydrogenase (LDH) in blood or fluid is less sensitive and specific, and is not routinely used. In addition, despite Ca^{125} antigen is elevated in these cases, this test is not recommended either as a routine diagnostic study (1, 2). Imaging studies such as ultrasound and CT scan are fundamental

for reaching a diagnosis, the latter being the most sensitive method for assessing the peritoneum (6).

Regarding the measurement of ADA levels with a cut-off point > 30 IU/mL (1, 3) and 36 IU/mL (7) for others, it can have a high sensitivity and specificity (96% and 98%, respectively) in the absence of immunosuppression or cirrhosis, (1), so that it is a very useful tool, especially in endemic areas with low possibility of taking samples for performing biopsies (1, 8).

ZN staining is positive in only 3% of cases and culture is still the gold standard, for which solid and liquid medium techniques are generally available, including the BD BACTEC automated blood culture method, which reduces the processing time by half (1, 9). In a systematic review, Sanai and Bzeizi reported positivity in 35% of cases (2).

As for immunological tests, tuberculin is not specific for active TB and it has a low sensitivity. Other tests such as interferon gamma (IFN-γ) measurement and specific immunoglobulin G (IgG) against mycobacteria are useful in ascites cases, but their availability is very limited due to their cost. Molecular tests such as PCR and ligase chain reaction (LCR) offer fast results, but their cost is high and sometimes their sensitivity is low (60-80%); in fact, LCR has a better performance, but is less available (1). In the case presented here, PCR test allowed confirming the diagnosis, which had been highly suspected based on clinical and imaging and laboratory findings.

Finally, peritoneal biopsy by means of laparoscopy is fundamental for histological confirmation and in the differential diagnosis of neoplasm; currently, percutaneous approaches are also being performed in non-fibroadhesive peritoneal TB cases (1, 2).

Peritoneal TB should be treated with the same treatment regime used for pulmonary TB, being 6 months the usual duration. However, some authors suggest extending treatment time to 9 or 12 months, especially in patients with HIV and who are not receiving antiretroviral therapy (1, 5). Our patient received supervised treatment for 9 months, achieving improvement of both clinical signs and laboratory values at the end of the first phase of treatment.

In conclusion, TB continues to be a highly prevalent disease. Furthermore, peritoneal TB is the most frequent type of gastrointestinal TB, and since it can occur with non-specific manifestations, a low threshold of clinical suspicion must be always maintained, even in patients who are not immunocompromised.

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Clinical case

Macroamylasemia at the Hospital Víctor Lazarte Echegaray in Trujillo (Peru): Case report

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Abstract

Macroamylasemia should be suspected in any patient with a persistent catalytic increase of plasma α-amylase but no other clinical signs of abdominal pain after ruling out other causes of pancreatic and extrapancreatic disease. The binding of α-amylase complexes with immunoglobulin, most commonly immunoglobulin A, characterizes this condition. Macroamylasemia is classified into three kinds. To prevent unnecessary procedures, it is critical to make a differential diagnosis of other conditions that can cause amylase increase. The present article reports the case of a 53-year-old female patient who was admitted to the emergency room with abdominal pain and hyperamylasemia, who was initially diagnosed with acute pancreatitis.

Keywords

Macroamylasemia; Hyperamylasemia; Acute pancreatitis.

INTRODUCTION

Macroamylasemia diagnosis is challenging when it is associated with abdominal pain, as it can lead to a false diagnosis of acute pancreatitis. Acute pancreatitis is characterized by pancreatitis-like abdominal pain, imaging findings of pancreatitis, and a three-fold increase in the plasma upper normal limit of the catalytic concentration of α-amylase and lipase enzymes (1-4).

However, said increase may also be related to pancreatic and extrapancreatic metabolic diseases and pancreatic duct anomalies (5). Non-pancreatic hyperamylasemia is mainly caused by salivary gland diseases (mumps, lithiasis), intestinal diseases (bowerl infarction, celiac disease, ulcerative colitis and peritonitis), chronic liver diseases, neoplasms, diabetic ketoacidosis, renal failure, ectopic pregnancy, polycystic ovary syndrome, head injury, and macroamylasemia (6-8). The existence of macroamylase was first described by Wilding in 1964 (6). The term was proposed by Berk in 1967 and published in several case reports (9).

Macroamylasemia is a rare benign condition characterized by the presence of hyperamylasemia or elevated serum α-amylase levels without elevation of α-amylase levels in urine, provided that kidney function is preserved (10). Macroamylasemia occurs in 0.1%-1.5% of the general population (nonalcoholic); amylase isoforms are encoded in chromosome 1p21 (11). It occurs more frequently in males, but the reasons of this predominance are unknown. Macroamylasemia is a condition in which serum amylase protein binds to other serum proteins such as immunoglobulins A (IgA) (up to 92%) and G (IgG) (<30%), among others (<5%), forming large macromolecule complexes that exceed 400 KDa (amylase in its active cytoplasmic form contains 496 amino acids with a molecular weight of 54 KDa) (11-13).

Macroamylasemia can be diagnosed indirectly by measuring amylase activity in urine; specifically, the amylase to creatinine clearance ratio (ACCR) can contribute to differentiating hyperamylasemia. This ratio is calculated using the following equation:

$$ACCR = (\text{amylase [urine]} \times \text{creatinine [serum]})/(\text{amylase [serum]} \times \text{creatinine[urine]}) \times 100.$$

An ACCR >5% is suggestive of acute pancreatitis.

An increased ACCR may also occur in diabetic ketoacidosis, surgery, and renal disease. An ACCR <1% is suggestive of macroamylasemia (11). Chromatography and polyethylene glycol (PEG) precipitation are the methods of choice for detecting macromolecules that contain macroamylase (6, 11).

CLINICAL CASE PRESENTATION

This is the case of a 53-year-old women with a history of high blood pressure (treated with losartan 50 mg every 12 hours) and cholecystectomy who was admitted due acute pancreatic abdominal pain. Epigastric pain on palpation was evidenced on physical examination. The following laboratory and imaging studies were performed: amylase: 1407 U/L; ultrasound: normal pancreas, 7.4 mm common bile duct, and mild left hydronephrosis. The patient was diagnosed with mild acute pancreatitis, for which she was hospitalized. Five days after hospital admission, a control amylase test was performed (1419 U/L; associated with absence of pain). She was then discharged and referred to the outpatient department to conduct further tests aimed at determining the causes of hyperamylasemia. **Table 1** summarizes the results of these tests on hospital admission and at 5 days, 3 months, 8 months, 10 months and 1 year in the outpatient service.

During the patient's follow-up, laboratory tests were performed to rule out associated diseases that could cause hyperamylasemia (**Table 1**). She also underwent an endoscopy in which a duodenal biopsy was performed, which in turn showed glandular architecture associated with chronic nonspecific infiltrate, intraepithelial lymphocyte count <40/100 epithelial cells, without atrophy. Besides, during colonoscopy diverticula were observed in the sigmoid colon. Regarding imaging studies, no lymphadenopathies were evidenced on a CT of the neck (soft tissue), and evidence of cancer was observed in the CT scan of the chest, abdomen and pelvis (**Figure 1**); likewise, a normal biliary tract and no signs of choledocholithiasis were evidenced during magnetic resonance cholangiopancreatography (**Figure 2**). Further tests included ACCR (0.02%) and a confirmation test for macroamylasemia, which was positive (**Table 2**). The patient was asymptomatic during her evaluation at the outpatient department.

DISCUSSION

It should be noted that our patient was a woman, as it has been described macroamylasemia occurs more frequently in males (11). In this case, the patient's abdominal pain on admission was associated with hyperamylasemia, which led to a wrong diagnosis of acute pancreatitis; 6% to 9.6% cases of hyperamylasemia are caused by macroamylasemia (14, 15). The highlight of our case is that no abdominal pain was experienced by the patient during the course of hyperamylasemia, so further testing was required to rule

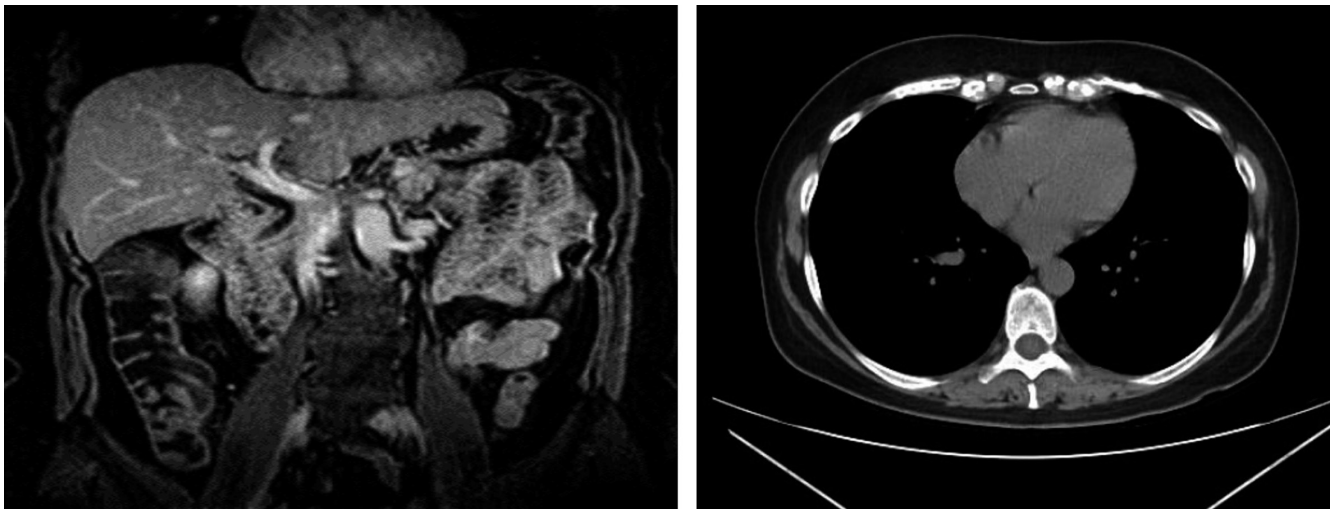

Figure 1. CT scan of the chest, abdomen and pelvis.

Table 1. Evolution of laboratory test results.

	On hospital admission	At 5 days	At 3 months	At 8 months	At 10 months	At 1 year
Amylase α (IU/L)	1407	1419	2445	2454	2495	1174
Lipase (IU/L)		32		---		
Creatinine (mg/dL)	0.48	---	0.54	---	---	---
Urea (mg/dL)	23	---	22	---	---	---
Creatinine clearance (mL/min)	120	---	107	---	---	---
Glucose (mg/dL)	106	---	88	90	---	---
AST/GOT (IU/L)	17	---	18	22	---	---
ALT/GPT (IU/L)	13	---	10	27	---	---
Albumin (g/dL)	4.50	---	4.54	4.43	---	---
Total protein (g/dL)	7.32	---	7.30	7.45	---	---
Globulin (g/dL)	2.82	---	2.76	3.02	---	---
Alkaline phosphatase	200	---	205	244	---	---
Gamma-glutamyl transpeptidase	40	---		14	---	---
Total bilirubin (mg/dL)	0.8	---	0.57	0.53	---	---
Triglycerides	156	---		66	---	---
Hemoglobin (g/dL)	12.8	---		12.9	---	---
Platelets mL/mm3	350.000	---		380.000	---	---
TSH (mIU/dL)	---	---	---	3.1	---	---
Free T4 (ng/dL)	---	---	---	1.83	---	---
ANA	---	---	---	---	Negative	---
VRDL	---	---	---	---	Negative	---
Rheumatoid factor	---	---	---	---	28.18	---
Total hepatitis B core antibody	---	---	---	---	Non-reactive	---
Hepatitis B, Australia antigen	---	---	---	---	Non-reactive	---
Hepatitis C Virus	---	---	---	---	Non-reactive	---
Elisa for HIV	---	---	---	---	Non-reactive	---
AMA	---	---	---	Negative		---

Source: Sistema de Atención Historia Clínica Hospital Lazarte Echegaray - Essalud (Medical Record Health Care System Hospital Lazarte Echegaray - Essalud). GOT: glutamic-oxalacetic transaminase (NV: 0-35 IU); GPT: glutamic-pyruvic transaminase (NV: 0-35 IU); TB: total bilirubin (NV: 0.3-1.2 mg/dL); DB: direct bilirubin (NV: 0-0.3 mg/dL); TP: total proteins (NV: 6-8 g/dL); ALB: albumin (NV: 3.5-5.5 g/dL); ALP: alkaline phosphatase (36-129 IU); GGT: gamma-glutamyl transpeptidase (NV: 8-78 IU); serum amylase (NV:0-100IU/L); T4 (NV: 0.8 to 1.9 ng/dL); TSH (NV: 0. 5-4.5 mU/dL); platelets (NV: 150-450 ml/mm3); hemoglobin (NV: 12-14 g/dL); serum creatinine (NV: 0.4 to 1.4 mg/dL); VRDL: The Viral and Rickettsial Disease Laboratory; NV: normal values.

out other pancreatic and extrapancreatic causes, as well as associations with other diseases. Celiac disease is the condition most frequently associated with macroamylasemia development; in this regard, Rabsztyn et al. (16), in a case-control study, concluded that a significant proportion of patients recently diagnosed with celiac disease have macroamylasemia; therefore, if a patient has macroamylasemia, celiac disease must be also considered. In our case, 6 biopsy samples were taken by means of an endoscopy, and in which a MARSH 0 score was reported, without criteria to carry out more tests to confirm or rule out the presence of celiac disease. Other macroamylasemia-

Table 2. Macroamylasemia study

	Result
Amylase clearance	0.02
Amylase in urine	19 IU/L
Serum amylase	1174 IU/L
Creatinine	0.5 mg/dL
Urine creatinine (24-hour urine collection)	43.9 mg/dL
Macroamylasemia*	Positive

*Chromatography; precipitation with polyethylene glycol (PEG). Source: Sistema de Atención Historia Clínica Hospital Lazarte Echegaray - Essalud (Medical Record Health Care System Hospital Lazarte Echegaray - Essalud). Amylase clearance (NV: <5); amylase in urine (NV: <460 U/L); serum amylase (NV: 0-100 U/L); serum creatinine (NV: 0.4-1.4 mg/dL).

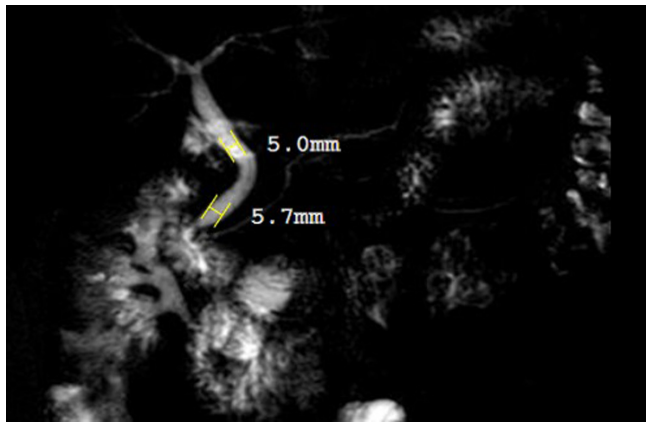

Figure 2. Magnetic resonance cholangiopancreatography.

associated diseases include chronic liver diseases (17), diabetes *mellitus* (18), rheumatoid arthritis (19), systemic lupus erythematosus (20), T-cell lymphoma (21), inflammatory bowel disease (22), asymptomatic HIV (23) and renal cell and thyroid carcinoma (16). All these conditions were ruled out in our patient.

Levitt et al. proposed the existence of two forms of macroamylasemia (24): the first one was characterized by the presence of malabsorption with an 11 S serum amylase resulting from the binding of normal-sized amylase by IgA immunoglobulin. In the second type, patients did not suffer from malabsorption, the sedimentation coefficient was 7 S and the complex was not the result of amylase binding to an immunoglobulin. Currently, 3 types of macroamylasemia have been described (**Table 3**) (25).

A very low ACCR (0.02%) and a short time to the positive result were observed in our patient; based on these findings, type 1 macroamylasemia was suspected, which was confirmed by means of chromatography and PEG precipitation. Thus, it can be concluded that this is a case of a type 1 macroamylasemia. Macroamylasemia must be considered in cases of persistent hyperamylasemia, even if the initial manifestation is abdominal pain, also ruling out other etiologies and associated diseases of importance.

Table 3. Types of macroamylasemia

Typo	1	2	3
Serum amylase	Persistently elevated amylase levels	Increased	Normal
Amylase in urine Decreased	Decreased or Normal	Decreased or Normal	Normal
ACCR	Very decreased	Disminuido	Decreased
Macroamylase concentration	Relatively high	Lower than type 1	Low
Time to result	Short	Long	Long

Source: taken from (25).

Conflict of interest

None declared by the author.

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Clinical case

Gastric volvulus in a nonagenarian patient: endoscopic and laparoscopic intervention. Case report

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Abstract

Gastric volvulus is a rare condition that can occur acutely or chronically and is accompanied by nonspecific symptoms. Its rapid identification is critical since it has high mortality rate and timely treatment determines the patient's prognosis.

The following is the case of an 89-year-old female patient who presented with atypical chest pain, with organoaxial gastric volvulus on chest X-ray, in whom endoscopic devolvulation was initially performed successfully. However, control imaging scans revealed recurrence. Therefore, surgical management included hiatoplasty and Toupet fundoplication, as well as percutaneous fixation gastrostomy, a procedure that was completed without complications and resulted in complete devolvulation without recurrence.

Keywords

Gastric volvulus; Endoscopic treatment; Gastropexy.

INTRODUCTION

Gastric volvulus is a rare condition characterized by abnormal rotation of the stomach along its long or short axis, leading to varying degrees of obstruction (1).

Its incidence reaches its peak after the fifth decade of life and adults account for 80% to 90% of cases. No association with sex or race has been reported (2).

Gastric volvulus is classified according to its duration (acute or chronic), etiology (primary or secondary) and the axis of rotation (organoaxial or mesenteroaxial).

Its symptoms are not specific; however, acute gastric volvulus has been associated with epigastric pain, nausea without vomiting and impossibility to advance the nasogastric tube (Borchardt's triad), while chronic volvulus, with peptic ulcer disease or biliary tract-related diseases such as cholelithiasis (3).

The following is the case of a nonagenarian patient who was admitted to our institution due to atypical chest pain, and in whom organoaxial gastric volvulus was documented as an incidental finding in the admission chest X-ray.

CASE

This is the case of an 89-year-old woman patient with a history of osteoporosis and multiple vertebral fractures who visited our health institutions looking for medical assistance due to having experienced the following symptoms

and signs during 4 days: nonradiating chest pain whose intensity increased with inspiration, together with dyspnea while in resting position. The patient did not refer experiencing any gastrointestinal symptom such as abdominal pain, nausea or emesis.

On physical examination on admission, the general condition of the patient was acceptable, agitation, tachycardia and diaphoresis were observed, as well as epigastric pain on deep palpation without signs of peritoneal irritation.

In a chest X-ray requested on admission due to suspicion of vertebral fracture, an ascending gastric chamber in the posterior mediastinum, associated with hydro-aerial level and suggestive of gastric volvulus was documented as an incidental finding (**Figure 1**).

Gastric decompression was started using a nasogastric tube, opioid administration was initiated for pain management, and intravenous hydration with isotonic fluids was started.

Subsequently, a contrast-enhanced CT scan of the chest and abdomen evidenced a hernia of the gastroesophageal junction, fundus and antropyloric region towards the thorax, as well as rotation of the stomach in its long axis, signs compatible with organoaxial gastric volvulus (**Figure 2**).

Given these imaging findings, the advanced age of the patient and her comorbidities, which made her a high-risk surgical patient, endoscopic management was decided, thus an endoscopic devolvulation was performed without any complication (**Figure 3**).

However, gastric volvulus recurrence was detected in a control chest X-ray performed 24 hours after the endoscopic procedure.

In view of this recurrence, surgical management was decided together with the general surgery service: laparoscopic hiatal hernia repair surgery (laparoscopic hiatoplasty and Toupet fundoplication) and percutaneous gastrostomy fixation.

The procedure was performed without complications, with an adequate evolution of the patient's condition during the postoperative period, tolerance to oral administration of food and improvement of thoracic pain. There was no evidence of recurrence in a control chest X-ray performed 72 hours after the surgical procedure.

DISCUSSION

Gastric volvulus is a rare condition characterized by abnormal rotation of the stomach along its long or short axis, which leads to varying degrees of obstruction (4).

Timely diagnosis and management determines the patient's prognosis, since it can lead to intestinal obstruction, vascular involvement and even intestinal strangulation, which can progress to necrosis or perforation.

Around 70%-80% of gastric volvulus cases affect adults over 50 years of age and its occurrence is associated with predisposing factors such as phrenic nerve paralysis and

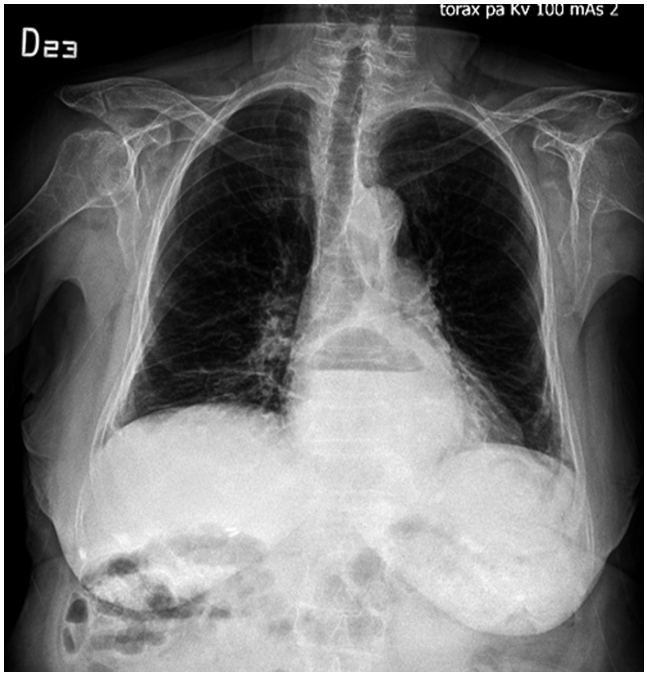

Figure 1. Chest X-ray: Ascending gastric chamber in the posterior mediastinum with hydro-aerial level.

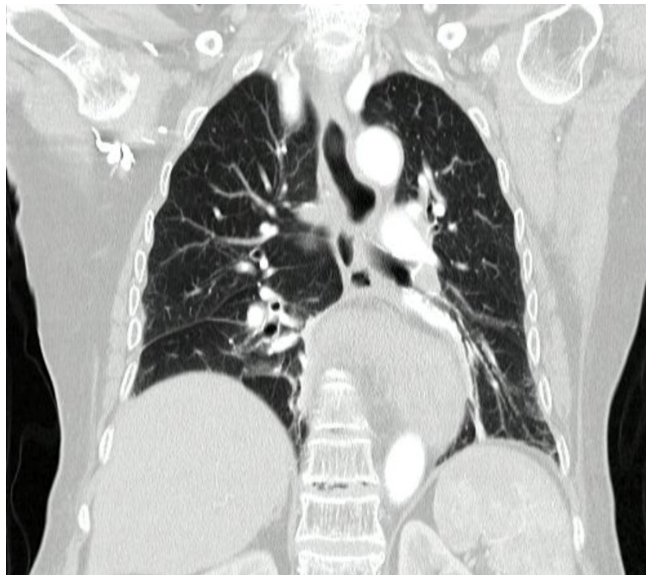

Figure 2. Contrast-enhanced CT scan: hernia of the gastroesophageal junction, fundus and antropyloric region towards the thorax and rotation of the stomach in its long axis.

some anatomical alterations of the diaphragm, abdominal organs or kyphoscoliosis (5).

There are two main types of gastric volvulus: organoaxial, where rotation of the stomach on its vertical axis occurs, and mesenteroaxial, in which rotation occurs on the horizontal axis (**Figure 4**).

Primary (idiopathic) gastric volvulus is defined as a volvulus caused by abnormalities of the gastric ligaments. Gastric fixation failure may occur as a result of agenesis, elongation or injury of the gastric ligaments due to neoplasia, adhesions or skeletal deformity (6, 7).

Secondary volvulus is defined as a volvulus caused by other anatomical abnormalities such as paraesophageal hernia, diaphragmatic hernia, diaphragm eventration and phrenic nerve palsy.

The classic finding of acute gastric volvulus on plain X-rays of the abdomen is the presence of a gastric bubble or hydroaerial levels in the upper abdomen or the chest.

In mesenteroaxial volvulus, there may be two gastric bubbles (one in the fundus and the other in the antrum), while in organoaxial volvulus there is only one bubble and the stomach is in a horizontal position.

CT scan has the additional advantage of showing the relationship between the stomach and surrounding structures, as well as anatomical abnormalities associated with secondary gastric volvulus.

Usually, acute volvulus management requires, as it was the case of our patient, endoscopic decompression, initial endoscopic devolvulation, percutaneous endoscopic gastrostomy, gastropexy and repair of predisposing structural defects to prevent recurrence (8). Yao-Chun Hsu et al., in a study in which 44 patients (median age of 71 years) with gastric volvulus who received conservative treatment in the presence of mild to moderate symptoms were followed-up for 36 months, reported that recurrence was observed in 64% cases and that none of the patients presented with acute complications during the follow-up period; however, laparoscopic surgery was required in one patient due to the presence of recurrent symptoms affecting the patient's quality of life (9, 10). The average recurrence-free duration was 3 months and the factors associated with recurrence were longer duration between the onset of symptoms and (1.6 months; p=0.065), previous thoracic or abdominal surgery (p=0.061) and peritoneal adhesions (p=0.015) (11).

On the other hand, it has been described that surgical management is superior to management based only on percutaneous endoscopic gastrostomy, as the latter does not prevent recurrence. Traditionally, gastric volvulus has been treated by means of surgery in combination with endoscopic techniques in some patients, including devolvulation alone or devolvulation plus one or two percutaneous gastrostomies (12). In patients with organoaxial volvulus, endoscopic approach is limited by the obstruction at the gastroesophageal junction, which prevents safe passage of the gastroscope and in turn makes more difficult guiding the position of the stomach; in addition, endoscopic management does not address the diaphragmatic disease seen in most gastric volvulus cases.

Several surgical methods for treating gastric volvulus have been described, including diaphragmatic hernia repair, gastropexy, partial gastrectomy due to necrosis, antral fundus gastrogastrostomy (Opolzer's operation) and gastropexy

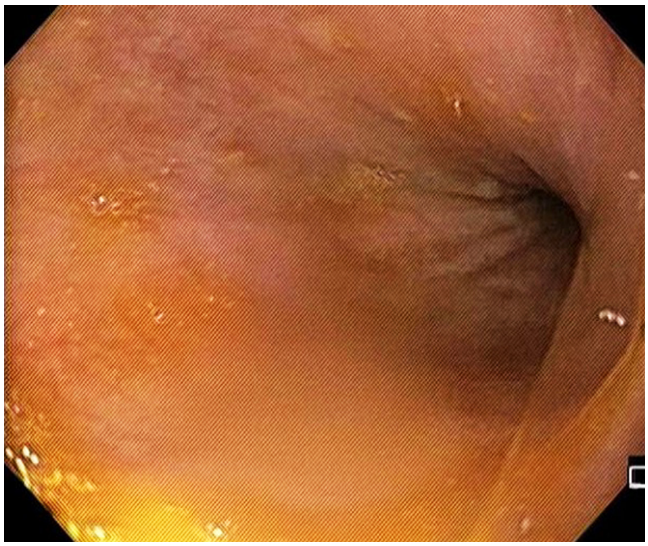

Figure 3. Image during upper endoscopy and endoscopic devolvulation.

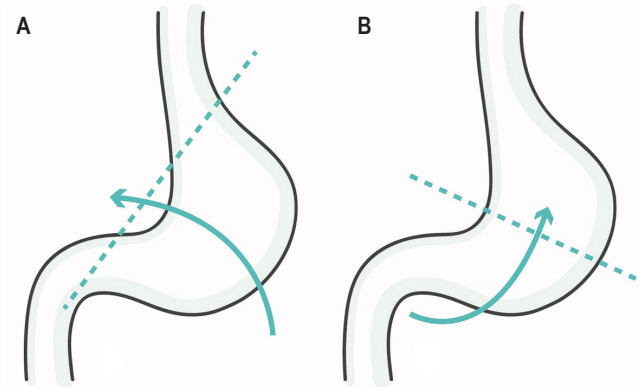

Figure 4. A. Organoaxial volvulus by rotation of the stomach on its longitudinal axis. **B.** Mesenteroaxial volvulus by rotation of the stomach on its transverse axis.

with fixation of the gastrocolic ligament (Tanner's operation), among others.

Combined management (surgery plus preoperative or intraoperative percutaneous endoscopic gastrostomy) favors that the gastrostomy tube acts as the main anchor of the stomach to the anterior abdominal wall, which allows the laparoscopic repositioning of the gastropexy sutures to achieve an optimal anatomical position of the stomach along its natural axis; besides, it has been described there is no difference in terms of the efficacy of combined management between performing endoscopic gastrostomy prior to or during surgery. The passage of the gastroscope through the esophagogastric junction or the lack of endoscopic devolution is a limiting factor for preoperative endoscopic gastrostomy (13).

Two techniques have been described to perform endoscopic devolvulation. First, the Alfa-loop maneuver, described by Tsang in 1995, which comprises six main steps, and in which an alpha loop is formed at the proximal end of the stomach affected by gastric volvulus by advancing the endoscope tip through the site of the stricture that produces the volvulus; subsequently the endoscope tip is brought into the duodenum by torquing the endoscope clockwise. Second, fluoroscopy based dual endoscopic technique, in which the adult gastroscope is brought into the duodenum, which favors the displacement of the stomach towards the abdominal cavity and the repositioning of the antrum maintaining its axis; then a pediatric gastroscope is passed next to the adult gastroscope and an endoscopic percutaneous gastrostomy is performed to fixate the anterior wall of the stomach to the abdominal wall (14).

In our case, in view of the gastric volvulus recurrence despite endoscopic management, and with the intention of performing gastric fixation to avoid a new recurrence, together with the general surgery service, a surgical approach consisting of a hiatoplasty and a Toupet fundoplication, in addition to percutaneous gastrostomy for gastric fixation purposes, was decided, which allowed achieving complete devolvulation, absence of recurrence and an adequate evolution of the clinical condition of the patient.

CONCLUSION

Gastric volvulus is a rare condition with a spectrum of clinical presentation ranging from chronic course of the disease characterized by nonspecific symptoms to acute clinical presentation, with sudden onset of symptoms and a high risk of mortality.

Clinical suspicion and timely diagnosis based on imaging findings is of great importance, as imaging tests allow for the identification of this condition, as well as the mechanism causing it and associated complications. Early endoscopy is necessary and treatment with endoscopic or laparoscopic gastropexy is required as a less invasive and viable alternative to a more aggressive surgical procedure in some older adults with significant comorbidities.

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Clinical case

Black hairy tongue associated with squamous cell carcinoma of the esophagus

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Abstract

Black hairy tongue (BHT) is a benign disorder characterized by dark coloration and hypertrophy with hyperkeratosis in filiform papillae on the surface of the tongue. Several intrinsic and extrinsic factors, including poor dental hygiene, smoking, drinking dark beverages, indiscriminate use of antibiotics, and some malignant diseases, have been proposed as potential causes. This is the case of a patient with advanced squamous cell carcinoma of the mid esophagus in conjunction with BHT, a previously unknown association.

Keywords

Black hairy tongue; Black tongue; Hyperpigmentation of the tongue; Lingual pigmentation.

INTRODUCTION

Black hairy tongue (BHT) is a benign condition in which the center of the tongue changes its color, from black to yellow, and has a hairy appearance due to hypertrophy and elongation of the filiform papillae (1). It has a variable prevalence and its occurrence is associated with multiple factors such as poor oral hygiene, tobacco use, antibiotic use (penicillin, erythromycin, doxycycline [2], linezolid [3], tetracycline [4]), and irritating mouthwashes (5). An association between BHT and systemic diseases such as HIV and malignancies has been described (6). We present the case of an elderly woman with squamous cell carcinoma of the middle esophagus and in whom BHT was an associated, incidental, unaesthetic, and asymptomatic finding.

PRESENTATION OF THE CLINICAL CASE

This is the case of a 78 years old woman born in Ubalá, Cundinamarca and living in Bogotá, with a history of hypothyroidism (treated with levothyroxine) and arterial hypertension (treated with enalapril at the time of consultation). The patient attended the digestive endoscopy service due to having experienced the following signs and symptoms for 1 month: dysphagia with retrosternal choking sensation and a 5 kg weight loss. The patient reported having black tongue for 7 years, a condition that was ignored in several consultations.

On physical examination she was in an acceptable general condition; vital signs: blood pressure (BP): 145/85 mm Hg; heart rate (HR): 76/min; respiratory rate (RR): 18/min;

oxygen saturation (SaO2): 92%; fraction of inspired oxygen (FiO_2): 24%; weight: 40 kg; height: 1.5 m; body mass index (BMI): 17.78 kg/m^2; and body temperature: 36°C.

During endoscopy, the tongue was found to have a dark blackish color on its dorsum, with a hairy appearance, without involvement of the borders or the tip, with a whitish depigmentation area in the central posterior part (**Figures 1** and **2**). In the middle esophagus (25 cm), on the right, left and anterior lateral walls, there is a nodular, infiltrative and friable lesion causing a 12 mm stenosis that can be crossed and reaches up to 30 cm, without distal esophageal involvement (**Figures 3** and **4**).

A non-keratinizing, infiltrating, poorly differentiated and ulcerated large squamous cell carcinoma was described in the pathology report.

At the time this case report was written, the patient is undergoing further testing to determine the treatment and management approach of the BHT syndrome by the odontology service.

DISCUSSION

Black hairy tongue (BHT) is a benign condition consisting of the darkening and hairy appearance of the dorsum of the

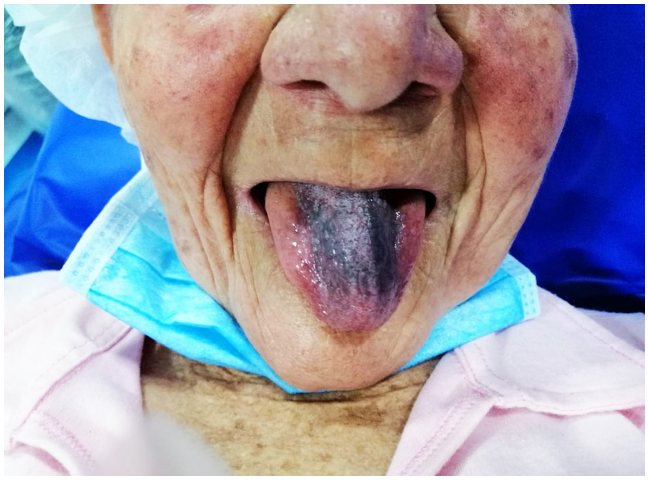

Figure 1. Patient in which the dorsum of the tongue is black, without involvement of the lateral borders of the tip.

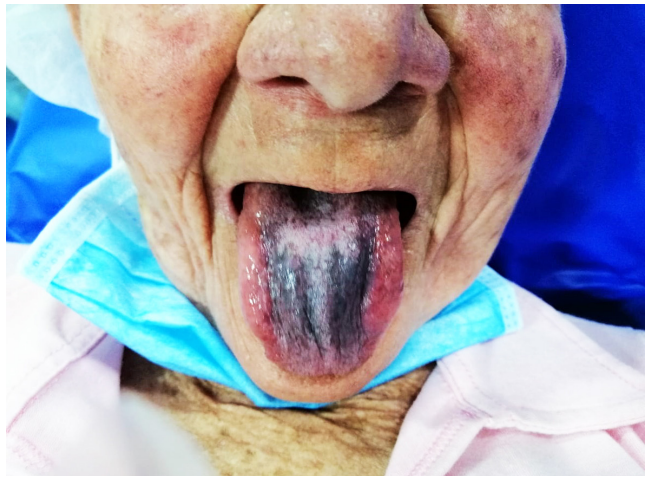

Figure 2. Patient with black hairy tongue (BHT) with whitish depigmentation in the central posterior part.

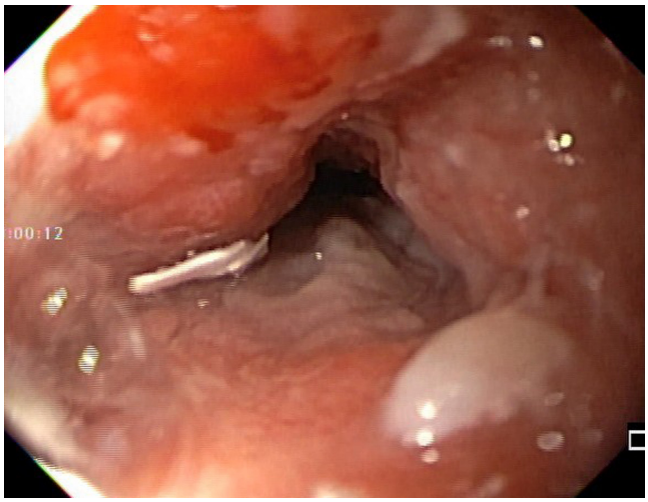

Figure 3. Endoscopy. Proximal border of squamous cell carcinoma in the middle part of the esophagus involving 80% of the wall and lumen.

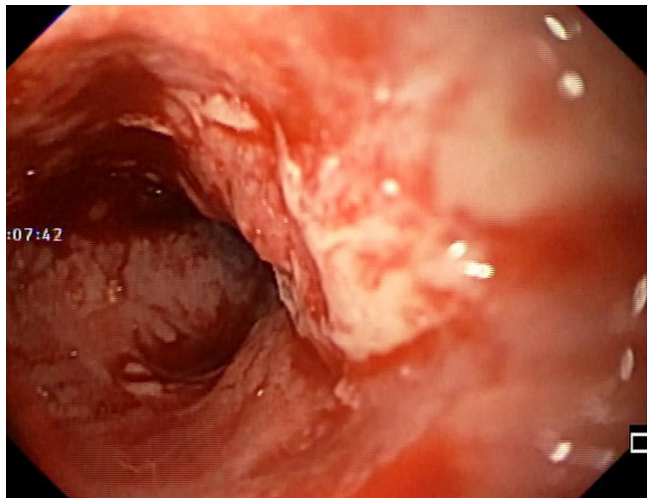

Figure 4. Endoscopy. Distal border of the carcinoma affecting the middle part of the esophagus.

tongue. It was first described by Amatus Lusitanus in 1597 (7, 8). Its prevalence is variable, although a prevalence as high as 11.3% has been described in some oral health studies, being more common in elderly men, heavy smokers, and black tea and coffee consumers (9, 10), HIV positive people, edentulous individuals, people with prostate cancer or B-cell lymphoma (6), and in patients undergoing antibiotic treatment (2-4). Clinically, a black plaque or membrane is observed on the dorsum of the tongue, without lateral borders or tip involvement (**Figure 1**) and, as in this case, without involvement of the central and posterior part of the tongue (**Figure 2**). Black is the most common color change, but can vary to brown, green or yellow (11).

BHT is usually asymptomatic, although symptoms such as nausea, loss of taste, halitosis, burning or tingling of the tongue have been described (12); however, the main annoyance for patients is its unpleasant esthetic appearance (13).

Hairy appearance is due to inadequate keratin desquamation (hyperkeratosis) over the filiform papillae, which elongate up to 18 mm × 2 mm. On the other hand, color change is caused by yeasts or anaerobic (such as *Porphyromonas gingivalis*) (14), chromogenic, amino acid-fermenting, and porphyrin-producing bacteria, and modifications resulting from environmental factors (tobacco, alcohol, oxidizing mouthwashes, antibiotics, antipsychotics, proton pump blockers, chemotherapeutic agents, radiotherapy, anti-HIV drugs, and xerostomia predisposing drugs) (7), which can be associated with alterations of the oral microbiome present in HIV infection, graft-versus-host disease, amyotrophic lateral sclerosis, trigeminal neuralgia or malignancy (11).

Differential diagnoses include "pseudo-BHT" conditions such as acanthosis nigricans, congenital lingual melanotic macules, congenital melanocytic nevi, premalignant leukoplakia, squamous cell carcinoma and hypertrophic infection by herpes simplex virus (15).

Clinical diagnosis is made by asking the patient in detail about the presence of the abovementioned predisposing factors. Gentle scraping of the tongue with a tongue depressor or a toothbrush may suggest BHT if the pigment dissipates; however, this procedure is not always easy, as it may require multiple attempts (16). A biopsy is usually not necessary, except when the lesion becomes atypical, refractory to treatment or symptomatic, thus suggesting a potential malignancy or systemic disease (17); however, when biopsy is performed, hyperkeratosis and accumulation of parakeratosis at the tip of the filiform papillae are reported (18). Dermoscopy is the diagnostic tool of choice; it allows the identification of shape and color changes of the filiform papillae; it is also useful in the evaluation of therapeutic success (18, 19).

The first line of treatment is based on suspending the medications associated with the condition, having excellent oral hygiene, quitting predisposing habits, and the generous brushing or scraping of the tongue to promote the desquamation of the papillae (17). Topical use of 3% hydrogen peroxide, suspension of oxidizing mouthwashes; fitting of dentures in edentulous patients (which promotes mechanical abrasion of the desquamated papillae when chewing solid food) have shown to have a good efficacy (20). In BHT resistant cases, papillae can be removed by burning-off or electrodesiccation with carbon dioxide laser (21). Second-line treatments, which are anecdotal and have no supporting evidence, include oral retinoids, antifungal agents, antibiotics, topical urea solution or triamcinolone, salicylic acid and gentian violet.

No cases of BHT and esophageal cancer association were found in the literature review conducted by us, so this is an association that should be taken into account.

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