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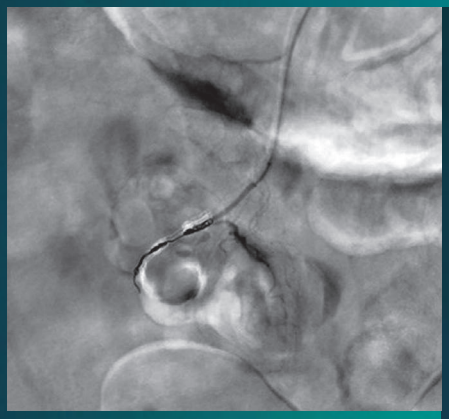

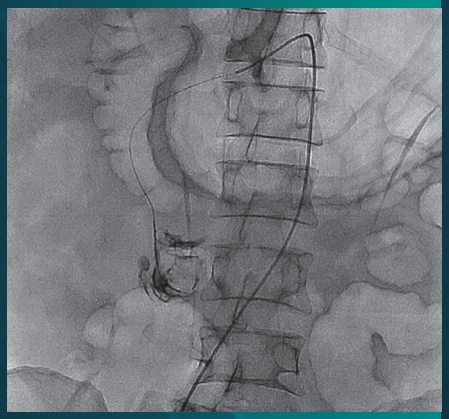

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Courtesy by the authors: Gianmarco Camelo-Pardo, Francisco José Ortega-Torres, Adriana Maritza León-Díaz, Cristian Eduardo Tarazona-León.

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Editorial

Remembering a rare pathology

Gustavo Landazábal-Bernal.[1*]

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This journal issue presents two articles on small bowel diverticula manifested by hemorrhage. Small intestine diverticula can be classified by origin (congenital or acquired), by the wall structure (true or false), and by location (duodenal, jejunal, jejunoileal, and terminal ileal). According to their origin, congenital diverticula are true when their wall includes all the layers of the intestinal wall (mucosa, submucosa, muscularis propria, and serosa); the most typical example is Meckel's diverticulum, described in 1598 by Fabricius V. Hilden, and it was not until 1812 that Johann Friedrich Meckel related it as a remnant of communication with the yolk sac[(1)]. It is present in 2% of the population. Of note is that congenital diverticula are also described, especially in the duodenum and sporadically in the rest of the small intestine. Acquired diverticula are usually false diverticula; their wall comprises the mucosa, submucosa, and serosa layers. They are the majority of jejunoileal and duodenal diverticula.

Their origin lies in pulsion mechanisms with incoordination of the neuromuscular activity of the intestinal wall with dyskinesias, causing high pressures. At the points where the perforating vessels penetrate the intestinal wall at the mesenteric border, progressive herniation of the submucosa and mucosa occurs, forming the false diverticulum; these vessels are more abundant in the proximal jejunum, precisely where these diverticula are more frequent, and are typically multiple[(2)]. The shaped diverticulum allows bacterial overgrowth that triggers malabsorption and possible steatorrhea.

From the perspective of their clinical manifestations, between 60% and 90% are asymptomatic, up to 25% present some symptoms, and 15% develop some complications. Small bowel diverticula can manifest in a chronic form with malabsorption associated with chronic abdominal pain or in an acute form with obstruction, pseudoobstruction, diverticulitis, perforation, or hemorrhage, as the cases reported in this publication[(3,4)]. In chronic manifestations, the diagnosis is made with clinical suspicion, which, due to their rarity, requires the physician's sharpness (incidence in autopsies of 0.06% to 5%). Noble's triad, consisting of diffuse abdominal pain, anemia, and dilation of thin loops[(5)], is described.

Depending on the manifestation, the diagnosis may be incidental to a surgical exploration for another cause or to radiological or endoscopic studies. In acute manifestations, especially those associated with bleeding, an upper or lower source of bleeding is ruled out with esophagogastroduodenoscopy and colonoscopy. At this point, it should be considered that since the highest incidence of diagnosis of diverticula in the small intestine is between 60 and 70 years of age[(6)], it is not uncommon to find associated diverticula in

the colon, hemorrhoidal disease, polyps, vascular malformations, and acid-peptic disease in different degrees of intensity. All these pathologies can distract from the diagnosis of diverticula in the small intestine, and only the persistence or intensity of bleeding makes it necessary to conduct other studies, which, in hemodynamically stable patients, can be capsule endoscopy, enteroscopy, magnetic resonance enterography, or contrast-enhanced tomography. Capsule endoscopy should be avoided in patients with large diverticula due to the possibility of becoming entangled in the diverticula[5].

Due to the intermittent nature of digestive bleeding, studies with radioisotopes allow several measurements to be taken at various times to detect active bleeding even without identifying the anatomical location, which helps the patient receive arteriography therapy[7]. In hemodynamically unstable patients, magnetic resonance angiography, CT angiography, or direct angiography is used. Ten percent of cases with bleeding require surgical management with resection of the diverticulum or the affected intestinal part. In patients with inflammation, it is preferable to resect the segment involved[1,2].

Lastly, we congratulate the authors of the articles on small bowel diverticula published in this issue for their detailed and engaging descriptions of the reported cases.

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Original article

Managing Low and Moderate Risk Obesity: Insights from a Colombian Reference Center's Experience with Liquid-Filled Intragastric Balloons

Cristian Flórez-Sarmiento,[1] Viviana Parra-Izquierdo,[2] Juan Sebastián Frías-Ordóñez,[3*] Elaine Jaimes-Valderrama,[4] Jesús David Castillo,[5] Charlyn Stefani Rodríguez,[6] Víctor Rodríguez,[7] María Isabel Piñeros,[8] Jenny Alvarado.[9]

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Abstract

Introduction: Liquid-filled intragastric balloons (IGBs) have emerged as a safe and effective option for managing overweight and obesity. However, there is limited information available regarding the implementation of liquid IGBs in individuals with low- and moderate-risk obesity. **Objective:** The objective of this study was to assess the implementation of liquid IGBs in low- and moderate-risk obese individuals in terms of weight loss, safety, and tolerance at four, six, and twelve months of treatment. **Materials and methods:** This prospective, descriptive observational study included 109 subjects with low- and moderate-risk obesity (body mass index [BMI] of 30-40 kg/m^2), who underwent endoscopic implantation of liquid-filled IGBs. The variables analyzed included sex, age, initial and final weight, percentage of weight loss, and side effects. **Results:** Out of the 109 subjects, 75.22% were women. The average weight at baseline was 87.22 kg, with an average BMI of 31.59 kg/m^2. Three different brands of IGBs were used: Orbera (n=103), Spatz3 (n=3), and Elipse (n=3). The average weight loss showed significant differences when analyzed by months and brands—Ellipse: four months (-4.6 kg), Spatz3: three months (-7 kg), Orbera: six months (15.2 kg), Orbera: twelve months (19.7 kg). The average reduction in BMI achieved was 27.71 kg/m^2. The complication rate was 2.75%, with two cases (1.83%) attributed to intolerance (abdominal pain) and one case due to acute appendicitis (0.91%). **Conclusions:** The findings of this study indicate that liquid-filled IGBs are a safe and effective procedure for managing low- and moderate-risk obesity. A minimum duration of twelve months with an IGB implantation is considered optimal for individuals with low- and moderate-risk obesity.

Keywords (DeCS – Health Sciences Descriptors)

Gastric balloon, risk, obesity, weight loss, obesity management, endoscopy.

INTRODUCTION

Obesity is a public health problem with high morbidity and mortality. It has been shown that a 5 kg/m^2 increase in body mass index (BMI) above 25 kg/m^2 is associated with an increased risk of all-cause mortality[(1)]. It is deemed a chronic and difficult-to-manage disease, which results in multiple metabolic, cardiovascular, joint, and psychosocial

complications. Furthermore, it has been described that achieving a sustained weight loss of 5% to 10% can prevent and reduce cardiovascular risk and other complications in people with obesity[2].

Initial management includes conservative measures such as caloric restriction, exercise, and behavioral changes. Pharmacotherapy is recommended in patients who fail to lose weight, and the surgical approach is reserved for highly obese people[3]. The intragastric balloon (IGB) is an intermediate step between medical and surgical management[4,5] and an attractive choice because it is considered a temporary (less than six months), reversible, minimally invasive, safe, and effective weight loss method[6-8]. A mean total body weight loss of 15.5% has been proven in overweight or obese adults one year after removal[7].

Currently, IGB models include those with fluid or air content; the most widely used are fluid-filled due to their lower rate of complications[9]. When placed, the IGB floats freely in the stomach, with a multifactorial mechanism of action and physiological and neurohormonal changes, leading to increased satiety and decreased gastric reservoir capacity and food intake[4]. It can be kept in the stomach for six months, and a new generation of IGB allows up to 12 months[10]. Today's most used IGBs include Orbera, Spatz 3, Reshape Duo, Bariatrix, Elipse, and Heliosphere. There is no precise indication in the literature regarding which to employ, so the best option is chosen according to the physician's criteria and experience in each technique[11]. In Colombia, there is little information about the results of implementing fluid-filled IGB in low- and moderate-risk obesity (BMI of 30–40 kg/m^2).

This study aims to evaluate the implementation of fluid-filled IGB in individuals with low- and moderate-risk obesity (BMI of 30–40 kg/m^2) regarding weight loss, safety, and tolerance at 4, 6, and 12 months of treatment.

MATERIALS AND METHODS

Study design and data extraction

A prospective descriptive observational study was conducted using convenience sampling that took as the source population patients with low- and moderate-risk obesity (BMI of 30–40 kg/m^2) at Clínica Palermo from January 1, 2019, to December 31, 2020. Clínica Palermo is a tertiary referral hospital and a national benchmark in gastroenterology. The study population consisted of patients ≥18 years of age, refractory to conservative treatment, and participants in a weight loss program. Individuals with a BMI > 40 kg/m^2 or with contraindications for IGB were excluded. All patients were informed and signed the informed consent.

Data collection

The medical records and the official report of the procedure performed were used as the primary source of information, collecting sociodemographic and clinical variables on admission. The variables of sex, age, initial and final weight, weight loss percentage, and side effects were analyzed. Complications were considered adverse effects attributable to IGB after two weeks of insertion, found during outpatient follow-up. Standard methods for quantifying weight loss, such as BMI and weight loss percentage, were used.

Procedure

The preprocedural weight loss protocol consisted of multidisciplinary outpatient follow-up (with a gastroenterologist and nutritionists). The IGB implantation was initially managed with a hypocaloric diet (1,000 cal/day) and physical activity.

One hundred nine patients were included and underwent endoscopic implantation of Apollo Endosurgery's Orbera, Allurion's Elipse, and Spatz 3 IGBs. Each patient needed a single IGB with a filling capacity of 500-700 mL (**Figure 1**). These procedures were performed under sedation by anesthesiology without endotracheal intubation.

Extraction was also performed under sedation in 106 patients without endotracheal intubation. Gastroscopes with a 2.8 mm working channel and standard accessories (needle catheter, foreign body forceps, and polypectomy loops) were used (**Figure 2**). Three patients presented with spontaneous expulsion (Allurion's Elipse).

Periodic follow-ups with gastroenterologists were conducted to assess efficacy and tolerance. Proton pump inhibitors (PPIs) were prescribed during the IGB stay, along with antiemetics and analgesics, for the first two weeks. Weight monitoring was performed in all patients before IGB implantation, at each follow-up control, and upon extraction.

Definitions

The ideal weight was considered 18.7-24.9 kg/m^2 for all adults, regardless of age (12), and an effective weight loss percentage of at least 10% of excess weight (13).

Statistical analysis

The database was prepared in Excel v. 2019. We completed the missing data with additional reviews of the information sources, and in the end, only complete data were analyzed. Data processing was conducted in the social sciences pro-

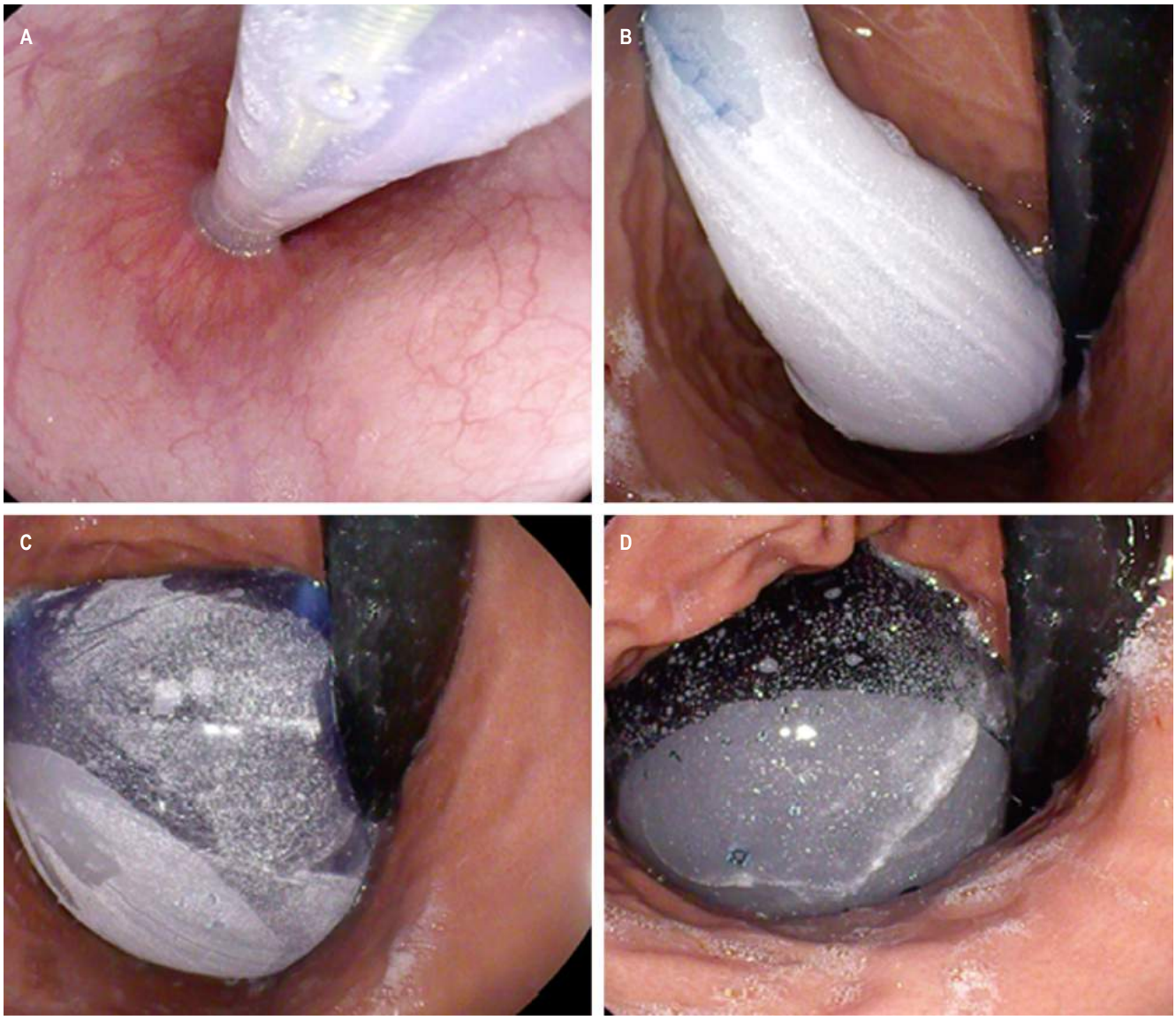

Figure 1. Fluid-filled IGB implant. **A.** Endoscopic view of the positioning of the IGB during implantation. **B.** Endoscopic view of the IGB filled with fluid. **C.** Endoscopic view of the IGB in an adequate position, completing the fluid filling. **D.** Endoscopic view of the IGB after filling is complete, with no fluid leak. Authors' archives.

gram SPSS v. 25.0. The arithmetic mean was used for the descriptive analysis of quantitative variables. At the same time, absolute and relative frequencies were employed for qualitative variables.

Ethical considerations

This study was approved by the ethics and research committee of Clínica Palermo, Bogotá, Colombia. The primary sources of information included clinical records. Its design met the requirements in Resolution 8430/1993 issued by the Colombian Ministry of Health, so it was regarded as a low-risk study. Confidentiality of the information collected was guaranteed. All patients were informed and signed the informed consent. None of the records had sensitive information about the identity of patients.

RESULTS

Of the 109 operated patients, eighty-two were women (75.22%). The average weight of the patients was 87.22 kg, with an average BMI of 31.59 kg/m^2. The main comor-

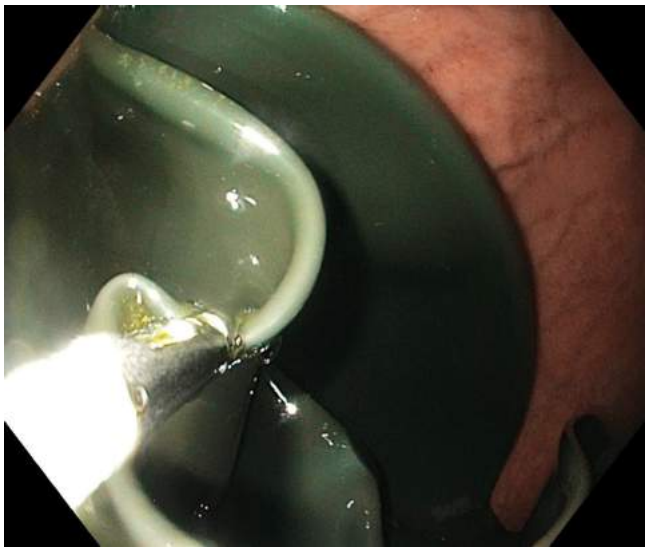

Figure 2. Endoscopic removal of the IGB. Endoscopic view of the empty balloon after suctioning the fluid. Authors' archives.

bidities at the beginning of treatment were high blood pressure (HBP; n: 23, 21.1%), type 2 diabetes (n: 18, 16.51%), mechanical joint pain in the lower limbs (n: 15, 13.76%), and obstructive sleep apnea-hypopnea syndrome (OSAHS; n: 9, 8.25%) (**Table 1**). Three brands of fluid-filled balloons were used (Orbera, n: 103; Spatz 3, n: 3; and Elipse, n: 3).

Table 1. Characteristics of patients treated with IGB at the beginning

Parameter	Statistics
Female sex (n: 82)	75.22%
Average age	33.44 years
Comorbidities	
- HBP (n: 23)	21.10%
- Type 2 diabetes (n: 18)	16.51%
- Joint pain (lower limbs) (n: 15)	13.76%
- OSAHS (n: 9)	8.25%

Table prepared by the authors.

The IGB was implanted for an average of 8.2 months, using fluid-filled devices in all cases. The average weight loss varied significantly between Elipse and Orbera, although there were very few cases with this first brand. Globally, a reduction of the average BMI to 27.71 kg/m^2 was achieved. The average weight loss had significant differences in the analysis by month and brand, respectively: Elipse: four months (-4.6 kg), Spatz 3: three months (-7 kg), Orbera: six months (15.2 kg), Orbera: 12 months (19.7 kg). **Table 2** shows the baseline anthropometric variables of the included patients and **Table 3** after IGB implantation.

Table 2. Baseline demographic and anthropometric characteristics of the patients on the day of IGB insertion

Parameter	Orbera (n = 103)	Spatz 3 (n = 3)	Elipse (n = 3)
Female sex, n (%)	80 (77.66)	2 (66.66)	2 (66.66)
Age, mean (SD)	33.2 (5.2)	36.4 (3.32)	38.5 (4.6)
Starting weight, mean (SD)	87.36 (8.31)	85.38 (7.17)	84.25 (5.92)
Excessive weight, mean (SD)	18.27 (3.46)	19.62 (4.62)	19.1 (4.03)
BMI, mean (SD)	31.34 (3.56)	36.78 (7.23)	34.98 (5.92)

IGB: intragastric balloon; SD: standard deviation; BMI: body mass index. Table prepared by the authors.

Given that the population sample was small and that this is a descriptive study, we could not evaluate statistically significant differences between assorted brands of IGB. However, a trend toward more significant weight loss was seen in periods of IGB implantation greater than six months (**Table 3**).

The balloon was removed after two months in three patients (2.75%), in two (1.83%) due to intolerance (abdominal pain), and one due to acute appendicitis (0.91%). No cases of acute pancreatitis or digestive bleeding were documented. There were no complications at the time of removal, neither with the procedure nor the sedation.

DISCUSSION

The fluid-filled IGB is a less invasive option for managing low- and moderate-risk obesity, particularly in cases of BMI greater than 25 kg/m^2, without optimal results after initial medical management[14,15]. Beyond this, it does not permanently interfere with the gastric anatomy or the size of the gastric volume due to interventions such as sutures, stomas, and thermal destruction of the mucosa, among others, used in other methods[5,11,16]. The main complications described in the literature include deflation or migration (up to 28.9% of cases), followed by minor side effects (0.2%-27%), nausea, and vomiting (18%)[16,17]. The present study found an overall frequency of complications of less than

Table 3. Anthropometric characteristics of the patients on the day of IGB removal

Parameter	Orbera, 12 months (n = 58)	Orbera, 6 months (n = 45)	Spatz 3 (n = 3)	Ellipse (n = 3)
IGB implantation time, months, mean (SD)	12 (0.8)	6 (1.1)	3 (0.2)	4 (0.5)
BMI reduction (kg/m^2) (mean ± SD)	8.12 ± 3.76	7.42 ± 3.34	3.3 ± 0.62	2.1 ± 0.3
Weight loss (kg), mean, (SD)	19.7 (6.3)	15.2 (4.32)	7 (1.83)	4.6 (0.23)
Excessive weight loss percentage (mean ± SD)	26.2 ± 2.3	22.4 ± 1.84	10.56 ± 0.92	8.5 ± 1.86

IGB: intragastric balloon; SD: standard deviation; BMI: body mass index. Table prepared by the authors.

3% in two patients (1.83%) due to intolerance (abdominal pain), approximating that described in the study by Sander et al.[18], in which there was an early removal of the IGB in 3% of the cases. Intolerance is characterized by persistent emesis for extended periods associated with abdominal distension, which can lead to the patient's dissatisfaction or lack of motivation[19]. This symptomatology is more attributable to all gas-filled IGB and less frequent in IGB with fluid content[11]. In our study, early removal of the IGB was required due to the risk of electrolyte imbalance, dehydration, and kidney failure in these patients. The percentage of intolerance found is as reported in the literature without finding any fundamental predisposing characteristic.

Other less frequent complications include gastric perforation, overfilling, intestinal obstruction, gastric dilatation and impaction[20]. None of these complications was reported in the population of our study, so their overall incidence is considered acceptable. One patient (0.91%) in the study had acute appendicitis. The manifestation of appendicitis is rare, as described in the literature[5], and may be a coincidence rather than a direct cause related to the IGB or the procedure. This study corroborates that the manifestation of appendicitis and the complications associated with the procedure requires the removal of the IGB.

Weight loss is the primary outcome of interest beyond comparison when evaluating the IGBs. The results in weight loss are heterogeneous in the different studies, with variable results concerning multiple factors[11]. Most studies establish as selection criteria patients with a BMI greater than or equal to 40 kg/m^2, with variable weight loss at six months of 17-21 kg[21,22]; however, few studies specifically assess the efficacy of fluid-content IGB in patients with low- and moderate-risk obesity in periods ranging from 6 to 12 months. In a retrospective study by Fittipaldi-Fernández et al.[23], the implementation of the IGB was evaluated in 5,874 subjects with overweight and any degree of obesity, with a predominant population of women (n = 4,081; 74.96%). According to the subgroups, 371 (6.81%) were overweight (BMI: 25-29.99 kg/m^2), and 1,848 (33.94%) were grade I obese (BMI: 30-34.99 kg/m^2), together totaling 37.7% of the total sample. Overall, there was a weight loss of 19.13 ± 8.86 kg; according to the obesity groups, there was a weight loss of 12.83 ± 4.51 kg and 16.2 ± 6.42 kg in the overweight and grade I obesity groups, respectively. In our cohort, we found a more significant weight loss at 12 months (19.7 kg) and a mean decrease in BMI of 3.88 kg/m^2. This figure is close to that described by Fittipaldi-Fernández et al.[23]. We can affirm that the results for weight loss are attributable to adequate regular multidisciplinary follow-up and the participants' motivation. Maintaining multidisciplinary management with nutrition and workout measures is vital to avoid weight regain after device removal.

In our study, when making the comparative analysis by sex, a higher percentage of weight loss was found in women. These findings are consistent with earlier comparative studies in which a more significant loss of excessive weight has also been noted in women[23,24]. However, this has been attributed to the lower basal excess weight in women[24], which may also be because, in our study, most of the population was women (75.22% of the cases). It is known that women are more willing to report gastrointestinal symptoms, request timely medical attention, receive recommendations for diagnostic tests, and adhere to treatment[25]. This study validates that women can receive prompt treatment for low- and moderate-risk obesity and achieve weight control goals in an optimal time. Further research is needed to clarify these findings.

Multiple studies have shown that 80% to 90% of weight loss is achieved during the first three to four months of IGB therapy; after this, the stomach accommodates, and the restrictive effect is partially lost, so an increase in the volume of the IGB is required to induce more significant weight loss[17]. The present study, evaluated the latest generation IGBs, which are

adjustable; in other words, after three months of insertion, the weight loss effect is lost, so it is necessary to add volume to the IGB to change its volume and weight and achieve better results[26].

Recent studies have corroborated the efficacy of the IGB brands used in this research. A meta-analysis in 2015, which included 17 studies with 1,638 patients, revealed an excess weight loss percentage of 25.44% (95% confidence interval [CI]: 21.47%-29.41%) and 11.27% total body weight loss at 12 months with Orbera IGB, which is considered an appropriate treatment option because it exceeded the intragastric preservation threshold and 5% total loss of body weight[27]. On the other hand, Schwaab et al. published a crossover study in 2020 in which 470 overweight and obese subjects were included, 144 of whom had a Spatz IGB implanted for up to 12 months, achieving total body weight loss of 15.5 ± 9.6%[28]. Regarding Elipse IGB, a meta-analysis by Ramai et al. examined seven studies with 2,152 patients and demonstrated similar results, with a total weight loss percentage of 12.2% (95% CI: 10.1-14.3, inconsistency index [I^2]: 94%) and excessive weight loss percentage of 49.1% (95% CI: 30.6-67.5; I^2 = 97%)[29]. Our study evaluated long-acting IGBs with a capacity of up to 12 months in the stomach and demonstrated better results and usefulness, as they allow more time for education on lifestyle changes, while short-acting balloons (less than four months) did not achieve significant weight loss. Although Orbera IGB was employed in more than 90% of the cases, corroborating its efficacy in therapeutic goals, the results were similar in Spatz and Elipse.

Limitations of this study include that it was a single-center study, and Orbera IGB was used in more than 90% of the subjects, preventing generalizability. Nevertheless, we could show the efficacy and complications of fluid-filled IGB in the adult population with low- and moderate-risk obesity, of which there is little literature in Colombia. It should be mentioned that only subjects older than 18 years were included, which limits its applicability to younger groups; however, the adult population included in the study is considered representative. The anthropometric evaluation of the patients was limited to bioimpedance. Other measures that could have added detail to the assessment of body changes and the impact of the IGB on body composition were not used. When evaluating the efficacy, other metabolic parameters such as glycosylated hemoglobin levels, lipid profile, and cardiovascular outcomes, which are of interest for this particular population, were not included. For being a retrospective study, the quality of the information may be affected when completing the medical records. Verification of clinical record data by at least two researchers could also decrease transcription bias.

CONCLUSIONS

The fluid-filled IGB is an attractive option for managing low- and moderate-risk obesity; it is a safe and effective procedure for achieving optimal weight loss goals.

Careful follow-up of the patient is paramount to avoid complications and support the efficacy of treatment; an IGB implantation period of at least 12 months is considered best for low- and moderate-risk obesity.

Since the IGB is a non-surgical and non-pharmacological temporary alternative for obesity, entirely reversible and repeatable, it should be especially recommended to patients with therapeutic failure of traditional weight reduction methods.

Ethics approval and participation consent

This research was reviewed and approved by the institution's Research Ethics Committee.

Consent for publication

The requirements in Resolution 8430/1993 issued by the Ministry of Health of the Republic of Colombia were met so that it was considered a low-risk study. Confidentiality of the information collected was guaranteed. All patients were informed and signed the informed consent. None of the records had sensitive information about the identity of patients.

Data and material availability

The data and material available for publication are in the manuscript, and no information is omitted.

Conflicts of interest

None stated by the authors.

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Authors' contributions

All authors contributed to each research stage (literature review, data collection, and composition) and approved the definitive version of the manuscript.

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Original article

Evaluating the Efficacy and Safety of Laparoscopic Heller Myotomy in Treating Achalasia

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Abstract

Introduction: Laparoscopic Heller myotomy (LHM) is widely recognized as the standard surgical treatment for esophageal achalasia. However, there is a lack of local data regarding the clinical characteristics of patients and the outcomes of this intervention. **Methodology:** This retrospective study analyzed patients who underwent LHM over an eight-year period. Demographic, operative, and postoperative variables were assessed. The Eckardt score was used to compare symptoms before and after the intervention. Continuous variables were presented as means. **Results:** Among the 39 patients assessed, 27 met the inclusion criteria. Of these, 51% were male, with an average age of 48 years. The average lower esophageal sphincter pressure was 36 mmHg. The mean operative time and bleeding were 133 minutes and 34 mL, respectively. The average length of the myotomy was 8.3 cm. Partial fundoplication was performed in all cases, and intraoperative endoscopy was conducted in 88% of the cases. Two intraoperative mucosal perforations occurred. The average length of hospital stay was 2.7 days. There was one medical complication but no mortality. Dysphagia significantly improved by 95%, and the mean Eckardt score decreased from 7.7 to 1.2 after surgery ($p < 0.001$). The average follow-up period was 24 months. **Conclusion:** LHM with partial fundoplication proves to be an effective and safe procedure for treating achalasia. It results in the resolution of dysphagia in 95% of cases and carries minimal morbidity. Therefore, LHM should be considered the definitive treatment of choice for achalasia.

Keywords

Esophageal achalasia, swallowing disorders, dysphagia, esophageal aperistalsis, Heller myotomy.

INTRODUCTION

Esophageal achalasia is a rare entity with an incidence of one and a prevalence of ten per 100,000 inhabitants in the United States[(1)]. It is mainly characterized by dysphagia and chest pain but has other associated symptoms such as regurgitation and weight loss. The pathophysiological mechanism is not clearly understood, although the symptoms are attributed to the absence of peristalsis of the esophageal body and the lack of relaxation of the lower esophageal sphincter (LES)[(2)]. Thus, the term achalasia comes from the prefix *a-* and the Greek word *khalasis,* meaning "no relaxation."

A high index of suspicion is required for the diagnosis since up to 40% of patients with achalasia may have a normal esophagogastroduodenoscopy (EGD)[(3)]. Contrast-enhanced radiography of the esophagus (esophagogram) classically shows dilatation of the esophagus and stricture at the esophagogastric junction with the "bird's beak" ending sign[(4)]. However, the esophagogram can have up to 30% false negatives. In advanced disease, a severely dilated,

angulated, and tortuous esophagus may be found and even have a sigmoid shape (megaesophagus)[5].

Esophageal manometry confirms the diagnosis[4]. In clinical practice, manometry has two techniques: conventional and high-resolution (HR)[6], the latter being more precise and allowing the achalasia type to be identified (I, II, or III), which can define the prognosis during treatment[7,8]. It has been concluded that type II responds better to any treatment, and type III predicts an adverse response[9].

International guidelines and expert articles have proposed logical treatment algorithms[10,11]. Pharmacological therapy with nitrates and calcium antagonists is the least effective option and is reserved for patients who, due to their clinical condition, are not candidates for invasive therapies[2]. Other management options include endoscopic botulinum toxin injection and endoscopic pneumatic dilation. Botulinum toxin is applied to the LES, and its effectiveness for dysphagia control is 50% at one year[12]. Pneumatic balloon dilations of achalasia have early effectiveness similar to surgery, but their effect diminishes with time. Almost 50% of patients are estimated to require a new dilation in the 5-year follow-up[13]. Peroral endoscopic myotomy (POEM) is the most recent management strategy, which consists of performing an endoscopic esophagogastric myotomy with encouraging initial results[14].

Surgical management with Heller myotomy is currently the standard for the definitive treatment of achalasia. Most studies show that surgery is more efficient than other alternatives, and, thanks to the laparoscopic approach, postoperative morbidity is very low[15]. In our setting, the clinical characteristics of patients with achalasia and the results of surgical treatment are unknown. This research aims to determine the degree of symptomatic improvement after laparoscopic Heller myotomy (LHM) and the morbidity of the procedure.

MATERIALS AND METHODS

Study type and patients

A retrospective descriptive study was carried out. Adult patients diagnosed with achalasia referred to LHM in two high-complexity healthcare facilities over eight years were studied. The information was obtained by reviewing medical records and telephone interviews with the patients.

Patients operated on via open surgery or from a thoracic approach, who could not be contacted by any means or with a previous myotomy were excluded. The variables explored were demographic and clinical characteristics, operative findings, postoperative complications, and follow-up.

The symptoms were assessed using the Eckardt symptom score, an instrument validated in the literature that includes the most relevant symptoms of patients with achalasia (dysphagia, retrosternal pain, regurgitation, and weight loss)[16]. The scale rates severity from 0 to 3, depending on the absence of the symptom (0) or its occasional (1), daily (2), or constant (3) presence. The total score is from 0 to 12, classifying the disease into stages: 0–1: stage 0, 2–3: stage I, 4–6: stage II, and > 6: stage III. Post-intervention stages 0 and I are defined as remission[17].

Procedure description

An American five-port surgical technique was used with the patient in the supine position with the operating bed tilted in reverse Trendelenburg. The dissection began on the left side, sectioning the short gastric vessels with an ultrasonic scalpel until the left crus of the diaphragm was identified. The pars flaccida is released, the left gastric artery and accessory hepatic artery are preserved, and if applicable, the phrenoesophageal membrane, both crurae, and the retroesophageal space are released. Once there is a circumferential dissection, an atraumatic traction of the esophagus is performed (with a Penrose drain), and its distal third is released at 360 degrees. The myotomy site is marked on the esophagus's anterior side, respecting the vagus nerve's left main trunk. The myotomy is then performed, which in most cases is performed bluntly with the help of two atraumatic forceps and, in others, with cautery. The length is, on average, 6 cm in the esophagus and 2 cm in the stomach. Intraoperative endoscopy is performed to verify the integrity of the mucosa, the length of the myotomy, and the complete opening of the cardia with insufflation of the endoscope (**Figure 1A**). The procedure is finished with a partial posterior (Toupet) or partial anterior (Dor) fundoplication at the surgeon's discretion (**Figure 1B**). Drains are not used, and conventional port site closures are performed. The patient can start clear oral liquids the next day and continue with a blenderized diet for two weeks.

Ethical considerations

This study complied with the current regulations of healthcare institutions' ethics and research committees and the research and bioethics committee of Universidad Antioquia. The confidentiality of the data obtained was guaranteed since only the researchers had access to the research instruments.

Statistical analysis

Continuous variables were described as means and ranges, while categorical variables were expressed as frequencies and proportions. For the comparison of continuous varia-

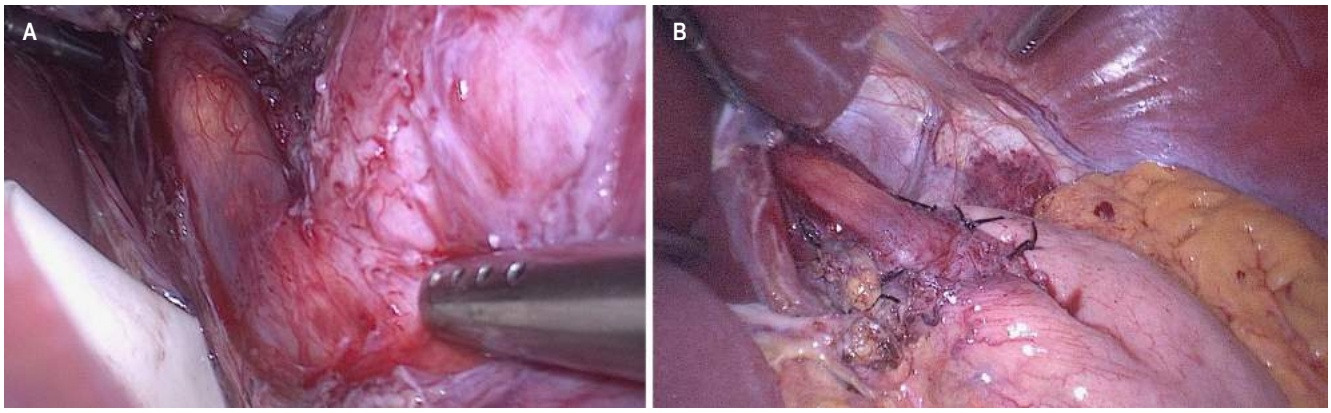

Figure 1. Surgical technique. **A.** Complete myotomy and verification with intraoperative endoscopy. **B.** Posterior partial fundoplication (Toupet). Source: Authors' archive.

bles, a Student's t-test was used. All statistical analyses were conducted with Stata v. 14 and GraphPad Prism 7.

RESULTS

A total of 39 eligible patients were identified, of whom 11 were excluded due to insufficient information and one due to a reintervention; therefore, 27 patients were included in the analysis. 51% were men, and the average age was 48 years. 53.5% of the patients had comorbidities. Achalasia symptoms' duration before surgery averaged 3.7 years (**Table 1**). All the patients underwent EGD, esophagogram, and esophageal manometry for diagnosis. Nine patients had AR manometry. Basal LES pressure had an average of 36 mm Hg. Three patients had prior endoscopic or medical treatment.

Operative time had an average of 133 minutes, the average length of the myotomy was 8.3 cm, and the mean bleeding was 34 mL (**Table 2**). Toupet-type fundoplication was performed in 25 patients. There were two intraoperative perforations of the esophageal mucosa that were repaired with separate 4-0 absorbable suture stitches, and in both cases, a Dor-type fundoplication was added. These two patients had a satisfactory postoperative evolution. In the intraoperative period, EGD was performed on 25 patients. The two mucosal perforations were confirmed by this means.

In the immediate postoperative period, 22 patients (88%) underwent an esophagram without reporting leaks or other complications. The average postoperative hospitalization was 2.7 days (1-14). A complication corresponding to infection associated with intravascular devices (phlebitis) occurred; this patient had a 14-day hospitalization for intravenous antibiotic treatment. There was no mortality in this series.

Table 1. Demographic and preoperative characteristics

Variable	Frequency/ Average	Percentage/ Range
Sex		
- Female	13	48.1%
- Male	14	51.8%
Age (years)	48	18-76
Cardiovascular disease	8	29.6%
Lung disease	2	7.4%
Metabolic disease	3	11.1%
Duration of symptoms before surgery (years)	3.7	1-20
Achalasia type		
- Type I	2	7.4%
- Type II	7	25.9%
- Not reported	18	66.6%
Basal LES pressure (mm Hg)	36	20-58

LES: lower esophageal sphincter. Table prepared by the authors.

The Eckardt score was obtained in 21 patients. The average preoperative total score was 7.7 versus 1.2 postoperative ($p < 0.001$). Dysphagia had pre- and postoperative means of 2.5 and 0.2, respectively ($p < 0.001$), and improved in 95% of patients. Similar results occurred with chest pain and regurgitation. Weight loss improved in 100% of patients ($p < 0.001$) (**Figure 2**). Regarding the severity of the disease, it was found that in the preoperative period, six patients were in stage II (28.5%) and 15 in stage III

(71.4%). After the intervention, 13 patients progressed to stage 0 (61.9%) and eight to stage I (38%).

The average postoperative follow-up was 24 months (1-87). A control esophagram and EGD were performed on six patients at the end of the year after the intervention. No other complications or recurrence were reported. Regarding gastroesophageal reflux (GER), five patients (18.5%) reported heartburn after surgery, and it was perceived as mild.

Table 2. Operative variables

Variable	Frequency/ Average	Percentage/ Range
Surgical time (minutes)	133	72-165
Myotomy length (cm)	8.3	6-10.5
Intraoperative bleeding (mL)	34	1-200
Fundoplication type: - Toupet - Dor	 25 2	 92.5% 7.4%
Mucosal perforation	2	7.4%
Intraoperative EGD	24	88.8%

EGD: esophagogastroduodenoscopy. Table prepared by the authors.

DISCUSSION

Local articles on achalasia have been published in the last decade; however, there needs to be precise information on the results of surgical management in our population[5,18,19]. The present study is the first to describe patient demographics, procedure-related characteristics, and clinical outcomes of the intervention at medium-term follow-up.

The patients had a distribution according to sex and age similar to that in the literature[20,21], with a shorter duration of symptoms than reported[22]. The frequency of symptoms was similar to other studies, and dysphagia was the main symptom[21,23,24].

The length of the myotomy was very similar to other reports, with ranges of 6-8 cm[25,26]. We believe that a 6 cm myotomy in the esophagus and 2 cm in the stomach is sufficient to relieve the obstruction without increasing the risk of mucosal perforation or bleeding. Mucosal perforation occurred in two patients (7%), a finding within the reported rate (6.9%-7.8%)[27-29]. Fortunately, patients with mucosal perforations detected and repaired in the same surgical act have a similar postoperative course to others, as observed in the present study. Intraoperative EGD was performed on 88% of patients to assess the myotomy and confirm mucosal integrity more objectively. According to the experts' recommendations, this intraoperative study is vital to guarantee better clinical results[30].

It is estimated that the incidence of GER is up to 47.6% in patients with Heller surgery without fundoplication compared to 9.1% when a fundoplication is added[31]. In this study, 92.5% underwent a Toupet fundoplication, and the remaining 7.4% had a Dor type. The precise recommendation is that the fundoplication should be partial since there is a greater risk of dysphagia with the complete one (Nissen type). Although there are no significant differen-

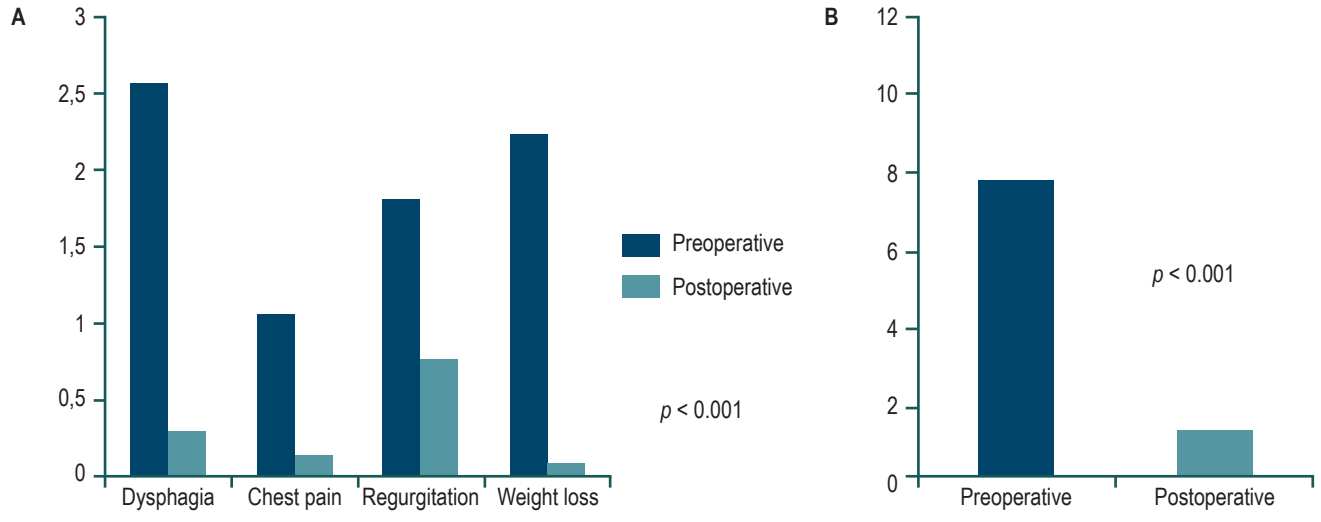

Figure 2. Comparison of symptoms by pre and postoperative Eckardt score. **A.** Comparison of averages by symptom type. **B.** Comparison of averages of the total score. p: Student's t-test. Prepared by the authors.

ces in performing an anterior partial (Dor) or a posterior partial (Toupet)[32,33], we are more inclined towards the Toupet-type fundoplication, which somewhat keeps the edges of the myotomy open and could prevent the formation of previous fibrosis and, consequently, the recurrence of dysphagia. We reserve the Dor type fundoplication for patients with perforation of the mucosa and in whom it is more logical to cover the suture line with the gastric fundus.

The surgeon's experience determined surgical time and was similar to other studies[25,26,31]. Hospitalization time was shorter than that mentioned in other reports[26,31]. In this study, only one postoperative complication of a medical nature not directly related to the procedure occurred. The series had no mortality, confirming that LHM in expert hands is a highly safe procedure associated with almost zero morbidity.

There is substantial evidence demonstrating the effectiveness of LHM. Four meta-analyses showed that surgical treatment is the most appropriate management for patients with achalasia since it is associated with 100% resolution of dysphagia in one year and 77% in five years on average[15,28,34,35]. In this series, the improvement in dysphagia was 95% with an average follow-up of 24 months, in addition to the fact that 100% of the patients ended up in stage 0 or I in the Eckardt score, placing them in the disease remission category.

POEM is a recent therapeutic alternative mainly available in international reference endoscopy centers[36]. An initial experience in four patients with good results was published in our country[37]. The effectiveness of this technique could be comparable to LHM, but there still needs to be robust information or long-term follow-up[38]. Its main disadvantages are that it requires general anesthesia and specialized endoscopic instruments, the long learning curve, and the impossibility of adding an antireflux procedure, which could result in *de novo* GER in up to 40% of patients[34].

Some limitations were identified in the study. First, control manometry was not performed to assess the impact of the intervention on LES pressure. This may be due to limitations inherent to our health system or the perception of the patient who considers further studies unnecessary after their symptoms improve. Still, it has been shown that Eckardt score values < 4 or stages < I correlate with manometry or esophagograms that show adequate esophageal function[39]. Since there is currently no clear recommendation on routine control studies such as EGD, esophagogram, manometry, or pHmetry, these should be performed depending on the patient's symptoms.

Another significant limitation is its retrospective nature and the low number of patients, mainly due to the low prevalence of the disease. Likewise, some patients were lost to follow-up, which reduced the information available for analysis. However, this study may be the starting point for new research that makes a more objective and complete evaluation of LHM results through esophageal anatomy and physiology studies. This would make it possible to measure essential changes in the evolution of the disease, such as the diameter of the esophagus, the pressure of the LES, and exposure to acid reflux, among others.

CONCLUSION

Laparoscopic Heller myotomy is an effective and safe procedure for treating achalasia. This modality remains the management standard, resulting in a medium-term improvement of dysphagia in 95% of cases and a global symptomatic improvement in all patients. It is associated with a short hospital stay and minimal morbidity.

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Original article

Parenteral nutrition: the prison that allows survival in the face of intestinal failure

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Abstract

Objective: Intestinal failure refers to a reduction in intestinal function that necessitates intravenous supplementation of macronutrients, water, or electrolytes due to the intestine's inability to absorb these substances adequately to maintain health and growth. This study aims to explore the experiences and challenges faced by patients enrolled in the intestinal rehabilitation program at Hospital Pablo Tobón Uribe in Medellín. **Methodology:** This qualitative study adopts a hermeneutic approach and utilizes grounded theory techniques. The sampling process involved both selective and theoretical sampling. A total of 20 semi-structured interviews were conducted, with eight interviews including contributions from family members. The data analysis commenced with open coding, followed by the grouping of codes into descriptive categories. Dimensions and properties were identified within these categories, and analytical categories were subsequently developed through axial and selective coding. This iterative process led to the emergence of the final paradigm matrix. **Results:** The study revealed that the healthcare system inadequately addresses the needs and expectations of patients with intestinal failure, leading to increased uncertainty about the disease's origin and future prognosis. Intestinal failure and its treatment disrupt various aspects of patients' lives, including personal, family, and work domains. Social stigmatization and rejection are prominent, underscoring the importance of support from family and close individuals in facilitating adaptation and revaluing life. **Conclusions:** Coping with the challenges of intestinal failure entails embracing the necessity of relying on parenteral nutrition, which is perceived as a prison that paradoxically enables survival.

Keywords

Intestinal absorption, intestinal failure, parenteral nutrition at home, qualitative research.

INTRODUCTION

Intestinal failure is the reduction of intestinal function that requires intravenous supplementation of macronutrients, water, or electrolytes, to the extent that the intestine does not achieve the minimum absorption to maintain health or growth[1]. Acute intestinal failure can have a frequency of 15% in patients with critical illnesses or during the perioperative period of abdominal surgery[2], while chronic intestinal failure can have a prevalence of close to 2-4 cases per million inhabitants[3]. Although rare, it dramatically impacts the patient and their family, and if left untreated, it results in death[4-6].

In the latter lies the need not only to consider the vision of the treating team in terms of quantitative variables but also to know the patient's view of our environment beyond analogous scales, demonstrating a significantly reduced quality of life compared to the healthy population[4,7]. This

work aims to understand the meaning of coping with the intestinal failure condition in our setting. It allows for an approach to the appreciation of the patient as a person and not as a disease, in addition to implementing strategies that facilitate coping with the disease and strengthen support networks that positively impact the reentry of these people into society.

MATERIALS AND METHODS

The research was conducted from a hermeneutic approach using grounded theory techniques such as open, axial, and selective coding[8]. The study population included patients older than 18 with a diagnosis or history of intestinal failure, treated by the intestinal rehabilitation group of Hospital Pablo Tobón Uribe since 2005, who agreed to participate and signed the informed consent. The exclusion criteria were critical condition, altered consciousness, or mental incapacity to answer the interview. Twenty semi-structured interviews were conducted with 20 participants (**Table 1**), eight of them in the company of their relatives at the discretion of the interviewees. With prior authorization, they were recorded not to lose information for analysis. Psychological support was also available, given the possibility of exacerbating stressful processes in remembering the situations experienced. In none of the cases was this support required.

The sampling was initially selective and theoretical in search of variations between the concepts until reaching theoretical saturation (when the new data collection no longer provided additional information)[9]. The analytical process was carried out with the coding and categorization techniques of the grounded theory. First, the faithful transcription of interviews was completed, from which the codes or first abstractions on the text were identified line by line to inductively group them into descriptive categories, properties, and dimensions for theoretical saturation[10]. Second, through axial coding, descriptive categories were related, and a phenomenon was detected, describing a context, its causes, action and interaction relationships, and consequences in the paradigm matrix typical of grounded theory (**Figure 1**).

The analytical process was systematic and interactive between stories, formulated codes, the abstractions that gave rise to the constructed categories, properties, and dimensions, all with the scientific literature reviewed during the research. Triangulation was carried out between researchers, the assumptions from which the researchers started were previously defined, and the analysis limitations were recognized[11].

This study was endorsed by the research and ethics committee of Hospital Pablo Tobón Uribe (Minutes 18/2015). Following Colombian regulations, the research proposed in this paper was classified as "risk-free"[12].

RESULTS

Parenteral nutrition as the prison that allows survival

The diagnosis of intestinal failure causes either anxiety, fear, and devastation or relief and joy. Feelings depend on experiences, expectations, knowledge, and the ability to assess the implications of the diagnosis. Attention immediately turns to treatment, in which parenteral nutrition plays a fundamental role. The perception of receiving parenteral nutrition is associated with weight gains and losses. It can mean well-being and life or represent a prison for being "handcuffed" to the machine. Management of intestinal failure involves changes to which the person adapts over time.

"(Parenteral nutrition) was for survival […] It's the hardest thing a human can live because you are tied to one place that you can't ever leave. It is as if you lost your freedom. It is a jail" (28-year-old woman).

Parenteral nutrition cycling is the opportunity one longs to reach for greater freedom. The news of the withdrawal of treatment may produce joy and be an omen of intestinal recovery. In other cases, it is assumed with fear due to difficulties in reaching goals, previous decompensation, and doubts about maintaining weight. Withdrawal can be abrupt in acute cases, while it is done more cautiously in chronic cases.

"I encouraged myself. If others had to be connected to a machine for 24 hours, I only had to do it for 12" (47-year-old woman). "They let me have it (parenteral nutrition) three days a week, but we were afraid. The doctor was very distrusting, precisely because of the whole process I had already gone through" (41-year-old woman).

Recovery from intestinal failure requires maintaining requirements orally. Suspension of oral feeding when hungry and thirsty can be a challenging experience, in which thinking revolves around food only, and recovering it is a reason for great joy. Conversely, overcoming the fear of eating can be difficult when eating has been associated with intolerance symptoms.

"(Suspension of oral feeding is) hard. I almost went crazy. Those carts passed by distributing the meals to each room and smelled [...] [I was] all year [alone in] a room. No, I wouldn't have endured it with another person there. Ha! I would have stolen food from them, um, because in the first surgery, I couldn't [...] drink anything or eat anything either. It was hot, and I got very thirsty. So, in the (shared) room, there was a mango juice drink (of another patient). I went to the bathroom and quietly grabbed the juice and drank it (laughs), and I got scolded" (39-year-old man).

Table 1. Consequences include adaptation to intestinal failure as the possibility of getting one's life back

Patient	Age	Sex	Year of onset of symptoms	Year of diagnosis	Functional classification**	Admission to intestinal rehabilitation	Pathophysiological classification	History	Longer hospitalization	Transplant candidate
1	36	M	2011	2011	III	2011	Short intestine	Trauma	One year	Yes
2	21	M	1997	2011	III	2009	Short intestine	Recurrent peritonitis	Two months	No
3	47	F	2008	2010	II-III	2017	Short intestine	Surgical complication	One month	No
4	61	M	1982	1982	II-III	1982	Short intestine	Ischemia	100 days	No
5	47	F	2010	2014	II-III	2014	Extensive mucosal disease	Crohn's disease	Three months	No
6	65	M	2010	2010	II-III	2010	Intestinal fistula	Colonic volvulus	Six months	No
7	41	M	2018	2018	III	2018	Intestinal fistula, short intestine	Trauma	15 days	No
8	35	M	2015	2015	II	2016	Extensive mucosal disease	Immunodeficiency	15 days	No
9	19	F	2019	2019	II-III	2019	Intestinal fistula, short intestine	Ischemia	6.5 months	No
10	63	F	1986	2007	I	2007	Short intestine	Multiple peritonitis	Three months	No
11	56	M	2012	2012	I	2013	Short intestine	Multiple peritonitis	4.5 months	No
12	41	F	1998	2018	I-II	2020	Extensive mucosal disease, mechanical obstruction	Crohn's disease	Two months	No
13	37	M	2007	2017	II-III	2018	Intestinal fistula, disease	Toxic megacolon, multiple peritonitis, idiopathic	Two months	No
14	41	F	2019	2019	II-III	2020	Intestinal fistula	Intestinal obstruction	Four months	No
15	62	F	2014	2014	I	2019	Mechanical obstruction, intestinal fistula	Neoplastic	Eight months	No
16	68	M	2017	2017	I-II	2021	Intestinal fistula, short intestine	Neoplastic	One month	No
17	35	F	2007	2007	I-II	2008	Short intestine	Ischemia	1.5 months	No
18	57	M	2021	2021	I	2021	Intestinal fistula, short intestine	Ischemia	One month	No
19	28	F	2016	2021	III	2021	Intestinal dysmotility	Idiopathic	Six months	No
20	39	M	1993	1993	III	2017	Intestinal fistula, short intestine	Multiple peritonitis	One year	No

**Functional classification: time when the patient required parenteral nutrition. I: weeks; II: months; III: years. Table prepared by the authors.

Intestinal transplantation may be an alternative in selected patients to manage intestinal failure. The news of the possibility of an intestinal transplant can cause joy because of the hope of eating again, having greater freedom, and a better quality of life. In other cases, the possibility may be received with bewilderment, anxiety, sadness, stress, or fear due to the implications and risks of complications. The information provided by health personnel in a timely and

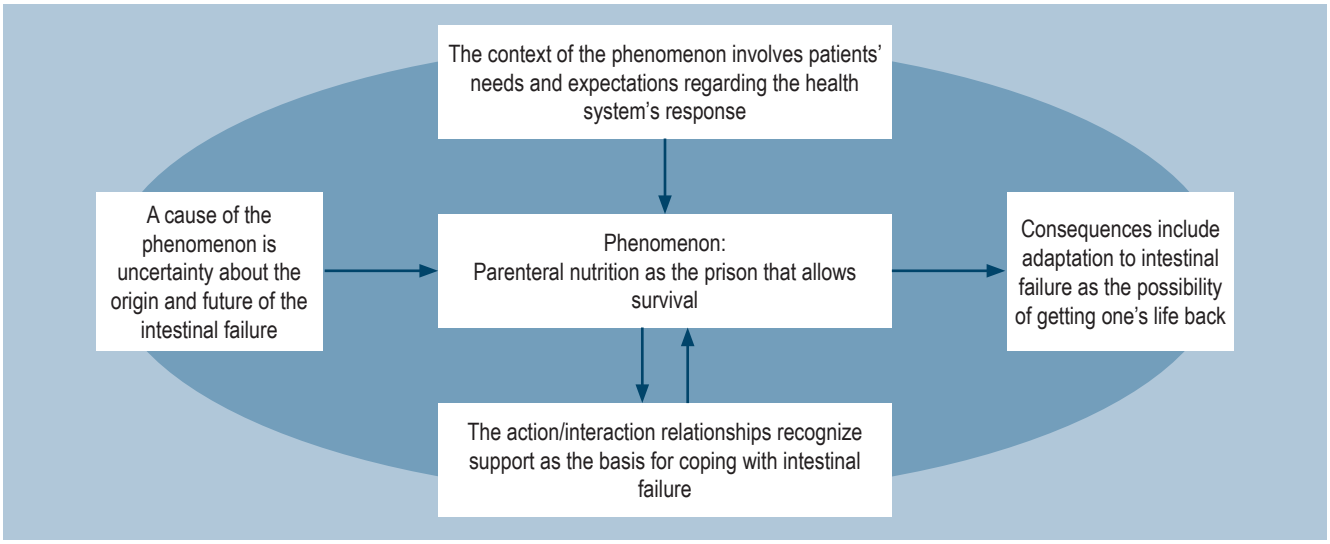

Figure 1. Paradigm matrix reflecting the main category of the research. Prepared by the authors.

complete manner is essential to weigh the possible risks and benefits amid uncertainty.

"They told me, 'Patient,' you're going for surgery (for the transplant), and I was happy to know that I was going to [...] be with my family again, to eat again, to walk again, to go out. It filled me with great happiness" (34-year-old man).

The intestinal transplant protocol can be long, while the call to attend surgery is unexpected. The transplant can provide more freedom and a better quality of life, but in other cases, complications recur, freedom is lost again, and it may be necessary to withdraw the transplant. However, the hope for a new attempt may persist.

"The transplant means a better quality of life because one has more freedom [...] I no longer have to think, 'I have to be at such time at home because I have to be put in a device to feed me.' Instead, having the intestine implies more freedom. You can eat, you can walk. What happened to the intestine? My body rejected it many times [...] The transplant changed my life, but I spent more time in the hospital than at home [...]. In my experience, with the transplant, there are many infections, many complications, many medications" (34-year-old man).

Patients' needs and expectations concerning the health system's response

Patients depend primarily on the public health system for health care, where there are difficulties dispensing drugs or supplies, causing disappointment, sadness, anger, and fear of not achieving health care and its consequences. Patients fight for and insist on the continuity of the service through administrative or legal means.

"It's very tough because she has a catheter, but I have to get all the supplies to clean her myself" (mother of a 28-year-old woman).

Similarly, health care is mediated by the health team-patient relationship. The patient expects to be listened to without dismissing their needs, notions, and contributions to treatment as the person who lives with the diagnosis and has knowledge from experience. Even in the face of uncertainty and unfavorable prognoses, the patient expects to hear an explanation about their condition and management alternatives and to have their needs met with diligence and empathy. Difficulties in the relationship between the health team and the patient impact care, which arise from the failure to meet expectations: from lack of skill and negligence in physical and emotional care to lack of communication and apathy. In addition, the monotony of health care and exhaustion have a negative influence. A deteriorated relationship results in impotence, anger, despondency, mistrust, and poor adherence. On the contrary, an adequate connection between the patient and the health team gives rise to trust, satisfaction, consolation, and hope, thus favoring management.

"When you arrive at the emergency room, they first say, 'ha, this one is coming to get some morphine [...]'. They did not believe me. I told the nurse, 'If you empty the reservoir, it will immediately fill with blood [...].' When she withdrew it, I was bleeding heavily, and she immediately ran to look for a surgeon" (37-year-old man).

Moreover, health care can be an economic challenge. Costs are high, while income is declining due to the labor impact of intestinal failure and treatment. Patients may need to work despite limitations, apply for disability pensions, try cost-cutting strategies, or financially depend on their families.

"I had to drive with Uber to cover the drugs the EPS (healthcare operator) did not give me for the fistula. So, I had to work during the day, arrive for the TPN (total parenteral nutrition) at night, and get up early to continue working after I was disconnected. While I am retired, my pension is a minimum wage" (39-year-old man).

Uncertainty about the origin and future of intestinal failure

Intestinal failure is marked by the onset of symptoms that lead to the search for diagnosis and treatment. It can be brief but sometimes significantly slow. Patience is required, but time sometimes breeds exhaustion and deterioration. The disease is accompanied by the uncertainty that runs between hope and fear. Finally, the diagnosis of intestinal failure allows initiation of treatment but may cast doubts regarding the etiology and prognosis. Judgments about the future can deprive patients of hope and inhibit them from moving forward.

"I have had Crohn's disease since 1998 when some symptoms started, but the diagnosis was clarified, and I started biological therapy in 2016" (41-year-old woman).

"The gastroenterologist told me, 'She's never going to eat again. Don't you ever give her a spoonful of food again [...]', I left crying. We left because he said, 'There's nothing to do. That's it.' I went home, but I was eager to continue fighting for her" (mother of a 28-year-old woman).

Hospital stays can become frequent and prolonged. The experience of hospitalization for some is just a change of bed. For others, it is a break from the challenges of daily life. In other cases, it can be overwhelming due to loneliness, isolation, the discomforts it brings, and the suspension of oral feeding while others eat. The need for hospitalization is acknowledged, but home is longed for.

"My lips were dry, cracked. I remember an ad for one (soft drink) that was taken out of a freezer, and gosh! I couldn't even speak" (65-year-old man).

"I have to be with this bag and empty it. Sometimes the smell is not pleasant [...]. Some patients did tell the nurses (they complained) about the smell and discomfort" (41-year-old woman).

Support as the basis for coping with intestinal failure

The support network arises from affection. It manifests itself in accompaniment, comfort, motivation, understanding, adaptation to the way of life, and addressing needs. It is crucial to cope with intestinal failure, particularly when the patient depends on others for their care. The lack of family support can contribute to deterioration and cause sadness, loneliness, isolation, and a feeling of abandonment.

"He said a few words to me, 'XX (the wife), you are my cane. If you fall, I fall [...]', If (you) have no one with you, that's worse than the disease" (68-year-old man and his wife).

The experience as a companion is challenging, especially in prolonged hospitalizations, due to insufficient space to rest and the need to continue with one's own life while accompanying the patient. Patients may consider the caregiver's position more complex than their own and prefer to be visited only to avoid a more negative impact on their relatives. Family members join efforts to cushion the impact and assimilate management. Learning helps them gain independence from health personnel.

"My youngest son dropped out of college. He stayed with me for six months, day and night, by my side" (65-year-old man).

Patients and their caregivers can also support each other, share lessons and experiences, and provide emotional support and assistance in support groups or social media, to the point of making new friends. Although the comparison with other patients gives us a better perspective on their condition, it is understood that each person has individual circumstances. Patients sometimes want to give back to society, prevent the suffering of others, and help in the research of intestinal failure.

"I started making Tik Tok videos of my life. Then, people from the United States, Germany, Spain, Ecuador, Peru, and Argentina began to write that they had also suffered from this condition. I met many people. We learned, and they learned" (28-year-old woman and her mother).

Adaptation to intestinal failure as the possibility of getting one's life back

Intestinal failure and its treatment can mean carrying out activities that change or interrupt projects and make you question the future, impacting the emotional sphere and vice versa. You feel pain, sadness, and frustration, and sometimes you reach depression with suicidal attempts. Professional and family support is essential.

"I had two suicide attempts. I was very depressed" (39-year-old man). "My and my wife's projects are to have children, but it has been difficult because they have told us to be aware of genetics" (35-year-old man).

Body image changes due to weight loss, ostomies, fistulas, hernias, and scars. Although this can take a backseat to health or being a source of pride as proof of the process undergone, it may also produce sadness, impotence, and

shame. Clothing and other cosmetic changes, such as surgical reconstructions, are made. The improvement of body image engenders motivation and well-being.

"Let my mom tell you (cries) [...]". "She was a girl with a gorgeous body. Now with these bags and scars [...], we hope the surgeons do everything they can to fix her tummy. More than anything, we want her fistula to close [...], as there are things that become irrelevant" (41-year-old woman and her mother).

The family is no stranger to the diagnosis. The diet, the activities, the coexistence, roles, the care of children, the projects, and even the city of residence change. Each member is impacted differently. There may be distancing in family relationships, sadness, frustration, fear, anguish, anger, and exhaustion. Patients sometimes feel guilty and try to lessen the family impact; they comfort, encourage, and try not to worry them. The family may come together out of love to face challenges or distance themselves to avoid them.

"I got disappointed [...]. I had a relationship then, and the person I was with left me... Of course, he would not put up with someone in this situation, but many people also came into my life. Sorry! (cries)" (47-year-old woman).

Intestinal failure brings labor and academic difficulties due to the time required for health care and living with an open abdomen, fistulas, and symptoms that limit activities. Some patients find support in the work environment when the employer understands the need for leaves, medical recommendations are followed, and working conditions are facilitated. In other cases, there is no consideration from bosses or colleagues. Despite trying to adapt by carrying supplies, implementing assistants, and finding spaces to care for their symptoms, the disease and its treatment result in job suspension, dismissals, resignations, or abandonment. Disrupting academic or work projects can impact income and independence and cause sadness and feelings of inferiority. Finally, patients may recognize the need to take a disability pension, which entails difficulty.

"When I already had a fistula, my first job was outside the city. I had to go into the ravines to wash the fistula, and peasants would stare at me. The bosses decided to leave me here in Medellín, but suddenly, I was in a meeting and shat myself" (39-year-old man).

Social life changes. Sometimes patients find understanding, assistance, and support among friends. They also adapt to continue to be socially active. However, in other cases, they may encounter rejection and cruel or reckless comments. The lack of understanding about the condition, added to the limitations, can lead to ending social activities with confrontations, sadness, impotence, and loneliness.

"We walk, and she keeps hiding behind us because she does not want anyone to see her. People start looking at her or nudging each other, which has ended up in fights" (mother of a 28-year-old woman). "I had more or less 20 to 25 bowel movements a day. I barely set foot in a mall because once I went to the restroom and heard people saying, 'It stinks in here!' That's horrible, knowing that you must get out and show your face" (61-year-old man).

Intestinal failure and its treatment can be a long, complicated, up-and-down, life-changing experience. Patients sometimes wish to change their current situation, to have acted differently, or not to have experienced the disease. They feel exhausted, guilty, and helpless, affecting their self-esteem. Some try to face the condition with optimism, resistance, and patience, but sometimes hope is lost. The patient is motivated by the desire to live, religion, children, family, and friends and learns from their care and to live with intestinal failure daily, changing their value system and how they see life and death. Recovery allows resuming activities, projects, relationships, freedom, and hope.

"Life has taught me. I maintain my ostomy and carry my things. Anyway, life taught me" (65-year-old man). "I live very happily. I think God allowed me to be born again, live, enjoy, help many people, and see life differently" (47-year-old woman).

DISCUSSION

The feeling of incarceration at home associated with TPN, as a central phenomenon in coping with the diagnosis, coincides with other qualitative research[13,14] in which TPN is consistently associated with loss of mobility and the need for staying at home and making adjustments in daily life, resulting in negative feelings toward the diagnosis and its management[13,14]. Other authors highlight that home care for administering parenteral nutrition was associated with the perception of greater rigidity in treatment[13].

The literature highlights that withdrawal at least one night a week is positively associated with and impacts well-being by resuming social activities and allowing patients to feel free and normal for a night[15]. Negative feelings are related to the risk of decompensation and not directly to the withdrawal of treatment. Nonetheless, the authors also cite the sensation of fatigue, hunger, and subsequent dehydration, which was not mentioned by the participants in our research[15].

About food, research found contradicting perceptions[14]. The need for food and inappetence and, oppositely, the restrictions on oral feeding and hunger significantly affect patients, as demonstrated by another study in which oral intake was an independent risk factor impinging on the quality of life[16].

The alternative to parenteral nutrition in selected cases is intestinal transplantation. As our patients perceived,

transplantation is associated with a better quality of life; however, long-term survival is a latent concern[17,18], which reinforces the idea of parenteral nutrition as a treatment that, despite providing a lower quality of life, represents the possibility of survival[17].

In addition to TPN, hospitalizations can be frequent and prolonged. Some studies describe them as positive because they signify a break from daily difficulties. Still, the perception of being hospitalized as a vital stressor detrimental to life[19] predominates, an assessment with which our interviewees agree.

Furthermore, the support network is essential[15]. It can come from the partner, family, friends, other patients, and even health personnel[13,15]. The literature suggests that the loss of independence varies according to the health condition, which denotes the feeling of loss of control, adding to the difficulty of asking for help[13,14]. A correlation has been found between support and scores on the hospital anxiety and depression scale, in which patients who perceived less support had higher levels of negative affect[20]. Support between patients has been shown to improve scores on quality of life and depression and decrease the incidence of catheter-related infection[21]. An innovative option is telemedicine support groups, where patients and their families interact in real-time[21], and other tools on social media[19].

Patients treated with home TPN experience a lower quality of life than the general healthy population and other patients with chronic diseases[16,17], which may be related to the negative impression of the diagnosis, the frequency of TPN administration, the restriction in the participation of activities considered valuable and routine[13-15], and the etiology of the disease. In the case of intestinal failure secondary to surgical complications, the patients reported a poorer quality compared to other causes[22].

Body image is also influenced by intestinal failure and its treatment. In other research, patients mentioned concern about the appearance of the catheter[13,14,19], the presence of an ostomy, and the need to hide changes in body image with changes in clothing that, in turn, would allow management[13,14,19]. Changes in body image increased self-consciousness, adversely affected self-esteem, and caused a loss of confidence that pushed them to reduce social interactions and, thus, increase isolation[13,14], as happened with our interviewees.

The authors underline patients' transition from sadness, frustration, worry, anger, anxiety, discouragement, and even depression to joy and hope[15,19]. In a study of 85 patients, 56% had clinical levels of anxiety or depression[20]. In another study, the use of antidepressants was correlated with the volume of parenteral nutrition, so patients with a high volume (three times greater) used antidepressants[23]. Besides, patients with poor support networks and of working age are more vulnerable to psychological impact[20].

From the patient's perspective, other research has identified the impact at the family level due to their limitation in carrying out activities, difficulty maintaining their role at home, exclusion, feelings of guilt, and concern for relatives distressed by the patient[14,15,19]. On the family side, 23% of family members reported a moderate to severe subjective burden on the domestic assistance scale[24]. Among the predictors that negatively influenced the perception of burden is the health condition of the relative of the patient with intestinal failure and the support received from health services[24].

Inability to continue working, dismissal, and the need to reduce working hours are frequently reported in the literature[13,14], a finding replicated in this research. This is corroborated by lower employment rates after starting TPN, especially in patients with intestinal failure secondary to surgical complications[25]. The consequences in the workplace have been associated with a negative impact on finances and, more significantly, anxiety and depression[15,20], which could be related to the perception of work as a goal, an identity, forced socialization, and a reason to get up in the morning[14].

A study with 196 patients found that the time and frequency of infusion, the duration of treatment, the social benefits of employment, the absence of benefits or pension, the intention to work, and age were significantly associated with return to work. The reasons for seeking employment after starting parenteral nutrition were the desire to contribute to society (48%), financial needs (20%), and social aspects (17%)[25].

From the patient's view, others have found different results: the refusal of home visits at night to not interfere with home health care and the impact of TPN on the ability and willingness to socialize due to exhaustion and stress produced by social situations[13,14]. A study mentioned limitations in movement, primarily due to the presence of an ostomy[13]. Similar to our findings, another study reported that friends' lack of understanding of the condition puts friendship to the test[15].

Research has referred to teaching care in the hospital but also has pointed out the particular learning of each patient and the adaptations in their personal, family, work, and social spheres for which hospital training is insufficient[13]. Patients must balance their lives to cope with intestinal failure and parenteral nutrition, sometimes making intestinal recovery possible and freeing them from the limitations imposed by diagnosis and management[15].

As limitations, we recognize that the emerging categories might not achieve the same depth since not all researchers have social sciences qualifications.

CONCLUSIONS

Facing intestinal failure implies the need for parenteral nutrition, which is perceived as a prison that paradoxically allows survival. The health system does not fully attend to the needs and expectations of patients with intestinal failure, creating uncertainty about the disease's origin and future. Intestinal failure and its treatment disrupt personal, family, and work life. Social rejection is marked. Family and close people's support is vital to adapt and revalue life.

RECOMMENDATIONS

Further research is needed on strategies to improve the independence of patients with intestinal failure in managing parenteral nutrition while maintaining safety and effectiveness. Emphasis should also be placed on forming and maintaining safe support networks for the patient and proper psychological assistance.

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Conflicts of interest

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Original article

Emerging Disease: A Case Series of post-COVID-19 Cholangiopathy

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Abstract

Introduction: Post-COVID-19 cholangiopathy is a novel condition characterized by biliary tract sclerosis and elevated alkaline phosphatase levels in critically ill patients. This case series aims to describe the experience of a Latin American reference hospital in managing this condition. **Methods:** This case series includes patients with confirmed coronavirus disease 2019 (COVID-19) who exhibited subsequent elevation of alkaline phosphatase levels exceeding three times the normal value. The patients also had documented bile duct abnormalities observed through cholangioresonance or endoscopic retrograde cholangiopancreatography (ERCP). The clinical presentation, imaging findings, complications, and treatment approaches are described. **Results:** Eight patients (56.5 ± 9.2 years old, 62.5% male) were included in the study. All patients had previously experienced severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) pneumonia and required mechanical ventilation. Four patients (50%) received sedoanalgesia with ketamine, and all eight patients (100%) received propofol. All patients developed infections, such as cholangitis or liver abscesses, caused by gram-negative bacteria. The peak alkaline phosphatase level during follow-up averaged 1646.12 ± 611.3. Imaging findings revealed intrahepatic (100%) and extrahepatic (87.5%) bile duct dilation. In 75% of cases, bile molds with a black appearance were extracted. Seven patients experienced recurrent cholangitis, and three patients were referred for pre-liver transplant consultation. **Conclusions:** Post-COVID-19 cholangiopathy is characterized by severe cholestasis, intra- and extrahepatic bile duct dilation, formation of bile molds, and recurrent cholangitis. In our study, a possible association between sepsis caused by gram-negative bacteria and the use of sedative medications is hypothesized. Further studies are necessary to establish the most appropriate management strategies for these patients, as they currently face unfavorable long-term morbidity and mortality outcomes.

Keywords

Cholangiopathy, SARS-CoV-2, COVID-19, cholangitis, sepsis.

INTRODUCTION

Elevation of liver injury markers in patients with coronavirus disease 2019 (COVID-19) is frequent. Elevated transaminases have been described in up to 14%-53% of patients[1]. Different studies describe elevated transaminases as a marker of inflammation and liver injury[2,3] related to increased disease severity and worse clinical outcomes.

A pattern of predominantly cholestatic liver damage is recognized, given by the elevation of bilirubin and alkaline phosphatase[4]. This new clinical entity, called *post-COVID-19 cholangiopathy*[4,5], is more frequent in critically ill patients[6,7] and is characterized by a severe lesion of the biliary tract. Various pathophysiological mechanisms are proposed, such as microthrombosis at the level of the bile ducts, sclerosing cholangitis in critically ill patients, and

direct injury caused by the virus. The frequency of this entity seems to be higher in patients with severe cases of COVID-19[6,7].

The number of reported cases of post-COVID-19 cholangiopathy is meager, and there are no reports in Latin America. This article describes the demographic, clinical, imaging characteristics, natural history, outcomes, and therapies used in eight cases of post-COVID-19 cholangiopathy managed at a university hospital in Colombia.

MATERIALS AND METHODS

This is a series of cases of patients diagnosed with post-COVID-19 cholangiopathy evaluated by the gastroenterology and hepatology services of Hospital Universitario San Ignacio in Bogotá, Colombia, between April 2020 and February 2022. We included adult patients who documented a cholestatic lesion with alkaline phosphatase levels above three times the standard value and abnormalities of the biliary tract on magnetic resonance cholangiography related to active or recent severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) infection (within six months), confirmed by positive laboratory results (positive polymerase chain reaction [PCR] or positive antigen), and who were examined in the outpatient clinic of the gastroenterology and hepatology services.

The patients' demographic data were analyzed, including their pathological history, liver biochemistry, COVID-19 severity at initial hospitalization, imaging findings, complications, and treatment used. The information was collected systematically based on the data from institutional electronic medical records. The recorded liver biochemistry values are the peak levels documented during medical care.

Categorical variables are reported as absolute and relative frequencies, and continuous variables as median and interquartile range or mean and standard deviation, depending on the data distribution. The Shapiro-Wilk test was used to test the assumption of normality. The analysis was performed using the Stata 16 statistical package.

RESULTS

Eight patients were included. **Table 1** summarizes the demographic and biochemical data, complications, and treatments received during the initial hospitalization.

All patients were diagnosed with pneumonia during hospitalization, required stay in the intensive care unit (ICU) and mechanical ventilation. The average length of stay in the ICU was 40.3 days, and the average time of orotracheal intubation and invasive mechanical ventilation was 20.3 days. The patients received different sedoanalgesia protocols, explained by the stay in three other institutions and periods; four patients (50%) received sedoanalgesia with ketamine and 8 (100%) with propofol.

Table 1. Demographic, biochemical characteristics, and complications during the initial hospitalization of the included patients

Variable	n = 8
Age, years, mean (SD)	56.5 (9.2)
Male sex, n (%)	5 (62.5%)
Latin American ethnicity, n (%)	8 (100%)
Comorbidities, n (%)	
- High blood pressure	2 (25%)
- Type 2 diabetes	3 (37.5%)
- Obesity	2 (25%)
- Cardiovascular disease	1 (12.5%)
- Previous liver disease	0 (0%)
- Dyslipidemia	2 (25%)
Blood biochemistry*, mean (SD)	
- AST	124.75 (68.4)
- ALT	114.75 (62.1)
- Alkaline phosphatase	1646.12 (611.3)
- Total bilirubin	13.77 (9.9)
Complications in initial hospitalization, n (%)	
- Multiple organ failure	0 (0%)
- Superinfection	8 (100%)
- Thrombosis	3 (42.8%)
Treatment used, n (%)	
- Corticosteroids	8 (100%)
- Anticoagulation	3 (37.5%)
- Propofol	8 (100%)
- Ketamine	4 (50%)
- Norepinephrine	8 (100%)

*Documented peak levels during care. ALT: alanine aminotransferase; AST: aspartate aminotransferase; SD: standard deviation. Table prepared by the authors.

All patients had bacterial superinfection that required antibiotic management, and gram-negative bacteria, including *Escherichia coli*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*, caused all these infections. Three (37.5%) patients had thromboembolic events (two with pulmonary thromboembolism and one with deep vein thrombosis) requiring anticoagulation therapy.

The average time from documentation of SARS-CoV-2 infection to diagnosis of cholangiopathy was 133 days, with the shortest period being 85 and the longest being 256 days. All patients had alterations in the bile ducts, detected in endoscopic retrograde cholangiopancreatography (ERCP) results. Eight patients presented with dilata-

tion of the intrahepatic bile duct, and seven had dilation of the extrahepatic bile duct. In four, there was evidence of a beaded appearance of the intrahepatic bile duct. Six (75%) patients had an extraction of unusual black material, and seven (87.5%) had recurrent episodes of cholangitis. Moreover, five patients had acute cholecystitis/choledocholithiasis preceded by the diagnosis of post-COVID-19 cholangiopathy.

Only one patient (12.5%) had a resolution of objective post-COVID-19 cholangiopathy findings, showed by a normal magnetic resonance cholangiography at follow-up. The remaining seven patients presented with worsening cholestasis and required multiple ERCPs for cholangitis management with stent replacement. Treatment with cholestyramine and ursodeoxycholic acid was indicated for three patients without improvement; they were referred to the liver transplant service due to the severity of their symptoms. Still, none had undergone transplantation at the time of the last follow-up. Six months after diagnosis, no patient had died, and three were in pre-hepatic transplant consultation.

Figure 1 shows one patient's ERCP and magnetic resonance cholangiography. **Figure 2** displays the extraction of the bile cast from another patient.

DISCUSSION

Cholangiopathy in critically ill patients is characterized by a cholestatic pattern secondary to liver injury from multiple pathologies[8], especially sepsis, trauma, and high-grade burns. Persistent damage occurs at the liver level once the underlying pathology has been resolved[9]. The literature proposes that one of the causes of cholangiopathy in critically ill patients is bile duct ischemia secondary to hypovolemia and hypoxia, aggravated by the everyday use of vasoconstrictor drug therapy[10]. Likewise, susceptibility to ischemia of the biliary tree is presented as a pathophysiological cause of this entity, explained by its unique supply of arterial blood[11].

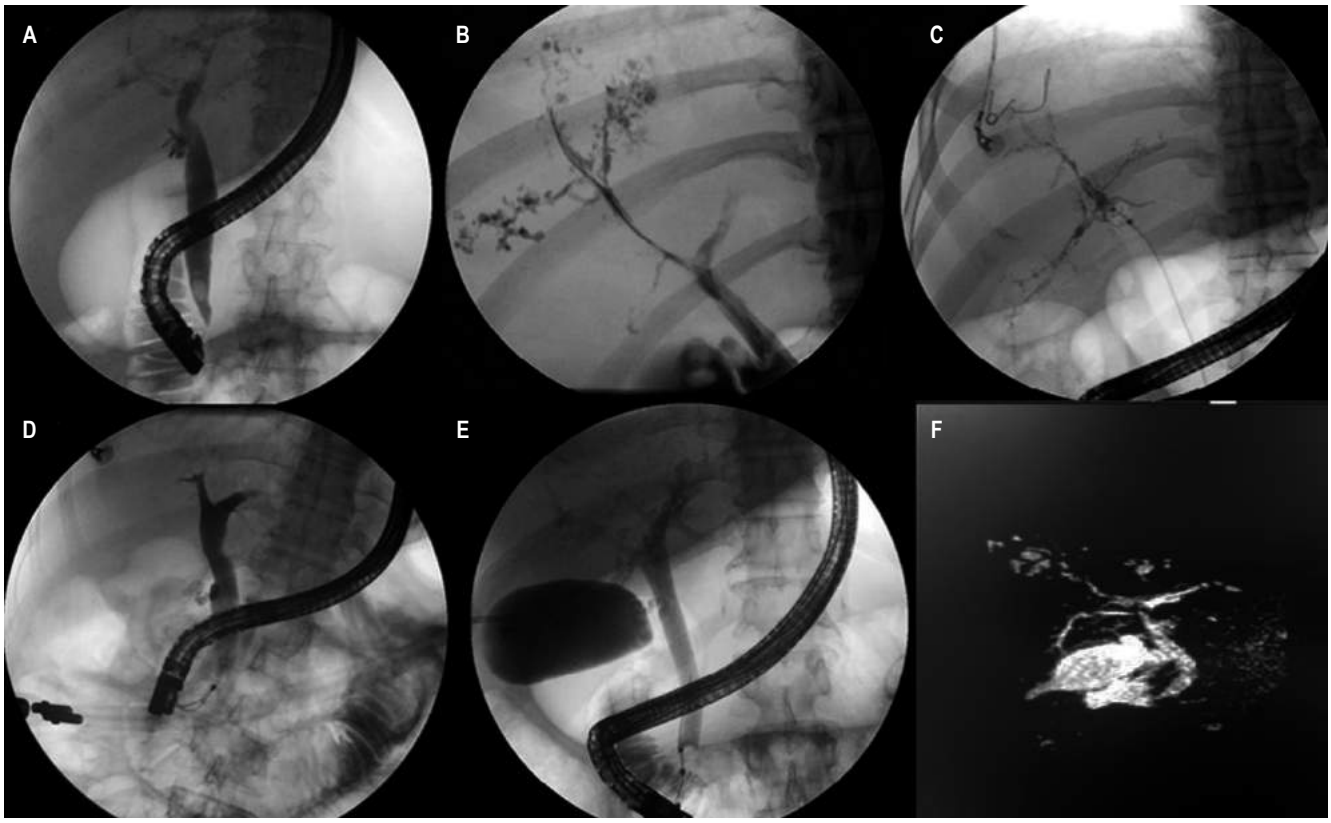

Figure 1. Imaging findings in post-COVID-19 cholangiopathy. **A.** Extrahepatic bile duct dilation on ERCP. **B.** Beaded bile duct of intrahepatic bile ducts on ERCP. **C.** Beaded bile duct in intrahepatic bile ducts on ERCP. **D.** Extrahepatic bile duct dilation on ERCP. **E.** Extrahepatic bile duct dilation on ERCP with beaded intrahepatic bile ducts. **F.** Extrahepatic bile duct dilation on magnetic resonance cholangiography. Source: Patient case series, Hospital Universitario San Ignacio.

Figure 2. Bile cast extracted on ERCP. Source: Patient case series, Hospital Universitario San Ignacio.

Post-COVID-19 cholangiopathy, as a new entity, has been reported by different authors, who have proposed differentiating the cholestatic pattern from the hepatocellular injury pattern described in moderate to severe COVID-19 infections[5]. However, there is insufficient information to determine whether this cholangiopathy corresponds to that previously reported in critically ill patients or is a separate pathology.

Our study reveals several characteristics that can contribute to understanding the pathophysiology of this disease. A significant proportion of the patients had comorbidities typically associated with more severe illness from COVID-19, such as high blood pressure (HBP) and type 2 diabetes mellitus (DM2), which could suggest susceptibility in these cases. New studies will be required to assess whether there is a genuine causal relationship.

Bacterial superinfection, exemplified by cholangitis and liver abscesses, was present in all our patients with post-COVID-19 cholangiopathy. The infection preceded the diagnosis of post-COVID-19 cholangiopathy, with documentation of gram-negative bacteria and high resistance patterns in many patients. In one of them, the condition became chronic to such a degree that it was considered incurable, so a multidisciplinary decision was made to continue broad-spectrum antibiotics indefinitely. Although sepsis is recognized as a predisposing factor for the development of cholangiopathy in critical patients[9,12], new studies will be required to clarify its role in the development of post-COVID-19 cholangiopathy.

Our study identified gallstone disease in five of the eight patients as contributing to the pathology. It has been described that COVID-19 may be a risk factor for the development of choledocholithiasis in patients with cholelithiasis[13]; nonetheless, its role in severe disease has not been defined. We believe that the presence of cholelithiasis and choledocholithiasis in a seriously ill patient predisposes to the development of cholangitis, which would contribute to the cholestatic lesion described in patients with severe COVID-19.

The biological expression of angiotensin-converting enzyme 2 (ACE-2) receptors has been recognized as the cell entry receptor for the SARS-CoV-2 virus[14], which explains the predilection of this pathogen for specific organs with high expression of these receptors. A study showed that ACE-2 receptors have increased expression in the bile ducts[15], which is considered one of the leading causes of potential damage at the liver and biliary levels. Hypoxia contributes to cholestatic liver injury, in which most patients with cholangiopathy have severe lung disease or pathologies that compromise oxygenation and ventilation[16].

It is striking that all of our cases occurred during 2021, even though we had many hospitalizations for COVID-19 at our institution in 2020. One possible explanation is the association of cholangiopathy with certain drugs. In our hospital, a change was made in the sedation protocols at the beginning of 2021, with which the use of ketamine, a drug that is extensively metabolized in the liver, was implemented more frequently. Ketamine has been associated with liver damage in multiple case series, initially in patients with recreational use of the drug and later also in patients with sedoanalgesia due to this drug[17]. A case report of two patients depicted post-COVID-19 cholangiopathy related to using ketamine[18], with the extraction of black bile casts and unusual appearance[12], which was consistently found in our study. The radiological findings were comparable to ketamine cholangiopathy, with biliary sepsis, intrahepatic and extrahepatic bile duct dilation, and biliary stricture[19]. Nevertheless, not all of our patients received ketamine before developing post-COVID-19 cholangiopathy. Propofol, used in all of our patients, has been related to the alteration of hepatobiliary transporters due to the release of cytokines, which increases the release of tumor necrosis factor-alpha (TNF-α) and interleukin (IL) 10, which has been associated with cholestasis[11]. However, this causality has only been seen with high doses of propofol (5-10 mg/kg/h), a quantity that none of our patients received. No studies assess the relationship between the use of ketamine and propofol and hepatobiliary injury in patients with COVID-19.

In our cases, only one patient did not have a recurrence of cholangitis and complications derived from post-COVID-19 cholangiopathy, with evidence of biliary lesion

resolution on follow-up magnetic resonance cholangiography. The use of ursodeoxycholic acid and cholestyramine, drugs frequently used to manage cholestasis in different pathologies[20], have not had beneficial effects in controlling recurrence.

As shown in our study, the severity and recurrence of the disease are characteristic in other case reports on post-COVID-19 cholangiopathy[4,5,7]. The prognosis of the disease appears to be ominous, as suggested by the fact that several of our patients have been referred for pre-liver transplant consultation. There needs to be more information on the success of this management and changes in the natural progress of the disease.

Our study expands the characterization of post-COVID-19 cholangiopathy in Latin American patients. Unlike other studies, there was no male preponderance, although the number of patients may limit these findings. To our knowledge, this series is the first to hint at a possible relationship between sepsis caused by gram-negative bacteria and the development of post-COVID-19 cholangiopathy. Likewise, the use of sedative drugs associated with liver disease, such as ketamine and propofol, is noteworthy.

Our study has limitations, and the main one is the number of patients, making it impossible to demonstrate the causality of the proposed factors; however, our data allow us to formulate hypotheses that can be formally tested in more extensive cohort studies.

CONCLUSIONS

Post-COVID-19 cholangiopathy is an emerging entity characterized by severe cholestatic liver injury associated with dilation of the intrahepatic and extrahepatic bile ducts, formation of bile casts, and recurrence of complications such as cholangitis. Our study proposes a possible relationship between the development of post-COVID-19 cholangiopathy with sepsis due to gram-negative bacteria and the use of sedoanalgesia. Complementary studies should evaluate this hypothesis.

Of importance is to evaluate in the future, with more extensive studies, the natural history of the disease, possible triggering factors, and prognoses to establish adequate management for patients with unfavorable long-term morbidity and mortality.

Conflicts of interest

The authors state that no financial or personal relationship with other individuals or organizations may have influenced this work.

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Original article

Economic burden of liver disease in Colombia

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Abstract

Introduction: Liver diseases have a significant impact on global morbidity and mortality rates, primarily attributed to cirrhosis and hepatocellular carcinoma. However, the true extent of their impact on patients, healthcare systems, and countries is often underestimated. **Materials and methods:** This descriptive, cross-sectional study aimed to determine the economic burden associated with premature deaths caused by cirrhosis and primary liver cancer. The economic assessment was conducted by analyzing potentially productive years of life lost (PPYLL) due to liver diseases in Colombia between 2009 and 2016. **Results and conclusions:** The total burden of liver disease accounted for 687,861 disability-adjusted life years (DALYs). Men experienced a higher number of years of life lost from mortality (YLL), while women had a greater number of years lived with a disability (YLD). The economic burden of deaths caused by cirrhosis and primary liver cancer exceeded USD 8.6 million, highlighting the urgency to enhance intervention strategies ranging from promotion and prevention to timely diagnosis and treatment.

Keywords

Economic burden, disability-adjusted life years, years of life lost from mortality, years lived with a disability, liver cirrhosis, liver neoplasms, liver disease.

INTRODUCTION

Liver disease is one of the leading causes of worldwide morbidity and mortality[1-3]. It is a slow process that persists for long periods and results in the progressive destruction of the liver; its timely diagnosis and treatment manage to prolong life expectancy and improve patients' quality of life[4]. Disease burden studies allow the gap between the current health condition and an ideal health condition free of disease and disability to be measured based on the disability-adjusted life years (DALYs) lost, calculated from the sum of years of life lost due to premature death (YLLs) and years lived with disability (YLDs)[5]. In 2019, the number of DALYs due to all causes amounted to 2.54 billion (2.29 to 2.81) worldwide[6].

Chronic liver disease and its complications have been included in global disease burden estimates; however, they are undervalued. Liver disease causes around 844 million cases and more than 2 million deaths annually, so its morbidity and mortality can be compared with other chronic

diseases[7]. It is responsible for the progressive increase in recurrent hospital visits and years of life lost due to chronic diseases[2,8,9].

The epidemiology of liver disease varies by etiology, sex, territory, age, and disease-specific risk factors[8,10,11]. It imposes a substantial health burden in many countries and reports a progressive increase worldwide since 1990, partly due to the growth and aging of the population[12]. In the case of Latin America, deaths from liver cirrhosis doubled between 1980 (1,503) and 2010 (3,674)[1].

Cirrhosis is considered a public health threat due to its high mortality, mainly due to alcoholic liver disease (ALD), metabolic disease-associated fatty liver (MAFLD), and chronic hepatitis C virus infection[13].

In Colombia, from 2009 to 2016, there were 649,887 cases of liver disease, the highest proportion of patients corresponding to metabolic disorders, cirrhosis, and viral infections[10]. Liver cirrhosis has become one of the leading causes of disease burden worldwide. In 2019, it caused 46 million (43-49 million) DALYs (1.82%, confidence interval [CI]: 1.64%-2.02% of total DALYs) and was responsible for more than one million deaths, equivalent to 2.6% of deaths globally[6].

In the early stages, the disease is usually compensated and asymptomatic, and patients may have a life expectancy similar to that of healthy adults; however, as the disease progresses and decompensates, it can be lethal in up to 80% of cases and frequent and prolonged hospital stays are required with treatments that include mainly liver transplantation, meaning a burden for patients, the health system, and the government[12].

The close relationship between the per capita consumption of liters of alcohol and the increase in the mortality rate from liver disease has been studied throughout the world, and it is decisive given the variety of non-communicable diseases attributable to consumption (fatty liver, alcoholic hepatitis, and cirrhosis)[3,9,14].

Non-alcoholic steatohepatitis (NASH) is an essential cause of liver disease worldwide[15]. In 2019, it caused around 168,000 deaths and 4.4 million DALYs (3.3-5.6) (0.17% of total DALYs)[6]. Viral infections affect the world population and have gained significant importance due to their considerable increase despite the available vaccines against hepatitis A and B[14]. In 2015, they caused 1.34 million deaths (primarily due to chronic liver disease [720,000] and primary liver cancer [470,000]), a number comparable to deaths from tuberculosis (1.37 million) and more than deaths from human immunodeficiency virus (HIV; 1.06 million) or malaria (0.44 million)[16,17]. This scenario does not show much variation compared to 2019, when hepatitis B and C were responsible for 1.1 million deaths and 1.3% of the total DALYs worldwide[6].

In 2019, liver cancer was responsible for 484,000 deaths and 12,000 DALYs (0.49% of total DALYs worldwide)[6]. It is the leading cause of death in many countries with medium and low sociodemographic indices; however, countries with high sociodemographic indices have shown an increase due to risk factors such as alcohol abuse, hepatitis B and C, and NASH[18].

Patients with liver disease pose challenges for health professionals; their quality of life is inferior, representing a significant economic burden for the country[4]. This disease's treatment is expensive and inaccessible in most of the world[1]. In Colombia, approaches have been introduced to determine the impact of liver disease; nonetheless, few publications support intervention initiatives in public policy. Therefore, it is necessary to provide an overview of the main etiologies of liver disease.

MATERIALS AND METHODS

Estimation of the disease burden

This descriptive cross-sectional study determined Colombia's economic and liver disease burden between 2009 and 2016. From the definition of the diagnoses concerned and the creation of disease categories (cirrhosis, portal hypertension, congenital and birth, pregnancy, non-cirrhotic alcoholic liver disease [NAFLD], inflammatory, metabolic, toxic, primary liver tumors [hepatic tumors], vascular, and viral infections), the data were analyzed by sex, year of care/death, ICD-10 primary diagnosis grouped into categories, age in five-year periods, and geographic location. The study used the Data Warehouse-Cube population databases of Colombia's Integrated Social Protection Information System (SISPRO, for its acronym in Spanish)[19] as the primary source of prevalence data and the registry of vital statistics (deaths) of the National Administrative Department of Statistics (DANE, for its acronym in Spanish)[20].

To calculate the prevalence and mortality rate of liver disease per year, it was adjusted for underreporting using Bennett Horiuchi's method, based on the intercensal estimate of deaths between 2009 and 2016[21].

In the global disease burden study, disability weights were defined for the diseases included in the studies; however, since these data were not available for all disease categories, disability weights were determined with a group of four experts in liver disease using the Delphi method[22]. We explained to them that the disability weights reflect the severity of the disease on a scale from 0 (perfect health) to 1 (death), exemplified by disability weights from the study conducted worldwide by the Global Burden of Disease (GBD) 2016[23].

Each expert was sent a format with the list of diagnoses grouped into disease categories, in which, according to their medical criteria, they defined the weight of disability. Two rounds were completed for expert consensus; in the second, the results of the first round were sent, obtaining the final values defined by the experts for each disease category, with which YLDs were calculated.

Prevalence and mortality data were included in the Microsoft Excel template according to the World Health Organization's (WHO) Manual [21], with the disability weights assigned by the experts for each disease category. The outcome variables for the disease burden given by DALYs were YLL plus YLD. The data was consolidated into a matrix by category for analysis. The disease burden was calculated based on life expectancy at birth for a society with low mortality[24,25], with an average of 80 years for men and 82.5 years for women, like Japan[26].

Estimation of the economic burden

The economic burden associated with premature deaths from cirrhosis and liver tumors was estimated through the economic valuation of the potentially productive years of life lost (PPYLL). For this, the method applied by the authors in previous studies[27-30] was used. The PPYLL was valued based on the productive period of people in Colombia, which ranges from 18-57 years in women and up to 62 years in men. The economic valuation of the PPYLL was discounted using an annual discount rate of 3% to achieve international comparability[31,32]. All costs were reported in 2019 US dollars, using the average market representative rate published by Colombia's Central Bank (1 USD = 3,281 Colombian pesos)[33]. The PPYLL was calculated as follows:

$$PPYLLi = \left[\begin{array}{l} Ap - 18, \text{ if } Ad \leq 18 \\ Ap - (sAdg + k), \text{ if } Ad > 18 \end{array} \right]$$

PPYLLi: potentially productive years of lost life of the individual; Ap: pension age (according to the sex of the individual); Ad: death age (adjusted by mid-term); sAdg: start age of the death age group; k: mid-cycle adjustment factor (for children under one year = 0.5; 1 to 4 years = 2; for the other age groups: 2.5).

The estimate of the economic burden associated with premature deaths caused by cirrhosis and liver tumors was modeled for two scenarios:

- Floor scenario (lower loss): PPYLLs are valued based on the annual minimum wage (AMW), calculated using the 2019 minimum monthly wage (COP 828,116). This value was multiplied by 13.5 months (12 calendar months + 1.5 months of social benefits).
- Ceiling scenario: It refers to the country's average productivity, evaluated as the gross domestic product per capita (GDPpc) of 2019 (COP 21,506,780)[34].

RESULTS

The burden of liver disease

Between 2009 and 2016, the total burden of liver disease represented 687,861 DALYs (1,835 x 1,000 people). By age group and sex, there is evidence of more DALYs in both sexes from age 30 (**Table 1**).

Table 1. Disability-adjusted life years (DALYs) and economic burden by sex and age group, liver disease, Colombia, 2009-2016

Age group	Men		Women		Total	
	DALY men	DALY/1,000	DALY women	DALY/1,000	Total DALY	DALY/1,000
0-4	5814	0.330	5584	0.332	11398	0.331
5-14	1966	0.056	2676	0.079	4642	0.067
15-29	6356	0.127	5914	0.122	12 270	0.124
30-44	24 900	0.686	15 547	0.402	40 448	0.540
45-59	84 219	3.021	52 584	1.714	136 802	2.336
60-69	139 309	13.477	151 583	13.038	290 892	13.245
70-79	63 549	11.729	77 288	11.568	140 837	11.640
80+	21 209	9.913	29 362	9.812	50 571	9.854
Total	**347 323**	**1.877**	**340 538**	**1.794**	**687 861**	**1.835**

Source: The authors.

Annual DALYs increased progressively between 2009 and 2014, from 1.59 to 2.13 DALYs per 1,000 people, with a subsequent decline in 2016 to 1.77 DALYs per 1,000 people (**Figure 1**). Of the total DALYs due to liver disease, 67% correspond to mortality and 33% to disability. When performing the analysis by sex, the proportion of DALYs due to mortality was higher in men than in women (37% vs. 30%); however, DALYs due to disability were higher in women than in men (19% vs. 14%) (**Figure 2**).

The main etiologies of liver disease burden were cirrhosis, liver tumors, and metabolic and viral diseases, with differences in burden due to disability and premature death (**Figure 3**, **Table 2**).

Liver cirrhosis had 307,412 DALYs (0.82 x 1,000 people), 58% in men. Of these, 245,651 DALYs were attributed to mortality (80%) and 60,793 to disability. Both men and women had the highest number of DALYs after 60. By year, it is evident that the highest DALY rates occurred between 2014 and 2015 (0.940 and 0.932 x 1,000 inhabitants, respectively) (**Table 2**).

Metabolic diseases had 109,280 DALYs (0.29 x 1,000 people), 43,535 DALYs (40%) in men, and 65,765 DALYs (60%) in women. Of the total DALYs, 3,800 (3%) correspond to mortality and 105,490 (97%) to disability. By age group, 82,366 DALYs (75.4%) belong to the 60-69 age group, followed by the 70-79 age group with 19,466

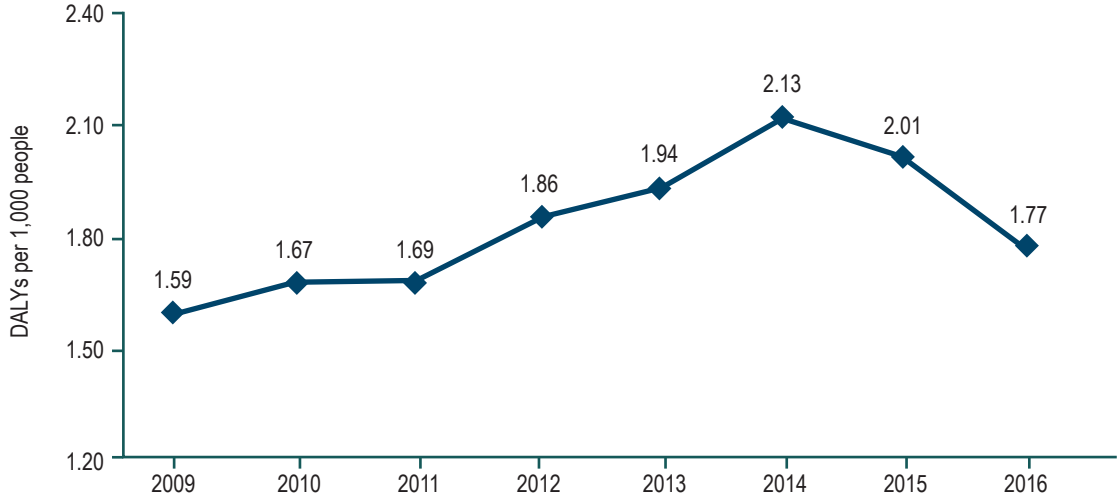

Figure 1. DALY trend due to liver disease x 1,000 people, Colombia 2009-2016. Source: The authors.

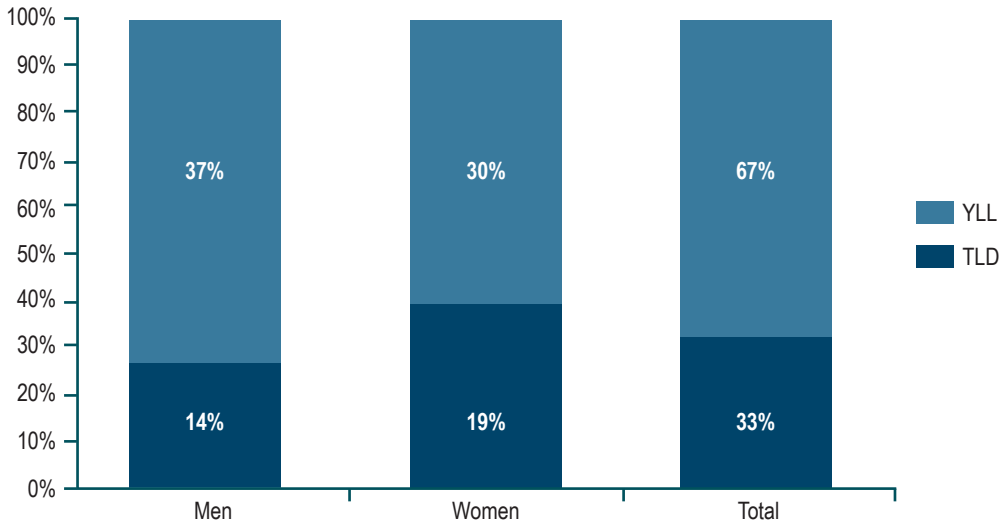

Figure 2. The proportion of YLLs and YLDs over DALYs due to liver disease in Colombia, 2009-2016. Source: The authors.

Table 2. DALYs, YLLs, and YLD by sex, Colombia, 2009-2016

DALY						
Category	**Men**	**Men *1,000**	**Women**	**Women *1,000**	**Total**	**Total *1,000**
Cirrosis	177 255	7.656	130 157	5.473	307 412	6.55
Congénitas y del nacimiento	3591	0.155	6975	0.293	10 567	0.22
Del embarazo	0	0.000	538	0.023	538	0.01
EHANC	6009	0.260	2052	0.086	8061	0.17
Hipertensión portal	3017	0.131	3088	0.130	6105	0.13
Inflamatorias	2757	0.119	4127	0.173	6884	0.15
Metabólicas	43 525	1.868	65 765	2.754	109 290	2.32
Tóxicas	3992	0.173	5262	0.221	9254	0.20
Tumores hepáticos	93 254	4.031	109 047	4.601	202 300	4.32
Vasculares	623	0.027	725	0.030	1348	0.03
Virales	13 300	0.576	12 802	0.540	26 102	0.56
Enfermedad hepática	347 323	1.870	340 538	1.794	687 861	1.83
YLL						
Category	**Men**	**Men *1,000**	**Women**	**Women *1,000**	**Total YLLs**	**%YLLs**
Cirrosis	150 968	6.526	94 683	4.020	245 651	53%
Congénitas y del nacimiento	2683	0.116	3295	0.135	5978	1%
Del embarazo	0	0.000	536	0.017	536	0%
EHANC	3852	0.166	609	0.023	4461	1%
Hipertensión portal	1625	0.071	1273	0.059	2898	1%
Inflamatorias	1295	0.057	1330	0.055	2625	1%
Metabólicas	1715	0.073	2086	0.088	3800	1%
Tóxicas	1551	0.068	1461	0.061	3011	1%
Tumores hepáticos	80 278	3.466	94 969	4.022	175 246	38%
Vasculares	346	0.015	269	0.009	615	0%
Virales	9347	0.405	7316	0.310	16 663	4%
Enfermedad hepática	253 659	10.952	207 826	8.800	461 485	100%
YLD						
Category	**Men**	**Men *1,000**	**Women**	**Women *1,000**	**Total de APMPs**	**% YLDs**
Cirrosis	26 287	1.091	35 475	1.484	61 761	27%
Congénitas y del nacimiento	908	0.038	3680	0.154	4588	2%
Del embarazo	0	0.000	3	0.000	3	0%
EHANC	2157	0.090	1443	0.060	3600	2%
Hipertensión portal	1392	0.058	1815	0.076	3207	1%
Inflamatorias	1462	0.060	2798	0.117	4259	2%
Metabólicas	41 810	1.727	63 679	2.665	105 490	47%
Tóxicas	2442	0.101	3801	0.159	6242	3%
Tumores hepáticos	12 976	0.540	14 078	0.592	27 054	12%
Vasculares	277	0.011	455	0.019	732	0%
Virales	3952	0.165	5486	0.231	9438	4%
Enfermedad hepática	93 663	3.882	132 712	5.557	226 375	100%

Source: The authors.

DALYs (17.8%). Metabolic diseases showed 0.413 DALYs x 1m000 people in 2014, followed by 0.356 in 2016 and 0.337 in 2015; the other years had less than 0.332 DALYs x 1,000 people (**Table 2**).

Liver tumors had 202,300 DALYs (0.54 x 1,000 people), of which 93,254 DALYs (46%) were in men and 109,047 DALYs (54%) in women. 175,246 DALYs (87%) were reported for mortality, and 27,054 DALYs (13%) for disability. When analyzed by age groups, there are 65,709 DALYs (32.5%) between 60 and 69 years, followed by 51,248 DALYs (25.3%) between 70 and 79 years, and 46,270 DALYs (22.9%) between 45 and 59 years. In 2014, there was a rate of 0.595 DALYs x 1,000 people, followed by 2012, 2014, and 2015 with rates between 0.558 and 0.561 DALYs x 1,000 people (**Table 2**).

Viral infections featured 26,102 DALYs (0.07 x 1,000 people), of which 13,300 DALYs (51%) correspond to men and 12,802 DALYs (49%) to women. 16,663 DALYs (64%) were registered for mortality, and 9438 DALYs (36%) for disability. 10,983 DALYs (42%) were reported between 60 and 69 years, followed by 4,506 (17%) between 45 and 59 years and 3,795 (15%) between 70 and 79 years, and the year 2016 had the lowest DALY rate (0.058 x 1,000 people). In the other years, they ranged between 0.068 and 0.078 x 1,000 people (**Table 2**).

The DALY, YLD, and YLL data for alcoholic liver disease portal hypertension, congenital and birth, pregnancy, inflammatory, toxic, vascular diseases, and NAFLD are found in **Table 2** because they do not represent a significant disease burden.

Economic burden of deaths from cirrhosis and liver tumors

For 2016, deaths in productive ages due to cirrhosis caused 9,064 YPLL (69.5% in those over 40) and 4,103 (62.8%) from liver tumors. These YPLYL due to cirrhosis produced an economic burden that ranged between 19.6 and 37.8 million dollars, and for liver tumors, between 8.6 and 16.5 million dollars (**Table 3**).

Figure 4 shows the economic burden of premature mortality due to cirrhosis and liver tumors by sex and age group. Most of the economic burden of cirrhosis occurs in men, especially those aged 35 years or older (**Figure 4A**), and it ascends to 54 years. In turn, the economic burden of liver tumors is higher in women in the 15-19 and 35-39 age groups; the burden is more significant in men in the remaining groups. A variable economic burden is noted in the first age groups, rising from over 35 to 49 and then decreasing to 59 years (**Figure 4B**).

DISCUSSION AND CONCLUSIONS

The total burden of liver disease represented 687,861 DALYs (1,835 x 1,000 inhabitants), with an increase between 2009 and 2014 (1.59 to 2.13 DALYs x 1,000 people) and a subsequent decrease in 2016 (1.77 DALYs x 1,000 people).

The highest proportion of DALYs was due to mortality (67%). Men had more YLL, and women exhibited the highest YLDs due to liver disease. This trend was maintained throughout the study period, which may be related to a longer life expectancy in women, biological factors (genetic,

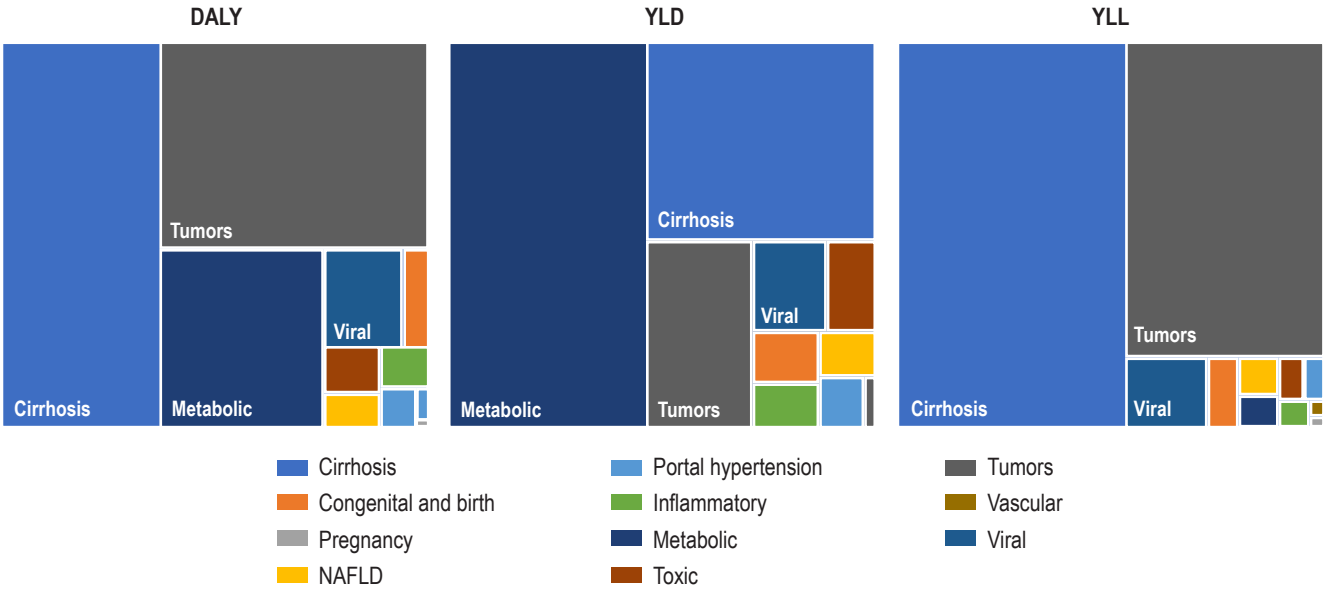

Figure 3. DALYs, YLDs, and YLL distribution due to liver disease in Colombia, 2009-2016. Source: The authors.

Table 3. Estimated PLYL and economic burden for cirrhosis and liver tumors, with and without discount. Colombia, 2016

Age group	Total PPYLL		PPYLL discount		Economic burden without discount*				Economic burden with discount *			
					Floor		Ceiling		Floor		Ceiling	
	F	M	F	M	F	M	F	M	F	M	F	M
Hepatic cirrhosis												
15-19	249	90	80	25	$ 847 305	$ 306 204	$ 1 630 010	$ 589 063	$ 271 523	$ 84 643	$ 522 345	$ 162 833
20-24	149	163	54	51	$ 506 182	$ 556 095	$ 973 772	$ 1 069 793	$ 182 567	$ 173 013	$ 351 215	$ 332 835
25-29	381	214	159	77	$ 1 298 467	$ 728 555	$ 2 497 937	$ 1 401 564	$ 542 916	$ 262 772	$ 1 044 440	$ 505 509
30-34	158	366	77	153	$ 539 194	$ 1 245 935	$ 1 037 279	$ 2 396 878	$ 261 356	$ 520 952	$ 502 786	$ 1 002 185
35-39	336	658	189	319	$ 1 144 412	$ 2 241 980	$ 2 201 572	$ 4 313 026	$ 643 067	$ 1 086 725	$ 1 237 106	$ 2 090 596
40-44	390	1007	254	566	$ 1 329 645	$ 3 431 601	$ 2 557 916	$ 6 601 571	$ 866 156	$ 1 928 284	$ 1 666 274	$ 3 709 551
45-49	450	1288	340	839	$ 1 533 219	$ 4 388 930	$ 2 949 542	$ 8 443 240	$ 1 157 845	$ 2 859 031	$ 2 227 414	$ 5 500 085
50-54	349	1501	305	1134	$ 1 188 428	$ 5 115 726	$ 2 286 248	$ 9 841 419	$ 1 040 412	$ 3 863 257	$ 2 001 501	$ 7 431 972
55-59	-	1315	-	1152	$ 0	$ 4 482 199	$ 0	$ 8 622 667	$ 0	$ 3 923 952	$ 0	$ 7 548 734
60-64	-	-	-	-	$ 0	$ 0	$ 0	$ 0	$ 0	$ 0	$ 0	$ 0
Total	2461	6603	1457	4315	$ 8 386 853	$ 22 497 227	$ 16 134 275	$ 43 279 221	$ 4 965 843	$ 14 702 628	$ 9 553 081	$ 28 284 300
Liver tumors												
15-19	166	90	53	25	$ 564 870	$ 306 204	$ 1 086 673	$ 589 063	$ 181 015	$ 84 643	$ 348 230	$ 162 833
20-24	74	326	27	102	$ 253 091	$ 1 112 191	$ 486 886	$ 2 139 586	$ 91 284	$ 346 026	$ 175 608	$ 665 671
25-29	64	143	27	51	$ 216 411	$ 485 704	$ 416 323	$ 934 376	$ 90 486	$ 175 181	$ 174 073	$ 337 006
30-34	53	122	26	51	$ 179 731	$ 415 312	$ 345 760	$ 798 959	$ 87 119	$ 173 651	$ 167 595	$ 334 062
35-39	336	152	189	74	$ 1 144 412	$ 517 380	$ 2 201 572	$ 995 314	$ 643 067	$ 250 783	$ 1 237 106	$ 482 445
40-44	281	322	183	181	$ 957 345	$ 1 098 112	$ 1 841 699	$ 2 112 503	$ 623 632	$ 617 051	$ 1 199 718	$ 1 187 056
45-49	307	539	232	351	$ 1 045 376	$ 1 837 227	$ 2 011 051	$ 3 534 379	$ 789 440	$ 1 196 804	$ 1 518 691	$ 2 302 361
50-54	281	393	246	296	$ 957 345	$ 1 337 445	$ 1 841 699	$ 2 572 920	$ 838 110	$ 1 010 002	$ 1 612 320	$ 1 942 999
55-59	-	456	-	399	$ 0	$ 1 552 140	$ 0	$ 2 985 941	$ 0	$ 1 358 824	$ 0	$ 2 614 049
60-64	-	-	-	-	$ 0	$ 0	$ 0	$ 0	$ 0	$ 0	$ 0	$ 0
Total	1561	2542	981	1530	$ 5 318 581	$ 8 661 714	$ 10 231 664	$ 16 663 042	$ 3 344 153	$ 5 212 964	$ 6 433 341	$ 10 028 482

*Amounts in 2019 US dollars. Source: The authors.

hormonal, autoimmune), and social and behavioral factors (tobacco and alcohol use)[35,36].

Deaths from cirrhosis created an economic burden that ranged between US 19.6 and 37.8 million, and from liver tumors between US 8.6 and 16.5 million, which can be significantly impacted by immunization against hepatitis B in the pediatric population and strategies against alcohol[6], implemented since 1992 and 2007, respectively[37,38].

In 2017, liver disease caused more than 1.32 million deaths globally in Europe, North America, South America, and Central Asia, and alcohol is the most common cause of liver cirrhosis. In some countries of the European region, approximately 2 million years of life are lost due to liver disease in people under 50 years of age (60%-80% due to alcohol)[39].

In 2012, cirrhosis and liver cancer in the United States were among the top 5 causes of death from gastrointesti-

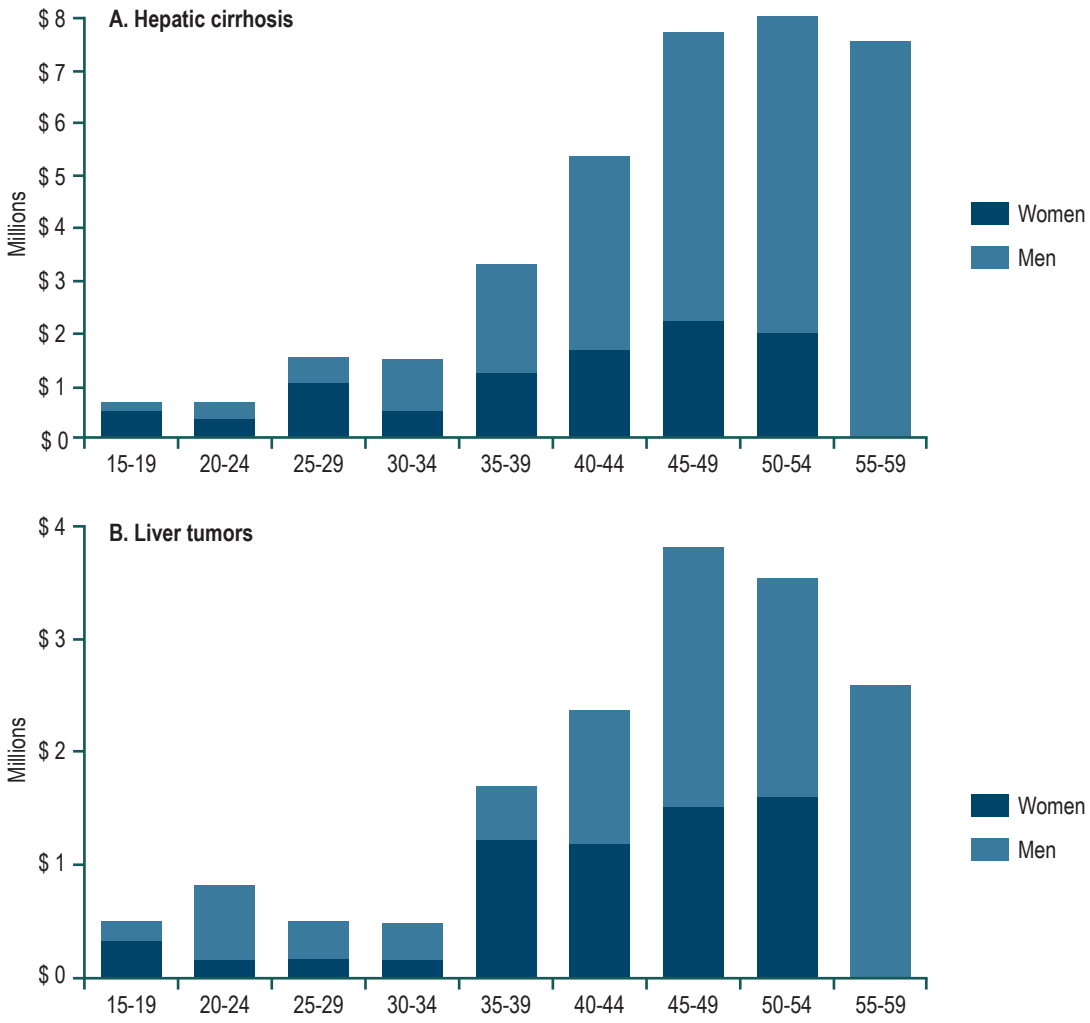

Figure 4. The economic burden associated with premature deaths from cirrhosis and liver tumors in Colombia, 2016. Source: The authors.

nal, liver, and pancreatic diseases[40]. In 2015, they were the 11th and 16th most frequent causes of death in the world, causing 1.16 million and 788,000 deaths, respectively, and when combined, they represent 3.5% of deaths worldwide[17]. These results are consistent with our findings, in which cirrhosis and primary liver tumors were Colombia's leading causes of death from liver disease.

By 2015, regionally, the highest proportion of deaths from cirrhosis and liver cancer was found in Latin America and the Caribbean, the Middle East, and North Africa[17]. Most liver cancers (83%) are diagnosed in less developed countries[41]; however, Fitzmaurice et al.[18] described that the chances of developing liver cancer are higher in countries with a medium sociodemographic index (SDI). In 2005, liver cancer in Santander, Colombia, represented 59.4 DALYs x 100,000 people, of which 89.7% correspond to mortality and 10.2% to disability[42].

The proportion in the distribution of mortality and disability does not show significant differences with our study since 202,300 DALYs (0.5 x 1,000 people) were estimated between 2009 and 2016, of which 87% correspond to mortality and 13% to disability. Considering the possibility of information systems underreporting mortality and prevalence in Colombia and studies worldwide, liver disease is related to geographic, socioeconomic, and sociocultural factors that lead to disparities with a significant impact on the health of the population and the country's development concerning disability and premature mortality outcomes[10,43,44].

Despite public health interventions related to immunization, healthy lifestyle habits (physical activity, diet), and measures to control alcohol use, the burden of liver disease in Colombia reflects the need to strengthen intervention strategies, from promotion and prevention to timely diagnosis and treatment, since economic and social expenses (drugs and technologies) can become unsustainable due to the increase in the disease burden[45].

LIMITATIONS

The study's main limitations in estimating cases and analyzing the population impact of public policy are the scarcity of epidemiological studies of liver disease in Colombia and underreporting in the information systems. This study does not include complications associated with the disease categories studied (such as variceal bleeding, ascites, hepatorenal syndrome, and portosystemic encephalopathy, among others, in the case of portal hypertension).

Care should be taken to interpret the data because the disease burden was assigned by disease category and does not include the severity scenario by disease category or other more complex situations in which multiple causes or risk factors contribute to disabilities or premature death individually.

The estimation of mortality costs was limited. Our analysis was performed from the perspective of the human capital method, which implied that friction costs were not considered. Some authors suggest that the friction cost method is an alternative to the human capital method. The latter would overestimate the costs associated with premature mortality because the production not obtained due to the death of a worker can be replaced by unemployed individuals[46-48]. This article justified the assessment of premature mortality due to liver diseases by selecting a floor scenario that illustrates these losses according to the annual minimum wage, which is close to 86.2% of the country's median salaries[49]. The second scenario, or ceiling scenario, is the country's average productivity evaluated as GDP per capita[50,51].

BIASES

Information bias regarding disability weights for all liver disease categories included in the study was controlled by expert consensus to assign values between 0 (perfect health) and 1 (death) because they were not fully defined in previous disease burden studies. Subjectivity bias in data analysis was contained by involving all researchers.

RECOMMENDATIONS

Despite national efforts to prevent and control chronic diseases, there is a substantial burden of liver disease in the Colombian population, requiring a more significant approach through strategies that contain, eliminate, or minimize the risk of developing the disease and its negative impact on the country, including the costs attributable to disability and premature mortality.

Our study shows that liver disease in Colombia and globally is a public health problem. It must be addressed with comprehensive strategies for prevention, control, treatment, and rehabilitation (particularly for patients with liver transplantation), with a multisectoral focus. Decisive public policy actions are required, such as vaccination (viral hepatitis, liver cancer), education on and restriction of alcohol use (cirrhosis), prevention and control of chronic non-communicable diseases such as diabetes and obesity (non-alcoholic cirrhosis), and of course, improved information systems to have the most reliable data to assess the impact of these public health measures.

Conflicts of interest

There were no conflicts of interest in the conduct of the research.

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Original article

Characterization of Achalasia Subtypes Based on High-Resolution Manometry in Patients at a Reference Hospital in Colombia

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Abstract

Introduction: Limited information is available regarding the clinical and manometric characteristics of different subtypes of achalasia. This study aims to describe these characteristics in patients treated at a prominent hospital in Colombia. **Methods:** This descriptive observational study included patients diagnosed with achalasia using high-resolution esophageal manometry at Hospital Universitario San Ignacio in Bogotá, Colombia, between 2016 and 2020. We documented the clinical manifestations, manometric findings, treatment approaches, and response to treatment based on the subtype of achalasia. **Results:** A total of 87 patients were enrolled, with a median age of 51 years, and 56.4% of them were female. The majority had type II achalasia (78.1%), followed by type I (16%) and type III (5.7%). All patients presented with dysphagia, 40.2% experienced chest pain, and 27.6% had gastroesophageal reflux. The clinical parameters, including integrated relaxation pressure value (IRP; median: 24 mmHg, interquartile range [IQR]: 19-33), upper esophageal sphincter pressure (UES; median: 63 mmHg, IQR: 46-98), and lower esophageal sphincter pressure (LES; median: 34 mm Hg, IQR: 26-45), were similar across the different subtypes. Esophageal clearance was incomplete in all patients. Among the 35 patients who received intervention, Heller's myotomy was the most commonly employed procedure (68.5%), followed by esophageal dilation (28.6%). All patients experienced symptomatic improvement, with a median pre-treatment Eckardt score of 5 (IQR: 5-6) and a post-treatment score of 1 (IQR: 1-2). **Conclusions:** Type II achalasia is the most prevalent subtype. The clinical and manometric findings, as well as treatment response, exhibit similarities among the different subtypes of achalasia. In Colombia, the outcomes of this condition align with those reported in other parts of the world.

Keywords

Achalasia, high-resolution manometry, dysphagia, esophageal motility.

INTRODUCTION

Achalasia is a disease with low incidence and prevalence, with an annual incidence of 1-5 cases per 100,000 individuals and a prevalence of 7-32 cases per 100,000 individuals worldwide[(1)]. It is a rare entity characterized by dysphagia for solids and liquids in 90% of patients, regurgitation of undigested food in 75%, chest pain in 50%, and heartburn in 40%[(2)]. Due to these symptoms, patients could present with weight loss, bronchitis, and recurrent pneumonia[(3)].

The gold standard for the diagnosis of achalasia is esophageal high-resolution manometry (HRM), revealing incomplete relaxation of the esophagogastric junction (EGJ) with the absence of organized peristalsis[(4)]. According to the Chicago 4.0 classification, three achalasia subtypes have been described, which are characterized by failure

to relax the lower esophageal sphincter (LES) and various patterns of esophageal contraction[5]: type I achalasia (formerly classic) exhibits an abnormal relaxation pressure integral (RPI) and 100% failed swallows (distal contractility integral [DCI] < 100 mm Hg/s/cm). Type II achalasia, or achalasia with esophageal compression, presents with abnormal RPI, 100% failed swallows, and panesophageal pressurization in at least 20% of swallows. Type III achalasia, or spastic, shows abnormal RPI, 100% failed swallows, and premature or spastic contractions in the distal esophagus in at least 20% of swallows[6,7].

There is limited information on the clinical characteristics of the achalasia subtypes[8-10]. The frequency of symptoms could be different in Colombia, considering the relatively high prevalence of Chagas disease.

This study aims to describe patients' clinical characteristics, manometric findings, and treatment according to achalasia subtype from a cohort of patients evaluated at a referral hospital for achalasia in Colombia.

METHODS

This observational descriptive study is based on a retrospective cohort that included patients with a manometric diagnosis of achalasia managed in the physiology and gastroenterology unit of Hospital Universitario San Ignacio in Bogotá, Colombia, between January 2016 and December 2020.

Based on the HRM findings, the Chicago 3.0 classification describes four large groups of esophageal motor abnormalities: achalasia, outlet obstruction at the EGJ, major alterations, and minor alterations[5]. This study included patients older than 18 who met the manometric criteria for achalasia according to this protocol[5]. Patients who had previously undergone surgery, dilations, or treatment with botulinum toxin were excluded. The institutional research and ethics committee of Hospital Universitario San Ignacio approved the study (MI 032-2021). Demographic data and information on symptoms were taken from a form systematically completed before entering the procedure.

HRM was performed with Medtronic®, Given Imaging (Medtronic, Los Angeles, California, United States), the same model used to develop the Chicago 3.0 and 4.0 classification. The following metrics were obtained: esophagogastric junction (EGJ) type, upper esophageal sphincter (UES) pressure, lower esophageal sphincter (LES) pressure, relaxation pressure integral (RPI), distal contractility integral (DCI), distal latency (DL) and the presence of complete or incomplete clearance of the bolus. The HRM was interpreted by a training fellow and an esophageal manometry-certified professor following the Chicago criteria version 3.0[5].

The first four seconds of maximum swallowing relaxation were averaged in the 10-second window to define the RPI, which begins with contiguous or non-contiguous UES relaxation, referenced for gastric pressure. Pan-pressurization with an isobaric contour is ≥ 30% mm Hg. Spastic/premature contractions occurred between UES relaxation and the point of contractile deceleration of less than 4.5 seconds associated with an DCI ≥ 450 mm Hg. The DCI was calculated by multiplying the amplitude, duration, and length of the distal esophageal contraction ≥ 20 mm Hg. Incomplete bolus clearance was defined as acid and bolus content that occurs with abnormal peristalsis and impaired salivation[6,7].

According to the Chicago 3.0 classification[5], the achalasia types were defined as follows: type I achalasia as RPI ≥ 15 mm Hg in the supine (primary) position and 100% failed peristaltic contractions without esophageal pressurization; type II achalasia as RPI ≥ 15 mm Hg in the supine (primary) position and 100% failed peristaltic contractions with esophageal pan-pressurization in ≥ 20% of swallows; type III achalasia as RPI ≥ 15 mm Hg in the supine (primary) position and 100% failed peristaltic contractions with spastic/premature contractions in ≥ 20% of swallows.

Additionally, the sphygmogram reports were reviewed from electronic clinical records. For all of them, the esophageal emptying time, termination with the "bird's beak" sign in the distal esophagus, LES stricture, and esophageal diameter (diameter of the lumen ≥ 30 mm)[4] were determined.

Response to treatment was evaluated for each technique used: esophageal dilation (RigiflexTM, Boston Scientific, Massachusetts, United States), Heller's myotomy, and POEM (peroral endoscopic myotomy)[4]. The severity of dysphagia symptoms was analyzed before and after treatment using the Eckardt score[11,12].

Absolute and relative frequencies describe qualitative variables. Quantitative variables such as median and interquartile range (IQR) were considered not to have a normal distribution. The assumption of normality was evaluated using the Kolmogórov-Smirnov test at a significance level of 5%. The Eckardt score was compared before and after the treatment with a paired t-test. Statistical analysis was performed using Stata (Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC).

RESULTS

Eighty-seven patients were included. The demographic, clinical, and manometric characteristics according to the achalasia type are shown in **Table 1**. Most of the patients had a diagnosis of type II achalasia (78.1%), followed by type I (16%) and type III (5.7%). The median age of involvement was 51 years, with a higher proportion of women

Table 1. Clinical and manometric features and esophagram findings in patients diagnosed with achalasia

Variable	Type I n = 14	Type II n = 68	Type III n = 5	Total n = 87
Clinical features				
Age, median (IQR)	51.5 (45-66.2)	43.5 (35-64.5)	57 (49.5-65)	50 (37-65)
Male sex, n (%)	6 (42.9)	31 (44.1)	1 (20.0)	38 (43.6)
Prevalent symptoms, n (%)				
- Dysphagia	6 (42.9)	19 (27.9)	2 (40.0)	27 (31.0)
- Dysphagia + chest pain	2 (14.3)	8 (11.8)	0 (0)	10 (11.5)
- Dysphagia + weight loss	0 (0.0)	1 (1.5)	0 (0)	1 (1.1)
- Dysphagia + chest pain + weight loss	1 (7.1)	10 (14.7)	0 (0)	11 (12.6)
- Dysphagia + chest pain + regurgitation	1 (7.1)	4 (5.9)	0 (0)	5 (5.7)
- Dysphagia + chest pain + weight loss + GERD	1 (7.1)	7 (10.3)	1 (20.0)	9 (10.3)
- Dysphagia + GERD	3 (21.4)	19 (27.9)	2 (40.0)	24 (27.6)
Manometric features				
UES pressure, median (IQR)	55 (35.5-89.5)	65 (47.7-105.0)	46 (35.5-50.0)	63 (46-98)
LES pressure, median (IQR)	29 (21.2-34.5)	35.5 (25.0-48.2)	43 (31.5-56.0)	34 (26-45)
RPI, median (IQR)	23 (18-31.5)	25.5 (19.2-4.7)	23 (19-41)	24 (19-33)
Incomplete bolus clearance, n (%)	14 (100)	68 (100)	5 (100)	87 (100)

LES: lower esophageal sphincter; UES: upper esophageal sphincter; GERD: gastroesophageal reflux disease; RPI: relaxation pressure integral; IQR: interquartile range. Source: The authors.

(56.4%). All presented with dysphagia, an isolated symptom in 31% of the cases. Other symptoms associated with dysphagia were chest pain (40.2%) and regurgitation or heartburn (5.6%). Regarding the manometric findings, the pressure of the UES and LES were similar in all achalasia types. The median RPI was 24 (IQR: 19-33), and bolus clearance was incomplete in all patients evaluated.

Table 2 presents the findings of the esophagogram, where imaging was available. In type I achalasia, esophageal dilation was not found, while 81.8% of the patients had it in type II achalasia. The bird's beak sign was present in 68.3% of the patients.

Response to treatment was assessed in 35 patients. The therapeutic option and the symptomatic response to the established treatment are shown in **Table 3**. For all achalasia types, Heller's myotomy was the most widely used intervention, and in all patients, the symptoms improved significantly, regardless of the treatment used. Eckardt median pretreatment was 5 (IQR: 5-6), and posttreatment was 1 (IQR: 1-2). Changes were similar in both type I achalasia patients (Eckardt mean 5.8 ± 2.0 vs. 1.4 ± 0.5; $p = 0.009$) and type II achalasia patients (Eckardt mean 5.7 ± 1.4 vs. 1.6 ± 0.8, $p < 0.001$).

DISCUSSION

Achalasia is a primary esophageal motor disorder of unknown etiology characterized by degeneration of the myenteric plexus, resulting in impaired relaxation of the EGJ, along with loss of organized peristalsis in the esophageal body. The most common form of achalasia is idiopathic and is seen mainly sporadically. This disorder can also be secondary to chronic infection by *Trypanosoma cruzi*, considered endemic in Latin America. Still, achalasia secondary to Chagas disease in Colombia has been reported with a low frequency of 13.1% of cases[13].

Most of our patients were women (56%), a finding that differs slightly from the world population, in which it occurs equally among men and women[4]. The average age of involvement was 51 years, which is related to other population groups, with averages of 20 to 60 years[4], and was similar for the achalasia subtypes, different from what

Table 2. Esophagram features in patients diagnosed with achalasia

Variable	Type I n = 6	Type II n = 33	Type III n = 2	Total n = 41
LES stricture, n (%)	6 (100)	6 (18.2)	1 (50.0)	13 (31.7)
Esophageal dilation and LES stricture, n (%)	-	27 (81.8)	1 (50.0)	28 (68.3)
Time between diagnostic esophageal manometry and esophagram, median number of days (IQR)	71 (4.5-143.5)	77 (30-126)	76.5 (58.7-94.2)	72 (17-120)

LES: lower esophageal sphincter; IQR: interquartile range. Source: The authors.

Table 3. Treatment of achalasia and change in dysphagia according to the Eckardt score after treatment in patients diagnosed with achalasia

Variable	Type I n = 5	Type II n = 29	Type III n = 1	Total n = 35
Treatment performed, n (%)				
- Esophageal dilation	1 (20.0)	9 (31.0)	-	10 (28.6)
- Heller's myotomy	4 (80.0)	19 (65.5)	1 (100)	24 (68.5)
- POEM	-	1 (3.4)	-	1 (2.9)
Eckardt pretreatment, median (IQR)	6 (4-6)	5 (5-6)	9	5 (5-6)
Eckardt posttreatment, median (IQR)	1 (1-2)	1 (1-2)	2	1 (1-2)
Days between treatment and posttreatment Eckardt measurement, median (IQR)	104 (86-149)	35 (27-68)	103	40 (27-90)

POEM: peroral endoscopic myotomy; IQR: interquartile range. Source: The authors.

was reported in Arab and French studies, whose patients with subtype I tend to be younger[14].

The most frequent symptom was dysphagia, followed by chest pain and symptoms of gastroesophageal reflux disease (GERD), findings similar to those published in the literature[4,15]. The HRM achalasia subtypes exhibited similar clinical symptoms, as described in a cohort of 108 patients in North America[16]. We also found that esophageal dilatation was much more prevalent in type II achalasia, as already reported in this population.

It is known that the severity of the symptoms can be evaluated by the Eckardt score, which makes it possible to assess and predict the response to treatment. A score ≥ 9 points indicates a failed POEM with a sensitivity of 87.5% (95% confidence interval [CI]: 47.3%-99.7%) and a specificity of 73.8% (95% CI: 64.4%-81.9%). A score of 0-1 corresponds to stage 0, 2-3 to stage I, 4-6 to stage II, and greater than 6 to stage III[11,12]. The present study found that symptoms improved significantly after the intervention in both type I and type II achalasia, regardless of the therapeutic intervention. These findings were consistent with data published by other authors[4,17-19]. Some authors have reported that the success rate with pneumatic dilation may be significantly higher in subtype II, compared to the other subtypes, and laparoscopic Heller myotomy could be the best treatment in subtype III[20,21]; however, further studies will be required to confirm these findings.

Our study is the largest in patients with achalasia in Colombia; however, we acknowledge that the sample size is relatively small for comparisons or formal hypothesis testing, including assessment of treatment response.

Despite the limitations, our data are remarkably similar to those found in the literature, suggesting that achalasia in Colombia behaves similarly to that reported in other parts of the world. More extensive multicenter studies will be required to evaluate the treatment response according to the achalasia type and treatment used.

Conflicts of interest

We state no conflicts of interest.

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Original article

Characteristics and Factors Associated with Inflammatory Activity on Liver Biopsy in Autoimmune Hepatitis Patients Aged 50 Years or Older

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Abstract

Introduction: Autoimmune hepatitis is a liver inflammatory disorder characterized by portal lymphoplasmacytic hepatitis with interface activity and lobular inflammation. **Objective:** The objective of this study is to identify clinical features associated with advanced age and significant inflammation in liver histology. **Methods:** This cross-sectional analytical study evaluated the medical records of adult patients with hepatitis who received treatment in the gastroenterology and hepatology ward of a tertiary university hospital. Bivariate analysis was conducted to identify characteristics associated with an age of 50 years or older and significant histological inflammatory activity. **Results:** A total of 47 patients were included, with a mean age of 42.8 ± 16.0 (43.0) years. Among them, 80.9% were women, and 31.9% were 50 years or older. Liver biopsy was performed on 31 patients, and 29.0% exhibited significant inflammation. When comparing age groups, individuals aged 50 years and older had a higher median γ-glutamyl transferase (GGT; 129 vs. 282 U/L; p = 0.034) and a higher proportion of significant inflammation (50% vs. 6.7%; *p* = 0.024). Patients with significant inflammation on liver biopsy had a higher mean age (63.7 ± 14.0 vs. 41.0 ± 14.4; p = 0.001) and a higher proportion of patients aged 50 years or older (85.7% vs. 66.7%; *p* = 0.024) compared to those with mild inflammation. **Conclusions:** Individuals aged 50 years and older exhibited a higher median GGT and a greater proportion of significant inflammation in liver histology.

Keywords

Autoimmune hepatitis, inflammation, γ-glutamyl transferase, aging.

INTRODUCTION

Autoimmune hepatitis is an inflammatory disorder of the liver that is likely to affect young and middle-aged women at a ratio of 2.4:0.9 compared to men[(1)]. It is characterized by histological and serological changes and the presence of autoantibodies in some patients[(2)]. Aminotransferases (formerly called *transaminases*) are located in hepatocytes and, when elevated, are sensitive indicators of hepatocyte injury[(3)]. On serum electrophoresis, approximately 80% of patients are expected to show hypergammaglobulinemia[(4)]. Antinuclear antibodies, smooth muscle antibodies, and liver and kidney microsomal antibodies may be present[(5)]. A liver biopsy is recommended unless the patient has contraindications, and the typical findings are interface hepatitis, rosettes, and plasma cell infiltration[(6)].

The accentuated liver inflammation may result in cirrhosis by activating stellate cells responsible for producing fibrotic tissue, as they are the primary source of liver myofibroblasts. The fibrosis process can be triggered by the

persistent presence of inflammatory cells such as infiltrating macrophages, hepatic macrophages (Kupffer cells), lymphocytes, and neutrophils[7]. Clinically, the challenge is finding markers that can be both sensitive and specific in predicting significant liver disease from the standpoint of inflammation and fibrosis.

This study aims to identify clinical features associated with age 50 or older and significant inflammation in liver histology.

MATERIALS AND METHODS

This analytical cross-sectional study evaluated medical records of adult patients with autoimmune hepatitis treated at the Gastroenterology and Hepatology Service of a tertiary referral University Hospital between January 2015 and December 2017. Patients with insufficient clinical and laboratory data in the medical records and patients who refused to participate were excluded.

The included individuals were analyzed regarding clinical, laboratory, and histological characteristics and their therapeutic response. Revised international criteria of the International Autoimmune Hepatitis Group were used to diagnose autoimmune hepatitis[8]. Data were collected from medical records and transferred to the Statistical Package for the Social Sciences (SPSS), v. 17.0 (Chicago, Illinois, United States). This study considered the following variables: age, sex, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), γ-glutamyl transferase (GGT), direct bilirubin (DB), serum albumin, prothrombin time (PT), antinuclear antibody, anti-smooth muscle antibody, and liver and kidney microsomal type 1antibodies (Anti-LKM1). ALT and AST were analyzed by the Clinical Chemistry System Dimension®, with ALTI Flex® and AST Flex® reagents at 37 °C. AP, GGT, DB, and serum albumin were also analyzed by the Clinical Chemistry System Dimension® at 37 °C. The reagent used for ALP was ALPI Flex®, and for DB, DBI Flex®. The PT was analyzed with a RecombiPlastin 2G® kit. All liver biochemical tests (AST, ALT, ALP, and GGT) were expressed in absolute numbers and three times the upper limit of normality (3 x ULN).

Regarding liver biopsy, the Brazilian Society of Pathology and Hepatology histological classification was used[9]. The following histological characteristics were observed: significant fibrosis (F ≥ 2), defined as a fibrotic portal expansion with portoportal septa or portocentral fibrotic septa or complete nodules; important portal inflammatory infiltrate (PII ≥ 2), defined as a sharp or very sharp increase in the number of portal lymphocytes; significant periportal inflammatory activity (PPA ≥ 2), defined as interface hepatitis or fragmentary necrosis, which may be discrete or present in extensive areas of numerous portal areas; and significant parenchymal inflammatory activity (PA ≥ 2), defined as focal necrosis of hepatocytes, surrounded by lymphohistiocytic aggregates at innumerable sites, with or without confluent necrosis, which may be extensive or multiple. Similarly, *significant inflammation* was defined as considerable inflammatory infiltrate, significant periportal inflammatory activity, and significant parenchymal inflammatory activity.

Statistical analysis

Continuous variables were described with central tendency and dispersion measures, while categorical variables were expressed in absolute numbers and proportions. Continuous variables were compared using Student's t or Mann-Whitney U test, and categorical variables using chi-square or Fisher's exact test when appropriate. A bivariate analysis was performed to identify characteristics associated with age equal to or greater than 50 and significant histological inflammatory activity. Spearman's correlation analysis was performed to determine whether biochemical and liver function tests were correlated with age. *P* values less than 0.05 were considered statistically significant. All the tests were biflow and ran by SPSS, v. 17.0 (SPSS; Chicago, Illinois, United States).

This study protocol conforms to the ethical recommendations of the Declaration of Helsinki of 1975 and was approved by the university's ethics and human research committee, number 1,147,617.

RESULTS

Case study analysis

Fifty-eight patients with autoimmune hepatitis were evaluated in the study period to decide whether they would be included. Eleven were excluded due to insufficient clinical and laboratory data. Forty-seven patients were included; their mean, standard deviation and median age were 42.8 ± 16.0 (43.0) years, and 80.9% were women.

Regarding liver biochemistry (**Table 1**), the individuals had the following means, standard deviations, and medians: AST: 428.1 ± 475.5 (175.0) U/L; ALT: 372.1 ± 355.9 (250.5) U/L; ALP: 209.4 ± 122.0 (185.0) U/L; GGT: 237.7 ± 256.1 (180.0) U/L; DB: 3.6 ± 4.6 (1.2) mg/dL; blood pressure (BP): 57.6 ± 21.9 (60.3); albumin 3.4 ± 0.9 (3.5) g/L; γ-globulins: 2.8 ± 4.0 (1.8) g/L.

Regarding the antibodies, 58.7% featured a positive antinuclear antibody with titers ranging between 1:80 and 1:2560, 78.3% with a speckled pattern, 17.4% with a homogeneous pattern, and 4.3% with a filamentous pattern. Anti-

smooth muscle antibody was positive in 52.2%, and 7.3% had positive anti-LKM-1. A few patients had more than one active antibody. Its distribution is shown in **Figure 1**.

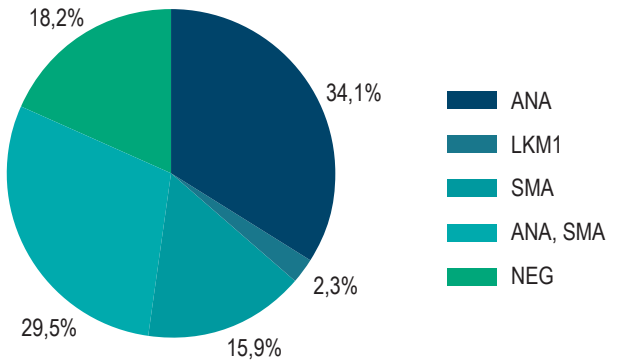

Figure 1. Distribution of the autoantibody profile in 58 patients with autoimmune hepatitis. ANA: antinuclear antibody; LKM-1: liver and kidney antimicrosomal antibody; SMA: anti-smooth muscle antibody; NEG: negative. Source: The authors.

Table 1. Clinical and laboratory features of 47 patients with autoimmune hepatitis

Clinical features	%	Mean ± SD	Median
Female	80,9		
Age		42,8 ± 16,0	43,0
AST (U/L)		428,1 ± 475,5	175,0
ALT (U/L)		372,1 ± 355,9	250,5
ALP (U/L)		209,4 ± 122,0	185,0
GGT (U/L)		237,7 ± 256,1	180,0
DB (mg/dL)		3,6 ± 4,6	1,2
PA (%)		57,6 ± 21,9	60,3
Albumin (g/L)		3,4 ± 0,9	3,5
γ-globulins (g/L)		2,8 ± 4,0	1,8
Histological features (n = 31)			
Significant fibrosis	64,5		
Significant periportal activity	60,0		
Significant parenchymal activity	33,3		
Significant portal inflammatory infiltrate	27,3		
Rosettes	18,5		
Plasma cell infiltrate	62,0		

AST: aspartate aminotransferase; ALT: alanine aminotransferase; ALP: alkaline phosphatase; DB: direct bilirubin; GGT: γ-glutamyl transpeptidase; PA: prothrombin activity. Source: The authors.

Thirty-one individuals underwent liver biopsy, and ten (32.3%) presented with cirrhosis. Significant fibrosis (F ≥ 2) was found in 64.5%, as well as significant periportal activity (PPA ≥ 2) in 60.0% of the patients. 33.3% had significant parenchymal activity (PA ≥ 2), and 27.3% had significant portal inflammatory infiltrate (PII ≥ 2). Plasmocytes were found in 62% and hepatic rosettes in 18.5% of the patients.

Features associated with age equal to or greater than 50

When compared in terms of age (**Table 2**), individuals aged 50 or older had higher median GGTs (129 vs. 282 U/L; $p = 0.034$), and a higher proportion of individuals had GGT levels equal to or greater than three times the UPN (92.3% vs. 50%; $p = 0.013$). Regarding the histological findings of liver biopsies, patients aged 50 years or older showed a higher proportion of significant periportal inflammatory activity (83.3% vs. 38.5%; $p = 0.041$), significant parenchymal activity (58.3% vs. 13.3%; $p = 0.037$), significant portal inflammatory infiltrate (50.0% vs. 8.3%; $p = 0.029$) and, therefore, a higher proportion of significant inflammation (50% vs. to 6.7%, $p = 0.024$).

Using Spearman's rank order correlation method, no relationship was found between age and biochemical (ALT, AST, FA, GGT) or function (BD, ALP, and albumin) test values.

Features associated with significant inflammation

When comparing individuals with significant inflammation in the liver biopsy and individuals with mild inflammation (**Table 3**), the first group had a higher mean age (63.7 ± 14.0 vs. 41.0 ± 14.4; $p = 0.001$), with a higher proportion of patients equal to or older than 50 years (85.7% vs. 66.7%; $p = 0.024$). There was no significant difference between the two groups regarding sex, biochemical tests, function tests, γ-globulins, autoantibodies, and significant fibrosis.

DISCUSSION

GGT is a well-known, established serum marker for steatosis and alcohol-related diseases. When associated with elevated alkaline phosphatase levels, it indicates cholestasis, highly suggestive of intra- or extrahepatic biliary injury. GGT, found in hepatocytes and biliary epithelial cells, is a sensitive marker for biliary tract diseases such as cholestasis, but not very specific[10]. It was also elevated in extrahepatic conditions such as acute coronary syndrome, renal failure, diabetes, dementia, and pancreatic disease. However, in these conditions, GGT is more likely to have increased due to oxidative stress caused by changes in homeostasis, thus leading to cell destruction, damage, and death[11,12]. Some drugs can also increase the levels of GGT in the blood[13].

Table 2. Clinical and laboratory features associated with age over 50 of 47 patients with autoimmune hepatitis

Features	< 50 years n = 32	≥ 50 years n = 15	p†
Female (%)	81,3	80,0	1,000
AST (U/L)*	464,9 ± 505,4 (230)	346,2 ± 407,2 (128)	0,461
AST 3 x ULN (%)	62,1	69,2	0,739
ALT (U/L)*	422,9 ± 410,5 (265)	267,1 ± 168,5 (211)	0,076
ALT 3 x ULN (%)	71,0	73,3	1,000
ALP (U/L)*	203,8 ± 136,5 (179)	218,5 ± 97,6 (219)	0,287
ALP 3 x ULN (%)	13,0	7,1	1,000
GGT (U/L)*	220,9 ± 294,5 (129)	271,4 ± 158,8 (282)	**0,034**
GGT 3 x ULN (%)	50,0	92,3	**0,013**
DB (mg/dL)*	3,6 ± 4,1 (1,7)	3,6 ± 5,8 (1,2)	0,784
PA (%)*	52,7 ± 27,2 (54)	64,3 ± 9 (66)	0,142
Albumin (g/L)*	3,5 ± 1,0 (3,5)	3,4 ± 0,8 (3,6)	0,795
γ-globulins (g/L)*	2,0 ± 0,9 (1,8)	4,3 ± 6,7 (2,0)	0,289
Non-organ specific autoantibodies			
ANA (%)	51,6	73,3	0,161
ANA titers ≥ 1:320 (%)	50,0	54,5	0,816
SMA (%)	48,4	60,0	0,460
LKM-1 (%)	7,1	7,7	1,000
Histological features (n = 31)			
Significant fibrosis	61,1	69,2	0,718
Significant periportal activity	38,5	83,3	**0,041**
Significant parenchymal activity	13,3	58,3	**0,037**
Significant portal inflammatory infiltrate	8,3	50,0	**0,029**

*mean ± standard deviation (median).† Pearson's chi-square test, Fisher's exact test, t-test, or Mann-Whitney U test, when applicable. 3 x ULN: three times the upper limit of normality; ALT: alanine aminotransferase; ALP: alkaline phosphatase; ANA: antinuclear antibody; AST: aspartate aminotransferase; GGT: γ-glutamyl transpeptidase; DB: direct bilirubin; LKM-1: liver-kidney microsome type 1; PA: prothrombin activity; SMA: smooth muscle antibody. Source: The authors.

Table 3. Clinical and laboratory features associated with significant inflammation in 31 biopsied patients with autoimmune hepatitis

Features	Little inflammation n = 22	Significant inflammation n = 9	p†
Female (%)	85,0	71,4	0,580
Age (years)*	41,0 ± 14,4 (40,0)	63,7 ± 14,0 (59,0)	**0,001**
≥ 50 years (%)	30,0	85,7	**0,024**
AST (U/L)*	565,2 ± 554,9 (293,5)	494,0 ± 543,8 (210,5)	0,787
AST 3 x ULN (%)	66,7	83,3	0,629
ALT (U/L)*	427,3 ± 419,5 (307,5)	388,3 ± 265,4 (439)	0,821
ALT 3 x ULN (%)	75,0	85,7	1,000
ALP (U/L)*	182,7 ± 102,1 (179)	263,9 ± 98,5 (235)	0,095
ALP 3 x ULN (%)	6,7	14,3	1,000
GGT (U/L)*	189,4 ± 150,3 (155)	292,1 ± 200,1 (293)	0,193
GGT 3 x ULN (%)	60,0	85,7	0,350
DB (mg/dL)*	4,4 ± 5,7 (1,9)	3,9 ± 3,2 (0,8)	0,526
PA (%)*	57,7 ± 19,9 (59)	54,7 ± 28,8 (64)	0,818
Albumin (g/L)*	3,6 ± 0,9 (3,6)	3,0 ± 0,9 (2,9)	0,241
γ-globulins (g/L)*	2,0 ± 1,0 (1,7)	2,6 ± 1,2 (2,6)	0,280
Non-organ specific autoantibodies			
ANA (%)	50,0	71,4	0,408
ANA titers ≥ 1:320 (%)	80,0	40,0	0,251
SMA (%)	40,0	85,7	0,077
LKM-1 (%)	5,6	0,0	1,000
Histological features			
Significant fibrosis	52,6	66,7	0,661

*mean ± standard deviation (median).† Pearson's chi-square test, Fisher's exact test, t-test, or Mann-Whitney U test, when applicable. 3 x ULN: three times the upper limit of normal; ALT: alanine aminotransferase; ALP: alkaline phosphatase; ANA: antinuclear antibody; AST: aspartate aminotransferase; GGT: γ-glutamyl transpeptidase; DB: direct bilirubin; LKM-1: liver-kidney microsome type 1; PA: prothrombin activity; SMA: smooth muscle antibody. Source: The authors.

Previous studies have shown a significant association between GGT levels and AST in patients with hepatitis C[14-16]. Another study has shown that a substantial number of patients with chronic hepatitis C virus (HCV) infection had elevated levels of serum GGT and a more intense level of necroinflammatory activity in patients with higher GGT. Thus, this enzyme has been proposed as a surrogate marker of significant inflammation in chronic hepatitis C[17]. Although these

are remarkable results, no studies indicate the role of GGT in the level of inflammation and fibrosis/chronic disease in patients diagnosed with autoimmune hepatitis.

A retrospective study of 23,597 healthy individuals found that the medians and interquartile ratios were higher in the very young compared with those 60 years of age or older (27.1 [18.8-41.7] vs. 22.5 [16.3-32.7] U/L, $p < 0.001$)[18]. This finding suggests that the observation of higher GGT levels in older patients in our study reflects the higher inflammatory activity found in this group, not age itself.

Autoimmune hepatitis is generally characterized by a bimodal age pattern at the onset, with a peak in children and adolescents and a second in midlife (fourth to sixth decades and especially in postmenopausal women). However, a considerably increasing number of patients are even older than 65-70 years[19]. Few studies have evaluated the clinical features of autoimmune hepatitis in older adults. In the Italian elderly, autoimmune hepatitis is usually asymptomatic, although the prognosis and response to treatment are like those of younger patients. However, no difference was observed in liver disease's histological/biochemical expression[20]. Onset at an early age, acute manifestation, hyperbilirubinemia, and the presence of HLA DRB1*03 characterize patients who fail corticosteroid treatment[21]. A North American study assessed 205 adults with defined autoimmune hepatitis type 1 and grouped them according to age of manifestation. Twenty-three percent of the patients were ≥ 60, and 15% were ≤ 30. Patients ≥ 60 years had a higher frequency of cirrhosis at onset than patients ≤ 30 years (33% vs. 10%, $p = 0.03$) and also failed corticosteroid treatment less frequently than patients ≤ 30 years (5% vs. 24%, $p = 0.03$)[22].

In China, elderly autoimmune patients have a higher frequency of cirrhosis at onset and a lower occurrence of treatment failure. Older patients had similar mean GGT levels (112.8 ± 82.8 vs. 121.9 ± 103.2 U/L; $p = 0.146$), and histological features were not evaluated[23]. In the United Kingdom, 164 patients with autoimmune liver disease were evaluated. When individuals aged 40 years or older were compared with those younger than 40 years, similar mean GGT levels (103.5 [8-820] vs. 190 [29-995] U/L; $p = 0.040$) and similar levels of histological grade of necroinflammatory activity (2 vs. 2 [mild]; p = 0.022), different data were observed in older patients[24] than those in the present study. A systematic review and meta-analysis demonstrated that GGT levels do not differ when comparing the elderly with the young (30 vs. 27 U/L; $p = 0.039$), and histological features were not examined[25].

A liver biopsy is necessary to diagnose autoimmune hepatitis, and establishing this diagnosis without histology should be an exception and limited to special clinical situations[26]. Portal lymphoplasmacytic hepatitis with interface activity and lobular inflammation is frequently found in autoimmune hepatitis[26,27]. Recently, severe necroinflammatory activity in autoimmune hepatitis has been associated with a serum level of 25(OH)D[28]. Unfortunately, vitamin D levels were not available in this study. When patients with hepatitis C were studied, severe interface hepatitis was associated with epidemiological features such as older age at both infection and biopsy and a higher prevalence of blood transfusion and alcohol abuse[29]. Also, in patients with hepatitis C, age > 40 years and the degree of inflammatory activity were associated with elevated levels of GGT[17].

In conclusion, individuals 50 or older had higher median GGT and a higher proportion of significant inflammation on liver histology. Moreover, considerable inflammation on liver biopsy was associated with advanced age.

Conflicts of interest

The authors state no conflict of interest.

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Review article

Rationality for the Use of Neuromodulation in Disorders of Gut-Brain Interaction (Functional Gastrointestinal Disorders)

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Abstract

Within the broad range of therapeutic options for managing functional gastrointestinal disorders, recently redefined as Disorders of Gut-Brain Interaction (DGBI) by the Rome Foundation in the Rome IV criteria, certain medications with antidepressant, anxiolytic, or antipsychotic effects are commonly employed. These drugs, now referred to as neuromodulators by the Rome Foundation, target the neurogastroenterological dysfunction associated with these disorders. Consequently, their clinical utility as psychiatric medications can now be leveraged to benefit patients with DGBI.

This narrative review aims to provide an updated and specific overview of the indications for neuromodulators in the primary DGBI. The first section of this review focuses on the rationale and justification for their use.

Keywords

Functional gastrointestinal disorders, neuromodulation, antidepressants.

INTRODUCTION

Digestive functional disorders have been redefined by the Rome Foundation in the Rome IV criteria with a new terminology called the *disorders of gut-brain interaction* (DGBI)[(1)], and these are the most common diagnoses in gastroenterology. These conditions are highly prevalent and affect up to 40% of people at any given time, and two-thirds of these people will have chronic and fluctuating symptoms, some of them of great intensity[(1)]. Given the broad spectrum of therapeutic possibilities with which DGBIs are addressed, the concept of *neuromodulation*, with drugs acting on the neurogastroenterological dysfunction of these disorders, extending from the central nervous system (CNS) to the enteric nervous system (ENS), has also been renamed by the Rome Foundation[(2)] since their use as psychiatric drugs in order to remove the stigma from them and take advantage of their therapeutic benefits.

This review aims to update and specify the indications for neuromodulators in the main DGBIs, and this first section addresses the reasons for their use.

RATIONALE

Brain-gut axis, its bases

The gastrointestinal (GI) tract has the vital function of acquiring nutrients through its motor, secretory, and absorptive functions. It constitutes a barrier for the luminal content that protects against potentially pathogenic and antigenic substances or substrates of food or own microbiota[3]. All of the above requires monitoring events in the intestinal wall and within the intestinal lumen to orchestrate reflexes that elicit appropriate patterns of motility, absorption, secretion, and blood flow to digest and absorb or to dilute and expel GI contents. The ENS and immune system mechanisms play a critical role in activating these reflexes by relaying sensory information to enteric reflex circuits, which provide local control and then inform the CNS to provide an afferent response via afferent pathways[3-5].

Enteric nervous system

It is universally known as the *intestinal brain*; it has a hierarchical neural organization whose objective is to regulate time after time the activity of GI glands, muscles, and circulation in such a way that patterns of secretion and motility are generated during the states and phases of digestion and interprandial periods[6,7]. The ENS has synaptic connections between sensory neurons, interneurons, and motor neurons. Interneurons are synaptically interconnected in neural networks, which process information about the state of the gut and contain a "library" of programs for different behavior patterns. Motor neurons innervate muscle, secretory glands, and blood vessels. The musculomotor neurons initiate or inhibit the contractile activity of the musculature and determine its force of contraction minute by minute. Secretory motor neurons stimulate the secretory glands to secrete chloride, bicarbonate, and mucus and determine the osmolarity and fluid content of the lumen[6,7].

The interaction of the SNE with the interstitial cells of Cajal (ICC) is a determining factor of each motility program stored in their library. ICCs are non-neuronal pacemaker cells that connect to form syncytial electrical networks that extend around the circumference and the long axis of the small and large intestines. ICC networks generate pacemaker electrical potentials (also called *slow electrical waves*) that spread across gap junctions in circular or longitudinal intestinal muscle, depolarizing the muscle to the threshold action potential and triggering contractions[8]. Generally, a normal ENS is essential for a healthy gut and the absence of irritating symptoms, such as those associated with the diagnostic criteria for any DGBI. Any neuropathic change in the ENS will most likely result in symptomatic bowel. Functional propulsive motility and its integration with specialized secretory functions cannot work without the ENS[7]. Pain originating in the GI tract ascends to the brain via the same trineuronal pathways that transmit noxious somatic stimuli (**Figure 1**).

Central processing via hubs and connectomes

Visceral stimuli from the periphery are transmitted to the dorsal horn of the spinal cord, where the first synapse occurs. The last primary synapse occurs on cell bodies within the brain. For the spinothalamic tract, the third-order neuron is within the thalamus, which acts as the main hub for the central pain matrix[9]. The thalamus is anatomically organized so that noxious signals from the spinal cord are sent to specific regions of the primary somatosensory cortex for signal localization. In contrast, cortical localization of visceral pain is typically less precise since the ascending signal from the spinal cord innervates at multiple levels, and visceral pain signal sources and somatic sources can be transmitted by the spinal cord and second-order neurons (viscerosomatic convergence). Within the central pain matrix, the thalamus sends signals to brain regions that process the emotional component of the pain signal, such as the amygdala, insula, anterior cingulate cortex, hippocampus, and nucleus *accumbens*. Under normal conditions, activating the central pain matrix provides the appropriate behavioral responses (unpleasant emotion, vigilance, or immobilization of the affected site) to promote recovery and learn to avoid it to prevent future injuries[3,9].

Currently, the interconnectivity of pain (visceral and somatic signals) processing nuclei and matrices seeks to be interpreted under the concept of *connectomes*[10], which bring together particular functional and neuroanatomical areas responsible for this function, as verified through multiple neuroimaging[11,12].

The afferent response after central processing is directed by descending projections from brainstem nuclei, including the periaqueductal gray, raphe nucleus, locus coeruleus, and lateral rostral ventral medulla down to the dorsal horn of the spinal cord, which modulates the transmission of afferent pain at the level of the first synapse. These descending pathways are controlled top-down by brain regions, particularly the amygdala and perigenual anterior cingulate cortex. Notably, these projections are primarily opioid, noradrenergic, and serotonergic in nature; as noted below, antidepressants can profoundly interfere with these modulatory processes (**Figure 2**)[3].

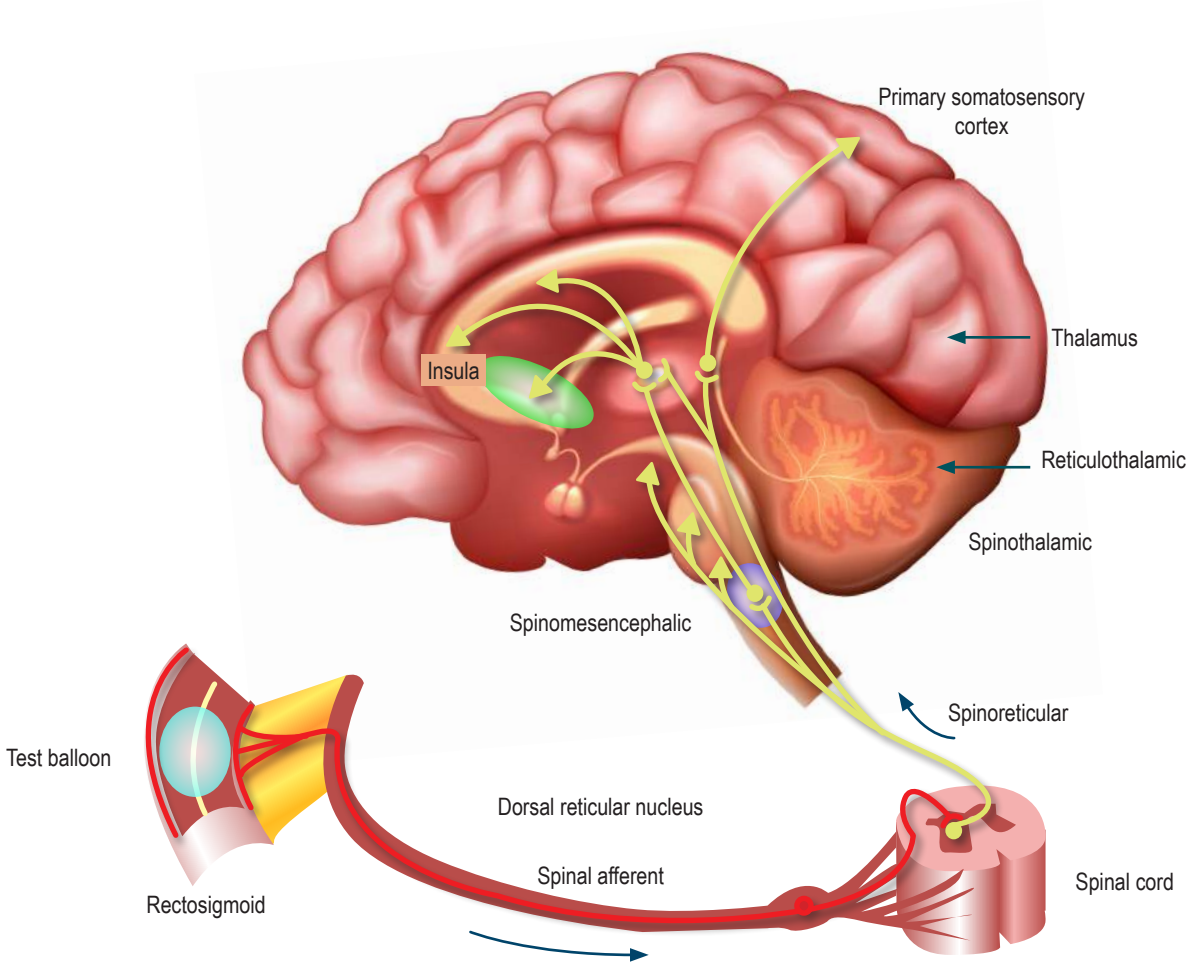

Figure 1. Afferent neural pathways in the DGBI[2]. Modified with permission from: Drossman DA et al. Gastroenterology. 2018;154(4):1140-1171.e1.

Hypersensitivity: Peripheral and central sensitization

Following an inflammatory event or GI injury, sensory neurons express receptors activated by mediators released from various source cells within the intestinal wall. Neurotrophins, for example, may play a role in axonal conduction and remodeling of sensory innervation after noxa. Both nerve growth factor and glial-derived neurotrophic factor are important in the adaptive response to nerve injury and inflammation[13]. Many other mediators from blood vessels, muscles, neurons, platelets, leukocytes, lymphocytes, macrophages, mast cells, glia, and fibroblasts are released during inflammation, injury, or ischemia. Some mediators act directly on sensory nerve endings, and others work indirectly, causing the release of other agents from nearby cells. It has been called *sensitizing inflammatory soup* since it contains amines, purines, prostanoids, proteases, and cytokines, which act on sensory nerve terminals to increase mechanical and chemical sensitivity. This activity as neuromediators, together with the neuropeptides that prevail after acute inflammation, induce phenomena known as *ENS neuroplasticity*, which would ultimately be responsible for the perpetuation of peripheral hypersensitivity (**Figure 3**)[13].

It has also been proposed that barrier dysfunction and intestinal permeability allow the passage of products and antigens from the GI microbiota, produce low-grade inflammation with multiple neuroimmune interactions, and can drive signaling and sensitization with hypersensitivity[14]. These afferent stimuli trigger reflexes that coordinate bowel function, such that sensitization can also cause hyperreflexia or dysreflexia and thus impaired transit, resulting in diarrhea or constipation, or both. Peripheral sensitization usually develops rapidly and is relatively short-lived. However, in persistent injury or inflammation, sensitization can be prolonged and lead to changes in gene expression. These genes can alter the expression of channels, receptors, or mediators in sensory neurons that modify the amount

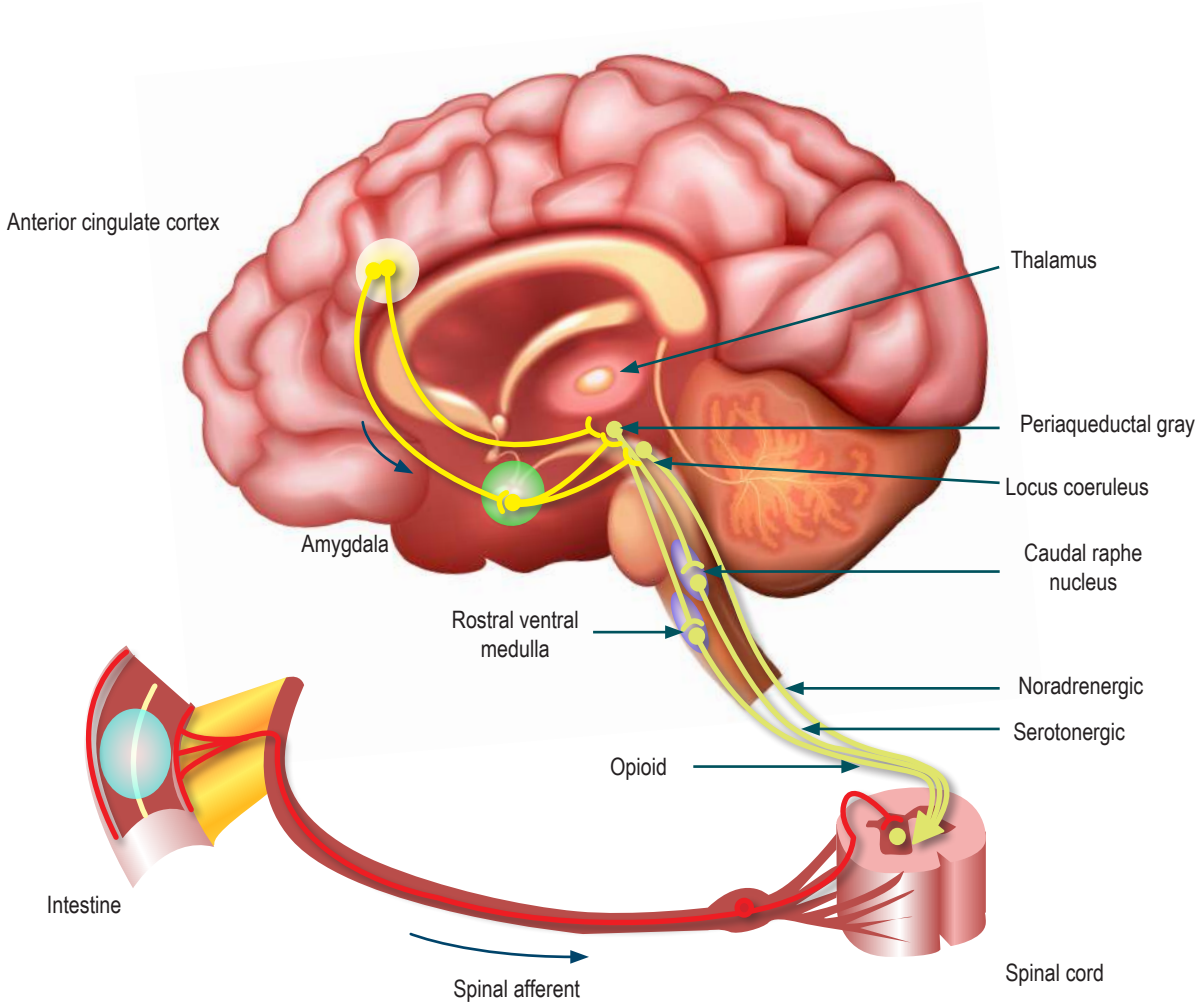

Figure 2. Afferent neural pathways in the DGBI[2]. Modified with permission from: Drossman DA et al. Gastroenterology. 2018;154(4):1140-1171.e1.

and pattern of neurotransmitters released by central nerve terminals in the brain and spinal cord. This changes how sensory signals are processed within the CNS, contributes to "central sensitization," and can prolong hypersensitivity beyond the acute period of injury or inflammation[12,13].

Sensory neurons send visceral signals to the ascending spinal pathways via glutamate and neuropeptide tides. These transmitter mechanisms are upregulated in response to inflammation or injury and contribute to hypersensitivity in the brain and spinal cord, where there are central neuroplastic changes called *central sensitization*, which contribute to chronic pain. Within the dorsal horn of the spinal cord, two mechanisms increase pain signals to the brain: increased synaptic transmission via glutamate, calcitonin gene-related peptide, and substance P in ascending excitatory pathways or decreased descending inhibitory modulation[3].

In the brain, sensitization can occur in second-order spinal neurons, such as the thalamus, periaqueductal gray (PAG), parabrachial nucleus, and locus coeruleus. Increased signaling from those nuclei promotes neuroplasticity and abnormal pain processing within the extended pain matrix (prefrontal cortex [PFC], anterior cingulate cortex, amygdala, insula), amplifying discomfort and negative emotions associated with chronic visceral pain or a decrease in the descending pain inhibitory system through the PAG and rostral ventral medulla[4]. Notably, the amygdala is a critical nucleus that integrates noxious visceral signals with anxiety/fear behaviors, and its hyperactivation could influence multiple central pain matrix nuclei and descending brainstem nuclei that modulate the amygdala function. Numerous neuroimaging studies have also shown functional, connectivity, and structure differences between irritable bowel syndrome (IBS) patients and

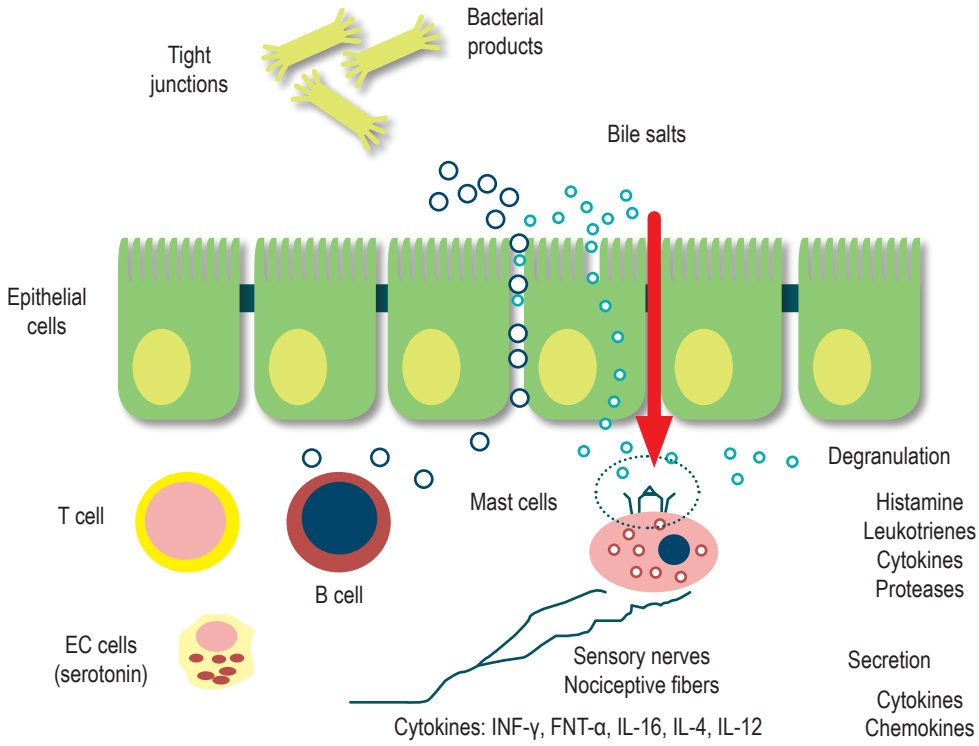

Figure 3. Peripheral sensitization: Intestinal permeability and local inflammatory response[15]. Modified from: Boyer J et al. Neurogastroenterol Motil. 2018;30(1).

healthy controls. Thus, central sensitization may promote chronic abdominal pain in IBS through the remodeling of connections both within the brain and spinal cord[16,17].

The brain-gut axis is the bidirectional neurohumoral communication system between the brain and the gut, which continuously sends signals about homeostatic information and the physiological condition of the digestive system to the brain through afferent (spinal and vagal) and humoral nerves of the ENS or "cerebral gut." Under normal physiological conditions, most of these gut signals are not perceived consciously. However, the subjective experience of visceral pain results from the conscious perception of directed gut-brain signals induced by noxious stimuli. It indicates a potential threat to homeostasis, requiring a behavioral response[18].

Visceral pain perception does not show a linear pattern but rather arises from a complex psychobiological process whereby the intensity of peripheral afferent input is processed and continuously modulated by cognitive and affective circuits in the brain and through descending modulators. These mechanisms help to understand the influence of cognitive and affective processes on the perception of GI symptoms in patients with DGBI and the therapeutic effect of interventions directed at these processes that constitute the basis for understanding DGBI as a model of gut-brain signaling disorders. In addition, dysfunction of these modulatory systems could allow non-noxious physiological stimuli to be perceived as painful or unpleasant (visceral hypersensitivity), leading to chronic visceral pain or discomfort, a hallmark of DGBI symptoms[18].

Aspects of a biopsychosocial model

The rationale for using neuromodulators has an even broader context when the factors contributing to developing functional gastrointestinal disorders (FGID)-DGBI are appreciated. Here, we highlight some of the most relevant: although there is evidence of the contribution of genetic, epigenetic, and cultural components, stressful life events (including sexual abuse, physical abuse, and emotional abuse, particularly during childhood), compared with controls. Patients with IBS report a higher prevalence of this type of adverse event, and, generally, this history is related to greater severity of FGID with worse outcomes, clinical stress, and impairment of daily functioning and quality of life (**Figure 4**)[18,19].

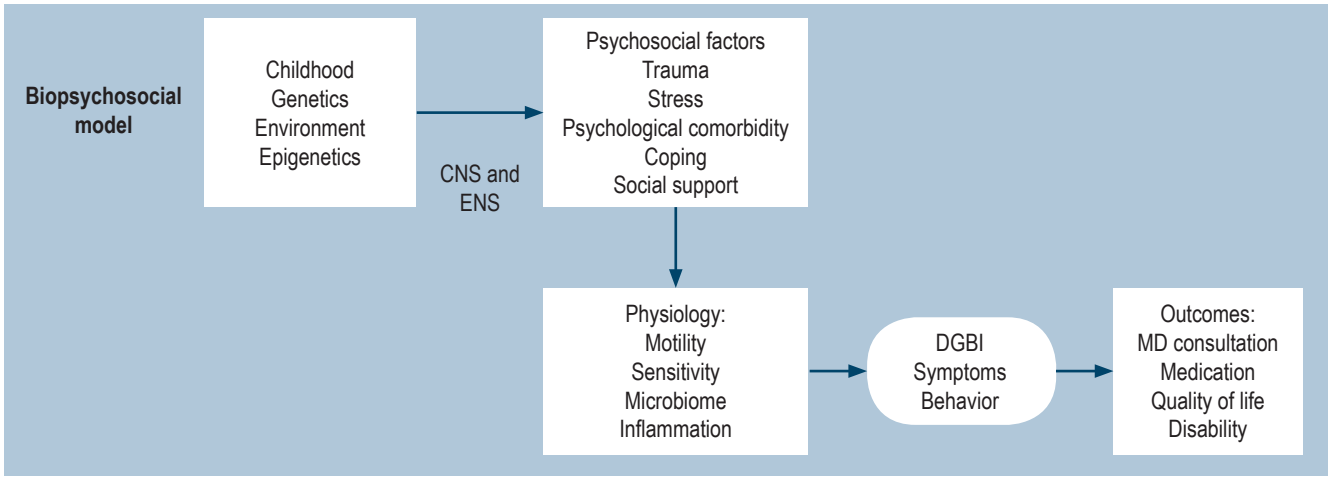

Figure 4. Biopsychosocial model for DGBI[2]. Modified with permission from: Drossman DA et al. Gastroenterology. 2018;154(4):1140-1171.e1.

Affective disorders

The overlap between depression and DGBI is around 30% in primary care settings and slightly higher in tertiary care. Depression can affect the number of functional GI symptoms experienced or DGBI diagnoses. Suicidal ideation is present between 15% and 38% of patients with IBS, and it has been related to hopelessness associated with the perception of the severity of the symptoms, the impact on the quality of life, and the variable and sometimes poor response to treatment. Likewise, the comorbidity of depression has been related to poor outcomes, increased use of medical services and cost of medical care, functional impairment, poor quality of life, and poor commitment to treatment outcomes[20].

Anxiety disorders

They are the most common psychiatric comorbidity in 30%-50% of patients with DGBIs. They can initiate or perpetuate symptoms through their association with arousal in response to stress and alter GI sensitivity and motor function, as well as sensitivity to anxiety itself, hypervigilance of the body, and the ability to tolerate discomfort and pain[20].

Somatic symptom disorder

The Diagnostic Manual of Mental Disorders, 5th Edition, modified the concept of *somatization* in favor of *somatic symptom disorders*. In the new diagnostic category, somatic symptoms may or may not have a medical explanation but are distressing and disabling and are associated with excessive and disproportionate thoughts, feelings, and behaviors for more than six months. This highly controversial approach shifts the experience of medically inexplicable symptoms as (unconscious) manifestations of psychological disorders towards abnormal cognitive and affective processes (e.g., excessive concern about the disease, concern about the body, and hypochondriasis) as contributors and consequences of symptoms[21].

Somatization is associated with GI sensorimotor processes, particularly pain, including gastric tenderness and emptying, symptom severity, and impaired quality of life in functional dyspepsia and IBS. It is also associated with the frequency of use of medical care and predicts a poor response or adherence to treatment. Therefore, assessing somatization by testing the severity of multiple somatic symptoms remains clinically useful. Somatization explains the frequent extraintestinal symptoms of IBS and the high co-occurrence between DGBI and other somatic symptom disorders (SSD), including interstitial cystitis, pelvic pain, headaches, and fibromyalgia[18].

Cognitive-affective processes

Some psychological processes may be superimposed; for example, when they include health anxiety (mainly GI), specific anxiety about other symptoms, attentional bias such as symptom hypervigilance, and catastrophizing have been linked to DGBI regardless of psychiatric comorbidity, and are essential treatment targets for cognitive-behavioral therapy (CBT)[22].

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Case report

Metastatic Crohn's disease: a difficult diagnosis from different perspectives

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Abstract

Metastatic Crohn's disease (MCD) is a rare cutaneous manifestation of Crohn's disease (CD). The simultaneous involvement of the vulva and oral region is uncommon in clinical presentations of MCD. We present the case of a middle-aged woman with a family history of autoimmunity who initially presented with oral and vulvoperineal involvement. Initially, Behçet's disease was ruled out, but histopathological studies of the vulva revealed findings compatible with MCD. The patient had no gastrointestinal symptoms, and fecal calprotectin levels were normal. Upper and lower endoscopic examinations and capsule endoscopy of the small intestine (SI) did not reveal any significant findings. Treatment with anti-tumor necrosis factor (anti-TNF) agents was initiated but resulted in paradoxical psoriasis with adalimumab and infliximab. Cyclosporine was also used, but the patient experienced intolerable tachycardia. After 18 months, the patient developed episcleritis and experienced diarrhea accompanied by cramp-like abdominal pain. Repeat upper and lower endoscopic examinations showed normal results, while capsule endoscopy of the SI revealed CD enteritis. The patient was diagnosed with CD of the small intestine, along with extraintestinal manifestations of vulvoperineal MCD, oral involvement, and episcleritis. Management with azathioprine and ustekinumab was initiated, resulting in significant clinical improvement. MCD poses a diagnostic challenge due to its unusual manifestations. It may present without gastrointestinal tract involvement, mimicking other conditions. Therefore, timely diagnosis and the selection of the most appropriate therapeutic strategy are crucial.

Keywords (DeCS)

Crohn's disease, inflammatory bowel disease, vulva, oral manifestations, cutaneous manifestations, granuloma.

INTRODUCTION

Crohn's disease (CD) is a chronic inflammatory disorder that can affect the entire length of the gastrointestinal (GI) tract from the oral cavity to the anus, characterized by abdominal pain, chronic diarrhea, and weight loss[(1)]. It can present with extraintestinal manifestations (EIMs) in up to 50% of cases, and 25% of the time, they can appear before intestinal involvement[(2)]. Metastatic Crohn's disease (MDC) is a rare cutaneous manifestation, and severe vulvar involvement is rare. It can present with lesions in the oral cavity, such as thrush, ulcers, lip edema, granulomatosis, dry mouth, abscesses in the salivary ducts, erythema, gingivitis, and glossitis. However, the simultaneous involvement of multiple severe oral lesions and the loss of numerous teeth are infrequent[(3,4)], so we present a case of severe oral involvement and vulvoperineal metastasis as the manifestation of CD.

CASE PRESENTATION

This is a female patient in the fourth decade of life with a family history of autoimmunity who presented with severe oral manifestations (**Figure 1**) requiring the extraction of 14 teeth, severe gingivitis (**Figure 2**), smooth tongue and glossitis (**Figure 3**), aphthous stomatitis, ulcers, lip edema, and angular cheilitis (**Figure 4**), without a clear cause on the part of oral pathology. There was associated vulvoperineal involvement (**Figures 5** and **6**) with ulcerated, inflammatory, erythematous, and infiltrated lesions. Behçet's disease was initially suspected, with a negative human leukocyte antigen B51 (HLA-B51) test, negative pathergy test, and no other systemic findings that would suggest it.

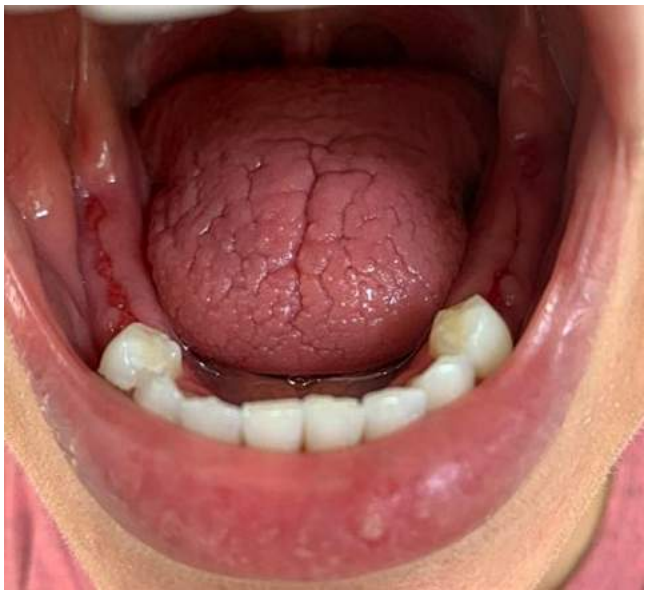

Figure 1. Dorsal tongue with depapilation and deep fissures without ulceration, findings compatible with glossitis resulting from oral xerostomia. Evidence of areas of post-extraction scarring in the lower alveolar ridge mucosa before implant treatment. Common nonspecific oral manifestations associated with inflammatory bowel disease (IBD). Authors' archives.

A vulvar biopsy showed marked edema of the dermis, dilated lymph nodes with perivascular and interstitial lymphoplasmacytic infiltrate, and noncaseating granulomas, negative for microorganisms. The results are compatible with MCD at this level, without gastrointestinal symptoms and calprotectin levels in the stool in normal ranges. Upper and lower endoscopic studies and small bowel (SB) capsule endoscopy were performed without alterations. Dermatology treated the patient with topical steroids and dentistry with dental implants. She was considered a patient with CD-type IBD with severe MEI. Although she did not have intestinal involvement, we decided to start treatment with anti-tumor necrosis factor (anti-TNF), initially with adalimumab, but she developed paradoxical psoriasis. Subsequently, management with infliximab was started again with the manifestation of severe paradoxical psoriasis, for which it was suspended (**Figure 7**). Cyclosporine was also used as an immunomodulator, and she presented with intolerable tachycardia.

Figure 2. Erythematous gums with enlarged interproximal dental papillae of generalized manifestation compatible with the diagnosis of gingivitis. Common nonspecific oral manifestation associated with IBD. Authors' archives.

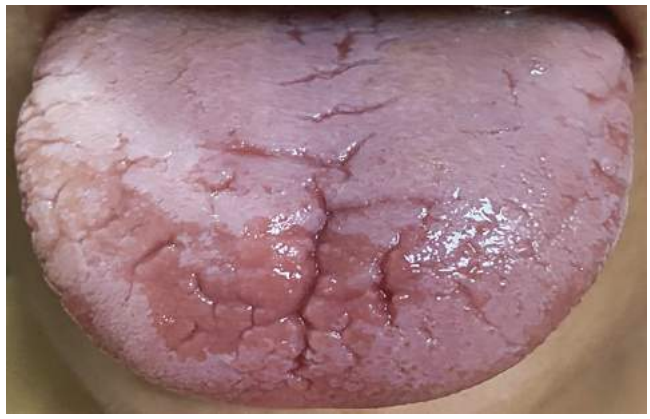

Figure 3. Smooth tongue and glossitis. Common nonspecific oral manifestation associated with IBD. Authors' archives.

Eighteen months after these symptoms, she exhibited episcleritis of the left eye (**Figure 8**) and began with colicky abdominal pain and an average of five diarrheal stools daily. High and low endoscopic studies were performed without alterations and a new SI capsule endoscopy revealed CD enteritis involving the duodenum, jejunum, and ileum (**Figure 9**). Therefore, the patient is considered to have SI CD-type IBD with EIM, vulvoperineal NCD, severe oral involvement, and episcleritis. She is being treated with azathioprine and ustekinumab, with significant clinical improvement.

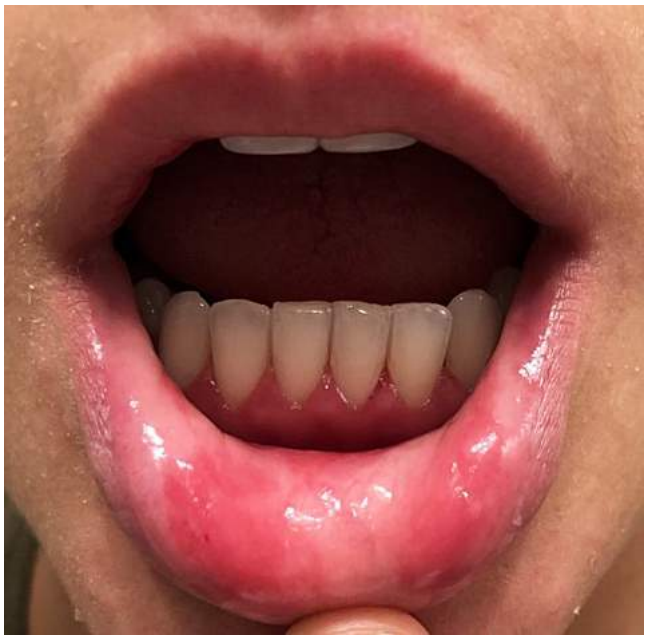

Figure 4. Multiple minor ulcerated lesions compatible with aphthous stomatitis. Authors' archives.

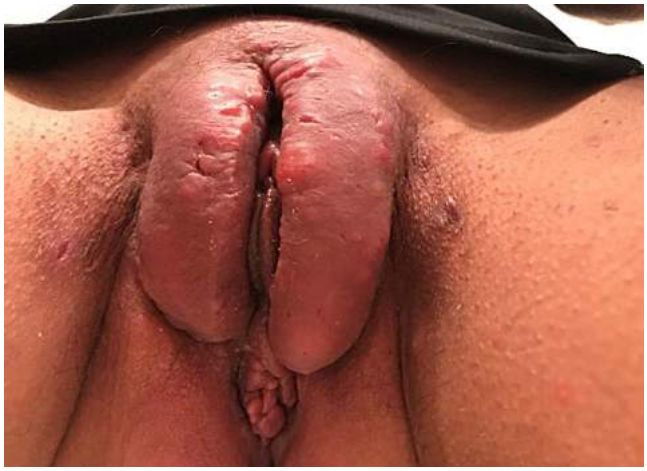

Figure 5. Vulvoperineal MCD involvement. Authors' archives.

DISCUSSION

The most frequent EIMs in CD are of the articular type and associated with colonic involvement. At the same time, severe vulvoperineal and oral MCD are rare, and their combination is scarce without previous intestinal involvement[2]. It has been described that in around 25% of cases of vulvar metastatic CD, its diagnosis may precede digestive CD[5], which complicates the situation and may cause a delay in diagnosis with significant physical, mental, and social morbidity. Thus, a multidisciplinary approach is required. In the description in the literature, there is no clear correlation between the activity of metastatic CD,

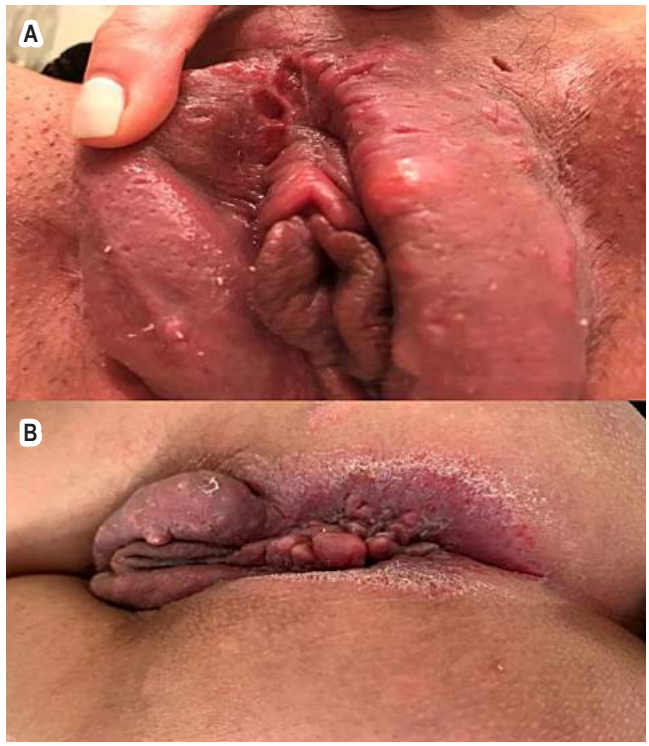

Figure 6. A. Vulvoperineal metastatic Crohn's involvement. **B.** Vulvoperineal MCD involvement. Authors' archives.

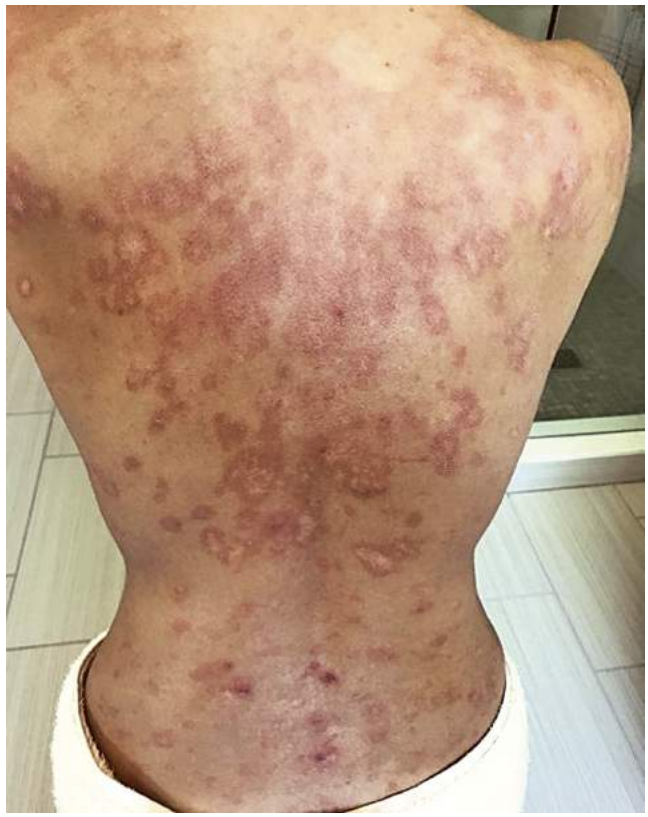

Figure 7. Paradoxical psoriasis secondary to the use of anti-TNF. Authors' archives.

Figure 8. Left eye scleritis. Authors' archives.

the intestinal clinical picture, and other MEI[6]. The clinical spectrum ranges from a mild and self-limited lesion to representing the main reason for consultation, so it conditions the treatment[4]. In the case presented, at the time of onset, the patient was without intestinal activity, and the most relevant clinical data was the cutaneous and mucosal involvement; likewise, articular and ocular manifestations were absent. A high level of suspicion of this GI entity must be maintained even if there are no intestinal manifestations. The refractoriness and severity of this condition require aggressive and comprehensive multidisciplinary management since EIM can become more severe and disabling than intestinal compromise.

MCD is the least frequent cutaneous manifestation of CD. It usually affects young adults. It can manifest as multiple or isolated lesions and affects the genital area and extremities, but it could also appear in any other body part[7]. The lesions can vary in morphology and occur as ulcers, plaques with or without ulceration, papules, or nodules. According to Barrett et al. (8), four main types of vulvar lesions can be observed: vulvar edema, ulceration, hypertrophic lesions in the form of pseudocondylomas acuminata, and chronic suppuration. The most common clinical manifestation is unilateral vulvar edema associated with chronic vulvar ulceration. It is typically asymptomatic, and the diagnosis is made when vulvar ulcers or hypertrophic lesions are discovered on physical examination. However, symptoms such as vulvar pain, pruritus, vulvar discharge, or dyspareunia have been described, as well as irritative urinary symptoms such as dysuria, among others[8]. In the case presented, the patient had ulcerated, inflammatory, erythematous, and infiltrated lesions found on physical examination. Given the suspicion of CD based on the clinical picture and histopathology, we proceeded to search for digestive manifestations of CD.

IBD-associated lesions in the oral cavity may precede intestinal manifestations in CD and become important when diagnosing it. Differential diagnoses are multiple and mainly include mycobacterial infection, hidradenitis suppurativa, pyoderma gangrenosum, erythema nodosum, sarcoidosis, and Behçet's disease[8]. The differential diagnosis with metastatic CD is difficult in the latter due to the tremendous clinical similarity. Because histology sometimes does not allow them to be differentiated[7], the diagnosis must be based on combining the clinical picture with the compatible biopsies. Granulomas in intestinal ulcers are usually employed to diagnose CD, and a positive skin pathergy test shows signs of Behçet's disease[9]. The histopathological diagnosis will be based on the finding of chronic or subacute inflammatory infiltrate and epidermal ulceration with aseptic non-caseating granulomas[10]. This

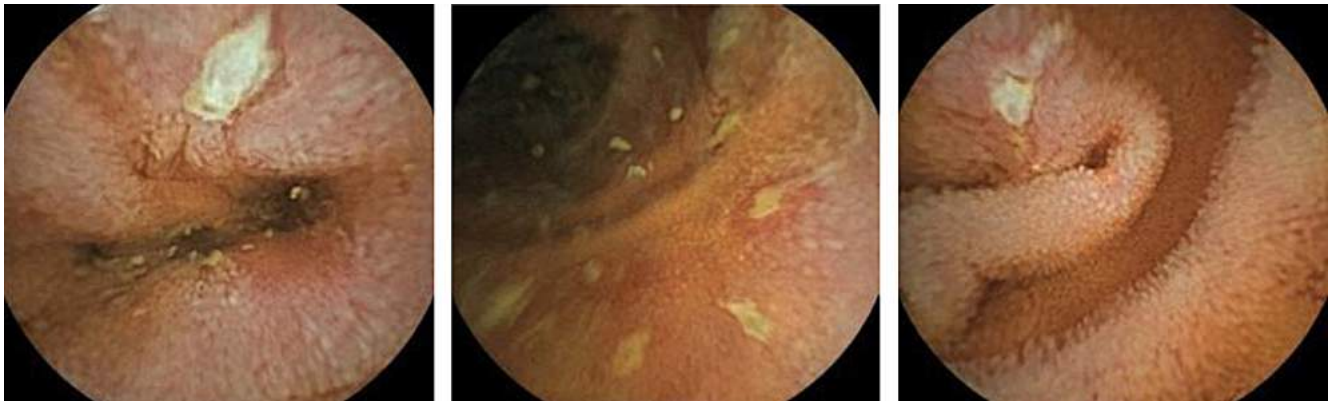

Figure 9. CD enteritis in a capsule endoscopy of the small intestine. Authors' archives.

case was diagnostically complex since the skin involvement preceded the intestinal involvement by more than a year, combined with the absence of other suggestive systemic findings, making it necessary to rule out Behçet's disease first. When HLA-B51 and pathergy test were found to be negative, histopathological studies were conducted on the vulvar lesions, with characteristic findings. Thus, the diagnosis was supported by the chronicity of the lesions, the histological findings, and the exclusion of other granulomatous and infectious diseases.

The therapeutic options are multiple; however, there is no specific treatment regimen since what is known about management is from case reports and a series of few patients whose response to different treatments has been variable and, in many cases, refractory. Most authors have reported a therapeutic response with metronidazole in monotherapy or combination with steroids. Other options include 5-aminosalicylates, antibiotics, and immunosuppressive agents such as azathioprine or cyclosporine[8]. The introduction of anti-TNF agents in CD has marked a milestone in management; nevertheless, their usefulness has been limited sometimes due to a lack of primary and secondary responses in a considerable proportion of patients[11]. Ustekinumab and vedolizumab are immunoglobulin G-1 (IgG-1) monoclonal antibodies, which have emerged as a therapeutic alternative for those cases that are refractory or intolerant to conventional treatments or anti-TNF agents and seem to be associated with a rapid and sustained clinical response, a safety profile, inflammatory cascade damping, and low immunogenicity[11]. In case of failure of pharmacological management, surgical excision can be considered in those patients with severe symptoms or deformities that interfere with the patient's social and private life[12]. This clinical case documented skin reactions with the anti-TNF drugs adalimumab and infliximab and intolerable tachycardia due to cyclosporine. Therefore, using ustekinumab was required, with significant and sustained improvement.

CONCLUSIONS

MCD poses a diagnostic challenge, especially since it can present without GI manifestations for years, and its clinical and histopathological findings can be seen in other conditions. The possibility of CD must be considered, and where possible, an early benefit in the patient must be sought with a timely diagnosis.

Authors' contributions

All authors contributed to the writing of the manuscript.

Conflicts of interest

None stated by the authors.

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Case report

Rare Association of Budd-Chiari Syndrome with COVID-19: A Case Report

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Abstract

Introduction: Severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) is a virus that can cause respiratory infections and pose a risk to patients' lives. While it primarily affects the airways, it can also lead to extrapulmonary clinical manifestations, such as hypercoagulable states, resulting in conditions like cerebrovascular disease, acute myocardial infarction, and, in rare cases, Budd-Chiari syndrome. **Clinical case:** This case involves a patient who was admitted to the emergency room with dyspnea on moderate exertion, progressive functional class deterioration, lower extremity edema, cough, fever, and weakness. The patient had a history of coronavirus disease 2019 (COVID-19) infection one month prior. Abdominal CT scan revealed subacute Budd-Chiari syndrome involving the middle sub-hepatic vein, along with right ventricle thrombosis, and a positive test for SARS-CoV-2. **Conclusions:** Budd-Chiari syndrome has multiple causes, primarily associated with hypercoagulable states or the presence of neoplasms that disrupt liver function or obstruct hepatic venous drainage. However, the understanding of the relationship between COVID-19 hypercoagulability and Budd-Chiari syndrome is still limited. Further research is needed to explore the heterogeneity of its pathogenesis in the context of the SARS-CoV-2 pandemic.

Keywords

Budd-Chiari syndrome, hepatic obstruction of venous outflow, coronavirus infections.

INTRODUCTION

Severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) can cause mild respiratory infections to life-threatening severe cases; however, its clinical manifestation is diverse. While it mainly affects the respiratory system, it can also result in infrequent extrapulmonary manifestations associated with hypercoagulability states[(1)].

Budd-Chiari syndrome (BCS) is defined as an obstruction of hepatic venous drainage, mainly caused by hypercoagulable states and the presence of neoplasms that alter the liver function or obstruct the vascular system[(2)], and its incidence ranges from 2.0 to 2.2 per million inhabitants[(3)]. We present the clinical case of a patient diagnosed with subacute BCS of the middle subhepatic vein associated with thrombosis of the right ventricle (RV) with a recent coronavirus disease (2019) infection (COVID-19).

There are few reported cases of BCS associated with COVID-19 infection, and this article shows the heterogeneous spectrum of clinical manifestation and pathogenesis of COVID-19 when causing BCS.

CASE REPORT

This is the case of a 36-year-old woman with a history of childhood hepatitis of non-specific etiology and vitiligo since childhood, with no history of alcohol consumption. She attended the hospital due to a clinical picture of 15 days of evolution consisting of dyspnea on medium exertion, progressive deterioration of functional class (NYHA III/IV), chest pain associated with productive coughing, unquantified febrile spikes, adynamia, and general malaise.

On physical examination, her vital signs were as follows: blood pressure (BP): 115/70 mm Hg and heart rate (HR): 80 beats per minute (bpm). She was jaundiced, the vesicular murmur was decreased in both lung bases, and the abdomen was not tender on palpation and was distended. Hepatomegaly, dullness on percussion on both flanks, positive ascitic wave sign, and splenomegaly were noted. Bilateral fist percussion was positive, and she presented with grade II edema in the lower extremities, skin without superficial or deep lesions, and generalized jaundice. Initial laboratory testing revealed hyperbilirubinemia (15.27 mg/dL) at the expense of direct bilirubin (9.41 mg/dL), transaminitis (alanine aminotransferase [ALT]: 56 U/L, aspartate aminotransferase [AST]: 79 U/L), normal partial thromboplastin time (PTT) (29.7 s) with daily monitoring (26.2 s), prolonged prothrombin time (PT) (20.5 s) with daily monitoring (13.2 s) and international normalized ratio (INR; 1.7), normal glycemia (78.4 mg/dL), hypoal-

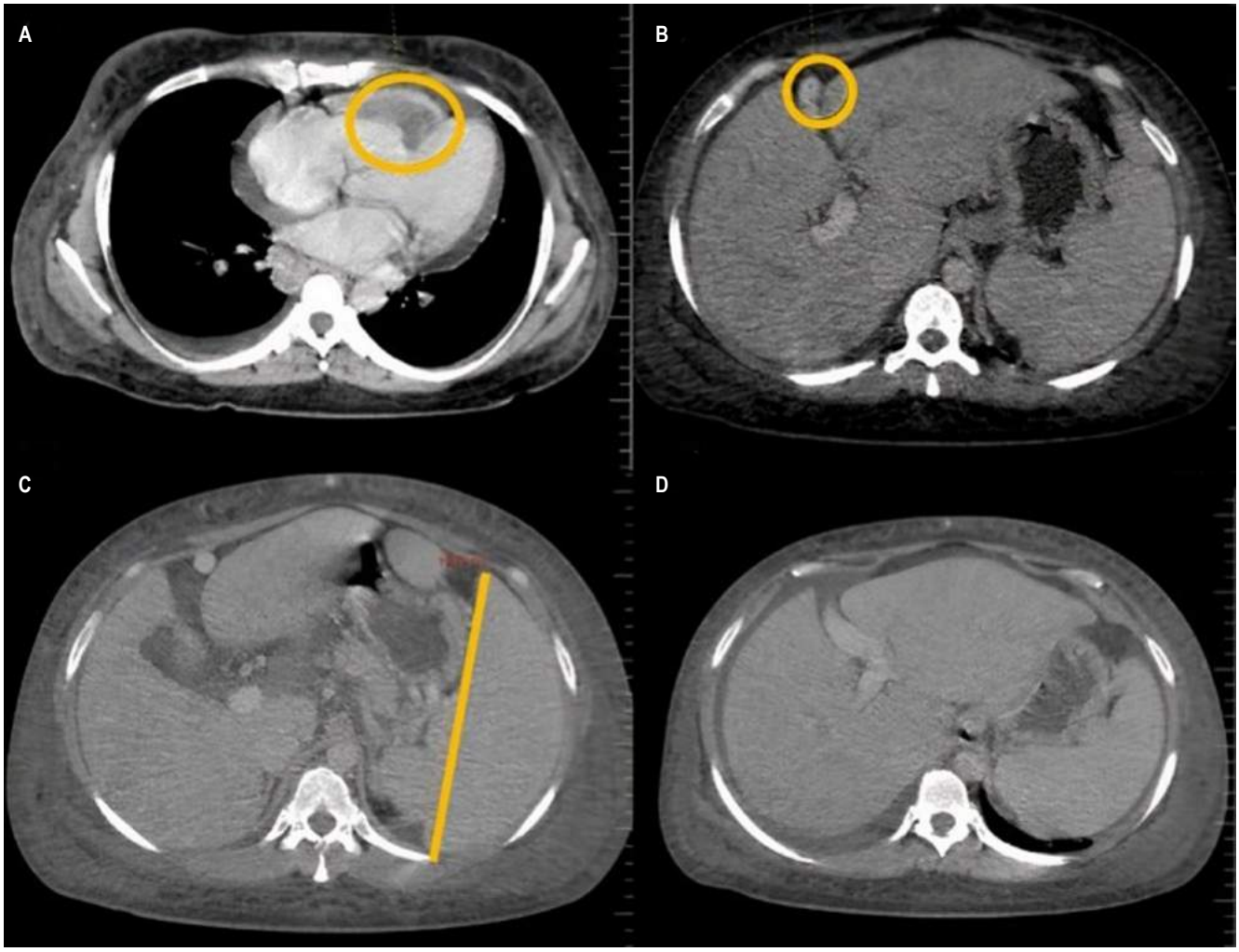

Figure 1. Contrasted CT revealing: **A.** Right atrial thrombosis; **B.** BCS detected by the absence of blood flow at the level of the outflow tract of the middle suprahepatic vein, hepatomegaly; **C** and **D.** Splenomegaly, ascites, and collateral circulation. Courtesy of the radiology department, Hospital Regional de la Orinoquia (HORO).

buminemia (2 g/dL), elevated alkaline phosphatase (3,478 U/L), normal amylase (24 U/ L), and elevated γ-glutamyl transferase (251 U/L).

Following the COVID-19 pandemic protocol, a nasopharyngeal swab was performed based on the polymerase chain reaction (PCR) technique, which was positive. Contrast-enhanced computed tomography (CT) of the abdomen revealed consolidations in the right lower lobe with pleural effusion, dilated right atrium, RV thrombosis, preserved intra- and extrahepatic bile duct, normal gallbladder, without lithiasis. BCS was detected by the absence of blood flow at the level of the outflow tract of the middle suprahepatic vein, portal hypertension, collateral circulation, hepatomegaly, splenomegaly, ascites, and lymph nodes, predominantly inguinal (**Figure 1**).

A chest CT confirmed the consolidation process and pericardial effusion (thickness: 7 mm). The transthoracic echocardiogram revealed a dilated right ventricle and two thrombi of equal echogenicity, one occupying most of the free wall and the other rounded, oscillating and protruding through the tricuspid valve (**Figure 2**), so anticoagulation with low molecular weight heparin (LMWH: 1 mg/kg/day) and diuretics was started.

The patient had mild to moderate ascites, but the clinician considered her a candidate for the invasive procedure with paracentesis. She was diagnosed with pneumonia of unclear etiology, post-COVID-19 respiratory distress syndrome, and subacute BCS of the middle suprahepatic vein associated with right ventricular thrombosis. During hospitalization, the patient clinically deteriorated due to temperature rises of up to 38.9 °C, arterial hypotension, and ventilatory failure. She required endotracheal intubation, vasopressor support, and a broad-spectrum antibiotic regimen; however, three hours later, she passed away.

The clinical characteristics of this patient are the typical manifestations of BCS. Since we did not notice associated clinical, paraclinical, and imaging findings that could be inferred from another diagnostic probability, we believe it was highly related to an infectious process caused by the SARS-CoV-2 virus.

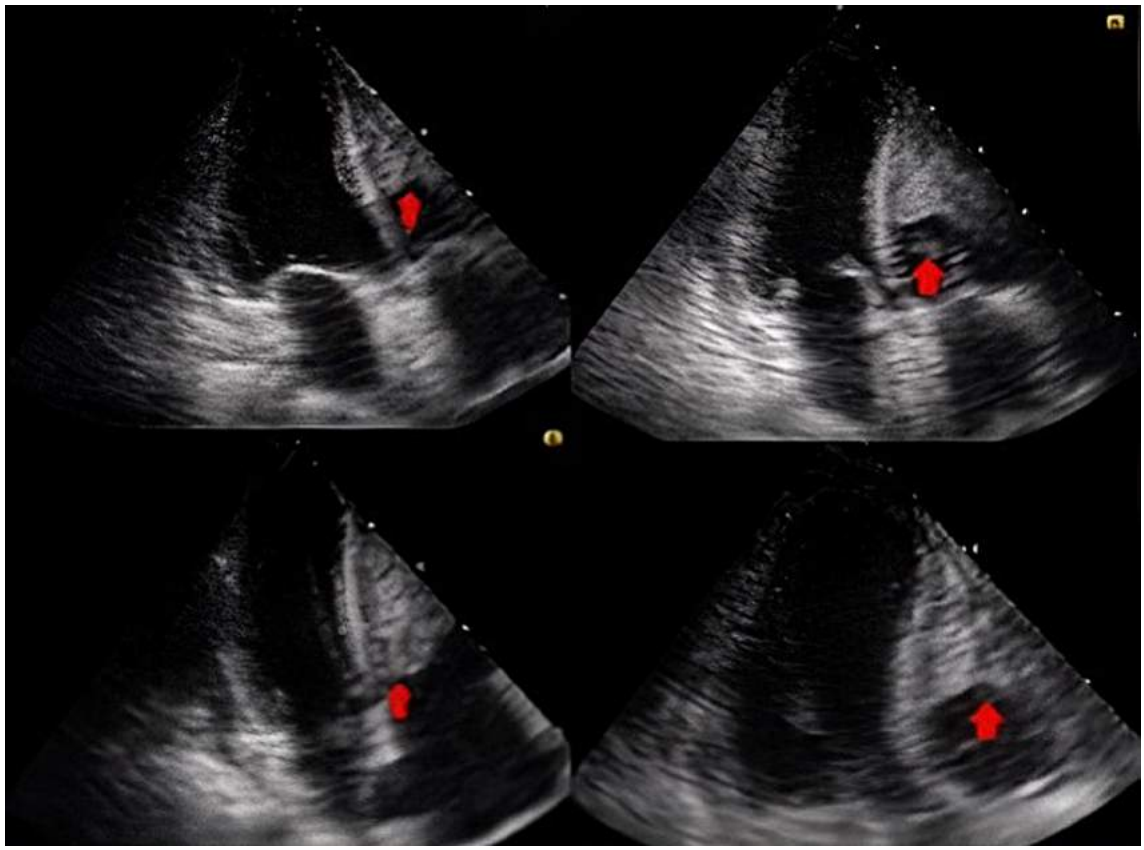

Figure 2. Transthoracic echocardiogram showing a thrombus covering most of the free wall of the right ventricle with another image of the same echogenicity, rounded, 1.6 x 1.6 cm, which oscillated and even protruded through the tricuspid valve. Courtesy of the radiology department, HORO.

DISCUSSION

SARS-CoV-2 infection continues to have significant clinical manifestations. Most cases present with mild symptoms that do not affect the quality of life. In rare cases, there may be hypercoagulability states caused by alterations in Virchow's triad and changes in serum levels of coagulation factors that put the patient at risk of ischemic pathologies such as cerebrovascular disease (5.7%), acute coronary syndrome (6%-7%), venous thromboembolic disease (deep vein thrombosis: 5.4%; pulmonary thromboembolism: 29%), and vasculitis, respectively[4-6].

Within the study of the pathophysiology of BCS, the presence of thrombophilia and alterations in the patient's coagulation is deemed an essential factor; therefore, it is most often related to neoplastic pathologies due to the hypercoagulable state that they can cause[7].

Taking into account the differential diagnoses that may be associated with BCS, those considered in this clinical case are liver cirrhosis, myeloproliferative disorders (polycythemia vera, essential thrombocythemia, or coagulation disorders), carcinoma (hepatocellular, adrenal, and renal), leiomyosarcoma and space-occupying lesions of the liver such as liver cysts and sarcomas. In addition, we inquired about the administration of oral contraceptives, which were discarded based on the questioning and the diagnostic aids described[7,8].

No clinical associations were found suggesting other history in the clinical case. The patient did not have alterations according to the age group, such as autoimmune diseases. She had a history of vitiligo since childhood, but there was no evidence of clinical reactivity, and she did not meet the criteria to indicate an autoimmune profile either. The main factor that predominated was a recent history of SARS-CoV-2 infection, which could explain the pathophysiological changes at the hematological level and the alterations in the vascular endothelium produced by COVID-19. We consider that the patient developed subacute BCS secondary to SARS-CoV-2 infection[9].

We conducted a literature review of published cases of these two clinical entities. We found few case reports[10-14], so we believe these findings are significant because we describe the diverse spectrum of the pathogenesis of COVID-19 and the heterogeneity in the clinical manifestation, as was this case of subacute BCS.

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Case report

A Case Report of Primary Hepatic Tuberculosis

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Abstract

This case report presents an incidental finding of primary tuberculosis in the liver of a 54-year-old female patient who had a history of multiple hospital admissions due to abdominal pain, jaundice, persistent fever, nausea with vomiting, weight loss, and asthenia. The evaluation involved considering differential diagnoses of cholangiocarcinoma, Caroli's disease, hepatocellular carcinoma, and hepatic tuberculosis based on the patient's history, imaging studies, and laboratory tests. The aim of this report is to provide healthcare professionals with a new diagnostic perspective when encountering patients with this ambiguous presentation, even in regions with low epidemiological incidence. Hepatic tuberculosis should be included in the differential diagnosis of patients with focal intrahepatic lesions or liver abscesses who have a history of recurrent hospitalizations and evidence on imaging studies.

Keywords

Hepatic tuberculosis, *Mycobacterium tuberculosis*, cholangiocarcinoma.

INTRODUCTION

The World Health Organization (WHO) estimates that about 25% of the world's population is infected with *Mycobacterium tuberculosis*. Generally, extrapulmonary tuberculosis occurs in approximately 12% of tuberculosis (TB) patients[(1)], and the most commonly affected sites are the mediastinal, retroperitoneal, and cervical lymph nodes, vertebral bodies, adrenal glands, meninges, and the digestive system[(2)]. Regarding the latter, the intra-abdominal manifestation only occurs in 3.5% of extrapulmonary TB. Notably, liver involvement occurs in up to 80% of the above cases[(3)]. Nonetheless, the manifestation of TB as a primary site in the liver represents less than 1% of the patients currently registered[(4)]. The authors Levine and Reed(5) agree on the first three forms of manifestation of hepatic TB as described below: granulomatous hepatitis accompanied by miliary TB, primary hepatic TB, focal tuberculoma, and tuberculous cholangitis or TB in the bile ducts. The most common symptoms for these scenarios are usually right upper quadrant pain, anorexia, weight loss, and fever. However, the literature describes the difficulty in

diagnosing due to the similarity of the clinical and imaging pictures to other well-described and more common pathologies, such as cholangitis, hepatocellular carcinoma, and cholangiocarcinoma[6].

CASE PRESENTATION

This is the case of a 54-year-old female patient with a known morbid history of arterial hypertension on regular treatment with atenolol 50 mg once daily and cholecystectomy (cholelithiasis) surgery. Her medical record includes multiple hospital visits in the last five years due to a recurrent clinical picture of diffuse abdominal pain predominantly in the epigastrium and radiating to the right hypochondrium, which was sometimes accompanied by non-thermometered fever, with no predominance of time, and fluctuating jaundice.

In the last five years, she was evaluated in different health centers, reporting laboratory studies, digestive screening (universal erythematous gastropathy, with *Helicobacter pylori* +), and colonoscopy without pathological findings. In addition, an abdominal resonance was performed, obtaining axial and coronal planes in T2, T1, T2FAT-SAT, FASE, and FS images, with and without contrast medium. They showed an enlarged liver and preserved morphology, with multiple cystic lesions randomly distributed in both liver lobes and an annular enhancement of the contrast medium (**Figure 1**). Magnetic resonance cholangiography was also performed, which revealed significant dilation of the intrahepatic bile duct, specifically the left one, and a well-defined cystic lesion with regular borders, which caused dilation of the extrahepatic bile duct (**Figure 2**). After injection of the contrast medium, a filling defect was observed, suggesting choledocholithiasis in the left hepatic duct. A biopsy was performed that did not report findings suggestive of malignancy, so we decided to manage the acute clinical picture with antibiotic therapy (carbapenems) only and periodic follow-up of the lesion.

On her last visit, the patient went to the emergency room with the symptoms described above, leukocytosis, increased bilirubin, cholestasis enzymes (**Table 1**), and jaundice in the sclera and mucous membranes. The diagnosis of cholangitis was assessed, for which an MRE cholangiography was performed, showing new findings in favor of multiple intrahepatic cystic lesions with an annular enhancement of the contrast medium and dilation of the intrahepatic and extrahepatic bile ducts. These findings were consistent with Caroli's disease. An intervention with endoscopic retrograde cholangiopancreatography (ERCP) was made, in which a sphincterotomy was performed before cannulation. The discharge of choledocholithiasis and seropurulent content consistent with cholangitis was observed, later placing a 10 Fr/9 cm plastic prosthesis (**Figure 3**).

We decided to take her to the operating room for left hepatectomy, with intraoperative findings of multiple cystic lesions (**Figure 4**). Hepatectomy was not performed, and a sample of the lesions described was taken for histopathological study purposes.

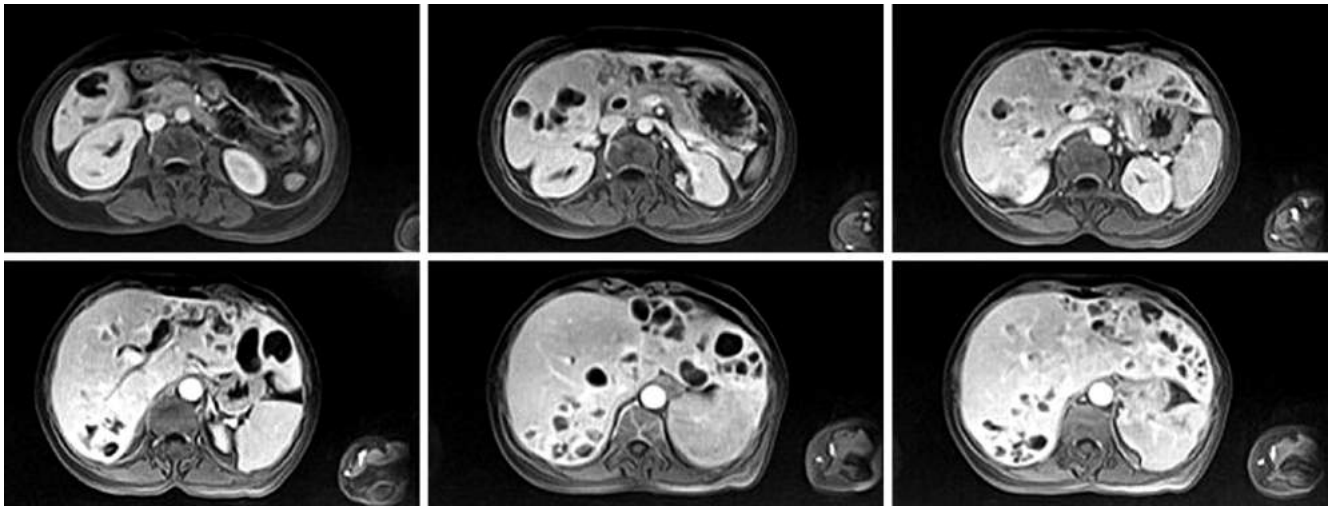

Figure 1. Abdominal resonance of axial and coronal planes. Liver measuring 22 cm in the longitudinal axis, regular borders, having multiple cystic lesions in both liver lobes with annular contrast enhancement. Source: Patient's medical record.

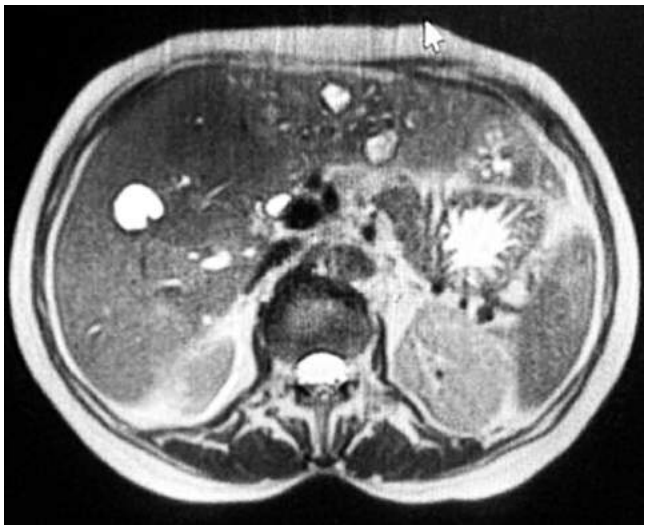

Figure 2. Magnetic resonance cholangiography showing dilation of the intrahepatic bile duct and a cystic lesion with regular borders. Source: Patient's medical record.

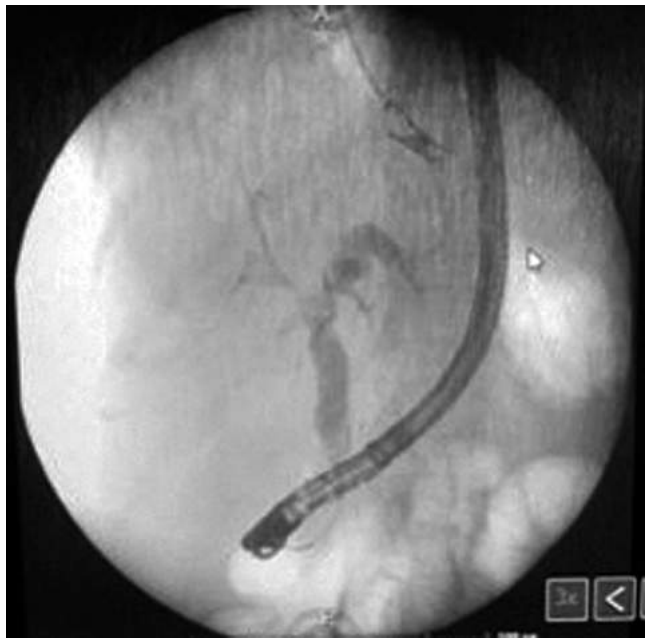

Figure 3. ERCP showing seropurulent content consistent with cholangitis. Source: Patient's medical record.

DIAGNOSTIC EVALUATION

Hepatic TB lacks pathognomonic clinical features or unique patterns in its manifestation; therefore, it is difficult to differentiate it from other more frequent pathologies that present with symptoms and imaging findings similar to hepatocellular carcinoma, intrahepatic cholangiocarcinoma, Klatskin tumor, and secondary liver abscesses[4]. Other approaches, such as fine needle aspiration cytology, have been used but are inconclusive. When evaluating the findings of ultrasound and computed tomography (CT), the usual results direct the presumptive diagnosis to malignancies or possible metastasis foci[5]. All of the above indicates the need for histopathological methods and GeneXpert as the reference test for definitive diagnosis. In this case report, the patient underwent different assessments (upper endoscopy, colonoscopy, magnetic resonance cholangiography, exploratory surgery, and liver biopsies) over the past five years due to the ambiguity of her clinical picture.

Three greyish-brown elastic fragments with whitish nodules, of which the largest measures 1.6 x 1 x 0.5 cm and the smallest 0.8 x 0.3 cm, were sent to the laboratory. The specimen was fully processed, and histochemical stains (reticulin, periodic acid Schiff [PAS], and Masson's trichrome) were performed for microscopic evaluation.

In the microscopic evaluation, hepatic tissue with alterations of the standard architecture was seen due to an extensive area of caseation necrosis. Outside, epithelioid cells, Langerhans-type giant cells, and fibrosis were found. In addition, a remnant of hepatocytes with distorted architecture and portal spaces having a fibrous expansion, hydropic degeneration, and sinusoidal congestion was detected. In some areas, there was ductal proliferation. The conclusion of the liver biopsy indicated a granulomatous inflammatory process with caseation necrosis compatible with *M. tuberculosis*. **Figure 5** shows a representation of the histological section. As a result, the pathology department suggested correlating the histopathological findings with the patient's symptoms.

Considering the pathological and clinical imaging reports, extrapulmonary TB was diagnosed, and antituberculosis treatment was started.

THERAPEUTIC INTERVENTION

In other case studies, the conventional antituberculosis regimen (isoniazid [INH], rifampicin [RIF], ethambutol [EMB], and pyrazinamide [PZA]) for six months has been the therapy of choice. Sometimes, it has been modified with micronutrient supplementation such as vitamin B6[7]. For this patient, the standard treatment of two months of quadru-

Table 1. Hematic biometrics

Test	Result
WBC	↑ 47.87
RBC	↓ 2.32
Hb	↓ 6.00
Ht	↓ 17.70
MCV	↓ 76.30
MCH	25.90
MCHC	33.90
PLT	↑ 484
Erythrocyte sedimentation rate (RSV)	↑ 140
Differential	
- Neutrophils %	↑ 91.50
- Lymphocytes %	1.00
- Lymphocytes #	0.78
- Monocytes #	1.57
- Neutrophils #	↑ 43.77
Chemistry	
- Amylase	62.0
- Lipase	42.8
- ALT	19.5
- AST	21.3
- Albumin	↓ 2.3
- Direct bilirubin	↑ 1.4
- Indirect bilirubin	↑ 1.1
- Total bilirubin	↑ 5.0

Test	Result
Chemistry	
- GGT	↑ 318.7
- Alkaline phosphatase	327
- BUN (urea)	↑ 47.9
- Creatinine	↑ 3.2
- Fasting glucose	↑ 113.0
- Potassium	4.8
- Sodium	↓ 124.4
- Calcium	9.1
- Phosphorus	↑ 6.1
- AFP	5.1
- CEA	1.7
- AC 19-9	15.6
- HIV, HBV, HCV	Negative
Autoimmune panel	
- Complement, IgG, IgG4, and anti-LKM-1	Within normal limits
- QuantiFERON-TB-GOLD	Negative
- Bacilloscopy	Negative
Miscellaneous tests	
- Procalcitonin	↑ 44.5
- D-dimer	↑ 1500
- Lactate	1.0
- C-reactive protein	↑ 248.9

AFP: alpha-fetoprotein; ALT: alanine aminotransferase; anti-LKM-1: type 1 liver and kidney microsomal antibodies; AST: aspartate aminotransferase; BUN: blood urea nitrogen; CA 19-9: carbohydrate antigen 19-9; CEA: carcinoembryonic antigen; WBC: white blood cells; GGT: γ-glutamyl transferase; RBC: red blood cells; Hb: hemoglobin; Ht: hematocrit; IgG: immunoglobulin G; MCH: mean corpuscular hemoglobin; MCHC: mean corpuscular hemoglobin concentration; MCV: mean corpuscular volume; PLT: platelet count; HBV: hepatitis B virus; HCV: hepatitis C virus; HIV: human immunodeficiency virus; RSV: respiratory syncytial virus. Taken from the laboratory of Centro de Salud Clínica Corominas.

ple therapy with INH, RIF, EMB, and PZA was considered, followed directly by another four months of dual administration of RMP and INH. However, extrapulmonary and disseminated forms of TB may sometimes require more extended treatment, as is the case of bone manifestation (nine months), lymphoid manifestation (six months), or involvement of the central nervous system (one year)[8]. After three months of therapy, the patient showed improvement and decreased symptoms. The reserved prognosis remains.

DISCUSSION

It is estimated that 6% to 38% of patients with intra-abdominal TB have evidence of pulmonary TB at diagnosis[3].

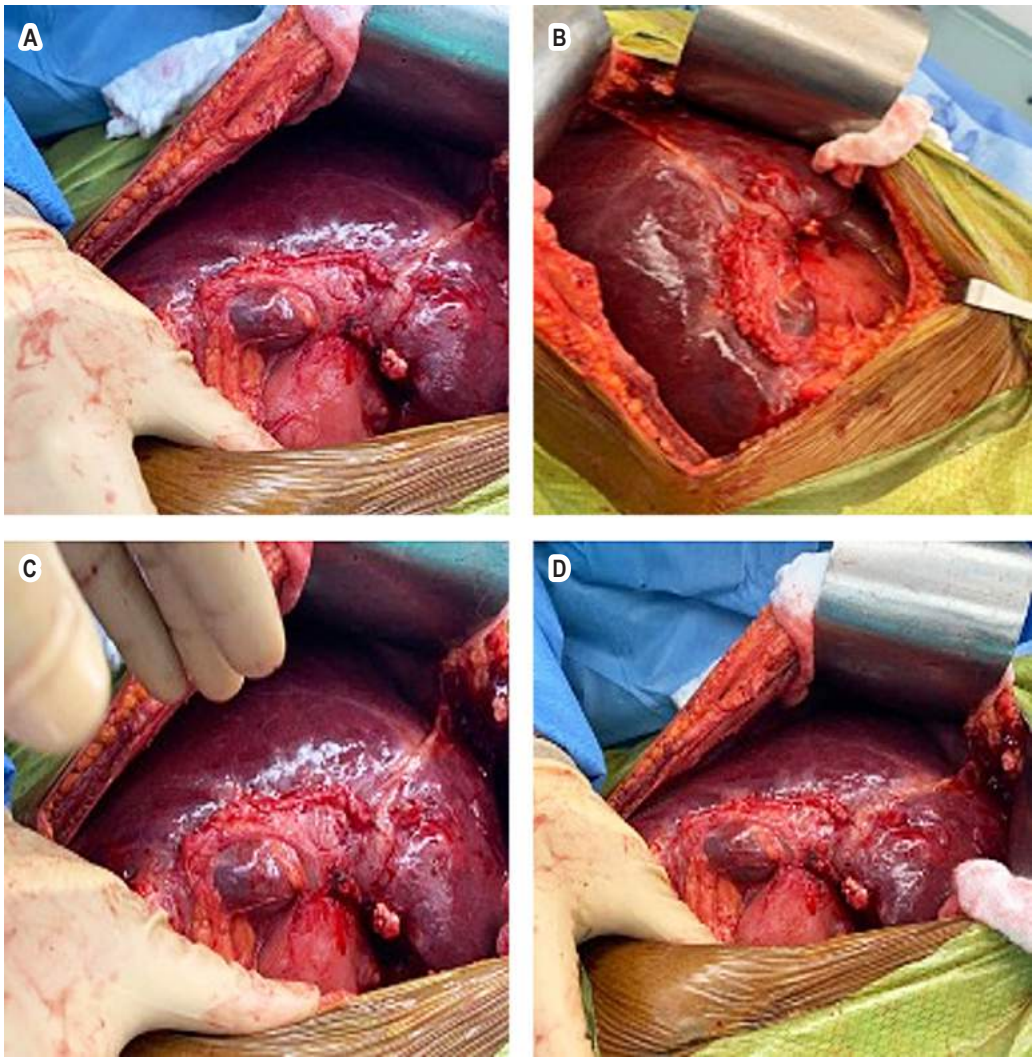

Figure 4. Gross findings on surgical exploration. Cystic areas with whitish, cheesy pasty content. Source: Patient's medical record.

The pathogenesis pathway includes a hematogenous bacillus spread from a pulmonary focus. In 2017, Schininà et al.[9] mentioned that of the 14 participants with hepatic TB included in their study, all had a liver lesion as a disseminated form of TB. However, hepatic TB as the primary infection focus is a manifestation with a particularly low incidence (less than 1% of TB cases worldwide)[4]. A systematic review published in 2015 by Hickey et al.[10] showed that, among the reported cases of hepatic TB, 79% corresponded to miliary TB, while only 21% to local hepatic TB. Regarding the pathogenesis proposed for disseminating TB to the liver in the case of primary hepatic TB, the migration of the bacillus *M. tuberculosis* from a focus in the gastrointestinal tract is described. It travels through the intestine towards the portal vein and from there to the liver, where, even under unfavorable conditions such as low oxygenation of the liver tissue, this bacillus grows in 1% of the cases[4].

Moreover, the manifestation of hepatic TB in the absence of miliary TB makes timely diagnosis and treatment difficult for health personnel by perfectly simulating other more frequent hepatic-biliary conditions[5]. Schininà et al.[9] reported that the most common symptoms in their study sample were right upper quadrant abdominal pain, night sweats, weight loss, fatigue, high fever, upper abdominal tenderness, and hepatomegaly on physical examination. This picture is similar to that of the patient under study but is non-specific for the disease. Hickey et al.[10] pointed out that in countries with endemic TB, TB was the leading cause of liver granulomas, and the presence of the latter is

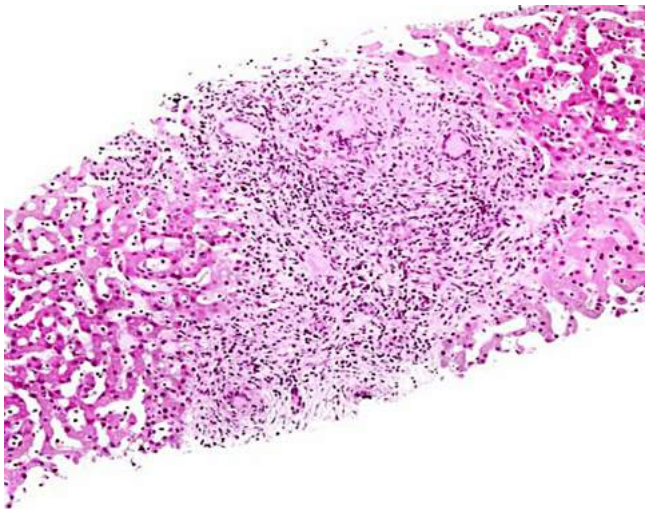

Figure 5. Histological section of liver tissue with giant cell granuloma. Source: Themes U. *Mycobacterium tuberculosis*[11].

highly suggestive of infection by the bacillus in endemic countries.

CONCLUSION

This case report is intended to motivate the medical community to maintain hepatic TB infection within the differential diagnoses in the face of non-specific and recurrent pictures to avoid unnecessary invasive surgeries and start timely treatment with antituberculosis therapy (ATT).

Patient perspective and consent

The hospital's ethics committee has granted an ethics waiver for the disclosure of clinical records for exclusively academic purposes.

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Case report

True Giant Diverticulum of the Left Colon. A Case Report

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Abstract

This abstract presents a clinical case of a male patient who exhibited clinical symptoms and tomographic findings of an abdominal mass in the descending colon. The diagnostic process and treatment are described, accompanied by a literature review. The review establishes the definition of the condition and its surgical indications. It is important to note that true giant diverticulum of the colon is a rare entity, with fewer than 200 reported cases in the literature.

Keywords

Diverticulum, colon, colectomy.

INTRODUCTION

The giant colonic diverticulum (GCD) is a rare clinical entity, with fewer than 200 reported cases[(1)]; it was first described in 1946 by Bouvin and Bonet[(2,3)]. It is a lesion originating from the antimesenteric border; the sigmoid is the most frequent site of manifestation. The size fluctuates between 4 and 30 cm, and they are generally simple and single lesions, but they can be multiple, considered an infrequent manifestation of colonic diverticulosis[(3)]. Among the reported complications are perforation, abscess, volvulus, infarction, and adenocarcinoma[(3,4)]. Segmental colectomy is regarded as the ideal treatment or diverticulectomy when the giant diverticulum is single[(5)]. We present this entity's case in a male patient in the fifth decade of life.

CASE PRESENTATION

This is the case of a 42-year-old male patient with no relevant pathological history. The patient initially consulted due to a two-year history of pain in the left hemiabdomen, associated with a sensation of mass and intestinal habit with periods of constipation and diarrhea. He made multiple consultations in which he was medically treated without improvement. A colonoscopy was performed on an outpatient basis with poor colonic preparation due to

fecal matter at the rectosigmoid junction. Double-contrast computed tomography (CT) of the abdomen reported dolichosigma and occupation of the colon-sigmoid junction with hypodense and heterogeneous material that reached a transverse diameter of 8 cm, giving rise to the suspicion of segmental fecal impaction in front of a bezoar. A control CT scan (**Figure 1**) was performed at Hospital Universitario San Ignacio, the findings of which suggested a bezoar in the lumen of the distal descending colon, not associated with intestinal obstruction, as the first possibility. He was assessed for colon and rectal surgery and considered a patient with a giant diverticulum in the descending colon, for which resection and anastomosis by laparotomy were prioritized. The intraoperative findings (**Figure 2**) showed a rounded lesion in the descending colon, towards the lateral edge of the antimesenteric surface, 10 x 8 cm, with a soft consistency. There were no postoperative complications, and he was discharged on day seven.

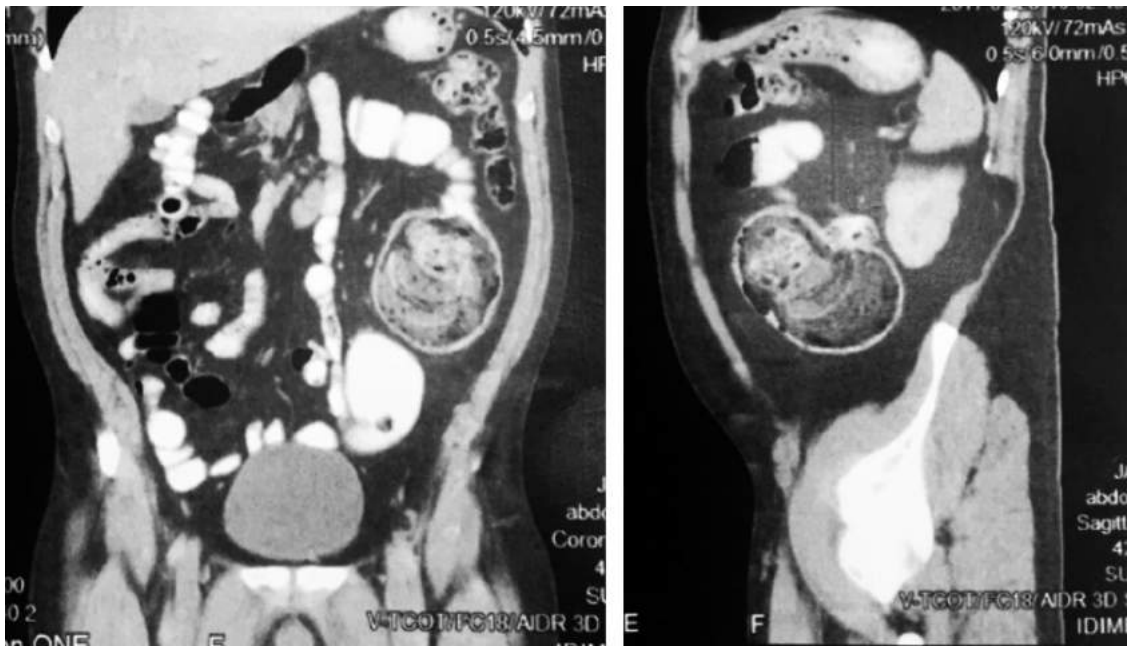

Figure 1. CT with double contrast, coronal and sagittal section (lesion indicated by the arrow). Source: Patient's medical record.

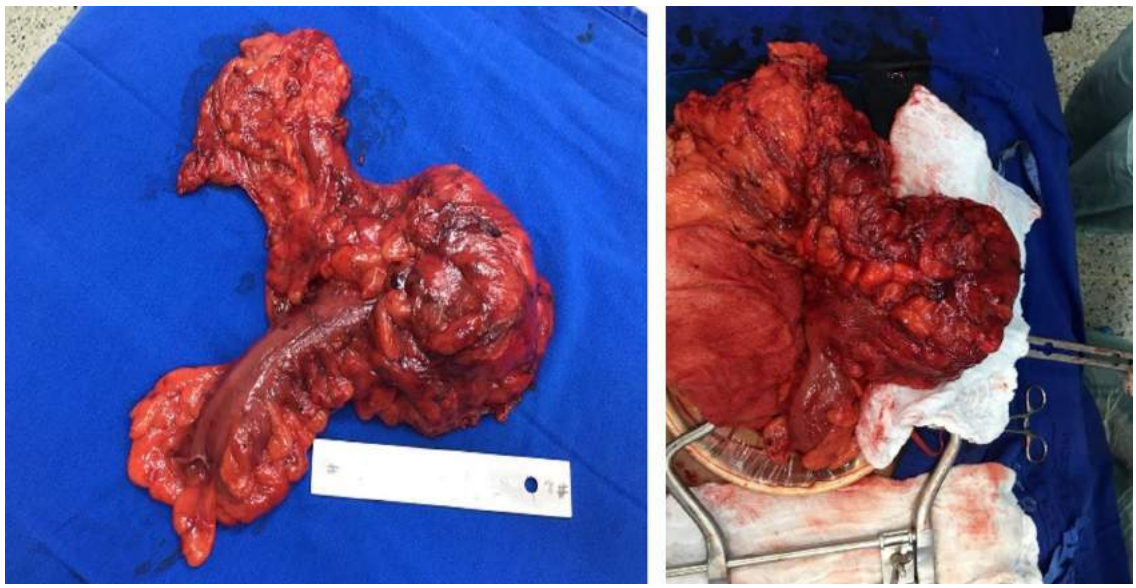

Figure 2. Intraoperative findings. Source: Patient's medical record.

In the anatomopathological findings, a large diverticulum with a small mouth is macroscopically described but with a cavity of 8.3 x 5 cm; when cut, abundant fecal content was found without perforations or masses (**Figure 3**). The microscopic diagnosis confirms a diverticular formation (**Figure 4**), with all the layers in the wall of the diverticulum corresponding to a true giant diverticulum.

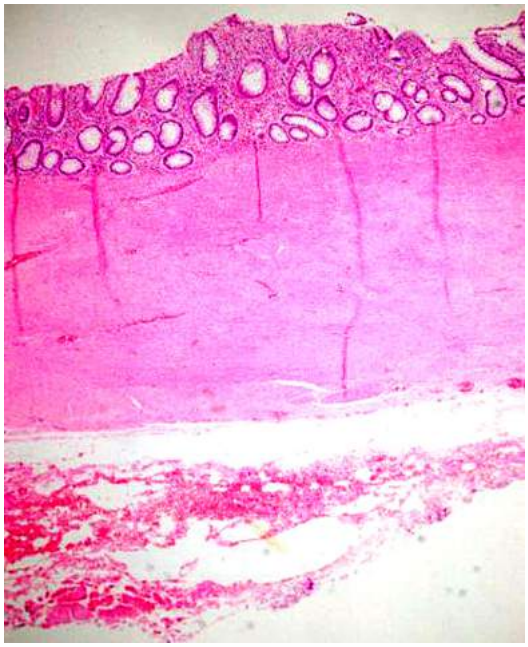

Figure 4. Pathological microscopic findings x 10 CAP. Source: Patient's medical record.

DISCUSSION

Colonic diverticula are herniations of the mucosa and muscular layer of the mucosa through a weakness in the muscular wall, where the arteries penetrate it[4,6]. These diverticula are usually of constant size and range between 0.5 and 1 cm in diameter[4]. These diverticular formations are considered false diverticula because they do not have all the typical layers of the gastrointestinal tract. Diverticula can be found throughout the entire colon. Still, in most cases, diverticular disease is located in the sigmoid colon[4], where diverticula average between 1 and 2 cm in size, in contrast to sigmoid diverticula, which are acquired and usually multiple[5].

Colonic diverticulosis is a common pathology in Western countries, mainly attributed to the low fiber intake in the diet[7]. The prevalence increases with age from the fourth decade onwards and is very frequent in advanced ages, affecting up to 70% of individuals in the seventh decade of life, mainly men[4]. This pathology is usually asymptomatic, but it can become complicated, and the most common is acute diverticulitis in 15% to 30% of patients with colonic diverticulosis, followed by bleeding[2,3,8].

GCD is a rare but well-known variant, defined as a diverticulum larger than 4 cm. 85% of GCDs are associated with diverticular disease[9], and 90% of these diverticula are located on the antimesenteric edge. They are generally simple and single but can be multiple[4]; their size fluctuates between 4 and 30 cm. It occurs more frequently between 60 and 80 years; however, it can be found in the age range between 38 and 86 years, both in men and women[1,2,10].

Clinically, the manifestation may vary. Abdominal pain is the most common symptom in 69% of cases, followed by constipation[10], sensation of abdominal mass, vomiting, rectal bleeding, and fever in up to 20% of cases; even so, the literature subdivides them into four clinical groups[3,9,10]:

1. Acute (30%-35%): Abdominal pain, fever, symptoms and signs of intestinal obstruction, and rectal bleeding.

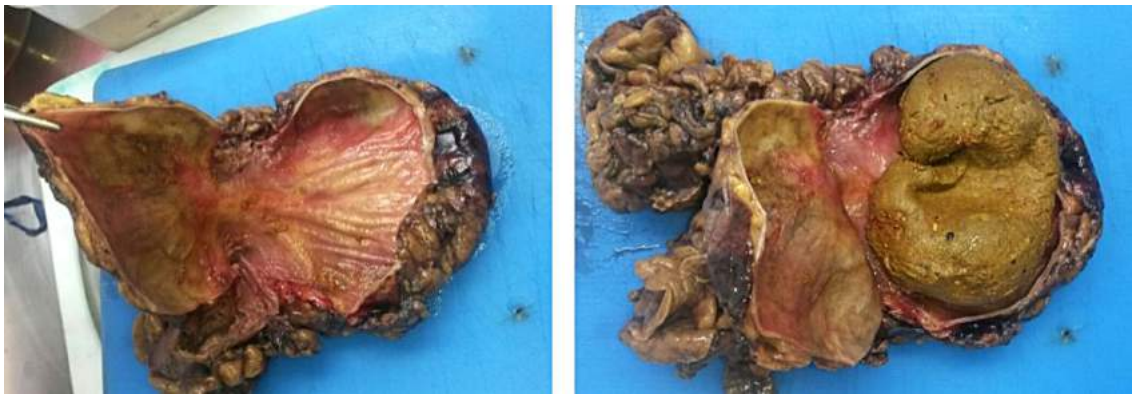

Figure 3. Pathological macroscopic findings with fecaloma. Source: Patient's medical record.

2. Chronic (35%): It occurs in one-third of patients and has nonspecific symptoms, such as abdominal discomfort, bloating, and constipation.
3. Complicated (10%-20%): It occurs in 6% of patients as an acute abdomen secondary to perforation, abscess, volvulus, urinary or intestinal obstruction, infarction, and even fistula formation, and extremely rarely, the appearance of adenocarcinoma within the GCD.
4. Asymptomatic (10%): It is detected as a mass on physical examination or as an incidental finding on imaging, in which a differential diagnosis should be made with other entities that appear as a cavity filled with air or with air-fluid levels such as volvulus, duplication cysts, duodenal diverticula, Meckel's diverticulum, abscesses, necrotic tumors, or emphysematous cholecystitis.

The most accepted pathogenic theory refers to a ball valve mechanism through which gas enters but cannot exit the diverticulum. The unidirectional air passage produces pressure elevation and pressure differences in the colon, with the gradual enlargement of the diverticulum[2].

Given the diagnostic suspicion of this entity, the test of choice is double contrast tomography. Typically, a round gas-filled structure is described with or without a hydroaerial level[2]. Colonoscopy frequently does not diagnose because the orifice of the diverticular neck can be hermetic to allow viewing, and contrast enemas can demonstrate communication of the diverticulum with the intestinal lumen in almost 70% of cases; however, recent publications suggest that the barium enema should be avoided due to the risk of perforation[11].

The histological classification proposed by McNutt in 1988 is still valid to this day. This classification subdivides GCD into three subtypes: pseudodiverticulum, inflammatory, and true or congenital, each with different microscopic characteristics[2].

The treatment of GCD depends on its clinical classification[1]. For uncomplicated and symptomatic GCD, it is primary resection of the diverticulum with margins and primary anastomosis. In the case of an acute abdomen secondary to perforation and peritonitis, the safest treatment is en bloc resection of the diverticulum and the affected colon associated with a terminal temporary colostomy.

CONCLUSION

The true giant diverticulum of the colon is a rare entity. We presented the clinical case of a patient who consulted on several occasions due to abdominal pain symptoms interpreted as irritable bowel syndrome, studied with colonoscopy and CT in which a lesion in the distal descending colon was finally documented. He underwent an exploratory laparotomy where a left hemicolectomy with colocolonic anastomosis was performed without complication. A mass was identified at the descending colon level corresponding to a fecaloma originating from a true giant diverticulum of the colon. Giant diverticula have been described in the context of diverticulosis in various colon segments. However, a true diverticulum at this level makes it a rare finding since they are mainly detected in the right colon, while pseudodiverticula are usually reported in the left colon. As noted in the reviewed literature, the treatment given to this patient is adequate; despite being a rare pathology, it should be considered a differential diagnosis given the possible complications that may arise.

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Case report

Recurrent Ascites: Uroperitoneum as an Overlooked Etiology

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Abstract

Ascites is a frequently encountered condition with diverse underlying causes. Among these, uroperitoneum is a rare etiology characterized by a non-specific clinical presentation, making it challenging to diagnose. A thorough approach and a high level of clinical suspicion are essential for accurate diagnosis. The measurement of creatinine levels in peritoneal fluid, serum, and the gradient between them plays a crucial role in achieving a correct diagnosis. In this case report, we present a patient with recurrent ascites and fluctuating elevation of azotemia, who was diagnosed with uroperitoneum through a meticulous diagnostic process. Following surgical intervention, the patient exhibited satisfactory clinical improvement without experiencing further recurrences.

Keywords

Ascites, acute kidney injury, uroperitoneum.

INTRODUCTION

Ascites is abnormal fluid accumulation in the peritoneal cavity[1]. In the Western world, cirrhosis is responsible for ascites in 80% of cases[2]; it is the most common complication of cirrhosis, occurring in up to 5%-10% of patients with cirrhosis each year[3]. Other etiologies include cancer (10%), heart failure (5%), and tuberculosis, among others[4]. Within this last group, uroperitoneum stands out, the incidence of which is unknown; there are only case reports and series in the literature. The leading cause of uroperitoneum is traumatic bladder rupture, which represents 96% of all cases. Another 3% is due to increased bladder volume in conditions with altered sensitivity, such as neurogenic and postpartum bladder with epidural anesthesia, and less than 1% is due to spontaneous rupture[5]. Additionally, a mortality rate of up to 47% has been documented, mainly due to septic shock if not diagnosed promptly[5].

In the initial study of ascites, the analysis of the peritoneal fluid and the calculation of the serum ascites albumin gradient (SAAG)[6] are essential. SAAG is calculated by subtracting the concentration of serum albumin and the peritoneal fluid; when greater than 1.1 g/dL, it allows the diagnosis of ascites secondary to portal hypertension with an accuracy of 97%, sensitivity of 93% and specificity of 47%[7,8]. However, sometimes it is impossible to establish a diagnosis with this initial approach, and the study must

be deepened[4,9]. Other studies that should be performed on ascitic fluid based on clinical suspicion are total protein, cytochemical, cultures, amylase, pH, and adenosine deaminase, among others[4]. Therefore, it is sometimes necessary to determine the gradient between ascitic fluid creatinine and serum creatinine in case of suspicion of uroperitoneum, which supports this diagnosis if greater than 1.0[10-12] both in cirrhotic and non-cirrhotic patients since it has been shown that the electrolytes, urea, and creatinine values in the ascitic fluid are similar to those in the serum[13,14]. We present the case of a patient with uroperitoneum due to a defect in the bladder dome who presented with abdominal pain and recurrent tension ascites associated with acute renal pseudo-injury with a fluctuating elevation of nitrogen gases.

CASE PRESENTATION

A 68-year-old man with a history of prostate carcinoma underwent a radical prostatectomy in 2016. As a complication of this procedure, there was a lesion in the right distal ureter that required ureterovesical reimplantation. Since 2019, he has had three hospitalizations for recurrent ascites that required evacuating paracentesis on several occasions. The ascitic fluid study showed a SAAG greater than 1.1 mg/dL during these hospitalizations, suggesting portal hypertension. The most common etiologies of ascites, including chronic liver disease, heart failure, malignancy, tuberculosis, autoimmunity, and thrombosis, were ruled out. Given the diagnostic uncertainty and imaging findings of particulate fluid with inflammatory characteristics, diagnostic laparoscopy was performed twice with a biopsy of the peritoneum and omentum, which revealed mature adipose tissue with chronic inflammatory infiltrate and reactive mesothelial cells with no evidence of neoplasia. In addition, the serum creatinine value was variable, mg/dL at times and, after permanent bladder catheterization, 0.8 mg/dL without any signs of obstructive compromise of the urinary tract on renal ultrasound.

He was admitted to our institution due to a fourth episode of ascites and abdominal pain. On admission, he had a blood pressure of 126/88 mm Hg, a heart rate of 100 beats per minute (bpm), and was afebrile. Physical examination revealed a distended but soft abdomen, a positive ascitic wave, mild pain in the hypogastrium, and no masses, hepatomegaly, or splenomegaly.

The diagnostic process began again; liver disease and thrombosis of the splanchnic axis were ruled out. Diagnostic and therapeutic paracentesis was performed, draining 3,600 mL of sallow fluid. SAAG was greater than 1.1 mg/dL. Proteins in the ascitic fluid were 1.58 g/dL, although particulate ascitic fluid was striking in the abdominal ultrasound, suggestive of infectious or inflammatory involvement. Microbiological cultures were negative, and other paraclinical tests were requested, as described in **Table 1**.

Table 1. Laboratory parameters on admission to the institution

Laboratory parameters	Results
Hemoglobin	16.1 g/dL
Hematocrit	45.9%
Leukocytes	7,740 cells per µL
Neutrophils	4,820 cells per µL
Lymphocytes	1,810 cells per µL
Platelets	339,000 cells per µL
ALT	16 UI/L
AST	18 UI/L
AP	153 UI/L
GGT	17 UI/L
Total bilirubin	1.24 mg/dL
Direct bilirubin	0.43 mg/dL
Albumin	4.06 g/dL
Sodium	140 mEq/L
Potassium	4.27 mEq/L
Chlorine	100 mEq/L
Phosphorus	4.46 mEq/L
Calcium	9.44 mEq/L
Creatinine	1.7mg/dL
BUN	30 mg/dL
Total serum protein	6.77 g/dL
Serum albumin	4.06 g/dL
Albumin in ascitic fluid	1.1 g/dL
SAAG	2.96 g/dL
Proteins in ascitic fluid	1.58 g/dL
Creatinine in ascitic fluid	7.44 mg/dL
Urea in ascitic fluid	144 mg/dL

ALT: alanine aminotransferase; AST: aspartate aminotransferase; BUN: blood urea nitrogen; AP: alkaline phosphatase; SAAG: serum ascites albumin gradient; GGT: γ-glutamyl transferase. Source: The authors.

Due to the recurrence of the symptoms, chronicity, absence of etiology after a detailed study, and taking into account the patient's surgical history, less frequent etiologies were considered a possibility of uroperitoneum. Creatinine was measured in the peritoneal fluid, the result of which was 7.44 mg/dL, and the gradient between fluid and serum was 5.74, which further increased the suspicion. Due to the uncertainty in the face of acute kidney injury and suspicion of urinary fistula, the nephrology service requested a voiding cystography with dynamic films, finding a bladder dome defect with active contrast extravasation into the peritoneal cavity, which confirmed the presence of uroperitoneum and explained the elevation of nitrogenous gases that simulated acute renal injury (**Figure 1**). To better characterize the genitourinary tract lesion and surgical planning, a urotomography was performed (**Figure 2**) with evidence of a defect in the bladder dome of 7.8 mm towards the right side in its anterior portion, with evidence of extraluminization of the contrast medium as a sign of rupture. After this characterization, he was scheduled for laparotomy with cystorrhaphy, performed at another institution.

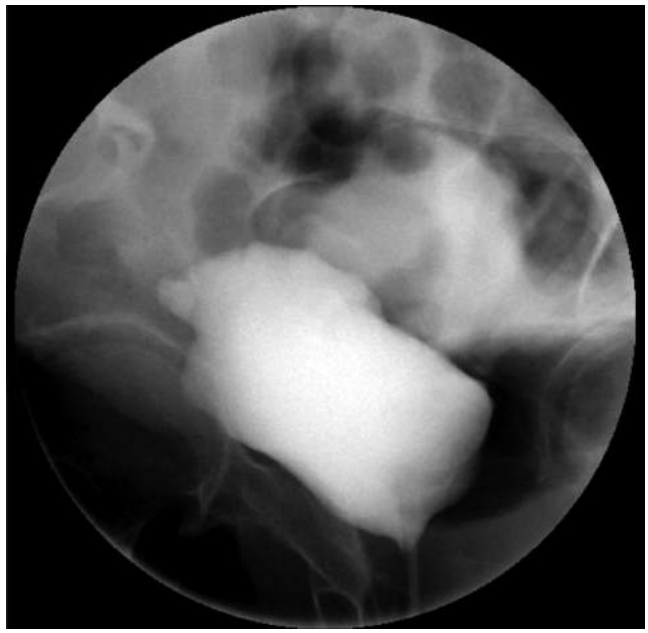

Figure 1. Voiding cystography. Authors' archives.

DISCUSSION

Uroperitoneum or urinary ascites is a rare entity defined as the presence of urine in the peritoneal cavity. It may be due to trauma, spontaneous rupture of the bladder, or perforation[10]. Moreover, it has been iatrogenically described as secondary to surgical procedures such as gastrointestinal[15], urological[16,17], gynecological[18], and obstetric[19] surgeries with an incidence of 0.11%[20]. The main risk factors identified for iatrogenic bladder injury are advanced age, recent chemotherapy or radiotherapy, and smoking[20]. It has also been associated with neurological conditions such as tabes dorsalis and multiple sclerosis[21,22]. There are reports in the literature related to radiotherapy and pelvic nerve fibrosis leading to the neurogenic bladder[23] and ureterovesical lesions resulting from lithiasis, tumors, and inflammation[24]. Spontaneous bladder rupture may be due to continuous irrigation, postpartum, and alcoholic intoxication[12,24,25]. There are three types of bladder rupture: extraperitoneal, the most frequent manifestation, in approximately 80% of cases; intraperitoneal, in up to 15%-20%; and combined[26].

The clinical manifestations of urinary peritonitis are not specific since sterile urine can be tolerated for several days and manifest through diffuse symptoms such as abdominal pain, dysuria, frequency, and urgency. There may also be oliguria or anuria and, in severe cases, peritonitis and septic shock if infected urine is present[27].

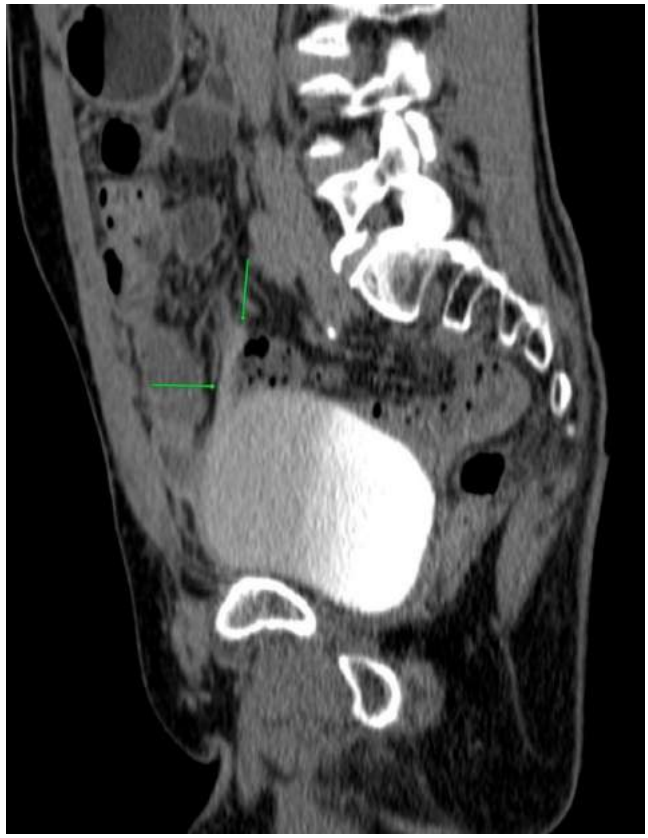

Figure 2. Sagittal section of contrasted urotomography. Green arrows indicate extravasation of contrast medium. Authors' archives.

Pseudorenal failure is defined as elevated serum creatinine, which mimics acute kidney injury, often of unknown etiology, after excluding traditional causes[28]. The uroperitoneum is characterized by increased serum creatinine due to the reabsorption of urinary creatinine mediated by the peritoneal membrane. In turn, chronic intra-abdominal urine leakage increases the abnormal reabsorption of toxic metabolites; thus, consideration should be given to this entity in the presence of acute kidney injury together with ascites or peritonitis, and electrolyte disturbances such as hyponatremia, hyperkalemia, and metabolic acidosis[10,27,29]. Calculating the gradient between creatinine in ascitic fluid and serum creatinine is instrumental, which gives a higher value to the diagnostic assumption if greater than 1[10-12], as happened in the case of our patient, whose result was 5.74.

Uroperitoneum is a difficult diagnosis, especially without a history of trauma or urologic instrumentation. Its form of manifestation is variable. It can occur as an acute abdomen with high associated mortality rates or as oliguric pseudo-acute kidney injury accompanied by azotemia, hyponatremia, hyperkalemia, metabolic acidosis, and increased nitrogen levels in the peritoneal fluid. Renal function usually improves when performing paracentesis or indwelling bladder catheterization[10,27,30-32].

Voiding cystography is the gold standard for diagnosing bladder rupture, with a sensitivity and specificity of 95% and 100%, respectively[33]. However, with the availability of new techniques, CT cystography has a performance comparable to voiding cystography, especially if injuries to other organs must be ruled out, which is common in traumatic bladder ruptures in multiple trauma patients[33,34].

Sam Kant et al.[10] described the case of a 74-year-old man with a history of ischemic heart disease and radical prostatectomy, who ten days after the procedure, presented with oliguric acute kidney injury, ascites, hyponatremia, hyperkalemia, elevated serum urea, and creatinine in the peritoneal fluid. Therefore, they suspected that the source of the abdominal fluid was a urinary focus, like the case described, except for the initial hydroelectrolytic disorder.

Ajape AA et al.[35] reported the case of a 62-year-old man with a history of prostatic hyperplasia who consulted for symptoms of abdominal pain, distension, and anuria of five days' evolution. His abdomen was distended and painful in the hypogastrium. Rectal examination revealed an enlarged prostate and abdominal ultrasound showed free fluid. All of this gave rise to the suspicion of a spontaneous bladder rupture confirmed by a voiding cystography. This case had a manifestation similar to the one we reported: pain, abdominal distension, and confirmation of the uroperitoneum with voiding cystography.

Bourgeois S et al.[26] informed the case of a 64-year-old woman with a history of transitional cell carcinoma of the bladder with subsequent laparoscopic nephroureterectomy. She was admitted due to acute colicky abdominal pain, abdominal distension, tender abdomen on palpation, and signs of peritonitis. From the paraclinical tests, a serum creatinine of 4.23 mg/dL and urea of 99.9 mg/dL stood out, with no hydroelectrolytic disorder. A simple tomography showed hypodensity compatible with the free intraperitoneal fluid, suggesting ascites. A prerenal acute kidney injury was suspected, and intravenous fluids were started without a subsequent drop in creatinine until bladder catheterization was performed. A diagnostic laparoscopy was performed, and biopsies were taken from the bladder due to its history of previous neoplasia, which was negative for malignancy. Then, when analyzing the ascitic fluid, elevated creatinine, and urea levels were found (although they were not described), thus confirming the uroperitoneum. This picture is similar to the one we report regarding clinical manifestations, the diagnostic process, the elevation of nitrogen compounds in the peritoneal fluid for the diagnostic approach, and the improvement in renal function after the bladder catheter insertion.

Furthermore, Gonzalo L et al.[32] detailed the case of a patient with a history of hypothyroidism and two deliveries, one of them with forceps and bladder rupture, who developed a picture of pain in the hypogastrium and accumulation of peritoneal fluid. A blood urea nitrogen (BUN) of 36 mg/dL and creatinine of 2.16 mg/dL stand out among the initial laboratory parameters. Subsequently, a non-inflammatory peritoneal fluid and a SAAG greater than 1.1 g/dL without liver disease were studied, for which a cystoscopy was performed, finding a vesicoperitoneal fistula, compatible with uroperitoneum, a complex diagnosis as in the case of our patient. Unlike this case, our patient's symptoms had a larvate and recurrent manifestation, with higher elevations of nitrogen gases.

It should be noted that the different series share the presence of hyperkalemia, increased BUN and creatinine, and improvement of nitrogen levels with permanent bladder catheterization, in addition to increased creatinine and BUN in the peritoneal fluid.

In the present case, the chronicity, the chronological order of the symptoms, their recurrence, the fluctuation in serum creatinine, and the sensible diagnostic approach adopted by our institution added to the history of radical prostatectomy allowed us to suspect a uroperitoneum first with subsequent imaging confirmation. Finally, the patient underwent urology surgery with repair of the bladder defect and has not had recurrences of the clinical picture.

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Case report

Laparoscopic Deloyers Procedure as a Salvage Technique for Colorectal Anastomosis: An Alternative to Total Colectomy

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Abstract

Introduction: The Deloyers procedure is a valuable technique used in reconstructing bowel transit following an extended left colectomy, a Hartmann-type colostomy, or repeated colon resections. It enables the creation of a tension-free colorectal or coloanal anastomosis. **Case presentation:** A 60-year-old female patient presented for consultation regarding the closure of a colostomy. Her medical history included segmental colectomy of the sigmoid and descending colon, resulting in a Hartmann-type colostomy due to complicated diverticulitis. The patient underwent laparoscopic surgery, during which a segment of the transverse colon with a short mesocolon was identified. Due to the complete release of the colon, a colorectal anastomosis could not be performed. As an alternative to preserving the ileocecal valve and achieving a tension-free colorectal anastomosis, the patient underwent the Deloyers procedure. **Discussion:** The Deloyers procedure involves tension-free anastomosis between the right colon and the rectum or anus. It includes complete mobilization and a 180° counterclockwise rotation of the hepatic angle and the right colon. The right and middle colic vessels are divided, while preserving the ileocolic pedicle and the ileocecal valve, thus avoiding the need for total colectomy and ileorectal anastomosis, which may yield unsatisfactory functional outcomes. **Conclusion:** The Deloyers procedure represents a viable alternative to ileorectal or ileoanal anastomosis, offering satisfactory functional outcomes.

Keywords

Colectomy, surgical anastomosis, colostomy, ileocecal valve.

INTRODUCTION

The Deloyers procedure is a technique that consists of an anastomosis between the right or transverse colon and the rectum or anus after complete mobilization and rotation of the right colon, preserving the ileocolic vessels. It is advantageous in reconstructing intestinal transit after an extended left colectomy, Hartmann-type colostomy closure, or iterative colonic resections. In these situations, when the residual colon cannot reach the rectal stump without tension, the Deloyers procedure for tension-free colorectal or coloanal anastomosis can be used as an alternative technique to avoid total colectomy and ileorectal anastomosis[1,2].

CASE REPORT

A 60-year-old woman attended the clinic for colostomy closure, a critical history in the medical record. Three years earlier, she underwent a segmental colectomy of the sigmoid and descending colon and was referred to with a Hartmann-type colostomy due to an episode of complicated diverticulitis. She had preoperative imaging studies; colon by rectal

enema indicated a rectal stump inferior to the promontory, and proximal ostomy colonoscopy showed a segment of the transverse colon and normal right colon.

The patient was taken to laparoscopic surgery, where four disposable trocars were used, two of 12 mm and two of 5 mm, and a short segment of the descending colon with a short meso was found. When freed entirely, the colorectal anastomosis could not be performed. Therefore, we decided to perform the Deloyers procedure using a completely laparoscopic approach. With advanced bipolar energy, the transverse colon was released, including the hepatic and splenic angle and the right colon. The middle colic vessels were ligated proximally with Hem-O-Lok clips, preserving the ileocolic vessels through which the colonic remnant will receive irrigation from the marginal arteries. Once complete mobilization of the colon was achieved, a standard appendectomy was performed since the caecum and distal ileum were going to be located in the hepatic position, which in the future would have diagnostic difficulties in the acute event of appendicitis. Subsequently, counterclockwise rotation was performed around the axis of the ileocolic vessels of the right colon to conduct the tension-free colorectal anastomosis with circular mechanical suture number 29. She had a satisfactory clinical evolution during the hospital stay, for which she was discharged on the third postoperative day.

DISCUSSION

The Deloyers procedure was first reported in 1964 by Dr. Lucien Deloyers. He performed complete mobilization of the right colon (**Figure 1**) and counterclockwise rotation around the axis of the ileocolic vessels, allowing colorectal or coloanal anastomosis with no tension and correct perfusion preservation[3].

It is generally performed by open surgery, although the Deloyers laparoscopic procedure is feasible and safe but requires trained teams[4]. Indications for this procedure are generally tumors of the left colon (e.g., splenic flexure), synchronous colorectal cancers, rectal resections, ischemia of the left colon after inferior mesenteric artery ligation, Hirschprung's disease, severe constipation, and reconstructions of complex intestinal transit, or iterative colonic resections when the anatomy is not favorable to allow a tension-free transversorectal or anal anastomosis[1,5,6].

The procedure aims to achieve a tension-free anastomosis of the right colon and rectum or anus after complete mobilization and 180° anticlockwise rotation of the hepatic angle and the right colon (**Figure 2**). The right and middle colic vessels are sectioned, with preservation of the ileocolic pedicle and ileocecal valve, avoiding the need for total colectomy and ileorectal anastomosis, for which functional results may be unsatisfactory (**Figure 3**)[1].

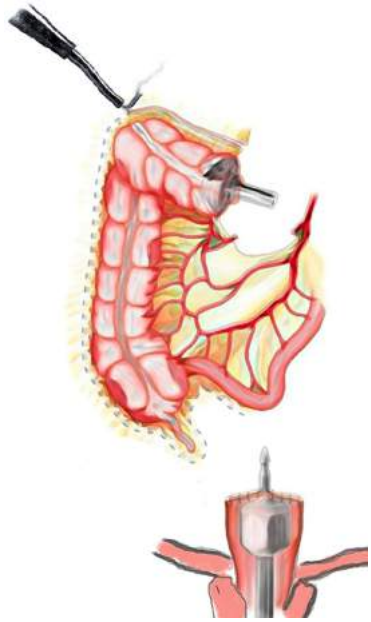

Figure 1. Release and mobilization of the right colon laparoscopically with monopolar energy and Hook forceps. Image owned by the authors.

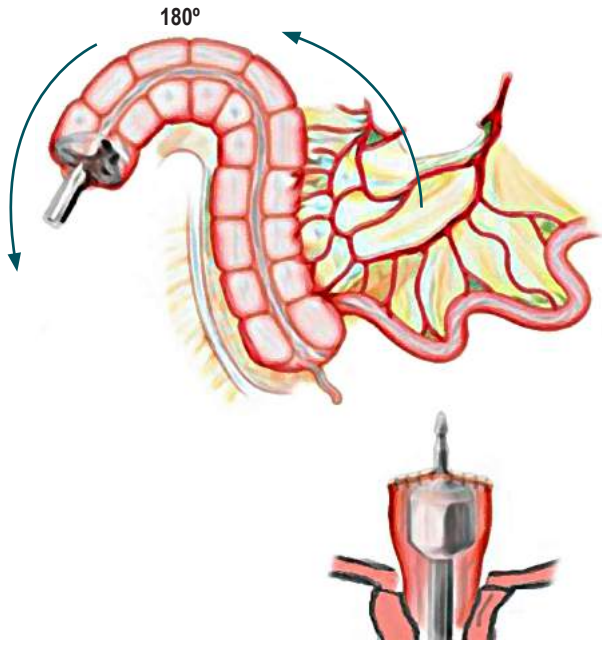

Figure 2. 180° rotation of the right colon on the ileocolic vascular pedicle. Image owned by the authors.

For the treating surgeon, it is vital to have a variety of surgical options to the conventional ones when reconstituting intestinal transit and to consider the Deloyers procedure as a safe technique and a possible alternative to ileorectal

anastomoses when there is not enough remaining colon length to perform a traditional colorectal anastomosis after a resection.

Our patient's procedure was performed using a completely laparoscopic approach, using advanced bipolar energy. The operating time was 3.5 hours. No intraoperative complications were recorded.

CONCLUSION

We deem the laparoscopic Deloyers procedure a safe and feasible technique and a viable alternative to the ileorectal or ileoanal anastomosis with satisfactory functional results.

Financial support and sponsorship

None.

Conflicts of interest

There are no conflicts of interest.

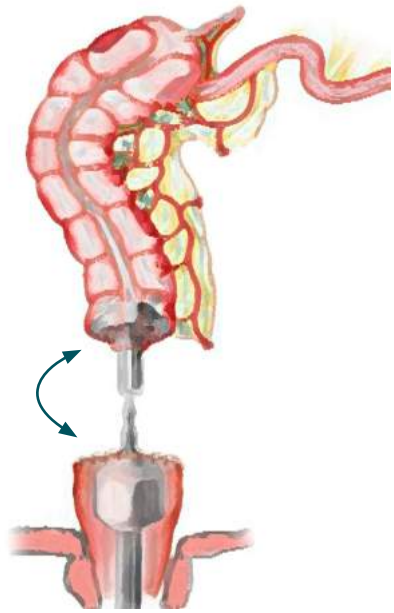

Figura 3. Anastomosis colorrectal sin tensión, preservando la válvula ileocecal. Imagen propiedad de los autores.

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Case report

Unusual Association of Intestinal Tuberculosis and Thalassemia: A Case Report

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Abstract

Introduction: Tuberculosis is an infectious disease that can be prevented and cured, but it is still associated with high morbidity and mortality rates. Disseminated tuberculosis, although rare, can occur in individuals with underlying pathologies that affect the immune system. Currently, there are limited reports on disseminated tuberculosis in individuals with congenital disorders. **Clinical case:** We present a case of a patient with a history of β thalassemia who was admitted to the emergency department with symptoms of abdominal pain and constitutional symptoms. The final diagnosis was disseminated tuberculosis. This case is of particular interest due to its atypical presentation, the initial suspicion of malignancy, and the extensive involvement of the disease despite the patient's absence of immunosuppression history. **Conclusions:** Disseminated tuberculosis in immunocompetent patients is a rare presentation associated with poor outcomes. The history of β thalassemia may be a risk factor to consider based on the metabolic pathways involved in the pathophysiology of both diseases.

Keywords

Tuberculosis, thalassemia, glutathione, iron, case report.

INTRODUCTION

Tuberculosis (TB) is a preventable and curable infectious disease associated with high morbidity and mortality worldwide; it was declared by the World Health Organization (WHO) in 1993 as a public health emergency[1,2]. Its primary clinical compromise is the lung, known as *pulmonary TB*; however, it can occur in other organs such as the pleura, lymph nodes, abdomen, genitourinary tract, and joints, among others, and together it is called *extrapulmonary TB*[3]. By 2020, 9.9 million cases of TB had been documented, with an estimated incidence of 127 cases per 100,000 people and an approximate mortality of 1.2 million people per year in patients without human immunodeficiency virus (HIV) coinfection and 214,000 people per year in patients with HIV coinfection[4]. It has been reported that patients with multiple comorbidities may be affected by TB infection[5]. Nonetheless, there are few reports on patients with underlying congenital disorders. We present the case of a 31-year-old patient with a history of thalassemia. He was admitted due to abdominal pain and constitutional symptoms, in whom neoplastic involvement was suspected upon initial approach, and intestinal TB was documented during the diagnostic process. The studies conducted for the characterization of the disease are provided.

CASE PRESENTATION

A 31-year-old male patient who worked as a farmer presented with a clinical picture of two years of evolution consisting of intermittent colicky abdominal pain in the right hypochondrium of moderate intensity and 4-5 stools a day of Bristol consistency 6, without mucus or blood. He reported the association with asthenia, adynamia, quantified weight loss of seven kilograms in the last six weeks, and nocturnal diaphoresis for two weeks. He had an increase in the intensity of abdominal pain in the previous five days associated with proctalgia and hematochezia, so he decided to attend the emergency room at our institution. On review by systems, he had respiratory symptoms that began eight days before admission due to dry cough and mMRC (modified Medical Research Council) dyspnea 3/4, associated with the appearance of ulcerated lesions in the anal region. The patient had a history of β-thalassemia with hepatosplenomegaly, for which he received a folic acid replacement and blood transfusions as needed; he also had a history of hepatitis A infection and a family history of colon cancer in his mother, diagnosed at age 52. On admission, the patient had tachycardia, diffuse abdominal pain on palpation, and palpable hepatomegaly over the right costal margin. The lymph nodes in the proper inguinal chain were not attached to deep planes or tender on palpation. The anal inspection revealed an ulcerated lesion around 9:00 clockwise with regular edges and no bleeding.

A clinical history of gastrointestinal neoplasia was considered because of the family history. An abdominal tomography with contrast was requested, which identified a concentric thickening of the wall of the ascending colon with slight enhancement and multiple mesenteric and retroperitoneal adenopathies (**Figure 1**). The paraclinical tests requested on admission documented normochromic normocytic anemia, lymphopenia, mild thrombocytopenia, elevated alkaline phosphatase, and hypoalbuminemia.

A colonoscopy was performed, which revealed multiple 5-mm ulcers with raised and defined erythematous edges at the level of the rectum, sigmoid, descending, and transverse colon, edematous mucosa covered by fibrin and erythema at the level of the hepatic flexure that diminishes friable lumen upon passage of the equipment, and an area of concentric stenosis with an inflammatory appearance. Colitis of infectious or inflammatory etiology was considered among the possible diagnoses. Biopsies of the mentioned areas were

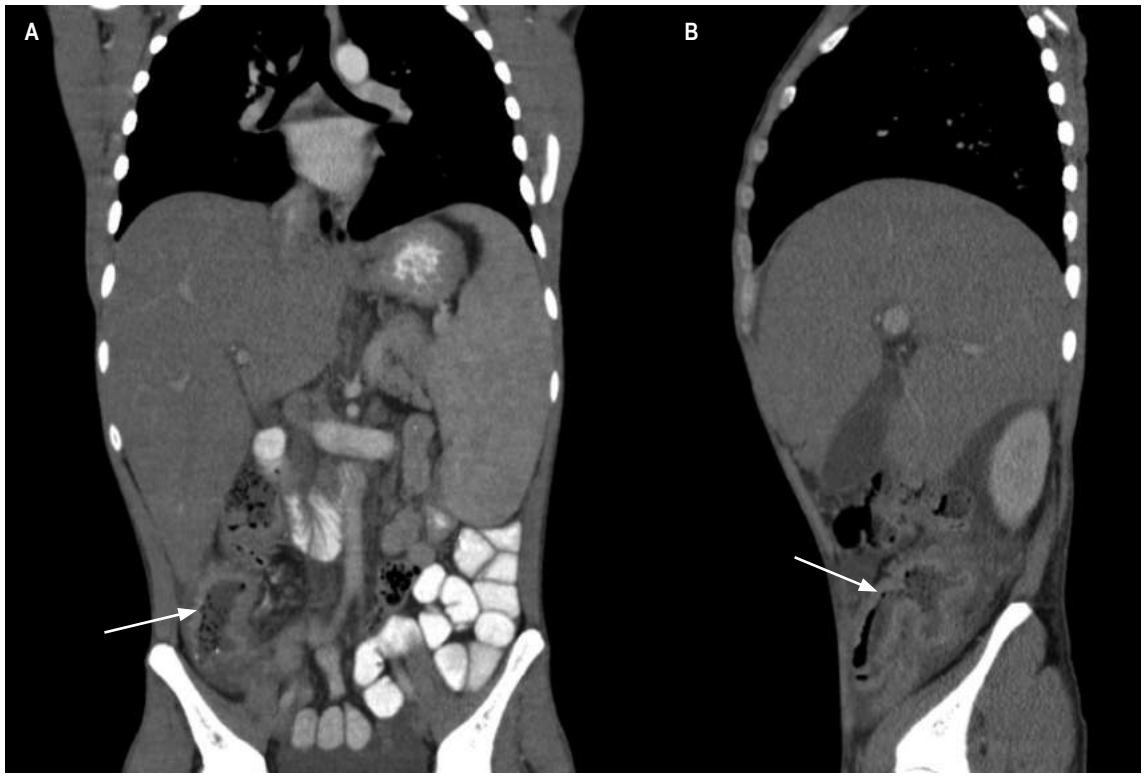

Figure 1. Contrast-enhanced coronal and sagittal computed tomography of the abdomen. **A.** Concentric thickening of the wall of the ascending colon with slight enhancement (arrow). **B.** Thickening of the distal ileum and ileocecal valve (arrow). Source: Patient's medical record.

taken, documenting findings compatible with granulomatous colitis (**Figure 2**). A rapid polymerase chain reaction test was performed to identify *Mycobacterium tuberculosis* and sensitivity to rifampicin (GeneXpert MTB/ RIF) in the tissue obtained in the colon biopsy, with a positive result for *M. tuberculosis* (**Table 1**). Due to respiratory symptoms, a chest tomography was requested, which reported micronodules of bilateral random distribution, some forming a budding tree pattern and predominated in the left upper lobe (**Figure 3**). Serial bacilloscopies found acid-fast baci-

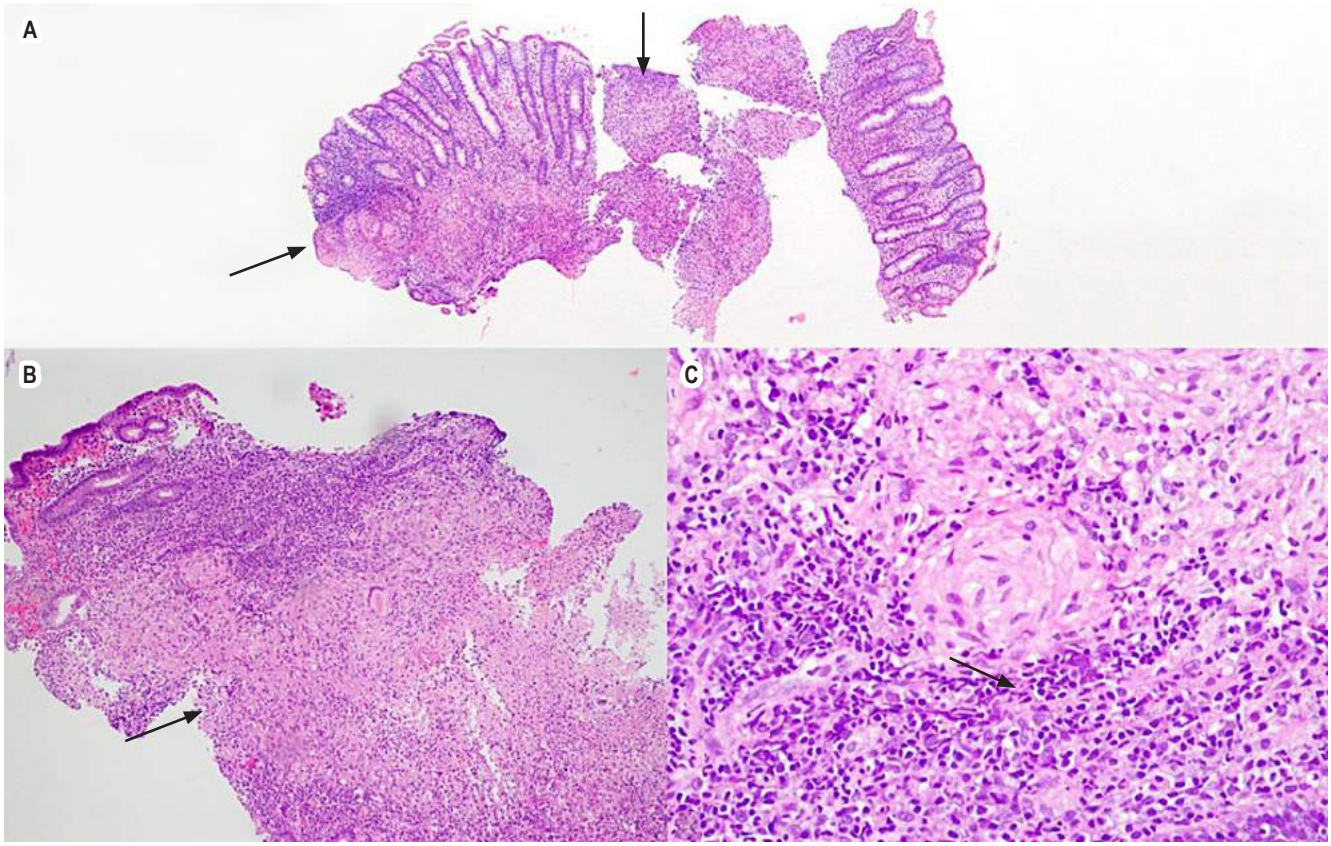

Figure 2. Granulomatous colitis with hematoxylin and eosin. **A.** 4x, colonic mucosa, arrows point to granulomas. **B.** 10x, the lamina propria shows the formation of well-defined granulomas and some neutrophil abscesses. **C.** 40x, epithelioid granuloma. Source: Patient's medical record.

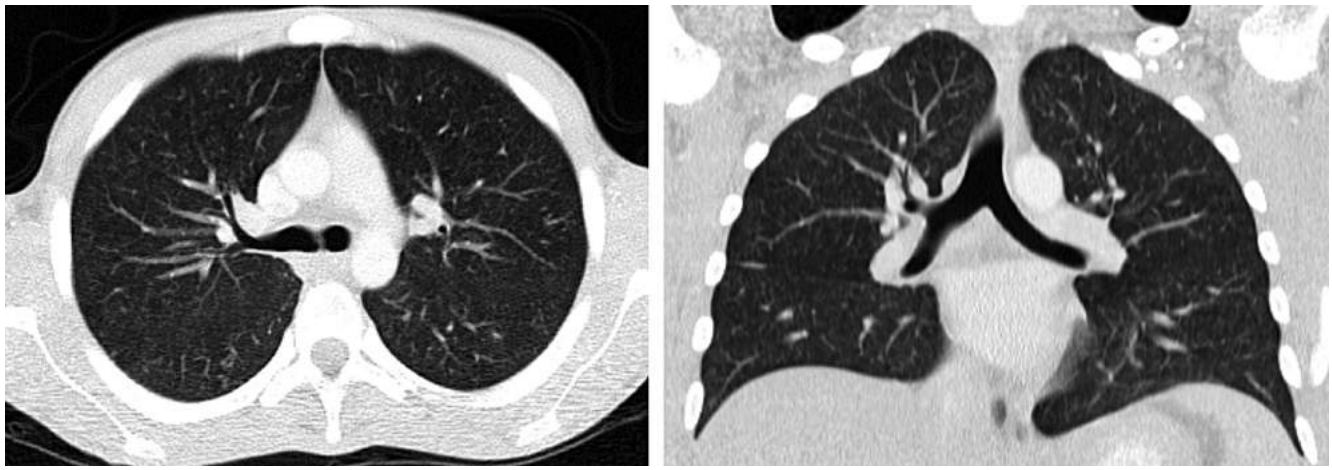

Figure 3. Coronal and cross-sectional high-resolution chest CT. Bilateral randomly distributed micronodules, some forming a budding tree pattern. Source: Patient's medical record.

Table 1. Summary of tests and results of the patient

Colonoscopy samples	
Transverse and right colon biopsy	Negative for malignancy Findings consistent with granulomatous colitis
PCR in rectal biopsy*	Sample positive for tuberculosis complex mycobacteria
Sputum	
Staining for AFB	Positive 1-9 AFB in 100 observed fields
PCR in sputum sample	Identification of *M. tuberculosis* by PCR: Detected Rifampicin resistance not detected
Lowenstein–Jensen culture	*M. tuberculosis*
MGITTM liquid culture medium	A positive culture for *M. tuberculosis* complex
Sensitivity tests* **	
Isoniazid	0.1 µg/mL sensitive (S)
Rifampicin	0.5 µg/mL sensitive (S)
Pyrazinamide	100 µg/mL sensitive (S)
Peritoneal fluid	
Gram stain in ascitic fluid	No germs observed
Ascitic fluid culture	Negative at 72 hours of culture
Cytological	
Appearance	Limpid
Color	Yellow
Leukocytes	234 cells/mm^3
Lymphocytes	74%
Monocytes	8%
Neutrophils	18%
Macrophages	118 in 100 leukocytes counted
Red blood cells	786 cells/mm^3
Cytochemical	
Glucose	98.19 mg/dL
Proteins	3.38 g/dL
Albumin	1.5 g/dL
Serum ascites albumin gradient	1.1
Microbiology	
Aerobic blood culture #2	Negative after five days of culture
Anaerobic blood culture #1	Negative after five days of culture
HIV test****	0.06 sec/CO; NOT reactive

*Real-time PCR using TaqMan probes for the IS6110 repeat region of tuberculosis complex mycobacteria.
**Real-time, nested, semi-quantitative PCR and melt peak detection. DNA detection (IS1081-IS6110) of *M. tuberculosis* (MTB) and detection of rpoB gene mutations associated with resistance to rifampicin.
***BACTEC MGIT 960 automated method.
****Chemiluminescent Microparticle Immunoassay (CMIA).
Source: Prepared by the authors with data from the patient's medical record.

llus (AFB), and the GeneXpert MTB/RIF test confirmed the diagnosis of TB and lung involvement with sensitivity to rifampicin.

An ophthalmology opinion was requested for the initiation of tetraconjugate treatment. In the assessment, an incidental finding in the left eye revealed a lesion with a granulomatous subretinal appearance consistent with ophthalmic involvement of TB. He was considered a patient diagnosed with disseminated TB, pulmonary, intestinal, lymphatic, and retinal involvement with sensitivity tests that confirmed sensitivity to isoniazid and rifampicin. Thus, tetraconjugate management was started with rifampicin 150 mg, isoniazid 75 mg, pyrazinamide 400 mg, and ethambutol 275 mg, each dose adjusted for weight. The first phase consisted of 56 doses, and pyridoxine, one tablet per day, was added. The patient was discharged.

He was re-admitted to our institution 20 days after discharge due to a clinical picture compatible with intestinal obstruction, for which an abdominal X-ray was taken, finding staggered air-fluid levels and the absence of distal gas. Medical management with a nasogastric tube and analgesia was indicated, and an abdominal tomography was requested with a new finding of ascites. A paracentesis was ordered in which 200 mL of sallow fluid was obtained, and the cytological study found leukocytosis at the expense of lymphocytes. In addition, the serum ascites albumin gradient (SAAG) confirmed a nonhypertensive fluid (**Table 1**), which, due to its cytochemical and cytological characteristics and a history of disseminated TB, was deemed ascitic fluid consistent with peritoneal TB. The obstructive symptoms resolved, and the abdominal pain improved, for which the patient was discharged from the hospital.

DISCUSSION

Disseminated TB is defined as TB infection in two or more non-contiguous sites resulting from lymphohematogenous dissemination of *M. tuberculosis*, which occurs due to a primary infection or reactivation of a latent focus[6,7]. The prevalence has been reported between 4.9% and 19.6% of patients diagnosed with TB, and patients with HIV coinfection have the highest probability of disseminated involvement (27.8%)[8-10].

Among the independent risk factors described for the development of disseminated TB are the use of immunosuppressive drugs, coinfection with HIV, liver failure or cirrhosis, duration of symptoms ≥12 weeks, bilateral lung involvement, weight loss, nocturnal diaphoresis, and absence of hemoptysis and dyspnea[10]. The most frequent clinical manifestations include constitutional symptoms such as fever and nocturnal diaphoresis and abnormal laboratory findings such as hypoalbuminemia (74.7%), elevated γ-glutamyl transferase (71.0%), alkaline phosphatase (66.4%), hyponatremia (58.9%), and anemia (43.9%)[11]. Mortality from disseminated TB has been reported in around 21% of patients monitored for six months, and levels of albumin, total bilirubin, creatinine, and time to start anti-tuberculosis treatment have been correlated as independent prognostic factors[10,11].

The thalassemias are a group of hemoglobinopathies in which the standard ratio of alpha globin to beta globin production is disrupted due to a genetic variant. This abnormal ratio of alpha to beta chains causes unpaired chains to precipitate, destroying red blood cell precursors in the bone marrow and leading to ineffective erythropoiesis and hemolysis[12].

In many areas where TB is endemic, thalassemia is also high, especially in Southeast Asia[13,14]. Sriwijitalai et al.[15] conducted a bioinformatic analysis of the biological pathways related to the antioxidant system in TB and thalassemia. They identified the pathway common to TB and thalassemia through glutathione, a pleiotropic antioxidant molecule showing antimycobacterial and immune-enhancing effects. The importance of the antioxidant pathway in TB has been demonstrated. Cao et al.[16] observed a significant decrease in intracellular glutathione levels in macrophages infected with *M. tuberculosis* compared to uninfected macrophages, indicating that *M. tuberculosis* infection can cause depletion of intracellular glutathione and, in turn, promote the survival and replication of *M. tuberculosis* within host cells. Regarding thalassemia, the clinical importance of the antioxidant pathway system is highlighted. β-thalassemia is known to cause oxidative stress induced by iron overload, and the glutathione system is the primary endogenous antioxidant that protects animal cells from oxidative damage[17].

Under oxidative stress, glutathione (GSH) donates reducing equivalents to free radical-scavenging enzymes, including glutathione peroxidase (GPx) and glutathione-S-transferase (GST). It is converted to its oxidized form, glutathione disulfide (GSSG). This GSSG can be reconverted to GSH by a reaction catalyzed by glutathione reductase (GR); therefore, a lower ratio of reduced to oxidized glutathione (GSH/GSSG) may indicate increased oxidative stress in cells. Kalpravidh et al.[18] found a 90% reduction in the GSH/GSSG ratio in patients with β-thalassemia compared to controls, suggesting lower GSH availability and more significant GSSG accumulation. The marked increase in GSSG in thalassemia patients was probably due to overutilizing cellular GSH, supported by 123% and 93% increases in GST and GPx activities, respectively. The GST enzyme detoxifies xenobiotics, including metabolites from oxidative reactions, by conjugation with GSH. At the same time, GPx is an antioxidant enzyme that reduces hydrogen peroxide to water using GSH as the reducing equivalent.

It has been widely reported that patients with marked deficiency in GSH production had impaired granulomatous effector responses against *M. tuberculosis*. Patients with thalassemia are prone to developing TB, which is explained by the GSH pathway[19]. Additionally, the functions of iron overload and susceptibility to infection have been previously described[20-24]. However, publications on the thalassemia model have been limited. Most studies have used hemochromatosis as a disease model for iron overload.

Ghozali et al.[25] reported on the types of variations of a metal transporter across the phagosome membrane, natural resistance-associated macrophage protein 1 (NRAMP1), in pediatric thalassemia patients with and without TB infection. They noted that NRAMP1 polymorphisms play an essential role in iron regulation, which is also necessary for MTB. Increased iron in patients with thalassemia may have a higher potential risk of TB[26].

The clinical case we present has several highlights, the main one being the manifestation of disseminated TB in an immunocompetent patient with a history of β-thalassemia, which had not previously been considered a risk factor for this manifestation. However, in the literature review, we found biological plausibility in the alteration in the GSH pathway, which confers risk to patients with thalassemia of developing TB due to alteration in the granulomatous effector response. Another critical point to consider is the presence of previously described risk factors for developing the disease, which was identified in our patient as a manifestation of symptoms ≥ 12 weeks, constitutional symptoms due to weight loss and nocturnal diaphoresis, and bilateral lung involvement, which implies a progression of the local disease that can precede systemic involvement. Additionally, abnormal findings in our patient's laboratory tests, such as hypoalbuminemia and anemia, have been correlated with mortality; however, during the follow-up of our patient, he only had one hospital readmission, and it was due to intestinal obstruction favored by the inflammatory process at the colonic level due to TB, which was resolved with medical management.

Cases described in the Colombian literature were reviewed. We found an extrapulmonary manifestation with compromise in the central nervous system[27], pericardium with cardiac tamponade as the first manifestation[28], sternum[29] in the pediatric population, and a case of a patient with diabetes *mellitus,* and thalassemia and pulmonary TB infection with multiple associated coinfections[30]. To the best of our knowledge, the case presented is the first report of a patient with thalassemia and disseminated TB; it sets a relevant precedent for future research and the expansion of differential diagnoses in similar cases.

CONCLUSIONS

Disseminated TB in immunocompetent patients is a rare manifestation associated with adverse outcomes. Therefore, prompt diagnosis is required to reduce disease-associated morbidity and mortality. The present case allows us to conclude that there should be an active search and similar diagnostic suspicion in patients with a history of β-thalassemia, given their immunological predisposition. However, more studies are required to define screening strategies in immunocompromised patients.

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Case report

A Rare Complication of Gastrointestinal Bleeding: Jejunal Diverticulosis. A Case Report

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Abstract

Introduction: Small intestine diverticula are a rare condition with an incidence of 0.6% to 2%. Their location at the level of the jejunum is a rare alteration, and their diagnosis is often delayed due to low clinical suspicion. The clinical manifestation of this pathology is related to the development of complications —15% to 30% of patients, with approximately 10% requiring surgical intervention. **Clinical case:** We present a case of a middle-aged adult patient who experienced a complication due to a bleeding jejunal diverticulum. The patient underwent surgical management, which resulted in a satisfactory outcome. **Objective:** This article aims to describe jejunal diverticulosis, a rare condition that can have a significant impact on affected individuals. Emphasizing its clinical suspicion as a differential diagnosis for gastrointestinal bleeding is crucial. Additionally, we discuss diagnostic methods and highlight various therapeutic options, including surgical management.

Keywords

Diverticulum of the colon, jejunum, gastrointestinal bleeding, therapeutic embolization.

INTRODUCTION

This article aims to describe jejunal diverticulosis, which, while rare, can compromise the life of those suffering from it; thus, its establishment as a differential diagnosis that causes gastrointestinal bleeding should be prioritized. It also clarifies diagnostic methods and shares the therapeutic options available, including surgical management.

Jejunal diverticulosis was first described in 1794 by Somerling, but it was not until 1906 that Gordinier and Sanpson informed the first case of a patient who underwent surgery for this pathology[1-4]. Diverticulosis occurs more frequently in the large intestine than in the small intestine, the latter with a reported incidence of 0.6%-2% in autopsy series and a reported radiological incidence of 2%-5%[5,6].

In small intestine diverticulosis, the most common site of manifestation is the duodenum, followed by the jejunum and ileum[6]; the former occurs in equal numbers in both men and women, while jejunoileal diverticula have a greater predominance in men than in women[7,8].

Pathophysiologically, diverticula are classified as true or false (pseudodiverticula) due to increased intraluminal pressure. The latter causes herniation of the mucosa and submucosa, mainly at the weakest points, which correspond to sites through which the vasa recta penetrate the

muscular layer of the intestine and are covered only by the serous layer[9-11].

The etiopathogenesis of small intestine diverticulosis is not clear. So, alterations in intestinal peristalsis, intestinal dyskinesia, and increased intraluminal pressure have been proposed as causes of this abnormality, which would result in the appearance of diverticula in the sites where the mesenteric vessels enter the muscular layer of the small intestine[9-11].

The clinical manifestation of these diverticula is related to complications, which occur in 15%-30% of patients, of which up to 10% require surgical management[1,2,12]. Among these manifestations or complications are diverticulitis and perforation, with percentages between 2% and 6%, obstruction between 2% and 4%, and gastrointestinal bleeding between 3% and 8%. The latter occurs because of erosion and ulceration of the mucosa, which compromises the mesenteric vessels around the neck of the diverticulum[1,2,13-16].

Generally, the diagnosis of small bowel diverticula is made incidentally on endoscopic retrograde cholangiopancreatography (ERCP), laparotomy, or enteroscopy[13-17]. The American Journal of Gastroenterology states that small bowel bleeding should be considered during regular upper and lower endoscopic studies[13].

Diagnostic methods involved in the study of gastrointestinal bleeding include upper and lower endoscopy, enterotest, scintigraphy, digital angiography, and computed tomography (CT)(18-20).

Upper digestive endoscopy is the primary diagnostic tool in studying upper gastrointestinal bleeding. Its sensitivity ranges from 92% to 98%, with specificity between 33% and 100%[18].

Colonoscopy is the first diagnostic method used in patients with lower gastrointestinal bleeding, with a sensitivity of 50% for detecting the location and cause of bleeding. However, its implementation is hampered by the need for prior bowel preparation, associated with inappropriate colon viewing if large amounts of blood or clots are present[18].

Capsule endoscopy is not feasible in an emergency setting, even though it can explore the entire small intestine since viewing is affected if there is an active massive hemorrhage[18].

Labeled red blood cell scintigraphy can be used to detect and locate the site of gastrointestinal bleeding. It has a sensitivity of 93% and a specificity of 95%; nonetheless, its value as a diagnostic test is limited since it has up to a 22% chance of false bleeding location[19].

Mesenteric angiography offers the advantage of detecting and making a therapeutic intervention through transcatheter embolization. It has a sensitivity between 40% and 86%, and ischemia is the main risk of this procedure[19].

Abdominal angiotomography is considered the first-line diagnostic method in a patient with suspected bleeding from the small intestine. It allows viewing the presence or absence of contrast material extravasation into the intestinal lumen. It has a sensitivity of 86% and a specificity of 95% for diagnosing acute gastrointestinal bleeding[20].

Once jejunal diverticula are identified as the cause of bleeding, resection of the affected segment of the jejunum with primary anastomosis should be performed[20].

CLINICAL CASE

A 48-year-old male patient with a history of gastritis was admitted to the emergency department, presenting with a three-day history of lower gastrointestinal bleeding, represented by hematochezia associated with a syncopal episode at the referral site. On admission, the patient was found hemodynamically stable and with severe anemia, for which an endoscopy and colonoscopy were performed with reports of "hiatal hernia" in the upper study and "presence of melena throughout the colon and distal ileum, without masses, polyps, or diverticula" in the lower study.

During the first three days of hospitalization, he persisted with hematochezia, hypotension, and severe anemia that did not correct despite being polytransfused. So, a mesenteric arteriography was requested, in which no lesions were found to explain the bleeding. The patient became hemodynamically unstable, for which he was transferred to the intensive care unit (ICU), requiring transfusion, vasopressor support, and invasive mechanical ventilation. In addition, he had a picture of hematemesis requiring upper digestive tract endoscopy that reported "angiodysplasia of the duodenal bulb, which received sclerotherapy." Due to the persistence of hemodynamic instability, lower gastrointestinal bleeding, and severe anemia, an abdominal CT angiography was performed, which revealed a "dilation in the ileal small intestinal segment, which could correspond to a Meckel's diverticulum, with extravasation of the contrast medium through this segment" (**Figure 1**). Then, a selective embolization was performed using arteriography (**Figures 2** and **3**).

The patient showed clinical improvement and hemodynamic stability, for which the vasopressor support was removed. Thus, we decided to schedule an intestinal resection. A median laparotomy was performed in which a single jejunal diverticulum was located 40 cm from the angle of Treitz (**Figure 4**), with residual blood content in the small intestine and colon. Then resection of the diverticulum and jejunojejunal anastomosis were performed. Finally, he was discharged from the hospital on the tenth day of hospitalization.

The pathology report described a 4 cm segment of the small intestine with a single pocket-shaped structure on the wall, corresponding to a jejunal diverticulum, with a recent thrombosis of the venous vessels and no ulceration or perforation.

DISCUSSION

Small intestine diverticulosis is a rare entity with even less common complications. The first reports of this pathology were made in 1794, and those of the first complications in 1853[5]; the prevalence of this pathology and its complications are low. The etiology is still unclear, although the currently most accepted aetiological theory indicates that

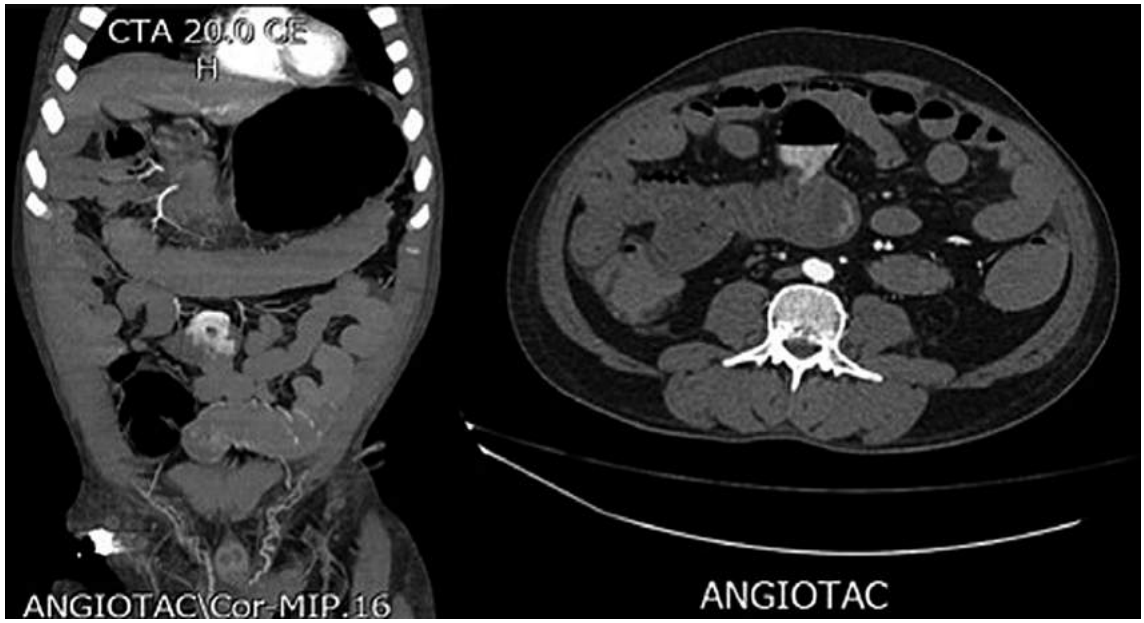

Figure 1. Computed axial tomography showing a thin-walled cystic structure with an air-fluid level corresponding to a jejunal diverticulum. Source: Radiology Service, Hospital Comuneros. Selected by the authors.

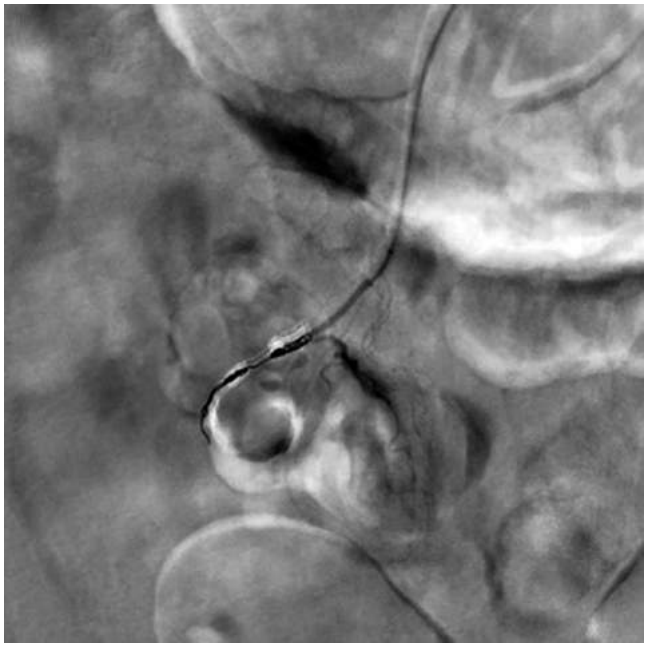

Figure 2. Angiographic embolization of the jejunal diverticulum highlighting a cystic figure compatible with a jejunal diverticulum. Source: Hemodynamics Service, Hospital Comuneros. Selected by the authors.

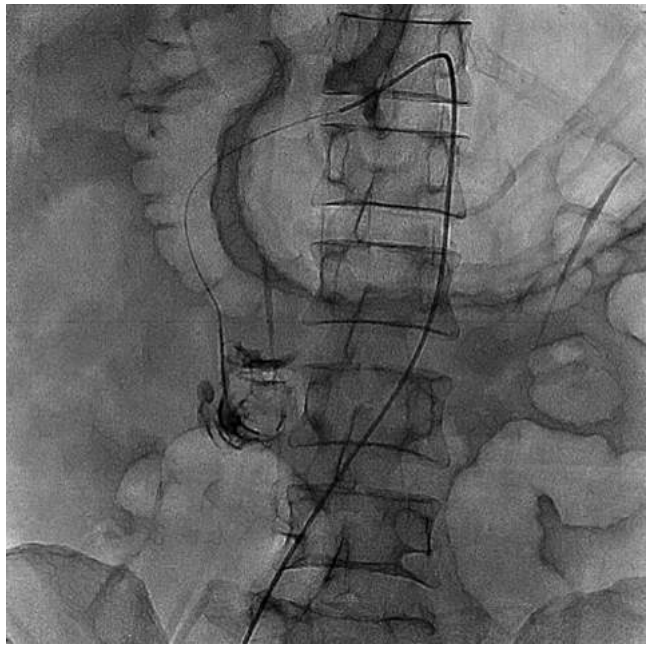

Figure 3. Angiographic embolization of the diverticulum. Source: Hemodynamics Service, Hospital Comuneros. Selected by the authors.

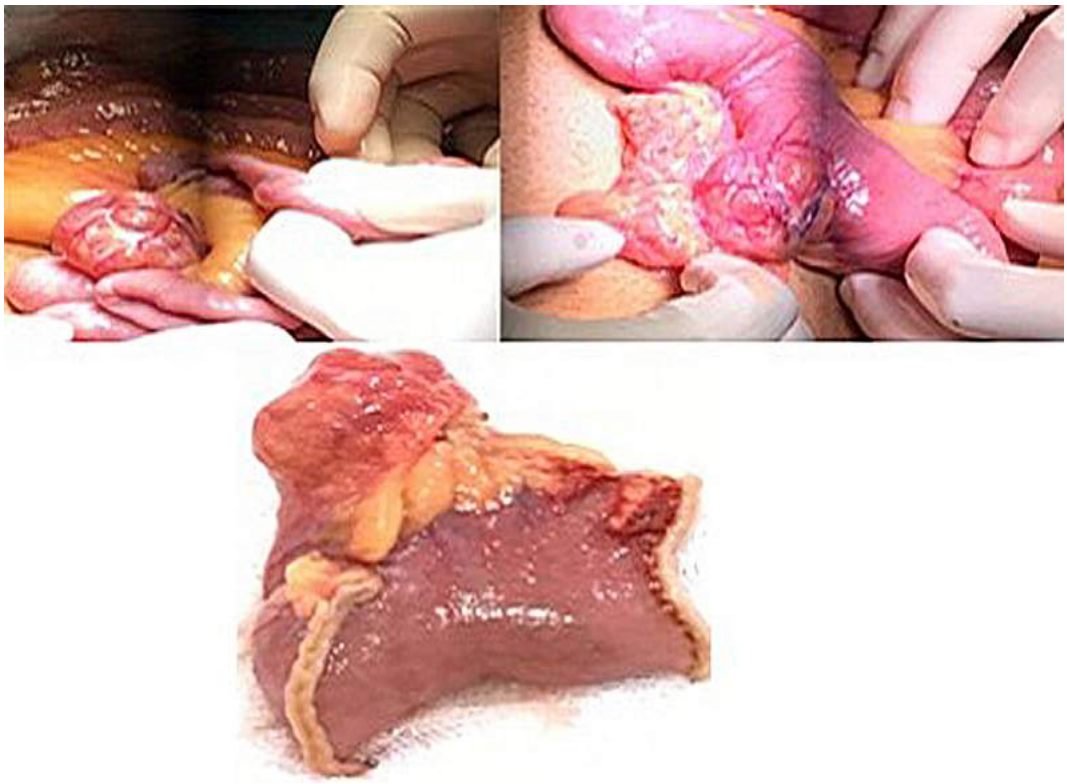

Figure 4. Macroscopic anatomical piece. Presence of an open diverticulum that allows its content to be observed. Source: Surgery Service, Hospital Comuneros. Selected by the authors.

the formation of diverticula can be caused by dysfunction or dyskinesia of the jejunal smooth muscle, which triggers an alteration in its contraction. It causes the development of weak areas, leading to herniation of the mucosa, submucosa, and serosa, but not the muscular layer (false diverticulum).

The case presented is very relevant given that both the clinical manifestation and the presence of complications of this pathology were found in a patient in the fifth decade of life. Notably, the clinical manifestation is more common around the seventh decade of life, as well as gastrointestinal bleeding, which occurs between 3% and 8% of the population with jejunal diverticula[7,8]. This complication should be considered for causal differential diagnoses of gastrointestinal bleeding since it does not have pathognomonic symptomatology that allows differentiation from other causes, hence the compromised hemodynamic status of patients, as in the previously described case, which required management in the ICU due to hemodynamic instability and severe anemia secondary to profuse and constant bleeding from the diverticulum.

Other complications in jejunal diverticula are diverticulitis and perforation, in 2%- 6% of the population with jejunal diverticulosis, and obstruction, in 2%-4%[8,9]. Chronic complications include chronic postprandial abdominal pain, emesis, diarrhea or constipation, weight loss, megaloblastic anemia, and steatorrhea; these symptoms reflect chronic complications such as malabsorption, obstruction, and bacterial overgrowth. As we have documented in all the studies reviewed in the literature, its non-specific chronic symptoms have led to this pathology being confused with others such as irritable bowel syndrome, acid-peptic disease, or cholelithiasis, resulting in erroneous diagnoses and, therefore, wrong treatments[14-16]. Being a rare pathology, its diagnosis is generally made incidentally.

According to the American Journal of Gastroenterology, small bowel bleeding should be considered when standard upper and lower endoscopic studies are available. During the review of the base articles, we found a clinical triad identified in 1971 by Nobles that alerted to the presence of jejunal diverticula, which consisted of diffuse abdominal pain, anemia, and dilated thin intestinal loops. Concerning our patient, Nobles' triad was added to typical endoscopic methods, which would make us suspect of thin loop diverticula[11,12].

The high and low endoscopic methods do not enable this pathology's diagnosis as they do not display the jejunum,

so the contrasted techniques are the first choice. At the same time, abdominal CT angiography is the first-line diagnostic method in patients in whom bleeding from the small intestine is suspected since this method reveals the existence or absence of extravasation of the contrast material in the intestinal lumen, as in the previous case. Mesenteric angiography is another critical diagnostic and therapeutic method, although this procedure's most relevant complication must be considered: ischemia[15-17].

The treatment will be chosen depending on the patient's complications. Among the options are the conservative method and the surgical method. The former is associated with complications such as diverticulitis or abscesses, and the latter, in the case of gastrointestinal bleeding, is of choice, which allows resection of the affected segment of the jejunum with primary anastomosis.

CONCLUSIONS

Jejunal diverticulosis is a pathology that goes unnoticed thanks to its low incidence and little knowledge, which is why it is not diagnosed and managed promptly. Managing diverticular disease of both the small intestine and the colon should focus on the symptoms or complications of patients.

We currently have several technological methods to make a more accurate diagnosis of this pathology, as is abdominal CT angiography, which shows whether or not there is extravasation of the contrast material in the intestinal lumen.

Conflicts of interest

The authors state no conflict of interest.

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Protection of people and animals

The authors state that no experiments were conducted on humans or animals for this research.

Data confidentiality

The work center's protocols for patient data publication have been followed.

Right to privacy and informed consent

The authors obtained the patient's informed consent. This document is in the possession of the corresponding author.

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Case report

Massive Gastrointestinal Bleeding Caused by Multiple Small Intestinal Diverticula: A Case Study

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Abstract

We report the case of a 71-year-old woman with multiple comorbidities who was admitted to the hospital due to hematochezia, without hemodynamic instability. Initial investigations, including colonoscopy and upper endoscopy, did not reveal the cause of bleeding. However, the patient experienced increased bleeding, anemia, and hemodynamic instability during her hospital stay. Subsequent selective angiography did not show any signs of active bleeding. In light of the persistent shock, surgical intervention was performed, which revealed blood originating from multiple diverticula in the jejunum.

Keywords

Gastrointestinal bleeding, diverticulosis, jejunum, ileum.

CASE PRESENTATION

A 71-year-old female patient was admitted to the emergency room with a history of arterial hypertension, type 2 diabetes *mellitus*, and chronic use of acetylsalicylic acid and consulted for hematochezia on multiple occasions with no other symptoms. On admission, she was found to be hemodynamically stable, with paraclinical tests showing microcytic and hypochromic anemia and elevated urea nitrogen. Preparation for colonoscopy was indicated, in which traces of recent bleeding without a clear cause were found. Upon reaching the distal transverse colon, it was impossible to advance despite multiple attempts due to a marked angulation, so the procedure was suspended. During follow-up, she persisted with bleeding associated with hemodynamic instability and anemia of 3 grams (hemoglobin [Hb]: 7.1 g/dL). Transfusion therapy of 2 units of packed red blood cells (PRBC) was indicated, and she was later taken to upper endoscopy, with no evidence of injury or bleeding. Mesenteric angiography was advanced without evidence of active bleeding. The patient persisted with hemodynamic instability, which required starting vasopressor support and management in the intensive care unit (ICU).

She was taken to surgery with a hemicolectomy plan due to suspicion of diverticular bleeding, with intraluminal blood in the small intestine. A manual inspection was performed, which revealed multiple multilobulated diverticula in the jejunum and a single diverticulum in the fourth portion of the duodenum. An intraoperative antegrade enteroscopy was performed with evidence of recent bleeding

and multiple clots in the previously mentioned diverticula, requiring resection of the compromised jejunal segment and diverticulectomy of the distal duodenal diverticulum with adequate bleeding control (**Figures 1** and **2**).

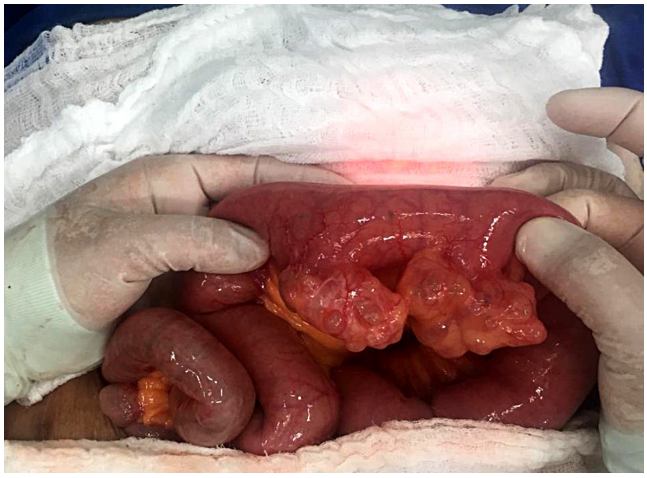

Figure 1. Intraoperative image showing diverticula in the jejunum. Source: Patient's medical record.

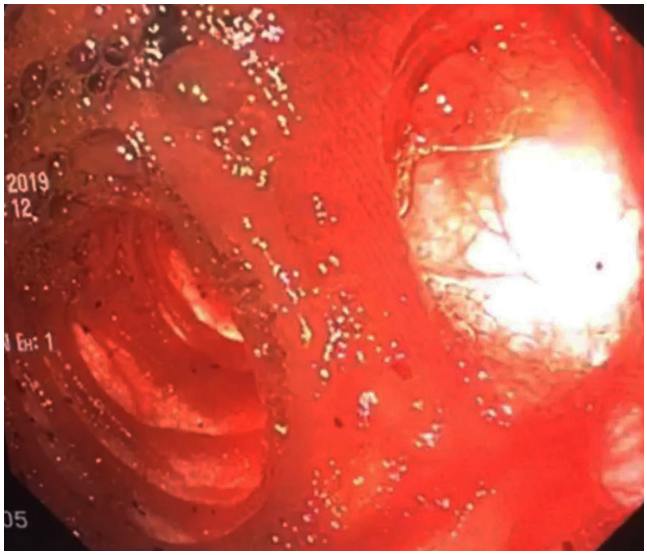

Figure 2. Image of the diverticulum in the jejunum by anterograde enteroscopy with active bleeding. Source: Patient's medical record.

DISCUSSION

The first reports of jejunal diverticulosis were described by Sommervit in 1794 and Cooper in 1807[1]. There are only case series in the literature due to its low incidence, approximately 0.5% to 7.1%[2]. However, depending on the identification tool, it can vary from 0.2%-4.5% in autopsies, 0.5%-2.3% in studies with contrast, 0.16%-27% in endoscopic retrograde cholangiopancreatography (ERCP), and up to 7.5% in endoscopic ultrasound (EUS; periampullary)[10]. It mainly affects men between 60 and 70[2,9]. Diverticula are acquired lesions with mucosal, submucosal, and serous involvement without the muscular layer, which is why they are considered false diverticula, which are fragile and thin. They frequently occur on the small intestine's mesenteric side, where the arteries enter the intestine[1,9]. However, manifestation on the antimesenteric edge has also been described[10]. They are more frequent at the level of the duodenum and more rarely at the level of the jejunum and ileum[9]. Three-quarters are represented by the periampullary diverticula[10]. Approximately 79% are located in the duodenum, and distal to it; 80% manifest at the jejunal level, about 15% in the ileum, and 5% in both, with multiple manifestations at the jejunal level, decreasing in quantity towards the distal part and sometimes with a single diverticulum in the ileum[9,10]. Diverticula form during periods of increased intraluminal pressure, such as inflammation or intestinal dyskinesia, which produces areas of high pressure in segments of the small intestine[10].

Most are asymptomatic and are found incidentally in studies for other causes[1], such as imaging studies or during abdominal surgery[9]. It is important to take these diverticula into account since most of the clinical manifestations can be variable (abdominal pain, nausea, dyspepsia, emesis, rumbling, altered bowel habits) or resemble a picture of bacterial overgrowth that causes malabsorption[9,10]; however, and although less frequent, it can manifest with severe conditions with a high mortality rate such as obstruction, perforation, volvulus, infection, and bleeding[1,8,9]. When these diverticula display secondary gastrointestinal bleeding, they vary since they can present with pictures of melena, hematochezia, and, in some cases, hematemesis, leading to the patient's clinical instability [3,6]. Bleeding from jejunal diverticula ranges from 3% to 8%, and although the manifestation is variable, as mentioned, most occur as rectal bleeding, which is confusing. When a patient presents to the emergency department with rectal bleeding, the most probable cause is considered to be lower gastrointestinal bleeding, in addition to having a high risk of mortality due to the delay in diagnosis[4]; however, current gastrointestinal bleeding guidelines mention that if a patient presents with rectal bleeding that causes hemodynamic instability, upper gastrointestinal bleeding should be considered[10]. It is believed that the bleeding mechanism of the jejunal diverticula is ulceration secondary to inflammation that affects an artery and causes bleeding[1].

Some reports described using drugs, such as warfarin and low-dose aspirin, as risk factors[1]. In the case of our patient who uses acetylsalicylic acid (ASA) for secondary cardiovascular prevention, it is advisable not to suspend it. Remember that its mechanism of action occurs through

the irreversible inhibition of cyclooxygenase-1, which mediates the synthesis of thromboxane; when ingesting the ASA, the synthesis of thromboxane returns to an average between 7 and 10 days; therefore, stopping ASA will have little impact on the initial clinical course due to the persistent antiplatelet effect of ASA in the first day or two after manifestation. By then, the patient will have undergone an endoscopic study with hemostasis. If ASA is suspended, it must be restarted once hemostasis is achieved since its effect will still be present. These two current recommendations have made it possible to demonstrate a decrease in mortality[11].

The mechanisms that could explain the increase in bleeding secondary to non-steroidal anti-inflammatory drugs (NSAIDs) are direct damage to the mucosa, disruption of intercellular integrity, and activation of neutrophils by bacteria[7]. Diagnosis is a challenge because initial studies such as upper endoscopy and colonoscopy have limitations in finding the site of bleeding at this level, so the algorithm for suspicion of bleeding from the small intestine must be continued, and studies such as videocapsule endoscopy or enteroscopy when the patient is hemodynamically stable should be advanced. Angiography is a valuable tool, especially in the context of instability, since it can help locate the lesion and make differential diagnoses based on the characteristics of the extravasation. It is considered the gold standard[5]. Management is generally surgical since embolization by arteriography is not practical in most cases; however, if the cause of the bleeding is not found, the recommendation is to perform a subtotal colectomy, but if found, it performing a resection of the affected segment with primary anastomosis is suggested. If it is found in several parts, an intraoperative enteroscopy can be helpful to find the source of bleeding and resect only this segment[9].

CONCLUSION

Bleeding jejunal diverticula are rare and difficult to diagnose as they can mimic signs and symptoms of upper or lower gastrointestinal bleeding. In this case, it presented with massive bleeding that the chronic intake of NSAIDs could have favored. Within the studies, selective mesenteric angiography is the gold standard for diagnosing active and fatal bleeding, but as in our case, it may not reveal the site. So, surgical management can be an essential tool for making a diagnosis and definitive treatment.

Ethical responsibilities

The authors state that no experiments were conducted on humans or animals for this research.

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