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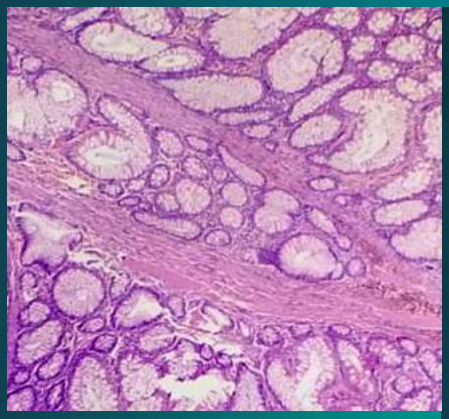

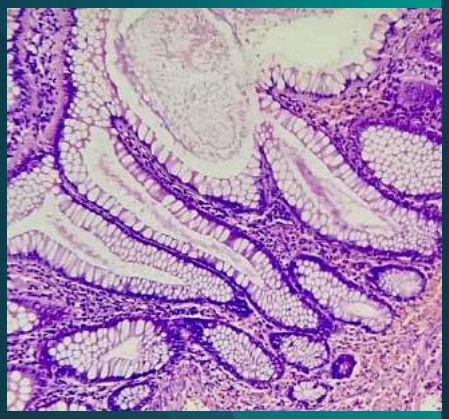

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Courtesy of the authors: Edgar Julián Ferreira-Bohórquez, Daniel Stiven Quintero-Rincón, Yulieth Vanessa Caro-Gamboa, María Camila Ayala-Forero.

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Editorial

Fatty Liver: A Heterogeneous Disorder with a High Global Prevalence

Mauricio Orrego.[1*]

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Non-alcoholic fatty liver disease (NAFLD) is the most prevalent liver disease globally and represents a real public health problem. NAFLD includes a spectrum of conditions, including hepatic steatosis, non-alcoholic steatohepatitis (NASH), and liver fibrosis, with the risk of progressing to cirrhosis, hepatocellular carcinoma (HCC), and eventually the need for liver transplantation[(1)]. The global prevalence of NAFLD in the adult population is estimated to be 23%-25% and varies by region; the areas with the highest prevalence are the Middle East (32%) and South America (30%), while Africa has the lowest (13%). The prevalence of NAFLD in 1990–2017 has increased from 8.2% to 10.9%[(2)], which has to do with the increased prevalence of obesity and type 2 diabetes mellitus worldwide[(3)]. Up to 20% of people with NAFLD may develop NASH. The development of NASH is the most critical stage in the pathogenesis of liver damage in patients with NAFLD.

Insulin resistance and obesity result in metabolic injury to hepatocytes, with activation of lipogenesis, lipid accumulation, and lipotoxicity exacerbating hepatocyte damage. Adipose tissue contributes to insulin resistance by secreting adipokines and cytokines (e.g., leptin and adiponectin). Endoplasmic reticulum (ER) stress causes the secretion of inflammatory, fibrogenic, and chemokine cytokines (e.g., interleukin-6 [IL-6], tumor necrosis factor-alpha [TNF-α], interleukin-1 beta [IL-1β], and transforming growth factor-beta 1 [TGF-β1]). ER stress is associated with changes in the microbiota (prevalence of *Firmicutes* over *Bacteroidetes* 13), increased gut permeability, the release of bacterial products such as lipopolysaccharides into the circulation, activation of Toll-like receptor-dependent signaling pathways (specifically TLR-4), and the recruitment and activation of inflammatory cells and myofibroblasts in the compromised liver[(4, 5)]. Liver fibrosis is the most crucial determining factor of liver-related and non-liver-related outcomes in patients with NAFLD[(6)].

Written by Dr. Prieto et al.[(7)], the article "Non-alcoholic fatty liver disease part 1: general aspects, epidemiology, pathophysiology, and natural history" in this issue provides a clear and concise review of general, epidemiological, pathophysiology, and natural history features of fatty liver.

A critical aspect of the review is the pathophysiology, emphasizing that NAFLD is a complex and very heterogeneous disorder derived from the interaction of multiple genetic, epigenetic, environmental, and cultural factors. All these elements combined lead to an accumulation of liver fat, insulin resistance, and hormonal and intestinal microbiota alterations, causing hepatocellular damage by forming oxygen-free radicals and activating liver fibrogenesis.

Another crucial part of the review is a forecast of what could happen in Colombia based on international data. It is estimated that, of 15 million people with fatty liver in Colombia, three million would have NASH. In three years, some 600,000 people could have stage 1-3 fibrosis, and of the patients with stage 3 fibrosis, 20% could develop cirrhosis with the consequent complications of liver failure and HCC. This analysis reveals that NAFLD is an actual public health issue; therefore, primary care physicians must be trained to timely detect fatty liver and make an adequate stratification to determine when to refer the patient to a specialist based on non-invasive fibrosis tests[8].

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Original article

Prevalence of Helicobacter pylori in patients undergoing upper digestive tract endoscopy at a referral hospital in Cali, Colombia, in 2020

Mauricio Sepúlveda,[1] Catalina Maldonado,[1] Juan Bravo,[2] Natalia Satizábal,[3] Andrés Gempeler,[4] Andrés Castro,[5] Juliana Escobar,[6] Jenifer Herrera,[7] Fernando Rosso,[8] Nelson Rojas,[9] Carlos Rojas.[1*]

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Sepúlveda M, Maldonado C, Bravo J, Satizábal N, Gempeler A, Castro A, Escobar E, Herrera J, Rosso F, Rojas N, Rojas C. Prevalence of Helicobacter pylori in patients undergoing upper digestive tract endoscopy at a referral hospital in Cali, Colombia, in 2020. Revista. colomb. Gastroenterol. 2022;37(4):355-361. https://doi.org/10.22516/25007440.868

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Abstract

Introduction: *Helicobacter pylori* infection has a high prevalence and distribution worldwide. Due to its association with the development of gastric adenocarcinoma, updates on its prevalence are of interest to the internist or gastroenterologist and policymaking. This study measured the prevalence of *H. pylori* and evaluated its association with endoscopic and histopathological findings in adults with an indication for upper GI endoscopy (EGD). **Materials and methods:** This analytical cohort study describes the prevalence of *H. pylori* and assesses risk factors associated with this infection in adult patients undergoing outpatient EGD for any medical indication in the endoscopy unit of a quaternary care university hospital between June and December 2020. Endoscopic and histopathological findings and the prevalence of *H. pylori* are described. To explore the risk factors, the chi-square (χ^2) test was used to evaluate differences in proportions and the Student's t and Mann-Whitney U tests for continuous variables according to their distribution. **Results:** 613 patients met the selection criteria and were included in the analysis. The most frequent indication for EGD was dyspepsia. The prevalence of *H. pylori* was 38.5% (95% confidence interval [CI]: 34.7-42.4%). **Conclusion:** *H. pylori* is a topic of great interest in gastrointestinal pathologies. The endoscopic search should take place in the antrum and body. Its presence was most common in patients with a normal esophagus, follicular nodular gastritis, duodenal ulcer, and acute inflammation upon the histological study. More studies are required to complement the local epidemiological behavior.

Keywords

Helicobacter pylori, prevalence, gastric neoplasms.

INTRODUCTION

Helicobacter pylori infection has a high prevalence worldwide[1,2]. In 2015, it was estimated that 4.4 billion people were infected, corresponding to more than half of the world's population[2]. In Colombia, a prevalence of 69.1% was found in 2003 based on data from 16 cities in all regions[3]. In Cali, the prevalence was reported at 63.1%[3]. Other studies have described lower frequencies, such as a study that reported a prevalence of 36.4% in Medellín[4].

H. pylori is relevant not only because of its high prevalence but also because of its relationship with the development of multifocal atrophic gastritis, gastric ulcers, and gastric adenocarcinoma[1,5,6]. This last relationship, establis-

hed by the International Agency for Research on Cancer (IARC), has led to the classification of this bacterium as a type 1 carcinogen[7]. *H. pylori* can increase the risk of gastric cancer by ten times[7]; thus, its eradication is crucial for the population of our country, where the incidence of this cancer is high. Additionally, gastric cancer is among the five types of cancer with the highest mortality[8]; reducing the prevalence of *H. pylori* could decrease the disease burden generated by this pathology.

There are several methods to detect H. pylori, most with adequate sensitivity and specificity. They are divided into non-invasive, such as serology, urea breath test, and stool antigen test, and invasive, such as histology, culture, rapid urease test, and polymerase chain reaction test[1, 5, 9]. In Colombia, the most used method is the histopathological study of gastric biopsies obtained through upper endoscopy (EGD). Some endoscopic findings may be related to the presence of *H. pylori*, such as diffuse erythema, mucus in the gastric mucosa, erythema foci in the gastric fundus, enlarged folds, edema, and the arrangement of collecting venules of the gastric mucosa[10].

The epidemiology of *H. pylori* infection has been described in international studies. However, recent reports on the prevalence of this infection in Colombia have yet to be identified. The prevalence of this infection and its related pathologies vary in the literature (69.1%–36.4%)[3, 4]. It is essential to know the local epidemiology to determine the need for changes in detection processes, propose eradication strategies, and reduce the burden of the disease. This study measured the prevalence of *H. pylori* in consecutive patients undergoing EGD for various indications and assessed risk factors and endoscopic and pathological findings connected with its manifestation.

MATERIALS AND METHODS

Design and participants

An analytical cohort study was carried out to describe the prevalence of *H. pylori* and evaluate the related risk factors in adult patients undergoing outpatient EGD for any medical indication at the endoscopy unit of a quaternary care university hospital between June and December 2020. We included patients over 18 years of age who underwent endoscopy and biopsy of the gastric mucosa of the antrum and body with at least two tissue samples for processing and histopathological description. Consecutive patients who met the selection criteria were included until completing the sample size. Patients with an indication for therapeutic endoscopy were excluded. The institutional ethics committee approved the study before its initiation.

Measurements and data collection

The information on the origin of patients and the use of proton pump inhibitors (PPIs) or antibiotics (ATBs) for any indication in the last month was taken from the medical records. The treating gastroenterologist or gastrointestinal surgeon described and recorded the endoscopic findings in the procedure report, from which the data of interest were extracted.

Pathology samples were fixed with 10% buffered formalin and embedded in paraffin blocks. Histological sections were stained with hematoxylin and eosin for regular study, and the Warthin-Starry technique was used to detect *H. pylori*. The histopathological evaluation was made according to the analogous visual scale described by Dixon et al., known as the *Sydney System*[11]. This classification assigns a semiquantitative description to each histological parameter, from 0 (normal) to 3 (severe or abundant), including neutrophil and mononuclear cell infiltrate, the intensity of atrophy, and the severity of intestinal metaplasia, and quantifies *H. pylori* colonization[1, 11].

Sample size and statistical analysis

The sample size was calculated with local data from 2003 that reported a prevalence of *H. pylori* of 63.1% in Cali[3]. With an estimated frequency of 50% prevalence and 97% confidence, a sample of 471 patients was calculated.

For data analysis, we employed STATA v.14® (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP). Continuous variables were described with measures of central tendency and dispersion according to their distribution, evaluated with the Shapiro-Wilk test. Absolute and relative frequencies were used to describe nominal or ordinal qualitative variables. The prevalence of *H. pylori* was reported with a 95% confidence interval (95% CI). We performed Chi-square ($\chi 2$) or Fisher's tests to assess differences in proportions, as appropriate, and Student's t and Mann-Whitney U tests depending on their distribution.

RESULTS

During the study period, 1,105 patients were identified for EGD, of whom 613 met the selection criteria and were included in the analysis. The reasons for being selected were, among others, patients with complete data, older than 18 years, and EGD and biopsy performed in the endoscopy unit.

The demographic and clinical characteristics of the population are shown in **Table 1**. The median age was 52 years

(interquartile range [IQR]: 38-62 years), and about two-thirds of the participants were women. Most patients who belonged to the prepaid, policy, or private social security scheme came from Cali, and their most common indication for EGD was dyspepsia.

Table 1. Demographic and clinical characteristics of the population taken to EGD

Characteristic	General (n = 613)	
Age*	52	(38-62)
Sex		
- Female	390	63.6%
- Male	223	36.4%
Social security scheme		
- Contributive and subsidized	57	9.3%
- Prepaid, policy, or private	556	90.7%
Origin		
- Cali	475	77.5%
- Another city	131	21.4%
- Rural area	7	1.1%
EGD indication		
- Dyspepsia	395	64.4%
- GERD	62	10.1%
- H. pylori control	32	5.2%
- Cancer screening	24	3.9%
- Chronic gastritis and metaplasia monitoring	14	2.3%
- Transplant protocol	12	2.0%
- Other EGD indication	88	14.4%
PPI use in the last month		
- No	416	67.9%
- Yes	197	32.1%
ATB use in the last month		
- No	544	88.7%
- Yes	69	11.3%

*Value stated as median (IQR).
GERD: gastroesophageal reflux disease; EGD: upper endoscopy; PPI: proton pump inhibitors; IQR: interquartile range. Source: The authors.

According to the histopathological study, the prevalence of *H. pylori* in this adult population with EGD indication was 38.5% (95% CI: 34.7%-42.4%). In most patients with *H. pylori,* it was identified in the antrum and the body, and in a minority of cases, in the antrum or the body (15%) (**Figure 1**). In the antrum, the presence of *H. pylori* was "abundant," while in the body, the categories "mild," "moderate," and "abundant" had similar frequencies (**Figure 2**).

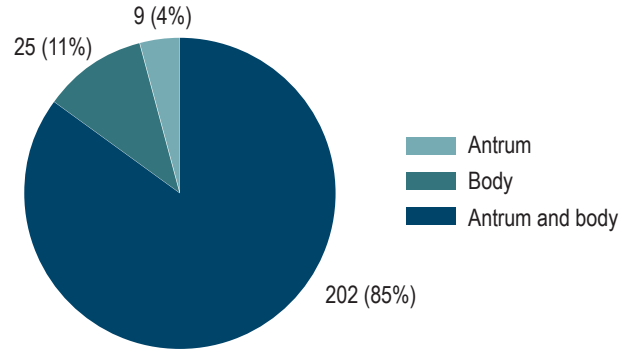

Figure 1. Anatomical location of H. pylori in patients taken to EGD. Source: The authors.

Table 2 shows the prevalence of *H. pylori* according to the EGD indication; the highest was observed in patients with an indication for *H. pylori* control. For the other indications, there were similar frequencies. **Table 3** presents the association of specific clinical characteristics and endoscopic findings with *H. pylori*. Patients diagnosed with *H. pylori* were young, and PPI use in the last month was reported to be lower in the group with *H. pylori*. There was no significant difference in the frequency of a history of dyspepsia between patients with and without *H. pylori*. Of the total number of patients with dyspepsia as an EGD indication, 41% were diagnosed with *H. pylori*.

Table 2. Prevalence of H. pylori according to EGD indication

EGD indication	Prevalence	95% CI
H. pylori control	50.0%	31.4%-68.6%
Dyspepsia	41.0%	36.2%-45.9%
Other EGD indication	35.2%	26.1%-45.6%
Transplant protocol	33.3%	13.8%-60.9%
GERD	30.6%	20.6%-43.0%
Cancer screening	25.0%	13.3%-42.1%

Source: The authors.

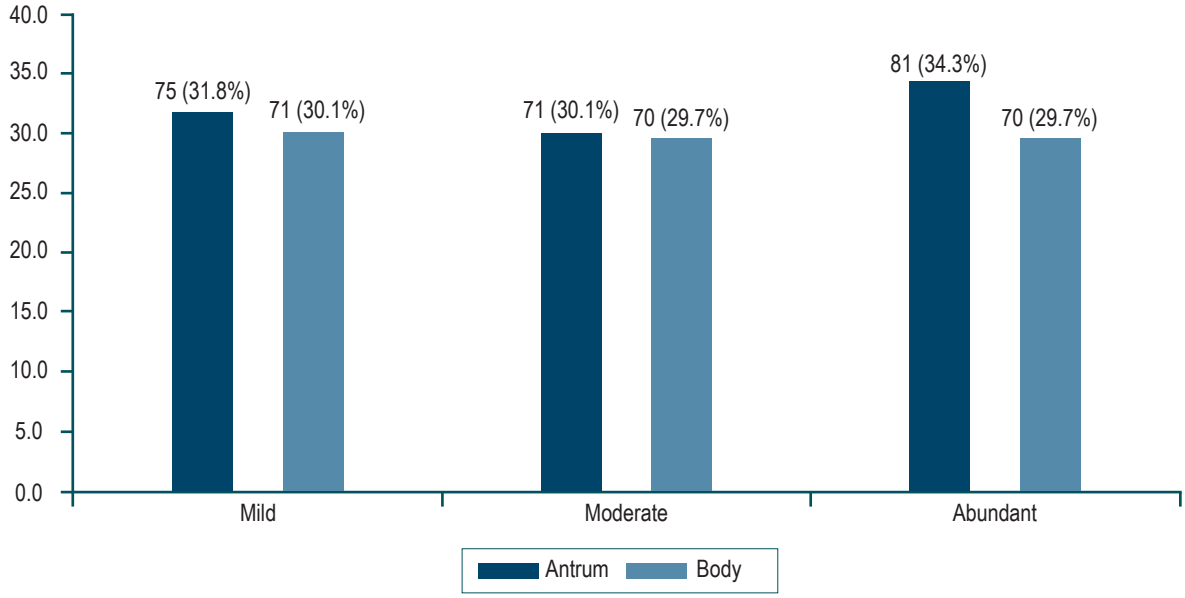

Figure 2. Amount of H. pylori in the antrum and body (n = 236 with H. pylori). Source: The authors.

A significant difference was observed for some endoscopic findings: a normal esophagus in patients with *H. pylori* was more frequent than esophagitis in patients without *H. pylori*. Mucosa with a nodular-follicular appearance in the antrum occurred in 4.4% of all patients, but it was highly specific for *H. pylori* infection (specificity: 98.9%; 95% CI: 97%-99%; likelihood ratio [LR+] = 9). An ulcer in the antrum was also frequent in patients diagnosed with *H. pylori*, although only 14 (2.2%) patients had it. Findings of possible atrophy and polyps in the body were more frequent in patients without *H. pylori*.

Table 4 introduces the histopathological findings related to *H. pylori*. Acute inflammation was noted in the antrum and body in 94.5% and 83.9% of patients infected with *H. pylori*; it was an infrequent finding in patients without *H. pylori* (5%-6%) and statistically significant. Atrophy and intestinal metaplasia in the antrum were not associated with *H. pylori*. The absence of this bacterium had a substantial relationship with atrophy and intestinal metaplasia in the body. The most frequent overall histopathology diagnosis was chronic non-atrophic gastritis (CNG).

DISCUSSION

This study in adult patients undergoing gastric endoscopy for any indication reports a prevalence of *H. pylori* infection of 38.5% (95% CI: 34.7%-42.4%). This infection was negatively related to PPI use in the last month and identified in younger patients, probably due to the older age of patients with indications other than dyspepsia and lower infection frequencies; however, it was not associated with other clinical characteristics. No relationship with the indication for endoscopy was identified, highlighting the considerable prevalence of infection even in indications other than dyspepsia. The eradication of *H. pylori* is a form of prevention accepted worldwide to reduce the incidence of gastric cancer, a common pathology connected with high morbidity and mortality[12-14].

The prevalence of *H. pylori* may vary widely depending on the study site and the inclusion of patients. In some studies, its manifestation has been linked to a low socioeconomic level. A higher prevalence has been reported in low- or middle-income countries with low levels of urbanization, sanitation, and access to drinking water[1, 2, 15]. These conditions are common in Colombia, where a high prevalence of *H. pylori* has been measured, such as that reported at 63% by Bravo et al. in 2003[3]. Nonetheless, more recent studies have described lower prevalences, such as the one obtained in this study and by Correa et al.[4] in Medellín, probably concerning a decrease in the risk factors for urban areas.

In studies in low- and middle-income countries, frequencies of *H. pylori* up to 50% mainly affect patients around ~10 years of age and adults around ~50 years of age, as shown in this study[4, 15, 16]. Reportedly, the male sex has been related to a higher prevalence of *H. pylori*[17, 18], unlike our study.

Table 3. Risk factors for H. pylori and related endoscopic findings

Clinical feature	H. pylori		*p*-value
	No (n = 377)	Yes (n = 236)	
Age	54 (41-64)	47 (34.5-58)	< 0.001
Female	242 (64.2)	148 (62.7)	0.711
EGD indication			
- Dyspepsia	233 (61.8)	162 (68.6)	0.085
- GERD	43 (11.4)	19 (8.1)	0.180
- Cancer screening	24 (6.4)	8 (3.4)	0.238
- H. pylori control	12 (3.2)	12 (5.1)	0.107
- Transplant protocol	8 (2.1)	4 (1.7)	0.775
- Other EGD indication	57 (15.1)	31 (13.1)	0.495
PPI use in the last month	138 (36.6)	59 (25.0)	0.003
ATB use in the last month	41 (10.9)	28 (11.9)	0.706
Endoscopic finding			
Esophagus			
- Normal	286 (75.9)	203 (86.0)	0.002
- Esophagitis	66 (17.5)	24 (10.2)	0.013
- Barrett's esophagus	2 (0.5)	0	0.526
- Ulcer	4 (1.1)	1 (0.4)	0.654
- Other	19 (5.0)	8 (3.4)	0.420
Antrum			
- Normal	5 (1.3)	2 (0.8)	0.712
- Possible atrophy	26 (6.9)	13 (5.5)	0.473
- Metaplasia foci	10 (2.7)	3 (1.3)	0.390
- Nodular-follicular appearance	4 (1.1)	23 (9.7)	< 0.001
- Erythematous gastropathy	353 (93.6)	219 (92.8)	0.631
- Erosive gastritis	63 (16.7)	29 (12.3)	0.128
- Ulcer	5 (1.3)	9 (3.8)	0.048
- Neoplasm	1 (0.3)	0	1.000
- Polyps	1 (0.3)	0	1.000
- Other	7 (1.9)	3 (1.3)	0.748
Body			
- Normal	270 (71.6)	184 (78.0)	0.019
- Possible atrophy	28 (7.4)	5 (2.1)	0.006
- Metaplasia foci	5 (1.3)	1 (0.4)	0.418
- Nodular-follicular appearance	10 (2.7)	7 (3.0)	0.761
- Erythematous gastropathy	54 (14.3)	34 (14.4)	0.838
- Erosive gastritis	10 (2.7)	5 (2.1)	0.727
- Ulcer	1 (0.3)	0	1.000
- Neoplasm	2 (0.5)	0	0.530
- Polyps	15 (4.0)	2 (0.8)	0.026
- Other	4 (1.1)	3 (1.3)	1.000
Duodenum			
- Normal	355 (94.2)	228 (96.6)	0.172
- Duodenitis	13 (3.4)	6 (2.5)	0.529
- Duodenal ulcer	0	2 (0.8)	0.148
- Other	9 (2.4)	0	0.015

Source: The authors.

The negative association with PPI and ATB use in the last month for any medical indication is explained by the suppressive effect of *H. pylori* described for this treatment, in addition to the potential impact of reducing the sensitivity of the diagnostic method[1, 5]. Therefore, it is advisable to suspend PPIs and ATBs before performing these tests[19, 20]. Using these medications could be considered an exclusion criterion; however, this study wanted to assess the relationships mentioned and did not exclude patients for this reason.

H. pylori colonizes the antrum more often in patients with normal acid secretion having few acid-secreting parietal cells. In subjects with impaired secretion, for example, due to PPI use or vagotomy, *H. pylori* colonize the body more frequently[21]. Thus, finding *H. pylori* in the antrum and body simultaneously is expected, with greater abundance in the antrum, as revealed in this study.

Erythematous gastropathy in the antrum, considered endoscopic gastritis[22], was present in almost all subjects. Like previous studies that report expected mucosa frequencies in the antrum that do not exceed 4% in the presence of *H. pylori*, only 0.8% of patients with *H. pylori* in our study had normal mucosa in the antrum[3, 23]. A higher frequency of nodular-follicular appearance findings in the antral mucosa in the presence of *H. pylori* was observed, with results similar to those informed by other authors[24, 25]. *H. pylori* has been identified in 95% of duodenal ulcers and 85% of gastric ulcers [26]. In this study, the two patients with duodenal ulcers had *H. pylori*.

Regarding the histopathological findings, on the one hand, a significant relationship was found between acute inflammation and *H. pylori* in the antrum and the body, as reported by Garg and Mysorekar; this is a hallmark finding of infection, which is rare in the absence of *H. pylori*[21, 27]. On the other hand, there was a negative association of *H. pylori* with gastric atrophy and intestinal metaplasia in the body. This association may be a consequence of previous treatment for *H. pylori* that eradicates the bacteria but does not reverse the histopathological changes in the mucosa[7]. According to the Sydney System, the most frequent global histopathological diagnosis was CNG (79.8%). Multifocal atrophic gastritis has diagnostic value for being a precursor lesion of malignancy[5]. Previous studies in the country found that the microorganism was associated with metaplasia, lymphoid follicles, and atrophy[4]. Concerning the endoscopic findings, this research has the limitation that, even though the six participating gastroenterologists have more than five years of experience, potential interobserver variability was not considered in this work.

Table 4. Histopathological findings

H. pylori		Pathology						Total
		Normal	CNG	MAG	MAG IM	Dysp	Ca	
Negative	n	23	279	4	68	1	2	377
	%	6.1%	74%	1.1%	18%	0.3%	0.5%	100%
Positive	n	0	210	0	26	0	0	236
	%	0%	89%	0%	11%	0%	0%	100%
Total	n	23	489	4	94	1	2	613
	%	3.8%	79.8%	0.7%	15.3%	0.2%	0.3%	100%

Ca: cancer; Dysp: dysplasia; MAG: atrophic gastritis; MAG IM: atrophic gastritis with intestinal metaplasia; CNG: non-atrophic gastritis. Source: The authors.

CONCLUSION

The prevalence of *H. pylori* in patients undergoing EGD for all indications is 38.5% and has similar values in all EGD indication subgroups. The endoscopic search should be in the antrum and the body. Follicular nodular gastritis in the antrum and duodenal ulcer is associated with *H. pylori*. Studies are required to evaluate the epidemiological behavior in the general population.

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Original article

2010 vs. 2019 ASGE criteria for choledocholithiasis in patients undergoing endoscopic retrograde cholangiopancreatography

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Abstract

Introduction: With the update of the American Society for Gastrointestinal Endoscopy (ASGE) 2019 guidelines, the criteria for patients with suspected choledocholithiasis became stricter when choosing who should be taken directly to endoscopic retrograde cholangiopancreatography (ERCP). This study aimed to compare patients taken directly to ERCP according to the 2010 vs. 2019 ASGE guidelines versus the 2019 guide. **Materials and methods:** A retrospective study of ERCPs performed between January 2016 and December 2018 evaluated the diagnostic performance of paraclinical and ultrasound variables individually and collectively to compare their sensitivity, specificity, predictive values, and high probability precision according to 2019 and 2010 guidelines regarding the presence of stones in ERCPs. **Results:** 386 patients underwent ERCP due to suspicion of choledocholithiasis; 84.5% were therapeutic procedures. The high probability group had a higher rate of therapeutic ERCP: 89.3% according to the 2019 guidelines compared to those of 2010 with 86.3% ($p < 0.001$). The sensitivity and specificity of high probability according to the 2010 guidelines were 86.8% and 25.0%, respectively, with a positive predictive value (PPV) of 86.3% and an accuracy of 77.2%. According to the 2019 guidelines, high probability showed lower sensitivity (74%) but higher specificity (51.7%), a PPV of 89.3%, and an accuracy of 70.7%. **Conclusions:** The implementation of the ASGE 2019 guidelines on the indications for ERCP should consider the resources of hospitals, especially in low- and middle-income countries. The ASGE 2010 guidelines show good sensitivity and precision to guide the performance of ERCP.

Keywords

Choledocholithiasis, endoscopic retrograde cholangiopancreatography, health systems.

INTRODUCTION

In 2010, the American Society for Gastrointestinal Endoscopy (ASGE) proposed a series of criteria to classify patients with suspected choledocholithiasis according to the probability of having or not having stones in the bile duct; high risk means a probability > 50%, medium risk between 10% and 50%, and low risk < 10%[(1)]. Over the years and the publication of several studies that demonstrated that by following these criteria, the rate of non-therapeutic endoscopic retrograde cholangiopancreatography (ERCP) was around 20%-30%[(2-7)], the ASGE decided to update the guidelines and published its new proposal in 2019[(8)]. The main objective of this modification is to reduce the diagnostic ERCP rate as much as possible, to avoid exposing patients to risks and complications of endoscopic manage-

ment, such as acute pancreatitis, bleeding, and perforation, among others[9]. However, the change significantly increased patients with medium probability, which involves imaging them to assess the bile duct before requesting ERCP. Many health institutions in Latin America do not have availability or timely access to this type of study, which could create the need to refer patients and, in turn, increase the days of hospital stay with the consequent increase in complications secondary to delay in the procedure and, probably, the impact on health care costs.

Our objective was to analyze the risk stratification for choledocholithiasis in a hospital in southwestern Colombia and compare the performance of high probability variables according to the ASGE 2010, as updated in 2019, in our patients.

MATERIALS AND METHODS

A retrospective cohort study was carried out on all patients older than 14 with suspected choledocholithiasis taken to ERCP at the San José University Hospital (HUSJ) in Popayán between January 2016 and December 2018. This institution performs around 900 laparoscopic cholecystectomies and 300 ERCPs per year.

We excluded (a) patients undergoing ERCP with a diagnosis of choledocholithiasis by magnetic resonance cholangiopancreatography (MRCP), endoscopic ultrasonography (EUS), contrast-enhanced abdominal tomography (CT) or previous ERCP; (b) failed ERCP (inability to channel the bile duct); (c) other causes of bile duct obstruction (neoplasms, benign strictures, parasites, among others); (d) ERCP for other causes (management of biliary fistulas, replacement of endoscopic prostheses, among others), and (e) incomplete medical records.

On the one hand, a patient is considered to have a high probability, according to the ASGE 2010, when having a very strong predictor (ultrasound bile duct stones, ascending cholangitis, serum bilirubin > 4 mg/dL) or both strong predictors (bile duct dilated, serum bilirubin 1.8-4 mg/dL). On the other hand, according to the ASGE 2010, the medium probability would occur in case of a strong predictor or at least a moderate predictor (altered liver function tests, age older than 55 years, gallstone pancreatitis).

In 2019, by modifying the criteria, patients with bile duct stones on ultrasound or other imaging, symptoms of ascending cholangitis, or bilirubin > 4 mg/dL with dilated bile duct were considered to have a high probability. Medium probability would involve abnormal liver function tests other than bilirubin, age > 55 years, or dilated bile duct on ultrasound or other imaging (acute pancreatitis of biliary origin is dismissed).

We requested the medical record numbers registered in the HUSJ Dynamics system of all patients with a CUPS code for ERCP performed between 2016 and 2018. The information was collected through the electronic form CLINAPSIS®. This study had the ethical endorsement of the HUSJ, Minutes No. 05/2019.

Measures of central tendency and dispersion were obtained for the quantitative variables. The frequencies for the qualitative variables were exposed. With the information obtained, we created univariate analysis tables to summarize the characteristics of the included population. Sensitivity, specificity, positive (PPV), negative (NPV) predictive values, and accuracy were calculated. We employed the statistical software SPSS v. 25 (Statistical Product and Service Solutions) for the analysis.

RESULTS

During the 2016-2018 period, 816 ERCPs were performed at the institution, of which 386 met the inclusion criteria (**Figure 1**). Of the total number of patients, 54.1% were women, the mean age was 59.4 years, and 26.4% (n = 102) had a surgical history of cholecystectomy (**Table 1**).

Accordingly, 19.7% of the patients presented with acute pancreatitis of biliary origin, and 27.7% were diagnosed with acute cholangitis based on the Tokyo 2018 criteria[10]. It was found that 62.7% had total bilirubin (TB) > 4 mg/dL, 21.5% had TB between 2 and 4 mg/dL, and 18.8% had values less than 2 mg/dL. Besides, 96.6% of the patients had liver profile abnormalities other than bilirubin (transaminases: aspartate aminotransferase [AST], alanine aminotransferase [ALT], and alkaline phosphatase) (**Table 1**).

Abdominal ultrasonography findings reported acute cholecystitis in 40.8% of patients, gallbladder lithiasis in 83.5%, and bile duct stones in 41.5%. Patients who presented with biliary sludge in the gallbladder and bile duct were included in the cholelithiasis and choledocholithiasis groups, respectively. Also, 76.2% had a dilated bile duct, considered > 6 mm in patients with gallbladder and > 8 mm with a history of cholecystectomy (**Table 1**).

The mean time from patient admission to ERCP was 2.6 days (standard deviation [SD] ± 2.6); 90.4% had a dilated bile duct, with a mean size of 12.8 mm (SD ± 5.8), according to the endoscopic report. Choledocholithiasis was detected in 84.7% of the patients undergoing ERCP, and 84.5% of the ERCPs were therapeutic since one of the patients had intrahepatic lithiasis, where endoscopic management was not possible. The total number of complications was 1.3% (n = 5): two severe pancreatitis cases, two mild pancreatitis cases, and one gastrointestinal bleeding without needing blood products or reintervention (**Table 1**).

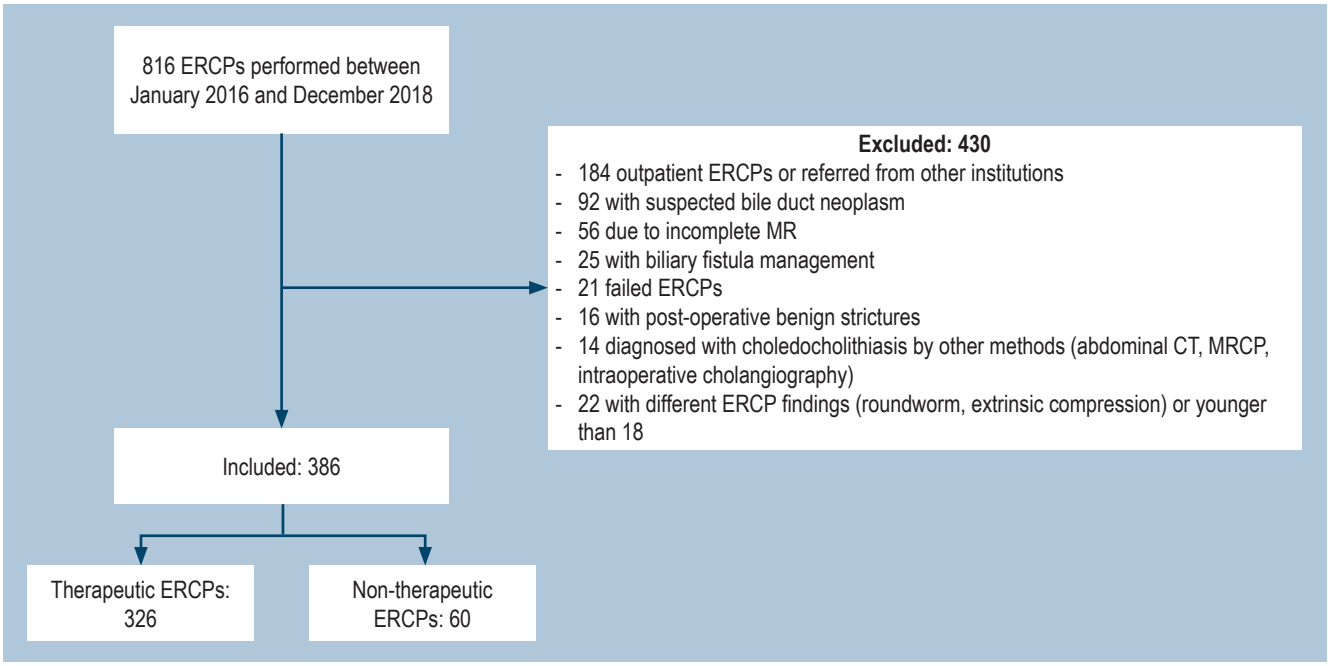

Figure 1. Patient selection. MR: medical record. Source: The authors.

The diagnostic yield of tests was calculated for patients with a high probability according to the ASGE 2010 and 2019 criteria. The most sensitive variable was bile duct dilation, with a sensitivity of 81%, followed by TB > 4 mg/dL (64%), and PPVs of 89.9% and 86.4%, respectively. Choledocholithiasis on ultrasound and symptoms of cholangitis were the most specific variables to detect bile duct stones, with specificities of 78.3% and 78.3% and PPVs of 91.9% and 87.9%, respectively. The patients who presented with cholangitis, hyperbilirubinemia greater than 4 mg/dL, and choledocholithiasis on ultrasound had specificities of 96.7% and a PPV of 95%. The sensitivity of bile duct dilation with total bilirubin greater than 4 mg/dL was 51.5% with a specificity of 75%, PPV of 91.8%, and NPV of 22.2% with an accuracy of 47.2 % (**Table 2**).

Patients were divided into high probability (HP) and medium probability (MP) of having choledocholithiasis according to the ASGE 2010 and 2019 guidelines. We calculated the percentage of patients with choledocholithiasis on ERCP and how many met very strong, strong, and moderate criteria according to the 2010 ASGE. Accordingly, we found that, of the 386 patients taken to ERCP, 328 (84.9%) met high probability criteria, of which 283 (86.2%) had choledocholithiasis, 301 met very strong and 27 strong criteria. Fifty-eight (15.1%) patients had medium probability, of which 43 (74.1%) were positive for choledocholithiasis, and 48 met strong and ten moderate criteria. When categorizing the patients according to the ASGE 2019 guidelines, 271 (70.2%) were classified as high probability, of which 242 (89.2%) presented with choledocholithiasis, and all met very strong criteria according to the ASGE 2010 (**Table 3**).

In our patient cohort, the sensitivity and specificity of high probability under the 2010 guidelines were 86.8% and 25.0%, respectively, with a PPV of 86.3% and a 77.2% accuracy. High probability, according to the 2019 guidelines, showed lower sensitivity (74%) but higher specificity (51.7%), a PPV of 89.3%, and an accuracy of 70.7% (**Table 4**).

DISCUSSION

The clinical manifestation spectrum in patients with suspected choledocholithiasis is broad and variable, so surgeons rely on guidelines and criteria for decision-making. Due to the high rate of diagnostic ERCP (20%-30%) under the ASGE 2010[2], we analyzed the therapeutic ERCP rate according to the high probability of the 2010 and 2019 guidelines. When categorizing the patients according to the 2010 guidelines, 328 met the high probability criteria, and the diagnostic ERCP rate in this group was 13.8%; with the 2019 criteria, there were 271 patients, and the non-therapeutic ERCP rate was 10.8%. The 2019 criteria were

Table 1. Characteristics of patients taken directly to ERCP for suspected choledocholithiasis

	n	%
Female	209	54.1
Mean age (SD)	59.4 (20.9)	-
Previous cholecystectomy	102	26.4
Clinical and paraclinical assessment		
- Acute pancreatitis of biliary origin	76	19.7
- Cholangitis, according to Tokyo 2018	107	27.7
- TB < 2	61	15.8
- TB 2-4	83	21.5
- TB > 4	242	62.7
- Altered liver profile other than TB	373	96.6
Abdominal ultrasonography findings		
- Acute cholecystitis	116	40.8
- Cholelithiasis	237	83.5
- Choledocholithiasis	160	41.5
- Dilated bile duct	294	76.2
ERCP findings		
- Days since admission to ERCP (mean SD)	2.6	-
- Therapeutic ERCP	326	84.5
- Choledocholithiasis	327	84.7
- Dilated bile duct	349	90.4
- Bile duct size (mm) (SD)	12.8 (5.8)	-
Post-ERCP complications		
- Pancreatitis	4	1.0
- Digestive bleeding	1	0.3
- Duodenal perforation	0	0

Source: The authors.

applied to the 328 who went directly to ERCP to analyze both results due to high probability per the 2010 guidelines. In this scenario, 29 patients (8.8%) would have diagnostic ERCP, which translates into a 41.7% reduction in the non-therapeutic ERCP rate.

When examining the paraclinical and ultrasound variables individually, we found that choledocholithiasis on ultrasound and cholangitis had specificities greater than 78% and PPV > 88%, which are lower than those reported in other studies, such as the one published in China. It analyzed 2724 patients with suspected choledocholithiasis who underwent ERCP, diagnostic imaging, or surgical exploration of the bile duct and reported specificities of 89.6% with a PPV of 91%[2]. Moreover, a study in the United States retrospectively analyzed 744 patients undergoing ERCP with indications of choledocholithiasis and showed specificities of 97% and a PPV of 93.7%[11]. Although the diagnostic yield of these variables in the different studies is diverse, they continue to form part of the high probability criteria in the 2010 and 2019 guidelines, under which patients should go directly to ERCP.

One of the significant updates to the 2019 guidelines was removing TB > 4 mg/dL as the only variable and adding bile duct dilation to define ERCP performance. Our study found that bile duct dilation was more sensitive than TB > 4 mg/dL (81% vs. 64%) with similar specificities (50% vs. 45%, respectively). By combining both variables, lower sensitivity and higher specificity were observed with a PPV of 91.8%, and the 2019 guidelines' objective of being more selective to reduce the rate of diagnostic ERCP was achieved. Our specificity was lower, and the PPVs were similar to the results of other research groups that reported specificities of 94%-96% and PPVs of 69%-85%[11, 12].

According to ASGE 2010, 86.2% of patients with high probability and 74.1% with medium probability were positive for choledocholithiasis. The 2019 criteria showed that 89.2% of patients with a high probability had bile duct stones compared with 73% of patients with a medium probability. Chandran et al.[11] reported similar results (67.7% vs. 82.5%, respectively). While not statistically significant, they considered that they are clinically relevant to reduce the rate of complications of endoscopic management when performing further imaging studies.

During the study period, the institution did not have EUS or MRCP available, which is why 15% of the patients taken to ERCP did not meet high probability criteria according to ASGE 2010 and did not undergo any prior imaging study, as recommended by the guidelines. When analyzing these patients, the probability of having choledocholithiasis was 74.1% according to the 2010 guidelines and 73.1% according to the 2019 guidelines. These data were higher than in the guidelines, which suggest probabilities between 10% and 50%[1], maybe because the majority met strong criteria, and only a small percentage met moderate criteria.

Few studies have compared the performance of patients classified as high-risk according to 2010 versus 2019 guidelines[11-13]. Hasak et al.[12] reported that, when using the 2010 guidelines, the sensitivity, specificity, PPV, NPV, and accuracy were 50.5%, 78.9%, 82.5%, 44.8%, and 60.1%, respectively, while when using the criteria of the 2019

Table 2. Diagnostic yield of the tests for high probability according to the 2010 and 2019 criteria

Variable	n	Sen	Spe	PPV	NPV	Accuracy
Individual						
- CL on US	147	45.1	78.3	91.9	20.8	38.1
- Cholangitis	94	28.8	78.3	87.9	16.8	24.4
- Dilated BD	264	81.0	50.0	89.8	32.6	68.4
- TB > 4	209	64.1	45.0	86.4	18.8	54.1
- TB 2-4	70	21.5	78.3	84.3	15.5	18.1
Aggregate						
- Cholangitis + CL on US + TB > 4	38	11.7	96.7	95.0	16.8	9.8
- CL on US + TB > 4	95	29.1	90.0	18.9	94.1	24.6
- Dilated BD + TB > 4	168	51.5	75.0	91.8	22.2	47.4
- Dilated BD + TB 2-4	55	16.9	91.7	91.7	16.9	14.2

CL: choledocholithiasis; Spe: specificity; Sen: sensitivity; US: ultrasonography; BD: bile duct. Source: The authors.

Table 3. Patients with a high and medium probability, according to the ASGE 2010 and 2019 guidelines

		2010		2019	
	Total n (%)	HP n (%)	MP n (%)	HP n (%)	MP n (%)
Number of patients	386	328 (84.9)	58 (15.1)	271 (70.2)	115 (29.8)
LC on ERCP	326	283 (86.2)	43 (74.1)	242 (89.2)	84 (73.1)
Very strong criteria*	301 (77.9)	301	NA	271	30
Strong criteria*	76 (19.6)	27	48	NA	76
Moderate criteria*	10 (2.5)	NA	10	NA	10

*According to ASGE 2010 guidelines. CL: choledocholithiasis; ERCP: endoscopic retrograde cholangiopancreatography; NA: not applicable; HP: high probability; MP: medium probability. Source: The authors.

Table 4. High probability diagnostic yield according to the 2010 and 2019 guidelines

Variables	2010	2019	*p*
Patients with HP (n) (%)	328 (84.9)	271 (70.2)	< 0.001
CL in patients with HP (n) (%)	283 (86.2)	242 (89.2)	< 0.001
Sensitivity (%)	86.8	74.2	
Specificity (%)	25.0	51.7	
PPV (%)	86.3	89.3	
NPV (%)	25.9	26.9	
Accuracy (%)	77.2	70.7	

CL: choledocholithiasis; HP: high probability. Source: The authors.

guidelines, the sensitivity, specificity, PPV and NPV, and accuracy were 65.8%, 78.9%, 86.3%, 54.1%, and 70.4%. In conclusion, although the 2019 criteria improve pretest performance, it is still in suboptimal ranges, and further EUS or MRCP-type studies should be considered before taking a patient to ERCP.

Chandran and colleagues[11] demonstrated a significant difference in the number of patients classified as high risk: 37% under the 2019 guidelines versus 60% with the 2010 criteria. Sensitivity was 37.8% vs. 61.2%, specificity 77.1% vs. 52.1%, PPV 95.5% vs. 94.9%, and accuracy 40.3% vs. 60.6% when comparing both guidelines. They considered it necessary to carry out a cost-effective analysis when applying the 2019 guidelines due to the significant increase in patients in the medium category. Another group that recently compared both guidelines[13] considers that the 2019 criteria reduce the number of diagnostic ERCPs and are a tool that improves risk stratification. Their data showed that the PPV increased by 79% according to the guides of 2010 to 83% according to those of 2019.

Our study obtained similar results when staging patients with the 2019 criteria. A lower number of patients were found in the high-risk category (70.2% vs. 84.9%), translating into much more specific criteria (51.7% vs. 25.0%) but less sensitive (74.2% vs. 86.8%) than those of the 2010 guidelines, considerably increasing the number of patients in the medium category. Accuracy was lower in the 2019 criteria (70.7% vs. 77.2%), a similar pattern to the previously mentioned studies. The PPV was higher in the 2019 guidelines (89.3% vs. 86.3%), with similar NPVs between both guidelines (26.9% vs. 25.9%).

Our ERCP complications were around 1%, well below what is mentioned in the current literature, reporting overall complications of 6%-15%, fatal complications of 1%-2%, and mortality of 0.4%[14, 15]. This result should be taken with caution, as it could be due to underreporting of complications, probably related to not including intra-ERCP bleeding, complications related to sedation, post-ERCP sepsis, complications of the 430 excluded ERCPs, or late complications that could be cared for in another hospital. In addition, most complications, for being minor, could not be correctly noted in the medical record or not identified during data collection. In our institution, there are no trainees; therefore, all procedures were performed by experts with many years of experience, and the literature documents lower complication rates in expert hands[16].

Our study has the limitations of being retrospective and single-center, which makes it susceptible to registration bias due to obtaining the data from medical records and restricts the generalization of results. In addition, it does not include all patients suspected of having choledocholithiasis, so an adequate measurement of the prevalence is not possible, especially of patients belonging to the medium probability category who were not taken for ERCP. Among its strengths, it is the first study that discusses the behavior of patients with choledocholithiasis taken to ERCP in the Cauca province, allowing the creation of guidelines that improve patient care at the San José University Hospital and motivate other institutions to conduct similar studies both in Cauca and in the rest of the country, as recommended by the Colombian Society of Gastroenterology.

CONCLUSIONS

Our results confirm that the new criteria for risk stratification and treatment of patients with suspected choledocholithiasis are less sensitive but more specific and become stricter when selecting patients who will be taken directly to ERCP so that the rate of non-therapeutic ERCP is decreased. However, the number of patients in the medium probability category increases considerably, which requires previous studies. Therefore, the implementation of the ASGE 2019 guidelines on the indications for ERCP should be considered in light of the resources of hospitals, especially in low- and middle-income countries. The ASGE 2010 guidelines show good sensitivity and accuracy in guiding ERCP performance.

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Original article

Stress, depression, anxiety, and eating habits in people with irritable bowel syndrome

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Abstract

Irritable bowel syndrome (IBS) is a disorder characterized by changes in bowel habits and affects 30% of the world's population. Although a connection has been found between the brain-gut microbiota axis, the development of IBS, and its association with the prevalence of mental disorders, the possible implications for people's eating habits are unclear. This article aimed to explore the relationship between stress, depression, anxiety, mental disorders, and eating habits in patients with IBS. A literature search was conducted in the PubMed, ScienceDirect, and VHL search engines. We found that people with IBS may have abnormalities in the brain microstructure and alterations in the brain-gut network associated with a longer duration of gastrointestinal symptoms and increased affective comorbidity. A relationship between stress, depression and anxiety, IBS symptoms, and changes in eating habits in different pathways is also suggested. All these may lead to restrictive eating practices, changes in appetite, nutrient inadequacy, even due to the same nutritional management in some cases, and, generally, deterioration in the quality of life of people with IBS. We recommend comprehensive management that involves not only pharmacological treatment for IBS symptoms and states of anxiety and depression but also psychological therapy, personalized nutrition, and improving lifestyles, such as physical activity and stress management.

Keywords

Irritable bowel syndrome, brain-gut axis, microbiota, stress, depression, anxiety, eating habits.

INTRODUCTION

Irritable bowel syndrome (IBS) is a functional gastrointestinal disorder affecting approximately 30% of the world population and is more common in women and developing countries. It is characterized by symptoms of chronic abdominal pain and change in bowel habits[1,2]. According to the criteria established by the Rome Foundation (Rome IV), it is classified into subtypes: IBS with diarrhea (IBS-D), IBS with constipation (IBS-C), IBS with mixed symptoms (diarrhea and constipation) (IBS-M), and IBS in patients who meet the diagnostic criteria, but do not fit into any of the above categories (IBS-U)[2].

It is a functional condition characterized by gut-brain axis (GBA) dysfunction. The altered functioning and balance of the GBA and the microbiota may trigger adverse reactions that cause the typical gastrointestinal symptoms of IBS[3]. One reason that can lead to this alteration is the chronic stress the patient is subjected to in their environment. Commonly, patients who have signs of depression and anxiety present

with symptoms such as abdominal pain, nausea, and decreased appetite, altering eating patterns[4]. Epidemiological data have shown that 40% to 90% of patients suffering from IBS also meet the criteria for diagnosing a mental disorder, especially depression and anxiety[1].

Even when the importance of the psychological factor in IBS has been recognized, information is scarce about how these altered mental states affect the relationship with food of the patient with IBS and to understand and devise strategies for optimal treatment.

Therefore, this article aimed to explore the relationship between stress, mental disorders, and eating habits in individuals with IBS. Hopefully, this article may help understand the existing relationships and make proposals to define strategies for clinical management with a comprehensive approach to the syndrome, especially in the nutritional field.

MATERIALS AND METHODS

Research on the relationship between mental disorders, stress, and eating in IBS is recent and imprecise. Thus, we decided to conduct a scoping review to determine the existing literature on the subject matter, particularly when it has not been extensively reviewed or is of a complex or heterogeneous nature[5].

We followed the five-step methodology suggested by Arksey and O'Malley[6] and the PRISMA extension for scoping review published in 2018, consisting of 20 essential items and two optional items to be included in this type of work[7].

The information search was carried out through PubMed, ScienceDirect, the Virtual Health Library (VHL) Regional Portal, and Google Scholar databases. The DeCS terms "*síndrome de intestino irritable*," "*depresión*," "*ansiedad*," "*estrés psicológico*," and "*hábitos alimentarios*" were used. Regarding the MeSH terms, only the term "irritable bowel syndrome" was employed due to the specificity of the search.

For this review, we built the following search equations: ((gut-brain axis) AND (microbiota) AND (irritable bowel syndrome [MeSH])), ((irritable bowel syndrome [MeSH]) AND (microbiota) AND (serotonin)), ((stress) AND (gastrointestinal symptoms)), ((anxiety) AND (gastrointestinal symptoms)), ((depression) AND (gastrointestinal symptoms)), and ((irritable bowel syndrome [MeSH]) AND (feeding behavior)).

The types of studies (clinical trials, systematic reviews, literature reviews, and meta-analyses), studies conducted in humans, and language (Spanish or English) were considered inclusion criteria. The time window was not considered as an inclusion criterion since, being a recent and heterogeneous research topic, there are few related publications. The articles' titles, keywords, and abstracts were considered selection criteria. We excluded publications or studies in the pediatric population or dealing with eating disorders or other inflammatory diseases of the digestive system, such as ulcerative colitis, Crohn's disease, or celiac disease (**Figure 1**).

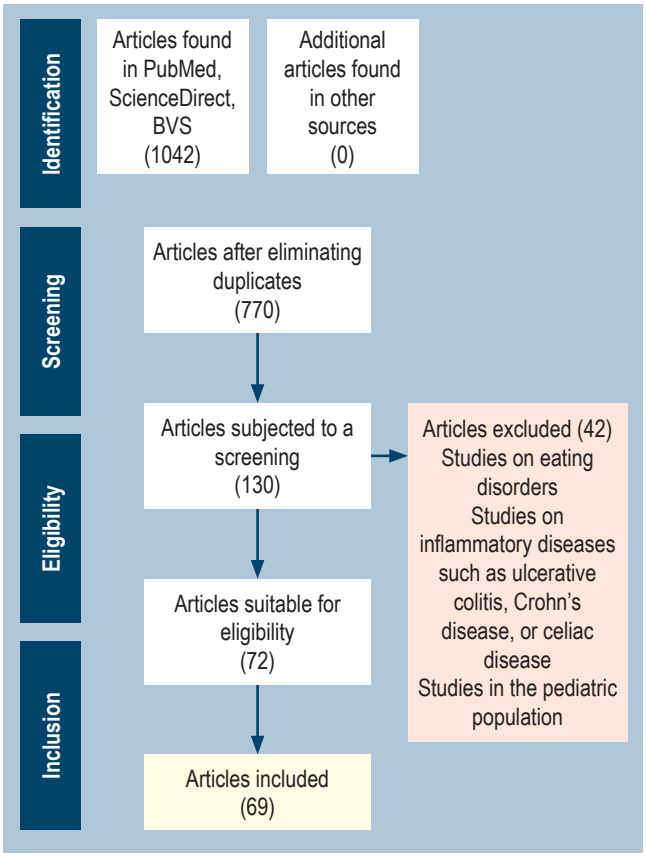

Figure 1. Flowchart of the study identification and selection process according to the PRISMA method for scoping review articles. Source: The authors.

After selecting the articles, an information extraction matrix was created in Excel, and the Mendeley reference manager was used. We employed the title, year, country, author(s), objective, materials and methods, and critical results fields for data extraction.

Finally, to summarize the findings, they were classified into the following lines of research: "mental disorders, stress, and gastrointestinal symptoms in patients with IBS," including the relationship between mental disorders (anxiety, depression, stress) and possible gastrointestinal symptoms involved in IBS; "eating habits in people who suffer from IBS," describing how the IBS symptoms may modify the eating habits of individuals who suffer from it, and "gut-microbiota-brain axis and IBS," involving the relationships between the central nervous system, intestinal microbiota, IBS, neurotransmit-

ters, and metabolites. The preceding describes the possible mechanisms that explain the associations between IBS, mental disorders, and eating habits.

RESULTS

Of the 130 articles selected for screening, 70 published between 2007 and 2021 were included, most of which correspond to 2021. Most of the articles published were from European and East Asian countries[4, 8-14], which is contradictory considering that these countries have the lowest prevalence of IBS[2]. On the one hand, most of the texts used were literature reviews that sought to establish the relationship between the gut-microbiota-brain axis and the development of IBS. On the other hand, clinical studies (randomized clinical trials and prospective studies) aimed to prove the variation in the microbial population of people with IBS and their concentration levels of short-chain fatty acids (SCFA) and serotonin. We also investigated clinical practice guidelines (CPG) for managing IBS and found four.

Mental disorders, stress, and gastrointestinal symptoms in patients with IBS

Hans Selye first defined stress in 1936[15] as the physiological response to psychological or genuine threats. When an acute stressor appears, a "fight or flight" response is triggered, preparing the body to defend itself and ensure its survival. However, when the stressor is chronic, it becomes harmful since it does not allow the achievement of basal homeostasis.

It has been noted that patients with IBS tend to have an increased response to stress, which has involved a possible mechanism contributing to the syndrome's pathology[14, 16]. The reason is that stress could induce changes in intestinal motility, permeability, and secretion, as well as visceral sensitivity that causes the reactivation of previous enteric inflammations and subsequent inflammatory stimuli[16, 17]; furthermore, it may alter the composition and function of microbiota[18].

Similarly, traumas during a person's life produce chronic stress that can lead to developing IBS[15]. Particularly, traumas experienced at an early age (sexual, physical, or psychological abuse, serious illness, or death of a parent, among others) have been associated with higher risks of suffering gastrointestinal discomfort and higher chances of suffering from inflammatory diseases in the digestive system such as IBS. These events may result in long-term epigenetic changes in the hypothalamic-pituitary-adrenal (HPA) axis, with altered negative feedback of glucocorticoids and increased susceptibility to stress-related disorders in adulthood[19].

In addition to a frequent number of people with IBS and stress, those suffering from IBS show a high prevalence of suffering from mental disorders such as anxiety and depression due to continuous exposure to stressful stimuli. Between 20% and 90% of patients with IBS suffer from severe psychiatric symptoms that may be diagnosed as a disorder[17, 20]. A prospective study conducted by Koloski et al.[21], with a 12-year follow-up of more than 1,000 individuals, found that those with high anxiety and depression were more likely to develop IBS.

Anxiety related to gastrointestinal symptoms is known as *specific gastrointestinal anxiety* (AGE) and influences the severity of symptoms and the quality of life of individuals with gastrointestinal diseases[22]. Van Oudenhove et al.[23] found an association between psychosocial morbidity (anxiety, depression, and somatization) and increased gastrointestinal symptoms. Specifically, they detailed that increased levels of anxiety and depression were related to the appearance of symptoms such as bloating, abdominal pain, and nausea in the postprandial period[24]. Studies have shown that higher levels of anxiety and depression lead to a more significant reduction in pain thresholds caused by a readjustment in the autonomic nervous system (ANS) and neuroendocrine pathways that increase pain perception[25].

Eating habits in people with irritable bowel syndrome

Stress and mental disorders in irritable bowel syndrome and its relationship with food intake

Stress and mental disorders increase or decrease eating, as exposure to stress produces both orexigenic and anorexigenic substances in the body[26]. Chronic stress increases the activation of the orexigenic pathways, which intensifies the intake of foods rich in calories and carbohydrates that are "appetizing" for the person and interrupts specific sensory satiety signaling, which results in the consumption of a particular food over and over again. In contrast, when there is an absence of foods rich in calories or that are appetizing, stress activates the anorexigenic pathways, so food intake decreases; activation of this pathway can be acute or sustained over 24 hours[27].

It has been shown that, under acute stress conditions, norepinephrine suppresses appetite and, together with other catecholamines, increases blood pressure and heart rate, and decreases blood flow in the digestive and renal systems and the skin[28]. Altered regulation of the HPA axis due to chronic stress modifies the production of cell fusion protein 1 (CFR1), which acts as an anorexigenic substance that influences food intake and energy balance. CFR1 is believed to decrease the synthesis of neuropeptide

Y (NPY) and its release and increase the production of leptin, known as the satiety hormone[19, 28].

Gastrointestinal symptoms and negative perceptions of food

Gastrointestinal symptoms have a high relevance in the perception of pleasure when eating, the selection of food, and participation in daily life activities. Usually, patients with a disease or syndrome related to the gastrointestinal system tend to develop negative perceptions of food and avoidance behavior in social situations due to the discomfort caused by the gastrointestinal symptoms of the pathology[29].

Fear and anxiety around gastrointestinal symptoms when eating increases restrictive or disordered eating practices, decreasing appetite due to gastrointestinal symptoms derived from eating[30]. Food restriction is a risk factor for disordered eating associated with reduced quality of life, maladaptive coping mechanisms, depression, and perceived stress.

Cuomo et al.[31] found that more than 60% of IBS patients reported the onset or worsening of gastrointestinal symptoms 15 minutes after meals, in addition to high food intolerance associated with reduced quality of life. According to the authors, this intolerance often makes patients identify and eliminate foods they do not tolerate. It was found that 62% of individuals with IBS limited or excluded foods from their diet[32]. A study with 1,717 Korean students revealed that individuals suffering from IBS tended to skip their daily meals frequently, unlike healthy subjects. These results were similar to those in other studies conducted with middle-aged people and a study conducted with nursing and medical students in Japan[33].

Petrillo et al.[34] found that 57% of the individuals who had decreased food intake met the criteria for psychiatric disorders and were also associated with abdominal distension, pain, irregular bowel habits, fatigue, and headache. Several studies that have evaluated daily eating patterns find a significant decrease in the intake of calories, protein, and carbohydrates, including fiber, and low values compared to the daily recommendation of micronutrients such as calcium, thiamine, and folates in individuals with IBS, in contrast to healthy controls[30, 34, 35]. Individuals with gastrointestinal diseases often have irregular schedules, skipped meals, and a more restricted intake.

In a study conducted by Melchior et al.[35] in 2021, 26% of patients with IBS reported that they frequently did not eat when hungry due to the same disorder, 54% stated that they often avoided food, and 31% said that they had an aversion to food. In a case-control study by Hayes et al.[36], patients with IBS had a risk factor of 3.96 for developing irregular eating habits compared to healthy controls.

Dietary recommendations for irritable bowel syndrome

Diet is critical, considering that 60% of patients with irritable bowel claim that certain foods worsen their symptoms. Generally, dietary indications to treat IBS symptoms include reducing the intake of lactose, fats, gas-producing foods (such as legumes, pulses, and broccoli, among others), a diet low in fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAP), which is the most common, and adequate fiber supply, especially soluble[37]. According to the 2016 Colombian CPG[38], with a strong recommendation but insufficient evidence, professionals state that the implementation and adherence to a low FODMAP diet are advised to treat patients with IBS who present with bloating, abdominal pain, and diarrhea because these carbohydrates increase intraluminal osmotic pressure and provide a substrate for bacterial fermentation, resulting in gas production, bloating, and abdominal pain[39].

However, in some articles, despite reducing some of these compounds in the diet, some people with IBS still show a degree of food aversion and restriction and report high severity in gastrointestinal symptoms[35]. The preceding can be related to the stress at eating time due to perceived gastrointestinal symptoms or other external stress situations and the same mental disorders that cause dysregulation in eating habits and appetite.

Diets based on eliminating foods to which patients with IBS are "intolerant" may increase the risk of developing avoidant/restrictive food intake disorder (ARFID). The DSM-5 defines it as a disorder that occurs when a disturbance in food intake causes the inability to meet appropriate nutrient or energy needs, leading to weight loss or nutritional deficiency and, in more severe cases, dependence on enteral feedings or dietary supplements. Usually, this disorder is not motivated by fear of gaining weight or dissatisfaction with body image but by low interest in eating or hyporexia, aversion to the sensory characteristics of some foods, or worry or fear of the consequences of eating certain foods[29, 40].

Most patients who develop ARFID have been prescribed a low FODMAP diet due to maladaptive eating behavior that pushes them to avoid the phase of food reintroduction, reducing their diet to only 10 "safe foods"[29, 41]. Notably, more than 70% of these patients already met the criteria for ARFID, low weight, or some mental disorder when prescribing the diet[29]. According to the data obtained by Mari et al.[42], greater adherence to a low FODMAP diet is associated with symptoms related to eating disorder behaviors. All patients who tested positive for an eating disorder had a percentage of adherence of 57.4% compared to 35.8% in those who tested negative for eating disorders.

In general, Kayar et al.[43] discovered that out of 200 patients, 118 (59%) were women, and 92 (41%) were men. The eating attitudes test (EAT) score was significantly higher in the IBS group (odds ratio: 5.3; 95% confidence interval [CI]: 4.3-9.3; $p < 0.001$). The number of subjects with an EAT score > 30 was significantly higher in the IBS group ($p < 0.001$). In addition, higher scores were found in female patients with IBS and younger ages, considering a broad age range between 18 and 65 years ($p = 0.013$ and $p = 0.043$, respectively). At the same time, there was no significant association between the IBS subtype and the EAT score ($p > 0.05$). However, the intensity and duration of IBS had a positive correlation with the EAT scores, which justifies some comments by other authors that the presence of IBS is linked to disordered eating and even with eating disorders such as anorexia nervosa, bulimia, and unspecified disorders[44].

Food restriction has also been related to the possibility of sub-adequacy in nutrient needs; for example, low dairy intake leads to insufficient calcium, vitamin B12, riboflavin, and vitamin D, or low fat intake may imply inadequate intake of fat-soluble vitamins. Patients suffering from IBS have been found to have low concentrations or deficiencies of vitamins A and riboflavin and minerals such as calcium and potassium[37].

Irritable bowel syndrome and abdominal obesity

Recent research, such as that of Akhondi et al.[45], has determined that IBS is more frequent among individuals with abdominal obesity compared to subjects with average weight (23.8% vs. 19%). This condition could be related to eating habits. Nonetheless, the association between IBS, obesity, and overweight was no longer significant after adjusting for possible confounding factors (odds ratio [OR]: 1.09; 95% CI: 0.82-1.44). In the categories of body mass index (BMI), they found no significant association between overweight (OR: 0.89; 95% CI: 0.62-1.27), obesity (OR: 1.05; 95% CI: 0.58-1.87), and the severity of abdominal pain. Abdominal overweight (OR: 0.96; 95% CI: 0.65-1.40) and obesity (OR: 1.61; 95% CI: 0.67-1.63) were not associated with the intensity of abdominal pain. Therefore, further research is required looking forward.

Gut-microbiota-brain axis and IBS, possible mechanism to explain the relationship of IBS symptoms with mental disorders and eating habits

At the core of the gut-brain (GBA) axis is the connection between the enteric nervous system (ENS) and the central nervous system (CNS), which creates direct "bottom-up" and "top-down" communication. Downstream, the ECI enables central regulation of gut function and facilitates gut responses to emotion and cognition; upstream, the responses to stimuli derived from the intestine influence the cognitive and emotional centers of the brain[46]. This modulation occurs through sympathetic and parasympathetic inputs from ANS neurons. It could be part of the mechanisms that explain the relationships between IBS gastrointestinal symptoms, mental disorders, and changes in eating habits.

Gut microbiota

The gut microbiota is the latest component of this network to be recognized. Commensal organisms in the gut have been shown to have the ability to directly influence the ENS and indirectly modulate ECI function[20] via numerous pathways, including the immune system, the recruitment of neuroendocrine signals, direct ENS pathways, and the vagus nerve, and the production of bacterial metabolites such as short-chain fatty acids (SCFAs), bile acids, serotonin, branched-chain amino acids, and peptidoglycans[9, 47, 48].

Mayer and colleagues[18] have proposed that signaling between the brain, gut, and microbiota may contribute to dyspepsia and that the microbiota may mediate the modulation of enteric reflexes that cause IBS-related symptoms. A local change in microbes in the gut microbiota leads to inflammation that may allow bacterial translocation along with an increase in proinflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and mediators such as serotonin, which induce increased sensitivity to pain and changes in motility, possibly through effects on the interstitial cells of Cajal[17, 49, 50]. This situation may be reinforced by mental disorders such as depression and anxiety that alter the flow of the ANS with increased levels of catecholamines, which in turn increase the production of an adrenocorticotropic-releasing hormone (CRF) and the secretion of cortisol (**Figure 2**)[17].

Moreover, it has been found that the intestinal microbiota composition in patients with IBS usually differs from that of healthy individuals. Several studies have identified that those individuals who suffer from the syndrome have a greater bacterial richness of *Ruminococcus* sp, *Clostridium* spp, and proteobacteria, which are linked to IBS symptoms, including visceral hypersensitivity and changes in SCFA values that are associated with altered levels of fecal cytokines. There are also deficiencies of *Bifidobacterium* sp, *Roseburia*, *Faecalibacterium*, and *Lactobacillus*, which help promote intestinal health[3, 11, 49, 51]. *Bifidobacterium* supplies a mucosal barrier that helps maintain intestinal homeostasis, and *Lactobacillus* is essential for increasing mucin production in the intestinal lining, preventing pathogenic microbes' adherence. Meanwhile, *Faecalibacterium prausnitzii* is a significant butyrate producer that promotes intestinal inflammation reduction and releases other important metabolites to improve the mucosal barrier function[4].

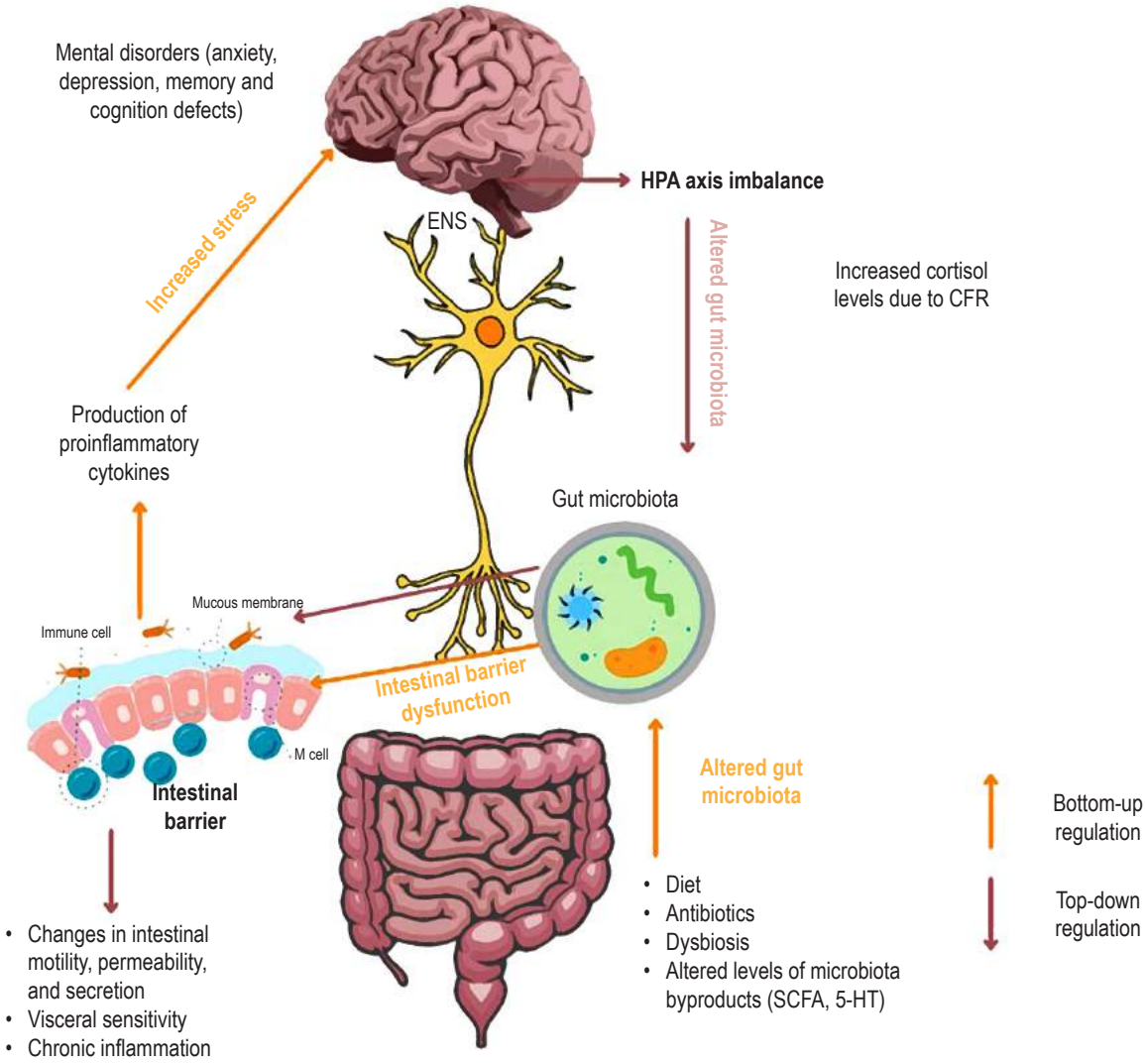

Figure 2. Alteration of the gut-microbiota-brain axis in IBS. The gut-microbiota-brain axis is connected through the enteric nervous system, creating two-way communication. Upstream, microbiota alteration by factors such as diet, antibiotics, or dysbiosis changes the concentration levels of the derivative metabolites (SCFA*, 5-HT**), which leads to intestinal barrier dysfunction. As a result, chronic inflammation and the production of proinflammatory cytokines can increase stress and cause an imbalance in the brain and the possible development of mental disorders such as depression and anxiety. Downstream, an imbalance in the HPA axis increases cortisol levels induced by CFR, causing the rise of the catecholamines that impact intestinal bacteria, intestinal inflammation, and changes in intestinal motility. *Short-chain fatty acids. **Serotonin. CFR: corticotropin-releasing factor; HPA: hypothalamic-pituitary-adrenal axis. Source: The authors.

The gut microbiota plays a vital role in neurodevelopment during the pre- and postnatal period and affective behavior in adulthood. Dysbiosis of the pregnant mother may alter the signs of normal development or induce inappropriate developmental stimuli[52]. Inflammation caused due to disruption of the gut microbiota results in a proinflammatory state that can affect neural development and the fetal immune system. Among the causes of maternal dysbiosis are the use of antibiotics, high fat intake, and physical or psychological stress that can suppress the production of immunoregulatory metabolites such as SCFAs or promote the production of proinflammatory metabolites[53]. The maternal gut microbiota can also affect circulating levels of serotonin (5-HT), which in turn alters fetal neurodevelopment because this metabolite regulates the division, differentiation, and synaptogenesis of neuro-fetal cells[54].

Disruption of the microbiome in the first years of life influences long-term adverse mental health outcomes

through its interaction with the gut-brain axis[55]. In neonates born vaginally, the gastrointestinal tract is colonized mainly by bifidobacteria, lactobacilli, *Bacteroidetes*, proteobacteria, and *Actinobacteria*. In contrast, those born by C-section have a higher amount of *Escherichia coli* and *Clostridia* and a lower amount of *Bacteroidetes* and bifidobacteria. Breastfed infants show a greater abundance of bifidobacteria, while in formula-fed infants, bifidobacteria, Bacteroides, clostridia, and staphylococci were found in equal amounts[56].

The species *Clostridium* spp., which, as mentioned, is usually found in more significant amounts in children born by C-section and fed with formula milk and in patients diagnosed with major depressive disorder and IBS, is responsible for producing acetic acid, which also seems to be increased in IBS[51]. Acetic acid plays a relevant role in suppressing appetite by activating acetyl-CoA carboxylase and its effect on the expression of regulatory neuropeptides in the hypothalamus[57], which could indicate that the levels of these hormones are altered when SCFA concentrations are limited due to a change in the gut microbiota composition. People with IBS have abnormal peptide YY (PYY) levels and abnormal cholecystokinin (CCK) responses to food intake, increasing rectal mechanosensitivity. Similarly, it has been identified that mood disorders, such as depression, are associated with genetic polymorphisms that can alter CCK and PYY levels[24, 56].

Short-chain fatty acids

Microbiota-derived SCFAs maintain intestinal homeostasis and have a dual role in immunity: anti-inflammatory, by strengthening the integrity of the epithelial barrier through upregulation of G protein-coupled receptors in the intestine, and induction and maintenance of regulatory T cells that enhance the integrity of the epithelial barrier. In contrast, in cases of dysbiosis, SCFAs induce mucosal inflammation via tryptophan hydroxylase 1 (TPH1) transcription and 5-HT production via the serotonergic pathway, accounting for low-grade inflammation in the pathogenesis of IBS[58].

Besides, 95% of these SCFAs are made up of acetate, propionate, and butyrate, produced from carbohydrates in the colon. Acetate and propionate regulate fatty acids and energy in the liver[51]. Butyrate is involved in the modulation of intestinal epithelial proliferation, apoptosis, and cell differentiation in the intestine and the inhibition of the nuclear factor kappa-light-chain-enhancer of activated B-cells (NF-κB) while maintaining the integrity of the intestinal barrier[49].

A study by Tana et al.[59] detected significantly higher levels of acetic acid and propionic acid in patients with IBS than in controls. However, other studies show that fecal SCFA of patients with IBS was characterized by lower levels of total SCFA, acetic acid, and propionic acid and higher levels of butyric acid[8, 60]. Although there is still no consensus on the differences observed in SCFA levels, alterations in SCFA composition and concentration are evident in patients with IBS, especially in patients with IBS-D, in whom differences in SCFA production by the colonic microbiota are associated with an accelerated rate of bowel transit and neuromuscular dysfunction[8, 10].

Serotonin

About 90% of the 5-HT in the human body is found in the gastrointestinal tract, mainly in enterochromaffin (EC) cells and myenteric interneurons[13]. Inflammation and the development of neurons are essential for peristalsis and intestinal secretion. 5-HT is related to pain, sensitivity, and reflexes through the activation of EC and enteroendocrine cells[16, 51]. It has been shown that abnormalities in the metabolism of this neurotransmitter may be associated with functional bowel diseases and anxiety disorders. Clinical studies have observed that patients with IBS-C have low postprandial serum 5-HT levels related to slow bowel transit. At the same time, high concentrations are more common in patients with IBS-D, which is related to a higher prevalence of depression and anxiety in patients with IBS-C, probably due to intestinal serotonin imbalance and reduced serotonin response in central and peripheral regions[16, 61].

Recent studies have discovered that the 5-HTTLPR polymorphic variation of the gene encoding the serotonin transporter protein (SERT) increases the expression of the transporter and enhances its activity, increasing serotonin uptake and, in turn, decreasing its effects on secretion and motility. Hence, this polymorphism may be found in patients with IBS-C[62-65].

Changes in serotonin concentrations are not only reflected at the level of intestinal metabolism. They can also alter intestinal signaling and visceral nociceptive processes, causing greater sensitivity to abdominal pain[66, 67].

The corticotropin-releasing factor signaling system

The CFR signaling system is a critical pathway in the biochemical mechanism by which the brain translates a stimulus into an integrated physical response. This system directly affects the gastrointestinal tract, producing proinflammatory effects primarily mediated by CFR1. The latter is expressed in enteric neurons and the intestinal mucosa layer, which delays gastric emptying and accelerates colonic transit[15, 68, 69]. CFR also plays a primary role in stimulating the HPA axis in response to physical or psychosocial stress: it increases catecholamine levels, which impact gut bacteria, and cortisol levels, which stimulate bile acid production in the liver and affect the microbiota[15, 69]. Evidence

suggests that patients with IBS have deregulation in the HPA axis in baseline conditions with an improved systemic response, which increases basal cortisol levels and anxiety symptoms[16].

DISCUSSION

Although in recent years, the information on the relationship between the psychological and metabolic factors that come together in IBS has increased, there is still a little-studied condition in these patients about these factors influencing IBS symptoms and changes in eating habits.

Among the mechanisms apparently associated with developing IBS are abnormalities in brain structure and the functioning of the gut-brain axis that cause a greater emotional response, higher visceral sensitivity, altered affective behavior, and changes in gastrointestinal function and gut microbiota composition. Structural and connective changes within sensory regions of the brain may result in increased abdominal pain sensation. They explain the increased affective comorbidity observed in IBS patients, especially as deficient modulation of the "upstream" gut-brain pathway and hyperactivity of the amygdala and anterior insula have been noted in anxiety disorders[20, 68].

According to the evidence, the relationship between gastrointestinal symptoms, mental disorders, and eating seems to occur in different pathways, many associated with the gut-microbiota-brain axis[11]. Gastrointestinal symptoms of IBS can be related to negative perceptions of food and changes in appetite. Mental disorders may change a person's eating habits, gastrointestinal function, and nutritional status, among other relationships[70]. Likewise, diet changes to manage IBS induce effects on food intake, mental state, and sub-adequacy of some nutrients (**Figure 3**).

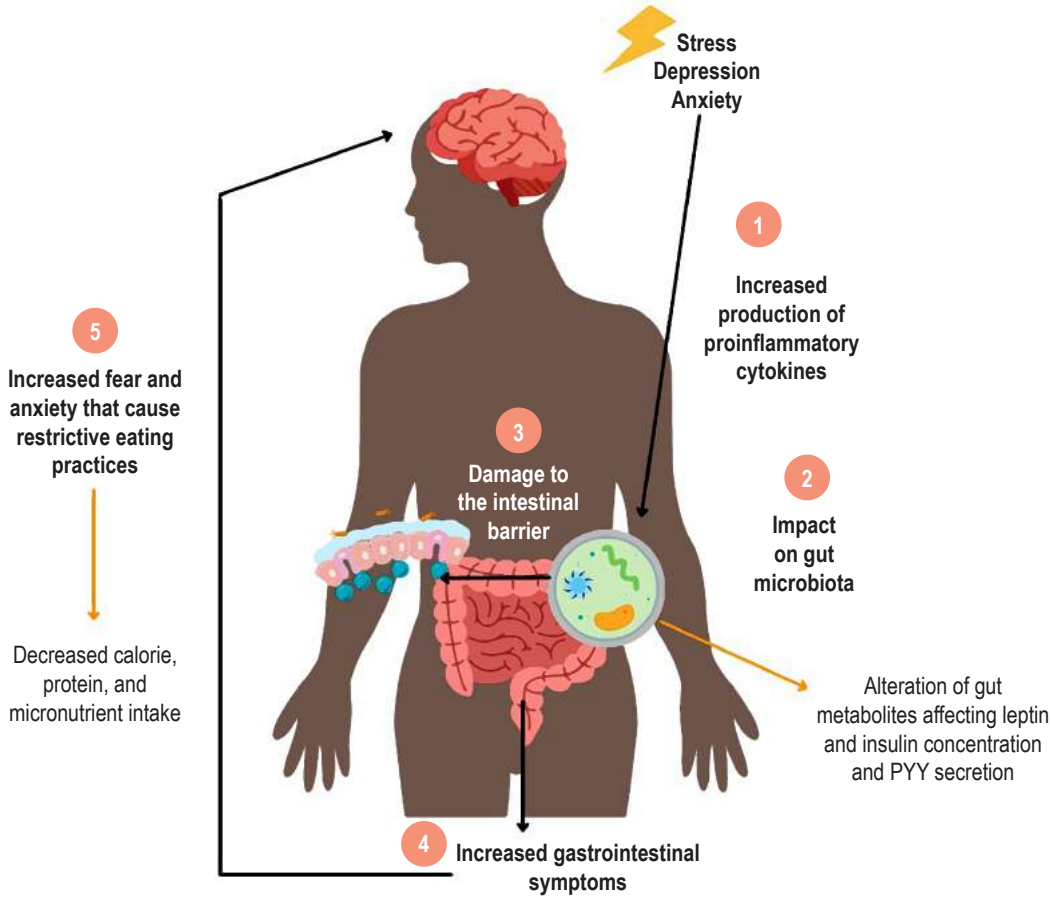

Figura 3. Modelo del rol de los trastornos mentales en la afectación del hábito alimentario de las personas con SII. **1.** El estrés psicológico, la ansiedad o la depresión aumentan la liberación de citocinas proinflamatorias. **2.** Estas citocinas impactan en la conformación de la microbiota intestinal, lo que puede alterar los niveles de metabolitos y, a su vez, los niveles de las hormonas que regulan el apetito. **3.** La pérdida del equilibrio bacteriano de la microbiota y el aumento de citocinas proinflamatorias causan daño en la barrera intestinal. **4.** Hay un aumento de los síntomas gastrointestinales como el dolor visceral, motilidad intestinal, distensión abdominal y generación de gases. **5.** El aumento de los síntomas gastrointestinales incrementa el miedo y la ansiedad al ingerir un alimento, lo que causa prácticas de alimentación restrictivas en el paciente con SII. Fuente: elaboración propia.

All the above supports the recommendations that for individuals with IBS, it is essential to establish comprehensive therapy that includes psychological and, if necessary, psychiatric treatment. It should always be accompanied by nutritional guidance that provides dietary alternatives based on recommendations that modify some dietary practices or the intervention of the low FODMAP diet, including a phase of personalization, and allow adequate nutrition and the prevention of future diseases.

It is relevant to include recommendations that promote lifestyle changes, such as physical activity or active breaks during working days, that help manage the stress of daily life and improve gastrointestinal function[71]. Psychological therapy in treating IBS not only helps to improve mood states but also has effects on pain perception, visceral hypersensitivity, and gastrointestinal motility, as well as possible favorable effects on appetite and food intake. Among the psychological therapies, relaxation, multi-component, and cognitive behavioral therapy stand out, which have been highlighted as more effective in patients with IBS[2].

As regards dietary recommendations, the subtype of IBS, the presence of a mental disorder, whether or not the patient already has low weight, and the risk of suffering from an eating disorder should be assessed before prescribing any restrictive diet[42]. The British Dietetic Association's 2016 guidelines[72] consider a low FODMAP diet, eliminating foods high in these carbohydrates for only four weeks. They also recommend the use of probiotics for four weeks. With less evidence, they advise controlling alcohol use and spicy and high-fat preparations. Meanwhile, with moderate evidence, the Canadian Association of Gastroenterology[73] recommends soluble fiber.

Gut dysbiosis and low-grade inflammation reflect the complexity of the relationship between the gut microbiota, the development of IBS, and mental disorders. The importance of regulating the microbiota from the prenatal period is suggested to ensure that the mother maintains healthy eating habits and that her pregnancy occurs in a calm environment, supported by the family and health personnel, and to prevent infections during pregnancy. The significance of breastfeeding infants is highlighted since it not only helps to develop and protect the baby's immune system but also promotes the formation of a healthy microbiota and could be or act as a protective factor against diseases such as diabetes, obesity, IBS, and the onset of mental disorders in adult life[55].

The world is currently experiencing a public health emergency due to the severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2), which is responsible for the coronavirus disease 2019 (COVID-19). The rapid increase in outbreaks worldwide led to the declaration of a global pandemic on March 11, 2020, and most governments instituted quarantines and lockdowns to reduce the number of new infections. Although there are still no conclusive data on the prevalence of IBS globally and regionally during the pandemic, it is clear that COVID-19 as an infectious disease has increased the number of cases of people with IBS and IBS-post-infectious (IBS-PI). It has had a significant impact on mental health globally, not only because of the psychological distress experienced in the acute phase of the illness but also because of the isolating environment and the uncertain sequelae of lockdown that create anxiety and panic[74]. The pandemic has probably affected the eating habits of citizens, who have resorted to increasing foods rich in carbohydrates and fats to feel comfort[75]. A study by Remes-Troche et al.[76] with 678 patients, in which the incidence of constipation symptoms was evaluated during the lockdown implemented to contain the spread of COVID-19 in Mexico, found that this change in eating habits increased the numbers of "new onset" constipation, a significant decrease in the number of stools, and harder stools.

Thus, the comprehensive management of IBS that encompasses the dietary and pharmacological treatment of symptoms and includes psychotherapeutic support is vital to guarantee a better quality of life for individuals suffering from IBS. Implementing a low FODMAP diet, as suggested by the CPG, or identifying intolerable food groups are excellent options to treat this syndrome; however, they are not usually effective in all patients. Complementary alternatives such as promoting physical activity or yoga should be considered, which, in addition to helping to improve gastrointestinal symptoms, can be a tool for managing mental disorders. Within the diet, increasing the intake of soluble fiber and water could help improve bowel transit, particularly in patients with IBS-C.

The possibility of using probiotics that protect and strengthen the intestinal microbiota could also be evaluated. Among these, *Bifidobacterium infantis* and *Lactobacillus salivarus* have been demonstrated to significantly reduce abdominal pain, bloating, and difficulty in bowel movement. It has also been found that the *Lactobacillus rhamnosus* strain could improve gastrointestinal symptoms of IBS and reduce symptoms associated with depression and anxiety[77]. In addition to probiotics, specific interventions aimed at modulating the gut microbiota in IBS are mentioned, including prebiotics, symbiotics, particular diets, fecal transplantation, and other possible future approaches useful for IBS diagnosis, prevention, and treatment[78].

It would be appropriate to conduct a more in-depth evaluation of the functioning of the CNS and ENS in patients suffering from IBS and some mental disorders. These aspects may lead to developing drugs and non-pharmacological therapies more specific to the etiology of IBS in each patient to guarantee a better quality of life.

CONCLUSION

A relationship was found in various pathways between stress, depression and anxiety, IBS symptoms, and changes in eating habits. Some of these relationships are explained to a considerable extent by the regulation in the gut-brain axis, which is probably not the only mechanism. Therefore, the gastrointestinal symptoms of IBS and changes in mood and eating may be associated similarly with variations in the regulatory function of the gut-microbiota-brain axis. Comprehensive management should involve not only pharmacological treatment for IBS symptoms or states of anxiety and depression but also psychological therapy[79] with a personalized nutritional management plan and healthy lifestyle recommendations involving physical activity and stress management[79, 80].

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Original article

Experience in endoscopic retrograde cholangiopancreatography management of postcholecystectomy biliary leak in a Colombian referral hospital

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Abstract

Introduction: Postcholecystectomy biliary leak is rare. Management is mainly endoscopic, but in the literature, there is no consensus on the first-line technique between sphincterotomy, biliary stent, or combination. **Materials and methods:** A case series study was conducted that included all ERCP performed at the San Ignacio University Hospital in Bogotá, Colombia, between January 2010 and March 2021 due to biliary leak after cholecystectomy. Demographic characteristics, clinical manifestations, resolution, adverse events, and hospital length stay were recorded according to the endoscopic technique. **Results:** 24 patients with postcholecystectomy biliary leak managed with ERCP were included. The median age was 59 years (interquartile range [IQR]: 53.5-67). In 75% the surgery was laparoscopic. The most frequent clinical manifestation was increased biliary drainage > 150 mL/24 hours (50%), followed by abdominal pain (39%). The main fistula's location was the cystic duct in 40%. Management with sphincterotomy was 25%, with a biliary stent, 8.4%, and combined, 66%; leak resolution occurred in 100%, 50%, and 87%, respectively, with a shorter hospital length stay in the combined management of 3.5 days compared to four days in sphincterotomy. Only one adverse bleeding event occurred in the sphincterotomy group. **Conclusion:** Sphincterotomy and combined therapy are options with reasonable resolution rates and low hospital length stay for managing postcholecystectomy biliary leak. Prospective, randomized, and multicenter trials will be required to define the best technique.

Keywords

Cholecystectomy, biliary leak, sphincterotomy, biliary stent, ERCP.

INTRODUCTION

Lithiasis of the gallbladder is a frequent reason for emergency and outpatient consultation[1-3]. It is managed by cholecystectomy[4, 5], which in recent decades has been mainly laparoscopic[6]. Among its complications are biliary fistulas, which occur in 1% of surgeries and whose risk factors include difficulty in the dissection and viewing of the bile duct due to inflammation[7-9], obesity, and anatomical variants[10-12]. Bile leaks may be due to direct injury during surgery, which frequently goes unnoticed[11, 13]. However, they may also occur due to bile duct stones that increase pressure in the duct or detach the clips[14]. The patient exhibits complications in the postoperative period, such as abdominal pain, collections, or biliary peritonitis[14, 15].

When there is no complete section of the biliary tree, the management of choice should be endoscopic retrograde cholangiopancreatography (ERCP), but the endoscopic method of choice needs to be clarified. Some studies show that papillotomy alone is better, while others suggest the insertion of plastic biliary stents or combined therapy[16-19]; this is why international scientific societies diverge in their

recommendations. On the one hand, the American Society for Gastrointestinal Endoscopy (ASGE) recommends sphincterotomy alone or placement of a biliary stent or nasobiliary drainage with or without sphincterotomy to decrease the pressure gradient between the bile duct and the duodenum[20]. On the other hand, the European Society of Gastrointestinal Endoscopy (ESGE) recommends only the placement of biliary stents without sphincterotomy, except in older adults, for whom it recommends sphincterotomy only to avoid another ERCP[21].

Given the contradictory recommendations on first-line endoscopic therapy, we decided to conduct a retrospective study to describe the experience in managing post-cholecystectomy biliary fistulas in a high-complexity care center and hypothesize about the technique with better clinical resolution and fewer complications to be evaluated in subsequent prospective studies.

MATERIALS AND METHODS

A descriptive observational case series study was carried out. From the medical record system of the San Ignacio University Hospital in Bogotá, Colombia, a tertiary care hospital, we identified the procedures performed under CUPS ERCP codes (511000, 518902, 512301, and 518801) between January 2010 and March 2021, both outpatient and inpatient. Medical records were reviewed, selecting patients whose indication for the procedure was suspected post-cholecystectomy biliary fistula. Patients under 18 years of age who received percutaneous or surgical management of the bile duct before ERCP were excluded. The identity of the patients was not referenced in the data analysis or the results reports. The institutional ethics committee approved the study.

The characteristics of patients and the procedures performed were collected from the information systematically documented in the medical record. The findings determined the presence of biliary fistula and its Strasberg-Bismuth classification during cholecystectomy surgery, reoperation, or ERCP. A high-grade biliary fistula was that viewed before the contrasting agent reached the intrahepatic bile duct, and low-grade was when the contrasting agent occupied the intrahepatic bile duct before viewing the leak[22, 23]. According to the specialist's criteria, the patients underwent sphincterotomy alone, a plastic biliary stent (7 Fr or 10 Fr), or combined therapy. The time from cholecystectomy to complication management by ERCP was recorded. Resolution of the biliary fistula was considered if any of the following five conditions were met: improvement of abdominal pain at 24 hours; resolved extravasation of contrast medium during ERCP; decreased abdominal drainage output < 150 mL for up to 72 hours; resolution of the abdominal collection in the imaging control by ultrasound, MRI, or tomography at seven days; or absence of fever, abdominal pain, jaundice, peritonitis, or abdominal collection seven days after drainage removal. The resolution time of the biliary fistula and the need for a new endoscopic, surgical, or percutaneous intervention were measured.

As patient safety measures, we established by the medical record if there was bleeding (melena, hematemesis, or drop in hemoglobin > 2 g/dL until day 7 of endoscopic therapy), acute pancreatitis (new or increased abdominal pain plus elevation of amylase > 3 times the upper limit of normal at 24 hours that would have required hospitalization > 2 days), cholangitis (fever > 38 °C *de novo* and cholestasis with increased bilirubin > 2 mg/dL up to 7 days), perforation (gas or contrast medium outside the digestive tract up to 7 days later), and mortality (death from any cause during hospitalization) after ERCP. The hospital stay after endoscopic therapy was measured.

Statistical analysis

Quantitative continuous data are expressed as means and standard deviation (SD) in the case of normal distribution (Shapiro-Wilk test) or as median and interquartile range (IQR) if this assumption was not met. Qualitative data are presented as absolute frequencies and percentages; no statistical tests were performed to compare these proportions, given the study design. We conducted the analysis using the statistical program Stata 16.

RESULTS

In the 11 years of observation, 2,436 ERCP procedures were performed, for which the indication was biliary fistula in 39 patients. Fifteen procedures were excluded: biliary fistula was ruled out in ten, three had failed cannulation, one received percutaneous management, and in another, the biliary fistula was secondary to a gunshot wound, leaving 24 patients for analysis.

The median age was 59; the youngest patient was 32, and the oldest was 76. Also, 54.2% were men. The type of cholecystectomy was primarily laparoscopic (87.5%). However, in three patients, it was necessary to convert it to open surgery due to inflammation secondary to a pyocolecyst, which prevented an adequate anatomical view of the bile duct (**Table 1**).

The most frequent clinical manifestation was increased bile production (greater than 150 mL in 24 hours) through the abdominal drainage lodged in the liver bed, which occurred in 12 patients, followed by 11 patients with increased abdominal pain after cholecystectomy. Abdominal collection > 3 cm documented by ultrasound, tomography, or

MRI (29.1%) and biliary peritonitis (12.5%) were associated with late management with ERCP of the bile leak (16 and 5 days on average, respectively) versus three days in patients without either of these two manifestations (**Table 2.**). The intraoperative finding of bile leak during cholecystectomy occurred in one-third of the patients. No patient had a fever as a manifestation of the fistula.

Table 1. Sociodemographic and clinical characteristics of the included patients

Characteristic	Value
Age in years, median (IQR)	59.5 (53.5-67)
Male sex, n (%)	13 (54.2%)
Type of cholecystectomy, n (%) - Open - Laparoscopic - Converted laparoscopic	 3 (12.5%) 18 (75%) 3 (12.5%)
Mean blood pressure in mm Hg, mean (± SD)	84 (± 14)
Heart rate per minute, median (IQR)	79 (71-90)
Temperature > 38.3 °C, n (%)	0 (0%)
Hemogram, median (IQR) - Leukocytes - Hemoglobin, g/dL - Platelets by thousands	 8400 (6300-12230) 12.2 (10.45-15.15) 306 (217-386)
Total bilirubin in mg/dL, median (IQR)	2 (0.6-4.9)
Alkaline phosphatase in IU/L, median (IQR)	176 (96-267)
Glutamic-oxaloacetic transaminase in IU/L, median (IQR)	52 (47-67)
Glutamic-pyruvic transaminase in IU/L, median (IQR)	88 (44-111)
Charlson comorbidity index > 2 points, n (%)	15 (62.5%)

SD: standard deviation; dL: deciliter; g/dL: grams per deciliter; IQR: interquartile range; IU: international units. Source: The authors.

Regarding complete blood count, only four patients had leukocytes greater than 12,000 cells/mm^3, bilirubin was greater than 3 mg/dL in 20.8%, and alkaline phosphatase had a median of 1.46 times the upper limit of normal. Still, there was no significant increase in transaminases (**Table 1**). Most patients with biliary fistula had comorbidities, with a Charlson index greater than 3 in 37%.

The biliary fistula was diagnosed during ERCP in 96% of the patients; only one was diagnosed by magnetic resonance cholangiopancreatography (MRCP) before endoscopic intervention. The most frequent location of the fistula was the cystic duct (40%), followed by the duct of Luschka (27%) and common hepatic duct (13%), which in the Strasberg-Bismuth classification represents 68% of type A and 22% of type D; in two patients the anatomical site of the leak could not be identified. Low-grade biliary fistulas predominated in 73%.

Table 2. Clinical manifestation upon diagnosis

Clinical manifestation	Value
Increased abdominal pain, n (%)	11 (39.2%)
Abdominal collection > 3 cm, n (%)	7 (29.1%)
Biliary peritonitis, n (%)	3 (12.5%)
Biliary drainage by abdominal catheter in mL/24 hours, n (%) - < 150 mL/24 hours - 151-300 mL/24 hours - > 300 mL/24 hours	 8 (40%) 6 (30%) 6 (30%)
Biliary fistula viewed during cholecystectomy, n (%)	8 (33.3%)
Residual choledocholithiasis	0 (0%)

mL: milliliters. Source: The authors.

Endoscopic management with papillotomy was performed in 25%, plastic biliary stents in 8.4%, and combined endoscopic therapy in 66%. Most patients' time from cholecystectomy to ERCP was longer than three days. The fistula was resolved in all patients with papillotomy, one of the two patients with a plastic biliary stent, and 87.5% of patients with combination therapy (**Table 3**). The patients with no resolution had high-grade fistulas, one with a Strasberg-Bismuth E2 lesion managed with hepaticojejunostomy and the other two with type D, one of whom underwent a new ERCP at week 6 with the placement of a fully covered metal biliary stent and resolved the fistula after three weeks. Patients treated early before 72 hours had a 100% resolution of the fistula compared to late patients (82%), and the mean hospital stay was shorter, with a median of three days versus four days.

Resolution time in 80% was less than three days; when differentiating by type of endoscopic therapy, papillotomy alone and combined had the same resolution time, with a median of 1.5 days (**Table 3**). In management with biliary stent alone, the only patient who improved did so after five days.

As adverse events after ERCP, there were no episodes of acute pancreatitis, perforations, cholangitis, or deaths. There was only one case of bleeding in a patient in the papillotomy group, which was resolved by endoscopic management with adrenaline.

Hospital stay independent of ERCP therapy had a median of four days (IQR: 2.25-9.75); in other words, 25% had a

post-ERCP hospitalization of fewer than three days, 50% between 3-7 days, and 25% greater than seven days. When evaluating by type of endoscopic management, the shortest duration of hospitalization was with combined therapy, with a median of 3.5 days (IQR: 2-9.75), followed by papillotomy with an average of four days (2.75-8.5). The two cases of plastic biliary stent had a hospital stay of six and 89 days. Patients managed before 72 hours had a median length of stay of three days, compared with four days for patients treated after 72 hours.

Table 3. Outcomes of endoscopic management in post-cholecystectomy biliary fistulas

Outcomes	Value
Endoscopic technique, n (%)	
- Papillotomy	6 (25%)
- Plastic stent insertion	2 (8.4%)
- Combined	16 (66.6%)
Time to perform ERCP, n (%)	
- < 1 day	5 (20.8%)
- 1-2 days	2 (8.3%)
- > 3 days	17 (70.8%)
Fistula resolution, n (%)	
- Papillotomy	6/6 (100%)
- Plastic stent insertion	1/2 (50%)
- Combined	14/16 (87.5%)
Fistula resolution time in days, n (%)	
- < 3 days	17 (80.9%)
- 4-7 days	4 (19%)

ERCP: endoscopic retrograde cholangiopancreatography. Source: The authors.

DISCUSSION

The present study describes the experience in endoscopic management of post-cholecystectomy biliary fistulas at a Colombian referral hospital. Our results show that the primary method of endoscopic therapy was papillotomy plus plastic biliary stenting, followed by papillotomy alone and biliary stenting alone, which was little used. The resolution was achieved in 100% of patients with papillotomy vs. 87% in combined therapy and 50% in the plastic biliary stent alone.

The compromise between men and women was similar; fistulas predominated between the sixth and seventh decades of life, which is consistent with the age of manifestation of cholelithiasis[24, 25]. Laparoscopic cholecystectomy was the method of choice for managing gallbladder disease in 87%, which for several decades has shown a shorter hospital stay and morbidity[6].

The main clinical manifestations were increased bile production through abdominal drainage and increased abdominal pain, which was associated with early management (median of three days). On the contrary, abdominal sepsis with collections and biliary peritonitis were less frequent (29% and 12%) and late. These findings are similar to other studies, such as Pandit et al., who found sepsis of abdominal origin in 35% of patients[26], which could suggest that timely diagnosis and management reduce complications. In our series of cases, the finding of biliary fistula during surgery was 33%, which is higher than that of other publications, with reports between 8% and 22%[26, 27], allowing for earlier endoscopic management in our study. Using imaging, such as ultrasound and tomography, was helpful in diagnosing abdominal collections. At the same time, MRCP was performed only in three patients and was diagnostic in one case, which contrasts with other studies in which its use was more significant[28].

In our study, the most frequent location of the biliary fistula was in the cystic duct (40%), the proportion of which was lower than in other studies: Rainio[27] reported this location in 64% and Haidar[29] in 79%. It was impossible to identify the fistula's origin in only 8% of our patients. High- or low-grade fistulas are not described in all studies[14], which is our strength, and we found that all patients who failed endoscopic therapy had high-grade fistulas. Sandha et al. noted that this fistula has better resolution with combined therapy[16].

As described, we had an overall resolution of biliary fistulas of 87.5%, with a time longer than three days from surgery to ERCP in most patients. This was called *expectant management* in the study by Abbas et al. [19], the most extensive retrospective study to date, with 1,028 patients, in which no differences in adverse events were found. However, we must analyze it carefully since they were variables requiring invasive hemodynamic, respiratory, or renal support that we did not assess in our study. We highlight that the three patients who failed had a prolonged average of 24 days from cholecystectomy to ERCP, which leaves the door open to research on the time to perform the ERCP.

It should be noted that, in our study, papillotomy plus plastic stent insertion had lower fistula healing rates than plastic stent insertion alone. This finding is different from the study by Mavrogiannis[30], in which no differences were found in healing rates, but more patients were assigned to these groups. The hospital stay of all ERCPs was shorter than that reported by Abbas[19], with a median of 11 days versus four days, and similar to Rainio's[27] and Chandra's[31]

results. Hospital stay was slightly shorter in patients who underwent ERCP before 72 hours and those who received combined therapy or papillotomy (3.5 versus four days). Adverse events in the study were low: only 4% had post-papillotomy bleeding, which was managed endoscopically. There was no mortality in our case series.

Our study has limitations, considering that a series of cases only allows for formulating hypotheses on the technique of choice for managing biliary fistulas. Our sample size is relatively small; specifically, the number of patients managed exclusively with plastic stent insertion is minimal, which does not adequately evaluate this management technique. The low prevalence of biliary fistulas prevents the collection of large case series; however, this is the most extensive series reported in Colombia. Prospective, randomized, multicenter studies will be required to define the techniques with the best rates of clinical resolution and adverse events.

CONCLUSIONS

This retrospective study found that early diagnosis of biliary fistulas is related to less development of collections, biliary peritonitis, and hospital stay. ERCP plays an essential role in diagnosing and managing post-cholecystectomy biliary fistulas, with good results in terms of resolution with sphincterotomy techniques alone or combined with plastic biliary stent and a low risk of adverse events. Although our study design does not allow direct comparison between methods, our data suggest that stent-only management may need to be improved. Randomized trials and meta-analyses will be required to compare the different management techniques directly.

Conflicts of interest

We declare no conflicts of interest.

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Original article

Cardiac hemodynamic variables and post-liver transplant outcomes in a transplant referral center in Colombia at 2,600 meters above sea level

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Abstract

Introduction: Hemodynamic assessment by Doppler echocardiography is essential in identifying systolic/diastolic changes as a predictor of outcomes in post-liver transplantation, from cardiovascular changes to graft dysfunction and mortality. **Materials and methods:** Retrospective cohort study. Patient with a liver transplant at the LaCardio hospital in Bogotá, Colombia, between January 2005 and July 2021. Analysis of sociodemographic variables, comorbidities, echocardiography, and intraoperative variables with primary outcomes such as early graft dysfunction, acute kidney injury (AKI), and mortality during follow-up. A classification and regression tree (CART) was performed. **Results:** 397 patients were analyzed; 54.4% were men, 71% had some degree of diastolic dysfunction and left ventricular hypertrophy (30.9%) with graft dysfunction in 8% and AKI in 21%, and a mortality of 15% during the study follow-up. In the CART model, mortality and graft dysfunction outcomes were related to a body mass index (BMI) < 19 or a combination of BMI between 19 and < 24 with dialysis. **Conclusion:** Echocardiographic variables, sarcopenia, AKI, or the requirement for renal replacement therapy are related to mortality and graft dysfunction outcomes.

Keywords

Liver transplantation, liver cirrhosis, ventricular dysfunction.

INTRODUCTION

Liver transplantation is a life-saving therapy in patients with end-stage liver disease. Multiple risk factors have been identified, and despite advances in immunosuppressive therapy and surgical techniques to improve post-liver transplant outcomes, graft rejection occurs between 23% and 64%[1,2]. It is imperative to understand the predictive factors related to adverse graft outcomes. Thus, identifying cardiovascular conditions without intervention before transplantation defines short- and long-term morbidity and mortality outcomes with the graft[3,4]. Post-transplant hemodynamic stress after reperfusion of the graft characterized by increased preload may result in multiple cardiovascular complications. The pre-transplant study protocol includes screening for traditional cardiovascular risk factors, coronary disease, and Doppler echocardiography analysis in the search for right or left ventricular dysfunction, portopulmonary hypertension, hepatopulmonary syndrome, and cirrhotic cardiomyopathy[5,6].

Cirrhotic cardiomyopathy is an entity with no diagnostic criteria yet established. However, the best-accepted definition is that of the Cirrhotic Cardiomyopathy Consortium (2019), made up of variables such as systolic/diastolic alterations, supported by the assessment of global longitudinal shortening (GLS) and electrocardiographic changes such as QT prolongation[7, 8]. This syndrome, which is usually not recognized in the initial phase, but rather in its decompensation, has gained importance in recent years as a predictor of outcomes such as heart failure, kidney injury, and even graft loss in the short and long term[3, 9-11]. Data on cardiovascular complications and deaths from heart failure are found in up to 70% after transplantation[12].

The discrepancy in some data, the insufficient evaluation of systolic/diastolic function parameters, incomplete data on the degree of diastolic dysfunction, imprecise determination of cardiac dysfunction in the final stage of cirrhosis with a physiological basis of a hyperdynamic state with high cardiac output, and non-adherence to echocardiographic assessment protocols limit the presentation of data in the literature[9, 11, 13].

Due to the importance of hemodynamic assessment by echocardiography in its correlation with post-transplant outcomes such as heart failure, graft dysfunction, and mortality, for which no specific data can be found in the literature in our setting, we describe the experience of a leading Colombian hospital in liver transplantation.

MATERIALS AND METHODS

Study population and data collection

Retrospective cohort study. Data were obtained from the medical records of the liver transplantation group at the La Cardio hospital in Bogotá, Colombia, from January 1, 2005, to July 31, 2021.

Demographic data, paraclinical examinations, history, and conditions related to the surgical procedure were taken from each patient's medical record.

Inclusion criteria

Patients older than 18 diagnosed with cirrhosis and stable disease undergoing liver transplantation.

Exclusion criteria

- Patients with acute liver failure without cirrhosis requiring transplantation
- Patients with retransplantation, transplantation of more than one organ, previous heart disease (ischemic or valvular)
- Glomerular filtration rate (GFR) < 30 mL/min/1.73 (calculated using the Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI]).

Within the institutional pre-transplant assessment protocol, data were taken from Doppler echocardiograms based on the diastolic ventricular assessment protocol of the American Society of Echocardiography/European Association of Cardiovascular Imaging (ASE/EACVI) guidelines[14]. Patients who underwent right heart catheterization were analyzed.

Outcomes

Our primary outcome was early graft dysfunction, defined as an abnormal liver profile in the first seven days post-transplant, as follows: bilirubin >10 mg/dL, international normalized ratio (INR) > 1.5, and alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 2,000 IU.

Another primary outcome was acute kidney injury during post-transplant hospitalization based on the Kidney Disease: Improving Global Outcome (KDIGO) guideline definition.

Mortality was assessed from liver transplantation to the study completion date, July 31, 2021.

Other outcomes were considered, such as the requirement for renal replacement therapy during the post-transplant period, infectious complications, transfusion support, and intraoperative arrest.

Statistical analysis

The sociodemographic and clinical characteristics are presented in frequencies and percentages for the categorical variables. For continuous variables, we employed the mean with standard deviation (SD) when the distribution was normal or the median with interquartile range (IQR) when this criterion was not met. The chi-square test or Fisher's test was performed to evaluate these comparisons according to the frequency of observations in the case of categorical variables. Student's t-test for independent samples was used to compare continuous variables. A p-value < 0.05 was considered statistically significant.

We set up a classification and regression tree (CART) with all the variables collected for comparison purposes[15]. The covariates selection for the model was based on biological and clinical relevance, as previously reported in the literature, and their statistical significance in the bivariate analysis. The CART algorithm quantified the weight of each variable and built risk profiles. This methodology contrasts with classical regression models in which the CART algorithm can

uncover modifier effects and complex interactions between variables. Statistical analysis was performed with R software version 3.6.3, and the CART model with the RPART (Recursive Partition and Regression Trees) package.

RESULTS

Within the established date, the study found 550 patients with liver transplantation, of which 397 had complete data and met the inclusion and exclusion criteria.

General characteristics

Of the total number of patients, the median age was 56 years at the time of liver transplantation, and 54.4% were men. At the time of the transplant, 75% had a functional class I, and the most frequent history includes arterial hypertension (15.8%), diabetes mellitus (24.1%), and smoking (25.44%). A Charlson index with a mean of 4.4 (SD ± 1.5) was calculated.

According to the etiology of cirrhosis, the main one was alcoholic (17.8%), followed by cryptogenic (16%), hepatitis C virus (HCV) (15.3%), and autoimmune hepatitis (12.5%).

At the time of liver transplantation, complications due to the pathology produced at least one ascitic episode or more (63%), encephalopathy (47%), variceal bleeding (34.2%), hepatocellular carcinoma (22.1%), hepatopulmonary syndrome (15.6%) and spontaneous bacterial peritonitis (8.3%). Regarding the staging of the pathology, 52.3% were in Child-Pugh B and 26% in Child-Pugh C, with an average Model for End-Stage Liver Disease (MELD-Na) of 16 (SD ± 6) (**Table 1**).

Hemodynamic variables: echocardiography and right heart catheterization

Of the 397 patients analyzed, all were evaluated by 2D Doppler echocardiography. We found an average LVEF of 62% (SD ± 6.4), 71% with diastolic dysfunction, but only 45 patients had type 1 diastolic dysfunction, and seven had type 2 diastolic dysfunction; left ventricular hypertrophy (30.9%), and presence of shunt compatible with hepatopulmonary syndrome (19%). Right heart catheterization was only performed in seven patients (**Table 1**).

Intraoperative and post-transplant variables

The anhepatic phase had a median of 57 minutes (IQR: 47-69), and the ischemic phase was 6.3 minutes (IQR: 5.7-8.2). Regarding the intraoperative complications, ten patients had a cardiorespiratory arrest, and 61.6% required transfusion support. The stay in the ICU was an average of two days. Only 32 patients presented with early graft dysfunction (8%); 21% presented acute kidney injury, and 29 required renal replacement therapy. Moreover, 29.2% exhibited infectious complications; the main ones were abdominal (39.6%) and pulmonary (21.5%). During the study period, there was a mortality of 15.1%.

Primary outcomes

The primary outcomes are summarized in **Table 2**.

Early graft dysfunction

Within the univariate Cox analysis, a relationship was found with the female sex ($p = 0.010$), transfusion support requirement ($p = 0.037$), acute kidney injury ($p = 0.0097$), and renal replacement therapy requirement ($p = 0.0002$).

Acute kidney injury

It was related to the male sex ($p = 0.054$), BMI ($p = 0.049$), Charlson index ($p = 0.0372$), episodes of encephalopathy before transplantation ($p = 0.0508$), LVEF ($p = 0.00059$), diastolic dysfunction ($p = 0.037$), LVH ($p = 0.00034$), anhepatic phase ($p = 0.016$), and infection ($p = 0.0004$).

Mortality

It was associated with hepatocellular carcinoma ($p = 0.036$), acute kidney injury ($p < 0.005$), renal replacement therapy ($p < 0.005$), and infection ($p < 0.005$).

CART predictive model

This method built a predictive model with mortality during the study, graft dysfunction, and acute kidney injury variables. The mortality during the study model found a mortality of 15%, in which patients with BMI < 19 had a 56% probability of dying. Meanwhile, with a BMI > 19 (98% of patients with fatal outcomes), patients who do not require dialysis have a 95% chance of survival. However, patients with a BMI > 19 and < 24 and requiring dialysis have a 55% chance of dying (**Figure 1**).

Concerning graft dysfunction, they were 8% of all patients. Patients with BMI < 19 had a 56% chance of graft dysfunction, and those with BMI > 19 and < 24 requiring dialysis had a 55% chance of death (**Figure 2**).

DISCUSSION

Globally, in 2017, approximately 1.5 million people had liver cirrhosis, whose main etiologies were NASH (60%), HBV (29%), HCV (9%), and alcoholic cirrhosis (2%); it produced 1.2 million deaths and was 3.5% of all causes of

Table 1. Characteristics of the study population

Patients, n	397
Age, years (median, IQR)	56 (45-62)
Sex (male:female), n	216:181
BMI, kg/m^2 (mean, SD)	25.7 ± 4.2
Functional class, n (%)	
- Class 1	298 (75)
- Class 2	90 (22.6)
- Class 3	8 (2)
- Class 4	1 (0.2)
Etiology of cirrhosis, n (%)	
- Alcoholic	71 (17.8)
- Cryptogenic	64 (16)
- HCV	61 (15.3)
- Autoimmune hepatitis	50 (12.5)
- NASH	42 (10.5)
- Primary biliary cirrhosis	39 (9.8)
- Secondary biliary cirrhosis	13 (3.2)
- HBV	13 (3.2)
- Other	44 (11)
History, n (%)	
- Hypertension	63 (15.8)
- Diabetes mellitus	96 (24.1)
- COPD	2 (0.5)
- Pulmonary hypertension	3 (0.7)
- SLE	4 (1)
- CKD	30 (7.5)
- Smoking	101 (25.44)
Complications of cirrhosis, n (%)	
- Ascites	250 (63)
- Variceal bleeding	136 (34.2)
- SBP	33 (8.3)
- Hepatopulmonary syndrome	62 (15.6)
- Encephalopathy	187 (47)
- Pruritus	19 (4.7)
- Hepatocellular carcinoma	88 (22.1)
Child-Pugh score, n (%)	
- Class A	86 (21.6)
- Class B	208 (52.3)
- Class C	103 (26)
- MELD-NA (mean, SD)	16 ± 6
Charlson index (mean, SD)	4.4 ± 1.5
Echocardiographic variables	
- LVEF (mean, SD)	62 ± 6.4
- TAPSE, n (mean, SD)	22 (25 ± 4.3)
- DD, n (%)	71 (17.8)
- Grade 1 DD, n (%)	45 (11.33)
- Grade 2 DD, n (%)	7 (1.7)
- Abnormal PASP, n (%)	88 (22.2)
- Increased DBP, n (%)	4 (1)
- LVH, n (%)	130 (30.9)
- RVH, n (%)	4 (1)
- Right ventricular dilatation, n (%)	12 (3)
- Presence of shunt, n (%)	79 (19)
Right catheterization variables (mean, SD)	n: 7
- mPAP	27.2 ± 9.5
- PVR	3.2 ± 3
- Wedge pressure	15.83 ± 5.3
- Cardiac index	4.3 ± 2.4
- Right atrium pressure	15.83 ± 5
Intraoperative variables	
- Anhepatic phase (median, IQR)	57 (47-69)
- Ischemic phase (median, IQR)	6.3 (5.7-8.2)
- Intraoperative cardiac arrest, n (%)	10(2.5)
- Days in ICU, median (IQR)	2 (2-4)
- Transfusion requirement, n (%)	244 (61.6)
Outcomes, n (%)	
Graft dysfunction, n (%)	32 (8)
AKI, n (%)	84 (21)
- KDIGO 1 AKI (%)	37.9
- KDIGO 2 AKI (%)	32.1
- KDIGO 3 AKI (%)	29.88
Dialysis requirement, n (%)	29 (7.3)
Infection, n (%)	116 (29.2)
- Abdominal	49 (39.6)
- Pulmonary	25 (21.5)
- Urinary	21 (18.1)
Bacteremia	6 (5.1)
Operative site	5 (4.3)
Other	10 (8.6)
Death, n (%)	60 (15.1)

DD: diastolic dysfunction; COPD: chronic obstructive pulmonary disease; CKD: chronic kidney disease; LVEF: left ventricular ejection fraction; RVH: right ventricular hypertrophy; LVH: left ventricular hypertrophy; BMI: body mass index; SLE: systemic lupus erythematosus; AKI: acute kidney injury; NASH: nonalcoholic steatohepatitis; DBP: diastolic blood pressure; SBP: spontaneous bacterial peritonitis; mPAP: mean pulmonary artery pressure; PASP: pulmonary artery systolic pressure; PVR: pulmonary vascular resistance; TAPSE: tricuspid annular plane systolic excursion; ICU: intensive care unit. Source: The authors.

death[16]. In data from local studies, it gains importance as an etiology of alcoholic cirrhosis, as shown in our study[17]. There are multiple risk factors in the pre-transplant study, and even its poor selection is related to a cost burden for the healthcare system[18]. Pretransplant detection of cardiac dysfunction is a predictor of adverse events after liver trans-

Table 2. Univariate Cox analysis of primary outcomes

Variables	Graft dysfunction			Kidney injury			Death		
	No GD	GD	*p*	No	Yes	*p*	No	Yes	*p*
Age (median, IQR)	56 (45-62)	52.5 (38.7-58.2)	0.03405083	55 (44-61)	58 (48.7-63)	0.0626625	56 (45-62)	58 (49-63)	0.19050336
Woman, n (%)	158 (87.8)	22 (21.1)	0.01052545	151 (83.4)	30(16.5)	0.05438623	149 (82.3)	32 (17.6)	0.24357336
Man, n (%)	206 (95.3)	10 (4.6)		162 (75)	54 (25)		188 (87)	28 (12.9)	
BMI (mean, SD)	25.8 ± 4.1	24.6 ± 4.9	0.11739833	25.5 ± 4	26.7 ± 4.6	0.04914905	26 ± 4.25	24.4 ± 3.9	0.01242746
FC I	276 (92.6)	22 (7.3)	0.55109023	234 (78.5)	64 (21.4)	0.24305443	251 (84.2)	47 (15.7)	0.09592338
FC II	80 (88.8)	10 (11.1)		72 (80)	18 (20)		79 (87.7)	11 (12.2)	
FC III	8 (100)	0		7 (87.5)	1 (12.5)		7 (87.5)	1 (12.5)	
FC IV	1 (100)	0		0	1		0	1	
Charlson index (mean, SD)	4.47 ± 1.55	4.06 ± 1.1	0.16534394	4.32 ± 1.5	4.7 ± 1.5	0.0372914	4.3 ± 1.5	4.7 ± 1.6	0.15445272
Etiology of cirrhosis, n (%)									
Alcoholic	69 (97.1)	2 (2.8)	0.13026919	55 (77.4)	16 (22.5)	0.9251709	63 (88.7)	8 (11.2)	0.67038578
Cryptogenic	60 (93.7)	4 (6.2)		53 (82.8)	11 (17.1)		56 (87.5)	8 (12.5)	
HCV	57 (93.4)	4 (6.5)		44 (72.1)	17 (27.8)		47 (77)	14 (22.9)	
Autoimmune hepatitis	47 (94)	3 (6)		40 (80)	10 (20)		43 (86)	7 (14)	
NASH	39 (92.8)	3 (7.1)		31 (73.8)	11 (26.1)		37 (88)	5 (12)	
PBC	33 (84.6)	6 (15.3)		33 (84.6)	6 (15.3)		31 (79.4)	8 (20.5)	
SBC	11 (84.6)	2 (15.3)		11 (84.6)	2 (15.3)		9 (69.2)	4 (30.7)	
HBV	12 (92.3)	1 (7.6)		10 (76.9)	3 (23)		12 (92.3)	1 (7.6)	
History, n (%)									
Hypertension	60 (95.2)	3 (4.7)	0.42588466	48 (76.1)	15 (23.8)	0.69396299	56 (88.8)	7 (11.1)	0.43822945
Diabetes mellitus	91 (94.7)	5 (5.2)	0.33522914	72 (75)	24 (25)	0.360296	82 (85.4)	14 (14.5)	0.99769806
COPD	2 (100)	0	1	1	1	0.89392224	2	0	1
PH	3 (100)	0	1	3	0	0.8483549	3	0	1
SLE	4 (100)	0	1	2	2	0.4212489	3	1	1
CKD	14 (100)	0	1	10 (71.4)	4 (28.5)	0.72013665	12 (85.7)	2 (14.2)	1
Smoking	97 (96)	4 (3.9)	0.12324534	78 (77.2)	23 (22.7)	0.74992213	88 (87.1)	13 (12.8)	0.57024989
Complications of cirrhosis, n (%)									
Ascites	233 (93.2)	17 (6.8)	0.3114414	194 (77.6)	56 (22.4)	0.507671	215 (86)	35 (14)	0.50759422
Variceal bleeding	124 (91.1)	12 (8.8)	0.83450994	110 (80.8)	26 (19.2)	0.55567329	120 (88.2)	16 (11.7)	0.23129388
SBP	31 (93.9)	2 (6)	0.91493425	25 (75.7)	8 (24.2)	0.81777885	30 (90.9)	3 (9)	0.45028031
Hepatopulmonary syndrome	58 (93.5)	4 (6.4)	0.80053717	54 (87)	8 (12.9)	0.11797885	56 (90.3)	6 (9.6)	0.26790479

Table 2. Univariate Cox analysis of primary outcomes (*continued*)

Variables	Graft dysfunction			Kidney injury			Death		
	No GD	GD	*p*	No	Yes	*p*	No	Yes	*p*
Complications of cirrhosis, n (%)									
Encephalopathy	169 (90.3)	18 (9.6)	0.3700466	139 (74.3)	48 (25.3)	0.05082367	160 (85.5)	27 (14.4)	0.83062933
Pruritus	16 (84.2)	3 (15)	0.40289368	19	0	1	16 (84.2)	3 (15.7)	1
Hepatocellular carcinoma	84 (95.4)	4 (4.5)	0.24972757	67 (76.1)	21 (23.8)	0.57802013	68 (77.2)	20 (22.7)	0.03647202
Child-Pugh score, n (%)									
Class A	79 (91.8)	7 (8.1)	0.48422153	65 (75.5)	21 (24.4)	0.66648793	71 (82.5)	15 (17.4)	0.64598336
Class B	194 (93.2)	14 (6.7)		167 (80.2)	41 (19.7)		176 (84.6)	32 (15.3)	
Class C	92 (89.3)	11 (10.6)		81 (78.6)	22 (21.3)		90 (87.3)	13 (12.6)	
MELD-NA (mean, SD)	15.9 ± 6.8	17.4± 7.7	0.28508139	15.8 ± 6.4	16.6 ± 8.5	0.89719791	16 ± 7	15.9 ± 8.2	0.50753706
Echocardiographic variables									
LVEF (mean, SD)	62.39 ± 6.5	61.2 ± 5.4	0.92794776	61.7 ± 6.5	64.4 ± 5.8	0.00059796	62 ± 6.3	64.1 ± 6.9	0.03786134
TAPSE, n (mean, SD)	25.5 (4.4)	25.3	0.93718292				25.3	30.1	0.18031438
Diastolic dysfunction, n (%)	65 (91.4)	6 (8.4)	1	49 (69)	22 (30.9)	0.03780355	57 (80.2)	14 (19.7)	0.3112245
PASP	80 (90.9)	8 (9)	0.86944739	68 (77.2)	20 (22.7)	0.81631308	68 (77.2)	20 (22.7)	0.03881794
Increased DBP, n (%)	3 (75)	1 (25)	0.74304706	4	0	0.67000042	3	1	1
LVH, n (%)	110 (89.4)	13 (10.5)	0.30260062	83 (67.4)	40 (32.5)	0.00034267	98 (79.6)	25 (20.3)	0.07329209
RVH, n (%)	4 (100)	0	1	3	1	1	3	1	1
RV dilation, n (%)	12 (100)	0	0.60608871	10 (83.3)	2 (16.6)	0.97293598	12	0	0.2751521
Presence of shunt, n (%)	71 (89.8)	8 (10.1)	0.60107922	60 (75.9)	19 (24.05)	0.58281122	66 (83.5)	13 (16.4)	0.84406117
Intraoperative variables									
Anhepatic phase (median, IQR)	57 (47-68)	60 (50-77)	0.16471272	56 (46-66)	60 (51 -75)	0.01654853	57 (47-68)	56 (50-73)	0.60601576
Ischemic phase (median, IQR)	6.3 (5.1-8.1)	6.4 (5.3-9)	0.54891242	6.3 (5.2-8.3)	6.1 (5-7.5)	0.3038509	6.2 (5-8)	6.9 (5.4-9)	0.05746276
Transfusion requirement, n (%)	219 (89.7)	25 (10.2)	0.03781268	189 (77)	55 (26)	0.48819885	205 (84)	39 (15.9)	0.53335917
AKI, n (%)	71 (84.5)	13 (15.4)	0.00970643		12 (41.3)		56 (66.6)	28 (33.3)	3.79E-07
Dialysis requirement, n (%)	21 (72.4)	8 (27.5)	0.00027098		17 (58.6)		7.9935E-11		
Infection, n (%)	104 (89.6)	12 (10.3)	0.38345075	78 (67.2)	38 (32.7)	0.00046397	87 (75)	29 (25)	0.00072601

PBC: primary biliary cholangitis; SBC: secondary biliary cholangitis; FC: functional class; GD: graft dysfunction; PH: pulmonary hypertension; HBV: hepatitis B virus. Source: The authors.

plantation, based on analysis of systolic or diastolic abnormalities[9, 11, 19]. Cardiac dysfunction leads to early mortality from cardiovascular causes (40%), followed by other causes of mortality, such as infections (27.2%) and graft rejection (12%)[20]. Even data have shown liver transplantation as a treatment for cardiovascular disorders, as reported by a study in which a decrease in biventricular dilatation and improvement in global strain post-transplantation were observed[21].

Regarding the findings in our study, no relationship was identified between LVEF and mortality during follow-up. The data are similar to the literature, in which no relationship was found with the mortality or post-transplant cardiac arrest outcomes[9]. However, in another study, a low LVEF is related to mortality[22]; even in the hyperdynamic state, it correlates with high LVEF, whose minimal variations are related to cardiovascular outcomes[10, 22]. Therefore, in assessing a patient with a hyperdynamic state associated with decreased peripheral vascular resistance, not only the evaluation of the systolic component becomes vital for diagnosing cirrhotic cardiomyopathy. An integration of variables such as those stipulated in the last CCC classification, with findings of LVEF < 50% and decrease in GLS > 18%, is also relevant, with careful assessment of the diastolic component considering the multiple variables that can affect preload based on electromechanical abnormalities such as QT prolongation[8].

Due to the complex assessment of cardiac dysfunction, there is no protocolized evaluation of this specific condition by echocardiography without following the latest recommendations for diagnosing cirrhotic cardiomyopathy. According to our study, there is no detail of the diastolic evaluation without the GLS and electromechanical component measurements. In the literature, systolic involvement is low, as shown in our study, where 100% of patients did not meet the criteria for systolic changes[22].

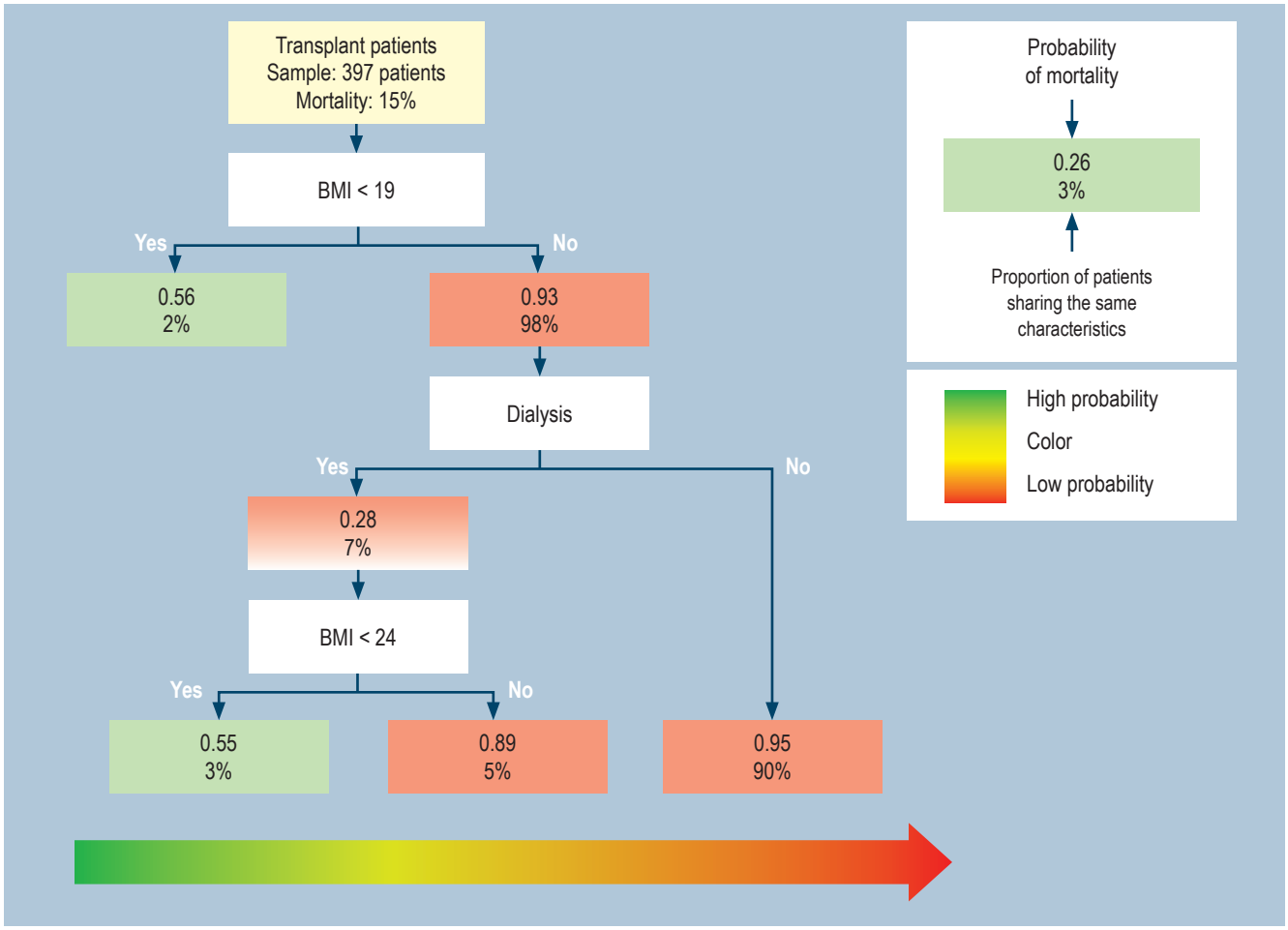

Figure 1. Distribution of transplant patients with mortality during the study, classified by risk groups in the regression tree (CART). This method builds a predictive model of three risk profiles with BMI < 19 and < 24, with or without dialysis requirement. Source: The authors.

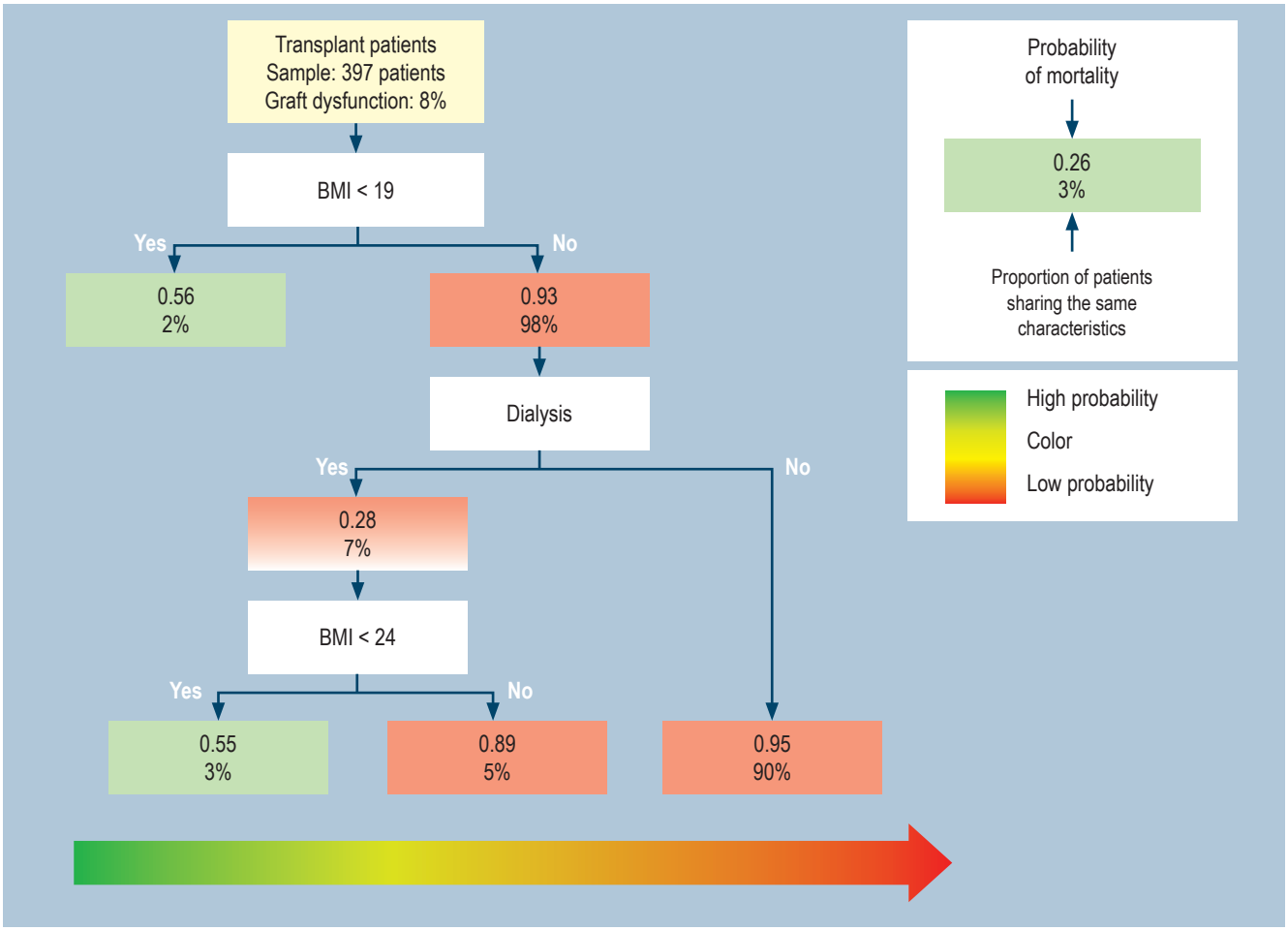

Figure 2. Distribution of transplant patients with graft dysfunction, classified by risk groups in the regression tree (CART). This method builds a predictive model of three risk profiles with BMI < 19 and < 24, with or without dialysis requirement. Source: The authors.

Some studies even reveal an incidence of only 2% of systolic involvement[13].

Although the CCC's latest classification of cirrhotic cardiomyopathy has an LVEF cut-off < 55%, data of LVEF < 60% in patients undergoing immunosuppression should have a closer follow-up, as it is a predictor of mortality and cardiovascular outcomes[23].

Among the findings of our study is that 17.8% presented with diastolic dysfunction, which does not agree with the literature since it shows a varied prevalence, possibly secondary to the non-standardization of echocardiographic variables. Reports in the literature have demonstrated that up to 66% of patients with end-stage liver disease have, according to the ASE classification, type 1 (53%) and type 2 (47%) diastolic dysfunction, with no type 3 patients[22], as found in our study (no findings of type 3 patients). Another study shows a prevalence similar to ours with data of diastolic dysfunction of 19%: mild (48%), moderate (30%), and severe (22%), and the findings of pre-transplant diastolic dysfunction were related to the risk of graft rejection, graft failure, and mortality[3]. Nevertheless, in our study, the finding of diastolic dysfunction was related to the development of acute kidney injury ($p = 0.0378$).

Additional echocardiographic variables, such as left atrial volume index (LAVI) > 40 mL/m^2, were associated with the risk of mortality within one year post-transplant[9]. The rate of moderate to severe tricuspid regurgitation is related to mortality since mild findings are expected in the patient's hyperdynamic state[24]; our study's data were not measured because they were found to be normal. Other findings are LVH, which occurs in 12% to 30% of patients with cirrhosis, an indication of possible diastolic dysfunction in the context of left ventricular remodeling in the patient's hyperdynamic state; in our

study, it was found in 30.9% of patients, with no relationship with mortality outcomes or graft dysfunction. These data differ from those in the literature, in which LVH was associated with mortality nine months after transplantation; it was more frequent in the elderly and patients with a history of arterial hypertension[25]. Even its presence before transplantation has been observed as a predictor of post-transplant echocardiographic deterioration[26]. However, the relationship between LVH and diastolic dysfunction was related to acute kidney injury, as shown by studies related to a low cardiac index in severe arterial vasodilation changes[22, 27, 28]; some data even show a correlation between a high LVEF and the deteriorating renal function possibly secondary to this hyperdynamic state[29]. Progressing to the requirement of renal replacement therapy was related in our study to graft dysfunction and mortality, as found in the literature, in which its relationship with mortality was noted, with an odds ratio (OR) of 14.18 (confidence interval [CI] 1.65-121.89; $p < 0.05$)[11].

Within our study, increased PASP was observed in 22% of the patients, which was related to mortality with $p = 0.038$; this finding may be related to increased left ventricular diastolic pressure and, therefore, be a marker of diastolic dysfunction. In one study, it was connected to the risk of cardiac events (hazard ratio [HR]: 1.79 [1.48-2.17]; $p < 0.001$)[29] and has even been directly associated in some studies with pulmonary artery pressure with catheterization, allowing for adequate screening with a detailed echocardiogram[30].

The transfusion requirement in the post-transplant period was related to graft dysfunction, and in the regression tree, to acute kidney injury in the initial stages and progression to dialysis. Previous studies have associated these findings with adverse post-transplant outcomes[31]. Another variable related to mortality and acute kidney injury was a post-transplant infection. These data are related to the literature concerning the immunosuppression state due to the pathology and the level of immunological activation to the infectious stimulus in a patient with a chronic inflammatory disease and hemodynamic dysregulation, causing mortality rates close to 50%[32].

Within the CART, the critical data related to mortality and graft dysfunction are low BMI, with a cut-off < 19 in our study, even related to renal replacement therapy. These data indirectly indicate sarcopenia since they show that 30%-70% of individuals with cirrhosis suffer from this condition due to the patient's degree of inflammation, chronic bacterial translocation, insulin resistance, hyperammonemia, and decreased testosterone. Previous data condition higher mortality (19 ± 6 months with sarcopenia vs. 34 ± 11 months without sarcopenia; $p = 0.005$)[33, 34]. Even data already related to post-transplant outcomes of skeletal muscle indices measured by tomography were linked to lower post-transplant survival[35].

CONCLUSIONS

Pre-transplant variables, from echocardiogram aids to previously associated conditions such as sarcopenia, considerations during liver transplantation, and the requirement or not of renal replacement therapy related to acute kidney injury are points of intervention and follow-up to reduce long-term complications and even impact the mortality of these patients.

LIMITATIONS

Data was derived from a retrospective study of a single hospital. The echocardiographic assessment shows incomplete data on the detail of the diastolic component, without GLS measurement and tricuspid regurgitation, among others, in addition to the protocolization according to the ASE, without considering the latest evidence under the CCC classification. As a retrospective cohort to date, there is no long-term follow-up of the patients.

Post-transplant cause of death, post-transplant medication, or type of immunosuppression were not included as variables possibly related to acute kidney injury. Nevertheless, in our institution, immunosuppression is mainly monitored by serum levels and guided by an expert group.

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Ethical considerations

The study was approved by the institutional ethics committee of the Fundación Cardioinfantil-La Cardio under minutes 06-2021.

Conflicts of interest

The authors have no conflicts of interest.

Sources of funding

The study was not funded.

Author contributions

All authors were involved in work conception, data acquisition, analysis and interpretation, paper writing or critical review of important intellectual content, and final approval of the version to be published.

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Original article

The usefulness of Giemsa staining to diagnose Helicobacter pylori in patients with preneoplastic lesions

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Abstract

Introduction: *Helicobacter pylori* is a bacterium associated with inflammatory and neoplastic gastroduodenal diseases. Histopathology is one of the diagnostic methods used for its detection, which has a sensitivity of 90% to 95% when there is a high density of *H. pylori*; however, the bacterium may be missed in low-density infections because routine hematoxylin and eosin (H&E) staining is not specific for its detection and has interobserver variability. This study aimed to determine the usefulness of complementary Giemsa staining for diagnosing *H. pylori* in preneoplastic lesions where the bacterium was found in low density. **Materials and methods:** A retrospective/prospective descriptive study was carried out that included 65 patients diagnosed with preneoplastic lesions. Gastric biopsies were stained with H&E and Giemsa and evaluated by two pathologists. **Results:** Giemsa staining analyzed 20.3% more cases of *H. pylori* than H&E, most with a low density of the bacteria. There were no statistically significant differences in the diagnosis of *H. pylori* according to the sample type. **Conclusion**: This study found that Giemsa staining improves the histopathological diagnosis of *H. pylori* in patients with preneoplastic lesions.

Keywords

Histological techniques, *Helicobacter pylori*, diagnosis, preneoplastic lesions, gastrointestinal diseases.

INTRODUCTION

Helicobacter pylori is a helical gram-negative bacillus with a worldwide prevalence of more than 50% in low- and middle-income countries and less than 50% in high-income countries[1]. In Colombia, the frequency varies according to different studies (41.7%-99.1%)[2-4]. *H. pylori* is associated with inflammatory and neoplastic gastroduodenal diseases and has been recognized as a definitive gastric carcinogen since 1994, according to the IARC (International Agency for Research on Cancer)[5]. In 2020 in Colombia, gastric cancer (GC) ranked second in incidence in men (4,989) and fifth in women (3,225)[6]. Chronic *H. pylori* infection leads to atrophic gastritis and intestinal metaplasia (IM), both considered preneoplastic lesions (PNL) of GC, which are potentially reversible when early and effective treatment is instituted to eradicate the bacterium[7, 8]. Therefore, early diagnosis and therapeutic management of the infection can reduce the risk of GC.

For *H. pylori* diagnosis, there are non-invasive and invasive methods. The former indirectly detect the bacterium or its products and include serology (sensitivity [Sen] = 76%-84% and specificity [Spe] = 79%-90%), fecal antigens (Sen = 69%-95% and Spe = 97.6%)[9], and the urease breath test (Sen = 96%-100% and Spe = 93%-100%)[10]. The latter are based on upper GI endoscopy (EGD) with biopsies and include the rapid urease test (Sen = 80%-95% and Spe = 95%-100%), microbiological culture (Sen = 70% and Spe = 100%), molecular tests (Sen = 91% and Spe = 100%), and histopathology (Sen = 90%-95% and Spe = 95%-98%)[11]. Histopathology has several advantages because it allows the diagnosis of the infection, determines the degree of inflammation of the gastric mucosa, and evaluates the presence of PNL[12].

On the one hand, for the histopathological study of *H. pylori*, it is advisable to carry out standardized sampling (Sydney protocol) in which several biopsies are taken from specific sites of the stomach, given the heterogeneous distribution of the bacteria that can lead to false negatives when selecting a single sampling site[11]. On the other hand, the stain routinely used for histopathological diagnosis is hematoxylin and eosin (H&E). This stain is usually sufficient in high-density infections, although it has a variable sensitivity between 69% and 93%; however, the density of *H. pylori* decreases with increasing PNL[13], so in patients with PNL, the sensitivity of H&E is less than 70%[14]. It has been reported that the exclusive use of H&E bypasses *H. pylori* with low density[15].

The implementation of the Sydney protocol improves the sensitivity and specificity in the diagnosis of *H. pylori*[16]. It consists of evaluating five samples, two from the antrum, two from the gastric body, and one from the angular incisure, which increases the probability of finding the bacterium. A previous study published by our group determined the presence of *H. pylori* not only in the gastric antrum but also in other samples used in the Sydney protocol[17].

Assessment of intestinal atrophy and metaplasia are best determined in the region of the angular incisure, which is also the site most likely to reveal dysplastic changes; hence the importance of this biopsy. This protocol, added to the use of special stains such as Giemsa, Alcian Blue, Periodic Acid Schiff (PAS), or Warthin-Starry, improves diagnosis, especially in patients with PNL[1, 14, 18].

Chahuan et al. demonstrated that, besides H&E, Giemsa staining is preferred because it is sensitive (42.6%-94%), easy to perform, cheap, widely available, and does not produce precipitates that can be confused with the bacterium[15]. Several studies show the superiority of Giemsa staining compared to H&E, whose sensitivity ranges from 28.7% to 83.9% in detecting the bacterium[15, 18, 19]. In addition, Giemsa staining reduces interobserver variability in the diagnosis of infection because it facilitates its viewing[17, 20].

Up to 75% of atrophic gastritis cases are associated with *H. pylori*. Still, the detection of the bacterium can go unnoticed[21], causing false negative results in the diagnosis and not allowing the patient to receive timely treatment for eradication[22], as demonstrated in previous studies[22-26].

In Colombia, no studies were found on determining the usefulness of special stains such as Giemsa for diagnosing *H. pylori* in patients with gastric PNL. Therefore, this study aimed to assess the effectiveness of Giemsa staining for diagnosing *H. pylori* in gastric biopsies of patients with PNL who attended seven healthcare institutions in three regions of Antioquia, Colombia, during 2016-2018.

MATERIALS AND METHODS

Study type

Descriptive, retrospective, and prospective.

Study population and eligibility criteria

This study derives from the CODI 2014-1062 project approved by the Research Ethics Committee of the Medicine School, Universidad de Antioquia. Individuals ≥18 years of age who attended seven healthcare institutions in three subregions of Antioquia (Valle de Aburrá metropolitan area, Oriente, and Urabá Antioqueño) were included. The participants came for EGD performance, and participation in the project was voluntary by signing the consent form.

We excluded individuals who received proton pump inhibitors (PPIs) or H2-histamine receptor antagonists during the 15 days before EGD or antibiotics within the last month; individuals diagnosed with upper gastrointestinal bleeding; anticoagulated patients or patients with coagulation disorders; pregnant women; people with previous surgical history in the upper GI tract; prior diagnosis of chronic severe diseases (renal, hepatic, decompensated heart failure, and decompensated diabetes *mellitus*), and people with a history of radiochemotherapy. From 272 individuals included in the previous study, a sample of 65 patients with a histopathological diagnosis of PNL (atrophic gastritis or intestinal metaplasia) was selected for this study. Patients with dysplasia were not included since this histopathological finding was not reported in the patients included[17].

Biopsy collection and processing

Five samples were taken from each participant following the recommendations of the updated Sydney protocol that include a sample of the greater curvature of the antrum (A1), lesser curvature of the antrum (A2), angular incisure

(I), greater curvature of the body (C1), and lesser curvature of the body (C2); a sixth sample was taken in cases where a tumor was found. Samples were stored and transported to the Las Vegas Clinic Cytology and Pathology Unit for processing. Samples from each patient were stained with H&E and modified Giemsa-Diff Quick.

Biopsy reading and histopathological diagnosis of H. pylori

All five Giemsa-stained biopsies were evaluated and blinded-read randomly by one of two pathologists and a third-year pathology resident. The presence or absence of the bacterium was determined as positive or negative by directly observing helical gram-negative bacilli with a light microscope (Leica® DM500). For its quantification, the visual analog scale of the updated Sydney protocol was used (absent, scarce, moderate, and abundant)[16]. The bacteria was searched in non-atrophic areas without intestinal mucosal metaplasia. The staining characteristics of the bacterium to specify in the H&E staining were monochromatism similar to the foveolar epithelium and, in the special Giemsa staining, the dark blue stain that stands out. In cases of discrepancies in the bacterium presence or quantification, the second pathologist and the pathology resident completed a third reading, agreeing upon the results.

Data analysis

The statistical package SPSS (IBM) v. 27 was employed. For the qualitative variables, we used the absolute and relative frequency distribution of the categories of the variables. The mean ± standard deviation (SD) was used for the quantitative age variable since a normal distribution was observed according to the Kolmogorov-Smirnov test. The ratio between the two stainings was defined based on a 2 x 2 table dividing the number of positive and negative matches by the total.

RESULTS

The study evaluated 325 gastric biopsies from 65 patients with PNL. The mean age was 54.4 years (SD: 16.4), and 63% (41) were female; 69.2% (45) of the participants lived in the metropolitan area of Medellín, 23.1% (15) in Oriente, and 7.7% (5) in Urabá Antioqueño.

Regarding the histopathological diagnosis of *H. pylori* infection, Giemsa staining had a positivity rate of 98.5%, lower than H&E (**Figure 1**).

When analyzing the presence of the bacterium at the biopsy site, *H. pylori* was more frequent in A1, A2, and I. The positivity for the diagnosis of *H. pylori* was higher with Giemsa staining in all anatomical sites (61.5%-72%), while H&E varied between 41.5% and 49% (**Figure 2**).

The proportion for positive and negative results between H&E staining and Giemsa staining was higher in the C1 samples, with 86.1%, and lower in A1, with 73.8% (**Figure 3**).

The proportion of samples positive for *H. pylori* evaluated with Giemsa staining was higher than H&E. The difference was more significant in the samples with a low amount of bacteria, with a statistically significant difference ($p = 0.035$) (**Table 1**).

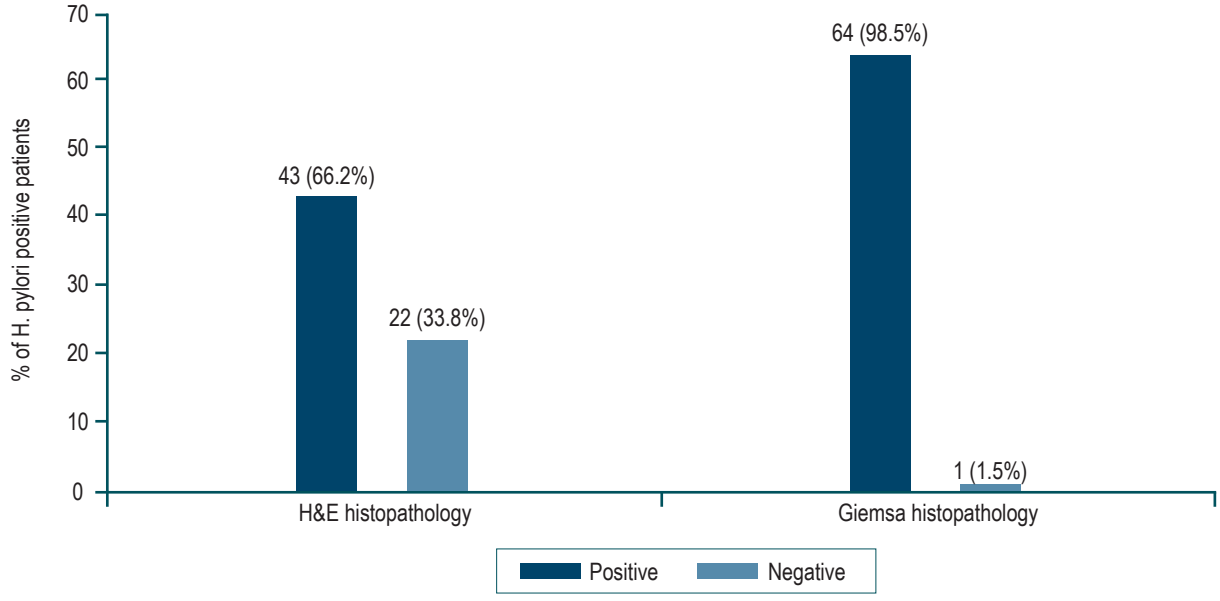

Figure 1. Distribution of patients according to the results of histopathological staining for H. pylori. Source: The authors.

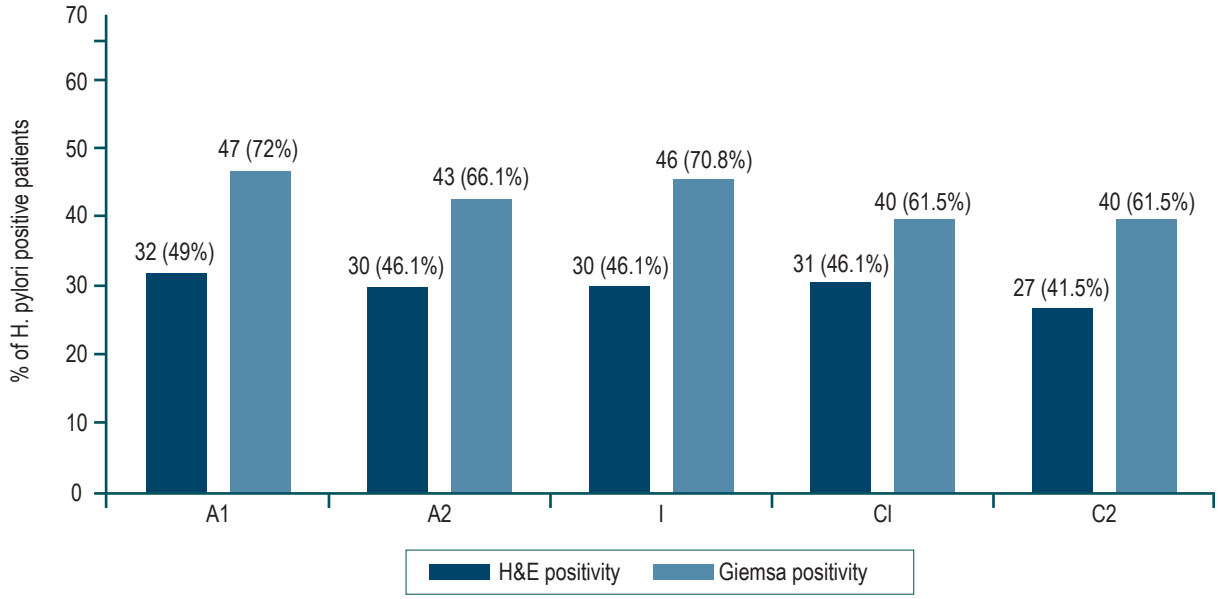

Figure 2. Distribution of positive H&E and Giemsa results for H. pylori by anatomical site. A1: greater curvature of the antrum; A2: lesser curvature of the antrum; I: angular incisure; C1: greater curvature of the body; C2: lesser curvature of the body. Source: The authors.

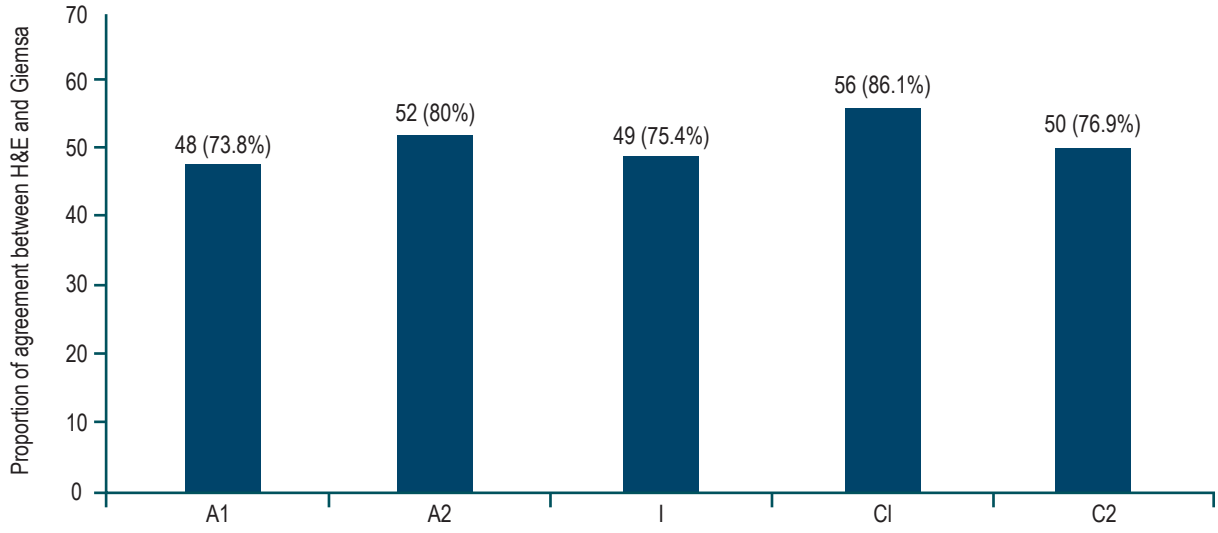

Figure 3. Agreement ratio between H&E and Giemsa. Source: The authors.

DISCUSSION

Several invasive and non-invasive methods are available for detecting *H. pylori*. Still, no test is the gold standard for diagnosis if sensitivity, specificity, cost, reproducibility, and speed are considered[11]. This study used two histological techniques (H&E and Giemsa) to diagnose *H. pylori* in patients with PNL (atrophic gastritis and intestinal metaplasia), whose bacterial density is low. According to the results, the Giemsa stain had a higher proportion of positivity in each of the five anatomical sites evaluated according to the updated Sydney protocol. This proportion was consistently higher in the group of samples with scarce bacteria.

The use of complementary stains has been evaluated in previous studies. Khan H et al. reported the need for other stainings such as Giemsa, PAS-AB, Warthin-Starry, and

Table 1. The proportion of positivity for H. pylori according to the infection density and staining used in each anatomical site

Sampling site	Amount of H. pylori											
	Scarce				Moderate				Abundant			
	H&E		Giemsa		H&E		Giemsa		H&E		Giemsa	
	n	%	n	%	n	%	n	%	n	%	n	%
A1	13	8.5	23	10.5	11	7.2	12	5.5	8	5.2	12	5.5
A2	8	5.2	21	9.6	13	8.5	10	4.6	9	5.9	12	5.5
I	10	6.5	25	11.4	10	6.5	12	5.5	10	6.5	9	4.1
C1	15	9.8	18	8.2	9	5.9	13	5.9	9	5.9	11	5.0
C2	14	9.1	19	8.7	8	5.2	13	5.9	6	3.9	9	4.1
Total	60	39.1	106	48.4	51	33.3	60	27.4	42	27.4	53	24.2

A1: greater curvature of the antrum; A2: lesser curvature of the antrum; I: angular incisure; C1: greater curvature of the body; C2: lesser curvature of the body. Number of positive cases for H&E: 153, and for Giemsa: 219. Source: The authors.

immunohistochemistry (IHC) in patients with low bacterial load (mild inflammation) associated with atrophic mucosa or after eradication therapy[27]. In our experience, the Giemsa stain was selected as complementary since it is reported in the literature for detecting *H. pylori* given its characteristics: economical, sensitive, easy to perform, and reproducible[9]. In a 2014 study, Boldt et al. found that Giemsa staining had higher sensitivity and specificity when compared to H&E[28]. Alkhamiss AS et al. found that the specificity of H&E for *H. pylori* is high (91.18%). Still, its sensitivity is low (66.67%) compared to Giemsa staining, whose sensitivity and specificity was high (93.33% and 100%, respectively), which suggests that Giemsa is a better option when compared to H&E[29].

This study noted that the H&E stain had a lower positivity rate (66.2%) compared to the complementary Giemsa stain (98.5%), as reported by Alkhamiss AS et al.[29]. For their part, Mawlood et al. said similar findings for Giemsa with a positivity rate of 93.5% and H&E of 83.9%[17]. Laine et al. found a similar sensitivity between the two stains (H&E: 92% and Giemsa: 88%). They highlighted that the specificity of Giemsa was significantly higher than the H&E stain (98% and 89%, respectively), which is why they recommend it for the diagnosis of *H. pylori*[18].

The proportion of samples positive for *H. pylori* with Giemsa was consistently higher than that with H&E in samples with low amounts of bacteria ($p = 0.035$), with diagnoses of an average of 20.3% more positive cases. It suggests that the H&E stain should be supplemented with an additional stain, such as Giemsa, when the amount of bacteria is low, as demonstrated by Moayyedi et al.[30] and by Vaira D et al. They determined that histological examination can miss low-density infections, mainly if performed only with H&E[31]. In these circumstances, the bacterium can easily be confused with cellular debris since H&E staining is not specific for *H. pylori*. Sabbagh P et al. proved that the accuracy of the histopathological diagnosis of *H. pylori* depends on the number and location of the biopsies collected[11].

This study could diagnose the *H. pylori* infection in samples from the five anatomical sites, which is consistent with what was reported by Lee JY et al. They mention that in cases of atrophic gastritis and intestinal metaplasia, there is a change in the usual colonization of the antrum towards the proximal stomach (body of the antrum and gastric fundus) as a result of hostile antral conditions, including increased pH, in which atrophy and metaplasia occur more frequently. The authors also reported that the gastric body is the appropriate biopsy site to detect *H. pylori* in patients with these lesions[32].

In Colombia, there is no consensus on the histological diagnosis of *H. pylori*. Sabbagh P et al. report that this method could make the diagnosis with a single gastric biopsy sample. However, multiple biopsies are recommended to increase diagnostic accuracy and sensitivity[11]. Generally, two different staining methods are employed: H&E for evaluating inflammatory cells and Giemsa for viewing the bacteria[11]. Alkhamiss AS et al., Makristathis et al., and Batts KP et al. suggested that studies complementary to H&E, such as Giemsa staining for the diagnosis

of *H. pylori*, should be performed only if the presence of an infection by the bacterium that cannot be viewed with H&E is highly suspected, such as cases with active gastritis or the formation of germinal centers[29, 33, 34].

Lee JY et al. also report that the specificity of histology can be improved by special stains such as Giemsa and immunohistochemical stains[32], the latter being used in other countries in cases of low bacterial density, atrophic gastritis with extensive intestinal metaplasia and chronic active gastritis without identification of H. pylori by standard staining. The IHC is more specific; however, it is more expensive, more technically challenging, and unavailable in all laboratories[9].

According to the Colombian Association of Gastroenterology clinical practice guideline for diagnosing and treating *H. pylori* in adults, routine basic staining with H&E and special staining with Giemsa is recommended to determine the presence or absence of *H. pylori*. IHC is reserved for cases with negative staining, active inflammation, post-treatment biopsies of MALT lymphomas, and when coccoid forms or other organisms cannot be identified with certainty[35]. According to Kocsmár É et al., the use of IHC is reasonable in cases that are negative with Giemsa staining and do not exhibit inflammatory activity and in which the etiological role of *H. pylori* is suggested by clinical, anamnestic, or other data[36].

CONCLUSION

In low- and middle-income countries, such as Colombia, it is increasingly critical that health systems find cost-effective and efficient alternatives to diagnose *H. pylori*. Giemsa staining proved helpful in the histopathological study of *H. pylori* in samples with low bacterial density, such as those from patients with PNL; however, its usefulness in evaluating non-atrophic gastric mucosa in ulcers and neoplasias is not ruled out. Giemsa staining could increase the sensitivity of the infection diagnosis and, thus, optimize the bacterium eradication treatment to reduce or reverse its progression to disease.

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Conflict of interests

The authors declare no conflicts of interest.

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Original article

Factors associated with muscle mass and strength in patients with liver cirrhosis: A cross-sectional study

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Abstract

Introduction: Sarcopenia is a frequent complication of cirrhosis and has been related to the progression of liver failure and increased complications, including mortality. This study aimed to determine the factors associated with muscle mass and strength in cirrhotic patients. **Materials and methods:** Cross-sectional, descriptive, analytical study. All adults who attended outpatient hepatology assessment with a diagnosis of liver cirrhosis were included. They underwent a nutritional examination that included anthropometric measurements, bioimpedanciometry, grip strength, and the Royal Free Hospital-Nutritional Prioritizing Tool (RFH-NPT) screening scale. A linear or logistic regression analysis was performed as appropriate. **Results:** 40 patients were included. The frequency of malnutrition was 17.5%, according to grip strength. The main determinants of muscle mass in the multivariate linear analysis were age, total body protein value, and total body water. Grip strength was also a significant predictor in univariate linear regression. Variables related to decreased muscle strength were the Child-Pugh score, history of ascites and hepatic encephalopathy, consumption of ammonium-lowering therapies, RFH-NPT score, and fat-free mass. **Conclusions:** The skeletal muscle mass of the cirrhotic patient was associated with age, changes in body composition, and grip strength. The muscle strength determinants were the disease's stage, the consumption of ammonium-lowering therapies, and the score on the RFH-NPT scale.

Keywords

Sarcopenia, hepatic cirrhosis, nutritional assessment, muscular strength.

INTRODUCTION

Sarcopenia is a common complication of cirrhosis and has been associated with the progression of liver failure and an increased rate of complications, including mortality[(1)]. Despite its manifest clinical importance, the risk factors related to decreased muscle mass and strength in cirrhotic patients have been poorly evaluated.

In addition to the fact that no method is superior to the others, assessing this group of patients is still controversial[(1)]. Among the available tools, grip strength has emerged as a simple, low-cost, and effective method to detect malnutrition in cirrhotic patients, which adequately predicts the incidence of major complications, the need for transplantation, and mortality compared to some clinical indices[(2)].

This study used different nutritional assessment methods, including grip strength, to determine the factors associated with muscle mass and strength in cirrhotic patients in our setting.

MATERIALS AND METHODS

A cross-sectional, descriptive, analytical study was carried out. Convenience sampling was defined. The population consisted of patients older than 18 who attended follow-up with outpatient hepatology in a medical center in Cartagena

de Indias, Colombia, between January 2022 and March 2022. They had an unequivocal diagnosis of liver cirrhosis per clinical (signs of decompensation and laboratory findings or upper GI endoscopy [EGD] demonstrating esophageal varices), ultrasound (increased liver surface nodularity, increased liver echogenicity, right lobe atrophy, hypertrophy of the left or caudate lobes, decreased liver size, portosystemic shunts), elastographic (Baveno VI definition > 15 KPa regardless of etiology)[3], or pathological (liver biopsy with evidence of severe fibrosis or cirrhosis) criteria.

We excluded patients in whom factors associated with malnutrition were presumed (patients diagnosed with human immunodeficiency virus [HIV] infection, hepatocarcinoma, stage V chronic kidney disease, on renal replacement therapy, with cognitive impairment that prevented an adequate caloric intake, or who had used oral steroids chronically in the month before the tests) or who, due to some physical limitation, could not undergo any of the required tests of the study.

All study subjects were in a follow-up protocol that included screening for hepatocellular carcinoma[4] and esophageal varices with EGD, as proposed in Baveno VI[3]. The Calès[5] classification was used to describe esophageal varices. The etiological diagnosis of cirrhosis was made following current international clinical practice guidelines[6-12]. Cryptogenic cirrhosis was determined in those cases where it was impossible to decide on any attributable etiology. Subsequently, all the subjects were scheduled for a day of nutritional assessment, including measurement of weight, height, body mass index (BMI), corrected body mass index, bioimpedanciometry, mid-arm circumference (MAC), triceps skin fold (TSF), mid-arm muscle circumference (MAMC), and grip strength, determination of ascites and peripheral edema, and application of the Royal Free Hospital-Nutritional Prioritizing Tool (RFH-NPT) screening scale.

The InBody 270® Segmental Multifrequency DSM-BIA body composition analyzer was used to determine weight. Dry weight was calculated following the European Association for the Study of the Liver (EASL) clinical practice guidelines for nutrition in patients with chronic liver disease[1]. The DETECTO® PHR portable stadiometer was used, with an accuracy of ± 0.005 m for each measurement. Dry BMI was calculated using the formula: dry weight/(height)[2]. The cut-off scores proposed by Campillo et al. regarding malnutrition[13] were used for the corrected BMI.

An experienced physician measured the TSF (mm) and MAC (cm) on the non-dominant arm of each patient with a tape measure and caliper. Measurements were made at the midpoint between the acromion tip and the olecranon process, with the patient sitting in a relaxed position. The average of two consecutive measurements for each variable was recorded.

The MAMC (cm) was calculated according to the following formula: MAMC = MAC - (TSF * 0.314)[14]. The values were classified according to the TSF and MAMC tables standardized for age and sex proposed by Bishop et al. in 1981[15] (**Appendix 1**), and moderate and severe malnutrition were diagnosed according to Campillo et al.'s criteria[16]. According to the manufacturer's recommendations, a trained physician performed bioimpedance analysis with the InBody 270® body composition analyzer.

Grip strength was measured in the non-dominant arm. The average (in kilograms) of two consecutive measurements was reported. The results were compared with the reference values put forward by Budziareck et al. in 2008[17], and malnutrition was defined as a value below the 5th percentile according to age group and sex. The Jamar hydraulic dynamometer was employed to guarantee the comparability of the measurements.

An expert doctor filled out the RFH-NPT nutritional screening scale, which consists of a questionnaire of basic questions that include the patient's feeding route, the presence of acute hepatitis, the state of fluid overload, the dry BMI, the degree of unintentional weight loss, and any acute comorbidity that modifies dietary intake. Nutritional risk was calculated based on Borhofen et al.'s scores[18].

The results of each patient's laboratory examinations were recorded three months before the nutritional assessment date to calculate the disease's prognostic indices.

Statistical analysis

Quantitative and categorical variables were described using mean (standard deviation [SD]) and percentages, respectively. A logistic regression or linear regression analysis was used, as appropriate, to identify the factors associated with muscle mass and grip strength. Results were expressed as odds ratio (OR) or regression coefficients (B). A p less than or equal to 0.05 was considered statistically significant.

Ethical aspects

We complied with all the ethical regulations for research in humans under Colombian Resolution 8430 dated October 4, 1993, which qualifies the present investigation as of minimal risk since no intervention made was invasive. The institution's ethics committee designed, disseminated, and approved a written informed consent form. All patients freely and independently agreed to participate in the study.

RESULTS

Sample description

Forty patients with a previous diagnosis of liver cirrhosis were included. No diagnosis was made *de novo* since all the patients were referred from other institutions. The majority were women (65%), and the mean age was 66. The diagnosis was confirmed mainly by elastographic (72.5%) and ultrasound (17.5%) methods, and only four patients (10%) had the definitive anatomopathological study. The most common causes of advanced chronic liver disease were nonalcoholic steatohepatitis (NASH) cirrhosis in 42.5% (17 patients) and cryptogenic cirrhosis in 25% (ten patients) (**Table 1**).

So, 77.5% were classified as category A (31 patients) on the Child-Pugh prognostic scale, and 22.5% as category B (nine patients). None were category C. Also, 42.5% (17 patients) had a history of decompensation, and the leading causes were ascites in 35% (14 episodes) and hepatic encephalopathy in 25% (ten episodes); 50% (20 patients) had esophageal varices, of which 45% (nine patients) were large. The mean modified MELD score was 13.37 points (**Table 1**).

Regarding the anthropometric variables, the average BMI of the population was 27.36 kg/m^2, the skeletal muscle mass was 25.18 kg, and the average grip strength was 15.62 kg (**Table 2**).

Table 1. Baseline characteristics of the patients

	Total sample n = 40
Age (years)	66 (4.58)
Average (SD)	
Identification	
- Women, n (%)	26 (65)
- Urban, n (%)	39 (97.5)
Personal history	
- High blood pressure, n (%)	18 (45)
- Type 2 diabetes mellitus, n (%)	15 (37.5)
- Chronic kidney disease, n (%)	6 (15)
- Smoking, n (%)	5 (12.5)
- Osteoporosis, n (%)	2 (5)
- Menopause*, n (%)	22 (84)
- History of ascites, n (%)	14 (35)
- History of hepatic encephalopathy, n (%)	10 (25)
- History of variceal bleeding, n (%)	4 (10)
Diagnostic information	
Etiology	
- NASH, n (%)	17 (42.5)
- Cryptogenic, n (%)	10 (25)
- AIH/PBC overlap, n (%)	4 (10)
- HCV infection, n (%)	3 (7.5)
- AIH, n (%)	3 (7.5)
- Alcoholic, n (%)	2 (5)
- SBC, n (%)	1 (2.5)
Varicose veins	
- Yes, n (%)	20 (50)
Varicose vein size	
- Small, n (%)	5 (25)
- Medium, n (%)	6 (30)
- Large, n (%)	9 (45)
Child-Pugh score	
- A, n (%)	31 (77.5)
- B, n (%)	9 (22.5)
- C, n (%)	0
- Modified MELD, n (%)	13.37 (1.16)

PBC: primary biliary cholangitis; SBC: secondary biliary cholangitis; AIH: autoimmune hepatitis; MELD: Model for End-stage Liver Disease; NASH: nonalcoholic steatohepatitis; HCV: chronic infection with the hepatitis C virus. Source: The authors.

Factors associated with skeletal muscle mass

Univariate linear regression found an association between skeletal muscle mass, male sex, and total body protein value. Grip strength also had a statistically significant relationship (b = 0.55; 95% confidence interval [CI]: 0.36-3.04; p = 0.0001) (**Table 3**).

Multivariate linear regression was performed with the variables that had a significant association with muscle mass in the univariate linear regression. Association was found with age, total body protein value, BMI, total body water, fat mass percentage, and fat-free mass. This analysis found no significant association between muscle strength and the male sex (**Table 4**).

Factors associated with muscle strength

Univariable linear regression was performed, noting that the main factors associated with muscle strength were male sex (b = 11.94; 95% CI: 8.5 to 15.3; p = 0.0001), age (b = -0.28; 95% CI -0.46 to -0.096; p = 0.004), chronic kidney disease (b = -6.11; 95% CI -10.92 to -1.31; p = 0.016), and fat-free mass (b = 4.01; 95% CI: 0.095 to 7.93; p = 0.045).

Multivariate linear regression was performed with variables that had a significant association with muscle strength in univariate linear regression. In this analysis, male gender was the only independent predictor of muscle strength (b = 10.79; 95% CI 7.17 to 14.42; p = 0.0001).

Table 2. Results of nutritional assessment

Anthropometry	
Triceps fold (mm) Average (SD)	20.18 (3.88)
Mid-arm circumference (cm) Average (SD)	27.37 (1.46)
Mid-arm muscle circumference (cm) Average (SD)	21.03 (0.78)
Grip strength (kg) Average (SD)	15.62 (2.23)
Bioimpedancemetry	
Weight (kg) Average (SD)	74.21 (5.23)
Size (m) Average (SD)	1.65 (0.02)
BMI (m/kg^2) Average (SD)	27.36 (2.16)
Total body water (kg) Average (SD)	39.06 (3.24)
Bone mineral content (kg) Promedio (DE)	3.78 (0.36)
Body fat mass (kg) Average (SD)	19.37 (4.97)
Fat mass percentage (%) Average (SD)	25.18 (5.78)
Skeletal muscle mass (kg) Average (SD)	27.36 (2.80)
Fat-free mass (kg) Average (SD)	54.83 (4.80)
Total body protein (kg) Average (SD)	9.73 (0.91)
Muscular strength	
Normal, n (%)	33 (82.5)
Decreased, n (%)	7 (17.5)

Source: The authors.

Accordingly, the data on gender and age were analyzed based on Budziareck et al.'s tables[17]. The variables related to the decrease in muscle strength were the Child-Pugh score, history of ascites and hepatic encephalopathy, use of ammonium-lowering therapies, RFH-NPT score, and fat-free mass (**Table 5**).

Table 3. Univariable linear regression: skeletal muscle mass

Relationship of variables with skeletal muscle mass			
Univariable linear regression			
Variable	**B**	**CI**	***p***
Male sex	10.56	7.98 a 13.14	0.0001
Age	-0.205	-0.36 a -0.04	0.01
High blood pressure	2.49	-2.44 a 7.43	0.3
Type 2 diabetes mellitus	-1.23	-5.67 a 3.21	0.56
Chronic kidney disease	1.49	-4.70 a 7.68	0.61
Smoking	-1.07	-9.45 a 7.29	0.78
Osteoporosis	-4.4	-11.68 a 2.87	0.21
Menopause	-0.75	-6.69 a 5.18	0.79
History of ascites	0.57	-6.78 a 7.94	0.87
History of hepatic encephalopathy	-2.4	-10.79 a 5.98	0.55
History of variceal bleeding	1.57	-6.43 a 9.58	0.68
KDIGO classification of chronic kidney disease	-0.04	-0.11 a 0.02	0.22
Child-Pugh score	-0.02	-0.15 a 0.10	0.71
BMI	-0.03	-0.06 a -0.006	0.01
Bioimpedancemetry			
- Total body water	0.39	0.17 a 0.60	0.001
- Mineral	0.17	-0.04 a 0.39	0.11
- Body fat mass	-0.02	-0.06 a 0.009	0.13
- Body fat percentage	0.061	0.01 a 0.11	0.017
- Fat-free mass	-0.16	-0.24 a -0.07	0.0001
- Total body protein	2.43	2.07 a 2.8	0.0001
Anthropometry			
- TSF	-0.002	-0.009 a 0.005	0.57
- MAMC	0.024	-0.003 a 0.05	0.08
- Grip strength	0.55	0.36 a 0.74	0.0001
- RFH-NPT	-1.38	-5.82 a 3.047	0.52

MAMC: mid-arm muscle circumference; RFH-NPT: Royal Free Hospital-Nutritional Prioritizing Tool; TSF: triceps fold. Source: The authors.

Table 4. Multivariate linear regression: skeletal muscle mass

Relationship of variables with skeletal muscle mass			
Variable	B	CI	*p*
Male sex	0.13	-0.01 a 0.27	0.07
Age	-0.005	-0.009 a -0.001	0.01
BMI	-0.048	-0.07 a -0.02	0.001
Total body water	0.52	0.33 a 0.70	0.0001
Total body protein	2.22	1.89 a 2.54	0.0001
Body fat mass percentage	0.28	0.01 a 0.04	0.0001
Fat-free mass	-0.21	-0.29 a -0.14	0.0001

Source: The authors.

Malnutrition prevalence

Taking into account the scores obtained in the RFH-NPT, 40% (16 patients) had a moderate and high risk of malnutrition. Regarding the standardized MAMC tables proposed by Bishop et al.[15], 37.5% (15 patients) had some degree of malnutrition. Based on the age and sex tables by Budziareck et al.[17], 17.5% (seven patients) presented with decreased muscle strength. According to the IMCC, 15% (six patients) had malnutrition.

DISCUSSION

The present study identified that the main determinants of skeletal muscle mass in cirrhotic patients were male sex, age, BMI, total body water, fat mass percentage, fat-free mass, total body protein, and grip strength.

Few works have tried to answer this question. In 2019, a study conducted by Sung et al.[19] demonstrated that grip strength (<18 kg for women; <26 kg for men), age (>60 years), history of hepatic encephalopathy, and elevated levels of *Wisteria floribunda* agglutinin-positive mac-2-binding protein (WFA^+-M2BP > 1.86 COI; a recent marker of liver fibrosis)[20] were the main predictors of loss of skeletal muscle mass in a population of cirrhotic patients.

Another study by Hiraoka et al. concluded that increased Child-Pugh score and decreased serum albumin levels were the most critical risk factors associated with decreased muscle mass and strength in patients with chronic liver disease[21]. Our study found no significant relationship between serum albumin levels and muscle mass or strength.

Table 5. Univariate linear regression: muscle strength according to Budziareck et al.'s sex and age tables[17]

Regresión lineal univariable			
Variable	OR	CI	*p*
Male sex	3.06	0.57 a 16.30	0.189
Age	1.01	0.94 a 1.08	0.686
High blood pressure	1.81	0.34 a 9.40	0.48
Type 2 diabetes mellitus	1.31	0.25 a 6.87	0.74
Chronic kidney disease	2.9	0.41 a 20.27	0.283
Smoking	1.2	0.11 a 12.81	0.87
History of ascites	6.66	1.09 a 40.7	0.04
History of hepatic encephalopathy	6	1.05 a 34.14	0.04
Presence of varicose veins	8.1	0.87 a 75.47	0.06
KDIGO classification of chronic kidney disease	2.49	0.83 a 7.39	0.1
Ammonium-lowering therapy	6	1.05 a 34.14	0.04
Serum albumin	0.85	0.2 a 3.6	0.82
Child-Pugh score	7.46	1.26 a 44	0.02
BMI	1.2	0.98 a 1.5	0.07
Corrected BMI	0.93	0.09:9.50	0.95
Bioimpedancemetry			
- Skeletal muscle mass	1.06	0.93 a 1.20	0.35
- Body fat mass	1	0.92 a 1.08	0.97
- Body fat percentage	0.97	0.90 a 1.04	0.42
- Fat-free mass	1.08	1 a 1.18	0.05
- Total body protein	1.21	0.82 a 1.79	0.32
Anthropometry			
- TSF	1	0.91 a 1.09	0.98
- MAC	1.03	0.84 a 1.27	0.752
- MAMC	1.07	0.79 a 1.45	0.65
Scales			
- Nutritional status according to the MAMC	0.49	0.49 a 2.43	0.813
- RFH-NPT	5.69	1.09 a 29.71	0.039

Source: The authors.

Regarding the other results, the relationship found between muscle mass and total body water could be explained by the fact that the water content of skeletal muscle mass is approximately between 70% and 75%, causing the total body water volume to increase at the expense of intracellular water in skeletal muscle fibers[22].

It is striking that, in our results, a negative association was found between skeletal muscle mass and fat-free mass. It could be speculated that the greater free mass in these patients is determined by increased extracellular water due to the pathophysiological processes typical of advanced chronic liver disease[23].

We also could demonstrate a significant relationship between muscle mass and strength, whose indirect measurement through grip strength has been emerging in recent years as a cost-effective, non-invasive tool in the early identification of malnutrition in cirrhotic patients[24] and even as a predictor of mortality[25].

Our analysis revealed similar results for muscle strength to those reported in previous studies. Significant relationships were found with male sex, age, presence and severity of chronic kidney disease, and fat-free mass. Sex was the only independent predictor in multivariate linear regression.

A study conducted by Nishikawa et al. in 2021 observed that in men, the main determinants of muscle strength loss were age, diagnosis of cirrhosis, glomerular filtration rate, and the ratio of extracellular water to total body water. Meanwhile, in women, they were the diagnosis of cirrhosis, serum albumin concentrations, the albumin:bilirubin ratio, prothrombin time, platelet count, and the ratio of extracellular water to total body water [26].

Consequently, considering the apparent differences between the sexes concerning muscle strength under Budziareck et al.'s tables[17], the population was discriminated by sex and age. It was shown that the variables most closely related to muscle strength were the Child-Pugh score, history of ascites, history of hepatic encephalopathy, use of ammonium-lowering therapies, RFH-NPT score, and fat-free mass. Some of these factors, such as the Child-Pugh score and history of encephalopathy, were also reported in Sung et al.'[19] and Hiraoka et al.'[21] works.

The use of ammonium therapies was related to decreased muscle strength. This finding is not surprising and can be explained by the fact that currently, the indication for these therapies is limited to the management of overt encephalopathy and secondary prophylaxis to prevent recurrences[27], which implies more advanced stages of chronic liver disease.

The RFH-NPT scale has been correlated with clinical deterioration, the severity of the disease (according to the Child-Pugh and MELD scores), and the appearance of different clinical complications such as ascites, hepatorenal syndrome, and hepatic encephalopathy. In addition, its application is an independent predictor of clinical deterioration and transplant-free survival, and improvements in this scale are associated with improved survival[18]. The most recent EASL guidelines support its use[1]. Our study revealed that it is the only screening scale significantly associated with muscle strength, so it is a good tool for identifying cirrhotic patients at risk of malnutrition.

In the present study, the prevalence of malnutrition ranged between 15% and 40% depending on the method used. This reflected the need for more uniformity among the available instruments and expressed the need for precise tools that can be used in daily practice. All this, added to the heterogeneous groups included in the studies, the severity of the disease, the etiology of cirrhosis, and the comorbidities presented, makes the prevalence of malnutrition in the literature vary greatly: 10% to 100%(28).

Taking into account that in our study, grip strength was the only nutritional assessment tool significantly associated with muscle mass, it could be determined that the most accurate prevalence of malnutrition was 17.5%. The high prevalence evidenced by the RFH-NPT score (40%) does not diminish its validity but, on the contrary, positions it as a good screening tool with excellent sensitivity.

The other measurements used in the nutritional assessment of cirrhotic patients did not have a significant association with each other or with the RFH-NPT. Thus, our results do not support using any of them (IMCC, MAMC, TSF, MAC) in daily practice.

The main limitation of our study was the sample size, considering that the collection of patients was restricted by the coronavirus disease 2019 (COVID-19) pandemic. Besides, there are no standardized national tables for anthropometric measurements (MAC, TSF, MAMC) or the grip strength values used in this study. To adequately interpret the results, local tables should be designed that account for our population's characteristics.

The main strength is that it is the first study that comprehensively evaluates the nutritional status of cirrhotic patients in Latin America.

CONCLUSIONS

The skeletal muscle mass of the cirrhotic patient was mainly associated with age, changes in body composition, and grip strength.

The main determinants of muscle strength were the stage of the disease, the use of ammonium-lowering therapies, and the score on the RFH-NPT scale. The latter seems to be a helpful tool for screening the nutritional status of cirrhotic patients in daily practice.

APPENDIX 1

Standardized TSF and MAMC tables for age and sex proposed by Bishop et al. in 1981[15]

Baseline TSF values distributed by age in US men

Age group	Sample size	Estimated population	Mean	Percentile						
Age		Millions	mm	5th	10th	25th	50th	75th	90th	95th
18-74	5261	61.18	12.0	4.5†	6.0	8.0	11.0	15.0	20.0	23.0
18-24	773	11.78	11.2	4.0	5.0	7.0	9.5	14.0	20.0	23.0
25-34	804	13.00	12.6	4.5	5.5	8.0	12.0	16.0	21.5	24.0
35-44	664	10.68	12.4	5.0	6.0	8.5	12.0	15.5	20.0	23.0
45-54	765	11.15	12.4	5.0	6.0	8.0	11.0	15.0	20.0	25.5
55-64	598	9.07	11.6	5.0	6.0	8.0	11.0	14.0	18.0	21.5
65-74	1657	5.50	11.8	4.5	5.5	8.0	11.0	15.0	19.0	22.0

†Values are given in units of mm. Table prepared from data collected during NHANES I from 1971 to 1974.

Baseline TSF values distributed by age in US women

Age group	Sample size	Estimated population	Mean	Percentile						
Age		Millions	mm	5th	10th	25th	50th	75th	90th	95th
18-74	8410	67.84	23.0	11.0†	13.0	17.0	22.0	28.0	34.0	37.5
18-24	1523	12.89	19.4	9.4	11.0	14.0	18.0	24.0	30.0	34.0
25-34	1896	13.93	21.9	10.5	12.0	16.0	21.0	26.5	33.5	37.0
35-44	1664	11.59	24.0	12.0	14.0	18.0	23.0	29.5	35.5	39.0
45-54	836	12.16	25.4	13.0	15.0	20.0	25.0	30.0	36.0	40.0
55-64	669	9.98	24.9	11.0	14.0	19.0	25.0	30.5	35.0	39.0
65-74	1822	7.28	23.3	11.5	14.0	18.0	23.0	28.0	33.0	36.0

†Values are given in units of mm. Table prepared from data collected during NHANES I from 1971 to 1974.

MAMC reference values distributed by age in US men

Age group	Sample size	Estimated population	Mean	Percentile						
Age		Millions	cm	5th	10th	25th	50th	75th	90th	95th
18-74	5261	61.18	28.0	23.8†	24.8	26.3	27.9	29.6	31.4	32.5
18-24	773	11.78	27.4	23.5	24.4	25.8	27.2	28.9	30.8	32.3
25-34	804	13.00	28.3	24.2	25.3	26.5	28.0	30.0	31.7	32.9
35-44	664	10.68	28.8	25.0	25.6	27.1	28.7	30.3	32.1	33.0
45-54	765	11.15	28.2	24.0	24.9	26.5	28.1	29.8	31.5	32.6
55-64	598	9.07	27.8	22.8	24.4	26.2	27.9	29.6	31.0	31.8
65-74	1657	5.50	26.8	22.5	23.7	25.3	26.9	28.5	29.9	30.7

†Values are given in units of cm. Table prepared from data collected during NHANES I from 1971 to 1974.

MAMC baseline values distributed by age in US women

Age group	Sample size	Estimated population	Mean	Percentile						
Age		Millions	cm	5th	10th	25th	50th	75th	90th	95th
18-74	8410	67.84	22.2	18.4†	19.0	20.2	21.8	23.6	25.8	27.4
18-24	1523	12.89	20.9	17.7	18.5	19.4	20.6	22.1	23.6	24.9
25-34	1896	13.93	21.7	18.3	18.9	20.0	21.4	22.9	24.9	26.6
35-44	1664	11.59	22.5	18.5	19.2	20.6	22.0	24.0	26.1	27.4
45-54	836	12.16	22.7	18.8	19.5	20.7	22.2	24.3	26.6	27.8
55-64	669	9.98	22.8	18.6	19.5	20.8	22.6	24.4	26.3	28.1
65-74	1822	7.28	22.8	18.6	19.5	20.8	22.5	24.4	26.5	28.1

†Values are given in units of cm. Table prepared from data collected during NHANES I from 1971 to 1974.

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Review article

Non-alcoholic fatty liver disease part 1: general aspects, epidemiology. pathophysiology and natural history

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Abstract

Fatty liver or NAFLD is defined by the presence of fat or steatosis in hepatocytes and covers a spectrum that goes from simple steatosis, through steatohepatitis (NASH), with inflammation and fibrosis and ending in cirrhosis. It is considered a global world prevalence close to 25% in the general population and is diagnosed between 40 and 50 years, with variations regarding the predominant sex and with ethnic differences, affecting more the Hispanic population. Fatty liver is associated with metabolic syndrome (MS), and obesity is considered the main risk factor for its presence and progression.

Fatty liver is a complex and very heterogeneous disorder in its pathophysiology, resulting from the interaction of multiple elements, genetic, epigenetic, environmental, cultural factors, etc. All this together leads to an accumulation of hepatic fat, insulin resistance, hormonal and intestinal microbiota alterations, generating hepatocellular damage through the formation of free oxygen radicals and activation of hepatic fibrogenesis.

The natural history of fatty liver is dynamic, patients with simple steatosis have a low risk of progression to cirrhosis, in patients with NASH this risk is increased, however, the process may be reversible, and some people will have spontaneous improvement. Fibrosis seems to be the determinant of overall mortality and outcomes associated with liver disease, it is considered that in all patients fibrosis worsens one stage every 14 years, in NASH it worsens one stage every seven years. Previous studies conclude that approximately 20% of cases of simple steatosis progress to NASH and that approximately 20% of them progress to cirrhosis, with the presence of hepatocellular carcinoma (HCC) in 5 to 10% of them.

Keywords

Non-alcoholic Fatty liver disease, pathophysiology, natural history.

INTRODUCTION

The first observations of patients with fatty liver date back to the 19th century[1]; nonalcoholic fatty liver disease (NAFLD), or fatty liver, as it is often called, was first described by Zelman in 1952 upon noting liver disease in very obese patients[2]. In 1980, Ludwig described the term nonalcoholic steatohepatitis (NASH) when observing a disease with histological changes similar to those in patients with alcoholic hepatitis but with negligible or absent alcohol use[3], a concept that continues to be valid. Fatty liver is the leading cause of consultation in hepatology services. However, it is also frequent in consultations with clinical specialists and primary care physicians due, on the one hand, to changes in habits in modern life, hypercaloric diets, and a sedentary lifestyle, and on the other, greater access to the healthcare system. The increasing use of diagnostic aids leads to occasional findings of "fatty liver" on imaging

(usually ultrasound) or elevated transaminases in asymptomatic patients[4], which is why all doctors must be prepared to treat it. Therefore, these two topics are reviewed.

DEFINITION AND DIAGNOSIS

NAFLD, or fatty liver, is defined by the presence of fat or steatosis in hepatocytes and spans from the initial stage, simple steatosis without inflammation and fibrosis, to steatohepatitis (NASH) with inflammation and fibrosis, to cirrhosis, the most advanced stage[5]. MAFLD (Metabolic-Associated Fatty Liver Disease) has recently been proposed to encompass the metabolic alterations associated with fatty liver[6]. A consensus must be awaited regarding this new definition that partly emerges because the fatty liver is a highly heterogeneous disease with multiple subgroups.

Fatty liver is diagnosed by hepatic steatosis on imaging (usually ultrasound) or liver biopsy in 5% or more of the tissue examined, with or without inflammation or fibrosis. Secondary causes of hepatic steatosis should be ruled out, such as:

- Alcohol use greater than 20 g/day for men and greater than 10 g/day for women;
- Intake of hepatotoxic drugs in the last six months before the study;
- Hepatitis B and C viruses, hemochromatosis, autoimmunity, and other causes of chronic liver disease[5].

EPIDEMIOLOGY

Younossi showed a global prevalence close to 25% in the general population, with significant variations depending on the region of the world evaluated; the Middle East and South America showed the highest prevalence, 32%, and 31%, respectively, followed by North America (24%), Europe (23%), and Africa (13%)[7]. In the United States, other studies have reported NAFLD prevalences of 10% to 46%[8, 9]. In Latin America, in a Mexican study with 2,503 individuals, NAFLD was detected in 14.3%, associated with overweight, obesity, and dyslipidemia[10]. In Chile, another study with 832 patients showed fatty liver in 23.4%[11]. In Colombia, we do not have exact prevalence data. Still, the 2015 National Nutritional Status Survey (ENSIN, for its acronym in Spanish) reported overweight in 19.1% of those surveyed between the ages of 13 and 17 and 38.4% of adults[12].

Of note is that the prevalence of NAFLD has been increasing over time, as demonstrated by comparing three periods of the National Health and Nutrition Examination Survey (NHANES). Between 1988 and 1994, the prevalence of NAFLD (defined as elevated levels of serum aminotransferases with no explanation, which could result in underdiagnosis) was 5.5%; between 1999 and 2004, it was 9.8%, and between 2005 and 2008, it was 11%, representing 47%, 63%, and 75% of chronic liver diseases during those periods, respectively[13].

Fatty liver is usually diagnosed between 40 and 50 years of age[14], with variation regarding the predominant sex: in some studies, it is women[3, 15-17], and in others, men[18-20].

There are ethnic differences in the prevalence of NAFLD[18, 21]. A study of liver triglyceride content in 2,287 subjects of a multiethnic population sample from the United States found a higher prevalence of hepatic steatosis in Hispanic Americans (45%) compared with white (33%) or black (24%) people[18]. A higher prevalence of obesity explains the higher prevalence in Hispanics.

Fatty liver, especially NASH, is associated with metabolic syndrome (MS)[5, 20-23]. Obesity is the leading risk factor since body mass index (BMI) and waist circumference positively correlate with fatty liver and disease progression[22]. Besides, 80% of patients are obese[24, 25], and 72% have dyslipidemia[25-27]. Type 2 diabetes (DM2) is found in 45% to 65% of patients with NAFLD and is directly and strongly associated with the severity and progression of fatty liver[5, 25-28]. The combination of obesity, systemic hypertension, dyslipidemia, and insulin resistance or diabetes independently increases the risk of severe fibrosis and cardiovascular disease[25, 28-30].

Fatty liver is the most frequent liver disease in obese children and adolescents and is associated with chronic systemic disorders such as hypertension, dyslipidemia, and increased risk of DM2 and cardiovascular diseases. In the pediatric population, the prevalence of fatty liver is estimated to be between 7.6% and 34%[31-33].

Fatty liver and obesity epidemics are global public health problems[5, 23, 27], and fatty liver is the fastest-growing indication for liver transplantation due to decompensated cirrhosis or HCC[34, 35].

PATHOPHYSIOLOGY

Fatty liver is a complex disorder and very heterogeneous pathophysiology resulting from the interaction of multiple genetic, epigenetic, environmental, and cultural factors. All this together produces hepatic fat accumulation, insulin resistance, hormonal alterations, and alterations in the intestinal microbiota, causing hepatocellular damage through the formation of oxygen-free radicals and activation of hepatic fibrogenesis.

Genetics

The first genome-wide association study in fatty liver (GWAS) showed the importance of heredity in the accumulation of liver fat and highlighted the susceptibility to the disease according to the individuals' genetic status[36].

Subsequently, studies on twins confirmed the hereditary component of steatosis and fibrosis[37]. Other association studies reported genetic variants related to the risk of fatty liver, responsible for encoding proteins that regulate the metabolism of hepatic lipids that lead to the accumulation of liver fat. These variants are associated with the development and progression of fibrosis[38, 39], whose phenotypic expression is triggered by dietary factors and adiposity[39]. The most important genes and their variants or polymorphisms (SNPs) are presented below.

PNPLA3 gene

It encodes a phospholipase, adiponutrin, which regulates the metabolism of triglycerides and retinoids[33, 39]. A single nucleotide polymorphism (SNP) of the gene, rs738409 (C > G), results in a sense variation (I148M) that inhibits the enzyme through a repressor that competitively binds to the adipocyte triglyceride lipase (ATGL) coactivator, causing a more significant accumulation of lipids (up to 75% more)[36, 40, 41]. Individuals with a G nucleotide variant have a 3.2 times higher risk of developing liver fibrosis, and NASH is more prevalent in GG individuals than in CC individuals (odds ratio [OR]: 3.49)[41]. The variant has been associated with steatohepatitis, fibrosis, and cancer. It has also been found to promote liver damage in alcoholic fatty liver, chronic hepatitis C, and infections that promote hepatic steatosis[39].

The frequency of the PNPLA3-I148M variant was correlated with the ethnic origin and the prevalence of fatty liver in the population, being common in the mixed population (frequency of 26%), more prevalent in the Hispanic population (49%), and less prevalent in the African one (12–17%)[36]. In addition, the penetrance of this variant in the European population is comparable to the effects of the monogenic liver disease mutation, with homozygous GG having up to a 12-fold higher probability of developing HCC in patients with NAFLD[42, 43].

TM6SF2 gene or transmembrane 6 superfamily member 2

The gene regulates the lipid content of hepatocytes by encoding an endoplasmic reticulum (ER) transmembrane protein associated with the clearance of very low-density lipoproteins (VLDL)[44]. Its polymorphism (SNP), rs58542926 (G > A), resulting in the E167K variant, was associated with high levels of liver triglycerides and an increased risk of advanced fibrosis[45]. On the contrary, this variant decreases the secretion of VLDL by hepatocytes and reduces the risk of cardiovascular disease[46].

MBOAT7 gene, membrane-bound O-acyltransferase domain-containing 7 (MBOAT7)

The MBOAT7 gene expression produces the enzyme lysophosphatidylinositol (LPI) acyltransferase, an endomembrane protein that catalyzes the production of phosphatidylinositol (PI), a component of cell membranes. Its SNP rs641738 has also been associated with increased fibrosis in fatty liver[47, 48].

GCKR gene, glucokinase regulatory gene (GCKR)

It is expressed in the liver and encodes a protein that acts as an allosteric inhibitor of GCK, the enzyme responsible for blood glucose homeostasis. Its SNP rs780094 genetic variant is associated with a higher fasting serum triacylglycerol level in fatty liver[49].

HSD17B13 gene, 17β-Hydroxysteroid dehydrogenase (HSD17B13)

Its SNP rs72613567 is protective and reduces the risk of fatty liver; it was associated with reduced alanine aminotransferase (ALT)[50, 51].

Genetic basis of insulin resistance

It has been associated with polymorphisms in the apolipoprotein C3 gene, interleukin 6 (IL-6), and adiponutrin[52-55], with altered transcriptional activity of the peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PPARGC1A)[52]. Additionally, other cytokines and adipokines involved in insulin receptor signaling seem to be altered in the omental adipose tissue of NASH patients[55].

Other genetic elements: non-coding RNA (ncRNA)

These RNAs do not code for functional proteins and are grouped according to their size, small (micro-RNA) and large, including long and circular RNAs. They regulate multiple biological pathways, lipid uptake, *de novo* lipogenesis, lipid oxidation, export of hepatic lipids, apoptosis, cell proliferation, or fibrosis[56]. At least a dozen micro-RNAs have been strongly associated with the development of fatty liver[56, 57]. As cell death increases with the progression of steatohepatitis, they are released directly or packaged in exosomes into the circulation, making them potential biomarkers for fatty liver status[58].

Excess lipid accumulation in the liver

The hepatic imbalance in the input and output of fats due to lifestyle changes caused by high-calorie consumption, sedentary lifestyle, metabolic syndrome, and hormonal and genetic alterations results in hepatic steatosis with excess triglycerides, free fatty acids (FFA), ceramides, and free cholesterol. It may occur due to excessive import of FFA from adipose tissue, decreased hepatic export of FFA (secondary to reduced VLDL synthesis or secretion), or impaired FFA β-oxidation. The primary sources of triglycerides are fatty acids stored in adipose tissue and newly processed fatty acids

in the liver through *de novo* lipogenesis[59, 60]. Additionally, *de novo* lipogenesis (DNL) has been reported to be upregulated in fatty liver patients. It is three-fold higher than in control patients, and this pathway may be pathogenetically more relevant in older patients and men[61, 62].

Increased visceral adipose tissue and intrahepatic fat correlate with increased gluconeogenesis, elevated FFA levels, and insulin resistance. Visceral fat has also been associated with liver inflammation and fibrosis in NASH patients independent of insulin resistance, an effect possibly mediated by IL-6 (proinflammatory cytokine)[63, 64].

INSULIN RESISTANCE

It is one of the primary mechanisms in the pathophysiology of fatty liver; it occurs in most obese and diabetic patients, although it can also be found in lean non-diabetic patients[65-67]. Insulin resistance triggers multiple events in lipid metabolism: increased peripheral lipolysis and triglyceride synthesis, increased FFA uptake by the liver, and, thus, accumulation of triglycerides in hepatocytes, resulting in a preferential shift from carbohydrate to FFA β-oxidation[65, 68, 69]. The molecular pathways that lead to insulin resistance are complex and not fully elucidated, but several molecules appear to interfere with the actions of insulin at the cellular level; for example, lipophilic bile acids have been shown to promote insulin sensitivity and decrease gluconeogenesis and hepatic triglyceridemia by binding to the farnesoid X receptor[70].

Gut microbiota

The human gut microbiome comprises 10 to 100 trillion microorganisms, primarily bacteria. It has ten times more intestinal microorganisms than human eukaryotic cells[71] and is susceptible to environmental and pathophysiological alterations, which is why it plays a fundamental role in the pathophysiology of fatty liver. The microbiota has been associated with direct and indirect injury to the liver cell through various mechanisms that produce lipotoxicity, oxidative damage, and secondary fibrosis[72-79]:

- Changes from the normal microbiota: bacterial overgrowth in the small intestine or changes in gut microbiota composition (for example, macronutrient composition in diets high in fructose and saturated fat).
- Increased intestinal permeability possibly associated with small intestinal bacterial overgrowth, changes in microbiota composition, and bacterial translocation.
- Increased production of endotoxins.
- Generation of toxic products, such as endogenous alcohol and acetaldehyde by bacteria and yeast at the colon level, and other metabolites of the gut microbiota such as N,N,N-trimethyl-5-aminovaleric acid (TMAVA). The latter reduces the synthesis of carnitine and oxidation of hepatic fatty acids, leading to hepatic steatosis.
- Deconjugation of bile salts and inactivation of hepatic lipotropes, such as choline.

In intestinal dysbiosis, defined as the imbalance between the resident microbial communities and the host, intestinal permeability increases may result in a pathological translocation of microbial products to the liver through the portal vein[73-75]. In this process, pathogen-associated molecular patterns (PAMPs) are produced, which are recognized by selective receptors in the liver, mainly Toll-like receptors, and provide a chronic innate immune response that releases damage-associated molecular patterns (DAMPs)[80]. Additionally, microbiota-derived metabolites, such as modified bile acids, choline, and ethanol, alter hepatic metabolism and trigger an inflammatory response[72, 75, 77-80].

Peptides and hormones

Leptin

It is a peptide produced in adipose tissue; its absence is associated with massive obesity in mice (ob/ob) and humans. Leptin induces dephosphorylation of insulin receptor substrate 1, making hepatocytes more resistant to insulin[81]. It appears that leptin resistance in the central nervous system, rather than in the liver, may be necessary for the pathogenesis of NASH, which was inferred by observing that leptin infusion into the central nervous system of mice with fatty liver corrected insulin resistance and fatty liver, while peripheral administration did not[82].

Adiponectin

It is another hormone secreted only in adipose tissue with beneficial effects on lipid metabolism. It improves β-oxidation of fatty acids in muscle and clearance of plasma lipids, inhibits tumor necrosis factor alpha (TNF-α) production in the liver, and produces direct anti-inflammatory effects[83]. Adiponectin appears to have some relationship with the modulation of insulin sensitivity, and low circulating hormone levels have been correlated with the severity of histopathological findings in NASH[84].

Resistin

It is a protein derived from adipose tissue associated with developing insulin resistance. In research with mice, resistin overexpression led to altered FFA levels, glucose intolerance, and hyperinsulinemia[85].

Incretins

These are gut-derived hormones, such as glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like pep-

tide-1 (GLP-1), that potentiate insulin secretion after food intake and play an essential role in glucose homeostasis[86].

Other proposed associated factors

Environmental factors

Modifiable risk factors, such as shift work and travel that disrupt normal eating and sleep-wake cycles, promote adiposity, metabolic syndrome, and nonalcoholic fatty liver disease[87]. Prolonged disruption of normal circadian rhythms in mice with fatty liver induces the development of nonalcoholic steatohepatitis by dysregulating crosstalk between two nuclear hormone receptors: the farnesoid X receptor (FXR) and the constitutive androstane receptor (CAR), resulting in FXR suppression, hepatic accumulation of bile acids, bile acid-induced CAR overactivation, and eventual CAR-dependent liver injury, fibrosis, and neoplasia[88-90]. Environmental toxins[91] and obstructive sleep apnea, which cause inflammation, have also been implicated as pathogenic factors[92, 93].

Hepatocellular damage

It is ultimately produced by the formation of free radicals due to the following:

- Induction of microsomal lipoxygenases of cytochrome p-450 from FFA;
- The switch to β-oxidation of FFA plus pre-existing defects in mitochondrial oxidative phosphorylation (significant mitochondrial structural abnormalities), which have been demonstrated by electron microscopy of hepatocytes from NASH patients, not observed in patients with simple hepatic steatosis[22, 64-70].

These two pathways together lead to hepatocellular damage and fibrosis through the activation of multiple processes such as nuclear factor kappa B (NF-κB), increased production of cytokines, activation of TNF-α, the complement system, plasma myeloperoxidase, and natural killer cells[65, 94-96].

Oxygen-free radical formation and lipid peroxidation can deplete antioxidant enzymes such as glutathione, vitamin E, beta-carotene, and vitamin C, rendering the hepatocyte more susceptible to oxidative injury. In this process, serum levels of xanthine oxidase produced by reactive oxygen species are increased compared to control patients, while the levels of multiple antioxidant enzymes are decreased[97, 98].

A correlation has been described between the severity of the disease and the increased expression of oxidative scavenging receptors[99]. Serotonin has been implicated as a source of reactive oxygen species in NASH; increased serotonin catabolism resulted in increased levels of reactive oxidative species and necroinflammation in an animal model[100].

Iron contributes to hepatocellular damage by forming oxygen-free radical species in its process of reducing Fe^{3+} to Fe^{2+}[101], associated with the development of NASH; an increase in iron has also been observed in patients with insulin resistance independently[102]. A higher liver iron concentration correlates with the severity of fibrosis in NASH[103].

The innate immune system plays a role in the progression of fatty liver[104, 105]. An adequate physiological immune response is essential for resolving liver damage and normal liver regeneration. In contrast, a persistent and exaggerated response of the innate immune system may lead to chronic inflammation of the liver and its consequences. PAMPs and DAMPs activate and maintain a pattern-recognition receptor-mediated innate immune response characteristic of fatty liver and a complex intercellular crosstalk between different innate immune cells, natural killer cells, T lymphocytes, macrophages, neutrophils, hepatocytes, and hepatic stellate cells (HSCs). The result defines the progression to steatohepatitis and fibrosis[105].

Apart from the death of hepatocytes by direct lipotoxicity and the release of DAMP, pyroptosis has been identified as a new form of programmed cell death in fatty liver, characterized by the activation and assembly of multiprotein complexes, called *inflammasomes*[106, 107]. The most studied is the nucleotide-binding domain, a leucine-rich repeats (NLR) family pyrin domain containing-3 (NLRP3) inflammasome. Once activated, the NLRP3 inflammasome cleaves procaspase-1 to its mature form (caspase-1), which later cleaves IL-1β, IL-18, and gasdermin D. IL-1 and IL-18 are highly proinflammatory cytokines released into the extracellular space partly through transmembrane pores formed by gasdermin D[108-109]. All pathophysiological factors are summarized in **Figure 1**.

Liver fibrosis is the pathological characteristic that predicts the various results associated with liver injury in fatty liver[110, 111] and its genesis, liver fibrogenesis, or scar formation. It is a dynamic process of extracellular matrix (ECM) accumulation in which the hepatic stellate cell (formerly known as *lipocyte*, *Ito cell*, or *perisinusoidal cell*) is its primary source in the normal and fibrotic livers[112].

Chronic liver damage paracrinely stimulates neighboring cells, such as sinusoidal endothelial cells, Kupffer cells, monocytes, and platelets, among others, producing an angiogenic stimulus with the formation of new blood vessels, sinusoidal remodeling and the release of multiple mediators such as platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF) and related receptors, and vasoactive mediators including nitric oxide and carbon monoxide[113]. All this together activates the stellate cells that increase the production of collagens (types I, III, and IV), several glycoproteins (cellular fibronectin,

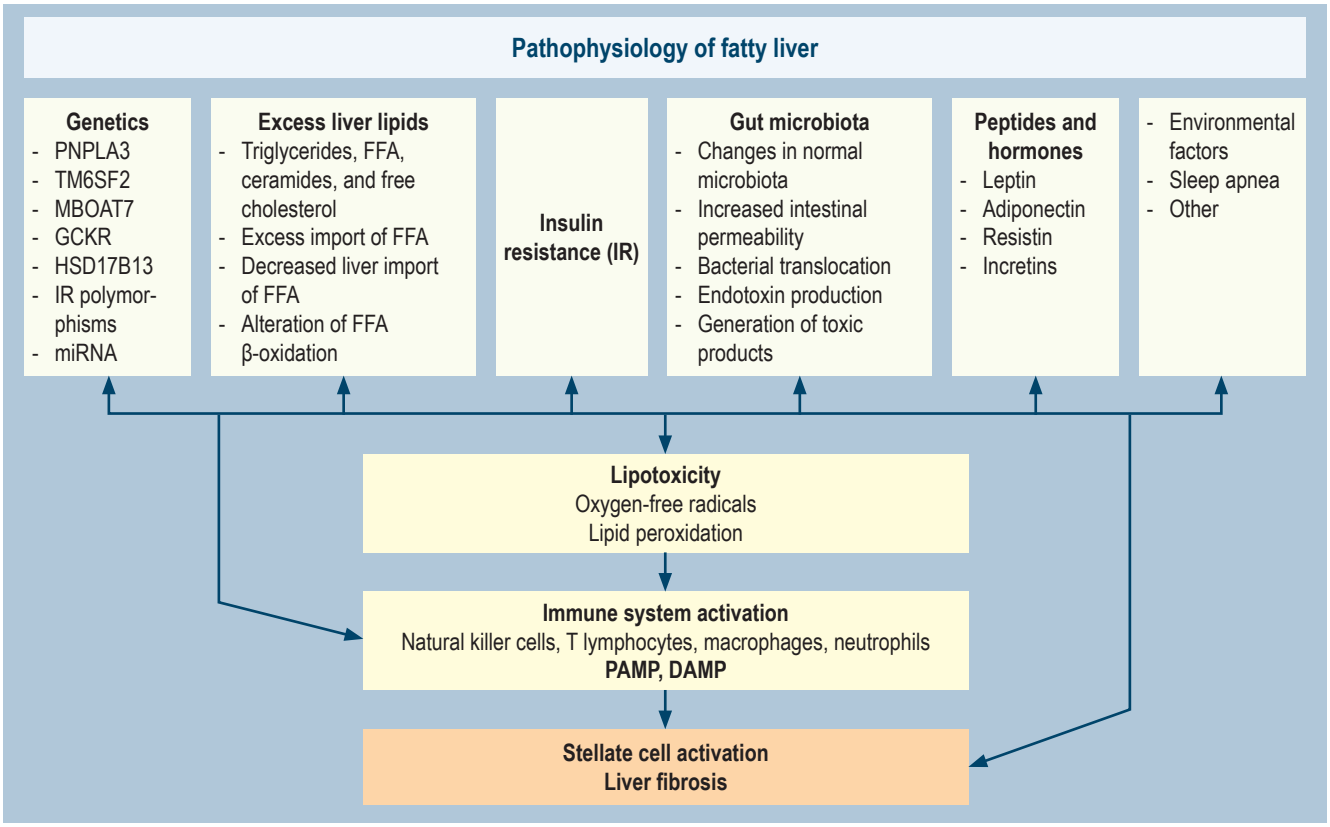

Figure 1. Pathophysiology of fatty liver. Source: The authors.

laminin, osteonectin, tenascin, von Willebrand factor), proteoglycans and glycosaminoglycans (perlecan, decorin, among others). It leads to a progressive accumulation and compositional change of the ECM that activates positive feedback pathways and further amplifies fibrosis through processes involving cell membrane receptors and other cytokines and adhesion proteins. One of these well-characterized pathways is that of integrins, a family of membrane proteins that control various cell functions, including gene expression, cell growth, and differentiation[114].

For its part, fibrosis reflects a balance between the production and degradation of the ECM, a delicate balance between calcium-dependent enzymes that specifically degrade collagens and non-collagenous substrates, known as *matrix metalloproteinases* (MMPs or matrixins), and related specific inhibitors, known as *tissue inhibitors of metalloproteinases* (TIMPs). The substitution of the low-density matrix for that of the interstitial type, characteristic of fibrosis, has consequences on the function of hepatocytes, hepatic stellate cells, and endothelial cells, which partly explains the synthetic and metabolic dysfunction observed in patients with advanced fibrosis[112-114].

NATURAL HISTORY

Paired biopsy studies showed that the natural history of fatty liver is very dynamic: patients with simple steatosis have a low risk of progression to cirrhosis, while in patients with NASH, this risk is increased; however, the process can be reversible, and some people will have spontaneous improvement[16, 115-120]. Fibrosis seems to be the determinant of overall mortality and the outcomes associated with liver disease[113, 114, 121, 122]. The damage caused by NAFLD can take many years to progress and is most often described in five stages, from 0 to 4, depending on the amount and distribution pattern of fibrosis found, similar to the METAVIR classification (F0-F4)[123].

In fatty liver, considering that the data are average figures and non-linear, in all patients, fibrosis worsens by one stage every 14 years, while in NASH, it worsens by one stage every seven years[120]. Previous studies conclude that approximately 20% of the cases of simple steatosis progress to NASH; of these, approximately 20% progress to cirrhosis, with hepatocellular carcinoma (HCC) in 5% to 10% of them[120, 124-126]. Recent analyses showed that 20%

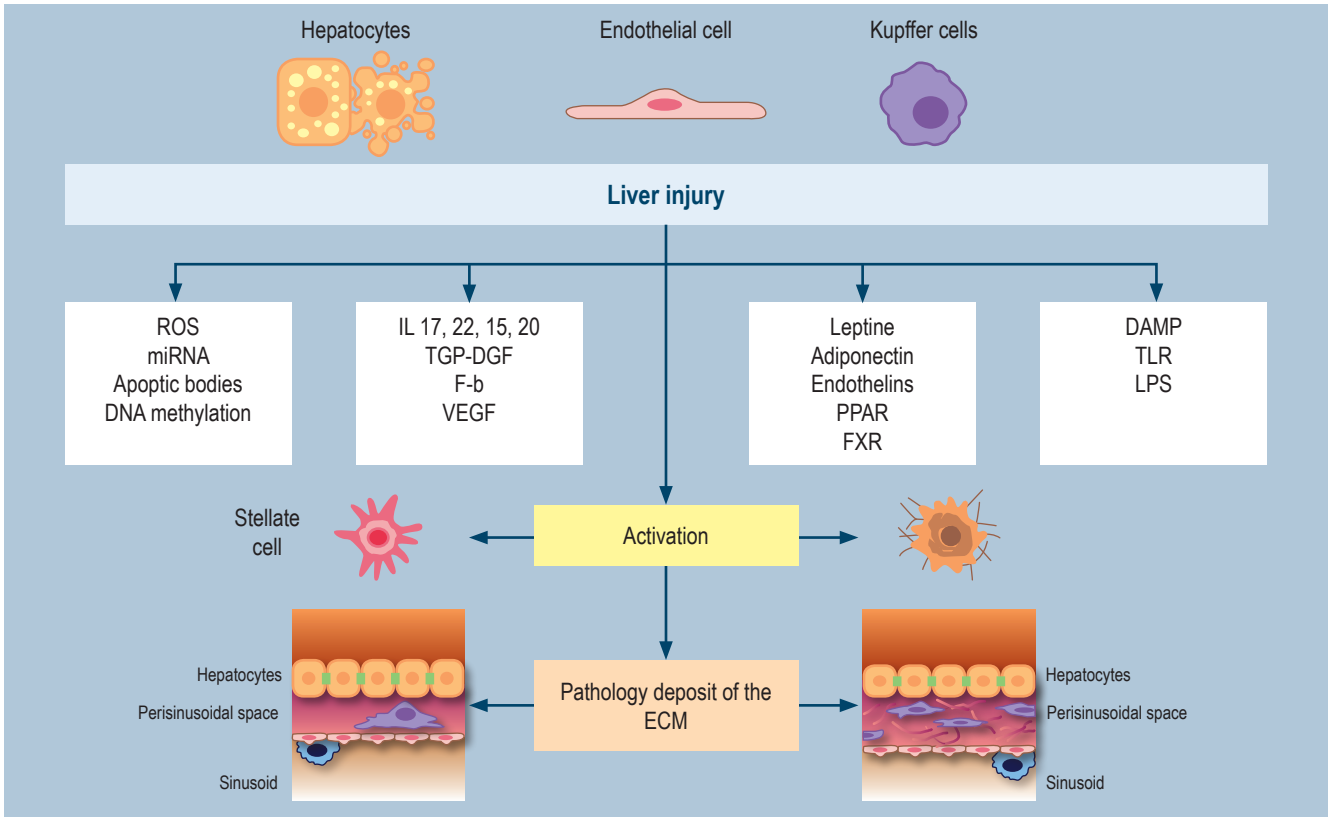

Figure 2. Hepatic fibrogenesis. Modified from: Tsuchida T et al. 2017;14(7):397-411; Friedman SL. Nat Rev Gastroenterol Hepatol. 2010;7(8):425-36; Kisseleva T et al. Nat Rev Gastroenterol Hepatol. 2021;18(3):151-166.

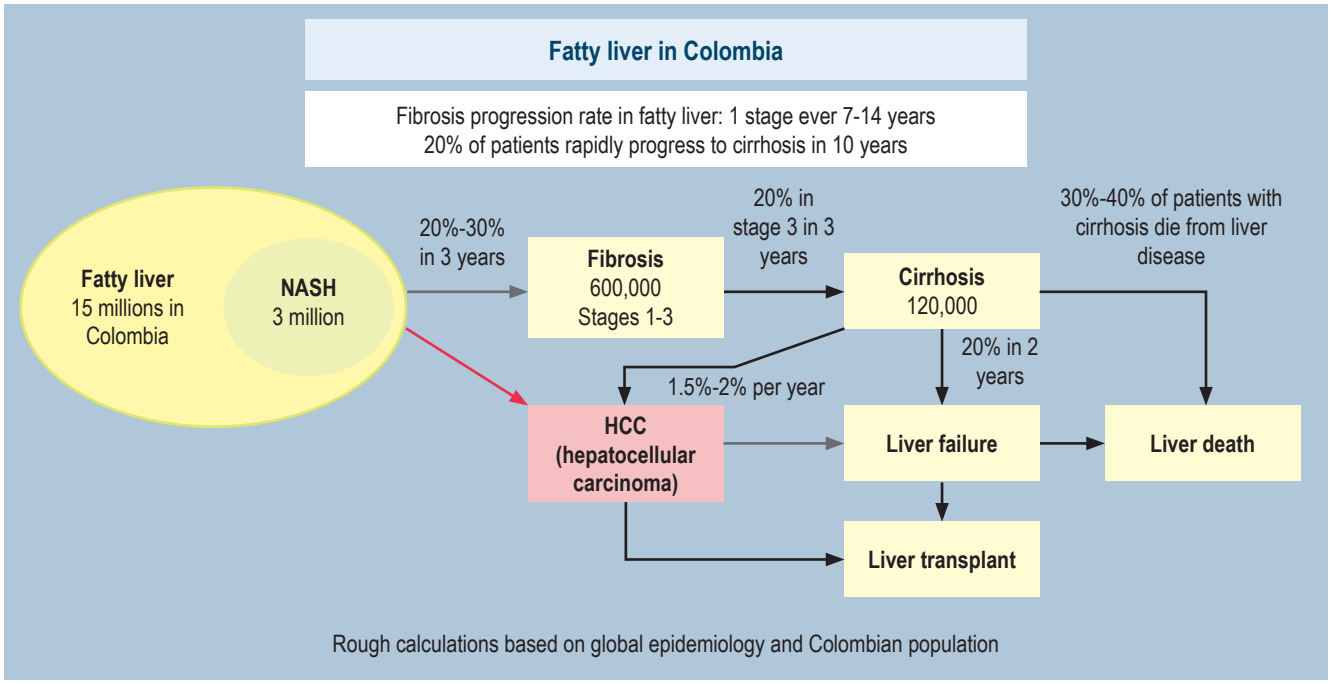

Figure 3. Fatty liver in Colombia (estimation with international data). Source: Adapted from[120, 125-128].

of patients with F3 progressed to cirrhosis in two years; of these, 20% of patients with compensated cirrhosis decompensated[127, 128]. These figures are called the 20% "rule" and corroborate the previous data. In some cases, the liver can be damaged much faster than these average numbers, and one in five patients with fibrosis are rapid progressors[120]; this could be due to fluctuations in the severity of metabolic risk factors, the impact of various (unhealthy) lifestyles, and genetic factors. NASH is now recognized as the leading cause of cryptogenic cirrhosis (**Figure 2**)[129]. Since in Colombia, there are no exact data on our natural history, **Figure 3** presents a forecast of the disease for our country based on international data.

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Review article

Hepatitis C virus reinfection: A review of the topic and case report

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Abstract

Chronic hepatitis C (HCV) infection affects 58 million people and is a significant cause of morbidity and mortality worldwide. HCV reinfection is a growing problem in people with risk factors such as heavy alcohol use, anal sex, group sex, and sharing needles and syringes. This type of infection is defined as a new HCV infection with a different viral genotype than the first infection in a patient after achieving a sustained viral response (SVR). Reinfection occurs, in part, due to the absence of promotion and prevention strategies. Taking this background into account, more pragmatic approaches have been proposed to control HCV infection and avoid reinfection, such as micro elimination.

This article reports the case of a patient with alterations in biochemical liver markers, for which a diagnostic test for HCV infection and then viral genotyping was requested. Infection by HCV genotype 1, subgenotype 1A, was evidenced. Management with direct-acting antivirals was started, and an adequate SVR12 was documented. Three months later, the patient returned, and the control tests showed a high HCV viral load, for which genotyping was requested, showing a new HCV genotype 4 infection.

Keywords

Direct-acting antivirals, hepatitis C virus, sustained virological response, reinfection, HIV/HCV coinfection.

INTRODUCTION

Chronic hepatitis C is a significant public health challenge. In 2019 approximately 290,000 people died of hepatitis C, mainly due to the development of end-stage liver disease (cirrhosis and hepatocellular carcinoma). There are currently 58 million people infected with the hepatitis C virus (HCV), and around 1.5 million new infections are reported yearly[(1)].

Chronic HCV infection triggers an inflammatory process that can progress to liver fibrosis, cirrhosis, hepatocellular carcinoma, and death[(2)]. Cirrhosis and liver decompensation are associated with a 2%-5% annual risk of death, and 15%-20% of people with liver disease die within the first year after decompensation[(3)]. In addition, chronic hepatitis C is one of the West's leading causes of liver transplantation (**Figure 1**)[(4-6)].

The World Health Organization (WHO) has established a global strategy against viral hepatitis. Its objectives include diagnosing 90% of cases and treating 80% of patients, achieving a 65% reduction in mortality associated with viral hepatitis by 2030[(7)]. Actively searching for cases with good admission to the healthcare system is imperative to accomplish these objectives since this information can guide interventions focused on reducing this disease in risk groups[(8)].

In addition to an active search and an adequate characterization of the population, it is necessary to have an antiviral treatment regimen to meet the WHO goal of control and elimination. An indication of cure of HCV infection is when a sustained viral response (SVR) is demonstrated, which is defined as the absence of the HCV genome in serum or plasma by assay (LLOD ≤ 15 IU/mL) at week 12 (SVR12) or week 24 (SVR24) after finishing the treatment. Viral clearance is also associated with normalizing serum levels of liver enzymes, improvement or disappearance of hepatic necroinflammation and fibrosis, and a decrease in extrahepatic manifestations of HCV infection[9].

Highly effective drugs are required to achieve this SVR. For a long time, the only therapy available for patients with hepatitis C was based on type I interferon. It had many limitations due to side effects and viral resistance, leading to therapy failure in many patients[10]. However, there are currently direct-acting antivirals (DAAs) that target viral proteins such as NS3 and its cofactor NS4A (protease inhibitors), NS5B (nucleoside or non-nucleoside viral polymerase inhibitors), and NS5A (viral replication complex inhibitors)[11]. These antivirals have a viral clearance rate close to 95%, even in cases of human immunodeficiency virus (HIV) coinfection, decompensated liver cirrhosis, and end-stage renal disease[12, 13]. DAA treatment regimens can be aimed at a specific genotype or pan-genome, which is the current preference. Viral genome sequencing (NS3, NS5A, and NS5B) before treatment is recommended in some cases where the risk of resistance is high for specific DAA regimes[10].

A recurrence (relapse or reinfection) should be suspected in case of a reappearance of viremia after SVR[14]. If it occurs after SVR12, it may be due to relapse, in which HCV persists in the individual and reappears due to the selection of a minority viral variant. This variant results from HCV RNA-dependent viral RNA polymerase activity that has no proofreading activity and therefore has a high error rate, resulting in genetic heterogeneity and the creation of quasispecies (**Figure 2**)[15]. In addition, late relapse has been described in some cases, detailing undetectable viral load levels after treatment (SVR) and the reappearance of the viral genome in the blood 24 weeks after the end of the DAA treatment regimen. Late relapse cases have been documented using deep sequencing; this methodology calculates genetic diversity in terms of the number of mutations per site in the quasispecies of the HCV genome isolated from a patient before treatment and during late relapse. This analysis is needed to prove a late relapse or reinfection with the same HCV genotype as the first infection because of the implications of the treatment regimen and creates the need to reconsider the follow-up time of a patient after completing the treatment regimen[16, 17]. Late relapse is a phenomenon facilitated by HCV infection of extrahepatic sites, as documented in peripheral blood mononuclear cells, dendritic cells[18, 19], and cells of the gastrointestinal mucosa[20].

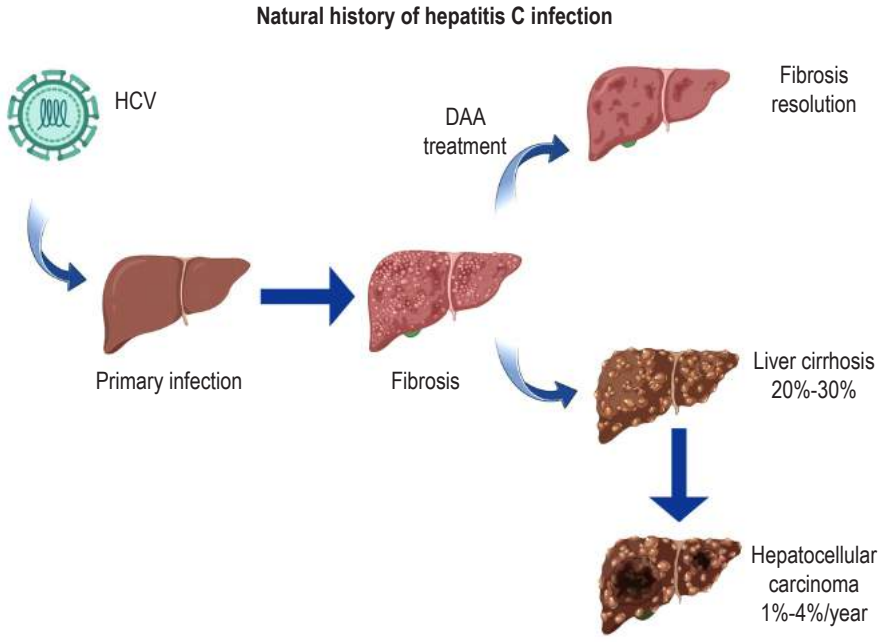

Figure 1. Natural history of hepatitis C infection. DAAs: direct-acting antivirals. Adapted from Lingala et al[3].

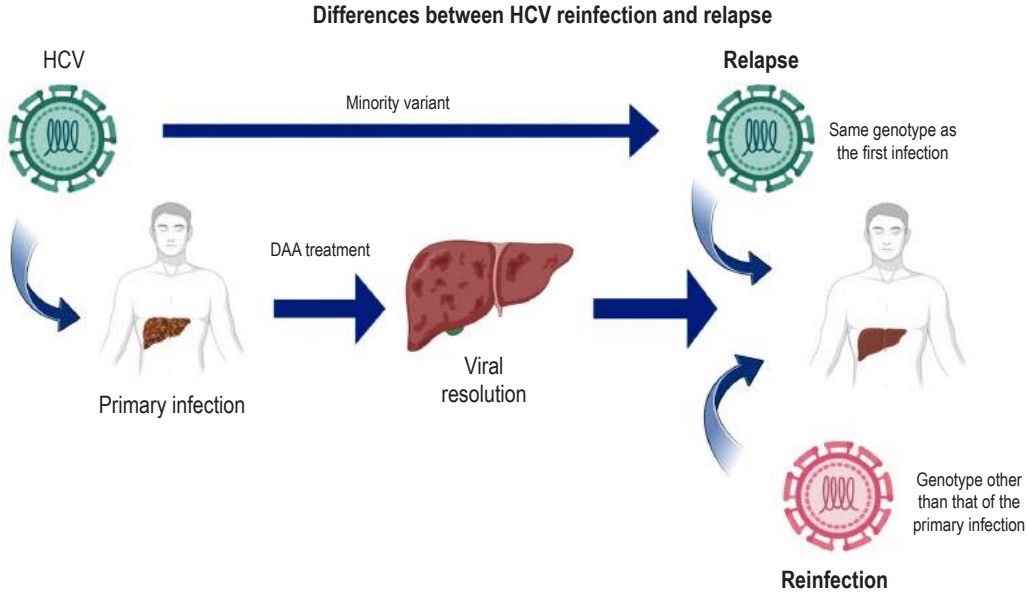

Figure 2. Differences between HCV reinfection and relapse. Source: The authors.

The possibility of reinfection should be considered in an individual after completing the treatment regimen with viral clearance. One of the most critical factors associated with reinfection is a humoral and cellular immune response with little activity against HCV. It should be noted that the response is specific to the viral genotype and, therefore, is susceptible to HCV genotypes other than that of the first infection[21-23]. The viral genotype should be characterized before and after treatment to distinguish between relapse and reinfection. Since reinfection corresponds to a new infection by another HCV genotype, the diagnosis of reinfection is established by detecting an HCV genotype different from the first infection[24-26].

With DAAs, virologic relapse rates after SVR12 are meager. Cases of a virologic relapse generally occur within the first four weeks after the treatment regimen, while reinfection can be defined as the detection of HCV viremia in persons with an SVR12 after completing treatment with a DAA regimen who have risk factors[8].

According to the European Association for the Study of the Liver (EASL), patients who achieve SVR should undergo viral load monitoring 24 weeks after completing treatment, mainly in populations with risk factors, such as people who inject drugs (PWID) and men who have sex with men (MSM). The cure for the infection can be deemed definitive when the HCV genome is undetectable at the time[27].

The American Association for the Study of Liver Diseases (AASLD) recommends check-ups every 6-12 months in people with risk factors or unexplained liver dysfunction to assess for HCV relapse or reinfection[28].

This article presents the first case of HCV reinfection in a patient with an SVR after DAA treatment.

HEPATITIS C VIRUS

HCV was discovered in 1989, and since then, clinical and basic science research has enabled progress in understanding its pathogenesis and the development of tools for diagnosis and treatment[29, 30]. So far, eight HCV genotypes and more than 90 subgenotypes have been characterized[31, 32]. HCV is a member of the family *Flaviviridae*, genus *Hepacivirus*. The viral genome is a single-stranded, positive-sense RNA of approximately 9.6 kb, encoding a single polyprotein cleaved into ten proteins: three structural proteins, the capsid protein (core), and two glycoproteins present in the envelopes (E1 and E2), as well as seven non-structural proteins, including two proteins necessary for virion assembly (p7 and NS2) and five proteins that form the viral replication complex (NS3, NS4A, NS4B, NS5A, and NS5B)[10].

HEPATITIS C INFECTION TRANSMISSION AND RISK FACTORS

HCV is primarily transmitted parenterally. It generally requires exposure to blood through transfusions, an iatrogenic route, the reuse of needles and syringes, and vertical transmission[33, 34].

The sexual transmission of HCV has been documented and associated with factors such as unprotected sex, fisting, and group sex. Furthermore, biological risk factors

have been described in the literature, such as ulceration or concurrent sexually transmitted infections and human immunodeficiency virus (HIV) infection[35, 36]. An increase in HCV cases acquired by this route has been observed since the 2000s, particularly in men who have sex with men (MSM) and people with HIV infection[37].

The importance of knowing the associated risk factors has been demonstrated in the study by Knick et al., in which they identified that the regions with a high incidence of HCV had less information about the risk factors than the inhabitants of low-incidence regions[38].

NATURAL HISTORY OF HEPATITIS C VIRUS

Hepatitis C is characterized by a transient infection in 15%-40% of cases and chronic infection in 60%-85% of cases. Spontaneous clearance of the infection involves an early, functional, sustained cellular and humoral immune response directed against multiple epitopes of viral proteins and is associated with host and virus variables[21-23].

Most patients develop specific antibodies against HCV in the early phase of infection. However, the role of neutralizing antibodies directed against conformational epitopes located on E1 and E2 glycoproteins in viral clearance is still controversial[23].

One of the evasion strategies of the immune response by the virus is the high genetic variability of HCV represented in the number of quasispecies throughout the evolution of the infection in an individual. The mechanisms described in persistent HCV infection include the depletion phenotype of CD8+ T cells ($CD127^{low}$ $PD\text{-}1^{high}$), decreased activity of CD4 T cells to express inhibitory molecules, such as programmed cell death protein 1 (PD-1), T cell immunoreceptor with Ig and immunoreceptor tyrosine-based inhibition motif domains (TIGIT), and cytotoxic T lymphocyte antigen 4 (CTLA-4), and the production of immunomodulatory cytokines, such as IL-10 and TGF-β by Treg lymphocytes[21-23].

After DAA treatment, an increase in the frequency of HCV-specific CD8+ T cells and a partially restored proliferative capacity have been described. These changes are due to the maintenance of a memory-like CD8+ T cell population and the disappearance of CD8+ T cells with a terminal depletion profile after HCV clearance. However, memory-like cells are not fully restored to the level of conventional memory-like CD8+ T cells, which sets up a pattern of functional exhaustion[21-23].

REINFECTION RISK FACTORS

A meta-analysis of 61 studies estimated reinfection rates of 0.95%, 10.67%, and 15.02% at five years in the low-risk, high-risk, and HIV coinfection groups, respectively[34]. Notably, most studies included in this review evaluated recurrence after treatment with interferon-based therapies.

Few studies assess reinfection rates in the DAA era; however, some experts speculate that DAA treatment may be associated with higher rates of reinfection due to the availability of antivirals, fewer adverse effects, and a high probability of cure, which may encourage risky behavior in people after healing from a first infection[8]. Ingilis P et al. published a retrospective cohort study that evaluated MSM reinfection in patients treated with DAAs; the authors found that the risk of reinfection in the study population was higher than in the control group (1.89 per 100 person-years; 95% confidence interval [CI]: 1.41-2.48) and that the reinfection rate was higher in this population treated with DAAs than in patients treated with interferon, although without statistical significance (hazard ratio [HR]: 1.05; 95% CI: 0.64-1.74; $p = 0.831$)[39].

For its part, a cohort study by the Madrid Registry (Madrid-CoRe Study) on patients with HIV/HCV coinfection treated with DAAs detected 12/177 cases of MSM reinfection (6.8%), representing an incidence rate of 5.93 per 100 people/year (95% CI: 3.37-10.44). In the same cohort, there were 5/1,459 cases of reinfection in PID (0.21 per 100 people/year)[40]. In a similar study, Smit and colleagues described the findings of the ATHENEA study from 2000 to 2019. ATHENEA is a national HIV infection observation registry established in 1998 that collects clinical data from adults and children in the Netherlands. Of a total of 23,590 cases, 1,269 diagnoses of primary HCV infection (incidence: 5.2 per 1,000 person-years [95% CI: 5.0-5.5]) and 274 HCV reinfections (incidence: 26.9 per 1,000 person-years [95% CI: 23.9-30.3]) were documented[41, 42].

It has been described that factors such as heavy alcohol use, reuse of needles and syringes, anal sex, and group sex are associated with HCV reinfection in patients with HIV infection and MSM. Moreover, it has been shown that mental health counseling reduces the risk of HCV reinfection (aHR: 0.24; 95% CI: 0.13-0.46)[43].

PREVENTION OF HEPATITIS C REINFECTION

One condition that facilitates reinfection is the absence of promotion and prevention strategies; consequently, this problem represents a significant burden for the health system and patients. Considering that no vaccine is available, the cornerstone of HCV infection control and elimination is DAA treatment, and therefore more pragmatic strategies have been proposed to avoid reinfection. Methods such as micro-elimination consist of adapting the WHO elimination objectives to small groups to address segments of the population individually and specifically. Thus, treatment

and prevention interventions could be made more quickly and efficiently and achieve HCV micro-elimination in specific subpopulations, such as people with HIV coinfection or inmates[44]. An example of this strategy is the Swiss HCVree trial, which aimed to evaluate this strategy in patients with HCV/HIV coinfection and MSM. The high rate of persistence of HCV infection, in combination with the high risk of transmission in these groups, make antiviral treatment a preventive intervention and a way to achieve HCV micro-elimination in MSM. This micro-elimination program resulted in a 57% and 84% decrease in the incident and prevalent HCV infections, respectively[45], over two years.

Adequate follow-up of patients after DAA treatment is also found in reinfection prevention strategies, as shown in a study in Japan. The follow-up of 1,392 patients with SVR was conducted via viral load in a sample obtained every six months. Of the total number of patients in follow-up, 434 (31.2%) continued with regular visits for more than ten years; none of the follow-up patients were positive during the study, demonstrating the importance of strict clinical surveillance[46].

The ideal prevention strategy for HCV infection is vaccination; however, the different evasion mechanisms of the HCV immune response, including genetic variability, have been a significant impediment to developing a vaccine[21-23].

Meanwhile, coinfection with two or more HCV genotypes has been described, particularly in populations such as PID, MSM, and individuals with HIV coinfection, among others. Of note is that the methods used in clinical practice limit the possibility of adequately demonstrating coinfections with two or more HCV genotypes, mainly when Sanger-type sequencing strategies are used, which generally only identify the predominant genotype. On the contrary, new-generation sequencing technologies allow the reading of all sequences, differentiating the majority genotype from the minority one.

In any case, pan-genotypic antiviral therapy is recommended in the vast majority of cases of reinfection or coinfection due to its high probability of SVR, which is a great advantage in developing countries, where the sequencing of a new generation is not very accessible. Nonetheless, the possibility of therapeutic failure should always be considered in case of coinfection with more than one genotype[47].

Another pillar in the multidisciplinary management of hepatitis C is the adequate screening and assessment of the patient's sexual partners to offer antiviral treatment and reduce incidence and complication rates. Although the patient is responsible for contacting and informing their partners, liaising with the health sector is necessary to offer education and opportunities to prevent and treat the disease.

The incidence rate of HCV infection in seronegative partners of individuals with a chronic condition has been described as 0%-0.6% in prospective cohort studies of monogamous heterosexual couples. Therefore, a higher incidence is expected in individuals with multiple partners; however, the study results are probably controversial because sometimes, recording risk factors and information about sexual partners is complex [48, 49].

HEPATITIS C REINFECTION TREATMENT

The effectiveness of DAA therapy for HCV infection is supported by both randomized controlled trials and real-life studies; still, in terms of HCV reinfection, the available data on the effectiveness of treatment is minimal, and as described above, reinfection can compromise the benefits of cure at the individual and population levels if not adequately treated[50].

The EASL recommendation on reinfection is to offer a new course of DAA treatment, with a three-month waiting period to allow possible spontaneous elimination, except if urgent treatment is needed[14].

The REACH-C study is an observational study that evaluated DAA treatment outcomes in 33 health services in Australia between March 2016 and June 2019. Of the 10,843 individuals starting DAA for the first time, 99 reinfections were reported. Treatment for reinfection occurred in 88 individuals for whom no resistance studies were requested. Regimens used to treat reinfection included glecaprevir/pibrentasvir (50%), sofosbuvir/velpatasvir (36%), sofosbuvir/ledipasvir (5%), sofosbuvir/daclatasvir (5%), grazoprevir/elbasvir (3%), and sofosbuvir/velpatasvir/voxilaprevir (1%).

The primary outcome was SVR12, similar to treatment for primary infection (95% vs. 95%; $p = 0.745$) and comparable in settings of primary, tertiary, and prison levels of complexity. The study concludes that the treatment of reinfection with pan-genotypic DAAs is highly effective and can be administered in non-specialized settings[50].

Still, Colombia only provides the sofosbuvir/velpatasvir combination (pan-genotypic regimen) as a therapy for treating HCV infection through the high-cost account due to its high effectiveness, the possibility of use even in patients with severe renal dysfunction, and the centralized purchase of drugs. Besides, because of the characteristic of the pan-genotypic regimen in Colombia, performing a genotype test before starting treatment is not recommended by clinical practice guidelines[51].

The preceding implies grave difficulty in managing patients with HCV reinfection due to the impossibility of both knowing whether it is a reinfection or a relapse and carrying out resistance studies to define adequate HCV therapy, especially in HIV-positive patients, whose predominant genotype in Colombia is genotype 4. Thus, it is vital

to perform the baseline assessment of the genotype before starting DAA to better guide treatment in those patients with clearly identifiable risk factors.

TESTING TO IDENTIFY RESISTANCE-ASSOCIATED MUTATIONS

One of the most intense debates in the pharmacological management of hepatitis C is the use of sequencing to identify resistance-associated mutations before treatment; however, access to tests is limited, and there is no consensus on test techniques, interpretation, and reporting. Highly effective treatments are currently available in cases of HCV infection with pre-existing resistance-associated mutations or substitutions (RAS). Therefore, many scientific societies do not recommend routine testing to identify RAS before treatment in DAA naïve people. However, the American Association for the Study of Liver Diseases recommends the RAS to identify the Y93H substitution in NS5A in previously treated or cirrhotic patients infected with HCV genotype 3 in whom it is intended to use sofosbuvir/velpatasvir (regimen available in Colombia). RAS testing is suggested for the intention to treat with elbasvir/grazoprevir and HCV genotype 1a infection, regardless of whether the patient has had prior treatment. Lastly, the AASLD guidelines recommend requesting RAS in patients previously treated and infected with genotype 1a, in whom it is intended to start ledipasvir/sofosbuvir[52, 53].

Moreover, the retreatment of patients who have failed after a regimen should be guided by knowledge of which drugs were given in previous treatment courses if resistance testing is not available or, if resistance testing is performed, by the response according to the observed resistance profile. Therefore, when available, RAS tests should guide the individualized choice of retreatment regimens, mainly if NS5A inhibitors were previously used[14].

In the case of reinfection, no studies recommend the use or not of molecular resistance tests; however, it is currently believed that they should have the same indications previously listed.

CLINICAL CASE

We present the case of a 37-year-old male patient with HIV infection being managed with lopinavir/ritonavir and abacavir. On physical examination, slight hepatomegaly was noted, with no additional stigmata of chronic liver disease. The liver biochemical profile revealed an alteration and positive anti-HCV, so further tests were requested to establish the diagnosis. HCV infection, genotype 1, and subgenotype 1a were confirmed. In addition, serological markers were detected that demonstrated a previous hepatitis B virus (HBV) infection. Besides, the liver ultrasound did not show signs of chronic liver disease, and the FIB-4 did not suggest advanced fibrosis (**Table 1**).

Table 1. Paraclinical results of the patient

Serum biochemistry	Result
Alkaline phosphatase	113 UI/L (44-147 UI/L)
Total bilirubin	1.67 mg/dL (0.1-1.2 mg/dL)
Direct bilirubin	0.64 mg/dL (< 0.3 mg/dL)
AST	27 U/L (0-35 UI/L)
ALT	56 U/L (0-45 UI/L)
GGT	31 (0-30 UI/L)
HBsAg	Negative
Anti-Hbc	Positive
Anti-Hbs	Positive
FIB-4	0.48
Anti-HCV	Positive
HCV RNA	254,287 UI/mL
HCV genotype	Genotype 1, subgenotype 1a

ALT: alanine aminotransferase; anti-Hbc: hepatitis B virus core antibody; anti-Hbs: hepatitis B virus surface antibody; AST: aspartate aminotransferase; FIB-4: fibrosis index 4; GGT: gamma-glutamyl transferase; HBsAg: hepatitis B surface antigen. Source: The authors.

Management was ordered with the pan-genotypic regimen for hepatitis C (sofosbuvir, an NS5B inhibitor, and velpatasvir, an NS5A inhibitor) for 12 weeks. The viral load at the end of the treatment was undetectable (<12 IU/mL), so SVR was confirmed. Additionally, serum levels in the normal range of liver enzymes (alanine aminotransferase [ALT]: 12 U/L; aspartate aminotransferase [AST]: 18 U/L) were demonstrated.

Three months later, the patient attended the follow-up appointment. According to the follow-up exams, viral load (HCV RNA: 8,354 IU/mL) was detected, for which the patient was questioned about possible risk behaviors.

After a thorough anamnesis, the patient reported unprotected sexual intercourse on five occasions with multiple partners. Therefore, genotyping was ordered, proving HCV genotype 4 infections. With this finding, we confirmed that the patient had HCV reinfection and prescribed a new treatment regimen with sofosbuvir and velpatasvir for 84 days and subsequent confirmation of SVR12.

CONCLUSION

We presented the case of a patient with HIV infection with an alteration in the liver profile and a diagnosis of HCV genotype 1, subgenotype 1a infection. The patient received DAA treatment, after which viral clearance was confirmed at 12 weeks of treatment. Three months later, reinfection was suspected due to elevated viral load and altered liver biochemistry, confirming HCV genotype 4 reinfection.

HCV reinfection is expected, mainly in MSM, HIV-infected individuals, and people with multiple sexual partners. Evidence and studies show the importance of being alert to the possibility of reinfection, so it is appropriate to perform HCV genotyping before starting treatment, even in cases with a pan-genotypic DAA regime. It is imperative to remember and insist on the caution that must be used to reduce risky behaviors. Effective treatment of HCV and consequent viral clearance do not induce a specific adaptive immune response against other HCV genotypes and, therefore, do not eliminate susceptibility to infection by the other seven HCV genotypes. Continuous education and multidisciplinary support are critical for these patients.

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Case report

Passenger lymphocyte syndrome due to anti-D antibodies in liver transplantation. Case report

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Abstract

Passenger lymphocyte syndrome (PLS) is a graft-versus-host complication in solid organ transplantation or hematopoietic stem cell transplantation. It is a major cause of immune hemolysis after transplantation caused by the production of antibodies by the specific clones of viable B lymphocytes transferred through the donor organ against the antigens of the recipient's red blood cells. It usually occurs in transplants with minor ABO or Rh mismatch. This descriptive study explains the case of a 54-year-old patient with O/Rh(D) positive blood group, with cirrhosis secondary to metabolic disease associated with fatty liver (NAFLD), who underwent liver transplantation from an O/Rh(D) negative donor. Nine days after the transplant, the patient presented with immune hemolytic anemia due to anti-D antibodies because of the transient B lymphocyte from the sensitized donor. The patient received support measures, transfusion of red blood cells, and immunosuppression with steroids, which stabilized the hemolytic parameters. In conclusion, this entity should be suspected in the case of acute hemolytic anemia in the post-transplant period.

Keywords

Direct Coombs test, hemolytic anemia, liver transplantation, case report.

INTRODUCTION

Liver transplantation is the therapy of choice in advanced or terminal stages of liver disease, acute liver failure with poor prognostic indicators, or primary liver tumors when the patient meets the criteria according to multidisciplinary pre-transplant analyses. The number of patients on the waiting list for organ transplants is increasing, but the availability of donors is insufficient. This outlook has favored organ selection from donors with minor incompatibilities[(1)], in addition to the development of immunosuppressive therapy and the prognosis of patients.

Liver transplantation is routinely performed with ABO system blood group compatibility (identical ABO). ABO is defined as compatible (e.g., type O donor to type B recipient), identical (same group), or incompatible (different groups, for example, type A donor to type B recipient); in the donor-recipient pairing, the Rh is not taken into account[(2)]. Only in emergent cases is liver transplantation performed with group incompatibility since survival is lower when transplanted with an incompatible ABO group, and there is a greater risk of complications and graft loss due to antibody-mediated rejection. In such cases, a different therapeutic approach is required

at centers experienced in liver transplantation with ABO incompatibility[3].

In any transplanted tissue, viable B-cell clones and plasma cells transfer from the donor into the recipient's circulation. Those "passenger" lymphocytes that survive and proliferate escape immunological surveillance due to the immunosuppression to which the recipient is subjected. In other words, there is no rejection of lymphoid clones, so when exposed to the antigen in the recipient's red blood cells, anti-isohemagglutinin or anti-Rh antibodies are produced, causing immune-mediated hemolysis[4].

The risk of hemolysis increases depending on the lymphocyte mass, and it is more common in heart and lung transplantation, followed by liver and kidney transplantation[5]. When these lymphocytes proliferate, they create an immune response, which can be primary or secondary, with the onset of hemolysis occurring in the first days to weeks after transplantation[6].

Passenger lymphocyte syndrome (PLS) is generally associated with mismatched ABO transplants. In other cases, it may occur in patients who receive an identical ABO organ, but there is a mismatch in minor red blood cell antigens between the donor and recipient. Liver transplantation has frequently reported antibodies against Rh antigens (D, C, c, E, e, and V) and, sometimes, alloantibodies against Jk, Kp, Fy, and M antigens, with which hemolytic reaction may happen[7, 8].

Below is the case of a patient with cirrhosis secondary to metabolic-associated fatty liver disease (MAFLD) with an O/Rh(D) positive blood type who received a liver transplant from an O/Rh(D) negative donor. During the postoperative period, he presented with immune hemolytic anemia due to anti-D antierythrocyte antibodies due to the donor's prior sensitization. It is a little suspected cause of acute autoimmune hemolytic anemia in the weeks following the transplant; therefore, given the increase in the number of procedures worldwide, it should always be considered.

CASE PRESENTATION

We present the case of a 54-year-old man with a history of hypertension, diabetes *mellitus*, and cirrhosis secondary to MAFLD, Child-Pugh B stage, MELD-Na (Model for End-Stage Liver Disease) score of 18 points, with multiple hospitalizations for hepatic encephalopathy and criteria for transplantation. On prior examination, an O/Rh(D) positive blood typing stands out, with negative irregular antibody screening and negative antiglobulin test (direct Coombs). Orthotopic liver transplantation was performed from a male O/Rh(D) negative donor with positive anti-D and anti-C erythrocyte antibodies due to previous sensitization in an unknown context. The ischemia time was five hours; there were no complications during the procedure or red blood cell transfusion requirement in the peri- or postoperative period. During the postoperative period, the patient required vasoactive support for a few hours, early extubation was performed, and elevated aminotransferases with an early cytolysis peak (aspartate aminotransferase [AST]: 588 U/L and alanine aminotransferase [ALT]: 413 U/L) were detected. Early immunosuppressive therapy with methylprednisolone and tacrolimus on day one was indicated. The ultrasound and Doppler follow-ups did not show any alterations. He was discharged on the fifth day after the intervention with tacrolimus at 0.1 mg/kg, prednisolone, and valganciclovir prophylaxis due to positive antibodies for cytomegalovirus in the donor and recipient, in addition to trimethoprim/sulfamethoxazole as prophylaxis against *Pneumocystis jirovecii*.

On the ninth day post-transplant, the patient attended the emergency room because he had jaundice, reddish urine, asthenia, adynamia, and hyporexia. The admission laboratory tests (**Figure 1**) documented severe anemia (7.1 g/dL, reference: 13-18 g/dL), hyperbilirubinemia at the expense of indirect bilirubin (total bilirubin [TB]: 5.01 mg/dL [0.2-1.2 mg/dL], indirect bilirubin [IB]: 3.63 mg/dL), elevated lactic dehydrogenase (531 U/L), consumed haptoglobin (<5 mg/dL), and positive direct antiglobulin test (Coombs) with evidence of anti-D alloantibody and renal compromise with elevated creatinine (Cr) (1.6 mg/dL). Abdominal ultrasound and portal Doppler were normal. Tacrolimus levels were in the normal range. A clinical manifestation related to passenger lymphocyte syndrome was considered, thus indicating management with intravenous fluids and transfusion of two O-negative RBC units associated with pulses of methylprednisolone 500 mg daily for three days. Hemoglobin (Hb) stabilization, hemolysis parameter control, and renal function improvement were achieved, and immunosuppressive management with prednisone at 1 mg/kg/day associated with tacrolimus was continued.

Outpatient follow-up has been carried out in the transplant unit without recurrence of the hemolytic process. The dose of steroids was gradually reduced, and tacrolimus levels have been maintained at targets with hepatocellular structure and function laboratory tests in the normal range: AST: 17 U/L, ALT: 12 U/L, gamma-glutamyl transferase (GGT): 13 U/L, BT: 0.50 mg/dL, IB: 0.32 mg/dL, direct bilirubin (DB): 0.18 mg/dL, alkaline phosphatase: 74 U/L, albumin: 3.39 g/dL, Hb: 15.2 g/dL, and tacrolimus: 6.8 ng/mL.

DISCUSSION

In the first 15 days after liver transplantation, anemia has different etiologies, such as bleeding, sepsis, medications,

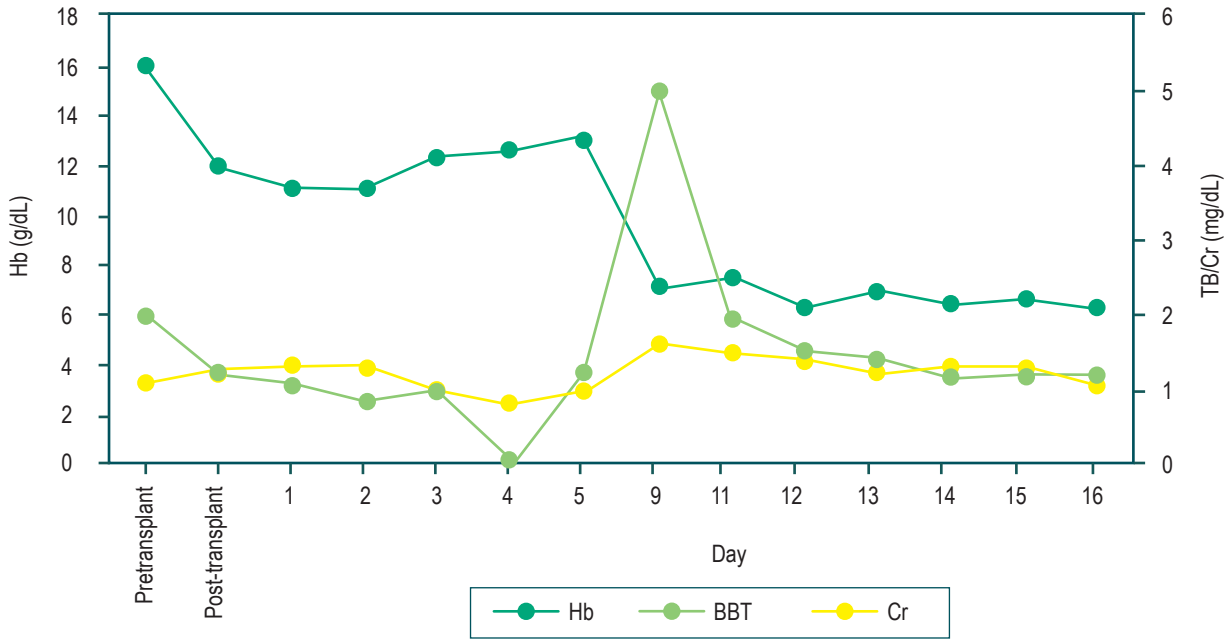

Figure 1. Report of Hb, BBT, and Cr levels. Source: The authors.

rejection, or hemolysis. The latter is a significant cause of anemia in this period and may derive from drugs, transfusions, hypersplenism, graft-versus-host disease, or incompatibility of the antigenic systems between donor and recipient[9]. In turn, the findings of jaundice and anemia make it necessary to rule out arterial or venous thrombosis, vascular stenosis, biliary complications, or sepsis[10].

Passenger lymphocyte syndrome (PLS) is a type of anemia that occurs after transplantation[11]. It is considered a subtype of graft-versus-host disease that affects patients in the first month, generally three to 24 days after solid organ or hematopoietic stem cell transplantation[6]. In the case described, the compromise occurred on the ninth day.

The incidence of PLS in solid organs depends on their lymphocyte mass, which is why it is more common in lung and heart transplants (70%), followed by liver and kidney transplants (40% and 17%, respectively)[5]. Moreover, 50% of patients develop antibodies in cases of incompatibility, but not all show evidence of hemolysis. In Ramsey's series in 1991, 12 cases of PLS occurred out of 1,200 liver transplants, for a prevalence of 1%[12]. In 2015, in a series of 1,217 liver transplants, Romero et al. reported 56 cases of ABO group incompatibility, of which 17.9% developed PLS, and of 147 patients with Rh incompatibility, 1.4% had PLS[8].

The viable B cells transferred in the donor graft proliferate and cause the entity due to the production of antibodies against specific antigens of the recipient's red blood cells, which produces a primary or secondary immune response[7]. This entity is a consequence of minor ABO or Rh system incompatibility and rarely of other minor antigenic systems of red blood cells (D, C, E, Jk, Kell, Fy, and M)[13]. Serum antibodies are predominantly of the immunoglobulin G (IgG) type, but in some cases, they are of the immunoglobulin M (IgM) type[13]. These tend to disappear within 3-6 months, except for anti-D, which can persist for up to a year[14].

Risk factors for PLS include previous sensitization by transfusion or pregnancy, group O donor versus a group A or B recipient, or treatment with cyclosporine[15]. In the case described, the recipient was O/Rh(D) positive, but the donor was O/Rh(D) negative, indicating that the latter was sensitized in an unknown context because of documentation of anti-D and anti-C in his serum and the detection of the anti-D alloantibody in the previously absent red blood cells of the recipient. Therefore, the cause of the hemolysis is attributed to the anti-D antibody.

Generally, the manifestation is mild and self-limited with spontaneous remission, although it can sometimes be severe[16]. In other cases, it may be subclinical and an incidental finding in follow-up laboratory tests or superimposed on perioperative complications. The severity will depend on three factors: the amount of transplanted lymphoid tissue, the isohemagglutinin titer of the donor's red blood cells, and the kinetics of post-transplant antibody

production[17]. Non-hemolytic variants, serological reactions, and even severe events such as liver rejection, hypotension, disseminated intravascular coagulation, and renal or multiorgan failure have been reported[5]. In the present case, the patient developed hemolytic anemia and acute kidney injury in KDIGO 1 (Kidney Disease: Improving Global Outcomes) stage.

Laboratory findings are consistent with acute hemolytic anemia, decreased haptoglobin, increased lactic dehydrogenase, increased reticulocytes, hyperbilirubinemia at the expense of indirect bilirubin, and peripheral blood smear with spherocytes, polychromasia, agglutination, or nucleation of red blood cells[18]. The direct antiglobulin test becomes positive in the transplanted patient, which is a good indicator in detecting antibodies derived from the donor's lymphocytes[6]. In our case, the hemolysis features described with a strongly positive direct antiglobulin test, previously negative in the pre-transplant assessment, were present.

Currently, there is no specific management but support measures and transfusion of red blood cells. It should be clarified that, for the latter, the recommendation is to transfuse units compatible with the donor or with negative antigens due to the risk of perpetuating hemolysis[6]. In the presence of bidirectional ABO group incompatibility, group O RBC units compatible with the donor and recipient should be transfused. Negative units should be used in the case of antibodies against minor antigens. For this reason, the patient received irradiated and leukoreduced O-negative RBC units.

Immunosuppressive or immunomodulatory therapy may also be required to induce remission in antibody production when hemolysis is severe or persistent. Administering glucocorticoids, whose dose is suggested to be increased to 1 mg/kg/day, with intravenous steroid pulses (250 to 500 mg of methylprednisolone) is the most widely used treatment and usually sufficient to resolve the clinical picture. The use of rituximab, intravenous immunoglobulin, or plasmapheresis has also been described in some cases[19]. Most therapeutic supports are based on observational studies or case reports. Clinical studies are required to define a practical approach, as well as the type and duration of treatment. In the case presented, there was a favorable clinical evolution and response with fluid intake, red blood cell transfusion, and methylprednisolone pulses. In case of recurrence, one can opt for the depletion of B cells and plasma cells using rituximab or plasmapheresis based on the pathogenic principle to remove immune complexes, complement components, and antibodies from the circulation[6].

PLS antibodies can persist at detectable levels from 12 days to 851 days post-transplant, so outpatient monitoring of hemolytic variables is essential[20]. The patient is being followed up in the transplant unit through a complete blood count, liver tests, hemolysis, and normal tacrolimus levels, with no evidence of alterations one year after the transplant, an unaltered liver profile, stable Hb, and immunosuppression levels according to the targets.

CONCLUSION

The diagnosis of passenger lymphocyte syndrome is challenging. It should be suspected in the presence of acute anemia in the first days and weeks of a liver transplant, especially if there is either group or Rh incompatibility or if there was positive antibody screening in the donor. Clinical and laboratory findings suggesting hemolysis, a positive direct antiglobulin test, serologic evidence of antibodies to red cell antigens, and the absence of another etiology of hemolysis favor the diagnosis. Management is defined according to the clinical manifestation. Most cases are resolved with support measures, blood transfusion, and, in some specific circumstances, steroids or other therapies. The patient's follow-up in the post-transplant period must be conducted with hemolytic parameters.

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Case report

Black esophagus associated with shock. About a case

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Abstract

Acute esophageal necrosis, also known as the *black esophagus*, is a rare pathology diagnosed by endoscopy that shows a black-looking esophageal mucosa. Its cause is unknown, but a multifactorial origin is attributed to it. An esophageal lesion of ischemic origin should be considered. We present the case of a 56-year-old patient with respiratory symptoms suggestive of a severe infectious process, with a rapidly progressive clinical picture and requirement of airway security, multimodal vasopressor, and organic support, and an endoscopic study due to clinical symptoms of upper digestive tract bleeding with evidence of lesions compatible with acute esophageal necrosis. Despite multimodal management in the intensive care unit, the patient died 34 days after hospital admission.

Keywords

Black esophagus, acute esophageal necrosis, ischemia, endoscopy.

INTRODUCTION

Acute esophageal necrosis, more commonly known as the *black esophagus*, is a rare entity with little clarity in its pathophysiology, reported since 1990, whose diagnosis is made endoscopically. The estimated prevalence of this pathology based on the medical literature is 0%-10.3%, and with the advent of endoscopy, 0.01%-0.28% based on retrospective[1-5] and prospective[6] studies. Given the rarity of this clinical entity and the lack of understanding of its pathophysiology, we describe the clinical case of a male patient with an endoscopic diagnosis of acute necrotizing esophagitis, treated at a tertiary care university hospital in Popayán, showing its evolution and outcome.

CASE PRESENTATION

We present the case of a 56-year-old male patient with a history of hypertension, asthma, chronic obstructive pulmonary disease, ichthyosis vulgaris, and obesity. He is under pharmacological treatment with amlodipine, carvedilol, indacaterol/glycopyrronium, and montelukast. He has been hospitalized multiple times for exacerbation of underlying lung disease.

He attended the emergency department for a two-week clinical picture consisting of progressive dyspnea associated with cough and purulent expectoration, fever, and chills. On admission, severe bronchospasm and hypotension refractory to fluid therapy were detected.

An admission chest x-ray reveals alveolar opacities in all four quadrants, multiple emphysematous bullae, "ground glass" appearance, and multiple linear images secondary to fibrous tracts in both lung fields. Laboratory tests revealed leukocytosis, neutrophilia, azotemia, severe respiratory acidemia, hypoxemia and hyperlactatemia, and elevation of acute phase reactants.

The septic shock of pulmonary origin was diagnosed, with criteria of severity and mechanical ventilation requirement. The patient was admitted to the intensive care unit (ICU) for comprehensive management with antibiotic coverage based on carbapenem and glycopeptide, bronchodilator therapy, intravenous steroids, and neuromuscular blockade due to poor coupling to invasive mechanical ventilation.

His clinical evolution was torpid; he required high ventilatory parameters and vasoactive support, increased leukocytosis, elevated nitrogen levels, and oliguria. The patient needed renal replacement therapy with hemodialysis from the fifth day of hospitalization.

On the ninth day of his stay in the ICU, the patient presented with hematemesis and sudden anemia. Upper endoscopy (EGD) showed, from 19 cm to the esophagogastric junction, sloughing of the mucosa with necrosis, adherent clots, diffuse bleeding in the layer and some areas, and deep involvement with exposure of the submucosa (**Figure 1**). He received treatment with a continuous infusion of a proton pump inhibitor, a transfusion of blood products, and antibiotic therapy. Esophageal

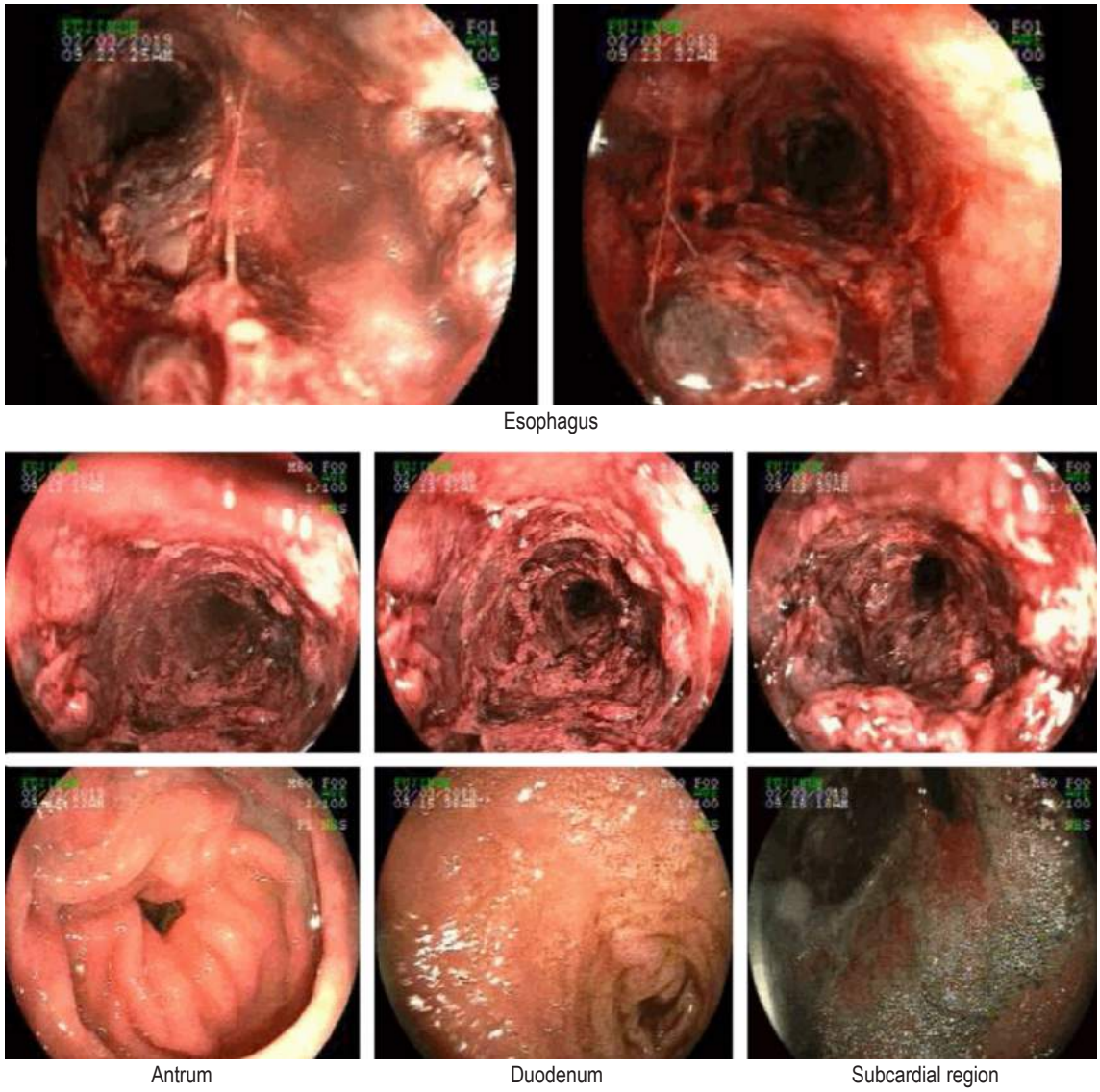

Figure 1. EGD: severe esophagitis, mucosal necrosis, and chronic gastritis of the antrum. Source: Authors' archive.

perforation was ruled out by cervical-thoracic-abdominal computed tomography (CT) scan.

The patient exhibits a persistence of prolonged refractory multifactorial shock. It was necessary to perform a tracheostomy and a percutaneous endoscopic gastrostomy.

On day 17 of hospitalization, a new follow-up EGD (**Figure 2**) showed erosions in the lower third of the esophagus with mottled erythema and erosions of the antrum and body.

The patient died on day 34 of hospitalization from worsening of his condition due to an infectious pulmonary event.

DISCUSSION

Acute esophageal necrosis or acute necrotizing esophagitis (AEN), also known as *black esophagus syndrome*, is a rare pathology that presents with an endoscopically defined alteration in the mucosa of variable severity.

The incidence is four times higher in men than women, and comorbidities are presented as an associated factor in all the cases reported in the literature, including diabetes *mellitus*, high blood pressure, alcohol abuse, chronic kidney disease, coronary disease, dyslipidemia, among others[7].

The pathophysiology of AEN generally involves a combination of multiple mechanisms. The "two hits"[8] hypothesis is considered the most widely accepted: the first is a state of hypoperfusion that damages the esophageal mucosa, leading to esophageal ischemia, generally seen in states of hemodynamic compromise and low flow. Subsequently, a second attack is caused by massive gastric acid reflux and impaired mucosal repair mechanisms present in weakened physical conditions[9].

There are multiple cases of AEN secondary to septic shock, where generalized vasodilation mediated by cytokines results in hemodynamic compromise and decreased perfusion pressure. Despite aggressive treatment with fluid therapy, vasoconstrictors, proton pump inhibitors, and empiric broad-spectrum antibiotic therapy, the outcome for these patients is commonly sepsis with multiple organ failure and death[10, 11].

The treatment of this entity is not standardized and is aimed at comorbidities and specific pathologies of the patient. Medical management is based on medication with a proton pump inhibitor or histamine receptor blockers until the clinical condition improves. Antibiotics are recommended in cases of suspected esophageal perforation, clinical deterioration, transplant recipients, cirrhotic patients, and patients on dialysis, reserving surgical intervention for patients with classic indications for it, such as esophageal perforation with subsequent risk of mediastinitis and abscess formation. Once the acute condition has been controlled, the requirement for dilations or stent placement should be defined in cases of poor response[12].

CONCLUSIONS

AEN is a pathology of rare incidence with a mortality rate of up to 50% whose endoscopic diagnosis is relatively simple due to its characteristic findings. Although such mortality is likely associated with shock or pan-esophageal disease, which conditions early suspicion of this pathology, intensive treatment and management of AEN possibly improve its mortality rate.

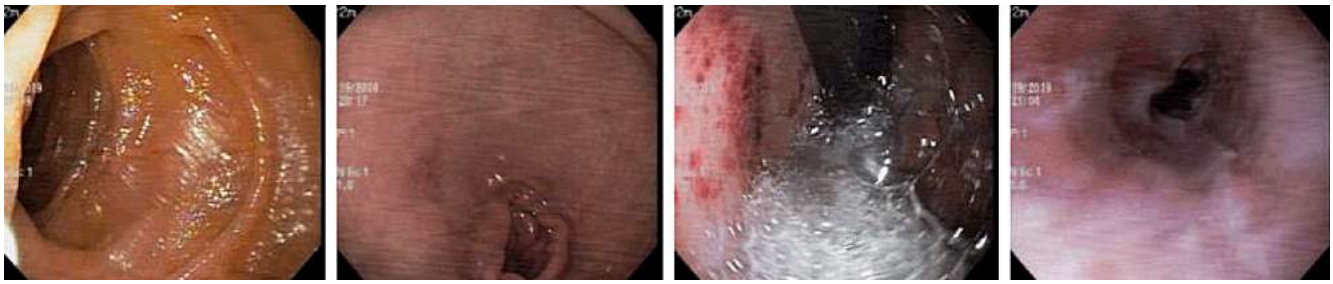

Figure 2. EGD: grade B esophagitis, erosive antral-body gastritis. Source: Authors' archive.

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Case report

Orthoptic liver transplantation in a patient with a positive SARS-CoV-2 test and its postoperative complications. Case report

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Abstract

Objective: To describe a case of liver transplantation in a patient with a positive result in the severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) test with success in the early post-transplantation, but who developed complications associated with immunosuppression and portal vein thrombosis without thrombophilia identified at a tertiary referral center in a Latin American country. **Case:** A 48-year-old patient diagnosed with liver cirrhosis secondary to non-alcoholic steatohepatitis (NASH) complicated by several episodes of portal hypertension ascites and hepatic encephalopathy was admitted for orthoptic liver transplantation. On initial examinations, he had a positive test for SARS-CoV-2 and was asymptomatic in the respiratory tract. The transplant was carried out successfully after the authorization of the infection committee. After the first postoperative month, he presented with diarrhea, ascites, and acute kidney injury. Tacrolimus levels at readmission were more significant than 10 ng/mL, and there was a significant clinical improvement with drug discontinuation. Finally, the patient required re-transplantation due to thrombosis of the portal vein and suprahepatic veins, although the etiology was not identified. **Conclusion:** One of the first reports of liver transplantation in a patient with recent recovery from COVID-19 and persistently positive tests is described. In the early post-transplant, there was a good response; however, after the first month, he had complications related to immunosuppression. This case also posits the possible association between SARS-CoV-2 and the development of thrombosis in the hepatic portal circulation.

Keywords

SARS-CoV-2, COVID-19, liver transplantation, hepatology, tacrolimus, portal vein, thrombosis.

INTRODUCTION

On December 31, 2019, hospitals in Wuhan, Hubei, China, reported a cluster of pneumonia cases of unknown cause at the time. On January 7, 2020, researchers isolated a new coronavirus from patients with pneumonia and named it SARS-CoV-2. On January 30, the World Health Organization (WHO) declared COVID-19 (as coronavirus disease 2019 has been known since February 11) a public health emergency of international concern that would later be recognized as a pandemic[1,2]. Over time, a broad association with extraintestinal manifestations has also been found[3]. Among them, there is a significant increase in the incidence of thrombotic events; notably, portal vein thrombosis (PVT) has been reported in patients with no other potential causes of thrombophilia other than a current or recent SARS-CoV-2 infection, as in the case we present[4].

There are various immunosuppression schemes after orthoptic liver transplantation[5]. One of the most frequently used is induction with corticosteroids and maintenance with tacrolimus. Nevertheless, it is necessary to know that this calcineurin inhibitor exhibits, in addition to numerous drug interactions, several adverse effects, including diarrhea, persistent ascites, and acute kidney injury. Therefore, in the liver transplant postoperative period, its serum level should be assessed to consider its adverse effects as a differential diagnosis of these complications[6-8].

CASE PRESENTATION

We present the case of a 48-year-old male patient with decompensated liver cirrhosis (Child-Pugh class B and Model for End-stage Liver Disease [MELD] 15) diagnosed one year ago, secondary to non-alcoholic steatohepatitis (NASH). During this period, he had multiple episodes of encephalopathy, ascites, and hypertensive portal bleeding, requiring hospitalization and ligation of esophageal varices. He was admitted to the Imbanaco Clinic for an orthoptic liver transplant because he had a compatible cadaveric donor. He was scheduled for the procedure 40 days before; however, it was not performed at the time as he had a positive polymerase chain reaction (PCR) test for SARS-CoV-2. Within the initial tests, the PCR for SARS-CoV-2 was again positive. The infections committee authorized the transplant considering that the positive sample corresponded to residual RNA in the absence of active infectious viral particles.

The liver transplant was performed with cold ischemia for five hours and 45 minutes and hot ischemia for 40 minutes, with vasopressor support, intraoperative bleeding of 1.7 liters, and transfusion of two RBC units, six cryoprecipitates, and a platelet pool. He was admitted to the intensive care unit (ICU) with no ventilatory support, vasoactive support with norepinephrine, and adequate urinary output. According to the protocol, immunosuppression was started with methylprednisolone at a dose of 200 mg/day in a tapering scheme as induction, and on the second day, tacrolimus XL at 7 mg/day for maintenance. After a hospital stay with no complications, preserved renal (creatinine 0.63 mg/dL, blood urea nitrogen 5.2 mg/dL) and liver function, hemodynamic stability, no respiratory symptoms or elevation of acute inflammatory reactants, and Doppler ultrasound of the transplanted liver within normal limits, he was discharged on the eighth post-transplant day with a prescription of tacrolimus XL at 9 mg/day, prednisolone 5 mg/day, and valganciclovir 450 mg every 12 hours.

One month after the transplant, the patient was readmitted due to a 10-day history of abdominal distension, increased frequency of liquid stools, no fever, and normal diuresis. On admission, he had abdominal pain and was normotensive, tachycardic, tachypneic, and euthermic. A portal Doppler revealed much ascitic fluid, and the transplanted liver appeared normal. The patient required an evacuatory paracentesis with albumin replacement at 8 g per liter; the administration of diuretics and the supply of intravenous fluids were started. Infectious etiologies were ruled out during the stay, with a viral load for *cytomegalovirus*, PCR for *Clostridium difficile*, and negative blood, urine, and stool cultures. Renal function showed a progressive deterioration with an initial creatinine of 2.33 mg/dL up to 4.04 on the fourth day of hospitalization. Tacrolimus levels were obtained at 10.7 ng/mL, so we temporarily suspended the drug. The following day, stools decreased to three in 24 hours and creatinine to 2.4 mg/dL, reaching normal ranges on the sixth day of hospitalization.

Sixty days after the transplant, the patient presented with diarrhea and ascites. Portal Doppler showed portal and suprahepatic veins thrombosis, confirmed by abdominal CT angiography (**Figure 1**). Anticoagulation was started, and the patient received approval for liver retransplantation. Tests to rule out thrombophilia were negative. Without a cause of the thrombotic event, a history of recent SARS-CoV-2 infection suggests a potential etiology.

DISCUSSION

It has been described that the risk of contagion in patients asymptomatic or with mild symptoms is low from day 7. Wölfel et al. virologically evaluated nine patients with mild COVID-19 and found that the virus replication rate decreases from day five, and there is a 5% probability of continuing beyond day 7[9]. The Centers for Disease Control and Prevention (CDC) recommends discontinuing isolation in patients with mild or moderate COVID-19 ten days after symptom onset, fever resolution for at least 24 hours without fever-reducing medications, and improvement of other symptoms. For asymptomatic patients, it should be ten days after their first positive PCR for SARS-CoV-2[10].

Regarding the indication for transplantation, there are reports of *solid organ* transplantation groups with different indications for surgery, with restrictions based on the decisions of the multidisciplinary team. Rouphael et al. published the case of a successful liver orthoptic transplantation in a patient with acute liver failure secondary to drug poisoning. The procedure was performed despite a positive initial PCR for SARS-CoV-2 after a risk exposure 6-10 weeks prior[11]. Some transplant groups suggest that patients be listed as active if six weeks have passed since they had an initial positive test for COVID-19 with at least

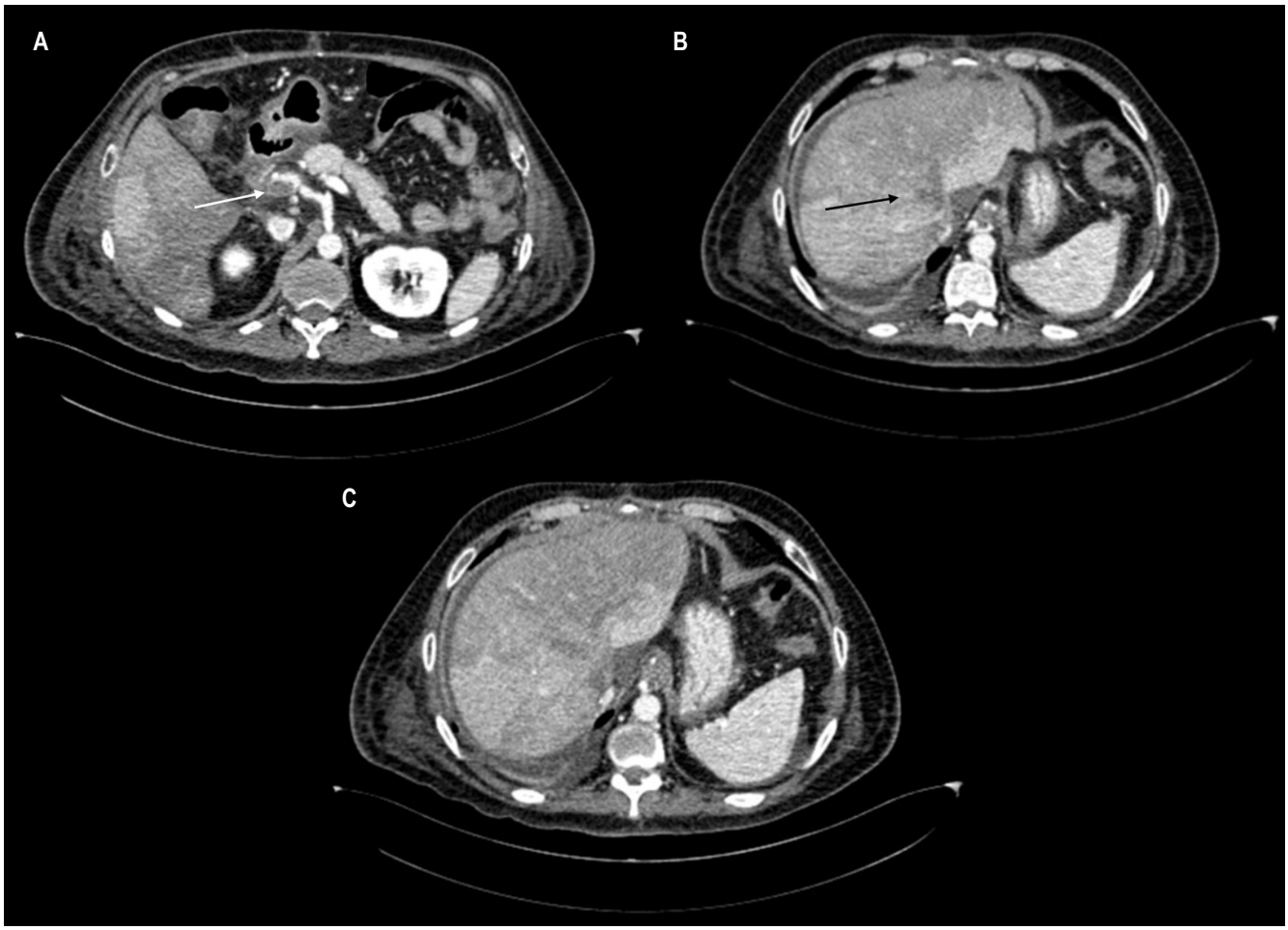

Figure 1. Computerized axial tomography (CT) of the abdomen. **A.** The axial plane reconstruction shows a thrombus with subtotal obstruction in the portal vein (white arrow). **B.** Total occlusion in the suprahepatic veins (black arrow), making up the diagnosis of Budd-Chiari syndrome. **C.** Hepatic areas of heterogeneous enhancement are a characteristic pattern of this syndrome.

four weeks without symptoms and that they not be retested with another PCR before transplantation if they are within three months of the initial positive test[12].

We present the case of a patient with a history of decompensated liver cirrhosis who was admitted for orthoptic liver transplantation; however, at first, it was not carried out because the PCR for SARS-CoV-2 was positive, despite not having respiratory symptoms. Forty days later, the patient continued to have a positive PCR. In this case, the infections committee regarded it as the persistence of non-infectious viral particles and authorized the orthoptic liver transplant.

It is speculated that COVID-19 has multiple pathophysiological mechanisms that trigger involvement in solid organs, including the liver. The vascular damage would be mediated by an altered coagulation process and the deterioration of the blood circulation or the endothelium. In Bergamo, Sonzogni et al. evaluated *postmortem* the histological characteristics of 48 liver samples in 47 patients positive for COVID-19 who died of severe respiratory failure with no history, signs, or symptoms of liver disease until the hospital stay. All presented with some degree of vascular thrombosis: partial portal (24), total portal (11), incomplete sinusoidal (7), and complete sinusoidal (6). In addition, variable degrees of phlebosclerosis, herniation, and portal fibrosis were reported[13].

A high incidence of thrombotic complications has been reported in critically ill patients with COVID-19. Klok et al. studied 184 patients with COVID-19 admitted to the ICU in the Netherlands to look for the composite outcome of ischemic cerebrovascular accident (CVA), myocardial infarction, or systemic arterial embolism. There was a mor-

tality of 22%, thrombotic complications in 75 cases, 65 pulmonary thromboembolisms, one deep vein thrombosis, two cases of upper extremity thrombosis, five patients with ischemic stroke, and two with systemic arterial emboli. Patients on chronic anticoagulation therapy on admission were associated with a lower risk of the composite outcome (hazard ratio [HR] 0.29; 95% confidence interval [CI] 0.091-0.92), whereas patients with thrombotic complications had a higher risk of death from any cause (HR 5.4; 95% CI 2.4-12)[3].

It has been shown how PVT may occur in patients without other possible identifiable causes. Borazjani reported the case of a 23-year-old asthmatic man with coronavirus pneumonia who presented with acute generalized abdominal pain, mild ascites, and PVT. Routine laboratory data regarding secondary causes of PVT were normal. In our patient, partial PVT and thrombosis of the suprahepatic veins were found, ruling out secondary causes of thrombosis. Progressive hepatomegaly occurred, which is why he underwent an orthoptic liver transplant again.

Apart from the history of recent recovery from SARS-CoV-2 infection, our patient had adverse effects caused by immunosuppression, specifically tacrolimus. He had diarrhea and prerenal acute kidney injury associated with hypovolemia one month after transplantation. When tacrolimus was discontinued, diarrhea stopped, and there was a progressive decrease in nitrogen concentrations until reaching normal levels. According to the American Society of Transplantation (AST) Infectious Diseases Community of Practice guidelines, after ruling out infectious etiologies of diarrhea in solid organ transplant recipients, it is necessary to consider reducing the dose of immunosuppressants and assessing the response[8]. In addition to episodes of vomiting or diarrhea, it has also been described that calcineurin inhibitor toxicity by itself may cause acute kidney injury post-transplantation, which is why drug levels should be measured and the dose adjusted according to the desired concentration[6]. Rodríguez et al. revealed that obtaining a trough concentration of tacrolimus between 6 and 10 ng/mL during the first 4-6 weeks after orthoptic liver transplantation reduces renal failure without simultaneously increasing the risk of acute cellular rejection. Then a progressive dose reduction should be achieved to reach a tacrolimus serum level between 4 ng/mL and 8 ng/mL in the long term[14].

CONCLUSION

There are recommendations from transplant groups regarding the isolation and surgical indications of the patient with COVID-19; however, these must be defined through institutional protocols and the infections committee. Once transplanted, multiple complications may occur in the patient who recently recovered from a SARS-CoV-2 infection; extrapulmonary complications with a thrombotic component must be recognized early. Furthermore, knowing the interactions and recognizing early the adverse effects of immunosuppression makes it possible to anticipate dose modifications to attain a safe and effective plateau concentration.

Ethics approval and participation consent

Ethical approval was not obtained for publishing this clinical case since it did not involve sharing the personal data and photographs of the patient in the article.

Publication Consent

Written informed consent was obtained from the patient to publish this case report and accompanying images. A copy of the written consent is available for review by the editor-in-chief of this journal.

Conflict of interests

The authors declare no competing interests.

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Case report

Double-balloon enteroscopy-assisted endoscopic retrograde cholangiopancreatography in a patient with total gastrectomy and roux-en-y reconstruction: A case report

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Abstract

Endoscopic retrograde cholangiopancreatography (ERCP) is a valuable procedure in managing biliopancreatic diseases. Patients with anatomical alteration of the gastrointestinal tract represent a technical challenge for multiple reasons. With techniques such as double-balloon enteroscopy (DBE), it is possible to perform ERCP in these patients. The case was first published in Colombia on a female patient with total gastrectomy with Roux-en-Y reconstruction and choledocholithiasis.

Keywords

Double-balloon enteroscopy, enteroscopy-assisted endoscopic retrograde cholangiopancreatography, total gastrectomy, Roux-en-Y reconstruction, altered gastrointestinal anatomy.

INTRODUCTION

Endoscopic retrograde cholangiopancreatography (ERCP) is a valuable procedure in managing biliopancreatic disease and is successfully performed in 85% to 95% of patients with normal gastrointestinal anatomy. In patients with gastrectomy and Roux-en-Y reconstruction, endoscopic instrumentation of the bile duct has lower success rates than ERCP in patients with preserved anatomy, increasing the need for more invasive and costly interventions[(1)]. ERCP in patients with anatomic abnormalities of the gastrointestinal tract, such as gastrectomy and Roux-en-Y reconstruction, is technically challenging for several reasons: the length of the biliopancreatic limb, the acute angle of the jejunojejunostomy, tortuosity due to adhesions, the difficulty in biliary cannulation, and the design (length) of the endoscopes[(2)].

Double-balloon enteroscopy (DBE) allows for diagnosing and treating various small intestine diseases, including therapeutic interventions in the bile duct in patients with altered gastrointestinal anatomy[3,4].

The first ERCP by DBE was reported in 2005, and since then, this procedure has been performed successfully in other countries[5]. The case we present below is the first of its kind published in Colombia in a patient with choledocholithiasis and altered anatomy due to a history of total gastrectomy with Roux-en-Y reconstruction due to gastric cancer.

CASE REPORT

We present the case of an 84-year-old female patient with a history of total radical gastrectomy and Roux-en-Y reconstruction for moderately differentiated gastric adenocarcinoma in 2012. She reported cramping pain in the right hypochondrium of nine hours of evolution, nausea, jaundice, and choluria. On physical examination, we found a jaundiced patient with normal vital signs, a tender abdomen in the right hypochondrium, and a negative Murphy's sign. The paraclinical tests identified a cholestatic profile (**Table 1**), a hepatobiliary ultrasound with cholelithiasis and normal bile duct, an MRCP with multiple gallstones, signs of acute cholecystitis in the initial phase, and dilatation of the extrahepatic bile duct (11-mm common bile duct) with microcalculi in its distal portion (**Figure 1**). After discussing the case, the general surgery and gastroenterology services decided to perform a laparoscopic cholecystectomy with intraoperative enteroscopy to manage choledocholithiasis.

Table 1. Initial paraclinical test results

Paraclinical test	Result	Reference value
Leukocytes	3000	
Neutrophils	2400	
Lymphocytes	400	
Hemoglobin	11.7 g/dL	
Hematocrit	37.5%	
Platelets	128.000	
Erythrocyte sedimentation rate	42 mm/hour	
Creatinine	1.15 mg/dL	
BUN	28 mg/dL	
Aspartate aminotransferase	282 U/L	0-35
Alanine aminotransferase	129 U/L	0-35
Alkaline phosphatase	159 U/L	30-120
Total bilirubin	4.62 mg/dL	0,3-1,0
Direct bilirubin	2.03 mg/dL	

Source: The authors.

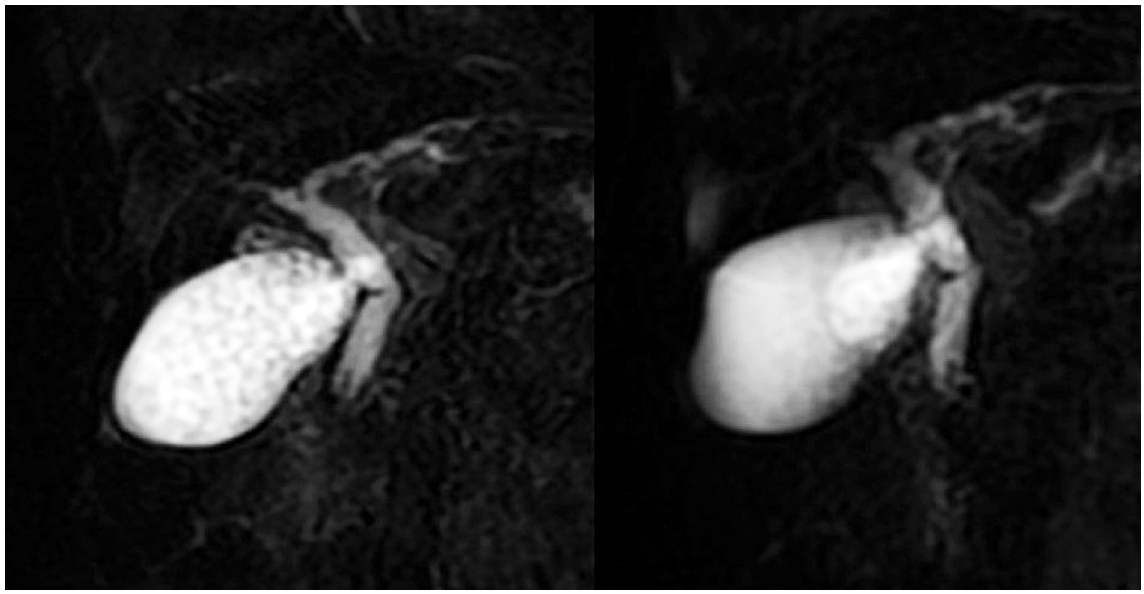

Figure 1. MRCP showing multiple gallstones, extrahepatic bile duct dilation, and choledocholithiasis. Source: Authors' archive.

Technique description

The patient was under general anesthesia, in the supine position. A short Fujifilm EI-580BT DBE was inserted orally (155 cm working length, 9.4 mm distal diameter, and 9.3 mm flexible portion diameter with a 3.2 mm working channel and overtube of 95 centimeters). We observed a normal esophageal-jejunal anastomosis and then advanced through the jejunum toward the jejuno-jejunal anastomosis (located 50 centimeters from the esophageal-jejunal anastomosis) (**Figure 2**).

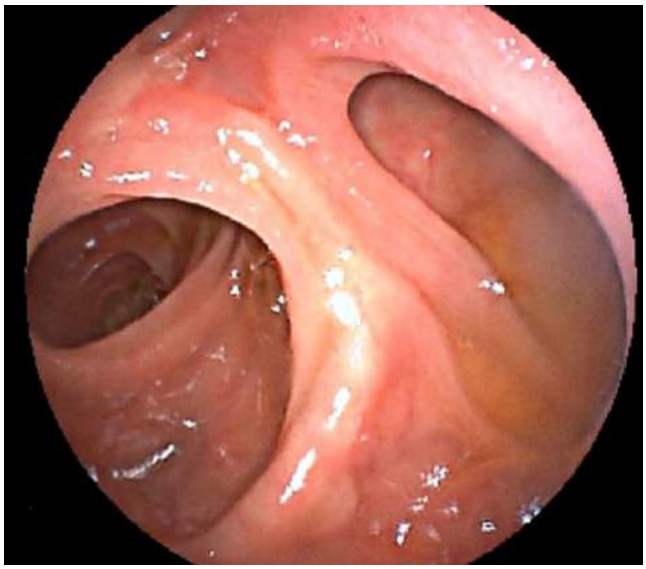

Figure 2. Jejuno-jejunal anastomosis. Source: Authors' archive.

We entered through the biliopancreatic loop (with the help of fluoroscopy) up to the duodenal stump (approximately 150 centimeters in length) (**Figure 3**). A normal-looking duodenal papilla was identified (in the upper quadrant) (**Figure 4**). Cannulation was attempted with a conical tip catheter, an arc papillotome, and a needle papillotome, but we could not advance the guidewire toward the bile duct. So, an inverted papillotome was used, advancing the hydrophilic guidewire toward the bile duct (**Figure 5**).

Cholangiography was conducted; we observed a normal intrahepatic bile duct and a dilated common bile duct measuring 12 millimeters in diameter, with a stone of 5 millimeters in its distal third and multiple gallstones (**Figure 6**). A papillotomy (**Figure 7**) and instrumentation of the bile duct with a 9-12 mm extractor balloon (**Figure 8**) were performed. We removed the calculus and biliary sludge (**Figure 9**) with no immediate complications.

During the extraction of the endoscope, we tattoed the mucosa of the biliopancreatic loop adjacent to the jejunojejunostomy for later identification in case of a new therapeutic procedure in the bile duct (**Figure 10**). The final x-ray showed the evacuation of most of the contrast medium from the bile duct (**Figure 11**). At this time, the surgery department performed the laparoscopic cholecystectomy.

The patient evolved satisfactorily, and the oral route was started the next day. Her liver biochemical profile was normal on the third postoperative day. She was discharged on the fifth postoperative day, ordering an outpatient follow-up in three weeks. Her liver biochemical profile was normal.

DISCUSSION

In patients with altered gastrointestinal anatomy, ERCP has lower success rates than patients with normal anatomy; therefore, achieving access to the bile duct endoscopically is challenging in these cases. In patients with a history of

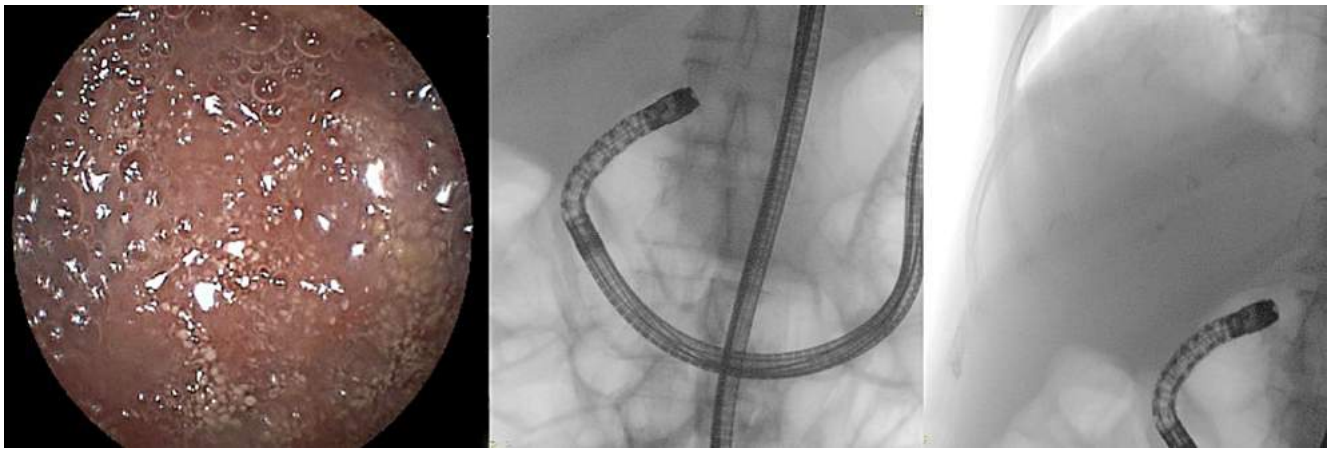

Figure 3. Duodenal stump by endoscopic and fluoroscopic vision. Source: Authors' archive.

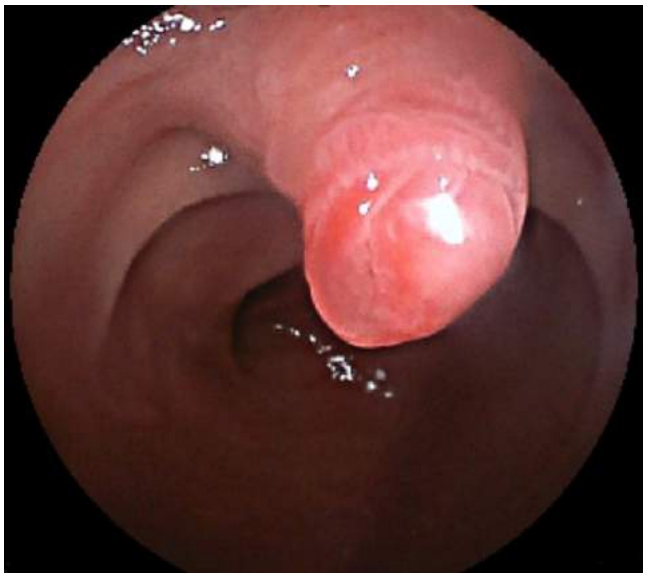

Figure 4. Duodenal papilla. Source: Authors' archive.

gastrectomy with Roux-en-Y reconstruction and biliopancreatic diseases amenable to endoscopic management, ERCP by DBE is a viable option[6].

Studies on this technique have reported that ERCP by DBE was successful in up to 87% of cases. It is deemed a safe intervention with low rates of significant complications, reporting adverse events in 0%-12%[7].

The procedure is less invasive, with less morbidity than the percutaneous route or the surgical approach. Once the duodenal papilla or the biliary-enteric anastomosis is reached, it is possible to perform the rest of the endoscopic interventions usually performed by conventional ERCP, such as sphincterotomy, stone removal, stent insertion, or dilation of the stricture or duodenal ampulla[5].

This laborious procedure requires a highly qualified team and takes longer than a conventional ERCP, with an average duration of 40 to 111 minutes[4]. In our case, the procedure was carried out successfully since biliary cannulation, papillotomy, and removal of the stone and biliary sludge from the common bile duct were achieved in a single intervention with no complications and excellent clinical evolution.

A short endoscope must be used for the ERCP accessories (cannula, papillotome, extraction balloons). Conventional DBEs have a length of 220 centimeters and are not suitable for ERCP accessories. Particularly difficult was the cannulation of the bile duct, which was only possible with an inverted papillotome because the DBE faces the papilla in a manner opposite to that of a conventional ERCP. Another difficulty is the absence of an elevator claw in the endoscope, which limits the mobility and direction of ERCP accessories.

For patients with cholecystocholedocholithiasis, there are several therapeutic options: pre-surgical ERCP[8] and laparoscopic common bile duct exploration (LCBDE, either transcystic or by choledochotomy)[9]. Both techniques have similar efficacy in resolving choledocholithiasis without significant differences in morbidity and mortality[10]. ERCP resolves choledocholithiasis in 88% of

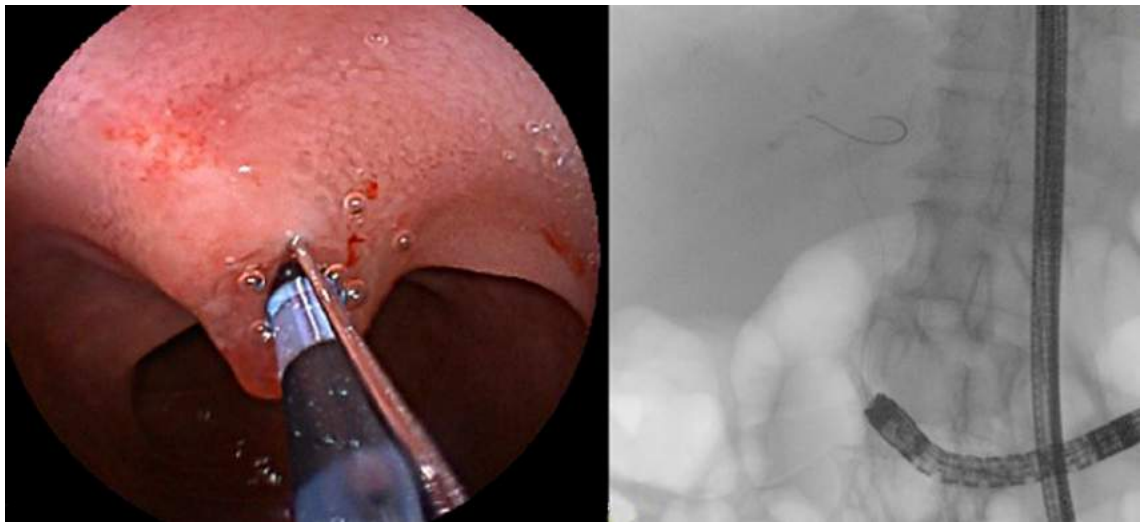

Figure 5. Cannulation with an inverted papillotome and advancement of the guidewire into the bile duct. Source: Authors' archive.

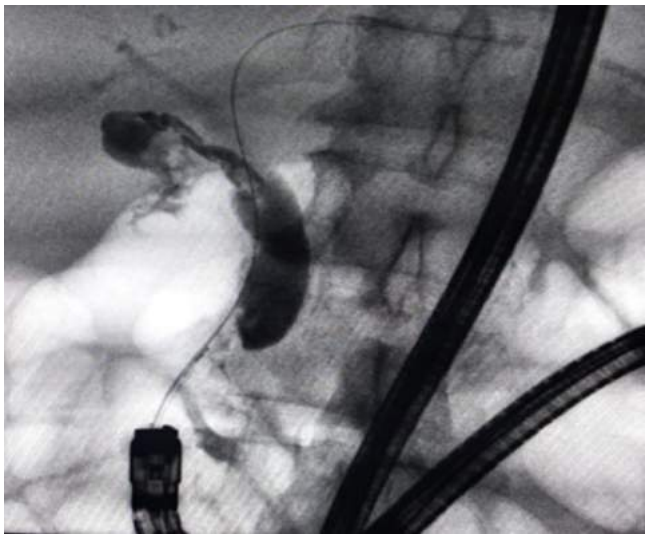

Figure 6. Cholangiography. Source: Authors' archive.

cases[11] and may result in major complications in 6%-15% such as acute pancreatitis (3%-10%), bleeding (0.3%-2%), cholangitis (0.5%-3%), and duodenal perforation (0.08%-0.6%)[12]. The LCBDE success rate is close to 90%, requires a surgeon expert in the technique, and can be associated with complications in 5%-15% of cases: retained stones (0%-5%), bile leak (2 3%-16.7%), pancreatitis (0%-3%), among others, such as basket impaction and bile duct narrowing[9]. Despite the efficacy and safety of LCBDE, one study found that only 7% of patients with choledocholithiasis were treated surgically, and 93% were managed with ERCP[13]. The cause of this discrepancy is multifactorial. The possible explanations are insufficient training in the technique, using instruments not routinely handled by the surgeon (dilating balloons, baskets, choledochoscope), and being a technique rarely performed[9].

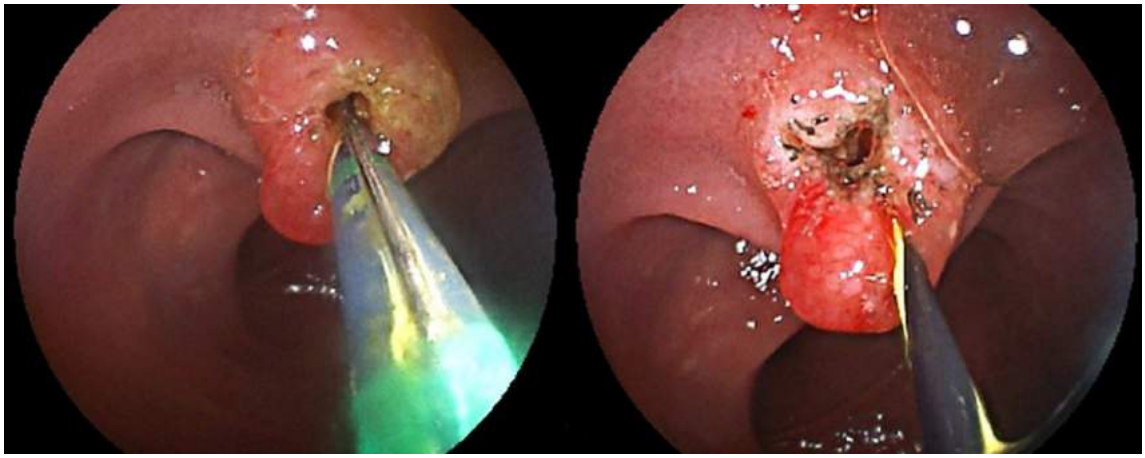

Figure 7. Endoscopic papillotomy. Source: Authors' archive.

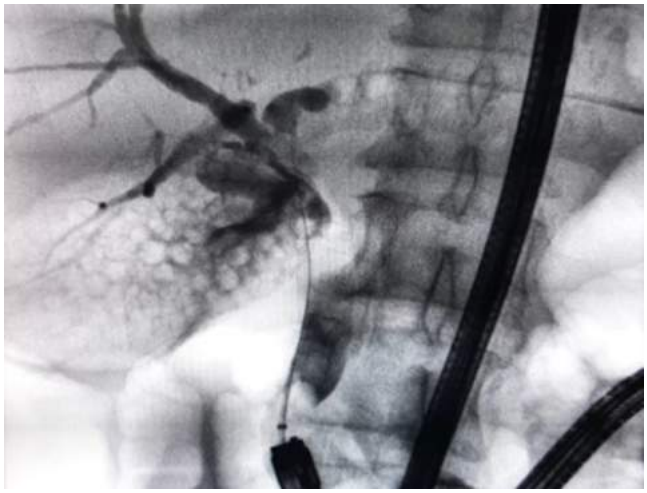

Figure 8. Instrumentation of the bile duct with an extractor balloon. Source: Authors' archive.

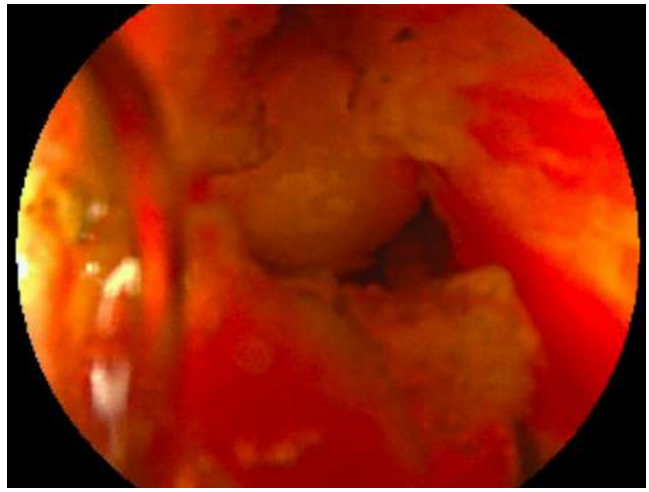

Figure 9. Gallstone. Source: Authors' archive.

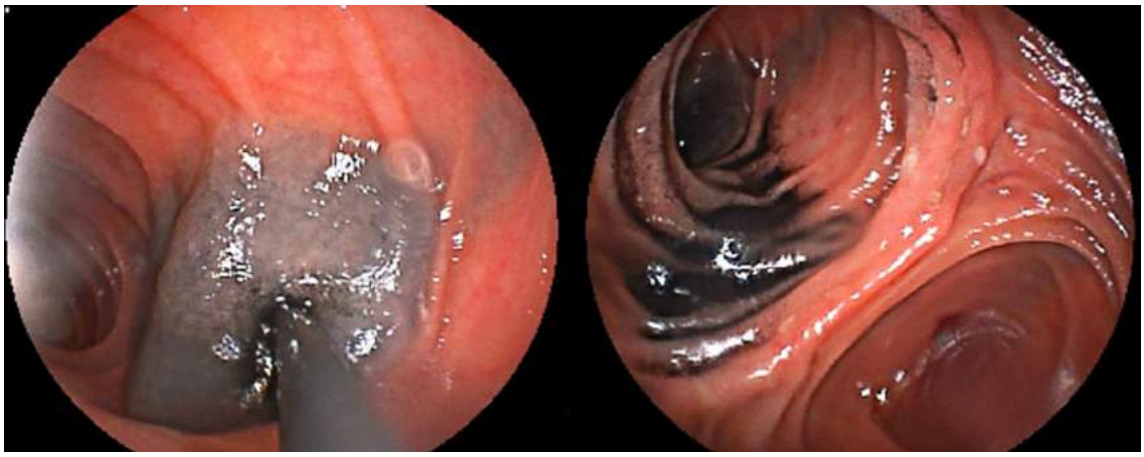

Figure 10. Biliopancreatic limb tattoo. Source: Authors' archive.

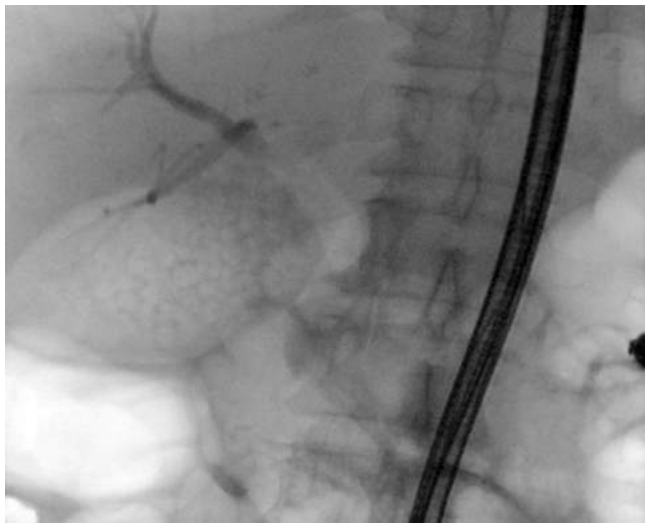

Figure 11. Final post-ERCP x-ray. Source: Authors' archive.

CONCLUSIONS

Managing choledocholithiasis in patients with altered gastrointestinal anatomy is a therapeutic challenge. DBE-assisted ERCP is an effective and safe method for patients with biliary pathology and a history of gastrectomy with Roux-en-Y reconstruction.

Conflict of interests

All the authors of this manuscript declare no conflicts of interest.

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Case report

Solid pseudopapillary neoplasm of the pancreas: A series of five cases and a literature review

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Abstract

Introduction: Solid pseudopapillary neoplasms of the pancreas represent around 3% of resected cystic pancreatic tumors. They occur more frequently in young women between the second and third decades of life. It is a tumor with little malignant potential located mainly in the tail; however, it can be found in any pancreatic anatomical location. **Materials and methods:** We reported five cases of four women and one man, between 16 and 36 years of age, who consulted mainly for abdominal pain. **Results:** Four patients underwent distal pancreatectomy without laparoscopic splenectomy, and one underwent laparotomy pancreatoduodenectomy. The tumor was completely and satisfactorily removed from all five patients. No metastasis was found. The tumors were located on the head (1), neck (1), and predominantly on the body and tail (3). The postoperative histopathological report confirmed the diagnosis in all five cases; in the youngest patient, a percutaneous biopsy had been performed before surgical intervention. **Conclusions:** Complete surgical resection of the tumor with preservation of the spleen is the treatment of choice in patients with solid pseudopapillary neoplasm of the pancreas.

Keywords

Pancreas, solid, pseudopapillary, neoplasia, tumor.

INTRODUCTION

Solid pseudopapillary tumor of the pancreas is also called *Frantz's tumor, solid and papillary tumor, solid-cystic tumor, papillary cystic tumor,* or *solid and papillary epithelial neoplasm*[1]. Lichtenstein was the first to report this entity in 1934[2], but Virginia Kneeland Frantz described its pathology in 1959[3], and Hamoudi et al. explained its electron microscopy characteristics in 1970[4]. The World Health Organization (WHO) classified it as a solid pseudopapillary neoplasm (SPPN) in 1996[5]. The prevalence has soared in recent years because of increased incidental detection of cystic pancreatic lesions on imaging such as computed tomography (CT) and magnetic resonance imaging (MRI) of the abdomen to study other causes[6]. The number of cases reported in the literature has increased seven times in the last two decades[6].

The present study reports five cases of SPPN and reviews its clinical, radiological, histological, treatment, and prognosis aspects.

MATERIALS AND METHODS

A series of five cases is reported, four women and one man between 16 and 36 years old, with a diagnosis of SPPN. The patients were diagnosed and treated between May 2017 and April 2020 at a tertiary care hospital in Bogotá, Colombia. The majority presented with similar symptoms, consisting of abdominal pain and distension. Two of the five patients had nausea, emesis, and fever; one had low back pain, and another exhibited weight loss. The tumor size and location were variable at the level of the head (1), neck (1), and body and tail (3) of the pancreas, with a distal predominance. Four spleen-preserving laparoscopic distal pancreatectomies and one open pancreatoduodenectomy were performed. For the literature review, we searched PubMed and Google Scholar; articles in Spanish and English were included, and no article was excluded due to the publication date.

CASE PRESENTATION

Case 1

A 27-year-old woman attended the emergency department due to diffuse and intermittent abdominal pain of two months associated with abdominal distension. An ultrasound and CT scan of the abdomen with a contrast medium revealed a cystic mass in the neck of the pancreas (3.6 cm x 3.6 cm x 3.5 cm) with high suspicion of a solid pseudopapillary tumor of the pancreas. Tumor markers CA 19-9 and carcinoembryonic antigen were negative. A biliopancreatic endoscopic ultrasound (EUS) was requested, which reported a lesion in the body of the pancreas distal to the splenoportal confluence, with elastography suggestive of a malignant lesion with a strain ratio of 180 (normal < 25).

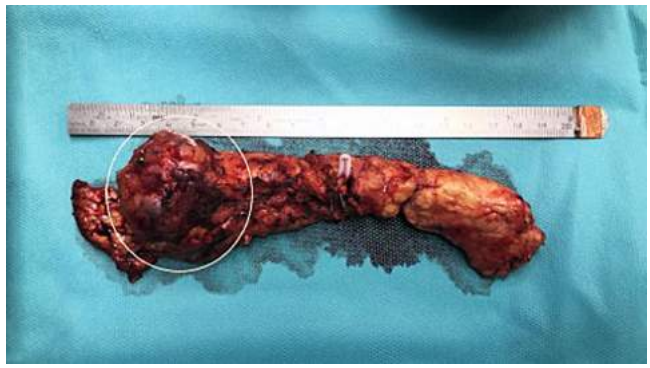

Figure 1. Tumor in the neck of the pancreas. Source: Authors' archive.

Distal pancreatectomy was conducted by spleen-preserving laparoscopy, finding an approximately 5 cm tumor in the neck of the pancreas (**Figure 1**) that did not compromise the vascular structures and lymphadenopathy on the hepatic artery, which was resected. The histopathological report confirmed the diagnosis of solid pseudopapillary neoplasm (**Figure 2**) with negative lymphadenopathy for the tumor. There were no postoperative complications.

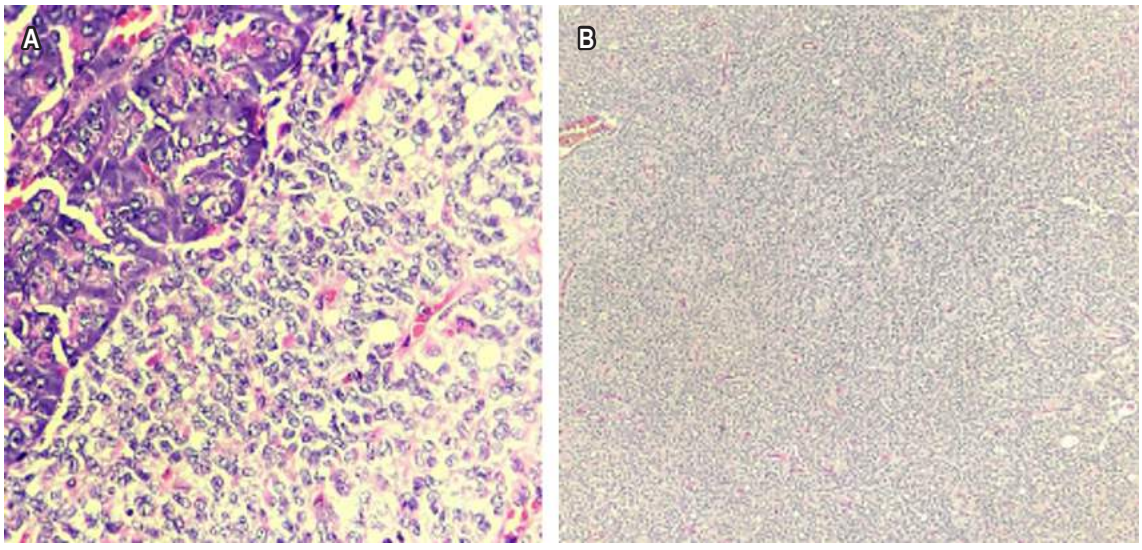

Figure 2. A. Tumor cells show an eosinophilic cytoplasm, some with perinuclear intracytoplasmic vacuoles and hyaline globules. **B.** Tumor lesions comprise solid nests of cells that aggregate around blood vessels and create a pseudopapillary architecture. Source: Authors' archive.

Four months after the intervention, the patient's condition was adequate, with modulation of abdominal pain. A follow-up CT scan of the abdomen with a contrast medium was performed with post-surgical findings of distal pancreatectomy and old splenic infarction.

Case 2

A 23-year-old female patient consulted the emergency department due to abdominal pain of a month's evolution associated with febrile episodes of 38 ºC, multiple emetic episodes, weight loss, and dysmenorrhea, with extra-institutional studies that ruled out an infectious focus. The CT scan of the abdomen with a contrast medium was consistent with a neoplastic mass in the body of the pancreas and compression of the gastric chamber. On admission, she had a hemoglobin of 9.4 g/dL and a platelet count of 608,000. An MRI of the abdomen (**Figure 3**) was requested with a protocol for the pancreas. It reported a mass in the tail measuring 10 cm x 8 cm with an anterior cystic component and a solid posterolateral component, a compressive effect on the viscera, and a poor view of the splenic vein, which suggested thrombosis. The splenoportal Doppler report did not document vascular alterations.

She was scheduled for distal pancreatectomy with laparoscopic splenectomy. During surgery, a 15-cm hypervascularized mass was resected. It adhered to the transverse mesocolon with fibrosis of the posterior face of the stomach in contact with the splenic artery and vein, which were dissected and preserved. There were adenopathies in the celiac trunk, which were resected and sent for frozen biopsy and did not report malignancy. A splenectomy was not conducted, and four units of packed red blood cells were transfused. In the postoperative period, she presented with anemia compared to the admission values (7.6 g/dL) and hypotension, for which she required additional transfusion support.

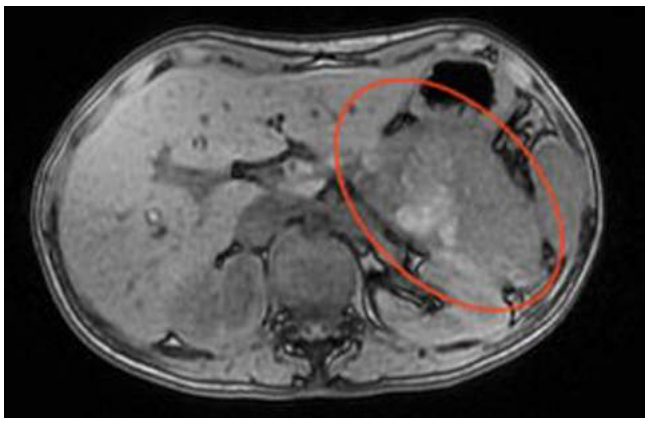

Figure 3. MRI of the abdomen with a contrast medium. Source: Authors' archive.

The patient was discharged and readmitted eight days later due to blood content greater than 300 mL in the drainage. A CT scan of the abdomen was performed with expected post-surgical changes, and a small amount of free fluid on the surgical bed was considered normal. The diagnosis of solid pseudopapillary neoplasm was confirmed with the histopathological report. At 16 months after the intervention, the patient was asymptomatic; a follow-up CT scan of the abdomen did not show a tumor relapse.

Case 3

A 36-year-old woman with a history of arterial hypertension was scheduled for distal pancreatectomy and laparoscopic cholecystectomy due to a solid pseudopapillary tumor of the tail of the pancreas and symptomatic cholelithiasis. During surgery, an 8 cm lesion was found near the body and tail of the pancreas with cystic content dependent on the main duct. It was resected with spleen preservation without complications. She had complex postoperative management due to pain, emetic episodes, and infection of the surgical site, for which analgesic, antiemetic, and antibiotic treatment was provided. The histopathological diagnosis (**Figure 4**) confirmed a solid pseudopapillary neoplasm. Two months after surgery, the patient developed a pancreatic fistula, which required percutaneous drainage with adequate resolution. At the last follow-up, 20 months after surgery, she was found to be asymptomatic.

Case 4

A 16-year-old female patient attended the emergency department for a week-long clinical picture of abdominal pain in the epigastrium, diarrheal stools, and unquantified fever associated with global headache. She had a history of autoimmune thrombocytopenic purpura at age 2. A total abdominal ultrasound revealed a retroperitoneal mass. Subsequently, a CT scan of the abdomen with a contrast medium was performed (**Figure 5**), which reported a neoplastic-looking focal lesion in the head of the pancreas; a mucinous cystadenoma or neuroendocrine tumor (NET) was considered as a differential diagnosis. Finally, a contrast-enhanced MRI of the abdomen showed a complex-looking mass attached to the head of the pancreas with no signs of invasion into adjacent structures, whose differential diagnoses were complex cystic neoplasm or NET.

We performed an ultrasound-guided percutaneous biopsy, reporting a solid pseudopapillary neoplasm, and a laparotomy pancreaticoduodenectomy with findings of a 9.5 cm x 7 cm solid tumor dependent on the head of the

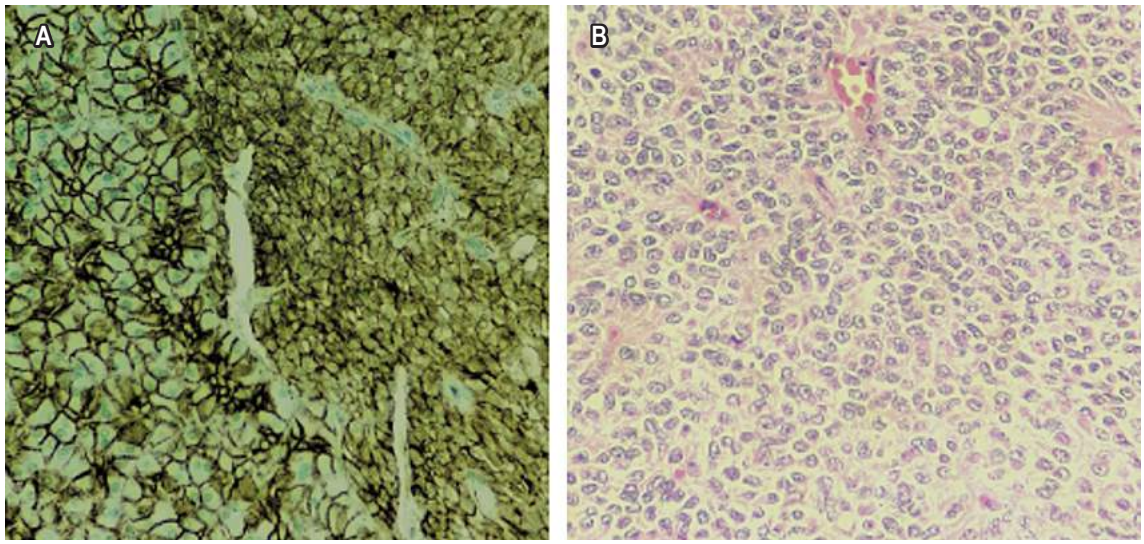

Figure 4. A. Immunohistochemical study for β-catenin shows abnormal nuclear expression in neoplastic cells (right) compared to regular membrane expression in adjacent pancreatic tissue (left). **B.** Tumor cells display nuclei with finely granular chromatin and irregular nuclear surfaces, some with characteristic longitudinal slits. Source: Authors' archive.

pancreas, distortion of the duodenal anatomy, feeding vessels of the gastroduodenal artery towards the tumor, bile duct of standard caliber, and enlarged periportal lymph nodes. The postoperative period elapsed in the intensive care unit (ICU) with an excellent clinical evolution. She was discharged without complications. Six months after surgery, she presented mild acute pancreatitis that resolved without complications. At the last follow-up, 17 months after surgery, she was found to be asymptomatic.

Case 5

A 21-year-old male patient consulted for a clinical picture of three months of evolution consisting of low back pain with no other associated symptoms. There were no relevant findings on physical examination. With the diagnostic impression of urolithiasis, a CT urogram was performed, revealing a 28 mm x 29 mm bilobed nodular image in the tail of the pancreas with calcifications inside, suggestive of a mucinous-type neuroendocrine (exocrine) tumor. Subsequently, an MRI of the abdomen was conducted with a protocol for the pancreas, noting a solid cystic lesion suggestive of a pseudopapillary tumor. The patient was scheduled for a spleen-preserving laparoscopic distal pancreatectomy. During tumor resection, a solid lesion was found in the tail of the pancreas, approximately 5 cm in diameter, homogeneous, hypervascularized, with irregular edges, which involved the splenic vein and artery, and no evidence of metastatic lesions.

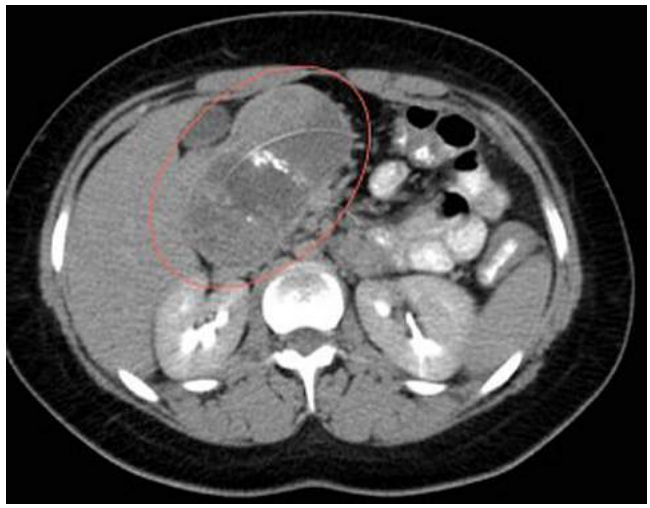

Figure 5. CT of the abdomen with a contrast medium. Source: Authors' archive.

The distal pancreas was dissected with the splenic artery and vein after identifying the superior mesenteric vein. We noted the described tumor, performed the ligation of the splenic vein and artery with distal and proximal Hem-O-Lock®, resected the infiltration of the tumor, and preserved the short gastric vessels and the left gastroepiploic artery. Subsequently, the distal pancreas was resected. The spleen was checked with adequate perfusion without signs of ischemia, infarction, or complications. Pathology diagnosed a solid pseudopapillary neoplasm.

He was readmitted 14 days later due to a six-hour history of epigastric pain radiating to the back, associated with emesis, and no fever. There were no signs of an acute abdomen. On admission, paraclinical tests were requested, showing leukocytosis with neutrophilia, direct hyperbilirubinemia without metabolic acidosis, electrolyte balance, preserved renal function, and unaltered amylase. An intra-abdominal collection was suspected, so broad-spectrum antibiotic and analgesic management was started. A contrast-enhanced CT scan of the abdomen reported a collection of approximately 62 mm x 138 mm x 50 mm in the surgical bed, with images suggesting multiple splenic infarcts and no other alterations. Interventional radiology drained 140 mL of residual hematic fluid with a report of positive amylase. He presented with a pancreatic fistula.

The patient had a good evolution with antibiotic management and drainage of the collection without requiring splenectomy. One month later, a follow-up CT scan of the abdomen was performed with a report of splenic infarcts without changes, distal pancreatectomy, and a residual collection of 33 mL, for which the catheter was withdrawn. Five months after the intervention, the patient's condition was adequate, and a follow-up CT scan of the abdomen revealed changes in distal pancreatectomy and no evidence of collection.

RESULTS

Four patients underwent laparoscopic distal pancreatectomy without splenectomy, and one underwent laparotomy pancreatoduodenectomy. The tumor was completely and satisfactorily removed from all five patients. No metastasis was found. The tumors were located in the head (1), neck (1), and body and tail (3) of the pancreas, with a distal predominance. The postoperative histopathology report confirmed the diagnosis in all five cases. An ultrasound-guided percutaneous biopsy had been performed on the youngest patient prior to surgical intervention.

DISCUSSION

SPPNs are defined by the fifth edition of the WHO Classification of Tumors of the Digestive System as low-grade malignant tumors composed of loosely cohesive epithelial cells that form solid, pseudopapillary structures and lack a specific line of pancreatic epithelial differentiation[7]. SPPNs are rare: they represent around 1%-3% of all resected cystic tumors[8]. They frequently occur in women between the second and third decades of life, and less than 10% are diagnosed in men[1]. In our series, 80% of SPPNs occurred in women. They were located mainly near the body and tail of the pancreas, although they can also involve the head and neck[9], as found in our series. Moreover, 1%-1.8% of SPPNs have an extrapancreatic location, mainly in the retroperitoneum, omentum, mesentery, stomach, duodenum, colon, liver, adrenal gland, ovary, testis, and lung[1, 10].

It has not been possible to establish which cells are involved in developing SPPN; they seem to derive from pluripotent stem cells of the genital ridges that join the pancreas during embryogenesis[11]. SPPN has been related to mutations in chromosome 11q, which contains genetic material for forming proteins such as cyclin D1, FLI-1, CD56, and the progesterone receptor[1, 12]. Even though SPPN expresses the progesterone receptor that makes it sensitive to hormones, which could explain its prevalence in women, its role in tumorigenesis has not been proven[13]. Additionally, there are mutations in exon 3 of the β-catenin gene, through which the Wnt signaling pathway is activated. It is enhanced by the BCL9 gene, which is present in this type of tumor, increasing the transcriptional activity and oncogenesis (**Figure 6**)[1, 12, 14].

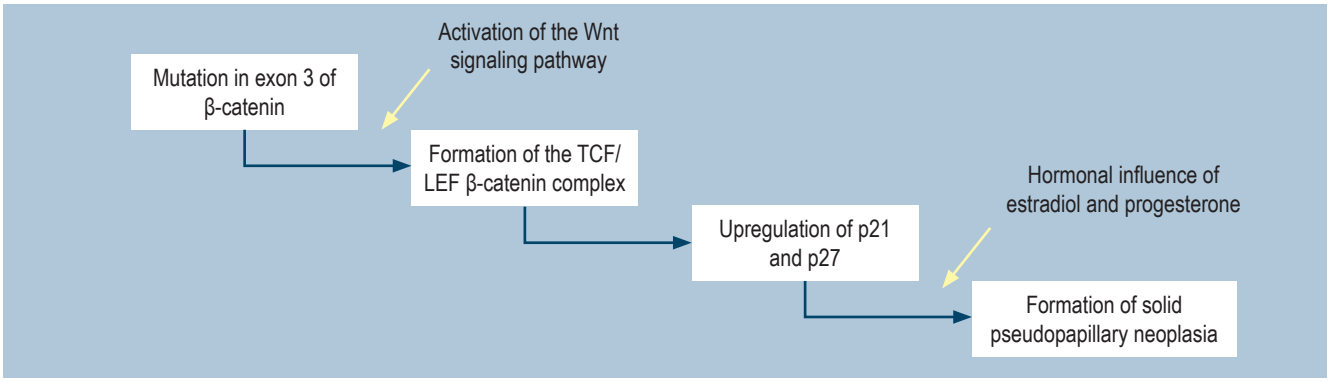

Figure 6. Physiopathology of solid pseudopapillary neoplasm of the pancreas[1]. Modified from: Lanke G et al. World J Gastrointest Endosc. 2018;10(9):145-155.

SPPN affects pancreatic exocrine tissue, which comprises acinar cells that produce digestive enzymes. They are pyramidal cells with granules surrounded by a membrane containing trypsinogen, chymotrypsinogen, procarboxypeptidase, proelastase, kallikreinogen, and prophospholipases A and B[15]. SPPNs are usually made up of different elements, such as hemorrhagic areas and calcifications, and feature a fibrous capsule[16]. Cytoplasmic vacuoles, granule nuclei, and hyaline globules may be present at the cellular level, aiding the diagnosis, as shown in **Figure 2A**[17, 18]. Additionally, there is a monomorphic, uniform, small to medium-sized cell population on a clean or hemorrhagic background and papillary structures, as shown in **Figure 2B**[11]. The confirmatory diagnosis is made through immunohistochemical studies that mainly verify the mutation of the β-catenin protein, as shown in **Figure 4A**[14]. The immunohistochemical panel proposed for diagnosing SPPN involves positive markers for β-catenin and CD99 (dot pattern) and negative markers for chromogranin, trypsin, BCL10, and E-cadherin[11]. EUS-guided fine needle aspiration (FNA), confirmed by immunocytochemistry on the cell block, is helpful for diagnosis, which excludes other pancreatic tumors[19]. EUS-guided fine needle biopsy (FNB) provides an adequate tissue sample for better diagnostic accuracy[1]. The histopathological study and immunohistochemistry allow the assessment of differential diagnoses (**Table 1**).

Table 1. Differential diagnosis of solid pseudopapillary neoplasm of the pancreas[1]

- Cystic adenoma
- Cystadenocarcinoma
- Microcystic adenoma
- Sarcoma
- Angiolymphoma
- Acinar cell cystadenocarcinoma

Modified from: Lanke G et al. World J Gastrointest Endosc. 2018;10(9):145-155.

This type of tumor usually has non-specific clinical manifestations, most of them caused by compression of the tumor against the normal pancreatic parenchyma (**Table 2**)[1, 20]. About 15% of patients are asymptomatic[20].

The imaging studies that can be performed are ultrasonography, CT, and MRI of the abdomen with a contrast medium (**Table 3**). CT and MRI of the abdomen are about 60% accurate in determining the correct histological diagnosis of cystic lesions of the pancreas. They are also a diagnostic tool that helps to differentiate aggressive lesions from non-aggressive ones in 75% to 90% of cases[21]. One of the common elements that can be seen in diagnostic images is an encapsulated lesion with solid and cystic components, intramural hemorrhage, fibrous capsule, and, occasionally, calcifications[22]. SPPN should be considered as the primary differential diagnosis when there is evidence of a large mass at the level of the body or tail of the pancreas, with defined contours, solid and cystic portions, and no internal septa[21, 23]. A study found that, in multislice computed tomography imaging, men generally have smaller lesions with a more significant solid component and calcifications than women[24].

Table 2. Clinical manifestation of solid pseudopapillary neoplasm of the pancreas[1]

- Epigastric and dorsal pain
- Early satiety
- Abdominal distension
- Jaundice
- Weight loss
- Nausea and vomiting
- Palpable abdominal mass

Modified from: Lanke G et al. World J Gastrointest Endosc. 2018;10(9):145-155.

We should differentiate this tumor from other pancreatic neoplasms because the cornerstone of treatment in these cases is surgical resection, which is curative in most patients[25]. Five studies compare the surgical approach: minimally invasive surgery versus open intervention with the different types of pancreatic resection depending on the location, pancreatoduodenectomy, central pancreatectomy, distal pancreatectomy, or enucleation (**Figure 7**)[26]. A distal pancreatectomy should be performed in tumors involving the body or tail with some vascular involvement[27]. This type of splenic-sparing surgery is currently preferred since it is associated with less morbidity, fewer infectious complications, a lower incidence of pancreatic fistula, and a shorter hospital stay[27-29]. In addition, a significant increase in platelet count has been documented after splenectomy, which has been associated with thromboembolic complications[30]. Finally, spleen preservation has been related to a better general condition in the long term[30].

Where possible, one should always try to preserve the spleen, even when the splenic vascular bundle is compromised and must be ligated. Splenic preservation can be achieved by spleen vessel-sparing distal pancreatectomy or the Warshaw surgical technique[31]. This technique involves

Table 3. Findings of solid pseudopapillary neoplasm of the pancreas according to the imaging study[21]

EUS	CT	MRI
- Well-defined circumscribed mass with a fibrous capsule	- Encapsulated mass with defined contours and a solid or cystic component	- A better view of the capsule and tumor extension
- A mass effect that compresses different structures with high echogenicity	- When the tumor has cystic characteristics, the degree of attenuation may vary depending on the extent of the hemorrhagic necrosis contained in the cyst	- On T1: A hypointense fibrous capsule with high-intensity internal bleeding
- Small tumor with a solid component	- Tumor with an attenuation coefficient of 20 to 50 Hounsfield units	- On T2: Heterogeneous signal intensity
- Large tumor with a cystic component showing posterior acoustic enhancement	- The cystic component varies in size according to the extent of necrosis, blood clots, and necrotic tumor tissue. However, it is not associated with the size of the tumor	- The solid portions are isointense or hypointense compared to the pancreatic parenchyma
- Low echogenicity mass with cystic areas suggestive of hemorrhagic necrosis		- Sometimes hyperintense foci are observed in the tumor, which may correspond to cellular debris or areas of hemorrhagic necrosis
		- With a contrast medium, the heterogeneous peripheral enhancement could be noted in the early arterial phase, and a subsequent heterogeneous filling of the lesion in the portal phase

Modified from: Tafur A et al. Rev Med. 2017;25(1):70-77.

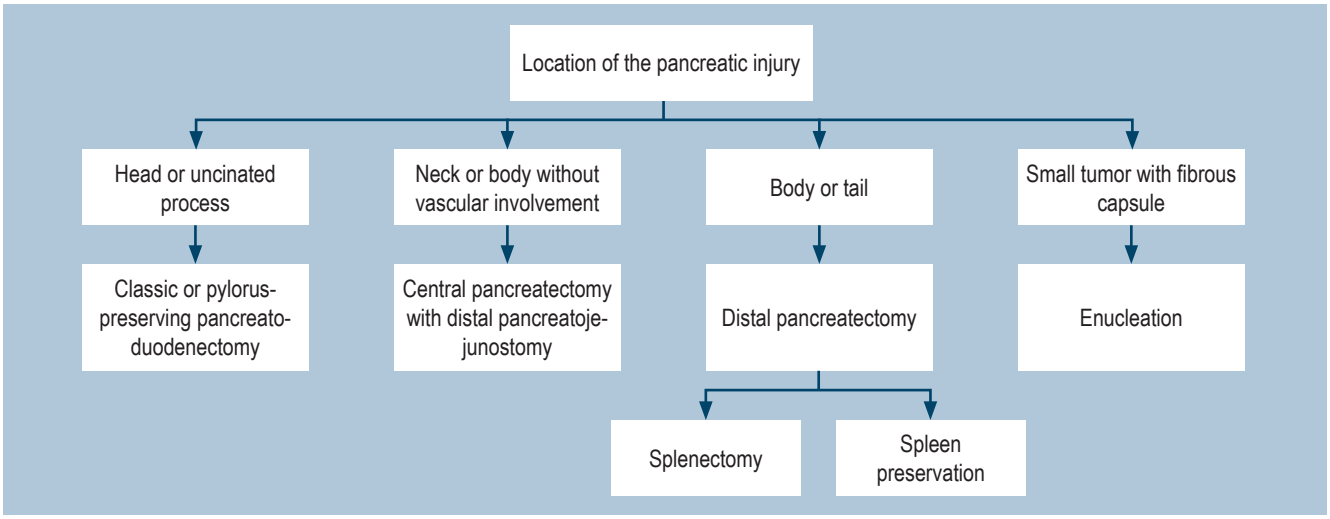

Figure 7. Algorithm to determine the type of pancreatic resection[25]. Modified from Liu M et al. Pancreatology. 2019;19(5):681-685.

ligating the splenic artery and vein, preserving the spleen's circulation by sparing the short gastric and left gastroepiploic vessels[32, 33]. A meta-analysis that compared the preservation of splenic vessels with the Warshaw technique showed that this technique had a significantly higher incidence of splenic infarction and gastric/epigastric varices, in addition to the fact that more patients with splenic infarction underwent splenectomy. Still, there were no differences between the two procedures regarding pancreatic fistula, morbidity, and hospital stay[31]. Likewise, splenic preservation using the

Warshaw technique is associated with less postoperative morbidity than splenectomy[34]. Currently, minimally invasive surgery is preferable because it is associated with shorter surgical time and postoperative stay. However, no intraoperative differences are associated with less blood loss, transfusion requirements, postoperative complications, mortality, or surgical resection margins[35-39].

In most patients, the disease is localized, and only 9%-15% have a local invasion or metastasis[6]. Malignancy cannot be easily predicted based on preoperative findings and immunohistochemical patterns[40]. Deep parenchymal invasion into the surrounding tissue is the most common pathological feature suggesting malignancy[41], in addition to lobulated margins and focal discontinuity of the capsule, exophytic growth pattern, solid-cystic component ratio, and Ki-67 index[40]. A recent meta-analysis confirmed that the risk of malignancy in SPPN increases with the gradual increase of the Ki-67 index[42].

The prognosis is generally good. The five-year survival is close to 97%, even in the presence of metastases, which shows that it is a relatively indolent disease compared to other pancreatic neoplasms[43]. Metastases occur mainly in the liver or peritoneum. The molecular alterations in SPPN with metastases are mutations with CTNNB1 activation and inactivation of epigenetic regulators such as KDM6A, TET1, and BAP1[44].

Recurrence after surgical resection of non-metastatic SPPN is 2%. The main risk factors for recurrence are being a man (odds ratio [OR]: 1.96), positive lymph nodes (OR: 11.9), R1 margins (OR: 11.1), and lymphovascular invasion (OR: 5, 5), all with $p < 0.05$[45]. Additionally, the size of the tumor (> 5 cm) and synchronous metastases have been associated with recurrence[46]. There is no specific classification system to predict results in SPPN. Although there are many factors, it has not been possible to consolidate a determining element related to recurrence[47]. Physiopathological similarities between pancreatic NETs and SPPNs have recently been found, with the association of the Ki-67 index as a factor that could reflect recurrence[48, 49]. The WHO introduced the Ki-67 index in 2017, an antigen used to study tumor growth rate for pancreatic NETs[47]. Tumor grade (**Table 4**), based on the Ki-67 index in pancreatic NETs, has been incorporated into SPPNs as a critical histopathological test to study tumor growth rates[48, 49]. Zou et al. conducted a study in which they related the tumor grade according to the Ki-67 index and the lesion size with recurrence after tumor resection. The grade based on Ki-67 was higher than that proposed by the American Joint Committee on Cancer with the TNM system to assess recurrence in SPPN[42]. A multicenter European study that included 149 patients who underwent complete resection of an SPPN found that preoperative EUS-guided FNA did not affect recurrence[50].

Table 4. Tumor grade associated with the Ki-67 index[47]

Grade 1	< 3%
Grade 2	3%-20%
Grade 3	> 20%

Modified from: Inzani F et al. Endocrinol Metab Clin North Am 2018;47(3): 463-470.

Lastly, an algorithm is presented for the correct diagnostic approach, treatment, and follow-up of patients with SPPN, considering the clinical manifestations and the complementary studies available in each institution (**Figure 8**)[1].

CONCLUSIONS

SPPN is a rare, low-grade malignancy that mainly affects young women. The signal symptom may be vague, or the patient may even be asymptomatic, so it is often diagnosed incidentally. Clinical findings, radiological imaging, and cytology constitute the basis of its diagnosis. Surgical resection of the tumor continues to be the mainstay of its treatment. Multiple surgical methods are used to resect these tumors depending on the part of the pancreas affected, its size, and the extent of local invasion.

Conflicts of interest

No conflict of interest was declared.

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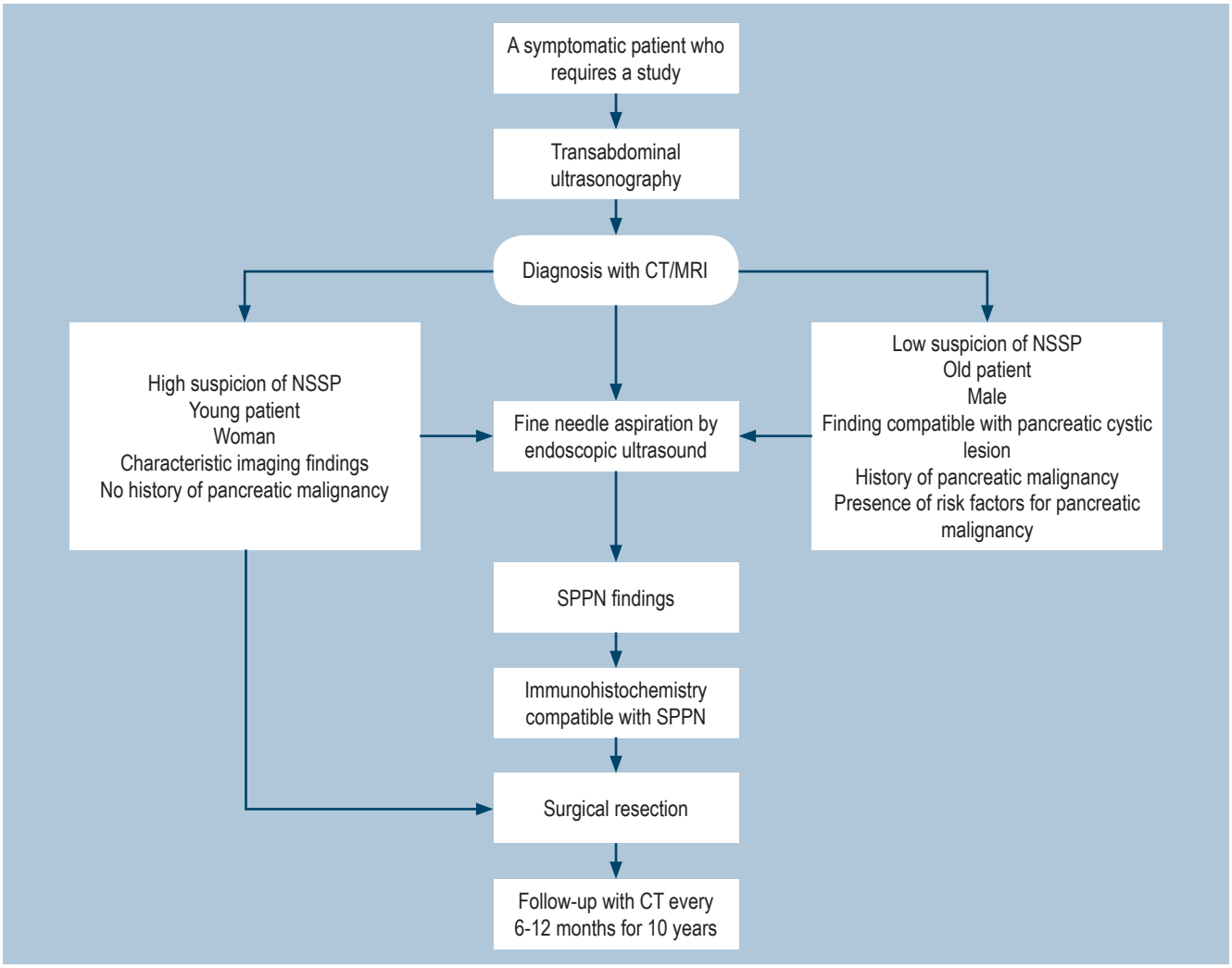

Figure 8. Algorithm for diagnosing, treating, and monitoring SPPN[1]. NMR: nuclear magnetic resonance; CT: computerized axial tomography. Modified from: Lanke G et al. World J Gastrointest Endosc. 2018;10(9):145-155.

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Case report

Acute pancreatitis due to ascaris in an adult from the urban area of Bogotá, regarding an unusual manifestation. Case report

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Abstract

Introduction: Acute pancreatitis is one of the most common entities affecting the gastrointestinal tract. Its most frequent causes are biliary and alcoholic; however, infectious causes, including parasitic ones, should not be ruled out. **Case:** We present the case of a 35-year-old man from the urban area of Bogotá who was admitted to the emergency department of the San Ignacio Hospital due to chest pain, with subsequent migration to the abdomen and associated gastrointestinal symptoms. Acute pancreatitis was diagnosed, biliary and alcoholic causes were ruled out, and the scan revealed a gastric endoluminal foreign body towards the intestinal loops; the diagnosis was confirmed endoscopically (*Ascaris lumbricoides*). The helminth was entirely extracted, and the intrahospital management was continued. As a complication, he had necrosis with associated collections in control images without multi-organ involvement. Finally, he was discharged due to adequate clinical evolution. **Conclusion:** Ascariasis is a rare cause of acute pancreatitis in adults in urban areas, even in developing countries such as Colombia. Its diagnosis and therapeutic management are carried out endoscopically with the extraction of the helminth. As in all cases of pancreatitis, a clinical follow-up should be conducted in search of associated complications and multi-organ involvement.

Keywords

Case report, acute pancreatitis, biliopancreatic ascariasis, infectious pancreatitis, *Ascaris lumbricoides*.

INTRODUCTION

Acute pancreatitis is one of the main pathologies of the gastrointestinal tract treated in emergency services worldwide[(1)]. Colombia's primary etiology is biliary (80%), followed by alcoholic (9%). Among the infectious causes, only 1.3% is due to ascariasis in some regions[(2)]. While usually mild and reversible, its manifestation can reach a mortality rate of up to 15%[(3)]. In severe cases, around 20-40% present with peripancreatic necrosis and organ dysfunction[(3)]. We present this case of severely compromised acute pancreatitis secondary to an uncommon infectious cause in our setting.

CASE PRESENTATION

We present the case of a 35-year-old male patient, a public transport driver, from Bogotá, with a two-hour history of

highly intense shooting retrosternal chest pain that radiated to the dorsal region and the epigastrium, with nausea, an emetic episode, and no other associated symptoms. He did not report any significant personal or family history or recent trips and did not smoke or drink alcohol.

The initial assessment found mild tachycardia (100 beats per minute), blood pressure and oximetry without alterations, and no additional findings upon cardiopulmonary auscultation or abdominal examination. An electrocardiogram was taken with sinus rhythm, finding no signs of myocardial injury or ischemia. Troponin I and D-dimer were taken in a chest pain study with typical values. The chest x-ray did not show consolidation or pleural effusion. Upon reassessment, he reported that the pain had migrated to the epigastrium with band irradiation, associated with multiple emetic episodes and a febrile peak, for which further studies were carried out to evaluate the acute biliopancreatic etiology and infectious involvement.

Markedly elevated amylase (2,902 U/L), a complete blood count with leukocytosis at the expense of neutrophilia (15,400 leukocytes/mL, 13,800 neutrophils/mL), and a slight elevation of alkaline phosphatase (254 U/L) with elevated transaminases ten times the upper limit (alanine transaminase [ALT]: 520 IU/L; aspartate aminotransferase [AST]: 441 IU/L) and no hyperbilirubinemia were documented. A diagnosis of mild acute pancreatitis is given by initial Atlanta classification, with an APACHE II score of 7 points. Management begins with the suspension of the oral route, analgesia, gastric protection, and fluid resuscitation.

In search of the biliary etiology, an abdominal ultrasound was performed, showing a bile duct and common bile duct without alterations, the gallbladder without signs of cholecystitis or cholelithiasis, evidence of perisplenic fluid, and multiple collections in the paracolic gutters. The other etiology studies were without alterations, including a lipid profile and serum calcium levels. A contrast-enhanced abdominal scan was then performed, identifying a thickening of the body and tail of the pancreas with edema and diffuse peripancreatic fluid, consistent with pancreatitis in the edematous phase. The presence of endoluminal lesions near the gastric cavity with passage towards the intestinal loops and a filling defect of tubular morphology towards the duodenal papilla, with a length of approximately 76 mm, identified as a foreign body (**Figure 1**) were striking; therefore, there was a high suspicion of ascariasis.

Antiparasitic management began with ivermectin, one drop per kilogram, and albendazole 400 mg daily for three days. An endoscopy of the digestive tract was carried out for viewing, noting an approximately 26 cm nematode at the second duodenal portion (**Figure 2**), whose proximal end is near the duodenal papilla and the distal end at the level of the duodenal lumen. It was removed with forceps, while the duodenum was thoroughly examined throughout its length with no evidence of another foreign body. Prophylactic antibiotic coverage with ampicillin/sulbactam was started, given the extent of the endoluminal compromise. Other possible causes related to pancreatitis were ruled out, with normal serum calcium (8.3 mg/dL) and a lipid profile with triglycerides less than 500 mg/dL. Therefore, it was considered that the directly related obstructive cause was pancreaticobiliary ascariasis.

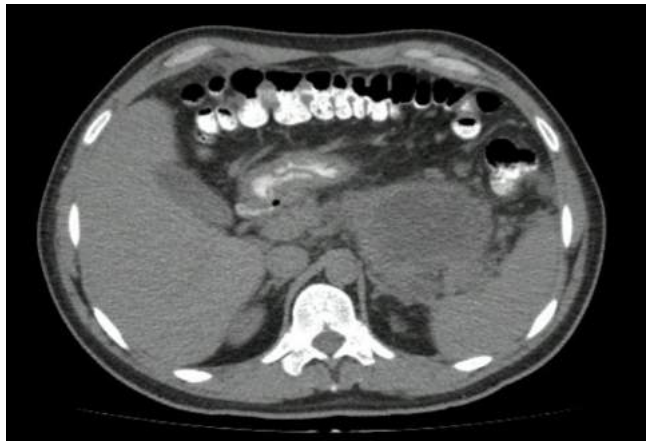

Figure 1. Abdominal tomography. Source: Authors' archive.

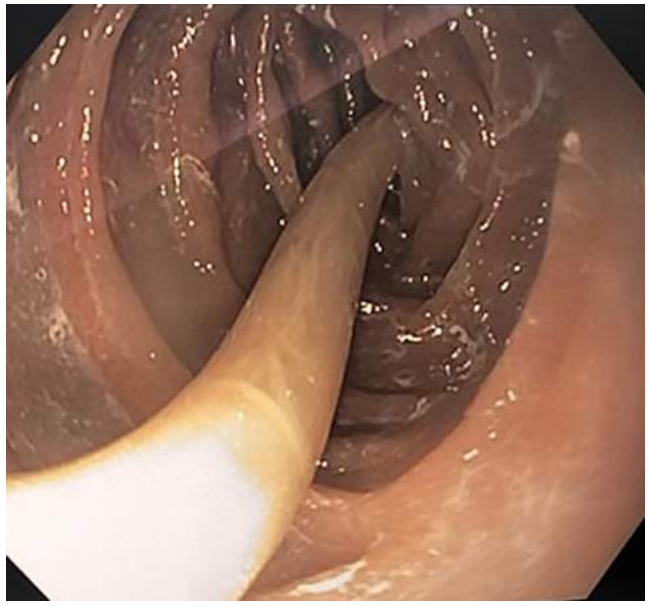

Figure 2. Endoscopic study. Source: Authors' archive.

On the fourth day of hospitalization, the patient presented with poor pain control, intolerance to the oral route, and signs of a systemic inflammatory response given by tachycardia, persistent fever, increased leukocytosis, and hyperlactatemia. Therefore, we decided to carry out an

imaging follow-up to evaluate the complications, showing thickening of the body, uncinate process, and tail of the pancreas without enhancement associated with more collections than in the previous study. The most extensive collection was approximately 170 cm^3 in volume, compatible with necrotic pancreatitis and associated intraparenchymal collections. A moderate-severe compromise was considered, with no signs of superinfection in collections. A procalcitonin test was performed with negative results. We decided to withdraw the oral route again, and the analgesic management was adjusted by the Pain Clinic group, with follow-up by the nutritional support group.

The patient exhibited good clinical evolution, hemodynamic stability, and adequate clearance of hyperlactatemia in the following days. The oral route was started with good tolerance, modulation of the signs of a systemic inflammatory response, and completion of antibiotic coverage for seven days. The patient completed 48 hours of tolerance with a soft diet. Progress was made in the diet, so we indicated discharge with outpatient follow-up by gastroenterology.

DISCUSSION

Acute pancreatitis is a frequent reason for consultation in emergency services worldwide, and its incidence has increased in recent years[4]. The manifestation of this entity may vary in terms of clinical involvement and possible complications[5]. This report presents an atypical case of pancreatitis not only because of its unusual clinical manifestation (chest pain and dyspnea as initial clinical symptoms) but also because of its etiology.

Pancreatitis generally has common clinical manifestations, which are defined by their diagnostic criteria (two out of three): characteristic abdominal pain (epigastric with band irradiation), amylase or lipase levels above three times the upper limit of normal, or findings suggestive of inflammatory changes in the pancreas by imaging[6]. Upon reaching its diagnosis, initiating directed management and monitoring its possible complications is essential[7]. Although different drugs have been studied, such as immunomodulators or antisecretory agents, the cornerstone of its treatment is adequate hydration, pain management, and restriction to the oral route[7-9].

After establishing its initial management, the next step is identifying its etiology. The initial approach must search for the most frequent causes in Colombia and the world. Biliary pathology is the leading cause of pancreatitis, followed by alcohol; thus, an upper abdominal ultrasound should be performed, and an appropriate history of alcohol use should be obtained from all patients. Although infrequent, the tumoral cause should be studied in patients older than 40[9]. By excluding the most frequent causes, other serological and imaging studies should be performed serially to find its etiology, including serum levels of triglycerides and calcium[1, 10]. In the case presented, there were no findings suggestive of biliary lithiasis etiology in the upper abdomen ultrasound, so we continued with serological tests and characterization by scan, which evidenced the cause.

About 10% of pancreatitis cases are related to infectious causes, with viral causes and tropical diseases being the most common. The parasitic cause is less frequent; however, it is an important entity, especially in developing countries[11]. Ascariasis is the parasitic cause most frequently related to pancreatitis, especially in children, occurring in approximately 23% of cases[11].

Ascaris lumbricoides infection occurs initially by ingesting the infective egg of the larva, which migrates towards the intestinal loops and penetrates the colonic mucosa. Finally, it settles in the liver and lung tissue through hematogenous dissemination, penetrating the bronchial tissue and the oropharynx, where it is swallowed again and continues its maturation cycle near the intestinal lumen. Approximately ten days after primary infection, the larva matures in the small intestine, where it can reside and increase in size for up to 12 months. Therefore, the clinical manifestations can be masked by even asymptomatic pictures and self-resolving infections; however, cases as severe as intestinal obstruction requiring surgical management and high morbidity and mortality rates may occur[12]. In cases of pancreaticobiliary ascariasis, most of them manifest as biliary colic or acute cholangitis and, less frequently, due to pancreatitis (6%) or in the form of liver abscesses[13].

Typically, cases of hepatobiliary pancreatitis go unnoticed or are little suspected, especially in adults in urban areas[14], as in our patient. The initial suspicion was given by the incidental findings on the first tomography, whose purpose was to evaluate the involvement of the pancreatic parenchyma and, thus, to look for other etiologies, such as anatomical variants or tumors, as described in the diagnostic algorithms when ruling out the most common causes of this entity[1, 4, 8]. With this first approach, the patient underwent an upper GI endoscopy not only for diagnostic confirmation but also for possible therapeutic management. Since the entire helminth could be removed, with no evidence of remains or distal compromise, it was not necessary to perform an endoscopic retrograde cholangiopancreatography (ERCP) for its total removal, as described in cases related to this etiology[13].

In addition to this management, based on removing the parasite from the gastrointestinal tract, the patient required intrahospital surveillance due to subsequent clinical deterioration. Therefore, as recommended in different management guidelines[3, 6, 9], an imaging follow-up was performed with evidence of progression of the necroinflammatory

involvement associated with necrotizing pancreatitis with collections; however, there were no imaging (gas) or clinical signs of infectious involvement. Since, at the time, he was under empirically established antibiotic management due to the high risk of endoluminal intestinal injury and bacterial translocation by the helminth, we considered not making any adjustments to the therapy and continuing with monitoring. The patient did not present with organic dysfunction or infectious deterioration; enteral nutrition was started with adequate tolerance. Finally, his discharge was indicated with imaging follow-up by gastroenterology.

This case is interesting for different reasons. First, as previously mentioned, it was an unusual manifestation due to the signal symptom of chest pain, even having ruled out potentially fatal causes such as acute coronary syndrome based on age and sex. Finding a "foreign body" near the duodenal papilla in the initial scan in looking for different etiologies of pancreatitis, having ruled out the most frequent ones, allowed its proper diagnosis and endoscopic therapeutic management. Furthermore, the presence of ascariasis in an adult residing in the urban area of Bogotá is noteworthy. Although ascariasis occurs more frequently in a tropical country such as Colombia than in others, it is odd to find it in a social and epidemiological context, such as our patient's[14, 15].

CONCLUSION

Acute pancreatitis is a common condition worldwide. Its manifestation is usually classic; however, unusual symptoms such as chest pain may appear as the initial manifestation. The most frequent etiologies must be ruled out without neglecting infections as causal factors. It is unusual to find a parasitic compromise in general, especially in adults from urban areas; however, it should not be dismissed as a differential diagnosis. In addition to the initial management in the emergency room, consisting of adequate hydration, restriction of the oral route, and analgesic management, the treatment of pancreatitis due to Ascaris must be completed endoscopically with the extraction of the helminth. Close clinical follow-up of patients with pancreatitis and monitoring for possible complications, regardless of their cause, is vital.

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Case report

Intestinal mucosal lesion associated with crystals: Case series and literature review

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Abstract

Crystal-associated mucosal injury is a crucial clinical picture in a subset of uremic patients who are given cation exchange resins such as sodium polystyrene sulfonate (Kayexalate) and sevelamer to treat hyperkalemia and hyperphosphatemia, respectively. Colonic necrosis in these patients is rare but may be associated with fatal gastrointestinal injury, with a mortality rate of 33%. Bile acid sequestrants are another type of resin that is theoretically biologically inert. Two cases of colitis associated with crystals are presented. The first patient had a history of multiple surgeries and pathologies of the gastrointestinal tract and was treated with cholestyramine. A sigmoidectomy was performed in which several crystal foci were found. The second patient had a history of chronic kidney disease requiring Kayexalate and attended the emergency department with severe lower GI bleeding. A partial colectomy was performed in which morphological changes related to the deposit of crystals were detected. Resins can cause a broad spectrum of malignant mucosal lesions, so early diagnosis is essential to reduce mortality and improve prognosis. However, it is uncertain whether the consumption of cholestyramine and kayexalate, as well as the deposition of their crystals in the GI tract, are the causative factor of mucosal damage. Therefore, resins should help establish the correct diagnosis and prompt medical treatment to avoid harmful results.

Keywords

Bile acid sequestrants, Kayexalate, crystal, necrosis, gastrointestinal tract

INTRODUCTION

Crystal-associated mucosal injury is an important clinical entity that has been gradually increasing, specifically, derived from the use of medications for chronic kidney disease (CKD). In patients with CKD, non-absorbable medications that facilitate ion exchange are part of the treatment options for electrolyte imbalances like hyperkalemia and hyperphosphatemia. There are 3 types of resins described in the literature: Bile Acid Sequestrants (BAS), Kayexalate, and Sevelamer. Kayexalate, a potassium-binding agent, and Sevelamer, a phosphate-lowering medication, are known for causing significant mucosal abnormalities. Nevertheless, literature is limited to case reports and a causal relationship has not yet been established, therefore little is known about the pathophysiological mechanism of mucosal injury.

The known pathologic effects of phosphate-lowering agents in the gastrointestinal tract were first described in

2013 by Swanson *et al*. in a case series of 15 patients with mucosal injury secondary to Sevelamer. Findings included ulceration, ischemic injury, necrosis, and inflammation[1]. Since then, few cases of symptoms associated with resin administration have been reported. Similar to Sevelamer, Kayexalate-related mucosal injury is rare but may be associated with fatal gastrointestinal injury; a systematic review reported a mortality rate of 33%[2].

BAS agents are another type of resin polymer that targets certain components in bile. These medications are mainly prescribed to treat diarrhea and hypercholesterolemia and have been safely used for several years[3]. Cholestyramine, a BAS agent, prevents the reabsorption of cholesterol found in bilis; therefore, it is prescribed for the management of hypercholesterolemia and atherosclerosis in patients with CKD. The agent has been associated with minimal adverse effects localized to the gastrointestinal tract without systemic repercussions. Accordingly, the main harmful effects described in the literature consist of esophagitis, gastritis, reactive gastropathy, erosion, and ulcers[3]. Although Cholestyramine is considered biologically inert and has been safely used for several years, we present a case series with histological description of 2 patients with crystal mucosal injury associated with Cholestyramine and Kayexalate consumption that required surgical treatment.

MATERIALS AND METHODS

Two specimens with histological similar crystals were collected from biopsies of two patients that arrived at our academic center over a 6-month period. Both samples were fixed with formalin and stained with hematoxylin and eosin. For each of the two cases, we evaluated the presence and distribution of the BAS crystals, mucosal injury and other conditions that could have contributed to the patient's clinical presentation.

RESULTS

Clinical Features

Case #1

An 86-year-old female patient underwent elective surgery for colovaginal and colovesical fistula with sigmoidectomy. The patient had a previous right colectomy in 2015 secondary to a malignant colonic tumor. She has a history of hypertension, gastritis, diverticulosis, and hypercholesterolemia that was being managed with cholestyramine.

Case # 2

An 83-year-old male patient presented to the emergency department with hematochezia associated with several blood clots, asthenia, adynamia, and dyspnea on exertion. On his arrival at our institution, he was hemodynamically unstable. He has a history of CKD with peritoneal dialysis requirement. Laboratory analysis revealed severe anemia (6.3 g/dL), creatinine of 8.4 mg/dL, and serum potassium of 6.4 mEq/L for which Kayexalate was administered. An endoscopic study was negative for upper gastrointestinal bleeding, but colonoscopy showed an abundance of clots in all colonic surfaces and multiple diverticula confined to the ascending colon.

The patient was admitted for radiological embolization followed by ICU admission, he required major hemorrhage protocol transfusion twice with over 10 units of blood. Finally, he was taken to the operating room where an exploratory laparotomy and subtotal colectomy were performed with aid of an intraoperative colonoscopy.

Pathologic Features

Case #1

Two resected colon specimens were studied in the pathology department and several diverticula were found. The diverticula had a wide base (measuring between 0.5 and 0.3 cm) surrounded with fibrosis and vascular congestion. Additionally, from the peri-intestinal adipose tissue, 5 nodular lesions were isolated; one of them with dimensions of 0.6cm x 0.5cm and the other one of 0.3 cm x 0.2 cm. As observed in **Figure 1** the diagnosis of diverticulosis associated with several intramural and mucosal crystal foci, very likely from cholestyramine, was made. It was not possible to state a causal relationship between the presence of crystals and the acute severe inflammation and perforation of the diverticula.

Case #2

The surgical pieces were analyzed in the pathology department. **Figure 2** shows a macroscopic picture of a colonic segment with multiple raised hemorrhagic lesions and microscopic examination showing crystals, ulceration, and ischemic necrosis.

DISCUSSION

Theoretically, the increased number of performed endoscopies, together with the increase in polypharmacy in the context of an aging population, should raise the probability of observing unintended side effects of therapeutic medications. Nevertheless, medication-induced injury is underrecognized and it is very uncommon for pathologists to report resins on specimens. An online survey performed in 2016 by the Rodger C. Haggitt Gastrointestinal Pathology Society informed that 75% of 99 pathologists with a GI

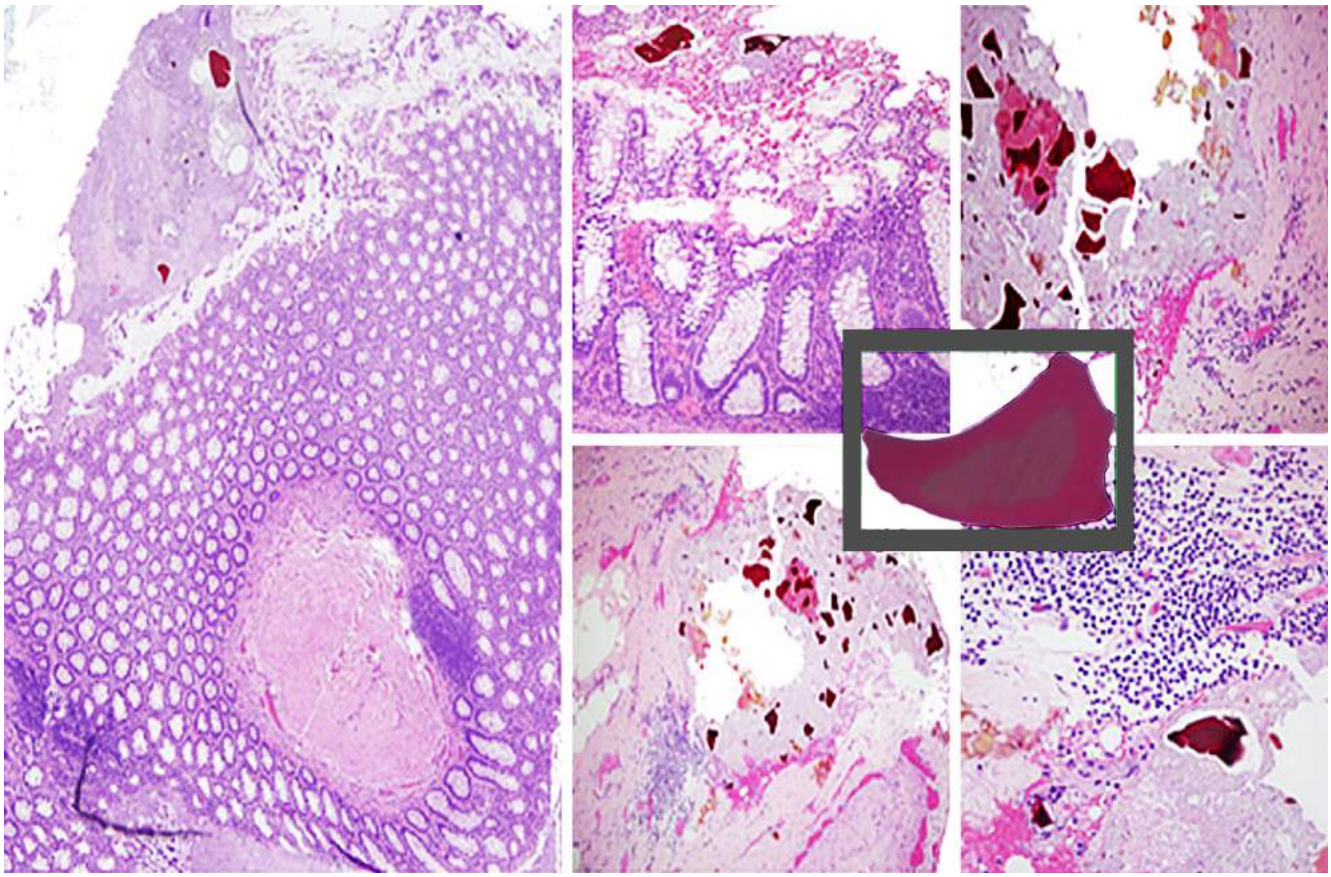

Figure 1. Sigmoid colon with complicated diverticular disease and areas of diverticulitis. Intramural abscesses and multiple magenta-colored crystals, with angled edges and salmon-colored striations on the inside. Additionally, crystals are found primarily on the mucosal surface, in close relationship to the diverticula.

subspecialty had never seen resin administration documented on the pathology[4].

Physiopathology

After an extensive review of the literature regarding mucosal injury derived from the use of cation-exchange resins, a cause-effect relationship has not yet been reported but literature has described the potential of Kayexalate to cause transmural colonic infarction due to rapid electrolyte shifts in the context of uremic patients who are vulnerable because of gastrointestinal vascular instability[5]. Particularly, factors that can predispose to injury aside from uremia, include slow gastrointestinal tract motility, immunosuppression medication, and hemodynamic changes associated with hemodialysis and surgery[6].

The use of cholestyramine has been described to lower the risk of BAS-associated mucosal injury since it diminishes the cytotoxic effects of deoxycholic acid therefore preventing endoplasmic reticulum stress that ultimately results in disruption of the mucosal barrier[7]. Although this is true, preliminary studies in rats showed an insignificant effect of cholestyramine treatment on preventing mucosal injury and they attributed this ineffectiveness to the pKa of bile salts converting them to their nonionized form at the gastrointestinal tract pH, impending cholestyramine-induced bile acid sequestration[8]. Nevertheless, no pathologic relationship with cholestyramine was described before and the exact mechanism is misunderstood; therefore, only an association can be established.

Diagnosis

Bile acid sequestrants are classically seen along the gastrointestinal tract as bright orange in hematoxylin-eosin with a rectangular shape and a glassy texture, nevertheless, as seen in **Figure 1**, non-classical morphology (usually focal) concerning shape, color and location can be observed depen-

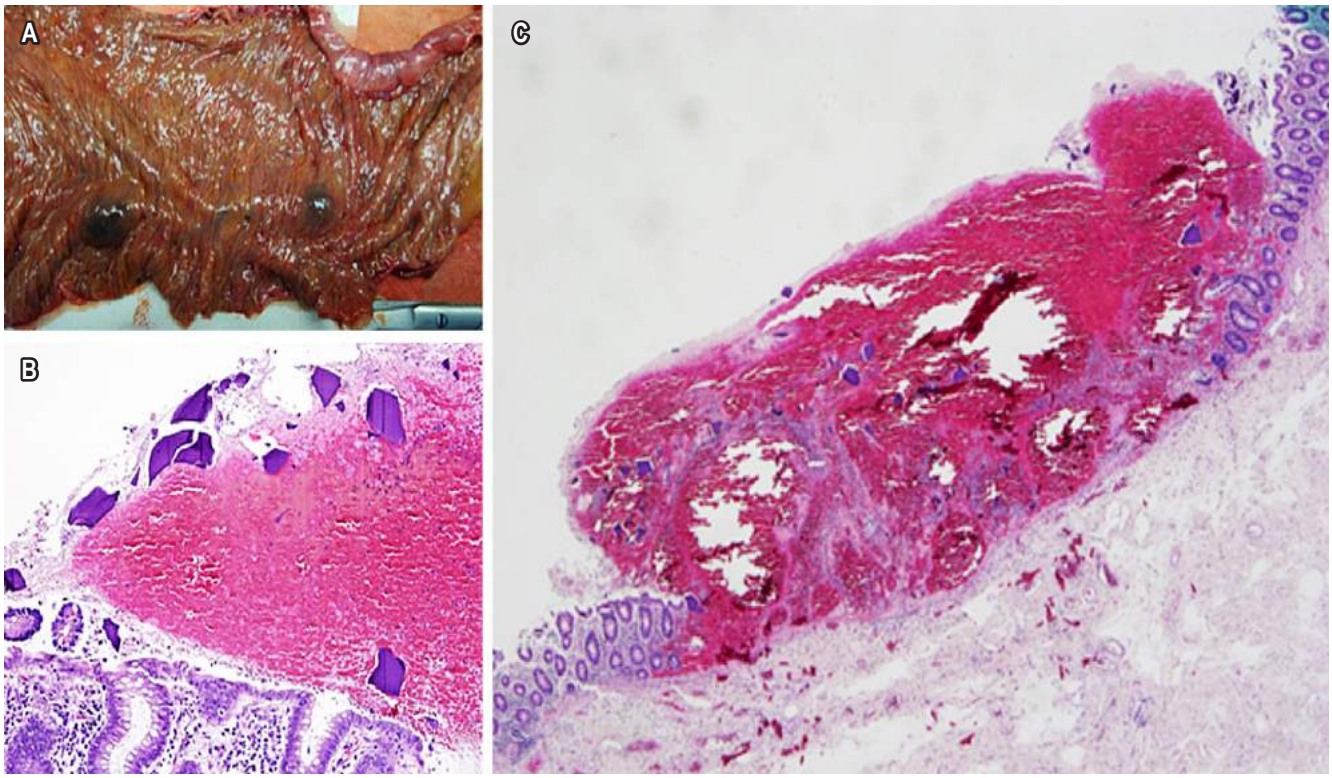

Figure 2. A. Colon segment with multiple hemorrhagic raised lesions. **B.** Hematoxylin and eosin 20 x closeup to appreciate crystal morphology. **C.** Hematoxylin and eosin 40 x closeup that shows ulceration and ischemic necrosis, presence of magenta-colored crystals in the surface of the hemorrhagic material.

ding on the variable substrate binding and background pH. In hematoxylin-eosin, BAS are eosinophilic polygonal crystals but can be dull yellow on acid fast bacillus special stains. They have been classically described as rectangular but recently rounded structures have been described as well[9]. Furthermore, crystals have been found not only in the GI tract but also in unusual locations such as cutaneous deposition, gall bladder in patients with biliary stenting, and in a separate surgical resection of a necrotic pancreas[4].

Moreover, Kayexalate's morphology is highly specific, showing rhomboid nonpolarizable, basophilic crystals with a mosaic pattern; its only differential diagnosis consists of cholestyramine-crystals which are also basophilic and angulated but with a greater opacity and no mosaic pattern[5]. Altogether, the best method to identify these crystals is acid-fast bacillus special stains where Sevelamer is seen as magenta-colored crystals, as presented in our case, Kayexalate as black-colored crystals and BAS as dull yellow crystals[3]. The high spectrum of crystal presentation tends to be focal, and the typical resin morphology should be found in the surroundings, therefore the slide must be scanned as a whole. Although there are several characteristics particular to each resin, most of the time they are histologically indistinguishable from each other, and accurate distinction is important since Kayexalate and Sevelamer have a stronger association with mucosal injury than Cholestyramine-crystals[3].

Treatment

Recognition and topline descriptive report of resins, particularly of Kayexalate and Sevelamer, in association with mucosal injury, should be treated as a clinical emergency for adequate monitorization and prevention of detrimental outcomes. Nevertheless, it is important to acknowledge that the effects of the medication are known to mimic other endoscopic and radiologic diagnoses in the esophagus, stomach, small intestine, and colon such as colonic pseudotumor[6]. Still, a low suspicion threshold must be considered since it is important to alert the clinician of the potentially dangerous consequences of Kayexalate and Sevelamer when a mucosal injury is observed in the specimen since Abraham et al. found that nearly 30% of patients with ileal or colonic injury had extensive necrosis requiring resec-

tion[10]. Therefore, recognition of resin crystals in histologic sections as a marker for resin-associated mucosal damage may aid in establishing the correct diagnosis for clinically or endoscopically misleading lesions.

Prevention

Even though a good number of cases relating to BAS-associated mucosal injury have been reported, no successful prevention or treatment other than surgical resection is mentioned[1, 2, 8-11]. One case report even described how gastrointestinal ulcers and bleeding started after the first dose of Kayexalate[12]. Because the mechanism behind crystal-associated mucosal injury is not well understood, the specific settings where resins must be used with caution are not yet established and no standardized recommendations are available. Nevertheless, it has been suggested based on one retrospective observational study carried out by Panagiotis I et al, that a low dose of BAS can be well tolerated and could effectively normalize electrolyte abnormalities[13].

CONCLUSION

In conclusion, given that it has been recognized that resins such as Sevelamer and Kayexalate can produce a large spectrum of fatal mucosal lesions, early diagnosis is critical to decrease mortality as well as improve prognosis. The latter makes it possible to indicate a feasible *association* between crystals in the colonic intestinal mucosa and critical inflammation. Nevertheless, establishing whether the consumption of Cholestyramine and Kayexalate and the deposit of its crystals in the gastrointestinal tract is the causal factor of mucosal injury, is uncertain. However, we cannot exclude their ability to cause mucosal injuries in specific settings and the presence of resins should prompt the pathologist to seek a related diagnosis to prevent deleterious outcomes.

Conflicts of interest and financing

The authors declare no conflict of interest or financing.

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Case report

Secondary Budd-Chiari syndrome associated with severe alcoholic hepatitis: A case report

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Abstract

Alcoholic hepatitis is an acute inflammation of the liver secondary to the consumption of alcohol in hepatotoxic amounts; various associated factors influence its pathophysiology. The diagnosis has three scenarios: probable, possible, and definite alcoholic hepatitis. Probable alcoholic hepatitis is based on compliance with clinical and laboratory diagnostic criteria; possible alcoholic hepatitis corresponds to cases that meet these criteria but with potentially confounding factors in the diagnosis, and the definite one is based on histopathology. Budd-Chiari syndrome is a rare, heterogeneous, potentially lethal entity characterized by thrombi in the suprahepatic veins and the inferior vena cava. The final diagnosis relies on imaging tests. Moreover, secondary Budd-Chiari syndrome is an even rarer entity, little studied, whose diagnosis is difficult due to its remarkable similarity to primary Budd-Chiari syndrome, both clinically and in diagnostic images, for which more complex and even invasive diagnostic methods must be used. Then, we describe an unusual case of a male patient with chronic alcohol consumption presenting with secondary Budd-Chiari syndrome associated with severe alcoholic hepatitis confirmed by liver biopsy and subjected to multiple imaging studies that ruled out thrombosis in the suprahepatic veins.

Keywords

Alcoholic hepatitis, Budd-Chiari syndrome, secondary Budd-Chiari syndrome.

INTRODUCTION

Alcoholic hepatitis is an acute inflammation of the liver secondary to alcohol use in hepatotoxic amounts and whose pathophysiology is influenced by various risk factors. On average, it affects people in the fourth and fifth decades of life, mainly males; however, in recent years, an increase in the incidence of alcoholic hepatitis has been described in women and young patients of both sexes, aged between 15 and 44 years[1].

This pathology is associated with drinking more than 50 grams of ethanol per day less than four weeks prior in a patient with chronic alcohol use for more than six months. It may affect patients without underlying pathologies or with chronic liver diseases, from steatosis to liver cirrhosis, and cause acute liver failure and acute-on-chronic liver failure (ACLF), both with bleak prognoses[1,2].

The diagnosis of alcoholic hepatitis is defined by criteria based on an adequate anamnesis, comprehensive and exhaustive physical examination, and compatible serological and imaging tests. Nonetheless, the final diagnosis is histopathological through liver biopsy[3].

Budd-Chiari syndrome is a rare, heterogeneous, and potentially lethal entity characterized by thrombosis in the suprahepatic veins (right, middle, or left), which involves their course and the possibility of affecting the inferior

vena cava (IVC)[4]. Timely diagnosis is essential, for which venous Doppler ultrasound is the first line diagnostic test[5]; however, magnetic resonance angiography has shown higher sensitivity (93%) and an area under the curve of 90.8%, compared to 88.4% and 86.6% for computed tomography angiography and venous Doppler ultrasound, respectively[6].

There is a similar identity, called pseudo-Budd-Chiari syndrome, which was first described in 1977 and is poorly known and studied. There is a paucity of scientific studies addressing it, and its pathophysiology needs to be clarified. Diagnosis is difficult due to its remarkable similarity to Budd-Chiari syndrome, both clinically and by imaging studies, so invasive diagnostic methods such as liver biopsy must be used[7].

Recently, the latest Baveno VII consensus considers Budd-Chiari syndrome as secondary when the mechanism of action of suprahepatic venous obstruction is associated with extrinsic compression, for example, by benign or malignant tumors or other entities that involve the liver parenchyma and are adjacent to the territory of the suprahepatic veins. Moreover, Budd-Chiari syndrome is considered primary in cases where its pathophysiology is purely related to suprahepatic vein thrombosis, as initially known[8].

CASE PRESENTATION

We present the case of a 51-year-old overweight male patient, a heavy transport driver, with a history of alcohol use for more than 20 years (> 60 g/day). After an episode of excessive alcohol use (> 360 g in ten hours), he was sick for 15 days and presented with jaundice in the sclerae and skin with notable progression, abdominal distension associated with pain in the right hypochondrium, and the subsequent appearance of edema in the lower limbs. The examination revealed hepatosplenomegaly painful on palpation, large-volume ascites, edema of the lower limbs (+++/+++), jaundice of the skin, and sclera (+++/+++). Neurologically, the patient was lucid and oriented in time, space, and person.

The tests taken on the patient on admission are shown in **Table 1**. The ascites fluid study was not pathological concerning infectious processes. The serum-ascites albumin gradient (SAAG) had a value of 2.11. Ascitic fluid, urine, and blood cultures were negative.

The patient underwent an upper GI endoscopy, which revealed mild portal hypertensive gastropathy and the absence of esophageal or gastric varices; the colonoscopy showed only medium-sized congestive internal hemorrhoids without other lesions. Abdominal ultrasound confirmed hepatosplenomegaly and determined the presence of abundant free fluid in the abdominal cavity. A Doppler ultrasound of the portal vein and suprahepatic veins was performed, revealing the left suprahepatic vein of 8.4 mm and visible flow, the middle filiform suprahepatic vein of 4 mm with a visible flow, and the right suprahepatic vein of 9.4 mm with no flow. These results suggest probable thrombosis related to probable Budd-Chiari syndrome.

Table 1. Admission laboratory analysis

TB	12.59
DB	7.53
AP	595
GGTP	817
GOT	159
GPT	74
Total protein and albumin	TP: 5.93; Alb: 2.9; globulins: 2.9
Leukocytes	L: 19,200; S: 88%; B: 2%
Hemoglobin	8.9 g/dL
Platelets	406,000
PT-INR/PPT	1.4-16/46
Peripheral blood smear	- White series: neutrophilia, reactive lymphocytes 2% - Red series: normochromic normocytic - Platelet series: some giant platelets
Coombs (R and L)	Negative
Creatinine/Urea	0.68 mg/dL/15
CRP	65
PCT	0.4
AFP	8.3
Anti-HCV	Not reactive
HBs-Ac	Not reactive
HB-Ac core	Not reactive
HBsAg	Not reactive
Ascitic fluid study	101 cells/mm^3; mononuclear: 88%; Alb: 0.79 g/dL; LDH: 55 U/L; protein: 1.5 g/dL

B: band; AFP: alpha-fetoprotein; Alb: albumin; Anti-HCV: antibodies against the hepatitis C virus; DB: direct bilirubin; TB: total bilirubin; AP: alkaline phosphatase; GGTP: gamma-glutamyl transpeptidase; HBs-Ac: specific antibody directed against the hepatitis B virus surface antigen; HB-Ac core: total core antibody to hepatitis B virus; HBsAg: hepatitis B virus surface antigen; PT-INR: prothrombin time with international normalized ratio; L: leukocytes; CRP: C-reactive protein; PCT: procalcitonin; TP: total protein; S: segmented; GOT: aspartate aminotransferase; GPT: alanine aminotransferase; PTT: partial thromboplastin time. Source: Clinical Pathology Service, Víctor Lazarte Echegaray Hospital.

Therefore, we decided to perform a venous magnetic resonance angiography. It showed thinning of the right suprahepatic vein with an irregularly thinned caliber of up to 3 mm, compatible with probable thrombosis and absence of signal emptiness proximal to the IVC; thin, threadlike courses of the left suprahepatic vein and the proximal portion of the middle suprahepatic vein, suggesting probable partial thrombosis; the portal vein of 13 mm, without signs of thrombosis. The radiological report of the venous magnetic resonance angiography found the portal vein with a preserved course and a thinning of the suprahepatic veins, suggesting a probable Budd-Chiari syndrome (**Figures 1** and **2**).

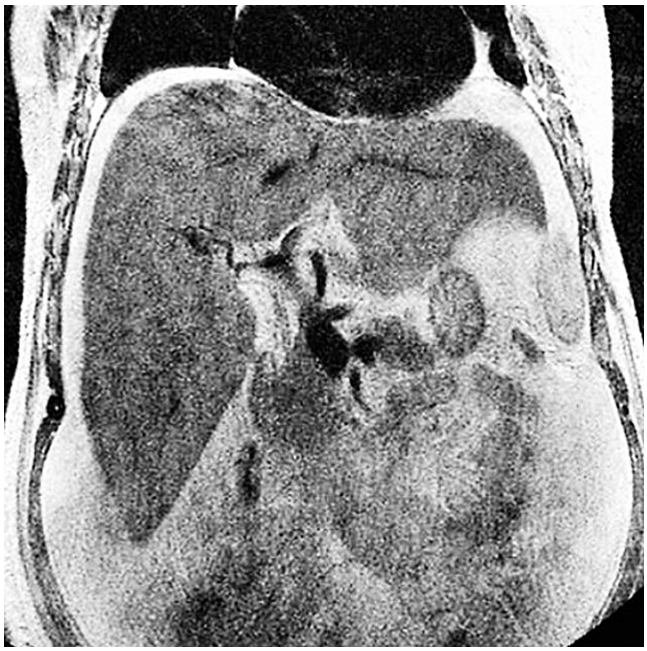

Figure 1. Thinning of the suprahepatic veins (MRI). Source: Radiology Service, Víctor Lazarte Echegaray Hospital.

Ultrasound-guided percutaneous liver biopsy was performed. The sample consisted of 15 portal triads. The histopathological report found liver parenchyma characterized by hepatocyte edema, Mallory-Denk bodies, acidophilic (apoptotic) bodies located predominantly in zone 3, associated with mixed inflammation (moderate portal inflammation and moderate interface hepatitis), necrosis in a 2-4 foci/10x patch, macrovesicular steatosis in 60%, diffuse fibrosis with the formation of centrilobular portal-vein bridges, without signs of cholestasis or congestion signs in the sinusoidal microvasculature. These findings are compatible with diagnosing non-cirrhotic alcoholic steatohepatitis with an Ishak fibrosis score of 3 (**Figures 3-5**). Thus, the absence of definitive histopathological criteria for Budd-Chiari syndrome was confirmed. Maddrey's discriminant function (32.6 points), Model for End-Stage Liver Disease (MELD) (21 points), and Glasgow Alcoholic Hepatitis Score (GAHS) (8.7 points) were calculated, arriving at a diagnosis of severe alcoholic hepatitis.

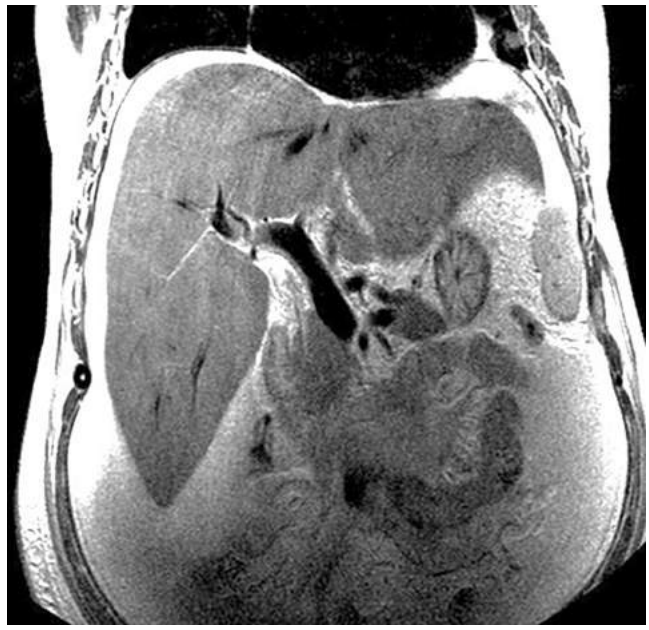

Figure 2. Thinning of the suprahepatic veins and portal vein of preserved caliber (MRI). Source: Radiology Service, Víctor Lazarte Echegaray Hospital.

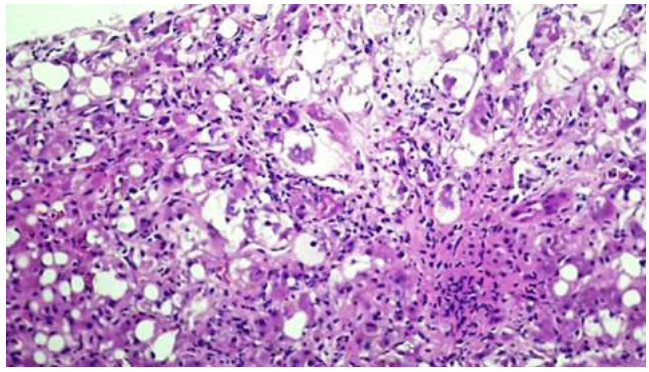

Figure 3. Macrovesicular steatosis and hepatocyte edema. Mallory-Denk body (arrow). Source: Pathology Service, Víctor Lazarte Echegaray Hospital.

Treatment based on corticosteroids was started: prednisone 40 mg/day orally with a planned schedule of 28 days and N-acetylcysteine 100 mg/kg/day for five days intravenously; anticoagulants were not administered. The Lille score was determined on the seventh day to control the response to corticosteroid-based treatment, which revealed a value of 0.08 (less than 0.45). Consequently, we decided to continue with the 28-day corticosteroid regimen.

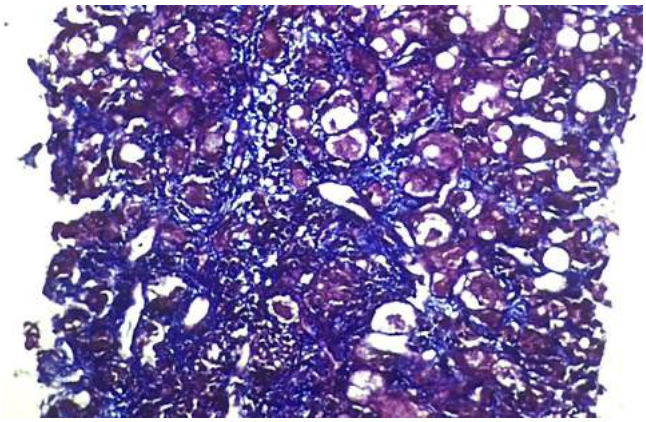

Figure 4. Masson's trichrome stain: bridging fibrosis. Source: Pathology Service, Víctor Lazarte Echegaray Hospital.

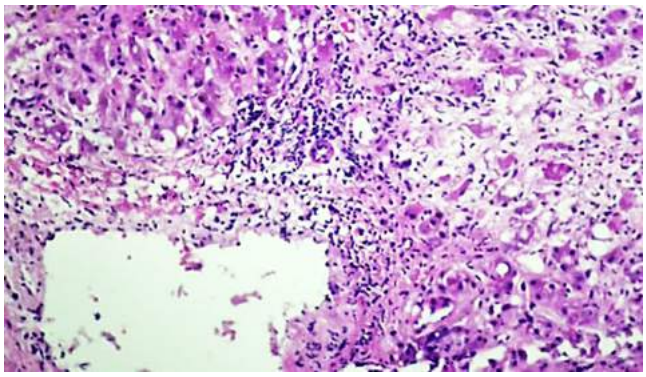

Figure 5. Inflammatory infiltrate, macrovesicular steatosis. Source: Pathology Service, Víctor Lazarte Echegaray Hospital.

After 28 days of completing the regimen, the follow-up analysis showed an improvement (**Table 2**) parallel to a good clinical evolution. The patient was discharged after 33 days of hospital stay in his baseline status as an independent person (carrying out his daily and personal care activities without help) with optimal functional status.

Table 2. Follow-up analytics

TB	3
DB	1.6
AP	620
GGTP	430
GOT	109
GPT	56
Total protein and albumin	TP: 5.3; Alb: 3.1; Alb/Glob: 1.2
Leukocytes	12,500
Hemoglobin	9.8
Platelets	260,000
PT-INR/PPT	1.3-15/43
Creatinine	0.5
Urea	22

Source: Clinical Pathology Service, Víctor Lazarte Echegaray Hospital.

DISCUSSION

The diagnosis of alcoholic hepatitis has three scenarios: probable, possible, and definitive alcoholic hepatitis. The probable one is based on the fulfillment of diagnostic criteria such as recent appearance or worsening of jaundice with or without ascites, with or without encephalopathy, associated with alcohol use in hepatotoxic doses (greater than 50 g/day) in less than four weeks prior by a person who uses alcohol chronically for more than six months. These criteria are accompanied by serological findings such as total bilirubin greater than 3 mg/dL, GOT and GPT greater than 50 IU/L and less than 400 IU/L, AST/ALT ratio greater than 2, GGTP greater than 100 U/L, serum albumin less than 3g/dL, INR greater than 1.5, leukocytosis greater than 12,000 associated with neutrophilia, variable degrees of anemia, or thrombocytopenia in cases of cirrhosis. The above excludes potentially confounding factors of the presumptive diagnosis[1,3].

Possible alcoholic hepatitis is identified when the indicated criteria are met but with potentially confounding factors, as in the present case: the possibility of Budd-Chiari syndrome concomitant with alcoholic hepatitis.

Finally, definitive alcoholic hepatitis is identified by confirmatory liver histopathological findings such as infiltration of inflammatory cells at the portal and periportal levels, with certain degrees of fibrosis, macro or microvesicular steatosis with ballooning of hepatocytes, megamitochondria, and Mallory-Denk bodies as pathognomonic findings of alcoholic hepatitis.

The entity known as pseudo-Budd-Chiari syndrome was first described in 1977[7]. Unlike Budd-Chiari syndrome, characterized by suprahepatic vein thrombosis, this syndrome has similar clinical and imaging findings. However, biopsies or autopsies fail to demonstrate suprahepatic vein thrombosis or histopathological findings compatible with the syndrome[7].

In a study conducted in 2002, Janssen et al. described three cases of patients with decompensated alcoholic

liver disease who had venous Doppler ultrasounds with a decreased flow in the suprahepatic veins but direct angiographies without thrombi in their lumen. Lastly, these patients underwent a liver biopsy without congestive histopathological findings due to a probable Budd-Chiari syndrome related to the initial diagnosis[9].

Similar results were found by Robles-Medranda et al. in the study they conducted in 2006, based on the pseudo-Budd-Chiari syndrome associated with alcoholic steatohepatitis and liver cirrhosis. They concluded that the imaging of a decreased flow near the suprahepatic veins, probably related to Budd-Chiari syndrome, was produced by an extrinsic compression of their lumen associated with an enlarged liver parenchyma resulting from a vast inflammatory pattern due to alcoholic steatohepatitis and not by intraluminal thrombi. Thus, anticoagulation was not considered within the prescribed therapy[10].

Sheth et al., in a study conducted in 2014, reported a case of alcoholic steatohepatitis masked by probable Budd-Chiari syndrome. After the liver biopsy, they determined that the mechanical compression exerted by the liver parenchyma on the suprahepatic veins is associated with the vast inflammatory infiltrate based on neutrophils and other inflammatory cells. They highlight the potential reversibility of this condition with medical treatment based on the administration of corticosteroids without the need for anticoagulation[11].

It should be noted that recently in the Baveno VII consensus, carried out in 2021 and published in 2022, this entity is considered a secondary Budd-Chiari syndrome because the mechanism of action of venous obstruction is associated with extrinsic compression, as mentioned above, which may occur, for example, due to a benign or malignant tumor. Nevertheless, we can extrapolate this designation to cases in which extrinsic compression occurs due to, for example, severely inflamed liver parenchyma, as in cases of severe alcoholic hepatitis[8].

CONCLUSION

In the case presented, severe alcoholic hepatitis is associated with imaging characteristics suggestive of Budd-Chiari syndrome, which creates confusion in the diagnosis and subsequent management of the patient. Reaching the diagnosis of secondary Budd-Chiari syndrome requires access to more complex or invasive methods, such as liver biopsy in cases like the present one. Therefore, more scientific evidence is needed to differentiate between both entities promptly and clarify on a scientific basis the best diagnostic and therapeutic course of action for these patients.

Conflict of interests

The authors declare not to have any interest conflicts.

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Case report

Pouchitis secondary to cytomegalovirus infection: Case report and literature review

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Abstract

Total proctocolectomy with ileal pouch is the surgical procedure of choice for ulcerative colitis refractory to medical treatment, and pouchitis is the most frequent complication. It can affect up to 50% of patients in the first five years of the procedure. Although the etiology is not well established, its manifestation could be related to dysbiosis resulting from fecal stasis in genetically susceptible individuals with altered immune responses. Typical symptoms of pouchitis, such as diarrhea, abdominal pain, tenesmus, urgency, fecal incontinence, and, less commonly, rectal bleeding, are nonspecific, and the diagnosis must be confirmed by endoscopic and histologic examination. Cytomegalovirus infection is an infrequent cause of pouchitis; however, it should be considered in patients with pouchitis refractory to initial antibiotic management. Diagnostic tests include serological tests such as the measurement of antibodies, antigenemia, and C-reactive protein (CRP) in blood. The treatment of choice is ganciclovir, an intravenous drug that can induce severe complications such as myelosuppression, neutropenia, and thrombocytopenia. Post-treatment endoscopic follow-up is recommended to ensure mucosal healing, especially when there is suspicion of Crohn's disease or involvement of the afferent loop on initial endoscopy.

Keywords

Ulcerative colitis, pouchitis, cytomegalovirus, proctocolectomy, ileal pouch.

INTRODUCTION

It is presumed that between 6% and 15% of patients with ulcerative colitis will require surgical management despite advances in drug therapy; this occurs mainly in cases of refractory disease or the development of colorectal carcinoma during the disease[(1)]. Total proctocolectomy with an ileal pouch is considered the first line of surgical treatment. Pouchitis is the most common complication, affecting approximately 20% of patients during the first year and nearly 50% in the first five years of the surgical procedure[(2,3)]. Different techniques for the creation of the ileal pouch and associated complications classified as early (in the first thirty days of the procedure) or late have been described[(4)] (**Figure 1**, **Table 1**).

CASE PRESENTATION

We present the case of a 32-year-old female patient diagnosed with refractory ulcerative colitis (RUC) since 18, who

required a total proctocolectomy with an ileal J-pouch and a protective ileostomy in 2010. Restitution of bowel transit was performed six months later. Since the first year of the surgical procedure, the patient had had between 2 and 3 episodes of pouchitis, for which she received antibiotic treatment (ciprofloxacin/metronidazole) that ultimately resolved the symptoms. In May 2020, the patient consulted again due to increased stool frequency (>10 in 24 hours), abdominal pain and bloating, rectal bleeding, and fecal incontinence. It was regarded as a new episode of pouchitis, so treatment with ciprofloxacin was started at 500 mg every 12 hours. An endoscopic assessment was requested and performed two months later, with evidence of multiple fibrin-covered ulcers and some pustular elevations with pseudomembranous formation. Biopsies were taken (**Figure 2**).

The histopathological report listed epithelium with changes marked by chronicity, including architectural distortion, lymphoplasmacytic infiltrate, intestinal metaplasia, and decreased intraglandular mucin with extensive neutrophil polymorphonuclear activity, crypt abscesses, and viral cytopathic changes compatible with cytomegalovirus (CMV) (**Figure 3**).

The patient remained symptomatic, did not respond to the antibiotic initially administered, and presented with an exacerbation of symptoms, so we decided to start antiviral treatment with intravenous ganciclovir plus ciprofloxacin. Twenty-one days of treatment were completed with a favorable clinical response and no documented adverse reactions to its administration. The patient was discharged due to the complete resolution of symptoms. Endoscopic follow-up was performed three months later, finding a noti-

Table 1. Complications associated with the creation of the ileal pouch

Early
Hemorrhage (suture line, pouch ischemia, intra-abdominal bleeding, intramural bleeding)
Sepsis (anastomotic leak, infected hematoma)
Portal thrombosis
Late
Intestinal obstruction
Pouch dysfunction - Mechanical causes (obstruction, stricture) - Pouchitis - Cuffitis - Irritable pouch syndrome
Pouch failure
Dysplasia or malignancy
Infertility

Source: Modified from[4].

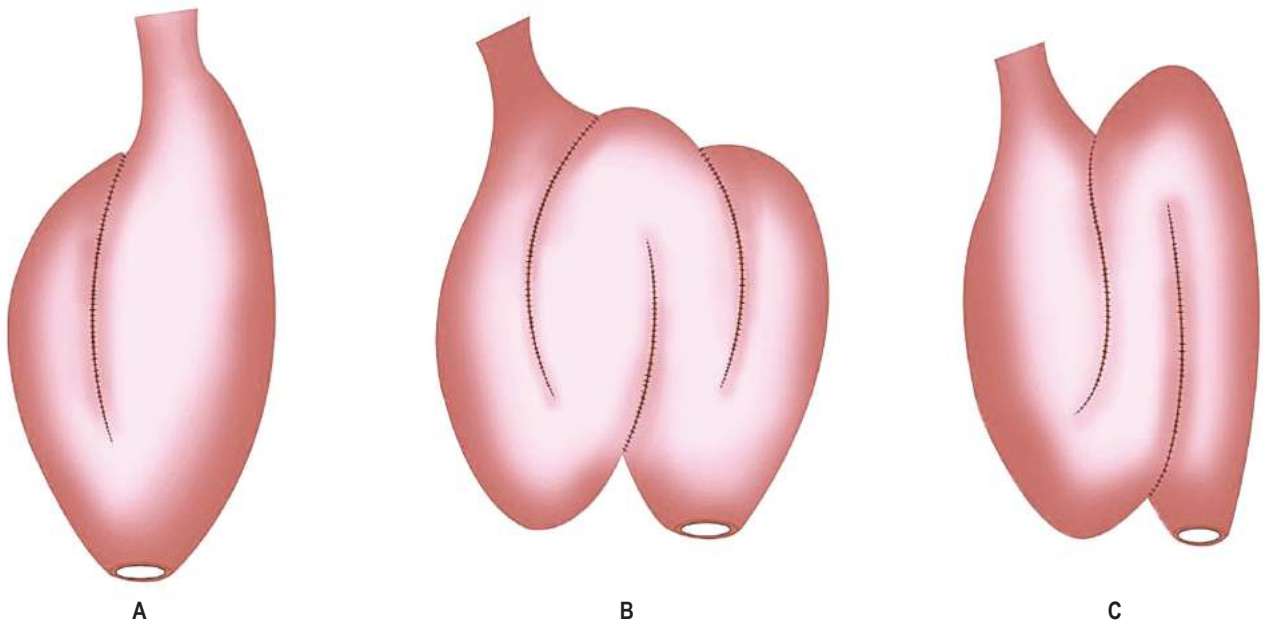

Figure 1. Types of ileal pouches. **A.** Ileal J-pouch. **B.** Ileal W-pouch. **C.** Ileal S-pouch. Source: Modified from[4].

ceable improvement compared to the initial study (**Figure 4**). Currently, the patient remains asymptomatic and is being treated with oral rifaximin.

DISCUSSION

Pouchitis is a non-specific inflammation of the ileal pouch whose pathogenesis is unclear. Nevertheless, it could be related to alterations in the microbiota of the pouch as a result of fecal impaction in genetically susceptible individuals with an altered immune response[5]. Typical symptoms are watery diarrhea, abdominal pain, tenesmus, urgency, fecal incontinence, and, less frequently, rectal bleeding; however, this clinical scenario is not specific. The diagnosis must be confirmed by endoscopic and histological changes to rule out other entities, such as irritable pouch syndrome or mechanical conditions associated with the surgical procedure[6]. The main endoscopic features

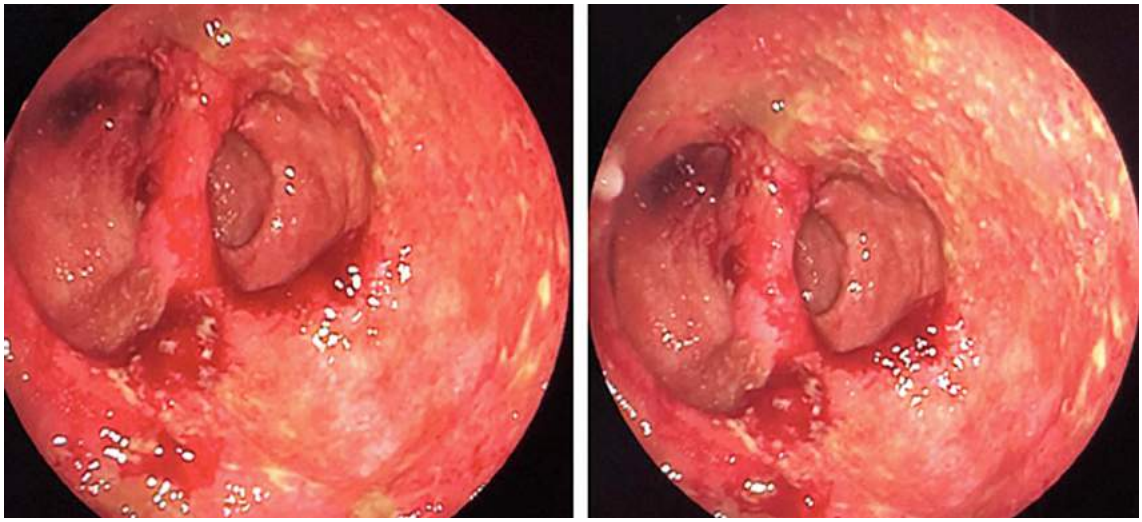

Figure 2. Endoscopic findings of pouchitis: edema, erythema, mucosal friability, fibrin-covered ulcers, and pustular elevations. Source: Authors' archive.

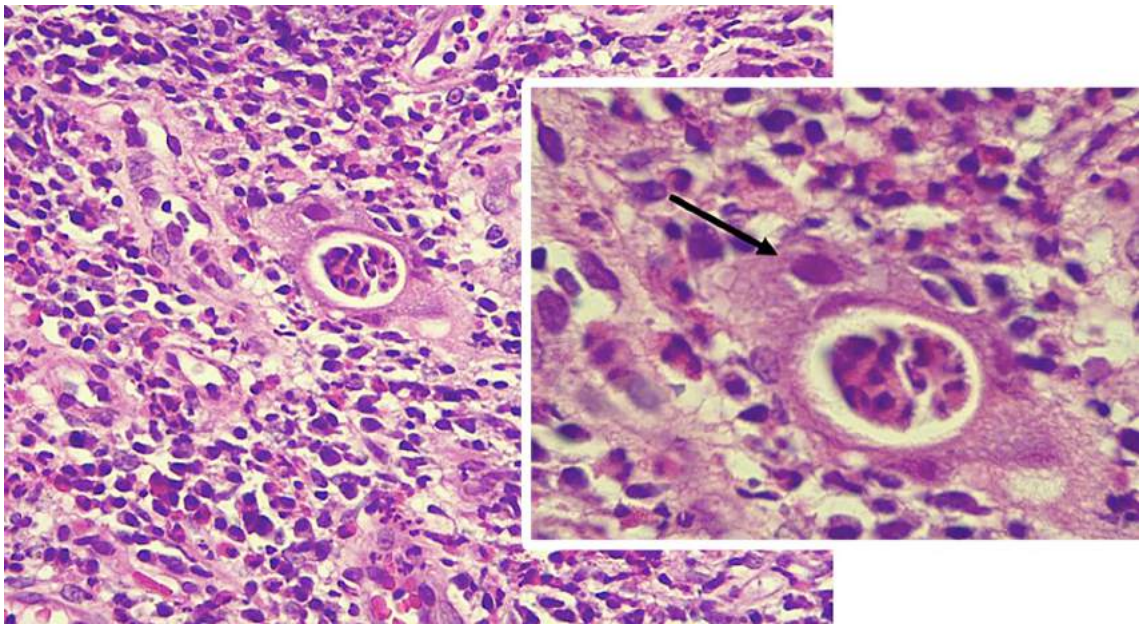

Figure 3. Histological findings in cytomegalovirus pouchitis. Mixed inflammatory infiltrates and cytomegalic cells with an enlarged nucleus, suspicious for cytomegalovirus inclusion (arrow). Source: Authors' archive.

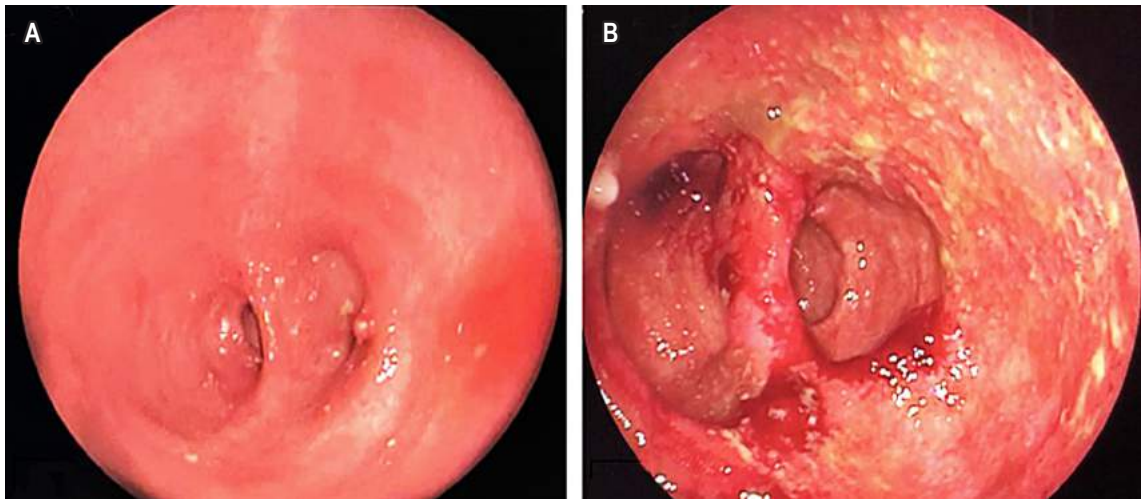

Figure 4. A. Endoscopic follow-up after treatment with ganciclovir. **B.** Endoscopy before antiviral treatment. Source: Authors' archive.

include erythema, edema, friability, hemorrhage, loss of vascular pattern, erosions, and ulcerations[7] (**Figure 2**).

It is advisable to take 4 to 6 pouch biopsies even in case of mild or absent inflammation (in mild forms, the endoscopic appearance may be normal) and 4 to 6 biopsies of the afferent loop to detect granulomas, ischemia, CMV inclusions, dysplasia, or ischemia[8, 9]. Typical histological findings are acute inflammation with neutrophil infiltration, crypt abscesses, or mucosal ulceration often associated with chronic changes such as villous atrophy, crypt distortion, and chronic inflammatory infiltrate[10] (**Figure 3**).

Once the diagnosis is made, the degree of disease activity should be established using the Pouchitis Disease Activity Index (PDAI). This index consists of a numerical scale that quantifies the severity of pouchitis and considers the clinical, endoscopic, and histological findings for its calculation[11]. Diagnosis requires a score ≥ 7. Since the histological report is not always available, the modified PDAI that only includes clinical and endoscopic criteria has been designed; the diagnosis, in this case, requires a score ≥ 5[12] (**Table 2**).

Pouchitis can be classified by the duration of the symptoms, as acute or chronic (longer or shorter than four weeks); by the response to antibiotics, as responders, dependent, or refractory; by the frequency, as infrequent, recurrent, or continuous (greater or less than three episodes per year); and by its etiology, as idiopathic (most cases) or secondary. The latter includes infectious causes (*Clostridium difficile*, CMV), mechanical complications related to the surgical procedure (ischemia or stricture), use of non-steroidal anti-inflammatory drugs, or Crohn's disease of the pouch[6, 10]. The probability of pouch failure is 3%-15%, mainly in patients refractory to antibiotic treatment; in this case, surgical management with resection of the pouch, a definitive ileostomy, or both may be required[6, 13].

Antibiotics are the first line of treatment, with response rates close to 80%; metronidazole and ciprofloxacin have proven effective[14]. Relapse after a first episode of pouchitis is typical, and about 20% will develop frequent relapses or refractory disease[2]. Those patients with three or more annual episodes despite antibiotic treatment are considered antibiotic-dependent[15], and probiotics are an effective option to maintain remission induced by antibiotic therapy[16, 17]. Other maintenance therapies, such as oral or topical rifaximin and mesalazine, have also been used and could be considered; however, the evidence is of low quality to advise its widespread use[18, 19]. In these patients, as in those who do not initially respond to antibiotic treatment, secondary causes should always be ruled out, and if documented, specific treatment should be indicated[2].

CMV infection is uncommon as a cause of pouchitis; nonetheless, it should be considered in patients who do not respond to initial antibiotic treatment. CMV is a double-stranded DNA virus belonging to the *Herpesviridae* family; humans are its only natural host, and ubiquitous in the adult population. Primary infection generally occurs in childhood and is usually asymptomatic in immunocompetent patients, followed by an indefinite period of residence in endothelial cells, fibroblasts, and cells of the myeloid lineage. Seroprevalence varies depending on age and ethnicity, with percentages close to 90% in older adults[20]. CMV lesions may occur due to primary infection or reac-

Table 2. PDAI index. Pouchitis defined as PDAI ≥ 7 or modified PDAI ≥ 5

I. Clinical criteria	
Number of bowel movements/day above normal	
- Same	0
- 1-2 more	1
- Three or more	2
Blood in the stool	
- No/Occasional	0
- Daily	1
Fecal urgency or abdominal cramps	
- Absent	0
- Occasional	1
- Usual	2
Fever > 38°C	
- No	0
- Yes	1
II. Endoscopic criteria	
Edema	1
Granularity	1
Friability	1
Loss of vascular pattern	1
Mucous exudate	1
Ulceration	1
Edema	1
III. Histological criteria	
Polymorphonuclear infiltration	
- Mild	1
- Moderate + crypt abscesses	2
- Severe + crypt abscesses	3
Low power field ulceration (average)	
- < 25%	1
- 25%-50%	2
- > 50%	3

Source: Taken from[12].

tivation of the latent virus. Reactivation occurs mainly in individuals with compromised cellular immunity; in patients with inflammatory bowel disease, the known risk factors for reactivation are advanced age, female sex, severe disease, and recurrent use of corticosteroids[21, 22]. Active CMV infection implies that it is detectable in blood or pathological specimens (biopsy), including histology, immunohistochemistry (IHC), or polymerase chain reaction (PCR) in tissue[23].

Diagnostic tests include serological tests such as the measurement of antibodies, antigenemia, and C-reactive protein (CRP) in blood. Immunoglobulin G (IgG) diagnoses previous contact, while IgM is very sensitive and specific for detecting acute infection or reactivation when accompanied by viremia[23]. PCR in the blood can be diagnostic, but no cut-off point differentiates latent from active infection. The sensitivity and specificity of antigenemia have been reported at 47% and 81%, respectively[20, 24]. Hematoxylin/eosin staining offers high specificity (92% to 100%) but low sensitivity (10% to 87%); IHC increases sensitivity from 78% to 93%[25].

Tissue PCR has high sensitivity (92%-96%) and specificity (93%-98%) and can be considered when IHC is negative in cases with high suspicion of CMV infection[26]. Despite the high sensitivity and specificity of the culture (45%-75% and 89%-100%, respectively), it lacks clinical utility since the results can take between two and four weeks[20].

Ganciclovir is the treatment of choice and must be administered as an intravenous infusion due to its low bioavailability by the oral route. The recommended dose is 5 mg/kg twice a day for 2 to 3 weeks; it can induce severe complications such as myelosuppression, neutropenia, and thrombocytopenia, as well as headache, nausea, vomiting, and hypotension, so these effects should be monitored regularly[20, 21]. This treatment usually requires hospitalization; however, it could be replaced by oral valganciclovir, although its efficacy is controversial[20]. There are data in the literature on follow-up after antiviral therapy. Still, endoscopic assessment is suggested to ensure mucosal healing, especially when there is suspicion of Crohn's disease or involvement of the afferent loop on initial endoscopy[20, 21].

CONCLUSIONS

Total proctocolectomy with ileal pouch is the treatment of choice for RUC, and pouchitis is the most frequent complication in these patients. CMV infection is rare, and a high index of suspicion is required for its diagnosis; however, symptoms in immunosuppressed individuals or those who do not respond to conventional treatment should always lead to suspicion of this condition.

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Case report

Peutz-Jeghers syndrome: Case report

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Abstract

Peutz-Jeghers syndrome is an autosomal dominant hereditary disease characterized by multiple hamartomatous-type gastrointestinal polyps associated with mucocutaneous hyperpigmentation.

A case of a 25-year-old male patient with a history of right hemicolectomy due to ileocolonic intussusception secondary to a giant polyp in the terminal ileum is reported. This patient consulted for rectal bleeding, with evidence on physical examination of dark brown hyperchromatic lesions on the buccal mucosa. A total colonoscopy was performed, noting multiple polyps. Endoscopic mucosectomy was conducted on some of them, being histopathologically compatible with hamartomatous polyps.

Keywords

Peutz-Jeghers syndrome, hamartomatous polyps, hyperchromatic lesions.

INTRODUCTION

Peutz-Jeghers syndrome (PJS) is a rare, autosomal dominant, hereditary polyposis associated with a high frequency of STK11/LKB1 gene mutations located on the short arm of chromosome 19[1, 4]. It is characterized by mucocutaneous pigmentation and multiple hamartomatous polyps, with an increased risk of gastrointestinal malignancy. It has also been associated with an elevated risk of gynecological, testicular, and thyroid cancer[1].

Mucocutaneous pigmentation is due to melanin-laden macrophages in the dermis and increased melanocytes at the dermal-epidermal junction, present in about 95% of patients. These usually appear in childhood around the mouth, nostrils, perianal region, fingers, and knuckles[2,5].

PJS polyps are usually located in the small intestine, mainly in the jejunum, followed by the colon, rectum, and stomach. They can also appear outside the gastrointestinal tract, including the renal pelvis, bladder, lungs, and nasopharynx[5]. Histological features include an elongated wave-shaped epithelial component, a cystic dilatation of the gland extending into the submucosa, and smooth muscle extending into the fronds of polyps[2].

The clinical diagnosis should be considered in an individual meeting at least one of the following criteria[1-3]:

1. Three or more histologically confirmed polyps

2. Peutz-Jeghers polyps, regardless of number, in a subject with a family history of PJS
3. Characteristic mucocutaneous pigmentation in an individual with a family history of PJS
4. Peutz-Jeghers polyps associated with characteristic mucocutaneous pigmentation

CLINICAL CASE

We present the case of a 25-year-old man from the urban area of the municipality of Barbosa (Santander), who was admitted to the emergency department due to diffuse abdominal pain of three years of evolution and rectal bleeding. He had a history of right hemicolectomy for acute abdomen secondary to ileocolonic intussusception due to a giant polyp in the terminal ileum measuring 45 cm x 42 cm. Upon checking the surgical specimen, another giant polyp was found in the jejunum, 80 cm from the angle of Treitz, both with hamartomatous histopathology. The physical examination on admission revealed multiple hyperchromatic dark brown macular lesions on the buccal mucosa, with no other relevant findings (**Figure 1**).

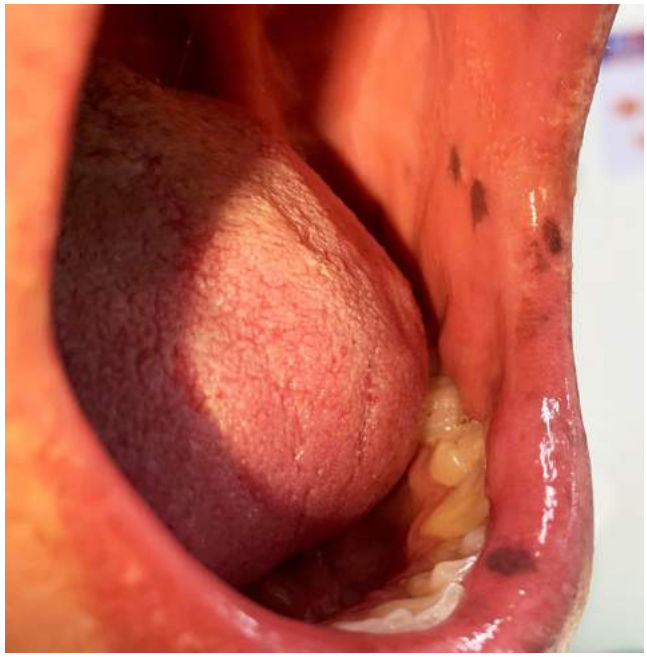

Figure 1. Hyperchromatic spots on the buccal mucosa. Source: Authors' archive.

The patient was hospitalized and underwent a colonoscopy, noting two 7 mm polyps near the rectum and two pedunculated polyps in the proximal transverse muscle measuring 20 mm x 15 mm (**Figure 2**) and 20 mm x 20 mm (**Figure 3**), respectively. An upper digestive endoscopy was also performed, documenting multiple sessile polyps (around ten) between the first and second duodenal portions, with diameters ranging from 4 mm to 12 mm (**Figures 4** and **5**). All colon polyps were endoscopically resected, and one of the largest duodenal polyps was removed.

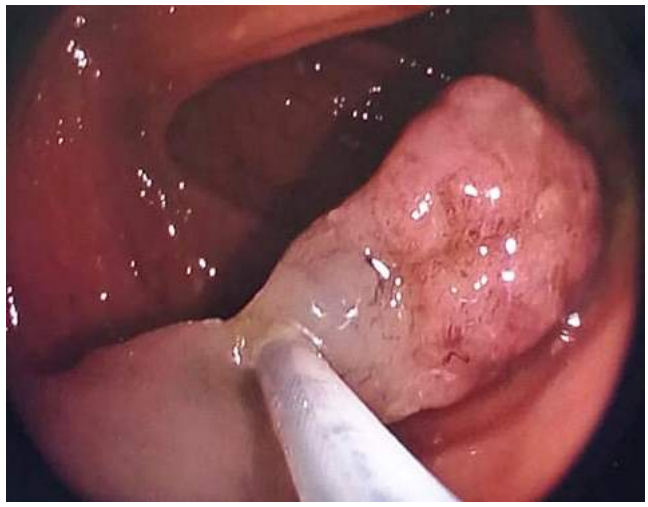

Figure 2. 20 mm x 15 mm pedunculated polyp of the transverse colon. Source: Authors' archive.

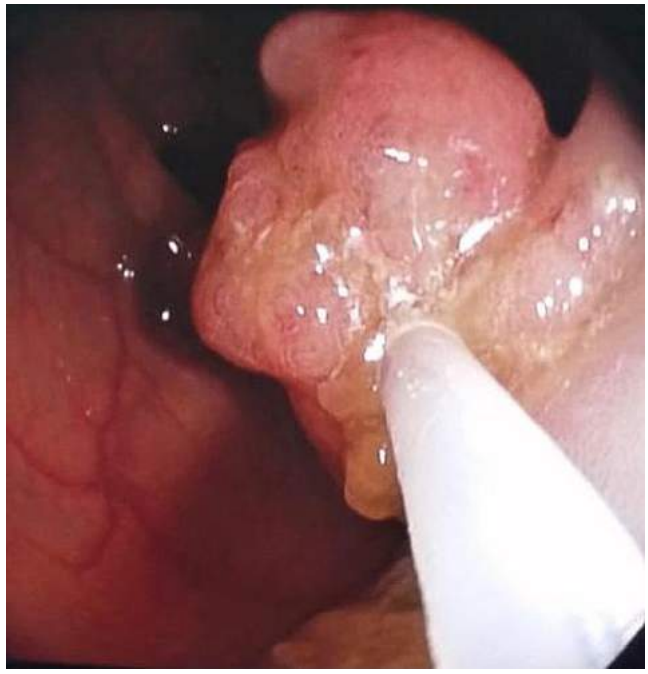

Figure 3. 20 mm x 20 mm transverse pedunculated polyp. Source: Authors' archive.

The histopathological report of the colon polyps was of the hamartomatous type, and one was a tubular adenoma without dysplasia (**Figures 6** and **7**). The resected duodenal polyp was reported as a hamartomatous polyp.

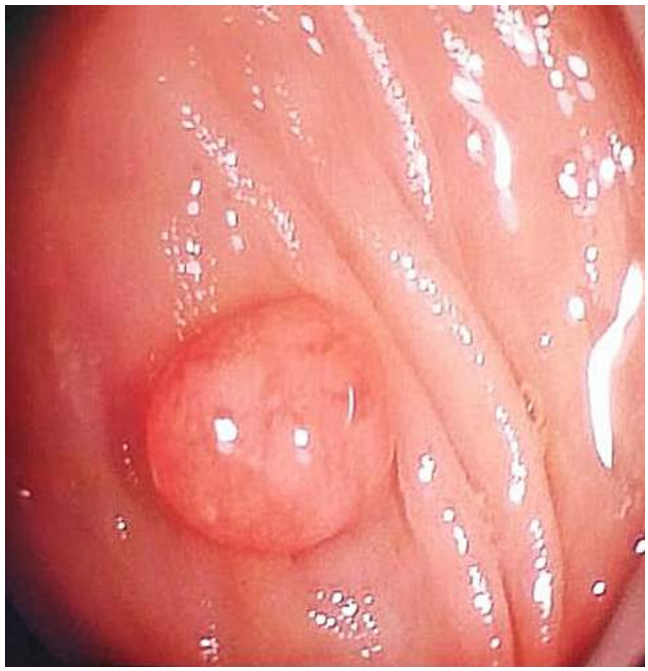

Figure 4. Hamartomatous-looking sessile polyp of the duodenum. Source: Authors' archive.

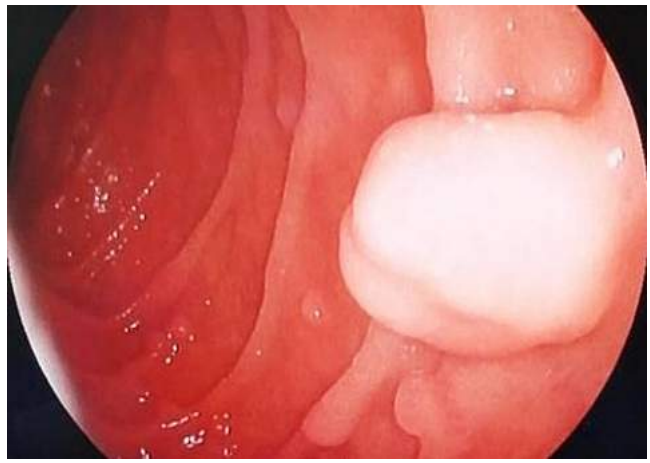

Figure 5. Hamartomatous-looking sub-pedunculated polyp of the duodenum. Source: Authors' archive.

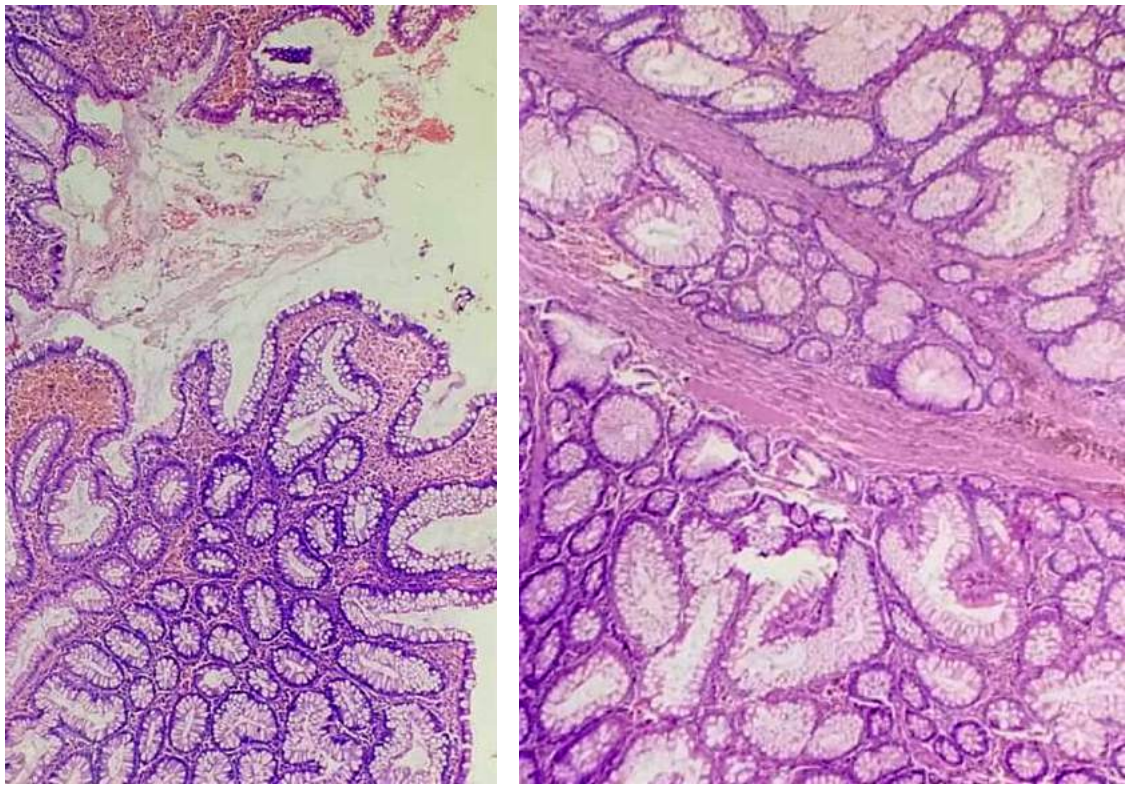

Figure 6. Polypoid lesions made up of glands of various shapes and sizes, supported by bands of smooth muscle fibers. Source: Authors' archive.

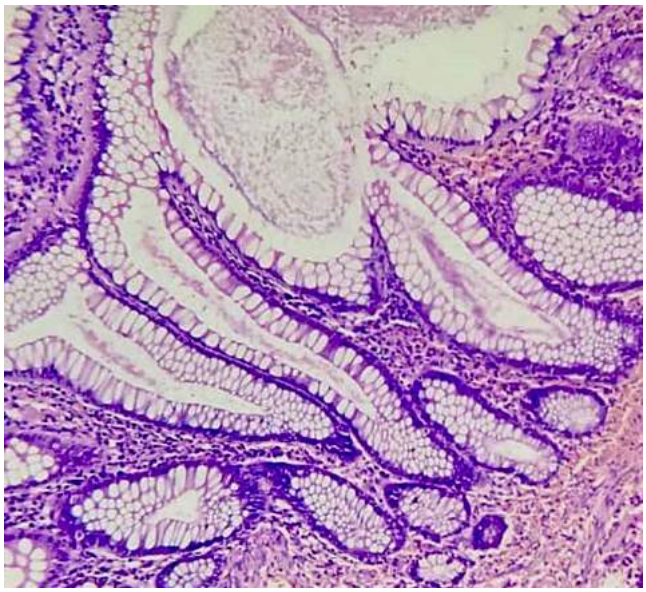

Figure 7. Different types of cells are present such as columnar, goblet, and endocrine cells. There are no signs of dysplasia. Source: Authors' archive.

DISCUSSION

Peutz-Jeghers syndrome is a rare, autosomal dominant disease with few reports in our country. According to Wu et al., it has an estimated incidence of one case per 25,000-300,000 live births. It may occur in any ethnic group and affects men and women alike. Its average age of diagnosis is 23 years, and the average age for cancer development is 42 years[6].

Moreover, according to Beggs et al., the first manifestation is often gastrointestinal obstruction due to intussusception by polyps, 69% of the time in the small intestine, and usually occurs between 6 and 18 years of age[2,6].

The main goal in effectively treating patients with Peutz-Jeghers syndrome is based on surveillance, prevention, and treatment of complications. Recommendations include[6-8]:

- Upper digestive tract endoscopy:
  - It is initially detected from the age of 12.
  - If polyps are found, repeat annually.
  - Repeat every 2-3 years until adulthood in the absence of polyps.
- Colonoscopy:
  - Initial screening starts at age 12 or earlier if symptoms are reported.
  - If polyps are found, repeat annually.
  - In the absence of polyps, repeat at intervals of 1-3 years.
- Pancreas:
  - Magnetic resonance cholangiopancreatography (MRCP), biliopancreatic endoscopic ultrasound, or both: from 25-30 years of age; repeat every 1-2 years.
- Breast:
  - Breast exam: clinical examination every six months from the age of 25.
  - Mammography: from the age of 25.
- Gynecological:
  - Papanicolaou smear: annually.
  - Transvaginal ultrasound: annually from the age of 18.
- Testicles:
  - Consider an annual exam and ultrasound starting at age 10.

Finally, in terms of prevention, we advise providing genetic counseling to couples with a family history of Peutz-Jeghers syndrome who wish to have children[6-10].

CONCLUSIONS

Peutz-Jeghers syndrome is a rare disease but with relevant clinical connotations. These patients have a 15-fold increased risk of gastrointestinal malignancy, although it has also been associated with extraintestinal neoplasms.

It is crucial to know its initial clinical manifestation: hyperpigmented mucocutaneous macules (present in more than 95% of cases), a positive family history of Peutz-Jeghers syndrome, and hamartomatous-type gastrointestinal polyposis.

Thus, a prompt diagnosis would be achieved to implement adequate surveillance, as previously recommended, to avoid complications such as intestinal obstruction secondary to intussusception and emergency surgical interventions and monitor the appearance of premalignant and malignant lesions.

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