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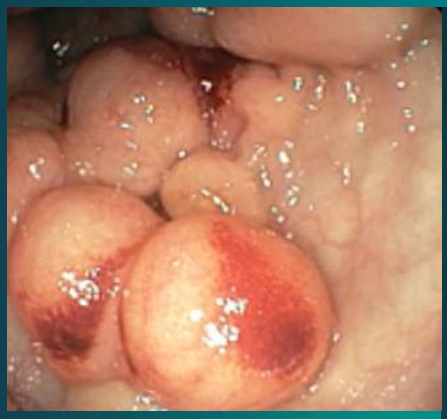

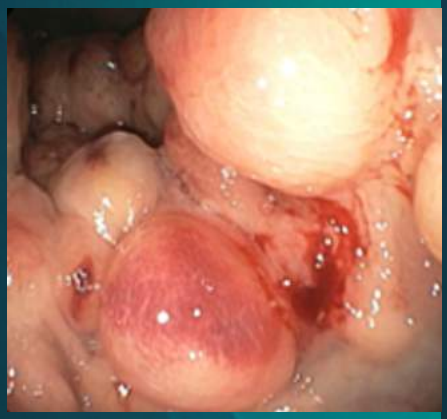

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Editorial

Autoimmune hepatitis: another look

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The understanding of autoimmune hepatitis has significantly evolved over the past decade, transforming from a rare pathology to a top-of-mind condition in hepatology consultations. Nevertheless, it is widely known that different populations exhibit distinct immunological behavior, indicating that our population's characteristics are probably different from those in areas with higher prevalence and incidence, like the Nordic countries. The most pressing challenges involve the low performance of diagnostic tools and the difficulty of treating specific populations, albeit in a small percentage. This situation has led to the treatment of false-positive patients or, in some cases, the failure to treat false-negative patients, with significant consequences.

The article "Characterization of Patients Diagnosed with Autoimmune Hepatitis in a Fourth-Level Hospital in Cali, 2014-2020"[(1)] provides insights into the clinical and paraclinical characteristics of patients with autoimmune hepatitis in our population. It also sheds light on the diagnostic challenges patients and clinicians face, which can lead to different treatment approaches. This study highlights some unique features, such as a higher association with autoimmune thyroid disease than other autoimmune pathologies, lower positivity for anti-smooth muscle antibodies (ASMA) in this group compared to literature reports, and a small number of patients with a simplified score greater than seven. It emphasizes the importance of describing our own statistics and population characteristics, which can aid in understanding the behavior of autoimmune hepatitis in our environment.

Expanding this information to a national database, in conjunction with findings from other institutions, would be beneficial in developing a clinical, diagnostic, and treatment algorithm tailored to our unique clinical and immunological expressions.

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Original article

Characterization of patients diagnosed with autoimmune hepatitis in a fourth level hospital from Cali, 2014-2020

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Abstract

Introduction: Autoimmune hepatitis (AIH) is a chronic inflammatory disease of the liver, rarely identified by clinicians to the point of being detected in late stages. It is rare, although there is a lack of epidemiological data. Early diagnosis has implications for the outcomes and development of advanced liver disease. This study describes sociodemographic, clinical, and laboratory characteristics, treatments received and their response and outcomes of interest in adult patients diagnosed with AIH treated at a university hospital in Cali, Colombia. **Materials and methods:** This observational historical cohort study included patients over 18 years of age of both sexes diagnosed with definitive AIH treated in the emergency services, outpatient clinic, intensive care, and hospitalization at the Fundación Valle del Lili University Hospital between January 2014 and December 2020. **Results:** 81 patients met the inclusion criteria; 86% were women. The median age was 49 (30–61), and autoimmune disease was comorbidity in 28.4%. Regarding pharmacological treatment, prednisolone and azathioprine were the most frequently used for induction and maintenance. The regimen of prednisolone or prednisolone with azathioprine was used in 79%. Four patients underwent liver transplantation, with no acute liver failure cases. There was only one case of mortality not related to AIH during follow-up. **Conclusion:** Patients with definitive AIH are mostly middle-aged adults and women, as found in the literature, with a low percentage of cirrhosis and, in earlier stages, low mortality and liver transplantation requirement. The low percentage of liver biopsy is the most critical limitation in the diagnosis and, therefore, in the outcomes of undiagnosed patients.

Keywords

Hepatitis, autoimmune, Cali.

INTRODUCTION

Autoimmune hepatitis (AIH) is a chronic inflammatory liver disease with a diverse range of clinical manifestations. The disease is characterized by progressive hepatocellular necroinflammatory activity and secondary fibrosis, as initially described by Waldestrom in 1950.[1] The pathogenesis of AIH is mediated by an immune reaction against autoantigens of the hepatocyte membrane, a loss of immune tolerance, and an increased risk of developing cirrhosis, hepatocellular carcinoma, and acute liver failure. Traditionally, two types of autoimmune hepatitis have been described, with type 1 accounting for 80% of cases and a female-to-male ratio of 3.6:1.[2,3] With a worldwide

incidence and prevalence of 1.37 and 17.44 per 100,000 inhabitants, respectively, AIH cannot be considered a rare phenomenon. The current study aims to describe the sociodemographic, clinical, and laboratory characteristics of AIH adult patients treated at a university hospital in Cali, Colombia, as well as the treatments received, their response to them, and relevant outcomes.

MATERIALS AND METHODS

This historical observational group study enrolled patients over the age of 16, of both sexes, who were diagnosed with autoimmune hepatitis (AIH) and treated at Hospital Universitario Fundación Valle del Lili between January 2014 and December 2020, in various clinical settings, including emergency, outpatient, intensive care unit, and inpatient services. We utilized the institutional medical records software system, SAP, to identify patients with an ICD-10 K754 diagnosis reported in their corresponding medical records upon admission, followed by subsequent screening (**Figure 1**) until finding the ones with a definitive diagnosis of AIH. To achieve this, we used the International Autoimmune Hepatitis Group (IAIHG) scoring system of 2008,[4] as specified in **Table 1**. In cases of overlap syndrome, we included patients with the necessary biochemical characteristics, autoantibody profile, hepatic histological findings, and cholangiographic findings.[5] We also gathered demographic, clinical, serological, histological, and treatment variables, as well as outcomes such as cirrhosis or a change in Child-Pugh score, transplantation, and death (related or unrelated to AIH).

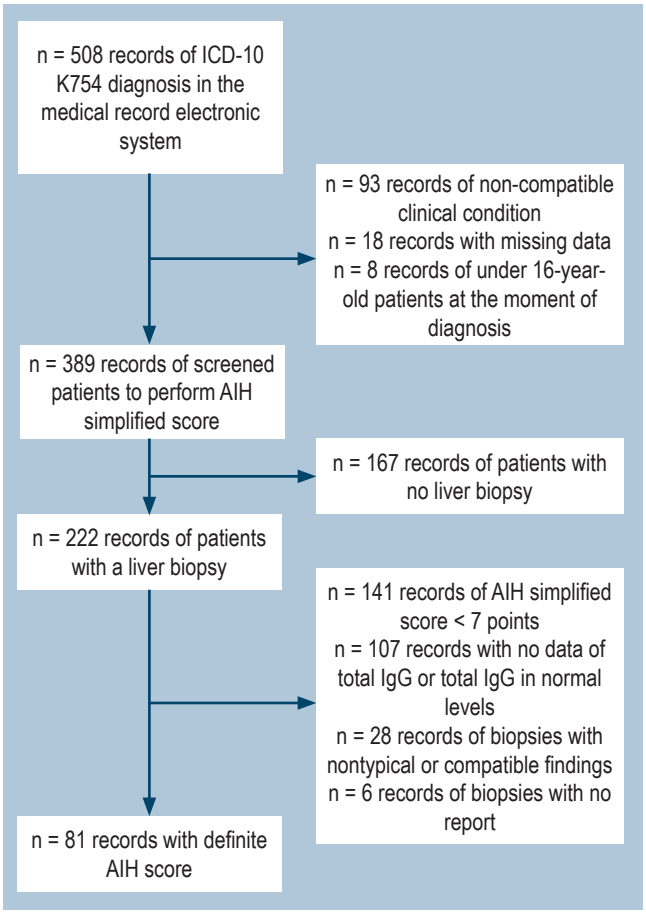

Figure 1. Screening diagram of the study. Source: Authors' own research.

Categorical variables are presented as absolute and relative frequencies, while continuous variables are reported as mean and standard deviation if they follow a normal or mean distribution and interquartile range (IQR) if they do not. The research conducted in this study is in accordance with international agreements on biomedical research set by the Council for International Organizations of Medical Sciences (CIOMS) and Resolution 8430 of 1993 of Colombia. As a risk-free study, informed consent was not required from participants; however, the researchers are dedicated to ensuring the confidentiality and privacy of all study subjects.

Based on the patients' clinical manifestation at the time of diagnosis, we categorized those who had no symptoms but showed abnormal liver profile test results as "asymptomatic with altered liver biochemistry."

The following are the clinical manifestations:

- Nonspecific symptoms: including asthenia, anorexia, pruritus, weight loss, and abdominal pain with evidence of liver biochemical alteration.
- Acute hepatitis: characterized by pain in the right hypochondrium, nausea, jaundice, and a pattern of hepatocellular damage evidenced in laboratory tests.
- Hepatic cirrhosis: identified by clinical signs of cirrhosis such as gynecomastia, telangiectasias, palmar erythema, collateral circulation, ascites, and encephalopathy, and biochemical signs such as hypoalbuminemia, thrombocytopenia, and prolongation of prothrombin time.
- Acute liver failure: indicated by acute hepatitis symptoms with coagulopathy and the development of encephalopathy in the first 26 weeks after the onset of jaundice, according to the definition of O'Grady et al.[6]
- *De novo* autoimmune hepatitis: observed in patients who received liver transplantation (without a pre-transplant diagnosis of AIH) and developed AIH in the post-transplant period.

The fibrosis stages of liver biopsy were evaluated using either the METAVIR score or transient elastography, when performed. The fibrosis stage was graded from F0 to F4, with F0 indicating the absence of fibrosis and F4 indicating advanced fibrosis with cirrhosis. Histological features

Table 1. Simplified criteria for the diagnosis of autoimmune hepatitis

Variable	Cut-off Point	Punctuation
ANA or SMA	≥ 1:40	1
ANA or SMA	≥ 1:80	2
Anti-LKM	≥ 1:40	2*
Anti-SLA	Positive	2*
IgG Serum	> Upper limit of normal	1
	> 1.10 times the upper limit of normal	2
Hepatic histology (evidence of hepatitis as a necessary condition)	Compatible with autoimmune hepatitis	1
	Typical of autoimmune hepatitis	2
Absence of viral hepatitis	Yes	2
≥ 6 points: Probable autoimmune hepatitis		
≥ 7 points: Definite autoimmune hepatitis		
Typical histology of autoimmune hepatitis: interphase hepatitis, lymphocytic/plasmacyte infiltrates in portal spaces with lobule extension, emperipolesis, and rosette formation.		
Histology compatible with autoimmune hepatitis: chronic hepatitis with lymphocytic infiltrate without the other typical findings of autoimmune hepatitis.		

*The maximum sum for autoantibody points is 2. ANA (antinuclear antibodies), LKM (liver kidney microsomal type-1 antibodies), SLA (antibodies against soluble liver antigen D), and SMA (anti-smooth muscle antibodies). Source: Hennes EM, et al.[4]

were classified as non-compatible, compatible, or typical of autoimmune hepatitis (AIH). Regarding treatment response, normalization of transaminases and immunoglobulin G (IgG) was considered *biochemical remission*. Clinical improvement and decrease in transaminases, without reaching normalization, were considered *partial remission*. Patients who did not experience a reduction of transaminase levels by at least 25% from the initial level when treatment began were classified as *non-response*. *Relapse* was defined as the elevation of alanine transaminase (ALT) greater than three times the upper limit of normal and elevation of IgG or worsening of histological findings after achieving remission with pharmacological treatment.

DATA MANAGEMENT AND STATISTICAL ANALYSIS

The password-protected BD Clinic platform and secure servers were used for consulting, downloading, and storing the collected data. Only individuals affiliated with the study had access to the database. Furthermore, each patient included in the study was assigned a study ID to ensure anonymity.

We randomly sampled 10% of the data to evaluate data quality and compared the typed data to the source documents. We randomly sampled another 10% of the data if inconsistencies were found. If the inconsistencies persisted, we reviewed the entire database.

RESULTS

A total of 81 patients met the inclusion criteria (**Figure 1**). Of these, 80.2% were women with a median age of 49 (interquartile range [IQR]: 30-61). Autoimmunity comorbidities were present in 28.4% of the patients. Among this subgroup, autoimmune thyroid disease was the most common (14.8%), followed by Sjögren's syndrome (6.2%), rheumatoid arthritis (3.7%), systemic lupus erythematosus (2.5%), and one case of systemic sclerosis. At the first consultation with the institution, acute hepatitis (43.2%) and biochemical alteration (24.7%) were the most common initial conditions, and there were no cases of acute liver failure. Hepatic cirrhosis, either clinical or diagnosed through non-invasive methods, was the initial condition for 17.3% of patients. By the end of the follow-up period, the percentage had increased to 22.2% of the population, with 72.2% in Child-Pugh stage A. Thirteen patients had the autoimmune hepatitis-primary biliary cirrhosis (AIH-PBC) overlap syndrome (**Table 2**).

Table 2. Clinical characteristics of patients with autoimmune hepatitis

Variable	n	%
Age*	49 (30-61)	
Sex		
- Female	65	80.2
- Male	16	19.8
Concomitant autoimmune diseases		
- None	58	71.6
- Autoimmune thyroid disease	12	14.8
- Sjögren's syndrome	5	6.2
- Rheumatoid arthritis	3	3.7
- Systemic lupus erythematosus	2	2.5
- Systemic sclerosis	1	1.2
Form of initial condition		
- Acute hepatitis	35	43.2
- Asymptomatic, only biochemical alteration	20	24.7
- Cirrhosis	14	17.3
- Nonspecific symptoms	12	14.8
- Acute liver failure	0	0.0
Cirrhosis during the follow-up period		
- No	63	77.8
- Yes	18	22.2
Cirrhosis stage (Child-Pugh score) n = 18		
- A	13	72.2
- B	5	27.8
- C	0	0.0
Overlap syndrome		
- No	68	84.0
- With PBC	13	16.0

PBC: primary biliary cirrhosis. Source: Authors' own research.

A cohort of 50 patients underwent histological analysis based on typical findings. The evaluation, which was conducted using either histological or elastography methods, revealed a prevalence of 29.6% for fibrosis grades 0 or 1.

The following laboratory parameters were obtained: aspartate aminotransferase (AST) levels of 154 U/L (75.5-711.5), alanine aminotransferase (ALT) levels of 150 U/L (79.5-509), total bilirubin levels of 1.6 mg/dL (0.71-5.0), alkaline phosphatase levels of 162 IU/L (100-280), and total IgG levels of 20 g/L (17.1-28.8). Among the patients, 88.9% had antinuclear antibody positivity equal to or greater than 1:80 dilutions, and 43.2% were positive for ASMA. The initial screening of the three cases evaluated showed no positivity for SLA or LKM antibodies (**Table 3**).

The most frequently used induction therapy for AIH was a combination of prednisolone and azathioprine, which was also used for maintenance during the follow-up period. However, induction therapy initiation was not reported for 7.4% of patients. Four patients required second-line therapies, specifically mycophenolate mofetil. Of the patients evaluated, 87% met response criteria, and relapses occurred in 13.6% (**Table 4**). Only one fatal outcome occurred, which was not directly related to the diagnosis of AIH (bacteremia in a patient diagnosed at the age of 26 with Child-Pugh B cirrhosis during prednisolone maintenance therapy). Four patients underwent liver transplantation, and another five patients were on the transplant list during the follow-up period. Nineteen patients experienced a change in Child-Pugh or progression to cirrhosis (**Table 5**).

DISCUSSION

The incidence of AIH is more prevalent in women, as observed in other studies conducted worldwide[7,8] and in Latin America[9,10], with a rate above 80%. About 28.4% of cases have at least one autoimmune comorbidity, which is lower than the rate reported by Karakaya et al.[11] However, the proportion of autoimmune thyroid disease is similar to that found in related studies[12,13], which may occur before or concomitantly with AIH. Acute hepatitis and asymptomatic manifestation were the most common, consistent with previous reports by Czaja[14] and Feld.[15] Furthermore, approximately 24.7% of cases had alterations in the hepatic biochemical profile, with transaminases being predominant in AIH and alkaline phosphatase in overlap syndromes. This finding is higher than that reported by Díaz et al.[9], indicating that the differential diagnosis remains broad despite the absence of treatment.

The clinical course of cirrhosis varies between studies. In our study, it was observed in 17.3% of cases, whereas a Japanese group showed grade 4 fibrosis (in definitive cases) in 8.3%.[16] Other studies consistently report that one-third of patients are diagnosed with cirrhosis, without distinguishing between classifications by score.[17,18]

Clinical guidelines underscore the importance of hepatic histology in confirming diagnoses, staging fibrosis, determining clinical prognosis, and ruling out differential diagnoses. In our study, of the patients who underwent ini-

Table 3. Pathology and laboratory characteristics of patients with autoimmune hepatitis

Variable	n	%
Histology (n = 81)		
- Typical findings	50	61.7
- Compatible findings	31	38.3
Degree of fibrosis by biopsy or FibroScan elastography (METAVIR index)		
- Grade 0	24	29.6
- Grade 1	24	29.6
- Grade 2	10	12.3
- Grade 3	5	6.3
- Grade 4 or established cirrhosis	18	22.2
Laboratory parameters		
- AST (UI/L)*	154 (75.5-711.5)	
- ALT (UI/L)*	150 (79.5-509)	
- Total bilirubin (mg/dL)*	1.6 (0.71-5.0)	
- Alkaline phosphatase (IU/L)*	162 (100-280)	
- Total IgG (gr/L)*	20 (17.1-28.8)	
Antinuclear antibodies (dilutions)		
- Negative	9	11.1
- 1;80	19	23.5
- Greater than 1;80	53	65.4
Anti-smooth muscle antibodies (dilutions)		
- Negative	46	56.8
- 1;40	15	18.5
- 1;80	5	6.2
- Greater than 1;80	6	7.4
LKM or SLA antibodies		
- Negative or not performed	81	100.00
- Positive	0	0.00

*Median and interquartile range. Source: Authors' own research.

Table 4. Treatments of patients with autoimmune hepatitis

Variable	n	%
Induction therapy		
- None	6	7.4
- Prednisolone	10	12.3
- Prednisolone + azathioprine	64	79.0
- Other	1	1.2
Response		
- No	10	12.3
- Yes	71	87.7
Relapse		
- No	70	86.42
- Yes	11	13.58
Maintenance therapy		
- Prednisolone	7	8.6
- Azathioprine	25	30.9
- Prednisolone + azathioprine	36	44.4
- Other	4	4.9
- ND	9	11.1
Second-line therapies		
- Not used	77	95.1
- Mycophenolate mofetil	4	4.9

ND: No data. Source: Authors' own research.

tial screening, 57% underwent histological assessment by laparoscopic or ultrasound-guided biopsy. Of those, 84.7% had findings compatible with or typical of AIH. However, the histological changes were not suggestive for 34 patients who had a biopsy because the definitive report was absent or the sample was inadequate. In addition, only 20.8% of the total screened had a simplified score of seven points or higher to confirm the diagnosis of AIH, indicating the ongoing underdiagnosis in low- to middle-income countries. Although other parameters included in the scores can lead to a diagnosis in accordance with recent guidelines,[19,20] we chose to use the definitive score as the inclusion criteria for patients who had a liver biopsy with a report of compatible or typical characteristics. From the initial screening, we obtained 50 patients with probable scores who had a biopsy and 55 patients with probable AIH without a biopsy report. These limitations also impede the accurate and serial assessment of fibrosis, which has implications for mortality.[21] The frequency of AIH-PBC overlap is similar

Table 5. Outcomes of patients with autoimmune hepatitis

Variable	n	%
Death during the follow-up period		
- No	80	98.8
- Yes	1	1.2
Liver transplantation		
- No	77	95.1
- Yes	4	4.9
On the transplant waiting list during the follow-up period		
- No	76	93.8
- Yes	5	6.2
Cirrhosis or change in the initial Child-Pugh to the last assessment		
- No	62	76.5
- Yes	19	23.5

Source: Authors' own research.

to that reported in the literature.[22] Based on the Paris criteria,[23] patients of Hispanic descent had a higher frequency of overlap than non-Hispanic patients (31% vs. 13%).

Early treatment is crucial as up to 17% of non-treated patients with interface hepatitis to diagnostic histology progress to cirrhosis within five years. Among them, 82% with bridging necrosis progress to cirrhosis and have a high mortality rate of 40%-50%. However, patients who receive appropriate treatment have a life expectancy comparable to those without AIH.[24] For the duration of this study's follow-up period, induction therapy consisted of a combination of prednisolone and azathioprine, which has similar benefits compared to prednisolone monotherapy[25] but with a lower incidence of adverse effects such as diabetes, obesity, osteoporosis, hypertension, and emotional lability.[27] Furthermore, only one case of pancytopenia due to azathioprine resulting in death was reported.

In terms of maintenance therapy, the data were more varied, with 75.3% of patients using an azathioprine-based regimen (either alone or in combination with low doses of prednisolone) and second-line therapy used in 4 patients (specifically, mycophenolate mofetil). According to the most recent 2019 American Association for the Study of Liver Diseases (AASLD) guidelines,[19] there have been no significant changes in pharmacotherapy that could account for a shift in treatment trends in our study. The percentage of relapses was comparable to that of another Colombian study[9] (mainly due to abandonment and poor adherence to therapy), with the vast majority occurring in the first 24 months, similar to what has been described by Czaja et al.[28] Additional factors related to relapse include the duration of adherent treatment and the length of time of inactive disease prior to drug withdrawal, psychological stress,[29] concurrent autoimmune disease, polypharmacy,[30] ALT and IgG levels at withdrawal, and prednisolone monotherapy, which have been linked to higher rates of cirrhosis development, death, and the need for a liver transplant.[31] These factors must be identified and evaluated during patient follow-up, particularly in countries where accessing treatment and specialized consultations is challenging.

Four patients (4.9%) with definitive AIH underwent a liver transplant, all of whom were under 40 years old. There were no mortality or acute liver failure cases during the follow-up period. The only death in this population was unrelated to AIH and occurred in a cirrhotic patient. Out of the 389 patients in the initial screening, 25 (6.4%) died, with eleven cases related to complications of cirrhosis (four with variceal hemorrhage, four from infections associated with spontaneous bacterial peritonitis [SBP] and bacteremia, one with hepatorenal syndrome, one with acute liver failure, and one with metastatic hepatocarcinoma). Fourteen deaths were not related to AIH, with six associated with bacterial and fungal infections not related to SBP, three related to non-hepatocellular neoplasms, two related to serious coronavirus infections caused by SARS-CoV-2, one due to massive bleeding in the immediate post-liver transplantation period, one due to acute graft dysfunction in less than 48 hours post-transplantation, and one due to non-variceal hemorrhage. Unlike Borssen's study[32], which reported 22% of deaths due to cardiovascular etiology, there were no deaths in this study due to this cause. Three patients died due to early post-transplant complications, with two deaths caused by massive bleeding requiring reoperation and one due to hyperacute graft dysfunction with no emergency indication for retransplantation.

The diagnosis of autoimmune hepatitis alone has been shown to increase the risk of cardiovascular and liver disease, as well as long-term extrahepatic malignancy, based on statistical data.[8] Without treatment, the prognosis is poor, with a 50% 5-year survival rate and only 10% survival at ten years, while immunosuppression leads to complete remission in 90% of patients.[33] Early diagnosis is beneficial, but detection during youth has been found to be an independent variable associated with incomplete response to treatment.[34] However, cirrhosis at the time of diagnosis remains an independent prognostic factor for non-response. This was observed in the German[35] and Canadian[15] groups, but it was not statistically significant in another study,[36] which

may be related to geographical and genetic factors in the populations studied. As of December 2020, fifteen patients were on the liver transplant waiting list.

Interestingly, patients who received a definitive score had lower rates of cirrhosis at the beginning of treatment, a high percentage of biochemical response, low relapse rates, and lower mortality. This may be attributed to the use of early histology as a diagnostic tool and treatment guide, as well as the early initiation of immunosuppression in the high percentage of non-cirrhotic patients at the time of diagnosis. Compared to patients who received probable scores, their characteristics and findings were similar to those reported in a study conducted by Fujita et al. No significant prognostic differences were reported in that study; therefore, patients with probable scores should be managed similarly.[16]

The low presence of patients with definitive scores in the available follow-up data may be attributable to several factors. Prior to their initial consultation, several of these patients were already receiving maintenance treatment, leading to sustained normalized total IgG levels consistent with their clinical response. Additionally, some patients had no baseline total IgG data or had autoantibodies with poor specificity (in 31 of 188 patients with typical or compatible liver biopsy findings, ANA and ASMA were negative). Despite the clear literature highlighting the importance of liver biopsy for diagnostic and prognostic purposes, 43% of patients screened for the simplified AIH score did not undergo it. This was due to a low pretest probability when evaluating the other components of the score (notably 35 patients with typical or compatible biopsies but with normal IgG and negative autoantibodies), clinical contraindications to the procedure, long-standing clinical response despite the absence of biopsy, and administrative difficulties in some cases.

Biopsies are not routinely used for assessing remission and follow-up of fibrosis.[37] This highlights the need for non-invasive techniques, such as liver elastography and measuring inflammatory markers, which have emerged as rapid tools. Transient elastography correlates positively with the histological fibrosis stage and has similar accuracy to other chronic liver diseases. However, liver inflammation can confound its interpretation, which may lead to overestimating liver stiffness. This is particularly important to consider in patients receiving immunosuppression. APRI, FIB-4, and AAR scores generally have low diagnostic accuracy.[38] Nonetheless, studies have shown that both the immunoglobulin/platelet and lymphocyte/platelet ratios are independently associated with the stage of liver fibrosis in untreated AIH.[39]

There is considerable debate regarding the diagnosis of AIH, as evidenced by the fact that 63 patients who did not undergo liver biopsy and six patients who did undergo biopsy with typical findings but negative autoantibodies were diagnosed with a probable score for AIH. Seronegative cases present a diagnostic challenge since patients can be diagnosed with AIH using the classic score but result negative with the simplified score, as reported by Sherigar et al.[40] This can result in AIH being excluded by the latter method. Furthermore, the low specificity of anti-AIH antibodies can add to the difficulties in diagnosis. In clinical practice, many of these are diagnosed with cryptogenic etiology.

CONCLUSION

As consistent with previous literature, middle-aged adults and women are the most common demographic for patients with definitive AIH. At the time of diagnosis and in earlier stages, a low percentage of cirrhosis was observed, which may account for the low mortality and absence of acute liver failure, as well as the low incidence of liver transplant requirement. However, more extended follow-up periods are necessary to obtain a more precise estimate of outcomes.

The limited use of liver biopsy represents a significant challenge to the accurate diagnosis of definitive AIH and, therefore, to clinical outcomes. Consequently, proposing non-invasive and more readily available diagnostic alternatives is crucial.

Conflict of Interests

The authors declare that they have no conflicts of interest.

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Original article

The Burden of Gastric Cancer Disease from 2010 to 2019 in Tunja, Boyacá, Colombia

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Abstract

Introduction: Gastric cancer (GC) is the first cause of death by neoplasm in Colombia, with 6,451 deaths in 2020. This pathology and its chronic manifestations pose a public health challenge. The objective is to estimate the disease burden of GC in Tunja, Boyacá, from 2010 to 2019. **Materials and methods:** An exploratory ecological study was conducted using disability-adjusted life years (DALYs) as the unit of measurement. The National Administrative Department of Statistics (DANE) mortality databases and prevalence information from the Integrated Social Protection Information System (SISPRO) records were used. Deaths and GC cases were pooled and then adjusted to control for bias. **Results:** In 2010-2019, 34.2 DALYs were lost for every 1,000 people secondary to GC in Tunja, 30.5 were due to years lost due to premature death, and 3.72 were due to years lived with disability. DALYs due to premature death were found to exceed DALYs due to disability. **Conclusion:** The morbidity burden of GC from 2010 to 2019 for Tunja was similar to that of other cancers because of years of life lost due to premature death, so public health efforts should be made to increase early detection.

Keywords

Gastric cancer, incidence, mortality, disability-adjusted life years.

INTRODUCTION

Gastric cancer (GC) is a global health concern that, despite an overall decrease since 1975, still occurs more frequently in men and people over 65 years of age.[1] As of 2020, it ranked fifth worldwide in incidence and fourth in mortality, with 768,793 cases.[2] In Colombia, the incidence was 8214 cases (7.3%) in the same year, making it the primary cause of death from neoplastic diseases, with 6451 deaths (11.7%).[2] This condition usually presents asymptomatically and is often diagnosed in Colombia at an advanced stage with limited treatment options.[3]

In Colombia, gastric cancer (GC) causes fewer years of life potentially lost than in other countries with similar incidence rates.[4] Boyacá is considered a high-risk area, along with other regions like Nariño, with mortality rates of 13.38 and 15.72 deaths per 100,000 inhabitants, respectively, in 2014.[5,6] As of 2021, both departments continued to have mortality rates above the national average of 5.26 deaths per 100,000.[7]

The burden of disease attributable to neoplasms during 2020 accounted for 0.75% of the total disability-adjusted life years (DALYs) worldwide, corresponding to 4,581,860 DALYs. Among neoplasms, GC contributed to 0.04% of the

global burden of disease, representing 246,437 DALYs. In Colombia,[8] the survival rate for GC during the 2010-2014 period was between 15.4% and 18.8%, significantly lower than the US average of 33.6% for a 5-year survival rate.[9] In some municipalities such as Bucaramanga (Santander), the 5-year survival rate for GC is as low as 11%,[10] highlighting the magnitude of the problem at the national level.

Previous studies have examined the burden of disease in Colombia, including those focused on GC.[4,11,12] However, given the unique characteristics of the Altiplano Cundiboyacense, a high plateau in the Eastern Andes Mountain Range, and Tunja (Boyacá), the highest capital city in Colombia with 179,263 residents, there is a need to investigate the burden of disease associated with secondary disability to GC in this high-risk population. While this study will not determine the prevalence of Helicobacter pylori in the city, the American Institute for Cancer Research has identified other factors, such as dietary habits (including salting of foods and low fruit consumption) and high alcohol consumption, which are prevalent in the department of Boyacá,[16] and may increase the risk of developing GC.[14,15]

It is worth noting that 95.6%[13] of Tunja's population resides in urban areas, and the city is situated at an altitude of 2775 meters above sea level.[17] According to some studies,[18,19] living at an altitude above 2000 meters could contribute to the development of GC.

This study aims to estimate the burden of GC in Tunja, Colombia, measured in DALYs, using prevalence data from the Ministry of Health and Social Protection and the methodology established by the World Health Organization (WHO).

METHODOLOGY

Type of Study

This is an exploratory ecological study on disease burden, which aims to estimate the potential years of life lost due to secondary disability to GC in Tunja, Boyacá, for the period from 2010 to 2019.

Source of Information

The study obtained information on GC mortality from the National Administrative Department of Statistics (DANE) and prevalence information from the Integrated Social Protection Information System (SISPRO) records. The Ministry of Health and Social Protection of Colombia centralizes the Individual Registry of Health Service Provision (RIPS), which is the main source of SISPRO.

Data from Tunja between 2010 to 2019 were collected to conduct the analysis, including GC-related International Classification of Diseases (ICD-10) codes from C160 to C169. These codes represent malignant tumors of various stomach parts, such as the cardia, gastric fundus, antrum pyloric, pylorus, and other regions not specified. We then identified patients with the main diagnosis codes for GC, categorized by sex, life cycle, report year, and residence in Tunja. To determine the prevalence of GC, the population denominator was obtained from DANE records,[20] which were grouped by life cycles per year.

Population at Risk

To define the population at risk for this study, we focused on the inhabitants of Tunja as people living in areas with a high prevalence of GC in Colombia are mainly located in the departments of Quindío, Cauca, Nariño, and Boyacá.

Ethical Considerations

This research adhered to the principles outlined in the Declaration of Helsinki[21] and Resolution 8430[22] of Colombia's Ministry of Health and Social Protection. As a retrospective documentary study, it was deemed risk-free research.

DATA ANALYSIS

DALYs were calculated using the WHO methodology, which involves adding together the YLL (years of life lost to premature death) and YLD (years lived with disability) measures. YLL indicates mortality attributable to the disease, while YLD indicates disease morbidity. The collected data from DANE and SISPRO were then organized into spreadsheets in MS Excel 365 for analysis. For the YLD calculation, we considered the weight per disability provided by the 2010 burden of disease study.[23,24] However, we opted to use the weight per disability suggested by the expert panel in a previous study[4] due to its applicability to the region. This study calculated a weighted weight of 0.278 for the time lived with GC in Colombia. We used a life expectancy at birth of 82.4 years for both men and women, and the expectation for each age range without discount rate or adjustment for age was used according to the five-year period.[23] Finally, we obtained the DALYs using the WHO staff[25] to calculate the burden of disease.

RESULTS

Based on the RIPS (Individual Health Service Provision Records) collected from 2010 to 2019, 583 patients with confirmed GC diagnosis were treated in Tunja, comprising 51.5% men and 48.5% women (**Table 1**).

Table 1. People treated with GC diagnosis by age group and sex in Tunja from 2010 to 2019

Age	Female	Male	Total
5-14	1	0	1
15-29	5	4	9
30-44	39	20	59
45-59	79	69	148
60-69	59	80	139
70-79	67	78	145
80+	33	49	82
Total	283	300	583

Source: Author's own research, based on information obtained from the RIPS, centralized by the Ministry of Health and Social Protection.

For the population aged over 30 years, the estimated 10-year prevalence of GC was 7.6 per 1000 men and 6.1 per 1000 women (**Table 2**).

Over the course of the decade under study, 79% of the GC diagnoses occurred in individuals between the ages of 45 and 79.

As for the estimated incidence (**Table 3**), cases increased during the life cycles of individuals aged 60 to 79. A total of 249 deaths were identified across six age groups: 15 to 29, 30 to 44, 45 to 59, 60 to 69, 70 to 79, and 80 or older. We calculated the YLL per 1000 inhabitants for these deaths using this data.

We calculated the number of years of life lost due to premature death caused by GC and found that men had a higher frequency of years lost compared to women (**Figure 1**).

Using the average reported disease survival rates for Colombia, the total DALYs were calculated by considering cases from each age group.[10] Over the 2010-2019 period,

Table 2. Prevalence of GC per 1000 inhabitants in men and women by life cycle f in Tunja from 2010 to 2019

Life Cycle	Men			Women			Total		
	Population	Cases	Prevalence	Population	Cases	Prevalence	Población	Cases	Prevalence
5-14	137 625	0	0	137 625	1	0.007	275 250	1	0.003
15-29	260 514	4	0.015	260 514	5	0.019	521 028	9	0.017
30-44	214 729	20	0.093	214 729	39	0.181	429 458	59	0.137
45-59	166 670	69	0.414	166 670	79	0.474	333 340	148	0.444
60-69	62 729	80	1.276	62 729	59	0.940	125 458	139	1.108
70-79	29 287	78	2.666	29 287	67	2.290	58 574	145	2.478
80+	15 275	49	3.213	15 275	33	2.162	30 550	82	2.687
Total	886 829	300	7.678	886 829	283	6.076	1 773 658	583	6.877

Source: Author's own research, based on information obtained from the RIPS, centralized by the Ministry of Health and Social Protection.

Table 3. Estimated incidence per 1000 inhabitants between 2010 and 2019 of GC in men and women per life cycle in Tunja

Incidence	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
15-29	0.000	-	0.046	-	-	0.045	-	-	0.043	-
30-44	0.000	0.065	0.063	-	0.179	0.117	-	-	0.055	0.054
45-59	0.000	0.001	0.367	0.179	0.436	-	0.083	0.728	0.079	0.386
60-69	-	0.002	-	1.239	0.940	2.232	-	1.019	1.364	1.107
70-79	0.005	3.521	-	-	2.615	-	-	0.002	1.412	2.660
≥ 80	3.130	0.006	-	4.819	2.326	1.124	0.002	5.371	6.309	-

Source: Author's own research, based on information obtained from the RIPS, centralized by the Ministry of Health and Social Protection.

the population of Tunja lost 34.2 DALYs per 1000 individuals as a result of GC, with a rate of 1.7/1000 inhabitants. Disability losses accounted for 10.9% of DALYs. The age group with the highest DALYs was 45-59 years, contributing to 34% of the total, followed by the 60-69 age group with 27.4% (**Table 4**).

DISCUSSION

GC is a significant contributor to morbidity and mortality rates in many parts of the world, with Asia and Central and South America experiencing the highest incidence and mortality rates. It is projected that there will be an 80%

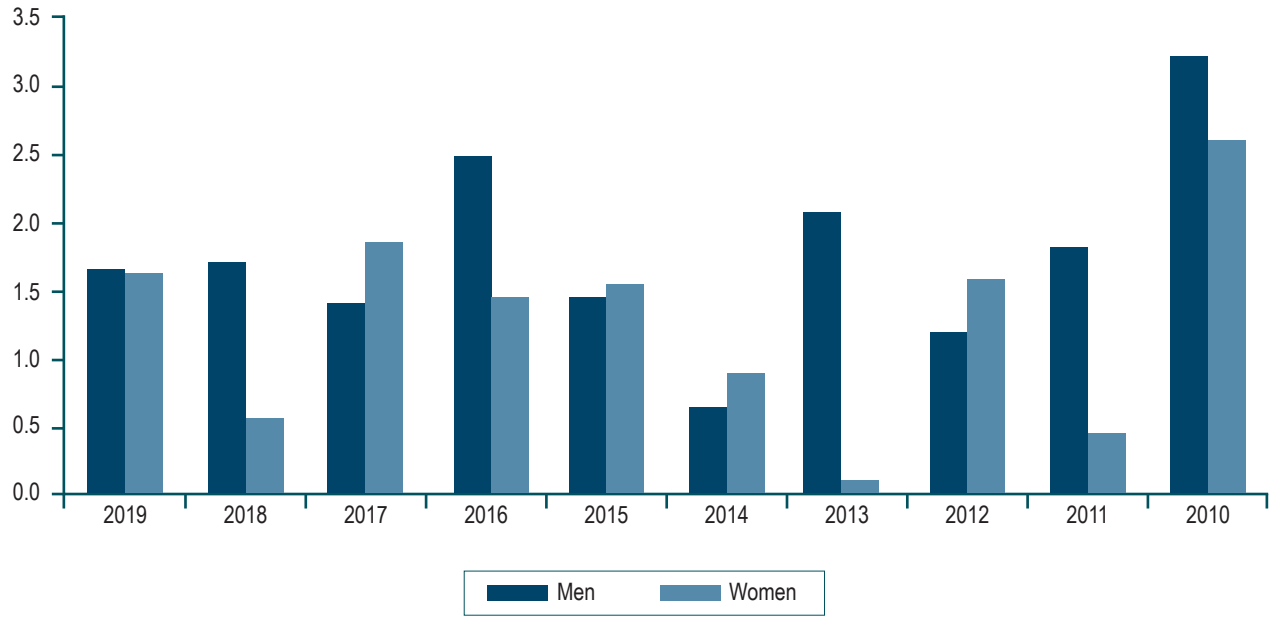

Figure 1. Years of life lost due to premature death secondary to GC according to sex in Tunja between 2010 and 2019 (per 1000 inhabitants). Source: Author's own research.

Table 4. Distribution of YLL, YLD, and DALY by GC in Tunja, according to year (rates per 1000 inhabitants)

Year	YLL		YLD		DALY	
	Men	Women	Men	Women	Men	Women
2019	1.7	1.64	0.3	-0.01	2.0	1.6
2018	1.7	0.59	0.3	0.42	2.0	1.0
2017	1.4	1.86	-0.1	0.11	1.3	2.0
2016	2.5	1.46	0.3	-0.16	2.8	1.3
2015	1.5	1.56	0.2	0.28	1.7	1.8
2014	0.6	0.91	0.2	0.03	0.9	0.9
2013	2.1	0.13	-0.1	-0.06	1.9	0.1
2012	1.2	1.60	0.5	0.36	1.7	2.0
2011	1.8	0.45	0.2	0.22	2.1	0.7
2010	3.2	2.61	0.6	0.10	3.8	2.7
Total	**17.7**	**12.8**	**2.4**	**1.3**	**20.1**	**14.1**

Source: Author's own research.

increase in its epidemiological behavior worldwide by 2030.[1,26] In Colombia, it was the leading cause of death from neoplasms in 2020[2] and the third most common cancer in terms of incidence.[27] Despite this, screening and early detection plans have been limited, particularly when compared to other prioritized cancers like cervical, breast, or prostate cancer. Moreover, screening plans have been further restricted due to the global impact of the severe acute respiratory syndrome coronavirus pandemic type 2 (SARS-CoV-2).[28] Therefore, this study aims to describe the burden of GC disease in Tunja over a decade based on official records, contributing to similar studies with comparable characteristics, as it is a high-land Colombian city with risk factors[16,29] typical of other municipalities with high or comparable mortality rates from GC.

Neoplasms are ranked as the second-highest cause of disease burden worldwide,[30] with variations in prevalence depending on geographic location. For example, in Korea, the estimated DALY for GC between 2000-2020 was 445/100,000,[24] while in nearby Mexico, it was 80/100,000 for men and 85.7/100,000 for women[31] from 2010 to 2014. In Colombia, the DALY was 172.7/100,000 in 2017[4] and 131.5/100,000 in 2006 in Santander.[32] In our study, the rate was found to be 170/100,000 inhabitants, which is consistent with the last reported figures in the country.[4] Sierra et al.[26] have also reported Colombia and South America as areas with high incidence and mortality due to GC worldwide, and our results validate the burden of secondary disability caused by GC in our region.

The authors of this study originally hypothesized a higher DALY due to GC in Tunja, Boyacá; however, the results showed 34.2 years of life lost during the studied decade, with a predominance of age between 45 and 59 years and a life expectancy of 82.4 years according to WHO and 77 years according to DANE.[33] This is noteworthy since—even though 89.1% of DALY was due to YLL (data consistent with the literature worldwide)—[33,34] the population described in this study is younger and predominantly female, which differs from that reported in other research at departmental,[35] national,[4] and global[36] levels, and may correspond to an information bias due to the data obtained from official secondary sources (SISPRO), which depend on satisfactory completion or diagnosis by the physician according to ICD-10. Nonetheless, despite the possible under-registration of SISPRO, this study found a higher prevalence of GC than predicted by the Global Cancer Observatory (GLOBOCAN) in 2020 for Colombia, with 22.82 cases per 100,000 inhabitants.[27]

These results offer valuable quantitative evidence that can be utilized to establish, prioritize, and assess public policies aimed at preventing and diagnosing gastric tumors at an early stage. Therefore, we recommend that the methods used in cities with long-term population registries, such as Bucaramanga and Cali, be employed in the department of Boyacá and Tunja to estimate and carry out continuous and descriptive evaluations of the affected population.

CONCLUSIONS

Tunja exhibited incidences akin to those reported by Triana JJ et al., Amaya Lara et al., Arias Sosa et al., and Caicedo A et al. Nevertheless, the disease burden detected in this study was primarily attributed to years of life lost due to premature death (89.1%). This underscores the pressing need to focus on screening, early diagnosis, periodic follow-up, early initiation of treatment, and population registry creation to enhance patient prognosis.

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Conflicts of Interests

The authors report that they have no conflicts of interest.

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Contribution

Dr. Barreto: data conception, acquisition, analysis, and interpretation of data. Dr. Limas: a critical review of intellectual content. Drs. Porras and Rico: a critical review of intellectual content and final approval.

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Original article

KRAS Gene Mutation in Patients Undergoing Liver Resections for Colorectal Cancer. Is There an Advantage to Anatomical Resections?

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Abstract

Introduction: Several factors have been described to make a prognostic assessment of patients with liver metastases due to colorectal cancer and to define the benefit of the surgical management of metastatic involvement; one of these factors is the status of the *KRAS* gene since its mutation is associated with worse outcomes. This study aims to describe the outcomes for a retrospective series of patients after liver resections for metastatic colorectal cancer concerning *KRAS* gene status. **Materials and methods:** The study involves a retrospective cohort of patients undergoing liver metastasectomy for colorectal cancer with *KRAS* mutation study from 2009-2013 at the National Institute of Cancerology in Colombia. Five-year survival analyses (overall and disease-free) were performed according to *KRAS* mutation status and the type of liver resection performed using the Kaplan-Meier estimate. **Results:** 35 patients undergoing liver metastasectomy were analyzed, of which 42.8% had KRAS gene mutation. Median overall survival was 34.2 months for patients with *KRAS*- mutant and 46.5 for non-mutant. The median survival for *KRAS*-mutant patients with anatomic resections was 43.5 months versus 23.5 months for nonanatomic resections. **Conclusions:** Performing anatomic resections during liver metastasectomy in patients with *KRAS* mutants could be associated with an improvement in overall survival. It is necessary to continue building the evidence for adequate decision-making in patients with *KRAS* mutants who will undergo liver resections.

Keywords

Colorectal cancer, liver metastases, metastasectomy, KRAS mutation.

INTRODUCTION

In 2020, colorectal cancer was the third most commonly occurring cancer, accounting for 9.5% of new cancer cases, and was also the fourth leading cause of cancer deaths worldwide.[1] Approximately 20% to 25% of patients with colorectal cancer have the metastatic liver disease at the time of diagnosis, and an additional 50% develop it in a metachronous scenario.[2,3] Among these patients, average survival without treatment is typically less than a year, ranging from 3.8 to 21 months.[2]

Hepatic metastasectomy, sometimes accompanied by ablation techniques, is the only potential cure for patients, with a survival average of 3.6 years and 5- and 10-year survival rates of 40% and 25%, respectively.[4] However, only 10-20% of patients with hepatic damage meet the criteria for surgical resection.[5] Nonetheless, the development of new approaches associated with perioperative systemic therapy has increased the number of potentially eligible patients for surgery to 30%.[3,6]

Several factors have been described to evaluate the prognosis of these patients and determine the benefit of surgical

management for metastatic involvement.[7] With a better understanding of the tumor biology of colorectal cancer, molecular biomarkers such as *KRAS* gene mutation have been integrated into prognostic scales. This gene has been extensively studied, and up to 50% of colorectal cancer cases have been reported to have this mutation,[3] which is associated with resistance to treatment with monoclonal antibodies against the epidermal growth factor receptor (EGFR). *KRAS* gene mutation occurs in up to one-third of patients with resectable colorectal cancer hepatic metastases and has a negative prognostic impact due to a higher frequency of extrahepatic metastases, poor response to systemic therapy, and lower overall survival after resection.[3,8] Some studies recommend hepatic metastasectomy, whenever possible, in patients without *KRAS* mutation and suggest evaluating other prognostic factors to decide on the treatment for patients with this mutation.[3,9]

Surgery remains the most promising option for a potential cure in patients with colon cancer and liver metastases. The liberal use of parenchymal-sparing surgery has increased the possibility of multiple synchronous resections, which can be used in cases of relapse.[10,11] However, it is essential to note that parenchymal sparing does not eliminate the need for proper resections to ensure the oncological safety of the procedure. While some studies suggest that narrow margins may yield similar outcomes to the 1-centimeter standard initially described,[12,13] it is currently recommended to evaluate factors such as molecular biology, including *KRAS* status, to determine the optimal margin of resection in these cases.[14]

This article aims to present the results of a retrospective study conducted at a renowned cancer treatment center in Colombia, focusing on patients who underwent liver resection due to metastases from colorectal cancer, with particular attention to their *KRAS* gene status. Additionally, the study aimed to assess the effectiveness of anatomical liver resections in patients with mutated *KRAS* in colorectal cancer.

MATERIALS AND METHODS

This retrospective cohort study includes patients over 18 years old who underwent liver metastasectomy surgery (including anatomic and non-anatomic resections) for colorectal cancer and had a *KRAS* mutation analysis performed at the National Cancer Institute in Colombia between January 1, 2009, and December 31, 2013. Patients with incomplete follow-up data were excluded to ensure the completeness of the analysis.

The study data were collected by reviewing medical records from the institution and entered into the RedCap program for analysis. Descriptive statistics, including absolute and relative frequencies, measures of central tendency, dispersion, or position, were calculated for qualitative and quantitative variables. The Kaplan-Meier method was utilized to estimate the five-year survival average (both overall and disease-free) in groups using univariate data for patients with mutated and non-mutated (*wild-type*) *KRAS*, and the results were analyzed and compared using graphs between patients who underwent anatomic and non-anatomic liver resections using the Logrank test with R-Project software version 3.6.2.

RESULTS

During the study period, 54 patients underwent liver resections for colorectal cancer, but only 35 of them had a study conducted for the *KRAS* gene (**Figure 1**). The patients had

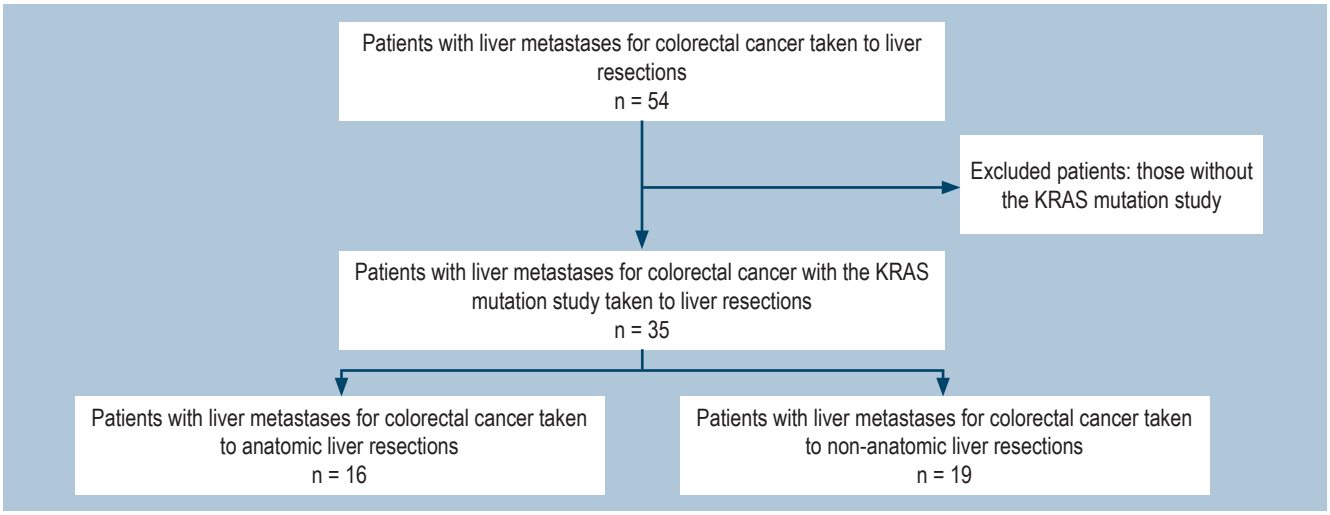

Figure 1. Flowchart of patients with liver resections for colorectal cancer 2009-2013. Source: Authors' own research.

an average age of 63 (ranging from 42 to 82 years) and a similar distribution between the sexes (57.1% male and 42.9% female). The rectum was the most frequent site of primary tumor location, observed in 40% of patients, followed by the sigmoid colon in 31.4% of cases, while the right colon had a lower frequency of 11.4%. Most patients (85.7%) had a moderate degree of histological differentiation. Among this group, 54.3% presented with stage IV disease, with isolated hepatic metastatic involvement in 84.2% and associated involvement with other organs in 15.8%. Prior to metastasectomy, high levels of carcinoembryonic antigen (CEA) were found in 82% of patients, with a value greater than 5 ng/dL and an average of 7 ng/dL in all patients, with no significant difference between those with mutated and non-mutated *KRAS* genes (**Table 1**).

KRAS Gene Mutation

Fifteen of the liver resections performed (42.8% of the total) were on patients with a *KRAS* gene mutation. Of these, 40% had a primary tumor in the left colon (descending or sigmoid), 26.7% in the rectum, and 33.3% in the right colon. In 60% of these patients, metastasis was synchronous. During follow-up, 73.3% of the patients experienced relapse, 19.2% of these relapses occurring exclusively in the liver, and 81.8% associated with another site (lung). The average number of metastatic liver lesions was four, with an average size of 4 cm.

Out of the total of liver resections, twenty patients had *wild-type KRAS* (57.1%). Of these, 45% had the primary tumor in the left colon, 40% in the rectum, and only 15% in the right colon. Both synchronous and metachronous scenarios were observed in this group in the same proportion. The mean number of metastatic liver lesions was four, and their mean size was 2.7 cm. Among these patients, 70% relapsed, with 64.3% being at the hepatic level and 50% associated with other sites such as the lung, lymph nodes, peritoneum, or bones (**Table 2**).

Chemotherapy and Radiation Therapy

Regarding the other types of therapies received, 31.43% of patients underwent neoadjuvant chemotherapy for the primary tumor, with a majority of patients (60%) receiving the 5-fluorouracil plus leucovorin combination, which was common among rectal tumors in this study. Additionally, 85.2% of patients received adjuvant therapy following resection of the primary tumor, with the majority (63.3%) receiving regimens based on 5-fluorouracil, leucovorin, and oxaliplatin. Only 16% of patients received targeted therapy, with 75% receiving anti-VGFR therapy and 25% receiving anti-EGFR therapy. Among the 45.7% of patients in the metachronous scenario, 11.4% received additional chemotherapy regimens before undergoing liver resection surgery, primarily based on 5-fluorouracil and irinotecan. However, all second hepatic relapse cases received systemic therapy prior to resection.

In the analysis of patients based on their *KRAS* status, 33.3% of patients with mutated *KRAS* and 30% of patients with *wild-type KRAS* received chemotherapy before undergoing liver resection. However, 85% of patients with mutated KRAS and 87% with *wild-type KRAS* received adjuvant systemic therapy. Furthermore, 28.6% of patients received radiotherapy for the locoregional management of primary rectal tumors.

Hepatic Resection

Among the patients in the synchronous scenario, only 10.5% underwent simultaneous liver resection with the primary tumor surgery. Non-anatomic segmental resections were performed in 54.3% (n=19) of patients. Anatomic resections were performed in 45.7% of the patients, with segmentectomy being the most frequent type of anatomic resection in 25.7% of cases, followed by combined resections (which included anatomic resection of several segments or non-anatomic resection) in 14.3%, and right or left hepatectomy in 5.7% and 2.9% of cases, respectively.

The study reported that R0 resection was achieved in 62.9% of patients, while 31.4% achieved R1 resection. In addition, two patients received surgical resection along with other local therapies for residual lesions. It is also worth noting that all patients who underwent a second liver resection were classified as R0.

Of the patients with mutated *KRAS*, anatomical resections were performed in 46.6% (n=16), with 13.3% undergoing combined resections. R0 resection was achieved in 80% of this group. For patients with *wild-type KRAS*, anatomic resections were performed in 50% of cases, with segmentectomies and combined resections being the most common types. In this group, 50% of resections were considered R0, 40% R1, and only 10% were considered R2 (**Table 3**).

Outcomes

The median follow-up duration for the study was 39 months. Unfortunately, 54.3% of the patients died from their oncological disease, while 5.7% died from other causes. At the end of the study, only 40% of the patients survived, and of these, only 28.5% were deemed disease-free and not receiving any active treatment (**Table 4**).

In the subgroup analysis based on *KRAS* gene status, it was observed that among patients with *KRAS* mutation, 60% of them died due to cancer-related causes, 6.7% died

Table 1. Clinical characteristics of patients who underwent liver resections for colorectal cancer

Characteristic	Statistics, n (%)
Age (years completed)	
- Median (min-max)	63 (42-82)
Sex	
- Man	20 (57.14)
- Woman	15 (42.86)
Primary tumor	
- Right colon	6 (17.14)
- Left colon	15 (42.86)
- Rectum	14 (40)
Neoadjuvant chemotherapy	
- No	23 (65.71)
- Yes	11 (31.43)
- No data	1 (2.86)
Synchronous metastasis	
- No	16 (45.71)
- Yes	19 (54.29)
Site of metastasis	
- Liver	16 (84.21)
- Liver + others	1 (15.78)
Hepatic and primary metastasectomy in a surgical time	
- No	17 (89.47)
- Yes	2 (10.53)
Treatment for metastases different from surgery	
- No	16 (94.12)
- Yes	1 (5.88)
Degree of differentiation of the primary tumor	
- Well differentiated	4 (11.43)
- Poorly differentiated	1 (2.86)
- Moderately differentiated	30 (85.71)
Clinical stage	
- II	5 (14.29)
- III	10 (28.58)
- IV	19 (54.28)
- No data	1 (2.86)
Relapses in a place other than the liver	
- No	31 (88.57)
- Yes	4 (11.43)
Site other than relapsed liver	
- Lung	4 (100)
Neoadjuvant chemotherapy to metastasectomy	
- No	31 (88.57)
- Yes	4 (11.43)
Tumor marker before metastasectomy	
- Median (min-max)	7.03 (1.33-88.5)
KRAS gene mutation	
- No	20 (57.14)
- Yes	15 (42.86)

Source: Authors' own research

Table 2. Clinical characteristics and outcomes of patients with mutated and wild-type KRAS

Characteristic	Mutated KRAS	Wild-type KRAS
Age (years completed)		
- Median (min-max)	66 (45-82)	59 (42-77)
Sex, n (%)		
- Man	7 (46.67)	13 (65)
- Woman	8 (53.33)	7 (35)
Primary tumor, n (%)		
- Right colon	5 (33.33)	1 (5)
- Left colon	4 (26.67)	12 (55)
- Rectum	5 (40)	8 (40)
Neoadjuvant chemotherapy, n (%)	9 (60)	
- No	5 (33.33)	14 (70)
- Yes	1 (6.67)	6 (30)
Clinical stage, n (%)		
- II	1 (6.67)	4 (20)
- III	5 (33.34)	4 (25)
- IV	9 (60)	8 (40)
- No data	-	1 (5)
Tumor marker prior to metastasectomy		
- Median (min-max)	6.98 (2.8-42.8)	8 (1.33-88.5)
Number of liver lesions		
- Median (min-max)	4 (1-12)	4(1-7)
Type of surgery for resection of liver metastases, n (%)		
- Right or left hepatectomy	1 (6.67)	2 (10)
- Another combined anatomical resection	2 (13.33)	3 (15)
- Non-anatomic segmental resection	8 (53.33)	10 (50)
- Anatomical segmentectomy	4 (26.67)	5 (25)
Measurement of increased liver metastasis (cm)		
- Median (min-max)	4 (0.7-8)	2.7 (1-12)
Resection status at metastasectomy, n (%)		
- R0	12 (80)	10 (50)
- R1	3 (20)	8 (40)
- R2	-	2 (10)
Progression-free survival, months		
- Median (min-max)	11.5 (0-24.8)	19.1 (1.9-46.2)
State at last contact, n (%)		
- Dead due to illness	9 (60)	10 (50)
- Dead due to another cause	1 (6.67)	1 (5)
- Alive with disease	4 (26.67)	6 (30)
- Alive without disease	1 (6.67)	3 (15)
Overall survival, months		
- Median (min-max)	34.1 (0.5-82.6)	46.4 (2.7-152.4)

Source: Authors' own research

Table 3. Characteristics of liver resections in all patients

Characteristics of liver resections	n (%)
Number of liver lesions	
- Median (min-max)	4.5 (1-12)
Surgery for resection of liver metastases	
- Right or left hepatectomy	3 (8.57)
- Other combined anatomic resections	5 (14.29)
- Non-anatomic segmental resection	18 (51.43)
- Anatomical segmentectomy	9 (25.71)
Measurement of increased liver metastasis (cm)	
- Median (min-max)	3 (0.7- 12)
Resection status at metastasectomy	
- R0	22 (62.86)
- R1	11 (31.43)
- R2	2 (5.71)
Chemotherapy adjuvant to metastasectomy	
- No	4 (11.43)
- Yes	29 (82.86)
- No data	2 (5.71)
Nonsurgical management of liver metastases, n (%)	
- Other	4 (11.4)
- Radioablation	2 (5.7)

Source: Authors' own research.

Table 4. Outcomes of patients who underwent liver resections for colorectal cancer

General patient outcomes	Statistics
Progression-free survival (months)	
- Median (min-max)	15.6 (0-46.2)
State at last contact, n (%)	
- Dead due to illness	19 (54.29)
- Dead from a different cause	2 (5.71)
- Alive with disease	10 (28.57)
- Alive without disease	4 (11.43)
Overall survival (months)	
- Median (min-max)	37.1 (0.5-152.4)

Source: Authors' own research.

from causes unrelated to cancer, and only 33% of patients were alive at the end of the study follow-up, out of which 80% had active disease. Conversely, in patients with *wild-type KRAS*, 50% had died due to cancer-related causes at the end of the study, and 66% had active disease among the living patients.

The study showed that the overall survival had a median of 37.1 months. When the analysis was based on the *KRAS* gene status, patients with mutated *KRAS* had a median survival of 34.2 months, while those with *wild-type KRAS* had a more prolonged median survival of 46.5 months. In the subgroup analysis based on the type of resection performed, patients with mutated *KRAS* who underwent anatomic resections had a longer median survival of 43.5 months compared to those who underwent non-anatomic resections with a median survival of 23.5 months. For patients with *wild-type KRAS*, the median survival was 34.5 months for non-anatomic resections and 41.3 months for anatomic resections.

DISCUSSION

Metastatic colorectal cancer is a complex condition characterized by significant biological variability. Therefore, it is essential to examine each case individually when considering locoregional and systemic management options.[15] With regards to liver metastases from colorectal cancer, various studies have investigated multiple clinical and pathological factors that can influence the prognosis and benefits of liver resection surgery. Some preoperative scoring systems have also been analyzed to support the selection of suitable candidates for hepatic resection.[7,16]

In recent decades, *KRAS* and *NRAS* gene mutations have been analyzed as biological markers. Studies have shown that these mutations are associated with resistance to monoclonal antibody therapy against EGFR in cases of metastatic disease.[17,18] Furthermore, these mutations are linked to a lower response rate to conventional management, faster disease progression, and poorer survival outcomes.[19]

The activation of the EGFR-activating-dependent RAS/RAF signaling pathway through receptor binding is caused by an oncogenic mutation in *KRAS*, leading to constant stimulation of proliferation, angiogenesis, resistance to apoptosis, and increased metastatic capacity.[20,21] Consequently, it can be inferred that EGFR inhibitors, which operate at a higher level than the activation of the *KRAS* pathway, are ineffective in patients with a mutation that sustains the active pathway.

Several studies have investigated the impact of *KRAS* gene status on the outcomes of patients with liver metastases due to colorectal cancer who undergo liver resection. However, the findings have not been consistent across studies, with some reporting adverse effects for patients with mutated *KRAS* while others not.[22-25] A meta-analysis conducted by Passiglia concluded that patients with mutated *KRAS* had worse outcomes in terms of recurrence and survival.[3]

Recently, some researchers have reported specific outcomes for patients with mutated *KRAS* when offered better

local surgical control with anatomic resections. This alternative has shown promise for improving survival rates compared to systemic therapies alone without local control of metastatic involvement. However, the results of studies on this topic are contradictory(**Table 5**).[26-28]

In our case series, 46.6% of patients with *KRAS* mutation and 50% with *wild-type KRAS* underwent anatomic resections, which were planned based on the number and location of metastatic lesions without considering the mutation status for the type of resection at the moment. We observed that in the group with mutated *KRAS*, anatomic resections resulted in an 85% higher average survival rate (43.5 vs. 23.5 months) compared to non-anatomic resections (**Figure 2**).

Several studies have demonstrated that patients with liver metastases due to colorectal cancer benefit more from surgery than from systemic management, with improved survival rates.[29-31] This benefit also extends to patients with mutated *KRAS*, who have a worse prognosis. In fact, studies have reported an average survival of 34 to 40 months for patients with mutated *KRAS* who underwent surgery, compared to only 10.6 months for those who received systemic management with chemotherapy alone.[32-34] In our study, patients with mutated *KRAS* who underwent anatomic resections

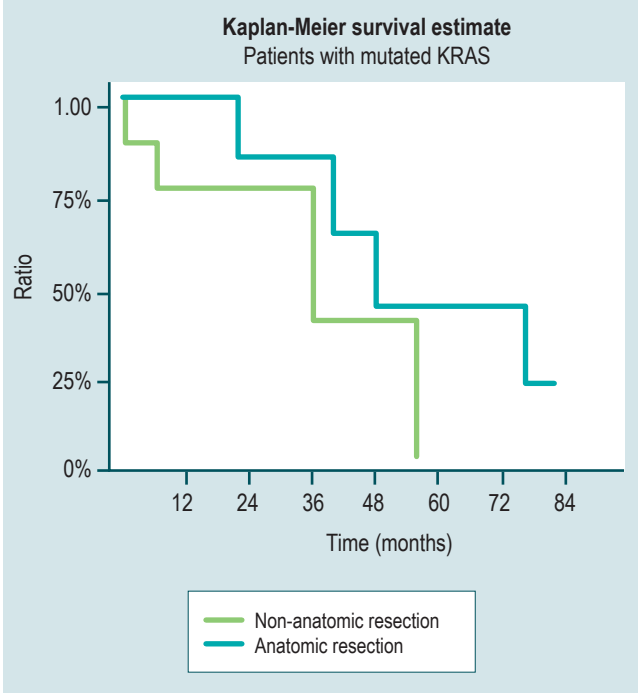

Figure 2. Overall survival of patients with KRAS mutation according to the type of resection. Source: Authors' own research.

Table 5. Studies reporting oncological outcomes according to the type of liver resection in relation to KRAS gene status in patients with liver metastases due to colorectal cancer

Study	Margonis et al.	Choi M. et al.	Kwai T. et al.	Acevedo et al.
Number of patients	389	250	290	35
Year	2017	2022	2022	2022
Oncology outcomes	DSF Anatomical KRASmut: 33.8 months Non-anatomical: 10.5 months	DSF Anatomical KRASmut: 11 months Non-anatomical: 9 months	5-year OS KRASmut Anatomical: 55% Non-anatomical: 53% KRASwt Anatomical: 81% Non-anatomical: 58%	Average OS Anatomical KRASmut: 43.5 months Non-anatomical: 23.5 months KRASwt Anatomical: 34.5 months Non-anatomical: 41.3 months
Comments	Non-anatomic resections are associated with worse DFS in patients with KRAS mutation tumors.	The presence or absence of the KRAS mutation did not show a significant association with DFS, regardless of the type of resection, and was not considered a significant prognostic factor.	Anatomic resection was an independent prognostic factor for DFS and OS in KRASwt patients. In contrast, anatomic resection was not associated with SLE or OS in KRAS mutation patients.	Anatomic resection was a factor associated with improved survival in patients with mutated KRAS.

KRASmut: KRAS gene mutation; KRASwt: wild state or no mutation of the KRAS gene; OS: overall survival; DFS: disease-free survival. Source: Authors' own research

had an average survival of 43.5 months, which was similar to the average survival of 41.5 months for those with *wild-type KRAS* who underwent anatomic resections. However, patients with mutated *KRAS* who underwent non-anatomic resections had a markedly lower average survival of 23.5 months, compared to 34.5 months for those with *wild-type KRAS* who underwent non-anatomic resections.

There is a limited number of studies that describe or recommend anatomic resections, particularly in patients with mutated *KRAS* status.[26-28] These studies have presented varying results regarding overall survival and disease-free survival. However, due to the higher frequency of micrometastases and R1 resections in this patient population,[34,35] achieving local control with parenchymal-sparing liver resections may be more challenging.

This paper has limitations as it is a retrospective study with relatively few patients. However, the results are consistent with those reported by other authors, showing better survival outcomes for patients with mutated KRAS who undergo greater margin or anatomic liver resections. Although there is still limited evidence, the results of this retrospective series are valuable and encourage further research to enable appropriate decision-making for patients with mutated KRAS who are candidates for liver resections, especially for those with unfavorable prognoses in different oncological outcomes.

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Conflicts of Interests

The authors of this article declare that they have no conflicts of interest in the development and publication of this paper.

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Original article

Endoscopic Findings in Patients with Moderate to Severe COVID-19: A Cross-sectional Study

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Abstract

Introduction: Severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) infection has diverse gastrointestinal manifestations, often requiring endoscopy. **Objective**: The primary objective is to describe the need for endoscopic procedures from a sample of hospitalized patients with moderate to severe coronavirus disease 2019 (COVID-19). The secondary objective is to describe the characteristics, findings, and interventions. **Materials and methods:** An observational, descriptive, cross-sectional study was conducted from May 2020 to December 2021 about indications, endoscopic findings, interventions, anesthesia requirements, and adverse events from a sample of patients with moderate to severe COVID-19 in whom gastrointestinal endoscopic procedures were performed for any indication. **Results:** Of 2,312 hospitalized patients with moderate to severe COVID-19, 2.72% required endoscopic procedures, with a predominance of men (75%), an average age of 65.7 years, and the majority for upper gastrointestinal endoscopy (68%). The most frequent indications were gastrointestinal bleeding (62%) and enteral access (28.3%). An ischemic compromise was documented in three patients. Of those with digestive bleeding, 9.5% required hemostatic therapy, and 65% were on ventilatory support and sedation during the endoscopic procedure. In half of these cases, anesthesiology support was required without periprocedural adverse events, nor was a negative pressure room required in any procedure. **Conclusions:** In patients with moderate to severe COVID-19 requiring gastrointestinal endoscopy, clinical judgment is necessary to define the relevance of the procedure; in many cases, conservative management may be considered.

Keywords (DeCS)

COVID-19, coronavirus, endoscopy, gastrointestinal bleeding, gastrointestinal diseases, gastrointestinal tract.

INTRODUCTION

The coronavirus disease 2019 (COVID-19) was initially believed to be a respiratory illness, but its potential consequences on other organs, including the digestive system, have become increasingly apparent over time.[1] The first confirmed case of COVID-19 with gastrointestinal symptoms was reported in the United States.[2] This discovery suggested the possibility of fecal-oral transmission, as the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was detected in stool samples, which drew further attention to the difficulty of assessing virus infectivity and potential alternative modes of transmission.[3] Studies conducted outside of China also described a higher inci-

dence of gastrointestinal symptoms,[4] including diarrhea, loss of appetite, nausea, vomiting, and abdominal pain. In addition, dysgeusia, anosmia, and gastrointestinal bleeding were reported upon admission or during hospitalization.[3]

SARS-CoV-2 infection is associated with gastrointestinal involvement and may require diagnostic and therapeutic endoscopic studies for patients with diverse clinical manifestations. The suspicion of intestinal bleeding is a common indication in hospitals, but multiple etiologies must be considered, including the underlying viral disease, medication consumption, coagulation disorders, and ischemic involvement.[1] The need for nutritional support also increases the need for endoscopic support.[3,5] Prior studies have found abnormal endoscopic findings in a significant proportion of the patients under study, ranging from mild to severe disease severity and displaying considerable heterogeneity in endoscopic findings.[5-7] It is reported that gastrointestinal involvement in COVID-19 patients is clinically relevant and that those with gastrointestinal symptoms often experience more severe clinical outcomes and require more intensive treatment.[8,9]

It had been proposed previously that the gastrointestinal tract could be a potential target of SARS-CoV-2 due to possible direct inflammatory effect on the gastrointestinal mucosa, as the virus binds to angiotensin-converting enzyme 2 (ACE-2) receptors that are constitutively expressed in the gastrointestinal tract.[10] However, previous studies[5,7,11] have shown heterogeneous findings and determined that most gastrointestinal manifestations are related to critical or prolonged illness rather than direct viral injury. In our setting, there is limited data on the severity of COVID-19 and its potential relationship with gastrointestinal involvement detected by endoscopic studies. Thus, the primary objective of this descriptive study is to report the need for endoscopic procedures in a sample of hospitalized patients with moderate to severe COVID-19, and the secondary objective is to describe the characteristics, findings, and interventions in detail.

METHODOLOGY

Study Design and Data Extraction

A cross-sectional descriptive observational study was conducted from May 2020 to December 2021, in which data from 2312 hospitalized patients who required endoscopic studies were collected from two third-level hospitals in Bogotá, Colombia. The study included patients aged 18 years or older diagnosed with moderate to severe COVID-19 who were hospitalized in the emergency room, general ward, or intensive care unit (ICU) and underwent endoscopic gastrointestinal procedures for any indication during their hospital stay. Subjects with mild COVID-19 and those who underwent endoscopic gastrointestinal procedures as outpatients were excluded.

Data Collection

For data collection, we relied on medical records and official reports of procedures, which served as our primary source of information. We gathered sociodemographic and clinical variables and analyzed information on indications, endoscopic findings, interventions, anesthesia use, and adverse events. The collected variables included age, sex, endoscopic indication, type of endoscopic study conducted, endoscopic findings, requirement for ventilatory support, need for sedation by anesthesiology during the procedure, requirement for hemostasis, and any adverse events encountered.

Definitions

The definition of *Moderate COVID-19* in this study was based on clinical evaluation or imaging showing evidence of lower respiratory disease and oxygen saturation (SpO_2) ≥ 94% in ambient air. *Severe COVID-19* was defined as having a SpO_2 < 94% in ambient air, a ratio between arterial partial pressure of oxygen and the inspired fraction of oxygen (PaO_2/FiO_2) < 300 mm Hg, a respiratory rate (RR) > 30 breaths per minute (brpm), or pulmonary infiltrates > 50%.[12] For cases of documented esophagitis, the severity was classified according to endoscopic findings using the Los Angeles classification.[13]

Statistical Analysis

We utilized MS Excel version 2019 to create the database. Any missing data was completed through further revisions of the sources of information, and only complete data were ultimately analyzed. The data was processed using the social sciences program SPSS version 25.0. Descriptive analysis utilized the arithmetic mean and standard deviation (SD) for quantitative variables, while absolute and relative frequencies were used for qualitative variables.

Ethical Considerations

The Ethics and Research Committees of Clínica Palermo and Clínica Infantil Santa María del Lago in Bogotá, Colombia, approved this study. Both hospitals are third-level care centers and local referral centers in gastroenterology. The study design followed the requirements established in Resolution 8430 of 1993 of Colombia's Ministry of Health and Social Protection, ensuring confidentiality and discretion with the collected information, and was considered low-risk research. All patients provided informed con-

sent, and no records contained sensitive information about patients' identities.

RESULTS

During the study period, 2312 patients with moderate to severe COVID-19 were hospitalized in the participating institutions, of which 63 (2.72%) were included in the study and underwent endoscopic procedures. Most of these patients were male (75%) and had an average age of 65.7 years. Of the total, 41 patients (65%) met the criteria for severe COVID-19, while 22 had moderate disease. Upper endoscopy (EGD) was the most common procedure, followed by colonoscopies and endoscopic retrograde cholangiopancreatography (ERCP). The most frequent indications for these procedures were gastrointestinal bleeding (62%), enteral access requirement (28.3%), and cholangitis (4.8%), among others (**Table 1**).

Table 1. Characterization of patients with moderate-severe COVID-19 requiring endoscopic studies

Characteristics (n = 63)	
Average Age (SD)	65.73 (13.91)
Sex	
- Male, n (%)	47 (75%)
- Female, n (%)	16 (25%)
Endoscopic indication	
- Bleeding, n (%)	39 (62%)
- Gastrostomy requirement, n (%)	14 (22%)
- Cholangitis, n (%)	3(4.8%)
- Catheter for nutritional support, n (%)	4 (6.3%)
- Abdominal pain, n (%)	1 (1.6%)
- Foreign body, n (%)	1 (50%)
- Intestinal obstruction, n (%)	1 (50%)
Endoscopic study	
- EGD, n (%)	51 (81%)
- Colonoscopy, n (%)	9 (14%)
- ERCP, n (%)	3 (4.8%)

ERCP: endoscopic retrograde cholangiopancreatography; EGD: upper endoscopy; SD: standard deviation. Source: Authors' own research.

Out of the 39 patients with suspected digestive bleeding, six (15.38%) required hemostatic therapy (**Table 2**), and all of them were treated with adrenaline sclerotherapy. The most commonly affected region by ulcers was the stomach, with seven out of nine patients, followed by the duodenum, with two out of nine patients. Ischemic involvement was documented in three patients, of which two had ischemic esophageal involvement (**Figure 1**), and the other had gastric ischemic involvement. These cases were observed in patients who met the severe COVID-19 definition and required ICU admission due to systemic thrombotic involvement. Gastrostomy was performed in fourteen cases (22%), and four required nasoenteral catheters (6.3%) (**Table 1**). ERCP was required in three cases, and findings of choledocholithiasis were documented (**Table 2**).

Table 2. Endoscopic findings of patients with moderate-severe COVID-19 requiring endoscopic studies

Endoscopic findings (n = 63)*	
Erythematous gastritis, n (%)	14 (22.2%)
Esophagitis, n (%)	10 (15.8%)
Ulcer, n (%)	9 (14.3%)
Hemorrhagic pangastritis, n (%)	6 (9.5%)
Changes due to epistaxis, n (%)	3 (4.8%)
Choledocholithiasis, n (%)	3 (4.8%)
Erosive gastritis, n (%)	3 (4.8%)
Diverticular bleeding, n (%)	2 (3.2%)
Erosive bulboduodenitis, n (%)	2 (3.2%)
Ischemic involvement, n (%)	3 (4.76%)
Neoplasm, n (%)	1 (1.6%)
No findings, n (%)	27 (42.8%)

*Patients may have more than one endoscopic finding. Source: Authors' own research.

During the endoscopic procedures, 65% (n = 41) of the patients were receiving ventilatory support and sedation. Of those cases, 22 required participation from anesthesiologists for general anesthesia due to their classification of III or higher in the American Society of Anesthesiologists (ASA) and multi-support therapy. No negative pressure room was used during any of the procedures, and no data were collected regarding the possible exposure and infection of endoscopy or anesthesia personnel during these procedures.

DISCUSSION

Despite the high burden of COVID-19, only 2.72% of the 2312 hospitalized patients with moderate to severe COVID-19 required endoscopy. Most EGD findings

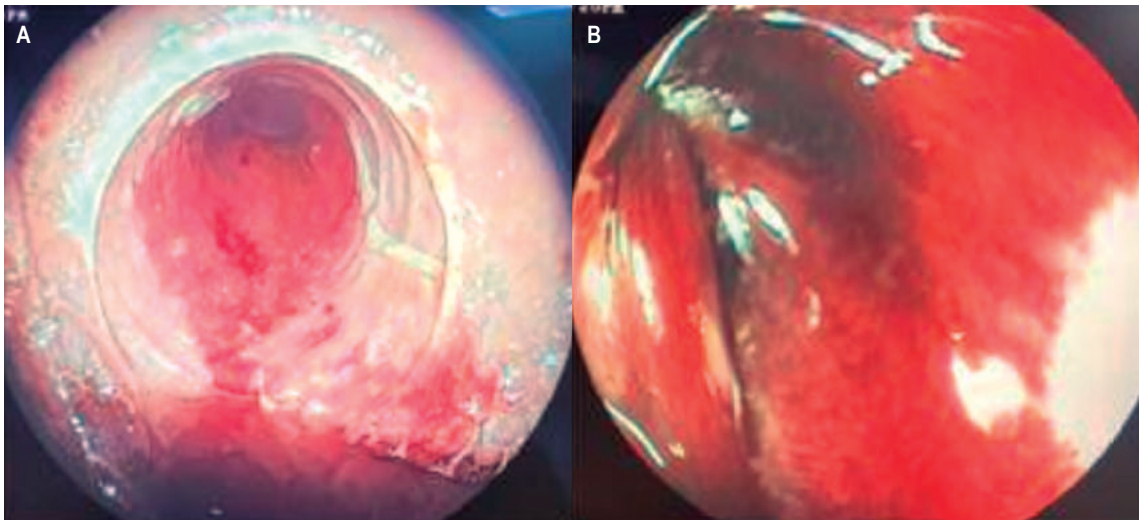

Figure 1. Endoscopic view of ischemic esophageal involvement. **A.** Detachment of areas of mucosa in an early stage of ischemic esophagitis. **B.** Advanced involvement in areas of necrosis. Images owned by the authors.

showed erythematous gastritis and esophagitis, while diverticular bleeding was the most common finding during colonoscopy. Gastrointestinal bleeding was the most common indication for EGD, likely due to interrelated factors such as medication use, predisposition to bleeding, or disseminated intravascular coagulation. We observed cases of esophageal and gastric ischemia, which may be secondary to thrombotic dysfunction resulting from excessive inflammation, platelet activation, and endothelial dysfunction. Findings in the upper gastrointestinal tract are consistent with those of previous studies conducted in Italy and the United States,[5,6,14] and are expected in severely ill patients. In contrast, we did not observe any findings of inflammatory pathology in the colon, which is similar to the outcomes of a study by Kuftinec et al.[5] Diverticulosis and hemorrhoids were the main colonoscopy findings in that study. Therefore, the indications and endoscopic findings are likely consequences of systemic disease rather than a direct viral lesion, which is consistent with the findings of previous studies.[5,7,11]

The majority of participants in this study were male and had an average age of around 65. It is worth noting the occurrence of hemorrhagic and ischemic findings, which suggest the presence of complications in patients with moderate-severity COVID-19. Previous studies[5-7,11,14] analyzed people aged 60 to 71, primarily male participants (56%-83.3%), with diabetes and hypertension as the main comorbidities and a higher rate of complications with respect to other age groups. Despite the limitations of this study, our findings highlight the importance of considering the male sex and advanced age as potential risk factors for ischemic damage in the gastrointestinal tract due to COVID-19. Further research is needed in this area. The role of the endoscopist is crucial in the comprehensive and multidisciplinary management of these patients.

Among the 63 patients in this study, 39 (62%) required endoscopy due to digestive bleeding, and six of these cases (15.38%) required hemostatic therapy, which was achieved through adrenaline sclerotherapy. Enteral access was only required in four cases (6.35%), and ERCP was necessary in three cases due to biliary obstruction, all of which were associated with choledocholithiasis with cholangitis. Diagnostic endoscopies accounted for most cases (36/63, 57.1%) and did not require interventional treatment. These findings are consistent with those of Kuftinec et al.[5] and suggest that conservative (non-endoscopic) treatment may be an appropriate option for most COVID-19 patients. The decision to perform an endoscopic study with possible intervention should be made by experts based on individual patient needs.

Despite the small sample size, we did not identify a significant increase in risk associated with endoscopic intervention or sedation in our patients. However, some studies have indicated a higher risk of sedation-related bronchoaspiration in patients undergoing colonoscopies under sedation compared to those without sedation (0.22% vs. 0.16%).[15,16] This is particularly relevant in patients with COVID-19 who have respiratory involvement and changes in mental state. At the time of the endoscopic study, 41 out of 63 patients (65%) were on ventilatory support and sedation, and 22 out of 41 (53.6%) required anesthesiology assistance for the procedure. No adverse events were docu-

mented during the peri-procedural period, and no negative pressure rooms were needed. These findings are similar to those of Kuftinec et al.,[5] which reported that approximately 50% of their patients required anesthesiology assistance for endoscopic procedures. Most procedures were performed in the ICU or digestive endoscopy unit, and none required a negative pressure room. Thus, the support of anesthesiology is essential to ensure the safety and comfort of clinicians in the peri-procedural management of these patients.

The study has several potential limitations, including a retrospective design and reliance on medical record reviews. Additionally, the study was conducted in only two third-level hospitals in Bogotá, Colombia, and thus, the results may not apply to other geographic locations with different resource availability. Furthermore, the sample size for patients undergoing EGD was small due to the national considerations for endoscopic procedures during the pandemic, which limited procedures to urgent or therapeutic purposes only. Other limitations include the inability to compare COVID-19 patients to those with negative results in the follow-up period and the lack of histological and microbiological analyses due to the endoscopic approach. Despite these limitations, this study sheds light on the wide range of gastrointestinal manifestations of COVID-19 that gastroenterologists and endoscopists should be aware of.

CONCLUSIONS

According to the findings of this study, less than 3% of patients with moderate to severe COVID-19 required gastrointestinal endoscopy. In addition, conservative management was generally employed, and there was a low frequency of endoscopic interventions. The indications for the procedures, as well as the endoscopic findings, interventional requirements, and need for anesthesia, were highly variable and consistent with what has been reported in previous literature. Therefore, clinical judgment is crucial in determining the necessity of endoscopies and prioritizing those that are urgent and therapeutic.

Ethical Approval and Consent to Participate

This research was reviewed and approved by the research ethics committee of each participating institution.

Consent to Publication

This study adhered to the guidelines outlined in Resolution 8430 of 1993 from the Ministry of Health and Social Protection of Colombia. Consequently, it was classified as low-risk research, ensuring confidentiality and discretion were maintained when collecting information. All patients were informed and provided informed consent. None of the records contained sensitive information regarding the patients' identities.

Availability of Data and Material

The manuscript contains all the data and material available for publication, and no information has been omitted.

Conflicts of Interests

The authors stated that they have no conflict of interest.

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The authors did not declare any source of funding.

Authors' contributions

All authors, VPI, JSFO, JPNM, HNM, KTCR, CNM, JC, and CFS, made contributions throughout all stages of the research, including literature review, data collection, and manuscript composition. The final version of the manuscript was approved by all authors.

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Original article

Whipple's Disease: A Systematic Review of the Literature

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Abstract

Introduction: Whipple's disease is a chronic systemic disease with a predilection for the digestive system, especially the small intestine. It was first described in 1907 by George H. Whipple, who named it *intestinal lipodystrophy*. It is caused by a gram-positive bacterium belonging to the *Actinomycetaceae* family called *Tropheryma whipplei*. **Objective:** To characterize patients with Whipple's disease. **Materials and methods:** A systematic literature review was carried out using the DeCS terms *enfermedad de Whipple* (*Whipple's disease*) or (*Tropheryma whipplei*) in the Pubmed/Medline, Scopus, Scielo, Science Direct, Embase, Cochrane Library, BIREME, Proquest, and Redalyc databases; 123 articles were analyzed. **Results:** 123 published articles corresponding to case reports and series were examined, noting a higher prevalence in males (70.6%). The most frequent manifestations were joint symptoms (61%), followed by weight loss (47.1%) and diarrhea (43.4%). The most used diagnostic method was polymerase chain reaction (PCR) (63.2%), followed by biopsy (50.7%) and pathological examination with PAS (periodic acid Schiff) granules (47.8%). The management most used was antibiotic therapy with a predominance of trimethoprim/sulfamethoxazole and ceftriaxone. **Conclusions:** Whipple's disease has a low prevalence, occurs more frequently in white people, mainly affects the elderly, has a predilection for the male sex, and is characterized as a chronic systemic disease with a predilection for the digestive system, especially the small intestine.

Keywords

Whipple's disease, *Tropheryma*, systematic review.

INTRODUCTION

Whipple's disease (WD) is a chronic systemic disease likely to manifest in the digestive system, particularly in the small intestine. It was first reported in 1907 by George H. Whipple, who named it *intestinal lipodystrophy*.[1,2] The disease is caused by a gram-positive bacterium, *Tropheryma whipplei* (TW), which belongs to the *Actinomycetaceae* family, and causes an infection with nonspecific symptoms. However, the typical symptoms usually start with arthralgia and then diarrhea, weight loss, fever, adenopathy, and, in some cases, neurological, cardiac, or ocular manifestations. Although atypical, the disease may also present as a febrile syndrome of unknown origin.[1-4]

This study aims to provide a systematic literature review that characterizes patients with WD.

MATERIALS AND METHODS

Type of Study

The systematic literature search for this study was carried out in accordance with the 2020 "Preferred Reporting Items for Systematic Reviews and Meta-Analyses" (PRISMA)

statement and the Cochrane Handbook for Systematic Reviews of Interventions, version 5.1.022.

Population

The study included all individuals who had been diagnosed with WD and had received treatment, as well as articles published from 2015 to 2021. The latest developments related to clinical presentations, diagnosis, laboratory tests, treatment, and prognosis were also taken into consideration.

Inclusion Criteria

We included case reports and case series articles published in English or Spanish within the last six years.

Exclusion Criteria

Studies, topic reviews, and editorial letters were excluded from our analysis.

Variables

The variables analyzed in this study were sex (male/female), country of origin, year of publication, medical history, clinical manifestations, laboratory tests, and medical management approaches used.

Search Strategies

Between September 1 and September 15, 2021, the researchers conducted a search using the following databases: PubMed/Medline, Scopus, Scielo, Science Direct, Embase, Cochrane Library, BIREME, Proquest, and Redalyc. The search terms used were "Whipple Disease" (Enfermedad de Whipple) or "Tropheryma", based on the DeCS [MeSH] system.

Search Restrictions

The search was restricted to literature related to humans and published in English and Spanish.

Data Extraction

The articles found in the literature search were recorded in an MS Excel database, and duplicates were removed. We discussed doubts and reasons for possible exclusions as a team and made consensus-based decisions. The statistical software SPSS version 22 was used to analyze the data. Descriptive statistics were used to conduct a univariate analysis and determine the absolute and relative frequencies of the qualitative variables, as well as measures of central tendency and dispersion for the quantitative variables. Finally, we reviewed the full articles to select those to be included in this study.

Biases

In this study design, it is important to control several biases. The first is related to poor population selection, which is why we created inclusion and exclusion criteria. The second one is measurement bias, which we addressed using a data collection sheet to be applied by the researchers. Finally, we had to deal with potential information gaps since the data come from case reports and case series records that may have incomplete information.

RESULTS

Selection of Studies

After implementing the search strategy as described, we initially identified 215 articles from the selected databases. However, we excluded 38 articles due to not meeting our search criteria. Following this, we screened the titles and abstracts of the remaining 177 articles and eliminated 24 articles. This resulted in 153 articles that were eligible for full-text review. After reviewing the full-text articles, we excluded 16 articles that did not meet the study's inclusion criteria, resulting in 137 articles. We then removed 20 duplicate articles, resulting in 117 published articles consisting of case reports and case series. We adhered to the PRISMA statement guidelines for the selection process of the included studies, and a flowchart outlining the study selection process can be found in **Figure 1**.

Sociodemographic Characteristics of Patients

The data interpretation regarding the most common age of onset for WD reveals that it can occur at any stage of life, with documented cases ranging from a 4-year-old girl to an 82-year-old man. However, the disease's highest prevalence falls within the approximate age range of 50 to 65 years, with 67 reported cases. Furthermore, a greater incidence was observed in the 50-58 (2.9%) and 63 (6.6%) age groups. Males showed a higher incidence rate, with 96 cases and a percentage of 70.6% out of the total cases.[1-117]

Clinical Characteristics

The researchers conducted an analysis of the clinical case series and identified the most common manifestations of WD. Arthralgia was found in 83 patients (61%), weight loss in 64 (47.1%), diarrhea in 59 (43.4%), fever in 45 (33.1%),

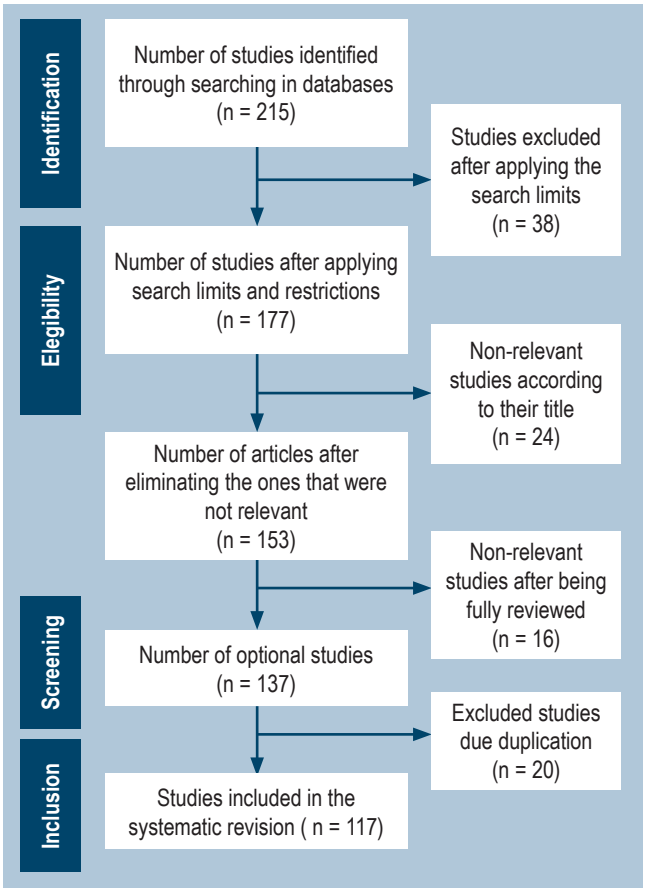

Figure 1. PRISMA flowchart. Source: Authors' own research.

abdominal pain in 31 (22.8%), and neurological symptoms in 30 cases (22.1%), as shown in **Table 1.**[1-117]

Based on the clinical cases analyzed by the research group, it was found that the three most commonly used diagnostic tools for generating a possible diagnosis were PCR for T. Whipple in 86 patients (63.2%), biopsy in 69 patients (50.7%), and pathological examination with positive staining for Periodic acid–Schiff (PAS) in 65 cases (47.8%). In addition, imaging findings from tests such as radiography, magnetic resonance imaging (MRI), and computed tomography (CT) were essential for the diagnosis, as they were helpful in 90 patients (66.2%). The erythrocyte sedimentation rate (ESR), high in 114 patients (83.8%), was also significant in aiding diagnosis.

Therapeutic characteristics

The results of the study showed that antibiotic therapy was the preferred approach for treating WD, with a high tendency towards the use of trimethoprim/sulfamethoxazole (61.0%), ceftriaxone (57.4%), and doxycycline (31.6%). Hydroxychloroquine (26.5%) and corticosteroids/prednisone (15.4%) were also used. Other antibiotic-based treatments, such as cefotaxime, meropenem, vancomycin, imipenem, tigecycline, and cefixime, were used less frequently. A detailed description of the results can be found in **Table 2.**[1-117]

In addition, other treatment options were employed to manage specific associated symptoms. These included methotrexate (1.5%), non-specified antibiotics (1.5%), nonsteroidal anti-inflammatory drugs (NSAIDs) (1.5%), ofloxacin/prednisone drops (0.7%), palliative stereotactic surgery (0.7%), caspofungin (0.7%), and gentamicin plus noradrenaline plus dopamine (0.7%), as reported in **Table 3**.

DISCUSSION

WD is a systemic condition caused by *Tropheryma whipplei*, a gram-positive bacterium. The disease is named after the Greek words *trophe* (food) and *eryma* (barrier) due to its association with poor absorption of nutrients. It was first described in 1907 by George Hoyt Whipple as a chronic and systemic disease linked to intestinal lipodystrophy. It was not until 1952 that its etiology was postulated to be bacterial, based on clinical improvement after antibiotic treatment. Electron microscopy findings in 1960 provided further evidence for this hypothesis, and its ribonucleic acid (RNA) was amplified using PCR in 1990. Cultivation of the bacterium was achieved in 1997.[42] The disease can occur at any age, as there are reports of cases from individuals aged 4 to 82.[1-117] While the highest prevalence is found among individuals between 50 to 65 years old, the disease onset can occur at any age. Males have a higher predisposition to the disease, with 96 cases reported and a percentage of 70.6.[1-117]

The clinical presentation of WD is variable and not specific, with different organs affected and requiring diverse treatments. The disease may manifest as gastrointestinal histological lesions or isolated neurological cases. Typically, joint involvement is the first clinical sign, as observed in 83 patients (61%), consistent with a study by Moreno García (60% of cases). Weight loss is present in 64 patients (47.1%), diarrhea in 59 (43.4%), fever in 45 (33.1%), abdominal pain in 31 (22.8%), and neurological symptoms in 30 cases (22.1%). Joint involvement typically appears as intermittent migratory arthralgia, arthritis, or both, without deformity. It usually affects multiple joints, although it can be oligoarticular in large joints.[9]

Ocular involvement is not common in WD and typically presents at a later stage. It should be considered when bilateral choroidal granulomatosis is observed in the context of an atypical systemic disease. A limited number of cases of ocular involvement in WD have been reported in recent

Table 1. Clinical characteristics

Prevalence	n	%	Prevalence	n	%
Clinical manifestations			Studies		
- Diarrhea	59	43.4	- Hemoglobin (anemia)	40	29.4
- Bloating	14	10.3	- Leukocytosis	21	15.4
- Rectal bleeding	3	2.2	- Neutrophilia	11	8.1
- Abdominal pain	31	22.8	- Increased ESR	114	83.8
- Dyspnea	19	14.4	- PCR for T. Whipple positive	86	63.2
- Headache	4	2.9	- Human rheumatoid factor	1	0.7
- Fever	45	33.1	- Anatomopathological examination with PAS granules	65	47.8
- Hyporexia	11	8.1	- Fecal occult blood	3	2.2
- Anorexia	7	5.1	- Imaging findings	90	66.2
- Weight loss	64	47.1	- Colonoscopy	9	6.6
- Asthenia	10	7.4	- Endoscopic findings	25	18.4
- Polyarthritis	25	18.4	- Biopsy findings	69	50.7
- Myalgias	7	5.1	- Autopsy	1	0.7
- Arthralgias	83	61.0			
- Adynamia	3	2.2			
- Fatigue	14	10.3			
- Weakness	10	7.4			
- Vomit	8	5.9			
- Neurological symptoms	30	22.1			
- Ophthalmoplegia	3	2.2			
- Cardiac symptoms	10	7.4			
- Tachycardia	3	2.2			
- Hyperpigmentation of the skin	9	6.6			
- Apathy	2	1.5			
- Irritability	2	1.5			
- Lymphadenopathy	24	17.6			
- Pericarditis	1	0.7			
- Endocarditis	2	1.5			
- Pleural effusion	3	2.2			
- Personality changes	4	2.9			
- Uveitis	5	3.7			
- Insomnia	2	1.5			
- Night sweats	12	8.8			
- Hypotension	4	2.9			
- Ocular symptoms	18	13.2			
- Depression and anxiety	5	3.7			
- Edema in lower limbs	18	13.2			
- Swelling of limbs	1	0.7			
- Paresthesia in lower limbs	3	2.2			
- Hypoesthesia and hyporeflexia	2	1.5			

PAS: Periodic acid–Schiff. Source: Authors' own research.

Table 2. Therapeutic features[1-117]

Prevalence	n	%
Therapeutic characteristics		
- Trimethoprim/sulfamethoxazole	83	61
- Ceftriaxone	78	57.4
- Metronidazole	1	0.7
- Vancomycin	3	2.2
- Penicillin	6	4.4
- Meropenem	7	5.1
- Tigecycline	2	1.5
- Doxycycline	43	31.6
- Cefotaxime	1	0.7
- Cefixime	2	1.5
- Imipenem	3	2.2
- Ciprofloxacin	1	0.7
- Hydroxychloroquine	36	26.5
- Corticosteroids or prednisone	21	15.4

Source: Authors' own research.

Table 3. Other treatment options

Prevalence	n	%
Therapeutic characteristics		
- NSAIDs	2	1.5
- Amoxicillin	1	0.7
- Gentamicin + Amoxicillin	1	0.7
- Caspofungin	1	0.7
- Ceftazidime	1	0.7
- Cyclophosphamide	1	0.7
- Co-trimoxazole	4	2.9
- Streptomycin	1	0.7
- Gentamicin + noradrenaline + dopamine	1	0.7
- Leflunomide	1	0.7
- Methotrexate	2	1.5
- Ofloxacin drops + prednisone drops	1	0.7
- Piperazine	1	0.7
- Sulfadiazine	1	0.7
- Non-specified antibiotic	2	1.5
- Stereotactic palliative surgery	1	0.7

Source: Authors' own research.

scientific literature, with eighteen cases identified in the review, representing a prevalence of 13.2%.[29]

According to Gundling F et al., central nervous system (CNS) manifestations occur in up to 15% of cases. These may occur rarely with little or no gastrointestinal damage, as isolated involvement, or associated with gastrointestinal disease. They may also occur as neurological relapse in previously treated disease,[58] which is consistent with reports of cases that found CNS involvement in 30 patients (22.1%). Histological alterations in the brain have been found in autopsies. This review found alterations in one case (0.7%) where WD organisms significantly affected several organ systems, confirmed by histochemical and molecular evaluation.

The frequency of cardiac involvement in WD varies widely among different studies. Our research found involvement in ten cases (7.4%), while other authors, such as Parodi R., reported a range of 17% to 55% of cases. Pericarditis is a common manifestation, while myocarditis is less frequent but can be the initial presentation of cardiac failure or sudden death. Endocarditis can also occur but is difficult to diagnose due to negative blood cultures, lack of fever, and valve destruction. Its diagnosis is confirmed through PCR analysis of surgically obtained valvular material.[9]

In terms of diagnosing Wilson's disease (WD), the three most commonly utilized diagnostic tools are the PCR for TW, biopsy, and anatomopathological examination with PAS granules. Fernández-Mondelo et al. propose two diagnostic criteria for WD: positive PAS staining in a small intestine biopsy and positive results in two tests (PAS, PCR, or immunohistochemistry) of TW from gastrointestinal or extraintestinal samples. Gastroscopy with biopsy remains the most frequently used technique for diagnosing WD. Macroscopically, a woolly, yellow, and pale mucosa alternating with an erythematous, erosive, or slightly friable mucosa in the post-bulbar region of the duodenum or jejunum is a characteristic finding. Biopsies taken at this level reveal positive foamy macrophages for PAS. Identifying the bacillus through PCR in the same duodenal tissue can confirm the diagnosis. In patients with suspected WD but

without gastrointestinal symptoms, samples should be collected from relevant anatomical sites such as synovial fluid and lymph nodes, among others.[91]

Differential Diagnoses

When joint symptoms are predominant, other rheumatic diseases should be ruled out before considering WD. In cases where joint disease does not improve or worsens with biological therapy, WD should be suspected. HIV infection can also present with similar symptoms, including enteropathy and wasting syndrome. If endocarditis is present, the most common pathogens should be ruled out first. The presence of systemic granulomas can be mistaken for sarcoidosis. In cases of abdominal involvement, other causes of malabsorptive syndrome should be investigated, such as celiac disease and other infections. A diagnosis of abdominal angina[9] should also be considered for patients with vascular disease.

The recommended treatment for WD includes antibiotics that can penetrate the blood-brain barrier, such as trimethoprim/sulfamethoxazole or ceftriaxone, to prevent neurological relapses.[8] In our research, we observed a preference for trimethoprim/sulfamethoxazole (83 cases; 61.0%) followed by ceftriaxone (78 cases; 57.4%). Currently, the recommended treatment involves ceftriaxone (2 g/day) or meropenem (3 g/day) administered parenterally, followed by trimethoprim/sulfamethoxazole (800-160 mg/ times daily) administered orally for at least one to two years. In cases of isolated neurological forms, ceftriaxone (2-4 g/day) is administered intravenously for 15-30 days, followed by trimethoprim/sulfamethoxazole (1600-320 mg/day) or doxycycline (200 mg/day) or cefixime (400 mg/day) until cerebrospinal fluid (CSF) PCR results are negative.[8]

The treatment goals for Whipple's disease are to minimize morbidity, prevent complications, and eliminate the infection. Without appropriate treatment, the mortality rate is almost 100%. However, the prognosis is favorable with complete antibiotic therapy.

Conflicts of Interests

The authors declare that they have no conflicts of interest in conducting this study. Additionally, all authors were involved in the design, data collection, analysis, interpretation, and drafting of the manuscript.

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Review article

Fatty Liver (part 2): Clinical Approach and Treatment

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Abstract

Patients with fatty liver are almost always asymptomatic; aminotransferases are usually elevated two to five times the expected value and are an important cause of initial consultation. All images can show fatty liver, and liver biopsy remains the gold standard for diagnosis. In any patient, non-invasive tests are an excellent alternative to biopsy to determine the degree of liver fibrosis and establish the stage of fibrogenesis. Weight loss and exercise are the fundamental pillars of the indicated treatment for all patients with overweight or obesity; a weight loss between 5% and 10% and a diet with caloric restriction of 500-1000 kcal/day, low in saturated fat and rich in Mediterranean diet products such as fruit, fish, vegetables, nuts, olive oil, among others, are recommended. There are other treatments, such as pharmacological measures and endoscopic and surgical procedures.

Keywords

Fatty liver, non-invasive diagnosis, clinical approach, treatment.

CLINICAL PROFILE

Most patients with nonalcoholic fatty liver disease (NAFLD) are typically asymptomatic, a common characteristic of liver diseases. Patients may sometimes report symptoms such as asthenia, adynamia, or pain in the right hypochondrium. As the disease progresses to advanced stages, signs and symptoms of portal hypertension or cirrhosis may manifest.[1] NAFLD is commonly seen in overweight or obese individuals, although it may also affect those with a lower body mass index.[1,2] Hepatomegaly due to fatty liver infiltration has been reported in 5% of patients with fatty liver and 18% of those with nonalcoholic steatohepatitis (NASH).[3-5] This condition may lead to abdominal pain, although other potential causes should always be considered.[1]

LABORATORY

Elevated aminotransferases, typically two to five times the normal value, often prompt patients to seek initial medical consultation. However, this elevation cannot predict the extent of liver inflammation or fibrosis. In addition, normal levels of alanine aminotransferase (ALT) do not rule out a diagnosis of fatty liver or significant histological damage.[6-8]

Other laboratory findings in patients with nonalcoholic fatty liver disease (NAFLD) include an elevation of alkaline phosphatase (AP) by two or three times the normal value, an increase in serum ferritin concentration, or elevated transferrin saturation.[9] A ferritin level greater than 1.5 times the normal value in patients with fatty liver is associated with advanced liver fibrosis.[10] Moreover, albumin, bilirubin, and coagulation times are only altered in advanced stages of cirrhosis.[9]

RADIOLOGY

Any imaging modality can show fatty liver. The most commonly used test is abdominal or hepatic ultrasound, and steatosis manifests as a diffuse increase in echogenicity of the liver parenchyma or a bright liver.[11] A meta-analysis using liver biopsy as the gold standard reported a sensitivity (S) and specificity (E) of 85% and 94%, respectively.[12] However, in obese patients and those with less than 30% fat content, these values are lower, with reported sensitivities ranging from 49% to 66% and specificities from 77% to 93.1%.[11,13]

Computed tomography (CT) can diagnose hepatic steatosis with a sensitivity of 82% and a specificity of 100% when the fat content is equal to or greater than 30%.[14] However, with lower fat contents, these values are reduced to 50% and 83%, respectively.[11] CT is a rapid method that does not depend on the operator, but it is important to consider the radiation exposure to which patients are subjected.

When nuclear magnetic resonance (NMR) is used in studies where liver biopsy is considered the gold standard test for detecting steatosis, sensitivity (S) has been found to range between 88% and 95% and specificity (E) between 63% and 98%, respectively.[15,16] However, when the detection of histological steatosis is reduced to ≥ 5%, reported S values range between 76.7% and 90.0%, and E values between 87.1% and 91%.

The proton density fat fraction (PDFF) estimated by magnetic resonance spectroscopy (MRS) is an accurate and reproducible non-invasive biomarker for hepatic steatosis.[17,18] However, spectroscopic sequences are not available on all scanners, and the technique is not routinely used due to its cost.

LIVER BIOPSY

Liver biopsy remains the preferred method for diagnosing fatty liver disease and accurately distinguishing between simple steatosis, steatohepatitis, and cirrhosis, which has prognostic implications and guides patient management, often motivating them to make beneficial lifestyle changes.[19-25] It is recommended in cases of:

- Patients at high risk of fibrosis or cirrhosis, such as those with obesity, diabetes, dyslipidemia, or serum ferritin levels greater than 1.5 times the upper limit of normal, when non-invasive tests cannot rule out advanced fibrosis.
- Patients with suspected but unconfirmed fatty liver after initial laboratory and imaging studies.
- Suspected advanced liver disease associated with fatty liver, peripheral signs of chronicity or cirrhosis, splenomegaly, and cytopenia.
- Need for determining the severity of the disease or excluding other phenomena.

Findings

To diagnose fatty liver through histology, a liver tissue sample must show the presence of 5% or more hepatocytes with steatosis. The severity of the condition can be classified as mild (5%-33%), moderate (34%-66%), or severe (>66%), based on the percentage of hepatocytes with steatosis present in the sample.[21,22]

Distinguishing simple steatosis from NASH requires a careful examination of the histological findings. Simple steatosis may exhibit lobular or portal inflammation with hepatocyte ballooning or hepatocyte ballooning without inflammation.[20,23] In contrast, NASH is characterized by the presence of hepatic steatosis combined with hepatocyte ballooning and hepatic lobular inflammation, typically observed in the acinar zone 3.[20,23] While fibrosis is not a necessary diagnostic feature, it may be present. As fibrosis progresses to cirrhosis, steatosis and inflammation may disappear, resulting in the diagnosis of "cryptogenic" cirrhosis.[23]

Several studies have demonstrated that histological parameters such as hepatocellular ballooning and inflammation, in addition to the age of patients, are the best predictors of fibrosis progression in fatty liver disease.[26] Other studies have shown that the presence of fibrosis in the initial biopsy or its progression in subsequent biopsies is strongly associated with adverse outcomes and increased mortality in fatty liver disease.[27,28] Therefore, assessing the presence of fibrosis in patients with fatty liver disease is crucial.

NON-INVASIVE DETERMINATION OF LIVER FIBROSIS

Non-invasive tests provide an excellent alternative to liver biopsy for determining the degree of liver fibrosis and establishing the stage of fibrogenesis (F0-F4) in any patient. A score ≥ F2 and advanced fibrosis ≥ F3[19,20,24,25,29] are considered significant fibrosis. Two categories of non-invasive liver fibrosis tests are available: serological and image-based. Combining them is the current trend, using whiche-

ver is locally available, resulting in fewer patients with an indeterminate fibrosis score and higher specificity.[25,29,30]

Serological Tests

Several serum marker products have been validated for the diagnosis of liver fibrosis, including:

- APRI
- FIB-4
- User ratings for NAFLD fibrosis
- BARD Score
- FibroTest/FibroSURE
- Hepascore
- FIBROSpect
- ELF score (panel of the European Hepatic Fibrosis Study Group)

While non-invasive tests can differentiate between patients with significant fibrosis (F2 to F4) and those without (F0 to F1), they are not as reliable in distinguishing between multiple stages of fibrosis, leading to indeterminate results in up to 65% of cases.[25,29,30] Some markers are still helpful in the field and include the following.

APRI or relationship between AST and platelets

The usefulness of APRI has been studied in patients with various diseases, including hepatitis C virus (HCV), human immunodeficiency virus (HIV), HIV-HCV coinfection, and alcoholic liver disease.[29] A meta-analysis of 40 studies found that an APRI cutoff point of 0.7 had a sensitivity of 77% and a specificity of 72% in predicting significant fibrosis (F2 to F4), and an APRI cutoff point of 1.0 had a sensitivity of 76% and a specificity of 72% in predicting cirrhosis (F4).[31] In patients with NAFLD, the ability of APRI to predict adverse liver-related outcomes was examined in a retrospective series of 320 patients,[32] and the area under the ROC curve (AUC) to predict these outcomes was 0.80. The AUC to predict liver death or transplantation was 0.63.

The FIB-4

The FIB-4 test combines platelet count, ALT, AST, and age and has typically been studied in the context of hepatitis C. It is also useful in predicting advanced fibrosis in fatty liver disease.[33] A study found that the area under the ROC curve (AUC) to predict adverse outcomes using FIB-4 was 0.81, and to predict death or liver transplantation, it was 0.67.[32] The test is interpreted using two diagnostic thresholds: a lower threshold of <1.30 to exclude advanced fibrosis and an upper threshold of >2.67 to confirm it.[29]

User Ratings for NAFLD Fibrosis

The NAFLD fibrosis score is calculated according to patient-age-based routine laboratory tests, including BMI, blood glucose levels, aminotransferase levels, platelet count, and albumin.[34] In a validation study, a high cutoff value (>0.676) was associated with an 82% positive predictive value for advanced fibrosis (F3 to F4) with a sensitivity of 43% and specificity of 96%, while a low cutoff value (< -1.455) was associated with an 88% negative predictive value with a sensitivity of 77% and specificity of 71%.[33]

BARD Score

The BARD score takes into account BMI, AST/ALT ratio, and the presence of diabetes mellitus.[35] A study of 126 patients with fatty liver found positive and negative predictive values for advanced fibrosis of 69% and 96%, respectively, with an AUC of 0.87.[36] Another study reported AUC values of 0.73 and 0.66 for predicting adverse outcomes related to the liver and liver death or transplantation, respectively.[32]

Image-Based Testing

Liver stiffness is determined using mechanical waves in a process called elastography, which measures the propagation speed through tissue. The most common type of elastography is ultrasound-based and includes FibroScan® (or transient elastography), real-time 2D shear wave elastography (2D-SWE) called SuperSonic®, acoustic radiation force impulse (ARFI) elastography, and magnetic resonance elastography (MRE). 2D-SWE and MRE combine elastography with conventional liver imaging in a single session.[37] While ultrasound-based tests are excellent at predicting healthy liver, advanced fibrosis, or cirrhosis, their accuracy in the intermediate stages should be interpreted with caution.[25,29,38]

Transient Elastography or FibroScan®

FibroScan® is the most extensively studied device for measuring liver stiffness. It utilizes two probes: the classic M and the XL, which were developed to optimize the measurement and reduce the failure rate in obese patients.[29,38,39] The two diagnostic thresholds with FibroScan® to exclude or suspect advanced hepatic fibrosis (≥F3) are < 7.9 kPa and > 9.6 kPa, respectively, with a negative predictive value of 96% and a sensitivity of 89%.[40] The indeterminate gray zone between the two thresholds accounts for 10%-15% of patients. Two-thirds of patients with a result > 9.6 kPa have advanced liver fibrosis, corresponding to a positive predictive value of 67%.[40] Although it can achieve a diagnostic

accuracy (AUC) greater than 0.92 for advanced fibrosis, it is less precise in patients with fatty liver in intermediate stages.[41]

Acoustic Radiation Force Impulse Imaging

ARFI uses a high-intensity and short-duration acoustic pulse to measure tissue displacement in the same direction.[42] The diagnostic ability of ARFI and TE for detecting hepatic fibrosis may be similar. In a study, the AUC for ARFI versus TE to diagnose fibrosis stage ≥ F2 was 0.77 and 0.74, respectively. For diagnosing fibrosis ≥ F4, the AUC for ARFI versus TE was 0.84 and 0.80, respectively. However, in patients without obesity, ARFI performed slightly better in diagnosing stage ≥ F4 fibrosis with an AUC of 0.92, a difference not observed with TE.[43]

2D Shear Wave Elastography, 2D-SWE, or SuperSonic®

SuperSonic® is an elastography technique that offers simultaneous real-time grayscale images of the tissue being studied. This technique is integrated into conventional ultrasound scanners, allowing both procedures to be performed in the same session.[37,38,44] A prospective controlled study on patients with fatty liver showed that SuperSonic® had an AUC of 0.84 for diagnosing stage ≥ F2 fibrosis, 0.88 for stage ≥ F3 fibrosis, and 0.93 for cirrhosis.[45] Other studies have reported similar results in diagnosing significant advanced fibrosis and cirrhosis.[46,47]

Magnetic Resonance Elastography

MRE, unlike ultrasound-based elastography, enables the examination of the entire liver and is not limited to a specific target for sampling. It is conducted using a standard MRI scanner equipped with extra hardware and software, and elastography and morphological imaging can be performed simultaneously. A meta-analysis revealed that the sensitivity and specificity for detecting fibrosis stage ≥ F2 were 79% and 81%, respectively; for fibrosis ≥ F3, they were 85% and 85%, respectively; and for cirrhosis, they were 91% and 81%, respectively.[48] MRE has also been compared to TE, with one study showing that MRE produced similar results to ultrasound-based TE,[49] while other studies found a higher technical success rate and improved diagnostic accuracy with MRE.[30,50]

As the prevalence of fatty liver continues to increase worldwide and locally, often linked to metabolic syndrome, it is important to assess the risk of progressive fibrosis leading to cirrhosis. All physicians who treat patients with fatty liver, particularly in primary care, internal medicine, and gastroenterology, should conduct risk classification studies.[51,52] To this end, we suggest following the algorithm outlined in **Figure 1**.

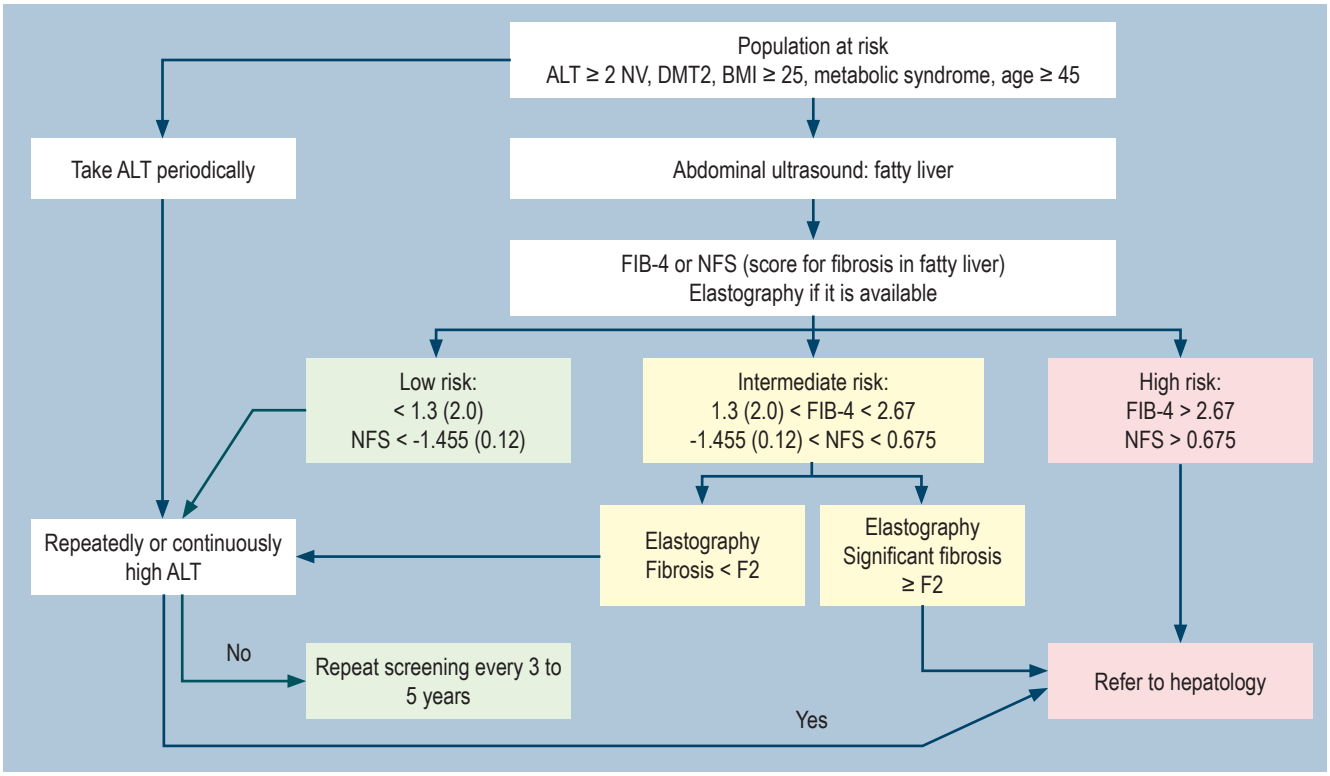

Figure 1. Liver risk algorithm in fatty liver.[51] DMT2, Diabetes Mellitus Type 2; NV: normal value. Modified from: Dietrich CG et al. World J Gastroenterol. 2021;27(35):5803-5821

TREATMENT

Most current short-term clinical trials are designed to achieve histological resolution, improve nonalcoholic steatohepatitis (NASH) without fibrosis progression, improve fibrosis by at least one stage, or improve biochemical parameters.[25,53,54] However, ideally, experts should focus on clinical outcomes such as a reduction in end-stage liver disease or liver transplantation due to fatty liver. Regarding type 2 diabetes, experts should also consider extrahepatic targets, such as cardiovascular or microvascular outcomes.[54]

Treatment for fatty liver disease is typically divided into four stages that progress in severity, as follows:

- Weight loss through a combination of diet and exercise
- Pharmacological measures
- Endoscopic procedures
- Surgical procedures

Weight Loss Following Diet and Exercise

Weight loss through diet and exercise is the fundamental and most critical treatment for all overweight (BMI > 25 kg/m^2) or obese (BMI > 30 kg/m^2) patients. For patients with simple steatosis, a weight loss of 5% to 7% of body weight is recommended, achieved at a rate of 0.5 to 1.0 kg per week. Patients with suspected or biopsy-proven NASH should aim for a 7% to 10% weight loss. If after reaching their weight loss target, the serum ALT level remains unnormalized (ALT < 20 for women and < 30 for men), patients should continue to lose weight until normalization is achieved.[19,20,24,25,55,56]

Diet

Based on current evidence, the best approach for weight loss is a combination of caloric restriction by at least 500-1000 kcal per day or a suitable diet low in saturated fat. However, adherence to these habits is crucial for successful weight loss.[30,57] The most recommended diet for patients with fatty liver is the Mediterranean diet (MD), which is rich in fruits, fish, vegetables, nuts, and olive oil, among others.[20,25,30,58,59] It has been shown to improve intrahepatic lipid content and insulin sensitivity.[60] The constituent elements of the Mediterranean diet are shown in **Figure 2**.

Exercise

Experts recommend performing moderate-intensity aerobic physical activity for 150-200 minutes per week in three to five sessions,[20,25,57] as it helps to maintain dietary weight

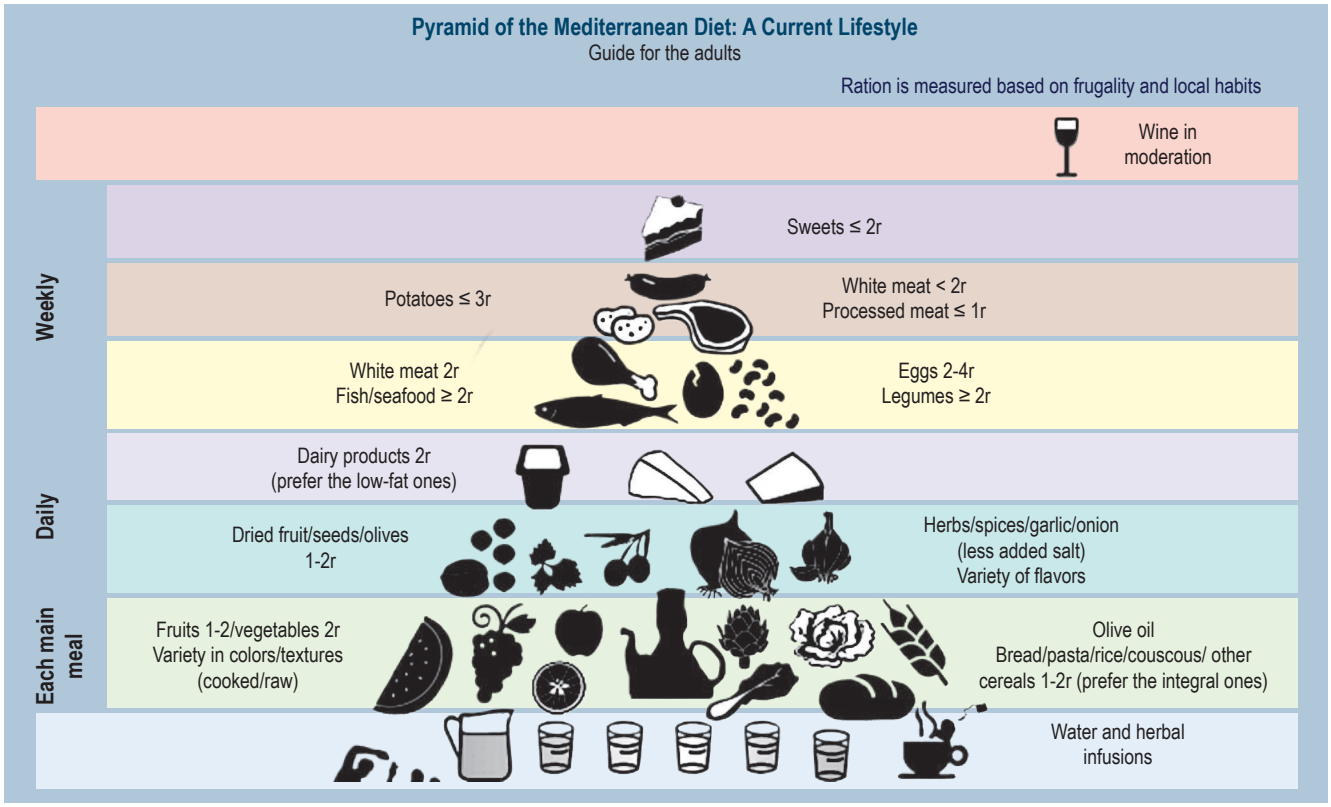

Figure 2. Mediterranean diet. Source: Mediterranean Diet Foundation

loss and may have independent benefits on liver fat and histology.[61] Studies suggest that exercise intensity and adherence to a training program are more important than the type of exercise performed, resulting in greater weight loss than education alone.[61,62] Moreover, physical activity has been linked to survival benefits for patients with fatty liver, especially for aerobic exercise, with longer physical activity associated with lower mortality risks due to cardiovascular diseases.[63,64]

Pharmacological Measures

Pharmacological treatments are recommended by the American Association for the Study of Liver Diseases (AASLD) mainly to improve liver disease and should be limited to individuals with biopsy-proven NASH and fibrosis.[19] The European Association for the Study of the Liver (EASL), the European Association for the Study of Diabetes (EASD), and the European Association for the Study of Obesity (EASO) guidelines recommend pharmacological treatment for patients with fatty liver with proven NASH and fibrosis ≥ F2, or patients at high risk of progression such as individuals with type 2 diabetes, metabolic syndrome, persistently high ALT, or high necroinflammation.[20]

NASH patients without diabetes

According to the AASLD, vitamin E is not recommended for treating fatty liver because the studies showing its usefulness did not include patients with diabetes mellitus or decompensated cirrhosis.[19] Despite a meta-analysis that found no histological improvement with vitamin E,[65] some studies suggest that doses of 800 IU/day may be beneficial. The largest randomized trial included in the meta-analysis (pioglitazone vs. vitamin E vs. placebo for the treatment of non-diabetic patients with NASH) found that patients who took vitamin E were more likely to improve their overall histological score (43% vs. 19%).[66] Another report found that patients who received vitamin E had a more significant decrease in ALT values. (48% vs. 16%).[67] The potential advantage of vitamin E may be related to its antioxidant properties. Therefore, vitamin E could be a reasonable treatment for patients with fatty liver and stage fibrosis ≥ 2 who do not have diabetes mellitus. However, it should be avoided in men with a high family history of prostate cancer. No dose ≥ 400 international units per day should be taken, as this has been inconsistently associated with increased all-cause mortality.

Patients with NASH and Diabetes

- Metformin is considered the first-line drug. However, it does not improve steatosis or liver histology in patients with or without type 2 diabetes. Despite this, it has been found to promote moderate weight loss.[19,20,24,25,30,68-70]
- Thiazolidinediones, specifically pioglitazone, have been shown to improve liver biochemical and histological parameters in patients with nonalcoholic steatohepatitis (NASH).[30] A meta-analysis demonstrated improvements in ballooning, lobular inflammation, and steatosis with thiazolidinediones, including fibrosis improvement with pioglitazone.[71] Long-term treatment may be necessary to achieve clinical benefits since the discontinuation of pioglitazone can reverse improvements.[72] In both diabetic and non-diabetic patients (type 2), pioglitazone has demonstrated histological reversal of NASH without worsening fibrosis.[73] Pioglitazone acts on the peroxisome-proliferator-activated receptor gamma (PPARγ) in adipocytes, leading to adipose tissue remodeling and increased adiponectin secretion, resulting in reduced lipolysis, insulin resistance, and hepatic lipid storage.[70,74] However, its use is limited in selected cases due to the potential side effects and risks, including weight gain, heart failure, and fractures.[20]
- Glucagon-like peptide-1 receptor agonists. Food-induced secretion of intestinal hormones, glucagon-like peptide-1 (GLP-1), and gastric inhibitory peptide (GIP) are collectively referred to as incretins. These hormones can enhance insulin secretion in pancreatic β cells in response to glucose stimulation. GLP-1 has also been shown to suppress glucagon secretion, delay gastric emptying and intestinal glucose uptake, and is involved in the central regulation of food intake and satiety.[75] For its part, GIP stimulates glucagon secretion. Glucagon-like peptide 1 receptor agonists (GLP-1 RA) are fundamental in treating type 2 diabetes and obesity because they induce weight loss, improve glycemic control, and produce beneficial changes in blood metabolism.[30,70]
  - Liraglutide effectively resolves NASH, reduces liver fat content, and decreases the likelihood of fibrosis progression.[70,76,77] The approved dosage for anti-diabetic use is up to 1.8 mg, while the recommended dose for weight loss is 3 mg.[78]
  - Semaglutide, at a dose of 0.4 mg once daily, has been shown to bring about histological resolution of NASH in patients with fatty liver disease and fibrosis.[70,76,79,80] Compared to liraglutide, semaglutide is more effective in reducing body weight in individuals with type 2 diabetes and is approved for weight loss in patients without diabetes as well. At present, it is the most potent among the available drugs for weight loss, leading to the recent approval

by the Food and Drug Administration (FDA) of a weekly subcutaneous dose of semaglutide at 2.4 mg for the management of chronic obesity in patients without diabetes.[76,80]

- Sodium-glucose cotransporter-2 inhibitors (SGLT2 inhibitors) effectively reduce blood glucose levels and induce moderate weight loss by causing renal glucose loss and resulting in a caloric deficit.[69,70,76,81] Recently, empagliflozin, an SGLT2 inhibitor, has been shown to significantly reduce liver fat content in patients with type 2 diabetes after 24 weeks of treatment.[81] However, there are few studies on SGLT2 inhibitors that correlate with histological endpoints, and they have few patients and short duration.[69,76] One study demonstrated improvement in the degree of steatosis, ballooning, and fibrosis with 25 mg per day of empagliflozin compared to placebo.[82]
- Dipeptidyl peptidase-4 inhibitors prevent the endogenous degradation of incretin, thereby prolonging the endogenous action of GLP-1. However, in clinical trials, dipeptidyl peptidase-4 inhibitors (DPP4i) have shown negative results for treating NAFLD,[69,70,76] except for vildagliptin, which has been shown to reduce liver fat.

Combination therapy involving different classes of medication has shown promise in the treatment of fatty liver. GLP-1 RA and SGLT2i have proven effective in reducing cardiovascular risk and are recommended as first-line therapies for patients with type 2 diabetes and established or high-risk cardiovascular disease (CVD). Possible combina-

Table 1. Diabetes treatment[70]

Medication	Hepatic fat	NASH/NAS Activity	Changes in weight	Cardiovascular effects	Side effects
Metformin	No changes	No changes	No changes	Potential benefit in ACD	Common gastrointestinal effects (diarrhea, nausea) Lactic acidosis Vitamin B_{12} deficiency
Pioglitazone	Decrease	Improvement	Increase	Potential benefit in ACD Increased risk of HF	Weight gain Fluid retention Increases the risk of fractures Increases bladder cancer
SGLT2i - Empagliflozin - Canagliflozin - Dapagliflozin	Decrease	Unknown	Decrease	ACD benefit of empagliflozin and canagliflozin HF benefit of empagliflozin, canagliflozin, and dapagliflozin	Risk of DKA from surgery Risk of bone fractures with canagliflozin Genitourinary infections Volume depletion Increases LDL
GLP-1 RA - Lixisenatide - Liraglutide - Semaglutide - Dulaglutide - Albiglutide - Exenatide	Decrease	Improvement	Decrease	ACD benefit of liraglutide, semaglutide, and dulaglutide	FDA indicates a risk of thyroid tumors in rodents Common gastrointestinal effects (diarrhea, nausea, vomiting) Pancreatitis
DPP4i - Saxagliptin - Alogliptin - Sitagliptin - Vildagliptin - Linagliptin	No changes	Unknown	No changes	Potential HF risk of saxagliptin	Pancreatitis Joint pain

GLP-1 RA: glucagon-like peptide-1 receptor agonists; DKA: diabetic ketoacidosis; ACD: atherosclerotic cardiovascular disease; HF: heart failure; DPP4i: dipeptidyl peptidase-4 inhibitors; SGLT2i: sodium-glucose cotransporter-2 inhibitors; LDL: low-density lipoprotein; NAS: NAFLD activity score; NASH: nonalcoholic steatohepatitis. Modified from: American Diabetes Association. Diabetes Care. 2021;44(Suppl 1):S111-S124.

tions include semaglutide/SGLT2i or low-dose pioglitazone combined with GLP-1 RA or SGLT2i.[69,70,76]

Other Treatments in General

- The primary benefit of statins is the reduction of cardiovascular risk. However, pilot studies have also suggested that atorvastatin may have a beneficial effect on aminotransferase levels in patients with NAFLD,[30,69,76] without any associated hepatotoxicity.[83]
- Omega-3 fatty acids have been shown to improve hepatic steatosis and AST levels in a meta-analysis on fatty liver.[84] However, when the analysis was limited to data from randomized trials, only improvement in hepatic steatosis was observed with the use of omega-3 fatty acids.

Table 1 provides a summary of the fundamental aspects of treatments for diabetes.

Future of Treatment for Patients with Fatty Liver and Type 2 Diabetes

Currently, double and triple agonists of GLP-1, GIP, and glucagon receptor in combination are being tested in phase 2 and 3 clinical trials for treating obesity and type 2 diabetes.[75] Tirzepatide, a dual GLP-1/GIP receptor agonist, demonstrated an average reduction in body weight of 9.5 kg (11.0%) with a weekly dose of 15 mg.[85,86] Another drug, Thesamorelin, a growth hormone-releasing hormone analog indicated for treating lipodystrophy in HIV, showed selective reductions in visceral and hepatic fat and weight loss, which has led to an ongoing study of fatty liver.[69,86] Resmetirom, a selective thyroid hormone receptor β (THR-β) agonist, was designed to improve NASH by increasing liver fat metabolism and reducing lipotoxicity.[69,86] In addition, Lanifibranor, a pan-PPAR agonist, achieved an improved combined resolution of

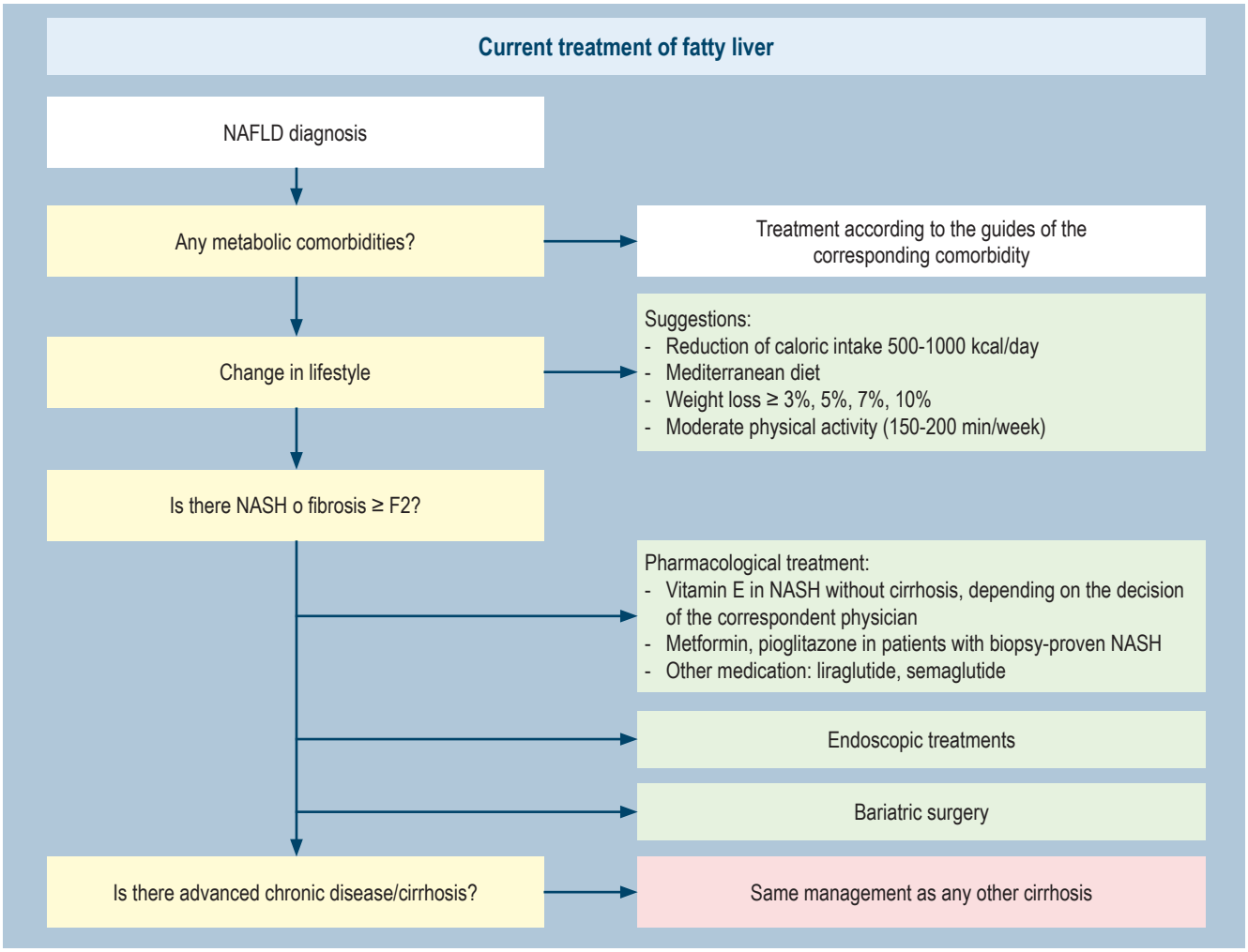

Figure 3. Treatment of fatty liver[57]. Modified from: Paternostro R et al. J Intern Med. 2022;292(2):190-204.

NASH and fibrosis in a dose-dependent manner in adults with type 2 diabetes and NASH.[69,86]

Endoscopic Procedures

Over the past ten years, the US FDA has approved six types of endoscopic bariatric and metabolic therapies (EBMT) as an alternative to bariatric surgery. Some of these therapies are reversible and have a lower cost and risk of complications than surgery.[87,88] Essentially, EBMT involves placing intragastric balloons or endoscopic intragastric sutures. The best-known options are the Orbera intragastric balloon system, the Obalon balloon system, and the OverStitch endoscopic suturing system (Apollo Endosurgery) for endoscopic sleeve gastroplasty (ESG).[87] These procedures are reserved for patients who do not achieve weight loss through diet, exercise, and medications and are at high risk of fibrosis progression. Endoscopic bariatric procedures have been shown to result in higher and sustained weight loss percentages, with regression of hepatic steatosis, steatohepatitis, and fibrosis occurring in 30% of patients.[89,90]

Surgical Procedures

Bariatric surgery is recommended for patients with NASH or advanced fibrosis without decompensated cirrhosis who have not achieved their weight loss goals after appropriate follow-up.[91] A systematic review reported improvement in steatosis in eighteen studies, decreased inflammation in eleven studies, and an improved fibrosis score in six studies.[92] However, four studies showed a deterioration in fibrosis, emphasizing the need for proper postoperative follow-up for all patients.

Bariatric surgery offers a viable option for achieving sustained weight loss and improving the histological components of NAFLD, as well as improving type 2 diabetes.[93] In addition, it has been shown to improve cardiovascular outcomes in both diabetic and non-diabetic obese patients.[94] However, bariatric surgery can also result in peri- or postoperative complications that should be taken into account.[92,95]

Finally, the current pillars of treatment are summarized in **Figure 3**.

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Case report

Cholestatic Jaundice Secondary to Portal Hypertensive Biliopathy Regarding a Case of Cavernous Transformation of the Portal Vein

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Abstract

Portal hypertensive biliopathy comprises the anatomical and functional abnormalities of the intra- and extrahepatic biliary tract, cystic duct, and gallbladder in patients with portal hypertension. The compromise of the bile duct usually occurs in portal obstruction due to the cavernous transformation of the portal vein (CTPV).

We present a case of a young patient with a recent history of portal hypertension and CTPV who presented with an episode of cholestatic hepatitis. Studies documented an image of nodular appearance with extrinsic compression of the distal bile duct compatible with a tumor-like cavernoma. Effective endoscopic treatment was performed using endoscopic retrograde cholangiopancreatography (ERCP), sphincterotomy, and biliary stenting.

Keywords

Portal hypertension, extrahepatic cholestasis, bile duct diseases, portal cavernoma.

INTRODUCTION

Portal hypertensive biliopathy is a condition that encompasses structural and functional anomalies of the biliary tract (intra- and extrahepatic), gallbladder, and cystic duct in patients with portal hypertension.[1] Bile duct changes are commonly observed in extrahepatic portal vein obstruction (EHPVO) due to normal bile duct compression by cavernous portal vein transformation.[2] Several terms have been used to describe this condition, such as portal biliopathy, portal cavernoma-associated cholangiopathy, or cholangiopathy associated with portal hypertension. However, the most widely accepted term is currently portal hypertensive biliopathy.[1] The bile duct involvement results from external compression from the enlarged venous plexuses that form in an attempt to decompress the portal vein obstruction caused by thrombosis.[3] The first cases linking EHPVO and cholestasis were reported in the 1950s,[4] and even today, the prevalence of this condition is not well established as its symptoms are rare (5%-15%).[5]

CLINICAL CASE

A 48-year-old man with a history of portal thrombosis and cavernous degeneration of the portal and portal hypertension presented to the emergency department after experiencing one week of jaundice, choluria, and generalized pruritus linked to asthenia and adynamia. The patient's

medical history included portal thrombosis with cavernous degeneration and secondary portal hypertension for one year without primary or secondary thrombophilia, and a previous variceal gastrointestinal hemorrhage treated with ligation. On admission, the patient was in regular general condition with normal vital signs and no alteration of consciousness. Physical examination revealed generalized jaundice skin and a protruding abdomen due to an abundant adipose panicle without abdominal pain or visceromegaly. Laboratory tests performed on admission (**Table 1**) showed hyperbilirubinemia, primarily from direct bilirubin, as well as elevated transaminases and cholestasis tests.

Table 1. Laboratory tests during hospitalization in the HPTU

Study	Income	Control
Hemoglobin	15.4 g/dL	13.2 g/dL
Hematocrit	45%	41%
Leukocytes	7400/mm^3	5410/mm^3
Platelets	147 000/mm^3	144 000/mm^3
Creatinine	1.09 g/dL	1.02 g/dL
Urea nitrogen	9 mg/dL	
AST	177 U/L	29 U/L
ALT	325 U/L	34 U/L
Total bilirubin	6.54 mg/dL	1.07 mg/dL
Direct bilirubin	3.72 mg/dL	0.57 mg/dL
Alkaline phosphatase	406 U/L	128 U/L
GGT	403 U/L	67 U/L
Chlorine	103 mmol/L	
Potassium	4.19 mmol/L	
Sodium	135 mmol/L	
Calcium	9.4 mg/dL	
Albumin	4.3 g/dL	
INR	1.1	
CRP	2.64 mg/dL	
Hepatitis C antibodies	Non-reactive	
Surface antigen for hepatitis B	Non-reactive	
IgM antibodies for hepatitis A	Non-reactive	
Tumor markers	Negative	

ALT: alanine aminotransferase; AST: aspartate aminotransferase; GGT: gamma-glutamyl transferase; IgM: immunoglobulin M; INR: international normalized index; CRP: C-reactive protein. Source: Authors' own research.

Due to cholestatic hepatitis syndrome and a history of chronic portal thrombosis, the patient underwent a contrast-enhanced computerized axial tomography (CT) scan of the abdomen. The results showed signs of chronic liver disease with chronic portal thrombosis, cavernous transformation, multiple venous collaterals, and splenomegaly (**Figure 1**). In addition, the scan revealed central bile duct dilation with a normal diameter common bile duct, which was further characterized by a magnetic resonance cholangiopancreatography (MRCP). The MRCP revealed an acute thrombosis of one of the collaterals in the hepatic hilum, causing central dilation and an excess of soft tissue with a nodular appearance restricting diffusion. These findings produced a mass effect in the distal common bile duct and were interpreted as a tumor-like cavernoma (**Figure 2**).

Subsequently, an endoscopic retrograde cholangiopancreatography (ERCP) was performed to bypass the bile duct and initiate enoxaparin anticoagulation at a dose of 1 mg/kg every twelve hours to resolve the acute thrombosis. During ERCP, stenosis was observed in the distal common bile duct of extrinsic appearance, while the proximal and middle bile ducts measured 6 mm in normal diameter. To treat this condition, a limited sphincterotomy and placement of a plastic stent measuring 10 French (Fr) x 7 centimeters (cm) were performed, resulting in abundant dark bile drainage (**Figure 3**). The patient had a good clinical evolution and did not present any complications after the procedure. Therefore, he was discharged with analgesic management, anticoagulation with low molecular weight heparins (LMWH), and ursodeoxycholic acid (UDCA).

One month after being discharged from the hospital, the patient attended an outpatient hepatology follow-up appointment. He reported no signs of jaundice, choluria, or acholia but mentioned occasional mild abdominal pain. The physical examination was unremarkable, except for palpable splenomegaly, 4 cm from the left rib cage. His paraclinical tests were within normal limits.

DISCUSSION

In the 1990s, it was discovered that between 80% and 100% of patients with extrahepatic portal vein obstruction (EHPVO) have concomitant portal hypertensive biliopathy (PHB), although most of them are asymptomatic.[6,7] This condition is more common in patients with EHPVO secondary to liver cirrhosis or idiopathic portal hypertension.[1] In terms of local epidemiology, Suárez et al. reported the first experience of a Colombian center in managing and treating PHB cases.[3]

PHB is closely related to the etiology of portal hypertension, which includes conditions such as liver cirrhosis,

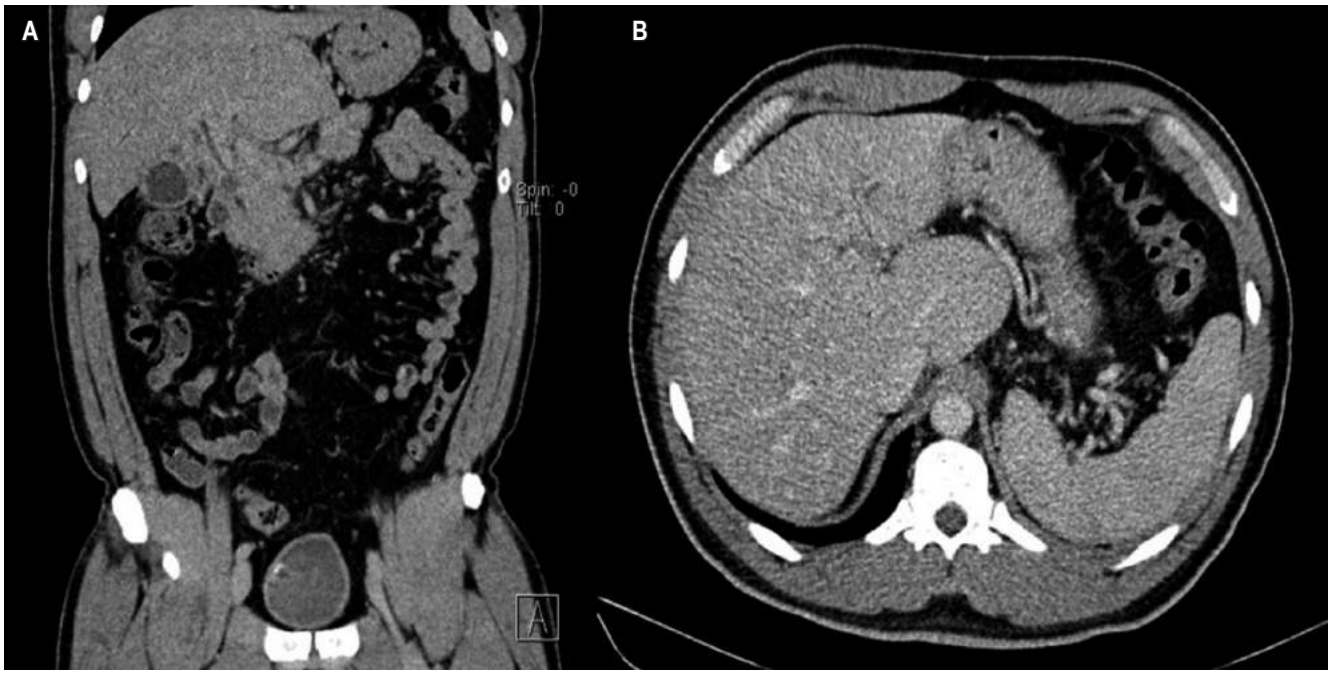

Figure 1. A. CT scan of the abdomen contrasted with findings of chronic liver disease and multiple venous collaterals. **B.** Findings of liver disease (nodularity of liver lobes) and splenomegaly. Source: Authors' archive.

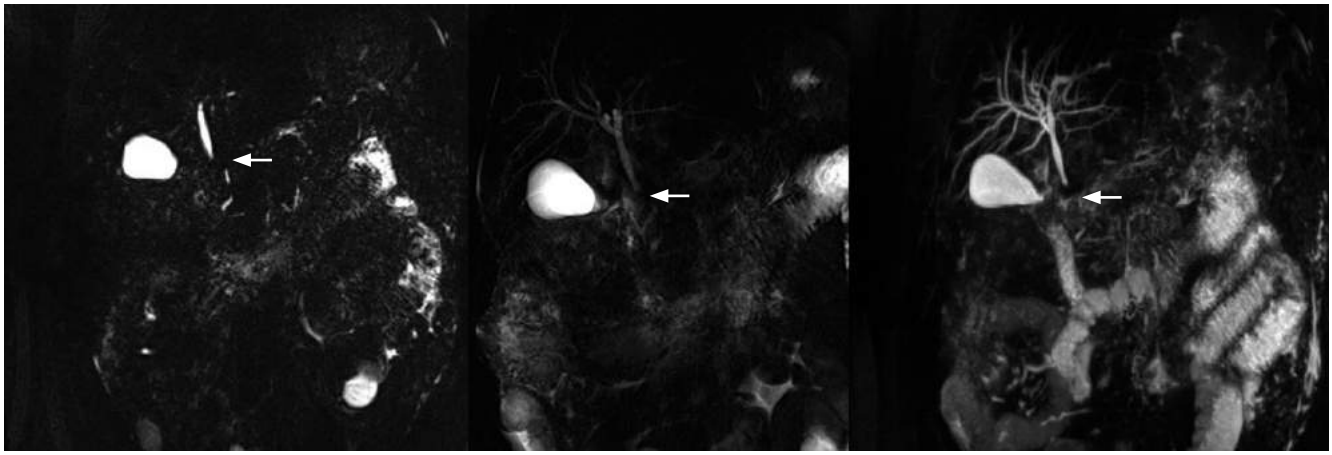

Figure 2. Stenosis in the distal common bile duct, with extrinsic compression image. Source: Source: Authors' archive.

neoplasms, coagulopathies, myeloproliferative disorders, or congenital liver fibrosis.[8] Although the pathogenesis of PHB is not entirely clear, it is well established that the venous plexuses of the bile ducts and gallbladder have a crucial role in the development of biliary obstruction.[7]

Portal hypertension slows portal blood flow, increasing the risk of portal vein thrombosis, which in turn causes the derivation of blood flow through portosystemic collaterals.[8] These collateral veins develop a dense vascular pattern and fibrous stroma in the peripancreatic region along the occluded portal vein, forming a portal cavernoma that provides an alternative route for blood flow around the thrombosed segment of the portal vein.[9]

The initial description of biliary changes observed in patients with portal cavernoma was performed in ERCP, mostly in individuals with biliary manifestations.[10] These descriptions were replicated and expanded with the increased use of MRCP.[11] This was a fundamental change in the diagnosis of the condition since the latter is more reproducible and has fewer risks concerning ERCP. Abnormal

findings include extrahepatic stenosis, intrahepatic biliary dilation, caliber irregularity, ductal ectasia, clefts, displacement, and ductal angulations.[12] Currently, there is a standardized nomenclature proposed by the working group of the Indian Association for the Study of the Liver (INASL) (**Table 2**).[10-12] The case described corresponds to extrinsic compressions/indentations (**Figure 3**), which were successfully resolved by ERCP and biliary stenting.

The initial identification of biliary changes in patients with portal cavernoma was conducted through endoscopic retrograde cholangiopancreatography (ERCP), primarily in individuals with biliary manifestations.[10] Subsequent observations of these changes were carried out through the increased utilization of magnetic resonance cholangiopancreatography (MRCP).[11] The use of MRCP represented a significant improvement in diagnosing this condition due

Table 2. Biliary findings corresponding to portal cavernoma-associated cholangiopathy

Imaging findings	Description/concept
Extrinsic compressions/indentations	Smooth impressions with the nodular outline. The indentation is more than a quarter of the width of the bile duct. Impressions can be multiple.
Superficial impressions	Smooth, noncontiguous impressions in the bile duct, less than a quarter the diameter of the bile duct
Irregular ductal contour	Fine, irregular, and wavy contour of bile duct walls due to contiguous superficial clefts, less than a quarter the diameter of the duct
Stenosis	Decrease in the ductal lumen, referring to a "downstream" segment of the duct. Narrow bile duct segments should offer some resistance to the extraction balloon and should produce a waistline. Stenoses can be divided into mild, moderate, or severe depending on whether the stenotic segment is > or < two-thirds the diameter of the adjacent normal segment.
"Upstream" dilation	Proximal dilation can be similarly classified as "mild to moderate" or "severe", depending on whether the dilated segment is between 1.5-2 and > 2 in diameter of the adjacent normal duct, respectively.
Bile duct angulation	An angle of < 145° between the proximal and distal bile duct is proposed.
Ductal ectasia	It is the dilated segment of the biliary tree without any obvious obstruction "downstream".

Modified from reference[10].

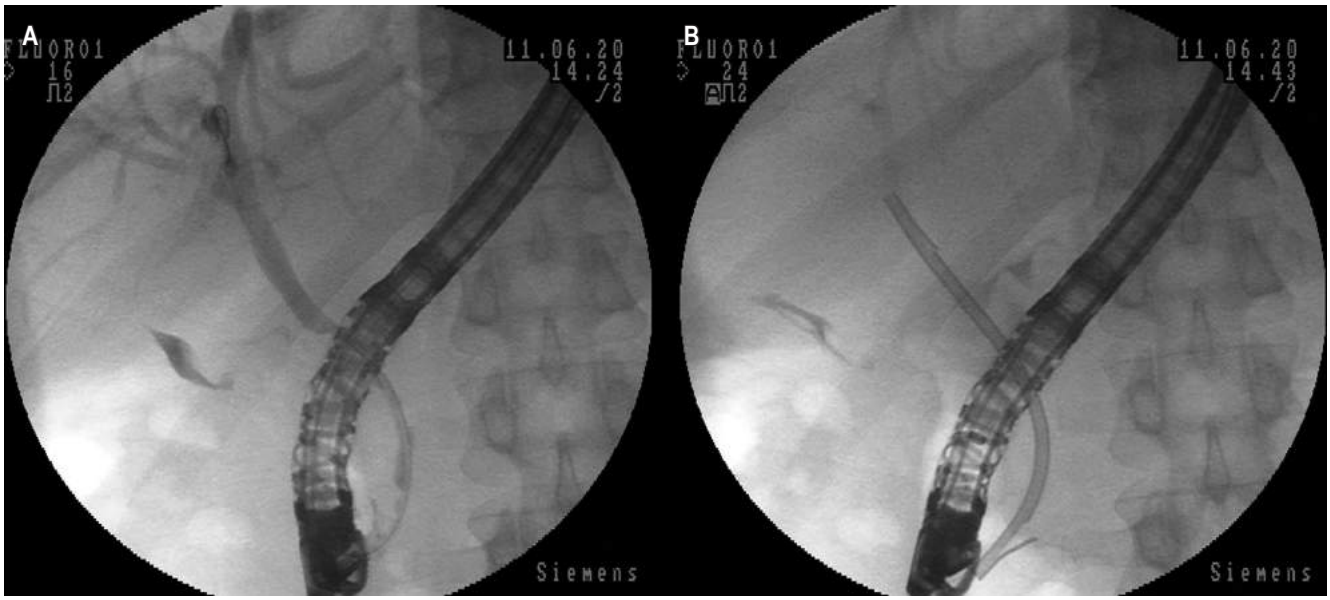

Figure 3. Images of ERCP. **A.** Decrease in diameter of the distal common bile duct with an appearance that impresses by extrinsic compression. **B.** Placement of plastic biliary stent, with evident elimination of the contrast medium of the bile duct. Source: Authors' archive.

to its greater reproducibility and reduced risks compared to ERCP. The biliary changes associated with portal cavernoma include extrahepatic stenosis, intrahepatic biliary dilation, caliber irregularity, ductal ectasia, clefts, displacement, and ductal angulations.[12] Currently, a standardized nomenclature has been proposed by the Indian Association for the Study of the Liver (INASL) working group (**Table 2**).[10-12] The present case corresponds to extrinsic compressions/indentations (**Figure 3**), which were successfully resolved through ERCP and biliary stenting.

The treatment strategy for symptomatic portal cavernoma depends on the mechanism that generates the symptoms, such as stones, stenosis, or both.[12] Biliary clearance/drainage and portosystemic shunt are the two main options available. The endoscopic approach includes sphincterotomy with gallstone removal (when present), dilation of stenosis with or without stent insertion, and biliary drainage. However, the treatment of biliary obstruction by portal cavernoma remains controversial due to the rarity of the condition. For Dumortier et al., the first step in managing biliary obstruction is through endoscopic management by ERCP, which effectively confirms the diagnosis and evaluates common bile duct patency.[13] Inserting a stent after sphincterotomy and gallstone removal allows the drainage of the bile duct and prevents the risk of early infectious complications.[13-15] Sphincterotomy alone is likely insufficient, based on the data observed by Perlemuter et al.,[16] in which recurrent cholangitis and death associated with cholangitis occurred in two of three cases in this series. Exclusively endoscopic management could avoid surgical procedures with hemorrhagic potential. Portosystemic shunt is generally proposed to treat hemorrhagic complications associated with portal hypertension.[17]

CONCLUSION

Portal hypertensive biliopathy is a rare condition that should be considered in patients with a history of portal hypertension who present with jaundice. The imaging patterns of this condition vary depending on the extent and location of the affected venous territory. Magnetic resonance cholangiopancreatography and ERCP with sphincterotomy and stenting are the current diagnostic methods of choice, and they may also serve as the preferred therapeutic approach in symptomatic patients.

Acknowledgments

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Conflicts of Interests

We declare that we have no conflict of interest.

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Case report

Diagnosis of a Case of Hepatotoxicity Due to Drugs and Herbal Supplements in a Hospital in Pasto, Colombia

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Abstract

The liver is a crucial organ in metabolism, and some substances can induce toxic hepatitis with high morbidity and mortality. Chemical and drug-induced liver disease is a diagnostic and therapeutic challenge since it requires extension studies to rule out other entities. We present the case of a 51-year-old female patient without underlying comorbidities, admitted due to symptoms of two-day evolution consisting of progressive jaundice, diarrheal episodes without acholia, or any other additional manifestation. Her condition was caused by the intake of nimesulide, two tablets a day for two days, for pain secondary to a mandibular cyst diagnosed in previous days. During her admission to the emergency room, the patient described chronic consumption of Herbalife® products daily for four years. She presented with elevated transaminases, prolonged prothrombin time (PT), and direct hyperbilirubinemia. Infectious and immunological diseases were ruled out. We decided to start antibiotic and vitamin K coverage. Finally, and by exclusion, a liver biopsy suggested an inflammatory process compatible with drug-induced hepatitis. The woman evolved favorably when the medication and dietary supplement were discontinued. In conclusion, this case constitutes an initial point in advancing research into hepatotoxicity by shared mechanisms of various substances simultaneously, such as what happened to the patient with the parallel use of Herbalife® and nimesulide.

Keywords

Toxic hepatitis, analgesics, nonsteroidal anti-inflammatory drugs, jaundice, dietary supplements, case report.

INTRODUCTION

The liver plays a critical role in protein synthesis and the storage of glycogen and fat-soluble vitamins, in addition to breaking down xenobiotic compounds, such as drugs.[1] Certain commonly used medications and substances, including over-the-counter drugs, have been known to cause toxic hepatitis.[2]

Liver disease caused by substances and drugs can mask the symptoms of acute and chronic liver diseases,[3-6] with varying degrees of severity. Although it is a rarely reported condition, toxic hepatitis has high morbidity and mortality rates and presents a challenge in terms of diagnosis and timely treatment, as it is usually detected only after liver damage has occurred.[3,4] Drug-induced liver injury is one of the most severe adverse reactions and is the leading cause of hepatotoxicity in many locations.[5]

When attributing hepatoxicity to supplements and drugs, it is necessary to exclude other causes, such as viruses, bacteria, autoimmunity, metabolic and vascular diseases,

alcohol, biliary pathology, and neoplasms, before making the diagnosis.[4,6] Although hepatoxicity induced by natural products is not commonly reported, it has piqued the interest of clinicians,[2,3] making it essential to document new cases. For example, some nonsteroidal anti-inflammatory drugs (NSAIDs) were withdrawn from the market due to severe hepatoxicity. These drugs accounted for almost 10% of cases of drug-induced liver disease, with seven NSAIDs being responsible for this adverse reaction.[7]

It is important to note that nimesulide, compared to other NSAIDs, causes a greater proportion and severity of adverse liver events.[8] The risk of hepatoxicity due to nimesulide also increases with longer consumption time and higher doses than conventional.[8,9]

Based on the above, we are presenting a case report of a woman who developed toxic hepatitis associated with the consumption of an herbal supplement (Herbalife®) and concomitant use of nimesulide. The patient was treated at a high-level complexity institution in Pasto, Colombia.

CLINICAL CASE

The patient was a 51-year-old female and professional with a BMI of 25.64 who sought medical attention (internal medicine) for a mandibular nodule. She had no relevant medical record. The physician initially prescribed nimesulide at a dose of two tablets of 100 mg per day for two days, assuming it to be an inflammatory process. The patient reported nausea and jaundice on the third day while denying other symptoms such as abdominal pain, fever, diarrhea, or vomiting. During her admission to the emergency room, the patient disclosed a history of chronic Herbalife® supplement consumption for four years, with a daily intake pattern of shakes. The patient sought medical care at a third-level healthcare institution due to the worsening of symptoms. In the initial differential diagnosis, inflammatory and viral pathologies were considered.

The patient was hospitalized and underwent a comprehensive diagnostic workup to determine the cause of her symptoms. Laboratory tests revealed elevated levels of transaminases, coagulation times, and other liver markers, as shown in **Table 1**. The blood count did not show leukocytosis, and the lipase test could not be processed due to reagent-related issues. The physical examination revealed adenomegaly in the mandibular region while ruling out the presence of other skin lesions or acute bleeding. The toxicology and internal medicine services evaluated the case, and a diagnosis of jaundiced syndrome with possible hepatoxicity was made.

In this case, the most relevant differential diagnoses considered were autoimmune hepatitis, pesticide-derived lesions (which were ruled out based on the patient's history and symptoms), hepatotropic viruses, alcoholic hepatitis, and biliary pathology.

The case study started with a neck ultrasound to assess the mandibular nodule, which incidentally revealed a subcentric right thyroid nodule and rounded adenomegaly in the right submandibular region with loss of a suspicious cortex-marrow relationship. Tests were then performed for hepatotropic viruses and other conditions, which yielded negative results. A fine-needle aspiration biopsy (FNAB) of the submandibular nodule showed indeterminate atypia of lymphoid cells. Based on these findings, the patient was treated with vitamin K (10 mg intravenously/day), hydration (Ringer's lactate), and antibiotics (ampicillin/sulbactam 3 g intravenously every six hours).

After the liver and bile duct ultrasound, hepatic steatosis, cholecystitis, and biliary sludge were detected. Consequently, the surgeons assessed the patient and requested both abdominal tomography (**Figure 1**) and magnetic resonance cholangiopancreatography (**Figure 2**). However, as hyperbilirubinemia persisted at the expense of direct hyperbilirubinemia, gastroenterologists performed an endoscopic retrograde cholangiopancreatography (ERCP). The ERCP revealed the papilla of Vater in the second flat duodenal portion, selective admission to the bile duct with bow papillotome plus hydrophilic guide. In addition, the contrast-enhanced cholangiography confirmed a normal caliber bile duct without stones, exploration of the bile duct with Dormia basket and extraction of biliary sludge and retained bile, and bile duct washing until clear bile drainage.

The patient had a non-obstructive liver condition with no stones in the bile duct. She improved due to her asymptomatic state, stable hemodynamics, decreased values of paraclinical controls (specifically bilirubin and transaminases), absence of an evident infectious process, and resolution of the mandibular adenopathy.

The patient underwent a liver biopsy (**Figure 3**), and the histopathological diagnosis revealed an inflammatory process of white line cells, which was compatible with a pattern of acute hepatitis with pericentral necrosis and apoptotic hepatocytes. It is important to highlight that the patient's clinical condition improved after discontinuing nimesulide medication and the dietary supplement. Thirty days after discharge, follow-up tests showed that liver function and transaminases were within normal parameters. In conjunction with the patient's clinical evolution, it indicates that the medication was the cause of the pathological process.

DISCUSSION

Toxic hepatitis can have various causes, such as the consumption of medications or xenobiotics like immunosuppressants, anti-tuberculosis drugs, antibiotics, and nonste-

Table 1. Complementary serum tests performed on the patient

Laboratory parameter	Admission	Day 7	Day 10	Discharge
Alkaline phosphatase	341 U/L	298 U/L	258 U/L	86 U/L
Amylase~	22.5 U/L	No data	No data	No data
Total cholesterol	175 mg/dL	No data	No data	172 mg/dL
Triglycerides	167 mg/dL	No data	No data	180 mg/dL
GGT	109 U/L	95 U/L	No data	60 U/L
Total bilirubin	10.8 mg/dL	2.90 mg/dL	No data	2.0 mg/dL
Direct bilirubin	6.7 mg/dL	0.00 mg/dL	No data	1.2 mg/dL
Indirect bilirubin	4.1 mg/dL	1.10 mg/dL	No data	0.8 mg/dL
Glycemia	88 mg/dL	110 mg/dL	No data	No data
Creatinine	0.69 mg/dL	No data	No data	No data
ALT	1160 U/L	987 U/L	574 U/L	272 U/L
AST	786 U/L	780 U/L	513 U/L	180 U/L
PT	15.8 s	16.7 s	13 s	No data
PTT	65 s	31 s	31 s	No data
Leukocytes	8555 10^3/µL	No data	No data	6700 10^3/µL
Hb	14.6 g/dL	No data	No data	12 g/dL
Hto	43.4%	No data	No data	40.2%
Platelets	130 10^3/µL	No data	No data	150 10^3/µL
*Hepatitis B and C negative Embryonal carcinoma antigen CA 19 negative Negative anti-smooth muscle Ab	HIV – negative serology	Negative CMV IgG- IgM	Negative Epstein-Barr IgG-IgM	Negative antinuclear, mitochondrial, and microsomal Ab

~There was no amylase follow-up due to the lack of reagent in the institution. *The clinical history reported that tests for hepatitis B and C (in addition to the last row) were non-reactive; however, numerical parameters were not provided as the patient's insurance company had the tests performed at an external institution, and the institutional report was qualitative. Ab: antibodies; ALT: alanine aminotransferase; AST: aspartate aminotransferase; CA: cancer; CMV: cytomegalovirus; GGT: gamma-glutamyl transferase; Hb: hemoglobin; Hto: hematocrit; IgG: immunoglobulin G; IgM: immunoglobulin M; PT: prothrombin time; PTT: partial thromboplastin time; HIV: human immunodeficiency virus. Source: HUDN (Hospital Universitario Departamental de Nariño) Clinical Laboratory.

roidal anti-inflammatory drugs (NSAIDs).[10] Analgesics are responsible for most cases of drug-induced liver injury.[10] In fact, up to 15% of patients using NSAIDs may experience at least one episode of transient elevation of transaminases.[11] Risk factors associated with the development of drug-induced liver injury include advanced age (60 to 70 years), female sex, pre-existing liver disease, and genetic polymorphisms in drug metabolism pathways according to ethnicity.[5,8]

The use of dietary and herbal supplements has become increasingly popular and has consequently had an impact on liver damage.[12] For instance, the consumption of Herbalife® products has been associated with varying degrees of liver damage, ranging from minimal changes to fulminant hepatitis that requires transplantation.[13] Herbal and dietary supplements contain a wide variety of ingredients, including vitamins, minerals, proteins, herbs, and other botanicals.[13,14] The nutritional information of these compounds typically includes a mixture of minerals such as calcium citrate, magnesium oxide, ferrous fumarate, sodium selenite, zinc oxide, manganese carbonate, chromium chloride [III], potassium iodide, cupric citrate, and potassium phosphate. Additionally, anti-caking agents such as silicon dioxide and

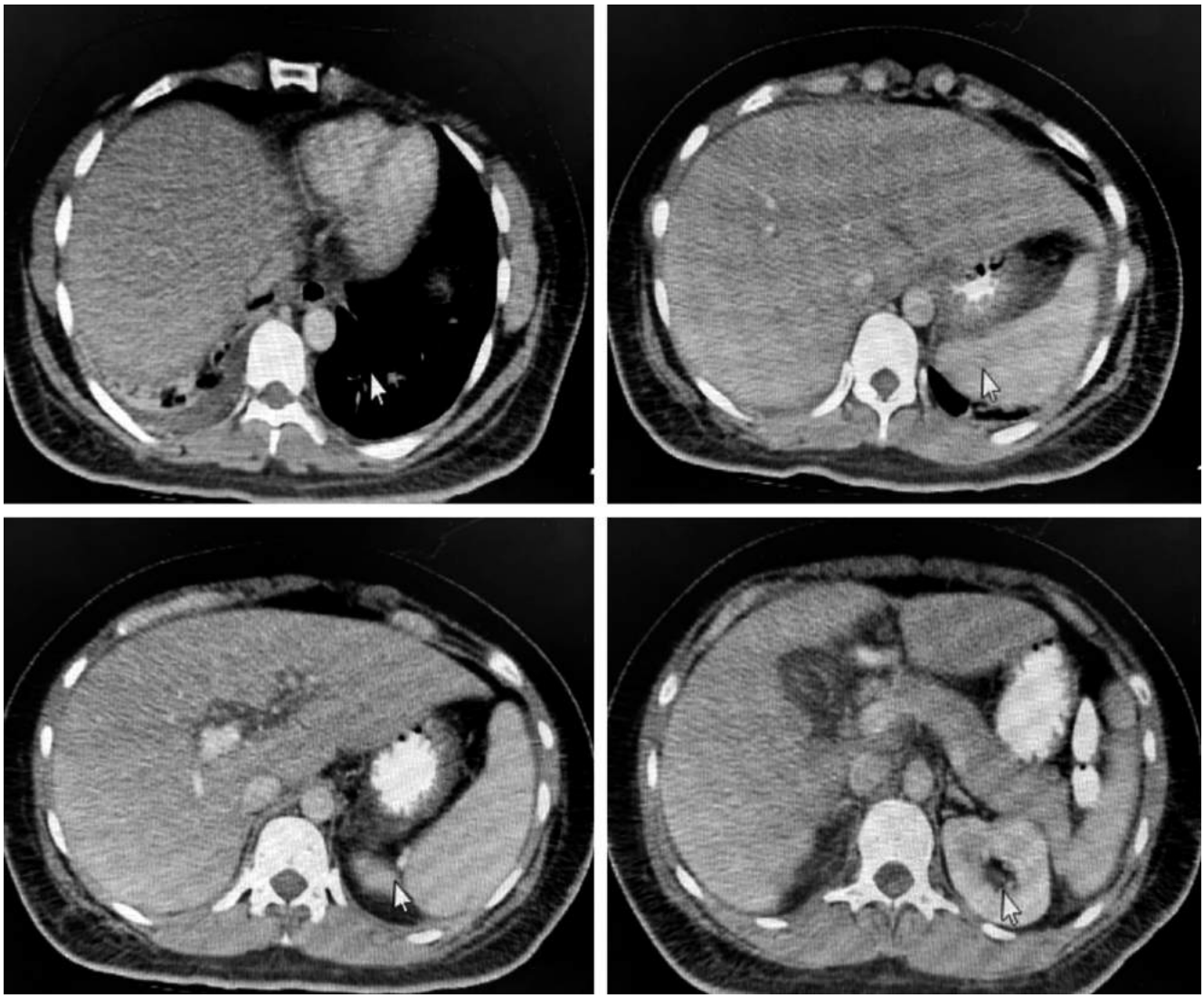

Figure 1. Computed tomography (CT) scan of the patient's abdomen. Right laminar pleural effusion with subsegmental atelectasis. Diffuse hepatic steatosis without focal lesions. Findings described at the pancreatic level suggest interstitial edematous process Balthazar C. Severity index 2. Right renal hypodense nodular image compatible with a cyst. Intra-abdominal laminar fluid. Courtesy of HUDN Radiology Department

botanical products such as shiitake mushroom, green tea leaf, oolong tea leaf, black tea leaf, pomegranate peel, parsley, dandelion, milk thistle extract, Echinacea purpurea, Echinacea angustifolia, Astragalus, and Schisandra are also commonly found in these supplements.[15]

Although they appear natural and safe, it is important to note that the safety of these substances remains controversial, as there is limited evidence available on their efficacy and toxicity.[14] Hepatoxicity resulting from the use of herbal products is often attributed to an idiosyncratic reaction rather than toxic damage.[13]

Recent publications have reported cases of toxicity caused by herbal supplements in various regions, including Asia (where traditional Chinese medicine is used), America (including the United States and Latin America), and Europe (such as Spain, Iceland, and France).[14,16] Specifically, Herbalife® products have been found to contain agents suspected of causing hepatoxicity, such as green tea extract, ginkgo, and saw palmetto.[12] In addition, hepatocellular damage is the predominant mechanism of liver damage caused by these extracts, followed by the mixed mechanism, among others.[12,13,16] The severity of liver damage caused by herbal supplements varies from mild to severe, and in some cases, can even lead to cirrhosis and liver failure that requires liver transplantation.[13]

Dietary and herbal supplements can lead to metabolic activation via the liver cytochrome P450 complex or intes-

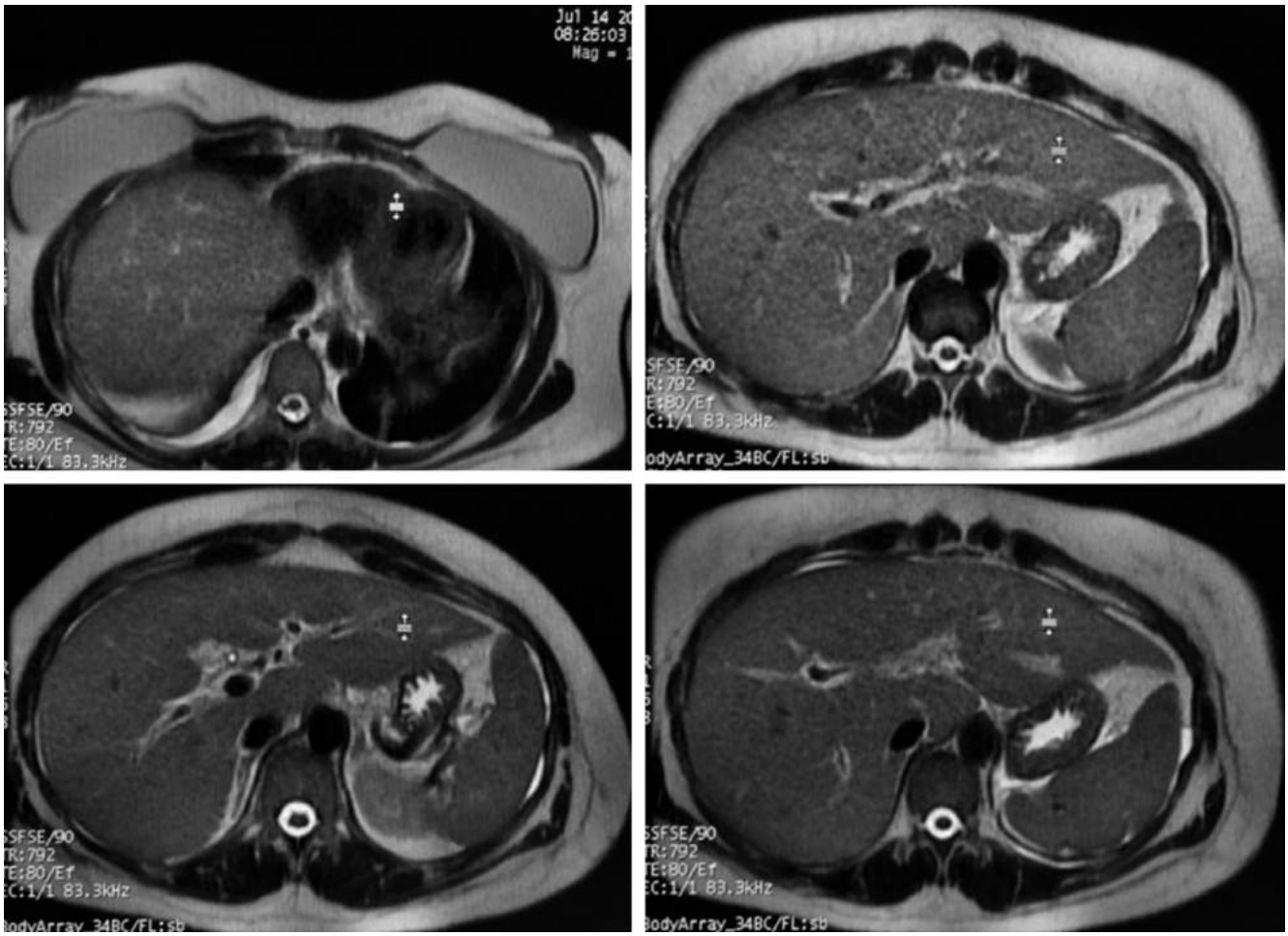

Figure 2. Magnetic resonance cholangiopancreatography of the patient. Edema of the gallbladder walls and biliary sludge inside. Stones that may cause obstruction are not observed in the vesicular lumen or the bile duct. Free liquid in Morrison's space and right parietocolic leak. Free fluid in the right lung base. Mild hepatomegaly. Courtesy of HUDN Radiology Department.

tinal bacteria, resulting in the production of toxic metabolites that can bind to reduced cellular glutathione, forming potentially toxic protein/DNA adducts.[17]

According to a study, patients with acute liver failure caused by herbal and dietary supplements are more likely to require liver transplantation compared to those caused by medication prescription.[18,19] Analyzing the toxicity of Herbalife® products can be complex as they may contain non-herbal chemical components that need to be evaluated as hepatoxicity precursors.[20] For example, contamination with *Bacillus subtilis* in Herbalife® products could potentially contribute to the hepatoxicity profile of this herbal supplement.[18]

In comparison to other NSAIDs, nimesulide is known to have a higher incidence of hepatoxicity, according to studies.[21,22] In fact, an integrative study found that approximately 45% of patients with adverse hepatic reactions due to nimesulide required liver transplantation or died from fulminant liver failure.[21] The toxicity caused by nimesulide may have a latency period ranging from 90 days to six months.[8] Recent studies have shown that most patients with nimesulide-induced hepatoxicity are women, elderly, and have jaundice,[8,21] which is consistent with the case presented in this report.

The mechanism responsible for nimesulide-induced liver damage remains unknown, and genetic association studies have yet to be conducted.[8] Potential mechanisms of hepatoxicity include the involvement of the adaptive immune system, bioactivation via oxidative stress production by nitroreductases, and the idiosyncratic metabolic hypothesis.[8]

However, further studies are needed to evaluate the risk of nimesulide-induced liver damage based on certain characteristics such as age, sex, dosage, and duration of

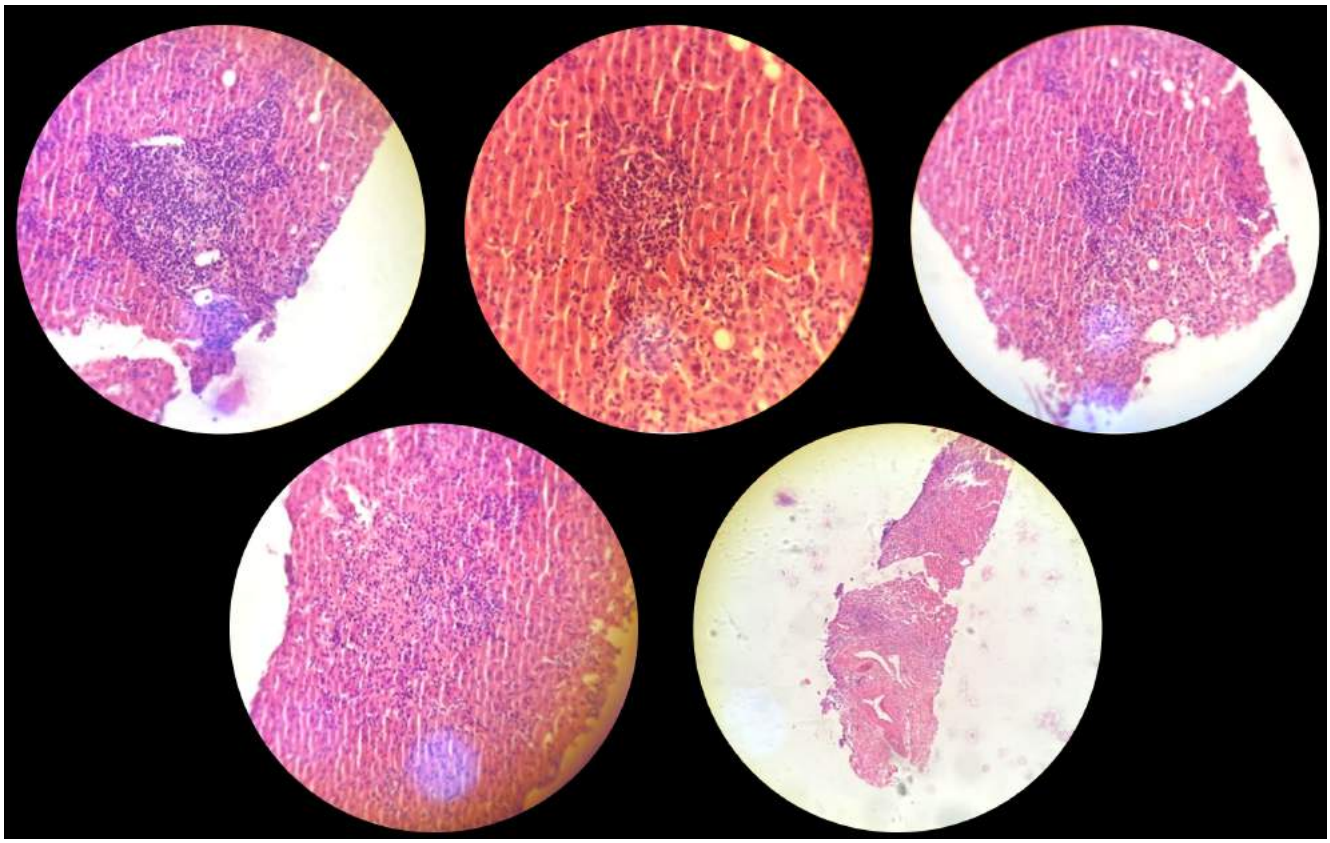

Figure 3. Liver biopsy images of the patient. Hematoxylin-eosin stain with unreported increase. Courtesy of the Pathology Department of the third-level institution in Pasto with reading extension (Dr. Fernando Bolaños Ordóñez).

treatment.[21] It should also be noted that the concomitant use of certain drugs and xenobiotics can potentiate the hepatotoxic effect. For instance, like Herbalife®, nimesulide is metabolized by cytochrome P450 isoenzymes.[17,22]

The liver biopsy on the patient revealed the presence of mononuclear inflammatory infiltrate and areas of necrosis in the liver tissue, leading to the histopathological diagnosis of acute drug-induced hepatitis based on the clinical context. However, a limitation of the study is that the findings could not be expanded upon to accurately support the diagnosis from the pathology. The elevated levels of both transaminases and an ALT/AST ratio of 1.4 to 1.5 suggest that the hepatic condition could have mixed with cholestatic predominance, according to López-Gil et al.[23]

The analysis of this case suggests a potential synergistic mechanism of hepatoxicity with the concurrent use of nimesulide and the Herbalife® dietary supplement, given that other possible causes of hepatoxicity were ruled out. Currently, there are no studies evaluating the possibility of a joint mechanism of liver toxicity, as observed in this case. Additionally, it is important to emphasize the need for regulations in the prescription of hepatotoxic drugs and the use of products without long-term medical indications, which may synergistically affect organs involved in the metabolism and excretion of xenobiotics.

CONCLUSION

The case mentioned above serves as a starting point for advancing research on hepatoxicity through shared mechanisms of multiple substances used simultaneously, such as the combination of Herbalife® and nimesulide, which both undergo metabolism via cytochrome P450.

Conflicts of Interests

The authors declare that there is no conflict of interest regarding the publication of this article.

Acknowledgments

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Case report

Lower Digestive Tract Bleeding in a Patient with Behçet's Disease: A Case Report

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Abstract

Behçet's disease is a chronic, multisystemic, and relapsing inflammatory pathology that frequently manifests with oral and genital ulcers and ocular and skin lesions. It rarely exhibits gastrointestinal involvement, which varies depending on the affected gastrointestinal segment; these have in common the predominance of ulcerated lesions and, consequently, a greater risk of bleeding from the digestive tract. A clinical case of a 28-year-old female patient who consulted for a clinical picture of melenic stools and oral ulcers is described. As a crucial clinical history, she had been diagnosed with Behçet's disease since adolescence, associated with severe gastrointestinal complications. An esophagogastroduodenoscopy was performed with findings of antral erythematous gastropathy and a colonoscopy with a report of ulcerated ileitis. Treatment with azathioprine and corticosteroids was indicated, significantly improving the clinical picture.

Keywords

Colombia, inflammatory bowel disease, ileitis, melena, Behçet's syndrome, vasculitis.

INTRODUCTION

Behcet's disease (BD), first described by Hulusi Behçet in 1937,[1] is a chronic inflammatory disease of unknown origin that affects multiple systems and primarily involves blood vessels of different calibers.[2] The disease is more common in countries located along the ancient Silk Road, in the Mediterranean region, and in the Middle and Far East, particularly in Turkey, Saudi Arabia, Iraq, Israel, China, and Japan, with a prevalence range of 7.2 to 420 cases per 100,000 inhabitants.[3]

According to the International Chapel Hill Consensus Conference, BD is classified as a vasculitis of variable vessels with an unknown etiology.[4] However, immunological mechanisms have been identified in its pathogenesis, which are linked to an increase in the activation of peripheral blood γ/δ T lymphocytes, the rise of Th1 cytokines, including interleukin (IL)-12, IL-18, interferon-gamma (IFN-γ), the presence of autoantibodies, circulating immune complexes, hypercoagulability, and activation of the vascular endothelium. Additionally, genetic mechanisms are involved through the presence of HLA-B*51 molecules and alterations in the aminopeptidase 1 enzyme of the endoplasmic reticulum and the receptors of IL-23 and IL-10.[5-7]

Behcet's disease presents with a variable clinical phenotype, with the most common phenotypes being mucocu-

taneous, with aphthous lesions on the skin, in the oral and genital mucosa (60%-90%), ocular in the form of panuveitis (45%-90%), and musculoskeletal expressed as mono- or oligoarthritis of large joints (11.6%-93%).[8] Gastrointestinal involvement occurs less frequently (8%-34%), with diverse clinical manifestations ranging from nonspecific symptoms such as abdominal pain, nausea, diarrhea, and digestive tract bleeding to complications such as ulcers, perforation, fistulas, abscesses, and intestinal ischemia.[9]

We present a case report of a 28-year-old woman with a history of BD who experienced gastrointestinal tract hemorrhage due to ulcerated vascular lesions in the intestinal mucosa. This case is particularly interesting because BD is less common in the Western hemisphere and typically involves a lower proportion of gastrointestinal manifestations.

CLINICAL CASE

A 28-year-old woman presented to the emergency department with a 48-hour history of four episodes of melenic stools, nausea, and mild diffuse abdominal pain. She also had ulcers in her oral mucosa for the past 15 days. The patient had a relevant medical history of Behcet's disease (2013), with secondary intestinal obstruction and perforation, and underwent two intestinal segment resections with colostomy and ileostomy at 13 and 19 years of age. She was treated for four years with azathioprine and colchicine, which were discontinued a year ago due to the resolution of symptoms. The patient had no other significant medical history. Paraclinical data is included in **Table 1**.

The patient underwent an esophagogastroduodenoscopy which showed erythematous antral gastropathy, and a total colonoscopy revealed the presence of a 10 mm ulcer with regular edges and fibrin at 3 cm from the colon anastomosis, a 12 mm ulcer with regular edges and fibrin at 5 cm proximal, and two ulcers of 4 and 7 mm in size with characteristics similar to the proximal 10 cm, for which biopsies of the center and the edge were performed. Additionally, a few aphthoid lesions were observed in the distal ileum, which is indicative of ulcerated ileitis with normal colon anastomosis (**Figure 1**). The biopsy of ileal mucosal fragments did not accurately represent the ulcers. However, it showed marked edema of the lamina propria, angiectasias associated with mononuclear and polymorphonuclear infiltrate that focally erode the superficial epithelium, and fragments with fibrinoleukocyte material, which suggested nonspecific inflammatory changes (**Figure 2**).

After the endoscopic studies, the patient was started on immunomodulatory treatment with azathioprine 50 mg orally (PO) every eight hours and prednisolone 1 mg/kg/day PO (60 mg/day). Nine months after hospital discharge, the patient had a satisfactory clinical course.

Table 1. Results of admission laboratory tests

Laboratories	Result	Reference values
Blood picture		
- Leukocytes	8,5 x 10^3/µL	4,5-10 x 10^3/µL
- Red blood cell count	3,8 x 10^6/µL	4,2-5,4 x 10^6/µL
- Hemoglobin	11,2 g/dL	12,5-16 g/dL
- Hematocrit	31,9%	37-47%
- Mean corpuscular volume	83,2 fL	79-101 fL
- Mean corpuscular hemoglobin	29,1 pg	29-35 pg
- EDR	13,2%	11%-16%
- Platelets	281,8 x 10^3/µL	150 -450 x 10^3/µL
Electrolytes		
- Potassium	3,4 mmol/L	3,5-5,1 mmol/L
- Sodium	137 mmol/L	136-146 mmol/L
- Chlorine	105 mmol/dL	101-109 mmol/L
- Magnesium	2,0 mg/dL	1,9-2,5 mg/dL
Renal function		
- Creatinine	0,89 mg/dL	0,55-1,02 mg/dL
- Urea nitrogen	18,6 mg/dL	7-25 mg/dL
Liver function		
- AST	26 U/L	0-35 U/L
- ALT	21 U/L	0-35 U/L
Acute phase reactants		
- CRP	0,16 mg/dL	0-0,5 mg/dL
- ESR	21 mm/h	0-20 mm/h

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP: C-reactive protein; EDR: erythrocyte distribution range; ESR: erythrocyte sedimentation rate. Source: Authors' own research.

DISCUSSION

The clinical case presents a patient with Behçet's disease (BD) and gastrointestinal manifestations secondary to ulcerated ileitis. This information is particularly relevant in the medical field due to the limited published literature and the low incidence of the disease in Latin America, including Colombia,[10,11] where only 523 cases of BD were identified and registered in the Comprehensive Information System for Social Protection (SISPRO) of the Ministry of Health and Social Protection from 2012 to 2016, resulting in a prevalence of 1.1 cases per 100,000 inhabitants. The disease is more prevalent among women aged 45-49 years and in the regions of Antioquia, Cundinamarca, and Bolívar.[11] The patient's clinical case is consistent with the findings of the aforementioned study, as she is a female patient from one of the regions with the highest reported cases of BD during a specific period from 2012 to 2016.

In countries where BD is prevalent, the clinical manifestations of the disease have been well characterized.

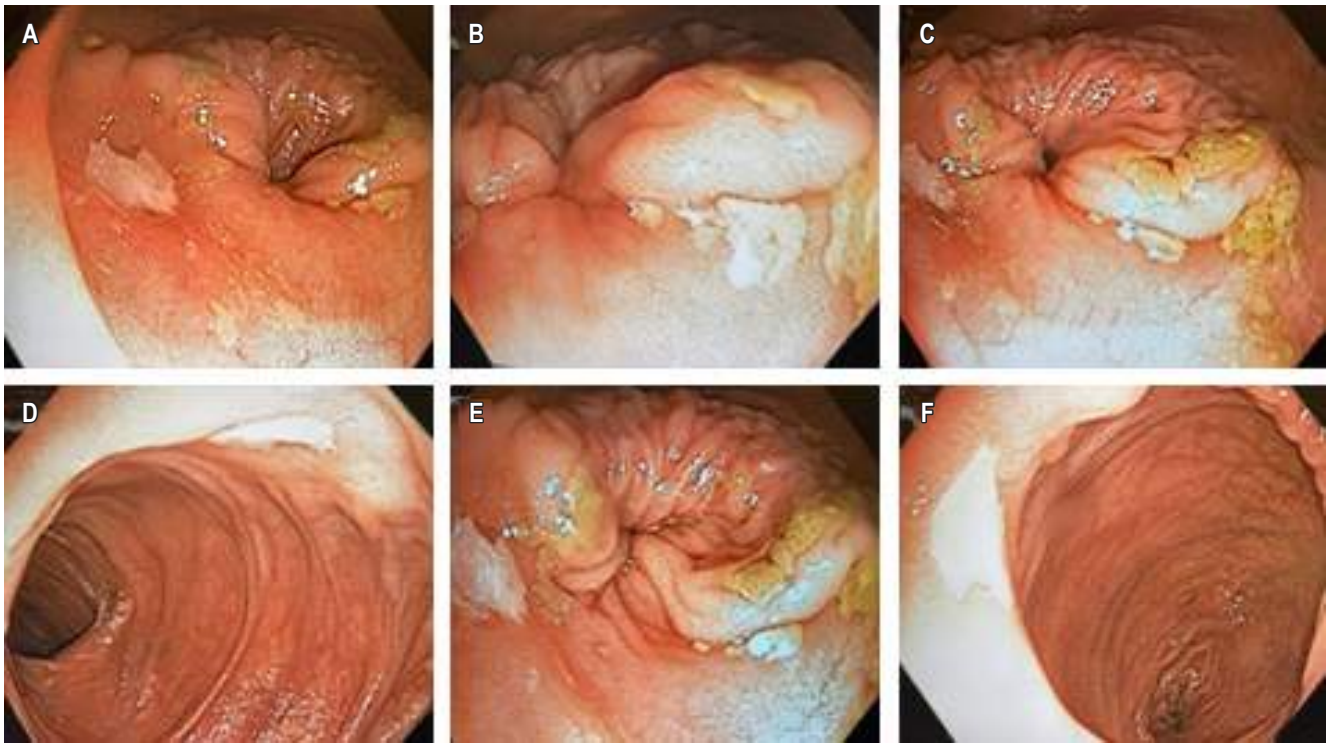

Figure 1. Total colonoscopy with findings of ulcerated ileitis. **A-F.** Well-defined ulcers with regular and slightly erythematous edges, with a fibrin background of the dimensions described in the clinical case. Source: Authors' archive.

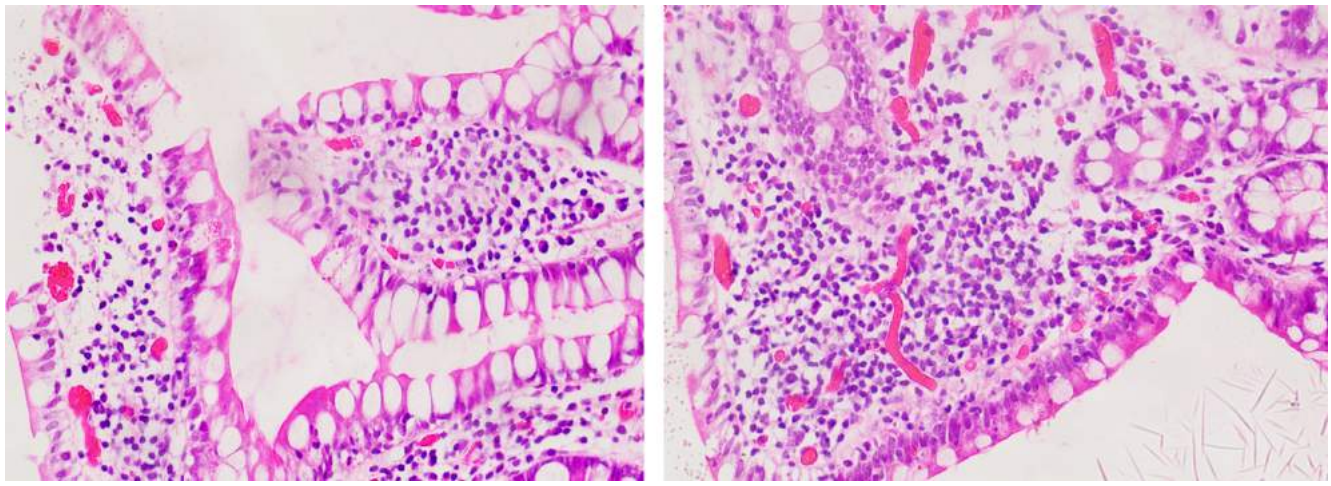

Figure 2. Histopathological findings of ulcer samples in the distal ileum. Findings of edema of the lamina propria and angiectasias associated with mononuclear and polymorphonuclear infiltrate eroding the distal epithelium. Courtesy of Edna Margarita Martínez Ortiz, Pathologist.

For instance, in Egypt, a study on 223 patients found that mucocutaneous (84.5%) and musculoskeletal (15.9%)[12] symptoms were the most common clinical phenotypes. Similarly, a study on 489 patients in China identified mucocutaneous lesions as the most frequent manifestation, while gastrointestinal ulcers were more common in patients over 40.[13] In contrast, the patient in this clinical case experienced recurrent gastrointestinal tract lesions since adolescence, which was the predominant clinical manifestation.

Furthermore, a study conducted in Colombia on 20 patients diagnosed with BD, with an average age of 40.6 ± 8.2 years, documented that the most common clinical pre-

sentations were recurrent oral ulcers (95%), genital ulcers (75%), and skin infections (60%), with 40% of patients presenting gastrointestinal manifestations.[14] Based on the gastrointestinal involvement described in the clinical case and the previously reported higher proportion of gastrointestinal manifestations in Colombian patients, it is suggested that further research be conducted to clinically and epidemiologically characterize BD cases in the country and evaluate the frequency of complications related to gastrointestinal involvement.

In regard to the subject, the involvement of the gastrointestinal tract in BD can vary based on its location. Esophageal involvement is rare and is typically demonstrated through ulcers, stenosis, and perforation. Ulcers in the stomach and duodenum may occur. However, complications such as perforation, gastrointestinal bleeding, fistulas, stenosis, and abscesses are more frequent in the jejunum, ileum, and colon.

In patients with BD, the terminal ileum and ileocecal region are commonly affected portions of the intestine.[15-17] Moreover, intestinal lymphangiectasias leading to protein-losing enteropathy have been reported.[18] In this clinical case, the patient experienced digestive tract hemorrhage resulting from ulcerated ileitis and a history of previous intestinal perforations that required surgery. This supports existing evidence indicating that digestive tract involvement is associated with a more severe clinical presentation and greater morbidity in patients with BD.

There are no pathognomonic symptoms or specific biomarkers for diagnosing BD, which is why various classification systems are utilized. The most commonly used system is the international criteria for BD, proposed by the international BD study group, which includes eye lesions, oral and genital ulcers, skin lesions, neurological and vascular manifestations, and a positive pathergy test (appearance of papules or pustules in epidermal areas that have had microtraumas).[19,20] In this clinical case, the patient was diagnosed with BD in 2013, with a predominance of oral ulcers according to the diagnostic criteria and a predominance of gastrointestinal manifestations. Therefore, given that BD is a multisystemic condition, in the presence of a patient with recurrent ulcerated lesions and gastrointestinal manifestations, it is important to prioritize endoscopic studies to assess vascular lesions caused by this disease.

The patient's endoscopic findings were consistent with ulcerated ileitis, making distinguishing between BD and Crohn's disease difficult. To differentiate between the two, endoscopic criteria have been proposed, such as the presence of limited ulcers with a round or oval shape, focal distribution (single or multiple), absence of aphthous lesions, or a paved appearance, which are compatible with BD.[21] In this case, the oval ulcerated lesions with regular edges focused on the distal ileum found in the patient are representative of BD.

The histopathological features of BD in the gastrointestinal tract include mononuclear infiltrates and perivascular mast cells, neutrophilic vasculitis, and acute and chronic inflammatory changes in the submucosa.[15] Despite the absence of clear evidence of ulcers in the histopathological report of the biopsies obtained during endoscopy, the edema of the lamina propria, along with mononuclear and polymorphonuclear infiltrates, may suggest the inflammatory changes that BD triggers in the gastrointestinal tract.

The pharmacological treatment of gastrointestinal involvement in BD varies depending on the severity of the clinical presentation. For mild cases, monotherapy with 5-aminosalicylate derivatives is recommended. In cases of moderate to severe severity, systemic corticosteroids are the first line of treatment. However, due to the side effects associated with high doses of corticosteroids, azathioprine has recently become relevant in managing such cases. In patients with severe gastrointestinal manifestations that do not respond to azathioprine, tumor necrosis factor inhibitors (infliximab or adalimumab) are preferred as third-line management.[22,23]

In this particular case, the patient had moderate-severe gastrointestinal involvement, as evidenced by the recurrence of her clinical profile and previous history of intestinal obstruction and perforation. As a result, treatment with corticosteroids and azathioprine was resumed, which resulted in an adequate clinical response.

CONCLUSIONS

BD is a rare condition in the Colombian population, and as it affects multiple systems, an interdisciplinary assessment is necessary to evaluate the involvement of various organs. Additionally, endoscopic studies are crucial for the early identification of vascular lesions that can lead to severe complications such as obstruction, perforation, and gastrointestinal bleeding. Timely initiation of immunomodulatory therapy can prevent such complications.

Additionally, BD should be considered among the differential diagnoses of inflammatory bowel diseases, considering the established diagnostic criteria and the differentiation of endoscopic findings inherent to this pathology.

This clinical case report serves as a starting point for future research in Colombia. Further studies should focus on the clinical and epidemiological characterization of BD cases, the determination of its incidence and prevalence in the Colombian population, and the identification of associated factors.

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Case report

Ulcerative Colitis Induced by Secukinumab in the Treatment of Ankylosing Spondylitis

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Abstract

Interleukin 17 (IL-17) inhibitors are approved for treating psoriasis, psoriatic arthropathy, and ankylosing spondylitis. IL-17 is involved in the pathogenesis of inflammatory bowel disease (IBD); however, paradoxical events have been reported using selective IL-17 inhibitors such as secukinumab, whose pathophysiological mechanisms have not been fully clarified. Although the incidence of IBD in this group of patients is low, the risk could be reduced by carefully assessing risk factors such as family history, gastrointestinal symptoms, and fecal calprotectin before starting treatment.

Keywords

Secukinumab, ulcerative colitis, ankylosing spondylitis.

INTRODUCTION

Interleukin 17 (IL-17) is a proinflammatory cytokine that has been linked to the pathogenesis of inflammatory bowel disease (IBD).[1] Selective inhibitors of IL-17, such as secukinumab (a monoclonal antibody approved for treating psoriasis, psoriatic arthropathy, and ankylosing spondylitis [AS]), have been paradoxically associated with exacerbations or the development of IBD. This seems to be due to the protective effect of IL-17 against inflammation by inhibiting the Th1 response and maintaining the epithelial barrier of enterocytes, thus preserving intestinal homeostasis.[2]

PRESENTATION OF THE CASE

A 43-year-old female patient with a medical history of ankylosing spondylitis (AS) since the age of 20, fibromyalgia, arterial hypertension, hypothyroidism, and latent tuberculosis treated in 2019 presented to the hospital with symptoms of diffuse abdominal pain and multiple bloody diarrheal stools (more than fifteen times a day) for a week. The patient had been treated with etanercept, adalimumab, abatacept, and since 2017, with secukinumab. On admission, the patient was tachycardic, dehydrated, afebrile, and had lower abdominal pain without signs of peritoneal irritation. Laboratory tests showed no alterations in blood count, and an ultrasound and tomographic study revealed wall thickening of the right colon with mucous enhancement, multiple mesenteric lymphadenopathies, and some free fluid at the bottom of the sac (**Figure 1**). Colonoscopy showed edema, erythema, mucosal friability, loss of vascular pattern, and ulcerations covered by fibrin from the rectum to the cecum, which are consistent with extensive ulcerative colitis (**Figure 2**).

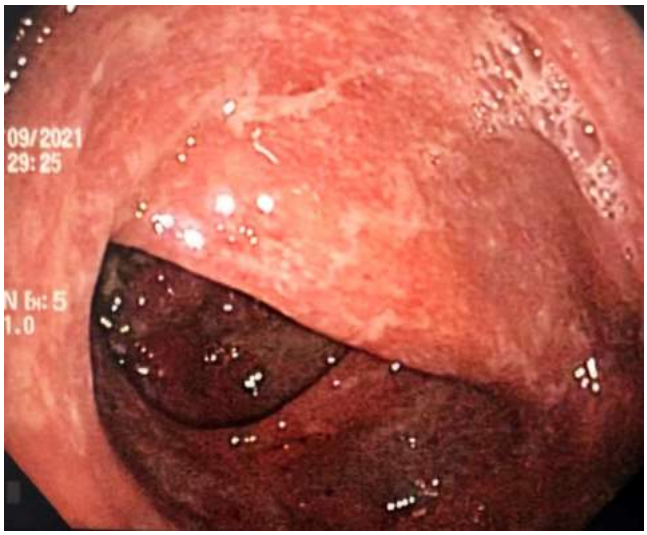

Figure 1. Tomographic findings. Thickening of the walls of the ascending colon with mucous enhancement (arrow). Source: Authors' archive.

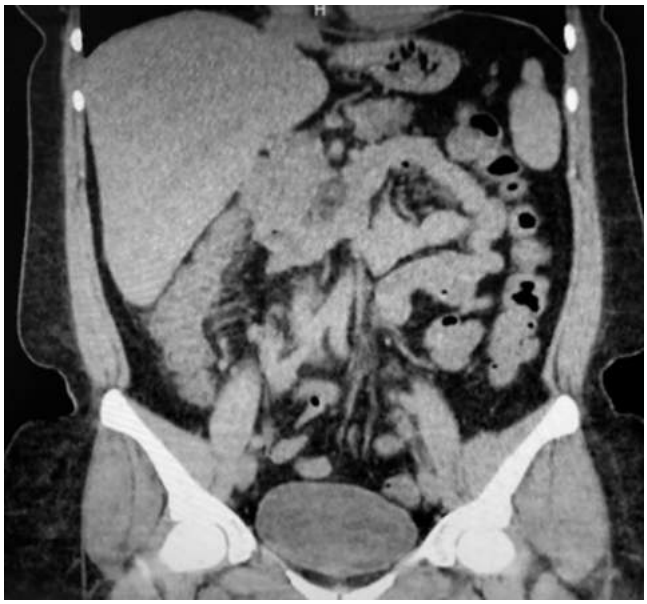

Figure 2. Endoscopic findings. Edema, erythema, loss of vascular pattern, and ulcerations covered by fibrin. Source: Authors' archive.

Based on the patient's symptoms and endoscopic findings, a diagnosis of severe ulcerative colitis was made, and treatment with intravenous corticosteroids, oral 5-aminosalicylic acid (5-ASA in granules), and enemas was initiated. The pathology report indicated that the patient had inflammatory bowel disease suggestive of severe ulcerative colitis without dysplasia or metaplasia. The patient's infectious profile showed only positive results for CMV IgG, normal liver function, and a fecal calprotectin level above 1000 ng/mL. Fortunately, the patient responded well to treatment and experienced a resolution of her symptoms. As a result, the corticosteroid treatment was gradually discontinued, and the patient was switched to tofacitinib in consultation with the rheumatology team.

DISCUSSION

Secukinumab is a human monoclonal antibody that specifically blocks interleukin 17A (IL-17A),[3] an inflammatory regulation molecule linked to the development of autoimmune diseases such as ankylosing spondylitis (AS), psoriatic arthritis (PA), and psoriasis. Additionally, murine studies suggest a role for IL-17A in maintaining gastrointestinal homeostasis and tissue repair by stimulating mucin production, which strengthens the bond between claudin and occluding proteins[5] and maintains intestinal barrier integrity.[4] Although spondyloarthropathies such as AS and PA (treated with secukinumab) share overlapping characteristics with inflammatory bowel disease (IBD), their immune mechanism is not well understood. It is noteworthy that at least 50% of patients with AS or PA exhibit histological changes of inflammation in colon samples, and approximately 7% may develop Crohn's disease or ulcerative colitis,[6] which suggests that they have a threefold higher risk of developing IBD compared to the general population.[7,8]

Blocking IL-17A, which is used as a treatment for AS, may lead to a possible deterioration of the intestinal epithelial barrier, which could initiate or worsen the phenotypes of IBD, such as ulcerative colitis or Crohn's disease.[3]

It has been reported that up to 7.8% of patients receiving secukinumab may present gastrointestinal symptoms associated with its administration.[9] However, most of them do not develop objective evidence of IBD or require treatment discontinuation. The incidence of new cases of IBD following secukinumab administration has been reported between 0.2% and 0.7%.[7,10,11]

Studies have reported that up to 7.8% of patients treated with secukinumab may experience gastrointestinal symptoms related to its use.[9] However, the majority of these cases do not result in the development of clear evidence of IBD or require treatment discontinuation. The incidence of new-onset IBD following secukinumab treatment has been estimated to range from 0.2% to 0.7%.[7,10,11]

While the incidence of IBD in patients treated with secukinumab is low, it is still recommended to carefully investigate the patient's family history of IBD or gastrointestinal symptoms before starting treatment.[7] Patients should be informed of the possibility of developing gastrointestinal adverse events. As some may present subclinical IBD, fecal calprotectin is suggested, and patients with normal values may be considered for treatment, although close moni-

toring for the appearance of gastrointestinal symptoms is essential. Those with elevated values should be evaluated to rule out an IBD diagnosis. For patients with active IBD, treatment initiation is contraindicated. For patients with a known diagnosis of IBD in the quiescent phase, other therapeutic options should be considered.[12] Currently, there are no known reported cases of secukinumab-induced or exacerbated IBD in Colombia.

CONCLUSIONS

Although the incidence of IBD in patients treated with IL-17 inhibitors is low, it is important to note that a significant percentage of patients receiving this group of medications may develop gastrointestinal adverse events that require monitoring and follow-up.

Performing a thorough evaluation of family history, previous symptoms, and fecal calprotectin levels before starting treatment is a proposed strategy to reduce the risk of developing IBD or worsening existing symptoms.

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Case report

Subserous Eosinophilic Colitis: A Case Report in a Private Hospital in Lima, Peru

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Abstract

Eosinophilic colitis is a rare gastrointestinal disease that belongs to the group of so-called primary eosinophilic diseases of the digestive tract. There are three types: mucosa, transmural (muscular), and subserous. We present the case of a 23-year-old male patient with a clinical picture of abdominal pain, nausea, chronic diarrhea, and ascites. Parasitic and other secondary etiologies were ruled out. Upper digestive endoscopy was not helpful. Colonoscopy revealed characteristics of inflammation in the distal ileum and ascending colon, the histological findings of which were consistent with eosinophilic colitis. The study of ascitic fluid was suggestive of eosinophilic ascites. The patient received induction treatment with prednisone 40 mg daily orally; remission was achieved after two weeks, and maintenance therapy based on prednisone was continued with the progressive withdrawal of the dose. Control of the disease was successful.

Keywords

Colitis, colonic eosinophilia, eosinophilic ascites, eosinophilic gastroenteritis.

INTRODUCTION

Eosinophilic colitis is a rare gastrointestinal pathology.[1] The classic concept of primary eosinophilic diseases of the digestive tract (EGID) is that they share a common factor: the infiltration of eosinophils into the mucosa without having a known cause of peripheral eosinophilia. Although the latter is not usually present in many cases (as in eosinophilic esophagitis or eosinophilic colitis), the symptoms are essential to suspect these pathologies.[2]

Since the first publication in Germany in 1937 by Kaijser on EGID,[3] isolated cases of these diseases have been presented in the literature, but currently, there are no clinical guidelines in this regard, particularly for eosinophilic colitis. The latter is a disease poorly studied and requires well-defined criteria for its diagnosis and treatment.

PRESENTATION OF THE CASE

The following is a case of eosinophilic colitis with coexisting ascites, diagnosed and treated in a private hospital in Lima, Peru. We received a 23-year-old male patient who had been ill for six months and reported a clinical profile characterized by oppressive heart-type abdominal pain in the epigastrium, which subsequently migrated to the mesogastrium, associated with nausea, general malaise, and loss

of appetite. After three months, liquid, mucus-free, bloodless, non-enteric stools began to appear approximately three to four times a day, only during daylight.

In our hospital, the first tests requested (on October 6, 2021) were the following: hemoglobin (13.7 g/dL), hematocrit (39%), leukocytes (8980 cell/μ L), eosinophils (38%), lymphocytes (15%), segmented neutrophils (40%), and platelets (208,000 cell/μL). From the main finding of peripheral eosinophilia, we began to look for etiologies, and the following results were obtained: *Toxoplasma gondii* immunoglobulin G (IgG) and M (IgM) negative, enzyme-linked immunosorbent assay (ELISA) for *Fasciola hepatica* negative, *Toxocara* IgG and IgM negative, immunoglobulin E (IgE) 67.3 IU/mL (normal), and antinuclear antibodies negative. The peripheral lamin described a red series of normal quantity and morphology, while the white series showed marked eosinophilia and normal morphology. The thrombocytic series resulted in a normal amount and morphology. Other outcomes were the following: lactate dehydrogenase (208 IU/L, normal), microglobulin β2 (1.33 mg/L, normal), HIV (negative), hepatitis A and B profile (negative), Epstein-Barr IgG and IgM (negative), cytomegalovirus (CMV) IgG and IgM (negative), antigenic test for severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) (negative), vitamin B_{12} (482.1 pg/mL, normal), total protein (5.66 g/dL), albumin (4.03 g/dL), C-reactive protein (CRP) (9.8 mg/dl), and glucose (105 mg/dL). The functional stool examination was diarrheal, without steatorrhea, starches, food remains, red blood cells, negative Thevenon test, and negative inflammatory reaction. Parasites in feces (six samples) were negative.

The treating clinicians decided to start the search for the gastrointestinal etiology of eosinophilia associated with gastrointestinal symptoms presented by the patient. First, he underwent an endoscopy in which moderate erythematous gastritis (histopathological examination: mild superficial chronic gastritis, without *Helicobacter pylori*, atrophy, or intestinal metaplasia) and nonspecific duodenitis (histopathological examination: mild chronic duodenitis with intraepithelial lymphocytes 8-10/100 epithelial cells, without typical findings of a specific disease) were found. Then, he underwent a colonoscopy that presented the following findings: in the distal ileum, from approximately 15 cm from the ileocecal valve to the distal, marked mucosa congestion was observed with "punched" erosions, punctate erythema, and loss of mucosal vascularization (**Figure 1**). On histopathological examination, moderate chronic ileitis was found with no specific findings. In the cecum, at the level of the ileocecal valve and proximal to the appendicular orifice, erythema of the mucosa and partial loss of mucosal vascularization were observed (**Figure 2**). There was a significant increase in eosinophils at the level of the lamina propria and crypts, which reached approximately > 200 eosinophils in a high-power field in the histopathological examination (**Figures 3** and **4**). This eosinophilic infiltrate was also accompanied by plasma cells, scarce lymphocytes, and cryptic abscesses, which are findings related to eosinophilic colitis.

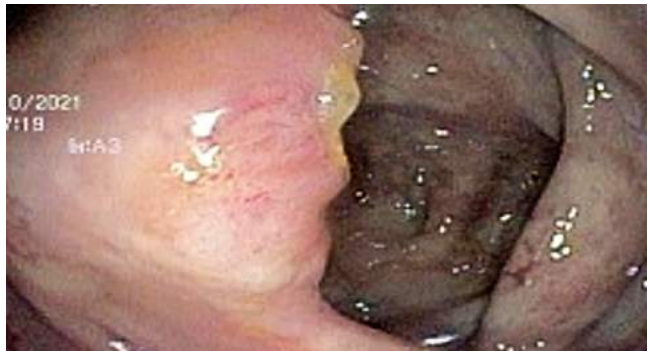

Figure 1. Distal ileum. Source: Gastroenterology Service of Clínica San Gabriel.

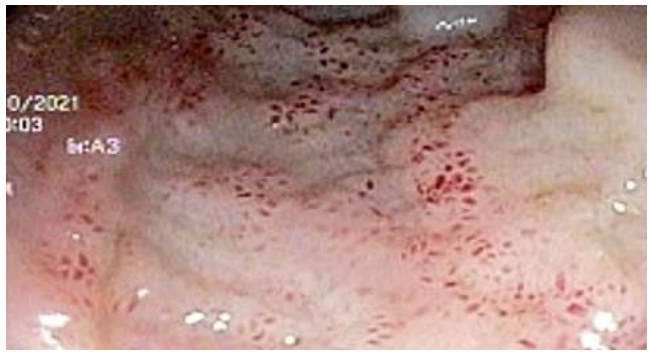

Figure 2. Cecum. Source: Gastroenterology Service of Clínica San Gabriel.

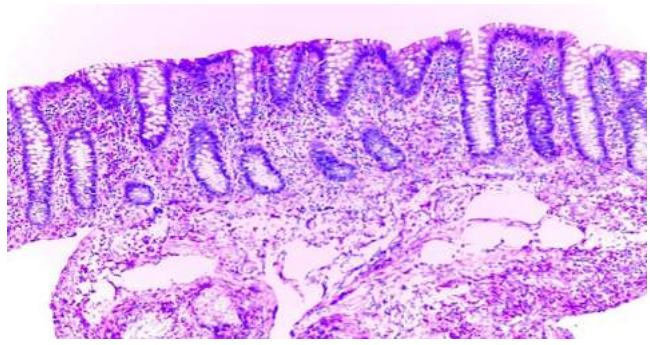

Figure 3. Biopsy of the cecum. Overview of the microscopic image. Numerous eosinophils surround the crypts. Source: Pathological Anatomy area of Clínica San Gabriel.

The patient underwent an abdominal ultrasound in which an abdominopelvic free fluid was observed, approximately 1150 mL, determined by the four quadrants: the

liver had its morphology preserved with no signs of cirrhosis, and the rest of the organs of the abdominal cavity were within normal parameters. Due to the not-so-abundant amount of ascitic fluid, it was decided to perform an abdominal paracentesis oriented under ultrasound guidance (by interventional radiology), in which turbid yellow fluid was obtained without any bad odor, from which approximately 120 mL were extracted for studies. The following were the rest of the results: ascitic fluid cytochemistry, cell count (3150 cell/UL), polymorphonuclear (90%), mononuclear (10%), Gram stain (negative), glucose (100 mg/dL), albumin (3.56 g/dL), serum-ascites albumin gradient (GASA) (1.18), culture (negative), and adenosine deaminase (ADA) (5.53 IU/L, normal).

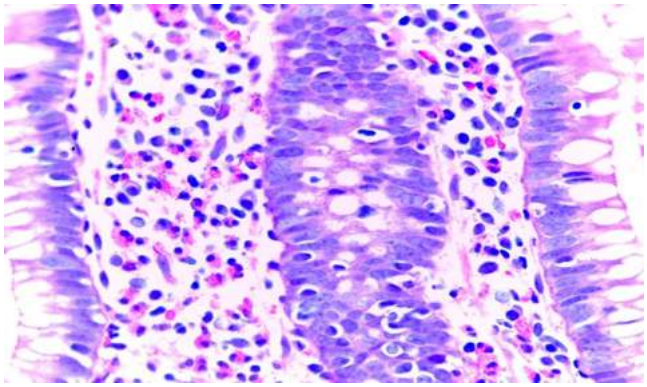

Figure 4. Cecum biopsy. It shows diffuse infiltration of eosinophils into the mucosa. Source: Pathological Anatomy area of Clínica San Gabriel.

With these findings, the diagnosis of subserous eosinophilic colitis was determined, so starting treatment with oral prednisone at doses of 40 mg per day for two weeks as induction therapy was decided. Blood count was monitored, and an improvement in symptoms and eosinophil count (successful clinical remission) was observed. Therefore, maintenance therapy was continued through progressive withdrawal of prednisone at a rate of 5 mg per week and reached up to 10 mg per day. The results were favorable (**Table 1**).

In the abdominal control ultrasound (15/12: after 30 days of maintenance therapy with prednisone), the liver of preserved morphology was observed, and there was no free fluid in the cavity. The rest of the organs had preserved characters.

DISCUSSION

Eosinophilic colitis is a gastrointestinal pathology that is part of the EGID group, along with eosinophilic esophagitis and eosinophilic gastroenteritis, which are defined by an excess count of eosinophils in the thickness of the wall of the gastrointestinal tract, without having an established secondary etiology. It is such a rare disease that, for example, in the United States, an overall prevalence of 2.1 per 100,000 people is reported, and it is more frequent in adults (1.6/100,000), unlike most EGIDs, which have an epidemiological inclination to pediatric populations. However, it is important to highlight that eosinophilic colitis has a bimodal pattern of

Table 1. Results of the patient's laboratory tests

	06/10	20/10	27/10 Initiation of induction therapy with prednisone	11/11 After 14 days of induction therapy	15/12 After 30 days of maintenance therapy
Hb (g/dL)	13,7	14,5	13,1	13,8	14,2
Hto (%)	39,3	40,1	37,2	40,6	41,9
Leu (cel/µL)	8980	11600	9710	10800	5300
Eos (%)	**38**	**41**	**43**	**2**	**4**
Eos (cel/µL)	**3430**	**4830**	**4590**	**160**	**220**
Lymph (%)	15		22	18	26
Seg (%)	40		30	73	59
CRP (mg/L)			9,8	0,49	0,7

Eos: eosinophils; Hb: hemoglobin; Hto: hematocrit; Leu: leukocytes; Lymph: lymphocytes; CRP: C-reactive protein; Seg: segmented. Source: Authors' own research.

presentation: first, in neonates and infants and then in adults. Due to its preponderance in urban and suburban areas, it may be related to high socioeconomic status or people with better levels of education.[4,5]

The clinical profile of EGIDs depends on the level of involvement of eosinophilia in the gastrointestinal tract wall. According to the Klein classification, there are three types: mucosa (57.5%), including nausea, vomiting, abdominal pain, digestive bleeding, diarrhea, and others; muscular (30%), including intestinal obstruction (presented even as recurrent sigmoid volvulus) and gastrointestinal motility disorders; and serous (12.5%), including ascites, meteorism, peritonitis.[6,7] Under this same criterion, we can say that the symptoms of eosinophilic colitis depend on the level of eosinophilic involvement, but they can co-occur in the same patient. Thus, in pediatric populations, there are clinical forms characterized by acute self-limited bloody diarrhea and, in adults, abdominal pain or chronic diarrhea, associated or not with the other symptoms described depending on the level of gastrointestinal involvement.[8] In another review, three types of disease that do not differ much from the previous ones are described: mucosal, transmural, and subserous (the latter, which is the reason for this publication, with ascites, the most benign and, in turn, the most infrequent of the three).[5]

The finding of ascites by ultrasound, with the results of the sample exposed above, gives the form of subserous presentation to this disease so rare in our setting. Similarly, there have been cases reported in the literature with the presentation of eosinophilic ascites associated with gastroenteritis or colitis, such as the one reported by Cuko et al.,[9] presenting a 37-year-old female patient whose leukocyte count in ascitic fluid was 8800, 94% polymorphonuclear (PMN), and with eosinophilic infiltrate in the duodenal mucosa. Likewise, in the case reported by Elsadeck,[10] a 41-year-old male patient was described with gastroenteritis and colitis associated with infiltration of eosinophils, plasma cells, and lymphocytes at the mucosal level, in addition to the characteristic findings of eosinophilic ascites. Finally, a case reported by Amado et al.[1] describes a 55-year-old woman presenting with subserous eosinophilic colitis potentially triggered by an herbaceous product (they do not describe it as an etiology of colitis).

To diagnose this disease, it is important to know its differential diseases, listed in **Table 2**, including some drugs such as gabapentin and pregabalin.[11] It is relevant to note that eosinophilic colitis can mask colon adenocarcinoma, such as in the case reported by Milne et al.,[12] or also be associated with another pathology such as Crohn's disease (*overlap*), as in the case described by Katsanos et al.[13] It is relevant to know that biopsies are important for the diagnosis of eosinophilic colitis. However, it is essential to differentiate it from the so-called *colonic eosinophilia* since, in the first one, the inflammatory infiltrate consists almost exclusively of eosinophils, unlike the second, in which there is a mixed inflammatory infiltrate and, generally, there is a known cause, such as allergies, drugs, inflammatory bowel disease, or infections, among others.[14] In fact, the study conducted by Arévalo et al.[15] found that, of 68 patients diagnosed with lymphocytic colitis (a subtype of microscopic colitis), there was a coexistence of 76.5% of elevated eosinophils in the colonic mucosa. The same study found that 51.4% of patients were diagnosed with eosinophilic colitis but only with biopsy, as the exclusion of other possible etiologies of eosinophilia is not described.

Table 2. Eosinophilic colitis: differential diagnoses[2]

Parasitic colitis
Eosinophilic gastroenteritis
Hypereosinophilic syndrome
Inflammatory bowel disease
Drug-induced colitis: - Nonsteroidal anti-inflammatory drugs - Rifampicin - Clozapine - Tacrolimus - Gold salts
Allogeneic bone marrow transplant
Other: Toulouse-Hunt syndrome, vasculitis (e.g., Churg-Strauss syndrome)
Acute radiation colitis

Taken from: Alfadda AA et al. Therap Adv Gastroenterol. 2011;4(5):301-9.

Endoscopic findings in patients with eosinophilic colitis are nonspecific. In fact, they may have a normal appearance in up to 70% of cases, so there may be overlap with diarrhea predominant-irritable bowel syndrome (IBS-D), as described by the study by Carmona-Sánchez et al.,[16] which found a prevalence of 4.7% of patients with eosinophilic colitis who had also been diagnosed as IBS-D. Other common manifestations include erythema, edema, decreased mucosal vascularization, erosions, and ulcers. Regarding the location of the lesions, they can be found more frequently in the right and left colon and as pancolitis in up to 11% of cases.[6] In our case, there were findings both in the distal ileum ("in punch" erosions, erythema, loss of mucosal vascularization) and in the cecum (erythema and loss of mucosal vascularization). In the other colon segments, there may have been the eosinophil counts necessary to diagnose eosinophilic colitis. However, the required samples were not obtained.

As already described above, a biopsy is essential. Nevertheless, eosinophils represent a normal component of inflammatory cells in the colon. Only they can vary in number in different colon segments, as they can also be part of the inflammatory infiltrate in various colon diseases.[17] Eosinophilic density is usually estimated semiquantitatively and requires counting the number of eosinophils by high-power fields (HPF) and the mean count. This density is not yet clearly established to determine the diagnosis of eosinophilic colitis. However, some options have been proposed, such as more than 60 (or even 100) eosinophils/HPF, usually observed in the cecum[18,19] or more than 40 eosinophils/HPF in at least two different segments of the colon.[6] The finding was more than 200 eosinophils/HPF in our case. The other findings that can be found in histology are mentioned in **Table 3**.

Table 3. Microscopic findings in eosinophilic colitis[6]

Histological characteristics	Prevalence in eosinophilic colitis
Inflammatory mucosal infiltrate	100
Intraepithelial eosinophils	77
Eosinophilic degranulation	51
Architectural distortion	42
Acute inflammation	26
Mucosal atrophy	23
Eosinophilic microabscesses	21

Taken from: Macaigne G. Clin Res Hepatol Gastroenterol. 2020;44(5):630-637

Treating this disease is sometimes difficult, and no international guidelines define it. However, it has been reported that an improvement in gastrointestinal symptoms is observed with corticosteroids, mainly prednisone. Thus, its use in doses of 1-2 mg/kg/day orally for eight weeks with its progressive withdrawal (induction and maintenance therapies) has achieved effectiveness between 80% and 100% of cases.[6,20] Clinical remission has also been achieved by induction therapy with oral prednisone (20-40 mg per day) for two weeks and subsequent maintenance therapy with progressive dose withdrawal, up to 5 mg daily.[5] This last scheme was the one indicated in the patient and caused him to have remission of symptoms, as well as the normalization of eosinophilia after two weeks of induction with prednisone at 40 mg daily and later with progressive withdrawal, achieving a normal eosinophil count again at four weeks and absence of ascites. Furthermore, this form of treatment was indicated in some cases, such as the one described by Yep Gamarra et al.,[21] which had a presentation of gastroenteritis with ascites, in that of Sánchez et al.,[22] and as in the case presented by Páramo-Zunzunegui et al.,[23] all with successful clinical remission.

In addition, there are other treatment schemes, such as the role of a hypoallergenic diet (even determined as a first therapeutic measure), anti-inflammatory agents such as mesalazine, immunomodulators such as azathioprine and antitumor necrosis factor (anti-TNF; infliximab and adalimumab) in refractory or steroid-dependent cases, and montelukast, among others.[8,24]

CONCLUSIONS

After having made a detailed description of our clinical case of subserous eosinophilic colitis, we can say that this is an uncommon disease and that management guidelines on this pathology are still pending. When a patient has eosinophilia associated with gastrointestinal symptoms, an exhaustive search should be carried out to rule out secondary etiologies and accurately diagnose eosinophilic colitis. Corticosteroids such as prednisone are important because they mitigate gastrointestinal symptoms and improve laboratory and imaging parameters.

Acknowledgments

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Case report

Congenital Paraduodenal Hernia: A Case Report

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Abstract

Paraduodenal hernia is a rare congenital anomaly that arises from an alteration in the midgut rotation during embryogenesis. Consequently, the small intestine becomes trapped in a sac of the posterior mesentery of the colon. This entity can compromise the intestinal segment's viability and the patient's life. Its diagnosis is difficult, rarely suspected, and often confused with other causes of abdominal pain. We present the case of a 29-year-old male patient with a documented paraduodenal hernia during surgery, its correction, and follow-up, in which no complications were reported.

Keywords

Abdominal hernia, small intestine, acute abdomen, surgical procedures.

INTRODUCTION

Paraduodenal hernia (PH) is an alteration that is part of congenital hernias. It is a rare condition, usually diagnosed during surgery.[1]

There are multiple types of congenital internal hernias. In order of frequency of appearance, there are the PH, pericecal, foramen Winslow, transmesenteric, perivesical, and omental hernias.[1] Internal hernias cause 1% of intestinal obstructions; within these, PH contributes 53%. It is more frequent in men than women, with an incidence of 3 to 1.

Despite its congenital nature, the complications that lead to its diagnosis occur between the third and fourth decades of life.[2] The risk of developing intestinal obstruction or perforation is 50% over a lifetime, with a mortality of 20% to 50%.[3-5] PH can be left-sided (75%) or right-sided (25%) and occur due to alterations in bowel rotation or poor fusion of mesenteric folds during embryogenesis.[1,3]

PRESENTATION OF THE CASE

This is a 29-year-old male patient with no medical or surgical history. He was admitted to the emergency department due to a 24-hour clinical profile of abdominal pain of sudden onset, colic type, located in the mesogastrium and left flank, accompanied by abdominal distension and emesis, radiating to the left paravertebral region and the left iliac fossa. Physical examination documented sinus tachycardia, distended abdomen, and pronounced deep palpation pain in the left hemiabdomen, with no signs of peritoneal irritation. Paraclinical studies showed leukocytosis (15,000 cells/µL), neutrophilia (12,750 cells/µL), and elevated

C-reactive protein (16 mg/dL). Initially, it was suspected to be urolithiasis with obstructive effect. The patient underwent a simple computerized tomography urogram (uroCT), which showed a conglomerate of intestinal loops located towards the left hemiabdomen with diffuse intestinal edema and scarce fluid between the loops (**Figure 1**).

They requested an assessment by our general surgery group. At the time of assessment, we found signs of peritoneal irritation in the patient, so he was scheduled immediately for surgery. Initially, he underwent a laparoscopic approach that showed great distension of the intestinal loops, so we decided to convert to open surgery, and we performed a median supra- and infraumbilical laparotomy. When we explored the abdominal cavity, we detected a left PH containing 2 meters of proximal small intestine within the hernial sac, proximal dilation to the site of obstruction, and the hiatus of entry to the sac with ischemia of the entire segment of the involved intestine. We proceeded to section the peritoneal fibrotic tissue capsule and reduced the content, restoring arterial flow and recovering the involved segment's viability. Subsequently, the capsule and the hernial sac were resected entirely. Finally, we verified that there was no hiatus in the abdominal cavity to avoid the risk of recurrence (**Figures 2**, **3,** and **4**). The patient evolved without eventualities and was discharged on the fourth postoperative day.

DISCUSSION

Embryologically, the intestine has been divided into foregut, midgut, and hindgut. PH occurs when there is an alteration in any part of the midgut formation, defined as all intestinal portions irrigated by the superior mesenteric artery (SMA), including the distal duodenum, jejunum, ileum, ascending colon, and proximal transverse colon.[3] Consequently, the embryonic development of the midgut is divided into two portions: prearterial and postarterial. The prearterial portion extends from the distal duodenum to the omphalomesenteric duct, while the postarterial portion begins distal to the omphalomesenteric duct to the proximal transverse colon. During the fifth week of gestation, the midgut is carried into the yolk sac, then rotates 90° counterclockwise on the axis of the SMA and returns to the abdominal cavity in the tenth week of gestation. At that time, said cavity is large enough to house this intestinal segment. The prearterial portion is on the right of the SMA, and the post-arterial portion is on the left. It presents a second rotation of 180° counterclockwise for a total of 270° and, finally, reaches its anatomical position. If this does not happen, a phenomenon of poor intestinal turnover occurs.[6]

PH occurs when there is some failure in the rotation of the prearterial portion of the small intestine when interposing in the fusion of the colon (postarterial) with the

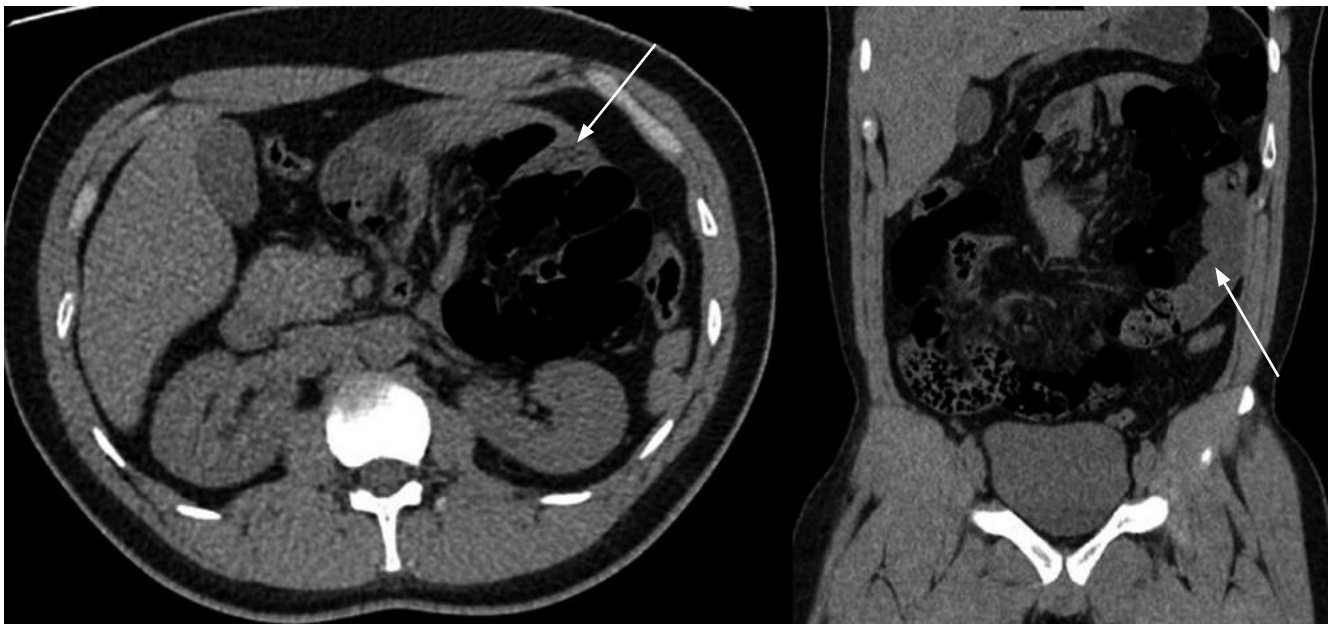

Figure 1. UroCT shows an axial and coronal section, respectively. The arrows point to the conglomerate of intestinal loops in the left hemiabdomen. Source: Authors' archive.

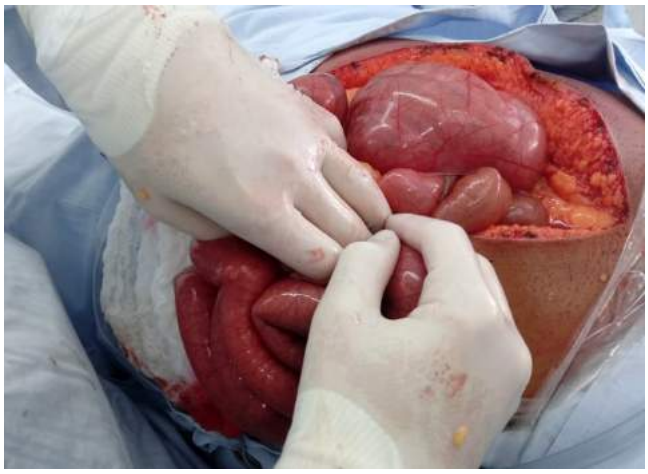

Figure 2. Laparotomy shows the hernial sac created by the retroperitoneal peritoneum of the Landzert fossa. Source: Authors' archive.

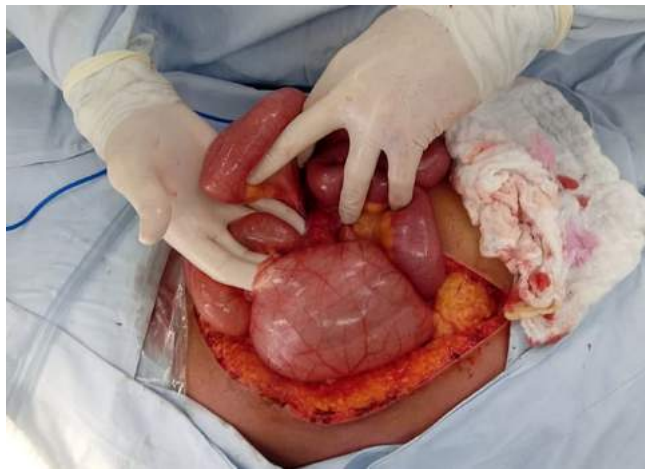

Figure 3. Surgeon's finger passes through the hiatus of the Landzert fossa, where intestinal loops come out. Source: Authors' archive.

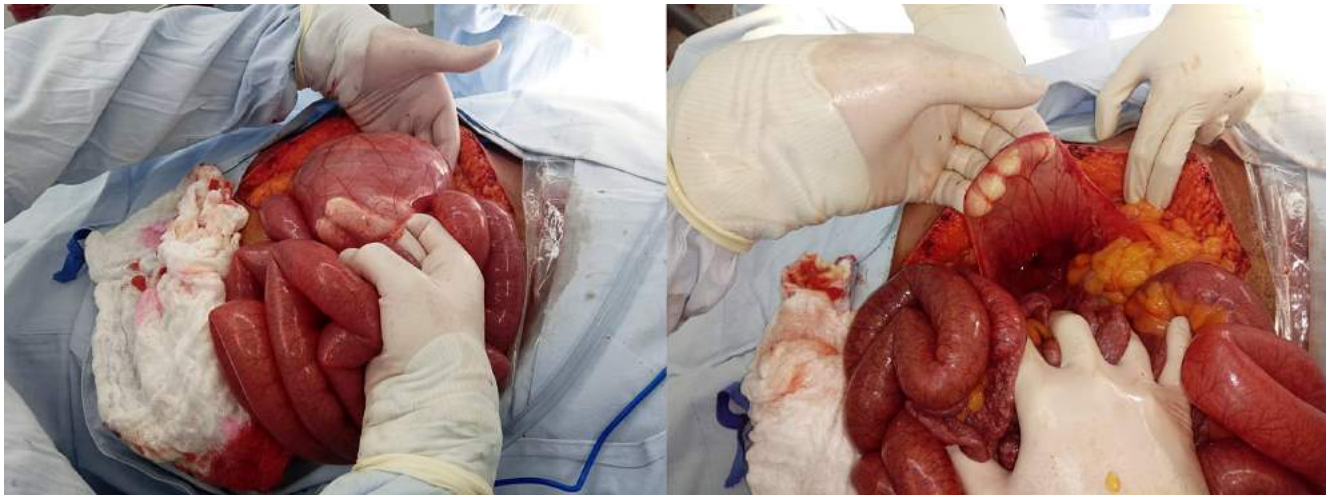

Figure 4. Hernial sac, before and after resection. Source: Authors' archive.

retroperitoneum, which creates the fosses where the hernia occurs: the Landzert fossa to the left of the SMA, with 75% frequency, and the Waldeyer fossa on the right side, with a 25% frequency.[3,7,8]

Concerning the clinical presentation, symptoms begin between the third and fourth decades of life (38.5 years of age on average).[9] 50% of patients present mild cramping abdominal pain, chronic, mainly postprandial, and exacerbated by Valsalva maneuvers with periods of complete remission. It can produce recurrent episodes of nausea, vomiting, chronic malabsorption, and weight loss. These symptoms usually change in characteristics or improve with changes in position. Patients present mild manifestations such as dyspepsia when the hernia is small and shrinks spontaneously. The other 50% of cases present acute abdomen due to sudden intestinal obstruction that can produce massive ischemia of the small intestine, especially when more than 40% of the intestine is involved.[1,3-5]

Physical examination showed no typical clinical signs: less than 20% of patients have a left upper quadrant mass with pain that varies according to the degree of incarceration and intestinal ischemia. In the reported case, the clinical presentation was complete intestinal obstruction with no prior symptoms.

Many PH cases are diagnosed incidentally on imaging, laparotomy, or autopsy.[2,5,9] Simple radiographic studies are not very specific, showing signs of intestinal obstruction with a conglomeration of intestinal loops towards the left side of the upper abdomen.[3] Contrasting studies such as tomography document a mass of regular, smooth edges with loops of small intestine encapsulated in the upper hemiabdomen, described as Donnelly's border. Additionally, anomalies can be seen in the mesenteric vessels consisting of their congestion, crowding, twisting, and stretching.[4,5,10]

If the PH is left-sided, we can observe a group of intestinal loops delimited by the pancreas, stomach, and ascending portion of the duodenum, to the left of the ligament of Treitz, behind the pancreatic tail, which displaces the inferior mesenteric vein to the left or between the transverse colon and the left adrenal gland. When the PH is right-sided, the accumulation of loops is located inferolateral to the descending portion of the duodenum, and we can observe an afferent loop of the jejunum and an efferent loop of the jejunum or ileus through the entrance hole of the Waldeyer's fossa.[3,5] The sensitivity and specificity of tomography are approximately 63% and 76%, respectively.[11] Diagnostic laparoscopy can be very useful in cases where the diagnosis cannot be verified with images.[2]

The treatment of these patients must comply with the fundamental principles of reducing the herniated intestine, verifying its viability, and repairing the hernial defect.[9] Surgery is always indicated, even in asymptomatic patients with incidental diagnosis, since PH has a 50% risk of incarceration throughout life.[6] Special care should be taken when opening the anterior sac since important vessels usually pass through it. In the case of a left-sided PH, it can pass the inferior mesenteric vein and the inferior mesenteric artery or the ascending branch of the left colic. In the case of a right-sided one, it can pass the middle colic artery with its right branch and the superior mesenteric vessels.[3,8]

In a left-sided PH, it is ideal to simply reduce the hernial contents and close the Landzert fossa with a non-absorbable suture. However, there are cases where it is impossible to perform it due to the pressure exerted by the intestines on the edge of the defect, so a herniotomy is necessary to release the intestine. At this point, the vascular care mentioned above is fundamental.[3] In our case, manual reduction of the hernial contents was not possible, and it was necessary to perform an anterior herniotomy with ligation of the inferior mesenteric vein to avoid uncontrolled bleeding. In this way, the ischemic intestine could be released, and secondary transmural necrosis could be avoided. The laparoscopic approach is safe and effective when performed electively. However, we decided to perform an open technique due to the patient's condition.

CONCLUSIONS

Congenital hernias are rare. Within this group, the PH is the most common; in turn, the left-sided PH is the one with the greatest frequency of appearance. Knowing this condition is essential to suspect it and be able to diagnose it. Depending on the patient's condition, treatment is always surgical, either open or laparoscopic.

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Case report

Recurrence in Patients with Epiploic Appendagitis: A Case Report

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Abstract

Epiploic appendagitis is a rare cause of acute abdominal pain. Management is self-limiting; however, some require surgical intervention. This case describes a 41-year-old female patient admitted to the emergency service for a clinical picture of an acute abdomen. On physical examination, the abdomen was soft, depressible, and painful on palpation in the left upper quadrant. A computerized axial tomography (CT) was requested, which revealed a hypodense oval image with a hyperdense center compatible with epiploic appendagitis. The patient received conservative therapy and was then discharged. Seven months later, the patient returned for an acute abdominal condition; complementary tests were negative, and she was treated again with conservative therapy. For 12 months, the patient has not relapsed. This case describes the recurrences in this rare pathology and the treatment that should be evaluated to avoid these relapses.

Keywords

Abdominal pain, recurrence, case reports (DeCS/BIREME).

INTRODUCTION

The epiploic appendages are anatomical structures that arise from peritoneal extensions. From 50 and 100 epiploic appendages originate in two rows (anterior and posterior) parallel to the external surface of the three longitudinal muscle bands of the large intestine.[1] As Sand et al. state, the epiploic appendix was first described in 1543 by Vesalius. However, it did not have clinical significance until 1853, when Virchow suggested that the detachment of the epiploic appendages could be the source of intraperitoneal bodies.[2] The term *epiploic appendagitis* (EA) was first described by Lynn in 1956, while the radiological features were defined by Danielson in 1986.[3-5] Epiploic appendagitis is a rare cause of acute abdominal pain and misdiagnosis resulting from inflammation, torsion, or infarction of the vascular pedicle of an epiploic appendix.[6] It appears as acute abdominal pain, which may be accompanied by fever, nausea, and vomiting, among others. The incidence of EA is 8.8 per million people[7] and is misdiagnosed in medical practice due to the lack of pathognomonic clinical features.[8] Treatment is usually self-limiting in most cases; however, this pathology can sometimes recidivate.

CASE REPORT

This is a 41-year-old female patient who first went to the emergency service on October 14, 2020, after two days

of intense pain in the left hemiabdomen of colic type and intensity 8/10 that did not expand to another area. In addition, twelve hours earlier, she reported nausea and general malaise. As part of her history, she manifested having had a transverse segmental cesarean section. At admission, the patient was awake, with vital signs within normal values (blood pressure [BP]: 120/70 mm Hg, respiratory rate [RF]: 20 breaths per minute [rpm], heart rate [HR]: 78 beats per minute [bpm], oxygen saturation [$SatO_2$]: 96% and afebrile). A physical examination of the digestive system revealed a soft, depressible abdomen with diminished hydro-air sounds and palpation pain in the hypochondrium and left flank. Laboratory tests revealed mild anemia (hemoglobin 9.3 g/dL).

The patient underwent an abdominopelvic computed tomography (CT) with contrast material, which evidenced that the liver, pancreas, spleen, and intestinal loops did not have any significant alteration, the stomach was partially distended with preserved walls and with a hypodense image of the oval fat density of 25 mm x 16 mm that contacts the anterior border of the descending colon, which contains inside a hyperdense image (the sign of the central point) compatible with EA (**Figures 1**, **2** and **3**). She started her medical treatment for pain with diclofenac 75 mg intramuscularly every twelve hours, paracetamol 500 mg orally in only one dose, metronidazole 500 mg orally every eight hours, and simethicone (gaseovet) 15 drops every eight hours. She was indicated to have a soft low-fat diet. The patient was discharged after two days on the following medications: paracetamol 500 mg (10 tablets), tramadol 50 mg (4 tablets), metronidazole 500 mg (9 tablets), and metoclopramide 10 mg (9 tablets).

Seven months later, the patient went to the emergency department again due to a clinical picture of acute abdomen. Her examinations showed an elevation of leukocytes and neutrophilia. Meanwhile, all other laboratory tests were within normal limits. Abdominopelvic CT showed inflammation of the epiploic appendages in the left colonic framework. She underwent symptomatic treatment with diclofenac 75 mg intramuscularly every 12 hours and paracetamol 500 mg orally once a day.

DISCUSSION

Anatomically, the epiploic appendix is a formation resulting from the duplication of the visceral peritoneum that surrounds the colon and covers a variable amount of pedunculated fat attached by a more or less narrow base to the external surface of the colonic wall. Most appendages are 1 to 2 cm thick and 2 to 5 cm long.[6] Inflammation of the epiploic appendix is known as *epiploic appendagitis*, which occurs due to a twisting of the epiploic appendages that leads to ischemia that subsequently becomes necrosis.[9] It is often a misdiagnosed disease that must be present within the differential diagnosis of an acute abdomen, which commonly resembles acute appendicitis, diverticu-

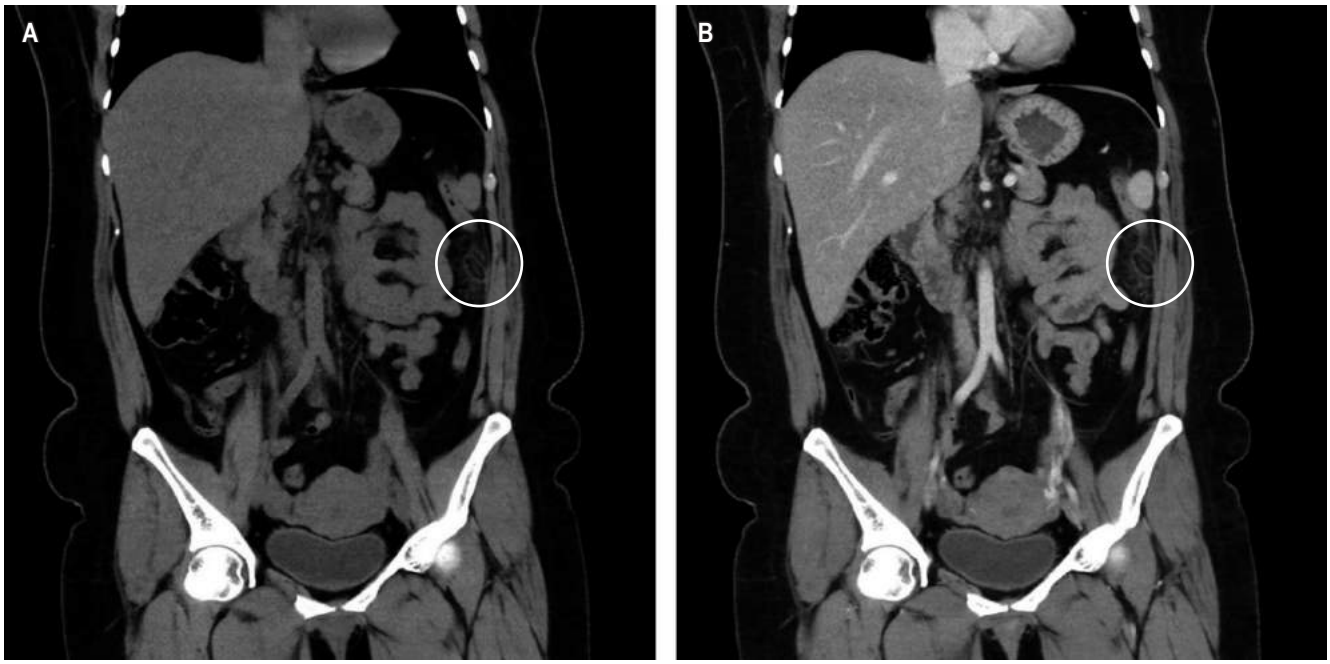

Figura 1. A. Appendagitis, coronal court S/C. **B.** Appendagitis, coronal court C/C. Source: Authors' archive.

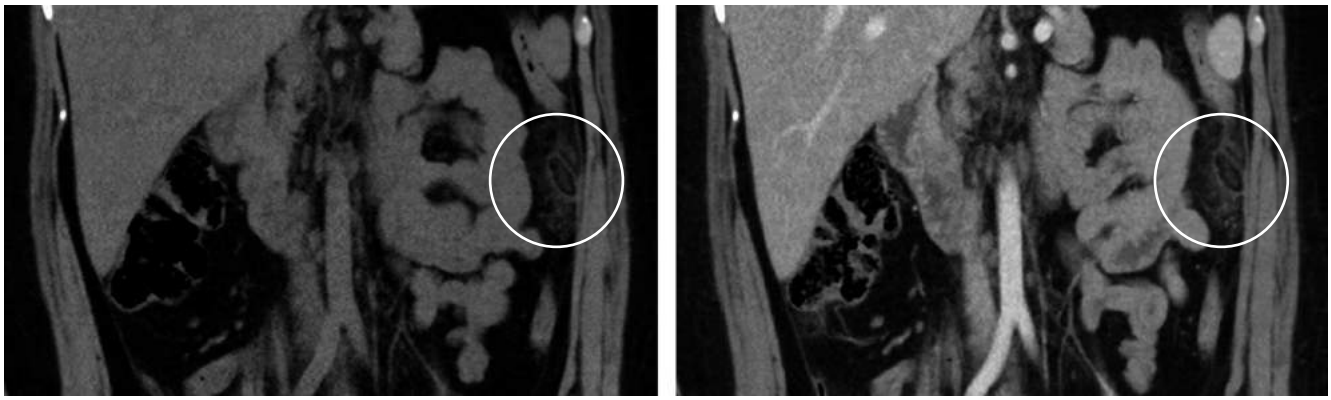

Figure 2. Hypodense image (circumscribed by a white circle) of fat density, oval, which contains a hyperdense image (the sign of the central point) inside compatible with epiploic appendagitis. Source: Authors' archive

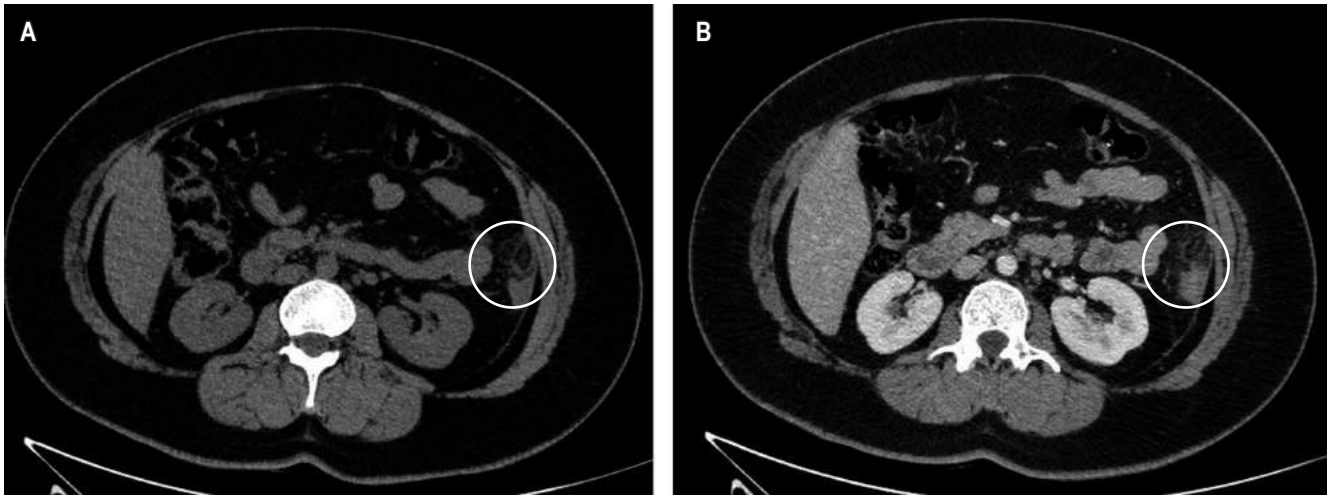

Figure 3. A. Appendagitis, horizontal cut S/C. **B.** Appendagitis, horizontal cut C/C. Source: Authors' archive.

litis, pelvic inflammatory disease, and ectopic pregnancy, among others.[9,10]

EA commonly begins with pain in the lower left quadrant (40%-60%), pain in the right lower quadrant (40%-50%), and pain in other locations, including the upper right and left quadrants (1.5%-10%).[11] An increase in white blood cells can hardly be found, so the possibility of laboratory aid, including their symptomatological nonspecificity, is dismissed, leading physicians to an incorrect diagnosis. Therefore, the chosen study is CT, and only 2.5% are diagnosed with the symptoms before surgery since normal epiploic appendages are not evident on CT but can be detected when inflamed or delineated by ascites.[12] Key features in CT include an ovoid lesion of fat density, also known as the *hyperattenuating ring sign*, mild thickening of the intestinal wall, and a central focus of high attenuation within the fat lesion that in recent studies has been described as *the central point sign*.[12]

EA is usually self-limited following conservative therapy. However, some cases need surgical management. Reports mention that some discharged patients have relapses, forcing them to go to the emergency room again.[13] Therefore, we conducted a systematic search in PubMed, Scopus, Scielo, CINAHL, BVS LILACS, Google Scholar, and articles related to the topic in English and Spanish, with the search terms "Epiploic appendagitis" and "Recurrence" or "Relapse", and we found eleven articles that met the terms of "recaída" and "relapso" in Spanish within the full text, whose characteristics are detailed in **Table 1**. Only seven patients out of 278 had a recurrence, which means 2.6% relapses. We consider it a small percentage. Relapses are not as common in these patients. However, there are

Table 1. Characteristics of included studies of patients with EA

Author	Country	Type of article	Number of patients included	Sex M/F	Age (SD)	Symptoms/ signs	Comorbidities (number of patients)	Diagnosis	Treatment	Recurrence time
Choi[16]	Korea	Observational, retrospective	56	23/33	45.4 (15.1)	Abdominal pain	Obesity (30)	CT	Conservative therapy, antibiotics	One patient recurred five years later.
Dogan[17]	Turkey	Observational, retrospective	39	34/5	36 (10.3)	Abdominal and groinal/ low back pain, nausea, vomiting, abdominal swelling, and dysuria	Does not report	CT	Analgesic therapy and antibiotics	No patient in one year of follow-up
García[18]	Spain	Observational, retrospective	17	3/14	57	Abdominal pain	Does not report	CT	Conservative therapy	One patient had an uncomplicated recurrence.
Hasbah-ceci[19]	Turkey	Observational, retrospective	20	13/7	43.2	Acute abdominal pain	Does not report	CT	Conservative therapy	No recurrence at 24 months of follow-up
Legome[20]	United States	Observational, retrospective	19	10/9	37.8 (10.4)	Abdominal pain, constipation (10%), diarrhea (10%), and fever (15%)	Does not report	CT	Antibiotic therapy	One patient recurred at two years of follow-up.
Lorente[13]	United States	Case report	1	0/1	66	Abdominal pain	Hypertension, hyperlipidemia, hypothyroidism, and cardiomyopathy	CT	Conservative therapy	Recurrence after nineteen months
Manto-glu[21]	Turkey	Observational, retrospective	39	29/10	44.4 (13.2)	Does not report	Does not report	CT	Conservative therapy	One female patient recurred after six months. Two male patients recurred at two and twelve months. 3-year follow-up
Ozdemir[4]	Turkey	Case series	12	9/3	40	Abdominal pain, nausea, and vomiting	Does not report	Ultrasonography and abdominal CT	Surgical and conservative therapy	Non-recurrence
Váz-quez[22]	Argentina	Observational, retrospective	73	54/19	45 (16)	Abdominal pain	Food transgression (7), overweight (26)	Ultrasound, CT scan	Conservative therapy and surgical therapy	Non-recurrence
Yang[23]	China	Case report	1	1/0	44	Abdominal pain	Does not report	CT scan with contrast	Not treated	Non-recurrence
Yousaf[24]	Pakistan	Case report	1	1/0	26	Abdominal pain	Does not report	CT	Conservative therapy	Non-recurrence

SD: standard deviation

currently minimally invasive techniques, such as laparoscopic surgery, which could help when there is a failure in conservative therapy, or an emergency intervention is needed. In that case, laparoscopic surgery shows better results.[14,15]

CONCLUSIONS

Relapses in patients with EA are uncommon. However, more studies are needed to evaluate this outcome in this condition. On the one hand, patients are treated conservatively with analgesics, but there are reports of cases treated surgically that would prevent a recurrence. For this, it is also necessary to evaluate the efficacy of new surgical therapies to resolve this pathology. On the other hand, it is fundamental to keep this pathology in mind within the differential profile of the acute abdomen due to its similarity to various diseases.

Authors' Contributions

Fabian A. Chavez-Ecos had the original idea, drafted, searched, and reviewed the final version. Mia Alejandra Gómez-Corrales wrote, extracted data, and reviewed the final version. Jackeline Alexandra Espinoza-Utani wrote, extracted data, and reviewed the final version. Carlos Alberto Dávila-Hernández wrote and reviewed the final version.

Conflicts of Interests

We declare that we do have no conflict of interest.

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Case report

Mixed Adenoneuroendocrine Carcinoma in the Ampulla of Vater: Case Report

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Abstract

A mixed non-neuroendocrine neuroendocrine neoplasm is a mixed neoplasm with a neuroendocrine component combined with a non-neuroendocrine component. It has a low incidence and limited studies, but with evidence of being an aggressive entity associated with poor survival. We present the case of a 58-year-old woman admitted with clinical symptoms of abdominal pain in the left hypochondrium associated with generalized jaundice and feverish spikes with an imaging diagnosis of bile duct dilation secondary to distal choledocholithiasis. Endoscopic retrograde cholangiopancreatography (ERCP) was performed, finding a significant papilla with a neoplastic appearance, which was biopsied and histopathologically analyzed. The diagnosis of mixed carcinoma with a component of high-grade poorly differentiated neuroendocrine carcinoma and a component of mucinous carcinoma was confirmed. Therefore, we decided to schedule a pancreaticoduodenectomy.

Keywords

Adenoneuroendocrine carcinoma, ampulla of Vater, MINEN, MANEC.

INTRODUCTION

Mixed neoplasms were first described in 1924 by Cordier as neoplasms in the gastrointestinal tract with two components: one neuroendocrine and the other adenocarcinoma.[(1)] In 1967, Levine proposed differentiating this neoplastic entity as independent of other neuroendocrine neoplasms.[(1)] Since then, multiple terms have been used for this diagnosis, such as mixed glandular-neuroendocrine compound carcinoma, carcinoid compound adenocarcinoma, mucin-producing carcinoid, and ex-goblet cell carcinoid adenocarcinoma, among others,[(2)] which leads to inconsistencies in the published data on this pathology.[(3)]

In 2000, Capella et al. first proposed the standardization of terminology to properly classify mixed neoplasms of the digestive tract.[(1)] In 2010, the World Health Organization (WHO) classified mixed neoplasms of the gastroenteropancreatic tract that contain a neuroendocrine and an exocrine component, and each of them must represent at least 30% of the neoplastic mass.[(4)]

The term mixed exocrine-endocrine neoplasia was subsequently replaced by mixed adenoneuroendocrine neoplasia (MANEC), a rare pathology composed of a group of neuroendocrine and exocrine neoplastic cells. However, it is believed that the term MiNEN (mixed neuroendocrine non-neuroendocrine neoplasms), proposed in 2016 by La

Rosa et al., better addresses the heterogeneous spectrum of possible combinations between neuroendocrine and non-neuroendocrine elements and the variability of morphologies, which are largely determined by the site of origin.[1] In 2019, the WHO established that mixed neuroendocrine neoplasms (TEN) are grouped in the conceptual category of MiNEN.[5]

Epidemiologically, the incidence of MiNEN is less than 0.01/100,000 cases per year. The rarity of this diagnosis, the limited quality of the published data, the use of inconsistent terminology, and the epidemiology of the treatment of patients with MiNEN remain nonspecific.[6,7] Nevertheless, according to the available evidence, this neoplasm is an aggressive element with a high-grade neuroendocrine component in most cases and is associated with poor survival outcomes, close to those of pure neuroendocrine carcinomas.[8]

The pathogenesis of MiNEN represents a topic of debate between pathologists and clinicians, in which three main theories have been proposed: the first theory suggests that neuroendocrine and non-neuroendocrine components arise independently, synchronously, from distinct precursor cells and fuse subsequently; the second states that the two components derive from a pluripotent progenitor, which acquires a biphenotypic differentiation during carcinogenesis; and a third theory assumes a common monoclonal origin of the two components, but neuroendocrine differentiation occurs in a non-neuroendocrine phenotype after the accumulation of molecular aberrations.[9,10] This last theory is based on the fact that non-neuroendocrine neoplasms in the gastrointestinal tract are generally located superficially close to the mucosa, while neuroendocrine neoplasms are located in a deeper area.[10]

Several studies have attempted to characterize the major genetic and epigenetic aberrations underlying MiNEN, with mutations in tumor-associated genes, including TP53, BRAF, and KRAS, and microsatellite instability emerging as potential triggers for MiNEs. However, to date, they are not clearly established yet.[10]

CLINICAL CASE

This is a 58-year-old woman with a history of hypertension and diabetes mellitus who does not require insulin and who consulted after 20 days of abdominal pain in the left hypochondrium, stabbing type, that expanded to the epigastrium with an intensity 6/10 on the analogous scale of pain associated with generalized jaundiced dye, acolia, choluria, and febrile peaks quantified up to 39 ºC. She underwent some laboratory studies that evidenced hyperbilirubinemia at the expense of direct bilirubin and elevated transaminases. The ultrasound showed hepatic steatosis, the gallbladder without stones inside associated with dilated intra- and extrahepatic bile duct with a common bile duct of 12 mm but did not show the cause of the obstruction. She also underwent a computed tomography (CT) scan and magnetic resonance cholangiopancreatography (**Figure 1**), which showed dilation of the bile duct secondary to distal choledocholithiasis, and it was decided to take her to endoscopic retrograde cholangiopancreatography (ERCP) to perform the management of obstructive biliary syndrome that had a probable biliary origin. However, a large papilla of neoplastic appearance of 3 centimeters at its greatest diameter was found without canalizing the bile duct. The patient underwent a biopsy and magnetic resonance imaging with double contrast (**Figure 2**) that reported choledocholithiasis, dilatation of the intra- and extrahepatic bile duct, and dilation of the intrapancreatic duct due to probable periampullary neoplasia.

The biopsy showed a villous adenoma with low-grade dysplasia. When no clinical-pathological correlation was obtained, the treating service proceeded to perform surgical treatment, and due to intraoperative findings of the bile duct, they decided to perform a biliopancreatic diversion plus pancreatectomy proximal to the open route. When performing the microscopic study, a mixed neoplasm characterized by a neuroendocrine carcinoma, a mucinous adenocarcinoma, and a villous adenoma with low-grade dysplasia were observed, the latter as a possible precursor of mucinous adenocarcinoma (**Figure 3**).

The patient underwent an immunohistochemical study in which they observed a positive marking in neoplastic cells of neuroendocrine carcinoma for chromogranin A, synaptophysin, cytokeratin 7, cytokeratin 17, thyroid transcription factor 1 (TTF-1), a proliferation rate of 98%; negativity for cytokeratin 20, homeobox caudal protein 2 (CDX2), and human epidermal growth factor receptor 2 (HER2) grade 0. Additionally, positivity was shown in mucinous carcinoma cells for cytokeratin 7 and a cell proliferation rate of 90%, and negativity for chromogranin A, synaptophysin, cytokeratin 20, TTF1, CDX2, and HER2 grade 0 (**Figures 4** and **5**). Microsatellite instability markers are preserved. These findings confirm high-grade neuroendocrine carcinoma associated with a component of mucinous carcinoma.

DISCUSSION

Mixed adenoneuroendocrine carcinomas (MiNEN) are biphasic carcinomas consisting of glandular epithelium and neuroendocrine cells. According to what the WHO stated in 2019, its denomination requires that each component represents at least 30% of the constitution of the carcinoma.[4,5] It is a rare neoplasm, and the cases in the

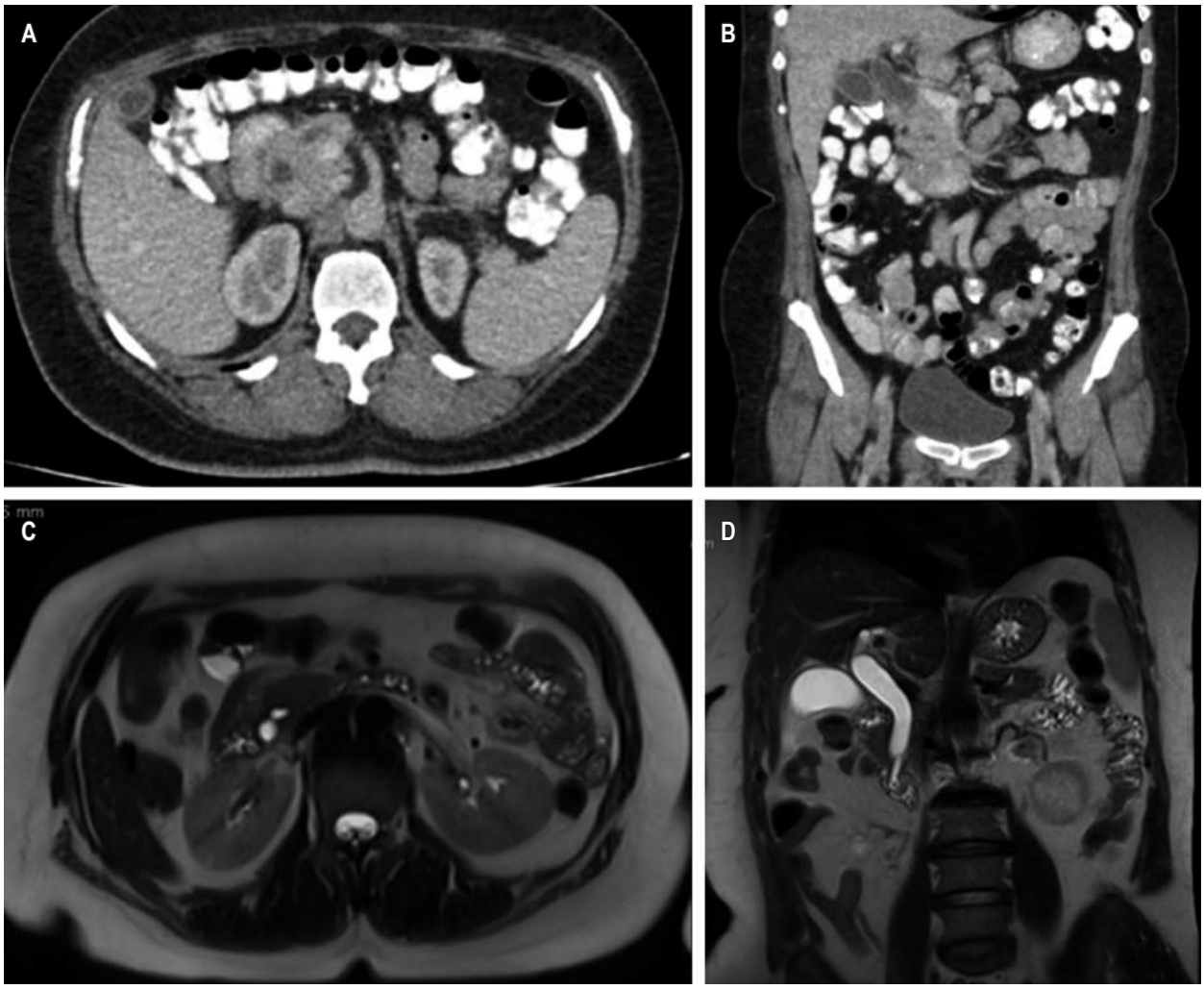

Figure 1. CT scan with evidence of intra- and extrahepatic bile duct dilation (**A**) axial section (**B**), and coronal section. Cholangioresonance shows dilation of the bile duct secondary to choledocholithiasis (**C**) in the axial section and (**D**) coronal section. Source: Authors' archive.

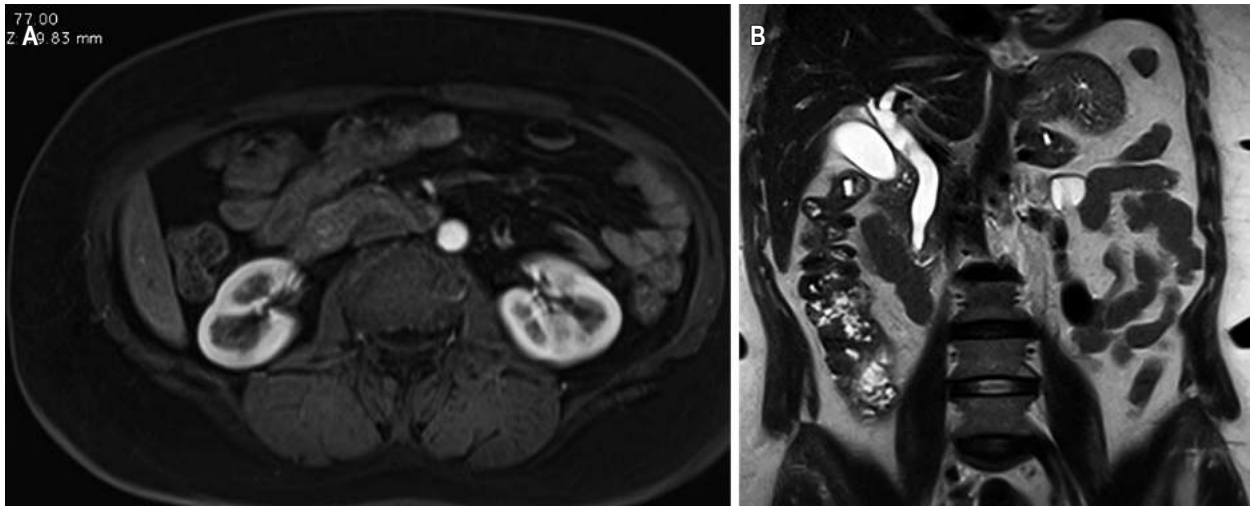

Figure 2. Magnetic resonance imaging contrasted with evidence of dilatation in the intra- and extrahepatic bile duct secondary to periampullary lesion (**A**) in the axial section and (**B**) coronal section. Source: Authors' archive.

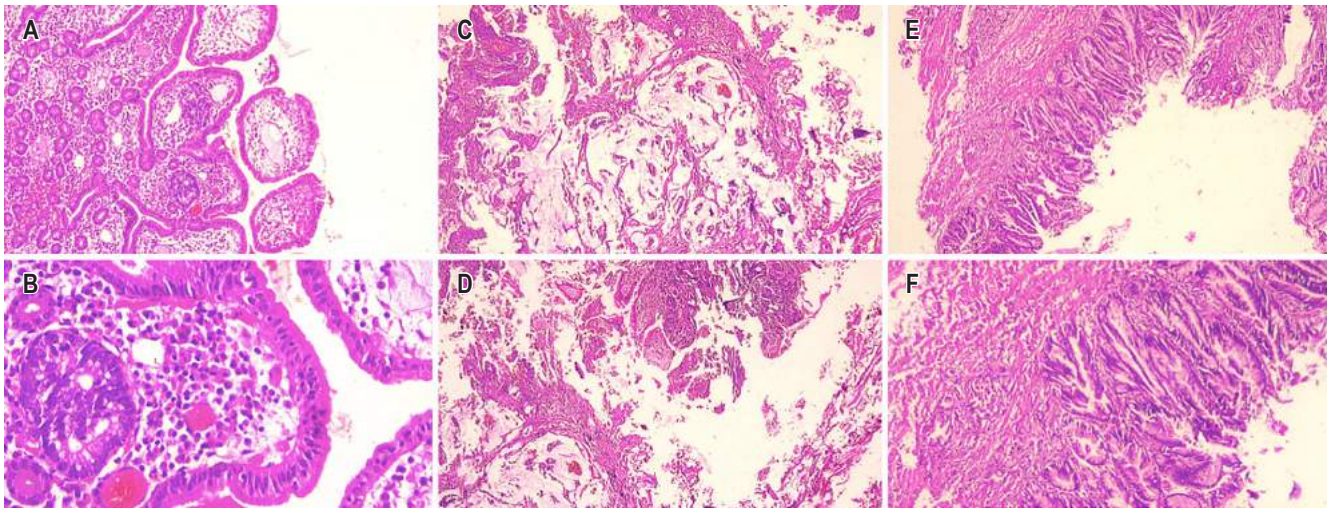

Figure 3. Microscopic vision with hematoxylin and eosin (H/E) 4x. Mixed adenoneuroendocrine tumor. **A.** 10x component of neuroendocrine carcinoma. **B.** 40x component of neuroendocrine carcinoma. **C** and **D**. 40x component of mucinous adenocarcinoma. **E** and **F.** 40x villous adenoma with low-grade dysplasia. Source: Authors' archive.

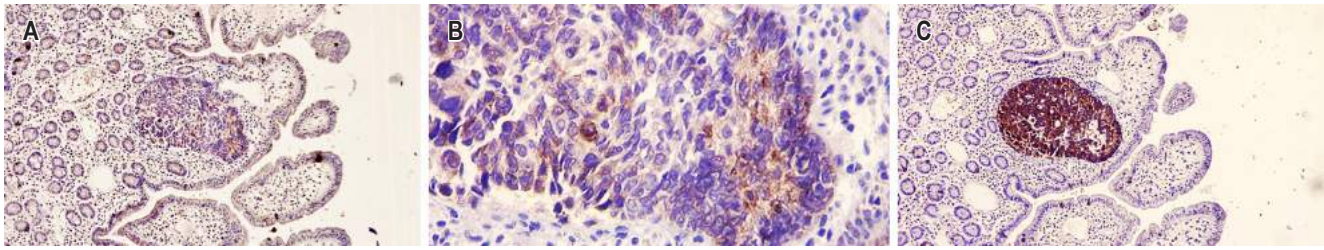

Figure 4. Immunohistochemical staining in neuroendocrine carcinoma. **A.** 10x weak immunohistochemical stain for chromogranin A. **B.** 1100x weak immunohistochemical stain for chromogranin A. **C.** 10x immunohistochemical stain with strong positivity for chromogranin A. Source: Authors' archive.

ampulla of Vater are uncommon. Only nineteen cases have been reported in this location. In the gastrointestinal tract, it is most common in the stomach and colon.[11]

In the case presented, the definitive diagnosis was made in multiple histological sections of paraffin and complementary immunohistochemical studies that documented the involvement of a mixed adenoneuroendocrine carcinoma of the ampulla of Vater, composed of neuroendocrine carcinoma (40%) and mucinous adenocarcinoma (60%), which confirmed the diagnosis of MiNEN according to the WHO, 2019.[5]

Symptoms are usually nonspecific and may be generalized. It is frequently abdominal pain, sometimes associated with emetic episodes. In the case presented, the main symptoms were jaundice, acolia, choluria, and febrile peaks. Due to the non-specificity of the obstructive symptoms that occur in these cases, making a clinical-radiological correlation with the pathology is of utmost importance.

This neoplasm located in the ampulla of Váter, as we mentioned previously, is a rare carcinoma, and its behavior is usually aggressive and of poor prognosis, so its treatment is surgical, as proposed in this case. Pancreatoduodenectomy is the most commonly used procedure in these cases, and this type of treatment should be associated with radiotherapy or chemotherapy.[6,11]

CONCLUSION

Mixed adenoneuroendocrine neoplasms are rare neoplasms with poor prognoses. Their diagnosis is difficult to make because the symptoms are not very specific, and their definitive diagnosis requires confirmation by histology and complementing with immunohistochemical studies.

Source of Funding

No funding was received to conduct the study.

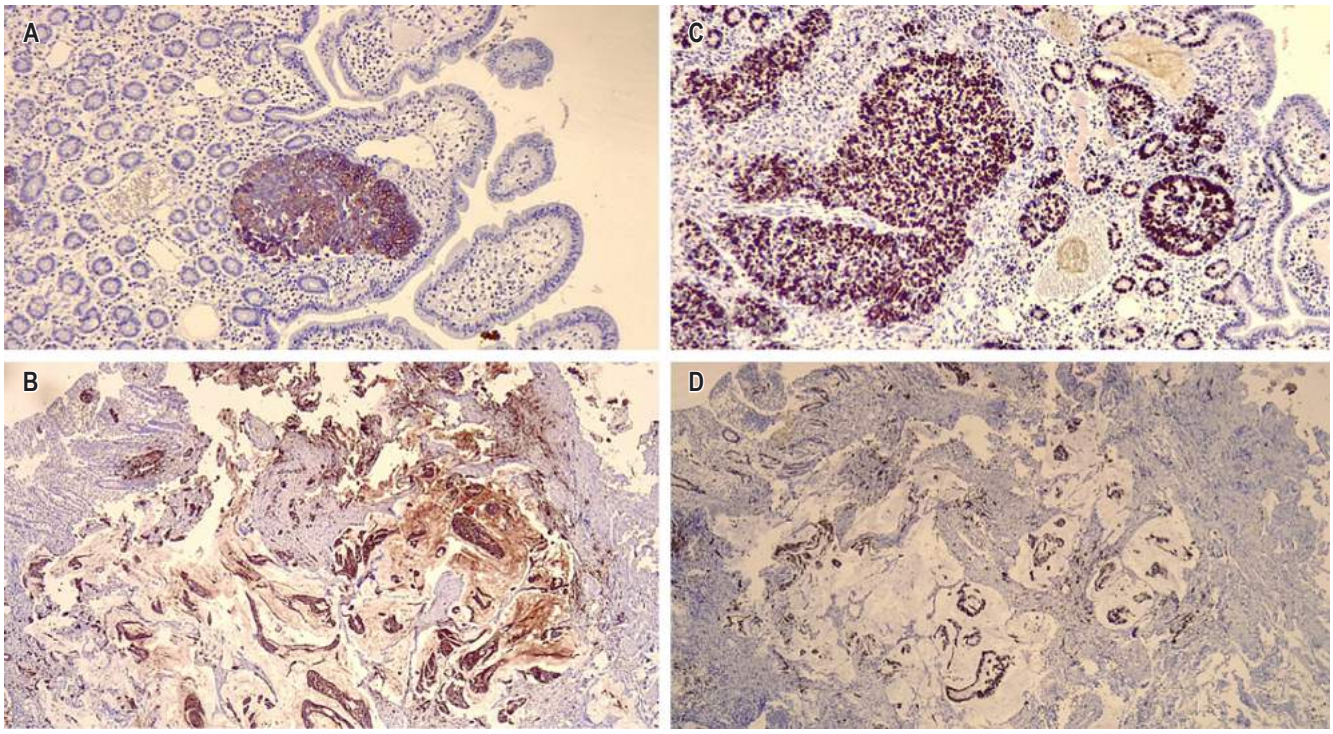

Figure 5. A. 10x positive immunohistochemical stain for cytokeratin 7 in the neuroendocrine adenocarcinoma component. **B.** 10x cytokeratin 7 positive immunohistochemical stain in the mucinous adenocarcinoma component. **C.** 10x cell proliferation index of neuroendocrine carcinoma of 98. **D.** 10x positive cell proliferation rate for most epithelial neoplastic cells. Source: Authors' archive.

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Case report

Spontaneous Biloma: A Case Report and Literature Review

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Abstract

Bilomas are collections of bile outside the biliary tree. The most frequent etiologies are iatrogenic and trauma. Cases of spontaneous or atraumatic bilomas are rare. Management of bilomas depends on the size and location and may include monitoring only; if the size is < 4 cm, there may be percutaneous or endoscopic intervention. The use of antibiotics depends on the clinical status of the patient. We describe the case of a man who presented with a spontaneous biloma eight years after laparoscopic cholecystectomy and, in addition to signs of choledocholithiasis, a stricture of the common bile duct. In patients with symptoms of biliary pathology, the diagnosis of biloma should be considered even without a history of trauma or recent surgery to initiate appropriate treatment early. Many cases are asymptomatic and resolve spontaneously but occasionally require percutaneous or endoscopic management.

Keywords

Bile ducts, cholecystectomy, biloma, endoscopic retrograde cholangiopancreatography, stents.

INTRODUCTION

The first description of a bilioma was made in 1884,[1] although the term bilioma was first introduced in 1979.[2] It refers to a collection of bile, which may or may not be encapsulated, located outside the biliary tree.[3] The most frequent causes include iatrogenesis and trauma.[3] The incidence of postoperative bilioma is 0.3%-2%.[3,4] The average time from cholecystectomy to the appearance of bilioma is two weeks.[5] The incidence of spontaneous or non-traumatic bilioma[6] is less frequent and, in adults, is associated with choledocholithiasis.[3] It is less frequently associated with hepatic infarction, abscesses, neoplasms, or extrapulmonary tuberculosis.[3] Patients may present abdominal pain, bloating, peritonitis, jaundice, and sepsis.[3] The average time between the onset of symptoms and diagnosis is between one and two weeks.[3,7] Ultrasound, with a sensitivity of 70%,[4] and computerized axial tomography, with a diagnostic yield of 90%[4], are the most frequently performed imaging studies. The percutaneous ultrasound-guided intervention has diagnostic and therapeutic utility and is recommended as the first line of treatment.[2,6] Management of patients may also include antibiotic treatment, especially in cases with sepsis. In cases

of asymptomatic collections < 4 cm, only surveillance is performed.[3] If percutaneous drainage does not resolve the condition, the patient may undergo endoscopic retrograde cholangiopancreatography (ERCP) with sphincterotomy and the option of stent insertion.[2] Among the differential diagnoses are cysts, seromas, pseudocysts, hematomas, and liver abscesses. On this occasion, we present the case of a patient with spontaneous bilioma.

PRESENTATION OF THE CASE

This is a 55-year-old man with a history of laparoscopic cholecystectomy eight years ago. He consulted after two days of abdominal pain in the upper hemiabdomen, more accentuated in the right hypochondrium, colic type, expanding to the back, and associated with fever and nausea.

Laboratory tests at admission found leukocytosis with neutrophilia, hyperbilirubinemia (total bilirubin: 2 mg/dL, direct bilirubin: 1.72 mg/dL), elevated alkaline phosphatase (148 U/L, normal: 35-104 U/L), elevated alanine aminotransferase (ALT: 89 U/L, normal: 0-41 U/L) and elevated C-reactive protein (CRP: 32 mg/dL). He had normal clotting times, electrolytes, azolates, aspartate aminotransferase levels (normal AST: 0-40 U/L), and amylase. Given the suspicion of cholangitis, he started an empirical antibiotic management with ceftriaxone and metronidazole.

The patient underwent an abdominal ultrasound that described dilation of the bile duct with these measurements: the right route (5 mm), the left one (4.8 mm), and the confluence (5.3 mm). A low amount of gas was also described at the level of the intrahepatic bile ducts. He also underwent a magnetic resonance cholangiopancreatography where they found a focal alteration in the subcapsular region of hepatic segment VI with an image of 34 x 31 x 37 mm, of heterogeneous content and similar images of smaller size, 10 and 13 mm, in segment VIII, suspicious of abscesses. Hepatic subcapsular fluid was also documented in the right lobe (112 mL) (**Figure 1**) and intrahepatic bile duct dilation with images of microlithiasis in the right hepatic duct near the confluence and in the intrapancreatic segment of the common bile duct. After 48 hours, an abdominal MRI was performed, and an increased volume of the hepatic subcapsular collection was found (**Figure 2**), so the patient was inserted into a multipurpose catheter. In the procedure, 1600 mL of purulent biliary-looking fluid was drained. The patient continued for five days with biliary drainage of 350-500 mL daily through the multipurpose catheter and with signs of an inflammatory response, so he was taken to ERCP.

ERCP showed a narrowing of the common bile duct at the junction of the proximal third with the middle third, with dilatation proximal to the confluence of the hepatic ducts (**Figure 3A**). Papilotmy was performed with dra-

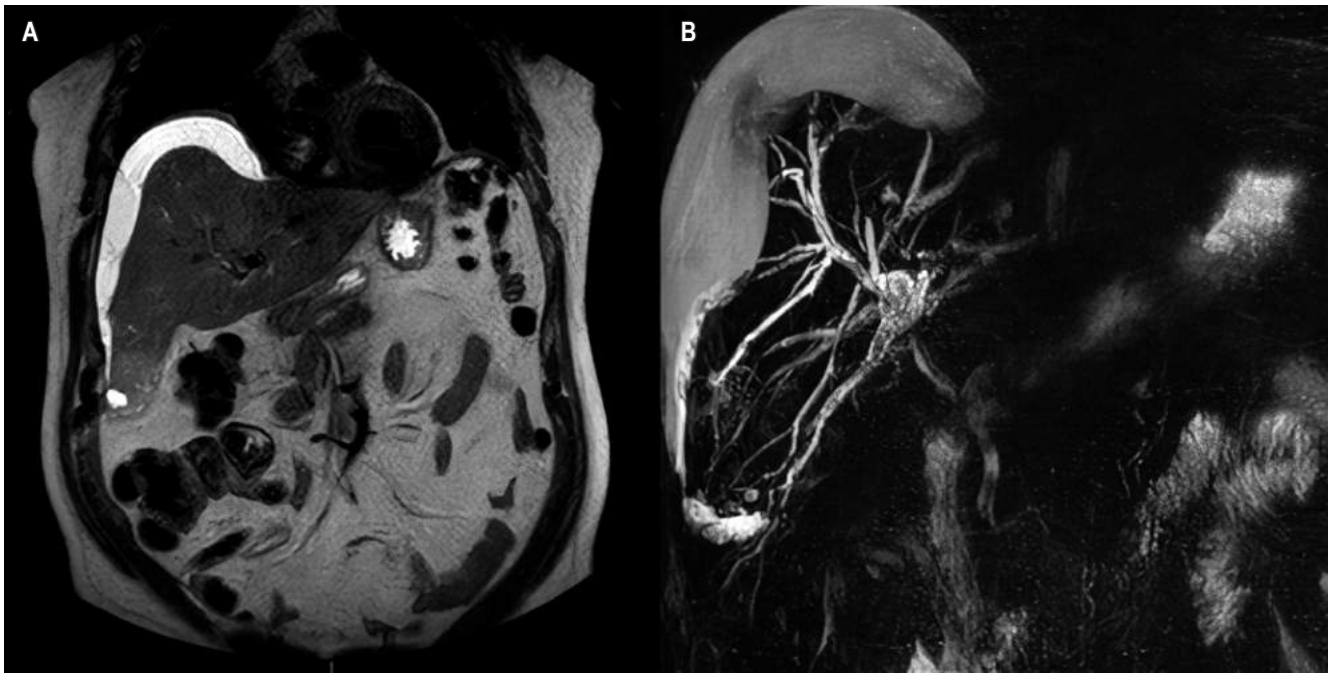

Figure 1. Magnetic resonance cholangiopancreatography. **A.** In sequence T2, subcapsular collection: bilioma. **B.** 3D reconstruction of the bile duct. Image Archive of Hospital Universitario Hernando Moncaleano Perdomo in Neiva.

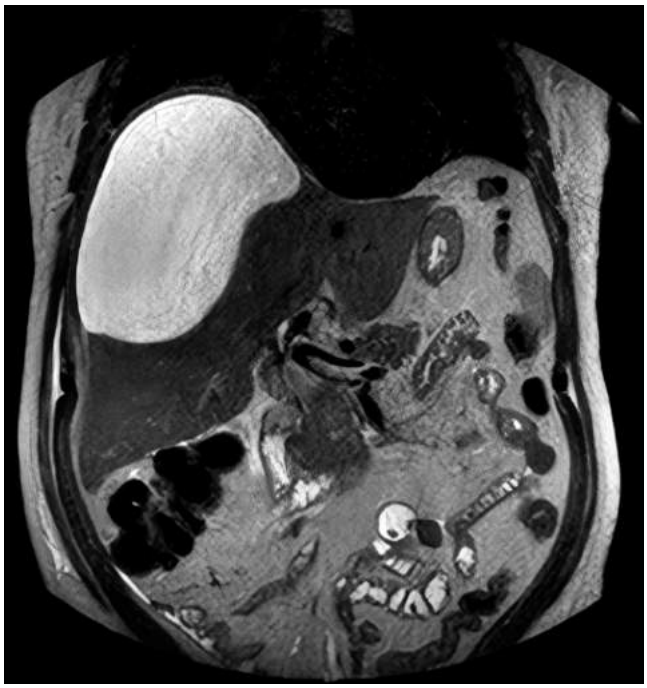

Figure 2. MRI of the abdomen. Increased volume of bilioma is observed. Image Archive of Hospital Universitario Hernando Moncaleano Perdomo in Neiva.

inage of purulent bile fluid and extraction of stones with basket and balloon. It was decided to insert a 10 cm Teflon stent of 10 Fr with adequate drainage (**Figure 3B**).

After the procedure, the patient required admission to the intensive care unit (ICU) and invasive mechanical ventilatory support (IMV). Antibiotic treatment was switched to fosfomycin + tigecycline + aztreonam by isolation in the drainage fluid through the carbapenem-resistant multipurpose catheter of Enterobacter cloacae multipurpose catheter by metallobetalactamase.

The patient subsequently presented a favorable evolution, with the tolerance of weaning from IMV the next day and discharge from the ICU. Signs of systemic inflammatory response disappeared on the second day after ERCP. The drainage volume through the catheter was < 50 mL from the third day after the procedure. The catheter was removed on the seventh day after ERCP. A control abdominal ultrasound showed that the residual collection was minimal. The patient was discharged upon completion of seven days of targeted antibiotic treatment with a stent removal plan upon completion of ten weeks.

DISCUSSION

The development of spontaneous bilioma is a rare phenomenon. Cases have been reported in the United States,[4,6]

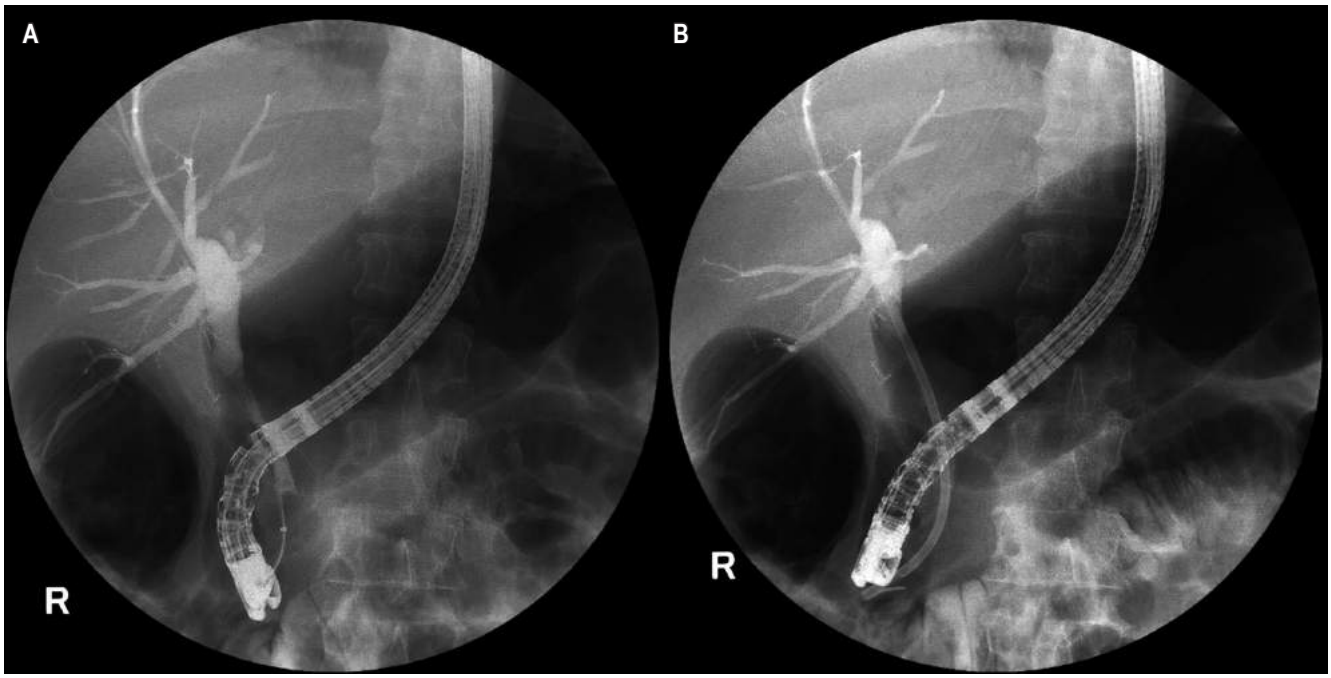

Figure 3. ERCP. **A.** Dilation of the bile duct at the junction of the proximal third with the middle third of the common bile duct, proximal dilation to the confluence of the hepatic ducts. **B.** After insertion of 10 Fr Teflon stent of 10 cm. Image Archive of Hospital Universitario Hernando Moncaleano Perdomo in Neiva.

Mexico,[1] Peru,[8] Brazil,[3] Serbia,[9] Italy,[5] and India,[2,7] and it is a condition that can occur in both men and women. In these reports, the symptoms presented by the patients include nausea, emesis, the presence of insinuated masses in the abdominal wall, acolia, and choluria,[2,3,5,8] in addition to the abdominal pain present in almost all cases.[1]

Our patient had a history of laparoscopic cholecystectomy for eight years, unlike other reported cases of patients without a pathological or surgical history.[2,3] There are case reports of biliomas presented five years,[7] nine years,[9] and 35 years[8] after an open cholecystectomy. Our case is the longest reported time between a laparoscopic cholecystectomy and the appearance of a spontaneous bilioma. The liver profile may be altered in all its parameters, partially altered as in our patient's case, or not altered at all.[2] Our patient presented choledocholithiasis like other cases described,[2,3,6] a condition frequently associated with spontaneous bilioma.

In our case, the patient initially underwent an ultrasound, and then, the lesion was better characterized by a magnetic resonance cholangiopancreatography and abdominal resonance. Magnetic resonance imaging has a diagnostic yield of around 95%.[4] Our patient required antibiotic treatment due to his septic state, with isolation of a multidrug-resistant germ.

Management included percutaneous drainage, but the patient persisted with abundant drainage and signs of systemic inflammatory response until five days later, so he was taken to ERCP with Teflon stent insertion. In the case of our patient, the increase in bile duct pressure, in addition to the obstruction due to choledocholithiasis proposed as an etiology of these cases of spontaneous bilioma,[6] was probably facilitated by stenosis of the common bile duct. For cases that do not resolve with this initial management, ultrasound-guided transmural drainage or transpapillary/transfistular access have been proposed as interventions.[10] In one case reviewed, drainage with a T-tube and cholecystectomy were performed after failure of ERCP with sphincterotomy. After the endoscopic intervention, the patient initially had a clinical deterioration but presented a favorable evolution, so he was discharged at the end of the 7-day antibiotic regimen. He could remove the multipurpose catheter due to minimal drainage, with ultrasound evidence of an almost complete reduction of the collection. This is the first case of spontaneous bilioma documented in Colombia.

CONCLUSION

The occurrence of spontaneous biliomas is an infrequently documented event, possibly because small lesions may be asymptomatic and resolve without specific treatment. In patients with bile duct intervention, this complication should be suspected, and appropriate imaging studies should be used to make the diagnosis early. Most cases resolve with percutaneous drainage, although the endoscopic intervention of the bile duct is necessary for some others.

Conflicts of Interests

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Case report

Pneumatosis Cystoides Intestinalis with Non-surgical Encapsulated Pneumoperitoneum: Case Presentation and Literature Review

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Abstract

Introduction: Pneumatosis cystoides intestinalis (PCI) is a rare entity characterized by cysts or air bubbles in the intestinal wall, usually asymptomatic. Its uncomplicated forms are managed conservatively, and the severe ones require surgical intervention. The presence of pneumoperitoneum is a disturbing radiological finding but not an indicator of surgical intervention. **Clinical case:** A 23-year-old man presented with weight loss, diarrhea, and rectal bleeding; a colonoscopy showed multiple violaceous cysts in the sigmoid and descending colon that collapsed after puncture and biopsies. Computed tomography (CT) confirmed the diagnosis and the presence of an encapsulated pneumoperitoneum. The absence of signs of potential lethality allowed conservative treatment with clinical remission during the first eight months of follow-up. **Discussion:** The pathophysiology of PCI is not well defined. Our patient's diagnosis was incidental when performing a colonoscopy for rectal bleeding. Asymptomatic encapsulated pneumoperitoneum should be interpreted as an important but not decisive sign of surgical intervention. Its presence, along with the medical history and physical, biochemical, endoscopic, and imaging examination, can prevent unnecessary surgery.

Keywords

Pneumatosis cystoides intestinalis, pneumoperitoneum, large intestine, colonoscopy, observation.

INTRODUCTION

Cystic intestinal pneumatosis (CIP) or pneumatosis cystoides intestinalis (PCI) was described by Du Vernoy in 1730.[1] It is a rare but well-identified clinicopathological condition characterized by the presence of bullae or aerial cysts in the subserosa of the small intestine and the submucosa of the colon,[2] especially transverse, descending, and sigmoid, with a higher proportion in men (2.4:1).[3] It is usually asymptomatic or with nonspecific symptoms such as abdominal pain, diarrhea, rectorrhagia, obstruction, flatulence, and rectal tenesmus,[4] and may be an incidental finding in colonoscopies and radiological studies. Histopathologically, it is characterized by cystic structures lined with histiocytes, giant cells, and granulomatous inflammatory reaction with eosinophils and elastosis.[5]

Etiologically, it can be primary or idiopathic (15%) and secondary, associated with other diseases (85%).[3,6] According to its clinical severity, it is classified as potentially lethal intestinal pneumatosis and benign intestinal pneumatosis (BPI).[4] The rupture of cysts can cause pneumoperitoneum, air in the omentum, or pneumoretroperitoneum in less than 3% of cases,[7] conditions that require either conservative or surgical management.

We present the case of a 23-year-old patient with four months of diarrhea and intermittent rectorrhagia. On colonoscopy, he was found to have cystic pneumatosis involving the sigmoid and descending, associated with acute infectious colitis. Computed tomography (CT) of the abdomen confirmed CIP and encapsulated pneumoperitoneum. After eight months of follow-up, he underwent conservative treatment with antibiotics and improved without surgery.

CLINICAL CASE

This is a 23-year-old male patient of urban origin, with four months of episodes lasting three days consisting of an increase in the frequency of bowel movements to three a day and one at night, of a liquid consistency, with mucus and blood, associated with abdominal distension, flatulence, pushing, and rectal tenesmus, in addition to the loss of 7 kg of weight. He had a history of isotretinoin treatment for acne for four years and a vaccine for 2019 coronavirus disease (COVID-19) with the first dose of the Pfizer vaccine. The stool test reported blastocystis hominis, Sudan III, in negative fecal matter and positive occult blood. It was treated as amoebic colitis with metronidazole and probiotic, rapidly improving diarrhea, but the patient had a symptomatic relapse eight days later.

On physical examination, vital signs were normal. He weighed 67 kg, was 1.78 m tall, and had a body mass index (BMI) of 21.15 kg/m^2, with no relevant findings. Laboratory tests reported C-reactive protein (CRP < 6.0), non-reactive human immunodeficiency virus (HIV), fecal calprotectin < 15, and carcinoembryonic antigen < 0.5, with normal liver and kidney profile. With a diagnosis of prolonged diarrhea and rectorrhagia under study, the patient underwent an upper endoscopy that led to the diagnosis of acute erosive gastritis and chronic diffuse corporoantral gastritis, Helicobacter pylori (-), and duodenal biopsies that ruled out celiac disease. In a colonoscopy, the rectal and colon mucosa between the splenic angle and the terminal ileum were normal, but there were multiple cystic, rounded, dark reddish confluent lesions up to 1.5 cm in the sigmoid and descending, with eroded overlying mucosa and soft on palpation with clamp (**Figures 1A** and **B**). When in doubt about the liquid or air content of the cysts, a fine needle puncture was performed in one of the largest cysts, with no fluid outlet and complete collapse of the cyst (**Figures 1C** and **D**). The same situation occurred when taking a biopsy of the wall of another of the cysts, which also had collapsed (**Figure 1E** and **F**). These findings are compatible with colonic cystic pneumatosis associated with acute erosive colitis of probable infectious or parasitic etiology. There was no abdominal pain, bloating, or other symptoms at the end of the colonoscopy.

CT of the abdomen with contrast showed multiple thin-walled air bubbles, without extravasation of contrast medium, predominantly of perihepatic distribution and, to a lesser degree, left subphrenic (**Figures 2A** and **B**), with multiple extraluminal air bubbles, located primarily in the descending and sigmoid colon walls (**Figures 2C** and **D**). Some of them were in clusters, adhered and adjacent to an "encapsulated pneumoperitoneum chamber" of approximately 160 mm larger diameter next to the splenic angle (**Figures 2E** and **F**), compatible with the endoscopic findings of PCI.

Cystic wall histopathology reported a chronic hemorrhagic inflammatory process with focal erosion, fibroblast proliferation with angiectasias, and multifocal reactive neovascularization. Comprehensive multidisciplinary analysis of PCI with asymptomatic pneumoperitoneum led to conservative treatment with tinidazole 500 mg twice a day for fifteen days, rifaximin 550 mg twice a day for fifteen days, pinaverio/dimethicone 100/200 mg twice a day for 30 days, esomeprazole 40 mg/day for 30 days, and insoluble fiber 20 mg/day for 30 days, with a relevant symptomatic improvement and disappearance of diarrhea and rectorrhagia, which was maintained until the 8-month follow-up.

DISCUSSION

Pneumatosis cystioides intestinalis is characterized by the presence of cysts with gas in the intestinal submucosa or subserosa and occurs in the large intestine in 46% of cases (especially in the sigmoid), the small intestine (27%), the stomach (5%), the small intestine and colon (7%), and very occasionally in the duodenum and rectum.[3,8]

Among the attributed pathophysiological mechanisms, there is inflammation, physical damage of the intestinal mucosa, nutritional imbalance, dysbiosis, gastrointestinal dysmotility, and immune dysfunction associated with predisposing factors such as surgeries with intestinal anastomosis, chemotherapy (rituximab, cetuximab), scleroderma, connective tissue diseases, lung disease, use of medications for diabetes (voglibose, acarbose), or use of trichloroethylene and inhibitors tyrosine kinase (sunitinib).[8]

Its etiology is imprecise and includes theories such as the "mechanical" one because intestinal obstruction increases intraluminal pressure and promotes cyst formation; "pulmonary" for chronic obstructive pulmonary diseases (COPD, asthma), where rupture of alveoli and subsequent pneumomediastinum cause air dissection along the aorta and mesenteric vessels, terminating air in the intestinal wall; "bacterial", because of the gas produced by intestinal bacteria that cross the mucosa and reach the submucosa; "chemical and nutritional deficiency", due to bacterial fermentation of carbohydrates with increased production of

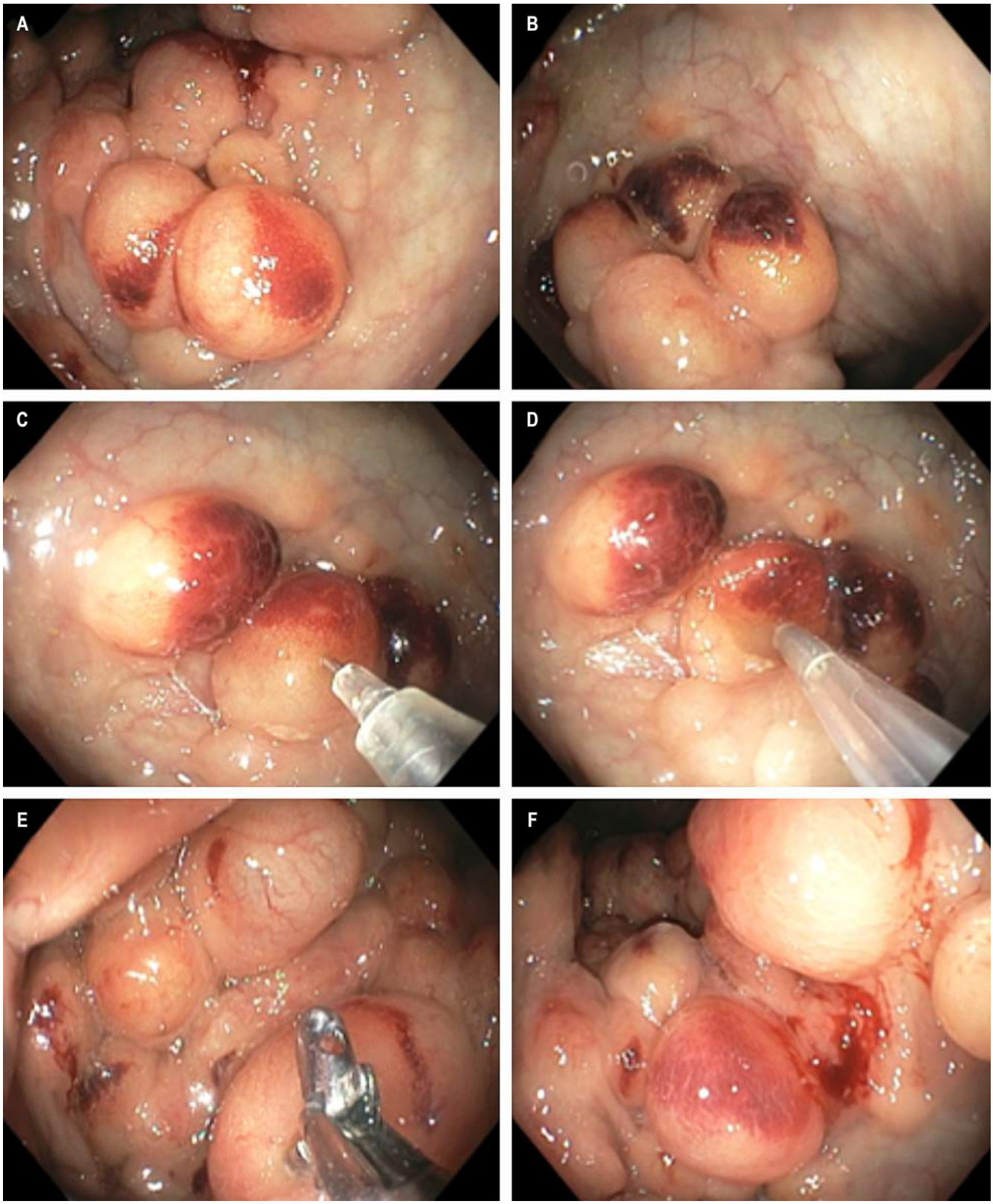

Figure 1. Colonoscopy. **A** and **B.** Multiple cluster cystic images in the sigmoid and descending, with eroded mucosa overlying by acute colitis. **C** and **D.** Fine needle puncture and air suction, no liquid outlet, with complete bubble collapse. **E** and **F.** Biopsy of the cyst wall with bubble collapse. Source: Authors' archive.

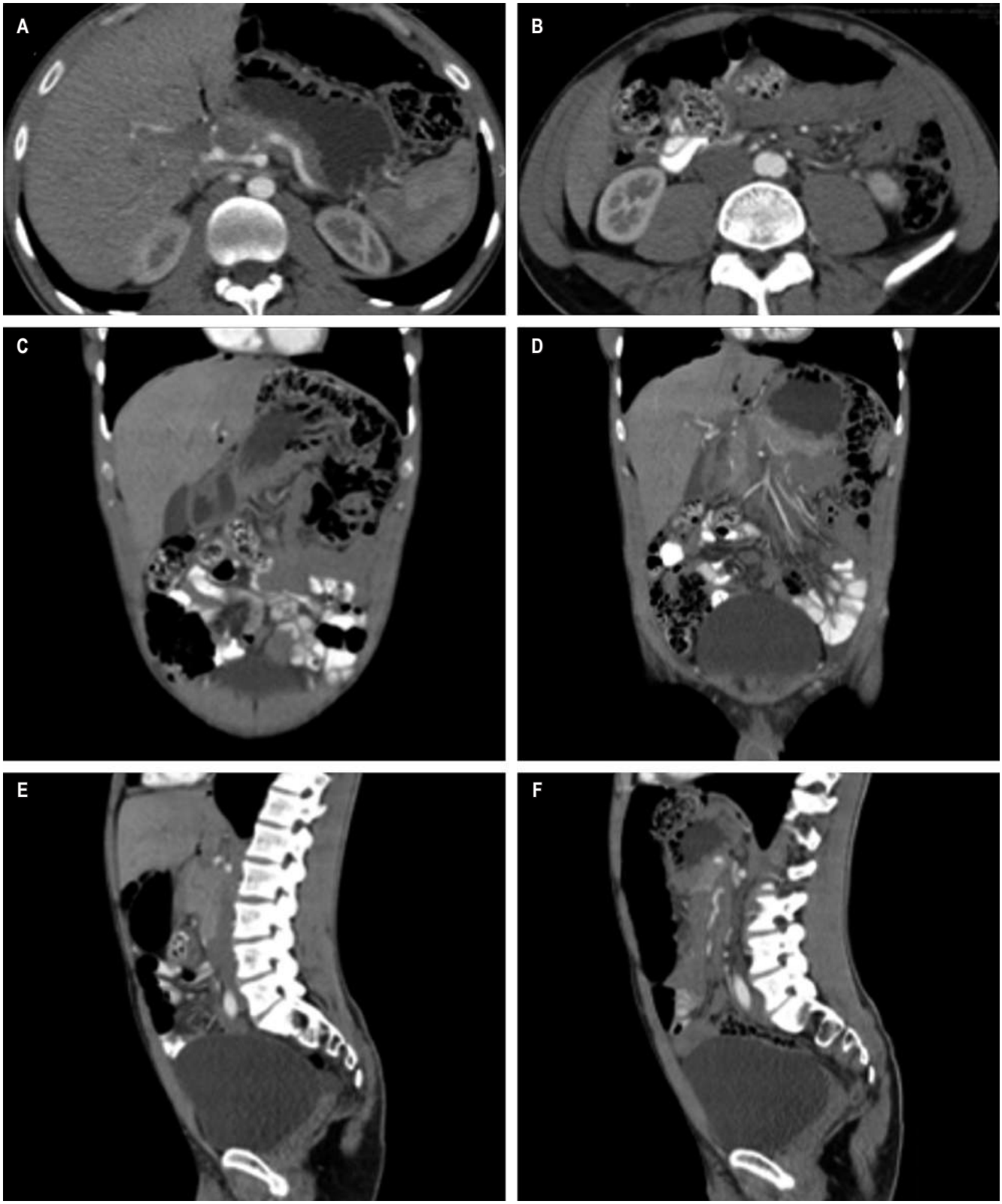

Figure 2. CT scan of the abdomen. **A** and **B.** Sagittal section. Cluster colonic cystic pneumatosis, with multiple thin-walled air bubbles, without extravasation of the contrast medium. **C** and **D.** Coronal section. Multiple extraluminal air bubbles located in the walls of the descending and sigmoid colon. **E** and **F.** Axial cut. Pneumoperitoneum in the anterior abdomen, 16 cm in diameter next to the liver and in continuity with the bubbles of the splenic angle of the colon. Source: Authors' archive.

gas that penetrates the intestinal wall; "immunological" or intestinal toxicity (use of chemotherapy and hormonal therapy) that generates air passage due to functional and organic dysfunction of the intestinal wall.[9]

The diagnosis can be suspected upon the finding by optical colonoscopy (OC) of intramural cysts in violet clusters, which simulate a liquid content due to the inflammation of the overlying mucosa, as well as by fine needle puncture, in which the collapse of the cyst is observed without a fluid outlet, or by appreciating the exit of bubbles from the cyst when taking biopsies underwater.[6]

Virtual colonoscopy and CT of the abdomen confirm the diagnosis by finding cysts that look like bunches of grapes or honeycombs in the intestinal wall, which show gas content in reconstructions with lung window. In cases of severe forms of PCI, intestinal dilation, arterial or venous occlusion, ascites, and porohepatic or portomesenteric venous gas can be observed.[4,9]

PCI is usually asymptomatic (even with pneumoperitoneum) or may have nonspecific symptoms. In these cases, treatment may be conservative through observation and follow-up,[4,6,8] hyperbaric oxygen therapy,[10] antibiotics (metronidazole, tinidazole, rifaximin, quinolones), Bifidobacterium probiotics, endoscopic therapy such as fine needle aspiration[6,11] or high-frequency electrosurgical resection of cystic walls or sclerotherapy. The use of plasma argon is not recommended due to possible explosion by methane,[8] and neither change of chemotherapeutic (cytostatic type or targeted molecular therapies and tyrosine kinase inhibitors for metastatic esophageal, pulmonary, renal, or other tumor pathology).[12]

In these patients, pneumoperitoneum should be considered an incidental sign. Other etiologies of non-surgical pneumoperitoneum should be ruled out, such as retained postoperative air or thoracic, gynecological, or abdominal causes, which in asymptomatic patients can resolve spontaneously so that unnecessary surgeries are avoided.[13]

Surgical intervention should be considered in symptomatic patients with abdominal pain, intestinal obstruction, bleeding, peritoneal irritation, acidosis, portal gas, and pneumoperitoneum, given the potential for ongoing ischemic colitis, necrosis, or intestinal obstruction.[2,14] The decision to undergo surgery should be based on the presence of associated risk conditions, a physical examination suggesting peritonitis, analytical predictors of poor prognosis (pH < 7.3, bicarbonate < 20 mL/L, lactate > 2 mmol/L, serum amylase > 200 U/L) or the presence of portal venous gas.[15] Pneumoperitoneum alone is neither a predictor of severity nor an indicator of emergency surgery.[13]

Surgically, PCI can be found in the sigmoid with chronic volvulus causing intermittent partial obstruction or perforation with peritonitis, which requires sigmoidectomy.[14,16] If no visceral perforation, peritonitis, or indication of bowel resection is found, surgery can be terminated, and conservative management can continue according to the etiological cause.[13]

There are no management guidelines for PCI; in most cases, it is done conservatively. In this patient, the incidental finding of pneumoperitoneum with no symptoms and a normal physical and paraclinical examination, without suspicion of peritonitis, allowed a non-surgical treatment based on antibiotics for the associated acute infectious colitis, and a symptomatic remission was obtained until the eighth-month follow-up. Colonoscopic, histopathological, and tomographic follow-ups will be carried out one year after diagnosis.

CONCLUSIONS

In patients with an incidental finding of PCI, diagnostic and therapeutic decisions should be rapid, based on multidisciplinary history analysis, physical examination, and biochemical, endoscopic, histopathological, and imaging analysis.

The finding of pneumoperitoneum in these patients should be an alarm sign but not an absolute indicator of surgical intervention.

Informed Consent

Written informed consent was obtained from the patient to publish the case and its attached images.

Conflicts of Interests

The authors declare that they have no conflict of interest.

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Tribute

Norman R. Barrett (1903-1979)

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Norman R. Barrett, an Australian, studied to become a physician and surgeon in Great Britain, where he worked practically all his life. He specialized in chest surgery in the United States. His particular interest was always the distal esophagus, of which he published more than 70 scientific articles, and is remembered mainly for the description of the esophagus lined by columnar epithelium, a condition later called Barrett's *esophagus*. It is an interesting peculiarity of the history of medicine that he is remembered by the name of a disease that, at first, he described wrong. He was listed as *the dean of thoracic surgery*.

He was born on May 16, 1903, in North Adelaide, Australia, and his parents were Catherine Hill Connor and Alfred Barrett. When he was ten, he moved to England with his family. He was educated in Cambridge at Eton College and Trinity College, did his medical and surgical training at St. Thomas Hospital in London, and graduated in 1928. In this institution, he specialized in surgery and worked there for the rest of his life.[1,2]

In 1935, he traveled to the United States to the Mayo Clinic. His purpose was to specialize in gastrointestinal surgery, but Dr. Donald Balfour brought him closer to thoracic surgery. When he returned to St. Thomas Hospital in London, he devoted himself to pulmonary tuberculosis and pulmonary hydatidosis surgery and promoted the enucleation of cysts to prevent effusions and contamination (a procedure known as the *Barrett technique*).[1,3]

In 1948, the thoracic surgery service was created, and he was appointed its first chief. In 1946, he wrote about the spontaneous rupture of the esophagus (Boerhaave syndrome) for the first edition of Thorax Journal, drawing on an original case of Morell Mackenzie and other reported cases and commented that the presentation of this condition is one of the most dramatic and most terrible situations in the field of surgery. His interest in the esophagus and the history of medicine were combined in this article, which seems to be described as a pleasure to read.[1,3]

Having thoroughly studied all aspects of this condition, Barrett only had to wait for a suitable case. A year later, on March 7, 1947, he carried out the first successful repair of this condition.[3]

Within his work, he showed interest in various topics of thoracic pathology, in which he made original contributions, such as gastroesophageal reflux, pulmonary hydatid cyst surgery, tumors of the chest wall, and the use of drains. He was the one who promoted Heller's operation for achalasia in England, which was accepted there before other countries.[2-4] Some of Barrett's most important works were directed to the method for the cytological examination of sputum in the diagnosis of lung neoplasms.[2]

The lower esophagus was his great interest. In 1950, he published in the British Journal of Surgery: "Chronic Peptic Ulcer of the Esophagus and Oesophagitis", in which he described a series of patients with ulcers in an intrathoracic tubular organ that appeared to be esophagus, except that it had gastric-like columnar epithelium, which Barrett interpreted as a segment of the stomach in the chest, generated by the traction of a congenital short esophagus. In his description, Dr. Barrett did not identify intestinal metaplasia in the columnar epithelium.[3,4]

Intestinal goblet cells in the esophagus lined by columnar epithelium were first described in 1951 by Bosher and Taylor.[5,6] Later, in 1953, Allison and Johnston pointed out that Barrett had made a mistake, and what he had described as the stomach was actually the esophagus lined by columnar epithelium.[3,4]

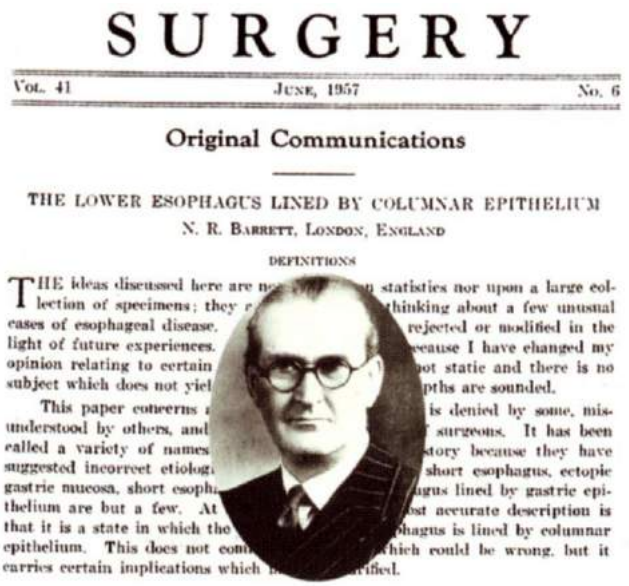
Allison and Johnston's arguments were finally accepted by Barrett in a report published in 1957, in which he suggested that the condition should be called *the lower esophagus lined by columnar epithelium* (**Figure 1**).[5,7]

In 1959, the idea that it was a metaplasia secondary to gastroesophageal reflux was accepted. However, Barrett never claimed to be the first to describe the distal esophagus covered by columnar epithelium and even mentioned nine possible previous reports. In 1953, it was Philip Allison in the Thorax Journal who coined the name *Barrett's ulcers* to chronic peptic ulcers of the esophagus with gastric-like epithelium, which was called *Barrett's esophagus*.[3,4]

He was an editor of Thorax Journal from its start in 1946 until 1971 and published more than 70 articles. He was characterized by beginning his writings with a detailed historical review of the subject and was very concerned that scientific articles had elegant writing, which demonstrated his brilliant inventiveness.[3,4]

He received distinctions such as Master of Surgery in 1935, President of the Thoracic Society of Great Britain and Ireland in 1962, and Honorary Member of the American Association of Thoracic Surgery. He taught at the Universities of Oxford, Cambridge, and Birmingham.[1] Moreover, he received the nickname "Pasty" (for the rosy appearance of his cheeks in his youth) and was well known by this nickname for the rest of his life.[2,3]

Barrett was diagnosed with Parkinson's at age 61. The physical effects of his illness were never severe, but he felt depressed about his deterioration and anxious about a future worsening. Barrett did not tolerate the new drug L-dopa, which triggered severe depression. He retired at age 65 and died on January 8, 1979, at age 75, due to a stroke. He was categorized as *the dean of esophageal surgery*.[1,3]



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Original Communications

THE LOWER ESOPHAGUS LINED BY COLUMNAR EPITHELIUM

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DEFINITIONS

THE ideas discussed here are no[t] statistics nor upon a large collection of specimens; they [a]re thinking about a few unusual cases of esophageal disease. [m]ay be rejected or modified in the light of future experiences. [B]ecause I have changed my opinion relating to certain [m]atter static and there is no subject which does not yiel[d] depths are sounded.

This paper concerns [a] is denied by some, misunderstood by others, and [b]y surgeons. It has been called a variety of names [h]istory because they have suggested incorrect etiolog[ies] short esophagus, ectopic gastric mucosa, short esoph[agus] lined by gastric epithelium are but a few. At [m]ost accurate description is that it is a state in which the [e]sophagus is lined by columnar epithelium. This does not con[t]hich could be wrong, but it carries certain implications which [m]odified.

Figure 1. Barrett's original work published in Surgery.[7]

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A comment about markers of severity of acute appendicitis

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The manuscript by Vargas-Rodríguez et al.[1] entitled *Markers of Severity of Acute Appendicitis: Diagnostic Test Study*, aimed to determine the possible markers of severity in acute appendicitis for diagnostic purposes and for the timely management of appendicitis and avoid possible complications, has been studied with great interest. A total of 239 patients were included, and the study concluded that the elevation of C-reactive protein (CRP) and neutrophil percentage > 85% are the acute phase reactants with the best diagnostic characteristics.

In their study, Delgado-Miguel et al.[2] included 1269 patients undergoing appendectomy and concluded that the neutrophil-lymphocyte index (NLI) can be considered the preoperative parameter with the highest sensitivity (84.2%) and specificity (83.8%) for predicting the absence of appendicitis in cases where there is any clinical suspicion. Furthermore, they point out that it is a simple and low-cost screening tool that should always be considered to avoid negative appendectomies.

For his part, in his systematic review, Dale[3] emphasizes that procalcitonin (PCT) does not help diagnose acute appendicitis, but he did identify higher rates of PCT in patients with complicated acute appendicitis. Statistically, the PCT level was significantly different ($p < 0.05$) under these two conditions.

In their meta-analysis, Krishnan et al.[4] analyzed mean platelet volume (MPV) levels and found that there was no significant difference in levels between children with acute appendicitis compared to healthy controls, which demonstrated the low usefulness of MPV for the diagnosis of this clinical condition. In contrast, in their meta-analysis, Tullavardhana et al.[5] clearly report that lower MPV values can be a marker to predict acute appendicitis but failed to demonstrate a prediction for complicated acute appendicitis and suggest continuing to use clinical scoring systems.

Ayeni et al.[6] support the use of neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) to stratify the risk of children with confirmed appendicitis in settings with limited economic resources or where the necessary diagnostic tests are not available. For NLR, they found a sensitivity of 70.3% and specificity of 70%, with a positive predictive value (PPV) of 84.6% and a negative predictive value (NPV) of 50.2%. For PLR, they found a sensitivity of 64% and specificity of 61%, with a PPV of 79.3% and NPV of 42%. They concluded that these markers are synergistic and reliable in predicting complicated acute appendicitis.

In conclusion, the approach to acute appendicitis represents a challenge due to the wide range of possibilities inherent to its symptoms. Nevertheless, the number of eva-

luations and analyses of alternative methods that allow more accurate decisions and more appropriate treatments is increasing. Therefore, it is worth highlighting the importance of carrying out studies such as these, which characterize populations to extrapolate to samples of similar characteristics and, through the analysis of severity markers in acute appendicitis, establish guidelines for a timely diagnosis and reduction of complications.

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