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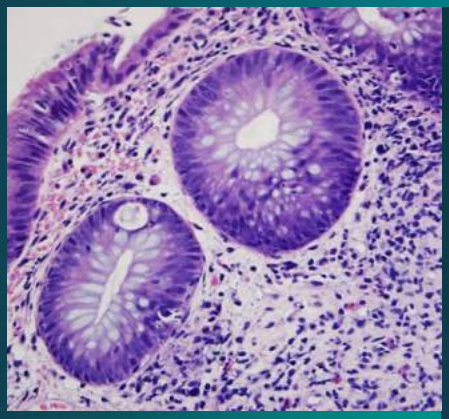

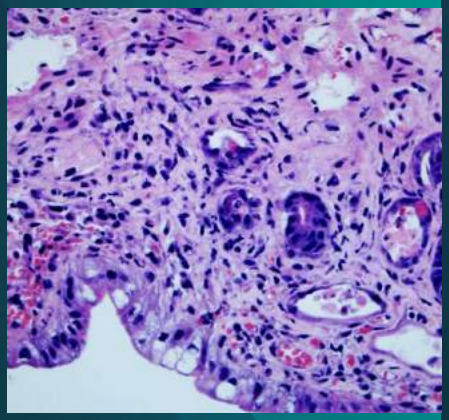

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Microscopic colitis: Case series and literature review

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Cover: *A. Colon compromised by GVHD. Colon histopathology with H&E (400 X). Shows crypt damage with basal apoptotic bodies and mixed inflammatory infiltrate in the lamina propria around the crypts. GVHD grade 1.*
B. Small intestine compromised by GVHD. Histopathology of the small intestine with H&E (400 X). An apparent decrease in the number of crypts with marked mucin depletion, presence of basal apoptotic bodies, and adjacent mixed inflammatory infiltrate stand out. Severe GVHD.
Article: Gastrointestinal involvement due to graft-versus-host disease
Courtesy by the authors: Álvaro Andrés Gómez-Venegas, Gabriel Mosquera-Klinger, Jhon Jaime Carvajal, Fabián Juliao-Baños, Andrés Goldstein-Rothstein, Juan Camilo Pérez-Cadavid, Juan Felipe Morantes-Rubiano.

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Editorial

COVID-19 and Liver Disease: A panorama that is being clarified

Rolando José Ortega-Quiroz.[1*]

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The COVID-19 pandemic, caused by the SARS-CoV-2 virus, has become a significant burden on economies and health systems worldwide. The disease course of COVID-19 ranges from asymptomatic —identified by antigen detection or rapid tests, polymerase chain reaction (PCR), molecular tests, and antibodies (before vaccination)— to multiorgan dysfunction and high mortality[1,2]. Perhaps rarely have we seen how research by multidisciplinary groups achieved results so rapidly in diagnosing, managing, and developing a highly effective vaccine to prevent severe manifestations of a disease. As of December 2021, all-cause mortality reports collected in more than 74 countries accounted for 6 million deaths, mainly in India (4.07 million), the USA (1.13 million), Russia (1.07 million), Mexico (798,000), Brazil (792,000), Indonesia (736,000), and Pakistan (664,000)[3].

The coronavirus (CoV) family displays a corona-like structure on its surface that is visible through electron microscopy. In humans, at least 7 types of this family result in disease, 4 of which are self-limiting, and 3 additional species (SARS-CoV-MERS-CoV and SARS-CoV-2) are highly pathogenic, causing severe respiratory disease. The SARS-CoV-2 is a single-stranded (positive polarity) RNA enveloped virus composed of a 30 kbp (kilobase pairs) genome, encoding 16 non-structural proteins and 4 structural proteins. The structural proteins of the surface include envelope (E), nucleocapsid (N), membrane (M), and *spike* (S), the main protein responsible for interacting with the host's primary receptor (ACE2), its co-receptor (neuropilin-1) and a transmembrane serine protease 2 (TMPRSS2). After the adhesion of the receptors, the virus envelope contacts the infected cell cytoplasm, generating endosomes (early or delayed) or endolysosomes. Then, the viral genome is released in the direction of the endoplasmic reticulum as a template (strand) for the translation of proteins. The assembly of the synthesized proteins occurs in the Golgi apparatus, where the virus is released, infecting other cells[4-6].

Risk factors associated with the severity of COVID-19 have been described, including age, metabolic comorbidities, heart disease, cancer, and immunosuppression. Multiple organ involvement is most evident during the acute phases of the disease. The most common manifestations include systemic, respiratory, gastrointestinal, cardiovascular, and neurological conditions. The severity of acute COVID-19 is associated with the post-COVID-19 syndrome, symptoms that persist for more than 6 months. Some of the most common manifestations include fatigue, brain fogginess, sleep problems, chronic headache, palpitations, muscle pain, nausea, and laboratory abnormalities: neutrophilia, anemia, thrombocytosis, and low albumin levels[7,8]. In addition, genetic predisposi-

tion to infection and to develop severe forms of the disease may exist. Genome-wide association studies (GWAS) have identified at least 13 genetic loci accounting for the response to infection[9].

Although the respiratory system represents the main entry point of the virus, the digestive tract represents a significant angiotensin-converting enzyme receptor 2 (ACE2) expression, mainly in the small intestine and colon. The SARS-CoV-2 mRNA has been detected primarily in the esophagus, stomach, duodenum, and rectum. As many as 64% of patients may remain positive for RNA in stool for several weeks by reverse transcription-polymerase chain reaction (RT-PCR) after negative nasopharyngeal tests. In patients with severe disease, histopathological findings show endothelial inflammation of the submucosal vessels of the intestinal wall, including interstitial edema, lymphocyte, and plasma cell infiltrate in the lamina propria of the stomach, duodenum, and rectum[10].

A study including 2036 hospitalized patients with COVID-19 showed that gastrointestinal symptoms occur in 59.7%. Some significant symptoms included nausea, diarrhea, loose stool, and emergencies. In addition, nausea can persist even after infection resolution[11].

In a healthy liver, the ACE2 receptors are expressed at low levels, mainly in cholangiocytes, liver sinusoidal endothelial cells (LSECs), and less frequently in hepatocytes. However, in patients with cirrhosis, ACE2 mRNA levels are 34-fold up-regulated, expressed by immunostaining in 80% of hepatocytes, which explains the high susceptibility to infection of this organ[12].

Liver involvement during COVID-19 has been associated with increased disease severity, prolonged hospital stays, ventilatory support, and mortality. Studies in hospitalized patients report a 3-5-fold elevation of aminotransferases in 20%-67% at entry and 61%-83% during hospitalization. Aspartate aminotransferase (AST) is generally higher than alanine aminotransferase (ALT), highlighting microvascular damage in COVID-19. Alkaline phosphatase and total bilirubin elevations occur in 20%–30% and 4%–16%, respectively, and cholestasis is described in an average of 15% of hospitalized patients, establishing a pattern of hepatocellular injury. It is unclear whether these changes occur before infection, are caused by the virus, or are related to events within the disease[13,14].

Alcohol etiology alone influences the outcome severity to date, and its consumption increased significantly during the pandemic[15,16]. No clear pattern has been demonstrated in patients with metabolic dysfunction associated with fatty liver disease (MAFLD) (where risk factors such as obesity and diabetes dominate), viral hepatitis, autoimmune hepatitis, or cholestatic diseases. Antiviral therapies may begin and continue, given the risk of reactivation with immunosuppressive drugs[17-19].

For patients with autoimmune hepatitis, the course of the disease is not at risk of a worse outcome, and immunosuppression is not associated with increased severity, so maintenance is recommended. The main predictor of complications in these patients is the presence of cirrhosis[20].

Nonetheless, given the previously described abnormalities, more studies are needed to define the short- and long-term consequences of SARS-CoV-2 infection in patients with underlying chronic liver disease[21].

Few case series have been published regarding histopathological changes in the liver during COVID-19. Changes range from fatty liver disease (55%), sinusoidal dilatation and congestion (34.7%), micro thrombosis (29.4%), fibrosis (20%), portal inflammatory infiltrate (13.2%), and invasive lobular carcinoma (11.6%). SARS-CoV-2 RNA has been detected in liver tissue *postmortem* studies in up to 55% of cases. At the same time, electron microscopy shows viral particles, mitochondrial edema, endoplasmic reticulum dilation, and apoptosis[22].

The mechanism by which liver injury occurs may be related to a direct cytopathic effect of the virus (currently unlikely), immune-mediated damage associated with the cytokine storm triggered by virus recognition due to innate immunity. Furthermore, it may be linked to hypoxic brain injury in patients with severe hemodynamic instability. Ultimately, drug-induced liver injury (azithromycin, hydroxychloroquine, non-steroidal anti-inflammatory drugs [NSAIDs], lopinavir/ritonavir, remdesivir, tocilizumab, tofacitinib, and dexamethasone) can cause it too[23,24]. Reactivation of preexisting diseases with the use of immunosuppressants (hepatitis B) is also a possibility. Also, the relationship between autoimmune hepatitis *de novo* and the different approved vaccines has been described[25]. Additionally, cholangiocyte injury in the form of cholangiopathy associated with the SARS-CoV2, a type of secondary sclerosing cholangitis (SSC), is possible[26].

An alternative mechanism to the described liver injury could be endothelial injury mediated by inflammation and thrombosis, caused by an inflammatory response to the virus and expressed by an increase in D-dimer, fibrinogen, von Willebrand factor(VWF), thrombomodulin and factor VIII. In addition, acute decompensation, associated with multiple organ failures and high short-term mortality, may occur in cirrhotic patients, leading to acute, chronic liver failure[27].

Cirrhosis is a risk factor for mortality. The Child-Pugh score system is the most prognosis assessment determinant for cirrhosis. Mortality in non-cirrhotic chronic liver disease patients was 8% at hospitalization, 20% in the intensive care unit (ICU), and 21% with mechanical ventilation. Child-Pugh A class was 22%, 40%, and 52%; Child-Pugh B was

39%, 62%, and 74%; Child-Pugh C was 54%, 79%, and 90%, respectively[28]. A collaborative study including 8941 cirrhotic patients with SARS-CoV-2 infection confirmed a mortality risk with a *Hazard Ratio* (HR) of 3.31 to 30 days[29]. The largest cohort of hospitalized COVID-19 patients in Latin America, which included 1611 patients, showed an alteration of the liver analysis at admission in 45.2%, with higher mortality of 18% versus 12% (< 0.001) compared to those with a normal profile[30]. An important aspect to highlight is the late diagnosis of hepatocarcinoma in cirrhosis, given the decrease in face-to-face consultations during the pandemic, hindering protocols for monitoring and detecting new cases[31]. Changes in screening schedules were reported in reference centers in 80%, and therapies were modified or canceled in 65% of cases[32].

Liver transplants were affected globally due to a significant decrease in donors[33]. The course of the COVID-19 disease is not different in transplant recipients, and no changes in immunosuppression should be made[34]. A recent European multicenter study evaluating the outcome in 243 patients transplanted with COVID-19 showed 25% mortality. The risk was more significant in those over 70 with comorbidities such as diabetes and chronic renal failure. The use of tacrolimus was associated with more prolonged survival. Therefore, maintaining the usual doses is recommended. No recommendations were made regarding other immunosuppressants such as mycophenolate mofetil[35].

The rapid production and clinical development of highly effective vaccines to prevent severe forms of COVID-19 reflect decades of research in immunology and biology. Vaccine safety represents one of the most critical challenges, particularly in special groups not included in approval trials. Another important aspect is the humoral response to vaccination in immunocompromised patients concerning immunocompetent ones. Due to their safety profile and high effectiveness, the mRNA (Pfizer, Moderna) and adenovirus vector (AstraZeneca, Johnson & Johnson) vaccines have gained more popularity[36]. The Centers for Disease Control and Prevention (CDC) recommendations prioritized patients with chronic liver disease and patients on the transplant list (even with one dose, a second dose should be transplanted at 6 weeks)[37].

Seroconversion in patients on the waiting list in one study reached 94.4%. No serious adverse events were observed, and no disease was documented in the first two months[38]. Similarly, the humoral response to mRNA vaccines in solid organ transplant recipients is slightly lower than in immunocompetent patients[39]. Protection is manifested by a 64% decrease in infection, 58% in symptomatic COVID-19, and 87% in mortality[40]. The recommendations point to vaccine boosts to achieve similar immunity.

As for antiviral drugs for COVID-19, there is little experience in patients with cirrhosis, given the possibility of drug-induced damage, becoming evident with toxicity from lopinavir/ritonavir and remdesivir[41].

A significant advance applicable during the pandemic refers to the Baveno VII guidelines. These guidelines recommend deferring endoscopy in cirrhotic patients with transient elastography <20 kPa and more than 150,000 platelets and initiating carvedilol administration in patients with a result >25 kPa, given the correlation with the presence of clinically significant portal hypertension (hepatic venous pressure gradient [GPVH] >10 mm Hg). Care in endoscopy units should be maintained due to the risk of transmission by micro-droplets of aerosols suspended in the environment[42].

Despite being based on an outpatient retrospective cohort, the study published in this issue of the journal provides essential insights into the epidemiology, behavior of the chronic liver disease, and abnormal liver tests, confirming, in this group, a low mortality rate. However, given their low number, these results do not apply to the population of cirrhotic and transplanted patients. Therefore, vaccination and monitoring complications such as hepatocarcinoma remain vital.

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Original article

Nonalcoholic steatohepatitis: An emerging cause of cirrhosis in Colombia

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Abstract

Introduction: Cirrhosis of the liver is a significant cause of morbidity and mortality in Latin America; the increased prevalence of metabolic syndrome in our population could be changing the epidemiological profile of patients with advanced chronic liver disease. **Aim:** To characterize a group of patients with cirrhosis of the liver at an outpatient hepatology care center in Cartagena de Indias, Colombia, and determine the contribution of nonalcoholic steatohepatitis (NASH) as an etiological factor in this population. **Materials and methods:** Retrospective, cross-sectional, analytical study. All patients who attended the hepatology follow-up with a diagnosis of cirrhosis of the liver were in the six-monthly follow-up protocol that included screening for hepatocellular carcinoma (HCC) and esophageal varices. **Results:** 346 patients were included, most were women (54.3 %). The first and second causes of cirrhosis were cryptogenic (35 %) and NASH (30.9 %), respectively, followed by viral hepatitis (17 %) and autoimmune diseases (9 %). Of these patients, 87.4 % were within categories A and B of the Child-Turcotte-Pugh score, and only 12.5 % (33 patients) were in stage C. Also, 60 % had at least one clinical decompensation, 38 % a history of variceal hemorrhage, and 4 % a diagnosis of HCC; 80.6 % of patients with NASH cirrhosis had diabetes, and 46.7 % were overweight. **Conclusion:** NASH cirrhosis is an emerging cause of advanced chronic liver disease in Colombia.

Keywords

Nonalcoholic fatty liver disease, cirrhosis of the liver, metabolic syndrome.

INTRODUCTION

Cirrhosis, or advanced chronic liver disease, is the final stage of all chronic diseases that affect the liver[(1)], a dynamic inflammatory process characterized by progressive fibrosis of the parenchyma and severe disruption of hepatic lobular and vascular architecture[(2)].

Any chronic aggression against the hepatic parenchyma will eventually result in cirrhosis[(3)]. Non-alcoholic fatty liver disease (NAFLD) remains the leading cause worldwide chronic liver disease[(4,5)]. As of 2017, the second most frequent liver transplant cause in the United States after hepatitis C virus (HCV) infection[(6)].

NAFLD is defined as a spectrum of alterations in the liver parenchyma. These alterations include the accumulation of triacylglycerol (TAGs)-rich microvesicular and macrovesicular lipid droplets without other secondary causes[(7)]. It primarily manifests in people with dyslipidemia, carbohydrate metabolism, and eating disorders. Like obesity, sedentary lifestyle, and high-calorie diet rates have increased, as has non-alcoholic steatohepatitis (NASH)[(4,5)]. An estimated 20% will have NASH from the total number

of patients diagnosed with NAFLD. In this group, between 3% and 20% will progress to cirrhosis, and between 4% and 27% will have hepatocellular carcinoma (HCC)[8,9].

In recent years, several studies have detected a NASH rate increase in Colombia as one of the main etiological factors of advanced chronic liver disease in specialized care centers in different geographical areas of the national territory[10-12]. These studies have been conducted in overly complex hospital reference centers, where patients in more advanced stages of the disease are usually admitted, possibly leading to an underestimation of the relevance of NASH as an aetiological factor of cirrhosis in our environment. Conducting this study in an outpatient hepatology center could more accurately reflect the relevance of NASH as a cause of advanced chronic liver disease in our country.

The main objective of this study was to describe a group of patients with liver cirrhosis. Additionally, to determine the contribution of NASH as an etiological factor of this population in Cartagena de Indias, Colombia, in an outpatient hepatology care center.

METHODOLOGY

A retrospective, cross-sectional, analytical study was conducted. Clinical records of patients were used as the primary source of information. This study took place between January 2013 and August 2020. The population consisted of all the patients visiting Centro Médico Gastropack for liver care monitoring in the city of Cartagena de Indias, Colombia, with a liver cirrhosis diagnosis through:

- Clinical criteria: Signs of decompensation and laboratory findings or an upper GI endoscopy (EGD) confirming the presence of esophageal varicose veins.
- Radiological criteria: Liver surface nodularity (LSN) increase, liver echogenicity at ultrasound examination increase, right lobe atrophy, hypertrophy of the caudate lobes, liver volume (LV) decrease, portosystemic collaterals, HCC.
- Elastography criteria: The Baveno VI > 15 kPa definition was used regardless of etiology[13].
- Pathological criteria: Liver biopsy with evidence of severe fibrosis or established cirrhosis.

The following paraclinical tests were systematically requested at the time of liver cirrhosis diagnosis to determine the etiology: Hepatitis B surface antigen (HBsAg), anti-HCV, protein electrophoresis, immunoglobulin G (IgG) levels, immunoglobulin M (IgM) levels, ceruloplasmin, ferritin, transferrin saturation index, total antinuclear antibodies, anti-smooth muscle antibodies, anti-mitochondrial antibodies, complete blood count, lipid profile, glycated hemoglobin (HbA_{1c}), creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, direct bilirubin, albumin, international normalized ratio (INR), alkaline phosphatase, and γ-glutamyltransferase as part of the staging of the degree of liver injury.

All study subjects were under a monitoring protocol that included screening for hepatocellular carcinoma (total abdominal ultrasound and measurement of alpha-fetoprotein every 6 months) [14] and esophageal varicose veins EGD as follows[13]:

- EGD was performed every 2 years in compensated patients without varicose veins in the EGD screening and persistent liver injury.
- EGD was performed yearly in compensated patients with small varicose veins and persistent liver injury.
- EGD was performed every 3 years in compensated patients –with no varicose veins in the EGD screening, for whom the etiological factor was controlled and had no other related risk factor.
- EGD was performed every 2 years in compensated patients –with varicose veins in the EGD screening, for whom the etiological factor was controlled and had no other related risk factor.
- EGD was performed every year in decompensated patients.

The CEAP classification[15] was used to describe esophageal varicose veins.

The etiological diagnosis of cirrhosis was made following the current international clinical practice guidelines. NAFLD diagnosis was conducted per the *American Association for the Study of Liver Diseases* (AASLD) of 2018[16]. HCV diagnosis infection was determined according to 2019 AASLD recommendations[17]. Chronic hepatitis B virus (HBV) diagnosis was determined according to the 2018 AASLD recommendations[18]. Autoimmune hepatitis (AIH) diagnosis was determined following the 2019 AASLD recommendations[19]. Alcohol-related liver disease diagnosis was determined using the 2019 AASLD diagnostic criteria[20]. Primary biliary cholangitis diagnosis was determined using the 2018 AASLD diagnostic criteria[21]. Primary sclerosing cholangitis diagnosis was determined according to the 2009 AASLD guidelines[22]. Cryptogenic cirrhosis was discerned in cases where determining attributable etiology was impossible.

Statistical Analysis

Percentages were used for the description of qualitative variables. To determine statistical significance, the difference between means and medians was compared among the quantitative variables, considering $p < 0.05$.

Ethical Aspects

This study did not entail any risk to the participants as no intervention was performed. All ethical standards for research in human beings given by Colombian Resolution 8430 of October 4, 1993, and the guidelines of the Declaration of Helsinki were met. This document was submitted to and approved by the Gastropack ethics committee.

RESULTS

In this study, 346 clinical records of patients with previous cirrhosis of the liver diagnosis were included. They visited outpatient monitoring by hepatology between January 2013 and August 2020. No diagnosis was made *de novo* because all patients were referred from other institutions. Neither was it possible to determine the time since diagnosis due to the lack of information in the medical records analyzed. Due to a lack of data, it was impossible to assess alcohol consumption in alcohol-related cirrhosis patients.

Most patients were women (54.3%). The diagnosis was mostly made using the clinical-radiological method (73.4%). Only 51 patients (14.7%) had the definitive pathological study (**Figure 1**). The most common causes of advanced chronic liver disease were cryptogenic in 35% of the population (121 patients) and NASH cirrhosis, 30.9% (107 patients) (**Figure 2**).

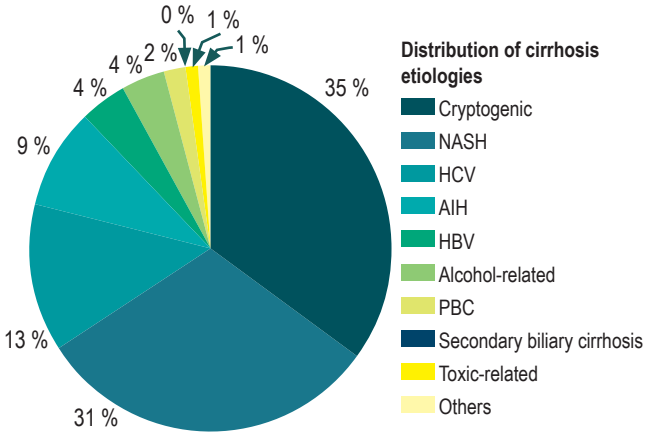


Figure 1. Distribution of cirrhosis etiologies. AIH: Autoimmune hepatitis; PBC: Primary biliary cholangitis; Secondary biliary cirrhosis; NASH: Non-alcoholic steatohepatitis; HBV: Hepatitis B virus; HCV: Hepatitis C virus.

No statistically significant differences were found in our study in terms of decompensation rates (p = 0.081). The highest decompensation percentages were found in patients with secondary biliary cirrhosis (100%) and toxic-related cirrhosis (100%). The lowest decompensation rates were found in patients with primary biliary cholangitis (PBC) (50%) and the category of other etiologies (50%) (**Table 1**).

Due to a lack of data during admission, the Child-Turcotte-Pugh prognostic scale was calculated in 76% (264 patients) of the study population. Of them, 51.1% (135 patients) were in stage A, 36.3% (96 patients) in stage B, and only 12.5% (33 patients) in stage C (**Table 1**). Of the total number of patients, 60.1% (208 patients) had a history of decompensation in the months before the outpatient evaluation. The main decompensation causes were ascites 36.7% (127 patients), upper GI bleeding in 23.6% of cases (82 patients), and hepatic encephalopathy in 22.5% (78 patients). Of the total number of patients evaluated, 62.1% (215 participants) had esophageal varicose veins evidenced in the EGD, of which 50.6% corresponded to large varicose veins (**Table 1**).

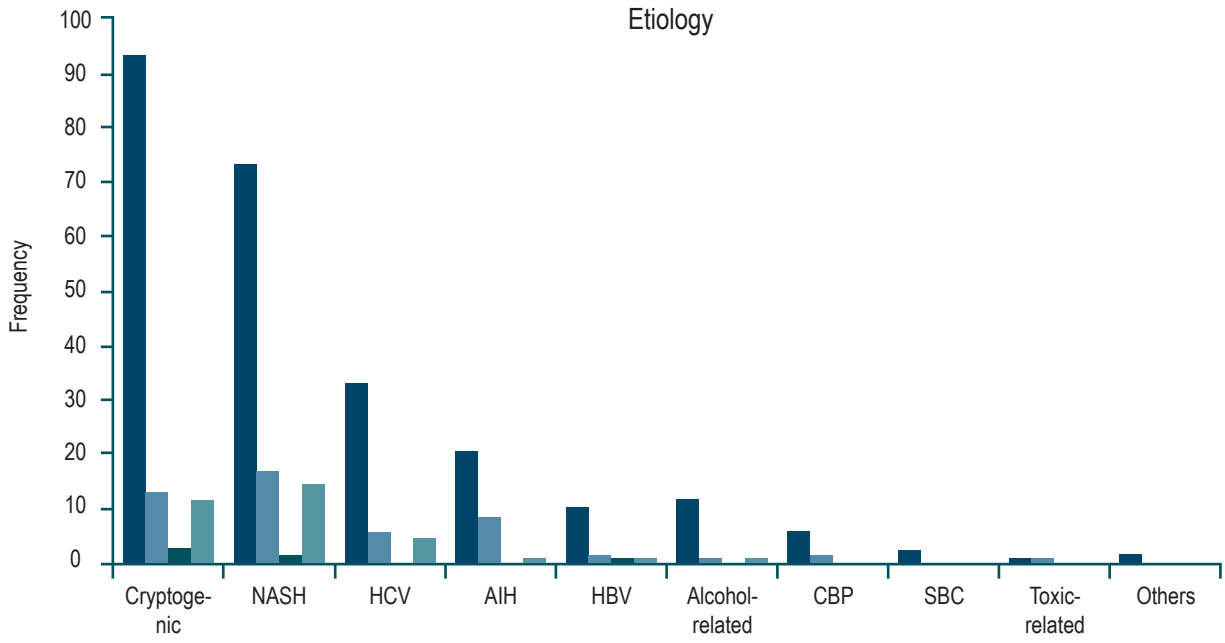
Among the different etiologies, there was a higher incidence of varicose veins in patients with secondary biliary cirrhosis in 100% (2 patients) and chronic HCV infection in 80.9% (34 patients). The lowest number of varicose veins incidence in patients was related to toxic and other different etiologies, 0%. Although, no statistically significant differences were evident (p = 0.062).

Regarding vein size, they were larger in secondary biliary cirrhosis patients with 100% of large varicose veins (2 patients) and 40% of cases (8 patients) in AIH (**Table 1**). Unfortunately, obtaining the body mass indices (BMI) for patients with non-NASH etiology cirrhosis was impossible due to a lack of information in the medical records.

Patients with NASH Cirrhosis

Of the total population, 107 patients showed a NASH cirrhosis diagnosis. The majority were women (54.2%). The diagnosis was mostly made using the clinical-radiological method (68.4%). Only 17 patients (15.8%) underwent the definitive anatomopathological study (**Figure 1**). Findings among these patients included 80.37% (86 patients) who had type 2 diabetes *mellitus* (T2DM), 46.7% (50 patients) were overweight (2 overweight patients; 48 obese patients), 41.12% (44 patients) had dyslipidemia, and 13% (14 patients) had primary hypothyroidism (**Table 2**).

Due to a lack of information, only the Child-Turcotte-Pugh prognostic scale in 85.9% (92 patients) was calculated. Of them, 60.9% (56 patients) were in class A, 32.6% (30 patients) in class B, and only 6.5% (6 patients) in class C (**Table 1**). Of the total population, 51.4% (55 patients) had a history of decompensation in the months before the outpatient evaluation. The main cause was ascites in 29.9% of cases (32 patients), followed by hepatic encephalopathy in 24.5% (26 patients) and upper GI bleeding in 21.7% (23 patients). Of the total number of patients evaluated with



	Cryptogenic	NASH	HCV	AIH	HBV	Alcohol-related	CBP	SBC	Toxic-related	Others
Clinical radiology	93	73	33	21	11	12	6	2	1	2
Biopsy	13	17	6	9	2	1	2	0	1	0
FibroSure test	3	2	0	0	1	0	0	0	0	0
Fibroscan	12	15	5	1	1	1	0	0	0	0

Figure 2. Diagnostic methods used discriminated by etiology. AIH: Autoimmune hepatitis; PBC: Primary biliary cholangitis; SBC: Secondary biliary cirrhosis; NASH: Non-alcoholic steatohepatitis; HBV: Hepatitis B virus; HCV: Hepatitis C virus.

NASH cirrhosis, 58.9% (63 participants) had esophageal varicose veins evidenced in the EGD screening, and 58.9% corresponded to large varicose veins (**Table 1**).

DISCUSSION

This study showed that NASH cirrhosis is the second most important cause of advanced chronic liver disease in our environment (30.9%), only below cryptogenic cirrhosis (35%) (**Figure 1**). However, it is worth noting that some of these patients could correspond to late-diagnosed NASH cirrhosis.

This finding, known as a *burnt-out phenomenon,* is well documented in the medical literature and refers to the paradoxical event that occurs in the most advanced fibrotic stages of the disease, in which the histopathological findings reveal little or no amount of fatty deposit, making definitive aetiological diagnosis difficult[22]. For this reason, NASH has been recognized as one of the leading causes of cryptogenic cirrhosis and accounts for most cases[24-26].

However, this relationship is not always easy to determine because the available studies are primarily retrospective, and not all the information necessary to establish a definitive etiology is available. In addition, in daily practice, many biopsies are performed in the advanced stages of the disease. Moreover, changes in lifestyle aimed at patients with metabolic risk factors could modify the appearance or progression of NASH, making the aetiological link even more difficult at the time of diagnosis. Thus, potentially explaining why the primary origin of cirrhosis in our study was cryptogenic.

The actual incidence of NASH cirrhosis remains unknown since the existing studies used different population groups, diagnostic methods, and other variable parameters with inconsistent epidemiological results[27]. Nonetheless, more recent data have shown an increase in the prevalence of NASH cirrhosis and advanced fibrosis associated with NAFLD between 2 and 2.5 times compared to results from previous years[28].

Table 1. Characteristics of Inpatients Classified by Etiology

Cause/variables (%)	Cryptogenic n (%)	NASH n (%)	HCV n (%)	AIH n (%)	HBV n (%)	Alcohol-related n (%)	PBC n (%)	Secondary Biliary Cirrhosis n (%)	Toxic-related (%)	Others n (%)	p
Gender											
- Women	65 (53.7)	58 (54.2)	27 (61.4)	23 (74.2)	5 (33.3)	0	5 (62.5)	1 (50)	2 (100)	2 (100)	0.001
Esophageal Varicose Veins											
- Yes	73 (64.0)	63 (64.2)	34 (80.9)	20 (74)	7 (63.6)	11 (78.6)	5 (71.4)	2 (100)	0	0	0.062
Size of Varicose Veins (VVs)											
- Small	18 (24.6)	22 (34.9)	14 (41.1)	4 (20)	5 (71.4)	5 (45.4)	2 (40)	0	0	0	0.119
- Medium	17 (23.2)	9 (14.2)	9 (26.4)	4 (20)	1 (14.2)	1 (0.09)	1 (20)	0	0	0	
- Large	26 (35.6)	22 (34.9)	6 (17.6)	8 (40)	0	3 (27.2)	0	2 (100)	0	0	
- Unclassified	12 (16.4)	10 (15.8)	5 (14.7)	4 (20)	1 (14.2)	2 (18.1)	2 (40)	0	0	0	
Red Dots											
- Yes	7 (9.5)	8 (12.6)	2 (5.8)	1 (5)	0	2 (18.1)	0	0	0	0	0.486
- No	47 (64.3)	37 (58.7)	25 (73.5)	14 (70)	5 (71)	6 (54.4)	3 (60)	1 (50)	0	0	
- No Reference	19 (26)	18 (28.5)	7 (20.5)	5 (25)	2 (28)	3 (27.2)	2 (40)	1 (50)	0	0	
Decompensation*											
- Yes	77 (63.6)	55 (51.9)	30 (68.2)	16 (51.6)	8 (53.3)	13 (92.9)	4 (50)	2 (100)	2 (100)	1 (50)	0.081
Ascites*											
- Yes	51 (42.1)	32 (30.2)	16 (36.4)	9 (29)	6 (40)	9 (64.3)	2 (25)	1 (50)	0	1 (50)	0.287
Hepatic Encephalopathy*											
- Yes	27 (23.3)	26 (24.5)	8 (18.2)	8 (25.8)	1 (6.7)	6 (42.9)	1 (12.5)	0	1 (50)	0	0.451
Hepatocellular Carcinoma (HCC)*											
- Yes	6 (5)	4 (3.8)	6 (13.6)	0	0	0	0	0	0	0	0.221
Upper GI bleeding*											
- Yes	25 (20.7)	23 (21.7)	13 (29.5)	7 (22.5)	3 (20)	7 (50)	2 (25)	1 (50)	0	1 (50)	0.409
Child-Pugh Classification*											
- A	33 (42.9)	56 (60.9)	18 (47.4)	12 (54.5)	8 (66.7)	2 (20)	4 (50)	0	0	2 (100)	0.05
- B	32 (41.8)	30 (32.6)	15 (39.5)	7 (31.8)	1 (8.3)	4 (40)	4 (50)	1 (100)	2 (100)	0	
- C	12 (15.6)	6 (6.5)	5 (13.2)	3 (13.6)	3 (25)	4 (40)	0	0	0	0	

*Note that data could not be obtained for all patients.

In the first reports made in Latin America, NASH was not among the most relevant causes of cirrhosis. It is probably related to the lack of awareness of the disease and the poor search for comorbidities[29]. More recent studies, such as the one conducted by García *et al.*, in 2020, in Argentina, have highlighted the increase in NASH cirrhosis diagnoses in recent years, identifying it as the third most important cause of cirrhosis (13.5%) and showing a significant increase when compared to the 1995-2002 period, in which no diagnosis was made[30].

Apart from the fact that population genetic differences could explain these variations, it is also true that the lack of uniformity in the diagnostic methods used and the absence of specific protocols for screening this population have led to a large number of patients with NAFLD being diagnosed in advanced stages of the disease.

Multiple descriptive studies of the population with liver cirrhosis have been conducted in Colombia. In 2013, Giraldo-Montoya *et al.* conducted a descriptive study in a cohort of patients with a previous diagnosis of advanced

Table 2. Comorbidities Found in Patients Diagnosed with NASH Cirrhosis

	NASH Cirrhosis		
	Yes n (%)	No n (%)	No information n (%)
DM2	86 (80,3)	21 (19,6)	0
Overweight	50 (46,7)	22 (20,5)	35 (32,7)
- BMI = 25-29.9 kg/m^2	48		
- BMI ≥ 30 kg/m^2	2		
Dyslipidemia	44 (41,1)	62 (57,9)	1 (0,9)
Primary Hypothyroidism	14 (13,1)	21 (19,6)	72 (67,2)

chronic liver disease in outpatient hepatology follow-up, which showed that NASH cirrhosis was the fourth most prevalent cause (11%)[10].

In 2016, Prieto *et al.* ranked NASH as the leading cause of cirrhosis (25.5%) in a group of patients in Bogotá who consulted outpatient monitoring for hepatology[12]. In 2017, Escorcia *et al.* conducted a retrospective, cross-sectional study in Barranquilla to describe cirrhotic patients under outpatient follow-up. In that study, they found NASH cirrhosis as the second most important cause of the advanced chronic liver disease (24.6%)[11].

Regarding previous local studies data, our study shows that there has been an increase in the proportion of these patients. In our population, 30.92% had a diagnosis of NASH cirrhosis, the highest number reported in recent years, which could be higher given that many of the patients with cryptogenic cirrhosis could correspond to late NASH cirrhosis diagnosis, as previously mentioned. This upward trend is related to the increased prevalence of metabolic risk factors nationally.

In Colombia, according to data from the Food and Nutritional Security Observatory (OSAN, for its acronym in Spanish), the prevalence of obesity went from 13.7% in 2005 to 16.5% in 2010 and 18.7% in 2015. In the same period, the prevalence of overweight went from 32.3% to 34.6% and 37.7% in 2015[31]. As a result, obesity has led to an increase in mortality and a higher risk of presenting chronic non-communicable diseases (NCDs) such as DM2, high blood pressure (HBP), dyslipidemia, and cardiovascular disease (CVD)[32] all risk factors for the development and NAFLD progression[33,34].

In our report, 46.7% of patients with NASH cirrhosis were overweight (2 overweight patients, 48 obese patients). Although this association could be even higher due to the retrospective nature of our study, about 33% did not have a BMI record, which could underestimate the prevalence in this cohort. In addition, some findings showed that 80.37% of these patients had DM2, correlating the results of Giraldo-Montoya *et al.,* who reported that 85.7% of their patients with NASH cirrhosis had diabetes[10]. Lower rates of dyslipidemia were found in our registries.

Regarding the prognosis of the disease, 51.1% of the global cohort was in Child-Pugh class A, unlike the study by Giraldo-Montoya *et al*[10], in which the majority corresponded to class B and C of the Child-Pugh, indicating that our population was diagnosed in earlier stages of the disease. Therefore, the findings offer a closer view of the general population's expected behavior.

Concerning the decompensation frequency, higher rates were found (both in the overall cohort and in the NASH cirrhosis cohort) when compared with the studies by García *et al*[30] and Escorcia *et al*[11] that were also performed in outpatient hepatology centers. Although they were lower when contrasted with the study Giraldo-Montoya *et al*[10] conducted on hospitalized patients, as expected.

Some studies have shown an apparent discrepancy in the risk of decompensation at 5 years between the different causes of advanced chronic liver disease. Alcoholic cirrhosis showed the highest rate of decompensation[35]. NASH cirrhosis ranks only below this, with a risk of decompensation at 5 years of 23.6 ± 7.8%[35]. Statistically, our study did not show significant differences ($p = 0.05$).

This study reveals an increase in the diagnosis of NASH cirrhosis in our country. This phenomenon may be related to the increased prevalence of reported overweight and obesity and the current awareness of the disease.

Due to the retrospective nature of our study, it was impossible to describe all the patients according to their BMI, which was a crucial datum, as stated in the discussion. However, this study's strength is that our trial was not conducted in a high-complexity hospital. Instead, this clinical trial took place in an outpatient hepatology care center, which offers a closer view of the general population.

CONCLUSIONS

Our results point to NASH cirrhosis as an emerging cause of advanced chronic liver disease in our environment.

In the future, the design of strategies aimed at reducing the burden of liver disease in Colombia should prioritize specific and comprehensive actions for patients with NAFLD, ensuring the rational and practical use of available resources.

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Original article

Gastrointestinal food allergy: Prevalence, characterization, and direct costs in a referral center in Bogotá

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Abstract

Introduction: The prevalence and incidence of gastrointestinal food allergy has increased in recent years with high associated costs, but usually with a good prognosis; nonetheless, in Colombia, information is scarce. This study intends to describe demographic variables, symptomatology, clinical picture, nutritional status, management, and natural history of the disease, determine its prevalence in the Colombian pediatric population by age group, and describe its direct costs. **Materials and methods:** The study was conducted in three phases. In the first, we estimated the prevalence of the disease from the review of the RIPS and MIPRES databases between 2015 and 2019. Secondly, we checked the medical records selected per the inclusion and exclusion criteria for characterization and costs. Lastly, through a telephone survey, we asked about the current state of the disease and its resolution. **Results:** The estimated prevalence adjusted for underreporting was 0.04 % for the pediatric population and 0.148 % for those under five. The most frequent diagnoses were allergic proctocolitis (59.3 %) and secondary functional gastrointestinal disorders (13.9 %). The most frequent allergen was cow's milk protein. Early management is related to an excellent nutritional prognosis. Direct costs are mainly related to using formulas (92 %) and medical appointments (3.4 %); 89 % of parents consider that the food allergy will resolve over time. **Conclusions:** This retrospective study is the most extensive in Colombia, drawing local conclusions that may be compared with other countries.

Keywords

Food hypersensitivity, gastrointestinal, pediatrics, characterization, prevalence, direct costs.

INTRODUCTION

Food allergy occurs due to an immune-mediated response to one or more allergens. They can manifest clinically in different systems, including the cutaneous, respiratory, or gastrointestinal systems, reflecting individual susceptibility[1]. This allergy varies according to its immunological mechanism, leading to different phenotypes[2]. The more delayed non-IgE-mediated responses are more difficult to identify, unlike immunoglobulin E (IgE)-mediated food allergies. There are no simple tests to confirm the clinical suspicion. The golden test for diagnosis is the elimination of the allergen and the reintroduction or challenge, observing the improvement of symptoms upon removal of the allergen and their reappearance with reintroduction. Children under 2 years can go through this rigorous open food challenge (OFC). However, older people undergo the double-blind placebo-controlled food challenge (DBPCFC)[3]. This is an expensive process that requires training. Additionally, symptoms of the challenge can take several days to appear[4].

The prevalence and incidence have increased over the years. The current series estimate a prevalence of 2% in the

general population. In children under 5 years of age, the series varies from 1% to 10% and reflects IgE-mediated allergies[5]. However, for non-IgE-mediated allergies, the evidence is limited given the clinical variability, the delayed symptoms development after exposure, and the lack of standardized diagnostic criteria. Hence, these results in many studies have selection biases and a lack of sensitivity in case findings[6].

Although each food could be considered a potential allergen, the list of those responsible, especially concerning the most severe reactions, is limited to a few food groups[7]. Cow's milk allergy (CMA) is the most frequent. In a study conducted in Utrecht in 804 children, 7% had suspected (CMA) experiencing dermatological (71%), gastrointestinal (60%), respiratory (13%), and other (36%) problems. Fifty-six percent of the children underwent the oral food challenge test, but none had a proven allergy. Despite this, 71% were subjected to an elimination diet and the use of therapeutic formulas for long periods. In summary, it was necessary to improve diagnostic methods[8].

These food allergies reportedly have a good prognosis. The resolution rate has been reported in 56% of children at 1 year, 77% at 2 years, 87% at 3 years, 92% at 5 years, and 97% at 15 years[9]. In a Finnish study, children with non-IgE-mediated reactions developed tolerance earlier than those with IgE-mediated responses, 64% versus 31% at 2 years and 96% versus 63% at 4 years[10].

The economic burden of food allergy in the United States in 2007 was estimated at USD 510 million in total costs, with USD 340 million in direct costs per year. In addition, there were critical indirect costs with work absenteeism in parents and caregivers, which affected the quality of life[11]. No regional studies analyze the direct expenses of gastrointestinal food allergy.

In Colombia, the literature on gastrointestinal food allergy is scarce. Only one CMA study with a small population sample has been conducted[12]. The objectives of this study include describing demographic variables, clinical symptoms, nutritional status, established management, and natural history of the disease. Furthermore, to know the disease prevalence in the Colombian pediatric population (by age group) and to describe its direct costs.

MATERIALS AND METHODS

A study was conducted in 3 phases. The first phase consisted of estimating the prevalence of the disease through a query of the data from the Individual Registry of Health Services Provision (RIPS, by its abbreviation in Spanish) and My Prescription (MIPRES, by its abbreviation in Spanish). In the second phase, a retrospective descriptive study of the medical records of a cohort from a second-level pediatric gastroenterology reference center in Bogotá was conducted. Finally, in the third phase, a descriptive cross-sectional study was conducted on the selected cohort through telephone surveys. The protocol was approved by the ethics committee of Cayre Colombia, a healthcare provider.

The prevalence of the disease in Colombia was defined by consulting the database of the RIPS and MIPRES systems. The last 5 years were consulted age-by-age for those under 18 through the Integrated Information System of Social Protection (SISPRO, by its abbreviation in Spanish) [13] using Excel® pivot tables. The ICD-10 K522 (allergic and dietary colitis and gastroenteritis) code was used. This code is the most closely related to the diagnosis of gastrointestinal allergy. The demographic information from the National Administrative Department of Statistics (DANE, by its abbreviation in Spanish) was used to estimate the national prevalence and prevalence by age group.

Between September 2011 and September 2020, the medical records were selected using the related ICD-10 codes, K-522 (allergic and dietetic colitis and gastroenteritis) and K20 (esophagitis). All patient records with a diagnosis confirmed by elimination-challenge test, or in the case of eosinophilic diseases, by histology results, were included. Ambiguous or incomplete medical records were excluded. The researchers reviewed all the records, filling in the data on a standard collection sheet to avoid errors. Relevant information was obtained on demographic data, clinical manifestations, time of evolution, birth type, first solid food, other personal or family allergies, nutritional status, diagnosis, management, and disease evolution. Direct costs were evaluated according to the number of pediatric gastroenterology consultations per year, endoscopies, colonoscopies, and allergy tests (specific IgE and skin prick test), based on healthcare providers (IPS, by its abbreviation in Spanish) contract prices. The median age of diagnosis and the median age of resolution were considered for the use of infant formula calculation. Eventually, the formula was adjusted for the average consumption of 2 cans per week, as previously published[14]. Parents or caregivers were interviewed through the telephone to find out the current status of the patients. They were asked about age and present symptoms, persistent need to avoid some food, presence of other allergic diseases, and parents' opinion regarding the resolution of the disease.

The data were tabulated in an Excel® sheet. The RStudio software version 1.4.1106 was used for the descriptive analysis. All the variables were classified according to their category (numerical or categorical), and the respective distribution analyses were made for each.

RESULTS

In the 2018 population census, the DANE published that Colombia had 48,258,494 inhabitants, including 23,501,887

people under 18. The RIPS database showed that 26,286 patients were reported from 2015 to 2019. The average prevalence of the investigated diagnosis in the population under 18 years of age was 0.02%. During the evaluated period, the group with the highest prevalence of allergic or dietary colitis and gastroenteritis was younger than 5 years, with an average of 0.074%. An analysis by year shows an increase in cases from 3,757 in 2015 to 8,807 in 2019 (all pediatric populations included [**Figure 1**]). The analysis in the MIPRES database of special formulas for children with the diagnosis studied reported an average prevalence of 0.006 % of formulated patients and a higher prevalence for children under 4 years of age, with 0.03 %. This is consistent with the RIPS report that shows an increase in formulation from 1537 products in 2017 to 4859 products in 2020 (**Figure 2**).

During the selected period, the IPS attended 7471 patients in the pediatric gastroenterology specialty. Medical records of 757 under the established ICD-10 codes were reviewed, and 472 (6.3%) were selected after applying inclusion and exclusion criteria, 219 (46.3%) were female, and 253 (53.6%) were male. The diagnoses were proctocolitis in 281 patients (59.3%), functional gastrointestinal disorders (FGIDs) in 63 (13.9%), eosinophilic esophagitis (EoE) in 51 (10.8%), immediate gastrointestinal hypersensitivity in 25 (5.3%), other eosinophilic diseases of the gastrointestinal tract in 9 (1.9%) and food protein-induced enterocolitis syndrome (FPIES) in 4 (0.84%). **Figure 3** shows the population distribution by diagnosis, age, and gender. According to gender, the median age in allergic proctocolitis (APC) was 3 months (0.4-9), and in

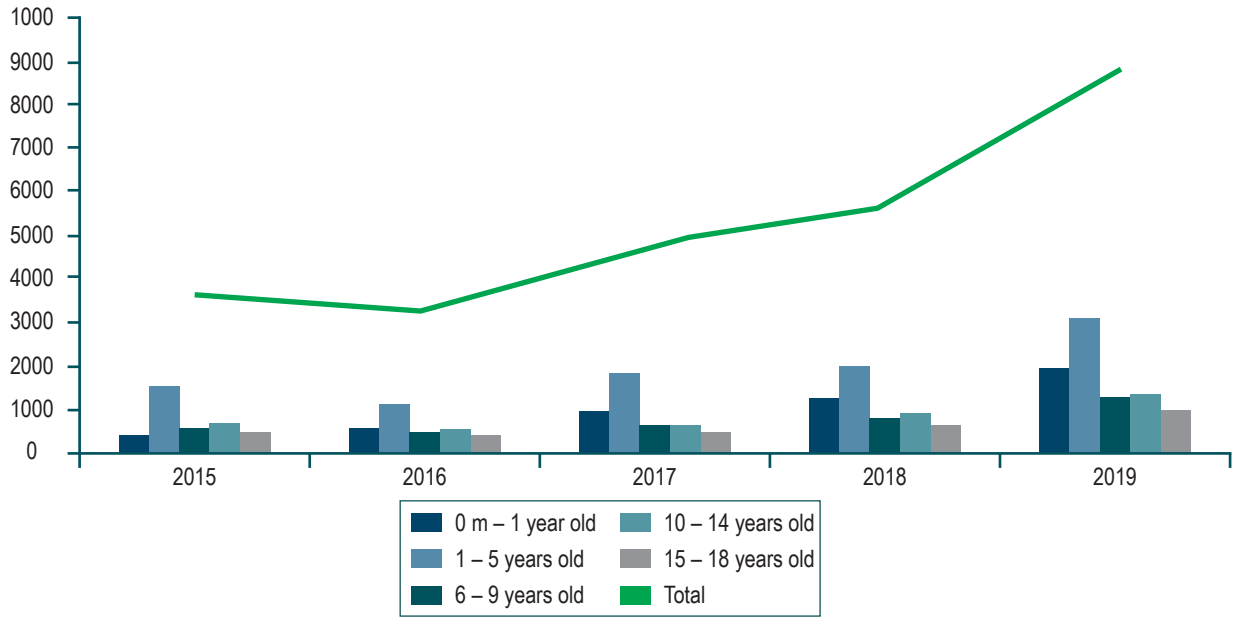

Figure 1. K522 allergic and dietetic gastroenteritis and colitis cases by age and year (RIPS).

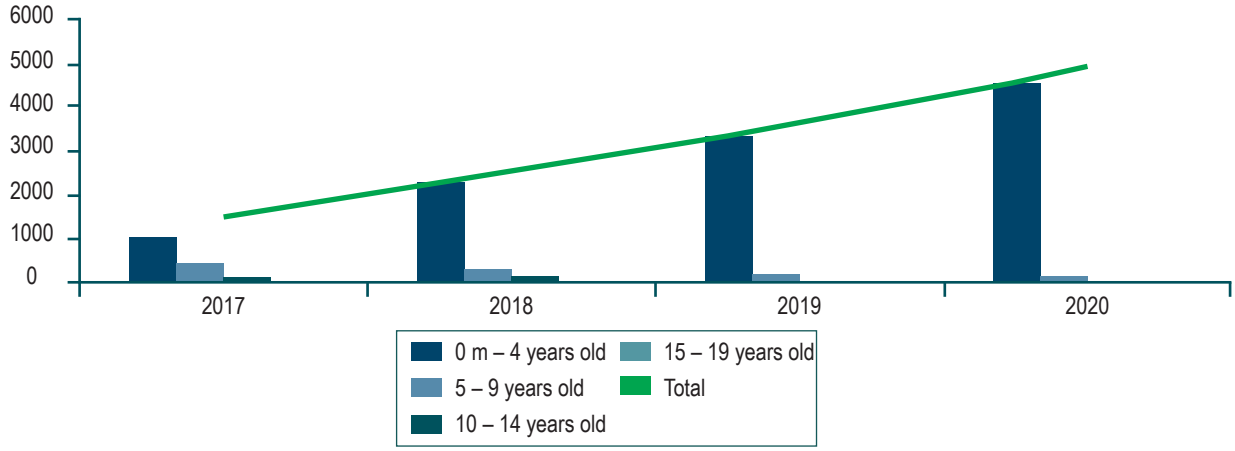

Figure 2. Special formulas for children diagnosed with allergic and dietetic gastroenteritis and colitis (number of products per year).

FGIDs, 3 and 4 months (1-15). Immediate gastrointestinal hypersensitivity and enteropathies showed a distribution between 12 and 24 months of life, and for eosinophilic diseases, the onset age was school age.

The main reasons for consultation were hematochezia in 275 patients (58.2%), diarrhea in 39 (8.26%), gastroesophageal reflux in 35 (7.41%), colic in 34 (7.2%), and others in 89 (18.8%). The median age at first consultation was 4 months, and most patients (75 %) were between 0.4 and 11 months old. Symptom evolution time at the first consultation showed a median of 3 months, most patients (85%) were seen before 6 months old. There were 272 patients (57.6 %) delivered by cesarean section, which was the dominant form of proctocolitis in 60 % of patients and FGIDs in 72 % of the patients (**Table 1**). Infant formula with CMP remained the first feeding at birth in 213 patients (61%) compared to 133 with breast milk (39%), distributed by diagnosis similar to birth type. Other allergic diseases reported on admission were atopic dermatitis (eczema) (13.3%) and asthma (3.8%). Most of the children (64%) had a family history of allergy. The type of feeding before the onset of the disease in infants was distributed as follows: Exclusive breastfeeding in 140 patients (29.6%), mixed breastfeeding in 225 patients (47.6%), and exclusive infant formula in 35 patients. (7.4%).

During the nutritional evaluation, the Z *score* for weight-for-age at the first visit showed a median of -0.64, height-for-age showed a median of -0.5 sd, and weight/height (W/H) in children under 2 years of age or body mass index (BMI) in older children had a median of -0.4 sd. A < -2 sd deficit was found specifically for weight/age in 13%, height/age in 10%, and W/H or BMI in 8%. At the first consultation, the W/H or BMI distribution by diagnosis and gender showed a greater nutritional involvement of enteropathies in females (**Figure 4**). In the follow-up, the last W/H or BMI Z *score* showed a median of -0.18, a ratio of patients with a (< -2 sd) deficit of 1.7%, and adequate nutritional management progress for the different types of diagnosis (**Figure 5**).

Dietary elimination of at least one allergen was required in 95.6 % of the population, where 91.3 % of the cases were CMA, followed by eggs in 4 %; in 14.6 % required 2 allergens elimination, and 5.5 %, 3 or more allergens were removed. Twenty-one patients who did not undergo dietary elimination belonged to the EoEs group.

Table 1. Diagnosis Related to Birth Type

	Vaginal Birth	Cesarean section	No information
Immediate gastrointestinal hypersensitivity	15	9	1
Proctocolitis	87	194	0
Enteropathy	22	13	1
Food protein-induced enterocolitis syndrome (FPIES)	3	1	0
Secondary FGIDs	18	47	1
Eosinophilic esophagitis (EoE)	7	4	40
Other eosinophilic FGIDs diseases	4	4	1

FPIES: Food protein-induced enterocolitis syndrome, GIT: Gastrointestinal tract, FGIDs: Functional gastrointestinal disorders.

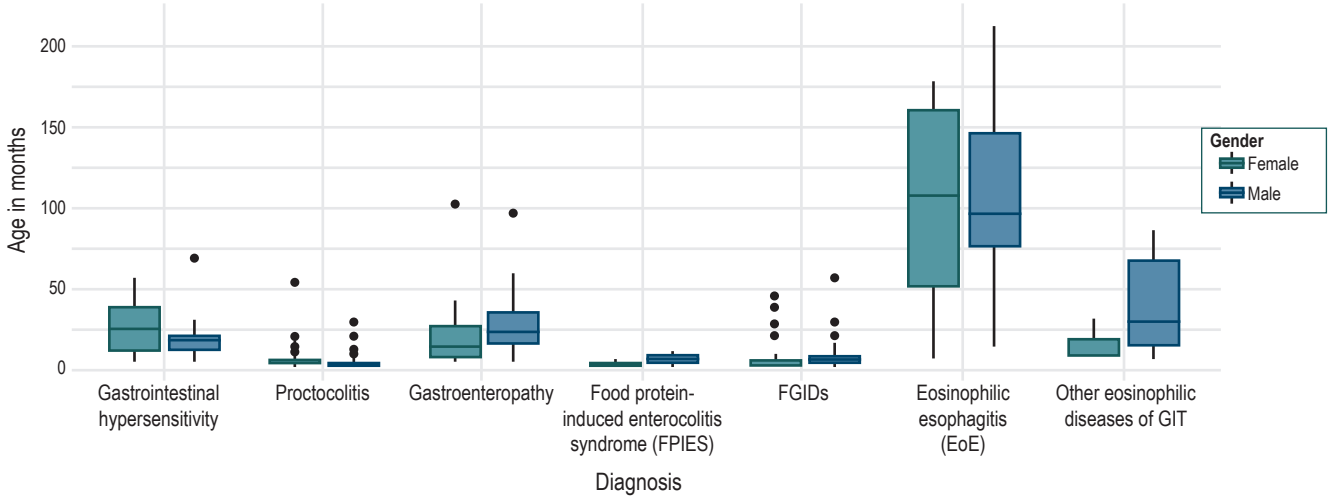

Figura 3. Distribution of the population by diagnosis according to age in months and discrimination by gender. FPIES: Food protein-induced enterocolitis syndrome, GIT: Gastrointestinal tract, FGIDs: Functional gastrointestinal disorders.

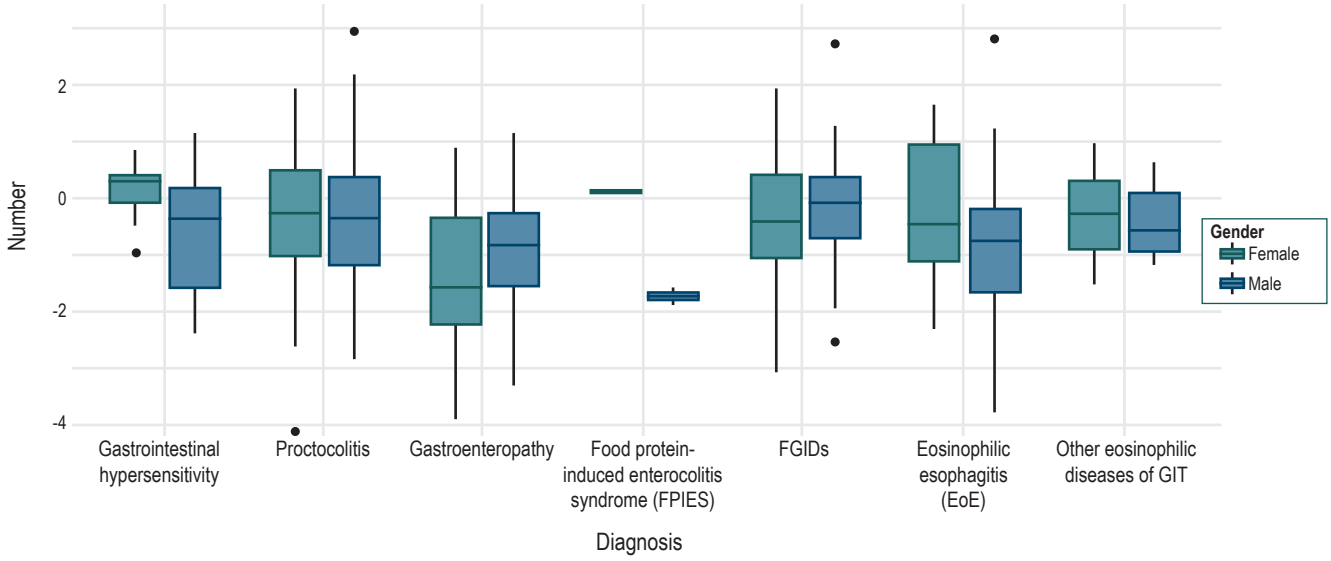

Figure 4. Distribution of the population according to the diagnosis by the weight/height ratio or BMI, discriminated by gender. FPIES: Food protein-induced enterocolitis syndrome, GIT: Gastrointestinal tract, FGIDs: Functional gastrointestinal disorders.

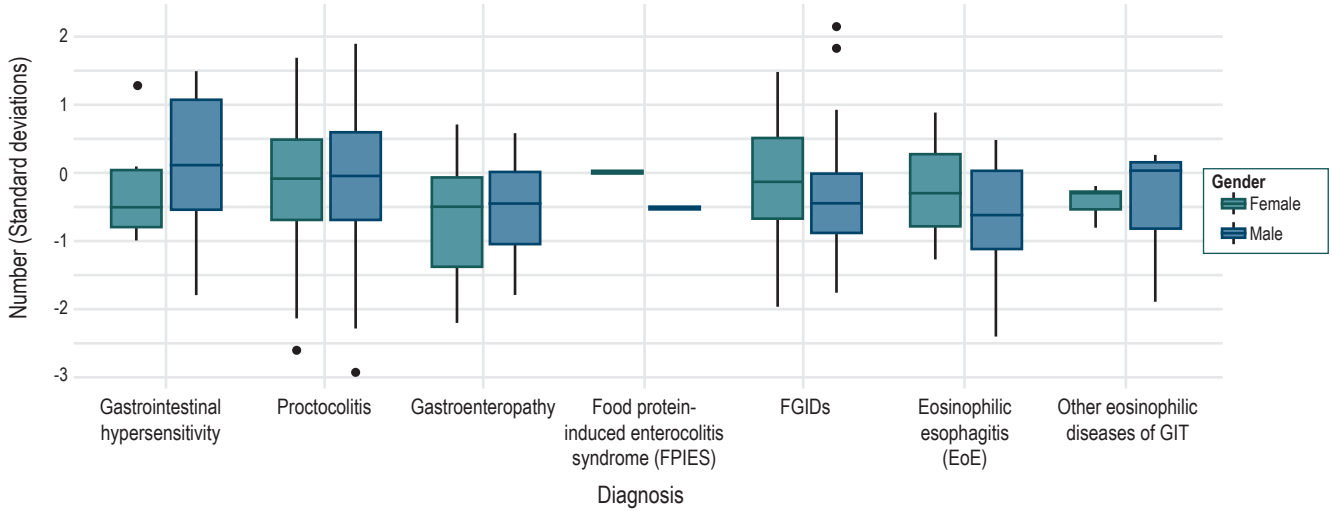

Figure 5. Distribution of the population according to the diagnosis by last weight/height ratio or BMI taken and discriminated by gender. FPIES: Food protein-induced enterocolitis syndrome, GIT: Gastrointestinal tract, FGIDs: Functional gastrointestinal disorders.

Some 29.2 % of the patients had no therapeutic formula prescription; 334 patients received a therapeutic formula, including 149 with casein extensively hydrolyzed formulas (EHF), 88 with amino acid (L) formulas, 78 with serum EHF formulas, 11 patients with soy formulas, and 8 with hydrolyzed rice formula. Distribution by diagnosis in **Table 2**.

The resolution age was established in 339 patients: Proctocolitis showed an 11-month median for both genders. FGIDs showed a median of 11 months for boys and 13 months for girls, and immediate gastrointestinal hypersensitivity showed a median of 24 months for boys and 43 months for girls. In enteropathies, there was a difference between genders with a later resolution age for males (a median of 45 months) compared to females (a median of 18 months) (**Figure 6**).

A total of 256 telephone surveys were conducted with a median age of 70 months (range: 10-293). The most frequent symptom was constipation (21.5%), followed by recurrent abdominal pain (9%), while 60% did not report any symptoms. Regarding the need to restrict some food in the diet, 87.5% said no dietary restriction, 7.4% reported CMP restriction, and 2.3% eggs, 20.7% of patients suffer

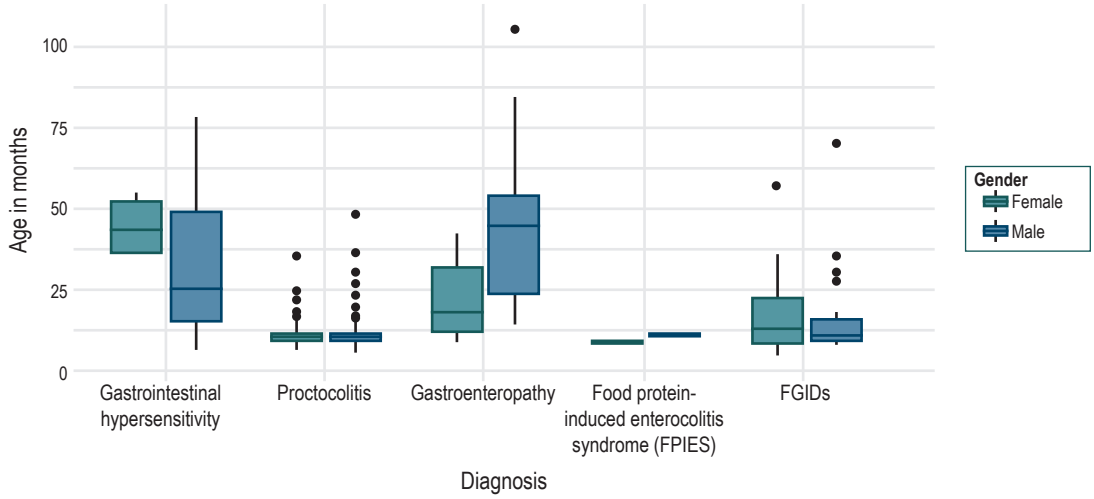

Figure 6. Distribution of the population according to diagnosis by resolution age and disaggregated by gender.

from allergic rhinitis, 12% from atopic dermatitis, and 12.9% have 2 or more allergic diseases, 57.4% denied the presence of other allergies, 89% of parents reported resolution of their child's food allergy.

The direct costs (Colombian pesos [COP], 2020) included the number of pediatric gastroenterology consultations per year, averaging 4, costing COP 160,000 per patient, 112 upper gastroenterology endoscopies for a unit cost of COP 321,000, equivalent to COP 76,170 per patient, 14 colonoscopies for a unit price of COP 425,000, corresponding to COP 12,606 per patient. Specific IgE measurement was performed in 121 patients with a cost per allergen of COP 74,000 for 6 allergens, equivalent to COP 113,822 per patient. Twenty-four patients took the skin prick tests for a unit cost of COP 180,000, equal to COP 9,152 per patient. Based on a 2-can consumption per week (8.5 cans per month), equivalent to 60 cans in total per patient, the average time of formula use was 7 months. Of 334 patients who received formula, 235 (70%) received HFE casein or serum, and 88 (26.3 %) received amino acid formula. Because these formulas were not being marketed at the time of the study and reference prices could not be obtained, 11 patients who received soy formula were not included in the cost analysis. The average price of the EHF for the period studied was COP 80,000 per can and COP 170,000 per can for the amino acid formula. In the cohort, the cost for the use of therapeutic formulas was COP 4,292,000 per patient. Total direct costs were COP 4,662,725 for each patient per year.

DISCUSSION

Childhood food allergy is a chronic disease that significantly affects patients, parents, and caregivers' quality of life. Although food allergies are one of the world's most common chronic non-communicable diseases (NCDs), publications on disease burden and quality of life are scarce.

This study calculated the prevalence of gastrointestinal hypersensitivity according to the RIPS reports. Considering the report of the National Health Observatory, which conducted a comparative study between the RIPS and the 2010 National Demographic and Health Survey (ENDS, by its abbreviation in Spanish), is likely to be lower than the actual result, estimating a 50% underreporting by diagnosis in chronic non-communicable diseases[15]. The prevalence would be 0.04% for the pediatric population and 0.148% for children under 5 years of age if this expansion factor is applied. Similarly, there are no reports of population-based studies in the region to adjust this rate for underdiagnosis or misdiagnosis. A survey conducted in 2012 by the World Health Organization (WHO) reported that more than half of the countries surveyed did not have prevalence and incidence data, and only 10% performed an adequate diagnostic confirmation, while by parental report, a significant overestimation was observed.

Based on adequate diagnostic methods, a prevalence of 10% has been estimated in preschool children in developing countries and a marked increase in frequency in the last 10 to 15 years[5]. Similarly, we observed an increase

Table 2. Diagnosis and Use of Therapeutic Formulas

	EHF Casein	EHF Serum	EHF Rice	Soy F	AAF	No formula
Immediate gastrointestinal hypersensitivity	4	3	0	2	3	13
Proctocolitis	117	53	6	4	54	47
Enteropathy	4	6	0	5	6	15
Food protein-induced enterocolitis syndrome (FPIES)	1	0	0	0	2	1
Secondary FGIDs	22	16	2	0	14	12
Eosinophilic esophagitis	1	0	0	0	4	46
Other GIT eosinophilic diseases	0	0	0	0	5	4

Soy F: Soy-based formula, AAF: Amino acid formula; EHF Rice: Extensively hydrolyzed rice formula, EHF Cas: Extensively hydrolyzed casein formula, EHF Whey: Extensively hydrolyzed whey formula; FPIES: Food protein-induced enterocolitis syndrome, GIT: gastrointestinal tract; FGIDs: Functional gastrointestinal disorders.

of more than 100% in the number of cases reported between 2015 and 2019 in the RIPS. A lower prevalence of patients was observed compared to that reported in RIPS in the MIPRES database. Although, the formulation trend increased by 216% from 2017 to 2020. Based on the EuroPreVall cohort, which investigated school-age children in 8 European countries, parents reported adverse reactions to foods in 16.2% of children; however, confirmatory testing found only between 1.4% and 3.8%[16]. In a survey conducted in the United States to 38,408 parents and caregivers, the estimated prevalence of food allergy was 7.6%, with peanuts (2.2%), milk (1.9%), and shellfish (1.3%) as the most common allergens. Among allergic children, 43% presented at least one severe reaction and 39.9% showed a response to multiple allergens[17]. Evidence is even more limited for the prevalence of non-IgE-mediated food allergies given the clinical variability of presentation, the late symptoms development after exposure, and the lack of uniform diagnostic criteria[6]. Schoemaker *et al.* reported the incidence of allergy to CMP based on the EuroPreVall cohort at an adjusted rate of 0.74% during the first 2 years of life[18]. However, in this study, non-IgE-mediated allergy to CMP was not documented in 5 of the 9 participating countries that contributed 6,500 children to the study, which is why some authors considered a lack of sensitivity in the search process and selection bias[19].

Our retrospective study focused on all gastrointestinal hypersensitivity phenotypes, and the diagnosis was confirmed in 6.3%. Vieira *et al.* reported a 5.4% allergy rate to CMP in children referred to gastroenterology centers in Brazil[20]. Meyer *et al.* reported 12.6% of non-IgE-mediated gastrointestinal hypersensitivities in a tertiary referral center[21]. This figure variability could relate to the type of reference center, phenotypes included, and potential regional differences. Half of our patients were in the first 4 months of age. An additional 25% were up to 11 months. This is consistent with the literature published in countries such as the United Kingdom and Brazil[20,21]. As previously published in a Colombian study of CMA, the most common digestive symptom was hematochezia (58.2%), followed by diarrhea 39 (8.26%), gastroesophageal reflux 35 (7.41%), and colic 34 (7.2%)[12]. The most common diagnoses were proctocolitis (59.3%) and secondary FGIDs, including gastroesophageal reflux disease and colic (13.9%), most of the frequent diagnoses in infants under 1 year of age. The majority of our population was in this age group. As previously reported, 50% of the patients were seen within the first 3 months of symptom onset in our clinic, with a short clinical course[12,22,23].

However, the cohort report by Meyer *et al.* is striking. They evaluated patients in tertiary care with an average evolution of 63 months[21]. These differences may be related to the referral processes of health systems to more complex institutions. A delay in the time of diagnosis has been linked to a higher nutritional deficit, as reported in the Meyer study, in which 54% of the patients had poor growth. In our cohort, 13% of patients had a deficit greater than -2 sd in weight for age, a remarkably similar figure to that reported by Vera in Colombia and Vieira in Brazil with 15%[12,20]. Some 29.6% of the patients were under exclusive breastfeeding. Although reports of epidemiological studies of patients presenting CMA under exclusive breastfeeding are scarce, we still rely on Host et al.'s study, which revealed a prevalence of 0.5% of CMA in 1749 infants in 1988[24]. Given the increase in frequency in recent years, a recent study investigating this field would be desirable.

As previously reported, cesarean delivery and the use of CMP formulas in the first 24 hours of life are more frequent, especially in patients with proctocolitis and FGIDs[25].

The natural history of CMA has been previously evaluated. We found an 11-month resolution for patients with proctocolitis and FGIDs, which is consistent with the literature. We observed in our study a delayed resolution of enteropathy in males, even though it has a non-IgE-mediated mechanism, which could be affected by a more

severe or extensive involvement[18]. Other factors affecting tolerance development include elevated IgE, multiple food allergies, and other allergic diseases such as asthma, rhinitis, and severe atopic dermatitis[23]. We found that 13% had atopic dermatitis and 3.8% had asthma, contrary to reports by Meyer *et al.,* of 42% for atopic dermatitis and by Vera *et al*., who reported an association with other allergic diseases between 35% and 52% in the first year of life[12,21]. A likely reason for this difference is that in our series, we investigated the association of these other allergic diseases at the time of diagnosis, which was for most of our patients at 3 months of age. However, when investigating the disease evolution in the telephone survey, parents reported the presence of allergic rhinitis in 20%, and 13% had 2 or more allergic diseases. Sixty-four percent of our patients had a positive family history of allergy, a risk factor previously reported in the literature[25]. The primary allergen was CMA 91.3%, which was the most frequent allergy, as previously reported by Dierick *et al*[26].

Of the patients who required formula use, 68% received EHF, and 26% received amino acids. The choice of the therapeutic formula is usually based on the physician's decision. Although, among the factors that affect the formula selection include the patient's age, risk of anaphylaxis, FPIES, severe allergy to CMP with complications such as malnutrition, anemia, or hypoalbuminemia, and adherence[3].

Cow's milk protein, egg, soy, wheat, fish, and nuts are among the most common allergens in pediatric EoE. Current dietary management focuses on eliminating 2 to 6 allergens, considering that very restrictive diets have a significant impact on nutrition, added to difficulties due to adherence[27].

In monitoring current status by telephone interview, the most frequently reported symptom was constipation (21.5 %), followed by recurrent abdominal pain (9 %), similar to the prevalence reported in Colombia for the general pediatric population[28]. Functional constipation is estimated to account for 25% of consultations in a pediatric gastroenterology service. Less than 10% of patients require food allergens elimination in their diet, and 89% of parents reported the resolution of food allergy in their children, confirming the favorable evolution of food allergy with age, understanding that this varies according to its different phenotypes[29].

A Turkish publication based on expert consensus estimated direct costs for patients with proctocolitis due to CMA over 2 years at USD 2116.05 and USD 2435.84 from the payer and societal perspectives, respectively. Direct costs included medical visits, laboratory tests, and treatment (formula or clinical nutrition). Eighty-nine percent of the cost is generated by food formula. In our study, the formula cost constitutes 92% of the direct costs evaluated. The second cost in our research was medical visits to the gastroenterologist (4 visits per year), which accounts for 3.4% of total costs. In the Turkish study, an average of 11 visits were made by patients, but other specialties were included; however, as in our research, it was the second highest cost[30].

This study has several limitations. In calculating the prevalence from the RIPS and MIPRES registries, we could not establish an adjusted rate for underreporting or underdiagnosis. The information was collected from a second-level referral center for pediatric gastroenterology, which may not represent the Colombian population in general, particularly in the most severe cases of gastrointestinal hypersensitivity. A time horizon of 9 years in a field under continuous investigation can affect the results due to the changes generated in the approach of these patients. The study includes all the diagnostic phenotypes of gastrointestinal hypersensitivity, generating a high variability in the characterization data.

CONCLUSION

Thus far, this is the most extensive retrospective study published in Colombia, covering the demographic and clinical characteristics, management, and natural history of gastrointestinal food allergies. Hence, making information comparison with publications in other countries possible. Additionally, this study includes an analysis of prevalence and associated direct costs. Nevertheless, prospective and multicenter studies are needed in this ever-evolving field.

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Original article

Microscopic colitis: Case series and literature review

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Abstract

Introduction: Microscopic colitis is a benign and multifactorial disease characterized by watery diarrhea and histological alterations in the colonic mucosa. The incidence of this disease is increasing, being diagnosed more frequently. **Materials and methods:** In this retrospective study, patients were examined employing colonoscopy and biopsy due to a diagnosis of chronic diarrhea in a gastroenterology unit throughout 22 months. Their diagnosis of colitis was confirmed by clinical picture and microscopic analysis. **Results:** In the study period, a total of 2849 colonoscopies were performed, 116 in patients with chronic diarrhea. We identified 15 patients with microscopic colitis, 12 were men (80 %), and only three were older than 60 (20 %). **Conclusion:** Unlike the world literature, this study found that microscopic colitis in our patients affects the male sex primarily (male/female ratio: 4/1) and occurs in young people, with an average age of 47.5 years (range: 21–82 years).

Keywords

Diarrhea, microscopic colitis, lymphocytic colitis, collagen, budesonide.

INTRODUCTION

In recent years, the incidence of microscopic colitis (MC) has been increasing, as has the interest in studying this disease, about which little is still known. Potential incidence increases causes include the increasingly easy access patients have to colonoscopy procedures and the gastroenterologists and pathologists' growing view and knowledge on the subject. In some populations, MC has reached and exceeded the incidence of inflammatory bowel disease (IBD), especially Crohn's disease (CD)[1,2].

This disease affects people over 60, especially females, with a female/male ratio of 9/1 in collagenous colitis (CC) and a lower proportion in lymphocytic colitis (LC)[3]. According to various studies, CC affects between 4.1 and 10/100,000 people/year. Lymphocytic colitis affects between 4.9 and 10/100,000 people/year; it is more common in whites and Jews and less common in Asians and Hispanics[4].

As for its etiology, it is a multifactorial disease. Recently, it has been related to immunological factors; thus, some authors consider MC an initial IBD stage. A histological study confirms the diagnosis, but there is no consensus regarding the number of biopsies required. Some studies recommend 8 biopsies in each colonic segment to achieve the diagnosis[5].

There are 3 types of microscopic colitis. First, in lymphocytic colitis, where chronic inflammation of the lamina

propria is observed, the diagnostic criterion is the presence of more than 20 lymphocytes per 100 epithelial cells. The second is collagenous colitis, where the diagnostic criterion is the thickening of the collagen layer > 10 µm. Third, Incomplete microscopic colitis (MCi), including mixed symptoms typical of MC but no histological changes described. The ratio of lymphocytes to plasma cells is < 10/100, or the collagen layer is < 10 µm thick, which is why several researchers consider that the two forms initially mentioned do not correspond to two different diseases but to two different stages of the same disease[5].

In Latin America, most publications related to this disease correspond to topic reviews or case presentations without determining the disease's frequency[6-9]. The main objective of this study was to determine the number of microscopic colitis cases in a given period at Hospital Central de la Policía in Bogotá, Colombia, and, second, to evaluate the age and gender characteristics of patients diagnosed with MC in our health subsystem.

MATERIALS AND METHODS

Retrospective study of patient cases in which the pathology results of biopsies taken from all patients who underwent colonoscopy for a diagnosis of chronic diarrhea for 22 months, between February 2018 and November 2019, were reviewed and whose histological results confirmed the diagnosis of MC. We reviewed the gastroenterology service database, the pathology reports, and the medical records of the patients included in the study.

- Inclusion criteria: patients over 18 years of age with a diagnosis of chronic diarrhea (more than 4 weeks) who underwent colonoscopy and biopsy, with the availability of the pathology report.
- Exclusion criteria: patients who were not biopsied or whose pathology result was unavailable.
- Variables analyzed: Gender, age, blood count findings, colonoscopy diagnosis, and histopathology.

This work was approved by the institutional committee of ethics and research and followed the current regulations of bioethical research.

Since this was a retrospective study, informed consent was not required from the patients based on the medical history review.

RESULTS

In the 22 months between February 2018 and November 2019, 2,849 colonoscopies were performed in our institution for different diagnoses. Indications in 116 cases were chronic diarrhea. Chronic diarrhea was reported in 116 cases, in which biopsies were taken, and a histopathological report was available, resulting in 15 patients diagnosed with MC (**Figure 1**) due to the finding of lymphocyte infiltration in the lamina propria or due to thickening of the collagen layer. According to histological criteria, some microscopic colitis was found in 12.9% of patients who were biopsied for chronic diarrhea (**Figures 2** and **3**).

Eighty percent of the patients (n = 12) were males, and only 3 patients were females. The median age was 47.5 years (range: 21-82 years) only 3 patients were older than 60. Colonoscopy was described as entirely usual in 60% of patients (n = 9), alterations were described in 6 of them, and only 2 patients received a clinical diagnosis of non-specific colitis. The diagnosis of MC was confirmed histologically in 15 patients: Three with MC, 1 with CC, and 11 with MCi (**Table 1**).

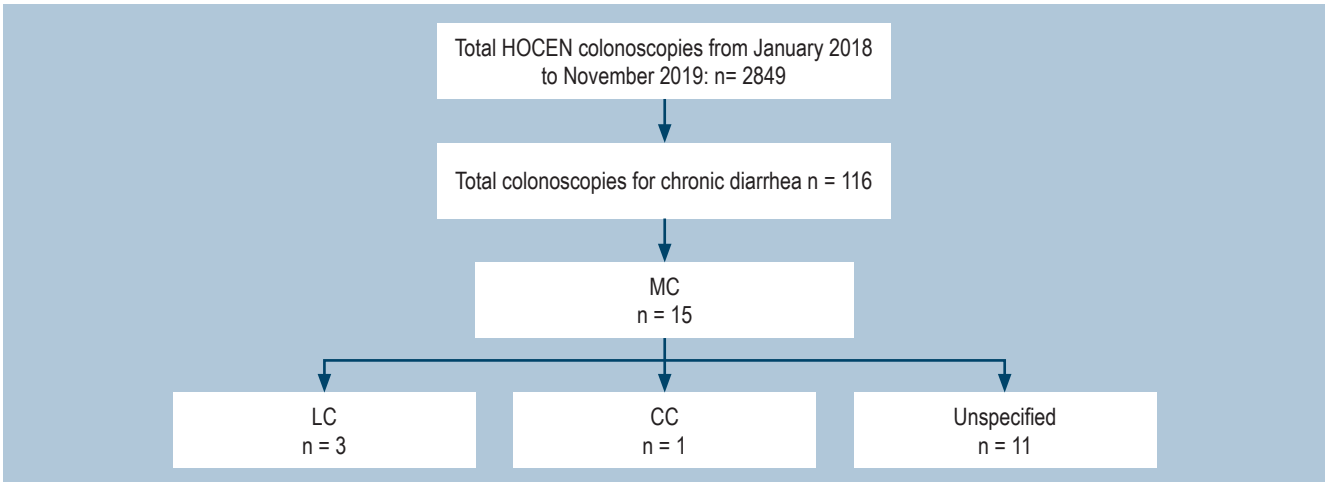

Figure 1. Histological findings of microscopic colitis in patients admitted for colonoscopy for chronic diarrhea.

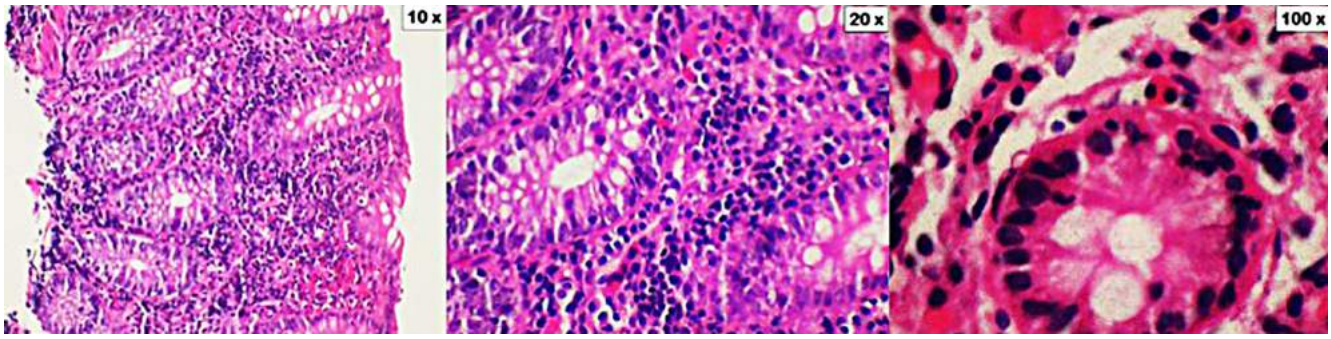

Figure 2. Lymphocytic colitis. The cuts show the mucosa of the colon distorted by a significant increase in intraepithelial lymphocytes (10x increase). In addition, there is a dense inflammatory infiltrate in the lamina propria consisting of lymphocytes, plasma cells, eosinophils, and occasional neutrophils (an increase of 20x and 100x). Coloration of hematoxylin and eosin (H&E).

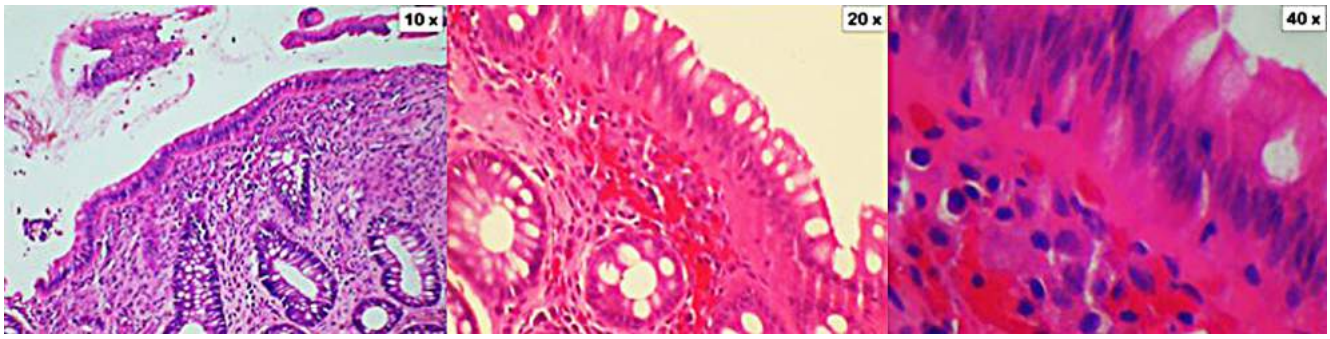

Figure 3. Collagenous colitis. The cuts show the mucosa of the colon distorted by the presence of a thickened subepithelial collagen band. Also, there are focal entrapment of capillaries, red blood cells, and inflammatory cells. In the lamina propria, there is a significant inflammatory infiltrate composed of lymphocytes, plasma cells, and eosinophils (10x, 20x, and 40x magnification). Coloration of hematoxylin and eosin (H&E).

Only one patient was found to have leukocytosis when reviewing the hemogram performed the month before the colonoscopy and biopsies. However, as in all the other patients, the total lymphocyte count was average (**Table 2**).

DISCUSSION

On the one hand, chronic watery diarrhea can occur due to various organic diseases, including IBD, MC, infections or intestinal bacterial overgrowth, and colon cancer. On the other hand, functional alterations can also cause this type of diarrhea, including Functional Diarrhea (FD) and Diarrhea-Predominant Irritable Bowel Syndrome (IBS-D). Current criteria for the diagnosis of these two entities are those described in the Rome IV classification and differ from each other by abdominal pain that is generally absent in FD and is very intense in IBS-D. Because many of the symptoms of these 2 diseases are similar to those caused by organic-type diarrhea, the final diagnosis is made by exclusion[3].

Currently, many authors include MC within the IBD group, alongside such significant pathologies as Chron's disease (CD) or ulcerative colitis (UC). However, it presents very different ages, symptoms, disease evolution, and treatment characteristics. Crohn's disease and UC are often considered systemic diseases, affecting not only the colorectal region but also frequently associated with other diseases and neoplastic complications, both of which have not been demonstrated concerning MC[10].

This disease was first described in 1976 by Lindström, who reported the case of a patient with watery diarrhea and CC. In 1982, Lazenby introduced the terms *LC* and *MC*. Epidemiological studies have shown an increasing incidence and prevalence, reaching levels similar to those of CD and UC. The incidence of MC has been increasing in the United Kingdom and the United States, although it appears to have stabilized in the latter[11].

Microscopic Colitis is characterized by non-bloody watery diarrhea associated with cramping-like abdominal

Table 1. Characteristics of Patients Diagnosed with Microscopic Colitis

Patient	Gender	Age (years)	Diagnosis by Colonoscopy	Histopathology
1	Male	37	Normal	LC
2	Male	31	Non-Specific Proctitis	LC
3	Male	35	Normal	LC
4	Male	64	Normal	CC
5	Male	82	Normal	(Non-Specific) Colitis
6	Female	53	Normal	(Non-Specific) Colitis
7	Female	48	(Non-Specific) Colitis	(Non-Specific) Colitis
8	Male	44	Colorectal Polyp	(Non-Specific) Colitis
9	Male	21	Normal	(Non-Specific) Colitis
10	Male	42	Normal	(Non-Specific) Colitis
11	Male	52	Rectal Polyps	(Non-Specific) Colitis
12	Female	58	Normal	(Non-Specific) Colitis
13	Male	35	Normal	(Non-Specific) Colitis
14	Male	35	Rectal Polyps	(Non-Specific) Colitis
15	Male	76	Diverticula	(Non-Specific) Colitis

Tabla 2. Hemogram of patients with microscopic colitis

Patient	Leukocytes	Hb	Platelets	Lymphocytes	%
1	5478	15.49	214 200	1890	33
2	7550	15.2	235 000	2570	34
3	6430	15.8	364 000	2780	43
4	11 750	15.06	525 700	2560	21
5	6510	16.9	216 000	1820	27
6	9060	18.1	219 000	3200	35
7	8280	15.67	237 800	1910	23
8	7100	16.4	261 000	2190	30
9	6250	15.1	281 000	2240	35
10	7980	17.1	261 000	2650	33
11	8540	17.3	167 000	3260	38
12	7990	13.3	194 000	2600	32
13	6830	16.9	153 000	1770	25
14	3757	16.3	140 000	1320	35
15	8120	16.3	203 000	2040	25

Hb: Hemoglobin

pain and occasionally weight loss. It occurs mainly in adults over 60 and is more common in women. An incidence rate of approximately 10/100,000 people per year has been reported[11].

In this study, 2 results were found opposite to what was mentioned in the literature: Eighty percent of the cases (n = 12) corresponded to male patients. Most patients (n = 12) were under 60 years old.

Pathophysiology

The causes of MC have not been clearly defined, and it is considered a multifactorial disease. Immune response, genetic susceptibility, and changes in epithelial barrier function have been implicated. These alterations promote increased mucosal permeability to antigens and bacteria. They facilitate inflammatory processes in the lamina propria, associated with the severity of symptoms, especially diarrhea, due to a decrease in sodium chloride absorption and active chloride secretion[4].

Some studies have linked MC to bile acid malabsorption (BAM). A Spanish study found that BAM was present in 43% of patients with MC, more commonly in LC (60%) than in CC (27%). Although cholestyramine treatment was met in 86% of patients, other studies have not demonstrated the same effect[12] Furthermore, MC has been linked to the human leukocyte antigen (HLA)-DQ2, which is associated with other autoimmune diseases and alterations of the fecal microbiota (depletion of the bacterium *Akkermansia muciniphila*)[10].

Risk Factors

In a systematic review and meta-analysis evaluating cigarette smoking as a risk factor, most studies found that smoking is a predisposing factor. Overall, patients who smoke are 3 times more likely to develop MC than non-smokers[13].

There are hypotheses involving the change of the gut microbiota in smoking patients, which leads to a dysbiosis that alters the epithelial barrier in the mucosa, contributing to the onset of diarrhea. Other factors such as alcohol intake and dietary factors have been mentioned[13].

Autoimmune disorders such as rheumatoid arthritis, thyroiditis, and celiac disease have been linked to the onset of MC. Furthermore, female hormonal factors and the consumption of medications such as nonsteroidal anti-inflammatory drugs (NSAIDs), proton pump inhibitors (PPIs), selective serotonin reuptake inhibitors, and low doses of aspirin have also been linked to MC onset[14].

Patient-related risk factors were not established because this is not the objective of this study and because of incomplete records of medical histories.

Diagnosis

Many clinical guidelines focus on the treatment of diarrhea. Although, the guidance regarding the diagnostic approach is generally poor. Therefore, it can lead to the improper use of diagnostic tests, causing loss of time, unnecessary expenses, discomfort in the patient, and inaccurate results. Unfortunately, MC remains largely unknown and is overlooked by front-line physicians, including some specialists, when treating patients with chronic diarrhea.

Microscopic Colitis displays a spectrum of symptoms ranging from mild, self-limiting episodes of diarrhea to debilitating and severe abdominal pain episodes, joint pain, fatigue, and weight loss. However, in no case has it been shown to have a mortality risk, nor has it been associated with the development of colorectal cancer. It significantly affects patients' quality of life, with an impact comparable to that of ulcerative colitis[15].

Through medical history, diseases with similar symptoms such as IBD, celiac disease, and IBS-D can be ruled out. Laboratory tests, including hemograms, are usually standard, as in the case of all our patients, and similar to radiological studies, can help rule out other diseases. Non-specific changes such as elevation of C-reactive protein (CRP) and anemia can be found. Fecal calprotectin and lactoferrin have low diagnostic accuracy. Sometimes subtle mucosal changes such as edema and altered vascular pattern may be observed, but colonoscopy is usually regular, which is the case in most of our patients[16]. Our setting recommends colonoscopy with biopsies for all chronic diarrhea patients.

A systematic review and meta-analysis evaluating 10 studies with more than 3900 cases found a combined prevalence of IBS-D symptoms in 33.4% of people with MC. Diagnosis should be based on the patient's clinical characteristics and confirmed by histology of step biopsies of the colon, minimum of 2 in each segment[17]. The number of segments and biopsies taken in our institution depends on each gastroenterologist's criteria and the procedure's findings. Samples of 3 segments (right, transverse, and left) are usually routinely taken.

Chronic inflammation of the lamina propria is observed in LC due to a proliferation of plasma cells, a decrease in the number of goblet cells, and the infiltration of more than 20 lymphocytes per 100 epithelial cells. In CC, the collagen layer thickens, which exceeds the standard upper limit of 7 µm. However, some authors consider thickening > 10 µm as diagnostic. In addition to these 2 histological subtypes, there

is MCi, which corresponds to the presence of clinical symptoms suggestive of the disease, with histological findings that do not meet the criteria above. In these cases, the number of lymphocytes and plasma cells is < 10/100 epithelial cells, and the subepithelial collagen is < 10 µm. These findings suggest that the 2 classic forms of MC may not correspond to 2 different diseases but 2 different stages in developing the same disease[5,10]. The above described corresponds to the diagnostic criteria used in the pathology department of our hospital.

So far, no specific biomarker has been found to assess disease activity. Indicators have been proposed that include the number of loose or liquid stools per day, nocturnal stools, abdominal pain, weight loss, and fecal urgency or incontinence. There is a direct correlation with MC and an indirect correlation with IBD. A study of 116 patients with CC found that patients had 3 or more stools per day, or one or more watery-looking stools, representing a negative effect on the patients' life quality[18].

Treatment

One of the fundamental pillars is eliminating all MC risk factors such as smoking, caffeine, dairy, and alcohol intake. Also, medications are recommended, especially aspirin, NSAIDs, lansoprazole, omeprazole, ranitidine, sertraline, and ticlopidine. Celiac disease and bile acid malabsorption (BAM), which may coexist with MC, should be ruled out[19].

Budesonide has been recommended as the medicine of choice in the treatment of MC for more than a decade. Medications such as prednisolone, mesalazine, and bismuth subsalicylate are second-line agents. Several randomized studies agree on the efficacy of budesonide in inducing remission in CC and CL. Meta-analyses have confirmed its effectiveness in controlling active MC, showing improvement before 2 weeks, given the absence of diarrhea. Therefore, the treatment of MC [20] has been recommended with this drug, the one our patients take. Responsiveness and monitoring were not analyzed as this was not the study's objective.

Twenty-eight patients were randomized in a double-blind placebo-controlled food challenge (DBPCFC) study evaluating the effectiveness of budesonide in patients with CC. Half of them received a placebo, and half received 3 capsules of 3 mg Budenofalk® (9 mg/day) for 8 weeks. A satisfactory response (50% decrease in stool quantity at week 8) was observed in 8 of 14 patients treated with budesonide compared to 3 of 14 placebo responders ($p = 0.05$). Histological follow-up was performed by comparing biopsies at weeks 0 and 8, with no changes in mean collagen band thickness but a significant decrease in lamina propria infiltration ($p < 0.001$). It was concluded that budesonide effectively induces a short-term clinical response in CC[21].

To compare the efficacy of budesonide and mesalazine in CC, a multicenter phase 3 study was conducted in 31 European centers, in which 92 patients were randomized into 3 groups (Budenofalk®, Salofalk®, or placebo) and a histological and clinical improvement (better stool consistency and improvement of abdominal pain) was observed in 80% of patients receiving budesonide, compared to 44% of patients receiving mesalazine ($p = 0.0035$)[22].

Currently, budesonide is recommended by the American Gastroenterological Association (AGA) as first-line therapy. Other studies have also demonstrated effectiveness in LC and maintenance of clinical remission with budesonide at doses of 4.5 mg for 12 months[23-26].

Azathioprine, 6-mercaptopurine (6-MP), and some biologics (anti-tumor necrosis factor alpha [anti-TNF-α]) have been used in microscopic colitis, especially in patients with refractory symptoms or steroid dependence. Loperamide at 2-16 mg/day helps control symptoms[19].

Corticosteroids are only recommended in patients refractory to budesonide treatment when budesonide is unavailable, and other etiologies such as celiac disease have been ruled out[26].

There is no consensus as to the criteria for referral. Each treatment must be individualized, determining to what point to extend it. Short-term treatment should be 6 to 8 weeks and continue for up to 12 months to avoid relapses[27].

Surgical treatment should be the last alternative and reserved only for patients who do not respond to medications. Small series have been reported in which subtotal colectomy, Ileoanal anastomosis, or ileal pouch-anal anastomosis (IPAA) have been performed[28].

As a possible bias, we should consider that it was impossible to view the total number of patients with chronic diarrhea assessed in the various consultations performed on patients at our institution. Furthermore, given that this was a retrospective study, it was impossible to evaluate the presence of associated risk factors explaining the high figures found.

CONCLUSIONS

In contrast to what is reported in the literature, we found that microscopic colitis affected especially young patients with a mean age of 47.5 years in this study. In addition, an unusual finding was that the male/female ratio was 4/1.

According to histological criteria, some microscopic colitis was found in 12.9% of patients biopsied for chronic diarrhea, a very high figure considering the incidence usually reported.

The objective of this study was to identify the presence of the disease in our population group. Given the findings, it is recommended to conduct prospective studies considering patients' history, treatment, and follow-up.

Conflicts of Interest

None.

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Original article

Hepatocellular carcinoma: A real-life experience in a specialized center in Bogotá, Colombia

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Abstract

Introduction: Hepatocellular carcinoma (HCC) is the most frequent malignant primary liver tumor globally. In 2018, it ranked sixth and represented the fourth cause of death from cancer; the five-year overall survival is 18 %. Most cases of HCC develop in patients with cirrhosis of any etiology, especially because of hepatitis B and C viruses, alcohol, and recently nonalcoholic steatohepatitis (NASH). **Aim:** To analyze the clinical characteristics, diagnostic methods, treatments, prognostic variables, and survival. **Materials and methods:** This retrospective descriptive study was conducted on a cohort of patients diagnosed with cirrhosis and treated between January 2011 and December 2020 at a health care center in Bogotá. The diagnosis of HCC was confirmed radiologically or by biopsy. We analyzed the information descriptively with absolute frequency measures in the case of categorical variables. For continuous variables, the information was summarized with measures of central tendency (mean or median) and their relevant measures of dispersion. **Results:** We included 152 patients diagnosed with HCC, with a mean age of 69.4 years; 51.3 % were men. The leading cause of HCC was nonalcoholic fatty liver disease (NAFLD), which accounted for almost a third of cases (32 %); other causes were alcohol (15 %) and hepatitis C virus (14 %). The median manifestation of the tumor was two nodules with a size close to 4 cm. Besides, 35 % of patients had a BCLC (Barcelona Clinic Liver Cancer) stage with curative options, and 25 % received curative treatment options. The first-line systemic therapy used in this cohort was sorafenib®, used in 35 patients (33.7 %). Survival curves showed that women, Child-Pugh class A, and BCLC stage 0 had higher median survival. Multivariate analysis showed a higher risk of death for males (hazard ratio [*HR*]: 2.16; confidence interval [*CI*]: 1.24–3.76), Child-Pugh class B (*HR*: 2.14; *CI* 1.16–3.95), and Child-Pugh class C (*HR:* 7.52; *CI* 2.88–19.57). **Conclusions:** NAFLD is the leading cause of HCC in this cohort. A third of patients are diagnosed in early BCLC stages with a curative treatment option, and 25 % are treated with curative therapies. Sorafenib was the first-line therapy in advanced HCC. Overall survival after diagnosis of HCC remains low, being necessary to join forces in the follow-up of patients with cirrhosis to improve these outcomes.

Keywords

Hepatocellular carcinoma, real life, survival, sorafenib.

INTRODUCTION

Hepatocellular carcinoma (HCC) or hepatocarcinoma (HCC) is the world's most common primary liver cancer. In 2018, HCC was the sixth most diagnosed cancer and represented the fourth cause of death from cancer, with 841,000 new cases and 782,000 deaths, respectively[1]. Men's incidence and mortality rate are 2 to 3 times higher in most

regions worldwide, representing the fifth highest number of global cases and the second leading cause of death[1,2]. Overall survival at 5 years is 18%[3]. Seventy-two percent of HCC cases occur in Asia, 10% in Europe, 8% in Africa, and 5% in North and Latin America. Zonal etiological differences explain these differences in prevalence[1,4]. Between 2007 and 2013, Colombia ranked seventh in mortality with a prevalence of 2.8 to 3.2/100,000 inhabitants, responsible for more than 10,000 of the 234,763 cancer deaths[5].

Cirrhosis of any etiology has a prevalence of 85% to 95% in patients with HCC and represents a significant risk factor for tumor development[6,7]. The incidence rate of HCC in patients with cirrhosis is estimated to be 2% to 4% per year[8], while it is believed that about one-third of patients with cirrhosis develop HCC at some point in their lives[9]. Globally, approximately 90% of HCCs are associated with a known etiology[2,10], 54% of cases are attributed to chronic hepatitis B virus (HBV) infection, 31% to infection by the hepatitis C virus (HCV), and 15% to other causes such as alcohol intake and exposure to aflatoxins. However, these calculations are rough estimates that do not reflect comorbidities and underestimate the impact of non-alcoholic steatohepatitis (NASH)/metabolic syndrome[10]. Recent data from the United States show that non-alcoholic fatty liver disease (NAFLD) in its form of NASH and metabolic syndrome contribute more to the burden of HCC than any other risk factor, including HCV[11] infection, mainly due to the high prevalence of NAFLD in the general population.

Radiological studies are essential for diagnosing liver tumors and contribute to their typing and staging. The non-invasive radiology diagnosis of HCC in the context of a patient with cirrhosis was accepted in 2001 when dynamic images demonstrated the typical pattern[12], which was updated in 2005[13], and which is the result of the characteristic vascular derangement that occurs during hepatic carcinogenesis[14], plus a high pretest probability of HCC before testing in the setting of cirrhosis. Typical findings include hypervascularity in the late arterial phase, defined as arterial phase hyperenhancement (APHE), according to the LI-RADS classification (*Liver Imaging Reporting and Data System*), and washout in the portal venous or portal delayed venous phases[14-16].

In patients at high risk of developing HCC (cirrhosis plus HBV or HCV, among others) and the presence of one or more lesions, the diagnosis can be made with contrast-enhanced and dynamic computed tomography (CT) or magnetic resonance imaging (MRI) with liver injury protocols, if the injury shows imaging criteria and is read as LI-RADS 5 (LR 5), is conclusive of HCC. In specialized centers, contrast-enhanced abdominal ultrasound can also be used for solitary lesions if the modality is available, although it is more widely used in Europe[15,16]. High-risk patients who do not have liver lesions can be monitored periodically by performing ultrasound with or without alpha-fetoprotein (AFP) levels every 6 months[15-17].

The *Barcelona Clinic Liver Cancer* (BCLC) staging system has been widely used for the HCC[18] approach, classifying patients into 5 categories or stages (0, A, B, C, and D) according to treatment and survival recommendations. Stages 0 and A have curative treatment options, with survival rates greater than 5 years. In stages B and C (intermediate and advanced), the therapeutic possibilities focus on slowing down the progression of the disease with survival between 1 and 5 years. Stage D (terminal) receives palliative care with survival of nearly 3 months[19].

We presented a cohort of patients diagnosed with HCC. They were monitored for 10 years in a specialized center in Bogotá, D. C., with the primary objective of analyzing the clinical characteristics, diagnostic methods, treatments, prognostic variables, and survival.

METHODOLOGY

A retrospective descriptive study of a cohort of patients treated between January 2011 and December 2020 at Centro de Enfermedades Hepáticas y Digestivas (Center for Liver and Digestive Diseases, CEHYD, by its abbreviation in Spanish) in the city of Bogotá.

As inclusion criteria, the confirmed cirrhosis and the concurrent diagnosis of HCC, confirmed radiologically or by liver biopsy, were considered. Radiologically, HCC was defined by CT or MRI before 2016 as an arterial phase hyperenhancement with portal venous or delayed phase washout reported on imaging[8,13]. Beginning in 2016, the LI-RADS liver imaging data and reporting system (standardized terminology and criteria system for interpreting and reporting liver CT and MRI exam results in patients with cirrhosis or at increased risk for HCC)[20] was used, and an LI-RADS 5 reading was required.

The medical records of the patients who met the inclusion criteria were reviewed, tabulating each patient's clinical history, laboratory data, and Child-Pugh staging. Regarding the tumor, we tabulated its cause, maximum size in cm according to the largest nodule, number of nodules, presence of vascular invasion, extrahepatic invasion, the primary treatment used, number of ablation sessions or transarterial chemoembolization (TACE), treatment duration in months with sorafenib as systemic therapy, and whether or not palliative treatment was indicated.

The information was analyzed using descriptive methods with absolute frequency measures in the case of categorical variables. Pearson's or Fisher's exact tests were used to evaluate the differences between the two groups. For continuous variables, the information was summarized with measures of

central tendency (mean or median) and their respective dispersion measure according to the normality of the distribution of each variable evaluated using the Shapiro-Wilk test. Additionally, the Wilcoxon rank-sum (Mann-Whitney U) test was used to assess differences between two groups for mean and median estimates, respectively.

Survival assessment was performed using Kaplan Meier analysis and univariate and multivariate Cox proportional hazards analysis. Time 0 was the date of diagnosis of cirrhosis, first decompensation, or diagnosis of HCC. The time of the event was the date of death. Patients were censored at the date of the last assessment. All analyzes were performed with the Stata version 13 statistical software package.

ETHICAL CONSIDERATIONS

This project was evaluated and approved by the ethics committee of the School of Medicine of Universidad Nacional de Colombia, Bogotá campus (minute No. 009-073 of May 13, 2021).

RESULTS

When analyzing the cohort of patients with cirrhosis and HCC, 238 were initially considered, and 86 were discarded due to inconclusive diagnosis or lack of complete clinical history data. Finally, 152 patients diagnosed with HCC were included, with a mean age of 69.4 years, 51.3% of whom were men. Clinical and laboratory characteristics are shown in **Table 1**.

The leading cause of HCC was NAFLD, in its form of NASH, which represented almost a third of the cases (32%), even more frequent in the group of women, where it reached 39% of the cases. In men, the leading cause was alcohol, followed by NASH (29.4% and 25.6%, respectively) (**Table 2**).

Regarding the tumor, the median presentation was 2 nodules close to 4 cm. Based on the BCLC system, 35% of patients had a stage with curative options (**Table 2**), and 25% received remedial treatment options. Of these, 11 patients received transplantation (**Table 3**). The first-line systemic therapy used in this cohort was sorafenib, used in 35 patients (33.7%) as primary treatment. Other 14 patients received sorafenib as secondary treatment, accounting for 49 patients treated. Of them, 15 reported side effects. Most side effects included hand-foot syndrome, diarrhea, and other gastrointestinal effects. In addition, variceal bleeding occurred in a patient treated with sorafenib (**Table 3**). As the primary non-curative treatment, palliative care was given to 17.3% of patients and 13.4% in 13.4%.

The results of the survival analysis are detailed in **Table 4**. There was evidence of 1.2, 2.4, and 3.2 deaths in 100 patients one month after the diagnosis of cirrhosis, first decompensation, and diagnosis of HCC, respectively. The survival curves from the diagnosis of HCC by Child-Pugh, BCLC stage, and primary treatment presented significant differences (**Figures 1** and **2**). The groups of women, Child-Pugh A and BCLC stage 0, showed higher median survival (**Figure 1**), as well as patients with transplant and radiofrequency ablation treatments (**Figure 2**), all with significant statistical differences.

The multivariate analysis (**Table 5**) showed an increased risk of death from the diagnosis of HCC in males (*Hazard ratio* [HR]: 2;16; confidence interval [CI]: 1.24-3 .76), fall under the B stage in the Child-Pugh (HR: 2.14; CI: 1.16 to 3.95) and Child-Pugh C (HR: 7.52, CI: 2.88 to 19.57), and having been treated with ablation (HR 4.27 CI 0.51 to 35.73), TACE (HR 10.74 CI 1.35 to 84.85), sorafenib (HR 17 .59 CI 2.31 to 133.79), and palliative care (HR 25.93 CI 3.17 to 211.48).

DISCUSSION

The experience of a center specializing in hepatology is presented in this study. The average age of the patients in this cohort agrees with that reported in the European guidelines (70 years)[16]. Furthermore, the age is similar to that recorded in a Latin American series (64 years)[21]. In this investigation, 51 % of patients were men, showing a ratio of almost 1:1 with women, data that contrasts with the international literature, where the ratio favors men 2 to 3 times[1,2] according to White in a series with 236,290 cases of HCC diagnosed between 2000 and 2012 in the United States, where 73% were men[22] and these figures are mainly explained by the HCV epidemic. We diagnosed more fatty liver and alcohol and proportionally less HCV, which is consistent with the trend shown in national registries[5], possibly explaining the male-female relationship found in our research.

In this cohort, the leading cause of HCC was NAFLD in its form of NASH, with a history of metabolic syndrome between 15% and 40%. In a study of cirrhosis published in 2016 with 419 patients, fatty liver was also the primary cause of cirrhosis (25%)[23]. Currently, this cohort of cirrhotic patients under follow-up reaches 1800, and fatty liver remains the primary cause[24]. In another cohort of Colombian patients, alcohol and NASH ranked as the first and second causes of HCC, respectively[25]. This is similar to data obtained in this study in males.

The Latin American series of HCC with 1336 patients shows HCC as the cause of HCV (48%), followed by alcoholic cirrhosis (22%), HBV infection (14%), and fatty liver (9%)[21]. However, it is worth mentioning that an estimated 25% of the world's adult population has NAFLD, according to a meta-analysis including more than 8 million people. The

Table 1. General Characteristics of Patients with HCC

Variable	Total n = 152 n (%)	Women n = 74 (48.6) n (%)	Men n = 78 (51.3) n (%)	Value *p*
Age at diagnosis		**Mean (SD)**		
	69.4 (9.4)	70.9 (8.4)	67.9 (10.0)	0.054*
Background		n (%)		
- Alcohol Consumption	72 (47.4)	7 (9.5)	65 (83.4)	< 0.001**
- DM	62 (40.7)	28 (37.8)	34 (43.5)	0.471***
- HTN	61 (40.1)	31 (41.8)	30 (38.4)	0.666***
- Obesity	49 (32.2)	25 (33.7)	24 (30.7)	0.691***
- Dyslipidemia	23 (15.1)	8 (10.8)	15 (19.2)	0.148***
- Coronary Disease	15 (9.8)	5 (6.7)	10 (12.8)	0.279**
Laboratories (n = 151)		**Median (IQR)**		
- Leukocytes	5610 (4490-6990)	5050 (4075-6462)	5830 (4835-7870)	0.0019****
- Neutrophils (%)	56 (50-66)	55 (50-65)	56 (49-66)	0.945****
- Lymphocytes (%)	28 (21-34)	30 (21-35)	27 (20-34)	0.436****
- Platelets	130k (91k-176k)	132.5k (91.7k-170k)	127k (90k-186k)	0.968****
- AST	61 (41.7-100.7)	61 (42-92.7)	63.5 (40.2-114)	0.504****
- ALT	49 (34-74)	48 (28-68)	52 (37-75)	0.083****
- GGT	164 (106-259)	150 (92-245)	190 (122-283)	0.032****
- Alkaline Phosphatase	166 (117-260)	158 (118-232)	190 (115-280)	0.299****
- INR	1.1 (1-1.3)	1.1 (1-1.3)	1.1 (1-1.2)	0.196****
- Total Bilirubin	1.2 (0.8-2)	1.1 (0.8-1.9)	1.3 (0.8-2.2)	0.216****
- Albumin	3.7 (3.1-4)	3.7 (3.1-4)	3.6 (3-4.1)	0.869****
- AFP	25.5 (5- 466)	20 (5-245)	27 (5-855)	0.89****
Esophageal Varicose Veins		**n (%)**		
- No	59 (38.8)	31 (41.9)	28 (35.9)	0.745***
- Small	34 (22.4)	16 (21.6)	18 (32.1)	
- Large	59 (38.8)	27 (36.5)	32 (41)	
Child–Pugh (n = 143)		**n (%)**		
- A	65 (45.5)	30 (43.5)	35 (47.3)	0.864***
- B	63 (44.0)	32 (46.4)	31 (41.9)	
- C	15 (10.5)	7 (10.1)	8 (10.8)	

*Two-sample t-test with equal variances.
**Fisher's exact test.
***X_2-Test.
**** Wilcoxon rank-sum (Mann-Whitney U) test.
ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, GGT: γ-glutamyltransferase, SD: Standard deviation, DM: Diabetes mellitus; HTN: Hypertension, INR: International normalized ratio, IQR: Interquartile range (p25-p75), Me = median.

Table 2. Characteristics of HCC

Variable	Total n = 152 n (%)	Women n = 74 (48.6) n (%)	Men n = 78 (51.3) n (%)	Value *p*
Causes of HCC		**n (%)**		
- NASH	49 (32.2)	29 (39.1)	20 (25.6)	
- Alcohol	24 (15.7)	1 (1.3)	23 (29.4)	
- HCV	21 (13.8)	16 (21.6)	5 (6.4)	< 0.001*
- NASH + alcohol	17 (11.1)	1 (1.3)	16 (20.5)	
- Cholestasis	13 (8.5)	11 (14.9)	2 (2.6)	
- Others	28 (18.4)	16 (21.6)	12 (15.38)	
HCC data		**Median (IQR)**		
Number of nodes	2 (1-3)	1 (2-3)	1 (1-3)	0.0021**
Size in cm	3.85 (2.2-7)	3.4 (2-7.2)	4 (2.7-7)	0.34**
BCLC Stage		**n (%)**		
- 0	10 (6.5)	6 (8.1)	4 (5.1)	
- A	45 (29.6)	26 (35.4)	19 (24.3)	0.407*
- B	49 (32.2)	22 (29.7)	27 (34.6)	
- C	35 (23.0)	16 (21.6)	19 (24.36)	
- D	13 (8.5)	4 (5.4)	9 (11.5)	
Terminal Stage		**n (%)**		
- Dead	95 (62.5)	42 (56.8)	53 (67.9)	0.154*
- Live	57 (37.5)	32 (43.2)	25 (32.1)	

*Fisher's exact test.
**Wilcoxon rank-sum (Mann-Whitney U) test.

prevalence rate in South America is 31%[26]. Therefore, NASH causing HCC may also be underdiagnosed. Additionally, recent data suggest that NASH cirrhosis contributes to developing HCC and is an increasingly important risk factor for its etiology in Western countries[10,27-29]. Accordingly, Singal AG *et al.* estimated an annual incidence rate of HCC in patients with NASH cirrhosis of 1% to 2%[27]. Another fatty liver study with many patients showed an HCC incidence with a follow-up rate of 1 per 100 person/years[29].

We monitor patients with cirrhosis in our center using abdominal ultrasound and AFP every 6 months[16,17]. The therapeutic approach follows the BCLC guidelines[19]. This surveillance accounts for 35% of patients diagnosed at treatable stages. Of the 104 patients for whom treatment data were available, approximately 35% received treatment (transplantation: 10.6% and radiofrequency ablation: 25%).

About 2 thirds of patients received non-curative therapies: TACE (17.3%), systemic therapy (33.7%), and palliative treatment (13.4%). About 64% of patients received this treatment, indicating a late diagnosis. From the first decompensation event, variceal bleeding, or presence of a mass on imaging, many patients are diagnosed with cirrhosis, data supported by a median HCC survival of 9.5 months after diagnosis. The median fluctuates between 6 and 20 months in the Cancer of the Liver Italian Program (CLIP) study[30].

Since 2006, sorafenib has been approved as systemic therapy for HCC in Colombia[31]. Sorafenib was the only therapy available until the second half of 2018 when rego-

Table 3. Treatment of HCC

Variable	Total n = 104 n (%)	Women n = 49 n (%)	Men n = 55 n (%)	Value *p*
Main Treatment				
- Transplant	11 (10.6)	3 (6.1)	8 (14.5)	
- Radiofrequency ablation	26 (25)	18 (36.7)	8 (14.5)	
- TACE	18 (17.3)	10 (20.4)	8 (14.6)	0.051*
- Sorafenib	35 (33.7)	13 (26.5)	22 (40)	
- Palliative	14 (13.4)	5 (10.2)	9 (16.4)	
		Me (IQR)		
Radiofrequency ablation sessions	1 (1-2)	1 (1-2.5)	1 (1-1.5)	0.3106**
Sessions with TACE	1 (1-2)	1 (1-2.2)	2 (1-2)	0.591**
Months with sorafenib	4 (2.25-8)	4 (3-10)	4 (2-8)	0.779**
Side effects of sorafenib	**n = 15**	**n = 7**	**n = 8**	
- Hand-foot syndrome	6 (40.0)	4 (57.1)	2 (25)	
- Diarrhea	2 (13.3)	1 (14.3)	1 (12.5)	
- Other dermatological	1 (6.6)	0	1 (12.5)	0.627*
- Bleeding during intake	2 (13.3)	0	2 (25)	
- Other gastrointestinal	3 (20.0)	1 (14.3)	2 (25)	
- Others	1 (6.6)	1 (14.3)	0	

*Fisher's exact test.
** Wilcoxon rank-sum (Mann-Whitney U) test.

Tabla 4. Survival Analysis

	Incidence rate * 100 (95%CI)	Median survival (months)	Percentile 25%-75% Percentile (months)
Cirrhosis Diagnosis	1.2 (0.9 to 1.4)	49.8	17.1 – 158.9
First Decompensation	2.4 (2.0 to 3.0)	26.3	8.8-63.3
HCC Diagnosis	3.2 (2.6 to 3.9)	15.9	6.4-50.2

rafenib was approved as a second-line treatment[32]. In this study, 35 patients received sorafenib as their primary treatment and 14 as a second or third option, with an average of 6.8 months of use for the 49 patients. Average survival rates between 4.6 and 12 months are mentioned in the literature[33-35]. Of the 14 patients with combined therapies, 8 had previously received radiofrequency ablation (5 later received TACE), and 6 had previously received TACE. Fifteen patients (30.6%) reported the usual side effects[31,34] in the following order a) hand-foot syndrome, b) gastrointestinal issues, and c) diarrhea.

Interestingly, 2 patients with platelets above 100,000 and regular INR experienced variceal bleeding while taking sorafenib. The first patient had large varicose veins with red dots that were not initially ligated due to administrative problems. The second patient, who had previously ligated varicose veins, bled at the beginning of the treatment, with unclear bleeding, after which he received sorafenib for 12 months without new episodes. On the other hand, although 54.5% of the patients had varicose veins, this was

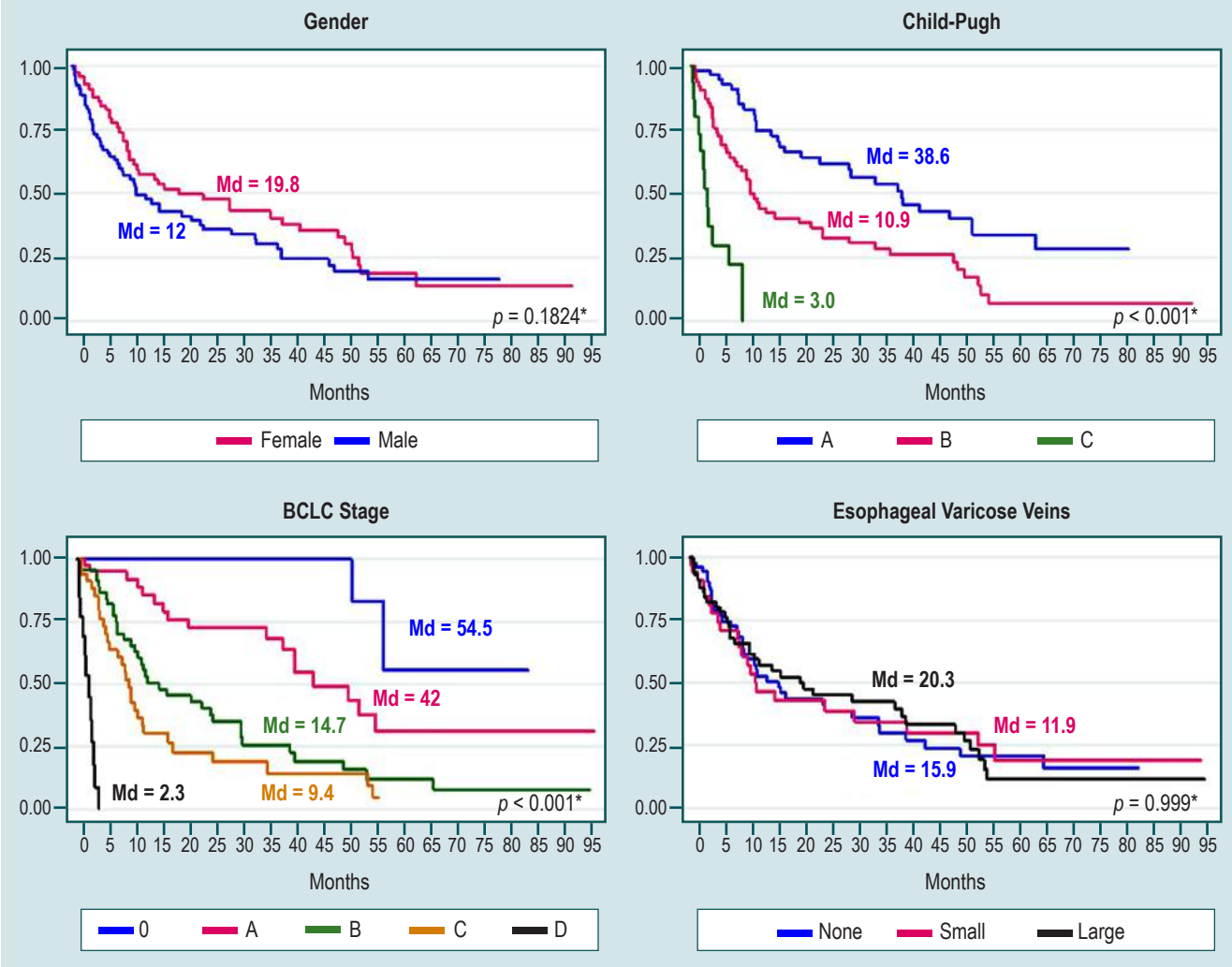

Figure 1. Survival curves of the risk of death from the diagnosis of HCC by gender, Child-Pugh, BCLC stage, and esophageal varicose veins. Kaplan-Meier survival estimates. *Log-rank test for equality of survival functions. Md: median.

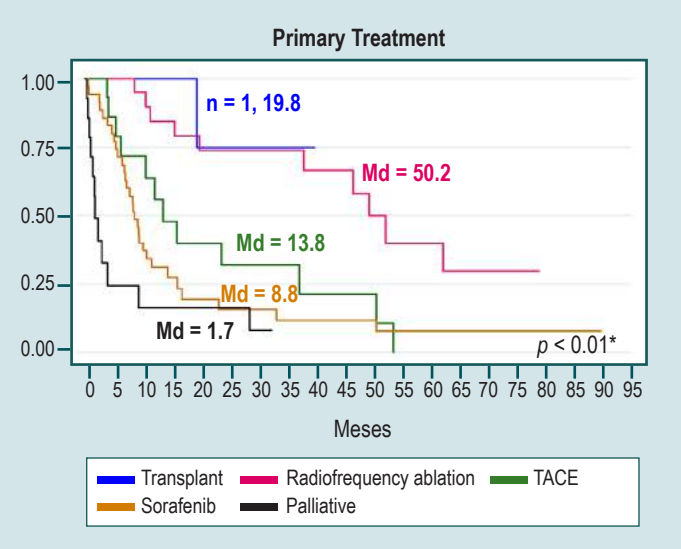

Figure 2. Survival curves of the risk of death from diagnosing hepatocarcinoma by primary treatment. Transplantation = 1 patient died after transplantation. Kaplan-Meier survival estimates. *Log-rank test for equality of survival functions. Md: median.

Table 5. Univariate and Multivariate Analysis of the Risk of Death from the Diagnosis of HCC.

	Univariate Analysis HR (95%CI)	Multivariate Analysis HR (95%CI)
Gender		
- Women	Reference	Reference
- Men	1.31 (0.87 to 1.97)	2.16 (1.24 to 3.76)*
Child-Pugh al diagnóstico HCC		
- A	Reference	Reference
- B	2.23 (1.41 to 3.54)*	2.14 (1.16 to 3.95)*
- C	11.39 (5.52 to 23.50)*	7.52 (2.88 to 19.57)*
Estadio BCLC		
- 0	Reference	
- A	2.75 (0.63 to 11.97)	
- B	7.03 (1.67 to 29.55)*	***
- C	10.89 (2.56 to 46.34)*	
- D	146.92 (28.79 to 749.58)**	
Várices esofágicas		
- No	Reference	Reference
- Pequeñas	0.98 (0.58 to 1.68)	0.64 (0.29 to 1.37)
- Grandes	0.99 (0.62 to 1.57)	1.18 (0.65 to 2.13)
Por tratamiento principal		
- Trasplante****	Reference	Reference
- Radioablación	2.20 (0.27 to 17.37)	4.27 (0.51 to 35.73)
- TACE	6.47 (0.83 to 49.95)	10.74 (1.35 to 84.85)*±
- Sorafenib	9.40 (1.27 to 69.19)*	17.59 (2.31 to 133.79)*±
- Paliativo	22.25 (2.88 to 171.79)*	25.93 (3.17 to 211.48)*±

*p < 0.05.
** Imprecise estimator due to the number of patients in this group (n = 13).
***Variable not included in the multivariate analysis due to imprecise estimators.
****1 patient died after the transplant. ± Inaccurate estimators due to the number of patients included.

not statistically significant in the overall survival of the patients. A study in Italy identified tumor deep vein thrombosis (DVT) as the strongest independent predictor of bleeding (HR: 15.4; 95 % CI: 1.84-129.6)[35], but none of the 2 patients in this study had it. The meta-analysis by Dai *et al.*, with 4720 patients who received sorafenib to treat HCC[36], showed a significant increase in the risk of low-grade bleeding events (relative risk [RR]: 1.99; 95% CI: 1 59-2.49; $p < 0.00001$), the second patient in our series could be in this group. Thus, we could say that one patient (2%) experienced low-grade bleeding associated with sorafenib in this cohort.

We acknowledge the limitations of the study as it is retrospective. However, this is a cohort of patients with HCC monitored for an extended period in Bogotá, drawing attention to the etiology, fatty liver, a frequent condition in our population. In the future, this condition could change the guidelines on its screening and follow-up as a risk factor for the development of HCC.

CONCLUSIONS

In this cohort, the leading cause of HCC is NAFLD, more than a third of patients are diagnosed in early BCLC stages with a curative treatment option, and 25% are treated with curative therapies. Sorafenib was the first line of treatment for advanced HCC. However, overall survival after diagnosis of HCC remains low, and it is necessary to join efforts in the follow-up of patients with cirrhosis to improve early diagnosis rates.

Disclosure

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Original article

Ergonomics in digestive endoscopy: Prevalence, types of musculoskeletal disorders, and risk factors in endoscopists in Colombia

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Abstract

Introduction: The practice of digestive endoscopy is a physically demanding activity, with musculoskeletal disorders present in 39 % to 89 % of endoscopists, associated with "excessive use" maneuvers. Due to a lack of knowledge of this problem in endoscopists in Colombia, the main objective is to determine the prevalence, types, and risk factors of musculoskeletal disorders in specialists and graduate students. The secondary objective is to identify the occupational impact, treatments used, and importance of prevention and education in ergonomics. **Materials and methods:** Analytical cross-sectional observational study. Electronic survey methodology, open from June 1 to 30, 2021. Purposive sampling of 450 endoscopists from four scientific associations and eleven graduate programs, including 50 questions in six groups according to the objectives. We validated 203 responses, with 131 confirmations of musculoskeletal disorders, the group on which the analysis was performed. **Results:** Global prevalence of musculoskeletal disorders of 64.5 % and prevalence in graduate students of 58.6 %. There was more significant involvement of the upper limbs (right shoulder, left thumb, right elbow), followed by lower back, neck, knees, and hips. Graduate students reported pain in the right hand/fingers (right thumb) and the lower back. There was no significant difference due to work factors, but there was a tendency for more reports when increasing the volume of procedures and years of professional practice. The labor impact showed 78 % absenteeism. The most used treatments were medication, physiotherapy, and rest; 93.8 % had not received ergonomic education. However, there is a positive perception (74.1 % to 90.9 %) of receiving formal training. **Discussion:** The prevalence reflected the health and safety problem for the endoscopist. Demographic risk factors plus those of the endoscopic practice give rise to an individualized risk framework that enables endoscopists to understand learning and training as a way to prevent musculoskeletal disorders in themselves and their work team.

Keywords

Ergonomics, endoscopy, injuries, musculoskeletal, occupational health.

INTRODUCTION

An upper GI endoscopy is a physically demanding activity[1]. The high prevalence of pain and musculoskeletal disorders (MSDs) associated with its practice (between 39% and 89% in practicing endoscopists)[2] has been linked to "overuse" injury[3] involving procedures where up to 40% of working time is spent[4].

In turn, ergonomics, a discipline responsible for the design of workplaces and the analysis and adaptation of tools and tasks following the physiological, anatomical, and psychological characteristics of workers, studies 4 aspects of endoscopists' interactions: Workspace, redesigns necessary to minimize risks, optimization of well-being beyond the physical well-being, and maximization of the overall performance of the service system[1].

Musculoskeletal disorders result from frequent and repetitive maneuvers, uncomfortable postures, prolonged times[5,6], and lack of breaks[7]. These situations are common to other professionals such as sonographers and laparoscopic surgeons[8,9].

The anatomical sites most commonly affected by MSDs include the thumbs, wrists[10-13], neck, lumbar region, shoulders[6], and hands[14]. In graduate students of gastroenterology, pain in the thumbs (more often in the left one), hands[3], right wrist, back, and neck[15].

Risk factors for MSDs include gender, length of time in practice, improper positions, the volume of procedures[4,7,11,12], and the performance of new procedures (endoscopic submucosal dissection [ESD], enteroscopy, endoscopic ultrasound [EUS], endoscopic retrograde cholangiopancreatography [ERCP], and cholangioscopy) due to their longer duration and technical demands[6,16,17].

Musculoskeletal disorders translate into duplication of occupational injury risk, affecting professional performance, usual work routine, and meeting work goals[18].

The primary objective of this study was to determine the prevalence, location, types of MSDs, and risk factors in endoscopists (including graduate students) in Colombia. The secondary objectives included identifying the occupational impact of MSDs and the treatments used. Additionally, determining the importance attributed by respondents to educational processes in ergonomics.

MATERIALS AND METHODS

Analytical cross-sectional observational study. Self-administered electronic survey methodology developed in Google Qualtrics including 50 questions on general demographics (age, gender, professional certification level, weight, height, dominance, glove size); Musculoskeletal disorders presence, types, and location (according to the Nordic musculoskeletal standardized questionnaire of pain, numbness, and discomfort in body areas); related risk factors (years of practice, number and type of procedures accumulated in the last 2 years and 2 months, general and specific working hours in the endoscopy room); occupational impact and types of treatment used; preventive ergonomic activities and education, and awareness of the importance of specific ergonomic training in endoscopy. According to the observations, the survey was adjusted on 2 occasions by 8 endoscopists, 2 graduate gastroenterology students, a physiotherapist, 2 nurses, and a medical equipment engineer for content and appearance validity verification.

The survey was conducted among a purposive sample of endoscopists from the following associations: Asociaciones Colombianas de Endoscopia Digestiva, Colombian Associations of Digestive Endoscopy (ACED, by its abbreviation in Spanish); Gastroenterología, Colombian Gastroenterology Association (ACG, by its abbreviation in Spanish); Coloproctología, Colombian Association of Coloproctology (ACCP, by its abbreviation in Spanish), and Cirugía, Colombian Association of Surgery (ACC, by its abbreviation in Spanish), sent to their electronic media and social networks to 240 members of the ACED, 420 of the ACG, 60 of the ACCP and 50 of the ACC. Also, the survey was sent to students from the 11 gastroenterology programs with an estimated number of 45.

After explaining its relevance and ensuring the anonymity of the responses, the survey remained open from June 1 to June 30, 2021. Informed consent was stated as implicit in answering the survey. In addition, a participation incentive was granted through educational and financial support allocated among participants on July 5, 2021. The ACED ethics committee approved this study.

STATISTICAL ANALYSIS

Descriptive statistics were used for demographic characteristics, with means and standard deviation (SD) for continuous variables and proportion for discrete variables. In addition, the Chi-square test (χ^2) and the Fisher's exact test were used for risk factors identification associated with MSDs related to workloads, types of procedures performed, and gender based on the observed percentage and to compare the distributions of nominal data and the χ^2 trend for ordinal data. A $p < 0.05$ was considered to determine significance. All analyses were performed with the free statistic JAMOVI *software*.

RESULTS

Regardless of the endoscopists' training and work environments, a 64.5% MSDs prevalence (in 131 of 203 validated responses) was found, while 35.5% (72) did not report MSDs. Twenty-nine graduate students responded, and 58.6% (17) reported MSDs (**Figure 1**).

In the 131 positive univariate analysis, the groups with the highest frequency (with significant differences) were men vs. women ($p < 0.001$); specialists versus graduate students ($p < 0.001$); right vs. left hand dominance ($p < 0.001$); glove sizes M and L vs. S size ($p < 0.001$), and the

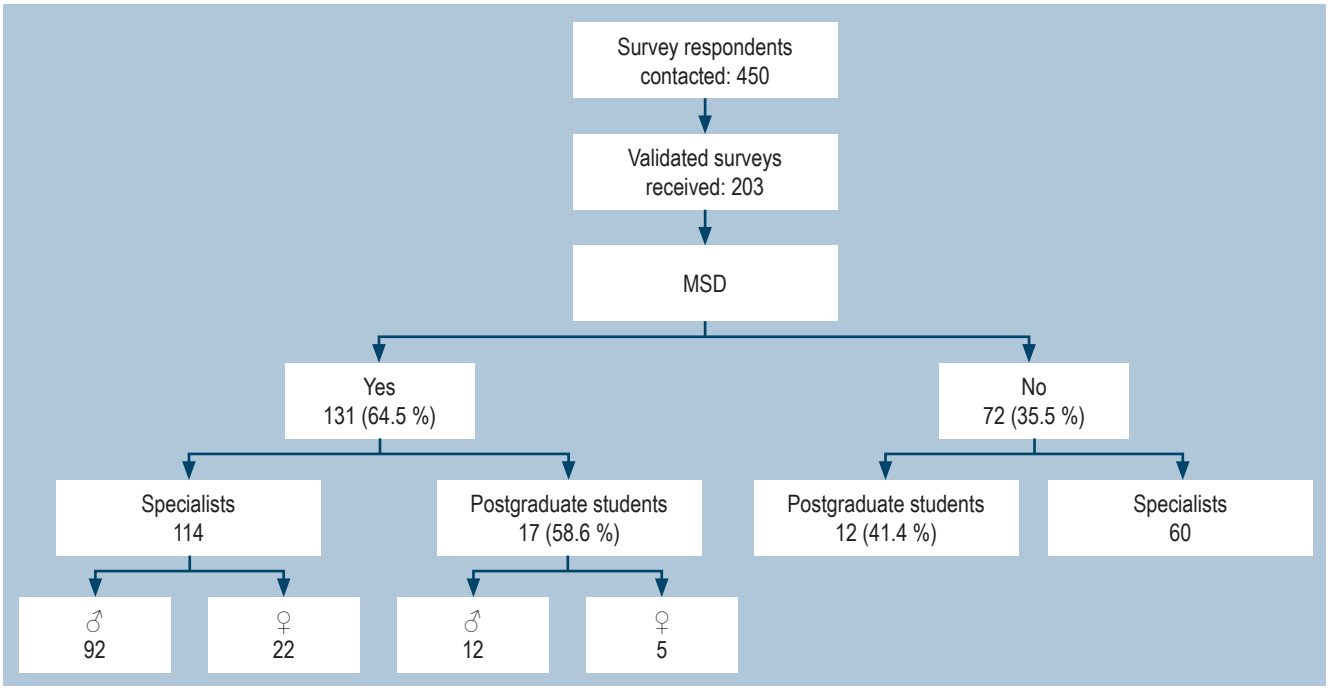

Figura 1. Respondent flow chart. Authors' elaboration.

use of Olympus technology vs. Fujifilm and Pentax (p < 0.001) (**Table 1**).

Since more than one MSD could occur per body segment, the 131 affected specialists reported 262 upper limbs injuries, over 85 reported neck-back injuries, and 41 reported lower limbs injuries. The most frequent complaints in the upper limb involved the right shoulder (n = 49, 48.7% of men, 60% of women), pain in the left thumb (n = 43, 60% of men, 50% of women). Although only 9 cases of carpal tunnel syndrome were recorded, it was the only type of MSD with a significant difference by gender (more frequent in men for both hands) (p < 0.011) (**Table 2**). In postgraduate students, there is a higher pain condition in the right hand-hand, especially the thumb.

Neck and back MSDs in specialists mainly involve the lower back (n = 21.95% of men) and neck (n = 19.79% of men, 21% of women). There were no significant differences by gender in both groups (p 0.058 in specialists and p 0.076 in graduate students) (p < 0.05) (**Table 3**). The most common involvement in postgraduate students was in the upper back (n = 7).

Lower limb musculoskeletal disorders in specialists occurred primarily in the hips (n = 15, 60% with bilateral involvement), knee pain (n = 15. 40% in the right, 26.7% bilateral). No significant difference was found by gender. In addition, no illness was reported in graduate students (**Figure 2**).

Absenteeism or work disability was reported in 89 specialists; 24.9% reduced the number of procedures and working hours. However, 14.6% (7 men and 6 women) had to discontinue specific endoscopic procedures associated with MSDs, which was significantly higher in female endoscopists (33.3% vs. 8.4%; p < 0.004). In addition, two male graduate students had to suspend specific procedures (**Figure 3**).

The most frequently used treatments for MSDs were medication (usually anti-inflammatory drugs), physiotherapy and rest, carpal tunnel splint to a lesser degree, steroid injections, and surgery. There were no significant differences by gender in any treatment. Fifteen specialists and 2 postgraduate students decided not to opt for any treatment (**Figure 4**).

In terms of risk factors, the most affected patients by MSDs (n = 54, including both genders) reported more than 20 years of professional practice (with a higher significant frequency in men from the 4-10 years of work practice group; p < 0.029) (**Table 4**). By age group, there was greater involvement of men between 51-60 years who fulfilled weekly working days between 24-48 hours and 49-60 hours. In addition, there was significant involvement in 34 endoscopists when working in the endoscopy room was less than 24 hours per week (**Tables 2** and **4**).

Injury reporting was higher when performing between 50 and 100 basic procedures, up to 50 advanced interven-

Table 1. General Characteristics of Respondents

Characteristics	n = 131 Fa (%)	χ^2 Test
Age by group (years)		
- 20-30	1 (0.76)	< 0.001
- 31-40	31 (23.6)	
- 41-50	32 (24.2)	
- 51-60	44 (33.6)	
- > 60	23 (17/5)	
Gender		
- Female	27 (20.6)	< 0.001
- Male	104 (79.4)	
Height		
- Mean (SD)	1.73 (0.09)	< 0.001***
- Median (IQR)	1.74 (1.68: 1.80)	
- Lower limit: Upper	1.50: 1.94	
Weight*		
- Mean (SD)	77.8 (13.0)	
- Median (IQR)	78 (68.5: 89)	0.039**
- Lower limit: Upper	50: 103	
Handedness		
- Right	122 (93.1)	< 0.001
- Left	9 (6.9)	
Glove size (n = 130)		
- Small	24 (18.5)	< 0.001
- Medium	62 (47.7)	
- Large	44 (33.8)	
Level of Education		
- Specialist	114 (87.0)	< 0.001
- Fellow r1	5 (3.8)	
- Fellow r2	9 (6.9)	
- Fellow r3	3 (2.3)	
Specialization		
- Gastrointestinal surgeon and endoscopist	31 (23.7) 6 (4.6)	< 0.001
- General surgeon	14 (10.7)	
- Proctologist	80 (61.1)	
- Gastroenterologist		
Video endoscopy system		
- Olympus	78 (59.5)	< 0.001
- Fujifilm	46 (35.1)	
- Pentax	7 (5.3)	

*No normal.
**Wilcoxon signed rank.
Test Student and test multinominal.
Fa: Absolute frequency; IQR: Interquartile range.

tional procedures, or up to 50 third-space interventional procedures in the last two months, and in the previous two years, more than 500 basic procedures, between 200 and 1000 advanced interventional procedures or between 200 and 1000 fluoroscopy-supported procedures (**Table 4**).

As for preventive measures, the study found that 96% of the specialists did not take intraprocedural breaks, while 62.9% paused between procedures. For training in ergonomics, 93.8% did not receive formal training, while 40% had self-taught training. Only 21% received didactic indications for ergonomic correction in the endoscopy room (**Table 5**).

Regarding awareness of ergonomics in endoscopy, 74% of the specialists would feel comfortable changing the way endoscopy is performed if this helped prevent injuries. While 93.75 % of the postgraduate students strongly agreed on the importance of ergonomic training, 81.25 % expressed their willingness to receive formal training on the subject (**Table 6**).

DISCUSSION

As a primary objective, an overall prevalence of 65.2% of MSDs was found in 203 specialists and postgraduate students in this representative sample of 45% from the estimated national population of 450 endoscopists as of June 2021, an intermediate figure compared to publications reporting 39% and 89%[2], similar to a study in Canada with a prevalence of 67% in ERCP endoscopists[19], and a European survey with a majority of 69.6 %[13].

The types of MSD reported included pain, musculocartilaginous, and joint discomfort in different segments of the upper limbs (less frequently in the neck, upper and lower back, and lower limbs), corresponding to areas that perform internal and external rotations (right shoulder, back, neck), flexion and extension (left thumb, neck, hips); torsion (wrists, elbows, hands, back); grasp (right thumb, right-hand fingers). Moreover, specific lesions of Quervain's tenosynovitis and carpal tunnel syndrome. This is consistent with reports in which its presence is associated with unsuitable endoscope design[10-13]. Other publications[2,13,14,16] confirm a greater involvement of the upper limbs, followed by neck-back and, in smaller numbers, lower limbs. In a survey on injuries during colonoscopies procedures, there was a higher frequency of injuries to the lumbar region (35.2%), neck (35.2%), and left thumb (33.9%)[20].

Postgraduate students reported increased involvement of the right hand and fingers (especially the right thumb). That report is inconsistent with a publication describing greater involvement of the left thumb[3]. In our students, it can be attributed to excessive gripping forces with biopsy forceps and other accessories at the beginning of their training.

Musculoskeletal disorders have been associated with risk factors for "overuse injury" (a term imported from sports) for repetitive movements and poor postures that generate repetitive stress; together with rotational and grasping forces, endos-

Table 2. Upper Limb MSDs in Specialists by Gender, Age Group, and Dominance

														N = 131
Types of MSD		**Specialist n = 114**												
		Male n = 92					**Total Fa (%)**	**Female n = 22**					**Total Fa (%)**	**P-value**
Upper limb		**20-30**	**31-40**	**41-50**	**51-60**	**> 60**		**20-30**	**31-40**	**41-50**	**51-60**	**> 60**		
Thumb involvement	Both				5	1	6 (17.1)		1	1			2 (25)	0.843
	Right		1	1	2	4	8 (22.9)			1		1	2 (25)	
	Left	1	2	5	10	3	21 (60)		1	1	2		4 (50)	
	Total	**1**	**3**	**6**	**17**	**8**		**0**	**2**	**3**	**2**	**1**		
Hand or finger pain	Both			1	7	2	10 (41.7)		2	2	1		5 (41.7)	0.424
	Right		1	3	3	1	8 (33.3)		1	3	2		6 (50.0)	
	Left			1	3	2	6 (25.0)				1		1 (8.3)	
	Total	**0**	**1**	**5**	**13**	**5**		**0**	**3**	**5**	**4**	**0**		
Hand-arm numbness	Both			2	4	3	9 (56.3)				1		1 (14.3)	0.095
	Right		1	1	1	1	4 (25)		1	3	1		5 (71.4)	
	Left				1	2	3 (18.8)			1	**2**		1 (14.3)	
	Total	**0**	**1**	**3**	**6**	**6**		**0**	**1**	**4**		**0**		
Carpal tunnel syndrome	Both			1	3	1	5 (71.4)						0	0.011
	Right						0		1		1		2 (100)	
	Left				2		2 (28.6)						0	
	Total	**0**	**0**	**1**	**5**	**1**		**0**	**1**	**0**	**1**	**0**		
De Quervain's tenosynovitis	Both				2		2 (20)		1	1			2 (40)	0.592
	Right				6	1	7 (70)				3		3 (60)	
	Left				1		1 (10)						0	
	Total	**0**	**0**	**0**	**9**	**1**		**0**	**1**	**1**	**3**	**0**		
Wrist pain	Both		1	3	3		7 (33.3)			1	2		3 (30)	0.576
	Right		2	3	3	1	9 (42.9)		3	2	1		6 (60)	
	Left	1	1		2	1	5 (23.8)			1			1 (10)	
	Total	**1**	**4**	**6**	**8**	**2**		**0**	**3**	**4**	**3**			
Elbow pain	Both			1	5	1	7 (22.6)		1		1		2 (28.6)	0.943
	Right		1	6	5	2	14 (45.2)			3			3 (42.9)	
	Left			5	3	2	10 (32.3)		1	1			2 (28.6)	
	Total	**0**	**1**	**12**	**13**	**5**		**0**	**2**	**4**	**1**	**0**		
Shoulder pain	Both			2	7	3	12 (30.8)			1			1 (10)	0.404
	Right		1	4	10	4	19 (48.7)			4	1	1	6 (60)	
	Left			2	2	4	8 (20.5)			2	1		3 (30)	
	Total	**0**	**1**	**8**	**19**	**11**		**0**	**0**	**7**	**2**	**1**		
Total		**2**	**11**	**41**	**90**	39		0	13	28	18	2		

copic support in uncomfortable positions, prolonged standing times, and the attempt to permanently relocate the visual field with the tip of the endoscope, they add to the cumulative trauma that worsens when associated with the large volume of procedures and number of years of practice[4,21].

The significant differences in risk factors included: Gender (greater involvement in males; $p < 0.001$), unlike an extensive series of 1698 participants, in which there was no difference by gender[22]. Also, a lower frequency of MSDs was associated with small glove size (compared to medium and large sizes; $p < 000.1$), contrasting publications linking most of the injuries to small hand size[22,23].

Other risk factors for women, including the combination of suboptimal endoscopic grip, lower muscle mass genera-

Table 3. Neck and Back MSDs in Specialists by Gender and Age Group

Types of MSD		N = 131 Specialist n = 114												P-value
		Male n = 92					Total Fa (%)	Female n = 22					Total Fa (%)	
Upper limb		20-30	31-40	41-50	51-60	> 60		20-30	31-40	41-50	51-60	> 60		
Neck and back														
- Neck pain	Yes No		1	5	5	4	15 (20.8)		1	1	1	1	4 (25)	0.058
- Neck pain, upper back pain	Yes No			1	1	4	6 (8.3)		1	3	2		6 (37.5)	
- Neck pain, upper back pain, lower back pain	Yes No			1	5	4	10 (13.9)		1				1 (6.3)	
- Neck pain, lower back pain	Yes No		1	1	3	1	6 (8.3)		1				1 (6.3)	
- Upper back pain	Yes No		1	4	3	1	9 (12.5)				1		1 (6.3)	
- Upper back pain, lower back pain	Yes No			3	1	2	6 (8.3)			2			2 (12.5)	
- Lower back pain	Yes No	1	4	7	4	4	20 (27.8)				1		1 (6.3)	
	Total	1	7	22	22	20		0	4	6	5	1		

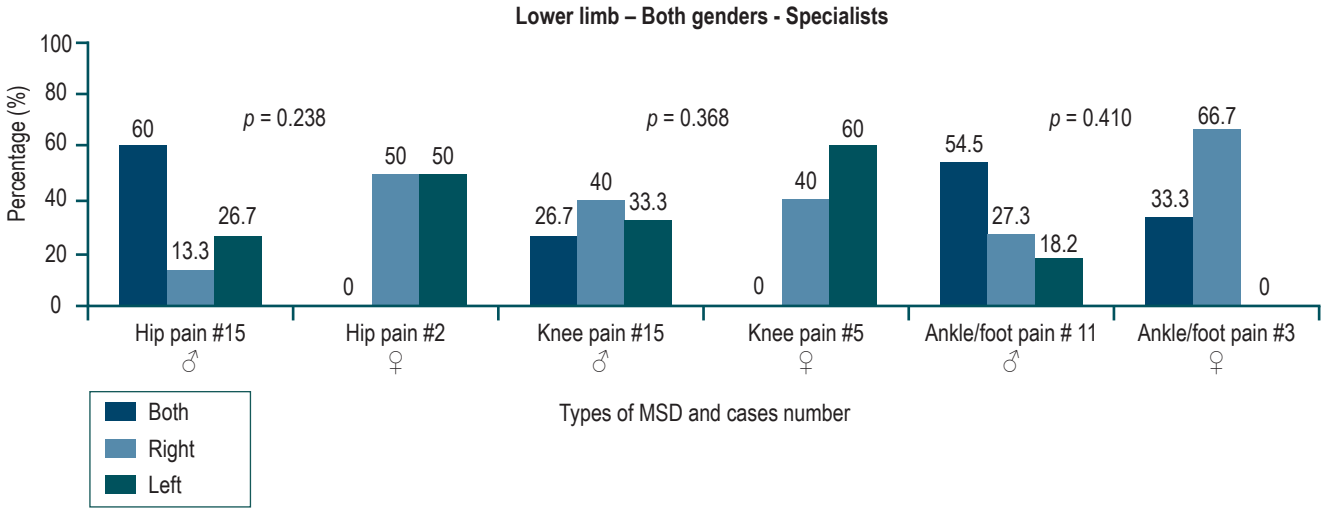

Figure 2. Musculoskeletal disorders in lower limbs in specialists by gender. Authors' elaboration.

ting prehensile strength in fingers[3,13,22,23], and endoscope inadequate ergonomic designs or procedure rooms[24], were not the subjects of this study. Although, they should be considered for future research.

Working conditions were evaluated as risk factors as follows: workload in years (accumulated and recent), number and type of procedures performed, and working hours dedicated to endoscopy. This research only found a significant difference ($p < 0.029$) for the group of 4-10 years of practice, resulting in more frequent MSDs in men than in women. When compared by gender, the remaining workload factors did not show significant differences.

Table 4. Characteristics of Cumulative and Recent Endoscopic Exercise in Male and Female Specialists and Postgraduate Students with MSDs

Characteristics of the endoscopic practice		Specialists			Postgraduate students		
Years of practice		Male n = 92 Total Fa (%)	Female n = 22 Total Fa (%)	Valor p	Male n = 12 Total Fa (%)	Female n = 5 Total Fa (%)	P-value
Accumulated years of endoscopic practice	< 3 < 4 4-10 10-20 > 20	1 (1.1) 5 (5.4) 13 (14.1) 24 (26.1) 49 (53.3)	0 2 (9.1) 8 (36.4) 8 (36.4) 4 (18.2)	0.029	11 (91.7) 0 0 0 1 (8.3)	5 (100) 0 0 0 0	0.50611
Two-year cumulative procedures							
- No. endoscopic procedures accumulated in the last 2 years (gastroscopy, colonoscopy, and basic interventional procedures)	< 200 201-500 501-1000 > 1000	4 (4.4) 6 (6.7) 42 (47.7) 38 (42.2)	2 (9.5) 3 (14.3) 7 (33.3) 9 (42.9)	0.437	2 (16.7) 3 (25) 6 (50) 1 (8.3)	1 (20) 3 (60) 1 (20) 0	0.487
- No. endoscopic procedures accumulated in the last 2 years (advanced interventionism (ERCP, EUS-FNA, enteroscopy, stent])	< 200 201-500 501-1000 > 1000	31 (54.4) 11 (19.3) 12 (21.1) 3 (5.3)	9 (75) 2 (16.7) 1 (8.3) 0	0.523			Un-known
- No. endoscopic procedures accumulated in the last 2 years (third space [DES, POEM, G-POEM, Z-POEM, D- POEM])	< 200 201-500	26 (92.9) 2 (7.1)	5 (100) 0	0.538			Un-known
- No. endoscopic procedures accumulated in the last 2 years (under radiology)	< 200 201-500 501-1000 > 1000	24 (51.1) 10 (21.3) 10 (21.3) 3 (6.4)	6 (60) 3 (30) 1 (10) 0	0.664	4 (57.1) 3 (42.9) 0 0	2 (66.7) 1 (33.3) 0 0	0.778
Cumulative procedures per week (averaged over 2 months)							
- No. endoscopic procedures per week (averaged over the last 2 months [gastroscopy, colonoscopy, and basic interventional procedures])	< 50 50 51-100 101-150 > 150	4 (4.5) 25 (28.1) 37 (41.6) 16 (18) 7 (7.9)	2 (9.5) 6 (28.6) 11 (52.4) 1 (4.8) 1 (4.8)	0.495	4 (36.4) 3 (27.3) 1 (9.10) 3 (27.3) 0	0 1 (20) 1 (20) 3 (60) 0	0.362
- No. endoscopic procedures per week (averaged over the last 2 months [advanced interventionism])	< 50 50 51-100 101-150 > 150	4 (9.3) 29 (67.4) 4 (9.3) 5 (11.60) 1 (2.3)	0 8 (100) 0 0	0.464	3 (42.9) 1 (14.3) 3 (42.0) 0	0 1 (100) 0 0	0.180
- No. endoscopic procedures per week (averaged over the last 2 months [third space interventionism])	< 50 50 51-100	2 (10) 17 (85) 1 (5)	0 2 (100) 0	0.841	5 (83.3) 1 (16.7) 0	0 0 0	Un-known
Hours worked per week (2 months)							
- General work	< 24 24-48 49-60 > 60	6 (7.2) 36 (43.4) 25 (30.1) 16 (19.3)	1 (4.8) 11 (52.4) 5 (23.8) 4 (19)	0.877	0 3 (25) 3 (25) 6 (50)	0 0 1 (20) 4 (80)	0.401
- Work in the endoscopy room	< 24 24-48 49-60 > 60	25 (29.1) 42 (48.8) 11 (12.8) 8 (9.3)	9 (40.9) 10 (45.5) 3 (13.6) 0	0.411	1 (10) 4 (40) 3 (30) 2 (20)	0 1 (20) 0 4 (80)	0.145

Table 5. MSD Prevention Behaviors and Ergonomics Training in Male and Female Specialists and Postgraduate Students

		Specialists			Postgraduate Students		
		Male n = 92 Total Fa (%)	Female n = 22 Total Fa (%)	Valor p	Male n = 12 Total Fa (%)	Female n = 5 Total Fa (%)	P-value
Regular breaks							
- Endoscopic intraprocedures	Yes No	2 (3.8) 50 (96.2)	0 12 (100)	0.490	0 7 (100)	1 (33.3) 2 (66.7)	0.107
- Between endoscopic procedures	Yes No	45 (60.8) 29 (39.2)	13 (65) 7 (35)	0.732	5 (55.6) 4 (44.4)	2 (66.7) 1 (33.3)	0.735
Training in ergonomics							
- Formal didactics of a program	Yes No	4 (4.9) 78 (95.1)	2 (12.5) 14 (87.5)	0.245	1 (10) 9 (90)	0 5 (100)	0.464
- Informal/self-taught didactics	Yes No	31 (36.5) 54 (63.5)	11 (55) 9 (45)	0.128	4 (40) 6 (60)	1 (20) 4 (80)	0.439
- Didactics within the procedure room	Yes No	17 (20.2) 67 (979.8)	2 (12.5) 14 (87.5)	0.470	3 (25) 9 (75)	0 5 (100)	0.218

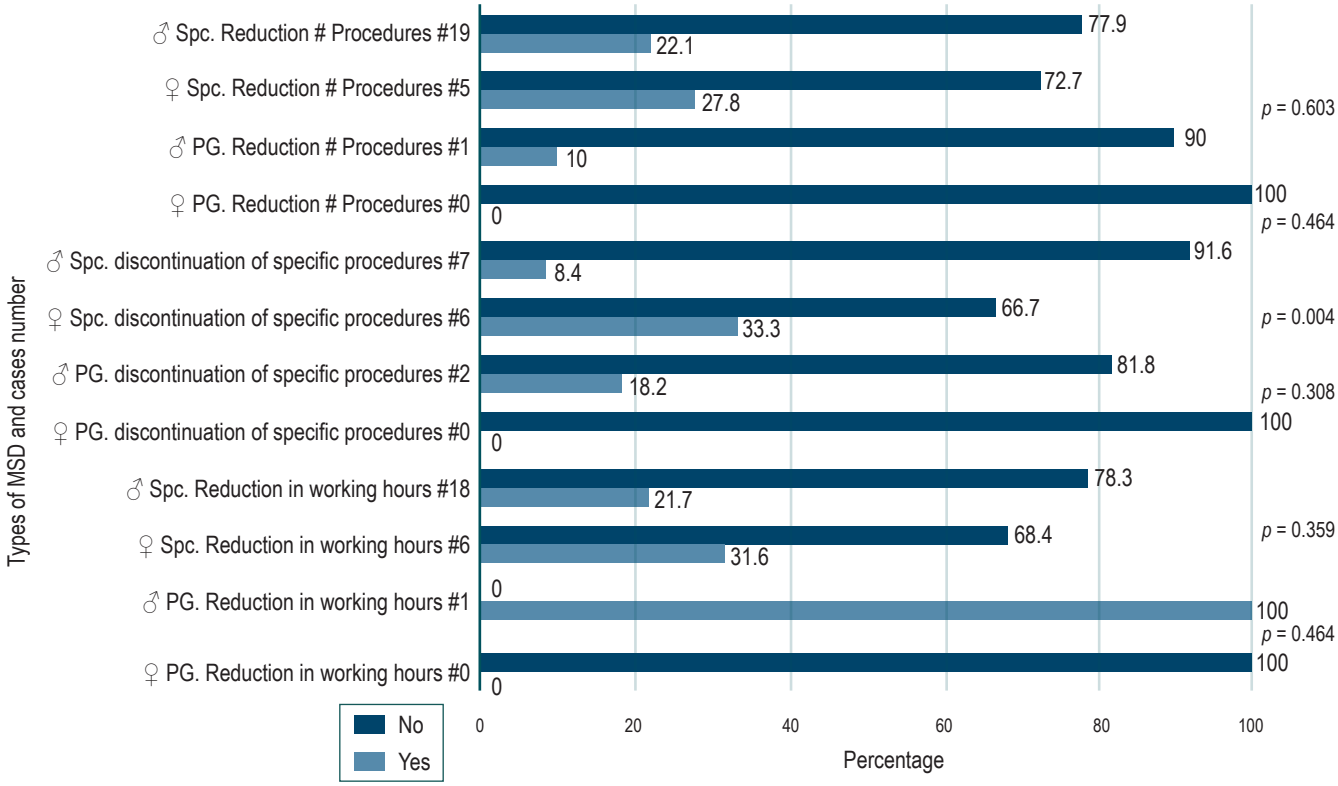

Figure 3. Occupational impact of MSDs in specialists and graduate students according to gender. Esp.: Specialists; PG: Graduate students; ♂: Male; ♀: Female. Authors' elaboration.

Table 6. Awareness of Ergonomics Endoscopy Training in Male and Female Specialists and Postgraduate Students

		Specialists		
		Male n = 92 Total Fa (%)	Female n = 22 Total Fa (%)	P-value
For practicing specialists				
- I am willing to change how I perform endoscopy if it helps me prevent endoscopy-related injuries.	Strongly agree Neither Agree nor Disagree Strongly disagree	62 (72.9) 8 (9.4) 15 (17.6)	12 (63.2) 1 (5.3) 6 (31.6)	0.366
- I am willing to receive and provide training to the endoscopy room care team on the prevention of overuse-related injuries in endoscopy	Strongly agree Neither Agree nor Disagree Strongly disagree	63 (74.10) 9 (10.6) 13 (15.3)	12 (66.7) 0 6 (33.3)	0.098

		Postgraduate Students		
		Male n = 12 Total Fa (%)	Female n = 5 Total Fa (%)	P-value
For postgraduate students-fellows				
- Ergonomic training during specialization is important	Strongly agree Neither Agree nor Disagree Strongly disagree	10 (90.9) 0 1 (9.1)	5 (100) 0 0	0.486
- I am willing to educate myself on what can help me prevent an injury related to performing endoscopies	Strongly agree Neither Agree nor Disagree Strongly disagree	9 (81.8) 0 2 (18.2)	4 (80) 0 0	0.211
- I would like to receive formal didactic training on how to prevent overuse injuries in endoscopy	Strongly agree Neither Agree nor Disagree Strongly disagree	10 (90.9) 1 (9.1) 0	4 (80) 1 (20) 0	0.541
- I receive training in the procedure room on how to prevent endoscopy-related injuries	Strongly agree Neither Agree nor Disagree Strongly disagree	3 (27.3) 5 (45.5) 3 (27.3)	2 (40) 2 (40) 1 (20)	0.872

Reports showed a tendency towards increased reporting in males (groups 51-60 years and 41-50 years), practicing for more than 20 years, working 24-48 and 49-60 hours per week; in addition to a higher number of basic endoscopic procedures, advanced interventional procedures or under fluoroscopy, both accumulated and recent. In the procedure room, the number of reported MSDs increased when the working day was less than 24 hours per week. This suggests that detraining caused by less practice may represent a risk factor.

Therefore, these results could not validate Pawa *et al.*[22], who reported higher odds of MSDs according to age (51.9 ± 12.3 years; $p < 0.001$), general gastrointestinal practice ($p < 0.001$), years of endoscopy practice (21.1 ± 12.0 years; $p < 0.001$), and the number of colonoscopies per week (between 11 and 30; $p < 0.001$) in univariate analysis, and, years of endoscopies practice and the number of hours performing endoscopies/week in a multivariate analysis.

The Japanese prevalence of 69% MSDs could not be confirmed in third space endoscopy (TSE) with MSDs (71% from the beginning of TSE and 48.8% with previous symptomatic worsening while performing echoendoscopes and ERCP)[17,25], probably due to the small amount of TSE in the current sample. However, the higher demands of time and technique could show an increase in this group in the future since these diagnostic and therapeutic modalities are rapidly expanding.

The occupational impact of MSDs was significant: Seventy-eight percent of specialists reported absenteeism and work disability. Absenteeism was much higher than in

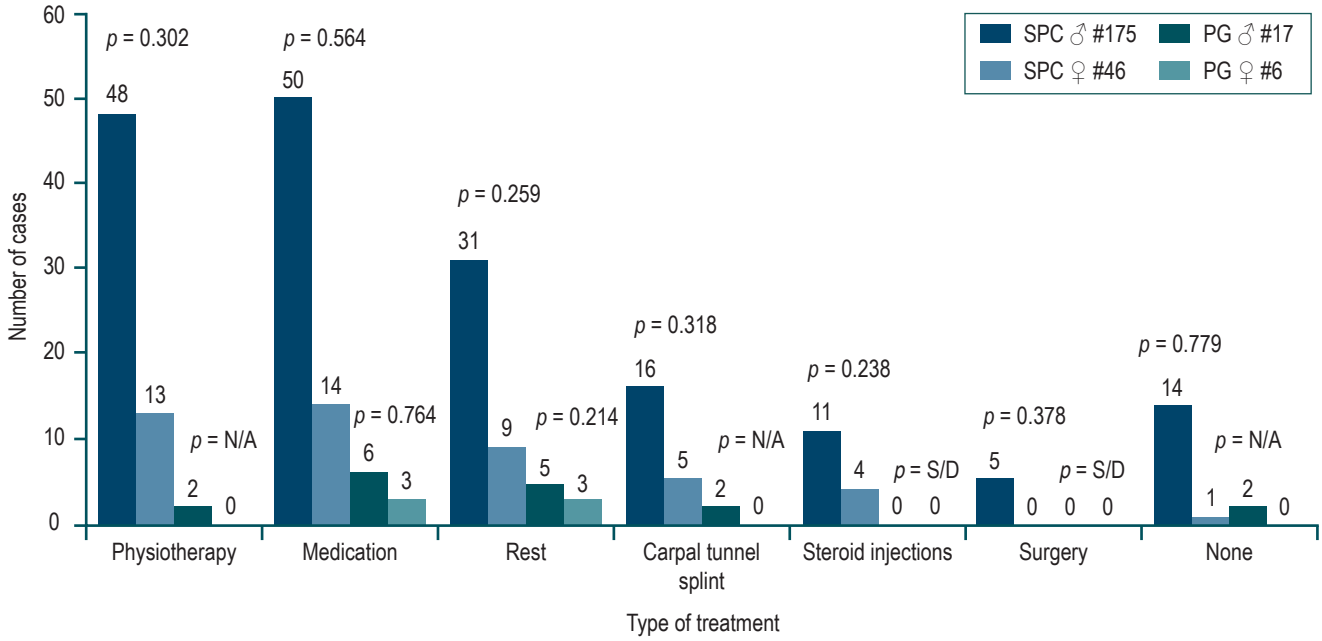

Figure 4. Treatment modalities for MSDs in specialists and graduate students according to gender. Esp.: Specialists; PG: Graduate students; ♂: Male; ♀: Female. Authors' elaboration.

other publications, with absence rates from work between 3% and 18.5%[4,13,15,26], 17.3% in endoscopists performing extended diagnostic and therapeutic procedures[6], and 9.7% in those performing colonoscopy procedures[20]. In terms of disability, this research found a significant difference with women discontinuing specific procedures more often (33.3% vs. 8.4%; $p < 0.004$). While disability accounted for only 2.2% of TSE research[17].

The most commonly used reported treatments included respectively: Medications, physiotherapy, rest, carpal tunnel splint or wrist splint treatment, steroid injection, no treatment, and finally, surgery. These behaviors coincide with therapeutic choices in TSE[17] and those performing colonoscopy[20]. In this study, many male endoscopists rejected any alternative, which may have influenced the high absenteeism rate.

Regarding the prevention of MSDs, 93.8% did not receive ergonomic training under formal didactics, a higher number than the 61.5% reported by Pawa *et al.*[22]. There was an intention of informal self-study training 40%, and 61.7% paused between procedures. These are inferior figures, possibly associated with the high prevalence found of MSDs. The positive perception of ergonomic training (74.1% in specialists, 90.9% in postgraduate students) enables a comprehensive preventive approach that must keep education and training as central elements[1,27,28].

Therefore, a proposal such as the Core Curriculum for Ergonomics in Endoscopy published by the American Society for Gastrointestinal Endoscopy (ASGE)[1] defines basic knowledge, technical skills, and non-technical skills by teaching the performance of endoscopy and the safety of the endoscopist with an ergonomic approach, including leadership and awareness of risk factors within the work team, supported by teachers who bring a level of understanding of competence the aspects mentioned above[29,30]. Prevention may include individualized studies and physiotherapy plans[24], ergonomic programs on colonoscopy simulators[31], and endoscope redesign tailored to gender needs. However, the advent of the customized endoscope is ideal, albeit inapplicable for the near future[32]. For some, the tremendous physical load demanded requires endoscopists to receive a training plan similar to that of an athlete, including 5 steps: Knowledge and appropriate use of equipment, preparation "for the game," teamwork, recovery, and reflection on the result, which keeps them physically "in the game"[28].

This study has limitations inherent to the application of surveys, such as response bias (likely reason for suffering from MSDs that overestimates the prevalence) and recalls bias. No detailed inquiry was made about other MSDs before endoscopic practice or potentially harmful habits such as excessive use of cell phones, nor was there any inquiry about healthy practices. Postgraduate students' participation was poor. Thus, their results are pretty limited, albeit interesting as a first approximation. Therefore, these results remained part of the report.

Study highlights: Despite the small sample size, it shows a response rate close to 50% of the estimated Colombian endoscopists population, constituting thus far the most extensive study of MSDs in endoscopy in the country. This study investigates various MSDs, professional practice characteristics, educational levels, and specific ergonomic training. Furthermore, it approaches impact according to gender.

CONCLUSIONS

The 65.2% MSDs prevalence rate evidences an occupational health problem for endoscopists. Consequently, further research and interventions in its prevention, diagnosis, and treatment should continue.

The type of MSD and the risk factors found are similar to those published (therefore, the pathophysiological mechanisms are shared). Hence, a common scenario can hasten the prevention and intervention measures already described.

Data from this study allows endoscopists' placement in the different groups surveyed to bring them closer to their risk factors and, consequently, to their prevention.

Numerous aspects require ergonomic improvements in endoscopy practice. If awareness, training, and prevention on the subject fail in this area, discussing the topic of "safe endoscopy practices" would remain a mere oxymoron[33].

Conflicts of Interest

The authors of this study declare that they have no conflicts of interest.

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Original article

Incidence and characterization of colorectal adenomas in the area of influence of a specialized institution

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Abstract

Aim: To locate and characterize colorectal adenomas endoscopically and histologically in a cohort of patients undergoing colonoscopy in Medellín, Colombia. **Materials and methods:** Descriptive cross-sectional study. We included patients older than 18 years who underwent colonoscopy between February and July 2020 at a specialized center in Medellín, Colombia. We determined the incidence of adenomas, their location in different segments of the colon, their endoscopic and histological characteristics, and cases of colorectal cancer (CRC) and high-grade dysplasia (HGD). **Results:** 992 colonoscopies were performed, finding colorectal polyps in 266 patients, of which 208 had adenomas. We resected 461 polyps, of which 336 were adenomas (72 %). The histological type with the highest representation was tubular (78 %). The location of adenomas was 37 % in the right colon, 25 % in the transverse colon, and 38 % in the left colon. CRC cases were nine per 1,000 patients, including advanced carcinoma and carcinoma *in situ* (HGD). **Conclusions:** Given the incidence of adenomas in the right and transverse colon, rectosigmoidoscopy is discouraged as a screening study for CRC. Tubular adenomas, sessile in appearance and tiny, predominated in the population studied. We recommend screening in the population over 40 years of age and the search for precursor lesions as strategies to reduce morbidity and mortality rates due to CRC.

Keywords

Colonoscopy, colorectal adenomas, colorectal cancer.

INTRODUCTION

The prevention of colorectal cancer (CRC) is an objective of public health in different countries worldwide. Primary prevention includes modifying risk factors in the lifestyle and diet of patients. In contrast, secondary prevention focuses on the surveillance and follow-up of patients with an average or high risk of developing the disease, such as 50 years of age or older, family history of CRC, familial adenomatous polyposis, or inflammatory bowel disease[(1)].

Carcinogenesis in CRC is a process that can take years and, therefore, allows identifying cancer precursor lesions that, when resected, would reduce the risk of developing the disease. There must be easy access to diagnostic and therapeutic colonoscopy programs.

The present study aims to describe the findings of a cohort of patients undergoing colonoscopy regarding the location and endoscopic and histological characterization of colorectal adenomas.

MATERIALS AND METHODS

A cross-sectional study was conducted in a gastroenterology institution in Medellín, Colombia, between February

and July 2020. All outpatients over 18 years of age admitted for colonoscopy after signing the informed consent were included consecutively.

A database was built from demographic, endoscopic, and histologic data obtained from colonoscopy and pathology reports. The study variables were age, sex, the scope of the examination, assessment of the quality of colon preparation using the Boston scale, endoscopic result, histological result, type of polyp, number of resected polyps, location of the polyps, aspect, size, presence of dysplasia, and presence of adenocarcinoma.

A total of 992 colonoscopies were performed in the study period by a team of seven gastroenterologists and interpreted by a group of two pathologists with training in gastrointestinal histopathology.

The colonoscopes used are high definition, with different light filters such as LCI (linked color imaging), BLI (blue light imaging), and NBI (narrow-band imaging) and magnification for lesion characterization. Polyp resection was performed with biopsy forceps or polypectomy snare, depending on the lesion size. The size of the lesion was estimated by comparing the polyp with the fully open biopsy forceps (7 mm in length) or the polypectomy snare (15 and 30 mm in diameter)[2] and classified according to the following criteria: minute (up to 5 mm), small (6–9 mm), and large (≥ 10 mm)[3].

The findings in the endoscopic report describe the size, quantity, and aspect of the resected polyps according to their location by colon segments. According to the Paris Classification, the endoscopic element was not included in the analysis.

A complete histological study of the polyps was performed, which were deposited in 10% buffered formalin and stained with hematoxylin and eosin to diagnose the histological type of each polyp (adenomatous, non-adenomatous), determine the grade of dysplasia according to the Vienna classification[4], and classify the adenoma according to its architecture as serrated, tubular, tubulovillous, or villous[5].

The institutional ethics committee approved the study, considering it without risk since no intentional intervention or modification of the biological, physiological, psychological, or social variables of the individuals who participated in the study was carried out. In turn, it contemplates the fundamental principles of research ethics following the Declaration of Helsinki version 2013[6] and the provisions of Resolution 008430/1993 issued by the Ministry of Health of Colombia[7].

Statistical analysis

The descriptive analysis of the population was carried out with the programs Excel version 2010 and Jamovi version 1.2.25. Absolute and relative frequencies were determined for qualitative variables and measures of central tendency and dispersion for quantitative variables. The chi-square association test was used for independent samples, estimating the odds ratio (*OR*) with its appropriate 95% confidence interval (*CI*). A statistically significant *p*-value < 0.05 was considered.

RESULTS

Data were obtained from the reports of 992 consecutive patients who underwent complete colonoscopy between February and July 2020 at a third referral gastroenterology institution in Medellín, Colombia. All patients included in the study met the criteria of the entire examination scope, the Boston scale result to assess the quality of colon preparation, and the measurement of colonoscope withdrawal time (≥ 6 minutes).

Sixty-one percent of the population with colorectal polyps are women, and the average age was 52.8 years, with a standard deviation of 14.7. The age range oscillated between 18 and 89 years. Demographic and follow-up variables are described in **Table 1**.

Five main indications for colonoscopy were identified: screening for CRC (47%), gastrointestinal symptoms (33%), personal history of polyps (15%), family history of CRC (3%), and positive fecal occult blood (2%). A greater indication for colonoscopy due to gastrointestinal symptoms was identified in women (OR: 1.36; 95%CI: 1.03–1.79; p = 0.029) and a personal history of polyps in men (OR: 1.72; 95%CI: 1.20–2.47, p = 0.003).

Two hundred sixty-six patients with colorectal polyps and 461 resected polyps were identified, characterizing 125 (27%) as non-adenomatous polyps (**Table 2**). In 32% of patients, more than one adenoma was resected.

The content of this article focuses on the characterization of adenomatous polyps. Adenoma detection was 21% (208 patients with adenomas out of 992 patients evaluated). In these 208 patients, 336 adenomas were resected. The most common macroscopic aspect was sessile (85%) and flat or pedunculated lesions to a lesser extent. Six mass-type lesions (2%) were identified: adenocarcinomas or adenomas with high-grade dysplasia (HGD). Of the resected lesions, 71% were categorized as minute (less than 5 mm), 18% small, and 11% large. One minute adenoma with HGD and eight larger advanced lesions were found.

The location of the adenomas was in the ascending (37%) and transverse (25%) colon. There were no statistically significant differences in the detection of adenomas between the right and left colon (**Table 2**).

Regarding the histopathology of the resected adenomas, three different types were identified (serrated, tubular, and

Table 1. Demographic information and characterization of adenomas

Variable	n (%)
Sex	
- Female	602 (61)
- Male	390 (39)
Age range	
- < 40	8 (3,8)
- 40-49	25 (12)
- 50-59	70 (33,7)
- 60-69	60 (28,8)
- 70-79	33 (15,9)
- > 80	12 (5,8)
Location	
- Rectum	39 (11,6)
- Sigmoid	56 (16,7)
- Descending	33 (9,8)
- Transverse	83 (24,7)
- Ascending	96 (28,6)
- Cecum	29 (8,6)
Size	
- ≤ 5 mm (minute)	240 (71)
- 6-9 mm (small)	60 (18)
- ≥ 10 mm (large)	36 (11)
Aspect	
- Flat	19 (6)
- Sessile	287 (85)
- Pedunculated	24 (7)
- Lump	6 (2)
Dysplasia grade	
- LGD	327 (97,3)
- HGD	5 (1,5)
- Adenocarcinoma	4 (1,2)

tubulovillous); 97% had low-grade dysplasia. We observed that the predominant histological type is tubular (78%), followed by the serrated type (18%). No villous adenomas were identified (**Table 2**).

Table 2. Histological type and location of polyps

	Right colon	Transverse colon	Left colon	Overall, n (%)
Adenoma				
- Serrated	17	7	38	62 (18)
- Tubular	105	73	84	262 (78)
- Tubulovillous	3	2	5	10 (3)
- Indeterminate	0	1	1	2 (1)
- Overall, n (%)	125 (37)	83 (25)	128 (38)	336 (100)
Polyp				
- Inflammatory	0	3	4	7 (6)
- Hyperplastic	20	17	81	118 (94)
- Overall, n (%)	20 (16)	20 (16)	85 (68)	125 (100)

Four new cases of CRC and five cases of HGD (considered carcinoma *in situ*) were obtained. In the case of these nine patients, five were men and four women, with a mean age at diagnosis of 69 years.

No cases of CRC or HGD were found in the studied population's rectum or descending colon.

DISCUSSION

A *polyp* is a visible protrusion that may develop on the surface of the colon or rectum. When it comes to an adenoma, it derives from the glandular epithelium and may have different grades of dysplasia or histological characteristics associated with a potential increase in malignancy[8,9]; therefore, they are widely known as precursor lesions of CRC. For its part, adenocarcinoma is an adenomatous lesion that invades the mucosa and whose transformation to a high grade of dysplasia and invasive carcinoma requires around ten years of evolution[10]. Characterizing the number, size, and histology of adenomas makes it possible to determine adequate follow-up periods[11] that minimize the risk of advanced or interval CRC in the population concerned.

Colonoscopy screening has effectively reduced CRC mortality and prevented 60%–80% of incident lesions due to adenoma resection[12]. In most cases, polypectomy was the procedure of choice for resection. However, some situations typical of the examination could have inadvertently affected the detection of adenomas, such as inadequate intestinal cleaning of the entire colon; polyps unnoticed by their size or appearance (minute or flat); CRC that does

not follow the adenoma-carcinoma sequence or particularly aggressive precursor lesions that transform from adenoma to carcinoma in a shorter period[13].

In the examinations carried out on women, there was a more significant indication for colonoscopy due to gastrointestinal symptoms (65%). Of note is that the clinical symptoms most strongly suggest CRC are rectal bleeding and weight loss[14] and that, generally, colorectal polyps are rarely accompanied by symptoms before progressing to CRC, except for some occasional abnormalities in the stool[15]. In our population, a higher incidence of adenomas was found in men, and the male sex is an established risk factor for colorectal adenomas[16].

Of the 208 patients with adenomas, 12% were 40–49 years old, suggesting the need to start CRC screening earlier for detection and resection of precursor lesions[17].

The prevalence of adenomas in the average risk population is between 10% and 20%[18]. In our case, it was 25%, corresponding to patients over 50 years of age with no pathology or history of associated risk in whom at least one colorectal adenoma was resected.

As for the location of adenomas, other authors reported no differences between the right and left colon[11], which matches the findings in the present study. Additionally, by identifying that 62% of all resected adenomas were obtained between the right and transverse colon, performing rectosigmoidoscopy in patients screened for CRC is not considered relevant.

Size is a significant risk factor for advanced adenomas[10]; those ≥ 2 cm are considered difficult to remove entirely for various reasons: visualization is limited, the borders are difficult to identify, and there is a higher risk of bleeding[19]. Four advanced adenomas not resected due to their large size were identified in the study population. Regarding those of minute size, an adenoma was resected with HGD, corresponding to 0.3%. The proportion of minute adenomas with HGD differs between studies, reporting values of less than 1% and between 3% and 4%[3,20]. This finding suggests resecting all adenomas regardless of their size (minute or small); depending on the grade of dysplasia, the risk of progressing to CRC increases, and cases of flat, minute or depressed lesions can also be carcinomas[21]. No complications such as perforation or bleeding were associated with the polypectomy procedure.

Nineteen flat-appearing adenomas (6%) were identified, a low percentage but predictable given the difficulty in detecting them; in Japan, the incidence of flat adenomas is between 8% and 40%[22]. Sessile adenomas can also represent technical difficulties for resection due to their proximity to the submucosa. In these cases, when performing the resection, the increased risk of bleeding or perforation is inherent[19].

Most of the adenomas studied had low-grade dysplasia and tubular histology and were resected with the hot or cold loop forceps technique[23]. Lesion detection and characterization were optimized using high-definition equipment with white light and virtual chromoendoscopy, so it was possible to differentiate an adenoma from a hyperplastic polyp with greater than 90% certainty[20].

In Colombia, CRC ranks fifth in cancer incidence, with 12 cases per 100,000 inhabitants. In the study population, the incidence was much higher, reaching nine cases per 1,000 patients, because the diagnosis was made in a referral center for digestive diseases[24].

CONCLUSIONS

Given the incidence of adenomas in the right and transverse colon, rectosigmoidoscopy is not recommended as a screening study for CRC. Tubular adenomas, sessile in appearance and diminutive in size, predominated in the population studied. Screening in the population over 40 years and searching for precursor lesions are advisable as strategies to reduce morbidity and mortality rates due to CRC.

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Original article

The behavior of liver diseases in a cohort of Colombian patients with COVID-19

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Abstract

Introduction: Severe acute respiratory syndrome type 2 coronavirus infection (SARS-CoV-2) is receiving the most attention now. The asymptomatic elevation of transaminases is typical in the liver, and liver involvement varies from 14 % to 78 %. The assessment of liver comorbidities is scarce, with prevalence ranging between 2 % and 11 %. **Aim:** To describe the behavior of a cohort of patients with liver diseases who fell ill with coronavirus disease 2019 (COVID-19). **Materials and methods:** This retrospective observational study analyzed the behavior of a cohort of patients with liver diseases who fell ill with COVID-19. **Results:** 543 patients became ill with COVID-19, of which 300 were women (55.3 %). The median age at diagnosis of liver disease was 52 years. The leading causes of liver disease were nonalcoholic steatohepatitis (49.5 %), cholestatic disease (7.7 %), and hepatitis C and B viruses (6.3 %). Alanine aminotransferase (ALT) had a median of 52 U/L (interquartile range [*IQR*]: 30–98) and aspartate aminotransferase (AST) 32 U/L (*IQR*: 23–62). Mortality due to viral infection was 5.7 %, with an incidence rate of 2.9 (95 % confidence interval [*CI*]: 2–4.2). **Conclusions:** It is a retrospective study but, until the preparation of the manuscript, it had been the first cohort in Colombia to describe the behavior of liver diseases in patients who become ill with COVID-19. No statistically significant differences were found between the causes of liver disease that confer a higher risk of mortality; however, having decompensated cirrhosis is the only condition related to mortality.

Keywords

Fatty liver, SARS virus, cirrhosis of the liver, mortality.

INTRODUCTION

Infection by the severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) called *COVID-19 pandemic infection* (from the English *novel coronavirus disease 2019*) is receiving the most attention now, and liver involvement is not alien to the viral infection. Asymptomatic elevation of transaminases is typical, and liver injury varies from 14% to 78%[1-5]. Gastrointestinal manifestations such as nausea, vomiting, abdominal pain, diarrhea, loss of appetite, dysgeusia, and liver chemical changes are increasingly being reported, especially in hospitalized patients[4,5].

In the meta-analysis by Dorrell *et al*[5], 62 studies were found that reported transaminase alterations with average alanine aminotransferase (ALT) of 34.8 (+/-16.1 U/L) and aspartate aminotransferase (AST) 39.0 U/L (+/-

17.3) among all patients with coronavirus disease 2019 (COVID-19), with a weighted average AST:ALT ratio of 1.15 (+/-0.20).

Liver damage may be directly caused by virus-induced cytopathic effects, considering that SARS-CoV-2 binds to the angiotensin-converting enzyme 2 (ACE-2) receptor to enter its target cells[6,7]. Data from two independent cohorts revealed a significant enrichment of ACE-2 expression in cholangiocytes (59.7% of cells) compared to hepatocytes (2.6% of cells), suggesting that SARS-CoV-2 could bind directly to ACE-2-positive cholangiocytes and produce alterations in liver function[8–10].

Among the liver diseases described and associated with severe cases of COVID-19, the main one was chronic hepatitis B infection, with 2.4% of severe cases. AST elevation is observed in approximately 18.2% of non-severe cases and 39.4% of severe cases, and ALT elevation in 19.8% of non-severe cases and 28.1% of severe cases.

Few studies have depicted hepatic manifestations, with one study in Wuhan, China, where the origin of the virus was initially described in a series of 99 patients. A decrease in albumin was observed in 98% of patients. At the same time, serum levels of AST, ALT, and bilirubin were elevated in 35%, 28%, and 18% of patients, respectively[11]. Similarly, in an analysis of 1,099 patients, elevated AST levels were noted in 18.2% of patients with non-severe disease and 39.4% of patients with severe disease[12].

Therefore, considering that the description of the hepatic manifestations of COVID-19 is scarce and that there is no record thereof in Colombia, the present study aims to explain the behavior of a cohort of patients with liver diseases who suffered from COVID-19.

MATERIALS AND METHODS

A retrospective observational study was conducted with a review of medical records that analyzed the behavior of a cohort of patients with liver disease who became ill with COVID-19.

Only patients older than 18 years who were under follow-up for liver disease at the Center for Liver and Digestive Diseases (CEHYD) from March 2020 to June 2021 were included. Pregnant patients and those under 18 years of age were excluded.

Statistical analysis

The variables of interest were compared with a description of the sociodemographic variables through frequency and central tendency measures. The variables with normal distribution were compared using the chi-square test, while the variables with abnormal distribution were analyzed using the Mann-Whitney test. Survival analysis was performed by comparing the variables related to mortality represented in Kaplan-Meier graphs and using the log-rank test. Results were presented as tables or graphs using Stata 13.0.

RESULTS

We reviewed a total of 1,937 medical records of patients under follow-up for liver disease with suspected SARS-CoV-2 infection, confirming the diagnosis by molecular tests (real-time polymerase chain reaction [RT-PCR] or antigens) in 543 patients, of whom 300 were women (55.3%).

The median age at diagnosis of liver disease was 52 years (interquartile range [*IQR*]: 40–61). The main associated comorbidities were high blood pressure (HBP) (23%), dyslipidemia (20.1%), and obesity (17.6%), and the leading causes of liver disease were, in order, non-alcoholic steatohepatitis (NASH; 49.5%), cholestatic disease (7.7%), hepatitis C and B virus (6.3%), and alcohol (4%), with a significant difference between them. Sociodemographic characteristics are shown in **Table 1**.

One hundred fifty-two patients (27.9%) were diagnosed with cirrhosis with statistically significant differences ($p < 0.001$), together with coronary heart disease ($p < 0.015$) for mortality.

The leading cause of cirrhosis was again NASH in 36.8% ($n = 42$), and 28.2% had a history of decompensation, and the most frequent were ascites (40%), followed by variceal bleeding (20 %).

Transaminases had higher values for ALT, showing a median of 52 U/L (*IQR*: 30–98), and for AST, there was a slightly elevated value with a median of 32 U/L (*IQR*: 23–62). Laboratory variables were taken before a diagnosis of SARS-CoV-2 infection.

Despite not having statistically significant differences in mortality, a higher proportion of DM, dyslipidemia, and obesity stands out in patients who survived, as shown in **Table 2**.

Mortality from COVID-19 was 5.7% ($n = 31$), with an incidence rate of 2.9 (95% confidence interval [*CI*]: 2–4.2) and a median survival of 18 days (*IQR*: 12–32). The only variable related to liver disease with statistically significant differences in mortality was cirrhosis decompensation ($p < 0.005$), as shown in **Table 2**.

In the survival analysis, no statistically significant differences were found between survival curves by sex, cause of HCC, diagnosis or not of cirrhosis, etiology of cirrhosis due to NAFLD, or alcohol use, as shown in **Table 3** and **Figures 1–5**.

Table 1. Sociodemographic characteristics and laboratory variables in all patients

Variable	Total n = 543 n (%)	Women n = 300 (55.3 %) n (%)	Men n = 243 (44.7 %) n (%)	P-value
Sociodemographic characteristics				
- Age at diagnosis Median (IQR)	52 (40-61)	53 (40-61)	51 (39-62)	0.628*
Background				
- DM	67 (13.3)	39 (13.8)	28 (12.6)	0.7ç
- Dyslipidemia	103 (20.1)	52 (18.1)	51 (22.6)	0.2ç
- Obesity	90 (17.6)	45 (15.6)	45 (20.0)	0.2ç
- Alcohol use	204 (37.5)	60 (20)	144 (59.2)	<0.001+
- HBP	118 (23.0)	66 (23.0)	52 (23.1)	0.976ç
- Coronary heart disease	26 (5.0)	15 (5.2)	11 (4.8)	0.863ç
- BMI Me (IQR)	26.5 (24.29.4)	26 (23-29)	27 (24.9-30)	0.002*
Laboratories (n = 151)		**Median (IQR)**		
- Leukocytes Me (IQR)	5950 (5000-7230)	5905 (4762-7157)	6190 (5070-7295)	0.2352*
- Neutrophils	54 (47-60)	54 (48-61)	52 (46-59)	0.0621*
- Lymphocytes	34 (27-39)	33 (28-39)	34 (26-41)	0.2057*
- ESR (mL/h)	7 (3-15)	8 (5-20)	5 (2-8)	<0.0001*
- Hb	15 (14-16)	14 (13-15)	16 (15-17)	<0.0001*
- HCT	45 (42-48)	43 (41-46)	48 (45-50)	<0.0001*
- Platelets	242000 (192 x103-288 X10^3)	260000 (207 x103-307x10^3)	218000 (178 x103-262 x 10^3)	<0.0001*
- Glycemia	94 (86-102)	91 (84-100)	96 (89-104)	<0.0001*
- Creatinine	0.8 (0.7-1)	0.7 (0.6-0.8)	0.9 (0.8-1.1)	<0.0001*
- Total cholesterol	193 (160-224)	196 (166-229)	188 (153-222)	0.0319*
- Triglycerides	143 (104-194)	138 (93-184)	147 (113-204)	0.0106*
- TSH	2.5 (1.5-3.6)	2.5 (1.5- 3.6)	2.4 (1.6-3.7)	0.7767*
Liver function				
- AST	35 (23-62)	33 (21-63)	35.5 (26-61)	0.1763*
- ALT	52 (30-98)	49 (23-101)	58 (36-95)	0.0064*
- Alkaline phosphatase	96 (74-136)	101 (77-142)	91 (72-134)	0.0279*
- Total bilirubin	0.7 (0.4-1.1)	0.6 (0.4-1)	0.7 (0.5-1.3)	<0.0001*
- Albumin	4.4 (4.1-4.7)	4.4 (4.1-4.6)	4.5 (4.2-4.8)	0.0007*
- AFP	2.5 (1.7-3.9)	2.3 (1.6-3.6)	2.7 (1.7-4.3)	0.0882*
Cause of liver disease				<0.001+
- Fatty liver	269 (49.5)	135 (45)	134 (55.1)	
- Alcohol	22 (4.1)	3 (1)	19 (7.8)	
- Virus	34 (6.3)	19 (6.3)	15 (6.1)	
- Cholestatic	42 (7.7)	36 (12)	6 (4.5)	
- Mixed (three or more)	14 (2.6)	7 (2.3)	7 (2.8)	
- Other	162 (29.8)	100 (33.3)	62 (25.5)	

ᶜChi-square. *Mann-Whitney test. ⁺Fisher's test. AFP: Alpha-fetoprotein; DM: Diabetes mellitus; Hb: Hemoglobin; HCT: Hematocrit; Me: Median; TSH: Thyrotropin; ESR: Erythrocyte sedimentation rate.

Table 2. Variables related to mortality from COVID-19 in patients with liver disease

Variable	Total n = 543 n (%)	Alive n = 512 (94.3) n (%)	Deceased n = 31 (5.7) n (%)	P-value
Clinical features				
- Women	300 (55.3)	283 (55.2)	229 (44.7)	0.962ᶜ
- Diabetes (n = 503)	67 (13.3)	63 (13.3)	4 (12.9)	1+
- Dyslipidemia (n = 512)	103 (20.1)	99 (20.5)	4 (12.9)	
- Obesity (n = 511)	90 (17.6)	87 (18.1)	3 (9.6)	
Alcohol use	204 (37.5)	188(36.7)	16 (51.6)	0.001
- Does not use	302 (59.6)	287 (60.4)	15 (48.3)	
- HBP	118 (23.0)	111 (23.0)	7 (22.5)	0.949ᶜ
- Coronary heart disease	26 (5.0)	21 (4.3)	5 (16.1)	0.015⁺
- Cirrhosis	152 (100)	74 (100)	78 (100)	<0.001ᶜ
Cause of cirrhosis				0.274⁺
- NASH	42 (36.8)	29 (39.1)	20 (25.6)	
- NASH + alcohol	10 (8.7)	1 (1.3)	16 (20.5)	
- Hepatitis C virus	8 (7.0)	16 (21.6)	5 (6.4)	
- Autoimmune	8 (7.0)	6 (8.1)	1 (1.2)	
- Alcohol	7 (6.1)	1 (1.3)	23 (29.4)	
- Other causes	20 (15.6)	8 (10.8)	12 (8.9)	
Decompensation				0.005⁺
- Ascites	12 (20.3)	6 (13.6)	6 (40.0)	
- Variceal bleeding	8 (13.5)	5 (11.3)	3 (20.0)	
- Encephalopathy	3 (5.0)	1 (2.2)	2 (13.3)	
- HCC	2 (3.3)	1 (2.2)	1 (6.6)	
- Jaundice	7 (11.8)	6 (13.6)	1 (6.6)	
- Coagulopathy	3 (5.0)	2 (4.5)	1 (6.6)	

ᶜChi square. *Mann-Whitney test. ⁺Fisher's test. HCC: Hepatocarcinoma.

DISCUSSION

We recognize the weaknesses of the study for being retrospective; however, until the writing of the manuscript, it is the first cohort in Colombia to describe the behavior of liver diseases in patients who become ill with COVID-19.

Similarities to other studies are found in which liver diseases have not posed an increased risk of SARS-CoV-2 infection. The descriptive studies published so far found that only a small number of patients with the condition (approximately 3%) have underlying chronic liver disease, and no statistically significant association between chronic liver disease and severity of COVID-19 or outcomes regarding mortality or severity of infection has been established[11,13–15]. The preceding is reflected in the incidence rate of 2.9, even considering that this study is based on

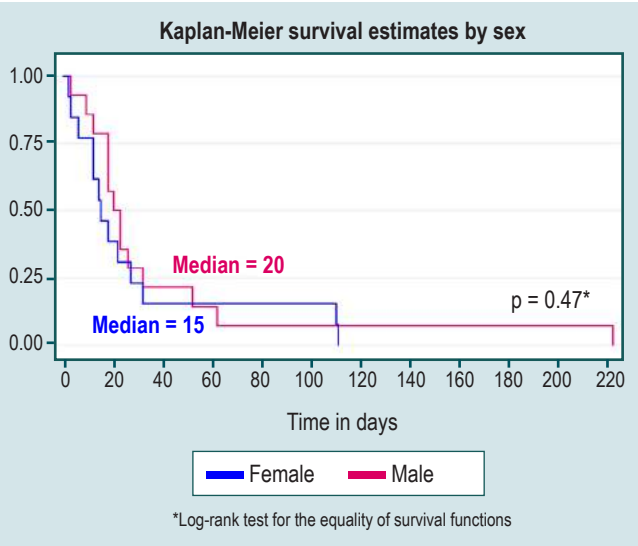

Figure 1. Survival analysis for the gender variable. Prepared by the authors.

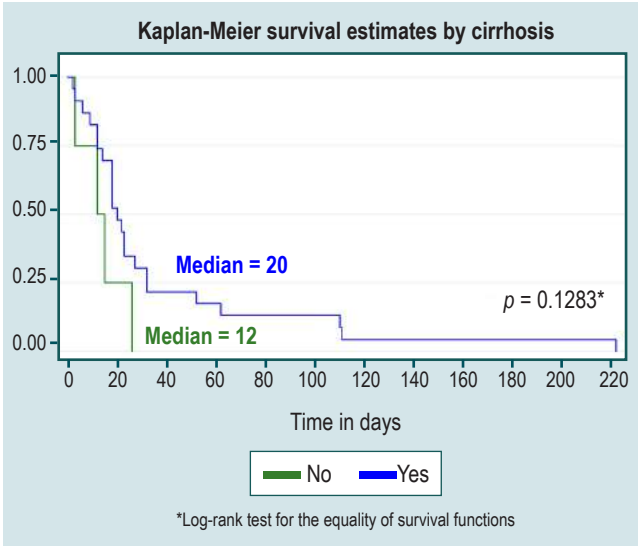

Figure 2. Survival analysis for the cirrhosis variable. Prepared by the authors

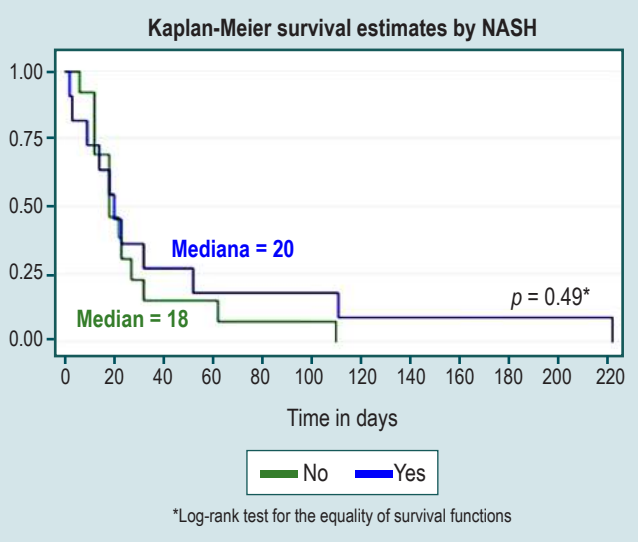

Figure 3. Survival analysis for the NASH variable. Prepared by the authors

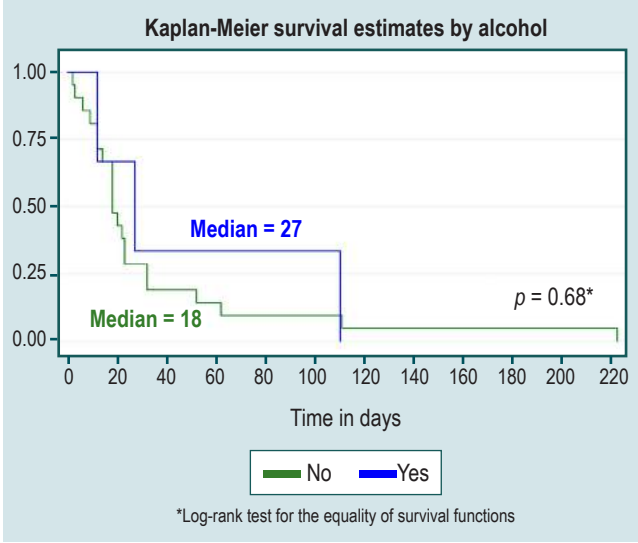

Figure 4. Survival analysis for the alcohol variable. Prepared by the authors

those patients who already have chronic liver disease. Furthermore, it reveals that mortality in this series is probably related to other factors and in those patients having advanced disease with decompensated cirrhosis from the perspective of liver disease.

No statistically significant differences were found between the causes of liver disease that represent a higher risk of mortality from SARS-CoV-2 infection in this series, contrary to what has been described in other latitudes. It has been shown that chronic diseases such as hepatitis B and C occupy the first places[12], even considering non-negligible rates of hepatitis C infection of 7% in the present study.

We ignore the transaminase behavior from the point of view of liver involvement, considering that baseline paraclinical tests are before infection. However, they show a slight elevation of ALT and AST. Other studies[5,11,12] show liver enzyme elevations with SARS-CoV-2.

Compared to global reports of patients with liver disease who develop COVID-19, such as SECURE-Cirrhosis and COVID-HEP. Mortality was similar at 13.8% for SECURE-

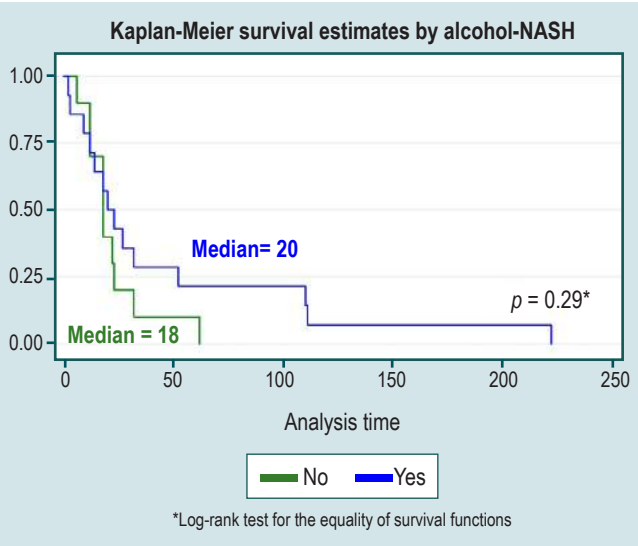

Figure 5. Survival analysis for the alcohol-NASH variable. Prepared by the authors

Tabla 3. Survival analysis

	Incidence rate * 100 (95%CI)	Median survival (days)	Percentile 25% - percentile 75% (days)
Positive diagnosis	2.9 (2 a 4.2)	18	12-32

Cirrhosis, but with a difference from COVID-HEP, in which 36.5% of deaths were found among patients with chronic liver disease and liver transplants[16,17].

Only one report of a transplanted patient was found, leaving the door open for research in this group of patients, who already have a higher risk of mortality from any cause because they are immunosuppressed patients. Nonetheless, this reinforces the concept of protection with immunization since this group of patients has a lower immunogenic response (approximately 50%), unlike those immunocompetent with responses close to 94%[18,19].

As it was a study conducted in an outpatient center, the primary liver disease was NAFLD associated with obesity and dyslipidemia, which until now has been briefly described in a few observational studies[20,21]. These found that mainly young patients and those with NAFLD have a higher risk of severe disease and a longer viral shedding time. However, fatty liver is frequently associated with other comorbidities such as diabetes or cardiovascular disease, which are also established risk factors for severe COVID-19 and could contribute to worse outcomes in these patients. Thus, there is a need for an adequate diagnosis of NAFLD to adequately define if it represents a cardiovascular risk factor in addition to chronic comorbidities, such as arterial hypertension or diabetes, once again reinforcing the concept of early vaccination in this population deemed a risk group.

Conditions of causality could not be established due to the characteristics of the study. Long-term observations are required to define the impact of liver diseases in severe cases of SARS-CoV-2 illness and determine potential therapeutic interventions in those patients with chronic liver diseases. Until now, there are discordant results as to whether or not they are a factor of more significant mortality from COVID-19[22,23].

CONCLUSION

Despite being a retrospective study, it is probably the first cohort of patients with liver diseases affected by SARS-CoV-2. Similarities and differences with other studies are found, but prospective studies are needed to assess the impact of chronic liver diseases on SARS-CoV-2 infection.

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Case report

Colo-umbilical enterocutaneous fistula as a rare complication of diverticulitis of the sigmoid colon

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Abstract

The care of patients with enterocutaneous fistula constitutes a significant challenge owing to the alterations it usually brings about. For successful treatment, it is necessary to manage fluids and electrolytes adequately, provide practical nutritional support, and control sepsis until its eradication; thus, many fistulae close spontaneously. We present the case of a 36-year-old male patient with a four-month history of fecal-like umbilical secretion. When performing the fistulogram, we confirmed a fistulous tract of 9 cm, which ended at the level of the sigmoid colon, a rare location. In cases where the enterocutaneous fistula does not close, and surgical treatment is indicated, it is imperative to maximize perioperative care, decrease surgical time, choose the correct surgical technique, and prepare the patient for surgery to avoid complications with a fatal outcome.

Keywords

Gastrointestinal fistula, abdominal pain, colon, sigmoid, laparotomy.

INTRODUCTION

Enterocutaneous fistula (ECF) is a common pathology, which sometimes occurs spontaneously as a complication of an underlying disease, and in others, it occurs due to surgical procedures. ECF is the most common form of intestinal fistulas[1], with a great diversity of manifestations, sometimes complex and very difficult to manage, reaching significant morbidity and mortality[2].

ECF is the abnormal communication between the interior of the gastrointestinal tract and the skin, with gastrointestinal fluids leaking through it for more than 24 hours[1,3-5]. The true incidence of ECF is not well determined, although an incidence of 1.5% to 16.9% has been reported after laparotomies. ECF represents 88.2% of all fistulas[6]. The world mortality due to fistulas before 1960 was 40%–65%, but the information compiled in the last decade estimates it at 3.5%–19%[1,2,4].

We present the case of a man who required surgical treatment for an unusual ECF that connected the sigmoid colon with the navel to highlight the importance of timely intervention to prevent complications.

CASE REPORT

We treated a 36-year-old male patient, 66 kg in weight and 1.64 m in height, for an average body mass index (BMI: 24.54). The patient reported a clinical picture of four months

of evolution, characterized by pain in the mesogastric and hypogastric region, increasing in frequency and intensity. He also had brown, foul-smelling discharge at the umbilical level reminiscent of feces due to its appearance and odor; it increased over time, reaching 300 mL in 24 hours.

Upon physical examination, the secretion described above was confirmed at the umbilical level. The abdomen was painful on deep palpation near the mesogastrium and hypogastrium without peritoneal reaction. The rest of the physical examination was negative. The necessary studies were performed to confirm the diagnosis of ECF, determine the patient's condition, and assess the need for surgery. The fistulography (**Figure 1A**) confirmed the fistulous duct and its communication with the sigmoid colon. Colon by double-contrast barium enema (**Figure 1B**) showed a fusiform narrowing of the entire sigmoid colon with diverticula. The diverticula were observed in the colonoscopy without finding a tumor mass. The blood count showed leukocytosis of 10.4 10 x^9/L, with a predominance of neutrophils (72.42%, normal range: 36–66).

Procedure performed and surgical findings

A supra- and infra-umbilical median laparotomy was performed, excluding the umbilicus and fistulous tract communicating the sigmoid colon with the navel. A fistulectomy with en bloc sigmoidectomy was performed (**Figure 2**). Another finding was an abscessed plastron made up of the sigmoid colon, bladder, and greater omentum; the pus was aspirated, and the devitalized tissues were removed (**Figure 3**). After the sigmoidectomy, an end-to-end seromuscular anastomosis was performed in a single plane with Vicryl 2/0; subsequently, the abdominal wall was sutured in planes.

The patient had a good evolution. After three days, a liquid diet was administered, he progressed the following day with a soft diet, and on the fifth day, he was discharged. The pathological diagnosis confirmed the presence of diverticula in the sigmoid colon with its fistulous tract.

DISCUSSION

There are various causes and risk factors that favor the formation of an ECF. A suture in any segment of the gastrointestinal tract can be the triggering factor for ECF when anastomosis dehiscence occurs, either due to errors in the technique, poor blood flow, anastomosis with tension, distal obstructions that cause distention near the suture line, and healing failure[1,3,5,6]. Crohn's disease causes 20%–30% of ECFs by spontaneous appearance or surgery compli-

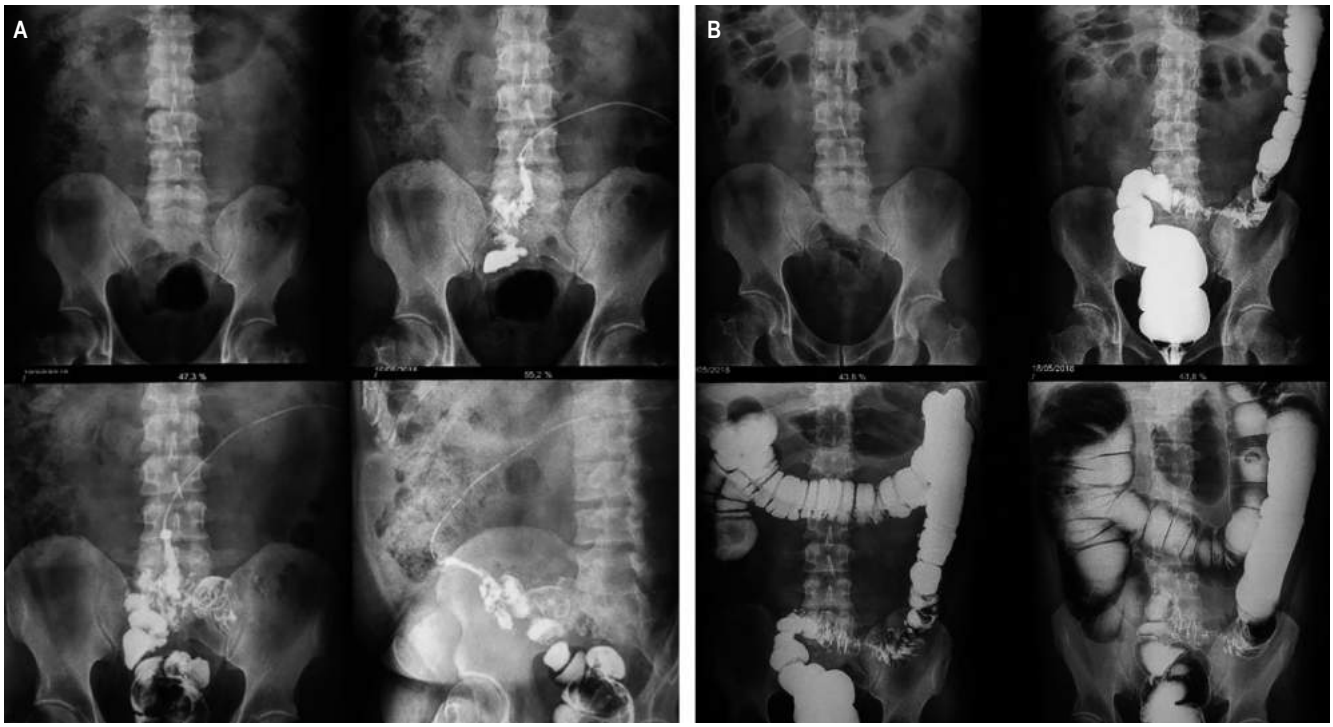

Figure 1. Fistulography. **A.** A fine probe was placed near the fistulous orifice in the umbilical region through which contrast was injected. The fistulous tract of 9 cm in length can be seen communicating with the sigmoid colon, filling it and the rectal ampulla. **B.** The colon by double-contrast barium enema showed a fusiform narrowing of the entire sigmoid colon with the presence of diverticula.

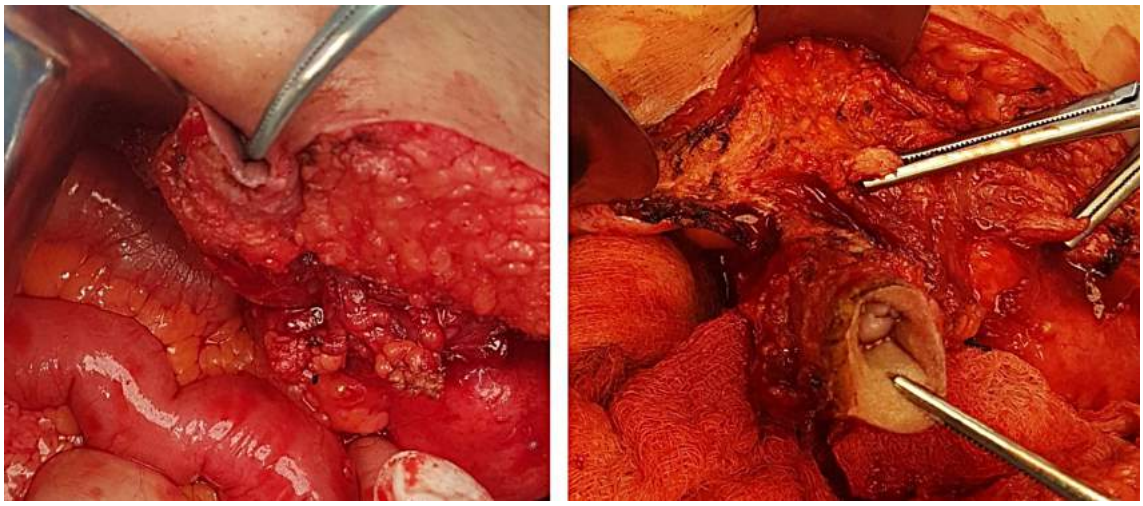

Figure 2. Moment of the surgery in which the navel is resected with the fistulous tract.

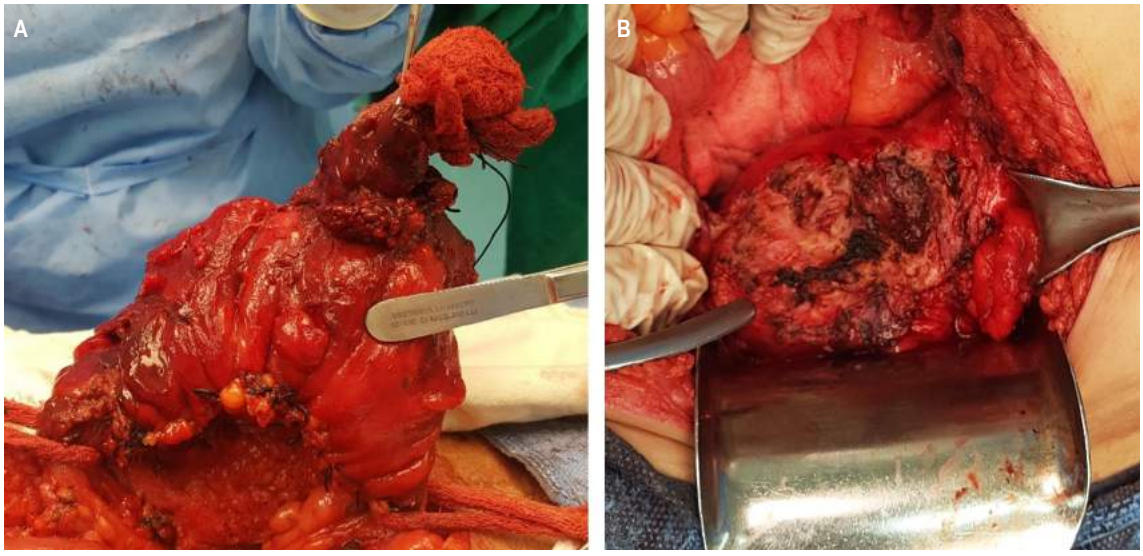

Figure 3. A. The sigmoid colon can be seen with its mesogastrium already ligated and sectioned, its two ends referred with gauze, and the fistulous tract in the medial part that communicates the sigmoid with the navel isolated with gauze. **B.** Bladder fundus where the sigmoid colon and greater omentum were adhered, forming an abscessed plastron. The bladder is shown after the plastron has been disintegrated and the devitalized tissue and pus removed.

cation[3,6,7]. Other causes are gastrointestinal resections, incisional hernia repair, intra-abdominal collection drainage, iatrogenic intestinal injury, foreign bodies, trauma, neoplasms, radiation, diverticular disease, and complicated intra-abdominal infectious pathologies such as tuberculosis, *Actinomyces*, amebiasis, typhoid fever, among others[2,3,5,6]. Our patient's ECF was spontaneous from a sigmoid colon diverticulum, as corroborated by the pathological diagnosis.

There are several described classifications of ECF, one of them is anatomical, which, due to the location of the fistula, can be proximal (gastric, duodenal, jejunal, proximal ileum), or distal (distal ileum and colon)[2]. The physiological classification determined by their output in 24 hours is considered low (less than 200 mL/day), moderate (between 200 and 500 mL/day), and high (more than 500 mL/day) output[1,3,6].

The diagnosis of ECF should be suspected by observing the exit of intestinal content through the skin. However, the definitive diagnosis is made by verifying an abnormal connection between the digestive tract and the skin. Computed axial tomography (CAT) can show the characteristics of the

fistula anatomy, detect associated collections and areas of intestinal obstruction distal to the fistula, and identify the underlying disease, among others[3,6]. A significant study that generally helps define ECF accurately is fistulography using water-soluble contrast, as in our patient, in which the connection of the navel with the sigmoid colon could be detected (**Figure 1**). A gastrointestinal study with contrast (intestinal transit or barium enema of the colon depending on suspicion of the affected intestinal section)[1] may also be helpful.

Initially, the approach is non-surgical. A comprehensive approach should be taken, and measures should be aimed at shortening the course of therapy, treating the disease that caused the ECF when possible, and taking care of the skin. In addition, hydromineral imbalance, malnutrition (present in 55%–90%), and sepsis must be avoided or corrected[1,4,6]. These are the most important aspects to control to achieve spontaneous fistula closure, which occurs in 20%–75% of cases without surgical treatment[1].

Early nutritional support is indicated to reverse catabolism. Enteral feeding is recommended as soon as possible to avoid intestinal villus atrophy and thus protect the intestinal mucosal barrier, preventing bacterial translocation. Sometimes, it is necessary to complement enteral nutrition with parenteral nutrition. Sometimes, total parenteral nutrition is indicated, mainly in patients with high-output ECF, to reduce output and facilitate healing[4,5,8]. In this case, enteral nutrition was always used, without resorting to parenteral nutrition, thus avoiding the complications it may cause.

Endoscopic therapies are more widely used through an endoluminal approach with a 3D printed patient-customized fistula stent, sealants, clips, and plugs[4,6,9]. A new treatment that has had good results is the combination of cyanoacrylate and polyglycolic acid sheets[10].

The patient and relatives should be informed of the need for a surgical approach when the ECF does not close spontaneously in two months, there is distal obstruction, neoplasms, or radiation enteritis, or there is evidence of mucosal eversion[1,4,6]. Antibiotic prophylaxis is essential in patients requiring surgery if the colon is compromised due to the greater risk of abdominal infections[11]. Once the need for surgery is determined, perioperative care, surgical time, and surgical technique are critical to achieving excellent outcomes[2]. Surgery must follow basic principles: resecting the fistulous tract with the affected intestinal segment, restoring intestinal transit, and reconstructing the abdominal wall[3]. In our patient, the navel was resected with the fistulous tract and sigmoid colon en bloc. We consider the timing of the surgical intervention to be appropriate and not to delay surgery due to the increase in symptoms and the abscessed plastron involving the sigmoid colon, bladder, and greater omentum, with a high risk of fistulization into the bladder.

The patients with the highest mortality are those with high-output fistulas since they lead to malnutrition, which causes death in more than 60% of cases[1]. However, the leading cause of more significant mortality in these patients is sepsis, reaching a figure of up to 85%[1,4]. In the operated patient, the fistula was not high output, and the sepsis was localized, contributing to his favorable evolution.

CONCLUSION

Once ECF has a surgical indication, surgery must be performed without delay and thus prevent other complications, with a meticulous surgical technique in the shortest surgical time. Despite progress, the persistence of sepsis and malnutrition is the leading cause of morbidity and mortality in patients with ECF.

Authors' contributions

Germán Brito-Sosa: Primary author, patient's physician, data collection, writing of the scientific article. Ana María Iraizoz-Barrios: Writing of the scientific paper, review, adaptation to the journal format.

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Erosive esophagitis secondary to radiotherapy: Case report

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Abstract

Erosive esophagitis secondary to radiotherapy is an unusual complication in the oncological treatment of thoracic tumors. This pathological entity is associated with multiple complications, which is a clinical challenge for health workers unfamiliar with the clinical manifestations. **Clinical case:** A 64-year-old woman with a 3-day clinical picture of chest pain radiating to the epigastrium with 10/10 intensity. On physical examination, she was tachycardic, hypotensive, and with intense pain in the upper hemiabdomen region; she had no signs of peritoneal irritation on deep palpation. Paraclinical tests showed no signs of local or disseminated infection, but endoscopy of the digestive tract reported post-radiation esophagitis. **Discussion**: Erosive esophagitis after radiotherapy occurs in less than 1 % of cases, and clinical manifestations such as dysphagia, odynophagia, and abdominal pain are common. Initial symptomatic management is preserved, with supportive measures such as intravenous hydration and proton pump inhibitors (PPIs). In case of intolerance to the oral route, therapy with nutritional support is indicated via nasogastric tube or gastrostomy in the most severe cases.

Keywords

Esophagitis, radiation-induced anomalies, breast neoplasms, sucralfate, omeprazole.

INTRODUCTION

Radiation esophagitis is a frequent complication due to exposure to radiotherapy, which manifests itself in treating certain types of cancer in advanced stages, such as lung and breast cancer[(1)]. However, this symptomatic erosive esophagitis requires a clinical, endoscopic, and histological assessment to confirm it because its manifestation is rare, affecting less than 1% of patients receiving radiotherapy[(2)]. Its pathogenesis is based on the effect caused by radiation on the basal epithelial layer, which reduces the mucosa and generates progressive denudation of the epithelium[(2,3)]. The acute manifestations of radiation esophagitis are dysphagia, odynophagia, and substernal discomfort, starting between two and three weeks after radiotherapy[(4)]. This paper aims to present the clinical and endoscopic manifestations of a patient with erosive esophagitis secondary to radiotherapy and to describe how this pathology was diagnosed.

CLINICAL CASE

We present the case of a 64-year-old woman with a two-week history of persistent burning chest pain of 10/10

intensity, predominantly in the epigastric region, radiating to the posterior area, and constantly associated with emetic episodes. She had symptoms of dysphagia and odynophagia, intolerance to oral solid and liquid foods, a history of type 2 diabetes *mellitus* (DM2), and moderately differentiated infiltrating lobular carcinoma. She underwent a right mastectomy in 2017, received tamoxifen therapy, and later in 2020, presented with chronic back pain and did not improve with analgesia. Consequently, she underwent an MRI of the thoracic spine, describing metastatic bone compromise near the sternum manubrium in the vertebral bodies of T11 and T12, the central region of the sacrum, and the sacroiliac joint. Two weeks prior, she received treatment with technical radiotherapy, extracranial radiosurgery near the T10-T12 dorsal column, doses/day of 700–2100 CGY, and chemotherapy with palbociclib, fulvestrant, and zoledronic acid.

On physical examination, she was found to be tachycardic, hypotensive, with intense pain of the upper abdomen on deep palpation, and no signs of peritoneal irritation (heart rate [HR] 120 beats per minute [bpm], respiratory rate [RR]: 20 breaths per minute [rpm], blood pressure [BP]: 90/50 mm Hg). Complementary studies showed mild anemia, leukopenia, no hypoalbuminemia, renal function within normal limits (hemoglobin [Hb]: 9.8 mg/dL, leukocytes: 1,100, neutrophils: 700, creatinine: 1.9 mg/dL, and albumin: 4g/dL). Coagulation and liver profiles did not show alterations, as did troponin and electrocardiogram (ECG), so the coronary disease was ruled out. Upper gastrointestinal endoscopy reported the following: from 20 cm of the dental arch to the z line, multiple fibrin-covered circumferential ulcerations with easy bleeding on contact, Los Angeles-Savary Miller IV grade D erosive esophagitis, post-radiation esophagitis, and gastropathy chronic antral (**Figures 1** and **2**).

The patient was managed symptomatically for one week with parenteral proton pump inhibitors (PPIs) (omeprazole), antiemetics, sucralfate, analgesics with opioids, and intravenous fluids. She had a favorable clinical evolution.

ETHICAL CONSIDERATIONS

The completion of the informed consent and its approval by the patient was carried out under Resolution 8430/1993.

DISCUSSION

Erosive esophagitis after radiotherapy produces general damage to the epithelium, which is limited by the number of doses used in the radiotherapy section. Thus, the concomitant use of chemotherapy increases the risk of developing esophagitis, becoming complicated with stenosis

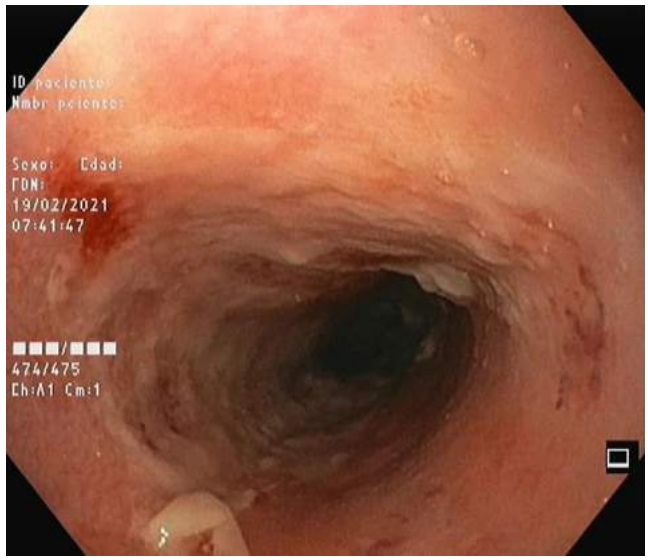

Figure 1. Esophageal injuries after radiotherapy.

six weeks after starting the event[5]. It is essential to bear in mind the incidence and severity of injuries caused by radiotherapy; the study by Maguire *et al* frequently described acute or late, but rarely severe, esophageal toxicities with high radiation levels without considering sociodemographic variables as prognostic factors[6].

The clinical information on radiation esophagitis described in humans is minimal. The studies carried out by Northway *et al* on opossums made it possible to see that radiation generated ulcers at the level of the gastric mucosa and dose-response anorexia, which occurred seven to ten days after radiotherapy[7]. It is vital to consider the chronic complications of radiotherapy, which appear between one and eight months, such as a decrease in primary peristaltic waves, decreased function of the lower esophageal sphincter, and necrosis due to focal coagulation of the mucosa. However, a mouse model produced by Phillips and Ross showed simultaneous areas of epithelial denudation and regeneration one to two weeks after radiotherapy, which would suggest early tissue regeneration[8].

In the study by Sasso *et al*, a case series with 29 participants was described after three weeks of radiotherapy treatment: 37% (n = 11) of the patients presented with esophagitis, which continued even after treatment for bronchial carcinoma[9]. Mascarenhast *et al* wanted to describe the incidence and nature of esophagitis in 38 patients who underwent radiation, resulting in endoscopic reports (esophagitis) similar to that described in the present case, considering that the patient received dual therapy for two weeks prior (radiotherapy and subsequent chemotherapy), which substantially increases the risk of developing the complication described in this article[10].

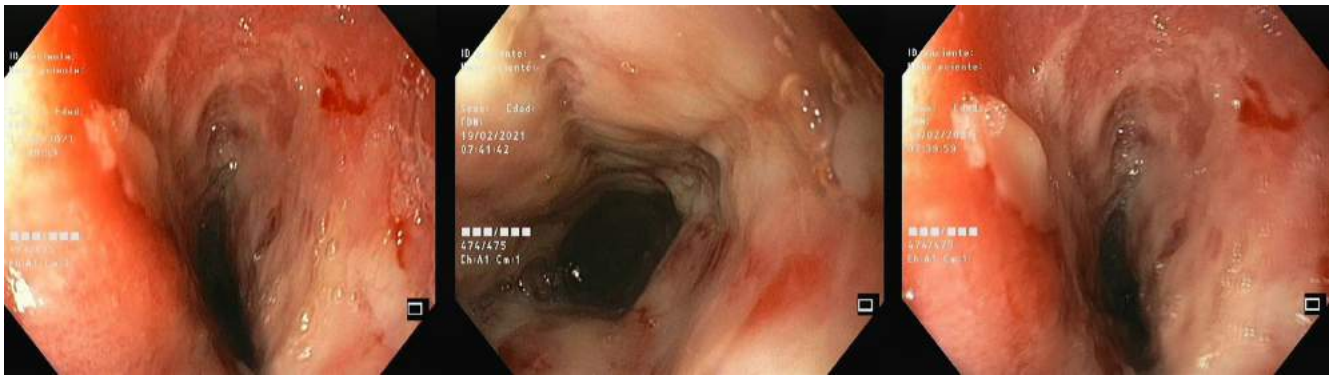

Figure 2. Esophageal injuries after radiotherapy with fibrin tissue.

The initial management of early complications is conservative, while endoscopic dilators for esophageal strictures are common in chronic cases. The way to prevent these difficulties is based on radioprotectors and inhibitors of the arachidonic acid metabolism pathway. The radiation modification can bring us closer to eliminating complications in normal esophageal tissue and improving the localized response in thoracic tumors[5]. Multiple pharmacological treatments have been proposed, such as nonsteroidal anti-inflammatory drugs (NSAIDs) and the prophylactic use of corticosteroids, in addition to nutritional support and treatment with PPIs or sucralfate to reduce mucosal exposure to the stimuli produced by radiotherapy, decreasing the risk of mucositis. Topical analgesics such as lidocaine slightly improve dysphagia, and antacids such as sucralfate may slightly improve food intake[9,11].

CONCLUSION

Erosive esophagitis associated with radiotherapy has a very low incidence, and its clinical manifestations are rare. Diagnostic methods are practical, considering the history of cancer with radiotherapy to rule out its etiology virtually since endoscopy of the digestive tract plus biopsy is the first diagnostic tool. Treatment is mainly based on symptom control and the constant use of PPIs, strict diet control, and essential nutritional supplements because these patients have a high risk of malnutrition and a compromised health condition.

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Case report

Giant pancreatic pseudocyst drainage by endoscopic cystogastrostomy: Case report

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Abstract

Introduction: The pancreatic pseudocyst is one of the late local complications of acute pancreatitis. For managing a giant pancreatic pseudocyst, there are multiple strategies. **Aim:** To present the case of a patient with a giant pancreatic pseudocyst managed by endoscopic cystogastrostomy. **Clinical case:** A 41-year-old woman developed a giant pancreatic pseudocyst as a complication of acute pancreatitis that was managed by endoscopic cystogastrostomy without endoscopic ultrasound guidance, with good evolution. **Conclusions:** Endoscopic cystogastrostomy, with or without the help of ultrasound endoscopy or lumen-apposing metal stent (LAMS), is a viable, safe, effective, and economical therapeutic option for selected patients with a giant pancreatic pseudocyst.

Keywords

Pancreatic pseudocyst, cystogastrostomy, endoscopy, pancreatitis, complications.

INTRODUCTION

The pancreatic pseudocyst is a liquid collection of debris, surrounded by fibers and inflammatory tissue and lacking epithelial coverage. It can be found partially or totally within the pancreatic parenchyma[1] and persists for more than six weeks after the condition onset[2]. It arises as a complication of acute[3] or chronic[4] pancreatitis, trauma[5], or other processes that affect the pancreatic duct[6].

The symptoms are usually abdominal pain, vomiting, nausea, and weight loss[7]. Diagnosis is made by transabdominal ultrasound, tomography, magnetic resonance, or endoscopy, the latter being the method of choice[8].

This manuscript intends to present the case of a woman with a pancreatic pseudocyst secondary to acute pancreatitis of unclear etiology and its evolution after endoscopic cystogastrostomy.

CLINICAL CASE

A 41-year-old woman from western Boyacá had a one-month history of severe epigastric pain and vomiting, exacerbated in the last 15 days. With no history of alcohol consumption, she attended the regional hospital. Abdominal tomography showed a pancreatic pseudocyst measuring 88 x 74 x 68 mm. She was administered analgesics and discharged; however, she was re-admitted due to the persistence of pain. The control abdominal tomography revealed continuance of the pancreatic pseudocyst in contact with the posterior wall of the les-

ser curvature of the stomach, for which she was referred to tertiary care.

On physical examination upon admission to our institution, the patient presented with a distended abdomen, pain, a palpable mass in the epigastrium, and no jaundice. The paraclinical tests showed a complete blood count without leukocytosis, hyponatremia, mild hypochloremia and hypokalemia, no metabolic acidemia, slightly increased lactate, mild hyperbilirubinemia, at the expense of direct hyperbilirubinemia, and mild amylasemia. Possible acute pancreatitis was considered. Therefore, we decided to perform a contrast-enhanced computed tomography of the abdomen, which reported a pseudocyst with an approximate volume of 1,460 mL in contact with the posterior gastric wall (**Figure 1**).

Upper GI endoscopy was performed, finding compression of the posterior stomach wall. Due to the impossibility of referral to a center with endoscopic ultrasound availability, we decided to drain it with endoscopic cystogastrostomy at the end of the eighth week.

The posterior stomach wall was incised near the antrum with an output of necrotic and pancreatic material of approximately 1,500 mL. The cystogastrostomy was dilated with a balloon of up to 18 mm in diameter in operating rooms (**Figure 2**). Endoscopic cholangiography was taken at the same surgical time, ruling out choledocholithiasis. Pancreatography was performed, finding dilatation of the pancreatic duct without disruption, followed by a pancreatic and biliary papillotomy.

On the third day after the primary intervention, the patient had signs of systemic infection, fever (39.2), leukocytosis, and positive procalcitonin (31.3). In the culture report of the pseudocyst fluid, there was *E. coli* growth. Piperacillin/tazobactam was administered for eight days, and endoscopic necrosectomies were performed under sedation every 24 to 48 hours (**Figure 3**).

On the third day after antibiotic treatment, normalization of acute phase reactants and improved liver function tests were observed. Thirteen washes were performed through endoscopic cystogastrostomy, achieving clinical and paraclinical improvement with discharge on day 45. Follow-up was conducted for six months, noting good evolution with no abdominal pain or relapses, no functional limitation, and weight gain.

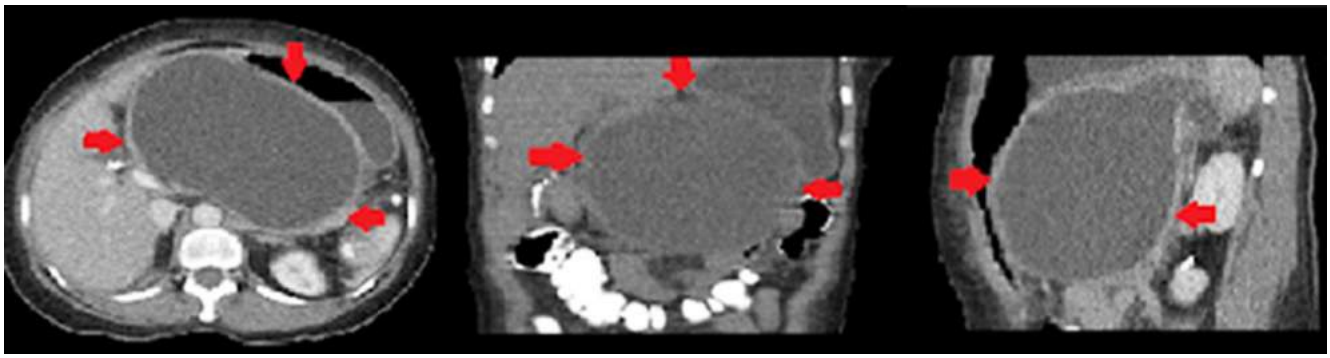

Figure 1. Computed tomography of the abdomen and pelvis. Presence of a 16 x 16 x 11 cm pancreatic pseudocyst, with no free fluid in the cavity.

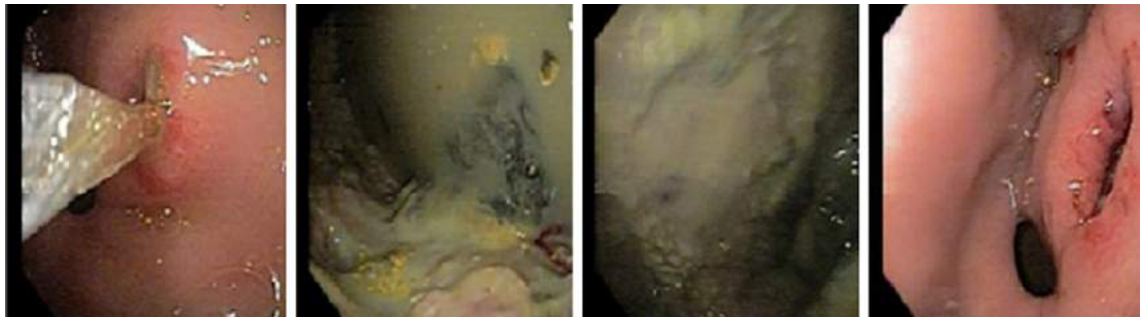

Figure 2. Pseudocyst drainage.

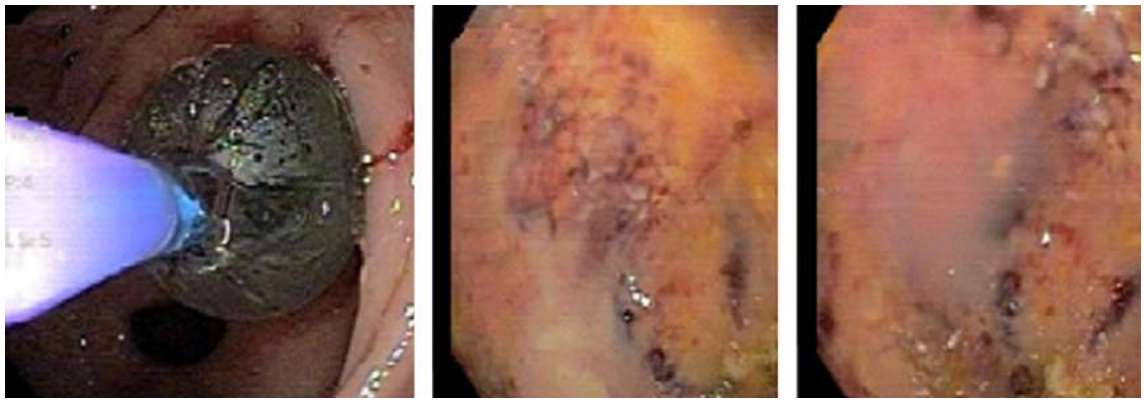

Figure 3. Evolution of endoscopic management.

DISCUSSION

The incidence of pancreatic pseudocyst is low (1 per 100,000 adults per year), while the prevalence is 6%–18.5%. According to the etiology, the pseudocyst appears in 20%–40% of cases of chronic pancreatitis, 70%–78% is associated with pancreatitis of alcoholic etiology, followed by chronic idiopathic pancreatitis in 6%–16% and chronic pancreatitis of biliary etiology in 6%–8%[9]. According to the Atlanta classification[10], giant pancreatic pseudocysts can occur after acute pancreatitis and have a diameter greater than 10 cm[11].

There are few observations in the literature on the management of giant pancreatic pseudocysts. One study found that expectant management is associated with higher morbidity and mortality compared to small pseudocysts, suggesting that early external drainage before clinical deterioration could be beneficial[12,13].

As described in the literature, the pseudocyst treatment was performed after the fourth week of onset in this case[14]. The choice of treatment for giant pancreatic pseudocysts is controversial. It includes observation, endoscopic drainage guided or not by endoscopic ultrasound, percutaneous drainage, and surgical interventions[15]. Currently, the endoscopic approach is preferred, as it is less invasive; it has a success rate of up to 95%[16]. If associated with ultrasound endoscopy, it has fewer complications and is more cost-effective[17], avoids external drainage (success rate of 98.3%, with recurrence of 2.5%[16], and has a high long-term success rate. Nonetheless, the form of drainage, whether transmural or transpapillary, is still divergent; when comparing them, they do not provide a more significant benefit in the treatment outcome.

In the guidelines of the Society of Endoscopic Gastroenterology of India[18], the use of the pigtail catheter is mentioned as a drainage method; however, in the case of pseudocysts with necrotic content, they recommend management with a metallic stent. The endoscopic approach showed advantages; recovery was adequate and without complications, despite lacking the help of endoscopy or LAMS, which are the techniques of choice for similar cases[19].

CONCLUSION

Endoscopic cystogastrostomy guided or not with endoscopic ultrasound and without luminal apposition stent is a viable, safe, effective, and economical therapeutic option for selected patients with a giant pancreatic pseudocyst.

Conflicts of interest

The authors state no conflicts of interest.

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Case report

Barogenic perforation of the esophagus: An unusual manifestation

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Abstract

Introduction: Typically, when esophageal perforation secondary to barotrauma is mentioned as the causal pathophysiological mechanism of perforation, the literature refers to spontaneous esophageal perforation or Boerhaave syndrome as an entity. It involves the longitudinal and transmural rupture of the esophagus (previously healthy) secondary to an abrupt increase in intraluminal esophageal pressure, frequently triggered during vomiting. However, in the medical literature, some reports list mechanisms of barotrauma other than this entity.
Case report: A 64-year-old female patient with a history of surgically managed gastric adenocarcinoma (total gastrectomy and esophagoenteral anastomosis) presented with stenosis of the esophagojejunal anastomosis, which required an endoscopic dilatation protocol with a CRETM balloon. The third session of endoscopic dilation was held; in removing the endoscope, we identified a deep esophageal laceration with a 4 cm long perforation at the level of the middle esophagus (8 cm proximal to the dilated anastomosis), suspecting the mechanism of barotrauma as the causal agent. She required urgent transfer to the operating room, where we performed thoracoscopic esophagectomy, broad-spectrum empiric antimicrobial coverage, and enteral nutrition by advanced tube during in-hospital surveillance. The control esophagram at seven days showed a small leak over the anastomotic area, which was managed conservatively. Imaging control at 14 days showed a decrease in the size of the leak, with good evolution and tolerance to the oral route. The patient was later discharged.

Keywords

Esophageal barotrauma, spontaneous esophageal perforation, Boerhaave syndrome.

CLINICAL CASE

We present the case of a 64-year-old female patient with a history of gastric adenocarcinoma surgically managed outside the institution (total gastrectomy and esophagoenteral anastomosis). She exhibited fibrotic stenosis of the esophagojejunal anastomosis with secondary esophageal dysphagia for solids. Extrainstitutional clinical follow-up was performed by gastroenterology, indicating endoscopic dilatation protocol with CRE balloon under general anesthesia. The patient underwent an esophagoscopy on 02/06/2019, noting a fibrous esophagojejunal anastomosis with a 3 mm residual lumen at 36 cm from the dental arches. An 8–10 mm CRE balloon was dilated on fluoroscopic and endoscopic views, leaving an 8 mm residual lumen.

A second esophageal dilation is performed two weeks later, and stricture of the anastomosis is observed again. This time, the biopsy is taken on a stenotic area with a 4-mm esophageal lumen, and then CRE balloon dilation is performed to 8–10 mm, leaving a 9-mm residual lumen. The patient was scheduled for a third endoscopic dilation on 03/04/2019 with a sequential dilatation protocol

with a CRE balloon to 11 mm (5 ATM) on a 9 mm stenotic esophageal lumen. Its diameter was increased to 10 mm, with evidence of mucosal tear expected at this level (**Figure 1**). After intervention and during endoscope extraction, a deep laceration with a 4 cm long perforation was identified on the middle esophagus towards the left posterolateral wall, with minor bleeding in the layer dependent on the laceration edges. The characteristics and location of the deep laceration (8 cm proximal to the recently dilated anastomosis, 28–32 cm from the dental arches) are striking, considering the easy non-traumatic entry of the gastroscope at the beginning of the procedure (**Figure 2**).

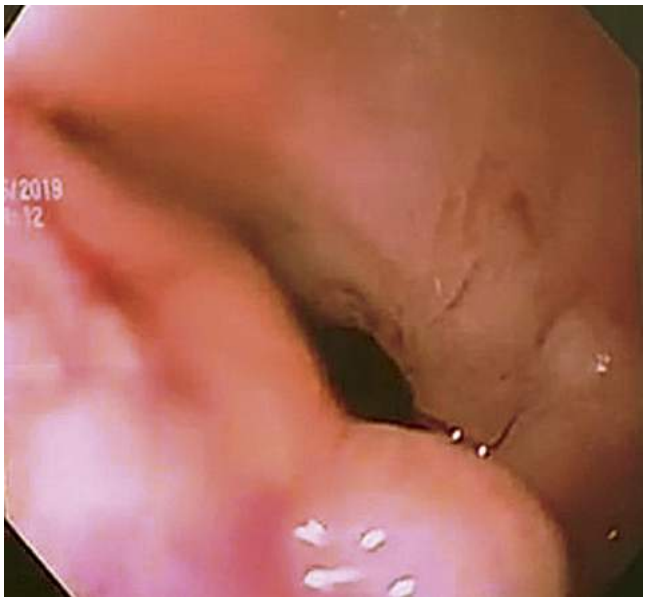

Figure 1. Fibrotic stenosis of the esophagojejunal anastomosis after CRE balloon dilation. A 10 mm residual lumen is observed after dilation in the presence of an expected mucosal tear.

Physical examination under anesthetic monitoring shows vital signs within normal limits, without hemodynamic instability or deterioration of ventilatory parameters. Supraclavicular subcutaneous emphysema with left predominance is regarded as positive. Findings related to a barogenic perforation of the esophagus are identified, considering the characteristics and location of the lesion and the chronology of events during the procedure. Thus, broad-spectrum empiric antimicrobial coverage is started immediately, and the gastrointestinal surgery service is called. Upon joint assessment, urgent transfer to the operating room for surgical and intraoperative endoscopic exploration is defined.

Thoracoscopy and endoscopic exploration are performed at the same surgical time. Through endoluminal transillumination with the gastroscope and on extraluminal view through the laparoscope, they detected a full-thickness esophageal perforation on the middle esophagus towards the left posterolateral wall, with 4 mm mucosal tear and 8 cm longitudinal muscle layer tear, and no evidence of contamination (**Figure 3A**).

After identifying the solution of continuity, a primary defect suture is performed with simple 2-0 PDS stitches, achieving adequate closure. Esophageal impermeability is verified at this level, an advanced feeding tube is passed under endoscopic guidance, and the left chest tube is inserted (**Figures 3B** and **3C**). The patient is then transferred to the recovery room. During in-hospital surveillance, the patient evolved adequately, achieving pain control and a progressive decrease in analgesia, with scant serosanguineous drainage through the left chest tube. The control esophagogram seven days after the event found a small solution of continuity, which communicated with a contained saccular image of 45 *x* 9 mm proximal to the defect area, with no outflow of contrast into the thorax or the mediastinum (**Figure 4A**). A new control esophagogram seven days prior shows a small leak with a decrease in size compared to the first imaging control; so the chest tube is removed, enteral nutrition is performed through an advanced tube, and oral administration is started with adequate tolerance. Hospital discharge will continue with outpatient follow-up (**Figure 4B**).

DISCUSSION

Esophageal perforation is a rare but catastrophic gastrointestinal pathology (incidence 3.1/1,000,000 inhabitants/year)[1,2], with high morbidity and mortality ranging between 10%–40%, being 10%–25% when treated in the first 24 hours and up to 40%–60% when management is delayed[3,4]. In their systematic review of the literature published in 2017, Sdralis *et al* reported an overall mortality of 13.5% based on the analysis of 39 studies (1,644 patients), with perforation of the thoracic esophagus being the most frequent location in 72.6%, followed by involvement of the cervical (15.2%) and abdominal (12.5%) esophagus[5].

Its etiology is variable, with iatrogenic (46.5%) being the most frequent cause. It has a risk of occurring in diagnostic esophagogastroduodenoscopy of 0.03%, increasing when therapeutic endoscopy is performed (0.5% in esophageal dilation, 1.7% in dilatation for achalasia, 1%–6% in varicose vein sclerotherapy, 4.6% in photodynamic thermal therapy, 5% in laser therapy, 5%–25% in stent insertion)[4]. It is followed in frequency by spontaneous perforation (37.8%), this being the most common cause of non-iatrogenic perforation, esophageal foreign body perforation (6.3%), traumatic perforation (penetrating and closed trauma), and finally perforation due to ingestion of caus-

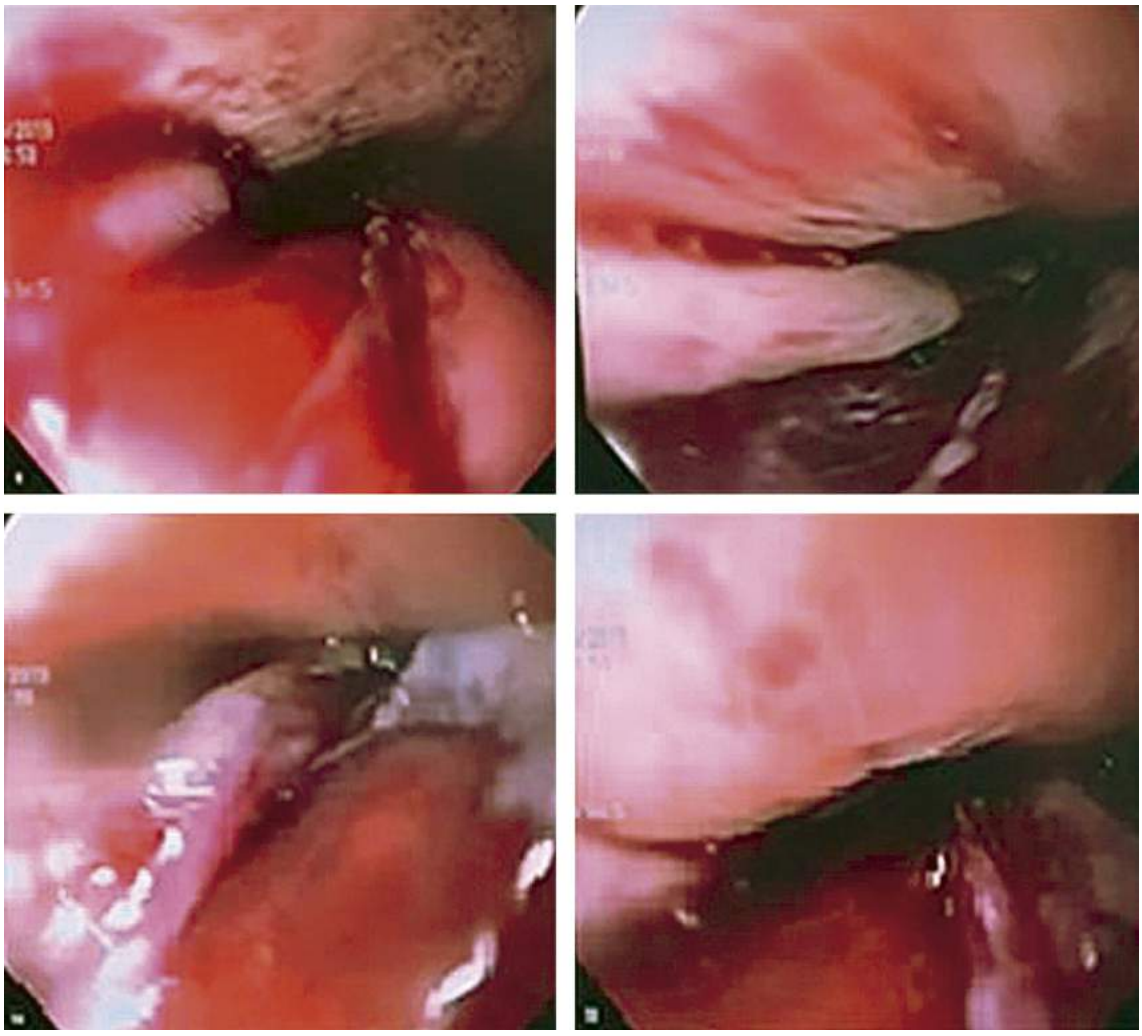

Figure 2. Spontaneous esophageal perforation is a 4-cm deep laceration, 8 cm above the newly dilated anastomosis.

tics (frequent in children)[1,5,6]. Typically, when esophageal perforation secondary to barotrauma is mentioned as the causal pathophysiological mechanism, the literature refers to spontaneous esophageal perforation or Boerhaave syndrome (BS), in honor of the Dutch physician Herman Boerhaave, who described the entity for the first time in 1724. It refers to the longitudinal and transmural rupture of the esophagus (previously healthy), secondary to an abrupt increase in intraluminal esophageal pressure caused by an increase in gastric content towards the esophagus due to an increase in intragastric pressure often triggered during vomiting. However, it is also reported in other events that require a Valsalva maneuver and even during sleep[7–11].

In this entity, the thickness rupture occurs more frequently in the distal 1/3 of the thoracic esophagus (80%), 3 to 6 cm above the diaphragm, on the left posterior wall (90%), with an average damage length of 2–10 cm[7,8]. Its clinical manifestations depend on the location of the perforation and the time of evolution[8]. Patients with perforation of the cervical esophagus exhibit pain in the neck and the upper half of the chest, while in those with more distal perforation, the pain is in the lower half of the chest and the upper left side of the abdomen. Mackler's triad (vomiting, chest pain, subcutaneous emphysema in the neck-thorax) and Anderson's triad (subcutaneous emphysema, tachypnea, abdominal muscle tension) are described as clinical aids to the diagnosis of this pathology. Nonetheless, subcutaneous emphysema, the characteristic sign of both triads, is present in only 14%–30% of cases, with an atypical course in 30%–50%[7]. Among the initial diagnostic

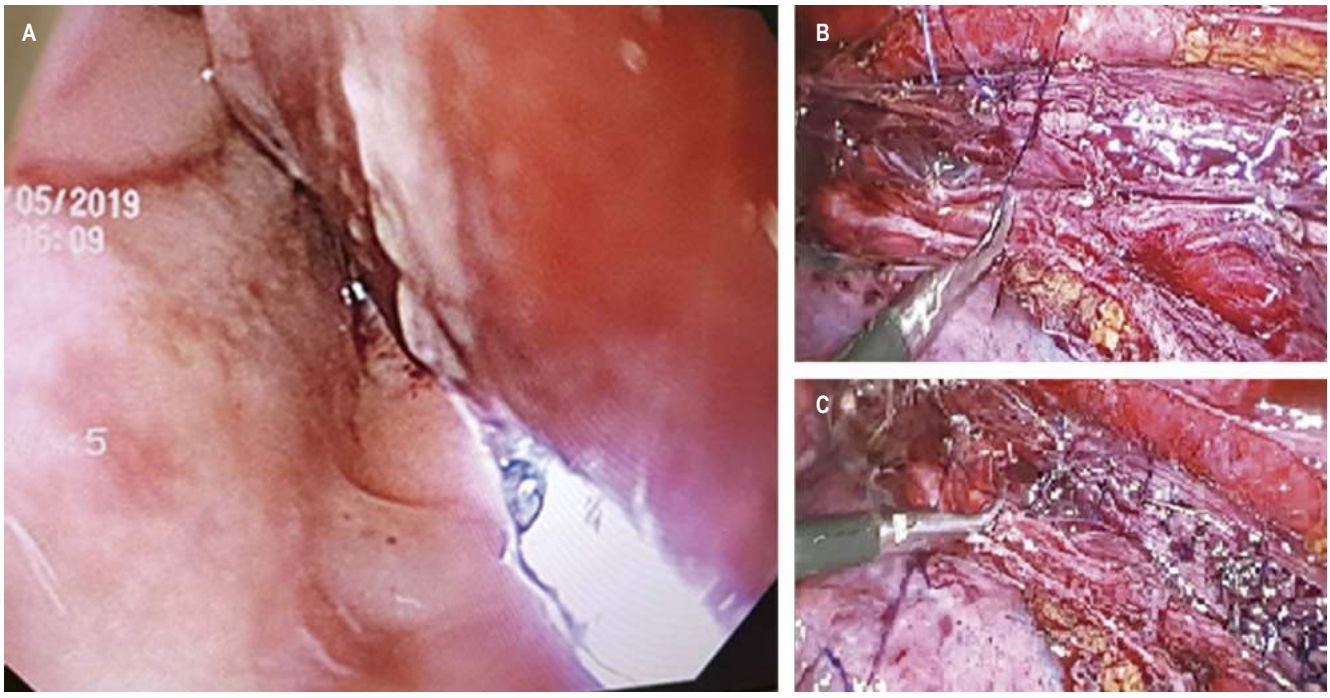

Figure 3. A. Endoscopic view of the esophageal perforation with external transillumination through the laparoscope. **B and C**. Thoracoscopy esophagography with simple stitches.

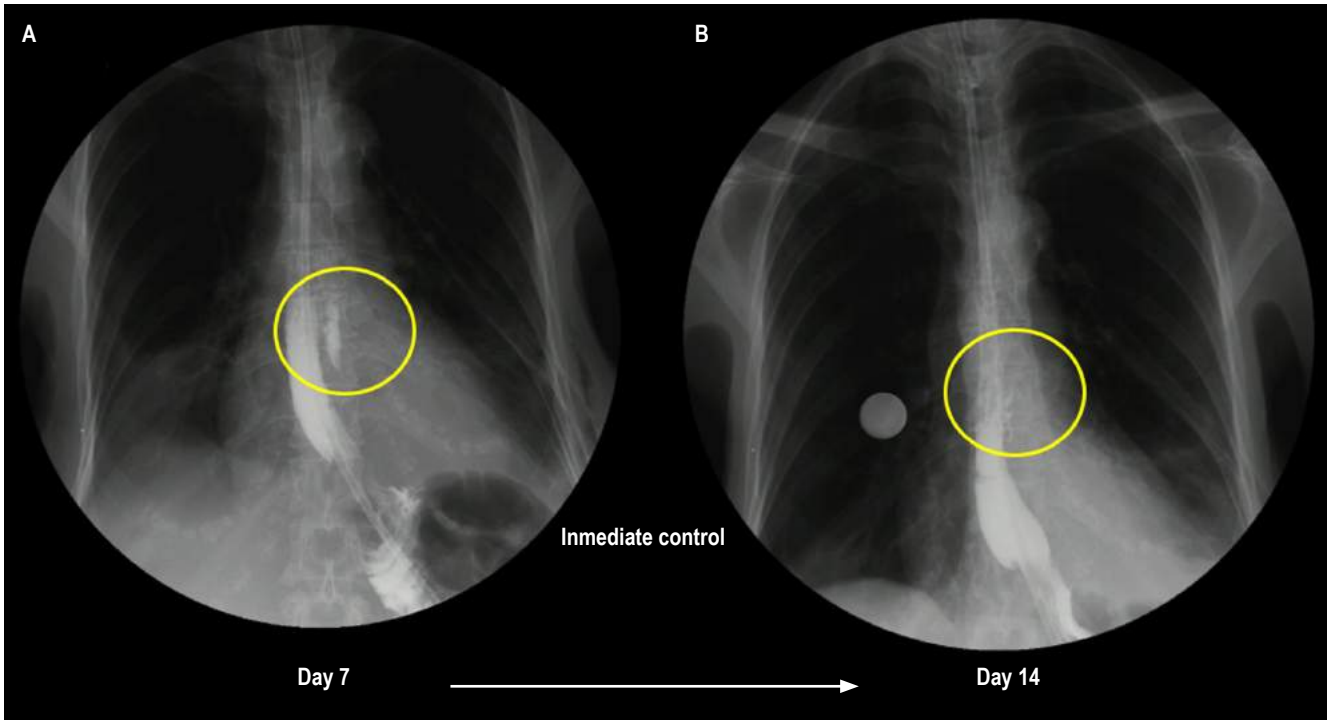

Figure 4. A. Control esophagogram seven days after the event: Minor solution of continuity, communicating with a contained saccular image of 45 *x* 9 mm proximal to the defect area. **B.** Control esophagogram 14 days after the event: Contained leak with a decrease in size compared to the initial imaging control (24 *x* 4 mm).

supports is radiography (subcutaneous emphysema, pneumomediastinum, pneumothorax, subdiaphragmatic air, pleural effusion), computerized axial tomography (CAT), and esophagogastroduodenoscopy, which, in cases of iatrogenic cause, is capable of detecting the defect promptly during the intervention[3,5,6,12].

As we said before, although BS is the representative pathology of barogenic perforation of the esophagus, the medical literature mentions mechanisms of barotrauma different from this entity[13–21]. In 1990, Gubbins reported the case of a 77-year-old patient with mid-esophageal stenosis, which was bridged over during gastroscopy. He retched during the procedure, with subsequent evidence of a perforation near the esophagogastric junction. The hypothesis of esophageal barotrauma as a causal mechanism is established. In 2002, Van de Louw published the case of a 56-year-old patient with a 3 cm linear esophageal perforation in the distal esophagus after requiring noninvasive mechanical ventilation, where the barotrauma mechanism was triggered by the positive pressure exerted[13]. Thus, in the case of our patient, considering the type of procedure and the site of the perforation (8 cm above the dilated stenosis), we hypothesize barotrauma as the causal mechanism of the esophageal rupture, triggered by an abrupt increase in esophageal intraluminal pressure during balloon inflation.

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Case report

Refractory iron deficiency anemia as an early manifestation of autoimmune gastritis in a teenager

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Abstract

Autoimmune gastritis is an underdiagnosed disease in the pediatric population due to the absence of specific signs and symptoms and late clinical manifestations. Iron deficiency anemia has recently been identified as an early hematological manifestation, allowing an early diagnostic approach. We present the case of a Colombian teenager, with no history of autoimmunity, with refractory iron deficiency. He underwent extension studies; biopsies and serology compatible with autoimmune gastritis were documented, requiring parenteral iron in its evolution. This pathology is underdiagnosed in our context since early diagnosis requires a high index of suspicion to prevent associated complications.

Keywords

Autoimmune gastritis, iron deficiency anemia, parietal cells, oxyntic glands, enterochromaffin cells, pernicious anemia, children, teenagers.

CLINICAL CASE

A 16-year-old male patient, from Boyacá, has a history of a syncopal episode associated with emesis and an incidental finding of iron deficiency anemia, hypochromia, and microcytosis without a clear cause, initially treated with polymaltosed iron folate and folic acid. Within his controls with pediatric hematology, refractoriness to treatment was documented, so he was referred to gastroenterology, where a first endoscopy of the upper digestive tract was performed. The initial biopsies showed non-atrophic chronic gastritis antrum of a follicular pattern at the level of the with mild activity, associated with *Helicobacter pylori* infection, for which tetraconjugate management was indicated for 14 days.

After eradication of the infection, ferrous sulfate 300 mg and ascorbic acid 500 mg twice daily were started to manage the iron deficiency; the patient returned to control due to the persistence of significant drowsiness and fatigue. His paraclinical tests (**Table 1**) showed the correction of the volumes but the persistence of iron deficiency despite an adequate intake.

A new esophagogastroduodenoscopy was performed with a body, antral and esophageal mucosa biopsy, finding chronic atrophic gastritis with extensive pseudopyloric

Table 1. Laboratory test records

	Reference values	Control # 1	Control # 2	Control # 3	Control # 4	Control # 5	Control # 6
Leukocytes (uL)	4500-11 500		8000	6800	6500	5700	7690
Neutrophils (uL)	1400-6500		4100	4000	3600	2600	4940
Lymphocytes (uL)	1200-3400		2800	1900	2100	2200	2130
Eosinophils (uL)	0-700		300	400	300	400	200
Hemoglobin (g/dL)	14-18	13.8	14	15.5	16.1	16.3	18.1
Hematocrit (%)	45-54	40.7	44.50	47.90	47.70	49.40	54.20
Mean corpuscular volume (fL)	80-100		73.6	82.4	83.5	87.20	94.10
Mean corpuscular hemoglobin (pg)	25.4-34.6		23.8	26.7	18.1	28.80	31.40
Distribution width (%)	11.5-18		18	14.90	16	16.8	12.5
Platelets (10^3/uL)	150-450		339	315	343	325	307
Ferritin (ng/mL)	23.9-336.2	3.74		9.2	18	116.4	60
Parietal cell antibodies	Positive >1/40				1/640		
Intrinsic factor antibodies	Negative (-)				(-)		
Gastrin (pg/mL)	13-115				274		

Source: Prepared by the authors.
In the fourth control, serological results compatible with the diagnosis of autoimmune gastritis were obtained. After the management of iron deficiency in the last controls, a normalization of hemoglobin and iron deposits was found.

metaplasia (antralization) and moderate activity in the body mucosa (oxyntic), associated with linear and nodular hyperplasia of neuroendocrine cells (enterochromaffin). The latter was highlighted by the immunohistochemical study for chromogranin (**Figure 1**). Meanwhile, in the antral mucosa, mild non-atrophic chronic gastritis was observed, with residual lymphoid aggregates, no acute inflammatory activit,y and evidence of bacilli with *Helicobacter pylori* morphology. The findings of chronic atrophic gastritis restricted to the oxyntic mucosa with hyperplasia of neuroendocrine cells (enterochromaffin) suggest autoimmune gastritis. Additionally, infection compatible with *Candida sp.* at the esophageal level was documented. Consequently, the autoimmune profile was completed based on the histological findings, the medical management was adjusted, and finally, the diagnosis of autoimmune gastritis was made given the presence of positive anti-parietal cell antibodies.

In subsequent controls, replacement with intravenous iron was necessary once. Currently, the patient does not require medical management. The last control esophagogastroduodenoscopy (**Figure 2**) showed corporoantral erythematous gastritis, whose biopsies showed a decrease in gastrin marking, which corresponds to the already known diagnosis, with paraclinical tests within normal limits.

DISCUSSION

Autoimmune gastritis is an underdiagnosed disease worldwide, especially in childhood, due to its asymptomatic nature[1,2], on the one hand, and the early treatment given to hematological alterations once identified without first investigating their etiological diagnosis, on the other[3].

Currently, autoimmune gastritis represents about 10% of gastritis cases in the adult population[1]. However, these estimates are not apparent in the pediatric population, where the average age of diagnosis is 12.3 years, with refractory iron deficiency anemia being the most common manifestation[2], as in our case.

Autoimmune gastritis is a chronic inflammatory disease that selectively affects the gastric body and fundus, particularly preserving the antrum[4]. It is characterized by antibodies against the proton pump H/K ATPase and, to a lesser extent, against intrinsic factors[1,2]. Autoimmune gastritis is known to cause pernicious anemia in older adults, with

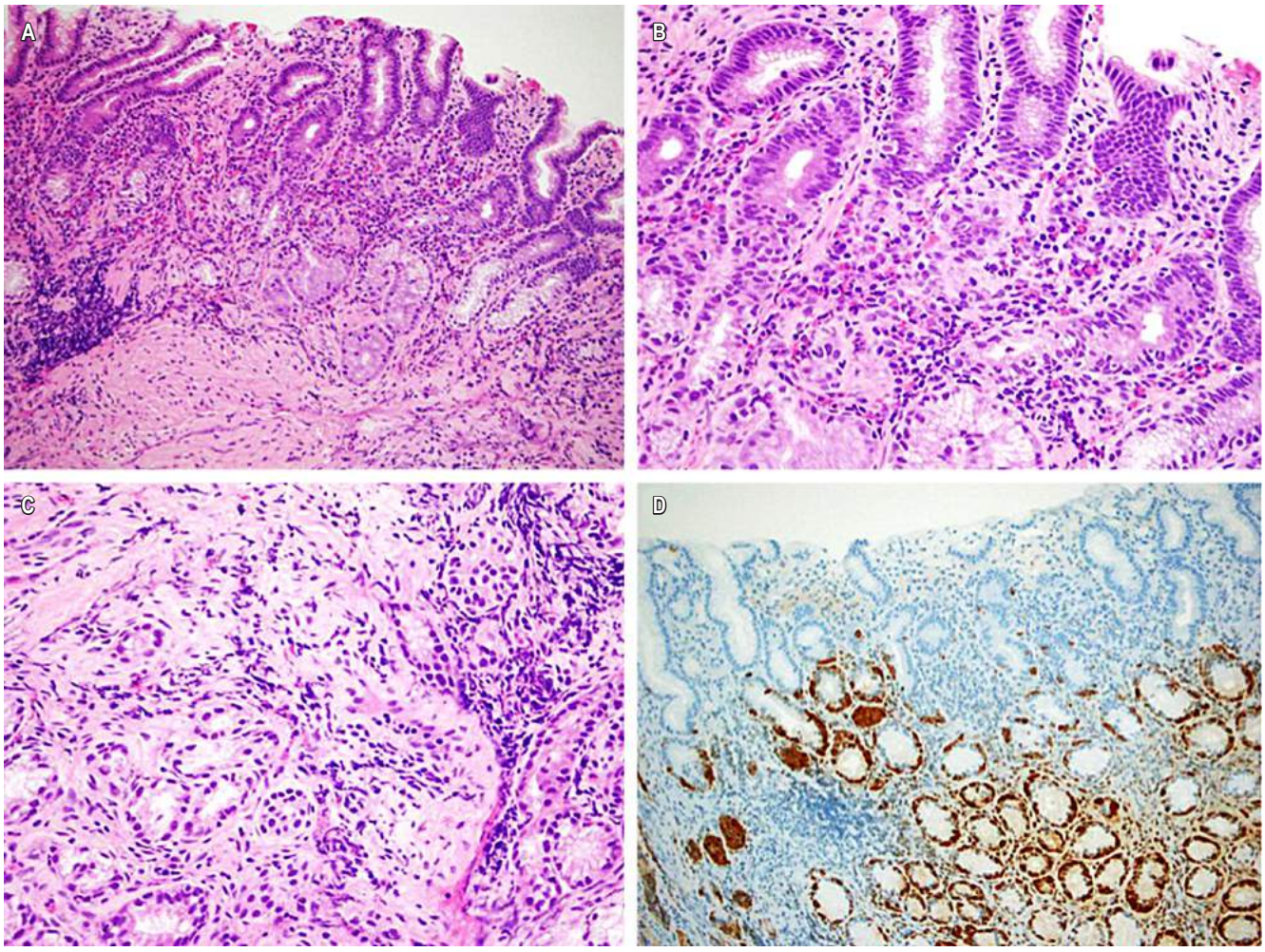

Figure 1. Body gastric mucosal biopsy. **A.** Oxyntic-type mucosa with loss of parietal cells and centralization of the mucosa, accompanied by a diffuse inflammatory infiltrate that compromises the entire thickness of the mucosa (Hematoxylin-eosin 100X). **B.** Lymphoplasmacytic inflammation in the lamina propria, rich in plasma cells and accompanied by eosinophils, noting permeation of the glands. **C.** Micronodules of neuroendocrine cells in the mucosa (Hematoxylin-eosin 400X). **D.** Immunohistochemical study for chromogranin confirmed a linear and nodular proliferation of neuroendocrine cells (100x). Source: Owned by the authors.

the classic manifestation of megaloblastic anemia and cyanocobalamin deficiency. Nonetheless, recent studies have linked iron deficiency anemia to this entity in much earlier stages, even in the pediatric population[1,2].

Currently, the etiopathogenesis of autoimmune gastritis is unknown. It is believed that it results from the interaction of genetic, hormonal, and environmental factors with still undefined defects in the immune response[3,5]; however, recent studies speak of the inappropriate activation of regulatory T cells[1]. Moreover, the association between autoimmune gastritis and *Helicobacter pylori* infection has been reviewed, finding molecular mimicry between bacterial antigens and proton pump receptors in parietal cells[4]. Some studies have shown the stimulation of T cells against parietal cells after infection, assigning it a role in the pathogenesis of autoimmune gastritis[3].

At a functional level, the involvement of the parietal cells, which produce intrinsic factors, is responsible for the malabsorption of cyanocobalamin and the subsequent development of megaloblastic anemia. Similarly, specific antibodies against intrinsic factors may trigger the same clinical manifestations[4].

Additionally, the secretion of hydrochloric acid[3] is compromised with a subsequent rise in gastric pH, affecting the solubilization and reduction of iron, processes that require an acidic environment to be effective and that, when failed, facilitate the development of iron deficiency[4,6]. Similarly, an alkaline climate favors the colonization of the stomach

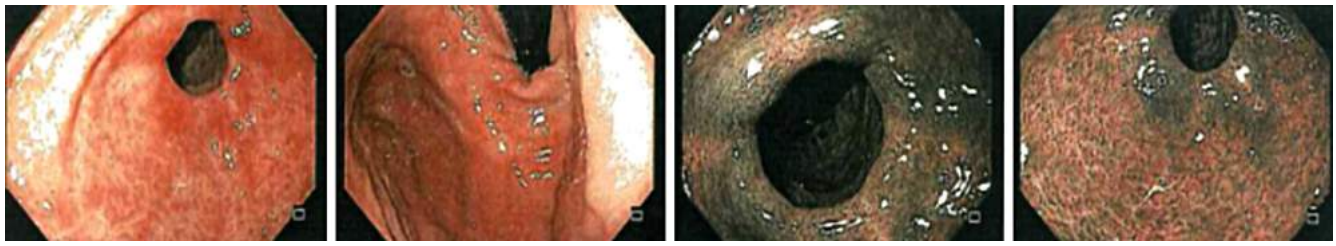

Figure 2. Esophagogastroduodenoscopy: Mucosa of the body with patchy erythema that does not show an atrophic border or additional findings. A review with narrow-band imaging (NBI) is performed to allow biopsies. Source: Owned by the authors.

by different microorganisms, as occurred in the case presented, which perpetuates a local inflammatory response[3]. In response to achlorhydria, there is a gastrin hypersecretory response, which favors the development of enterochromaffin cell hyperplasia and neuroendocrine tumors[3,4].

Regarding the clinical manifestations of the disease, autoimmune gastritis is usually silent until a significant degree of glandular atrophy is reached. Then it can present with weakness, pallor, and other nonspecific symptoms secondary to anemia[4,5], as in our patient, who started with episodes of syncope. The age of occurrence is usually variable and correlates with hematological manifestations[7]. Young patients typically have iron deficiency anemia refractory to treatment, while older adults show symptoms related to megaloblastic anemia secondary to chronic consumption of cyanocobalamin reserves[1–4,6].

The diagnosis is based on antibodies against parietal cells, intrinsic factors, or H/K ATPase[3,4]. A positive serology not only supports the diagnosis but also informs about the hematological involvement and the degree of atrophy[4]. Currently, different gastrointestinal panels in the world allow the identification of fundic atrophy; these include biomarkers such as levels of pepsinogen I and II, the ratio between these two, and gastrin levels[4,5].

Furthermore, it is crucial to carry out endoscopic studies in which focal gastritis at the body level, a loss of the anatomical folds characteristic of this region, and the presence of pseudopolyps can be viewed[1,3,7]. A representative sample must be available to make an adequate histopathological diagnosis, considering the topographic location due to the focal nature of autoimmune gastritis and the need to distinguish *Helicobacter pylori* infection[1–3].

The histopathological spectrum of autoimmune gastritis is vast and includes four phases, sometimes overlapping. The first phase consists of a lymphoplasmacytic infiltrate in the lamina propria, which is usually diffuse and accentuated at the base of the mucosa. The second phase is characterized by the destruction of the oxyntic glands with a consequent pseudopyloric metaplasia ("antralization of the mucosa"), in addition to diffuse lymphoplasmacytic infiltrate in the lamina propria. The third phase comprises progressive destruction of the oxyntic glands accompanied by intestinal metaplasia or pancreatic acinar metaplasia. The final step is a total replacement of the oxyntic glands by a metaplastic epithelium and the absence of a prominent inflammatory component[5].

Another characteristic finding of autoimmune gastritis is linear and nodular hyperplasia of enterochromaffin cells in response to achlorhydria, leading to the development of type 1 neuroendocrine tumors[5].

Follow-up should be conducted with markers of atrophy, complete blood count, and screening for autoimmune diseases[4]. As with other conditions of this nature, pre-existing or family history is associated with a higher risk of suffering from other autoimmune disorders, most commonly thyroiditis and type 1 diabetes *mellitus*[1,3,4]. There was no family history of autoimmunity in the case presented, and evaluation of other autoimmune diseases was negative.

The management of these patients is aimed at controlling hematological manifestations and preventing their progression[3]. Iron deficiency anemia is corrected by supplementation of the element according to baseline requirements[1,2] and, in the case of refractoriness, defined as *failure to respond to oral iron treatment* for at least two months[6], the administration of intravenous iron is chosen to replenish its deposits[6]. In advanced cases with pernicious anemia, management focuses on controlling cyanocobalamin reserves[2,3].

So far, there is no certainty about the prognosis of these patients. Studies show a decrease in the progression of the disease but not a reversal of the changes established[2]. Additionally, as it is a chronic inflammatory process that involves changes in the epithelial lining, the risk of gastric cancer in these patients should not be neglected[7]. An endoscopic control is recommended every five years to monitor for preneoplastic lesions and evaluate their progression[1,2].

CONCLUSION

Autoimmune gastritis must be recognized as a disease that occurs in the pediatric population. Although its symptoms are nonspecific, the incidental finding of iron deficiency anemia refractory to treatment should suggest its diagnosis. Early identification allows treatment and implementing strategies to prevent its progression. Currently, treatment focuses on the control of identified deficiency anemia, in addition to endoscopic follow-up, for the early detection of preneoplastic lesions and malignancy in the region in adulthood.

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Case report

Gastrointestinal involvement due to graft-versus-host disease

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Abstract

Graft-versus-host disease is a common complication after stem cell transplantation. The digestive tract is affected in many patients who suffer from it, with consequences that can be fatal. The proper approach, which includes endoscopic studies, allows ruling out differential diagnoses and managing the disease early.

Keywords

Graft-versus-host disease, digestive system, gastrointestinal tract, transplant, stem cells.

INTRODUCTION

Graft-versus-host disease (GVHD) is a frequent complication of allogeneic stem cell transplantation caused by an immune response of donor lymphocytes against the recipient patient[(1)]. The incidence of GVHD in this transplant is estimated to be as high as 39%–59%, with first-year mortality of 31%[(2)]. The skin, the gastrointestinal tract (GIT), and the liver are the main organs affected. The GIT is affected in up to 74% of cases and may be exclusively compromised in 17% of cases; 67% of cases with digestive compromise show diffuse involvement of both the upper and lower GIT[(3)]. We present three cases of patients treated at the Pablo Tobón Uribe Hospital (HPTU) in Medellín with suspected GVHD and gastrointestinal involvement and their diagnostic approach.

CASE 1

A 26-year-old male patient diagnosed with B-cell acute lymphoblastic leukemia received induction therapy with the high-risk PETHEMA-LAL protocol and three consolidation cycles with PETHEMA. Subsequently, he had a systemic relapse with compromise in the central nervous system. High-intensity chemotherapy with IDA-FLAG, cytarabine, and intrathecal therapy was administered, achieving morphological remission with residual marrow disease, for which he required new chemotherapy for

bone marrow transplantation (BMT). Haploidentical transplantation of hematopoietic progenitors was performed with his mother as a donor. He was admitted on day 24 after the transplant due to acute diarrhea, generalized mucocutaneous jaundice, and diffuse erythematous macular exanthema with scaling. Paraclinical tests revealed pancytopenia and an altered liver profile with a mixed pattern (hepatocellular and cholestatic). Given the suspicion of GVHD, empirical management was started with high doses of methylprednisolone, requesting endoscopic studies. Esophagogastroduodenoscopy (EGD) revealed relevant findings in the mucosa of the first and second portions of the duodenum with focal areas of patchy atrophy and absence of villi, with no inflammatory changes and normal gastric mucosa (**Figure 1**).

The ileum was accessed through a colonoscopy, finding a diffuse atrophy of the mucosa, absence of villi, and marked friability with easy bleeding and sloughing on rubbing, moderate bleeding, and even the formation of small submucosal hematomas when taking biopsies (**Figure 2**). The colonic mucosa was normal. The histopathological study of the biopsies of the duodenum and the ileum confirmed the acute grade 4/4 GVHD (**Figure 3**). The patient's evolution was torpid with persistent diarrhea, high fecal output, digestive bleeding, hydro electrolytic disorders difficult to manage, multiple transfusions of blood components, and development of bacteremia due to *Klebsiella pneumonia*, and hypoxemic respiratory failure. He presented with acute, severe GVHD refractory to steroids, with poor prognosis criteria, whose outcome was death 56 days after hospitalization.

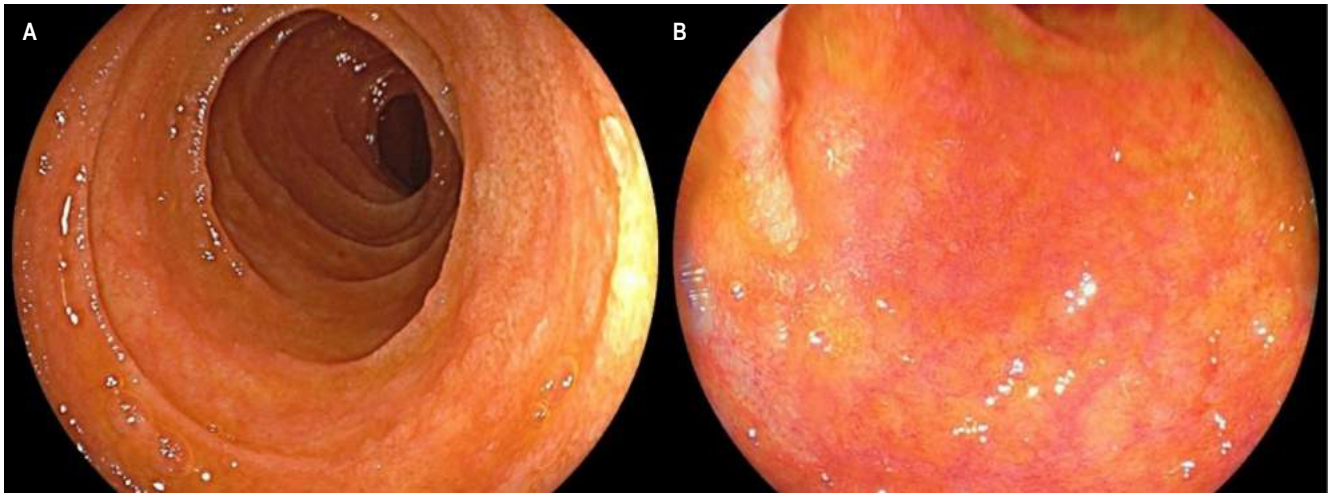

Figure 1. Compromise due to GVHD in the duodenal mucosa. **A.** Endoscopic view with a white light showing a reduction in the size and thickness of the duodenal folds, with an atrophic-looking mucosa. **B.** View with LCI (linked-color imaging) chromoendoscopy in which thinning of the mucosa was found, with signs of atrophy and shortening of villi.

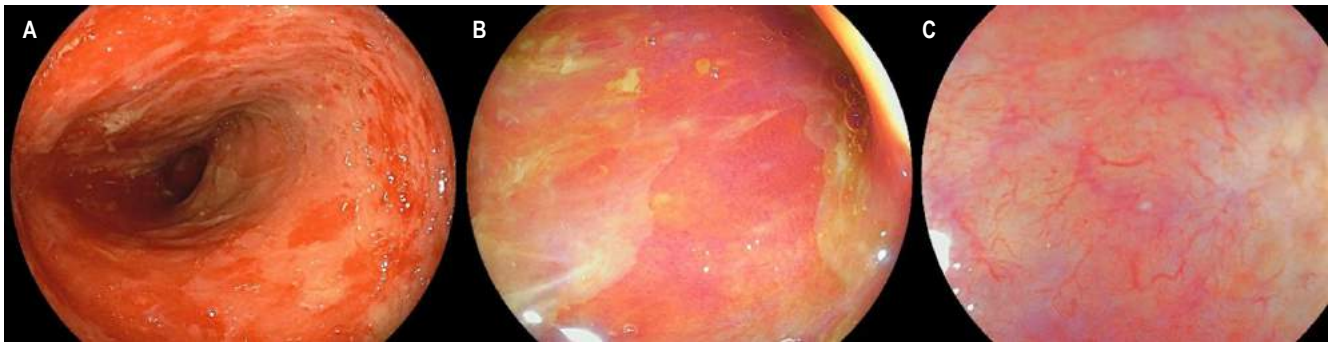

Figure 2. Compromise due to GVHD in the terminal ileum. **A.** White light endoscopic view demonstrating patchy sloughing of the ileal mucosa, atrophy, and marked friability. **B.** LCI view that shows an area of denudation without villi, findings confirmed in **C** when evaluated by LCI with magnification.

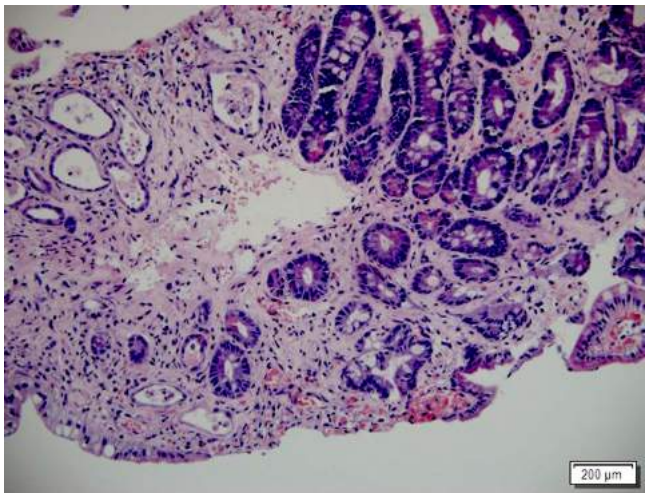

Figure 3. Small intestine compromised by GVHD. Small intestine biopsy with hematoxylin and eosin (H&E: 200 X). Destruction of crypts with changes in their shape and size, some atrophic with basal apoptotic bodies, and denudation of the superficial epithelium. Severe GVHD.

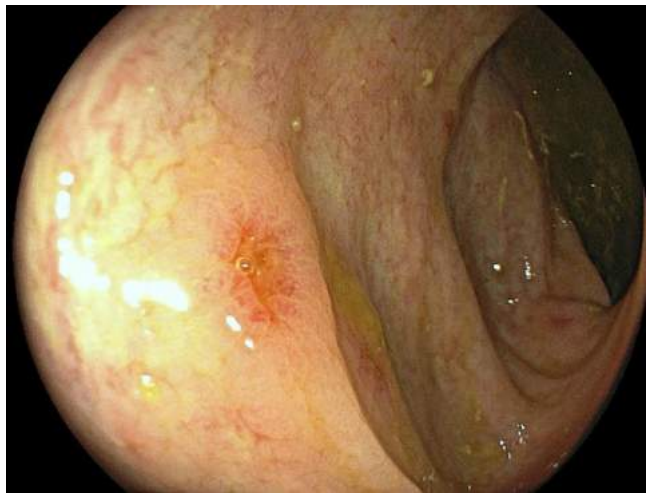

Figure 4. Colonic ulceration due to GVHD. Single ulceration in the colon with congestive edges.

CASE 2

We present the case of a 17-year-old male patient diagnosed with T-lymphoblastic lymphoma, who initially received induction and reinduction therapy with the GRAALL Lysa protocol (cytarabine + idarubicin), achieving remission of his disease. He underwent haploidentical hematopoietic stem cell transplantation with his father as the donor. He developed a diffuse macular rash, predominantly in the extremities during the transplant. Skin biopsy confirmed the diagnosis of acute GVHD with grade 3/4 skin involvement. On day 32 after the transplant, he presented with fever, abdominal pain in the hypogastrium and both iliac fossae, and liquid stools without mucus or blood. Computed axial tomography (CAT) of the abdomen documented inflammatory changes in the ileocecal region and signs of terminal ileitis; thus, endoscopic studies were requested. The EGD revealed flat patchy erythema in the stomach without inflammatory changes in the duodenum. Colonoscopy revealed congestive mucosa of the ileum with multiple superficial, irregular ulcers with flat edges and a smooth surface. Furthermore, in all the colonic tracts, including the rectum, small punctate ulcers with fibrin in the center and flat congestive edges were observed (**Figure 4**). The histopathological study confirmed the diagnosis of acute GVHD in the ileum grade 3/4, right colon 1/4, left colon 3/4, and rectum 4/4 (**Figures 5** and **6**). Immunohistochemistry (IHC) on these samples was negative for cytomegalovirus (CMV).

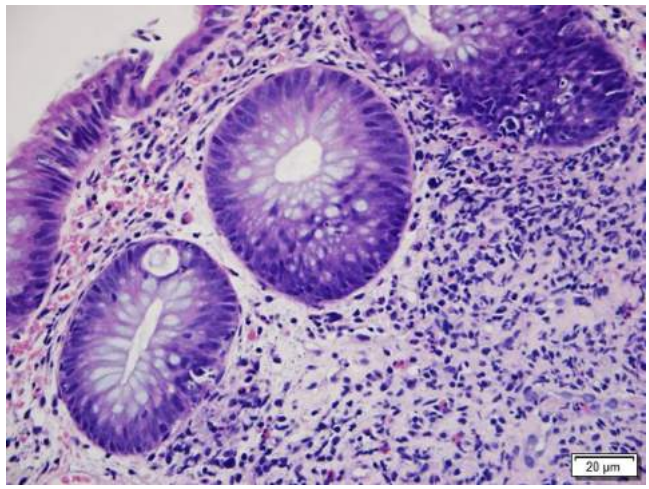

Figure 5. Colon compromised by GVHD. Colon histopathology with H&E (400 X). Shows crypt damage with basal apoptotic bodies and mixed inflammatory infiltrate in the lamina propria around the crypts. GVHD grade 1.

Initially, management was provided with high doses of methylprednisolone with partial response. Thus, around day 15 of the disease, we decided to carry out endoscopic control with EGD, not showing any relevant findings, and colonoscopy, which even showed a worsening of the findings in the ileum with sloughing of the mucosa, diffuse atrophy without villi, and no changes on the ulcerations in the colon. These manifestations correlated with the pro-

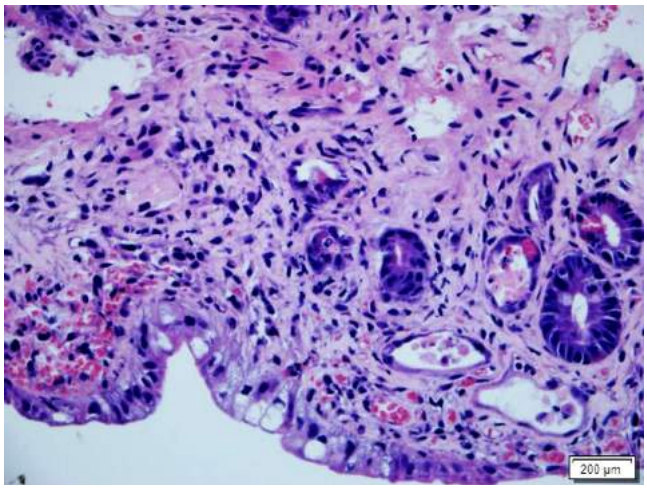

Figure 6. Small intestine compromised by GVHD. Histopathology of the small intestine with H&E (400 X). An apparent decrease in the number of crypts with marked mucin depletion, presence of basal apoptotic bodies, and adjacent mixed inflammatory infiltrate stand out. Severe GVHD.

gression of acute GVHD to grade 4/4 but was also positive for CMV on IHC in biopsies. Management with ganciclovir was started, followed by ruxolitinib for second-line management of GVHD. Nevertheless, the clinical evolution was towards deterioration, with worsening liver involvement due to GVHD and progressive anemia due to digestive bleeding. Rescue therapy with infliximab was even started without any response, which finally resulted in the death of the patient after 58 days of hospitalization.

CASE 3

A 41-year-old female patient diagnosed with acute myeloid leukemia and myelomonocytic maturation underwent a hematopoietic stem cell transplant after induction with a HIDAC chemotherapy scheme (high-dose cytarabine) plus midostaurin due to refractoriness to the first induction with a 7 x 3 scheme with cytarabine and idarubicin. Haploidentical transplantation of hematopoietic progenitors was performed with her brother as a donor. She was admitted on day 34 post-transplant with a two-week clinical picture consisting of diarrheal stools without mucus or blood, associated with crampy abdominal pain, nausea, and hyporexia. The clinical condition was generally acceptable, with no shock or inflammatory response signs. The paraclinical tests noted anemia of standard volumes and normal hepatic and renal functions. Given the suspicion of GVHD, an EGD were performed without pathological changes and a colonoscopy with evidence of mucosa of the left colon, sigmoid, and rectum with focal areas of congestion and aphthoid microerosions. Biopsies suggested acute GVHD in the duodenum grade 1/4 and in the rectum and sigmoid 3/4.

Given the acuteness of the condition, infectious colitis and positive *Clostridium difficile* toxin fecal colitis were suspected, with no other clinical signs suggestive of GVHD. Management included oral vancomycin for ten days with an adequate initial response, although with a subsequent recurrence of symptoms; therefore, she was hospitalized two months later. A high and low endoscopy control was performed, finding only ulcer scars in the colon with biopsies suggestive of GVHD grade 1/4 with negative IHC for CMV. Due to the positive serum viral load for CMV, oral valganciclovir was provided with improved digestive symptoms. Finally, it was not clear whether the patient's digestive manifestations corresponded to GVHD or changes due to multiple infectious processes.

DISCUSSION

GVHD is a frequent complication in patients undergoing allogeneic stem cell transplantation. However, cases have also been reported in patients undergoing autologous stem cell transplantation, solid organ transplantation, or after blood transfusions[1]. There are two variants of the disease: acute and chronic. Previously, a distinction was made between both types from the onset of the complication (acute if within the first 100 days of transplant). However, the 2005 consensus, as ratified by the 2014 National Institutes of Health (NIH) consensus, established that the difference between both types is based on clinical criteria according to the organs compromised instead of a specific time window[4].

GVHD is a multisystemic disorder: The main organs affected are the skin, GIT, and liver[5], and digestive involvement is the most difficult to manage and the one associated with the worst prognosis since it represents the leading cause of mortality related to GVHD[4–7]. The main risk factors for acute GVHD include major histocompatibility complex (MCHC) disparity, chronic myeloid leukemia, patient and donor age, history of acute GVHD, graft procurement method, and mismatch of sex, mainly when the recipient is male, and the donor is female[6,8].

The pathophysiology of GVHD is not entirely elucidated; tissue damage is considered to be mainly mediated by donor T cells and proinflammatory cytokines[6]. It begins with the first phase of tissue injury, resulting from the myeloablative regimen with chemoradiation therapy prior to the donor graft, with subsequent production of proinflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin (IL) 1, 2, and 6, among others. They increase the expression of cell adhesion molecules, costimulatory molecules, and CMHC antigens, activating antigen-presenting cells[9]. Subsequently, there is activa-

tion, proliferation, and differentiation of the donor's T cells towards the Th1, cytotoxic T, and Th17 subtypes, culminating in a cytotoxic effect with tissue damage[1].

In the GIT, immune deregulation produces a disturbance in the intestinal epithelium, specifically in the stem, Paneth, and goblet cells[6]; in fact, histologic severity in intestinal GVHD is categorized according to the degree of crypt damage, and preservation of Paneth cells in duodenal biopsies is inversely correlated with disease severity, response to treatment, and transplant-related mortality[7]. It has also been suggested that an imbalance in the intestinal microbiota may play a role in developing GVHD, as there is a relationship between the innate and adaptive immune systems and intestinal bacteria. Factors such as the myeloablative regimen prior to transplantation, broad-spectrum antibiotics, immunosuppressive drugs, and the addition of donor lymphocytes influence this imbalance[6,7].

The diagnosis of the acute variant is clinical. The NIH consensus criteria subclassify it as classic, with typical symptoms given by the appearance of an erythematous maculopapular rash, cholestatic hepatitis, and GIT symptoms such as diarrhea, nausea, vomiting, and abdominal pain within the first 100 days of transplantation[10], or as a persistent, recurrent or late-onset form when typical symptoms appear after 100 days[4]. The diagnosis can be confirmed with a histopathological study of the skin or GIT[1]. Acute GVHD can affect any segment of the GIT, usually in a patchy manner, and the manifestations in this system can be very subtle and nonspecific, posing a diagnostic challenge. In the oropharynx, it can exhibit mucositis that can be difficult to differentiate from that induced by myeloablative treatment, although the latter is expected to manifest within the first three weeks after the transplant and, afterward, could be explained by GVHD[6].

Gastroduodenal involvement shows mild and insidious symptoms such as loss of appetite, early satiety, dyspepsia, and weight loss, which can progress to incessant emesis, epigastric pain, and digestive bleeding[3]. The large and small intestines can also be affected, and diarrhea is the initial manifestation, usually occurring two weeks after the transplant[6]. Diarrhea is usually of the secretory type and is up to several liters per day in severity; as the inflammatory process progresses, a loss of proteins can occur through the mucosa. It generates mucus and, finally, bloody stools in the context of complete denudation of the epithelium, particularly in the ileum[9]. Mucosal injury with protein loss can result in malabsorption and malnutrition[6].

The chronic variant can have a more varied manifestation involving multiple organs, including the lungs, hepatobiliary system, musculoskeletal system, GIT, and skin[1]. The diagnosis is made by identifying pathognomonic signs and symptoms, which, if present, are sufficient for diagnosis, such as poikiloderma in the skin or stenosis in the GIT[4]. Lastly, a subtype of the chronic variant is also described, characterized by symptoms typical of the acute variant simultaneously; this subtype is known as overlap syndrome and carries a worse prognosis than the classic chronic variant[10].

Endoscopic studies are a fundamental piece in the study of GVHD. Generally, they perform well and are safe, with low complication rates[11]. The GVHD manifestation varies depending on the extent and severity and can range from patchy mucosal areas with mild and superficial erythema to ulcerations with sloughing and complete mucosal denudation (**Table 1**). Endoscopic techniques with magnification favor the detection of subtle changes such as shortening and reduction of the number of villi in the duodenum and ileum[12]. From the histological point of view, the severity of the findings will be defined by the degree of cell apoptosis in the crypts, necrosis, or, as in endoscopy, the evidence of complete mucosal denudation (**Table 2**).

Table 1. Freiburg classification

Grade	Endoscopic finding
1	Normal mucosa
2	Patchy erythema
3	Aphthoid lesions or focal erosion
4	Confluent erosions, ulceration, or mucosal denudation

Modified from[13].

Table 2. Severity classification

Grade	Pathological finding
1	Increased apoptosis in the crypts
2	Apoptosis with cryptic abscesses
3	Individual crypt necrosis
4	Total mucosal denudation in areas

Modified from[6].

Given the broad spectrum of GIT manifestation, the performance of endoscopic studies in diagnosing GVHD is variable, with sensitivity and specificity of 34%–89% and 65%–79%, respectively, and an agreement between the endoscopy and histology as low as 38%[13,14]. These are also used to rule out other differential diagnoses such as mycophenolate enteritis and colitis, infection by germs such as CMV, *C. difficile*, or common enteric viruses (adenovirus, rotavirus, norovirus, among others). Particularly

in the context of CMV, given the high infection rates in bone marrow transplant patients (up to 15%) and the importance of its diagnosis, it is always advisable to perform an IHC or polymerase chain reaction (PCR) study on biopsies in tissue. Similarly, infection by *C. difficile* can occur between 12% and 27% in this group of patients, which is why it should also be ruled out before considering the diagnosis of GVHD[15]. Therefore, biopsies are always recommended, both for healthy mucosa and for mucosa with inflammatory changes[6].

The diagnostic yield of endoscopic studies with biopsies is variable: 67%–80% for EGD, 58%–80% for rectosigmoidoscopy (RSC), 83%–87% for colonoscopy, 87%–100% for ileocolonoscopy, and 92%–93% for EGD with RSC[11,13]. Several studies suggest that CRS with biopsies of the distal colon could be more accurate in diagnosing acute GVHD (82%–95%); therefore, it is considered the initial study of choice, in addition to its easy preparation and performance[13]. The guidelines of the American Society for Gastrointestinal Endoscopy (ASGE) to approach diarrhea endorse this recommendation and suggest performing EGD in cases where CRS does not provide a diagnosis or if upper digestive symptoms are present[16]. Another guide published by the same society for taking samples in endoscopy suggests two approaches: RSC with four biopsies of the rectum and left colon; if no diagnosis is obtained, add EGD with biopsies of the body, antrum, and duodenum (four in each segment), or ileocolonoscopy with four biopsies of the distal ileum, right, transverse, left, and rectosigmoid colon[17]. In cases where CMV is suspected, performing RSC alone could be insufficient; performing a complete colonoscopy would be ideal. When taking biopsies, areas with very severe inflammation should be avoided due to the difficulty in interpretation for the pathologist and to reduce the risk of hematomas (in patients with thrombocytopenia) and even perforation, particularly in the duodenum and ileum[11]. Similarly, prophylactic antibiotics are recommended in patients with a neutrophil count < 500 cells/μL.

Endoscopic findings can also predict response to steroid management. A recent study of 44 patients with acute GVHD, of whom 45% were considered steroid-resistant, found that macroscopic findings in the ileum, histological findings in the ileum and colon, and the presence of granulation tissue in biopsies were predictors of refractoriness to steroid therapy[18]. In patients with therapeutic failure in the first line of management, repeating endoscopic studies could be considered to reassess the stage of the disease, objectify the degree of response, and rule out differential diagnoses (up to 25% of patients with therapeutic failure could have an infection by CMV in the second endoscopic review)[19]. Finally, some small studies of patients with suspected GVHD and capsule endoscopy have found high sensitivity (100%) and negative predictive value (NPV). As in conventional studies, the findings are usually patchy and range from erythema to erosions or ulcerations[20–22]. Generally, its use is recommended in patients with a high suspicion of GVHD who cannot tolerate conventional studies due to their clinical condition.

The standard GVHD treatment is high-dose steroids, particularly methylprednisolone 1–2 mg/kg/day in divided doses or prednisolone (1 mg/kg/day). In colonic compromise due to GVHD, the use of budesonide MMX has been described[6,23]. The response to steroid therapy is variable; up to 31%–57% of patients may be steroid-resistant[24]. Oral intake should be discontinued in patients with severe digestive symptoms, providing parenteral nutrition. For upper digestive symptoms, proton pump inhibitors (PPIs) and sucralfate are suggested. The use of non-steroidal anti-inflammatory drugs (NSAIDs) and opiates, including loperamide, should be avoided due to the risk of bleeding and ileus. The use of octreotide and cholestyramine has been described to control diarrhea, but potential adverse effects and the risk of alteration in the absorption of other medications must be contemplated[25,26].

CONCLUSION

In the three cases presented, we found a broad spectrum of GVHD manifestation, from mild symptoms and changes in the mucosa, due to erythema and erosions, to severe symptoms, such as bleeding, diarrhea difficult to manage, and extensive changes in the intestine with denudation of mucosa and severe atrophy in the small intestine. Magnification, particularly in the small intestine, was deemed helpful where there was a significant correlation between endoscopy and biopsies concerning atrophy. The risk of complications associated with endoscopic procedures should be considered, particularly bleeding and perforation. Although they did not occur in our cases, there were signs such as submucosal hematomas with biopsies that alerted us to the limitation in the number of samples to take. It is essential to rule out differential diagnoses, especially infectious ones, which could impact the patient's outcomes. As we saw in our cases, repeating the endoscopic studies could be helpful in follow-up and excluding infection by opportunistic germs. Due to their clinical condition, adherence to the ASGE recommendations should be pondered in high-risk patients, only performing CSR for diagnosing GVHD, but bearing in mind that ileocolonoscopy allows for a complete diagnostic approach.

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Case report

Anal canal lymphoma: Case report and literature review

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Abstract

Introduction: Primary tumors of the anal canal other than carcinomas are rare entities; among them, anal canal lymphomas are extremely unusual and pose both a diagnostic and therapeutic challenge for the coloproctologist. **Case presentation:** A male patient with positive human immunodeficiency virus (HIV) with proctalgia and mass sensation at the perianal level. A concentric thickening of the walls of the lower rectum was documented by magnetic resonance imaging, with colonoscopy and biopsies with histopathology compatible with plasmablastic lymphoma. Therefore, a diverting colostomy was performed and, subsequently, the hematology service indicated chemotherapy with the EPOCH scheme. **Discussion:** Lymphoma of the anus represents 0.2 % of anorectal tumors, most of these are non-Hodgkin's lymphomas; Hodgkin's disease at the anorectal level is even rarer. The population with the highest risk of this entity is HIV-positive patients, such as the patient in this case, although other associated factors are described in the literature.

Keywords

Anal lymphoma, plasmablastic lymphoma, colorectal cancer, anorectal cancer.

INTRODUCTION

Malignant neoplasms of the anal canal are rare diseases, and anal lymphoma is one of the least frequent, comprising approximately 0.2% of anorectal tumors. it affects primarily young adult men in a 6:1 ratio; a critical factor associated with these tumors is human immunodeficiency virus (HIV) infection[(1)]. The low incidence of this pathology represents a diagnostic and therapeutic challenge for both clinical oncology and colorectal surgery groups. Cancers of the anus and anal canal represent approximately 2.4% of all gastrointestinal neoplasms[(1)]. They are the majority of these squamous cell cancers; however, there are other types of less frequent tumors, including lymphoma of the anus, which is a diagnostic and therapeutic challenge.

CLINICAL CASE

A 33-year-old male patient with a history of stage C3 HIV infection was admitted for a clinical picture of approximately three months of evolution consisting of sensation of perianal mass and pain, anal discharge, and intermittent rectal bleeding. On physical examination, a mass of approximately 4 x 5 cm was observed at the level of the anal

canal, protruding through it. Digital rectal examination revealed an ulcerated, exophytic, friable mass that extended from the anal ridge up to 5 cm, infiltrated the external anal sphincter, and was in contact with the puborectalis muscle.

Within the extension studies, he had a contrast-enhanced magnetic resonance imaging (MRI) of the pelvis that showed a concentric thickening of the walls of the lower rectum, with an exophytic lesion that compromised the anal canal and extended towards the intergluteal soft tissues. The anal canal lesion had a longitudinal extension of 63 mm with an anteroposterior (AP) diameter of 73 mm and a transverse diameter of 40 mm with an adequate cleavage plane between the walls of the rectum and the seminal vesicles. The image described in the lower rectum made contact with the prostate posterior contour with nodes in the mesorectal fat with a diameter of up to 7 mm.

With this result and the findings upon physical examination, we decided to perform a rectosigmoidoscopy, finding a circumferential mass that extended from the anal rim to 5 cm, compromising 100% of the lumen and 95% of the circumference. It was obstructive and did not allow the team to advance, from which biopsies were taken (**Figures 1** and **2**). The histopathological report was a plasmablastic lymphoma with a positive immunophenotype for CD38, MUM-1, Ki67 95%, and CMYC in 70% of the tumor cells; and negative for cytokeratins, AE1/AE3, CD20, CD3, CD5, CD30, cyclin D1, Bcl2, Bcl6, PAX5, and CD10.

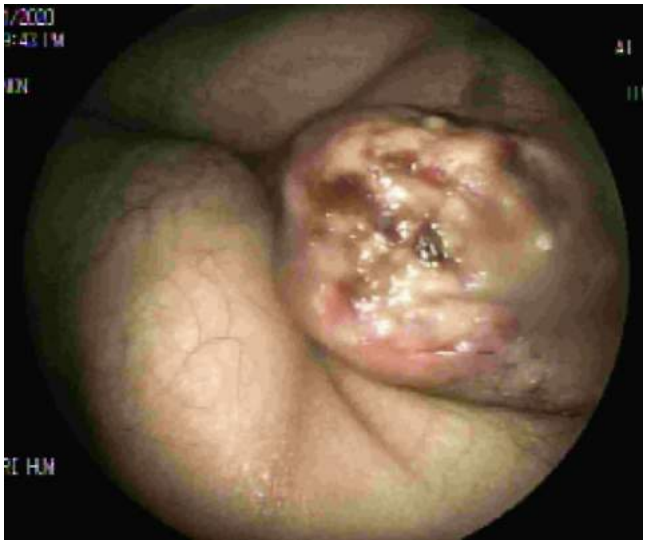

Figure 1. Mass at the level of the anal rim.

The diagnosis of plasmablastic lymphoma was made. We decided to perform a laparoscopic diverting colostomy, without complications during the postoperative period. Due to the patient's history of HIV, in-hospital studies were performed that showed a CD4+ lymphocyte count: 23 cells/mm^3 and a viral load of 16,803 replicates, with an indication to start chemoprophylaxis with trimethoprim/sulfamethoxazole and antiretroviral therapy with tenofovir, emtricitabine, and efavirenz.

Staging studies showed an abdominal computerized axial tomography (CT) scan with hepatosplenomegaly and a contrast-enhanced chest CT without evidence of lymphadenopathy or pulmonary nodules suggestive of secondary neoplastic disease. He was assessed by the haemato-oncology department, which considered that the patient had a stage IV BX plasmablastic lymphoma according to the Ann Arbor classification. We opted for management with systemic chemotherapy DA-EPOCH scheme for six cycles, with a partial response after the third cycle.

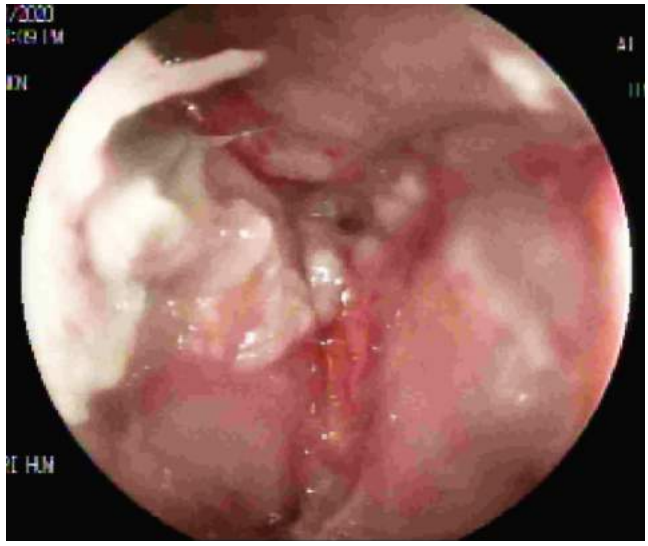

Figure 2. Mass with complete obstructive effect in the anal canal.

DISCUSSION

Cancers of the anus and anal canal represent approximately 2.4% of all gastrointestinal neoplasms[1]. They are the majority of these squamous cell cancers; however, there are other types of less frequent tumors, including lymphoma of the anus, which poses a diagnostic and therapeutic challenge.

Lymphoma of the anus represents 0.2% of anorectal tumors, most of which correspond to non-Hodgkin's lymphomas; Hodgkin's disease at the anorectal level is even rarer[1]. This pathology affects more young adult men in a ratio of 6:1; an important associated factor is HIV infection, mainly when the CD4 count is < 100 mm^3. Nevertheless, in recent decades, active antiretroviral therapy has decreased the incidence of HIV-associated lymphoma[2]. Anorectal lymphoma can be classified as primary if it refers to a primary neoplastic process of anorectal origin and secondary

if it is a generalized neoplastic process in which anorectal involvement is caused by lymph node metastases[3].

As already mentioned, primary colorectal lymphomas usually tend to be of the non-Hodgkin type; however, in some patients immunocompromised by HIV, the anorectal involvement could be of the Hodgkin type[4]. In this particular population, the involvement of the anal canal can reach up to 26%[3,5].

The clinical manifestations of anorectal lymphoma are similar to those of adenocarcinoma of the rectum. The most frequent is the sensation of a perianal mass, chronic ulceration, and bleeding; in turn, B symptoms such as weight loss, abdominal pain, or fever may occur[4]. It is a problematic pathology; sometimes, the symptoms or diagnostic studies are misinterpreted. The clinical manifestation described in the world literature is diverse, from cases diagnosed postoperatively after hemorrhoidectomy[6] to perianal abscesses[7]. Therefore, obtaining adequate samples that allow histopathological diagnosis is vital for establishing appropriate treatment.

Anal canal lymphoma is usually a tumor associated with HIV infection; however, other risk factors are described in the literature for its development, such as long-standing ulcerative colitis, transplant patients, pelvic radiotherapy, and immunodeficiencies of other causes[5]. Regarding diagnosis, imaging studies impede adequate differentiation from other types of lesions and most of the time, they are performed to evaluate the regional extension of the disease and rule out extranodal involvement[4]. The histopathological study provides the definitive diagnosis. Nonetheless, it continues to be a challenge because there are more than 60 varieties of non-Hodgkin's lymphomas with different histological provide. It is often necessary to obtain multiple biopsies and various immunohistochemical markers that allow a definitive diagnosis[4,8]; the most common are diffuse large B-cell non-Hodgkin's lymphoma and plasmablastic lymphoma, as in the previously described case.

Currently, the treatment is controversial, and there is no consensus about it; the most important thing is to define the extent of the disease, classify the type of lymphoma, and whether or not it is associated with HIV. Most studies suggest that the treatment of primary anorectal lymphoma could be surgical through oncological resection when it is a localized disease (Ann Arbor stages I–II), in which imaging findings classify it as potentially resectable. For example, high lesions could be treated with anterior resections of the rectum, while lower lesions that compromise the sphincters can be treated with abdominoperineal resections[9,10]. For advanced lymphomas (Ann Arbor stages III–IV), the treatment is systemic chemotherapy, of which there are multiple schemes[11]. Traditionally, multiple chemotherapy regimens have been administered for anal lymphomas, and the most used is CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone); nonetheless, adequate response and survival rates have not been achieved with this scheme[10,12].

Due to the low frequency of this pathology, most studies conducted to date are retrospective and with a relatively low number of cases, without showing significant differences in overall survival and response to treatment; however, more recent studies suggest an improvement in survival with more intensive chemotherapy schemes such as EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin)[13].

Radiotherapy treatment in lymphomas of the anus can be complementary, especially in local recurrences or in patients who underwent local resections with positive margins[4]. The overall survival rate is poor for anal lymphoma. Before highly active antiretroviral therapies (HAART), survival was eight months; now, the 5-year overall survival is 50% in localized disease, while for advanced disease with regional or distant metastatic lymph node involvement is 24% at five years[4].

CONCLUSION

Primary lymphoma of the anus is an infrequent entity, representing approximately 0.02% of all anorectal tumors; primary lymphomas of this location are usually non-Hodgkin's type, the population with the most significant relationship to this entity are HIV positive patients, and its management is surgical in early stages (Ann Arbor I and II). For more advanced lesions (Ann Arbor III and IV), treatment must involve systemic chemotherapy with EPOCH.

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Case report

Splanchnic vein thrombosis as a manifestation of latent myeloproliferative neoplasm associated with sticky platelet syndrome

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Abstract

Vein thrombosis of unusual sites such as the splanchnic region continues to be not only a diagnostic but also a therapeutic challenge for the clinician due to its manifestation and associated pathologies. Latent JAK2 (Janus kinase 2) positive myeloproliferative neoplasm associated with sticky platelet syndrome is unusual. We present a clinical case of a 38-year-old female patient who presented with sudden onset abdominal pain of a possible vascular origin. Splanchnic thrombosis was diagnosed in latent myeloproliferative neoplasm by identifying the JAK2V617F mutation and sticky platelet syndrome via platelet aggregometry. Off-label anticoagulation with rivaroxaban 20 mg/day was administered. During her outpatient follow-up, she did not suffer any new thrombotic episodes.

Keywords (MeCS)

Thrombosis, thrombophilia, neoplasm, anticoagulants, hematological diseases.

INTRODUCTION

The venous thromboembolic disease has positioned itself as a condition of interest in public health, given its high morbidity and mortality, particularly the one related to unusual sites that pose a diagnostic and therapeutic challenge[(1)]. Thus, it should be specified that splanchnic thrombosis refers to that located in the portal, mesenteric, or splenic vein or the hepatic venous flow; they are generally uncommon and occur in the context of hereditary thrombophilias (21%), infectious or inflammatory disorders, neoplasms, or liver cirrhosis. It has nonspecific manifestations, abdominal pain being the most common symptom (50%), followed by gastrointestinal bleeding and ascites[(2,3)].

Thrombophilias have been frequently related to venous thromboembolic disease. These can be classified as primary when they are hereditary, as in the case of sticky platelet syndrome, and secondary if they are associated with an acquired risk factor such as the Janus kinase 2 (JAK2) mutation[(4)], documented in up to 32.7% of patients with splanchnic venous thrombosis[(3)].

Classically, this mutation has been associated with Philadelphia chromosome-negative myeloproliferative neoplasms (MPN) such as polycythemia vera (96%),

essential thrombocytosis (55%), and primary myelofibrosis (65%)[5]. The latent condition of this type of neoplasia refers to the sole identification of the JAK2 mutation without peripheral alterations such as cytopenias and with normal erythropoietin levels. Recognizing it is becoming increasingly important given the clinical spectrum that will give rise to the natural evolution of the disease[6].

Besides MPNs, it is crucial in thrombosis of unusual sites to consider other etiologies such as sticky platelet syndrome, an autosomal dominant disease characterized by abnormal platelet aggregation. For its diagnosis, a platelet aggregometry with epinephrine and adenosine diphosphate (ADP) must be performed; the platelets are exposed to low concentrations of these substances, assessing the response against standard parameters for the test[7]. It has been associated with arterial (21%) and venous (13%) thrombotic events, generally recurrent; its manifestation can be related to any state of hypercoagulability, the most frequent being factor V Leiden mutation[8].

A case of splanchnic thrombosis is presented below as the initial manifestation of latent MPN associated with sticky platelet syndrome.

CLINICAL CASE

A 38–year-old woman was admitted to the emergency department due to a clinical picture of sudden onset. It was characterized by acute pain with visceral nociceptive features, initially located in the epigastrium with subsequent generalization and radiating to the bilateral lumbar region, with an intensity of 9/10 on the visual analog scale (VAS) for pain. She had no extenuating or exacerbating factors. The clinical picture was associated with sweating, nausea, and vomiting of food content. The patient referred to it as the first episode of this type of symptomatology. She had no relevant pathological, family, gynecological, or pharmacological history, and the symptom systems review was negative. On physical examination, her blood pressure (BP) was 100/50 mm Hg and heart rate (HR) 99 beats per minute (bpm). She exhibited abdominal distension and diffuse pain on palpation, predominantly in the upper abdomen, with no signs of peritoneal irritation.

Due to the sudden-onset pain characteristics, it was deemed sensible to rule out a vascular origin, for which a contrast-enhanced abdominal tomography was performed, showing thrombosis of the portal vein without cavernous transformation. An endoscopy of the upper digestive tract was performed, finding large esophageal varices of 7 mm in diameter, tortuous from 27 cm to the Z line, with maximum insufflation occupying more than a third of the lumen of the esophagus. On the surface of the varices, cherry-red spots classified as F3 and cardinal varices were observed, and the esophageal varices were ligated. However, the abdominal pain persisted, and laparoscopy was considered. Serohemorrhagic fluid and ischemic jejunal loop were found in a segment of 20 cm to 5 cm of the ligament of Treitz, with no necrosis, mesenteric venous engorgement, and preserved pulses.

The content was aspirated, and no additional surgical procedure was considered. Subsequently, we decided to perform an abdominal angiography, revealing thrombosis of the splenic and mesenteric veins and intrahepatic portal vein with collateral circulation and physiological splenorenal shunt associated with splenomegaly and permeabilization of the left gastric vein (**Figure 1**). Anticoagulation was indicated with low molecular weight heparin (LMWH) and a non-selective β-blocker.

Since the leading causes of thrombosis in these sites are thrombophilias, relevant tests were performed (**Table 1**). Only one JAK2V617F mutation was identified, and the blood count showed findings related to mild anemia. Thus, erythropoietin (EPO) level tests were requested, which were within normal parameters, leading us to consider a latent MPN.

In addition, platelet aggregometry was performed, revealing hyperaggregation at two concentrations with both ADP and epinephrine (**Figure 2**) classified as type 1 sticky platelet syndrome (SPS). Once she showed clinical improvement, anticoagulation was indicated in an off-label or unapproved manner with rivaroxaban 20 mg/day.

DISCUSSION

We present the case of a young adult female patient who had sudden abdominal pain as an initial manifestation, one of the symptoms that creates the most confusion in an emergency department due to the multiple differential diagnoses of this condition. The sudden appearance is alarming due to the possible related etiologies, among which visceral perforations or vascular alterations (rupture or ischemia)[9] stand out. Given the preservation of vital signs and absence of peritoneal irritation, contrast-enhanced abdominal tomography was performed first, showing thrombosis in the portal vein and, subsequently, splanchnic venous thrombosis was confirmed using angiotomography (unusual site of thrombosis). Other causes, such as gynecological ones, can be ruled out. It is crucial to remember that this is the most frequent symptom in this type of pathology[3].

In patients under 40 years of age with splanchnic thrombosis, searching for primary thrombophilias such as factor V Leiden mutation, prothrombin, antithrombin III, protein S and C deficiencies, homocysteine, sticky platelet syndrome, and secondary thrombophilias such as syndrome chronic antiphospholipid and MPN is essential to define

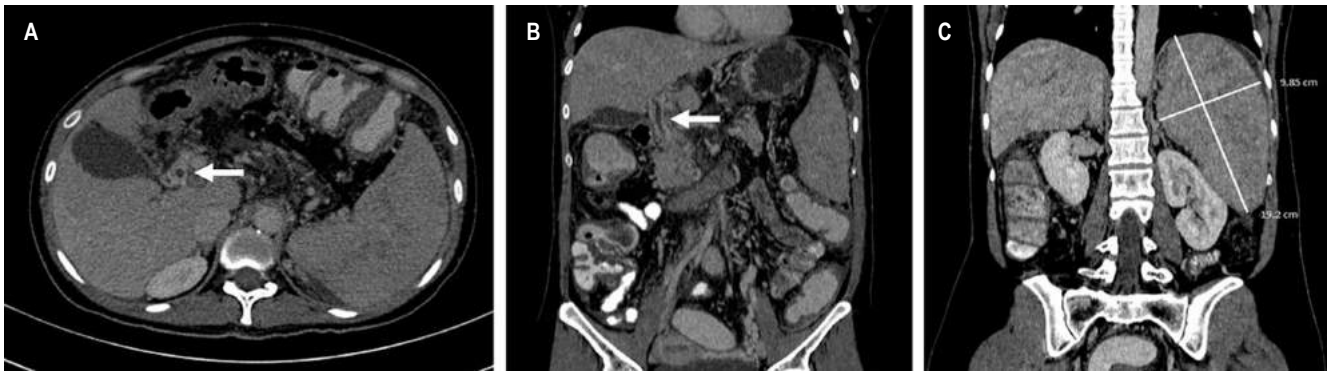

Figure 1. A. There is no adequate opacification of the portal vein (white arrow). **B.** Portal vein, multiple serpentine vascular images going to the hepatic hilum are observed in its course, suggesting portal hypertension (white arrow). **C.** Splenomegaly (white line).

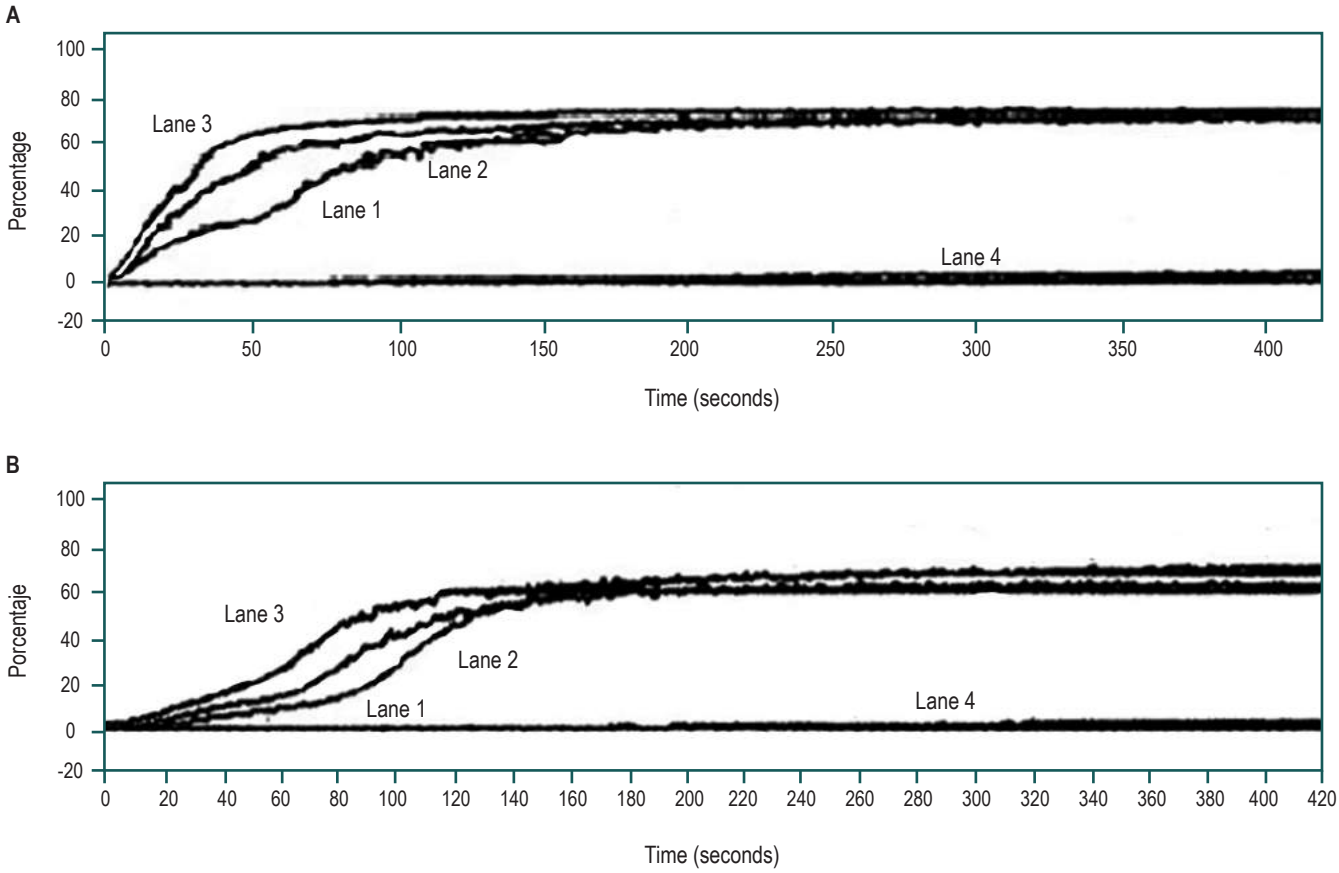

Figure 2. A. Platelet aggregation study with ADP compatible with sticky platelet. Lanes: 1: No platelet hyperaggregation with ADP at a concentration of 2.3 µM; 2: Platelet hyperaggregation with ADP at a concentration of 1.2 µM; 3: Platelet hyperaggregation with ADP at a concentration of 0.6 µM; 4: Negative control with 0.85% saline solution (SS). **B.** Platelet aggregation study with epinephrine compatible with sticky platelet. Lanes: 1: No platelet hyperaggregation with epinephrine at a concentration of 11 µM. 2: Platelet hyperaggregation with epinephrine at a concentration of 1.1 µM; 3: Platelet hyperaggregation with epinephrine at a concentration of 0.6 µM; 4: Negative control with 0.85% SS.

Table 1. Paraclinical tests performed during the patient's hospitalization

Tests	Patient value	Reference value
Factor V Leiden mutation	Negative	Negative
Prothrombin gene mutation	Negative	Negative
Antithrombin III	87.2%	75%–125%
Protein C	77.2%	65%–140%
Protein S	65.2%	52%–118%
Homocysteine	9.11	5–12 µmol/L
Flow cytometry for PNH	Negative	Negative
JAK2V617F mutation	Positive	Negative
Factor VIII	74.9	50%–150%
Factor IX	54.5	50%–150%
Factor XI	58.2	50%–150%
Erythropoietin	14.3	4.3–29
D-dimer	100	0–500 µg/mL
LDH	169	140–280 U/L
Lupus anticoagulant	Negative	Negative
Anticardiolipin	IgM: 3.7 IgG: 1.8	Less than 10 U/mL Less than 10 U/mL
Anti-β_2-glycoprotein 1 antibodies	IgM: 2.2 IgG: 2.7	Less than 5 U/mL Less than 5 U/mL
Antinuclear antibodies	Negative	< 1:80
Complete blood count	Leukocytes: 4550 Hb: 11.8 MCV: 81 Platelets: 244,000	3,700–10,100 UL 12–16 g/dL 80–100 150–400,000 µL

Hb: Hemoglobin; PNH: Paroxysmal nocturnal hemoglobinuria; IgG: Immunoglobulin G; IgM: Immunoglobulin M; MCV: Mean corpuscular volume.

long-term therapeutic strategies[10]. Other alterations such as PNH must be ruled out, which takes on significant relevance. Its identification is an independent factor for mortality[11], ruled out by peripheral blood flow cytometry.

The patient in the clinical case had two conditions that increased the risk of venous thrombotic events, such as the JAK2 mutation in the context of latent MPN and sticky platelet syndrome[4–8]. Notably, its prevalence is quite rare, so this would be one of the first cases reported with this association.

Regarding the treatment of splanchnic thrombosis, it is based on early anticoagulation to improve vessel recanalization and avoid complications; however, the risk of bleeding is high, especially in patients with esophageal varices[5]. In recent years, the efficacy of rivaroxaban vs. warfarin in resolving thrombosis (86% vs. 45% for warfarin) and improving late recanalization with no recurrence of thrombotic events and no bleeding episodes has been proved[12]. A prospective cohort from the Mayo Clinic, where the safety of direct-acting oral anticoagulants (DOAC) was evaluated, included 63 patients with unusual thrombosis, primarily women (63%). Non-inferiority was noted in the risk of recurrence of thrombotic events and bleeding with DOACs (rivaroxaban and apixaban) compared to LMWH[13]. The first-line treatment for sticky platelet syndrome is aspirin[14]. In the present case, given the evidence of factors that increased the risk of recurrent thrombosis, we decided to start indefinite anticoagulation as an off-label or unapproved measure with a direct factor Xa inhibitor (rivaroxaban 20 mg/day). Nonetheless, due to the high risk of bleeding in this patient caused by esophageal varices and a lack of clinical trials evaluating dual therapy together with aspirin, its use was not considered in this context. With this therapeutic approach, the patient has had an outpatient follow-up for 15 months and has not presented with new symptomatic thrombotic episodes.

CONCLUSION

When evaluating acute abdominal pain of sudden onset, the correct application of semiology is critical to identify the patient who requires medical or surgical management. Besides, it is necessary to rule out vascular origin as a causal factor. The proper use of diagnostic aids such as abdominal tomography helps exclude or confirm potential etiologies, considering the age group and clinical manifestation. Venous thrombosis of unusual sites, such as splanchnic thrombosis, is a low-prevalence entity, which poses not only diagnostic but also a therapeutic challenge for the clinician due to its manifestation and associated pathologies such as primary (platelet syndrome sticky) and secondary (latent MPN) thrombophilia. All of the above is relevant when establishing an effective treatment, in this case, anticoagulation, improving the patient's prognosis and quality of life.

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Conflicts of interest

None was declared by the authors.

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Case report

Modified amoebic liver abscess: Case report

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Abstract

We present the case of a 56-year-old black female patient from a rural area in the Morón municipality, Ciego de Ávila province, Cuba. She was admitted with symptoms of dysentery with several days of evolution and a later episode of high fever, compromised general status, and abdominal pain located in the right hypochondrium. Analytical studies reported leukocytosis with a predominance of polymorphonuclear cells, *Entamoeba histolytica* was found in the stool study. Abdominal ultrasound reported a mixed image of 110 x 84 mm in the upper right lobe of the liver, as confirmed by computed tomography. This image was interpreted as a possible liver abscess. The patient received antimicrobial treatment for four weeks without a good response, thus requiring surgical intervention. She evolved favorably and was discharged after 21 days.

Keywords

Liver, abscess, imaging diagnosis, surgical treatment.

INTRODUCTION

A liver abscess (LA) is a collection of pus surrounded by a fibrous capsule that, depending on its etiology, can be pyogenic or amoebic[1]. It occurs with low frequency in first-world countries, and between 5 and 22 cases are recorded per 100,000 hospital admissions, with a predominance of males between the third and sixth decade of life[2]. Mortality is reduced from 50% to 10% after percutaneous intervention guided by ultrasonography or tomography[2].

The risk factors associated with amoebic liver abscess (ALA) are male gender, the third and fifth decades of life, alcoholism, oncological diseases, immunosuppression, and living in endemic areas, among others[3].

Despite being an infectious pathology with accessible diagnostic methods and management options, LA continues to cause high morbidity and mortality in developing countries[4]. In the last century, there has been a decrease from 75%–80% to 10%–40% in mortality due to LA thanks to pharmacological advances, specifically in the area of antibiotics and interventional processes; however, it must be considered that timely diagnosis would contribute to improving prognosis and mortality[5].

The cardinal elements to establish the diagnosis include clinical history, laboratory tests, and imaging studies. These elements are not enough to clearly differentiate between an amoebic abscess, a pyogenic abscess, or a malignant disease. With the existence of risk factors and a suspicious lesion, a potential amoebic infection can be assumed, as long as it is corroborated by other tests[4].

Comorbidities such as the development of intra-abdominal sepsis without an apparent cause or malignant processes in advanced stages darken the prognosis and increase mortality more than the abscess concerned. The most frequent causes of death in this type of patient are usually sepsis and multi-organ failure[3].

Our goal is to present the clinical characteristics, diagnosis, and specific therapeutic management of this patient and of a rare entity in our environment. It will serve as a guideline to conduct research on the diagnosis and treatment of this disease and as a reference for the future management of similar cases.

CLINICAL CASE

A 56-year-old black female patient was admitted to the Internal Medicine service for a 14-day history of dysentery with a severe compromise of her general condition, fever of 38–39 degrees, and pain in the right hypochondrium. Complementary tests were indicated, starting antimicrobial treatment with the clinical suspicion of complicated intestinal dysentery.

Complementary exams

Analytical studies

Table 1 shows the differential blood count.

Table 1. Differential blood count results

Hb	9.0 g/L
Leukogram	15.8 x 10^9
Polymorphonuclear leukocytes	0.70
Lymphocytes	0.28
Platelet count	300 x 10^9
Coagulation time	10 minutes
Bleeding time	1 minute
Prothrombin time	Control: 14 minutes, patient: 17 minutes
Erythrocyte sedimentation rate	107 mms
C-reactive protein	25 mg/L
Blood glucose	8.1 mmol/L
Creatinine	58.7 mmol/L
Serum amylase	86 pcs/L
Total bilirubin	76 mmol
Total proteins	45 g/L
Albumin	26 g/L
Urea	4 mmol/L
Uric acid	296 mmol/L
Cholesterol	3.0 mmol/L
Triglycerides	1.22 mmol/L
GPT	107 IU
GOT	98 IU
Alkaline phosphatase	370 IU/L
VDRL	Not reactive
HIV	Negative
Blood and stool cultures	Negative
Microscopic examination of feces	Positive for *Entamoeba histolytica*

Hb: Hemoglobin; GOT: glutamic oxaloacetic transaminase or aspartate aminotransferase (AST); GPT: Glutamic pyruvic transaminase or alanine aminotransferase (ALT); HIV: human immunodeficiency virus; VDRL: Venereal disease research laboratory test. Source: Prepared by the authors.

Abdominal ultrasound

A heterogeneous liver is appreciated with two mixed images; the largest one of 110 x 84 mm with echolucent areas inside that could be related to degeneration, of average size, and does not exceed the costal margin. The gallbladder has no alterations. The right kidney measures 100 x 40 mm, and the 9 mm parenchyma has microlithiasis in the middle calyceal group without dilatation of the system. The left kidney measures 118 x 45 mm, and the parenchyma of 15 mm has no lithiasis or dilatation of the system. The bladder is empty. There is no free fluid in the abdominal cavity (**Figure 1**).

The liver is of average size with two closely related hypodense images and thick walls; the largest one of 114 x 92 mm, of liquid density, located in the right lobe immediately below Glisson's capsule concerning subsegments VI and VII. The gallbladder has thin walls without stones, and there is no dilatation of the bile ducts. The pancreas and spleen are of standard size and density. The kidneys are of average size and position; there is good parenchyma without ectasia or lithiasis. The bladder is empty. There is

no free fluid in the abdominal cavity and no intra-abdominal adenopathies (**Figure 2**).

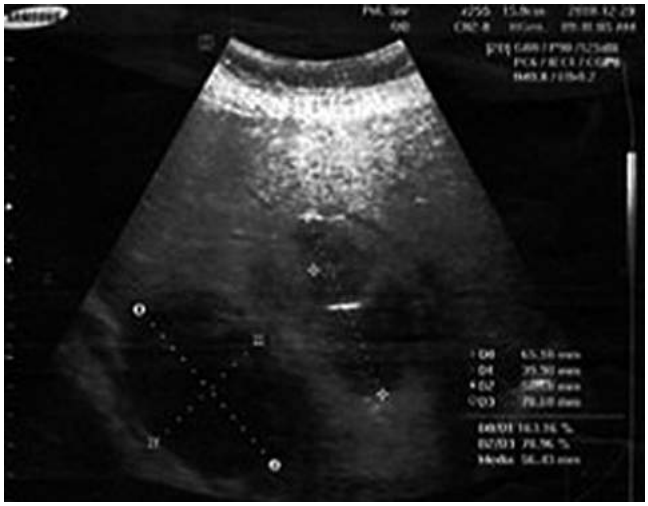

Figure 1. Liver ultrasound. Diagnostic impression: Multiple LAs. Contrasted abdominal computerized axial tomography (CAT) No. 0077-19. Source: Owned by the authors.

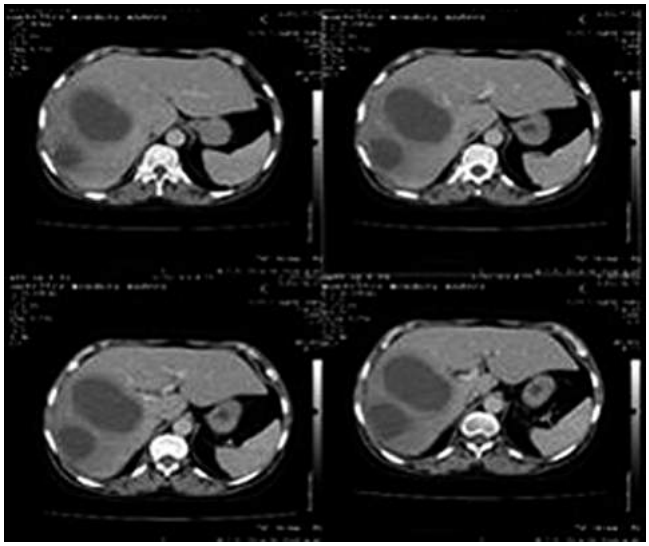

Figure 2. Contrast-enhanced CT of the liver. Diagnostic impression: LAs. Conclusive gastroduodenoscopy of erythematous erosive gastritis. Source: Owned by the authors.

Surgery

We decided to perform a laparotomy because of the poor response to the imposed medical treatment and the failure of the ultrasound-guided percutaneous puncture approach. A supraumbilical right transrectal incision was made, deepening it with the electrocautery by planes until reaching the abdominal cavity. An approximately 10 cm resistant area was found in the upper part of the right lobe of the liver in close relation to the diaphragm. It was carefully punctured, confirming the diagnosis that, due to the characteristics of the pus, it could be pyogenic and initially amoebic. A sample was taken for culture and antibiogram. The entire area of the abscess was subsequently unroofed, and 600 mL of creamy yellow pus was aspirated. The cavities were digitally explored for being multiloculated; it was washed with abundant physiological saline, carefully applying povidone-iodine to prevent contamination of the rest of the cavity (**Figure 3**). Counter-opening drainages were set, and the cavity was closed by planes. Subsequently, the patient went to the Intensive Care Unit for three days; then, she was transferred to the Intermediate Care Unit and to the Surgery Room, where the antibiotic treatment was completed. An antibiogram was received 72 hours after surgical drainage, which was positive for *Escherichia coli*.

A medium-sized serous right pleural effusion (700 mL) was diagnosed and resolved with thoracentesis on the fourteenth day. The culture with antibiogram reported no bacterial growth. The patient evolved favorably and was discharged after 21 days.

DISCUSSION

Amebiasis is the second leading cause of death from the parasitic disease worldwide; in Cuba, it has been proven that amebiasis is not one of the most frequent parasitisms, even though ALA is the most frequent extraintestinal manifestation of *Entamoeba histolytica* infection[6].

Most LAs are polymicrobial, mainly caused by the combination of enteric and anaerobic bacteria[1]. Liver infection can originate from the bile duct (40.1%), portal vein (16.1%), infection of neighboring organs (5.8%), liver trauma (4.5%), cryptogenic (26, 2%), or other (7.3%), as the starting point of appendicitis, septic disease of the pelvis, pyogenic cholecystitis, diverticulitis, peritonitis secondary to hollow viscous perforation, infected hemorrhoids, and any other cause of septic origin[7,8].

Within the bacterial etiology, Enterobacteria such as *Escherichia coli* and *Klebsiella* are recognized as capable of developing pyogenic abscesses, in addition to anaerobic enterococci and streptococci, among which *Streptococcus milleri* is the most frequent species. The immunosuppression of HIV infection, chemotherapy, and transplantation has increased the number of fungal abscesses and opportunistic germs[4].

Poor sanitation, low socioeconomic status, decreased access to clean water, high population density, immunosuppressive conditions, HIV infection, and homosexuality are considered risk factors for acquiring amoeba infection, especially in the male sex. While in the female sex, protective factors such as iron deficiency due to menstrual loss,

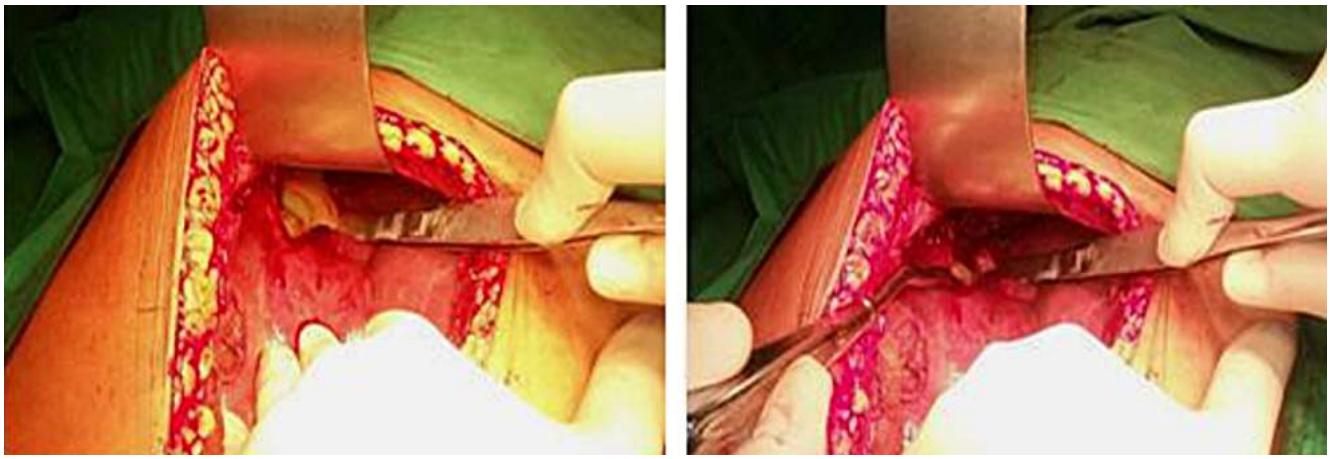

Figure 3. Abscess cavity during laparotomy. Source: Owned by the authors.

hormonal changes, and a lower tendency to use alcohol are described, causing minor hepatocellular damage (mainly to Kupffer cells)[9].

Due to the effect of the mesenteric blood flow of the portal vein, there is a predisposition of more than 80% of the location of LAs in the right lobe, mainly in segments VI and VIII. Single abscesses can be of hematogenous or portal origin with a higher incidence between 60%–70%, while multiple abscesses have their origin in the bile duct with a lower incidence (30%)[8].

The symptoms recorded in a pyogenic liver abscess (PLA) have been diverse, mainly due to its pathology. PLAs have shown clinical variability over time. Fever, jaundice, and pain associated or not with cholangitis or pylephlebitis, as traditionally known, have given way to subclinical forms[3].

There are symptomatologic differences concerning single or multiple abscesses, the latter with a more significant systemic impact. The clinical differences between amoebic and pyogenic abscesses are not notable since more than 90% of patients present with fever, weight loss, malaise, abdominal pain, chills, myalgia, headache, pruritus, nausea, vomiting, diarrhea, and in the most severe cases, shock and mental confusion[3].

Jaundice and right upper quadrant pain, aggravated by percussion, are some signs found on physical examination. Nonetheless, other patients only present with fever, before which we must think of an LA, especially if the fever origin is unknown. In addition, respiratory symptoms are apparent, such as cough and pleuritic pain radiating to the right shoulder when in the presence of subdiaphragmatic abscesses[8]. In both types of abscesses, 80% of patients have symptoms established in days or weeks prior to diagnosis, typically in less than two to four weeks[7].

Leukocytosis associated with anemia and accelerated sedimentation rate is frequently associated with LA. In liver function tests, enzymes sometimes appear elevated, mainly transaminases, alkaline phosphatase, and bilirubin. Our results showed elevated liver enzymes and a higher frequency of hypoalbuminemia associated with pyogenic abscesses compared to other studies[8].

Abdominal ultrasound is a non-invasive, low-cost method with a sensitivity that ranges between 85%–95%, making it the diagnostic method of choice. Besides, it can be used to guide the aspiration and culture of the abscess. CT has a higher sensitivity (95%–100%) and helps identify other intra-abdominal pathologies[10].

There is a broad spectrum within the differential diagnosis, so a high index of suspicion is needed after a thorough history and physical examination. Possible causes can be infectious and non-infectious, including[5] Hodgkin's and non-Hodgkin's lymphoma, acute leukemia, pathology of the bile duct (cholangitis and cholecystitis), acute diverticulitis, acute appendicitis, visceral perforation, mesenteric ischemia, acute pancreatitis, and pulmonary embolism.

Treatment and mortality in patients with PLA were addressed in 1938 by Ochsner and DeBakey, who established surgery as the treatment of choice; however, in recent decades, new diagnostic and non-surgical treatment options have been introduced[11].

Management should include drainage of the abscess, whose techniques include percutaneous drainage guided by ultrasound or tomography, catheter drainage, drainage by endoscopic retrograde cholangiopancreatography (ERCP), specifically in those cases with an obstruction of the bile duct attached to the stent placement, and laparoscopic drainage or open surgical drainage[3].

There are differences in the management of abscesses larger than 5 cm. Some authors prefer surgical intervention to percutaneous drainage with a lower range of treatment error, although there are no differences in the clinical picture's morbidity, mortality, and duration. The conduct of LA drainage varies depending on their size; if they are smaller than 5 cm, it is more feasible to perform needle aspiration or catheter drainage. When the size is larger than 5 cm, placement of a drainage catheter is preferable since needle aspiration has been associated with a therapeutic failure of up to 50% in these cases[12].

The established antibiotic regimen and its duration may vary depending on the culture results, the number of abscesses, their size, and clinical improvement and should last between two and four weeks. The administration of antibiotics with combined antimicrobial therapy (third-generation cephalosporins plus metronidazole or piperacillin-tazobactam) is only effective in Las smaller than 5 cm in diameter, which report *Escherichia coli*, *Klebsiella pneumoniae*, Bacteroides, enterococci, and anaerobic streptococci as causative germs. Vargas *et al* describe a high resistance to fluoroquinolones and ampicillin[5].

Mora *et al*[13] reported a clinical case of LA in which the causal germ was of the genus *Pediococcus*, specifically *Pediococcus pentosaceus*. It was initially managed with the administration of piperacillin-tazobactam and metronidazole, puncture, and percutaneous drainage, whose evolution was torpid. Thus, it was necessary to make gradual readjustments in its treatment until administering meropenem and vancomycin to obtain a favorable evolution.

The indications for surgical aspiration combined with antibiotic therapy include: 1. High possibility of rupture when it comes to a cavity larger than 5 centimeters; 2. Left lobe abscesses have a high risk of communicating with the pericardial sac; 3. Failed response to treatment after one week[11].

In the last three decades, percutaneous drainage has been displacing traditional surgical drainage coupled with the use of antibiotics to become the treatment of choice, except in cases of multiple abscesses difficult to access or when medical treatment has not shown a notable improvement[12]. Combined management in any of the three ways (aspiration plus direct drainage, drainage plus percutaneous catheter placement, or surgery) is reported in 52% of studies, most of which used surgical management[10].

The combination of laparoscopic drainage and antibiotic therapy is possible in selected patients or those in whom percutaneous drainage has failed. Laparotomy is reserved for cases with a greater possibility of opening the abscess to the peritoneal cavity or when the necessary conditions to perform percutaneous puncture or laparoscopic access are available[14].

In other situations, including multiple abscesses, multilocular abscesses with dense content, poor response after seven days of percutaneous drainage, dimensions equal to or greater than 110 mm or more than 500 mL, those adjacent to the diaphragm, those of the left lobe due to the risk of pericarditis, failure of the previous methods, and patients with more than one criterion, surgical drainage is the treatment of choice[14].

In 50% of patients, the liver returns to its standard size after a few weeks, with radiological improvement observed between three and nine months later[15]. Between 10% and 20% of patients exhibit complications related to an extension to neighboring structures or rupture of the abscess, mainly to the pleuropulmonary space (pleural effusion or empyema), and less frequently, subphrenic abscess, peritonitis, pericarditis, and the haemobilia. Its mortality is reduced with early diagnosis and adequate treatment. Factors that increase the risk of death include shock, adult respiratory distress syndrome, disseminated intravascular coagulation, immunosuppression, severe hypoalbuminemia, diabetes, ineffective surgical drainage, and malignancy[16]. In Cuba, the advantages of non-surgical interventional management have also been observed as a management option combined with antibiotic therapy[6].

In our case, the management of combined antibiotics (third-generation cephalosporins, aminoglycosides, and metronidazole) was chosen, which covered the amoebic and pyogenic etiology from the beginning with poor results. The dimensions of the abscess, its proximity to the diaphragm, the failure of the ultrasound-guided percutaneous puncture approach, and the patient's clinical deterioration made laparotomy necessary.

CONCLUSION

The case was concluded as a modified ALA, serving as a reference for future management of this entity.

Informed consent

Informed consent was obtained and is available upon request. The Ethics Committee and Scientific Council of our institution approved the design and methodology of the study.

Conflicts of interest

The authors certify no conflict of interest.

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This work was self-financed by the authors.

Authors' contribution

The study conception, the search for updated information, the writing of the manuscript, the review and approval of the final report, and the agreement of responsibility for all aspects of the work and its result involved Armando Rivero-León and Margis Núñez-Calatayud.

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César Roux and his Roux en Y Anastomosis: 130 Years of History

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The discovery, implementation, and development of asepsis, antisepsis, and anesthesia techniques allowed, coupled with the development of formal and better-structured programs and training in medicine and surgery, accessing body cavities considered inscrutable temples in the human being, such as the abdomen and the skull. Since then, and historically, there have been notable characters in the world of surgery, not only for their intellectual abilities that gave them a superior understanding of the human body in their time but also for their manual skills that led them to transcend in the history of surgery. One of these characters is César Roux, inventor and precursor of the surgery that bears his name*: L'anse en Y selon Roux* or Roux-en-Y anastomosis (**Figure 1**).

Figure 1. César Roux at the age of 42 (1899). Courtesy of Dr. Gustavo Martínez-Mier. Martínez-Mier G, Reyes-Devesa HE. César Roux. El cirujano y su anastomosis. Cir General. 2005;27(2):171-75.

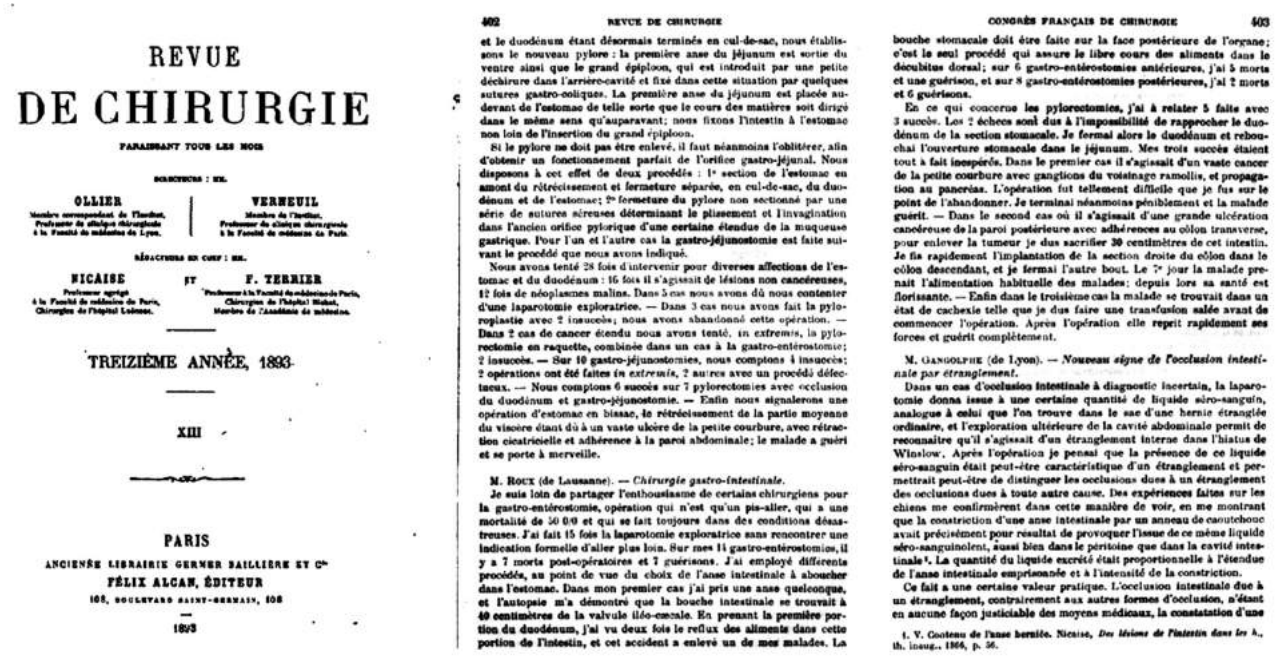
César Roux was born on March 23, 1857, in Mont-la-Ville, Switzerland. He was the fifth of eleven children, and his father was a school inspector. He studied medicine at the

University of Bern between 1874 and 1880, a university whose faculty included Theodor Langhans in pathology and Theodor Kocher in surgery. It was under the mentorship of Theodor Kocher that Roux undertook further training in surgery for three years at the University Hospital of Bern. He was early noted for his surgical skills that would bring him recognition in the scientific community of the time and would later lead him, at the age of 30, to be the chief of surgery at the Canton Hospital in Lausanne, Switzerland. Although his interest in surgery encompassed many areas, Roux had a particular interest in gastrointestinal surgery, and his contributions in this area were the most representative.

The first performance of a Roux-en-Y gastrointestinal reconstruction in a human was performed in 1892 as a treatment for anthropyloric obstruction, a general pathology that concerned and occupied the minds of great surgeons of the time, such as Theodor Billroth. This procedure was performed by adapting Anton Wölflers' technique presented at the 12th Congress of the German Society of Surgery from an experiment in canines in which a Y-shaped anastomosis was performed with an end-to-side jejunojejunoanastomosis and a gastrojejunoanastomosis. In 1893, César Roux published his experience with 29 patients and detailed the steps to follow for his procedure (**Figure 2**), which included the section of a loop of jejunum at 15 to 30 cm from the ligament of Treitz, creating an afferent loop 10 to 12 cm long. The efferent loop (Y-loop) was anastomosed with the posterior wall of the stomach in a retrocolic position, and the anastomosis between the afferent and efferent loops was performed in an end-to-side position in three layers (**Figure 3**).

By 1897, Roux published his experience with the intervention in 50 patients and additional details about the procedure. Although the initial mortality was 21%, with a refinement of the technique, it was reduced to 11%, reasonably low mortality if one considers that Roux did not select low-risk patients and performed the procedure on all those in which it was technically possible even when they presented with tumor involvement. One of the main complications of this procedure was the appearance of ulcers at the edges of the gastrojejunoanastomosis, resulting in bleeding, pain, and perforations and causing the original technique to be modified by a side-to-end gastrojejunostomy that gave rise to the reflux of biliary and pancreatic secretions that neutralized gastric secretions. So, Roux abandoned his original procedure in 1911. Additionally, with the appearance of drugs that help control gastric secretion and vagotomies, the Roux-en-Y anastomosis fell into oblivion. Half a century later, this procedure was adopted again in multiple gastrointestinal surgical procedures with some modifications but keeping the basic principles described initially by César Roux[1,2].

César Roux was also the first person to surgically remove a pheochromocytoma by adrenalectomy, seven months ahead



REVUE

DE CHIRURGIE

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402 REVUE DE CHIRURGIE

et le duodénum étant désormais terminés en cul-de-sac, nous établissons le nouveau pylore : la première anse du jéjunum est sortie du ventre ainsi que le grand épiploon, qui est introduit par une petite déchirure dans l'arrière-cavité et fixé dans cette situation par quelques sutures gastro-coliques. La première anse du jéjunum est placée au-devant de l'estomac de telle sorte que le cours des matières soit dirigé dans le même sens qu'auparavant; nous fixons l'intestin à l'estomac non loin de l'insertion du grand épiploon.

Si le pylore ne doit pas être enlevé, il faut néanmoins l'oblitérer, afin d'obtenir un fonctionnement parfait de l'orifice gastro-jéjunal. Nous disposons à cet effet de deux procédés : 1° section de l'estomac en amont du rétrécissement et fermeture séparée, en cul-de-sac, du duodénum et de l'estomac; 2° fermeture du pylore non sectionné par une série de sutures séreuses déterminant le plissement et l'invagination dans l'ancien orifice pylorique d'une certaine étendue de la muqueuse gastrique. Pour l'un et l'autre cas la gastro-jéjunostomie est faite suivant le procédé que nous avons indiqué.

Nous avons tenté 28 fois d'intervenir pour diverses affections de l'estomac et du duodénum : 16 fois il s'agissait de lésions non cancéreuses, 12 fois de néoplasmes malins. Dans 3 cas nous avons dû nous contenter d'une laparotomie exploratrice. — Dans 3 cas nous avons fait la pyloroplastie avec 2 insuccès; nous avons abandonné cette opération. — Dans 2 cas de cancer étendu nous avons tenté, in extremis, la pylorectomie en raquette, combinée dans un cas à la gastro-entérostomie; 2 insuccès. — Sur 10 gastro-jéjunostomies, nous comptons 4 insuccès; 2 opérations ont été faites *in extremis*, 2 autres avec un procédé défectueux. — Nous comptons 6 succès sur 7 pylorectomies avec occlusion du duodénum et gastro-jéjunostomie. — Enfin nous signalerons une opération d'estomac en bissac, de rétrécissement de la partie moyenne du viscère étant dû à un vaste ulcère de la petite courbure, avec rétraction cicatricielle et adhérence à la paroi abdominale; le malade a guéri et se porte à merveille.

M. Roux (de Lausanne). — *Chirurgie gastro-intestinale.*

Je suis loin de partager l'enthousiasme de certains chirurgiens pour la gastro-entérostomie, opération qui n'est qu'un pis-aller, qui a une mortalité de 50 0/0 et qui se fait toujours dans des conditions désastreuses. J'ai fait 15 fois la laparotomie exploratrice sans rencontrer une indication formelle d'aller plus loin. Sur mes 14 gastro-entérostomies, il y a 7 morts post-opératoires et 7 guérisons. J'ai employé différents procédés, au point de vue du choix de l'anse intestinale à aboucher dans l'estomac. Dans mon premier cas j'ai pris une anse quelconque, et l'autopsie m'a démontré que la bouche intestinale se trouvait à 40 centimètres de la valvule iléo-cæcale. En prenant la première portion du duodénum, j'ai vu deux fois le reflux des aliments dans cette portion de l'intestin, et cet accident a enlevé un de mes malades. La

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bouche stomacale doit être faite sur la face postérieure de l'organe; c'est le seul procédé qui assure le libre cours des aliments dans le décubitus dorsal; sur 6 gastro-entérostomies antérieures, j'ai 5 morts et une guérison, et sur 8 gastro-entérostomies postérieures, j'ai 2 morts et 6 guérisons.

En ce qui concerne les pylorectomies, j'ai à relater 5 faits avec 3 succès. Les 2 échecs sont dus à l'impossibilité de rapprocher le duodénum de la section stomacale. Je fermai alors le duodénum et rebouchai l'ouverture stomacale dans le jéjunum. Mes trois succès étaient tout à fait inespérés. Dans le premier cas il s'agissait d'un vaste cancer de la petite courbure avec ganglions du voisinage ramollis, et propagation au pancréas. L'opération fut tellement difficile que je fus sur le point de l'abandonner. Je terminai néanmoins péniblement et la malade guérit. — Dans le second cas où il s'agissait d'une grande ulcération cancéreuse de la paroi postérieure avec adhérences au côlon transverse, pour enlever la tumeur je dus sacrifier 30 centimètres de cet intestin. Je fis rapidement l'implantation de la section droite du côlon dans le côlon descendant, et je fermai l'autre bout. Le 7e jour la malade prenait l'alimentation habituelle des malades; depuis lors sa santé est florissante. — Enfin dans le troisième cas la malade se trouvait dans un état de cachexie telle que je dus faire une transfusion salée avant de commencer l'opération. Après l'opération elle reprit rapidement ses forces et guérit complètement.

M. Gangolphe (de Lyon). — *Nouveau signe de l'occlusion intestinale par étranglement.*

Dans un cas d'occlusion intestinale à diagnostic incertain, la laparotomie donna issue à une certaine quantité de liquide séro-sanguin, analogue à celui que l'on trouve dans le sac d'une hernie étranglée ordinaire, et l'exploration ultérieure de la cavité abdominale permit de reconnaître qu'il s'agissait d'un étranglement interne dans l'hiatus de Winslow. Après l'opération je pensai que la présence de ce liquide séro-sanguin était peut-être caractéristique d'un étranglement et permettrait peut-être de distinguer les occlusions dues à un étranglement des occlusions dues à toute autre cause. Des expériences faites sur les chiens me confirmèrent dans cette manière de voir, en me montrant que la constriction d'une anse intestinale par un anneau de caoutchouc avait précisément pour résultat de provoquer l'issue de ce même liquide séro-sanguinolent, aussi bien dans le péritoine que dans la cavité intestinale[1]. La quantité du liquide excrété était proportionnelle à l'étendue de l'anse intestinale emprisonnée et à l'intensité de la constriction.

Ce fait a une certaine valeur pratique. L'occlusion intestinale due à un étranglement, contrairement aux autres formes d'occlusion, n'étant en aucune façon justiciable des moyens médicaux, la constatation d'une

1. V. Contenu de l'anse herniée. Nicaise, *Des lésions de l'intestin dans les h.*, th. inaug., 1866, p. 36.

Figure 2. Original publication in the *Revue de Chirurgie* journal of the article in which César Roux describes his technique.

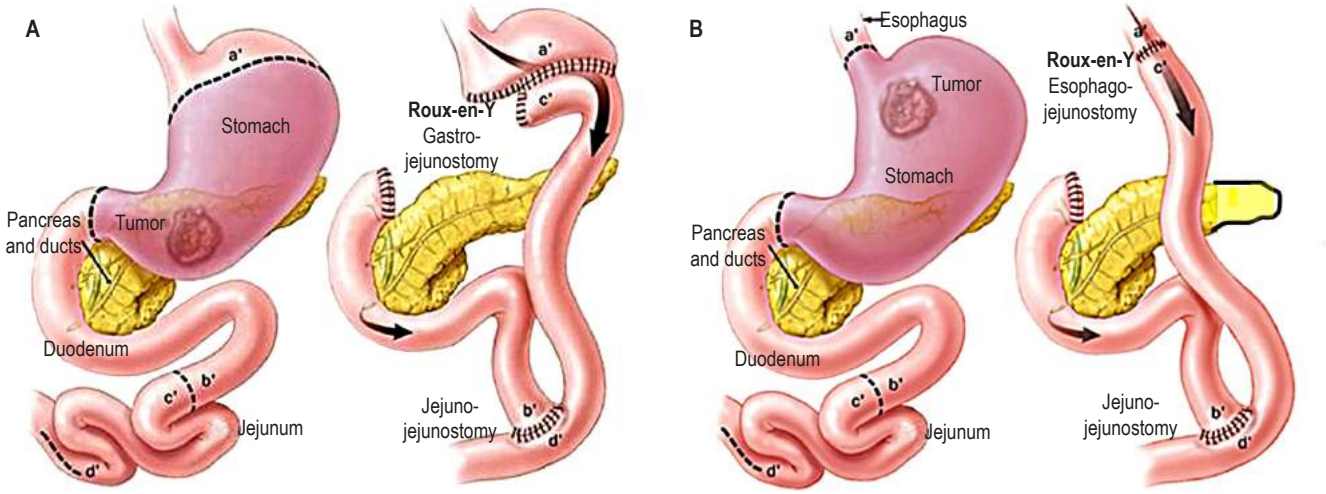

Figure 3. A. Subtotal gastrectomy and Roux-en-Y reconstruction. **B.** Total gastrectomy and Roux-en-Y reconstruction.

of Charles Mayo[3]. Thanks to his tireless work and dedication to teaching and the welfare of his patients, César Roux enjoyed great prestige in Europe and was a prominent member of some of the most critical medical societies of the time, such as the Paris Surgical Society and the St. Petersburg Military Medical Academy; besides, he received several recognitions and awards throughout his career as a surgeon[4].

Personally, different nuances of his character are described: a good sense of humor, but sometimes a strong temperament, an excellent vocation for work, and an outstanding commitment to his patients' care. Harvey Cushing, who visited Lausanne in October 1900, describes him as "…a diamond in the rough who has worked his way into one of the best clinics in Switzerland. It is wonderful to see."

In 1934, after returning to private practice, Roux died suddenly in his office; Switzerland declared national mourning. Roux left a surgical legacy that has endured for more than a century[3].

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