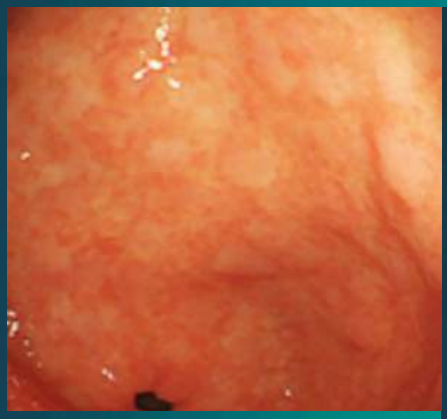
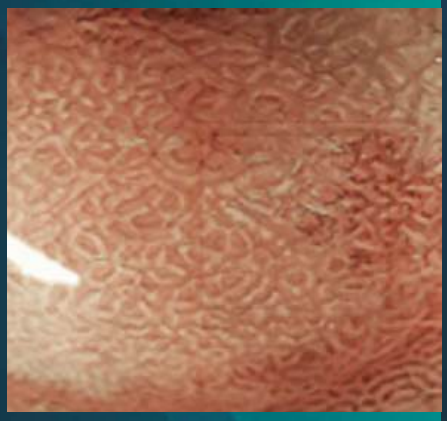
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Article: Strategies to Optimize Early Endoscopic Detection of Gastric Cancer
Courtesy of the authors: Nicolás Zuluaga-Arbeláez, Raúl Pinilla-Morales, Mario Rey-Ferro, Martín Alonso Gómez-Zuleta.

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Editorial

Gastric Cancer: Prevention is Our Duty

David B. Páramo-Hernández.[1]

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Although the global incidence of gastric cancer is showing a downward trend[(1)], in Colombia it remains the third most common malignant neoplasm among men[(2)]. Mortality rates are still high and alarming. In 2023, in Colombia, according to data from the National Administrative Department of Statistics (DANE), stomach cancer was the tenth leading cause of death in the country, with 5309 deaths and an average rate of 10.3 x 100,000 inhabitants[(3)]. At the National Cancer Institute, gastric cancer was the leading cause of death from malignant neoplasms in men (16.5%) and the third leading cause in women (8.6%)[(4)]. Although there are significant regional variations, these figures may reflect the national average. The study presented by Limas et al. reveals a concerning local reality characterized by the late detection of digestive neoplasms and a notably high mortality rate, with an average survival of 5 months and a maximum of 2.3 years[(5)]. This situation requires contribution from both scientific societies and professionals in the field, specifically aimed at primary and secondary prevention activities, which are briefly mentioned below.

Regarding primary prevention, measures aimed at preventing the onset of neoplasia and reducing the incidence of gastric cancer, coupled with the aforementioned general decline in incidence, support the role of lifestyle modifications, physical exercise, nutrition, use of medications, and other environmental factors in the carcinogenesis of gastric cancer. Thus, the following have been proposed: a decrease in the prevalence of *Helicobacter pylori*, improvements in food storage and hygiene, a reduction in smoking, and an increase in the use of antibiotics, all of which have been linked to the changing epidemiology of gastric cancer[(1,6)]. Among the nutritional factors, some seem to increase the risk of developing cancer, such as the consumption of salt, nitrites and nitrates, alcohol, coffee, and meat, while others seem to play a protective role, particularly the intake of fruits, vegetables, and vitamins[(6)].

H. pylori eradication is considered the most effective primary prevention strategy for gastric cancer. Multiple studies have shown that community eradication of *H. pylori* can modestly reduce the incidence of gastric cancer. Systematic reviews and meta-analyses have also shown that eradication therapy significantly reduces the incidence of gastric cancer and related mortality, particularly in high-risk populations[(7)].

Secondary prevention aimed at the early diagnosis of incipient disease (without clinical manifestations) includes actions for early detection, timely referral, and appropriate treatment, all of which are essential for disease control. In some countries with a high incidence of gastric cancer, such as Japan and South Korea, endoscopic screening of the

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general asymptomatic population is a common secondary prevention strategy. This approach aims to detect precancerous lesions or cancers at an early stage, thus improving outcomes. In Colombia, screening is not yet a health policy. However, due to the high regional variation in incidence rates, the recommendation is to monitor patients with precancerous conditions, such as intestinal atrophy and intestinal metaplasia[8]. Additionally, the possibility of non-invasive biomarkers, such as pepsinogen levels, has been explored. These biomarkers could help identify individuals at higher risk of gastric cancer who may benefit from endoscopic surveillance. Emerging technologies for early detection and risk stratification are also recommended to improve prevention strategies[9]. In this regard, the review by Zuluaga et al.[10], published in this issue, highlights the potential for improvement in the timely diagnosis of gastric cancer[10].

Thus, raising awareness of responsibility in all stages of prevention of a neoplasm, which significantly affects patients and whose ominous outcome urgently needs to be modified, is essential.

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Original article

Incidence and Survival of Digestive Tract Cancer Detected by Endoscopy with Histological Confirmation in a High-Risk Region of Colombia

Luis Manuel Limas-Solano,[1] Clara Patricia Barreto,[2*] Juan Carlos Vega.[3]

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Abstract

Introduction: Cancers of the digestive tract are among the leading causes of mortality from non-communicable chronic diseases, both in Colombia and worldwide. These malignancies are often asymptomatic in their early stages, which significantly impacts survival rates and poses a major public health challenge. This study aimed to analyze survival rates following histopathological confirmation of digestive tract neoplasms detected through endoscopy at a regional referral center. **Methods:** A retrospective cross-sectional study was conducted, reviewing biopsy results from endoscopies and colonoscopies performed between 2018 and 2020. Sociodemographic variables were analyzed, and survival rates were assessed using the Kaplan-Meier method and the Log-Rank test. **Results:** A total of 133 cases of gastrointestinal neoplasms were identified: 66.1% in the stomach (n = 88), 23.3% in the colon (n = 31), and 10.6% in the esophagus (n = 14). The median age was 66.7 years (interquartile range [IQR]: 59–79), with a predominance of male patients. Follow-up data showed a median survival of five months from diagnosis to death, with a maximum survival of 2.3 years. **Conclusion:** The majority of patients diagnosed with digestive tract cancer at the regional referral center were male and presented with advanced-stage disease, as reflected in the short survival times observed.

Keywords

Endoscopy, cytopathology, signs and symptoms, gastrointestinal neoplasms, survival analysis.

INTRODUCTION

Cancer is one of the leading causes of mortality in the world due to chronic non-communicable diseases, with approximately 10 million deaths annually. Among these, gastrointestinal cancers occupy the first places in incidence and mortality rates[(1)]. In Colombia, by 2022, gastrointestinal cancers, including liver, gallbladder and pancreatic cancer, were responsible for 33.1% of cancer deaths[(2)], highlighting their clinical, economic and social impact.

In the United States, colorectal cancer deaths have steadily declined since 1980, thanks to dietary changes, screening programs, and better access to treatment[(3)]. In contrast, this type of cancer remains a major cause of mortality in Colombia[(4)]. In 2023, according to data from the National Administrative Department of Statistics (DANE), stomach cancer was the tenth leading cause of death in the country, with 5309 deaths. Meanwhile, esophageal and colorectal cancers accounted for a total of 5540 deaths. In the department of Boyacá, stomach cancer was the fifth leading cause of death, with 156 deaths, followed by esophageal and colorectal cancers, with 152 deaths[(5)]. Esophageal cancer has a high incidence and prevalence worldwide and was responsible for 4.3% of deaths from gastrointestinal neo-

plasms in 2022[1], with dismal survival rates (15% to 25% at 5 years) due to its aggressive nature[6,7]. In Colombia, colon cancer is more concentrated in urban centers such as Bogotá, Quindío and Risaralda[8].

These gastrointestinal neoplasms have a multifactorial origin and are associated with *Helicobacter pylori* infection[9,10], living at altitudes above 2000 meters above sea level[11,12], and behavioral factors such as obesity, smoking, and alcohol consumption[13,14], all of which may influence survival[15]. Boyacá is a mountainous department located in central Colombia, which has been identified in previous studies as a high-risk area for the development of gastrointestinal cancer[16]. This situation, combined with the high consumption of tobacco and alcohol in the region[17], motivated the present analysis of the survival of patients with a histopathological diagnosis at a departmental referral center.

MATERIALS AND METHODS

A retrospective cross-sectional study was conducted in a high complexity center in the department of Boyacá, with the objective of characterizing patients over 18 years of age with positive histopathological findings for neoplasms. Between 2018 and 2020, a total of 5935 endoscopies and 1982 colonoscopies were performed, and biopsy results positive for neoplasia were identified. The patients included in the study presented with gastrointestinal symptoms such as abdominal pain, bleeding, anemia or weight loss and, during the endoscopic procedure, macroscopic lesions of malignant appearance. Additional variables, such as TNM classification or surgical specimen analysis, were not included.

Sociodemographic information was obtained from electronic medical records (Servinte Clinical Suite), and histopathological information was collected from pathology reports. Data were stored in a database in Excel 365 and analyzed with IBM SPSS software[18].

Sociodemographic variables included age, sex, origin, social security system affiliation, date of diagnosis and date of death. Other variables included the degree of differentiation, location of the lesion and presence of *H. pylori* (for cases of stomach cancer), and the history of exposure to cigarettes and alcohol intake. The categorization of gastric lesions followed the classification of Lauren and Jarvi[19,20], grouping them into intestinal or diffuse types. Staging was not considered because it included outpatients who did not receive follow-up at the institution.

For the calculation of survival, the time in days that elapsed between the histological diagnosis and the date of death was recorded, which was obtained from the records of the Administrator of the Healthcare Social Security Resources (ADRES). The distribution of quantitative variables in gastric neoplasms was verified using the Kolmogorov-Smirnov test due to the large sample size, while for esophageal and colorectal neoplasms, the Shapiro-Wilk test was used. The medians and their confidence intervals were estimated using the Mann-Whitney U test. For nominal variables, frequency and position measures were calculated, applying the chi-square test or the Fisher's test to assess statistical significance, with a 95% confidence interval (CI).

Survival analysis was performed using the Kaplan-Meier method and curves were compared using the Log-Rank statistical test. The study followed the principles of the Declaration of Helsinki, was approved by the ethics committee of the Hospital Universitario San Rafael de Tunja (Act 0011-2021) and was considered a risk-free investigation, complying with the standards of good clinical practice[21].

RESULTS

During the study period, 133 malignant neoplasms of the gastrointestinal tract were reported. Of these, 18 patients received surgical management during the same hospitalization. In cases of esophageal cancer, no patient underwent surgical resection with curative intent. A total of 64.2% (n = 9) received palliative care through stent insertion, while the remaining patients were either undergoing additional studies or had such an advanced disease that no palliative care could be provided.

The median age was 66.7 years (interquartile range [IQR]: 59-79), with a range between 24 and 92 years. All age groups were represented; however, the highest incidence was observed in the 60-69 age group (25.5%), followed by the 70-79 age group (24.8%). According to sex, a male predominance was observed, with 73 cases (55.3%) (**Table 1**). It is noteworthy that between the ages of 20 and 39 years there were more cases of malignant neoplasms in women. The youngest patient and the oldest patient had gastric adenocarcinomas.

Table 1. Sociodemographic Characteristics of the Population Under Study

Variable		n	%
Sex	Female	60	45%
	Male	73	55%
Health Insurance System Regime	Subsidized	104	78%
	Contributory	21	16%
	Special	8	6%
Origin	Tunja	55	42%
	Other cities in Boyacá	74	55%
	Other departments	4	3%

Table created by the authors.

In the distribution of neoplasms of the gastrointestinal tract, the highest proportion corresponds to gastric cancer, with 66.2% (n = 88), followed by colorectal carcinoma, with 23.4% (n = 31), and esophageal cancer, with 10% (n = 14) (**Figure 1**).

The most frequent histologic type was adenocarcinoma (n = 114, 85%), with a predominance of the intestinal subtype, which manifested more frequently in patients older than 60 years (**Table 2**).

Upon classification, according to the histological type of neoplasm found, it was determined that adenocarcinoma of the intestinal type was the most frequent, followed by the diffuse type (**Table 3**).

A review of the history according to the location of the neoplasm showed that 12.9% of the patients with colorectal cancer smoked, while 54.2% of the gastric neoplasms had the presence of *H. pylori* (**Table 4**).

On consulting the ADRES data, it was found that, as of April 25, 2023, 87.9% (n = 117) of the patients had died. A survival analysis was conducted on these 117 subjects, who were followed for 4.8 years. Survival was evaluated according to the degree of histopathological differentiation, which showed a statistically significant difference (p = 0.049). Median survival was 22 months from diagnosis to death (95% CI: 16.2-27.8), with a median of 109 days (95% CI: 34.7-183.2) and a maximum survival time of 3.7 years (**Figure 2**).

A total of 87 samples from the esophagogastric junction and stomach were analyzed. In 17.2% of the cases, the presence of *H. pylori* could not be determined due to the lack

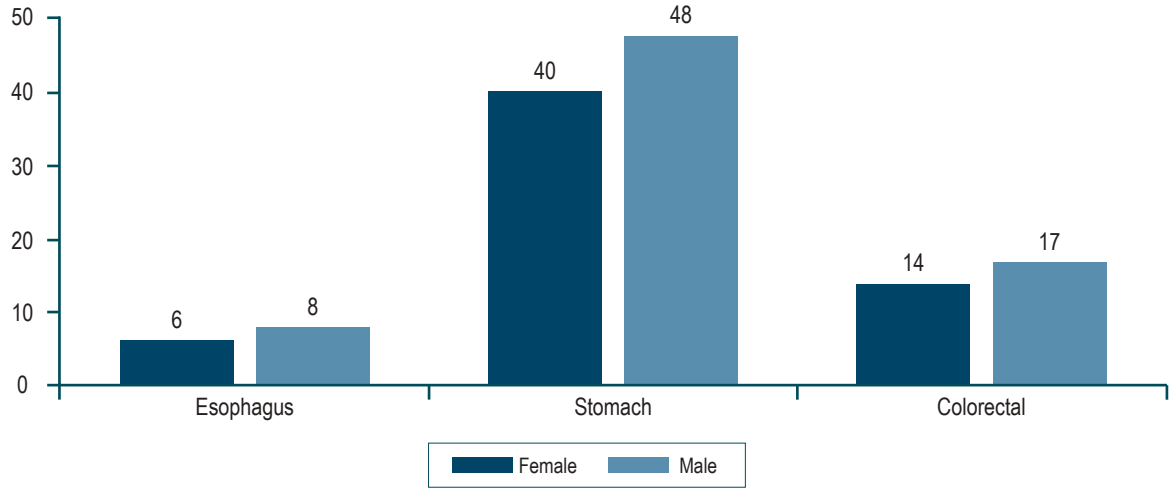


Figure 1. Anatomical Distribution of Gastrointestinal Neoplasms According to Sex. The image is the property of the authors.

Table 2. Distribution of Gastrointestinal Neoplasms According to Age, Sex, Type and Anatomical Localization

Variable n (%)		≤29 years n (%)	30 to 59 years n (%)	≥60 years	*p** n (%)	Total
Sex	Female	3 (75)	11 (37)	46 (46)	0.30	60 (45)
	Male	1 (25)	19 (63)	53 (54)		73 (55)
Neoplasm	Adenocarcinoma	4 (100)	27 (90)	84 (83)	0.93	115 (85)
	Carcinoma	0 (0)	0 (0)	9 (9)		9 (7)
	Lymphoma	0 (0)	2 (6)	4 (5)		6 (5)
	Mesenchymal	0 (0)	1 (4)	3 (3)		4 (3)
Localization	Esophagus	0 (0)	3 (10)	11 (11)	0.63	14 (10)
	Stomach	4 (100)	21 (70)	63 (63)		88 (66)
	Colorectal	0 (0)	6 (20)	25 (26)		31 (24)

Table created by the authors.

Table 3. Histological Classification of Neoplasms According to the World Health Organization[22]

Type of neoplasm	Frequency	Percentage
Adenocarcinoma	2	1.5%
Tubular-pattern adenocarcinoma	7	5.3%
Diffuse-type adenocarcinoma	14	10.5%
Intestinal-type adenocarcinoma	84	63.2%
Mucinous adenocarcinoma	1	0.8%
Adenocarcinoma in situ	3	2.3%
Metastatic adenocarcinoma	1	0.8%
Mixed adenocarcinoma (intestinal pattern)	2	1.5%
Mixed adenocarcinoma (tubular and diffuse pattern)	1	0.8%
Squamous cell carcinoma	7	5.3%
Neuroendocrine carcinoma	1	0.8%
Carcinoma or lymphoma	1	0.8%
Lymphoma	1	0.8%
Diffuse large B-cell lymphoma	1	0.8%
B-cell lymphoma	3	2.3%
Mantle B-cell lymphoma	1	0.8%
MALT-type B-cell lymphoma	2	1.5%
Mesenchymal neoplasm (GIST or mucinous origin)	1	0.8%
Total	133	100

GIST: gastrointestinal stromal tumor; MALT: mucosa-associated lymphoid tissue. Adapted from: Bosman F, et al. 4th edition. World Health Organization; 2010.

Table 4. Distribution of Neoplasms by Location in Relation to the Presence of *H. pylori*, Alcohol and Tobacco Consumption

Location n (%)		Esophagus n (%)	Stomach n (%)	Colorectal
H. pylori	Absent	13 (92.9)	38 (45.8)	0
	Present	1 (7.1)	45 (54.2)	0
Tobacco use	Yes	3 (21.5)	10 (12)	4 (12.9)
	No	11 (78.5)	73 (88)	27 (87.1)
Alcohol consumption	Yes	1 (7.1)	17 (20)	6 (19.3)
	No	13 (92.9)	66 (80)	25 (80.6)

Table created by the authors.

of a report and the transfer of the slide to the family; in contrast, 32.1% of the samples tested positive for this microorganism. A survival curve was generated, in which the presence of *H. pylori* did not show statistical significance on survival ($p = 0.45$) (**Figure 2B**).

Based on the findings presented in the survival curve according to the degree of differentiation, and given the clinical significance, survival by type of neoplasm and site of appearance was also verified (**Figures 2C** and **D**). These were not significant, since they obtained a *p*-value of 0.57 and 0.298, respectively. When evaluating the median survival according to the variables studied (**Table 5**), it was observed that people who use tobacco and present poorly differentiated neoplasms have a lower survival, while people under 60 years of age show a higher survival.

DISCUSSION

The present study is relevant because it provides unpublished information on the incidence and survival after histopathological diagnosis of digestive tract cancers in samples obtained endoscopically in a referral center in the department of Boyacá. In Colombia, a continuous increase in the incidence and prevalence of gastrointestinal tract neoplasms is projected, with the exception of gastric cancer[16]. The median age at diagnosis is slightly higher than that reported in Latin America[23-26]. In addition, colorectal, gastric and esophageal cancers are more frequent in men[27], which is consistent with data from regional and international studies[2,28-30].

When comparing the survival presented in other parts of the world and that reported in Colombia[26,31,32], a lower survival was found in our population, which could be attributed to sociodemographic factors or late diagnosis. Although the type of affiliation to the social security system does not seem to be a determining factor, it is possible that this low survival rate is influenced by the fact that more than 50% of the population studied belongs to the subsidized regime and resides in the area of influence of the institution, in the department of Boyacá[33].

Given the high prevalence of *H. pylori* infection reported in Colombia (63.4%)[34], its relationship with survival was analyzed, despite the fact that more than 10% of the data on gastric cancer were not available. Thus, it was observed that, together with the degree of differentiation, the presence of *H. pylori* is associated with a decrease in survival.

The main strength of the study is that it was conducted in a referral center that serves people from several surrounding areas, which allowed histological confirmation of the diagnoses. However, the size of the sample, the absence of tumor staging, the assessment by oncology in the absence of this institutional service and the lack of analysis of

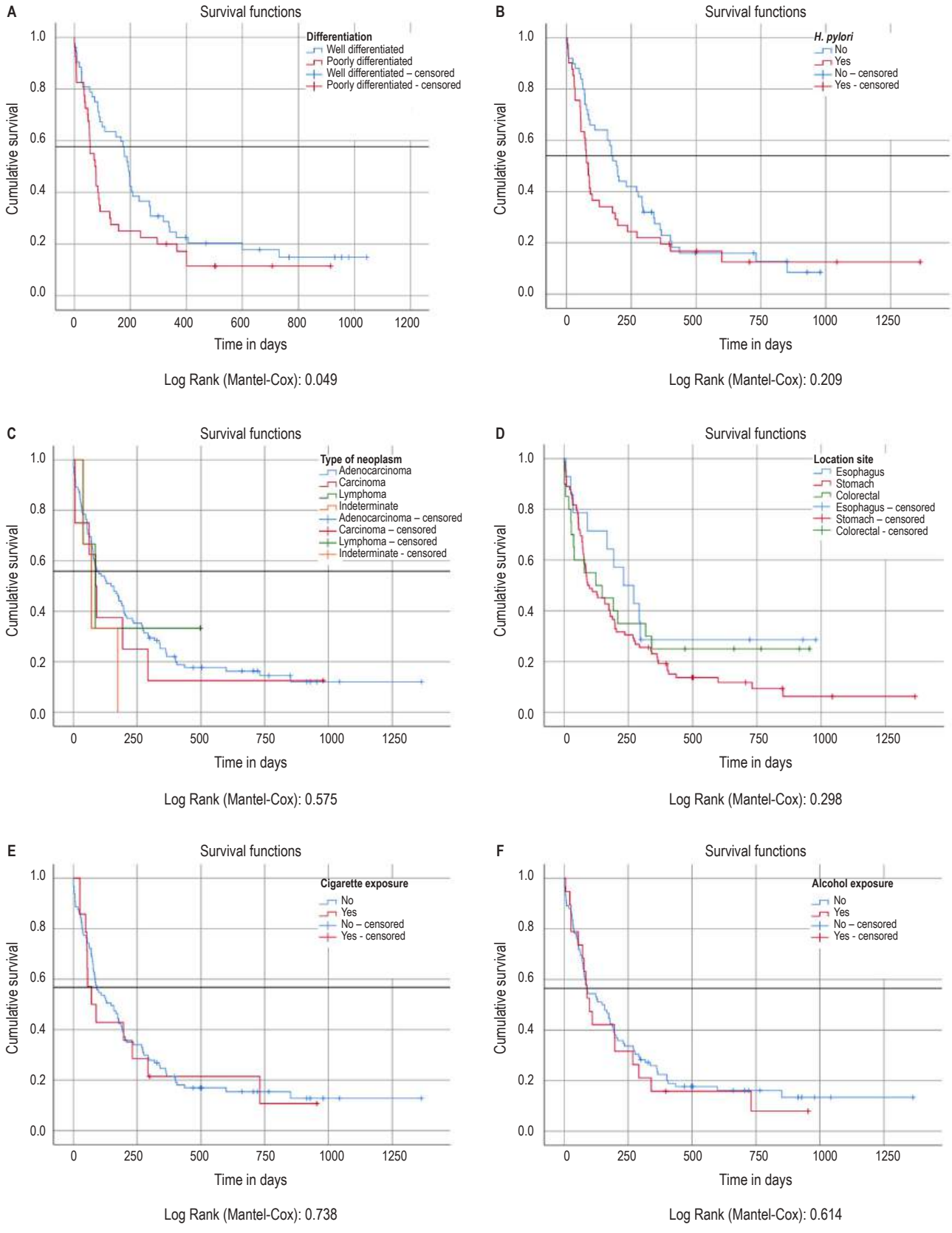


Figure 2. Survival According to Different Variables of Interest. Images property of the authors.

Table 5. Median survival by type of variable

Variable		Estimate (days)	95% confidence interval	
			Lower limit	Upper limit
Age	Under 60 years	236	107.3	364.6
	Over 60 years	92	32.4	151.5
Sex	Female	130	52.8	207.1
	Male	92	0.0	195.2
Differentiation	Well differentiated	191	170.8	211.1
	Poorly differentiated	74	46.7	101.2
Neoplasm	Adenocarcinoma	148	76.2	219.7
	Carcinoma	88	47.8	128.2
	Lymphoma	86	10.7	161.2
	Poorly differentiated	71	16.5	125.4
Localization	Esophagus	231	87.9	374
	Stomach	92	32.3	151.7
	Colorectal	123	0.0	274.2
H. pylori	Absent	193	157.3	228.6
	Present	84	66.4	101.5
Alcohol consumption	Absent	148	69.9	226
	Present	99	63.4	134.5
Tobacco use	Absent	148	76.0	219.9
	Present	71	10.4	131.5
Global		127	57.9	196

Table created by the authors.

additional comorbidities, especially due to the limitations imposed by the Covid-19 pandemic, represent important limitations[35,36].

In conclusion, it highlights the importance of implementing screening to detect these neoplasms in early stages in high-risk patients, given that the cancers diagnosed in this study were in advanced stages, resulting in short survival. It is essential to increase awareness of risk factors and promote healthy lifestyles (no alcohol or smoking). Further studies involving multiple institutions and interdepartmental collaborations are also required to identify factors associated with the observed poor survival, including the role of *H. pylori* in this population.

CONCLUSION

The population treated with endoscopies at a departmental referral center for digestive tract neoplasms is primarily composed of men, who were diagnosed at advanced stages, which was reflected in limited survival. This situation could be positively impacted by the implementation of screening programs, community education on risk

factors, and improvements in the quality of endoscopy at primary care levels.

Authors' contribution

All authors contributed to the planning, data acquisition, analysis, interpretation of the data, critical review of the intellectual content, and final approval.

Conflicts of interest

None.

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Original article

Delphi Consensus on Quality Indicators for Pediatric Digestive Endoscopy by the Latin American Society of Pediatric Gastroenterology, Hepatology, and Nutrition

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Abstract

Introduction: There is a global concern regarding the need to improve performance in endoscopic procedures, and Latin America is no exception. A high-quality endoscopic study requires appropriate indications, accurate diagnosis and therapy, and minimal risks. The PEnQuIN consensus, developed by experts from North America and Europe, established standard quality indicators for pediatric endoscopy across three phases: pre-procedure, intra-procedure, and post-procedure. This study aims to develop a consensus among experts on quality indicators for pediatric digestive endoscopy in Latin America. **Methodology:** Based on the available scientific evidence, statements were defined and subjected to real-time Delphi consensus rounds. The process continued until an agreement of at least 80% was reached among participants, with a Cronbach's alpha exceeding 0.8. The panel comprised 24 pediatric gastroenterologists selected using a modified questionnaire similar to that employed in the California cohort studies. **Results:** Of the 44 initial statements, consensus was reached on 36, which were established as quality indicators for pediatric digestive endoscopy. Eight indicators achieved unanimous agreement. The Cronbach's alpha for this Delphi questionnaire was 0.85. The indicators were categorized into 13 pre-procedure measures, 20 intra-procedure measures, and 3 post-procedure measures. **Conclusions:** The quality indicators developed through the Delphi Consensus are applicable to any pediatric endoscopy unit. They are easy to implement and align with established healthcare quality and endoscopy standards. These indicators can be measured and, when applied, help reduce disparities in human and material resources among countries.

Keywords

Healthcare quality management, endoscopy, consensus, quality indicators, health care.

INTRODUCTION

Quality in gastrointestinal endoscopy requires the use of indicators through which performance can be evaluated, leading to improvements, reduced risks, and fewer complications[1]. Globally, there is growing concern about delivering high-quality medical care, with increasing interest in improving performance in endoscopic procedures. This performance is evaluated by healthcare quality institutions[1,2]. A high-quality endoscopic procedure aims to ensure that the patient undergoes a properly indicated endoscopy, with an accurate diagnosis, performed by an experienced professional using appropriate equipment, technique, and preparation. It also requires a comprehensive endoscopy report that is suitable for both the patient and caregivers[1–3].

In the evaluation of digestive endoscopy, various indicators are considered, some related to the period before the procedure, and others to the intra- or post-procedural stages. These indicators are usually assessed through a checklist that includes characteristics describing whether the procedure was performed and the condition of the mucosa observed, which are incorporated by institutions as part of standardized checklists[4]. Guidelines on quality endoscopy in adult patients emphasize specific quality indicators in colonoscopy, such as a minimum cecal intubation rate of 90%, withdrawal time of at least nine minutes to detect signs of colorectal cancer, and an adenoma detection rate of at least 20%[5].

Another important aspect highlighted in adult endoscopy reports is the quality of bowel preparation (Boston scale), as well as information on reaching the cecum, visualization of the ileocecal valve, photographic documentation, recording of the number, location, and characteristics of polyps detected, and the management provided. These elements help determine recommended surveillance intervals in cases of colon cancer and inflammatory bowel disease [6,7]. Unlike in adults, these indicators are not as well established in children. However, in cases of inflammatory bowel disease, reports do include the performance of colonic mucosal biopsies, with the recommended number and distribution for this patient group, or biopsies from targeted sites using specialized imaging techniques. Colonic mucosal biopsies are also performed in patients with chronic diarrhea, and all colonoscopy-related complications are recorded [7,8].

In relation to upper gastrointestinal endoscopy, the presence of quality metrics has not experienced as much of an upturn as in colonoscopy. For example, a minimum of five gastric biopsies is recommended, along with retroversion to examine the gastric fundus; however, there is no standardized preparation scale for upper endoscopy. Most publications on adults regarding quality indicators in gastroscopy are disease-oriented, focusing on outcomes such as the detection of Barrett's esophagus, metaplasia follow-up, identification of *Helicobacter pylori*, gastric cancer, and the number of biopsies taken for celiac disease[9]. In pediatrics, quality indicators are more clearly defined for certain conditions, such as infectious gastritis or duodenitis caused by bacteria or parasites, as well as for gluten-related or allergic-related disorders.

This scenario has led to the use of adult endoscopic quality indicators as a starting point for reviewing stan-

dards in the pediatric population. However, without formal validation, in 2017 the Pediatric Endoscopy Quality Improvement Network (PEnQuIN) outlined international standards for gastrointestinal procedures in children. These indicators can be used to assess quality and are grouped into three phases: preprocedural, intraprocedural, and postprocedural[10].

There are public or private institutions in Latin America with inequalities that may condition differences in the conditions for performing endoscopic studies and limited available resources with basic technology that may influence the quality of endoscopic studies. According to statistics from the Economic Commission for Latin America and the Caribbean (ECLAC), poverty in Latin America reaches nearly 60% in parts of northern South America and Central America. In contrast, the southern region reports much lower poverty rates, around 15%, as seen in southern states of Brazil, Uruguay, and Chile[11]. A study conducted by Pierre et al. in 2017 identified 256 pediatric endoscopy centers (PECs) across 13 countries, 42% of which were public. The highest availability (69%) was found in Argentina, Brazil, and Venezuela, followed by 23% in Chile, Colombia, Mexico, and Peru, and the remainder distributed across Bolivia, Costa Rica, Ecuador, Uruguay, El Salvador, and Nicaragua. Regarding training centers in pediatric gastrointestinal endoscopy (CEEDP), a total of 39 centers were reported across the region, with 67% located in Argentina and Brazil, each having 13 centers. In contrast, Venezuela, Mexico, and Peru each reported three centers. In most cases, training in pediatric endoscopy is carried out within the specialty training programs[12].

The Endoscopy Working Group of the Latin American Society for Pediatric Gastroenterology, Hepatology and Nutrition (LASPGHAN), in view of the disparities in the number of centers, trained personnel, and available resources, has convened specialists in this field—those with expertise and training in pediatric gastrointestinal endoscopic procedures—to review quality standards in endoscopy. Drawing on their endoscopic, clinical, and academic experience, the group aims to establish consensus-based parameters that can bridge the differences among countries and be implemented during endoscopic procedures. The objective of this study was to develop an expert consensus on quality indicators for pediatric digestive endoscopy in Latin America.

MATERIALS AND METHODS

The Delphi process was carried out through an ad hoc platform, with face-to-face online discussions[13]. The 24 Delphi panelists were selected based on their expertise in the field, using a modified version of the criteria employed by the California courts in the United States to determine the qualifications of a legal medical expert witness[14]. All participants were able to comment on and rate each statement using a five-point Likert scale (1: strongly agree, 2: agree, 3: neutral, 4: disagree, 5: strongly disagree). Consensus was defined *a priori* as 80% agreement or disagreement among panelists on the Likert scale. In addition, according to established Delphi processes, text boxes appeared after panelists entered their responses to each statement, so that they could provide comments and suggest modifications, if desired. These were reviewed and used to modify statements in subsequent survey rounds. The study facilitator (CMT) was not allowed to vote or comment on the statements. Ethical approval was not required since the study did not use patient data or biological material.

Some of the authors independently conducted a systematic review of current literature. This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[15]. The authors reviewed the literature currently published in the PubMed, Scopus, and Web of Science databases, searching for full-text articles in English and Spanish published between 2010 and 2023. The search included English and Spanish keywords such as: "colonoscopy quality, quality of digestive endoscopy in children, endoscopic preprocedure, endoscopic procedure, endoscopic postprocedure, endoscopy consensus, digestive endoscopy consensus, consenso (consensus), indicadores de calidad de la endoscopia (quality indicators of endoscopy), colonoscopia (colonoscopy), calidad de la endoscopia digestiva en niños y adultos (quality of digestive endoscopy in children and adults), endoscopia de preprocedimiento (preprocedure endoscopy), intraprocedimiento (intraprocedure), y postprocedimiento (postprocedure)". Additional important studies cited in the reference list of the selected articles were evaluated. The reviewers independently selected the articles. Based on all the documentation obtained, 44 statements or questions were prepared, divided into three categories: preprocedure, intraprocedure and postprocedure.

The Cronbach's alpha coefficient was used to determine the internal consistency of the assessment tool after each round[16]. The Cronbach's alpha value demonstrates how closely related a set of test items is as a group, and it ranges from 0 to 1, with 1 corresponding to 100% consistency. The final round of consensus was defined by achieving a Cronbach's alpha >0.80. Categorical variables were expressed as proportions.

RESULTS

A total of 24 panelists from 12 Latin American countries participated. Of the 44 initial statements drafted as quality indicators in pediatric digestive endoscopy, consensus was

reached on 36 statements. Unanimous agreement was reached on 8 of these indicators, representing 22.22%, and on the remaining 28 statements, 77.77%; agreement reached a level of 80% or higher after the fourth round.

In the adjustment process, considering the panelists' responses, consensus was not reached after the first round on 8 premises, which were reviewed, and two were corrected and merged. These premises addressed pre-existing conditions in patients, and only those findings potentially related to the endoscopic procedure would be mentioned in the endoscopy report. Other medical or surgical comorbidities would be described in the medical record. This statement reached an acceptance level of over 80% in the second round.

Four premises oriented to the preparation of the patient before the endoscopic study (previous diet, recommendations for preparation, medication and preparation time) were grouped in a statement as a protocol prior to the study, and this would be written in the medical record given the importance for the endoscopic procedure. The remaining two statements were removed due to their low acceptance: one suggested documenting in the medical record whether auxiliary support equipment is available, and the other referred to including the duration of the procedure in the report, with 47% and 62% acceptance, respectively.

The Cronbach's alpha achieved in this Delphi questionnaire was 0.85. Thirteen indicators were classified for the pre-procedure, numbered 1 to 13, and are aimed at documenting the identification of the patient, the endoscopist, the patient's complete clinical information regarding personal history, gastrointestinal pathologies, and comorbidities, as well as including informed consent and identification of endoscopic and anesthetic risks (**Figure 1**).

The 20 indicators included in the intraprocedural phase (from 14 to 33) are aimed at complying with the quality standards of the procedure, such as the description of the areas examined, the visualization of important areas like the gastric fundus (retroversion) and gastric antrum, biopsy (location and quantity), application of therapy, iconography (photodocumentation or video), classifications used, patient preparation for colonoscopy, and mentioning whether difficulties were encountered during the endoscopic study, as well as providing information to the patient and their family. The indicators agreed upon unanimously were located within the intraprocedural phase.

In the postprocedural phase, three key indicators for patient evaluation and follow-up are highlighted. **Table 1** shows the selected quality indicators.

DISCUSSION

This work is the first consensus in Latin America on quality indicators in pediatric endoscopy in which all reported

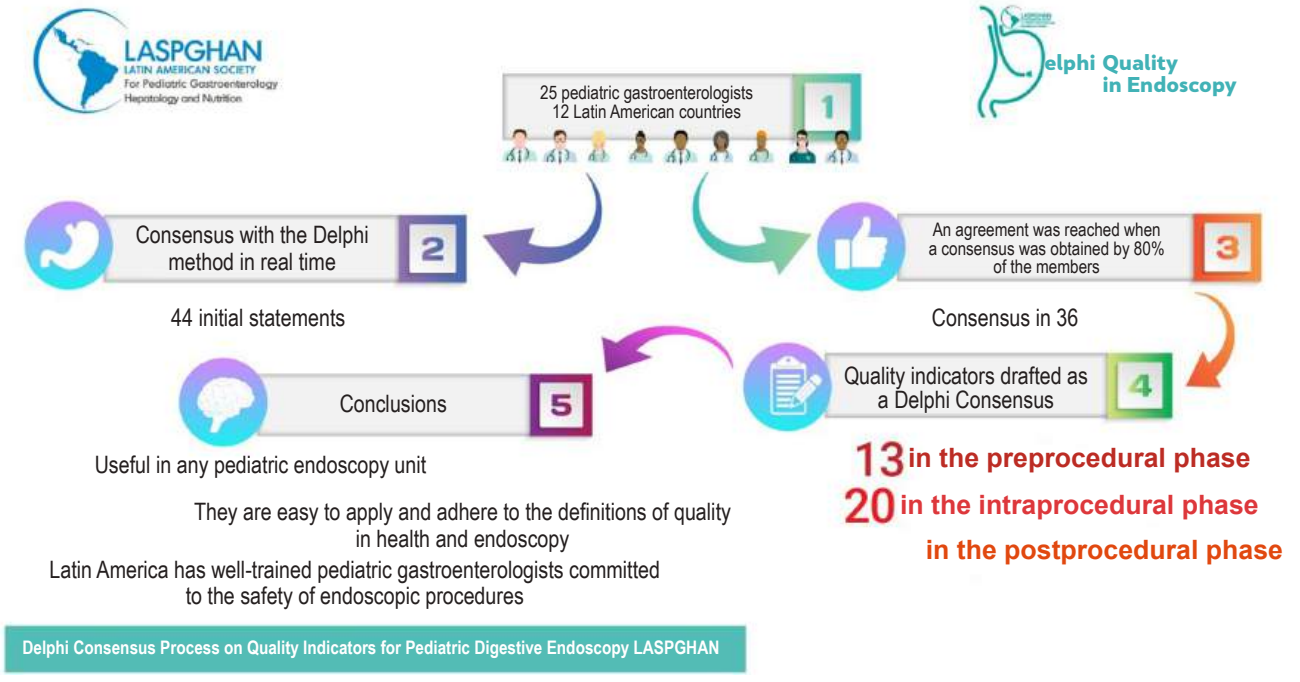


Figure 1. Delphi Consensus Process on Pediatric Digestive Endoscopy Quality Indicators of the Latin American Society of Pediatric Gastroenterology, Hepatology, and Nutrition (LASPGHAN) The image is the property of the authors.

Table 1. Agreement on Quality Indicators for Digestive Endoscopy Reached Through Consensus

Indicators	Agreement*
Preprocedural	
1. Include the patient's name in the report	95
2. Include patient identification data in the report	82
3. Include the patient's biological sex in the report	86
4. Describe the name of the person responsible for the procedure and whether he/she is a pediatric gastroenterologist, intern/resident/fellow in pediatric gastroenterology	91
5. Attach to the medical record the signed informed consent and assent document (according to age) prior to the procedure	90
6. Mention in the report any previous pathologies or surgical conditions that may be related to the endoscopic findings during the procedure	83
7. Register in the medical record the ASA anesthetic risk scale determined prior to the endoscopic procedure	85
8. Describe in the report the indication for the endoscopic procedure	95
9. Describe in the medical record the protocol and whether the patient showed tolerance to the indicated colonic preparation	82
10. Describe in the medical record the time in hours of fasting prior to the performance of upper and lower endoscopy	86
11. Mention in the medical record if medication was prescribed prior to the endoscopic procedure	95
12. Describe in the report the technical specifications of the type or characteristics of the equipment used	90
13. Describe in the report the type of anesthesia or sedation used	91
Intraprocedural	
14. Describe in the report the scale used in the evaluation of the quality of colonic preparation	96
15. Describe in the report each area examined during the procedure	100
16. Indicate in the report whether gastric retroversion was achieved	100
17. Describe in the report if the second portion of the duodenum is reached	100
18. Describe in the report details of the biopsy collection (anatomical site of collection, type of collection)	95
19. Describe the endoscopic diagnostic impression in the report	100
20. Describe in the report if there is control of digestive bleeding	95
21. Describe in the report the result of the therapy used	95
22. Mention in the report the classifications used according to the endoscopic findings	80
23. In the case of an ulcer, describe in the report the exact biopsy site (central or peripheral)	100
24. Describe in the report if a *Helicobacter pylori* test was performed	86
25. Describe in the report the collection of four biopsies from the second portion of the duodenum and at least one from the bulb when investigating celiac disease	100
26. Include segmental iconographic documentation (photographic or video) in the report	81
27. Describe the ileal intubation validation by photographic documentation in the report	95
28. Describe in the report the dosage and route of administration of drugs used by endoscopy.	86
29. Describe in the report if there was interruption or premature termination of the procedure due to a problem related to sedation/anesthesia	100
30. Describe in the report if there was an interruption or premature termination of the procedure due to an endoscopy-related problem	100
31. Describe in the report the complications before and during endoscopy	96
32. Document in the medical record that verbal or written information was provided regarding endoscopic findings, biopsy review scheduling, and follow-up	90
33. Describe in the report the findings of the examination on the day the colonoscopy or esophagogastroduodenoscopy was performed	96
Postprocedural	
34. Describe in the report the need for follow-up with the patient or their caregivers to review pathology reports	90
35. Describe in the medical record whether warning signs and post-endoscopy care instructions were explained or provided in writing	80
36. Describe in the medical record whether post-endoscopy complications were documented	90

*Blue indicates unanimity (100% agreement); yellow indicates more than 80% agreement. Table created by the authors.

aspects were considered and the selected indicators were adjusted to the definitions of quality in health and endoscopy. They were subdivided into three phases: 13 preprocedural phase indicators, 20 intraprocedural phase indicators, and 3 postprocedural phase indicators. This categorization was based on the importance of implementing actions that can influence the quality of the procedure not only during its performance, but also in the preparation and follow-up stages.

The World Health Organization (WHO) defines quality of care as the degree to which health services for individuals and populations increase the likelihood of desired health outcomes and are consistent with current professional knowledge[17]. When considering this definition in relation to endoscopy quality, it encompasses the healthcare system, facilities, personnel, training, technical skills, clinical quality, and the experience of both the patient and the caregiver. In this regard, the PenQuIN consensus defines a quality indicator as a measure of the process, performance, or outcome of pediatric endoscopy services used to determine the quality of endoscopy[10].

In general, quality indicators have been divided into three categories: structural, process and outcome[18]. Structural measurement refers to the physical and functional infrastructure of the endoscopy room, disinfection processes, monitoring of procedure compliance, and measurement of prophylactic medication administration rates or adverse events, among others[10,19,20]. This consensus did not include the evaluation of hospital facilities or available resources due to differences in income, technological resources and quantity between public or private institutions, which would have made agreement difficult and could widen the gap between Latin American countries, nor did it include guidelines or position statements on safety indicators and accreditation for endoscopy[10,21].

The indicators drafted in this consensus were framed within the process measurement and evaluate the performance of endoscopic exploration. Some differences can be observed in the indicators written before, during and after the procedure with respect to reports in the literature[10,19,20]. However, these do not affect their application and can be implemented without inconveniences in all centers. This allows the individual or group performance of endoscopists, as well as the execution of a safe and quality endoscopic procedure. At the local level, these indicators can be implemented with the aim of standardizing high-quality endoscopy across all phases of the process, and they can also be applied in endoscopy programs regardless of the center.

In the preprocedural phase, 46.15% of the indicators reached the minimum consensus required, being between 80% and 86%. The main difficulty was the repetition in the report of data already recorded in the medical record, such as personal data, sex, American Society of Anesthesiologists (ASA) anesthesia score and history of surgical pathologies. In relation to the inclusion of informed consent as an indicator, this was considered a fundamental parameter of quality in endoscopy, in accordance with the recommendations of the different literatures[1-3,10,10,19,22]. In addition, it not only provides information to the patient or his caregiver about the procedure but also brings benefits to the doctor-patient relationship, protecting the patient and the endoscopist from future legal aspects[23,24]. Additionally, it ensures that the family has an adequate understanding of what will be performed, risks, benefits, diagnostic or therapeutic alternatives and complications, as well as when bowel preparation is indicated and the timeliness of the procedure.

Another important indicator voted during the preprocedural phase was the ASA score, which classifies health status and predicts operative risk. This score, along with the administration of medications during patient preparation for the endoscopic study, is considered essential. Different societies and authors recommend the use of ASA as a parameter with evidence; its inclusion in surgical or endoscopic safety checklists is suggested because it can prevent errors and, consequently, have a positive impact on patient morbidity and mortality[10,19,25]. Several studies emphasize that, in terms of safety, younger and smaller patients with higher ASA scores are at greater risk of experiencing complications during gastrointestinal procedures[26,27]. For this reason, the American Society for Gastrointestinal Endoscopy (ASGE) and the American Academy of Pediatrics (AAP) recommend adapting sedation plans according to the ASA score[28-30], as adopted in this consensus.

During the intraprocedural phase, unanimous agreement was reached on indicators related to the appropriate indication for endoscopy, which must be documented and closely linked to the endoscopic procedure itself, the areas examined, biopsy sampling, and reporting of adverse events such as interruption of the procedure. These elements are crucial and determine the effectiveness of the examination. These indicators are in accordance with what has been established in other consensuses, such as PenQuIN, which mentions among its standards and indicators that pediatric endoscopic procedures should be performed in their entirety, the review of all areas is relevant, the acquisition of adequate biopsies and performance of interventions are convenient, and all are related to the indication for endoscopy[10].

It has been mentioned that the indications for digestive endoscopy in adults and the endoscopic quality indicators are clear and serve as a reference, are widely available and evaluate the effectiveness or exploration, mostly directed to cancer surveillance and in colonoscopy to the detection of adenoma[18,19]. However, they are not applicable to the pediatric population due to significant differences in indications, possible diagnoses, distribution of biopsies, among others.

Therefore, indicators related to pediatric pathology, such as bleeding, detection of *Helicobacter pylori*, ulcers, celiac disease, and the validation of ileal intubation as an important metric in inflammatory bowel disease, were added to the intraprocedural phase, in alignment with the indications reported in the literature[31]. Similarly, biopsies obtained during pediatric endoscopic procedures are primarily aimed at assessing congenital disorders, autoimmune conditions, allergic reactions, and other inflammatory processes, in contrast to adult populations, where biopsies are more commonly performed for cancer detection[18,19].

The guidelines for young children, school-aged children, and adolescents developed by the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and the European Society of Gastrointestinal Endoscopy (ESGE) include recommendations for both diagnostic and therapeutic esophagogastroduodenoscopy and ileocolonoscopy. These guidelines represent a consensus on best practices based on the evidence available at the time of writing. However, the authors noted that they may not be applicable in all cases and should be interpreted in the context of specific clinical situations and resource availability[31]. This observation is relevant and has been taken into account in this consensus, in which the selected indicators can be adapted to any basic clinical setting regardless of access to advanced technologies.

The PEnQuIN consensus defines the intraprocedural period as extending from the administration of sedation or insertion of the endoscope to the withdrawal of the instrument. This period includes all technical aspects of the procedure, including completion of the examination and therapeutic maneuvers[10]. This consensus also pointed out the inclusion in the endoscopy report of bleeding control and therapeutic maneuvers, as well as the classifications used as quality indicators similar to those defined in PEnQuIN.

Photo-documentation was another primary indicator considered in this consensus because of its recent appearance as proof of the endoscopic procedure, together with the use of video-documentation. Photodocumentation has been established as a quality indicator since 2008. In 2016, the European Society of Gastrointestinal Endoscopy (ESGE) began defining specific anatomical landmarks to be photographed, ranging from 10 to 21 images. The goals were to highlight key anatomical areas, document the extent of the examination, and capture mucosal characteristics, including cleanliness[32]. The PEnQuIN consensus specifies the importance of demonstrating with photographs or videos all the abnormal findings visualized[10]. Accurate and appropriate image documentation is an essential part of gastrointestinal endoscopy reports. It should be routinely performed in both upper and lower gastrointestinal endoscopies, and information systems must incorporate this relevant data[32].

It is known that the quality indicators for colonoscopy were the first to be described. These encompass various aspects, such as the total procedure time (integrity/extent of the examination), cecal and ileal intubation rates, quality of bowel preparation, and whether the colonoscopy was complete[10,19,30,33-37]. Only the quality of colonic preparation and validation of ileal intubation were included in the intraprocedural phase, as these are two parameters directly associated with the quality of the endoscopic study. This decision is supported by the report of the Endoscopy Committee of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN), which considers the quality of bowel preparation and ileal intubation rate as the most important indicators among multiple metrics described[38]. A retrospective review of all colonoscopies performed from November 2011 to October 2015 at a tertiary pediatric center was added. Demographic data and characteristics such as the presence of training personnel were collected, and the reported quality data included procedure indication, quality of bowel preparation, extent of colonoscopy, and confirmation of location, with validation of ileal intubation through photography or histology[39].

An outstanding aspect in pediatrics is the validation of colon preparation scales, which are standardized and validated in adults, such as Ottawa, Chicago, Aronchick, and Boston[38]. A Latin American study used the Boston Bowel Preparation Scale in children in a prospective study and found that the overall cecal intubation rate, when associated with adequate bowel cleansing, increased from 65% to 91.30%, which constitutes a key factor in the quality of pediatric colonoscopy[40]. Although other aspects such as the ileal and cecal intubation rates and procedure time reflect the quality of the endoscopy, they also involve additional considerations such as the endoscopist's expertise and the learning curve. It is known that the average duration of colonoscopy can be influenced by resident participation, ileal and cecal intubation failure due to severe disease, technical difficulties, and inadequate bowel preparation[33,41]. It is also noted that the ileal intubation rate depends on the underlying pathology[30]. Therefore, these parameters should preferably be included in broader and more specific colonoscopy evaluation consensus guidelines.

The postprocedural indicators were framed around informing the patient or family about the need for follow-up, recognition and documentation of adverse events, assessment of patient satisfaction, and communication of histopathology results. They also included preventive indicators regarding the need to inform patients about potential complications and warning signs. These parameters reached an agreement level of 80%, similar to what was observed in the preprocedural parameters, particularly in one indicator that refers to documenting in the medical

record that instructions and warning signs were provided to the patient. In practice, this information is usually included in the discharge instructions and explained verbally. However, it is argued that it must also be recorded in the medical record, as it is a medico-legal document.

The postprocedural period begins at the moment the endoscope is withdrawn from the patient for subsequent follow-up[36,42]. High-quality endoscopic care is not only based on technical competence, but also encompasses elements related to the overall patient experience[1,10]. Postprocedural indicators, as a general metric of care quality, are important in assessing patient and caregiver satisfaction with the procedure. The PEnQuIN consensus[10] emphasizes the evaluation of the experience, whether through standardized telephone calls, email, or paper-based surveys. It is up to each Latin American institution to adopt the system that best fits its context.

Finally, another point of discussion focused on which quality indicators should be included in the medical record and which in the endoscopy report. It was agreed that nine indicators should be documented in the medical record, as it is a fundamental tool for comprehensive medical care, containing information on the patient's health status, preserving data over time, and providing details on risks, medications, and comorbidities. The remaining 27 quality indicators were included in the endoscopy report. Currently, several studies consider comprehensive endoscopy procedure reports to be a written communication tool for physicians, patients, or family members. These reports also serve as medico-legal documents of the endoscopic record and reflect adherence to quality standards and indicators with favorable outcomes[22,42-45].

Latin America has well-trained pediatric gastroenterologists who are committed to the safety of endoscopic procedures, and the development of a consensus was of great importance for advancing pediatric digestive endoscopy, as well as for optimizing diagnosis and therapy. The document outlining quality parameters for endoscopy is easy to implement and includes essential metrics that ensure safe digestive endoscopy in children, aligned with proper technique and in accordance with international standards. It can be applied in any Latin American country, regardless of disparities in healthcare, available resources, or whether the hospital is public or private, serving as a means to standardize the endoscopic procedure across its three phases: preprocedural, intraprocedural, and postprocedural. It is concluded that the quality indicators drafted as a Delphi Consensus can be used in any pediatric endoscopy unit, are easy to apply, and align with health and endoscopy quality definitions. These indicators are measurable and, when used, help to reduce disparities in human and material resources among countries.

RECOMMENDATIONS

- The dissemination of this endoscopy quality consensus in the Latin American region can promote the performance of responsible digestive endoscopy, with technique and control of execution and risks.
- Pediatric gastroenterologists in training can learn quality standards, apply them and contribute to the development of the specialty in the region.
- Considering the quality indicators, pediatric gastroenterologists can ask their staff to comply with all phases of the procedure (pre-, intra- and post-procedural) for a quality digestive endoscopy.
- The pediatric gastroenterologist, when preparing his work team, can ask the institutions for the indispensable resources to comply with all the indicators of the endoscopy quality consensus, given that they are adapted to public and private institutions with limited resources.
- Informed consent and ASA classification should be the responsibility of the pediatric gastroenterologist, with the latter not being solely the responsibility of the anesthesiologist.
- The use of the indicators drafted allows the preparation of a report that is equivalent throughout the region, which facilitates interinstitutional communication between countries and between scientific societies and can be used in research studies.
- Digestive endoscopy is constantly changing, technology is advancing, and the written indicators can be expanded and easily adapted to new situations.

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Conflicts of interest

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Original article

Incidence of Hepatocellular Carcinoma in Patients with Chronic Hepatitis B Infection: A Retrospective Cohort Study (2013–2023) in Lima, Peru

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Abstract

Introduction: Chronic hepatitis B virus (HBV) infection increases the risk of hepatocellular carcinoma (HCC). HCC-related mortality ranks as the second leading cause of cancer death worldwide. This study aimed to determine the incidence of HCC in patients with chronic hepatitis B infection within a Peruvian population. **Materials and Methods:** This was a retrospective, observational cohort study of patients with chronic HBV infection treated at the Hospital Nacional Arzobispo Loayza between 2013 and 2023. **Results:** A total of 84 patients were included. The median age was 46 years, and 29% had liver cirrhosis at the start of the study. The median follow-up period was 66 months (range: 64–87). At baseline, 87% of patients were receiving antiviral therapy. The cumulative incidence of HCC at 5 and 10 years was 1.2% and 2.5%, respectively. **Conclusions:** Over a ten-year follow-up period, the low incidence of HCC in patients with chronic HBV infection may be associated with timely treatment and individualized monitoring. Further research is needed to validate these findings.

Keywords

Chronic hepatitis B, incidence, hepatocellular carcinoma, antiviral therapy, liver cirrhosis.

INTRODUCTION

Hepatocellular carcinoma (HCC) in Peru is not uncommon, and its capital, Lima, has the highest incidence in our continent (4.78 x 100,000 inhabitants), and the first cause is Hepatitis B infection[1,2]. Chronic hepatitis B infection has an oncogenic potential and a tendency to develop HCC in patients without liver cirrhosis[3]. In several cities in the interior of Peru, chronic Hepatitis B infection is endemic[1], which has probably contributed to the current scenario, in which HCC mortality is the second leading cause of death from cancer[4]. It is important to highlight the identification of people at high risk of developing HCC among chronic hepatitis B carriers, with an emphasis on treatment and follow-up. For this reason, different predictive models for the development of HCC have been developed and validated[5]. Potential clinical applications of these risk scores include prognosis and patient selection for antiviral therapy and individualized surveillance.

In Peru, little information is available on the incidence of HCC in patients with chronic hepatitis B infection. The importance of recognizing patients at higher risk lies in a more active follow-up, considering that only up to 40% of patients with HCC can achieve a functional cure due to late diagnosis[6].

In view of the above, the present research work aims to determine the incidence of HCC in patients with chronic

hepatitis B infection in a Peruvian population at a national referral hospital.

MATERIALS AND METHODS

It is a retrospective observational cohort study. Our study applied the STROBE checklist for observational studies. The clinical records of patients with chronic hepatitis B virus infection at the Hospital Nacional Arzobispo Loayza attended between 2013 and 2023 were evaluated. The inclusion criterion was mono-infection with hepatitis B virus, defined by the presence of positive surface antigen (HBsAg) for at least six months and a follow-up of at least five years in our center. Patients with co-infection with human immunodeficiency virus (HIV), previous diagnosis of HCC, co-infection with other viral hepatitis and patients under immunosuppressive treatment for autoimmune diseases at the start of follow-up were excluded.

Procedures and variables

The demographic and biochemical variables of the medical records that met the selection criteria were evaluated. Risky alcohol consumption was defined with consumption ≥20 g of alcohol per day or ≥140 g per week for men and ≥10 g of alcohol per day or ≥70 g per week for women[7]. The diagnosis of liver cirrhosis was made based on clinical, biochemical, imaging, and elastographic parameters, as well as liver biopsy when available[8]. A diagnosis of HCC was made with the presence of LI-RADS-5 lesions or observations on three-phase contrast-enhanced tomography[9]; diabetes mellitus was defined by two fasting glucose measurements of >126 mg/dL or glycosylated hemoglobin >6.5%; hypertension was defined as systolic pressure ≥140 mm Hg or diastolic pressure ≥90 mm Hg on at least two occasions; obesity was considered as body mass index >30, and dyslipidemia was defined by a high-density lipoprotein (HDL) level <40 mg/dL in males, HDL <50 mg/dL in females, low-density lipoprotein (LDL) >160 mg/dL, or triglycerides >150 mg/dL.

Additionally, seven predictive indices for hepatocellular carcinoma were calculated at the beginning of the study:

- REACH-B: this score was calculated using sex, age, alanine aminotransferase (ALT), hepatitis B e antigen (HBeAg), and HBV DNA levels, with values assigned according to the criteria established by Yang et al.[10]. Subsequently, based on the total score, the 5-year HCC risk was classified as follows: low (0-5 points), intermediate (6-11 points), and high (12-18 points).
- PAGE-B: This score was calculated using sex, age, and platelet count, with point values defined by Papatheodoridis et al.[11]. Based on the total score, the risk of HCC was classified as low (<10 points), intermediate (10-17 points), and high (>17 points).
- mPAGE-B: this score was calculated using sex, age, platelet count, and albumin levels. Points were assigned according to the method described by Kim et al.[12]. Based on the total score, HCC risk was stratified as low (≤8 points), intermediate (9-12 points), and high (≥13 points).
- aMAP: to apply the risk formula established by Fan R et al.[13], the following variables were used: sex, age, platelet count, albumin levels, and total bilirubin. Based on the resulting score, HCC risk was classified as low (0-50 points), intermediate (51-60 points), and high (61-100 points).
- CU-HCC: to calculate the total score as established by Wong et al.[14], the following variables were used: age, HBV DNA viral load, albumin levels, total bilirubin, and presence of cirrhosis. Based on the final score, patients were classified as low risk (<5 points), intermediate risk (5-19 points), and high risk (>19 points).
- GAG-HCC: In order to apply the formula described by Yuen et al.[15], the variables used were sex, age, HBV DNA viral load, and presence of cirrhosis. Based on the score, patients were classified as low risk (<100 points) and high risk (≥100 points).
- LSM-HCC: In order to estimate the risk, the variables used were age, HBV DNA viral load, albumin levels, and liver transient elastography. Scores were assigned based on the publication by Wong G et al.[16]. According to the total score, patients were classified into two groups: low risk (0-10 points) and high risk (11-30 points).

Follow-up data were collected retrospectively from medical records up to the last recorded evaluation, diagnosis of HCC, or date of death.

Statistical analysis

Qualitative variables were expressed as absolute frequencies and percentages. Quantitative variables were expressed as medians and interquartile ranges. The cumulative incidence of HCC at 5 and 10 years was evaluated. RStudio version 4.2.1 statistical software was used for the analysis.

Ethical considerations

The study protocol was approved by the ethics committee of the Hospital Nacional Arzobispo Loayza (No. 041-DG-HNAL/2023). The study was developed in accordance with the recommendations of the latest update of the Declaration of Helsinki (Fortaleza, Brazil, October 2013). The present study did not require informed consent, since

no intervention was performed. In addition, patients' personal information was encrypted to prevent identification. The data collected were stored and managed exclusively by the authors of the study.

RESULTS

Patient characteristics

A total of 135 medical records were evaluated and, after applying the selection criteria, 84 patients were included in the study (**Figure 1**).

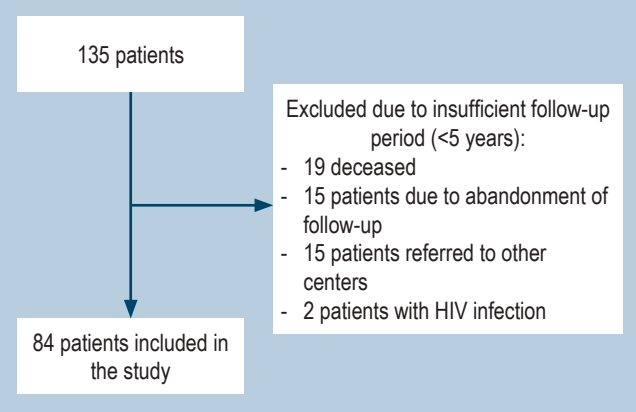


Figure 1. Flow Chart for Patient Selection in the Study. The image is the property of the authors.

The median age was 46 years, 55% of the population was male and 29% had a diagnosis of liver cirrhosis at the beginning of the study, using the Baveno VII criteria (clinical, biochemical, imaging or elastographic criteria). The median follow-up was 66 (64-87) months. Among the comorbidities, risky alcohol consumption was the most prevalent (15%), followed by dyslipidemia and obesity (8% and 6%, respectively). At the time of inclusion in the study, 87% of the patients were under medical treatment with antivirals (73 patients with tenofovir disoproxil fumarate).

Complete biochemical and elastographic data were obtained from 68 patients at baseline, which are summarized in **Table 1**. According to the HCC predictive indices, more than 50% of patients were categorized as low HCC risk for aMAP, CU-HCC, GAG-HCC and LSM-HCC indices (**Figure 2**). Mortality at the end of the study was 18% (15 patients) (**Table 2**). Of the 15 patients, seven had liver cirrhosis (five died due to cirrhosis-related decompensations and two from HCC-related complications), and only one patient did not achieve a virological response during follow-up.

Table 1. General Characteristics of the Study Population

Clinical features	n = 84
Age (years)	46 (35-60)
Sex (%)	
- Male	46 (55)
- Female	38 (45)
Arterial hypertension (%)	3 (4)
Diabetes mellitus (%)	2 (2)
Alcohol risk consumption (%)	13 (15)
Dyslipidemia (%)	7 (8)
Obesity (%)	5 (6)
Fibrosis stage (%) (evaluated in 68 patients)	
- F1	33 (49)
- F2	11 (16)
- F3	6 (9)
- F4	18 (26)
Liver cirrhosis (%)	24 (29)
- Hepatitis B	21 (88)
- Alcohol + hepatitis B	3 (12)
Hepatitis B treatment (%)	73 (87)
Stages of infection at baseline (%)	
- Chronic inactive carrier	42 (50)
- HBeAg-negative chronic hepatitis	34 (40)
- Immunotolerant	4 (5)
- HBeAg-positive chronic hepatitis	4 (5)
Immunologic profile at baseline (%)	
- HBeAg positive	29 (35)
- Anti-HBe	41 (49)
Viral response to treatment (%)	70/73 (96)
Seroconversion to anti-HBe (%)	14/29 (48)

Anti-HBe: antibody against hepatitis B antigen; HBeAg: hepatitis B virus antigen. Table created by the authors.

Table 2. Causes of Death in the Study Population

Cause of death	n = 15 (%)
Hepatic cirrhosis decompensation	
- Gastrointestinal bleeding	3 (20)
- Spontaneous bacterial peritonitis	1 (7)
- Ascites	1 (7)
Community-acquired pneumonia	2 (13)
Covid-19 pneumonia	2 (13)
Sudden cardiac arrest	3 (20)
Complicated urinary tract infection	1 (7)
Hepatocellular carcinoma	2 (13)

Table created by the authors.

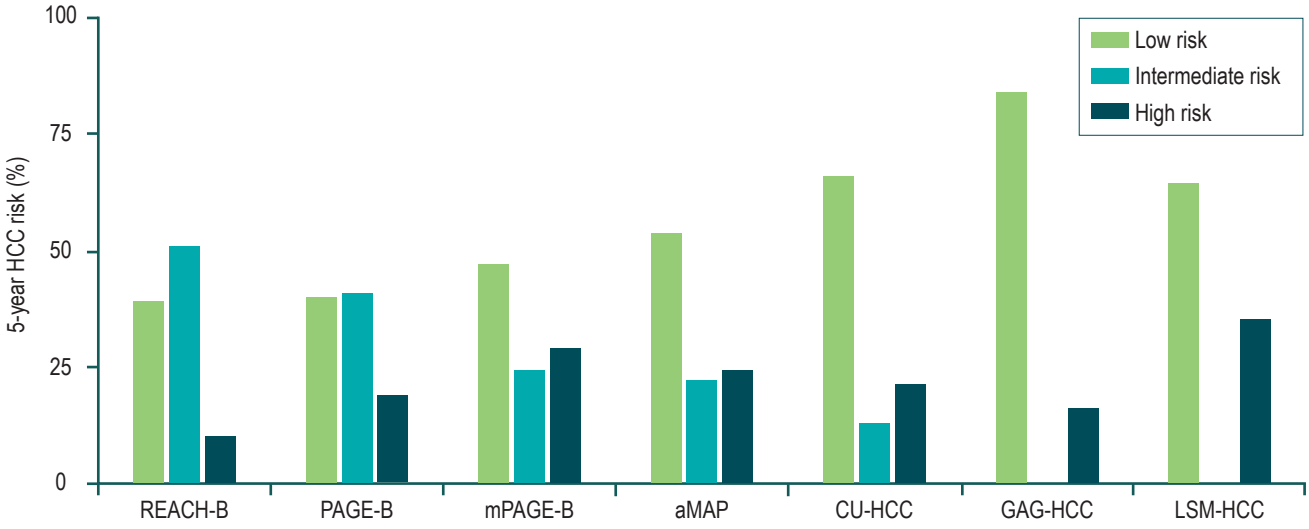


Figure 2. Categorization of Hepatocellular Carcinoma Risk According to the Predictive Index. The image is the property of the authors.

Cumulative incidence of hepatocellular carcinoma

At the end of the study, two people with liver cirrhosis since the start of the follow-up were diagnosed with HCC during the semiannual screening. The cumulative incidence of HCC at 5 and 10 years was 1.2% and 2.5%, respectively (**Figure 3**). Both cases were classified as high-risk according to the predictive indices used for cirrhotic patients at the beginning of the study. Likewise, they did not exhibit high-risk alcohol consumption or metabolic risk factors. It is important to highlight that only one patient with HCC in the follow-up achieved virological response (serum HBV DNA levels < 2000 U/mL).

DISCUSSION

To our knowledge, the present research work is the first Peruvian study that evaluates the incidence of hepatocellular carcinoma in patients with chronic hepatitis B virus infection over a ten-year period. Our result shows a long-term cumulative incidence lower than previously reported in our region[17-20]. Despite not having a control group, the present retrospective cohort demonstrates a decrease in the presence of HCC in patients under correct follow-up and treatment of hepatitis B virus infection. This result could be related to the higher percentage of patients under antiviral treatment (87%) and of patients with liver cirrhosis (29%), factors linked to the development of HCC.

The percentage of HCC is low compared to that published by Porto de Macedo et al. (2.5% vs. 3.5%)[17] and by Ferreira da Silva et al. (1.2% vs. 2.7%, cumulative incidence at 5 years)[18]. This result is related to the higher percentage of patients under antiviral treatment in our study (87% vs. 40-55%, respectively) and to an acceptable virological response (96%). Other risk factors for HCC include alcohol consumption and obesity[21]. However, these comorbidities did not prove to be the most prevalent in our follow-up cohort (15% and 6%, respectively). The two patients with HCC did not present these comorbidities and only one of them achieved a viral response. However, both patients had a diagnosis of liver cirrhosis, a proven risk factor for the development of HCC[3].

With respect to hepatitis B virus, the viral load determines a greater progression to hepatic fibrosis and greater development of HCC[22]. Antiviral treatment with tenofovir significantly reduces viral load in up to 95% of patients after twelve months of treatment, a result superior to that of entecavir[23]. In a meta-analysis by Choi Won-Mook et al.[24], which included 15 non-randomized studies and 61,787 patients, treatment with tenofovir was associated with a significant decrease in the incidence of HCC compared to entecavir (hazard ratio = 0.80 [0.69-0.93]; p = 0.003). Based on the above, the low number of patients with HCC in our study could be explained by the considerable proportion of patients treated with tenofovir (87% of patients with antiviral treatment), with a good virological response in the population studied (96%). The 13% who did not receive antiviral treatment had an HBV DNA <20,000 IU/mL at baseline follow-up, which confers a lower risk of developing HCC[25]

Regarding the distribution of the stages of chronic hepatitis B virus infection, a large percentage of patients (65%)

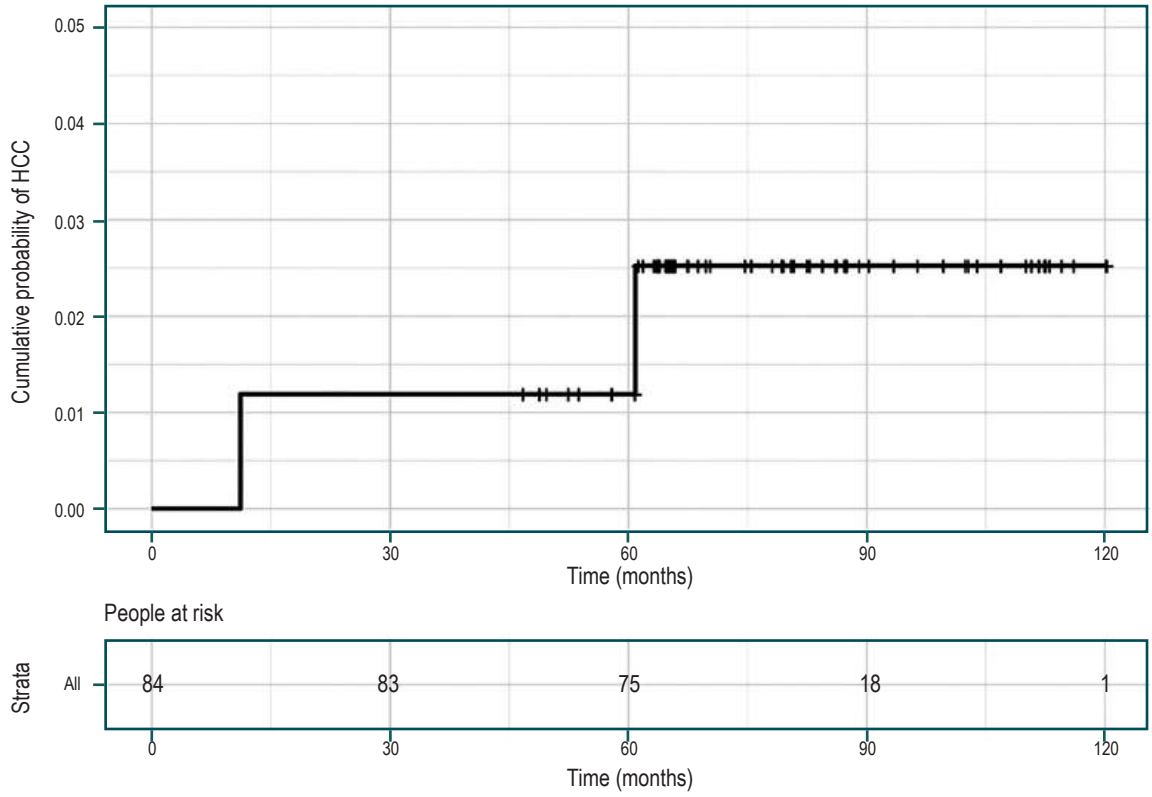


Figure 3. Cumulative Incidence of Hepatocellular Carcinoma in Patients with Hepatitis B Infection. The image is the property of the authors.

were HBeAg negative and had a seroconversion to anti-HBe under antiviral treatment of 48%. Hsu Y et al.[26], in their nine-year follow-up study in patients with HBeAg seroconversion, detected an incidence of HCC of 2.2%, a result similar to our study (2.5%). In addition, patients defined as immunotolerant have a higher risk of HCC than chronic inactive carriers[27]; however, initiation of antiviral treatment in well-selected immunotolerant patients would decrease the risk (immunotolerant patients with HBV DNA titers ≥20,000 IU/mL and older than 40 years)[25]. This characteristic of our population, added to the number of patients under treatment, could have influenced our findings.

Regarding primary prevention of HCC, the Latin American Association for the Study of the Liver (ALEH) does not specify the initiation of HCC screening in patients with hepatitis B virus infection without liver cirrhosis[28]. Currently, there are several long-term predictive indices for HCC in patients with or without liver cirrhosis and chronic hepatitis B infection[29]; however, validation of these indices in Latin American populations remains limited[17,18]. The two patients who developed HCC during follow-up had high scores on the predictive indices (PAGE-B and mPAGE-B) used in patients with liver cirrhosis. Despite this, the insufficient number of events does not allow any conclusions to be drawn regarding the usefulness of predictive indexes in other populations.

In Peru, the positive impact of hepatitis B vaccination as a national strategy for the reduction of complications of chronic infection, such as the development of HCC, has been corroborated[30]. Adding to this effort, in 2018, national guidelines for the treatment and follow-up of patients with chronic hepatitis B infection were published, recommendations based on the guideline published by the European Association for the Study of the Liver (EASL) [31]. Although the findings of the present study cannot be generalized to other populations, proper application of the guidelines would decrease the incidence of HCC, especially in patients who achieve virologic response. Based on the findings of this study, the importance of strict HCC surveillance in patients with liver cirrhosis from the time of diagnosis can be emphasized, as this risk factor may play a decisive role in the development of malignant liver lesions[3].

Limitations of the present study are associated with the retrospective nature of the investigation and the potential

incomplete data in the medical records. It is imperative to point out that the size of the population and the few events in our study (two patients with HCC) do not allow us to perform analyses to correlate variables, which could influence the explanation and inference of the findings. The small sample size was influenced by the referral of patients to their respective healthcare centers and by patient attrition during follow-up. The development of multicenter studies could reduce these limitations and biases in the future.

CONCLUSION

The low cumulative incidence of HCC, over a ten-year period, could be explained by compliance with timely treatment and follow-up of patients with hepatitis B virus infection in an independent Peruvian cohort. Further investigations with a larger sample of patients are necessary to validate the findings of the present study.

Authors' contributions

RZH, JGR and CCV contributed to the conceptualization and methodology of the study. RZH, WCC, EM and RM were in charge of data collection. RZH performed the statistical analysis. RM, WCC, JGR and CCV validated the results. All authors were involved in the transcription and approval of this manuscript.

Conflicts of interest

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

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Original article

Proton Pump Inhibitors and Quality of Life in Patients with Globus Pharyngeus: An Observational Study

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Abstract

Introduction: Globus pharyngeus accounts for up to 4% of otolaryngology consultations. There is no consensus in the literature regarding its treatment; however, most studies agree that gastroesophageal reflux is the primary etiological factor. **Objective:** To determine whether treatment with proton pump inhibitors is associated with changes in the quality of life of patients with globus pharyngeus. **Methods:** This prospective observational study included patients who attended otolaryngology outpatient consultations between January and December 2022 and were diagnosed with globus pharyngeus. All patients underwent a comprehensive otolaryngologic evaluation, and the following assessment tools were used before and after three months of treatment: the Reflux Symptom Index (RSI), the Reflux Finding Score (RFS), the Glasgow-Edinburgh Throat Scale (GETS) for globus pharyngeus, and the SF-36 Quality of Life Questionnaire. **Results:** The study population consisted of 35 patients, 27 of whom were women (77.1%), with an average age of 55.2 years. Improvement was observed in all RSI scale parameters. Quality of life improved after treatment in the domains of bodily pain, vitality, social functioning, emotional role, and mental health. **Conclusions:** In this observational study, treatment with proton pump inhibitors significantly improved symptoms associated with globus pharyngeus.

Keywords

Globus pharyngeus, quality of life, proton pump inhibitors, gastroesophageal reflux.

INTRODUCTION

Globus pharyngeus is a common condition that may account for up to 4% of otolaryngology consultations[(1)]. Its prevalence in the general population is approximately 12.5% in the United States[(2,3)], and up to 45% of healthy volunteers in a study conducted in the United Kingdom reported experiencing it[(4)]. It has a peak incidence in middle age, with an average age of onset of 43 years (range: 22 to 71 years)[(5)]. Some authors have reported a higher prevalence among women[(6)], while others have found similar rates in both men and women[(7)]. This is a poorly understood condition, often difficult for patients to describe. It is associated with a wide range of symptoms and significant interpersonal variability, which has limited the development of standardized diagnostic and treatment protocols.

Due to the lack of consensus on the etiology of globus pharyngeus, there is no standardized algorithm for its diagnosis and treatment. An example of this is a study conducted in the United Kingdom, where 14% of otolaryngologists did not perform any diagnostic tests in patients presenting with globus pharyngeus symptoms and instead prescribed treatment with proton pump inhibitors (PPIs). The remaining 86% investigated the symptoms using a

variety of methods, including esophagogastroduodenoscopy (61%), barium swallow (56%), or a combination of both approaches (17.5%)[8].

Although several studies have reported an association between globus pharyngeus and psychosomatic disorders, such as anxiety and depression[9,10], there is only one known study that evaluates quality of life before and after initial otolaryngology consultation, without providing any specific treatment other than patient education. In this study, conducted by Pia Järvenpää et al. in 2017[11], 30 patients with globus pharyngeus underwent physical examination and nasofibro-laryngoscopy. The evaluation also included the Reflux Finding Score (RFS), as well as questionnaires such as the Reflux Symptom Index (RSI), the Dysphagia Handicap Index (DHI), and the 15D Quality of Life Questionnaire. The results showed that patients with globus pharyngeus had higher disability scores, which improved after four months of follow-up without any specific treatment. Furthermore, up to one-third of patients declined additional testing following the initial consultation[11].

Although this study suggests a possible psychosomatic origin for this condition, the role of PPI therapy has not been extensively studied. This appears contradictory, considering that laryngopharyngeal reflux has been regarded as the primary etiology of globus pharyngeus[7,12]. The aim of this study is to determine the relationship between PPI treatment and changes in quality of life in patients with globus pharyngeus.

METHODOLOGY

This research study was approved by the Department of Research and the Ethics Committee of the School of Medicine at the Universidad de Cartagena. An observational, prospective linear study was conducted, based on a before-and-after design. It included 35 conveniently selected patients who attended outpatient otolaryngology consultations at Gastropack Medical Center and ORL del Caribe in Cartagena between January and December 2022, presenting globus pharyngeus as their main reason for consultation. Patients between 18 and 75 years of age were included. Exclusion criteria were: incomplete questionnaire data; current or recent (within the past year) treatment with PPIs; suspected diagnosis of other upper aerodigestive tract conditions; or alarm symptoms suggestive of malignancy of the upper digestive tract, such as weight loss, dysphagia, odynophagia, or symptom lateralization.

Prior to signing the informed consent form, all patients underwent a comprehensive otolaryngologic evaluation, including nasofibrolaryngoscopy. The Reflux Symptom Index (RSI), the Reflux Finding Score (RFS), the Glasgow-Edinburgh Throat Scale (GETS) for globus pharyngeus, and the SF-36 questionnaire were administered to assess quality of life. Esomeprazole 40 mg was prescribed every 12 hours for 3 months. After the treatment period, the RSI, RFS, GETS, and SF-36 assessments were repeated. All survey data were collected directly by the principal investigator via telephone.

The RSI is a scale used to assess the degree of laryngopharyngeal reflux symptoms. It is based on nine items scored from 0 to 5, depending on the severity of the symptoms, with a maximum score of 45. A score greater than or equal to 13 is indicative of laryngopharyngeal reflux[13]. The GETS scale was designed to evaluate patients with globus pharyngeus symptoms, estimating the presence and severity of common throat complaints on a scale from 0 to 7. The last two items are questions that help establish a relationship between globus and the patient's quality of life[14]. The RFS is an endoscopic findings scale developed to analyze the laryngopharyngeal changes caused by laryngopharyngeal reflux. The maximum score is 26, and a score of 7 or higher is considered highly suspicious for this condition[15].

For the estimation of quality of life, the recommendations established in the SF-36 manual were followed. After the administration of the questionnaire, the following steps were carried out:

1. Homogenization of the response direction by recoding the 10 items that required it, ensuring that all items followed the gradient of "the higher the score, the better the health status."
2. Calculation of the sum of the items that make up the scale (raw score of the scale).
3. Linear transformation of the raw scores to obtain scores on a scale between 0 and 100 (transformed scores of the scale).

For each dimension, the items were coded, summed, and transformed into a scale ranging from 0 (the worst health status for that dimension) to 100 (the best health status)[16].

The statistical analysis was performed using Jamovi software. Numerical and categorical variables were expressed as the mean (standard deviation [SD]) and as percentages, respectively. In addition, to determine the normality of the sample, the non-parametric Shapiro-Wilk test was applied. A significance level of 5% was set.

To determine the relationship between quality of life and proton pump inhibitor treatment, the mean difference was estimated using the Student's *t*-test for paired samples in variables with a normal distribution. For variables with a non-normal distribution (physical function, physical role, general health, social function, and emotional role), the Wilcoxon signed-rank test was used. Additionally, to assess the relationship between treatment and changes in the RSI, GETS, and RFL, the difference in medians for pai-

red samples was estimated using the Wilcoxon signed-rank test, as these variables had a non-normal distribution. This was done by comparing the scores from the questionnaires before and after initiating PPI treatment.

RESULTS

Finally, 35 patients were available for analysis. Of these, 77.1% (n = 27) were women. The mean age was 55.2 years (SD: 14.5). The mean scores of all RSI items significantly decreased statistically. On the one hand, the severity of symptoms such as throat clearing, occasional or paroxysmal cough, and the sensation of a lump or needle in the throat showed the greatest reduction after treatment. On the other hand, symptoms such as dysphonia or other voice issues, as well as difficulty swallowing, showed the least change by the end of the treatment (**Table 1**).

When evaluating the GETS scale, scores decreased considerably across all assessed symptoms. The difference was statistically significant for all items except for "swelling in the throat." The symptoms that showed the greatest reduction in severity were the sensation of discomfort in the throat, the amount of time spent thinking about the throat, phlegm in the throat, and the constant urge to swallow (**Table 2**).

Regarding the endoscopic findings of the patients after antisecretory treatment, the most frequent observation was the presence of erythema/hyperemia in the larynx limited to the arytenoids, in 57.1% of patients. Only 8.6% (n = 3) had a positive RFS score (>7 points) for laryngopharyngeal reflux, indicating that imaging abnormalities are not necessarily required to determine the presence of the symptom. One does not exclude the other (**Table 3**).

The SF-36 dimension with the highest score prior to treatment was physical functioning, with a mean of 50.8, followed by social functioning, with a score of 49.1. The lowest scores were observed in the physical role and emotional role dimensions, with scores of 25 and 24, respectively. An increase was observed in all SF-36 subscales after treatment, and in five out of the eight dimensions, the differences reached statistical significance (bodily pain, vitality, social functioning, emotional role, and mental health) (**Table 4**).

DISCUSSION

The present study predominantly included female patients (77%), with a mean age of 55.2 years (± 14.5). The mean age among women was 52.3 years, while among men it was 65 years, reflecting an earlier and more frequent presentation in females. This finding is consistent with most reports in the global literature, which describe a higher prevalence in women, as observed in the studies by Drossman et al., Thompson et al., and Harvey et al.[2–4]. However, a higher percentage of arterial hypertension (HTN) and diabetes mellitus (DM) was found in this sample. This can be partially explained by the older mean age of the study population compared to other studies, in which the average age ranges from 45 to 52 years[17–19].

The most prevalent medical histories in the sample were, in order, HTN, tobacco use, type 2 DM, and alcohol consumption. Contrary to current assumptions, this study

Table 1. RSI Symptom Scale Differences Before and After Proton Pump Inhibitor Treatment

RSI scale items	Pretreatment	Posttreatment	Difference	*p*
Dysphonia or other voice problem	1.9	1.1	-0.8	0.001
Clearing of the throat	3.2	1.7	-1.5	<0.001
Presence of excessive mucus in the throat or postnasal drip	2.3	1.4	-0.9	0.001
Difficulty swallowing food, liquids or pills	1.6	0.8	-0.8	0.002
Coughing after eating or lying down	1.5	0.6	-1.0	0.001
Feeling of choking or obstruction	2.2	1.1	-1.1	<0.001
Occasional or paroxysmal cough	2.3	1.1	-1.3	<0.001
Sensation of a lump or a needle in the throat	3.2	1.8	-1.4	<0.001
Retrosternal burning, chest pain, indigestion, sour regurgitation	2.0	1.0	-1.0	<0.001

Table created by the authors.

Table 2. Difference in GETS Scale Item Scores Before and After Treatment

Symptom of the GETS scale	Pretreatment	Posttreatment	Difference	*p*
Sensation of having something stuck in the throat	2.6	1.6	-1.1	<0.001
Sore throat	2.2	1.3	-0.9	0.005
Throat discomfort/irritation	2.9	1.3	-1.6	<0.001
Difficulty swallowing food	1.7	0.7	-1.0	<0.001
Sensation of throat closing	1.8	1.0	-0.8	0.009
Swelling in the throat	0.9	0.6	-0.3	0.208
Phlegm in the throat	3.1	1.4	-1.7	<0.001
Cannot clear throat when swallowing	2.2	1.3	-0.9	0.004
Constant urge to swallow	2.9	1.2	-1.7	<0.001
Food sticks when swallowing	1.4	0.6	-0.8	0.002
How much time do you spend thinking about your throat?	4.5	2.3	-2.2	<0.001
At the moment, how annoying do you find the sensation in your throat?	4.9	2.5	-2.4	<0.001

Table created by the authors.

found that only a small percentage (5.7%) of patients had a history of diagnosed depression or anxiety. According to various authors, psychiatric disorders such as depression, generalized anxiety, and panic disorder may be present in up to 44% of patients with globus pharyngeus[20]. Moreover, in Rasmussen's study, 84% of participants presented with anxiety, mainly related to fear of having cancer[18].

After evaluating reflux-related symptoms, the sensation of throat clearing was identified as the most severe symptom, followed by the sensation of a "lump" or "needle" in the throat. These discomforts often overlap with and are easily confused with the general symptom of globus pharyngeus, making it difficult to establish a specific diagnosis of laryngopharyngeal reflux. Such a diagnosis would require additional diagnostic tools, such as esophagogastroduodenoscopy or 24-hour esophageal pH monitoring, to differentiate these pathologies[21]. Patients in this cohort did not report typical symptoms of gastroesophageal reflux disease, which are usually common in that condition, such as a history of chronic gastritis, heartburn, sour regurgitation, or chest pain[22,23]. This may be explained by the fact that patients were recruited from an otolaryngology clinic, where it is less common for referred individuals to present with predominantly gastroesophageal symptoms.

Patients' perceived quality of life was low from the beginning of the study. Most reported a fair health status that had remained the same or worsened over the past year. This finding is consistent with the literature, such as the study by Harris et al. on stressful life events and the onset of globus pharyngeus[20], in which patients with globus pharyngeus reported more discomfort and more stressful life events during the two months prior to symptom onset compared to controls. These findings support the idea that emotional disorders may play a causal role in the onset of globus pharyngeus rather than being a consequence of the symptom.

Moreover, regarding their physical health, patients in the present study reported reduced work performance and limitations in carrying out daily activities. With respect to emotional problems, they reported doing less than they would like to, experiencing pain that interfered with work-related tasks during the past month, and feeling exhausted and fatigued over the past week. Notably, nearly half of the patients reported being less careful in carrying out their job duties, difficulty engaging in social activities due to low mood, and nervousness. These findings are supported by previously published studies, such as that by Dr. Järvenpää[11], in which patients with globus pharyngeus had lower quality-of-life scores at their initial otolaryngology consultation. These findings are relevant because they highlight the connection between globus pharyngeus and impairment in key areas of the patient's life, particularly in their occupational and emotional well-being.

The literature describes that patients who do not show significant symptom improvement despite treatment with

Table 3. Endoscopic Findings on the RFS Scale

Findings	Score	Frequency	Percentage
Subglottic edema	Absent	33	94.3
	No information	2	5.7
Ventricular obliteration	Absent	33	94.3
	No information	2	5.7
Erythema/ hyperemia	Absent	9	25.7
	Arytenoids only	20	57.1
	Diffuse	4	11.4
	No information	2	5.7
Edema of vocal folds	Absent	29	82.9
	Mild	1	2.9
	Moderate	3	8.6
	No information	2	5.7
Diffuse laryngeal edema	Absent	13	37.1
	Mild	11	31.4
	Moderate	8	22.9
	Obstructive	1	2.9
	No information	2	5.7
Granuloma/ granulation tissue	Absent	32	91.4
	Present	1	2.9
	No information	2	5.7
Thick endolaryngeal mucus	Absent	25	71.4
	Present	8	22.9
	No information	2	5.7

Table created by the authors.

Table 4. Difference of the Subscales of the SF-36 Quality of Life Survey Before and After Treatment

Quality of life aspect	Pre-	Pos-	Difference	*p*
Physical function	50.8	54.3	3.5	0.116
Physical role	25	28.6	3.6	0.262
Bodily pain	47.7	54.9	7.2	0.027
General health	47.1	49.5	2.4	0.166
Vitality	44.3	55.5	11.2	0.003
Social function	49.1	58.6	9.5	0.029
Emotional role	24.8	34.7	9.9	0.02
Mental health	43.4	49.9	6.5	0.029

Table created by the authors.

PPIs often have an underlying, uncontrolled anxiety disorder[24]. Although only two patients (5.7%) in this study had a prior diagnosis of anxiety or depression, the average emotional role score on the quality-of-life scale was significantly reduced. This finding suggests a probable underdiagnosis of psychiatric conditions among patients with globus pharyngeus, who may also benefit from referral to and treatment by psychology or psychiatry specialists. It should be noted that no validated scales were used in this study to objectively diagnose anxiety or depression in the participants.

When analyzing quality-of-life scores based on patient self-perception, the domains that showed statistically significant improvement after treatment with PPIs were bodily pain, vitality, social functioning, emotional role, and mental health. No other studies were found that specifically evaluated changes in quality of life following antisecretory treatment in patients with globus pharyngeus. However, there are studies assessing quality-of-life changes in patients with gastroesophageal reflux disease after PPI treatment, such as the study by Aanen et al., in which the most notable improvements after treatment were observed in emotional role and vitality[25].

Regarding the improvement in RSI-assessed symptoms, all showed statistically significant improvement. The most notable improvements were in occasional coughing after eating (66% improvement), throat clearing (52%), and the sensation of a lump or needle in the throat (56%), which were the most severe symptoms reported by patients before treatment. Prior to initiating PPI therapy, the mean RSI score was 20.3 points, and 26 out of 35 patients (74%) had an RSI above 13 points, a threshold considered suspicious for laryngopharyngeal reflux[13]. After treatment, the mean RSI score was 10.6 points. Very similar data were found in a recently published study by Boom et al.[15] in which their patients with globus pharyngeus had a mean RSI score of 18.8 points at baseline, with 76% of patients having a score greater than 13, and a post-treatment RSI score of 10.3 points after two months of PPI therapy.

Regarding symptom improvement on the GETS scale, the most consistently responsive symptoms were "wanting to swallow all the time," "phlegm in the throat," "throat discomfort," and "the sensation of having something stuck." As for the endoscopic findings prior to antisecretory treatment, evaluated using the Reflux Finding Score (RFS), the most relevant signs observed were: erythema/hyperemia in the larynx and mild to moderate diffuse laryngeal edema in more than half of the patients; thick laryngeal mucus in approximately 25% of the patients; and mild to moderate edema of the vocal folds in just over 10%. However, only three patients (9%) had a positive RFS score for laryngopharyngeal reflux, despite all of them reporting symptoms of globus pharyngeus. This suggests that a negative RFS result does not rule out the presence of the symptom nor the potential benefit of antisecretory treatment. The mean RFS score in this study was 3.6 points, which contrasts with findings in the literature, such as in the study by Dr. Boom et al.[15], where the mean score was 5 points and 25% of the patients had a positive RFS score for laryngopharyngeal reflux prior to treatment.

In the literature, the Reflux Finding Score (RFS) has been reported to have a sensitivity of 87.8% and a specificity of 37.5% for detecting patients with pharyngeal reflux, as confirmed by the reference standard, which is pH monitoring[26,27]. Shilpa et al. found in their study that the RSI and the RFS were complementary and showed a strong correlation with the diagnosis of laryngopharyngeal reflux. They also concluded that after three months of treatment with PPIs, 70% of their patients showed improvement in the RFS[28]. This association between the presence of globus pharyngeus and signs suggestive of laryngopharyngeal reflux could be further clarified through larger studies that include a greater number of patients and hospital centers. It is also important to consider that the RFS is a subjective assessment and may show interobserver variability, which could account for differences found between studies. In patients who do not show improvement in symptoms with antisecretory treatment, it is also essential to evaluate for functional voice disorders, as several studies have described a causal relationship between these two pathologies[29,30].

In this study, a generic quality of life scale such as the SF-36 was used, which may have limited the precise evaluation of some important aspects of quality of life in these patients. However, there is currently no specific questionnaire available to assess quality of life in globus pharyngeus, and the scale used has already been widely validated in other pathologies. Moreover, a potential placebo effect or Hawthorne effect from the treatment with PPIs cannot be ruled out, considering that patients had a low prevalence of typical gastroesophageal reflux symptoms, low scores on the RFS scale, and, additionally, the absence of a control group.

CONCLUSIONS

PPI treatment was associated with improved symptoms and quality of life in patients with globus pharyngeus. Randomized controlled studies are needed before generalizing these results.

LIMITATIONS

Although globus pharyngeus is a common symptom in otolaryngology consultations, the sample size in this study is relatively small due to the strict exclusion criteria used, aimed at reducing biases from comorbidities and treatments with PPIs or other medications that could affect the results. It should be noted that there is no specific questionnaire to assess the quality of life of patients with globus pharyngeus. Therefore, other physical, emotional, or social disorders unrelated to the condition may interfere with the improvement or worsening of the patients' perceived quality of life in this study.

Finally, since this is a study on globus pharyngeus, no objective test, such as pH monitoring, was conducted to confirm or rule out the presence of gastroesophageal or laryngopharyngeal reflux in the patients. Instead, the diagnostic algorithm suggested by Zerbib et al. was followed, where patients with globus pharyngeus and no alarm esophageal symptoms underwent laryngoscopy and started a therapeutic trial with PPIs[31].

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Original article

Characterization of Liver Cirrhosis in Patients Hospitalized at a University Hospital in Colombia

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Abstract

Introduction: Cirrhosis is a chronic, diffuse, and irreversible liver disease that represents the final stage of various liver conditions caused by different etiologies. **Objective:** To characterize patients with liver cirrhosis treated at a hospital in Boyacá. **Methodology:** A retrospective, cross-sectional descriptive study was conducted, including patients over the age of 18 who were treated at the Hospital Universitario San Rafael in Tunja with a diagnosis of liver cirrhosis of any etiology between January 01, 2016, and December 31, 2021. **Results:** The age range of the study population was 28 to 89 years, with men accounting for the majority (77.51%). The most frequent complications observed were ascites and hepatic encephalopathy. A total of 12.8% of patients required admission to the intensive care unit (ICU), 38.7% were classified as having decompensated disease (Child-Pugh C), and the overall mortality rate was 34.6%. **Conclusions:** Cirrhosis imposes a significant financial burden on both the healthcare system and patients. The primary cause of cirrhosis in this population was alcohol consumption, a modifiable risk factor. The higher prevalence in men may be attributed to greater exposure to risk factors, such as alcohol consumption, which is common in the country. The mortality rate for this condition remains high, and given the natural course of the disease, it significantly impacts patients' quality of life, leading to an increased number of years lost due to disability and premature death.

Keywords

Cirrhosis, alcoholism, liver, mortality, ascites.

INTRODUCTION

Cirrhosis is a chronic and diffuse liver disease triggered by various etiologies, with the most common being alcohol consumption, hepatitis virus infection, and non-alcoholic steatohepatitis[1,2]. Regardless of its etiology, the mechanisms leading to cirrhosis are shared. They begin with hepatocyte necrosis or lysis, resulting in the loss of hepatic parenchyma and inflammation. Healthy hepatic parenchyma is progressively replaced by fibrotic tissue and regenerative nodules, ultimately leading to liver failure, portal hypertension, and hepatocellular carcinoma[3,4].

Early identification of the clinical features of cirrhosis allows physicians to guide their diagnostic strategy, reverse causal factors, establish timely treatment, and prevent complications[5]. Unfortunately, the diagnosis of cirrhosis is often made late nowadays, which means that management is primarily focused on treating complications of the decompensated disease. As a result, many patients eventually require liver transplantation. This leads to a significant impairment in their quality of life and, evidently, represents a major public health issue[3].

According to 2019 data from the National Administrative Department of Statistics (DANE), Boyacá is one of the

departments with the highest prevalence of alcohol consumption[6]. This factor is the leading cause of cirrhosis worldwide and accounts for a high rate of morbidity and mortality, resulting in a significant impact on the quality of life of individuals affected by the disease, particularly in developing countries such as Colombia[7,8].

In 2018, the World Health Organization (WHO) estimated that alcohol consumption was responsible for three million deaths annually worldwide[5]. Alcohol is the most common cause of liver damage in approximately 60% of reported cases in Europe, North America, and Latin America[9,10], where higher mortality rates due to cirrhosis secondary to alcohol consumption have been reported in countries such as Peru, Nicaragua, and Mexico[8,9]. In Colombia, the situation is similar. Although there is insufficient information regarding the clinical and sociodemographic characteristics of affected patients, some studies focused on the populations of Antioquia and Barranquilla show a high prevalence of the disease[10-12].

Given the high mortality rate, the complexity of the disease, and its poor prognosis, it is crucial to emphasize the need for timely and early diagnosis. This is especially important for populations such as Boyacá, which shows a high prevalence of alcohol consumption and presents sociodemographic characteristics different from those studied in other regions of the country. Therefore, the objective of this study is to describe the sociodemographic and clinical characteristics of patients with liver cirrhosis.

MATERIALS AND METHODS

Type of study

A descriptive, cross-sectional, retrospective study was carried out.

Population and selection criteria

The target population included all patients over 18 years of age who were treated at the Hospital Universitario San Rafael de Tunja for liver cirrhosis of any etiology between January 1, 2016, and December 31, 2021, excluding those with incomplete medical records.

Data collection and analysis

Data collection was carried out by the investigators. Initially, the list of patients was identified using the International Classification of Diseases (ICD-10) code; subsequently, a Google Forms instrument was adopted to collect all the variables from the medical records.

The variables considered included: age at the time of cirrhosis diagnosis, sex of the patient, disease progression time, sociodemographic characteristics (place of origin, education level, social security affiliation, and type of health insurance), etiology of liver cirrhosis (alcoholic, autoimmune, viral, non-alcoholic fatty liver disease, drug-induced, secondary to hemochromatosis, primary biliary, secondary biliary, or unclassified), presence of complications (ascites, hepatic encephalopathy, spontaneous bacterial peritonitis, esophageal varices, gastrointestinal bleeding, hepatorenal syndrome), and the time of evolution between cirrhosis diagnosis and the diagnosis of these complications. Additionally, the presence of comorbidities (arterial hypertension, diabetes mellitus, chronic kidney disease, rheumatoid arthritis, gastric ulcers), number and duration of hospitalizations, the time between each hospitalization in patients with more than one admission, patients requiring management in an intensive care unit (ICU) and number of days spent in the ICU, patient mortality, time from disease diagnosis to death, and age at the time of death were recorded.

The database was registered in Excel version 2013 and analyzed using SPSS statistical package version 22. Univariate analysis was performed through descriptive statistics for each group, determining absolute and relative frequencies for categorical variables; for quantitative variables, measures of central tendency (mean, median) and measures of dispersion (standard deviation and interquartile range) were calculated.

Ethical considerations

Based on Resolution 8430 of 1993, this study is considered a no-risk investigation. Authorization for the review of medical records was obtained from the Ethics and Research Committee of the Hospital Universitario San Rafael de Tunja (Minutes No. 053).

RESULTS

Selection of participants

During the study period, a total of 312 medical records were collected. However, during the review process, 23 records were excluded for the following reasons: 15 corresponded to patients with incomplete medical records with missing information, and 8 had ICD-10 coding that did not match the diagnosis of liver cirrhosis.

Sociodemographic characterization

The minimum age of the evaluated population was 28 years, and the maximum age was 89 years. The majority were male,

accounting for 77.51%. A relevant finding is that the most frequent etiological agent was alcohol consumption. However, the type or degree of alcohol consumption is not known, as it could involve non-distilled alcohol, such as "guarapo" or "chicha," which are frequently consumed in agricultural regions during working hours to quench thirst (**Table 1**).

Table 1. Sociodemographic characterization

Variables		Total (n: 289)	%
Sex	Female	65	22.49
	Male	224	77.51
Type of regime	Contributory	37	12.80
	Subsidized	252	87.20
Etiology	Alcoholic	244	84.43
	Autoimmune	12	4.15
	Primary biliary	10	3.46
	Secondary biliary	1	0.35
	Non-alcoholic fatty liver disease	5	1.73
	Drug-induced	1	0.35
	Idiopathic	10	3.45
	Hemochromatosis	4	1.38
	Viral	2	0.69
Educational Level	None	6	2.08
	Not available	196	67.82
	Primary	65	22.49
	Secondary	13	4.50
	University	9	3.11

Table created by the authors.

Comorbidities and complications

The most frequently occurring complications were ascites and hepatic encephalopathy (**Table 2**).

Prognosis

A total of 12.8% required hospital stay in the ICU, 38.7% were classified as Child-Pugh C disease, and the mortality rate was 34.6% (**Table 3**).

DISCUSSION

Cirrhosis follows an evolving course marked by different clinical stages. For a long time, it has been recognized that the natural history of cirrhosis is dominated by a prognostic milestone represented by the development of complications related to portal hypertension and liver dysfunction, such as gastrointestinal bleeding, hepatic encephalopathy, jaundice, and ascites formation. This led to the division of the disease course into two distinct clinical states: a compensated phase, characterized by preserved quality of life and an average survival exceeding 12 years, and a decompensated phase, marked by the onset of complications, with an average survival reduced to 2-4 years[3,5].

Table 2. Comorbidities and complications

Variables		Total (n: 289)	%
Ascites	No	131	45.33
	Yes	158	54.67
Hepatic encephalopathy	No	158	54.67
	Yes	131	45.33
Spontaneous bacterial peritonitis	No	272	94.12
	Yes	17	5.88
Esophageal varices	No	170	58.82
	Yes	119	41.18
Gastrointestinal bleeding	No	164	56.75
	Yes	125	43.25
Arterial hypertension	No	209	72.32
	Yes	80	27.68
Diabetes	No	256	88.58
	Yes	33	11.42
Rheumatoid arthritis	No	280	96.89
	Yes	9	3.11
Biliary lithiasis	No	245	84.78
	Yes	44	15.22
Gastric ulcers	No	205	70.93
	Yes	84	29.07

Table created by the authors.

In the compensated phase, patients are typically asymptomatic or present with nonspecific symptoms. During this stage, the liver is still able to perform its essential functions, and the patient's quality of life remains relatively stable. In contrast, the decompensated phase is characterized by the onset of evident symptoms such as ascites, hepatic encephalopathy, jaundice, gastrointestinal bleeding, and other severe complications. These events can lead to prolonged hospitalizations, liver transplantation, and even

death[13-16]. Acute decompensation is defined by the rapid development of one or more major complications, such as grade 2 or 3 ascites, acute hepatic encephalopathy, gastrointestinal bleeding, or acute bacterial infections. Additionally, the study defined multi-organ failure as a criterion for diagnosing acute-on-chronic liver failure (ACLF), which can worsen the prognosis and increase mortality[13-16].

Table 3. Variables to establish the prognosis

Variables		Total (n: 289)	%
ICU	No	252	87.20
	Yes	37	12.80
Child-Pugh Scale	Class A	47	16.26
	Class B	91	31.49
	Class C	112	38.75
	Not available	39	13.49
In-Hospital Mortality	Within 48 hours	36	12.46
	After 48 hours	64	22.15
	No	189	65.40

Table created by the authors.

Clinical events occurring during a period following acute decompensation can help classify patients into different groups based on disease progression. This classification identifies clinical trajectories that reflect various levels of instability and mortality risk[13-16].

Cirrhosis is the final result of chronic liver diseases, secondary to excessive alcohol consumption, viral hepatitis, or non-alcoholic fatty liver disease, which is becoming increasingly common due to the rise in obesity, type 2 diabetes mellitus, and sedentary lifestyles[3,4]. In our findings, the male sex represents the vast majority of cases, which contrasts with other studies conducted in Colombia, where a higher prevalence of cirrhosis in females was reported [10,17-19].

The population affiliated with the contributory health regime was a minority. In Colombia, two other studies have reported the type of affiliation to the health system, finding that 77.1% and 60% of the population, respectively, were affiliated with the contributory regime[10,20]. The reason why the majority of the population in our study had subsidized health coverage is partly due to the characteristics of the population covered by the hospital, which is mainly composed of agricultural workers from the central region of the country.

The main etiologies of liver cirrhosis in our population are consistent with findings from other studies, in which alcoholic, autoimmune, and viral causes are among the most frequent[10,17,21]. Globally, one-quarter of cirrhosis-related deaths are attributable to alcohol consumption[22]. Furthermore, in the Americas, there is a noticeable shift from predominantly viral etiologies toward an increase in alcohol-related cirrhosis. This trend is associated with improved control of viral diseases and a rise in alcohol consumption[23].

The variable of educational level emerges as a factor of particular relevance. Although the lack of complete data across the entire population limits its analysis, education remains an important factor. Most cases of cirrhosis occur in individuals with low levels of education, which is also related to the high prevalence of alcoholic liver cirrhosis and affiliation with the subsidized health insurance regime. This suggests an association between low educational level, poverty, and alcohol consumption, as individuals engaged in agricultural work do not typically consider "guarapo" or "chicha" as alcoholic beverages, but rather as drinks to quench thirst during workdays. Prospective studies are needed to evaluate the composition of these substances and, in this way, address a multidimensional problem that requires an interdisciplinary approach, considering both medical and sociocultural aspects. The interrelationship among these factors highlights the need for a comprehensive and collaborative understanding to effectively address this issue and its determinants[23].

Up to 50% of patients with cirrhosis, particularly those with alcoholic etiology, may experience decompensation with the development of ascites[9,24], a figure consistent with our findings. However, it is notably higher compared to other national studies, where prevalence ranges from 13% to 36%[10,18]. This can be mainly explained by the high proportion of patients with alcohol-related cirrhosis in our population.

Spontaneous bacterial peritonitis is a serious complication in cirrhotic patients with ascites, and its prevalence ranges from 10% to 25% among hospitalized patients[24]. However, in our population, it was a rare complication, possibly due to the high prevalence of gastrointestinal bleeding and, consequently, the administration of antibiotics, which could reduce the frequency of this complication.

The prevalence of esophageal varices increases with the progression of liver disease (Child-Pugh class A: 43%, class B: 71%, class C: 76%)[25]. Approximately 50% of patients with newly diagnosed cirrhosis have esophageal varices, and peptic ulcers are present in 35% of cases[26,27]. These figures are lower than those reported in our population. Nonetheless, our figures also remain lower compared to other studies conducted in Colombia: Vélez et al. reported a prevalence of 62.1%[17], and Escorcia & Marrugo reported 62.6%[10].

The prevalence of overt hepatic encephalopathy at the time of cirrhosis diagnosis ranges from 10% to 14%, and from 16% to 21% in decompensated cirrhosis[28,29]. National

studies are also consistent with international literature, reporting prevalences between 5.6%[18] and 22.5%[10]. The higher figures observed compared to other studies may be related to the high prevalence of alcohol-related cirrhosis, which is associated with a greater number of cases of hepatic encephalopathy.

The most common comorbidity was arterial hypertension. Our findings are consistent with the frequency of hypertension in the general Colombian population, considering that the reported national prevalence of arterial hypertension is 28.14%[30,31]. The second most common comorbidity was type 2 diabetes mellitus[32-34]. This latter finding aligns more closely with the general population prevalence and with our reported prevalence of diabetes in cirrhotic patients. However, compared to other studies, the frequency of this condition remains high, possibly due to specific dietary habits of the regional population, which are based on high carbohydrate consumption.

The high percentage of patients with rheumatoid arthritis in our population is noteworthy, considering that, according to the latest audited and analyzed period reported by the Cuenta de Alto Costo de Colombia (Colombian High-Cost Account), corresponding to the period between July 1, 2020, and June 30, 2021, only 0.27% of the Colombian population is affected by this pathology[35]. Among the group of cirrhotic patients with autoimmune etiology, one patient (8.3%) had arthritis as a comorbidity. This suggests that as autoimmunity becomes a more common etiology of cirrhosis in our setting, the occurrence of polyautoimmunity in these patients also increases.

The frequency of the history of biliary lithiasis in our population of cirrhotic patients was higher than what has been reported in the literature. In the general population, the prevalence of this condition is approximately 10%, and in Colombia, it is 8.6%[36]. However, this could be related to the local epidemiology of lithiasis, highlighting the need for further local research on this topic.

CONCLUSIONS

Liver cirrhosis is a pathology that generates high costs for both the healthcare system and the patient. The main cause of cirrhosis is alcohol consumption, a modifiable risk factor. There is a higher prevalence in males, which is attributed to exposure-related factors. The mortality rate of this condition is high, and according to the natural course of the disease, the patient's quality of life is significantly affected, increasing the years of life lost due to disability and death.

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Authors' own resources.

Conflicts of interest

The authors state that they have no conflicts of interest.

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Original article

Characterization of Patients with Lactose Intolerance at a Gastroenterology Diagnostic Center

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Abstract

Introduction: The estimated global prevalence of lactose intolerance is 68%, while in Colombia, it reaches up to 59%. Primary lactase deficiency is the most common cause of lactose intolerance and malabsorption in adults. The lactose hydrogen breath test (HBT) is a routinely used diagnostic tool for this condition. **Methodology:** All lactose hydrogen breath tests (HBTs) conducted between August 2020 and September 2023 at the Gastropack medical center in Cartagena were reviewed. These tests were performed on patients presenting with symptoms such as abdominal pain, bloating, and diarrhea during gastroenterology consultations. Medical records were analyzed, and all clinical and sociodemographic variables were documented to characterize the population with lactose intolerance. **Results:** Out of 397 hydrogen breath tests performed between August 2020 and September 2023, 62 were identified as lactose HBTs. Of these, 24.4% were female patients, with an average age of 47 years. The most common symptoms included abdominal pain (71%), bloating (66.1%), diarrhea (30%), and flatulence (29%). Additionally, 38.7% of patients had a prior diagnosis of irritable bowel syndrome (IBS). Overall, 51.6% of the tests were positive for lactose intolerance. Among IBS patients, 44% tested positive for lactose intolerance. No statistically significant differences were found between patients with and without lactose intolerance. **Conclusion:** This study did not identify specific factors associated with lactose intolerance. Although the sample size was relatively small, performing lactose hydrogen breath tests is recommended in patients with suggestive symptoms and in those with conditions that share similar symptoms, such as IBS. This approach can help prevent unnecessary dietary restrictions that may negatively impact patients' quality of life and nutritional status.

Keywords

Lactose intolerance, abdominal pain, diarrhea, irritable bowel syndrome.

INTRODUCTION

Lactose is a disaccharide composed of D-galactose and D-glucose. It is the primary source of sugar in milk and the main carbohydrate in human milk, necessary for the proper growth of newborns(1). The enzyme lactase, which is required for the adequate absorption of lactose from breast milk, is present from the 8th week of gestation, with a maximum peak expression at birth(2).

Primary lactase deficiency is the most common cause of malabsorption and lactose intolerance (LI) in adults. It is secondary to two single nucleotide polymorphisms in the lactase gene on chromosome 2q21, which leads to a genetically programmed progressive decrease in lactase synthesis and impaired lactose absorption at the enterocyte level. This creates an osmotic load in the intestinal lumen, which in turn causes osmotic diarrhea. When fermented by the gut microbiota, it leads to the formation of short-chain fatty acids,

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hydrogen, carbon dioxide, and methane, resulting in symptoms such as abdominal pain, bloating, and flatulence[3].

The terms "lactose malabsorption" and "lactose intolerance" should be differentiated. Lactose malabsorption refers to any cause of an inability to absorb lactose in the small intestine due to low activity or absence of the lactase enzyme. In contrast, lactose intolerance (LI) refers to the point at which the lactose load exceeds the residual activity of the lactase enzyme, leading to the onset of symptoms[1].

LI is a very common condition worldwide, with an estimated prevalence of approximately 68%[4]. Studies conducted in Colombia show an approximate prevalence of 59% using hydrogen breath tests following lactose loading, and up to 80% based on genotypic studies[5,6]. The prevalence of LI varies greatly depending on geographic location, ranging from 20% in Europe to as high as 100% in South Korea[4]. The actual prevalence of LI is difficult to estimate because significant differences exist between ethnic groups, and the variability of diagnostic methods complicates the interpretation of results.

The nonspecific nature of its symptoms and the overlap with other conditions, such as irritable bowel syndrome (IBS), can lead to underdiagnosis and prevent some patients from receiving the appropriate treatment and recommendations for managing their symptoms, which ultimately results in a decreased quality of life. Identifying risk factors can help make an early diagnosis, which can improve symptoms and enhance the quality of life for patients.

OBJECTIVE

The objective of this study was to identify the factors associated with lactose intolerance in a group of patients who attended a gastroenterology diagnostic center for symptoms of bloating, abdominal pain, and diarrhea, with or without a previous diagnosis of IBS or dyspepsia.

METHODOLOGY

A retrospective cross-sectional study was conducted, including patients over 18 years of age who visited the gastroenterology clinic for symptoms of bloating, abdominal pain, and diarrhea, with or without a prior diagnosis of IBS or dyspepsia. These patients underwent a lactulose hydrogen breath test (LHBT) between August 2020 and September 2023. All medical records were reviewed, and clinical variables such as abdominal pain, bloating, constipation, diarrhea, nausea, and flatulence were recorded, as well as sociodemographic variables, including a history of hypertension, diabetes mellitus, dyslipidemia, and smoking.

The study protocol was carried out in accordance with the principles of the Declaration of Helsinki for medical research and Resolution 8530, which regulates clinical research in Colombia. The privacy of medical records was respected at all times. The institutional ethics committee approved the protocol, and it was considered a minimal-risk study for patients. Quantitative and qualitative variables were expressed as mean (SD) and percentages, respectively. Hypothesis testing was performed using a Student's t-test or Chi-square test, as appropriate. Statistical significance was set at $p \leq 0.05$.

Lactose load hydrogen breath test

Four weeks prior to the study, the use of antibiotics and any endoscopic procedures that could cause variations in the intestinal microbiota were suspended. 24 hours before the study, the consumption of dairy products, fruits, or fruit juices, as well as fiber, beans, peas, cabbage, leeks, onions, or garlic, was restricted. 12 hours before the procedure, smoking and chewing gum were prohibited.

Study procedure

After a 14-hour fast, each patient was given 25 g of lactose dissolved in 250 mL of water. Breath hydrogen samples were taken at 15, 30, 45, 60, 90, 120, 150, and 180 minutes, along with an assessment of symptoms at each sample collection point. The hydrogen breath test was considered positive if a level of >20 parts per million (ppm) was detected at 80 minutes after the lactose administration.

RESULTS

Out of a total of 397 hydrogen breath tests conducted between August 2020 and September 2023 at the Gastropack medical center, 62 LHBTs were identified. Of these, 24.4% were women, with an average age of 47 years. Additionally, 38.7% had a prior diagnosis of IBS. A total of 51.6% of the tests were positive, with a direct proportional increase to age, as the highest number of affected patients was found in those over 50 years old (40%) (**Table 1**). The most frequent symptoms were abdominal pain (71%), followed by abdominal distension (66.1%), diarrhea (30%), and flatulence (29%) (**Table 2**). Comorbidities found included hypertension (17%), dyslipidemia (9%), and hypothyroidism (5%) (**Table 3**).

In patients with lactose intolerance, the average age was 49 years, and 25% were female. A total of 44% (11/24) of patients with IBS were lactose intolerant. They had few comorbidities, such as hypertension, dyslipidemia, or hypothyroidism. The most frequent symptom was abdominal distension (24%), followed by abdominal pain (21%), diarrhea (12%), and flatulence (10%). When comparing

Table 1. General characteristics of the population

Variable	n = 62
Sex	
- Male	75.8% (47)
- Female	24.2% (15)
Age (SD)	47.7 (16.2)
Irritable bowel syndrome	38.7% (24)
Lactose intolerance	51.6% (32)
Age ranges in patients with lactose intolerance	
- Range between 20 and 30 years	6.3% (2)
- Range between 31 and 40 years	28.1% (9)
- Range between 41 and 50 years	21.9% (7)
- Over 50 years	40.6% (13)

Table created by the authors.

Table 2. Clinical manifestations of the population

Variable	n = 62
Abdominal pain	71% (44)
Abdominal distension	66.1% (41)
Constipation	19% (12)
Diarrhea	30.6% (19)
Emesis	1.6% (1)
Nausea	6.5% (4)
Flatulence	29% (18)

Table created by the authors.

Table 3. Personal history of the population

Variable	n = 62
Personal history	
- Arterial hypertension	17 % (11)
- Dyslipidemia	14.5% (9)
- Cardiovascular disease	4.8% (3)
- OSAHS	3.2% (2)
- Hypothyroidism	8.1% (5)
- Type 2 diabetes mellitus	1.6% (1)
- Smoking	4.8% (3)

OSAHS: obstructive sleep apnea/hypopnea syndrome. Table created by the authors.

the age of patients with and without lactose intolerance, no statistically significant difference was found. Although the symptoms of abdominal distension, diarrhea, and flatulence were more frequent in the lactose-intolerant group compared to patients without lactose intolerance, no statistically significant differences were observed (**Table 4**).

DISCUSSION

Of all the patients who underwent the hydrogen breath test, 38.7% had a history of IBS, and of the patients with lactose intolerance (LI), 34% had concomitant IBS. This finding supports the existing interrelation between these two conditions and also broadens the scope of potentially affected patients, considering that the global prevalence of IBS ranges from 9% to 23%[7].

Previous studies have shown a clear relationship between LI and IBS. In a 2016 case-control study conducted in Germany, which evaluated the comorbidity burden reported in 6758 medical records of patients with and without LI, it was found that the presence of IBS was five times more common in patients with LI[8]. Some authors attribute these findings to the fact that many patients with LI are misdiagnosed as having IBS.

In a prospective study conducted in the Netherlands in 2001, 70 patients with a prior diagnosis of IBS were recruited, and LI was detected in 24.3% of them. There were no differences in symptoms between patients with a positive lactose tolerance test and those with a negative result. However, after following a lactose-free diet, gastrointestinal symptoms improved statistically significantly in these patients[9].

Another study conducted in Italy, aimed primarily at identifying patients with LI among those with a prior diagnosis of IBS, enrolled 259 IBS patients and 108 control patients. Among the IBS patients, 79.9% tested positive for the hydrogen breath test, compared to 25% in the control group, with a statistically significant difference (p <0.001). These findings highlight the importance of ruling out lactose intolerance in patients with a prior IBS diagnosis[10].

In contrast, a study conducted in 2004 found no relationship between both conditions and suggested that the diagnosis of LI in patients with IBS may result in false positives, as IBS itself is associated with bacterial overgrowth, which can distort hydrogen breath test results. Furthermore, the continuous consumption of dairy products in intolerant patients may be linked to persistent irritation of the gastrointestinal tract, which could ultimately evolve into IBS[11, 12].

Regarding symptoms, patients with LI more frequently presented with abdominal distension, diarrhea, flatulence, and nausea compared to those without LI, although these differences were not statistically significant. These findings are consistent with the fact that the symptoms of LI are sha-

Table 4. Characterization of patients with and without lactose intolerance

Variables	With lactose intolerance n = 32 (%)	Without lactose intolerance n =30 (%)	*p*-Value
Female	25 (8)	23.3 (7)	0.87
IBS	34.4 (11)	43.3 (13)	0.46
Age (SD)	49.2 (15.8)	44.9 (16.5)	0.3
Arterial hypertension	9.4 (3)	26.7% (8)	0.07
Dyslipidemia	15.6 (5)	13.3 (4)	0.79
Hypothyroidism	12.5 (4)	3.3 (1)	0.18
Smoking	9.4 (3)	0 (0)	0.08
Abdominal pain	65.5 (21)	76.7 (23)	0.33
Abdominal distension	75 (24)	56.7 (17)	0.12
Constipation	12.5 (4)	26.7 (8)	0.15
Diarrhea	37.5 (12)	23.3 (7)	0.22
Nausea	9.4 (3)	3.4 (1)	0.35
Flatulence	31.3 (10)	26.7 (8)	0.69

SD: standard deviation. Table created by the authors.

red by many other conditions, including IBS, inflammatory bowel disease, celiac disease, and even malignant gastrointestinal conditions[13].

In 2010, a systematic review was conducted to evaluate the diagnostic value of the most common gastrointestinal symptoms of LI (diarrhea, abdominal pain, abdominal distension, flatulence, and constipation), and the results were highly heterogeneous. For example, diarrhea had a sensitivity ranging from 30% to 80%, and specificity ranging from 32% to 84%. Similar trends were observed with the other symptoms, which supports the assertion that symptoms alone are insufficient for diagnosis[14].

The diagnostic value of self-reported lactose intolerance remains a topic of debate. On one hand, many more individuals seem to attribute their symptoms to lactose intake than what objective tests are able to confirm. On the other hand, some patients have a positive hydrogen breath test for lactose intolerance, but they have not recognized the association between dairy consumption and the presence of symptoms[15,16].

There are different tests to evaluate lactose intolerance. In our study, we used the hydrogen breath test, which has the advantage of being widely available and having an adequate diagnostic performance, with a sensitivity of 78% and specificity of 98%[17].

The importance of an accurate diagnosis lies in avoiding unnecessary restrictions on dairy foods in the diet, as this could be associated with demineralization and subsequent reduction in bone density[18]. These phenomena have previously been demonstrated in children aged 3 to 10 years[19]. In adult patients, a prospective study in postmenopausal Korean women evaluated the consumption of dairy products, including milk and yogurt, and the incidence of osteoporosis. The study found that women with a high intake of these dairy products had a 48% lower risk of osteoporosis in the radial bone compared to those who did not consume them[20].

The impact of dairy consumption on cardiovascular risk has also been evaluated. A meta-analysis of 22 studies found a 12% reduction in the total risk of cardiovascular disease and a 13% reduction in the risk of presenting acute coronary syndrome with the consumption of dairy products[21].

No factors associated with LI were identified, so it is recommended to rule it out in patients with compatible symptoms, even if these symptoms are similar to those found in other pathologies. This helps avoid unnecessary dietary restrictions that could affect patients' quality of life and nutritional status.

This study has limitations, including its retrospective, single-center design, limited to a sample of patients from the gastroenterology clinic. Additionally, the symptoms taken

from the medical records may have a bias of underreporting of clinical manifestations in some of the cases studied.

CONCLUSION

In the present study, no factors associated with lactose intolerance were identified. Although the number of patients is not very large, it is recommended to perform the lactose overload hydrogen breath test in patients with symptoms suggestive of this condition, as well as in diseases with similar symptoms, such as IBS. This will help avoid unnecessary dietary restrictions that could affect the quality of life and nutritional status of the affected patients.

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Review article

Research and publish. Part 5. How to present and evaluate an observational study: cohorts

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Abstract

Introduction: Cohort studies are a fundamental design in epidemiological and clinical research, allowing the evaluation of associations between exposures and health outcomes over time. Their longitudinal structure enables the estimation of disease incidence and the calculation of association measures such as relative risk. However, these studies present methodological challenges, including selection bias, information bias, and confounding, which must be addressed through appropriate design and analytical strategies. **Methods:** To enhance the quality and transparency in reporting cohort studies, the STROBE Statement provides a detailed guide on key aspects to include in a scientific article, such as participant selection, exposure and outcome measurement, and statistical methods used. **Results:** In the interpretation of cohort studies, the JAMA Evidence framework facilitates the assessment of study validity through a three-step approach: identification of bias risk, analysis of the magnitude and precision of the association, and determination of the applicability of findings in clinical practice. **Conclusion:** Cohort studies are essential for generating health-related evidence, but their validity relies on rigorous execution and proper critical appraisal. The use of tools such as STROBE and JAMA Evidence improves the quality of reporting and interpretation, strengthening their impact on biomedical research and clinical practice.

Keywords

Cohort, epidemiology, observational studies, relative risk, validity (epidemiology), evidence-based medicine.

INTRODUCTION

Cohort studies are a key design in epidemiological and clinical research, used to evaluate the relationship between exposures and health outcomes. Their main characteristic is the longitudinal follow-up of a group of individuals, which allows for the estimation of disease incidence and the assessment of its relationship with specific risk factors[(1)]. Unlike cross-sectional studies, which only allow the evaluation of prevalences at a single point in time, cohort studies can determine if an exposure precedes the outcome and estimate the relative risk[(2)].

Types of cohort studies

Cohort studies can be classified based on the timing of exposure measurement and the structure of the study population.

Prospective cohort studies

In this design, researchers identify and select participants before the outcome of interest occurs. Exposed and non-exposed groups are defined and followed over time to assess the incidence of the disease. A key advantage is the ability to measure exposures accurately and establish the

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temporal sequence between exposure and disease, which reduces information bias[1].

A classic example is the Framingham study. It was one of the most influential cohort studies in cardiovascular epidemiology, initiated in 1948 in Framingham, Massachusetts. Key risk factors for cardiovascular diseases, such as smoking, hypertension, and dyslipidemia, were identified[1,3].

Retrospective cohort studies

In this design, both the exposure and the outcome have already occurred by the time the study begins. Medical records, databases, or clinical histories are used to reconstruct the exposure history and assess the incidence of the disease. While this method is more time- and cost-efficient, it can be limited by the quality of available data and information bias[1].

An example is exposure to radiation and cancer. Retrospective studies in Hiroshima and Nagasaki have evaluated the incidence of cancer among atomic bomb survivors, using historical records to determine exposure and follow individuals over the years[1,4].

Ambispective cohort studies

This design combines both prospective and retrospective elements, using historical data to assess past exposures and continuing to follow individuals in the present and future. This approach allows for the use of prior information, which can be complemented with prospective data.

An example is the British birth cohort of 1946. This study began with perinatal data and has followed participants into adulthood, gathering information on multiple exposures throughout their lives[1].

Special cohort studies

There are methodological variations that can enhance the efficiency and precision of cohort studies.

- *Multiple cohort studies*: These studies compare two or more groups of individuals with different levels of exposure. For example, workers exposed to a chemical agent can be compared to unexposed workers in the same industry[1]. One example is the study on asbestos exposure. A study compared workers exposed to asbestos with office employees and evaluated the incidence of mesothelioma[1].
- *Matched cohort studies*: In this design, each exposed participant is matched with an unexposed individual with similar characteristics, such as age and sex, reducing the effect of confounding variables[1]. One example is studies on smoking and lung cancer. Several studies have matched smokers and non-smokers based on factors such as age and socioeconomic status, improving comparability between the groups[1].
- *Nested cohort studies*: These studies combine the advantages of cohort and case-control studies. Within an established cohort, cases of the disease are identified and compared with a randomly selected subset of controls from the same cohort, reducing costs and improving study efficiency[1]. An example is the *Nurses' Health Study*. This study has used a nested cohort design to investigate risk factors for breast cancer and other chronic diseases, leveraging its extensive prospective database[5].

Advantages and disadvantages of cohort studies

Despite their benefits, cohort studies present methodological challenges that should be considered (**Table 1**).

Table 1. Advantages and disadvantages of cohort studies

Advantages	Disadvantages
They allow to evaluate incidence and relative risk	They are expensive and require long follow-up periods
They establish the temporal sequence between exposure and disease	There may be loss to follow-up of participants
They avoid memory biases common in retrospective studies	They may require large sample sizes
They allow the study of multiple outcomes from a single exposure	Exposure to confounding factors that are difficult to control

Adapted from: Gordis L. Elsevier; 2013[1].

Main biases in cohort studies

Cohort studies can be subject to biases that affect the validity of their results, including the following:

- Selection bias: This occurs if the comparison groups are not representative or if there are systematic differences in the inclusion of participants[1].
- Information bias: This arises when the measurement of exposure or outcome is inaccurate. It is especially relevant in retrospective studies that rely on previous records[1].
- Confounding: This happens when an external variable is associated with both the exposure and the outcome, thus biasing the observed association[1].

Cohort studies have been fundamental in epidemiology and clinical research, as they provide crucial information on risk factors and preventive strategies in public health. Their implementation requires rigorous design to minimize biases and maximize the validity of findings. The choice between a prospective, retrospective, or nested design

depends on the study's objectives, the availability of data, and the resources available. Despite their challenges, the impact of these studies on risk identification and the formulation of public health policies is undeniable[1].

METHODS

Presentation of a cohort study according to *STROBE*

The *STROBE Statement* (Strengthening the Reporting of Observational Studies in Epidemiology) is an international guideline designed to improve the quality and transparency in the presentation of observational studies, including cohort studies[6]. Its goal is to ensure that authors provide sufficient information for readers to assess the validity of the findings, minimizing biases and promoting reproducibility.

Key elements of *STROBE* in a cohort study

STROBE includes 22 items, several of which are essential for the methods section of a scientific article. Below are the most relevant points for a cohort study.

Study design

- Explicitly state that it is a cohort study and specify whether it is prospective, retrospective, or ambispective.
- Justify the choice of design based on the research question.
- Describe the hypothesis and the expected direction of the association.

Example of phrasing: "A prospective cohort study was conducted to evaluate the relationship between benzodiazepine exposure and the risk of falls in older adults, with a five-year follow-up."

Selection of participants

- Inclusion and exclusion criteria: clearly define the criteria used to select participants.
- Recruitment methods: indicate whether participants were identified from medical records, surveys or population sampling.
- Define the source of the cohort: explain whether it comes from a hospital database, epidemiological database or pre-existing cohort.

Example: "Patients aged ≥65 years treated in healthcare centers affiliated with the National Health System between 2015 and 2020 were included. Patients with prior history of fractures or neuromuscular disease were excluded."

Definition of exposure and outcome

- Exposure measurement: describe how exposure was determined (clinical history, self-report, biomarkers, etc.).
- Outcome measurement: explain how the diagnosis or event of interest was established (radiological confirmation, laboratory tests, among others).
- Covariates and confounding: explain how confounding factors were addressed through matching, stratification, or statistical models.

Example: "The primary outcome was the incidence of severe falls, defined as those requiring hospitalization. Benzodiazepine exposure was defined as continuous use for ≥3 months according to the electronic medical record."

Bias minimization

STROBE recommends documenting strategies to minimize the following biases:

- Selection bias: use of propensity score matching or strict inclusion criteria.
- Information bias: application of standardized methods to measure exposure and outcome.
- Confounding: adjustment by multivariate models or sensitivity analysis.

Example: "to minimize confounding bias, the analysis was adjusted for age, sex, comorbidities, and polypharmacy using a Cox regression model."

Sample size and statistical power

- Explain the calculation of the sample size based on the expected incidence of the outcome and the minimum detectable effect.
- Justify whether the sample is sufficient to detect statistically significant differences.

Example: "the sample size calculation determined that 8000 participants were required to detect a 20% difference in the risk of falling with a power of 80% and a significance level of 5%."

Statistical methods

- Specify the methods used to analyze the data.
- Indicate how missing data were handled.
- Include the measures of association used, such as risk ratio (RR), hazard ratio (HR) or odds ratio (OR).

Example: "a Cox regression model was used to estimate the adjusted hazard ratio, and a sensitivity analysis assessed the impact of missing data."

RESULTS

Critical appraisal of a cohort study according to *JAMA Evidence*

To properly interpret the results of a cohort study, the *JAMA Evidence* guide, which proposes a three-step structured approach, should be applied[7].

Step 1: Bias risk assessment

The first step is to determine whether the study minimized biases that could affect internal validity.

Comparability of the groups:

- Did the groups start with the same risk of outcome?
- Were initial differences adjusted by statistical models?
- Were known confounding factors controlled for?

Example: "the benzodiazepine-exposed group had more comorbidities than the non-exposed group, so a propensity score adjustment was made."

Evaluation of the outcome:

- Were the same methods used to assess outcome in both groups?
- Was there a risk of surveillance bias?

Example: "the outcome was determined by standardized hospital diagnoses, minimizing information bias."

Complete follow-up:

- Was the loss rate less than 20%?
- Were there differences in follow-up between the groups?

Example: "the follow-up rate was 95% in both groups, which reduced the impact of loss-to-follow-up bias."

Step 2: Assessment of the magnitude and precision of the association

The second step is to assess the magnitude and precision of the association between exposure and outcome.

Magnitude or strength of the association:

- Measures such as relative risk (RR), hazard ratio (HR) or odds ratio (OR) are reported.
- RR values close to 1 indicate a weak association, whereas values >2 suggest a stronger relationship.

Example: "prolonged use of benzodiazepines was associated with an increased risk of falls (adjusted HR: 1.52; 95% CI: 1.32-1.75)."

Estimation accuracy:

- It is evaluated by observing the confidence intervals (95% CI).
- A wide CI suggests uncertainty, while a narrow CI indicates greater precision.

Example: "the 95% CI did not include unity, indicating that the association is statistically significant".

Step 3: Clinical applicability

The third step is to determine whether the findings can be applied in medical practice.

Comparability with the clinical population:

- Are participants representative of patients in clinical practice?

Example: "the study included only hospitalized elderly adults, which limits the generalizability to outpatient populations."

Follow-up duration:

- Was it enough to capture the outcome?

Example: "the mean follow-up was 6.2 years, which made it possible to evaluate long-term effects."

Magnitude of absolute risk:

- The absolute risk is compared between groups.

Example: "the absolute risk of falls in benzodiazepine users was 12.3%, compared with 8.5% in the control group (number needed to treat [NNT]): 25)."

CONCLUSION

Cohort studies are essential in epidemiological and clinical research as they allow for the evaluation of the relationship between exposures and outcomes over time. Their longitudinal design enables the estimation of disease incidence and the calculation of relative risk, which contributes to the identification of risk factors and public health prevention strategies.

To ensure proper presentation in scientific publications, the *STROBE Statement* provides a structured framework that promotes transparency and reproducibility in studies. Additionally, critical evaluation based on *JAMA Evidence* allows for the assessment of the internal and external validity of findings through an analysis of bias risk, the magnitude of the association, and clinical applicability.

In conclusion, the proper implementation, presentation, and evaluation of cohort studies are key to ensuring their validity and utility in health decision-making. The use of methodological checklists such as *STROBE* and *JAMA Evidence* strengthens the rigor of these studies and guarantees their impact on biomedical research and clinical practice.

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Review article

Strategies to Optimize Early Endoscopic Detection of Gastric Cancer

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Abstract

The impact of gastric cancer on the Colombian population is alarming. It is essential to promote strategies that enhance early detection by leveraging available diagnostic tools. This approach can significantly improve patient outcomes. This article presents methods aimed at enhancing the quality of endoscopic procedures and providing key insights to facilitate accurate interpretation of endoscopic findings. The goal is to establish a solid foundation for the precise identification of malignant or precancerous lesions, ultimately leading to better clinical outcomes for this patient population.

Keywords

Stomach Neoplasms, endoscopy.

INTRODUCTION

Gastric cancer (GC) is currently a global health problem, ranking fifth in incidence and fourth in cancer-related mortality[1]. In Colombia, as of 2020, the incidence was 8,214 cases, and it stood out as the leading cause of death from neoplastic diseases, with 6,461 deaths, reaching a national average of 5.26 deaths per 100,000 inhabitants[1,2]. Notably high mortality rates were reported in departments such as Boyacá and Nariño, with 13.38 and 15.72 deaths per 100,000 inhabitants, respectively, in 2014[3,4]. In addition, the prognosis in Colombia is concerning. Survival rates for the 2010-2014 period ranged from 15.4% to 18.8%[5]. In fact, Santander reported a five-year survival rate of only 11%[6]. These grim figures stand in stark contrast to the global cancer survival surveillance data (CONCORD-3), where low-incidence countries like the United States have an estimated survival rate of around 30%, and high-incidence countries such as Korea and Japan reach nearly 70%[7].

This raises an urgent question: what are we doing differently? While acknowledging Colombia-specific risk factors, such as the high prevalence of *Helicobacter pylori*[8], a critical component must be considered: the low detection rate of early gastric cancer (EGC).

IMPORTANCE

The label of early gastric cancer (EGC), defined as an adenocarcinoma limited to mucosa and submucosa regardless of lymph node involvement[9], is perhaps the one with the greatest impact on patient prognosis The 5-year survival rate for EGC in recent series exceeds 90%[10], whereas for advanced gastric cancer, it can be as low as 11%.

In Western countries, the detection rate is low. In Japan, up to half of all gastric adenocarcinoma resections are performed for EGC, while in South Korea, the rate ranges between 25% and 30%[11-13]. In contrast, in North America and Europe, EGC accounts for only 15% to 21% of detected gastric adenocarcinomas[12–14]. In Latin American countries such as Peru and Colombia, detection rates are 15.6% and 21.5%, respectively[15,16].

This significant gap has been attributed to factors such as the higher incidence of EGC in East Asia and differences in the interpretation of gastric histology in Asian centers[17], factors that are difficult to modify. However, other important variables can be addressed, such as the implementation of early detection programs. For example, Japan increased EGC detection from 15% to 57% following the introduction of screening programs[11,12]. Another actionable factor is the improvement of the quality and interpretation of upper gastrointestinal endoscopy (UGE) to enhance the detection of EGC and precursor lesions. The miss rate for EGC during UGE can be as high as 25% in Western studies, and among endoscopists with less than 10 years of experience, this rate may reach up to 32.4%[18].

Innovative methods are currently being developed to further improve detection. Among them, gastric endocytoscopy stands out as one of the new endoscopic techniques. It offers ultra-high magnification, allowing cellular-level visualization of the gastrointestinal mucosa and enabling a more detailed prediction of malignancy risk[19]. Additionally, the development of artificial intelligence programs has surpassed the EGC detection rate of expert endoscopists[19]. Non-invasive methods are also emerging as promising tools for early EGC detection, including circulating tumor DNA (ctDNA) biomarkers, microRNAs (miRNAs), long non-coding RNAs (lncRNAs), and circular RNAs (circRNAs)[20].

In contrast, in Colombia, despite alarmingly high mortality rates, strategies already described in the literature to increase EGC detection have not been consciously and systematically adopted. Therefore, the objectives of this article are to raise awareness among Colombian physicians and to present, in a concise and straightforward manner, useful strategies for increasing EGC detection in the country.

GASTRIC CANCER SCREENING

Regarding screening, countries with a high incidence of gastric cancer (>20 per 100,000 inhabitants), such as South Korea and Japan, perform UGE every two years starting at the ages of 40 and 50, respectively[21-23]. Some Colombian authors have proposed adopting these strategies at a national level[24]; however, the clinical practice guidelines of the Colombian Association of Gastroenterology and the National Cancer Institute of Colombia conclude that there is insufficient evidence to make a recommendation on this matter[25,26]. As a result, they maintain only the same recommendations for primary prevention, monitoring precursor lesions, and performing UGE in patients with uninvestigated dyspepsia over the age of 35[25,26]. These sole recommendations are established because screening programs are not sustainable in countries with developing economies[27].

Additionally, as proposed by Januszewicz et al., early detection strategies should be adapted based on the incidence in a given region. In Colombia, a country with an intermediate incidence (10-20 per 100,000 inhabitants), nationwide screening programs are not supported in terms of cost-effectiveness[27]. However, the identification of high-risk subpopulation should be considered, so they can be included in early detection programs. These programs should include active screening and eradication of *H. pylori*, and, as suggested by Januszewicz et al., existing screening programs, such as Colombia's colorectal cancer screening program, in which all individuals over the age of 50 undergo colonoscopy, should be leveraged. This represents an opportunity to perform UGE simultaneously[27]. In this way, early evaluation can be achieved, leading to the detection of either EGC or precursor lesions, allowing for resection of the former or close follow-up of the lesions.

STRATEGIES TO IMPROVE THE QUALITY AND INTERPRETATION OF UPPER GASTROINTESTINAL ENDOSCOPY FOR THE DETECTION OF EARLY GASTRIC CANCER

As the American Robert Schuller once said, "Spectacular achievement is always preceded by unspectacular preparation." Seemingly minor details, such as proper preparation, should not be underestimated, as they are essential to achieving optimal visualization of the gastric mucosa. The following key points have been proposed to support this goal.

Use of mucolytics and defoaming agents

Foam and adherent mucous content hinder proper visualization of the gastric mucosa. Therefore, in Japan, pronase is

systematically used as a mucolytic, in combination with the defoaming agent dimethylpolysiloxane[26]. In Colombia, due to the unavailability of these drugs, an alternative mixture has been recommended. It consists of 100 mL of water mixed with 2 mL of acetylcysteine (200 mg/m) and 0.5 mL (40 mg/mL) of dimethicone, administered 30 minutes before the procedure[28]. This has been shown to improve visualization of the gastric mucosa, optimize procedure time, and enhance endoscopist satisfaction[29].

Use of antiperistaltic agents

Constant peristaltic movement within a cavity characterized by multiple folds, curvatures, and variable distensibility can hinder the visualization of small lesions. Therefore, although there is no current evidence showing that this measure increases the detection of EGC, its use is recommended in cases of intense peristaltic activity[28].

The options include:

- Hyoscine butylbromide (10-20 mg intramuscular [IM] or intravenous [IV], single dose).
- Glucagon (1 mg IV, single dose).
- Peppermint oil (20 mL of 0.8% sprayed directly as an aerosol).

Hyoscine, which is readily available and low-cost, should be avoided in patients with glaucoma, prostatic hyperplasia, severe heart disease, or paralytic ileus[28]. Glucagon, in contrast, has a safe cardiovascular profile but is more expensive, less available, and contraindicated in diabetic patients or those with a history of pheochromocytoma. Peppermint oil is the safest option but is expensive and not widely available[28].

Adequate insufflation

Proper insufflation of the gastric chamber is essential to fully expose the mucosa and to avoid missing lesions hidden among the gastric folds. But what exactly constitutes adequate insufflation during UGE? In laparoscopic surgery, insufflation is pressure-controlled, which optimizes visualization and helps prevent adverse effects. In contrast, gastroenterologists rely on subjective assessments. Inadequate insufflation may result in missed lesions, whereas over-insufflation may lead to secondary complications, ranging from mild issues, such as post-procedural distension or pain, to more severe outcomes, including Mallory-Weiss or Boerhaave syndrome due to barotrauma. There is a lack of literature and evidence to determine the optimal pressure. However, preliminary findings showed that an average pressure of 10 mm Hg in the gastric cavity was well tolerated by endoscopists, allowing lesion detection without adverse effects[30].

Visualization time

Inevitably, the more time spent observing a given area, the more precisely it will be examined, thus increasing the likelihood of detecting a lesion, including EGC. This hypothesis, tested by Teh et al., demonstrated that the "slow endoscopist" (with an average UGE duration of 8.6 minutes) is three times more likely to detect a neoplastic lesion (cancer and dysplasia only) in the stomach compared to a "fast endoscopist" (with an average UGE duration of 5.5 minutes; odds ratio [OR]: 3.42; 95% confidence interval [CI]: 1.25-10.38)[31]. Notably, the European Society of Gastrointestinal Endoscopy (ESGE) includes a minimum duration of 7 minutes from endoscope insertion to removal as a quality indicator[32].

Remembering blind spots

A number of areas are commonly overlooked during the evaluation of the gastric mucosa. Therefore, it is essential to consciously assess these points[33]:

- Cardia (angle of His).
- Greater curvature of the proximal gastric body.
- Posterior wall of the gastric body.
- Lesser curvature of the antrum.
- Pylorus.

Photodocumentation

To avoid blind spots during the evaluation of the gastric mucosa, K. Yao, MD, proposed a systematic screening protocol for the stomach (SSS)[34]. The SSS begins in the gastric antrum. Using anterograde vision, photos are taken of the four quadrants of the antrum, the distal body, and the middle-proximal body. Then, in retroflexion, photos are taken of the four quadrants of the gastric fundus and the cardia, as well as three photos of the middle/proximal body and the incisura, for a total of 22 endoscopic photos (**Figure 1**).

In this regard, in Colombia, F. Emura, MD, described the systematic alphanumeric-coded endoscopy (SACE), which includes the entire upper digestive tract, evaluating 8 regions and 28 areas (**Figure 2**)[35].

INTERPRETATION OF ENDOSCOPIC FINDINGS

Determination of the risk of early gastric cancer development

Chronic gastritis associated with *H. pylori*, gastric atrophy, and intestinal metaplasia are the main risk factors linked to

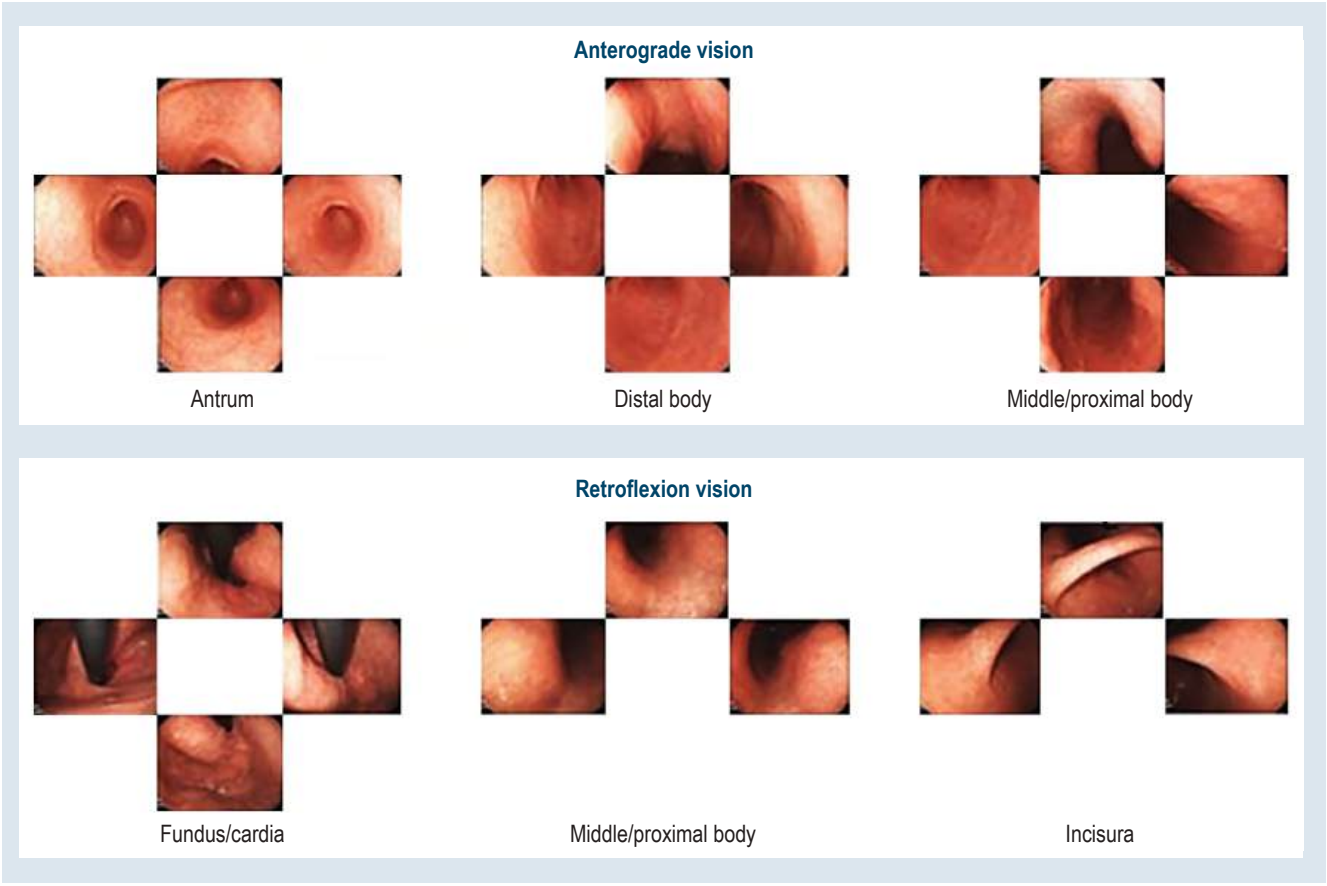


Figure 1. Systematic Screening Protocol for the Stomach (SSS). Adapted from: Toyoshima O, et al. World J Gastroenterol. 2020;26(5):466-77[38].

the development of EGC[36]. Although these conditions are defined histologically, endoscopic findings that predict such pathologies can be identified during the procedure.

Gastric atrophy

Atrophy, defined as the loss of glandular tissue, is endoscopically identified by a pale mucosa, visible submucosal vessels, and flattening of the gastric folds[36]. The Kimura-Takemoto classification (**Figure 3**), which shows a 69.8% concordance between endoscopic and histological assessment and good reproducibility (weighted kappa of 0.76; 95% CI: 0.71–0.80)[41], allows for grading the severity of atrophy. Severity is based on its extent: mild (C1-C2), moderate (C3-O1), or severe (O2-O3) atrophy predicts the 5-year risk of EGC at 0.7%, 1.9%, and 10%, respectively. Severe atrophy reflects a hazard ratio of 9.3 (95% CI: 1.7–17.4) when compared with no atrophy or mild atrophy[37].

Gastric intestinal metaplasia

With standard white light endoscopy (WLE), this condition can be identified by the presence of whitish plaques surrounded by mixed areas of pink and pale mucosa, creating an irregular surface appearance[39]. However, the diagnostic accuracy of WLE is limited when compared to image-enhanced techniques such as narrow-band imaging (NBI), which detects gastric intestinal metaplasia (GIM) with a sensitivity of 87% versus 53% for WLE ($p < 0.001$)[39]. The use of NBI is recommended to identify suggestive features such as the "light blue crest" sign, "irregular marginal zone," and "white opaque substance" (WOS) (**Figure 4**)[39].

It is recommended to classify these findings using the EGGIM score (**Table 1**), based on the percentage of metaplasia (greater or less than 30%) in the antrum, incisura, and body. Each region is scored accordingly, and if the total score exceeds 4, there is a strong correlation with histological severity (OLGIM stage III/IV), with an area under

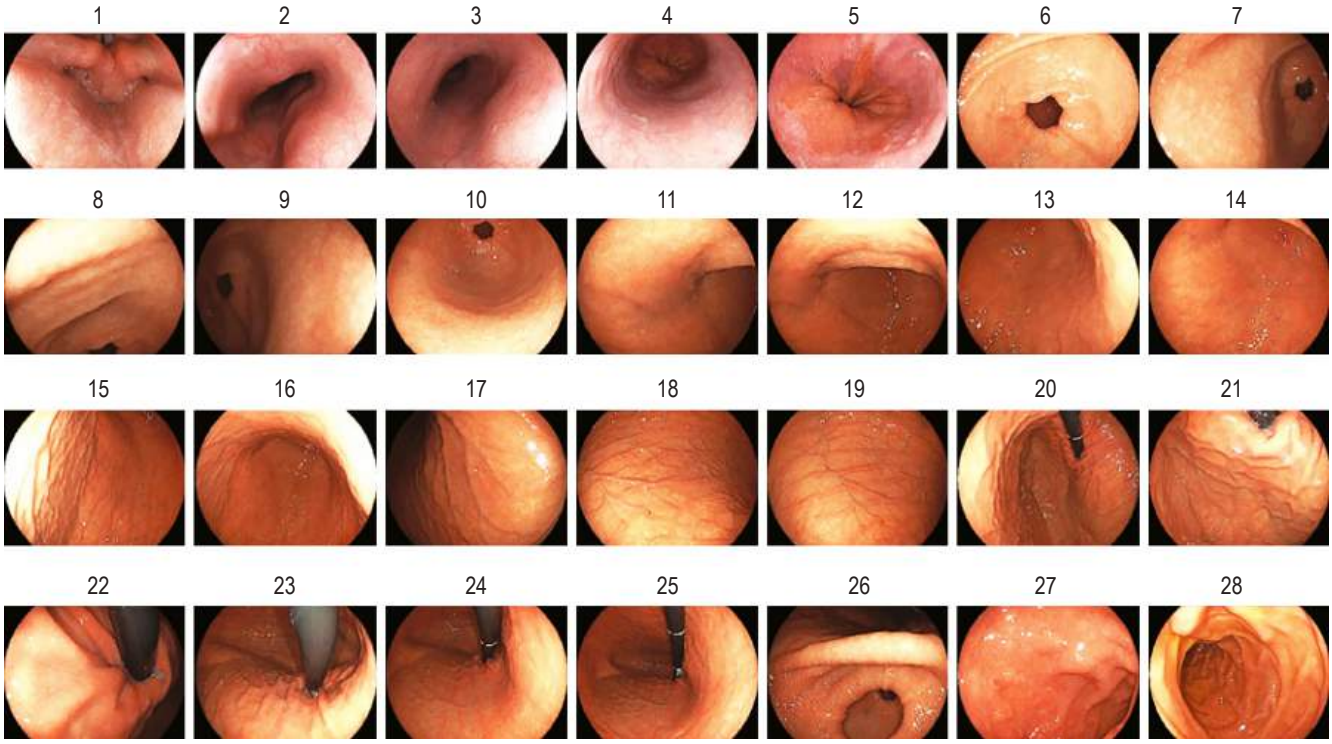


Figure 2. Reconstructed illustration of a Complete Photodocumentation of the Upper Gastrointestinal Tract. **1.** Hypopharynx. **2.** Esophagus, upper third. **3.** Esophagus, middle third. **4.** Esophagus, lower third. **5.** Esophagogastric junction. **6.** Pyloric canal. **7.** Antrum, anterior wall. **8.** Antrum, lesser curvature. **9.** Antrum, posterior wall. **10.** Antrum, greater curvature. **11.** Lower third, anterior wall. **12.** Lower third, lesser curvature. **13.** Lower third, posterior wall. **14.** Lower third, greater curvature. **15.** Middle third, anterior wall. **16.** Middle third, lesser curvature. **17.** Middle third, posterior wall. **18.** Middle third, greater curvature. **19.** Upper third, greater curvature. **20.** Upper third, anteroposterior wall. **21.** Fornix. **22.** Cardia. **23.** Lesser curvature, upper third. **24.** Lesser curvature, middle third. **25.** Lesser curvature, lower third. **26.** Angular incisure. **27.** Duodenal bulb. **28.** Duodenum, second portion. Adapted from: Waddingham W, et al. F1000Res. 2018;7:F1000 Faculty Rev-715[40].

the curve of 0.96 (95% CI: 0.93-0.98) and a sensitivity and specificity of 89% and 95%, respectively[41].

Chronic *Helicobacter pylori* Gastritis

Multiple endoscopic findings have been described in association with *H. pylori* infection. O. Toyoshima, MD, identified those findings with true statistical significance and proposed the Kyoto classification score[38], which is based on the sum of five endoscopic findings: atrophy, intestinal metaplasia, enlarged folds, nodularity, and diffuse redness (**Table 2**). A score ≥2 indicates active *H. pylori* infection with an accuracy of 82%, and a score ≥4 suggests an increased risk of gastric cancer[38].

As a protective factor, the presence of a regular arrangement of collecting venules (RAC) in the gastric body has a high negative predictive value and is a reliable endoscopic marker for ruling out *H. pylori* infection[42].

KEY FINDINGS FOR IDENTIFYING EARLY GASTRIC CANCER

After proper preparation and the identification of risk findings, the next step is to recognize lesions suspicious for malignancy. Polypoid or ulcerated lesions are easily noticeable and generally do not pose a diagnostic challenge for the endoscopist. Here, we focus on outlining guidelines to help detect suspicious neoplastic changes in superficial lesions, which can easily go unnoticed or be mistaken for changes similar to focal gastritis[34].

Findings with Standard White-Light Endoscopy

If WLE is the initial approach, it is important to be aware of signs suggestive of neoplasia. These include[43]:

- Mucosal discoloration (erythema or pallor) or asymmetric color distribution.

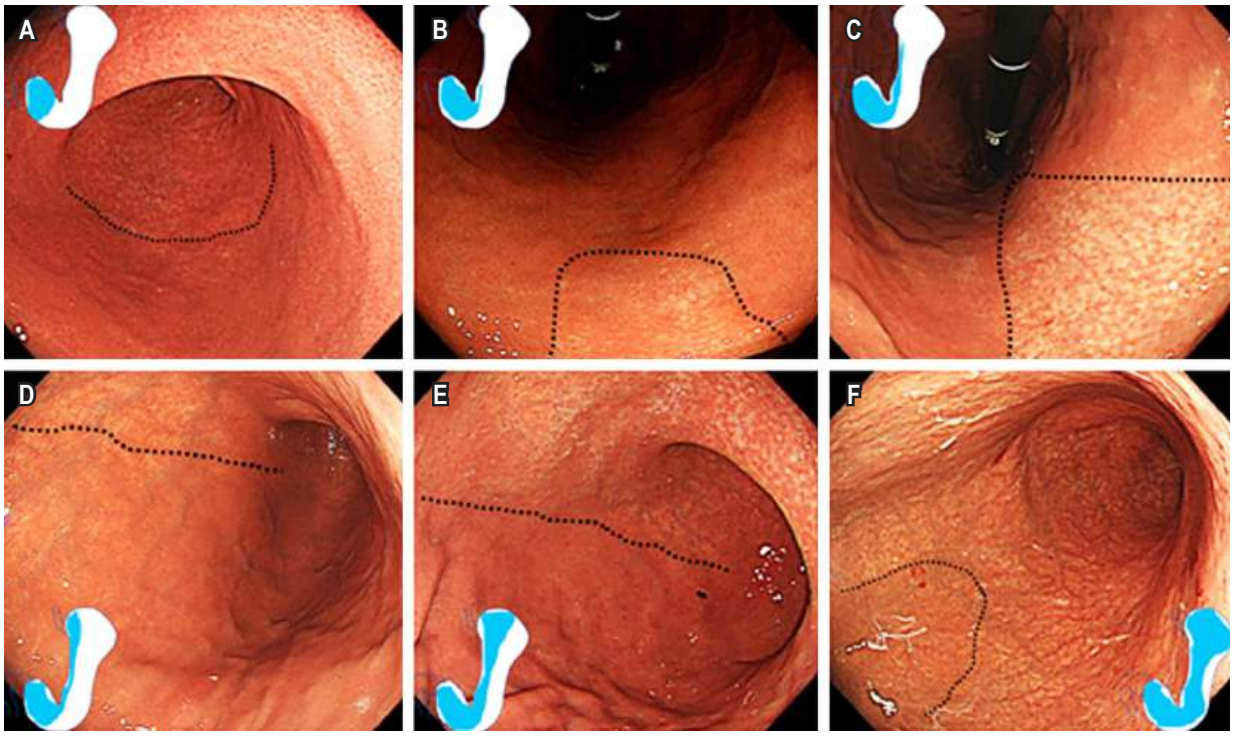


Figure 3. Kimura-Takemoto classification. **A.** C1 (atrophy is limited to the antrum). **B.** C2 (atrophy is limited to the minor area of the lesser curvature of the body). **C.** C3 (atrophy involves the main area of the lesser curvature of the body but does not extend beyond the cardia). **D.** O1 (atrophy extends to the gastric fundus passing over the cardia between the lesser curvature and the anterior wall). **E.** O2 (the atrophic border of the body compromises the anterior wall). **F.** O3 (atrophy is generalized involving the anterior wall and greater curvature). Adapted from: Toyoshima O, et al. World J Gastroenterol. 2020;26(5):466-77[38].

Table 1. Endoscopic Grading of Gastric Intestinal Metaplasia

	Lesser curvature of the antrum	Greater curvature of the antrum	Incisura	Lesser body curvature	Greater body curvature
Without GIM	0	0	0	0	0
≤30% GIM*	1	1	1	1	1
>30% GIM*	2	2	2	2	2
GIM Score					

*Percentage of affected surface area. GIM: gastric intestinal metaplasia. Modified from: Esposito G, et al. Endoscopy. 2019;51(6):515-21[41].

- Macroscopically irregular mucosa.
- Confluence of gastric folds.
- Narrow folds or abrupt interruption of folds.
- Localized mucosal opacity.
- Loss of mucosal gloss or changes in light reflection.
- Spontaneous bleeding.

This evaluation alone is insufficient to diagnose small EGC, measuring less than 1 cm. When comparing the diagnostic accuracy, sensitivity, and specificity of WLE versus magnifying narrow-band imaging (M-NBI), the diagnostic values were as follows: diagnostic accuracy of 90.4% for M-NBI vs. 64.8% for WLE, sensitivity of 60.0% vs. 40.0%, and specificity of 94.3% vs. 67.9%, respectively. The accuracy and specificity of M-NBI were significantly higher than those of WLE (p <0.001)[34]. The combination of both modalities is superior to the exclusive use of either one[34]. Therefore, concomitant use is recommended.

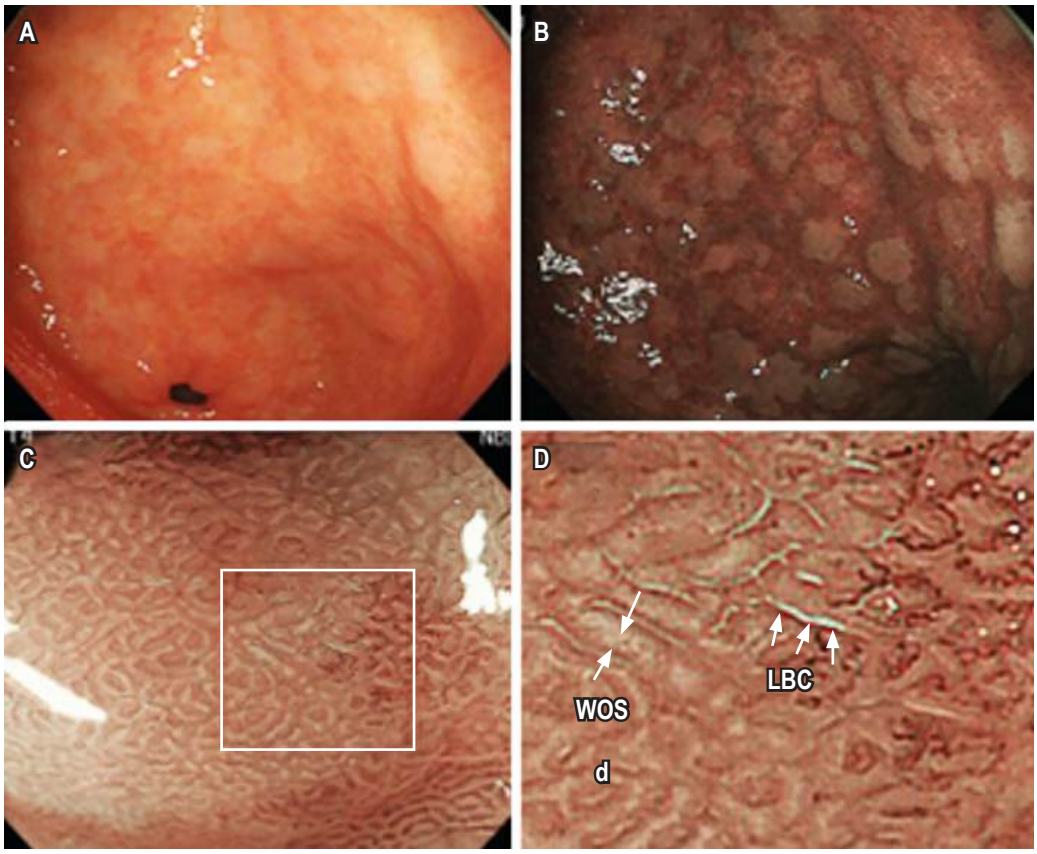


Figure 4. Endoscopic Findings of Gastric Intestinal Metaplasia. **A.** White-light endoscopy image with gastric intestinal metaplasia clearly visible as whitish plaques. **B.** Narrow-band imaging enhances mucosal contrast and highlights patches of gastric intestinal metaplasia. **C.** Magnifying endoscopy reveals light blue crests (LBC) on the epithelial surface; in some cases, white opaque substance (WOS) can be seen in the intermediate part of the crypt openings. **D.** Corresponds to the white square in image **C.** Adapted from: Waddingham W, et al. F1000Res. 2018;7:F1000 Faculty Rev-715[40].

Table 2. Kyoto Score

Endoscopic findings		Score
Atrophy (Kimura-Takemoto)	C0-C1 C2-C3 01-03	0 1 2
Metaplasia	Antrum Antrum and body	1 2
Diffuse erythema	Mild with RAC Severe	1 2
Thickening of gastric folds (>5 mm)	Absence Presence	0 1
Nodular surface	Absence Presence	0 1

RAC: regular arrangement of collecting venules. Modified from: Toyoshima O, et al. World J Gastroenterol. 2020;26(5):466-77[38].

Findings with Magnifying Narrow-Band Imaging

M-NBI enables the assessment of the microanatomy of the glandular epithelium. This allows for the identification of a clear demarcation line (DL) between the lesion and the normal mucosa, as well as the evaluation of microvascular (MV) and microsurface (MS) patterns in potentially suspicious lesions. Based on these observations, Yao et al.[34] developed the VS (vessel and surface) classification system, which categorizes microvascular and microsurface patterns as regular, irregular, or absent (**Figure 5**).

Microvascular Pattern

- Regular: mucosal capillaries exhibit a uniform, homogeneous morphology, with symmetrical distribution and regular arrangement.

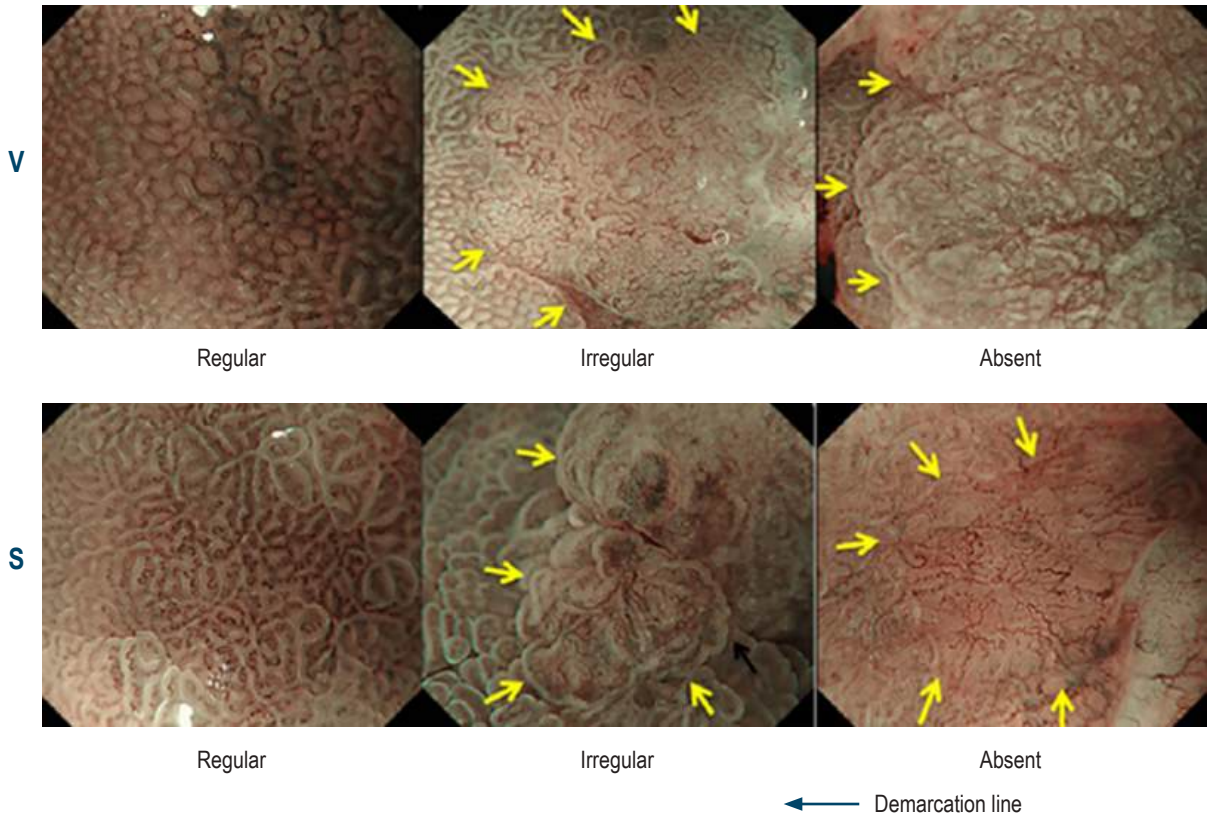


Figure 5. VS classification (vessels and surface). Modified from: Yao K. Ann Gastroenterol. 2013;26(1):11-22[34].

- Irregular: characterized by heterogeneous morphology, asymmetrical distribution, and irregular arrangement. Tortuous, branched, or aberrant vessels are observed, with or without a network.
- Absent: the subepithelial microvascular pattern is obscured due to the presence of WOS, which prevents proper visualization of the surface.

Microsurface Pattern

- Regular: the morphology of the marginal crypt epithelium shows a uniform linear/curved/oval/circular structure, with homogeneous and symmetrical distribution, and a regular arrangement.
- Irregular: the marginal crypt epithelium presents a heterogeneous morphology, asymmetrical distribution, and irregular arrangement. When WOS is present in an irregular manner, it may also be interpreted as an irregular microsurface pattern.
- Absent: neither the structure of the marginal crypt epithelium nor the WOS is visible.

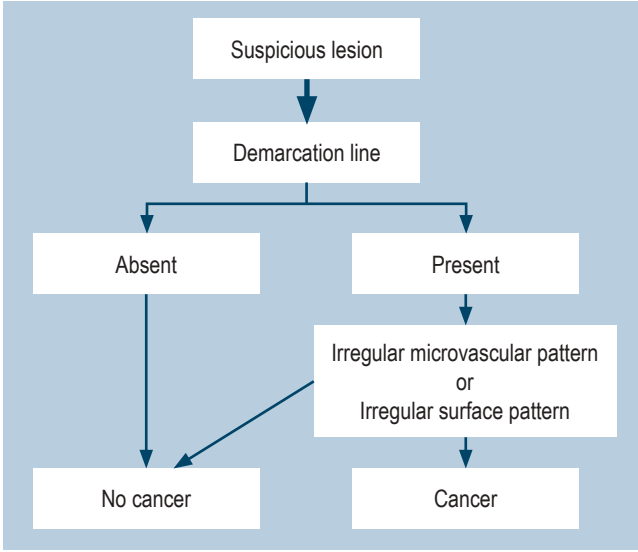


Figure 6. MESDA-G Diagnostic Algorithm. Modified from: Muto M, et al. Dig Endosc. 2016;28(4):379-93[43].

Based on these findings, it was determined that a lesion showing a DL along with either an irregular microsurface or an irregular microvascular pattern can be diagnosed as high-grade dysplasia or EGC, with a diagnostic accuracy of 97%[43]. This principle was endorsed by the Japan Gastroenterological Endoscopy Society, the Japanese Society of Gastroenterology, and the Japanese Gastric Cancer Association, and was summarized in the MESDA-G algorithm (Magnifying Endoscopy Simple Diagnostic Algorithm for Early Gastric Cancer) (**Figure 6**)[43]. It provides a simple and rapid method for endoscopic identification of EGC.

CONCLUSION

Colombia is a country with high mortality from gastric cancer, making the implementation of early detection strategies essential. Achieving high-quality endoscopy that facilitates lesion detection, along with the knowledge required for accurate interpretation of endoscopic findings, will increase the detection of EGC and optimize the follow-up of precursor lesions. This will positively impact the clinical outcomes of the Colombian population affected by this condition.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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Case report

Wilkie's Syndrome: A Rare Cause of Chronic Abdominal Pain in a Young Patient

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Abstract

Wilkie's syndrome is classified among vascular compression syndromes, with a low incidence rate. This case report details a young patient who presented with chronic abdominal pain, symptoms of chronic intestinal obstruction, and significant weight loss. Following multiple hospitalizations and a contrast-enhanced abdominal CT scan, the patient was diagnosed with superior mesenteric artery syndrome (SMAS). After initiating medical therapy, the patient's condition improved significantly. This report also includes a literature review on the topic and underscores the importance of maintaining a high index of clinical suspicion to ensure timely diagnosis and appropriate guidance for medical or surgical management.

Keywords

Superior mesenteric artery syndrome, duodenal mesenteric compression syndrome.

INTRODUCTION

Superior mesenteric artery syndrome (SAMS), also known as Wilkie's syndrome, Cast syndrome or chronic duodenal ileus, was first described by Carl von Rokitansky in 1842. In 1907, Bloodgood reported laterolateral duodenojejunostomy as the treatment of choice for this condition. However, it was not until 1921 that Wilkie published the first series of successful surgical cases[(1)]. This condition is characterized by aortomesenteric impingement at the duodenal level causing chronic gastrointestinal symptoms[(2)]. It is a diagnostic challenge since it is a rare syndrome. We present the case of a young patient with a history of chronic abdominal pain and significant weight loss.

CLINICAL CASE

This is a 34-year-old male patient with a history of open appendectomy and multiple visits to the emergency department between April 2021 and January 2022 (a total of five visits for the same complaint), with an average hospital stay of 3-4 days. During his most recent visit, he was admitted on January 4, 2023, with a five-day history of intermittent episodes of dyspepsia and colicky abdomi-

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nal pain, predominantly in the epigastric and mesogastric regions. Pain intensity was reported as 8/10 on the visual analog scale. The pain worsened with food intake and was occasionally accompanied by vomiting and early gastric fullness. In the review of systems, two episodes of hematemesis and a weight loss of 30 kilograms over six months were reported. Vital signs at admission were as follows: blood pressure (BP): 123/70 mm Hg, heart rate (HR): 67 beats per minute (bpm), respiratory rate (RR): 18 breaths per minute, temperature: 36°C, oxygen saturation: 93% on room air, and blood glucose: 87 mg/dL. The patient's weight was recorded at 54 kg, height at 171 cm, and body mass index (BMI) at 18.5 kg/m^2. Extended laboratory workup ruled out anemia, renal abnormalities, electrolyte disturbances, acute and chronic gastroenteric causes, pancreatitis, gastrointestinal infections, human immunodeficiency virus (HIV), and syphilis. A total abdominal ultrasound showed no signs of cholecystitis, cholelithiasis, collections, or masses. Upper gastrointestinal endoscopy revealed chronic gastritis, and the patient was prescribed a quadruple therapy for *Helicobacter pylori* eradication.

In previous hospitalizations, the patient had received symptomatic pain management with partial improvement. Due to persistent abdominal pain, the Internal Medicine team ordered a contrast-enhanced computed tomography (CT) scan, which revealed dilation between the second and third portions of the duodenum. A transition zone was identified at the level of the aortomesenteric clamp, with a reduced angle of less than 8° between the superior mesenteric artery and the aorta, and an aortomesenteric space measuring only 5 mm. There was no evidence of left renal vein dilation or stenosis. These findings are consistent with a diagnosis of aortomesenteric duodenal compression syndrome (**Figure 1**).

Given the findings and recurrent pain symptoms, the patient was referred to a quaternary care facility for a joint evaluation by vascular surgery and gastroenterology. Medical management was determined, guided by clinical nutrition. The nutrition team prescribed a high-carbohydrate, high-protein fractionated diet. In addition to the dietary plan, postural measures were implemented, along with gastric decompression via nasogastric tube as needed, which led to marked improvement. After three weeks, the patient was discharged with a weight of 56 kg and a BMI of 19.2 kg/m^2, with follow-up scheduled in outpatient clinics for clinical nutrition, internal medicine, and gastroenterology. It should be noted that the patient declined surgical management. During hospitalization, the patient gained 2 kilograms with medical management; however, follow-up was lost after discharge, and it was not possible to determine whether this weight gain was maintained over time.

DISCUSSION

Superior mesenteric artery syndrome, also known as Wilkie's syndrome, is a rare vascular disorder with an incidence ranging between 0.2% and 0.78%[3]. It predominantly affects women[4,5], with an average age among reported cases of 33.5 years[6]. Given its rarity, it is noteworthy that this case occurred in a male patient. Due to its low incidence, it is essential to rule out more common conditions in the evaluation of patients with unintentional weight loss, as

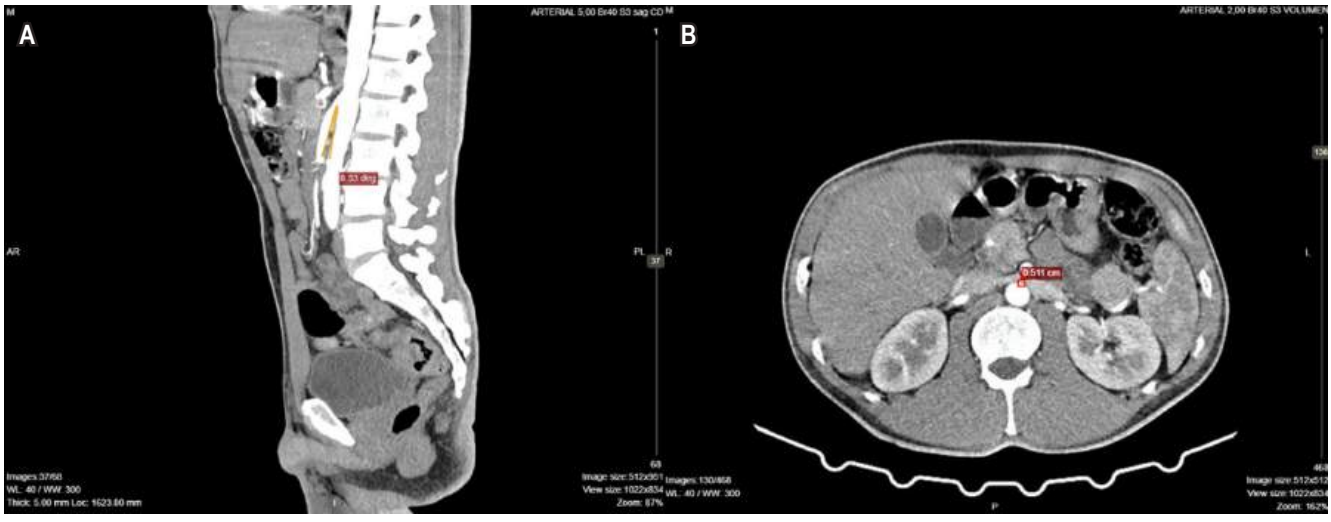


Figure 1. Double-Contrast Total Abdominal Tomography. **A.** Sagittal section, arterial phase. The aortomesenteric clamp is visualized at an angle of 8º. **B.** Cross section, arterial phase. The aortomesenteric distance of 5 mm is visualized. Images property of the authors.

was done in this case. Acute and chronic infectious causes, acquired immunosuppression, neoplastic diseases, malabsorption syndromes, medications or psychotropic substances, metabolic disorders, renal, hepatic, and psychosocial conditions were all ruled out. An esophagogastroduodenoscopy, performed as part of the initial work-up, revealed an incidental and unrelated finding of chronic gastritis. Gastric mucosa biopsy showed the presence of *H. pylori*, for which eradication therapy was initiated. It is important to highlight that this endoscopy did not reveal any duodenal segment dilatation, a finding that is often reported due to vascular compression at this level in patients with Wilkie's syndrome. However, it is important to note that a normal endoscopy does not rule out the diagnosis of vascular compression.

Wilkie's syndrome is characterized by a reduction in the aortomesenteric angle from a normal average of approximately 45º, with a typical range between 25° and 65º[3,7,8], to an angle of less than 22º-25º[3,4], or by an aortomesenteric distance of less than 8-10 mm (**Figure 2**)[3]. This narrowing results in mechanical compression of the duodenum, which in turn leads to symptoms of chronic intestinal obstruction (**Table 1**)[6,8,9]. In addition, this condition may coexist with left renal vein compression, which together may cause hematuria, varicocele, left flank pain, or renal vein thrombosis, findings consistent with the so-called *Nutcracker syndrome*[3]. In Colombia, the coexistence of these two syndromes has been documented, such as in the case reported by Suárez, Rivera, et al.[10]. Given this context, the radiological findings in this case are of particular importance, especially the absence of left renal vein involvement. Other scan findings typically include gastric distension, loss of mesenteric fat, and duodenal distension distal to the vascular compression (third portion of the duodenum)[3].

Table 1. Most Common Gastrointestinal Symptoms in Wilkie's Syndrome

Symptom
- Abdominal pain (59%): postprandial, diffuse or localized in the epigastric region, relieved in the left lateral decubitus position.
- Postprandial nausea or emesis of gastric or bilious contents (40%-50%)
- Gastroesophageal reflux
- Hyporexia-anorexia
- Weight loss

Table created by the authors.

The patient in this case presented with an aortomesenteric angle of 8° and a distance of 5 mm. Although there is no subclassification dependent on the degree of narrowing

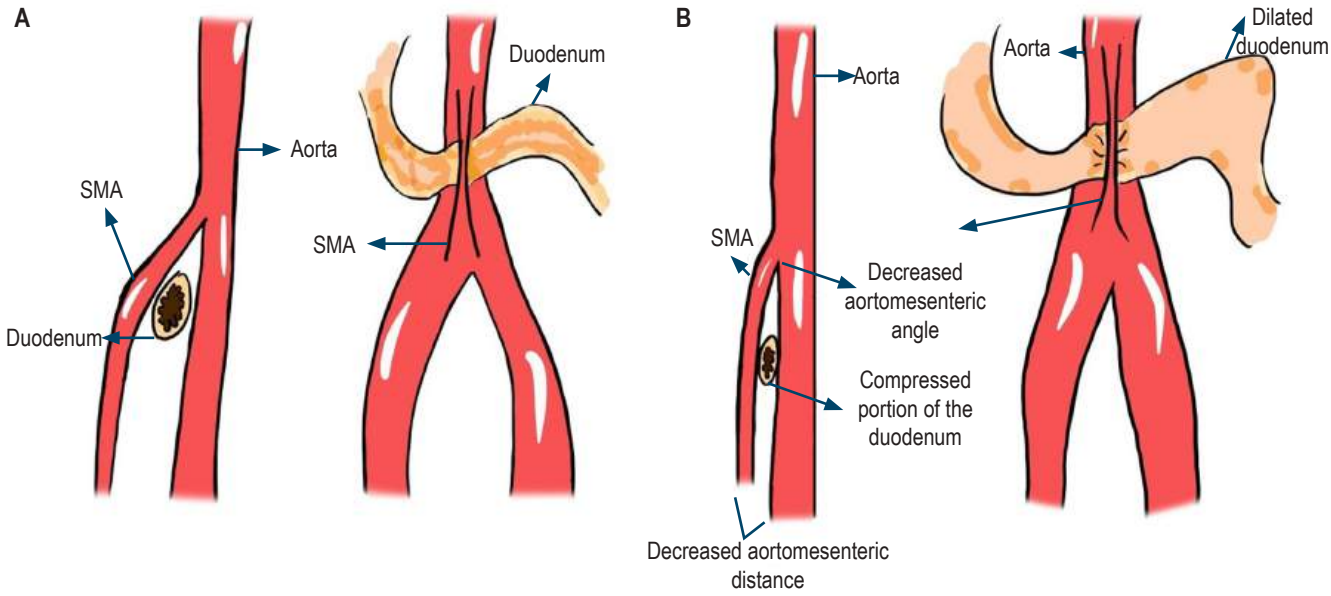


Figure 2. Mechanism of aortomesenteric compression in Wilkie's syndrome. **A.** Normal illustration of the aortomesenteric space. **B.** Compression of the third portion of the duodenum due to narrowing of the aortomesenteric angle to less than 22°-25°. The aortomesenteric distance is less than 10 mm. This narrowing leads to chronic gastrointestinal symptoms. SMA: superior mesenteric artery. The image is the property of the authors.

or the distance from the angle, we consider these values significant enough to explain the symptoms described in the case. Wilkie's syndrome can be either congenital or acquired. Risk factors for the acquired form include weight loss secondary to malignancy, bariatric surgery, eating disorders, heart failure, spinal surgeries that cause vertical traction, trauma, burns, prolonged hospitalizations, malnutrition, chronic infectious processes, or malabsorption syndromes, all of which lead to a rapid loss of intra-abdominal mesenteric fat and a consequent reduction in the diameter and angle of the clamp[3,6,8]. This patient did not present any related risk factor, as in 40% of the cases described in the literature[11]; however, it is considered that the weight loss in recent months may have been not only a consequence of the narrowing but also contributed further to the severity of the symptoms due to the loss of mesenteric fat[8].

Clinical diagnosis requires high diagnostic suspicion[6], especially in patients with abdominal pain and postprandial emesis associated with significant weight loss[7]. This case highlights the importance of timely diagnostic suspicion, which can reduce healthcare system costs related to hospitalization, improve the patient's quality of life, and prevent excessive weight loss that worsens symptoms. Although this condition has a broad range of imaging-based diagnostic tools, contrast-enhanced abdominal CT has been proposed as the method of choice[3,6,8]. Abdominal ultrasonography, when performed by an expert, allows for reliable measurement of the angle between the aorta and the superior mesenteric artery[8].

Initially, treatment is conservative[3]. Due to its low incidence or underdiagnosis, there are no recognized percentages or studies comparing symptom remission between conservative and surgical management. Nevertheless, it is acknowledged that most patients show a favorable response to conservative treatment, as was the case here, with a six-week therapeutic trial. This approach is aimed at gastric decompression through a nasogastric tube, intravenous fluid administration, correction of electrolyte imbalances, antiemetics, postural measures, and high-calorie diets via feeding tubes advanced to the jejunum until the patient can tolerate oral intake[6], in order to promote weight gain[8], along with parenteral nutrition[3,9].

Patients who do not respond to medical management benefit from surgical treatment[8], which includes gastrojejunostomy, loop duodenojejunostomy, Roux-en-Y duodenojejunostomy, or the Strong's procedure (division of the ligament of Treitz)[6,7]. Among these, duodenojejunostomy is the procedure of choice[8], as it has shown the lowest rate of perioperative complications, although there are no studies directly comparing the different surgical interventions.

CONCLUSION

Wilkie's syndrome is a rare medical condition, which requires a high degree of diagnostic suspicion, especially in patients with a history of hyporexia-anorexia, postprandial emesis, and weight loss. Early imaging of the abdomen may reveal findings regarding the aortomesenteric angle and help rule out other conditions that cause abdominal pain and signs of chronic intestinal obstruction, particularly when using contrast-enhanced CT. Conservative treatment guided by nutritional support may be sufficient in most cases of Wilkie's syndrome. Surgery is indicated in those who fail conservative management, with excellent perioperative outcomes, especially with laparoscopic duodenojejunostomy, although studies comparing the various interventions are lacking. Early diagnosis can prevent weight loss and worsening symptoms. However, due to the condition's low incidence, there is currently no early diagnostic or screening tool available to identify these patients in a timely manner. For this reason, the authors encourage clinicians to consider this diagnosis in patients presenting with the aforementioned symptoms and previously described risk factors, particularly when the evaluation of unintentional weight loss does not yield results that explain the ongoing symptomatology.

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Case report

Diaphragmatic Disease: Case Report and Literature Review

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Abstract

Diaphragmatic disease of the small intestine, named for its microscopic appearance of concentric rings of fibrotic tissue, is a rare condition with nonspecific symptoms that leads to small bowel strictures. The primary risk factor is prolonged use of nonsteroidal anti-inflammatory drugs (NSAIDs). Presenting symptoms are vague and may include chronic abdominal pain, iron deficiency anemia, weight loss, and constipation. Imaging studies often reveal findings suggestive of adhesions or a mass causing primary small bowel obstruction, making a definitive diagnosis challenging; histopathological confirmation is required. We present the case of an 88-year-old female patient who developed primary intestinal obstruction due to diaphragmatic stricture in the distal ileum, attributed to long-term acetylsalicylic acid use for her underlying comorbidities.

Keywords

Intestinal obstruction, small intestine, anti-inflammatory drugs, gastrointestinal tract.

INTRODUCTION

Small bowel diaphragm disease, named for the microscopic appearance of concentric rings of fibrotic tissue, is an uncommon pathology with nonspecific symptoms, causing small bowel stenosis[(1)]. The main risk factor is the consumption of nonsteroidal anti-inflammatory drugs (NSAIDs) for prolonged periods[(2)]. Presenting symptoms are nonspecific, including chronic abdominal pain, iron deficiency anemia, weight loss and constipation. Imaging studies generally reveal findings related to adhesions or mass causing primary small bowel obstruction[(1)], which makes definitive diagnosis difficult and ultimately confirmed by histopathology. The following is the clinical case of an 88-year-old female patient who presented with primary intestinal obstruction due to diaphragmatic stenosis in the distal ileum due to chronic consumption of acetylsalicylic acid for her underlying comorbidities.

CLINICAL CASE

This is an 88-year-old female patient with a history of cervical cancer treated with radiotherapy. She presented with a one-week history of generalized abdominal pain, associated with episodes of nausea and vomiting, dietary intolerance, and intermittent diarrhea. Upon admission, a non-contrast abdominal computed tomography (CT) scan was performed due to a prior anaphylactic reaction to contrast medium. The scan revealed an intestinal obstruction with a transition zone at the level of the distal ileum

(**Figure 1**). An exploratory laparotomy was scheduled for the same day, given the suspicion of a primary obstruction. Intraoperatively, three consecutive and progressive segments of circumferential stenosis were found, measuring 15 cm in length, creating a transition zone. These findings were initially considered to be related to the side effects of the radiotherapy the patient had previously received. Given these findings, a resection and anastomosis of the affected segment was performed without complications. The patient showed a satisfactory postoperative course, with gradual tolerance to oral intake (clear liquids, full liquids, soft, and solid diet) and the presence of bowel movements, which allowed for discharge.



Figure 1. Intestinal obstruction with a transition zone in the distal ileum. Simple abdominal CT scan, with an arrow pointing to the transition zone, with stenosis in the distal ileum. The image is the property of the authors.

During the outpatient assessment, 10 days after discharge, the patient was in good condition, pain-free, tolerating a normal diet and with an unaltered bowel habit. The pathology result was reviewed, showing stenosed intestinal folds due to a non-neoplastic lesion that expands the submucosa, a finding very consistent with diaphragmatic stenosis disease associated with nonsteroidal anti-inflammatory drugs (NSAIDs) (**Figures 2** and **3**). Based on this report, the patient was questioned about chronic NSAID use, and the finding was attributed to the use of acetylsalicylic acid (ASA), as it was the only medication from this group to which she had been chronically exposed (100 mg/day for the past five years) due to her underlying conditions. It was decided to refer her to internal medicine for evaluation to determine long-term management and whether to continue the medication.

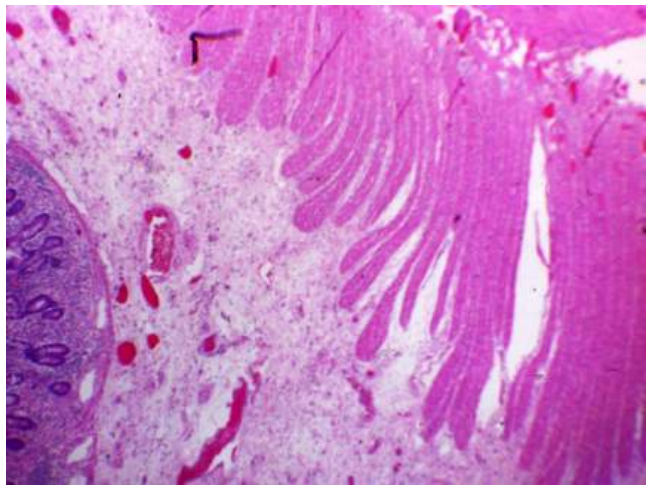


Figure 2. Magnified view at 10x. Shows details of the vertical alignment of muscle fibers and the accompanying vascularized fibrosis, forming an appearance consistent with a circular fold. The image is the property of the authors.

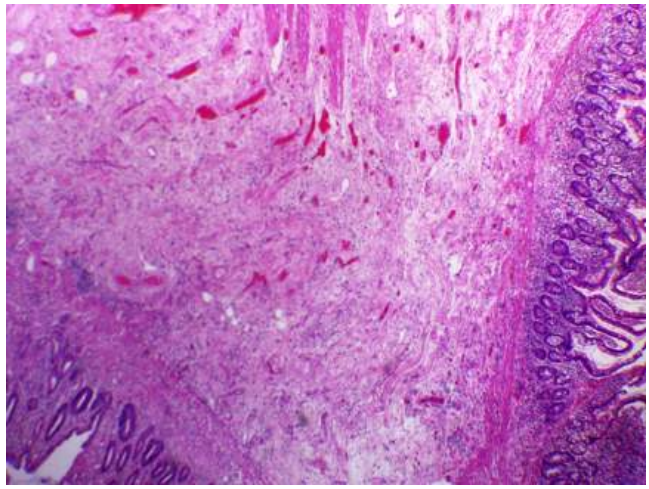


Figure 3. Panoramic view at 4x magnification. It shows how muscle fibers and fibrosis push the epithelium. The image is the property of the authors.

DISCUSSION

Diaphragm disease was first described by Lang et al. in 1988. They reported on seven patients with chronic NSAID use who developed small bowel stenosis. Histopathological analysis revealed lesions resembling perforated diaphragms, which led to the name by which the condition is currently known[3]. Its incidence is difficult to determine due to the limited number of cases reported; however, the literature states that over 50% of patients taking NSAIDs experience some degree of small bowel mucosal injury, and among

these, approximately 2% will go on to develop diaphragm disease[1,4]. Nonetheless, many cases remain undiagnosed due to the nonspecific nature of symptoms, as well as the limited awareness of this pathology among general surgeons.

The pathogenesis of the disease is not clearly defined. It is believed to be caused by the combination of an inflammatory response, fibrosis, and mucosal remodeling within the lumen of the small intestine that has been exposed to NSAIDs for prolonged periods[2]. Ulceration caused by the inhibition of cyclooxygenase 1 (COX-1) leads to microischemia, which is the initial step in the formation of the "diaphragms," described as circumferential stenotic lesions. The disease process is limited to mucosa, while the other layers of the intestine are not affected[5].

The disease can be located anywhere in the gastrointestinal tract, but the cases reported in the literature are mostly found in the small intestine, with the ileum (83%) and jejunum (17%) being the most common sites. However, it is less frequent in the distal ileum, making our case even rarer[2]. This occurs despite recent reports indicating that colonic diaphragm disease is associated with slow-release, enteric-coated NSAIDs, as these have a longer half-life, allowing them to reach the colon before being fully absorbed[6,7].

Risk factors include being female, with a 3:1 ratio, advanced age, as this population is more likely to use analgesics for prolonged periods, and finally, the prolonged use of NSAIDs[2,8]. The use of NSAIDs for at least three to five years is most commonly described, although the literature reports cases with only two months of use that also lead to stenosis, with no documented minimum dose that causes the disease[9,10]. Clinical manifestations are very nonspecific. The onset of the disease can be more insidious, with a wide variety of abdominal symptoms, generally of long duration, including pain, distension, weight loss, and soft stools associated with increased frequency. In more acute presentations, the disease may debut with intestinal obstruction and, in some cases, may even progress to intestinal perforation[5].

Among diagnostic imaging techniques, plain abdominal radiography has no utility, and contrast studies are not specific, as diaphragms can closely resemble circular folds, which may lead to confusion. Computed tomography (CT) often lacks the resolution needed to clearly visualize the "diaphragms". However, CT enterography and magnetic resonance imaging (MRI) may be useful for diagnosis. Still, making differential diagnoses is challenging, as the appearance of the strictures is very similar to Crohn's disease and radiation-induced enteritis. Nonetheless, MRI may offer a better assessment of the strictures[7,11].

Regarding endoscopic methods, due to anatomical distribution, esophagogastroduodenoscopy and colonoscopy are not useful. In contrast, double balloon enteroscopy has been effectively used as a diagnostic method, both preoperatively and intraoperatively. However, it has two limitations: its high cost and limited precision in lesion localization[12]. Nevertheless, it is highly useful intraoperatively when diaphragm disease is suspected, as it allows for intraluminal evaluation of additional affected segments of the small intestine that should be resected to prevent symptom recurrence[1]. Capsule endoscopy has been used as an alternative diagnostic tool, but the risk of retention in areas of stenosis must be considered[6]. Definitive diagnosis is made through histopathological examination, which reveals characteristic lesions such as thickening of the muscularis mucosae with ulceration at the apex of the diaphragms, fibrotic changes in the lamina propria, as well as neovascularization, nerve fibers, and eosinophils within the mucosa[6,12].

Treatment is based on two key components: discontinuation of NSAID use and surgery, with the latter being the cornerstone of treatment. Laparoscopic treatment remains highly debated and appears to have limitations, as the lesions affect only the mucosa and submucosa, leaving the serosa intact and thus undetectable macroscopically. This may lead to missed lesions. In contrast, laparotomy allows for meticulous palpation of the lesions, revealing areas of thickening and stenosis. However, if the lesions are not easily localized, intraoperative enteroscopy is recommended, as it allows for intraluminal evaluation of the affected segments. Definitive treatment consists of complete resection of the involved sections of the intestine to prevent recurrence[12]. Some case reports in the literature describe the usefulness of stricturoplasty as a surgical option in patients with extensive involvement, in whom the risk of short bowel syndrome after resection is considerable. However, the risk of therapeutic failure and recurrence is as high as 50% of cases, mainly due to incomplete resection, either because the full extent of the lesions is not recognized or because NSAID use continues[1,2,4,13,14].

Recently, endoscopic balloon dilation has been considered an alternative therapeutic option, with a very low risk of perforation due to the fibrotic characteristics of the lesions, mucosal thickening, and an intact muscular layer. However, a major limitation is that in most cases, the diagnosis is made based on the histological report of the resected lesions[6,15].

Finally, among the differential diagnoses, Crohn's disease shares similarities with diaphragm disease. However, in Crohn's disease, the entire thickness of the intestinal wall is affected, and granulomas, characteristic of the latter, are absent[5]. Radiation enteritis is particularly relevant in patients with a history of radiotherapy. Macroscopically,

intestinal mucosa shows edema, erythema, and neovascularization. Histopathological features include fibrotic lesions associated with progressive obliterative endarteritis, a vascular manifestation that leads to exaggerated submucosal fibrosis and sclerotic changes. These findings were not documented in our case, and it was ultimately histopathology that enabled the differential diagnosis[16,17]. Other differential diagnoses should also be considered, such as neuromuscular and vascular hamartomas, which resemble NSAID-induced small bowel enteropathy[6,18].

CONCLUSION

Diaphragmatic intestinal stenosis secondary to NSAID use is a rare cause of intestinal obstruction in adults, making it important to suspect in patients with chronic NSAID use, including ASA. Double-balloon enteroscopy is a diagnostic method that can be highly useful both preoperatively and intraoperatively. However, in most cases, the diagnosis is based on the histopathological report when performed by expert pathologists. Its treatment is surgical, involving complete intestinal resections of the affected segment whenever possible, along with discontinuation of anti-inflammatory medications to prevent the development of new lesions.

Conflicts of interest

The authors declare that there is no conflict of interest.

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Case report

Acute Pancreatitis Secondary to Hypertriglyceridemia: Case Report

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Abstract

Acute pancreatitis is characterized by a reversible inflammatory process affecting the pancreas. The most common causes include biliary tract obstruction and alcohol consumption. However, between 4% and 10% of cases are linked to hypertriglyceridemia, with serum triglyceride levels exceeding 1,000 mg/dL. While the exact pathophysiology remains unclear, prevailing hypotheses suggest two main mechanisms: the direct toxic effect of free fatty acids on pancreatic tissue and vascular obstruction caused by chylomicrons due to reduced genetic expression of lipoprotein lipase (LPL). Treatment focuses on lowering triglyceride levels to below 500 mg/dL. Although few interventions have proven effective, insulin therapy and anticoagulation are generally recommended. This report presents the case of a young male patient diagnosed with acute pancreatitis associated with hypertriglyceridemia, along with a review of the underlying pathophysiology and management strategies for this condition.

Keywords

Pancreatitis, hypertriglyceridemia, insulin.

INTRODUCTION

Acute pancreatitis is a reversible inflammatory process of the pancreas; the most common causes are bile duct obstruction and alcohol consumption[1]. In Colombia, the prevalence is similar between men and women, with the condition affecting more individuals between the ages of 50 and 70. In this population, approximately 50% of cases are of biliary origin, and 19% of cases have no identifiable cause. Mortality in severe cases can reach up to 8%[1,2].

Hypertriglyceridemia is the third most common cause of acute pancreatitis (APHTG), contributing to 10% of cases. It is estimated that this percentage may rise to 50% during pregnancy, making it one of the main etiologies in this population group[3,4]. The link between hypertriglyceridemia and acute pancreatitis was first identified by Speck in 1865, and since then, numerous studies have explored this relationship[5].

Complications associated with APHTG have been found to be more severe than those caused by other forms of pancreatitis[6]. Therefore, early and aggressive management is crucial. The main treatment described involves insulin infusion to reduce serum triglyceride levels through its action on lipoprotein lipase and hormone-sensitive lipase[7].

CLINICAL CASE

This is a 38-year-old male patient with a history of dyslipidemia, overweight (body mass index [BMI]: 26.8 kg/m^2), and a previous episode of pancreatitis of undetermined

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etiology. He was admitted for a 24-hour history of progressive abdominal pain, starting in the epigastrium and radiating in a band-like pattern, with no signs of peritoneal irritation, and associated with oral intolerance. Paraclinical tests showed a glucose level of 140 mg/dL, lipase of 8050 IU/L, amylase of 963 IU/L, and a normal liver profile. A biliary obstructive process was ruled out through a total abdominal ultrasound, and triglyceride levels were 5780 mg/dL. He was diagnosed with mild pancreatitis secondary to hypertriglyceridemia (APACHE-II score of 0 points).

A significant decrease in hemoglobin levels was observed, from 17.2 mg/dL to 8.9 mg/dL. However, no obvious cause of loss, such as gastrointestinal bleeding or signs of hemolysis, was identified, and thus, hemodilution was considered as a possibility. Treatment was started with insulin infusion at 0.5-1 IU/kg/h, maintaining blood glucose levels between 140 and 180 mg/dL, and enoxaparin 80 mg every 24 hours. Triglyceride levels were reduced by the second day of treatment (**Table 1**). The patient's symptoms gradually decreased, allowing for the restoration of oral intake. No complications associated with pancreatitis were reported.

Table 1. Laboratory reports

Laboratory test	Day 1	Day 2	Day 3	Day 4	Day 5
Triglycerides (mg/dL)	5780	1887	665	499	
Leukocytes (10^3/µL)	10.60	7.57		6.26	5.08
Hemoglobin (g/dL)	17.2	15.6		10.1	8.9
TB/DB (mg/dL)	0.7/0.2				
AST/ALT (U/L)	29/27	33/20			
Lactic acid (mmol/L)	2.10	1.40			
Amylase (IU/1)	963				
Lipase (IU/L)	8.050				

ALT: alanine aminotransferase; AST: aspartate aminotransferase; DB: direct bilirubin; TB: total bilirubin. Table created by the authors.

ETHICAL CONSIDERATIONS

The patient's informed consent was obtained and completed to collect clinical and paraclinical data for the purpose of writing the article, ensuring the confidentiality of the patient's personal information.

DISCUSSION

Acute pancreatitis secondary to hypertriglyceridemia (APHTG) occurs when triglyceride (TG) levels exceed 1000 mg/dL; the time required for elevated triglycerides to cause pancreatic injury is not well established[8]. It primarily affects young patients, in contrast to those with pancreatitis from other etiologies[3,9]. It has been observed that men make up two-thirds of the total patients affected by APHTG[3,7,10].

When diagnosing APHTG, it is crucial to determine the etiology of hypertriglyceridemia. This can be primary (usually polygenic), including patients with hyperlipidemia from groups I (increased chylomicrons), IV (increased VLDL), and V (increased chylomicrons and VLDL), which are particularly associated with this disease; or secondary to conditions such as diabetes, obesity, human immunodeficiency virus (HIV), estrogen use, medications like tamoxifen, or pregnancy. The latter increases the risk of developing pancreatitis associated with hypertriglyceridemia (**Table 2**)[4,7,9,10].

Table 2. Primary and secondary causes of hypertriglyceridemia

Primary causes (genetic)	Secondary causes
Type I hyperlipidemia	Obesity
Type IV hyperlipidemia	Diabetes mellitus
Type V hyperlipidemia	Renal disease: nephrotic syndrome
	Pregnancy (second and third trimester)
	Viral hepatitis
	Hypothyroidism
	Excessive alcohol consumption
	Medications: estrogens, tamoxifen, chlorthalidone, thiazides, β-blockers (non-selective and cardioselective).

Table created by the authors.

The pathophysiological mechanism of APHTG is unclear. Under normal conditions, a substance involved in the removal of triglyceride-rich lipoproteins, called lipoprotein lipase (LPL), is produced in adipocytes and myocytes. LPL is matured by lipase maturation factor 1 (LMF1). After its release, it is transported to the capillary endothelium, where it acts on triglyceride-rich chylomicrons, hydrolyzing them into chylomicron remnants and hydrolyzing triglyceride-rich lipoproteins into fatty acids and glycerol. These products are then transported to the liver, skeletal muscle, myocardium, and adipocytes for utilization. A deficiency in LPL disrupts the plasma degradation of chylomicrons, leading to an increase in free fatty acids in the serum of these patients[4,9].

In the pathophysiology of APHTG, a first hypothesis is proposed: the increase in free fatty acids due to the reduced activity of LPL, causing direct damage to the pancreatic tissue. Under normal conditions, these fatty acids are not toxic when bound to albumin or hydrolyzed by LPL. However, in APHTG, the albumin's capacity for transport is exceeded, which increases toxicity, leading to enzymatic degradation of the pancreas by endothelial lipase and lysolecithin in the acinar tissue, resulting in hemorrhages. Cellular injury leads to an increase in intracellular calcium levels and inhibition of mitochondrial complexes I and V, promoting necrosis and inflammation[9].

A second hypothesis suggests that chylomicrons obstruct the distal circulation of the pancreas, causing ischemia, which exposes the tissue to pancreatic lipase and triggers the inflammatory cascade[4,6,7]. Additionally, all these conditions lead to the activation of trypsinogen, a precursor to trypsin, which damages pancreatic acinar cells and ultimately promotes the development of pancreatitis[3].

Recent studies have identified a third mechanism related to a genetic decrease in LPL, typically of an autosomal recessive nature. Mendelian randomization analyses have shown that variants of LPL, such as APOA5, APOC3, ANGPTL3, and ANGPTL4, are associated with elevated serum triglycerides and an increased risk of pancreatitis[9].

The clinical manifestations of APHTG are similar to those of any other etiology of acute pancreatitis, including abdominal pain, nausea, and vomiting. However, the suspicion that the cause is hypertriglyceridemic is supported by the presence of the previously described risk factors[11].

The diagnosis of APHTG is made following the same criteria used for other forms of acute pancreatitis. This involves identifying at least two of the following three factors: the presence of characteristic abdominal pain, elevation of pancreatic enzymes to more than three times the upper limit of normal (ULN), and radiologic evidence confirming pancreatitis. In the initial approach to pancreatitis, the use of contrast-enhanced computed tomography is indicated only in particular cases; therefore, it was not performed in this case (**Table 3**)[12]. It is important to note that in approximately 50% of patients with APHTG, serum or urinary amylase levels at the time of diagnosis may be low or normal. This is due to interference with colorimetric reading[7,9]. Therefore, amylase levels are not useful to confirm or rule out the diagnosis of APHTG[5,6,13,14].

Additionally, pseudohyponatremia may occur for the same reasons, which normalizes as triglyceride levels decrease[7,9].

The initial management of APHTG, as in any case of pancreatitis, includes several key interventions. First, fluid replacement with crystalloids is essential, with careful monitoring to avoid fluid overload[15]. Second, pain control, early initiation of oral intake as tolerated, and strict glycemic control (target range: 140 to 180 mg/dL) are crucial. Finally, emphasis is placed on the importance of reducing triglyceride levels[13,16].

There are various options to lower triglyceride levels, including the use of insulin, heparins, and plasmapheresis. The choice of therapy also depends on the severity of the patient's symptoms, assessed through the Revised Atlanta Classification and other severity scoring systems[7]. These therapies aim to reduce the development of complications such as necrotizing pancreatitis and organ failure, both of which significantly contribute to increased mortality[17].

Table 3. Indications for contrast-enhanced computed tomography scanning

Indications
1. The diagnosis of acute pancreatitis is uncertain.
2. Patients with hyperamylasemia, severe clinical pancreatitis, abdominal distension and tenderness, fever >38.8° and leukocytosis for screening complications.
3. Ranson score >3 or APACHE score >8.
4. Patients who do not improve after 72 hours of conservative medical therapy.
5. Acute change in clinical status, such as new fever, pain, and shock after initial successful medical therapy.

Adapted from: Busireddy KK, et al. World J Gastrointest Pathophysiol. 2014;5(3):252-70 [12].

Insulin

Intravenous insulin has been used for over a decade to lower serum triglyceride (TG) levels by enhancing lipoprotein lipase activity, which accelerates the metabolism of chylomicrons and VLDL into glycerol and free fatty acids for absorption[14]. Additionally, it decreases the activity of hormone-sensitive lipase, leading to reduced breakdown of adipocytes into triglycerides and, consequently, lowering the circulation of free fatty acids. The general regimen involves a continuous infusion of 0.1 to 0.2 units/kg/hour until triglyceride levels fall below 500 mg/dL, while maintaining serum glucose levels between 150 and 200 mg/dL in cases of hyperglycemia. Insulin is able to decrease triglyceride levels from 50% to 75% in 2 to 3 days[11,13,18].

Heparin

Heparin is used as a measure to lower triglyceride levels due to its ability to activate LPL. Reports describe the use of heparin either alone or in combination with insulin,

administered through different routes and at various doses. However, although heparin has been found to produce an initial increase in LPL levels, this is quickly followed by hepatic degradation of LPL, leading to a rise in chylomicron levels. Therefore, there are significant doubts as to whether these transient effects are truly beneficial[11,18].

The duration of heparin's action has been described as 30 to 120 minutes, based on studies in healthy patients using it as monotherapy. As a result, the combined use of intravenous insulin and heparin is recommended[19,20]. Subcutaneous heparin dosing is described as 5000 units every 12 hours[20].

Plasmapheresis

Plasmapheresis has been proposed as an effective and rapid measure to remove triglycerides from the serum if the patient does not have associated hyperglycemia and there are no contraindications such as hemodynamic instability or inability to obtain venous access. To achieve triglyceride levels <500 mg/dL, three days of plasmapheresis are required. It is important to note that this therapy is highly expensive and available only in specialized medical centers. In addition, there is no clear evidence regarding its impact on morbidity and mortality[11,16]. To date, there is limited published information on its use in cases of acute pancreatitis; however, a few reports suggest better outcomes in cases of severe APHTG, defined by triglyceride levels >2000 mg/dL[18]. Some authors even recommend albumin as an alternative to plasmapheresis to avoid complications associated with plasma infusion[13].

Traditionally, APHTG has been believed to carry a worse prognosis compared to pancreatitis of other etiologies. However, the evidence is not entirely clear. In a retrospective study, APHTG was found to be associated with a higher recurrence rate and a more severe clinical course[3,9].

Prevention

Long-term management of hypertriglyceridemia is very important to prevent the development of recurrent pancreatitis. Treatment strategies include the use of fibrates and long-term therapies with omega-3 fatty acids, in addition to dietary measures and strict alcohol abstinence.

Currently, other available options include pemafibrate, a selective synthetic agonist of the PPARα nuclear receptor. This compound has been shown to reduce plasma triglyceride levels by enhancing LPL activity, lowering triglyceride levels by 26% to 28% within the first four months of treatment[21].

Among molecular therapies, ANGPTL3 inhibitors are noteworthy. Under normal conditions, this protein acts mainly as an inhibitor of LPL and endothelial lipase. Evinacumab has been shown to be effective in reducing cholesterol levels by 47% and triglyceride concentrations by 51%[9,22].

Finally, a recently published meta-analysis evaluated the incidence of pancreatitis in patients receiving Volanesorsen®, an oligonucleotide targeting APOC3 messenger RNA to reduce triglyceride levels. Among patients who received the medication, no cases of pancreatitis were reported during the four-month follow-up period[23].

Future Perspectives

The supramolecular protein mTOR complex 1 (mTORC1) is essential for the production of VLDL-triglycerides, which are exported by the liver and delivered to peripheral tissues. High-fat diets activate the mTORC1/S6K1 pathway, leading to an autophagic response in pancreatitis. Although drugs such as sirolimus increase the risk of pancreatitis, rapamycin (the precursor of sirolimus), a TOR inhibitor, has been evaluated in pancreatitis models. It has been shown to restore autophagic flow and to reduce the adverse effects of hypertriglyceridemia. However, there is no human evidence supporting this effect[24].

CONCLUSION

Acute pancreatitis secondary to hypertriglyceridemia is a rare condition, which is why there are no established protocols for its diagnosis and treatment. A triglyceride level greater than 1000 mg/dL in the presence of pancreatitis should raise suspicion for this diagnosis. It is important to be familiar with the pathophysiology for the use of insulin and heparin in the management of this condition during the acute phase.

Conflicts of interest

None.

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Case report

Endoscopic Retrieval of Migrated Coils in the Biliary Tract: Case Reports and Literature Review

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Abstract

Embolization is a widely used procedure for managing both vascular and nonvascular conditions. However, the potential migration of coils into the biliary tract has been documented in medical literature, with clinical presentations often resembling biliary obstruction caused by choledocholithiasis. This report discusses two cases of coil migration into the biliary tract following arterial embolization and their subsequent endoscopic removal. Endoscopic management is the preferred approach; however, the technique used depends on the patient's clinical condition and anatomical considerations.

Keywords

Biliary tract obstruction, choledocholitiasis, therapeutic embolization, foreign body migration.

INTRODUCTION

Embolization is a versatile procedure used in the treatment of a wide range of vascular and non-vascular pathologies. However, potential complications are also complex and varied. The success rate of hepatic embolization can be as high as 86%, while the associated morbidity can reach up to 58%, usually related to bile leaks, hepatic abscesses, or necrosis[1]. Migration of coils or clips used in surgical procedures into the biliary tract has been reported in the literature, typically as a result of necrosis or fistulization of adjacent structures. Other theories include bacterial or fungal superinfection of pseudoaneurysms and coils, leading to subsequent inflammation and erosion[2-5].

PRESENTATION OF CASES

Case 1

This is a 60-year-old male patient who presented in 2018 with recurrent choledocholithiasis (history of cholecystectomy in 2012). He underwent endoscopic retrograde cholangiopancreatography (ERCP) and biliary stent insertion due to a mismatch between the size of the stones and the distal biliary tract. Furthermore, three additional endoscopic procedures were performed without achieving complete stone removal. In January 2019, the patient consulted for an episode of cholangitis, which was managed with percutaneous biliary drainage. As a late complication, a pseu-

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doaneurysm of the right hepatic artery developed, requiring emergent embolization with coils. In February 2019, he underwent open biliary exploration, sphincterotomy, and sphincteroplasty. He reconsulted in 2020 for residual choledocholithiasis and required endoscopic drainage and biliary stent insertion on two occasions.

In May 2022, the patient presented with jaundice. An ERCP was performed, revealing a 15 mm stone in the left hepatic lobe, which could not be extracted. Therefore, electrohydraulic lithotripsy via choledochoscopy was scheduled. During this procedure, multiple choledocholithiasis was identified in relation to migrated foreign bodies (coils) in the biliary duct (**Figures 1** and **2**). The stones and most of the visible coils were successfully removed, a biliary stent was left, and a new endoscopic procedure was scheduled. However, the patient reconsulted for another episode of cholangitis, and a medical board decided to perform a biliary-enteric bypass as definitive management.

Case 2

This is a 54-year-old female patient who underwent laparoscopic cholecystectomy in 2022, resulting in bile duct injury and a biliary fistula. Postoperatively, she required ERCP and stent insertion, as well as management of haemobilia with hemodynamic repercussions secondary to a pseudoaneurysm of the right hepatic artery, which required emergency embolization with coils. She was admitted to the gastroenterology service for a scheduled ERCP and biliary stent removal eight months after the initial procedure. Fluoroscopic imaging revealed a linear foreign body within the biliary tract, which was successfully extracted using a Dormia basket (coils) (**Figure 3**).

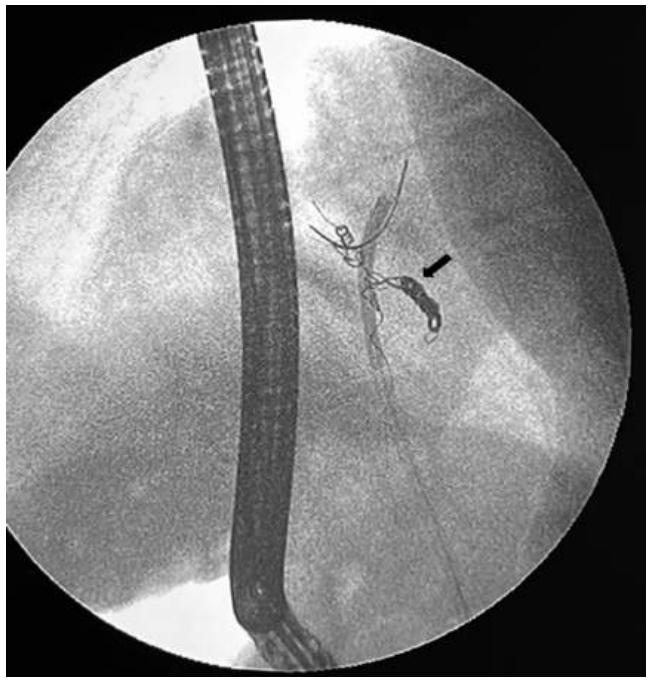


Figure 1. Fluoroscopic view, foreign bodies (coils) within the biliary tract (arrow). The image is the property of the authors.



Figure 2. Endoscopic view of the biliary tract with coils inside, using the Spyglass® system. The image is the property of the authors.

DISCUSSION

The migration of intravascular coils into the biliary tract is uncommon and may promote stone formation, increasing the risk of cholangitis, recurrent abdominal pain, and biliary strictures[6]. Their extraction has been described in the literature in several case reports using conventional endoscopic methods, percutaneous approaches, or surgical techniques[5-9]. However, due to the low frequency of this complication, evidence and information are limited, and therefore, management must be individualized based on the patient's symptoms, clinical course, and anatomy[10-12].

Endoscopic extraction through ERCP is ideal in the absence of anatomical alterations such as biliodigestive bypass or gastrectomy. Nevertheless, it is important to consider that fluoroscopic imaging may not always allow for the identification of foreign bodies, which are often embedded within stones and may present clinically as recurrent choledocholithiasis, as described in the first case.

Cholangioscopy using the Spyglass® system, through direct visualization of the biliary tract, allows not only for confirmation of the diagnosis but also for treatment, either through ERCP or via the percutaneous (transhepatic) route. It has become the endoscopic technique of choice for the extraction of foreign bodies from the biliary tract and for addressing associated secondary conditions such as choledocholithiasis[13]. However, surgical management may be required in some cases if definitive resolution is not achieved with this method.

CONCLUSIONS

The migration of foreign bodies into the biliary tract is unusual and serves as a contributing factor to stone formation and other complications. Clinical presentation is similar to that of primary or secondary biliary obstruction due to choledocholithiasis, and endoscopic extraction, whenever possible, is the treatment of choice.

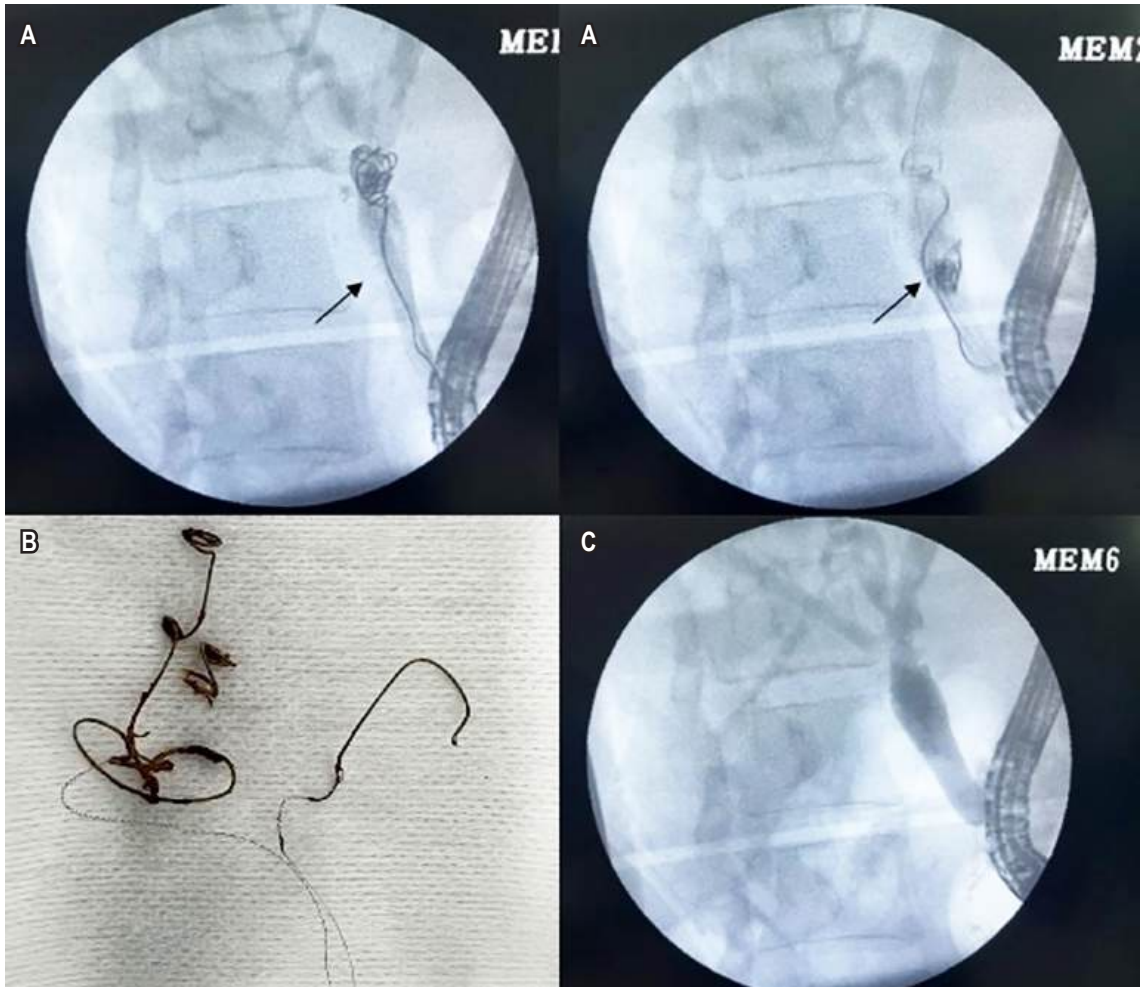


Figure 3. A. Fluoroscopic view, foreign bodies (coils) within the biliary tract (arrow). **B.** Coils extracted. **C.** Final cholangiogram. Images property of the authors.

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Case report

Incidental Finding of a Neuroendocrine Tumor in the Distal Ileum: A Case Report

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Abstract

Introduction: Neuroendocrine neoplasms (NENs) are rare, with an estimated annual incidence of 1.05 cases per 100,000 people. Over the past 30 years, their incidence has been on the rise, though the exact causes remain unclear. **Case Presentation:** We report the case of a 56-year-old female patient with a history of treatment-resistant hypertension since 2022. She was referred to gastroenterology due to diffuse, colicky abdominal pain, accompanied by bloating and two loose bowel movements per day for the past two years. A colonoscopy with ileal intubation revealed a 15 mm sessile polypoid lesion in the distal ileum, located 5 cm from the ileocecal valve. An octreotide scan identified an intraluminal lesion in the distal ileum with somatostatin receptor overexpression, as well as an enlarged right ileocolic lymph node. The patient underwent laparoscopic surgery, which included a right hemicolectomy, distal ileum resection, and retroperitoneal lymphadenectomy. The final histopathological diagnosis confirmed a grade 2 ileal neuroendocrine tumor measuring 1.5 x 1 cm, extending into the muscularis propria without lymphovascular or perineural invasion. Surgical margins were tumor-free. To date, the patient has not required adjuvant therapy during follow-up. **Conclusion:** This case highlights the importance of routine colonoscopy with ileal intubation, as it can facilitate the early detection of distal ileal neuroendocrine tumors, allowing for timely treatment and improved patient prognosis.

Keywords

Carcinoid tumor, small intestine, colonoscopy.

INTRODUCTION

Neuroendocrine neoplasms (NENs), previously known as carcinoid tumors, originate from the neuroendocrine cells found in the skin, lungs, gonads, pancreas, and gastrointestinal tract[(1)]. They are rare, with an estimated annual incidence of 1.05 cases per 100,000 inhabitants. Although considered a rare disease, the incidence has increased eightfold over the past five decades[(2)]. The exact causes of the appearance of these tumors are not known[(3)].

Primary NENs are most frequently located in the gastrointestinal tract (62%-67%) with greater involvement of the small intestine (45%), rectum (20%), appendix (16%), colon (11%), pancreas (5%-10%) and stomach (7%)[(4)]. NENs arising from the small bowel (SB-NEN) are considered rare malignant neoplasms, which are further classified as well-differentiated neuroendocrine tumors (NETs) and poorly differentiated neuroendocrine carcinomas (NECs), according to the 2022 World Health Organization (WHO) classification[(5)].

This case presents a NET in the distal ileum in a patient with nonspecific symptoms, diagnosed during a colonoscopy with ileocecal intubation.

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CLINICAL CASE

This is a 56-year-old female patient with a history of difficult-to-manage hypertension (HTN) since 2022. In the search for the origin of the HTN, she underwent various studies: a normal total abdominal ultrasound, an abdominal and pelvic MRI with contrast, which revealed pancreatic cysts, and an endoscopic ultrasound with biopsy, which provided a histological diagnosis of mucinous pancreatic cysts. She was referred to gastroenterology due to diffuse colicky abdominal pain associated with bloating and two soft stools per day, which had been present for two years. A colonoscopy with ileal intubation was performed, revealing a 15 mm sessile polypoid elevated lesion in the distal ileum, 5 cm from the ileocecal valve (**Figure 1**). The pathology report from the lesion biopsies showed the presence of a well-differentiated, low-grade NET (Grade I), with a mitotic count of 0-1 per mm^2, CKAE1/AE3: positive, focal, extranodal extension, and strong positivity for synaptophysin, chromogranin, and enolase (**Figure 2**).

An endoscopic capsule was ordered to rule out other lesions in the small intestine, which confirmed the lesion in the distal ileum, with no other significant findings (**Figure 3**).

The patient underwent other paraclinical tests: hemoglobin: 12 g/dL, platelets: 424,000, glycemia: 90 mg/dL, creatinine: 0.68 mg/dL, alkaline phosphatase: 92 U/L, γ-glutamyl transferase (GGT): 56 U/L, alanine aminotransferase (ALT): 31 U/L, aspartate aminotransferase (AST): 20 U/L, total bilirubin: 1.10 mg/dL, direct bilirubin: 0.29 mg/dL, indirect bilirubin: 0.72 mg/dL, albumin: 4.8 g/dL, lactate dehydrogenase (LDH): 168 U/L, insulin: 7 mU/L , 5-hydroxyindoleacetic acid: 6.8 mg/24 hours, chromogranin A: 7.8 ng/mL, fecal calprotectin: 80 μg/g.

She was evaluated by oncological surgery, where an octreotide scan was ordered. This imaging showed the endoluminal lesion in the distal ileum with somatostatin receptor overexpression and an ileocolic right lymphadenopathy (**Figure 4**). A chest CT scan showed no evidence of metastasis. The patient underwent laparoscopic surgery, which included a right hemicolectomy with retroperitoneal lymphadenectomy.

The final histopathological diagnosis was a grade 2 ileal NET, measuring 1.5 x 1 cm in diameter, with extension into the muscularis propria without lymphovascular or perineural invasion, and tumor-free resection margins. A total of 3 of the 22 resected lymph nodes showed tumor involvement, with extranodal extension present at 1 mm and metastasis size measuring 6 mm. Immunohistochemistry of the surgical specimen revealed positive synaptophysin, positive chromogranin, CD56+, Ki-67: 4%-5%, and a mitotic index of 3 mitoses per 10 high-power fields. The patient has not required adjuvant treatment during follow-up to date and has had good clinical progression, with improvement in abdominal pain and better control of HTN.

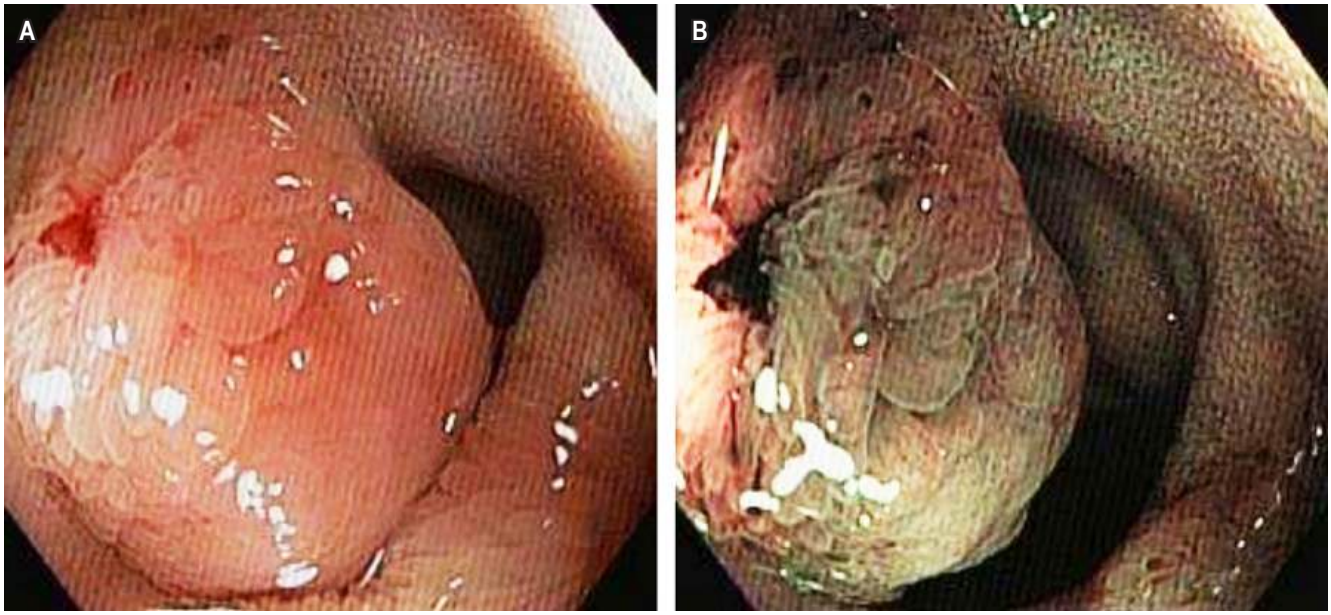


Figure 1. Ileocolonoscopy. Sessile polypoid lesion (Paris classification: 0-Is) in the distal ileum. **A.** Image with white light. **B.** Image with digital chromoendoscopy. Images property of the authors.

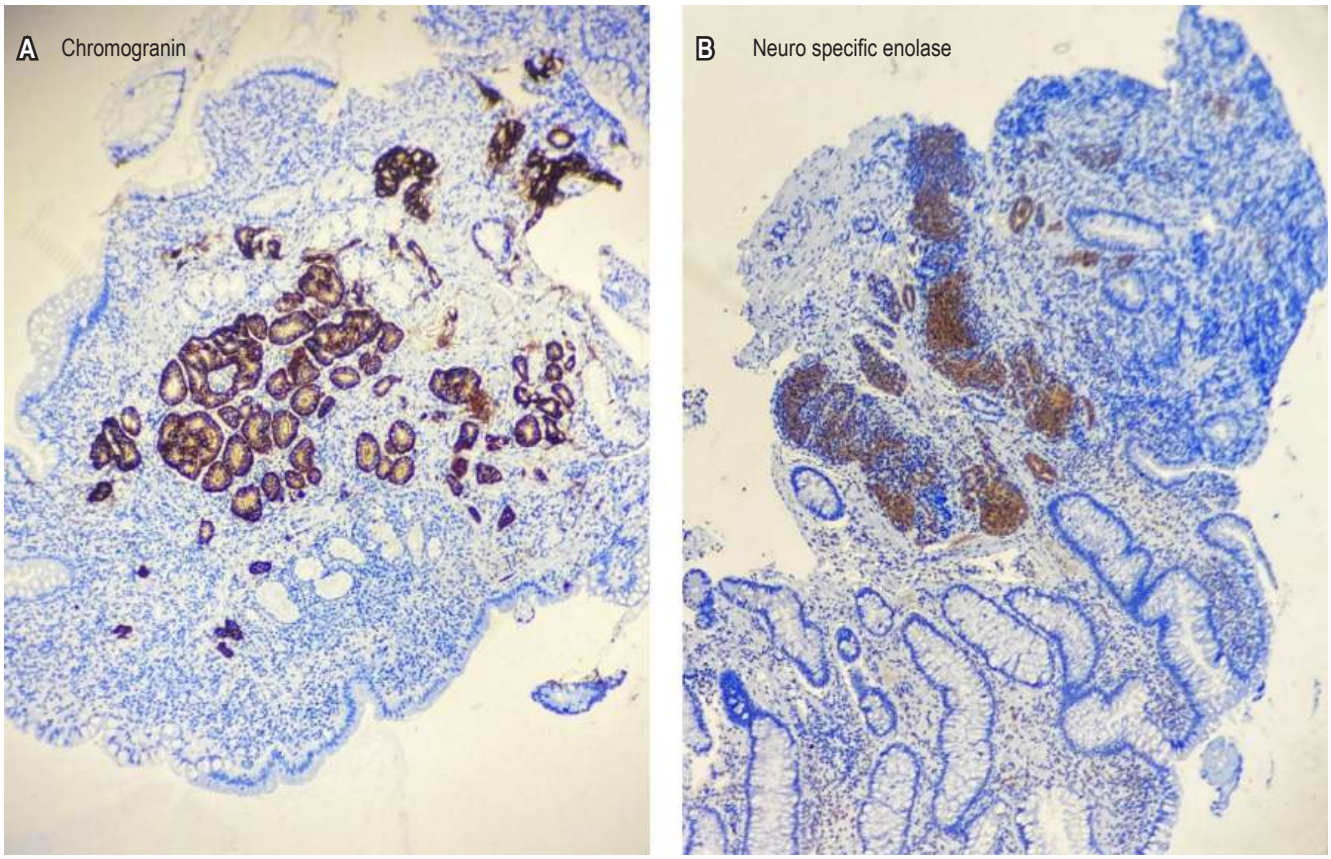


Figure 2. Biopsy of the ileal sessile polypoid lesion. **A.** Positive chromogranin. **B.** Positive enolase. Images property of the authors.

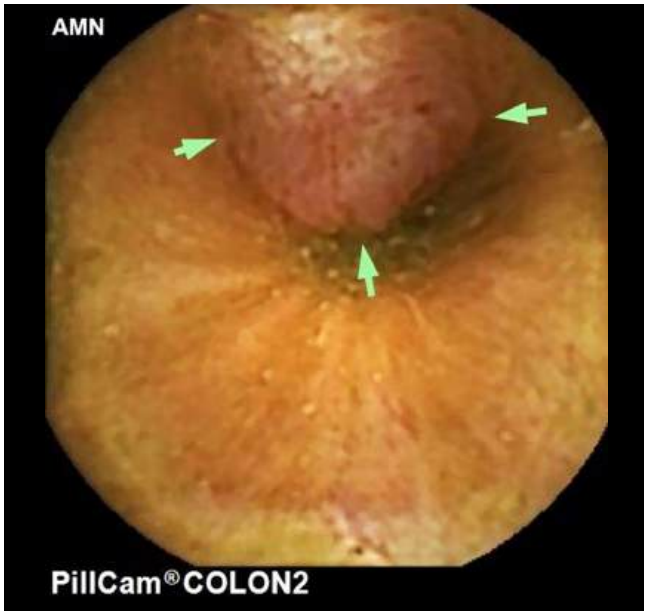


Figure 3. Endoscopic capsule. Sessile polypoid lesion (Paris classification: 0-Is) in the distal ileum. The image is the property of the authors.

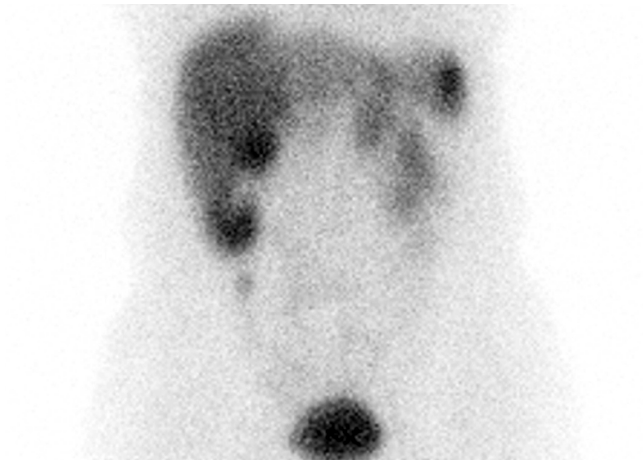


Figure 4. Octreotide scan shows focal nodular uptake in the right flank. The image is the property of the authors.

DISCUSSION

The first description of a small bowel NET was made by Lanchas in 1867, who described a polypoid tumor in the small intestine. In 1890, Ransom described the symptoms of diarrhea and dyspnea in a patient with a lesion in the ileum and hepatic metastases, which would later be known as carcinoid syndrome[6]. NETs are classified according to their signs and symptoms into non-functional and functional types. On the one hand, non-functional NETs present with signs and symptoms related to the tumor's location, such as abdominal pain or obstruction. Functional NETs, on the other hand, have symptoms associated with the secretion of amines and peptides, particularly serotonin, as seen in "carcinoid syndrome," which presents with facial flushing, a sensation of heat in the face and neck, chronic diarrhea, and dyspnea. However, functional NETs may present with other symptoms depending on the hormone secreted, such as in cases of gastric overproduction leading to Zollinger-Ellison syndrome, or the secretion of adrenocorticotropic hormone (ACTH), which causes Cushing's syndrome[6]. In our case, the patient presented with a non-functional NET and nonspecific symptoms, such as abdominal pain.

The WHO classifies NETs based on their histopathology into three grades: Grade 1: low grade, well-differentiated with a mitotic count of <2 per 10 HPF or Ki-67 index <3%; Grade 2: intermediate grade, well-differentiated with a mitotic count of 2-20 per 10 HPF or Ki-67 index 3%-20%; and Grade 3: high grade, poorly differentiated with a mitotic count of >20 per 10 HPF or Ki-67 index >20%. NECs are characterized by poor differentiation and a mitotic count >20 per 10 HPF or Ki-67 index >20%[7]. According to the tumor's extent, it is classified into stages based on the TNM system (**Table 1**).

Patients in stage 3 paradoxically had better survival rates than those in stages 1 and 2. However, this lack of a hierarchical prognosis by stage may be due to insufficient lymph node dissection, which can lead to poor staging. Furthermore, survival analyses of patients with these tumors are limited because the data include cases diagnosed between 2010 and 2016, during the seventh edition of the American Joint Committee on Cancer (AJCC) staging system. With significant changes in the eighth and ninth editions, such as the inclusion of the pathological category (pN2), it is expected that this prognostic stratification will improve[2].

NETs can be sporadic or associated with genetic syndromes, such as multiple endocrine neoplasia (MEN1, MEN2A, MEN2B), von Hippel-Lindau disease, or neurofibromatosis type 1[7]. The majority of SB-NENs are asymptomatic, and 80% to 90% present with hepatic metastases at the time of diagnosis. Among these, 20% will develop carcinoid syndrome[8]. Diagnostic aids for detecting SB-NEN include multi-phase contrast-enhanced computed tomography (CT), contrast-enhanced magnetic resonance imaging (MRI), and somatostatin receptor studies, such as somatostatin receptor scintigraphy, positron emission tomography-computed tomography (PET/CT), or positron emission tomography-magnetic resonance imaging (PET/MRI), with the latter providing higher diagnostic performance. In cases of suspected SB-NET, ileocolonoscopy, deep enteroscopy, and capsule endoscopy are useful for diagnosis, staging, and detecting synchronous lesions[5,9].

Table 1. American Joint Committee on Cancer (AJCC) TNM classification and survival rates of ileal NEN

Stage	TNM	Description	5-year survival rate
Stage 1	T1, N0, M0	T1 = invades lamina propria or submucosa and measures ≤1 cm.	87.37%
Stage 2	T2 or T3 N0, M0	T2 = invades muscularis propria or measures >1 cm. T3 = invades through the muscularis propria the subserosal tissue without penetration of the overlying serosa.	84.16%
Stage 3	T1, T2, T3 or T4 N1, N2; M0 T4, N0, M0	T4 = invades visceral peritoneum (serosa) or other organs or adjacent structures. N1 = regional lymph node metastasis, <12 nodes. N2 = large mesenteric masses (>2 cm) or extensive nodal deposits (≥12), especially those enclosing the superior mesenteric vessels.	90.62%
Stage 4	TX, T0, T1, T2, T3 or T4 NX, N0, N1, N2 M1	TX = primary tumor cannot be evaluated. NX = regional lymph nodes cannot be assessed. M1 = distant metastasis.	76.67%

Adapted from: Chauhan A, et al. CA Cancer J Clin. 2024;74(4):359-67[2].

In patients with functional NETs, biochemical tests are performed to identify the causal substance of the symptoms: serum or 24-hour urinary 5-hydroxyindoleacetic acid (5-HIAA), plasma chromogranin A (CgA), and tests for Cushing's syndrome[10]. However, CgA should not be used for detection purposes, as elevated levels are found in patients with chronic kidney disease, atrophic gastritis, and inflammatory bowel disease. It is, however, useful for monitoring[5].

The treatment for non-metastatic SB-NETs consists of open intestinal resection with regional lymphadenectomy of at least eight lymph nodes, along with bimanual palpation of the entire small intestine to rule out synchronous lesions. In patients with unresectable metastatic disease, a conservative approach is preferred, including imaging follow-up, treatment with somatostatin analogs (octreotide), and surgical intervention in cases of intestinal obstruction[4,10,11]. For SB-NETs that do not respond to first-line therapy, second-line treatments such as everolimus or peptide receptor radionuclide therapy with lutetium Lu 177-dotatate (^{177}Lu) are available[10]. Treatment algorithms are presented in **Figures 5** and **6**.

For patients treated with surgery and complete tumor resection (curative surgery), follow-up for grade 1 and 2 tumors should be performed every 6 to 12 months, while for grade 3 tumors, it should be done every 6 months. In cases of unresectable metastatic SB-NETs, follow-up should be every 3 to 6 months for grade 1 and 2 tumors, and every 3 months for grade 3 tumors. During follow-up, measurements of CgA, 5-HIAA, three-phase CT scan, or somatostatin receptor-based imaging studies are required if recurrence or metastasis is suspected[11].

In the present clinical case, a grade 2 neuroendocrine neoplasm was diagnosed incidentally in a patient with nonspecific gastrointestinal symptoms (abdominal pain). This highlights the importance of routine colonoscopy with ileocecal intubation in the early detection of lesions, which allows for timely therapy and positively impacts patient prognosis.

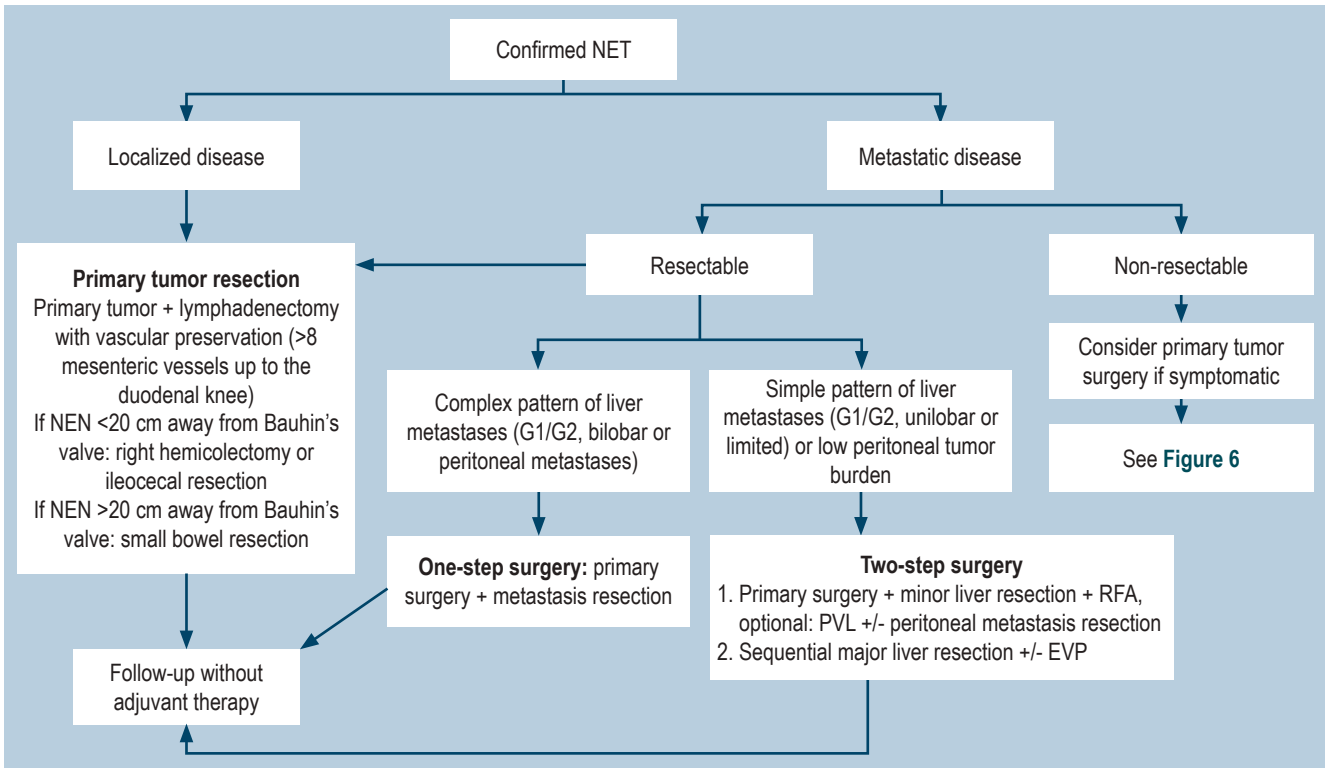


Figure 5. Treatment algorithm for SB-NETs. PVE: portal vein embolization; PVL: portal vein ligation; RFA: radiofrequency ablation. Adapted from: Oronsky B, et al. Neoplasia. 2017;19(12):991-1002[4].

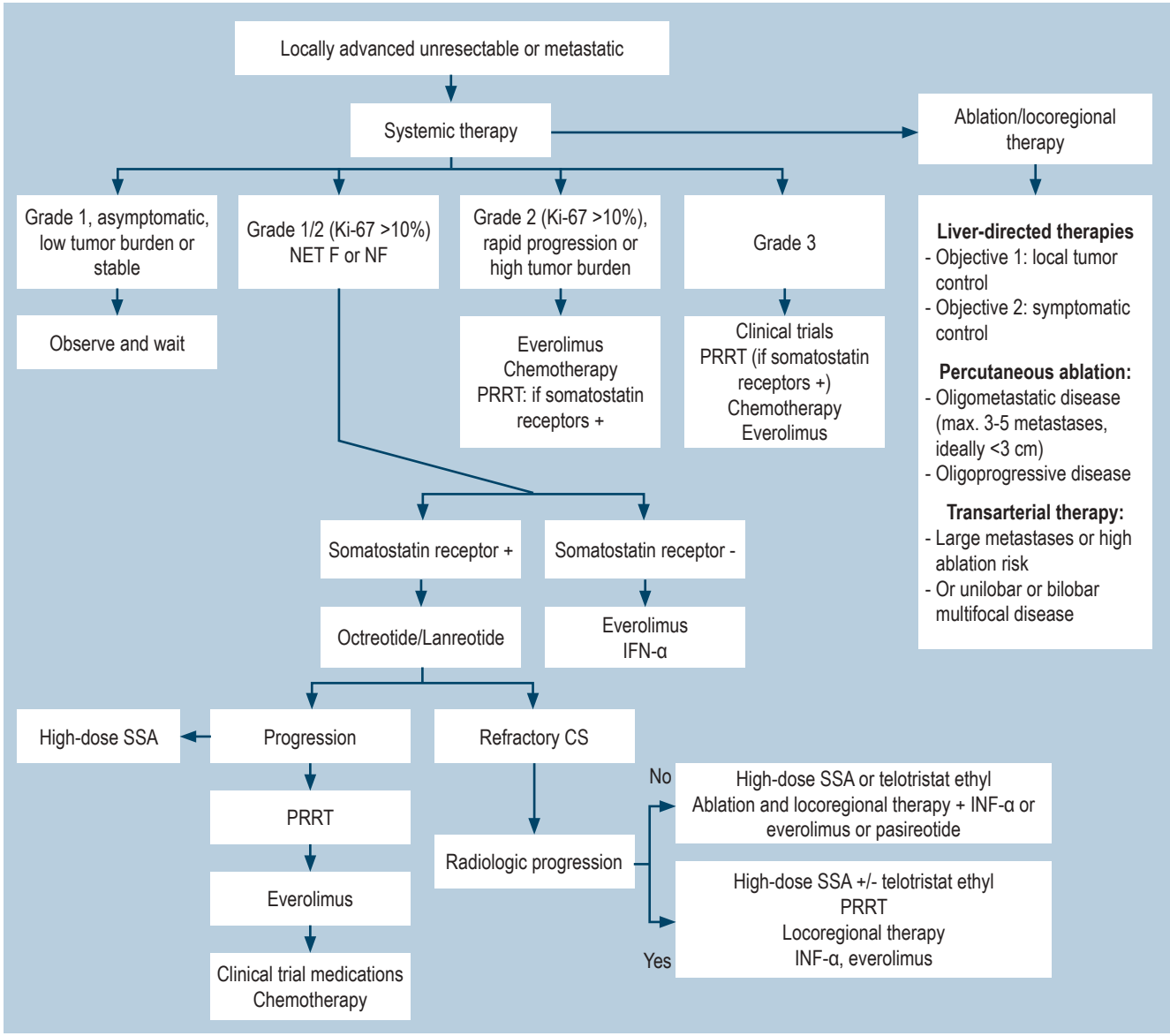


Figure 6. Treatment algorithm for SB-NETs. CS: carcinoid syndrome; PRRT: peptide receptor radionuclide therapy; SSA, somatostatin analogues. Adapted from: Oronsky B, et al. Neoplasia. 2017;19(12):991-1002[4].

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Case report

Acquired Superior Mesenteric Artery Syndrome: A Case Report with Associated Mortality

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Abstract

Introduction: Superior Mesenteric Artery Syndrome (SMAS) is a rare vascular-origin intestinal obstruction affecting the third portion of the duodenum. It is often underdiagnosed due to its multiple confounding factors, leading to delays in diagnosis and a high morbidity and mortality rate. The primary underlying mechanism is significant weight loss, and it is more commonly seen in young women. Current treatment approaches include either medical management or minimally invasive surgery. **Case Presentation:** We present the case of a 61-year-old woman with a six-month history of insidious abdominal pain and recurrent episodes of vomiting, accompanied by severe weight loss. Imaging studies confirmed a diagnosis of SMAS, which was secondary to tumor recurrence in metastatic breast cancer. Conservative management was initiated; however, the patient ultimately succumbed to infectious complications. **Conclusions:** SMAS is a rare and challenging condition to diagnose. Various underlying factors contribute to significant weight loss, which is central to its pathophysiology. Computed tomography (CT) and magnetic resonance imaging (MRI) are the preferred diagnostic modalities. While conservative management remains the first-line treatment, it is associated with a high recurrence rate. Surgical intervention, though an option, carries substantial morbidity risks due to the complexity of the procedure.

Keywords

Superior Mesenteric Artery Syndrome, intestinal obstruction, weight loss, breast neoplasm, duodenal obstruction.

INTRODUCTION

Superior mesenteric artery syndrome (SMAS) is a rare condition, first described by Rokitansky in 1842. It results from extrinsic intestinal obstruction due to vascular origin, occurring at the third portion of the duodenum. This condition is caused by a reduction in the angle between the superior mesenteric artery and the aorta[1]. The prevalence is unknown, with varying incidences reported in imaging studies, ranging from 0.013%-0.78% up to 2.67% in patients with constipation[1,2]. Currently, it is an underdiagnosed condition due to its nonspecific symptoms. In fact, 10.8% of patients with SMAS were previously treated for dyspepsia[3]. All of this leads to a delay in diagnosing a condition with a reported mortality rate of approximately 33%[4,5].

This report presents the case of a 61-year-old woman with fatal outcomes due to tumor relapse from a breast neoplasm in the context of SMAS.

PRESENTATION OF THE CASE

This is a 61-year-old woman with a history of primary clinical hypothyroidism and right breast cancer diagnosed two years prior, currently in remission (following neoadjuvant therapy and mastectomy). She was admitted due to a six-month clinical course characterized by progressive colicky pain in the epigastrium and mesogastrium, occurring postprandially. In the last 20 days, she developed episodes of vomiting with food content and occasionally bile, leading to oral intolerance and a weight loss of approximately 10 kg. Initial tests revealed hypokalemia (2.8 mEq/L), hypochloremia (94 mEq/L), and metabolic alkalosis, accompanied by signs of dehydration. These abnormalities were adequately corrected. Other tests, including thyroid function tests, were within normal limits.

An abdominal X-ray was performed, showing dilated intestinal loops with abundant fecal material and the presence of gas in the rectal ampulla. After performing an intestinal lavage with a nasogastric tube, an upper gastrointestinal endoscopy was conducted, revealing erosive grade B esophagitis according to the Los Angeles Classification. No pyloric syndrome or obstruction was observed in the examined areas.

A contrast-enhanced abdominal CT scan was performed, showing evidence of a distended gastric chamber and first and second portions, with collapse of the distal third portion at the level of the superior mesenteric artery (SMA). The aortomesenteric angle was 22° and the aortomesenteric distance was 7 mm (**Figures 1** and **2**). Additionally, blastic lesions were noted in the iliac bones and vertebral bodies.

In the context of tumor relapses in the patient with sarcopenia, along with clinical and imaging findings of SMAS, initial management focused on parenteral nutritional recovery and concurrent oncological treatment. The patient developed complications during her hospital stay, including pulmonary-origin sepsis, which led to a fatal outcome.

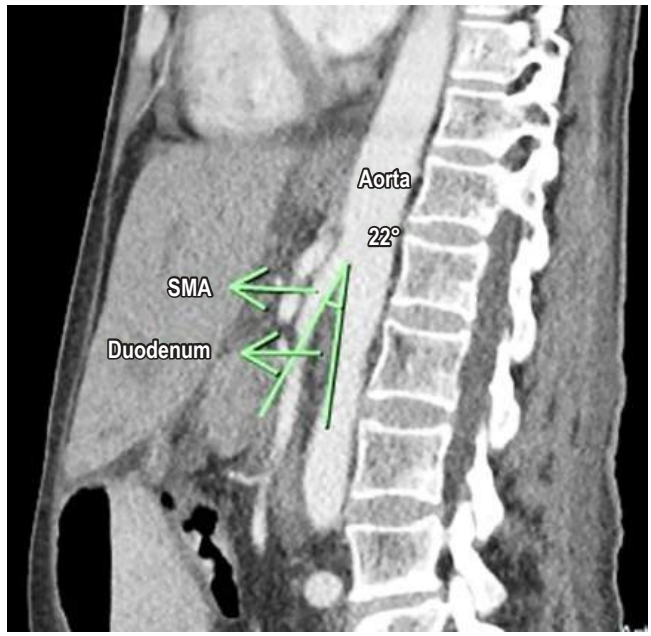


Figure 1. Contrast-enhanced abdominal CT scan in the sagittal section showing an angle of 22° between the aorta and the superior mesenteric artery. The image is the property of the authors.

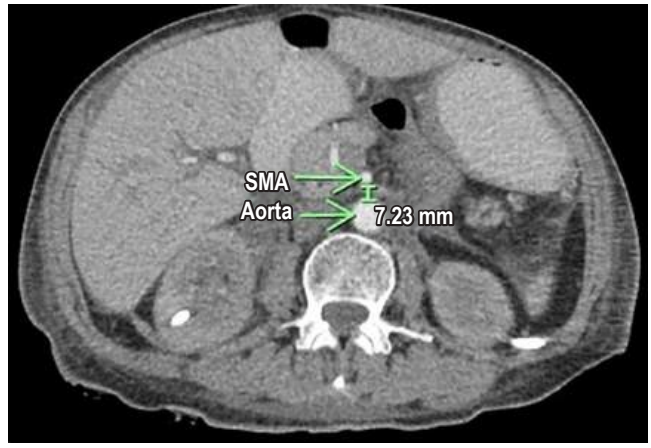


Figure 2. Contrast-enhanced abdominal CT scan in axial section showing an aortomesenteric distance of 7.3 mm. The image is the property of the authors.

DISCUSSION

SMAS, also known as Wilkie's syndrome, cast syndrome, mesenteric duodenal obstruction, or aorto-mesenteric compass syndrome, was first described by Carl Freiherr Von Rokitansky in 1861. However, it was Wilkie in 1927 who published a case series of 75 patients, which is why the syndrome is named after him[6,7]. As of 2022, there are 730 articles with 2400 reported cases[1]. Its incidence is low, estimated to be between 0.1% and 0.3% of the general population. However, in specific conditions such as anorexia nervosa (2.73%)[8] and functional dyspepsia (10.8%)[3], the prevalence remains unknown. SMAS is more commonly seen in women than in men, with a female-to-male ratio of 3:1, and an average age of onset of 23 years (range: 10-40 years). However, there has been a growing number of reports in individuals over the age of 40 (range: 0-91 years)[1,9].

The third part of the duodenum, which is the longest and narrowest, passes between the aorta and the superior mesenteric artery (SMA) from right to left. Both vessels are covered by retroperitoneal fat and lymphatic tissue, which act as cushioning and reinforcement, allowing the duodenum to pass unobstructed between them[10]. The SMA arises from the front section of the abdominal aorta

behind the pancreas at the level of the L1 vertebra, creating an acute angle with the aorta. Typically, the angle between the aorta and the superior mesenteric artery is around 45° (range: 38°-65°), and a normal aortomesenteric distance is described as between 10 and 28 mm[1,7]. When there is a decrease in the available space for the duodenum, intestinal compression occurs due to the vascular structures. An angulation between the abdominal aorta and the superior mesenteric artery is described as ranging from 6° to 25°, with an aortomesenteric distance between 2 and 8 mm[11].

This syndrome can be either congenital or acquired. The congenital type is associated with malrotation, low take-off of the superior mesenteric artery, Ladd's bands, idiopathic peritoneal adhesions, a shortened and thickened mesenteric root, and a more cephalic or hypertrophied position of the Treitz ligament[1,6]. The acquired type results from weight loss (due to cancer, bariatric surgery, chronic infections, burns, eating disorders, intestinal surgeries, malabsorption, rheumatoid arthritis, among others), which leads to a reduction in the perivascular fat surrounding the abdominal aorta and the SMA[12].

The clinical symptoms are nonspecific and can be either acute or chronic, sometimes starting insidiously. Symptoms include postprandial epigastric pain (59%), nausea (40%), vomiting (50%), early satiety (32%), weight loss, and anorexia (32%). Obstruction can progress rapidly, leading to distal ischemia, with consequences such as lactic acidosis and even death[12]. A key diagnostic point is that abdominal pain worsens in the supine position and improves in the lateral decubitus position (knees-to-chest position) or with the Hayes maneuver (applying pressure below the umbilicus in a cephalad direction, which relieves pain by reducing mesenteric tension)[1,12].

Abdominal X-ray is typically the first radiological study, showing findings consistent with high intestinal obstruction, such as a dilated gastric and gastroduodenal chamber. Other studies that may help include, on the one hand, an upper barium contrast study showing gastroduodenal obstruction with improvement upon position changes, and on the other hand, abdominal ultrasound, which could be helpful in measuring the aortomesenteric angle. Currently, contrast-enhanced tomography and magnetic resonance imaging are the preferred studies for measuring the aortomesenteric angle and distance, offering detailed views of adjacent structures[11]. An endoscopic study is necessary to rule out any mechanical cause of obstruction[7].

Among the described complications are hypovolemic shock, aspiration pneumonia, severe electrolyte imbalance, gastrointestinal mucosal damage (peptic and biliary acid reflux), emphysema, necrosis, gas in the portal vein, pneumoperitoneum, pancreatitis, and even sudden death (secondary to electrolyte imbalance and acidemia)[1].

The treatment is based on two main pillars: symptom relief and nutritional replenishment. Conservative medical management includes gastrointestinal decompression with the passage of a nasoenteric tube, the use of prokinetics (e.g., metoclopramide), feeding in small amounts, positional repositioning or the Hayes maneuver, and total parenteral nutrition to improve nutritional status and increase the aortomesenteric angle by increasing perivascular adipose tissue. The duration of conservative management is variable; however, after 4-6 weeks without improvement, surgical treatment should be considered[1,10,13,14]. Surgical management is the treatment of choice if there is no response to conservative management and in patients with multiple abdominal interventions, immobility, and atherosclerosis of the SMA[1]. There are no clinical trials comparing medical versus surgical management, but a cohort study has shown recurrence rates of 71.3% versus 15.8%, respectively[15]. The three available surgical options are gastrojejunostomy, duodenojejunostomy, and the Strong procedure. Duodenojejunostomy is the most common surgical procedure and appears to have the best outcomes, with a success rate of 80%[13,16]. Open duodenojejunostomy was traditionally the preferred approach; however, the current standard of care favors minimally invasive techniques, including ultrasound-guided endoscopic gastroenterostomy[17].

CONCLUSION

SMA syndrome is an underdiagnosed condition associated with mortality, and in adults, it is linked to any situation that leads to overall weight loss. Its diagnostic approach relies on a combination of clinical evaluation and imaging studies (CT or MRI). Management should be individualized, as conservative treatment has a high recurrence rate, while surgical management carries significant morbidity.

Conflicts of interest

The authors declare no conflict of interest.

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Case report

Subcapsular Hematoma Following Endoscopic Retrograde Cholangiopancreatography (ERCP): Complex Cases Requiring Open and Endovascular Intervention – Case Reports

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Abstract

Endoscopic retrograde cholangiopancreatography (ERCP) is an essential diagnostic and therapeutic procedure for managing biliopancreatic disease; however, it carries a complication rate of up to 6.85%. Subcapsular hepatic hematoma is a rare occurrence, which in most cases can be effectively managed with conservative and expectant medical care. In certain exceptional situations, invasive corrective interventions such as angiography with vascular embolization or open surgical exploration are required. This report presents two cases of young adult female patients with no significant pre-existing comorbidities who developed abdominal pain, anemia, and hypotension following ERCP. They were subsequently diagnosed with post-ERCP subcapsular hepatic hematoma. Both patients underwent comprehensive treatment through a multidisciplinary approach, requiring different interventions—one with percutaneous endovascular management and the other with open drainage—both yielding equally favorable outcomes.

Keywords

Abdominal pain, endoscopic retrograde cholangiopancreatography, hematoma, therapeutic embolization.

INTRODUCTION

Endoscopic retrograde cholangiopancreatography (ERCP) is essential in the treatment of biliopancreatic diseases. The performance of ERCP carries a potential risk of complications, which can range from trivial incidents to life-threatening conditions. The overall complication rate (pancreatitis, bleeding, perforations, and infections) occurs in approximately 6.85% of cases, with a related fatality rate of 0.33%[(1)]. Hepatic subcapsular hematoma post-ERCP is an uncommon event; however, like any bleeding, it has the potential to lead to fatal outcomes. Treatment is typically conservative, while invasive interventions such as angiography, endovascular approaches, or open surgical interventions are reserved for patients with refractory hemorrhage. Two cases involving young patients with different clinical courses are presented.

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DESCRIPTION OF CASES

Case 1

This is a 31-year-old female patient in late puerperium who presented with abdominal pain in the epigastrium and right hypochondrium. The hepatobiliary ultrasound revealed cholelithiasis without cholecystitis, with intrahepatic biliary and common bile duct dilation of 7.7 mm. The magnetic resonance cholangiopancreatography (MRCP) showed evidence of a normal-caliber intrahepatic bile duct, with heterogeneous material within the common bile duct. The patient underwent ERCP, which revealed a type 1 papilla with successful bile duct cannulation on the first attempt, a wide medial papillotomy, and extraction of biliary sludge with a balloon extractor. The procedure ended without complications, and no contrast was observed in the pancreatic duct. Eight hours after the procedure, the patient developed sharp, high-intensity pain in the right hemithorax extending to the ipsilateral shoulder, associated with nausea and epigastric pain. Therefore, a contrast-enhanced abdominal computed tomography (CT) scan was performed, which identified an extensive subcapsular collection in the hepatic lobe with hypodense areas lacking enhancement with contrast medium (**Figure 1**). In addition, in association with the imaging findings, a 5 g/dL decrease in hemoglobin was documented.



Figure 1. Hepatic hematoma (206 x 81 x 160 mm) involving the right hepatic lobe on the axial CT scan. Contrast densities associated with the hematoma are observed, showing signs of active bleeding. The image is the property of the authors.

Medical management was initiated, and surgery was not considered necessary initially. The patient received hydration resuscitation and empirical antibiotic coverage. During monitoring, there was hemodynamic deterioration, requiring transfusion support with three units of red blood cells. An aortogram with selective hepatic artery angiography was performed, revealing intraoperative findings of a flush in the area related to hepatic segments VII and VIII, prompting selective embolization of the segment VII and VIII hepatic artery with helix coils (**Figure 2**). The procedure was completed without complications. The patient showed satisfactory progress following the intervention.

Case 2

This is a 35-year-old female patient who underwent laparoscopic cholecystectomy for cholecystitis six months prior to admission. She presented with a one-day history of epigastric and right hypochondrium pain, associated with nausea, multiple emetic episodes, and choluria. Upon initial evaluation, no signs of peritoneal irritation were found. Paraclinical studies revealed leukocytosis (19,260 WBC/mm^3) and neutrophilia (86%), along with abnormalities in the liver profile (elevated alanine aminotransferase [ALT], aspartate aminotransferase [AST], and alkaline phosphatase). A possible obstructive biliary syndrome was suspected, with an intermediate suspicion of choledocholithiasis. Therefore, an MRCP was performed, showing dilatation of both intrahepatic and extrahepatic bile ducts (common bile duct 11 mm) due to the presence of multiple stones smaller than 10 mm in the intrapancreatic portion of the common bile duct. The patient then underwent ERCP, during which a selective biliary cannulation was successfully performed, followed by cholangiography. The common bile duct was identified as 14 mm, with a 12 mm mobile filling defect inside and distal bile duct disproportion. In addition, a sphincterotomy was performed, revealing bile sludge and abundant pus drainage. A retrieval basket was advanced, and yellow pigment stones were extracted. Subsequently, a 10 Fr x 9 cm plastic biliary stent was placed, with adequate drainage.

Approximately 3 to 4 hours after the procedure, the patient developed sudden right hypochondrium abdominal pain, accompanied by marked hypotension. A hemoglobin drop from 12 g/dL to 9 g/dL was recorded. Finally, a contrast-enhanced abdominal CT scan was performed, revealing a large subcapsular hepatic collection, of approximately 1055 mL in volume, with hyperdense content consistent with a subcapsular hepatic hematoma (**Figure 3**).

The patient was transferred to the intensive care unit for hemodynamic monitoring, where conservative management was initiated with fluid resuscitation, transfusion support, and empirical antimicrobial therapy with piperacillin-tazobactam. Given the persistent decline in hemoglobin levels (down to 7.9 g/dL despite receiving transfusion

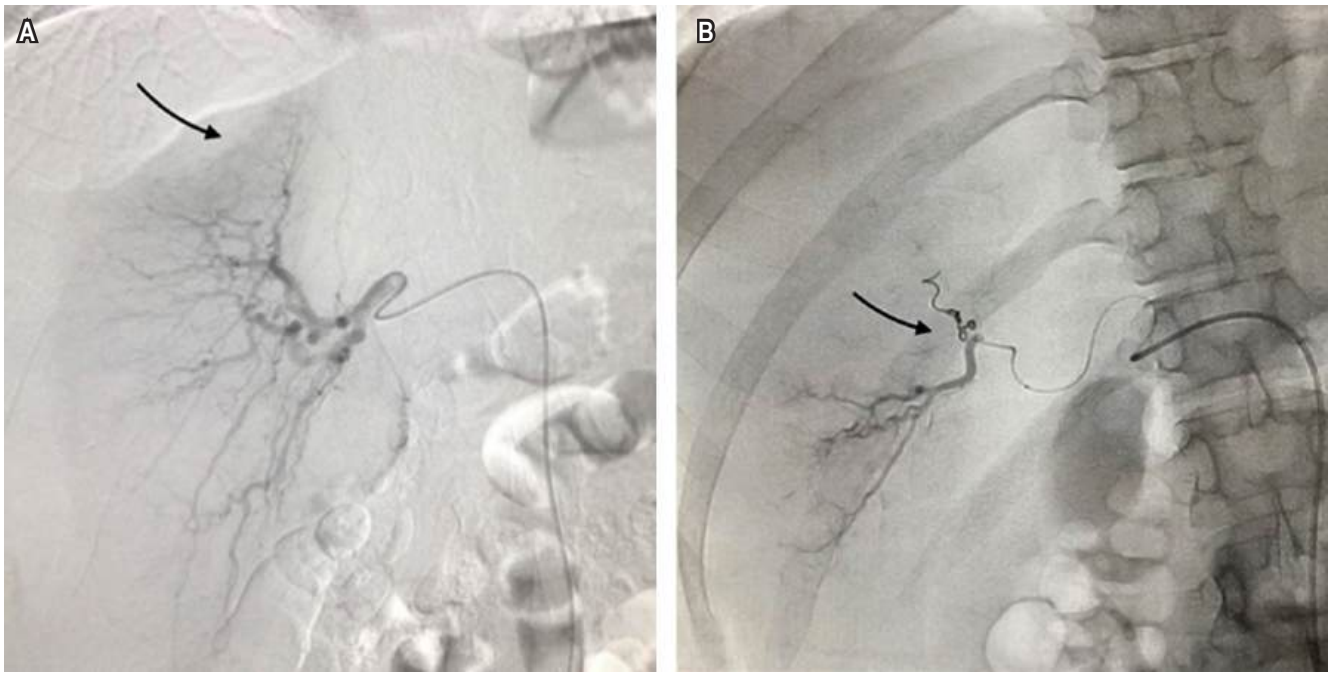


Figure 2. A. Supraselective arteriography. Note the right hepatic artery. Poor contrast washout at the level of the hepatic segment (arrow), suggestive of hepatic bleeding. **B.** Selective embolization of the hepatic artery branches for segments VII and VIII. Images property of the authors.

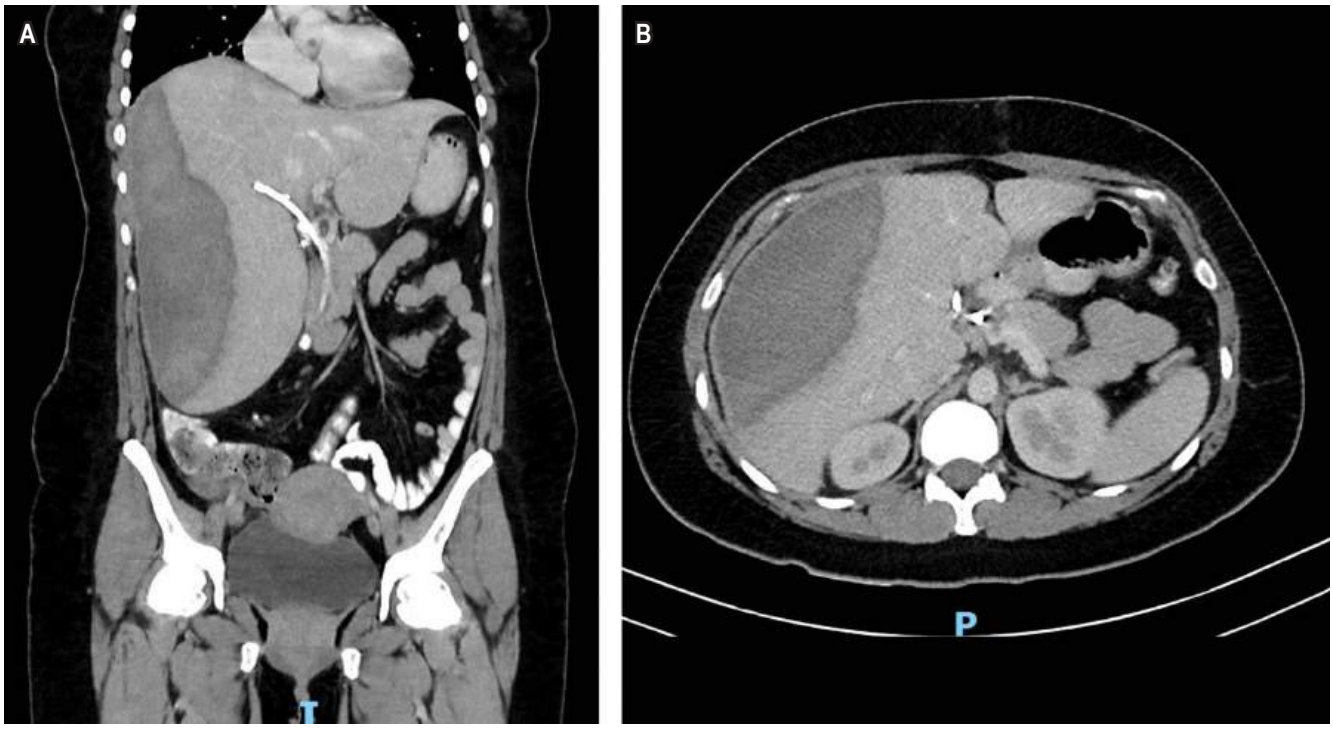


Figure 3. Subcapsular hepatic hematoma measuring 246 x 127 x 65 mm in the right hepatic lobe. **A.** Coronal section. **B.** Axial section view. Images property of the authors.

support), along with progressive thrombocytopenia (down to 42,000 platelets/μL), the surgical team considered the need for exploratory laparotomy. During the surgical exploration, findings of a ruptured subcapsular hepatic hematoma and layered bleeding in segments IV and V were identified, and bleeding control was performed along with drainage of 2500 mL of hemoperitoneum and cavity packing. In the second surgical procedure, complete hemostasis was achieved with Surgicel® and drainage of the residual hemoperitoneum of 800 mL with closure of the cavity. The patient subsequently showed progressive improvement until discharge.

DISCUSSION

ERCP is a diagnostic and therapeutic medical procedure currently useful for the management of biliopancreatic disease. Its origins date back to 1968, when it was initially used as a tool for the direct observation of the biliary tree. Subsequently, the technique was modified with the introduction of sphincterotomy in 1974, leading to the expansion of the procedure[2].

Compared to other endoscopic procedures, ERCP carries a potential risk of complications ranging from trivial or minor to major or life-threatening. The most common ERCP-related adverse event is acute pancreatitis (AP). Infection is one of the most morbid complications of ERCP, with an associated fatality rate of 7.85%. On the one hand, septic complications of ERCP include ascending cholangitis, hepatic abscess, acute cholecystitis, infected pancreatic pseudocyst, and infection following perforation of a viscus. On the other hand, hemorrhagic complications may occur, with post-sphincterotomy bleeding being the most frequent, reported in 1.4% of all procedures, indicating moderate, non-severe bleeding[1].

Among the main post-ERCP complications is gastrointestinal bleeding, which can be clinically significant and accounts for 0.1% to 2% of complication cases; other non-clinically significant bleeding events are more frequent, accounting for 10% to 30% of cases[3].

Post-ERCP hepatic subcapsular hematoma is a very rare but potentially serious complication. The actual incidence of subcapsular hematomas is likely underestimated, and the currently available literature on this condition mainly consists of case reports. It is considered that this complication may result from accidental puncture of intrahepatic vessels by the guidewire during exploration of the biliary tree; however, cases of post-ERCP hepatic subcapsular hematoma without prior guidewire use have been documented, leading some authors to suggest that it may also result from hepatic contusion during traction-extraction with the retrieval basket[3,4].

The clinical presentation of this complication may initially be nonspecific, as it shares common postoperative symptoms such as abdominal pain, nausea, and vomiting. However, it is important to recognize alarm symptoms that, according to reported cases, appear within hours after the procedure and may guide early diagnosis. The most frequent findings include abdominal pain (91.7%), anemia (43.8%), hypotension (29.1%), and fever (20.8%). It can be concluded that most cases of post-ERCP hepatic subcapsular hematoma occur early, within the first 72 hours after the procedure, although in unusual cases, diagnosis may be delayed up to five days post-procedure[3-5].

In our reported cases, the onset of abdominal pain occurred early, within the first 12 hours. In Case 1, the onset of abdominal pain was recorded 8 hours after the ERCP procedure, whereas in Case 2, abdominal pain began within 6 hours after ERCP. In both cases, hypotension was identified, accompanied by symptoms suggestive of low cardiac output, along with clinically significant anemia, characterized by a hemoglobin drop >2 g/dL. Laboratory findings, in addition to the clinical presentation, can further support diagnostic suspicion and may include expected abnormalities such as leukocytosis and cholestasis. The diagnostic methods of choice for post-ERCP hepatic subcapsular hematoma involve ultrasound evaluation, contrast-enhanced abdominal computed tomography, or abdominal magnetic resonance imaging. Contrast-enhanced abdominal CT offers certain advantages due to its ability to specifically define the hematoma's size, location, and any particular patterns of parenchymal involvement. A review found that, in most cases, hematomas are located in the right hepatic lobe (95%), with an average size of approximately 116 x 93 mm. Development of a post-ERCP hepatic subcapsular hematoma in the left hepatic lobe was rarely identified[5].

The management of post-ERCP hepatic subcapsular hematoma should always involve a multidisciplinary approach focused on the patient's specific needs, depending in a particular and individualized manner on the patient's hemodynamic status and clinical progression. Standard comprehensive management typically includes early interventions such as strict bed rest and pain control, monitoring of hemodynamic variables in intermediate care units, aggressive intravenous fluid resuscitation (preferably with balanced crystalloids as the fluid of choice), broad-spectrum empirical antibiotic coverage (targeting anaerobes, gram-negative, and gram-positive bacteria) based on laboratory findings, and transfusion support with blood components as needed[6].

In the cases described, a broad and comprehensive multidisciplinary approach was implemented, based on goal-directed resuscitation and empirical antibiotic coverage. Additionally, due to a significant drop in hemoglobin

levels in the acute postoperative setting, early transfusion of blood components was performed.

It is essential to assess the response to the established management, closely monitor hemoglobin levels, and maintain continuous surveillance of the hemodynamic status in the intermediate or intensive care unit. However, it is not possible to reach a definitive conclusion regarding the strict indications for the need for invasive intervention or percutaneous drainage due to the significant clinical heterogeneity in the limited published cases. In any case, it can be conceptualized that, once non-invasive clinical interventions have been ensured, a more invasive approach (open exploration or percutaneous intervention) should be considered in cases documenting hemodynamic instability, signs of peritoneal irritation, or lack of improvement with conservative management. Nonetheless, management should be individualized based on each patient's particular conditions, the availability of services, and local expertise[5].

CONCLUSIONS

Post-ERCP hepatic subcapsular hematoma is a potentially fatal condition that must always be considered in patients presenting with clinical deterioration following the procedure. Clinical suspicion should be high in cases presenting with the triad of abdominal pain, anemia, and hypotension. The management of this condition requires a comprehensive and multidisciplinary approach, which should include hemodynamic surveillance, monitoring of perfusion parameters, transfusion support if necessary, and optimal collaboration between medical and surgical services.

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Case report

Association Between Ulcerative Colitis and Pulmonary Embolism: A Case Report

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Abstract

Introduction: Inflammatory bowel diseases (IBD) include Crohn's disease (CD) and ulcerative colitis (UC), conditions that primarily affect the intestines but can sometimes lead to extraintestinal complications such as venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE). **Case Report:** A 39-year-old woman was admitted with a 12-hour history of left-sided chest pain radiating to the ipsilateral scapular region, worsened by breathing and positional changes. She reported a prior episode of deep vein thrombosis in her right leg. Laboratory tests revealed microcytic hypochromic anemia and thrombocytosis. Imaging studies showed findings suggestive of pulmonary infarction, with a CT pulmonary angiogram confirming a thrombus at the segmental branch of the right lower lobe, accompanied by right-sided pleural effusion and atelectasis. Further evaluation for anemia, including a colonoscopy, revealed acute-phase pancolitis with minimal bleeding. An autoimmune panel was negative. Treatment was initiated with anticoagulation, mesalazine, and methylprednisolone. **Conclusions:** Thromboembolic complications occur in approximately 1% to 8% of patients presenting with active inflammatory bowel disease and are associated with increased morbidity and mortality. The underlying pathophysiological mechanisms likely involve a hypercoagulable state, platelet aggregation, impaired fibrinolysis, and genetic predisposition. Identifying risk factors and implementing appropriate therapeutic measures are crucial to preventing future thromboembolic events. The preferred prophylactic anticoagulation therapy is low-molecular-weight heparin, which is recommended for hospitalized patients at high risk during active disease phases.

Keywords

Ulcerative colitis, pulmonary embolism, inflammatory bowel disease, inflammation, coagulation.

INTRODUCTION

Inflammatory bowel diseases (IBD) include Crohn's disease (CD) and ulcerative colitis (UC), pathologies that mainly affect the intestine[(1)] and in some cases can generate extraintestinal complications[(1)]. Venous embolism includes pathologies such as deep vein thrombosis and pulmonary embolism, which are usually known complications of inflammatory bowel diseases[(1,2)].

It is estimated that the incidence of these complications is 0.26% annually in both CD and UC[(3)]; however, the actual risk remains unclear due to methodological designs and the heterogeneity of the studies conducted. Despite this, one of the main factors involved in this relationship is the inflammatory process, with key markers such as elevated C-reactive protein and thrombocytosis[(4,5)].

The objective of this article is to present the case of a patient with UC who presented pulmonary embolism as a complication.

CLINICAL CASE

This is a 39-year-old woman from Tunja, Colombia, who presented with a 12-hour history of left-sided chest pain

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radiating to the ipsilateral scapular region. The pain worsened with breathing and positional changes. She reported a history of secondary anemia diagnosed five months earlier.

On physical examination, a heart rate (HR) of 115 beats per minute (bpm), blood pressure (BP) of 113/70 mm Hg, a temperature of 36.5 °C, and a weight of 53 kg were documented. Mucocutaneous pallor and tenderness to palpation were noted at the fourth intercostal space between the posterior axillary line and the left midclavicular line, with no other abnormalities observed. Admission laboratory tests revealed microcytic hypochromic anemia and thrombocytosis (**Table 1A**), while chest X-ray showed signs suggestive of pulmonary infarction (retrocardiac wedge-shaped opacity) (**Figure 1**).

Based on the findings, it was determined that the patient had a high probability of pulmonary thromboembolism, likely secondary to deep vein thrombosis and microcytic hypochromic anemia. Therefore, confirmatory studies were expanded, three units of red blood cells were transfused (admission hemoglobin: 5 mg/dL) (**Table 1B**), and anticoagulation with enoxaparin 80 mg daily (1.5 mg/kg/day) was initiated.

On the second day of hospitalization, a chest CT angiography (CT angio) report was received, showing a thrombus at the level of the right lower lobar segmental branch, right pleural effusion, and atelectasis (**Figure 2**).

Once the diagnosis of pulmonary embolism was confirmed, further studies were conducted to evaluate the cause of the patient's chronic anemia. An esophagogastroduodenoscopy (EGD) was performed, which revealed a hiatal hernia and chronic antral gastritis. Meanwhile, colonoscopy reported active ulcerative pancolitis in the acute phase with scant bleeding (**Figure 3**), explaining the cause of the iron-deficiency anemia. Given these findings, treatment was initiated with mesalazine 1 g orally every 12 hours and methylprednisolone 70 mg intravenously every 24 hours for three days. Anticoagulant therapy was also maintained, as there was no evidence of active bleeding.

On the fourth day of hospitalization, given the diagnosis of active ulcerative pancolitis complicated by pulmonary embolism and microcytic anemia, the patient was evaluated by the gastroenterology department. The treatment was adjusted by increasing the mesalazine dose to 3 grams per day. Additionally, due to the risk of recurrent thrombotic events and potential cardiac complications, a transthoracic echocardiogram was ordered, which showed normal ventricular function without signs of pulmonary hypertension.

Once the treatment with intravenous corticosteroid was completed (sixth day of hospitalization) and upon evidencing an adequate clinical and paraclinical evolution (**Table 1B**), it was decided to discharge the patient with recommendations, follow-up appointments, outpatient examina-

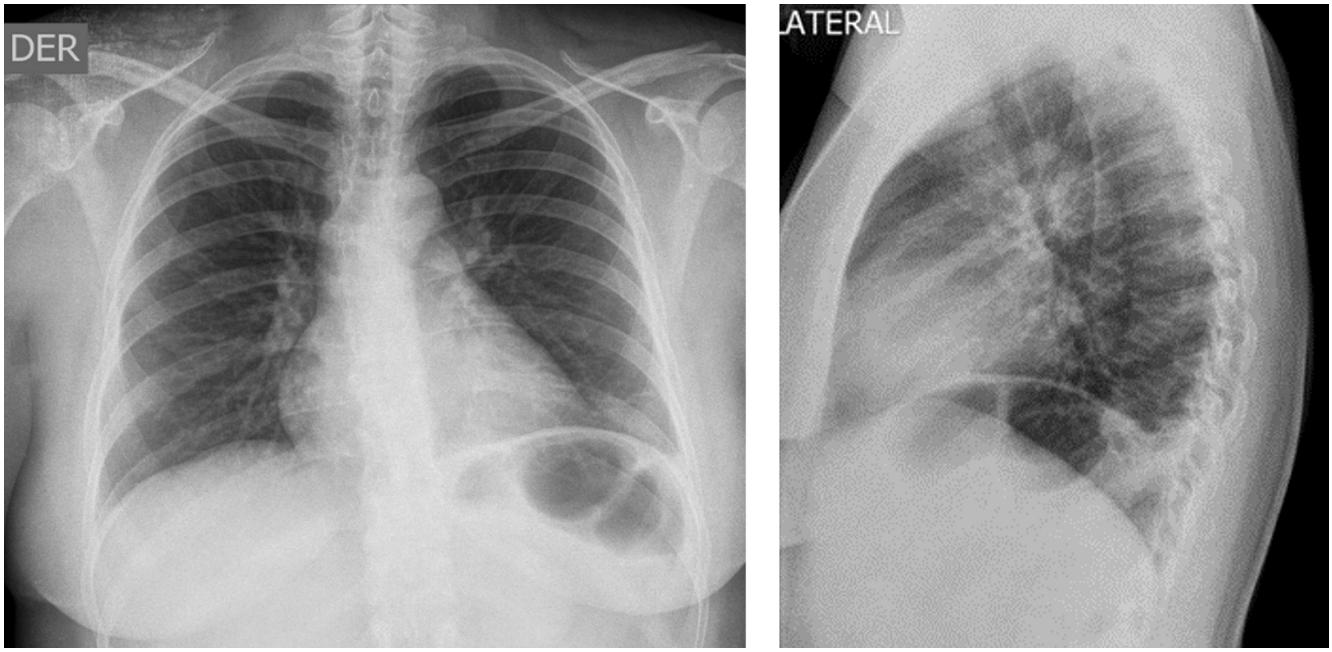


Figure 1. Chest X-ray. Findings suggestive of pulmonary infarction (retrocardiac wedge-shaped opacity) Images property of the authors.

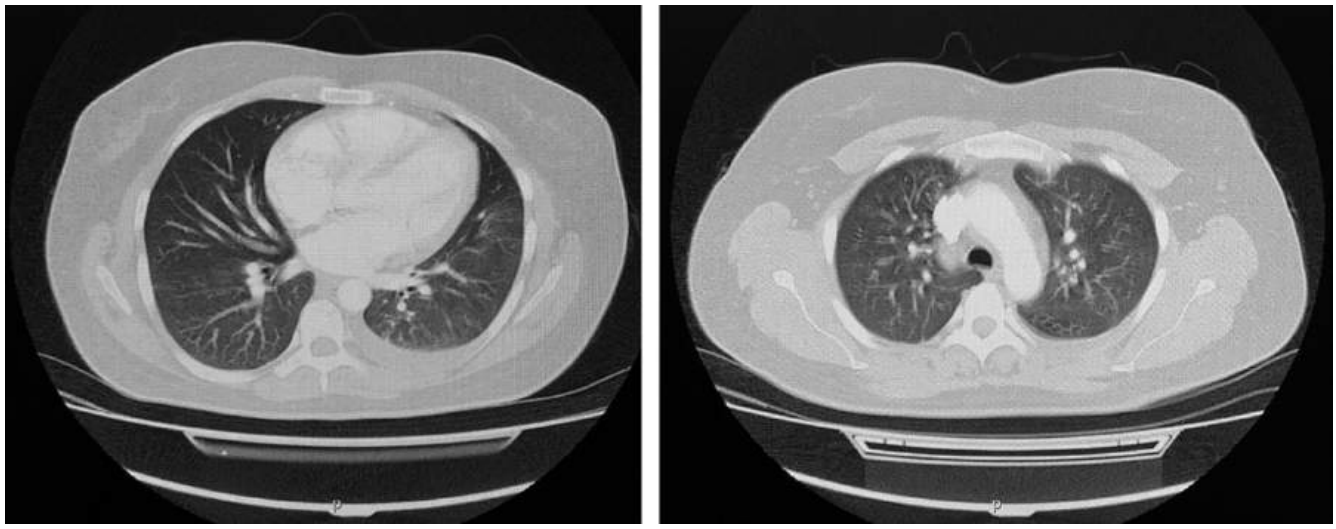


Figure 2. Chest CT angiography: thrombus at the level of the right lower lobar segmental branch, right pleural effusion, and atelectasis. Images property of the authors.



Figure 3. Colonoscopy. Findings revealed active ulcerative pancolitis in the acute phase with scant bleeding. Images property of the authors.

tions and alarm signs in the event of requiring assistance again in the emergency department.

One month later, the patient was reassessed in an outpatient consultation. Complementary studies ruled out other immunological diseases (**Table 1C**), and a colon biopsy revealed epithelial erosion, increased lymphoplasmacytic infiltrate, formation of lymphoid nodules, basal plasmacytosis, abundant neutrophils with crypt involvement, microabscesses, and depletion of goblet cells. These findings confirmed that the patient had active UC without dysplasia, and the established treatment was continued.

DISCUSSION

Thromboembolic complications of inflammatory bowel disease (IBD) have an estimated prevalence of 1% to 8%; however, postmortem studies report an incidence of 39%. Patients presenting with newly diagnosed IBD have a 3- to 4-fold increased risk of developing venous thromboembolism (VTE) compared to the general population[6-8]. Pulmonary embolism increases the risk of morbidity and mortality in this patient group, with reported mortality rates ranging from 18% to 25% in patients with IBD[9].

There are likely risk factors that contribute to the presentation of the condition, such as age 60 years or older with IBD, pregnancy, active and extensive IBD with complications (stenosis, fistulas, or abscesses)[10,11], obesity, smoking, family history of thromboembolic disease, use of oral contraceptives or hormone replacement therapy, immobility[8,12], dehydration, need for surgery, and being a carrier of central catheters[13]. Other hematological abnormalities have been found to be associated with thrombotic risk, such as anemia and hyperhomocysteinemia, as well as electrolyte imbalances or patients on corticosteroid treatment[13]. In our case, the patient had a history of deep vein thrombosis, along with findings of microcytic hypochromic anemia and thrombocytosis, which were considered attributable risk factors for the presentation of pulmonary embolism.

Among the pathophysiological events involved in the risk of thromboembolism, several hypotheses are described that point to the active state of IBD as an initial requirement. There is a state of hypercoagulability associated with an increase in procoagulant factors, such as factors V and VIII, and a decrease in anticoagulant factors like antithrombin III, protein C, and protein S[6,9]. The involvement of autoantibodies such as anticardiolipin (aCL) and lupus anticoagulant (LA) has also been suggested as precursors in the hypercoagulable state[7].

Similarly, thrombocytosis or platelet activation and aggregation occur due to the expression of markers such as GP53, CD-40 ligand, and P-selectin[13], which induce microvascular damage and cytokine activation. There are

Table 1. Laboratory tests

Diagnostic tests	Result	Reference
A. Admission tests		
Creatinine (mg/dL)	0.52	0.3-1.1
Plasma glucose (mg/dL)	89	74-106
Leukocytes (x 10^3/µL)	9.38	4.5-11.0
Neutrophils (%)	46	50-70
Lymphocytes (%)	45	20-40
Hemoglobin (g/dL)	5	11.0-16
MCV (fL)	9	80-99
MCHC (g/dL)	20	32-36
Platelets (x 10^3/µL)	848	150-450
Troponin # 1 (ng/mL)	0.004	0.0-0.3
B. Control tests		
Leukocytes (x 10^3/µL)	9.82	4.5-11.0
Neutrophils (%)	35	50-70
Lymphocytes (%)	47	20-40
Hemoglobin (g/dL)	8.2	11.0-16
MCV (fL)	9.4	80-99
MCHC (g/dL)	26	32-36
Platelets (x 10^3/µL)	767	150-450
Immunological tests	**Result**	**Reference**
C. Complementary tests		
Coagulation Protein C Activity (%)	93	70-130
Anti-dsDNA IgG Antibodies	Negative	>1:10
Anticardiolipin IgG Antibodies (GPL/mL)	2.06	>18
Anticardiolipin IgM Antibodies (MPL/mL)	1.36	>18
Antinuclear Antibodies (ANA)	Negative	>1:160
Extractable Nuclear Antigen, IgG Antibodies (EIA Units)	1.29	20-39
Anti-SSA (Ro) IgG Antibodies (EIA Units)	0.87	
Anti-RNP IgG Antibodies (EIA Units)	1.44	
Lupus Anticoagulant	1.3	
Citrullinated Peptide (Anti-citrulline) (U/mL)	<1	>5.0

MCHC: mean corpuscular hemoglobin concentration; dsDNA: double stranded DNA; GLP: glucagon-like peptide; IgG: Immunoglobulin G; IgM: Immunoglobulin M; MLP: mean levels of cardiolipin antibodies; RNP: ribonucleoprotein; SSA: anti-RO antibody; MCV: mean corpuscular volume.

decreased plasma concentrations of tissue plasminogen activator (tPA), the main activator of the fibrinolytic system, along with an increase in plasminogen activator inhibitor and thrombin-activatable fibrinolysis inhibitor, suggesting that fibrinolysis is also altered[7]. Additionally, genetic factors such as factor V Leiden, factor II, and mutations in the plasminogen activator inhibitor type 1 gene are involved in the development of thrombotic manifestations[6,9].

Therapeutic measures recommended for the prevention of thromboembolic events include hydration, the use of below-the-knee compression stockings (especially for venous thrombosis of the extremities), correction of vitamin deficiencies (particularly B6, B12, and folate), and an active lifestyle that involves constant mobilization. Prophylactic anticoagulant therapy is recommended for high-risk patients who are hospitalized during the active phase of the disease or those who have undergone surgical procedures. Recommendations are based on the use of low molecular weight heparin (LMWH) as the treatment of choice. Alternatively, unfractionated heparin or fondaparinux at low doses can be used. The risk-benefit of extending prophylaxis after hospital discharge for individuals with a higher risk of venous thromboembolism remains unknown; however, long-term treatment with vitamin K antagonists (warfarin, acenocoumarol, and fluindione) or non-vitamin K antagonists (dabigatran, apixaban, edoxaban, and rivaroxaban) is recommended for outpatient care [10,14-17].

CONCLUSIONS

Thromboembolic complications have an estimated prevalence of 1% to 8% in patients presenting with active-phase IBD. Pulmonary embolism, in turn, increases morbidity and mortality. The potential pathophysiological events involved include disruption of platelet aggregation, fibrinolysis failure, and genetic conditions that promote hypercoagulable states. It is crucial to identify risk factors and implement therapeutic measures to prevent future thromboembolic events. The prophylactic thromboembolic therapy of choice is LMWH, which is recommended for high-risk patients hospitalized during the active phase of the disease.

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Conflicts of interest

The authors state that they have no conflicts of interest.

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Case report

Conservative Management of Esophageal Perforation Due to Foreign Body: A Case Series of Four Patients

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OPEN ACCESS

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Abstract

Introduction: The most common cause of esophageal perforation today is diagnostic and therapeutic procedures. However, perforation caused by a foreign body accounts for 10% to 35% of cases, with a mortality rate of up to 18%. **Method:** This case series presents patients diagnosed with esophageal perforation who were treated conservatively over a two-year period at the Hospital Regional de Moniquirá, Colombia. **Results:** Six patients experienced esophageal perforation due to a foreign body. Of these, four were successfully managed without the need for surgery. **Conclusions:** Conservative treatment of esophageal perforation is a valid approach for selected patients who meet Cameron's criteria and can undergo strict follow-up.

Keywords

Esophagus, foreign bodies, esophageal perforation, conservative treatment, patient selection.

INTRODUCTION

Esophageal perforation caused by accidentally ingested foreign bodies presents a diagnostic and therapeutic challenge for the medical team. Between 57% and 80% of foreign bodies become impacted in the cervical esophagus, 26% in the thoracic esophagus, and 17% at the esophagogastric junction[1,2]. Foreign bodies account for 10% to 35% of the causes of esophageal perforation[3-5] and are associated with a mortality rate of up to 18%. Currently, the most common cause of esophageal perforation is related to diagnostic and therapeutic procedures[6].

One of the earliest documented descriptions of esophageal perforation corresponds to Hermann Boerhaave, who in 1723 observed the spontaneous rupture of the esophagus of Baron Van Wasserman, Grand Admiral and Commander of the Dutch fleet[6,7]. In 1947, Barrett[8], Olsen and Clagett[9] described the first attempts to repair an esophageal injury.

Foreign bodies pass through the digestive tract without causing damage and without requiring intervention in 80% of cases. Between 10% and 20% of cases require endoscopic removal, and less than 1% require surgical management. In the United States, the ingestion of foreign bodies has an incidence among adults of between 3 and 5.3 per 100,000 inhabitants and is associated with 1,500 deaths per year[10].

The management of esophageal perforation must be individualized, taking into account the third of the esophagus

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in which the perforation occurs, the extent of esophageal damage, the cause or mechanism of the injury, the patient's health condition, and the time elapsed between the perforation and medical attention. Based on these factors, treatment may include conservative management, endoscopic management, or surgical management[10].

At the Hospital Regional de Moniquirá, 42 patients with foreign bodies in the esophagus were treated over a two-year period, between December 2021 and November 2023. Six of these patients presented with esophageal perforation. One patient was not considered a candidate for conservative management due to not meeting Cameron's criteria and required surgical management. Another patient with esophageal perforation also did not qualify, as he experienced a massive hemorrhage episode six hours after admission in the intensive care unit (ICU) and died. The remaining four patients, who underwent conservative treatment, had a favorable clinical course. All four patients presented poor dental health as a probable predisposing factor for the accidental ingestion of foreign bodies, being either partially or totally edentulous.

The patients' information was obtained with authorization from the Scientific Submanagement of the Institution, along with approval for its publication.

CLINICAL CASES

Case 1

This is a 59-year-old male patient who, after ingesting chicken, presented to the emergency department with dysphagia and a sensation of a foreign body at the cervical level, with 48 hours of evolution. Clinically, he had normal vital signs and no subcutaneous emphysema. Upper digestive endoscopy revealed a chicken bone impacted in the esophagus, 22 cm from the dental arch (**Figure 1A**). After removal with foreign body forceps, a 3 mm perforation was identified in the esophageal wall (**Figure 1B**). Cervicothoracic computed tomography (CT) showed a small amount of gas and a contained leakage of contrast medium at the periesophageal level (**Figure 1C**).

Conservative treatment was performed, including enteral nutrition through a nasojejunal tube and administration of ampicillin-sulbactam at a dose of 3 g intravenously (IV) every 6 hours.The patient had an adequate clinical course; therefore, oral feeding was resumed on the tenth day, and he was discharged.

Case 2

This is a 75-year-old female patient who, after ingesting chicken, presented to the emergency department with dysphagia for solids and liquids and a sensation of a foreign body at the cervical level, with 96 hours of evolution. On physical examination, her vital signs were normal, and there was no subcutaneous emphysema. During the upper digestive endoscopy, a chicken bone was observed impacted in the esophagus, 16 cm from the dental arch (**Figure 2A**). It was removed using foreign body forceps (**Figure 2B**), and an 8 mm perforation was identified in the esophageal wall (**Figure 2C**). Cervicothoracic computed tomography (**Figure 2D**) showed tissue thickening, with gas at the esophageal level and in the retropharyngeal space.

Due to the patient's stable clinical condition, a conservative treatment approach was chosen. This included enteral feeding through a nasojejunal tube and the administration of ampicillin-sulbactam at a dose of 3 g IV every 6 hours. Given her favorable progress and good oral intake tolerance, she was discharged on the tenth day.

Case 3

This is a 62-year-old female patient who, after consuming rib broth, presented to the emergency department with

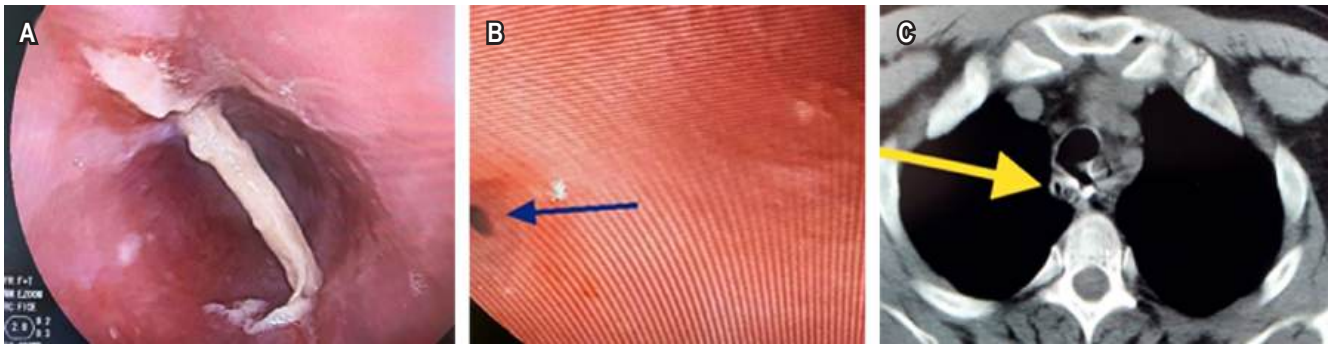


Figure 1. Foreign body located in the esophagus. **A.** Foreign body. **B.** Perforation in the esophageal wall. **C.** CT scan showing gas and contained contrast medium. Images property of the authors.

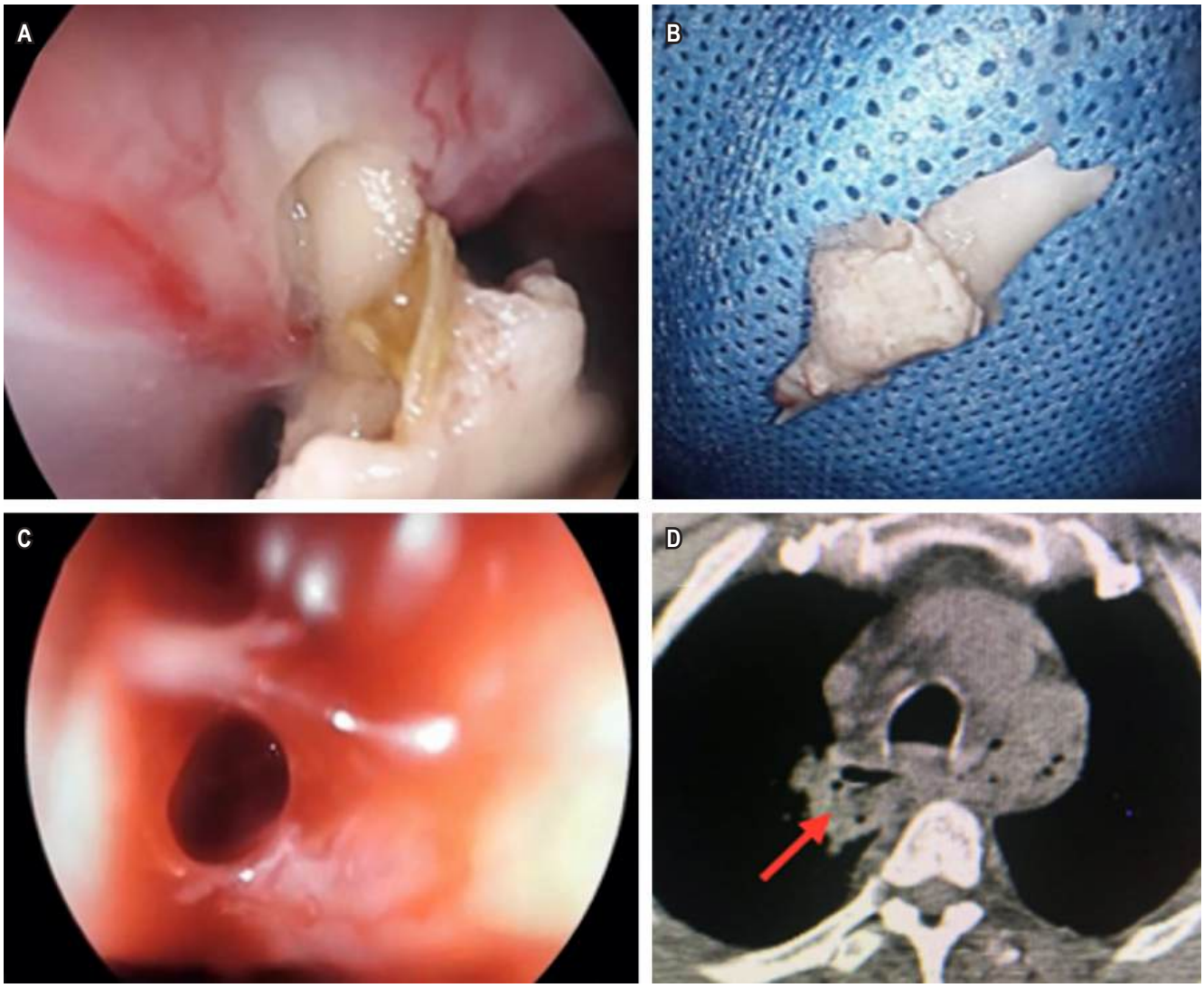


Figure 2. Presence of a foreign body in the esophagus. **A.** Impacted foreign body. **B.** Foreign body. **C.** Perforation in the esophageal wall. **D.** Gas at the esophageal level and in the retropharyngeal space on CT scan. Images property of the authors.

dysphagia and a sensation of a foreign body at the cervical level, with 24 hours of evolution. Vital signs were normal, and there was no evidence of subcutaneous emphysema. During the upper gastrointestinal endoscopy, a beef bone spicule impacted in the esophagus was observed at 14 cm from the dental arch (**Figure 3A**), and it was extracted using foreign body forceps (**Figure 3B**). A mirror-image perforation of 3 mm, caused by the ends of the foreign body, was identified in the esophageal wall (**Figure 3C**). Cervicothoracic computed tomography showed the presence of gas at the mediastinal and periesophageal levels.

A nasoenteral feeding tube was placed, and broad-spectrum antibiotic therapy was initiated with piperacillin/tazobactam at a dose of 4.5 g IV every 8 hours. Given the patient's good oral intake tolerance and favorable clinical progress, she was discharged on the eighth day.

Case 4

This is a 60-year-old male patient who presented to the emergency department with progressive dysphagia and a sensation of a foreign body at the cervical level, 120 hours after ingesting fish. He had no subcutaneous emphysema, and his vital signs were normal. The esophagogastroduodenoscopy revealed a deep longitudinal tear in the esophageal wall with signs of perforation (**Figure 4A**), but the foreign

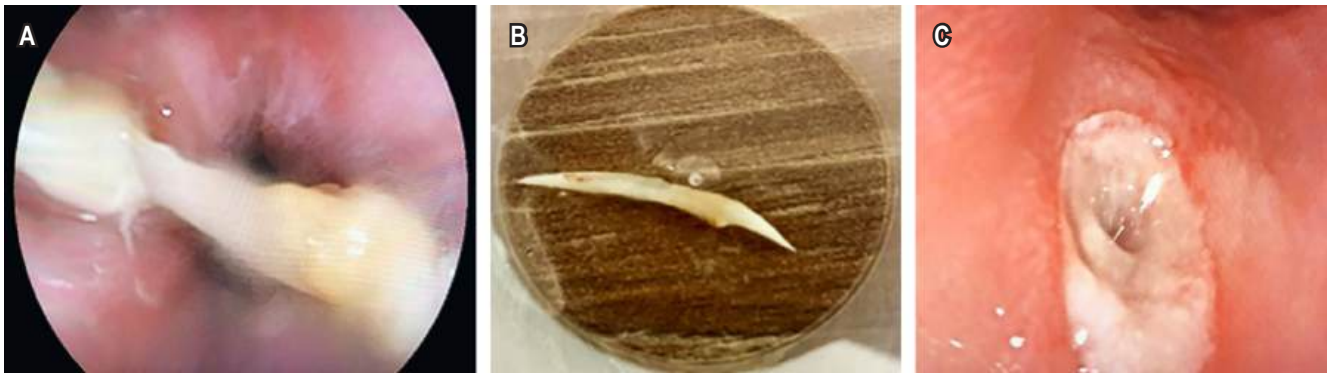


Figure 3. Presence of a foreign body in the esophagus. **A.** Foreign body impacted on both sides of the esophageal wall. **B.** Foreign body extracted. **C.** Perforation in the esophageal wall. Images property of the authors.

body was not identified. Cervicothoracic CT showed gas at the mediastinal and periesophageal levels, with a foreign body located at the periesophageal level (**Figure 4B**). A cervical X-ray also showed the foreign body at the periesophageal level (**Figure 4C**).

The patient was treated with enteral nutrition via a nasojejunal tube and broad-spectrum antibiotic therapy with piperacillin-tazobactam at a dose of 4.5 g IV every 8 hours. The progress was satisfactory, and on the ninth day, a follow-up endoscopy showed a longitudinal scar at the level of the cervical esophagus with adequate re-epithelialization (**Figure 4D**). The patient was discharged on the tenth day. Two weeks later, the patient underwent left anterolateral cervicotomy due to persistent pain in the cervical region. The foreign body was successfully extracted (**Figure 4E**). The patient was discharged 48 hours postoperatively with satisfactory recovery.

Table 1 shows the paraclinical results of the four patients, who were monitored through outpatient consultations at 4 and 8 weeks, remaining asymptomatic.

DISCUSSION

Esophageal perforation is a rare condition, with causes including endoscopic instrumentation (59%), spontaneous occurrence (15%), foreign bodies (12%), trauma (9%), surgical lesions (2%), neoplastic conditions (2%), and other causes (2%)[11]. A retrospective descriptive study published in 2022 identified a total of 15 patients with this condition between 2000 and 2019, of whom 80% required surgical treatment[12]. In our institution, a higher percentage of cases occurred within a shorter period, with six patients diagnosed with esophageal perforation over two years. Four of these patients were treated conservatively, the fifth required surgery due to not meeting Cameron's criteria, and the remaining patient presented with massive hemorrhage six hours after admission to the ICU and died.

The symptoms most commonly presented after the ingestion of foreign bodies are dysphagia, cervical pain, the sensation of a foreign body in the pharynx or cervical esophagus, hypersalivation, chest pain, dyspnea, subcuta-

Table 1. Paraclinical tests of patients

Patient	Admission paraclinical tests			Discharge paraclinical tests		
	Leukocytes	Neutrophils (%)	CRP	Leukocytes	Neutrophils (%)	CRP
Case 1	16.060	85,1	48	6090	60,3	<6
Case 2	16.970	92,1	192	8180	59,6	48
Case 3	8070	83,7	101	3630	38,0	24
Case 4	10.700	82,4	98	5780	50,5	27

Table created by the authors.



Figure 4. Foreign body located in the esophagus. **A.** Longitudinal perforation of the esophagus. **B** and **C.** CT scan and X-ray showing the foreign body in the retropharyngeal space. **D.** Healing wound observed during follow-up endoscopy. **E.** Foreign body extracted. Images property of the authors.

neous emphysema, fever, tachycardia, and tachypnea[12]. All the patients included in this series presented dysphagia and the sensation of a foreign body, with no tachycardia and no subcutaneous emphysema, so clinically, perforation was not suspected upon admission.

The diagnosis is aimed at establishing the presence of the foreign body in the upper digestive tract, or signs of perforation such as dissection of the periesophageal or mediastinal spaces by gas, or indirect signs of the presence of the foreign body at this level, such as rectification of the cervical spine due to antalgic positioning and increased retropharyngeal or retroesophageal space on cervical X-rays. Paraclinical tests help assess criteria for systemic inflammatory response, and a complete blood count, C-reactive protein, and other relevant tests should be requested depending on the patient's condition[13].

Due to the risk of perforation or aspiration, an endoscopic examination should be performed on all patients suspected of having a foreign body in the upper digestive tract, as was the case with all the patients presented. The examination should systematically assess the base of the tongue, soft palate, tonsillar fossae and their pillars, palatine tonsils, the supra-epiglottic space, pyriform sinuses, anterior commissure, posterior commissure, vocal folds, hypopharynx, cricopharynx, esophageal lumen along its entire length, the gastric chamber, and the duodenum[14-16].

The extraction of the foreign body should be performed very carefully to avoid further tissue damage from improper traction, in order to prevent inadvertent perforation. Excessive bleeding, which could indicate vascular injury, subcutaneous emphysema, respiratory difficulty, or a decrease in pulse oximetry, should always be monitored, as it may suggest pleural or airway injury. During the foreign body extraction, proper fixation is essential to prevent loss of the foreign body and possible migration into the airway. After the foreign body is removed, a thorough reassessment of the esophageal wall should be conducted to rule out potential perforations[15,16].

In the case of perforation or suspected perforation, performing a cervicothoracic computed tomography allows for the assessment of the extent of gas dissection in the mediastinal and cervical tissues, the presence of cervical or thoracic collections, and potential injury to neighboring structures or organs. This will help determine the management approach to be followed[17], as was done with the patients presented.

The factors for determining the conservative management of esophageal perforation in the middle or thoracic third were established in 1979 by Cameron[18] and are known as Cameron's criteria:

- Early diagnosis
- Contained fistula in the neck, mediastinum, or between the mediastinum and the visceral pleura
- Drainage of the perforation into the esophageal lumen
- Availability of diagnostic imaging and a surgical specialist
- Injury not occurring on neoplastic tissue, nor associated with distal obstruction
- Absence of symptoms of sepsis

In 1997, Altorjay[19] published his 15-year experience with conservative management in 20 out of 86 patients with esophageal perforation, with a mortality rate of 10%. In 2020, Liao[20] published a retrospective review of 270 patients with esophageal perforation caused by a foreign body over an 8-year period, treated conservatively, with a healing rate of 94.8% and a mortality rate of 1.1%.

Complications that can arise when conservative management is implemented include mediastinitis, the formation of abscesses or mediastinal collections, and empyema, when the perforation site does not maintain adequate drainage into the esophageal lumen, leading to infection spread. Active bleeding can also occur due to vascular injury or an aortoesophageal fistula[21].

Endoscopic treatment requires proper supplies and trained personnel. It includes defect closure with the placement of traditional TTS (through the scope) and OTSC (over the scope clip) clips, which have generally been used for lesions up to 10 mm in size. However, there are reports of successful closure for larger lesions with a success rate of 89% when the perforation is identified early (i.e., within the first 24 hours). Early identification allows for leakage control and reduces the risk of mediastinitis[7, 22, 23]. The placement of fully covered self-expanding esophageal stents shows a healing rate ranging from 13% to 69%, with mortality rates between 0% and 33%, and stent migration between 6% and 35%. These stents should be removed after 4 to 6 weeks to prevent bleeding or tissue penetration, which could complicate their removal[22, 24].

Vacuum therapy in patients with a periesophageal cavity that needs drainage allows for closure by granulation with healing rates of 70% to 100%. It is recommended to change the sponge every 5 to 7 days[24, 25]. Tissue glue has been successfully used for 2 mm perforations resulting from the removal of food impacted in the esophageal lumen[7].

Based on the clinical characteristics of the presented patients and the endoscopic findings, these alternative therapeutic approaches for initial management were not considered and were reserved as second-line treatment options, which were ultimately not used.

According to the guidelines from the *World Journal of Emergency Surgery*, patients without transmural necrosis of the esophageal wall are candidates for non-surgical management but require close clinical, laboratory, and imaging monitoring if necessary. Once the perforation is documented, nasoenteral feeding should be administered. Oral intake can be resumed as soon as proper swallowing is restored, pain is reduced, and it is deemed that the esophageal lesion has healed[26]. These guidelines were followed for the patients presented.

Surgical treatment is aimed at draining the periesophageal spaces, suturing the perforation with or without the placement of reinforcement muscle patches, or performing derivational surgeries with partial or total esophageal resection. The mortality associated with esophageal perforation can range from 12% to 36%[27, 28].

CONCLUSIONS

In every patient diagnosed with a foreign body, esophageal perforation should be ruled out, even if clinical signs such as tachycardia or subcutaneous emphysema are not present. Conservative management of esophageal perforation is a valid option for selected patients who meet Cameron's criteria and can be closely monitored, allowing for the detection of changes that may indicate the need for definitive surgical management.

We consider it highly important that future studies be conducted with methodological designs that allow for stronger recommendations regarding the treatment of these patients.

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Case report

Drug-Induced Pancreatitis Due to Deferasirox: A Case Report

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Abstract

Pancreatitis, or inflammation of the pancreas, is a common reason for medical consultation, particularly in emergency departments when patients present with abdominal pain. It represents a significant financial burden on healthcare systems, as one in three cases progresses to moderate or severe pancreatitis, leading to increased morbidity, mortality, and complications. Currently, the primary causes of pancreatitis include obstructive biliary and non-biliary factors, resulting from reflux and the absence of enzyme flow into the intestine. This leads to enzyme activation within the pancreatic tissue, causing self-digestion. Alcohol consumption and hypertriglyceridemia contribute to cellular toxicity due to the metabolic breakdown of these substances. Drug-induced pancreatitis is a rare condition associated with antibiotics, analgesics, and antidepressants. Deferasirox, an iron chelator primarily used in patients requiring frequent blood transfusions to prevent iron overload, has rarely been linked to pancreatitis. However, available data suggest a possible correlation, and the pharmaceutical manufacturer lists pancreatitis as a potential adverse effect in the drug's technical specifications. This report presents the case of a 71-year-old female patient who developed moderate to severe pancreatitis without major complications. Physicians ruled out the most common causes of pancreatitis and concluded that the triggering factor was the iron-chelating agent deferasirox.

Keywords

Pancreatitis, acute pancreatitis, abdominal pain, deferasirox, Exjade.

INTRODUCTION

Inflammation of the pancreas, known as pancreatitis, is a common condition. It is the leading cause of gastrointestinal-related consultations in the United States, resulting in significant morbidity and mortality, as well as increased healthcare costs. This condition accounts for up to 275,000 hospitalizations annually, with an incidence ranging from 13 to 45 cases per 100,000 inhabitants per year in the United States[1,2].

It is important to note that the three abdominal diagnoses associated with the highest healthcare costs are gastrointestinal bleeding, gallbladder disease, and pancreatitis, representing an expenditure of over 12 billion dollars annually. In 2018, pancreatitis accounted for up to 195,000 emergency department visits and 562,000 outpatient visits in the United States, with up to 65.6% of these patients requiring hospitalization, and an average cost per hospitalization of 23,472 dollars per patient[3,4].

In Colombia, the two main etiologies are biliary pancreatitis and alcohol-related pancreatitis. Most cases are mild and follow a satisfactory course; however, up to 30% are moderate to severe cases, with mortality rates rising dramatically from 5% to 35%. In the country, the incidence is 34 cases per 100,000 inhabitants[5,6].

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In developed countries, gallstone obstruction has been reported to account for 38% of cases. The mechanism by which pancreatitis develops is related to the lodging of a gallstone in the biliary tract, causing obstruction. This leads to increased ductal pressure and decreased flow, which causes the enzymes produced in the exocrine pancreas to be activated in its interior[7]. Alcohol is considered the second most common cause, although its pathophysiology is not clearly established. Studies have described that alcohol can be partially metabolized by the exocrine pancreas through oxidative and non-oxidative mechanisms. However, during degradation and elimination, the molecule first binds to fatty acids, forming lipophilic fatty acid ethyl esters. These molecules are well tolerated by pancreatic cells at low concentrations; however, when accumulation occurs, they interfere with the calcium gradient required for exocytosis and also cause mitochondrial toxicity by disrupting oxidative phosphorylation, leading to a secondary drop in adenosine triphosphate levels and resulting in cell death[8].

A controversial and rare cause is hypercalcemia. Patients with conditions associated with elevated serum calcium levels may develop pancreatitis, as the deposition of calcium salts is cytotoxic to pancreatic cells. Moreover, the increase in extracellular calcium concentrations enhances the release and subsequent activation of trypsinogen, triggering pancreatic autodigestion[9].

PRESENTATION OF THE CASE

The patient is a 71-year-old woman with a history of myelodysplastic syndrome associated with chronic anemia, requiring transfusion support every 25 days as indicated by the hematology department. She was being treated with deferasirox. She presented with abdominal pain predominantly in the epigastric region, associated with multiple episodes of vomiting with food content. Management with omeprazole, sucralfate, and sodium alginate was initiated; however, the patient did not respond to treatment, and additional studies were performed (**Table 1**).

In this context, a diagnosis of pancreatitis was considered, and additional studies were requested to determine the possible cause. An abdominal ultrasound was performed, which did not reveal any abnormalities; however, the pancreas could not be evaluated due to gas interposition. The report noted a postcholecystectomy status. Magnetic resonance cholangiopancreatography (MRCP) showed an increase in pancreatic size and diffuse signal intensity, with alteration of the adjacent fat. Peripancreatic fluid was observed, extending bilaterally to the anterior pararenal space and toward the paracolic gutters, as well as the perihepatic and perisplenic regions. In addition, ectasia of the extrahepatic bile duct was reported, without evidence of any obstructive cause (**Figure 1**).

Table 1. Laboratory tests

Test	Observed value	Reference value
Amylase	721 U/L	28-100 U/L
Lipase	1539 U/L	13-60 U/L
ALT	103.6 U/L	0-31 U/L
AST	97.8 U/L	0-32 U/L
Total bilirubin	1.41 mg/dL	0-1 mg/dL
Direct bilirubin	0.96 mg/dL	0-0.3 mg/dL
Indirect bilirubin	0.45 mg/dL	
Hemogram		
Hemoglobin	9.1 g/dL	12.3-15.3 g/dL
Leukocytes	13.2 10 3/µL	4.5-11.3 10 3/µL
Platelets	210 10 3/µL	150-450 10 3/µL
Serum calcium	10 mg/dL	8.8-10.2 mg/dL
Triglycerides	88.7 mg/dL	0-150 mg/dL
CRP	5.8 mg/dL	0-5 mg/L

ALT: alanine aminotransferase; AST: aspartate aminotransferase; CRP: C-reactive protein. Table created by the authors.

The patient presented clinical and paraclinical findings consistent with pancreatitis. After ruling out the most common causes, a consultation was requested with the gastroenterology department, where it was determined that this was a case of moderately severe pancreatitis. As further studies were carried out to determine the origin, an endoscopic ultrasound was performed, which reported acute pancreatitis without biliary duct dilatation, without lithiasis, with absence of the gallbladder, and a normal papilla.

The patient showed gradual but steady improvement, with increasing tolerance to the initial diet and its progression, along with better control of abdominal pain. Since no typical causes of pancreatitis were found, the patient's medication history was reviewed again. A possible association between the iron chelator and pancreatitis was identified. These reports describe that this association is more frequent in pediatric patients, probably due to the higher incidence of hematologic disorders, although there remains a risk when using deferasirox in adult patients. The hematology team agreed with this etiological approach and discontinued the administration of this drug. The patient

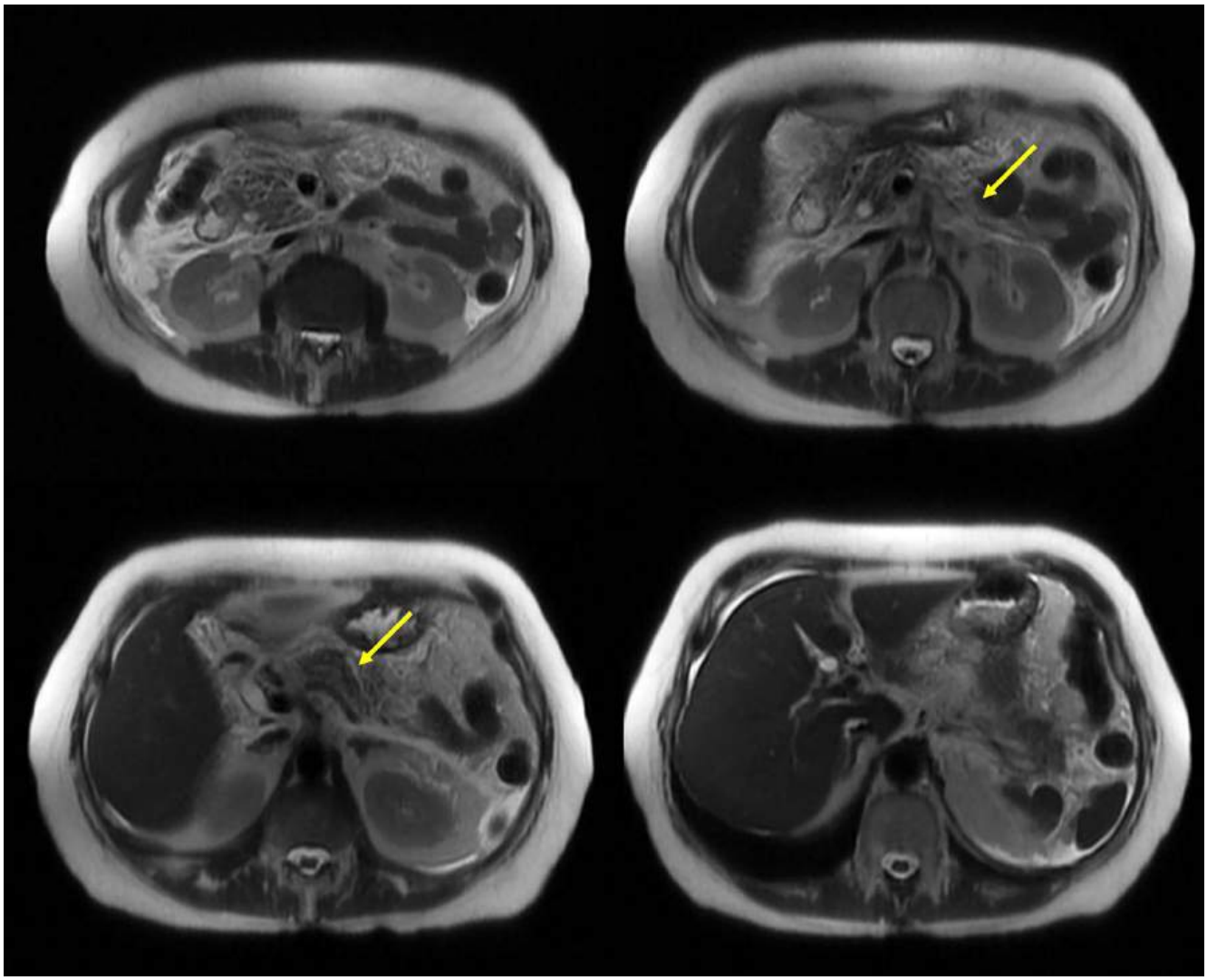


Figure 1. Abdominal MRCP: The pancreas shows a diffuse increase in size and signal intensity, with alteration of the adjacent fat. There is peripancreatic fluid extending bilaterally into the anterior pararenal spaces and along the paracolic gutters, as well as into the perihepatic and perisplenic regions. Images property of the authors.

ultimately had a favorable clinical course, with normalization of biochemical parameters, and was discharged from the hospital. The next step is to assess whether the patient will require reinitiation of an iron chelator due to the frequent and multiple transfusions, while considering the risk of recurrent pancreatitis.

DISCUSSION

Deferasirox is an iron-chelating drug developed by Novartis and approved by the U.S. Food and Drug Administration (FDA) in 2005 for the management of iron overload, a common condition in patients requiring frequent blood transfusions due to various pathologies[10]. It works by forming irreversible bonds with ferric iron in a 1:1 ratio, leading to the subsequent fecal elimination of the formed complex, thereby removing the excess iron. It is important to mention that there are no endogenous systems that respond to the increase in iron levels, there are only mechanisms to store it[11].

The first study demonstrating its efficacy was published in *The Lancet* in 2003, which included patients with β-thalassemia requiring frequent transfusion support. The results showed that, compared to a placebo, it reduced iron

levels and also had an appropriate safety profile[12]. Later, in 2006, a study was published in the journal *Blood* that included patients with β-thalassemia and compared deferasirox with deferoxamine in terms of reducing hepatic iron concentration. This study demonstrated slightly greater effectiveness, though not statistically significant; however, deferasirox is an oral agent, which, compared to slow infusion or subcutaneous administration, also showed an appropriate safety profile. Gastrointestinal symptoms were common but self-limited in less than eight days. The administration of these drugs also resulted in a mild elevation of transaminases in most patients, and in two cases, treatment was discontinued due to drug-induced hepatitis[13].

In the randomized studies, pancreatitis related to deferasirox was never mentioned. However, there is a follow-up study in which one case of acute pancreatitis was reported as an adverse effect[14]. In 2015, the Health Sciences Authority (HSA) issued an alert describing a review of VigiBase, the World Health Organization's (WHO) database, which identified 14 possible cases of pancreatitis related to this drug. In three of these cases, confusion with other medications could have occurred. However, in the remaining 11 cases, deferasirox was the only drug associated, prompting the company to investigate the correlation. Health professionals were advised to exercise caution when using the drug and consider the potential risk, even though it is a rare event[15,16]. In 2021, Novartis developed a manual for patients using deferasirox that includes pancreatitis as a possible adverse effect of this agent[17], and various monitoring entities included this potential adverse effect in the medication's precautions[18,19].

In the presented case, the patient was definitively diagnosed with pancreatitis based on the clinical presentation, laboratory results, and imaging. She was managed by a multidisciplinary team, including specialists in internal medicine, gastroenterology, and hematology. The primary causes of pancreatitis were objectively ruled out, and the treating team, based on evidence and clinical experience, determined it to be a case of drug-induced pancreatitis caused by deferasirox.

CONCLUSIONS

Drug-induced pancreatitis can be a challenging diagnosis, especially in the case of iron chelators, given their limited use and relative infrequency. It is important not to overlook common causes and to subsequently individualize the diagnosis for each patient. In these cases, having a multidisciplinary team of experts is crucial to offer the best approach and management for each patient. This report does not aim to discourage the use of the drug in question, but rather to inform the scientific community about the existence of this potential condition.

Conflicts of interest and ethical issues

Informed consent was obtained from the participant in this case report. This research is based on medical records, and there was no direct contact or intervention with the patients; all data collection was conducted by researchers based on the medical records. No patient was at risk due to the interventions.

All behaviors and actions carried out by the researchers are in accordance with the Belmont Report. All data were collected and analyzed in an appropriate and transparent manner with the active participation of the corresponding author and certified in good clinical practices by the NIDA clinical trial networks.

The researchers openly declare that they have no financial support of any kind, and this research project is purely academic. Due to the methods of this study, no budget was necessary, and the members of the research team declare their absolute commitment to the collection and analysis of data without any financial interests.

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Letter to the editor

Not everything is celiac disease

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After reading the clinical case published by Urbano et al. regarding a patient with diffuse digestive symptoms and findings suggestive of celiac disease[1], I would like to offer the following considerations. First, the diagnosis of celiac disease is made by a combination of clinical symptoms, in addition to paraclinical and histological findings.

Regarding the paraclinical findings, the presence of positive celiac disease antibodies is mentioned, with a cutoff of 1.1 and a result of 1.4. However, diagnosis of the disease requires that transglutaminase antibody values reach a value of more than 10 times the cut-off point, and even the detection of anti-endomysial antibodies[2]. In the case of the patient, it would be appropriate to complement the studies to meet this criterion.

Additionally, the case mentions the histological findings showing a Marsh 1 and Marsh 2 score. However, there is no evidence of villous atrophy, which makes this diagnostic criterion a real challenge, since lymphocytic duodenosis (>25 intraepithelial lymphocytes per 100 epithelial cells) in the absence of villous atrophy is not specific for celiac disease[2-4], but may be a manifestation of multiple mimicking conditions of infectious (tropical sprue, bacterial overgrowth or *Helicobacter pylori*), drug or even immune origin (immunodeficiencies or autoimmune enteropathy)[3]. In these cases, it could be referred to as a non-atrophic type of celiac disease; however, further evidence would be needed to support this diagnosis.

I consider that this case could be considered as a potential celiac disease, given the presence of antibodies and a biopsy with no evidence of villous atrophy. This would need to be confirmed by histocompatibility testing for HLA-DQ2 and HLA-DQ8, which, if negative, would virtually exclude the possibility of celiac disease[2,5].

Unfortunately, in Colombia the prevalence studies of celiac disease have been based predominantly on the detection of antibodies[6], which generates an underdiagnosis and a lack of knowledge of this pathology in our community. For this reason, it is important to consider the different clinical and paraclinical aspects for an adequate diagnosis of an entity that would force a radical change in life habits.

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Response to the letter to the editor: Not everything is celiac disease

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I thank you in advance for your interest in the clinical case *Celiac disease, a silent enemy: a case report*[(1)]. I consider of great relevance the contribution and the profound academic discussion on the diagnostic challenge of an underdiagnosed pathology, based on the sum of clinical, paraclinical and histological criteria, which allow for a comprehensive approach. Unfortunately, at present, there are no diagnostic scales for celiac disease and there are few national and local studies on celiac disease.

It is worth noting that, according to the literature, the clinical presentation of the exposed patient is highly suggestive of celiac disease, as it presents a malabsorption syndrome (iron-deficiency anemia, chronic diarrhea, weight loss, vitamin deficiencies, hypertransaminasemia, chronic pancreatitis, depression, among others). As for the paraclinical tests, and despite the upper limit titers of anti-transglutaminase antibodies, it is important to remember their high sensitivity and specificity for the diagnosis of celiac disease together with the other clinical and histological criteria. The anti-endomysial antibodies and histocompatibility markers HLA-DQ2 and HLA-DQ8 are pending authorization from the patient's health benefit plan administrator. In relation to the histological findings, it should be noted that the prevalence of celiac disease diagnosed by biopsies is approximately 0.7%, which would not exclude the diagnosis in the absence of villous atrophy.

Finally, it is worth mentioning that during the follow-up of the case, the patient reported that, to date, the management that has most positively impacted the improvement of her symptoms has been a gluten-free diet, which would support the diagnosis of celiac disease.

We appreciate your comments and will take them into account for future publications.

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Regarding the characterization of the population as a tool of external validity

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Dear Mr. editor,

We have read with great interest the article published by Aponte-Martín et al. entitled *Improving colonoscopy preparation using information and communication technologies (ICT), randomized clinical trial*[(1)]. The authors used information and communication technologies (ICT) to improve the quality of patient preparation for colonoscopy through the use of an educational video. We highlight the suitability of using ICT for these types of patients, not only because of the easy and unlimited access to necessary information for the proper procedure but also because we have observed that, in Colombia, the use of these technologies has steadily increased over the past five years, particularly among the adult and elderly population[(2)], which is the main focus for the application of this examination. Therefore, it is essential to have an appropriate characterization of the population, especially with regard to variables that may seriously affect the results of the clinical trial.

In the aforementioned study, no clear description was provided regarding age, socioeconomic status, and educational level for the different working groups. This not only leaves room for potential biases in the assessment of bowel preparation and adenoma detection but also decreases the external validity of the results, as they cannot be extrapolated to the general population due to the lack of sociodemographic information about the study sample. We believe that it is essential to take into account the various social variables and determinants that affect patients' ability across different regions of Colombia to access and view the video in a timely manner. Although there are areas with high rates of ICT usage, such as Bogotá (84.3%), Meta (82.6%), and Cundinamarca (77.7%) among individuals over the age of five, there are other departments, such as Vichada (12.7%) and Vaupés (21.4%), where the proportion of the population using ICT is significantly lower[(2)].

Other factors to consider include the low rate of ICT use in small towns (41%) and remote rural areas (34.3%). Age is also a relevant variable, as only 40.84% of adults between the ages of 65 and 69, and just 20% of adults aged 70 and older, reported using ICT. This represents a significant barrier when implementing this type of intervention or assessment tool[(3)].

Additionally, it is important to highlight the lack of rigor in verifying whether the video was actually viewed, as patients were simply asked during the follow-up visit whether they had watched the video or not. This method allows for false positives that cannot be filtered and may introduce a social desirability bias, which should be considered when conducting the study. This contrasts with the methodology used in the

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study by Hayat U et al., where access codes were employed and patients were not directly asked, thereby reducing this type of bias[4–6]. This, combined with the subjectivity involved in describing the clarity of the instructions on how to access the video, raises concerns, especially considering that the material consisted of a printed envelope containing the video link. Since the individuals who received it were between 30 and 84 years old, there is a considerable likelihood that many may have experienced difficulties using the tools required to view the video.

Moreover, by explaining the study to patients and making them aware that they were being observed, the results, although statistically significant as demonstrated by the authors, may have been influenced by the Hawthorne effect, which positively alters patients' behavior simply because they know they are part of a study. Furthermore, the article mentions that pilot tests were conducted to assess the ease of access to and viewing of the video; however, beyond stating that such tests were carried out, no further details are provided regarding the outcomes or findings.

Finally, the article concludes by recommending the routine use of this technological strategy; however, it also points out a "possible limitation of the study, which is that the population involved consists of middle and high-income patients, who may have had greater access to internet technologies"[1], as mentioned by the authors. Due to this, the results and conclusions derived from this research could not be extrapolated to the general population, let alone implement this practice in a systematic and routine manner.

In conclusion, we believe that various factors that could have directly affected the results were overlooked in this study. Furthermore, a clear description regarding the age, socioeconomic status, and educational level of the sample used was not provided, so the results cannot be applied to the Colombian context, nor can they be verified with the methodology provided by the authors. In addition, we propose the use of a method similar to that of Hayat U et al., so as to have more than the patient's testimony and reduce the possibility of false positives. Additionally, it is recommended to add some sort of code at the end of the video, which should be provided by the patients during the follow-up consultation, without informing them about its existence beforehand. This would verify their engagement when accessing the video.

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