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Editorial

Revista Colombiana de Gastroenterología 2021-2023

Ricardo Oliveros-Wilches.[1*]

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The journal's motto, "A journal by everyone and for everyone," must fulfill its objective. It must be a journal by and for all members, which translates into active participation in each role we play so that the journal becomes remarkable in importance, reference, impact, quality, and content of scientific articles.

In our environment, scientific journals are supported by a university or some association, and these are judged substantially by their scientific production, represented in the quantity and quality of papers their scholars or members publish periodically. Some ethical standards provide that a scientific journal of a university or association is not intended to be the publication body of its own research. In other words, with some exceptions, high-impact journals should not be backed by the scientific production of their house (endogamy). For us, these approaches are hard to adopt.

Furthermore, the incentive for researchers to publish in national journals is extremely poor, beyond philosophical convictions. Thus, the vicious circle that "the journal has no impact factor because high-impact articles are not published" cannot be broken.

Another aspect to highlight is that every day, we need national articles to be referenced within the bibliography, i.e., that every time we publish an article, we can know what has been published in national literature.

The editorial board's work is based on the process comprising the reception of the manuscripts, their preliminary evaluation, the assignment of expert peers, the acceptance or rejection of the article following the opinions of these reviewers, the layout, and the publication of approved papers.

The journal has continued to publish four issues per year. For this last quarter, a supplement issue titled "Colombian Consensus on Pediatric Inflammatory Bowel Disease" was published (1).

In the last two years (01/01/2021 to 12/31/2022), we received 235 articles, of which 155 were accepted and 102 were rejected. The acceptance rate is 59%, and the rejection rate is 41%.

On March 1, 2023, a webinar was held on "Case Reports in Medical Literature," with Dr. Scott R. Steele as a guest and Dr. Juan Carlos Reyes as the moderator.

We continue working with Biteca, which manages the journal's OJS platform and provides permanent support.

In the last 12 months, the average number of visits to the journal ranged between 2,500 and 3,600 per month.

In the editorial process, the assignment and selection of expert reviewers are vital for the paper to have an accurate assessment, review, and relevant recommendations.

QR Code

Biteca enabled the "QR Block" OJS plugin for us, generating a QR code for the page accessed. This option improves user experience since it can be shared on different digital media.

Statistics

We have updated the public view of our website traffic statistics to information already collected by Google Analytics since January 2023. These statistics show the countries visiting our journal (**Table 1**) (2).

Table 1. Visits to the journal by country in the last year (11/01/2022–11/01/2023)

	Country	Sessions	Views
1	Colombia	43,626	
2	Mexico	37,661	
3	Peru	21,652	
4	Spain	19,418	
5	Argentina	12,786	
6	Chile	9300	
7	Ecuador	9184	
8	Bolivia	4322	
9	Venezuela	4212	
10	USA	3366	
11	Guatemala	2046	
12	Dominican Republic	1583	
13	Costa Rica	1324	
14	Panama	1169	
15	Uruguay	1087	
16	Paraguay	1081	
17	El Salvador	1066	
18	Honduras	989	
19	Cuba	932	
20	Nicaragua	900	

Similar Articles

Biteca updated the "similar articles" plugin, which displays related articles, including those that share a keyword. This option improves user experience since readers are suggested other articles that may be of interest.

Through Biteca, our recent publications have been uploaded to the digital preservation system Pórtico. The content saved and preserved to date ranges from volume 29, issue 4 (October–December 2014) to volume 38, issue 4 (October–December 2023).

Digital preservation is one of the fundamental components of scientific communication. It guarantees that the published content is indefinitely preserved whether the journal or the institution that finances it closes. Digital preservation is a fundamental requirement of internationally recognized databases such as DOAJ and PubMed. To check your journal's preservation status, go to https://www.portico.org/. Type the journal's ISSN "2500-7440" in the search box and click search.

Finally, the journal is achieving its objectives, and its editorial process is closer to the ideal every day. It will be of immense importance for the Association and its members to understand that the journal by "everyone" will improve its goals and purposes and have a higher impact if members participate.

REFERENCES

1. Vera Chamorro JF, Sánchez Franco C, Vargas Sandoval M, Mora Quintero DV, Riveros López JP, Sarmiento Quintero F, et al. Consenso colombiano de la enfermedad inflamatoria intestinal pediátrica. Rev. colomb. Gastroenterol. 2023;38(Supl No. 1):1-75. https://doi.org/10.22516/25007440.943
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Original article

Dyssynergic Defecation Concerning Proctalgia Fugax: An Observational Study

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Abstract

Introduction: There is no clarity about manometric findings in patients with proctalgia fugax; evidence shows different results. This study aims to evaluate dyssynergic defecation through anorectal manometry in Colombian patients in two gastroenterology centers in Bogotá, Colombia. **Materials and methods:** A cross-sectional descriptive observational study in adult patients with proctalgia fugax undergoing anorectal manometry and treated in two gastroenterology centers in Bogotá between 2018 and 2020. **Results:** 316 patients were included, predominantly women (65%), with a median age of 45.2 (range: 18-78; standard deviation [SD]: 28.3). Four percent of patients had hypertonicity, 50% were normotonic, and 46% were hypotonic. Regarding manometric parameters, 50% had normal pressure, and 46% had anal sphincter hypotonia; 76% had a normal voluntary contraction test. Dyssynergic defecation was documented in 5% of patients, and the most frequent was type I, followed by type III. A rectoanal inhibitory reflex was identified in all patients, 42% with altered sensory threshold and 70% with abnormal balloon expulsion. There was an agreement between the results of the anorectal manometry and the subjective report of the digital rectal exam by the head nurse who performed the procedure. **Conclusions:** The data obtained in the present study suggest that proctalgia is not related to the elevated and sustained basal contracture of the sphincter but neither to the alteration in voluntary contraction since most patients have typical values.

Keywords (DeCS)

Anorectal disorders, anorectal manometry, proctalgia, dyssynergic defecation, gastrointestinal diseases.

INTRODUCTION

Proctalgia fugax is defined as recurrent, inconsistent episodes of stabbing rectal pain not associated with defecation for three months. Episodes can last seconds to 30 minutes, disrupting daily activities and waking the patient at night. Once organic pathologies such as inflammatory bowel disease, fissures, thrombosed hemorrhoids, and prostatitis, among others, have been ruled out, a functional pathology must be studied[1]. Manometry is a diagnostic test that measures pelvic floor muscle function and is helpful in proctalgia fugax. However, results may vary between patients and healthy people and between centers without being standardized[2–5].

Moreover, the rectoanal inhibitory reflex (RAIR) should always be observed in anorectal manometry. This reflex is vital since it is modulated by the myenteric plexus of the autonomic nervous system and produced by the release of nitric oxide and vasoactive intestinal polypeptide. Its absence remains the main element for diagnosing Hirschprung's disease on manometry. Nonetheless, it is also possible not to find it or to find it incompletely in patients with post-circular myotomy and low anterior resection of the rectum[6].

Proctalgia is chronic anal pain with an organic or functional origin. Any organic pathology must be ruled out before considering a case of proctalgia fugax. It is believed that anal sphincter spasms, compression of the pudendal nerve, and psychological factors such as anxiety and obsessive-compulsive disorders are related to its appearance. Although some situations, such as sexual intercourse, defecation, emotional stress, or menstruation, can trigger pain, it is not established[7]. The diagnosis is based on the Rome IV criteria, which require recurrent episodes of anorectal pain unrelated to defecation and lasting only seconds to minutes. Before diagnosis, it is necessary to exclude other causes through tests such as digital rectal examination, laboratory studies, sigmoidoscopy, magnetic resonance imaging (MRI), and transrectal ultrasound (TRUS)[4].

Current evidence regarding manometric findings in these patients is not very clear. Some reports show that biofeedback on patients with dyssynergic defecation simultaneously improves the symptoms of proctalgia fugax. The present study aims to approach the manometric characteristics in a sample of subjects with proctalgia fugax and estimate the presence of dyssynergic defecation through anorectal manometry.

MATERIALS AND METHODS

Study design and data extraction

This cross-sectional descriptive observational study included 316 patients with symptoms of proctalgia fugax undergoing anorectal manometry for any indication between 2018 and 2020.

Eligible adult patients had to have complete information on year of birth, age, sex, and active clinical follow-up at each study institution and anorectal manometric evaluation.

Data collection

Information was gathered over four years on different dates in the various hospitals included in the study. Medical records and anorectal manometry results were used as primary sources of information. Sociodemographic and clinical variables such as age, sex, and functional parameters at the anorectal level were collected.

Technical aspects

During the anorectal manometry scan, several parameters are measured to evaluate the function of the gastrointestinal tract. These include anorectal resting pressure, measured over 20 seconds and extended to one minute if ultraslow waves are detected. The maximum voluntary contraction pressure is also measured through three maneuvers of 20 to 30 seconds with 30 seconds of rest between them. Additionally, extrinsic nervous integrity is assessed with a cough maneuver performed with and without 50 mL of air in the balloon. The defecatory maneuver carried out with three attempts and with and without 50 mL of air in the balloon at 30-second intervals is also evaluated. Finally, the RAIR and rectal sensitivity are examined during distension of the rectal balloon, with increments of 10 to 20 mL[2].

Definitions

A condition suggestive of proctalgia fugax was considered as a case with a history of recurrent episodes of anorectal pain unrelated to defecation and lasting only seconds to minutes, according to the Rome IV criteria, and which, by medical criteria, had been organic causes were excluded through tests such as digital rectal examination, laboratory studies, sigmoidoscopy, MRI, and TRUS[1].

Statistical analysis

The database was created in Excel version 2019. Missing data were filled in with new reviews of data sources, analyzing only complete data at the end. Data were processed using the social science program SPSS version 25.0. We used the median, range, standard deviation, and minimum and maximum values for the descriptive analysis of quantitative variables and absolute and relative frequencies for qualitative variables.

Ethical considerations

The study's design considered the requirements in the Declaration of Helsinki, version 2013, and Resolution 8430/1993 issued by Colombia's National Ministry of Health. It was deemed risk-free research, guaranteeing the confidentiality of the information collected. Informed consent was not necessary in its implementation. No records contained sensitive information about the patient's identity. This research was reviewed and approved by the research ethics committee of each participating institution.

RESULTS

Three hundred sixteen patients were included, predominantly women (65%), with a median age of 45.2 years, a minimum age of 18, and a maximum age of 78 years (**Table 1**), all with symptoms of proctalgia fugax according to the Rome IV criteria.

Table 1. Baseline characteristics of the patients (n = 316)

Number of patients (n = 316)	
Parameter	**Value**
Age, median (range), years	45.2 (18-78; DE: 28.3)
Sex	
- Male, n (%)	98 (31)
- Female, n (%)	218 (69)

Table prepared by the authors.

Manometric parameters

At a manometric level, we found 50% normal pressure, 46% hypotonia of the anal sphincter, and 4% hypertonia; the voluntary contraction test was normal in 76% and abnormal in 24%. A pattern of dyssynergic defecation was documented in 5% of patients, and the most frequent was type I, followed by type III (**Figure 1**).

Regarding other parameters, we identified a RAIR in all patients, alteration in the sensory threshold in 42%, and abnormal balloon expulsion in 70%. There was an agreement between the findings of the basal pressures of the anal sphincter by manometry and the subjective report of the digital rectal examination by the head nurse who performed the procedure.

DISCUSSION

When analyzing the variables, it would be expected that proctalgia be associated with elevated levels of resting pressure and contraction of the anal sphincter. Still, only 4% of patients (mostly women) showed hypertonicity; 50% were normotonic, and 46% were hypotonic. This finding suggests that proctalgia is not necessarily related to an elevated and sustained basal contracture of the sphincter nor an alteration in voluntary contraction since most patients in this study had average values.

The diagnosis of proctalgia fugax relies on the symptomatic characteristics and the exclusion of other pathologies as the cause of pain. Physical examination, rectoscopy, and anoscopy results are usually normal in these patients. TRUS and MRI findings are typically normal, although hypertrophy of the internal anal sphincter (IAS) has been recorded in some cases. Anorectal manometry can detect increased tone of the IAS with a paroxysmal lack of relaxation[8–10].

Furthermore, dyssynergic defecation is a lack of synchronization between abdominal contractions and the functioning of the anal sphincter, together with insufficient relaxation of the IAS and a paradoxical contraction of the striated sphincter muscles during defecation[9,11,12].

There are four types of dyssynergic defecation[8,13]:

1. Type I is when the individual can produce adequate intrarectal pressure and pushing force, but there is

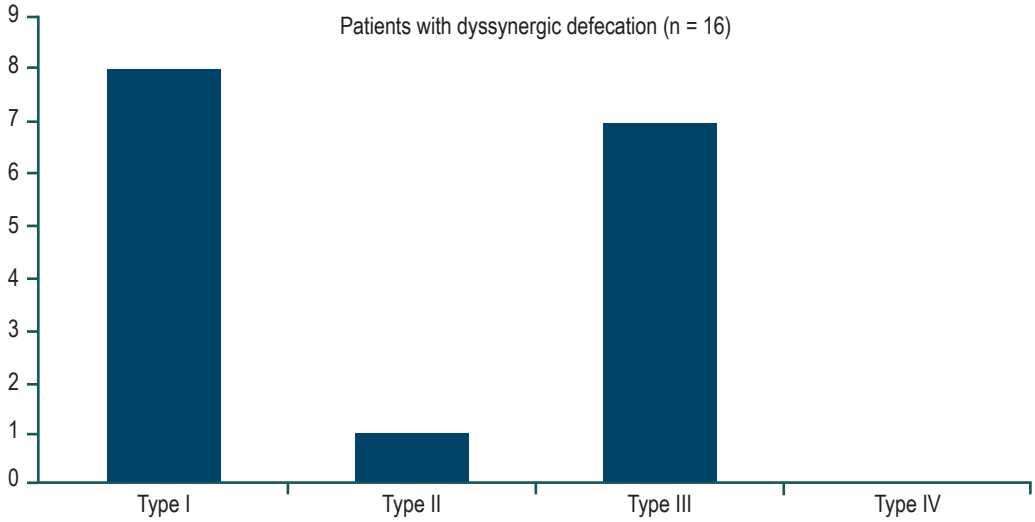

Figure 1. Frequencies of dyssynergic defecation patterns in patients with proctalgia fugax (n = 16). Figure prepared by the authors.

no anal relaxation; in fact, there is an increase in anal sphincter pressure.
2. Type II is when the individual cannot produce adequate pushing force, and there is an increase in anal sphincter pressure.
3. Type III is when the individual can produce adequate pushing force, but anal sphincter relaxation is absent or incomplete with insufficient decrease in anal sphincter pressure.
4. Type IV is when the individual can produce adequate pushing force, but anal sphincter relaxation is absent or incomplete and has a worse response to biofeedback therapy.

In our study, the manometric findings do not reveal a defined pattern, and this is reflected in this group of patients, in whom the pressure, contraction, and sensory threshold tests are non-specific. Their values may vary in any direction. However, regardless of the cause of this symptom, a pattern of dyssynergic defecation in 5% of patients suggests a correlation with proctalgia fugax. Therefore, two points stand out about the relationship between these two entities: First, the most frequent types of dyssynergic defecation found were types I and III; in both situations, an adequate defecatory effort is generated (increased intra-abdominal pressure). Still, in the former, there is a paradoxical contraction of the anal sphincter. In the latter, the relaxation of the anal sphincter is incomplete or absent, which confirms a non-anatomical functional alteration in the outflow tract or defecatory mechanism, resulting in an abnormal balloon expulsion test in 70% of patients. Second, the RAIR is positive in 100% of patients with proctalgia, and the first sensation or sensory threshold is expected in 58% of patients, indicating that the myenteric innervation and reflex arcs of the lower motor neurons are intact and that the problem is poor muscle coordination in the outflow tract.

Because the most frequent pattern scores in the present study were types I and III, it can be correlated with the data obtained in another study. The literature also mentions that a typical pattern involves an increase in intrarectal pressure accompanied by anal sphincter relaxation. A study of 100 patients using a robust 6-sensor manometry system identified four patterns of functional defecatory disorders (FDD). Two patterns, types I and III, describe dyssynergic defecation. The type I pattern is characterized by an elevation of intrarectal pressure (≥ 45 mm Hg) and anal pressure, reflecting contraction of the anal sphincter. The type III pattern is characterized by an increase in intrarectal pressure (≥ 45 mm Hg) with absent or insufficient relaxation (< 20%) of the anal sphincter. Inadequate propulsion (intrarectal pressure < 45 mm Hg) may be associated with paradoxical contraction (type II pattern) or insufficient relaxation (< 20%) of the anal sphincter (type IV pattern). A test performed a month later showed that the abnormal patterns could be reproduced in 51 of 53 patients[9,10].

On the other hand, to treat proctalgia fugax, the literature usually relies on techniques that reduce the pressure of the IAS. The main option is conservative treatments, although no permanently curative results have been observed. These conservative treatments include warm water baths, topical 0.2% glyceryl trinitrate, salbutamol inhalation, local anesthetic block, or injection of botulinum toxin into the anal sphincters. In case of thickening of the IAS and high pressures at rest, considering limited internal anal sphincterotomy is suggested[5].

Finally, the study has some limitations that should be noted, including its retrospective nature based on information reviewed from medical records of patients treated in an outpatient setting, which may have affected data accuracy. Due to the scarcity of information in the study, exposure information is subject to measurement error.

CONCLUSION

The data obtained in the present study suggest that proctalgia is not related to the sphincter's elevated and sustained basal contracture but to the alteration in voluntary contraction since most patients have typical values.

The RAIR is present in 100% of patients with proctalgia fugax, and the first sensation or sensory threshold is normal in 58% of patients. The preceding indicates that the myenteric innervation and the reflex arcs of the lower motor neurons would be intact and that the problem is possibly poor muscle coordination in the outflow tract. However, we suggest that more studies be conducted to continue providing a scientific basis for the relationship between proctalgia fugax and dyssynergic defecation.

Ethical approval and consent for participation

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

Consent for publication

The study's design considered the requirements in the Declaration of Helsinki, version 2013, and Resolution 8430/1993 issued by Colombia's National Ministry of Health. It was deemed risk-free research, guaranteeing the confidentiality of the information collected. Informed consent was not necessary.

Availability of data and material

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

Conflicts of interest

None declared by the authors.

Sources of funding

None declared by the authors.

Author contributions

All authors contributed to all stages of the research (literature review, data collection, and writing) and approved the final version of the manuscript.

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REFERENCES

1. Drossman DA, Hasler WL. Rome IV - Functional GI disorders: Disorders of gut-brain interaction. Gastroenterology. 2016;150(6):1257-61. https://doi.org/10.1053/j.gastro.2016.03.035
2. Ciriza De Los Ríos C, Mínguez M, Remes-Troche JM, Lacima G. High-resolution and high-definition anorectal manometry: Rediscovering anorectal function. Rev Esp Enferm Dig. 2018;110(12):794-805. https://doi.org/10.17235/reed.2018.5705/2018
3. Bjoern MX, Perdawood SK. Manometric assessment of anorectal function after transanal total mesorectal excision. Tech Coloproctol. 2020;24(3):231-6. https://doi.org/10.1007/s10151-020-02147-3
4. Fox M, Markopoulos K, Flückiger M. Investigations of anorectal function. Ther Umschau. 2021;78(9):513-21. https://doi.org/10.1024/0040-5930/a001304
5. Rao SSC, Bharucha AE, Chiarioni G, Felt-Bersma R, Knowles C, Malcolm A, et al. Anorectal disorders. Gastroenterology. 2016;150(6):1430-1442.e4. https://doi.org/10.1053/j.gastro.2016.02.009
6. Ciriza De Los Ríos C, Ruiz De León San Juan A, Díaz-Rubio García M, Tomás Moros E, García Durán F, Muñoz Yagüe T, et al. Diferencias en las presiones del canal anal y la sensibilidad rectal en pacientes con incontinencia anal, estreñimiento crónico y sujetos sanos. Rev Esp Enferm Dig. 2010;102(12):683-90. https://doi.org/10.4321/S1130-01082010001200002
7. Carrington EV, Heinrich H, Knowles CH, Rao SS, Fox M, Scott SM, et al. Methods of anorectal manometry vary widely in clinical practice: Results from an international survey. Neurogastroenterol Motil. 2017;29(8):e13016. https://doi.org/10.1111/nmo.13016
8. Nakao A, Okamoto Y, Sunami M, Fujita T, Tsuji T. The oldest patient with gallstone ileus: Report of a case and review of 176 cases in Japan. Kurume Med J. 2008;55(1-2):29-33. https://doi.org/10.2739/kurumemedj.55.29
9. Meza Madrid D, Hani de Ardila AC, Costa VA, Leguízamo AM, Puentes Leal GA, Ardila Hani AF. Cómo realizar e interpretar una manometría anorrectal de alta resolución. Rev Colomb Gastroenterol. 2019;34(4):404-10. https://doi.org/10.22516/25007440.411
10. Krogh K, Chiarioni G, Whitehead W. Management of chronic constipation in adults. United Eur Gastroenterol J. 2017;5(4):465-72. https://doi.org/10.1177/2050640616663439
11. Kitaguchi D, Nishizawa Y, Sasaki T, Tsukada Y, Ito M. Clinical benefit of high-resolution anorectal manometry for the evaluation of anal function after intersphincteric resection. Color Dis. 2019;21(3):335-41. https://doi.org/10.1111/codi.14528
12. Villarreal AD, Barney VAC, Hani A, Leguizamo AM, Ardila A, Madrid DM. Update of high-resolution anorectal manometry interpretation using the London classification. Rev Colomb Gastroenterol. 2019;34(4):411-5. https://doi.org/10.22516/25007440.484
13. Cho HM, Kim H, Yoo R, Kim G, Kye BH. Effect of biofeedback therapy during temporary stoma period in rectal cancer patients: A prospective randomized trial. J Clin Med. 2021;10(21):5172. https://doi.org/10.3390/jcm10215172

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Original article

Using High-Resolution Anoscopy to Detect Anal Dysplasia Due to Papillomavirus in Patients with Inflammatory Bowel Disease

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Abstract

Introduction: Anal squamous cell carcinoma is rare, but its incidence and mortality have been increasing globally; 90% of cases are related to human papillomavirus (HPV) infection[1,2]. Patients with inflammatory bowel disease (IBD) have a higher risk of infection with this virus; an incidence of 5.5 per 100,000 patients has been identified in the IBD group compared to 1.8 in the non-IBD group[3]. **Materials and methods:** A descriptive case series study was conducted with 21 patients with IBD and no perianal symptoms between January and July 2022 at the Institute of Coloproctology in Medellín. They underwent anal cytology, HPV genotyping, and high-resolution anoscopy after explanation and acceptance of the procedure. If lesions were found, ablative treatment was performed. **Results:** 23% of this cohort had low-grade squamous lesions, while 14.2% had high-grade lesions with dysplasia changes during anoscopy. Besides, 90.4% had positive HPV genotyping, of which 76.1% were high-grade. **Conclusions:** Our study suggests that this series of patients with IBD behaves as a high-risk group for developing premalignant lesions in association with HPV. High-resolution anoscopy is a cost-effective, painless, and affordable method that, in expert hands, may impact the diagnosis and management of premalignant lesions and decrease the incidence of anal cancer in patients with IBD.

Keywords

Human papillomavirus, inflammatory bowel disease, anal dysplasia, anal cancer, high-resolution anoscopy.

INTRODUCTION

Anal intraepithelial neoplasia (AIN), or squamous intraepithelial lesion (SIL), is a premalignant lesion. It is a precursor to squamous cell carcinoma, strongly associated with oncogenic strains of the human papillomavirus (HPV), specifically subtypes 16 and 18, risk factors due to behaviors associated with the acquisition of this virus, such as human immunodeficiency virus (HIV) infection, smoking, receptive anal intercourse, and a history of cervical intraepithelial neoplasia (CIN)[1].

Anal squamous cell carcinoma (ASCC) is rare, and among specific high-risk populations, its incidence may exceed that of colon cancer. Patients with inflammatory bowel disease (IBD) have a higher risk than the general population: An incidence of 5.5 per 100,000 patients has been identified in the group with IBD compared to 1.8 in the group without IBD[2].

It is known that the prevalence of AIN, as well as its progression to carcinoma of the anal canal, is higher in immunosuppressed patients and associated with a prolonged inflammatory state. It favors the persistence and decreases

the viral clearance of HPV in the transition zone of the anal canal, increasing the possibility of developing premalignant lesions and, consequently, anal cancer. Besides, prolonged management with anti-tumor necrosis factor (anti-TNF) and steroids causes a loss of cell cycle regulation, which alters viral clearance.

It is possible to detect precursor lesions of anal cancer mainly through anal cytology and high-resolution anoscopy (HRA)[3]. Currently, there are no recommendations for HPV screening of the anal canal in patients with IBD. Therefore, we conducted a study to confirm the presence of premalignant lesions related to HPV in this area that could explain the high risk of cancer in these patients and develop a screening algorithm in which HRA is the cornerstone for the diagnosis and treatment of premalignant lesions[4].

At present, surveillance protocols define that cytology or HRA is restricted to men who have sex with men (MSM), HIV carriers, recipients of solid organ transplants, and patients using immunosuppressive medications such as chemotherapeutics and steroids, among others[5,6].

This work aims to reveal the incidence of dysplasia and ASCC in a series of cases of patients who suffer from IBD and are at potential risk of developing these conditions[7–9].

METHODS

A descriptive case series study was conducted with patients under follow-up for IBD, without perianal symptoms, between January 2022 and July 2022 at the Instituto de Coloproctología ICO S. A. S. in Medellín. They underwent anal cytology, HPV genotyping, and HRA after explanation and acceptance of the procedure. If lesions were found, ablative treatment was performed.

RESULTS

We included a total of 31 patients with ulcerative colitis (UC; 10 women [47%] and average age of 35.2 years [19–58 years]) with an average disease duration of 4.4 years (0.5–12 years) and an extension of colitis according to the Montreal classification: E1: 7 (17%), E2: 8 (18.5%), and E3: 6 (14.5%).

Thirty-two percent (10) of the patients were under follow-up with conventional therapy (mesalazine, azathioprine). Notably, 6 (19%) of the patients required steroids (prednisolone) in the last year, with an average duration of 6 weeks. The remaining 68% (21) presented with failure of the first management line and were under treatment with biologics (20 with anti-TNF and 1 with vedolizumab).

Cytology was positive for HPV in 23 patients (74.2%). We found atypical squamous cells of undetermined significance (ASCUS) in 10 (32.3%) patients, low-grade squamous intraepithelial lesion (LSIL) in 8 (25.8%), high-grade squamous intraepithelial lesion (HSIL) in 5 (16.1), and normal results in 5 (16%). Cytology was not performed in 3 (1%). HPV genotyping was positive in 28 (90.3%) patients, of which 76.1% were high-risk strains. During anoscopy, dysplasia was found in 11 patients (35.5%), condylomas in 5 (16.1%), and normal results in 15 (48.4%).

When the anoscopic findings were positive for dysplasia/condylomas, they contrasted with concomitant medication. Dysplasia and anti-TNF use was found in 9 (56%) patients, dysplasia and a history of steroid use in 8 (50%), condylomas and anti-TNF use in 5 (31.3%), and condylomas and a history of steroid use in 7 (44%). Importantly, there were no positive anoscopic findings in patients under conventional therapy or vedolizumab.

So we must ask: Should we add a new risk population group to the literature?

DISCUSSION

What is the reality of anal cancer?

In Colombia, no national record of neoplasms allows us to describe the incidence of ASCC. Still, it is a rare neoplasm that constitutes less than 5% of all gastrointestinal cancers.

According to recent publications, it has been seen that in healthy men, it went from 0.8 cases per 100,000 inhabitants in the early 1990s to 1.3 cases per 100,000 by 2012. There is also a more proportional growth in women who have suffered cervical neoplasms. According to data for 2017 from the Surveillance, Epidemiology, and End Results (SEER), a program of the National Cancer Institute (NCI) in the United States, there were about 10,000 cases yearly.

A global incidence is estimated at 1.8 cases per 100,000 individuals, increasing along with mortality; 90% of cases are related to HPV infection. In fact, few doctors know that anal cancer is more common in women in the general population than in men. If the groups commonly called high-risk are analyzed, such as HIV-infected patients or MSM, the figures for anal cancer are exponentially higher than in the general population (1.8/100,000). The incidence of anal cancer in MSM with HIV (-) is 35/100,000, while in MSM with HIV (+) it is 131/100,000[10].

What is HPV, and why is it an oncogene?

HPV is a small, non-enveloped papovavirus with double-stranded DNA, whose sexually transmitted infection is the most common pathogen in humans[11]. It is now recognized that HPV infection is responsible for almost all cervical cancers, 95% of anal cancers, 65% of vaginal cancers, 50% of vulvar cancers, and 35% of penile cancers, as well as a

significant number of head and neck cancers. Almost 63% of new cases and 61% of deaths will occur in women[1].

There are about 200 subtypes based on the genetic sequence of the major capsid protein L1. Approximately 40 subtypes are transmitted by contact between mucosal epithelia, and subtypes 16, 18, 31, 33, 35, 52, and 45 are high risk; they represent the most critical carcinogenic group involved in ASCC: they are isolated in 91% of these tumors, but only serotypes 16 and 18 are responsible for 79% of anal cancers[12].

HPV infects keratinocytes and incorporates the E6 and E7 oncogenes into the host genome. These oncogenes subsequently induce the degradation of p53 and Rb, two crucial tumor suppressor proteins typically found in cells, and the inactivation of retinoblastoma family products, ultimately resulting in chromosomal or microsatellite instability. If these processes are not controlled without these proteins, normal cells can mutate into cancer cells following a sequence from dysplasia to neoplasia[10].

The Centers for Disease Control (CDC) suggests that "more than 80% of sexually active people will be infected with at least one HPV serotype at some point in their lives." It is estimated that, worldwide, one million people become infected daily, with a prevalence of 79 million.

In the vast majority, HPV is asymptomatic, and the infection often disappears on its own thanks to cellular scavenging and shedding mechanisms. However, it can also be subclinical, microscopically detectable (anal cytology/HRA), or latent (i.e., an infection that manifests clinically months or years after exposure), but also macroscopically evident (condyloma) (**Figure 1**). HPV infection can also start in one part of the body and then migrate to another part (initially beginning in the genitals and then infecting the anus, without necessarily having occurred at this level).

A study of 431 women found that 42% were positive for anal HPV DNA at enrollment, but after a 1.3-year follow-up, that number rose to a total of 70%, and 50% of these developed anal HPV infections during this period, but 58% also cleared their infections during the subsequent follow-up period[13].

Moreover, the risk of anal cancer in women is linked to the presence of other tumors in the anogenital region, probably related to everyday exposure to HPV due to anatomical proximity (both the cervix and the anal canal act as reservoirs that will favor mutual infection by proximity, regardless of its initial anatomical location). Thus, patients presenting with neoplasia in this region will have a considerably higher risk than those with a second neoplasia in the anogenital region[14].

Risk factors for HPV infection include sex with uncircumcised men, a partner who has had many sexual partners, and first sexual contact at an early age, as well as patients who have had a solid organ transplant (kidney, liver, among others), are undergoing chemotherapy or radiotherapy (leukemia, lymphomas), use biologicals, are chronic steroid users, have diabetes, among others, which conse-

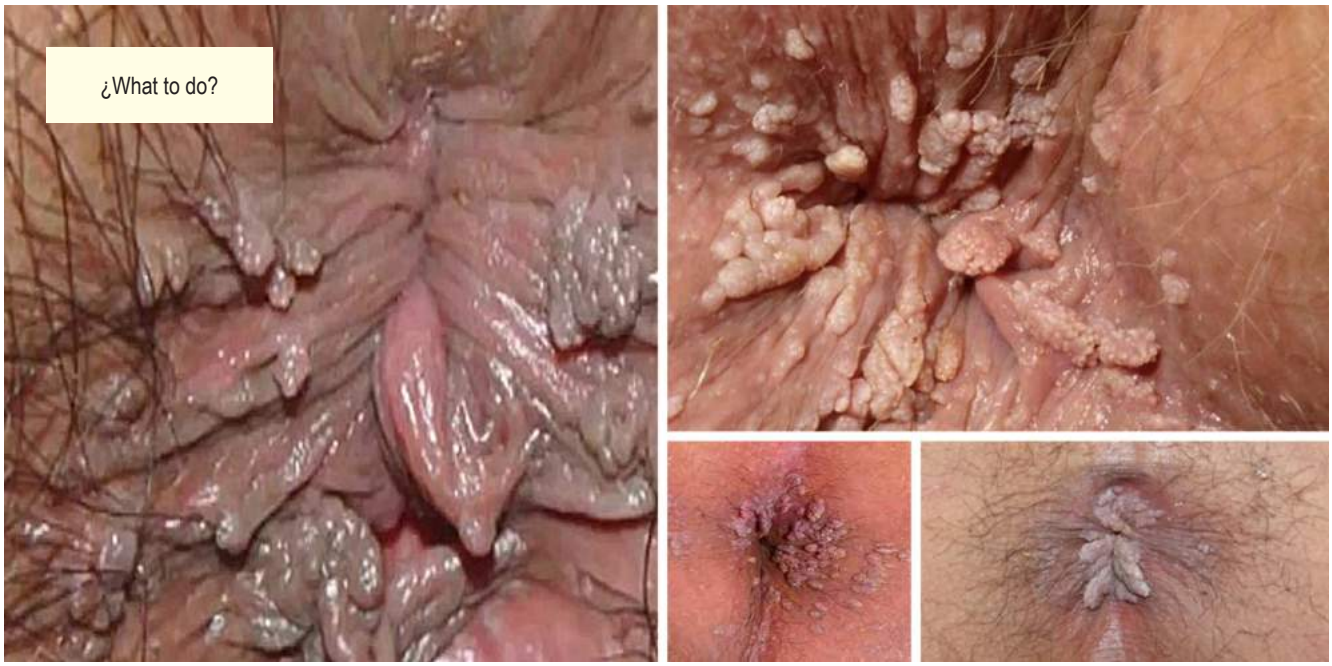

Figure 1. Anal and perianal condylomas. Source: Authors' archive.

quently follow immunosuppressive treatment. Specifically, several studies have reported rates of anal carcinoma up to 10 times higher than the general population in patients with kidney transplants[15].

What is anal dysplasia?

AIN is defined as dysplastic cells in the anal canal. However, cytologically, abnormal squamous cells of the anus are classified as ASCUS, atypical squamous cells (high-grade squamous intraepithelial lesion cannot be ruled out), LSIL, and HSIL[10]. It has also been confirmed that lesions classified as low-grade dysplasia (LGD) can undergo spontaneous regression without any treatment (50–70%) or progress to high-grade dysplasia (HGD) (20%). Approximately 10% of patients with HGD may progress to epidermoid carcinoma within three years after detection of the lesion.

The American Society of Colon and Rectal Surgeons recommends using the term *low-grade squamous intraepithelial lesions* (LSIL). The term comprising Bowen's disease, carcinoma *in situ*, AIN II, AIN III, moderate dysplasia, and HGD is *high-grade squamous cell intraepithelial lesions* (HSIL) and are considered cancer precursor lesions or ASCC[16].

In a case report, Sha et al. found that 5.3% of IBD patients were HPV-positive with ASCUS. In this cohort, there were no cases of LSIL, HSIL, or ASCC[17].

The gold standard for the diagnosis of AIN is HRA-guided anal biopsy, and it is currently classified into LGD and HGD based on the appearance of dysplastic cells that affect the epithelium from lesser to greater depth, respectively.

Both incidence of and mortality from anal cancer are becoming more common, with a 2.2% increase in new cases each year for the last decade and a 3.75% increase in mortality rates each year over the previous two decades[10]. Therefore, closer surveillance (3 to 4 months) should be considered because HSILs have been shown to recur within six months after treatment, and for having a high-grade lesion, the patient should be considered at higher risk of developing additional anal dysplasia than the general population[18].

Why is inflammatory bowel disease oncogenic?

IBD is an inflammatory entity that favors alterations in cellular immunity. In a systematic review that included 11 studies of referral centers (1940 to 2005), the incidence of ASCC was 0.02 per 1000 patient-years in patients with Crohn's disease (CD) and 0.009 per 1000 patient-years in patients with UC; that is, similar to that of the general population[19].

It is known that in CD, there is a reduction in human defensins. These proteins are found in the immune system cells in the genital mucosa, helping against viral infections. They inhibit cutaneous and mucosal HPV, acting as a natural barrier against HPV.

Human α-defensins 1, 2, 3, and 5 have been shown to inhibit HPV in the skin and mucous membranes, which may account for an increased risk of HPV infection in IBD patients[2]. Most cases of ASCC that develop in patients with CD are diagnosed in the perianal manifestation of early onset in life with a long-term disease (>10 years)[17,19].

Is the risk of cancer increased when associated with HPV and IBD?

The pathogenesis of IBD-related anal cancers is believed to be associated with disease-related mechanisms that include local and systemic changes, chronic inflammation, HPV infection, decreased function of defensins, specifically in CD, and drug-induced immunosuppression, which produces changes in the processes of proliferation, senescence, and cell death, as well as in DNA mutation and methylation.

There is a correlation between HPV infection and IBD: HPV is more common in patients with IBD, with a 3- to 5-fold increase in changes in cervical cytology in women with IBD compared to the general population[20]. There are several possible explanations for this correlation. HPV is likely a passenger virus that implants more frequently in IBD patients due to the weakened immune system, which is characteristic of these individuals. Another possibility is that the inflammation caused by IBD provides a hospitable environment for HPV to flourish. Interestingly, a PCR-based study demonstrated that all ASCC patients who were immunosuppressed as a result of IBD treatment tested positive for high-risk HPV variants[21].

In a recent French study, 469 patients subject to consecutive procedures (median age: 54 years, 52% women), including 112 who received immunosuppressive therapies and 101 with IBD (70 with CD), underwent routine colonoscopies. HPV DNA in anal tissues was detected in 34% of subjects and high-risk HPV serotypes in 18%. Serotype 16 was the most prevalent genotype (seen in 7%), followed by 51, 52, and 39. High-risk serotypes were detected in a significantly higher proportion of samples from women (23.1%) than from men (12.8%) (p = 0.0035) and in a substantially higher proportion of patients with CD (30.0%) than without it (18.1%) (p = 0.005). Overall, 84/101 (83.2%) IBD patients were on immunosuppressive therapy at the time of the study (75.8% vs. 85.7% for UC and CD patients, respectively, p = 0.25). Of these, 30.8% had infections with high-risk strains, compared to 16.6% of unexposed patients (p = 0.15)[22].

In a study of 26 IBD patients, half of whom were taking immunomodulators, 81% of patients were found to carry anal HPV (80% had ≥1 high-risk HPV type), and 42% of

patients had abnormal anal cytology. All patients taking a thiopurine had >1 high-risk anal HPV detected. Among patients who underwent biopsies, 38% had LSIL and 15% had HSIL. Of the group with dysplasia (LSIL/HSIL), 43% were taking immunosuppressants[17].

ASCC in patients with IBD has a poor prognosis, with a 5-year survival of 37%, according to the only systematic review available[19]. The general population's 5-year survival rate after ASCC diagnosis exceeds 60%[23]. Therefore, IBD patients should be screened for HPV and, if positive, monitored for the development of cancer, specifically in patients with long-standing perianal disease[19].

The mainstay of treatment for HPV anal dysplasia has traditionally been surgical excision. However, its effectiveness may be limited, with high morbidity and disastrous functional and anatomical sequelae, such as anal stricture or fecal incontinence. Therefore, the modern approach that has been established as a management standard at the Instituto de Coloproctología ICO S. A. S. is based on two approaches: HRA-directed ablative therapy and ablative medical therapy based on the use of 5-fluorouracil together with methotrexate in a scheme of 5 days of active application twice a day, spaced by nine days of rest for a total of 16 weeks.

HPV vaccines, such as Gardasil 4 or 9 and Cervarix, effectively reduce infection rates, but their effectiveness has not been studied in people with IBD.

Does anti-IBD treatment promote HPV infection?

The treatment of IBD, except for aminosalicylates, is based on immunomodulation (azathioprine, methotrexate, and 6-mercaptopurine) or immunosuppression with biological agents such as tumor necrosis factor blockers (anti-TNF) (infliximab, adalimumab, golimumab, and certolizumab pegol). These drugs impair cellular immunity and are associated with higher rates of viral, bacterial, and fungal infections, with increased risk in those using combination therapy, which may result in a higher rate of HPV-associated diseases, including genital warts, dysplasia, anogenital, and even oropharyngeal cancer.

In one cohort, ASCUS's overall prevalence was 7% (8.8% in the IBD group vs. 2.6% in healthy controls). This is similar to the prevalence in other low-risk populations (3.9–10%) but lower than that of AIN reported in other high-risk populations (19.6–28%), such as those with genital dysplasia or a history of transplant[17].

According to a recent meta-analysis, long-term exposure to immunosuppressive therapy in IBD could promote HPV-associated cervical dysplasia and cancer (odds ratio [OR] = 1.34, 95% confidence interval [CI]: 1.23–1.46)[24]. Another study documented that the relative risk of inducing cervical cancer was 1.65 for 5-aminosalicylic acid (5-ASA) and 3.45 for thiopurines (both with p-values >0.05)[25].

However, there are controversial data, as expressed in an article in which no differences were found in cytological alterations and the presence of HPV in the anal canal between patients with CD and a control group of healthy people. On the contrary, in other retrospective case series, the authors concluded that anal squamous neoplastic lesions in IBD are associated with HPV infection, and ASCC seems to be associated with perianal CD[11,26].

A prospective study of 230 IBD patients demonstrated a significant increase in viral warts in the group receiving AZA/6-MP compared to those not receiving immunosuppression (17.2% vs 3.3%, p = 0.004). Abnormal Pap tests in women with IBD compared to controls (42% vs. 7%, p = 0.001) and also in women with a history of exposure to immunosuppression back the recommendation of HPV vaccination and regular gynecological examinations in women[11].

TNF is the cornerstone in multiple cellular processes, such as the regulation and maintenance of homeostasis of the immune system, inflammation, and host defense[27–29]. One article investigated patients using anti-TNF-α medications and found that 21.1% were positive for HPV infection in the genital region[30]. In recent years, there has been a resurgence of interest in the parallels between chronic inflammation and cancer, and it is not surprising that TNF-α has become the focus of this research.

Given its close development with inflammatory processes and its participation in the apoptosis signal, its significant role has been seen in the modulation of HPV infection since, in infected cells, it helps stop the replication and spread of the virus. Increased expression of TNF-α has been observed in HPV infection in both normal cervical tissues and cervical cancers, supporting the importance of TNF-α in the response to HPV and the subsequent carcinogenesis[31].

TNF-α suppresses the expression of the E6 and E7 oncogenes at the translation level in human cells infected by HPV16 by binding to its type I receptor[31,32], induces apoptosis in normal and infected cells by HPV16, and stimulates the inflammatory response by regulating cytokines and other inflammatory regulators. Therefore, TNF-α blockade may increase the risk of HPV reactivation and ultimately lead to host cell apoptosis. Screening and vaccinating patients receiving TNF-α antagonists is essential[31–34].

The association between cervical dysplasia and TNF-α blockade therapy is well documented, given the latter's fundamental role in the control of viral infection, including HPV. Therefore, therapeutic inhibition of TNF-α may increase the risk of HPV reactivation and cause cervical dysplasia and carcinoma, as noted in patients with

rheumatoid arthritis and CD. Wadstroem et al. analyzed the risk of cervical dysplasia in patients with rheumatoid arthritis treated with anti-TNF. They found that they had an increased risk of high-grade cervical dysplasia (hazard ratio: 1.36 CI: 1.01 to 1. 82) and invasive cervical cancer (hazard ratio: 2.10, CI: 1.04 to 4.23) compared to women without biological treatment[35].

Another study by Kane et al. included CD patients exposed to immunomodulators, including prednisone, purine analogs, methotrexate, and infliximab, who underwent Pap smears and compared their cytology over two years with those of a control population. Women exposed to immunosuppressive therapy for more than six continuous months were more likely to have abnormal cytology (p = 0.001) than the control population[36]. Nonetheless, upon closer examination of individual studies, the evidence regarding cervical abnormalities attributable to thiopurines and anti-TNF is still inconclusive[37].

This opens the door to questioning whether the long-term use of anti-TNF blockers or immunosuppressants in patients with IBD may increase the risk of anal cancer, taking into account the close link with HPV clearance. However, it should be recognized that the CESAME cohort did not demonstrate an association between thiopurine use and anal cancer (either adenocarcinoma or ASCC) in IBD patients, although the crude risk in the subgroup of perianal CD patients exposed to thiopurines was of 0.42 per 1000 patient-years. Furthermore, the TREAT and ENCORE registries have not demonstrated an excess of anal cancers in patients treated with infliximab[38–40].

The consensus statement of the European Crohn's and Colitis Organization (ECCO) only recommends vaccination in women suffering from IBD to prevent cervical cancer. However, unfortunately, there are no specific recommendations for HPV prophylaxis to prevent ASCC in patients with IBD[41,42].

Given the well-established similarities between cervical and anal HPV-related diseases, recent CDC guidelines have recommended HPV vaccination for children of both sexes at age 11 or 12 and for men and women at high risk of AIN or CIN or any previously unvaccinated person under 26 years of age[43].

In studies of MSM who are HIV-negative, the sensitivity of anal cytology reported in the literature varies, ranging between 47% and 70% for the detection of AIN of any grade. HSIL anal cytology correlates well with high-grade AIN (i.e., AIN II or III), so direct anal examination and tissue biopsy are recommended after any abnormal anal cytology result[44].

If abnormal cytology is detected on anal cytology examination, the next step in the management of AIN is HRA to attempt to localize the source of atypical cells. HRA involves examining the squamocolumnar junction, anal canal, and perianal skin under magnification using a colposcope. During anoscopy, a lidocaine-lubricated anoscope is inserted through the anus. Then a swab soaked in a 3–5% acetic acid solution is inserted into the anal canal while the anoscope is removed for one minute. Acetic acid causes an "acetowhite change" in areas of the abnormal transitional epithelium; the mucosa is carefully inspected for changes characteristic of AIN, including flat or slightly raised areas of thickened mucosa with or without abnormalities in the vascular pattern. Lugol's iodine is then applied similarly, but in this case, the lesions do not stain with iodine (negative for Lugol's stain) because iodine is glycophilic, and the dysplastic tissues lack glycogen and appear thick mustard in color. Any suspicious Lugol's iodine-negative lesion, including condylomas, atypical surface configurations, stippling, mosaicism, or atypical vessels, is biopsied under direct visualization (**Figures 2**, **3**, and **4**).

Figure 2. High-resolution anoscopy. Source: Authors' archive.

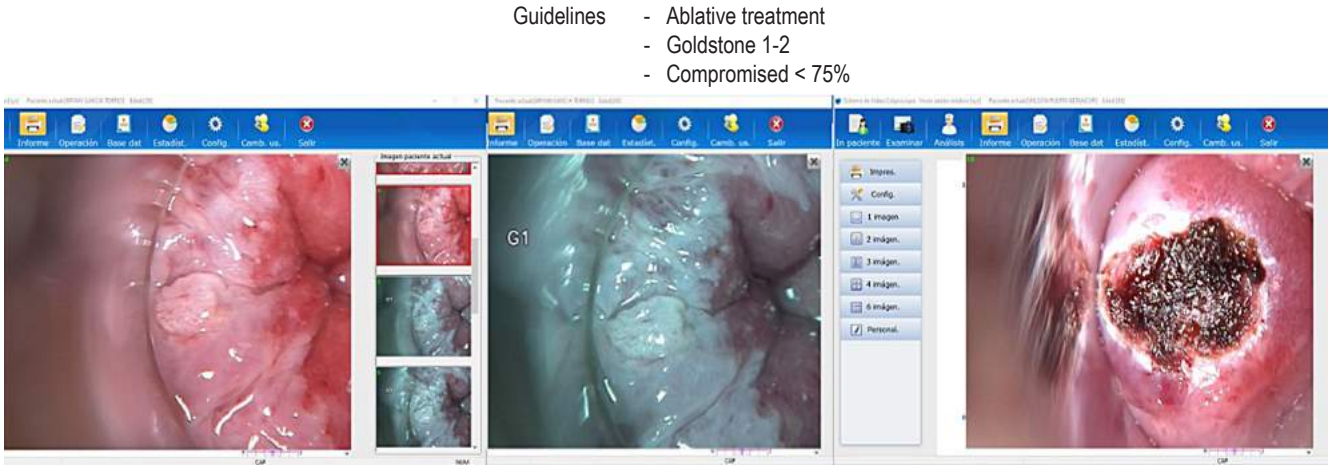

Figure 3. Ablative treatment through high-resolution anoscopy. Source: Authors' archive.

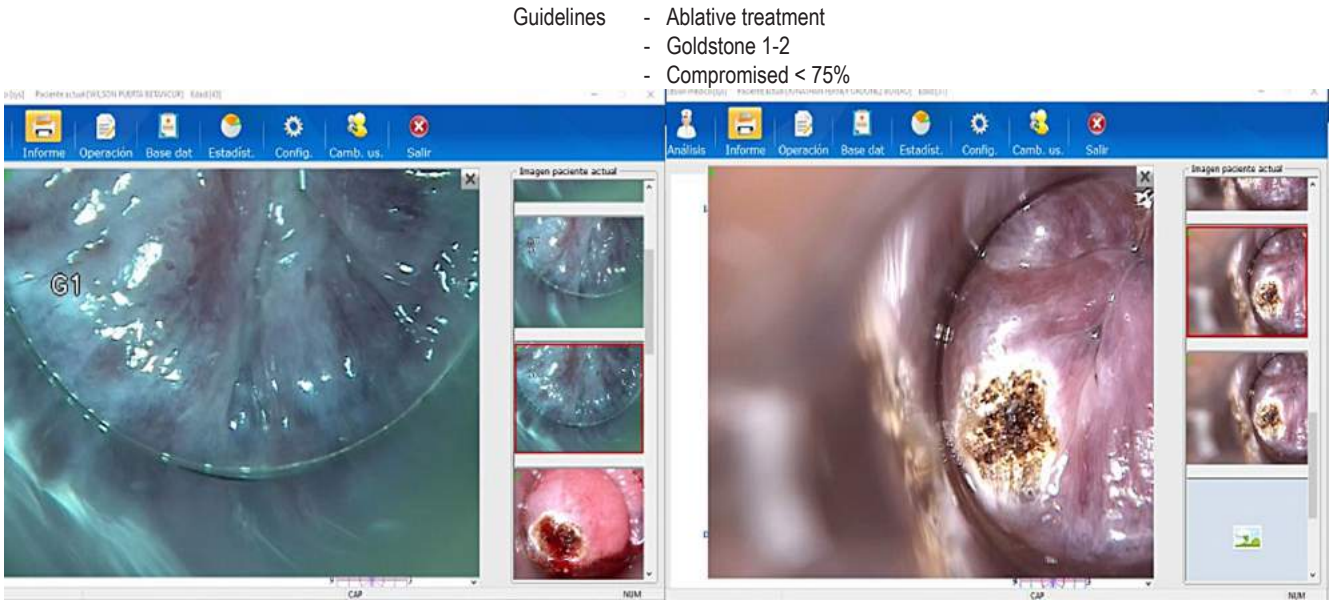

Figure 4. Ablative treatment through high-resolution anoscopy. Source: authors' archive.

HRA is considered superior to standard anoscopy, as demonstrated by Camus et al., who reported that in a population of 102 patients (68% men, 57.3% HIV positive; mean: 1.6 lesions), only 38.7% (65/168) of all lesions observed with HRA were visible with standard anoscopy[45].

Although HRA is generally considered safe for patients and is not difficult for clinicians to perform, considerable training time is required to recognize anal lesions, especially those that may have a subtle appearance. Due to the limited number of patients with atypical findings associated with AIN in the general population, HRA is ideally performed in specialized centers[46].

Strategies to reduce HPV infection

Behavioral factors also play a role in preventing HPV infection. Stopping smoking, in addition to promoting and educating about safer sexual practices, can reduce the prevalence of people infected with HPV and, in turn, could reduce the incidence of anal cancer risk caused by HPV in patients with IBD.

Anal cytology performed by trained personnel detects precancerous and intraepithelial lesions that could eventually lead to invasive anal carcinoma. As a screening tool, it is as sensitive for detecting anal cytological abnormalities

in high-risk patients as it is for cervical cancer and contributes to the careful selection of patients for HRA.

AIN can be diagnosed with screening strategies such as anal cytology and HRA, thus avoiding progression to anal cancer, with an acceptable cost and low morbidity.

The risk of non-fistula-related ASCC in UC patients is the same as in the general population. It does not justify an anal cancer screening program in IBD patients who are not at specific high risk due to associated HIV infection or a personal history of anogenital condyloma.

CONCLUSION

Our study suggests that anal squamous neoplasia in IBD is associated with HPV infection and that ASCC appears to be associated with perianal CD. In addition to careful perianal examination, anal HPV screening could be considered in patients with IBD. Still, it seems too early to provide clear recommendations for screening a specific subset of patients. A prospective study is needed to confirm these findings. Although based on low-level evidence from uncontrolled studies, annual perianal examination with or without anal cytology could be considered in IBD patients with long-standing perianal fistulizing disease, anal stricture, or known HPV infection.

Additionally, IBD patients with other risk factors for HPV infection, such as a history of receptive anal intercourse, MSM, history of sexually transmitted diseases (including HIV), multiple sexual partners, and history of anogenital cancer (cervical, vulvar or vaginal) should also be screened to prevent anal cancer[11].

Our study demonstrates that patients with IBD behave as a high-risk group for developing premalignant lesions in association with HPV, such as dysplasia in 35.5% and condylomas in 16.1%. Vaccination reduces the rate of high-grade anal intraepithelial neoplasia related to high-risk HPV strains by 75%. In patients with IBD, the ECCO recommends routine prophylactic HPV vaccination for both women and men, according to national guidelines[47].

The persistent inflammatory state, the use of steroids, and anti-TNF play a vital role in decreasing HPV viral clearance, so a more exhaustive study should be carried out in patients with IBD, establishing the frequency of lesions and the viral genetic profile that could be related to the development of anal cancer.

HRA is a cost-effective, painless, and affordable method that, in expert hands, can efficiently diagnose and treat premalignant lesions and decrease the incidence of anal cancer in patients with IBD.

To date, through ICO Seguro, we are the first program designed and implemented in Colombia that comprehensively guarantees the education of health personnel and patients and the detection, treatment, and monitoring of populations at risk of anal cancer (**Figure 5**).

Figure 5. The human team of the Instituto de Coloproctología ICO specialized in high-resolution anoscopy. Source: Authors' archive.

Nevertheless, in the end, there are more questions than answers: Are there specificities in the prevalence and serotype distribution of HPV infection in patients with IBD compatible with other established risk factors for HPV infection (smoking, sexual practices)? Does immunosuppression increase the risk of HPV-related ASCC and intraepithelial precursor lesions in patients with IBD and HPV infection? Is the excess risk of non-fistula-related ASCC in patients with CD associated, at least in part, with local or systemic chronic inflammation? What are the optimal frequency and surveillance modes between digital examination, cytology, and HRA?

REFERENCES

1. Roberts JR, Siekas LL, Kaz AM. Anal intraepithelial neoplasia: A review of diagnosis and management. World J Gastrointest Oncol. 2017;9(02):50-61. https://doi.org/10.4251/wjgo.v9.i2.50
2. Savio MC, Svoboda Baldin RK, Nóbrega NL, Nicollelli GM, Brenner AS, Borges da Rocha P, et al. Prevalence of Anal Intraepithelial Lesions in Patients with Inflammatory Bowel Disease. J Coloproctol. 2021;41(3):222-227. https://doi.org/10.1055/s-0041-1730425
3. Vuitton L, Jacquin E, Parmentier AL, Crochet E, Fein F, Dupont-Gossart AC, et al. High Prevalence of Anal Canal High-Risk Human Papillomavirus Infection in Patients With Crohn's Disease. Clin Gastroenterol Hepatol. 2018;16(11):1768-1776.e5. https://doi.org/10.1016/j.cgh.2018.03.008

4. Palefsky JM. Practising high-resolution anoscopy. Sex Health. 2012;9(6):580-6. https://doi.org/10.1071/SH12045
5. Sendagorta E, Herranz P, Guadalajara H, Bernardino JI, Viguer JM, Beato MJ, et al. Prevalence of abnormal anal cytology and high-grade squamous intraepithelial lesions among a cohort of HIV-infected men who have sex with men. Dis Colon Rectum. 2014;57(04):475-481. https://doi.org/10.1097/DCR.0000000000000095
6. Oon SF, Winter DC. Perianal condylomas, anal squamous intraepithelial neoplasms and screening: a review of the literature. J Med Screen. 2010;17(01):44-49. https://doi.org/10.1258/jms.2009.009058
7. Cranston RD, Regueiro M, Hashash J, Baker JR, Richardson-Harman N, Janocko L, et al. A pilot study of the prevalence of anal human papillomavirus and dysplasia in a cohort of patients with IBD. Dis Colon Rectum. 2017;60(12):1307-1313. https://doi.org/10.1097/DCR.0000000000000878
8. Richel O, Hallensleben ND, Kreuter A, van Noesel CJ, Prins JM, de Vries HJ. High-resolution anoscopy: clinical features of anal intraepithelial neoplasia in HIV-positive men. Dis Colon Rectum. 2013;56(11):1237-42. https://doi.org/10.1097/DCR.0b013e3182a53568
9. Camus M, Lesage AC, Fléjou JF, Hoyeau N, Atienza P, Etienney I. Which lesions should be biopsied during high-resolution anoscopy? Prospective descriptive study of simple morphological criteria. J Low Genit Tract Dis. 2015;19(2):156-160. https://doi.org/10.1097/LGT.0000000000000064
10. Limoges-Gonzalez M, Al-Juburi A. Anal Intraepithelial Neoplasia. J Clin Gastroenterol. 2017;51(3):203-207. https://doi.org/10.1097/MCG.0000000000000721
11. Ruel J, Ko HM, Roda G, Patil N, Zhang D, Jharap B, et al. Anal Neoplasia in Inflammatory Bowel Disease Is Associated With HPV and Perianal Disease. Clin Transl Gastroenterol. 2016;7(3):e148. https://doi.org/10.1038/ctg.2016.8
12. Poggio JL. Premalignant lesions of the anal canal and squamous cell carcinoma of the anal canal. Clin Colon Rectal Surg. 2011;24(3):177-192. https://doi.org/10.1055/s-0031-1286002
13. Goodman MT, Shvetsov YB, McDuffie K, Wilkens LR, Zhu X, Ning L, et al. Acquisition of anal human papillomavirus (HPV) infection in women:the Hawaii HPV cohort study. J Infect Dis. 2008;197(7):957-966. https://doi.org/10.1086/529207
14. Shvetsozv YB, Hernandez BY, McDuffie K, Wilkens LR, Zhu X, Ning L, et al. Duration and clearance of anal human papillomavirus (HPV) infection among women: The Hawaii HPV cohort study. Clin Infect Dis. 2009;48(5):536-546. https://doi.org/10.1086/596758
15. Nyitray AG, Carvalho RJ, Baggio ML, Lu B, Smith D, Abrahamsen M, et al. Age-specific prevalence of and risk factors for anal human papillomavirus (HPV) among men who have sex with women and men who have sex with men: the HPV in men (HIM) study. J Infect Dis. 2011;203(1):49-57. https://doi.org/10.1093/infdis/jiq021
16. Steele SR, Varma MG, Melton GB, et al. Practice parameters for anal squamous neoplasms. Dis Colon Rectum. 2012;55(7):735-49. https://doi.org/10.1097/DCR.0b013e318255815e
17. Shah SB, Pickham D, Araya H, Kamal A, Pineda CE, Ghole S, et al. Prevalence of anal dysplasia in patients with inflammatory bowel disease. Clin Gastro Hepatol. 2015;13(11):1955-1961. https://doi.org/10.1016/j.cgh.2015.05.031
18. Messick CA, Rodriguez-Bigas MA. Anal Dysplasia. Surg Oncol Clin N Am. 2017;26(1):33-43. https://doi.org/10.1016/j.soc.2016.07.005
19. Slesser AA, Bhangu A, Bower M, Goldin R, Tekkis PP. A systematic review of anal squamous cell carcinoma in inflammatory bowel disease. Surg Oncol. 2013;22(4):230-7. https://doi.org/10.1016/j.suronc.2013.08.002
20. Bhatia J, Bratcher J, Korelitz B, Vakher K, Mannor S, Shevchuk M, et al. Abnormalities of uterine cervix in women with inflammatory bowel disease. World J Gastroenterol. 2006;12(38):6167-6171. https://doi.org/10.3748/wjg.v12.i38.6167
21. Wong AK, Chan RC, Aggarwal N, Singh MK, Nichols WS, Bose S. Human papillomavirus genotypes in anal intraepithelial neoplasia and anal carcinoma as detected in tissue biopsies. Mod Pathol An Official J United States Can Acad Pathol Inc 2010;23(1):144e50. https://doi.org/10.1038/modpathol.2009.143
22. Vuitton L, Jacquin E, Parmentier AL, Crochet E, Fein F, Dupont-Gossart AC, et al. High Prevalence of Anal Canal High-Risk Human Papillomavirus Infection in Patients With Crohn's Disease. Clin Gastroenterol Hepatol. 2018;16(11):1768-1776.e5. https://doi.org/10.1016/j.cgh.2018.03.008
23. Abramowitz L, Mathieu N, Roudot-Thoraval F, Lemarchand N, Bauer P, Hennequin C, et al. Epidermoid anal cancer prognosis comparison among HIV+ and HIV- patients. Aliment Pharmacol Ther. 2009;30(4):414-21. https://doi.org/10.1111/j.1365-2036.2009.04026.x
24. Allegretti JR, Barnes EL, Cameron A. Are patients with inflammatory bowel disease on chronic immunosuppressive therapy at increased risk of cervical high-grade dysplasia/cancer? A meta-analysis. Inflamm Bowel Dis 2015;21(5):1089-97. https://doi.org/10.1097/MIB.0000000000000338
25. Hutfless S, Fireman B, Kane S, Herrinton LJ. Screening differences and risk of cervical cancer in inflammatory bowel disease. Aliment Pharmacol Ther. 2008;28(5):598-605. https://doi.org/10.1111/j.1365-2036.2008.03766.x
26. Guzela VR, Sobrado Junior CW, Nadal SR, Villa LL, Mota GR, Gonçalves AP, et al. Is there a higher frequency of anal dysplasia and infection by human papillomavirus in Crohn's

disease patients? Braz J Med Biol Res. 2022;55:e12141. https://doi.org/10.1590/1414-431x2022e12141
27. Gaiotti D, Chung J, Iglesias M, Nees M, Baker PD, Evans CH, et al. Tumor necrosis factor-alpha promotes human papillomavirus (HPV) E6/E7 RNA expression and cyclin-dependent kinase activity in HPV-immortalized keratinocytes by a ras-dependent pathway. Mol Carcinog. 2000;27(2):97-109. https://doi.org/10.1002/(sici)1098-2744(200002)27:2<97::aid-mc5>3.0.co;2-v
28. Idriss HT, Naismith JH. TNFα and the TNF receptor superfamily: Structure-function relationship(s). Microsc Res Tech. 2000;50(3):184-95. https://doi.org/10.1002/1097-0029(20000801)50:3<184::AID-JEMT2>3.0.CO;2-H
29. Balkwill F. TNF-alpha in promotion and progression of cancer. Cancer Metastasis Rev. 2006;25(3):409-16. https://doi.org/10.1007/s10555-006-9005-3
30. Handisurya A, Lázár S, Papay P, Primas C, Haitel A, Horvat R, et al. Anogenital human papillomavirus prevalence is unaffected by therapeutic tumour necrosis factor-alpha inhibition. Acta Derm Venereol. 2016;96(4):494-498. https://doi.org/10.2340/00015555-2298
31. Ram A, Noël JC, Marmol V, Benhadou F. Occurrence of an invasive cervical epidermoid carcinoma in a patient receiving TNF-α blocking therapy for hidradenitis suppurativa. JAAD Case Reports. 2018;4(9):857-859. https://doi.org/10.1016/j.jdcr.2018.06.014
32. Khodabandehlou N, Mostafaei S, Etemadi A, Ghasemi A, Payandeh M, Hadifar S, et al. Human papilloma virus and breast cancer: the role of inflammation and viral expressed proteins. BMC Cancer. 2019;19(1):61. https://doi.org/10.1186/s12885-019-5286-0
33. Ali KS, Ali HY, Jubrael JM. Concentration levels of IL-10 and TNFα cytokines in patients with human papilloma virus (HPV) DNA and DNA cervical lesions. J Immunotoxicol. 2012;9(2):168-72. https://doi.org/10.3109/1547691X.2011.642419
34. Jin L, Sturgis EM, Zhang J, Huang Z, Song X, Li C, et al. Association of tumor necrosis factor-alpha promoter variants with risk of HPV-associated oral squamous cell carcinoma. Mol Cancer. 2013;12:80. https://doi.org/10.1186/1476-4598-12-80
35. Wadström H, Frisell T, Sparén P, Askling J; ARTIS study group. Do RA or TNF inhibitors increase the risk of cervical neoplasia or of recurrence of previous neoplasia? A nationwide study from Sweden. Ann Rheum Dis. 2016;75(7):1272-8. https://doi.org/10.1136/annrheumdis-2015-208263
36. Kane S, Khatibi B, Reddy D. Higher incidence of abnormal Pap smears in women with inflammatory bowel disease. Am J Gastroenterol. 2008;103(3):631-636. https://doi.org/10.1111/j.1572-0241.2007.01582.x
37. Magro F, Peyrin-Biroulet L, Sokol H, Aldeger X, Costa A, Higgins PD, et al. Extra-intestinal malignancies in inflammatory bowel disease: results of the 3rd ECCO Pathogenesis Scientific Workshop (III). J Crohns Colitis. 2014;8(1):31-44. https://doi.org/10.1016/j.crohns.2013.04.006
38. Beaugerie L. Inflammatory bowel disease therapies and cancer risk: where are we and where are we going? Gut. 2012;61(4):476-483. https://doi.org/10.1136/gutjnl-2011-301133
39. Lichtenstein GR, Feagan BG, Cohen RD, Salzberg BA, Diamond RH, Chen DM, et al. Serious infections and mortality in association with therapies for Crohn›s disease: TREAT registry. Clin Gastroenterol Hepatol. 2006;4(5):621-630. https://doi.org/10.1016/j.cgh.2006.03.002
40. Colombel J, Prantera C, Rutgeerts PJ, Panes J, Fleig WE, D›Haens G, et al. No new safety signals identified in Crohn›s disease patients treated with infliximab in an interim review of the ENCORE registry. Gastroenterology. 2008;134:A-472. https://doi.org/10.1016/S0016-5085(08)62209-X
41. Rahier JF, Ben-Horin S, Chowers Y, Conlon C, De Munter P, D›Haens G, et al. European evidence-based consensus on the prevention, diagnosis and management of opportunistic infections in inflammatory bowel disease. J Crohns Colitis. 2009;3(2):47-91. https://doi.org/10.1016/j.crohns.2009.02.010
42. Gaidos JKJ, Bickston SJ. HPV infection and vaccination in patients with inflammatory bowel disease. Pract Gastroenterol. 2012;36(10):27-31.
43. Petrosky E, Bocchini JA, Hariri S, Chesson H, Curtis CR, Saraiya M, et al. Use of 9-valent human papillomavirus (HPV) vaccine: updated HPV vaccination recommendations of the advisory committee on immunization practices. MMWR Morb Mortal Wkly Rep. 2015;64(11):300-304.
44. Panther LA, Wagner K, Proper J, Fugelso DK, Chatis PA, Weeden W, et al. High resolution anoscopy findings for men who have sex with men: inaccuracy of anal cytology as a predictor of histologic high-grade anal intraepithelial neoplasia and the impact of HIV serostatus. Clin Infect Dis. 2004;38(10):1490-1492. https://doi.org/10.1086/383574
45. Camus M, Lesage AC, Fléjou JF, Hoyeau N, Atienza P, Etienney I. Which lesions should be biopsied during high-resolution anoscopy? Prospective descriptive study of simple morphological criteria. J Low Genit Tract Dis. 2015;19(2):156-160. https://doi.org/10.1097/LGT.0000000000000064
46. Albuquerque A. High-resolution anoscopy: Unchartered territory for gastroenterologists? World J Gastrointest Endosc. 2015;7(13):1083-1087. https://doi.org/10.4253/wjge.v7.i13.1083
47. Rahier JF, Magro F, Abreu C, Armuzzi A, Ben-Horin S, Chowers Y, et al. Second European evidence-based consensus on the prevention, diagnosis and management of opportunistic infections in inflammatory bowel disease. J Crohns Colitis. 2014;8(6):443-68. https://doi.org/10.1016/j.crohns.2013.12.013

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Original article

Diagnostic Efficacy of Fecal Calprotectin in Inflammatory Bowel Disease: Systematic Literature Review

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Abstract

Introduction: Inflammatory bowel disease is a group of pathologies that include ulcerative colitis and Crohn's disease, which have similar manifestations. Currently, the diagnosis and monitoring of this disease rely mainly on endoscopic studies. Still, this method can hardly be applied to periodic disease monitoring as it is expensive, invasive, and not readily available. Fecal calprotectin is widely known, easy to use, and affordable, and it is currently the best-characterized biomarker for this pathology. **Materials and methods:** The research design is a systematic diagnostic test validation literature review. A search was conducted in different databases using the QUADAS-2 checklist to evaluate the methodological quality. **Results:** The initial search yielded 352,843 articles published chiefly in PubMed, followed by Scopus and Science Direct. After multiple filters, 221 papers were selected and wholly reviewed. They were evaluated with inclusion and exclusion criteria, with 18 articles being chosen. **Conclusions:** Fecal calprotectin is a reliable surrogate marker of endoscopic activity in IBD. However, there is a lack of consensus on delimiting a cut-off point and improving applicability and diagnostic accuracy. Colonoscopy remains the gold standard in all studies.

Keywords

Inflammatory bowel disease, fecal calprotectin, approval of diagnostic tests, biomarker, diagnostic efficacy.

INTRODUCTION

Inflammatory bowel disease (IBD) is a group of pathologies that include ulcerative colitis (UC) and Crohn's disease (CD), which have similar manifestation patterns, but their differences allow classification[1,2]. CD is characterized by transmural and fistulizing involvement, affecting the entire gastrointestinal tract and the perineal region, while UC presents with mucosal compromise limited to the colon only[1].

The recent guidelines of the European Crohn's and Colitis Organization (ECCO) for diagnosing UC and CD describe no established "gold standard" but suggest diagnosis through clinical, laboratory, imaging, endoscopic, and histopathological findings[2]. The use of genetic and serological tests is not recommended[2].

Currently, the diagnosis and monitoring of IBD is mainly based on the direct evaluation of the mucosa on endoscopic studies, which provide information on the extent and severity of the lesions and possible complications[3,4]. However, this method can hardly achieve periodic disease monitoring given its high cost, limited availability, and invasive nature[3,4]. Fecal calprotectin (FC) is widely available, easy to use, affordable, and currently the best-characterized biomarker in IBD.

Multiple studies have shown that FC is a reliable marker that evaluates the presence or absence of endoscopic activity and severity[4]. It is superior to C-reactive protein (CRP) and other fecal biomarkers[3]. Still, no consensus exists on the evidence for using FC or its diagnostic validity.

This paper will note the limitations of the current diagnostic strategy and the importance of defining a more accessible diagnostic and follow-up method. It will also show the availability of biomarkers. One of them is FC, a non-invasive diagnostic aid that would distinguish IBD from functional pathologies and, in turn, identify relapses in both CD and UC. Thus, for this research, we opted for the systematic literature review e since it allows us to identify, condense, and evaluate the current information about the diagnostic accuracy of FC in adult patients with IBD.

MATERIALS AND METHODS

The research design is a systematic literature review (SLR) validating diagnostic testing using the PICOT question strategy. The SLR thoroughly followed the recommendations of the PRISMA checklist.

A comprehensive and systematic search strategy was devised to identify available and relevant studies. We used MeSH and DeCS terms in the different databases: PubMed, Scopus, Science Direct, OVID, Cochrane Library, Scielo, Web of Science, and Virtual Health Library. No language restrictions were applied.

We made search records and exported the results of the searches to the Rayyan software, in which the articles were selected by title and abstract. In case of disagreements, the two researchers made the selection by consensus. Duplicates were discarded using the same software, and subsequently, we created an Excel matrix with the selected articles to include/exclude those meeting the inclusion/exclusion criteria.

The research included all studies available in full text conducted between 1992 and July 2022 and published in English, Portuguese, and Spanish that evaluated FC as a diagnostic method in adults with an established diagnosis of IBD by another diagnostic method. Conversely, we discarded studies that included patients diagnosed with another pathology that alters FC or performed in animals and papers with incomplete data that did not have the variables for data analysis.

With the group of articles rigorously selected by the title and abstracts, we continued reading the full text to evaluate its eligibility and, thus, obtain the studies for the synthesis of the information and define the level of evidence with the help of the QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies) tool.

To evaluate the methodological quality of the diagnostic method studies, we employed the QUADAS-2 checklist for diagnostic accuracy studies using the four domains: patient selection, index test, reference standard, flow and timing, and their relevant applicability[5]. This tool is fully available on the website, was adapted for our type of study, and was applied by both researchers. This tool is designed to assess the quality of primary diagnostic accuracy studies, but not to replace the review data extraction process, and should be used in addition to primary data extraction.

Sensitivity, specificity, and positive and negative predictive values were determined to measure diagnostic efficacy. Besides, measurements such as the cutoff point and area under the curve were considered in the studies that allowed it[6]. After verifying the quality of the information, we organized and documented the research selected for comparison by characteristics, design, population, sample, and study conditions and thus created a matrix with the evidence.

The SLR is an information synthesis study, i.e., a study of studies that do not have individuals (neither human beings nor animals) as their object of study. Nonetheless, this SLR was evaluated by the Universidad de Caldas ethics committee, obtaining the respective endorsement. In addition, an attempt was made to reduce biases and thus avoid improper manipulation of information.

RESULTS

The initial search for selection yielded 352,843 articles published mainly in PubMed, followed by Scopus, Science Direct, Cochrane Library, OVID, and Web of Science, and in Spanish, LILACS and Scielo. Due to the large number of search results, we performed a first filter by title, resulting in 7,584 articles. Then, using the Rayyan software (Intelligent Systematic Review), 2,196 duplicates were detected and discarded. A total of 5,388 papers were reviewed by title and abstract with double-masked dynamics, mainly rejecting studies with animals and pediatric and obstetric populations. We excluded studies that evaluated the treatment, not diagnostic accuracy, and those that involved serum calprotectin. Articles available in English, Spanish, and Portuguese were selected only. Finally, 221 articles were chosen and thoroughly reviewed. This process is summarized in **Figure 1**.

At this point, we reviewed the full-text articles, verifying that they evaluated the diagnostic accuracy of FC, that the study population did not have another pathology that could affect the results of FC, and that they had all the data to allow the evaluation of accuracy diagnostic. Therefore, 19 articles written mainly in English were included in the SLR.

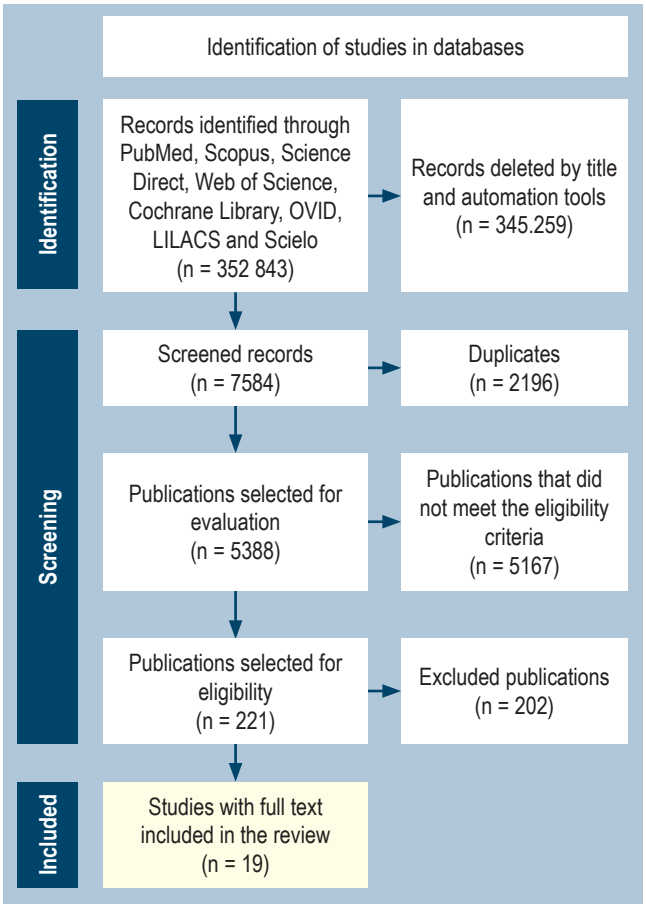

Figure 1. Flowchart of the article selection process. Figure prepared by the authors.

The final result of the SLR, presented in **Table 1**, included 18 articles written mainly in English between 2004 and 2019, especially in 2018, with five articles, the year in which the largest number of publications occurred. The most frequent study design was prospective cohort-type (61.1%), followed by retrospective cohort and cases and controls (15.8% each), and one cross-sectional observational study (5.5%).

The majority of studies were conducted in a population with a final or presumptive diagnosis of IBD. Furthermore, in one of the articles, the population studied was patients who presented with gastrointestinal symptoms suggestive of IBD, and healthy people were found as a control group in two of the articles.

The studies were carried out in the adult population, as indicated in the inclusion criteria; however, two articles did not include the age of the participants. Five of the 18 studies chosen did not differentiate the sex of the participants, while in eight studies (44.4%), male participants predominated, and in the remaining 26.1%, females predominated.

In all articles, the exclusion criteria were that the study subjects had not consumed non-steroidal anti-inflammatory drugs or antibiotics during the three months before enrollment, did not suffer from concomitant severe diseases, were not pregnant, and did not use alcohol.

Of the total number of studies, 14 studied clinical activity to determine the risk of relapse, two analyzed FC to distinguish between IBD and an organic disorder such as irritable bowel syndrome (IBS), one evaluated both problems, and another used FC to assess progression in both UC and CD.

In 94.4% of the articles, the diagnosis of IBD was made through endoscopic studies such as total colonoscopy or sigmoidoscopy, and only one used an indium white blood cell (WCS) scan for this purpose.

The Montreal classification, used mainly in UC, was employed to classify IBD progression. This scale was used in three studies where the primary phenotype was inflammatory (B1), followed by stenosing (B2). The Mayo scoring, also validated to categorize clinical activity in UC, was used in 11 of the 18 studies, in which relapse or active disease was concluded with a score greater than 2; in one study, it was established from 4 points, and seven studies applied the Crohn's disease activity index (CDAI), which documented 150 mg/g as a cutoff point for clinical activity or, otherwise, remission. The simple endoscopic score for Crohn's disease (SES-CD), the Harvey-Bradshaw index, in which only five CDAI variables are used, and the Truelove-Witts index in UC were also used in the articles to define flares.

FC was used as a diagnostic method in all articles, as specified in the inclusion criteria; 13 of the articles reported that the feces were frozen at -20 ºC to be later processed, one article mentioned between -2 and -4 ºC, and in another, the samples were frozen at -80 ºC. In contrast, three articles did not refer to their sample-taking and handling protocol. Six articles showed that the sample processing method was enzyme-linked immunosorbent assay, four studies were processed with qualitative test assay method, and three studies with fluorescence enzyme immunoassay.

In all the selected articles, summarized in **Table 2**, the ROC curve was used to determine the best cutoff value of the FC; however, there is no consensus on the cutoff points, which range from 48.5 to 710 µg/g. These values significantly varied in sensitivity, from 70% to 100%, while the specificity values found were more heterogeneous: from 50% with a cutoff point of 15 µg/g to 100%. The positive (LR+) and negative (LR-) likelihood ratios were calculated for all the papers, concluding that, according to the LR+, in four articles, the FC allows confirming the disease with high certainty and managed to have a very low LR- that is highly relevant to rule out disease. Still, three articles referred to these values with poor relevance to confirm and rule out the pathology.

Table 1. Characteristics of the selected studies

#	Author and year	Design	Sample quantity	Aim	Reference standard
1	Kennedy (2019)	Retrospective cohort	918 patients	Relapse	Total colonoscopy
2	Costa (2005)	Prospective cohort	79 consecutive outpatients	Relapse	CDAI
3	Chen (2021)	Cases and controls	143 outpatients and inpatients and 108 volunteers	Relapse	Total colonoscopy
4	Dolwani (2004)	Cases and controls	30 patients: 8 with CD and 22 with UC	Relapse	Total colonoscopy and biomarkers (CRP and ESR)
5	García-Sánchez (2010)	Prospective cohort	135 patients: 66 with CD and 69 with UC	Relapse	CDAI and TW
6	Chang (2014)	Cases and controls	104 patients: 20 healthy, 26 with IBS, and 58 with IBD	Relapse	Total colonoscopy
7	Walker (2018)	Retrospective cohort	789 patients	To distinguish between IBD and IBS	Total colonoscopy
8	Gaya (2005)	Prospective cohort	35 CD patients	Relapse	CDAI and WCS
9	D'Haens (2012)	Prospective cohort	87 patients with CD and 39 with UC	To distinguish between IBD and IBS	Total colonoscopy and biomarkers (CRP and ESR)
10	Kostas (2017)	Retrospective cohort	149 patients: 113 with CD and 36 with UC	Relapse	Total colonoscopy and biomarkers (CRP and ESR)
11	Mooiweer (2014)	Prospective cohort	164 patients: 74 with UC and 83 with CD	Relapse	Total colonoscopy and fecal hemoglobin
12	Urushikubo (2018)	Observational, cross-cutting	131 patients with UC	Relapse	Total colonoscopy with biopsies
13	Kwapisz (2015)	Prospective cohort	130	Relapse	Total colonoscopy
14	Onisor (2018)	Prospective cohort	140 patients with UC and 40 with IBS	Relapse	Total colonoscopy with biopsies
15	Lee (2018)	Prospective cohort	93 patients: 55 with UC and 38 with CD	Relapse	Total colonoscopy and biomarkers (PCR)
16	Smith (2014)	Prospective cohort	97 patients with CD	Relapse	CDAI
17	Dong Ju Kim (2018)	Prospective cohort	106 patients with UC	Relapse	Total colonoscopy
18	Un Dhaliwal (2014)	Prospective cohort	311 patients: 144 with IBS, 148 with IBD, and 19 with other causes	Relapse and to distinguish IBD from IBS	Total colonoscopy

Table prepared by the authors.

To evaluate the methodological quality of the diagnostic methods studies, the QUADAS-2 checklist for diagnostic accuracy studies was used as a questionnaire with yes/no questions that classified the domains as having high or low risk[34]. This tool is fully available on the website, was adapted for our type of study, and was applied by both researchers.

With the data organized in the Excel matrix, as shown in **Table 3**, we could note that, in Domain 1 (patient selection), there are 13 studies with a low risk of bias. In Domain 2, there is a higher frequency of concern about an increased risk of bias in six studies. In contrast, in Domain 4 (which focuses on the bias that the flow and timing of patients

Table 2. Diagnostic accuracy assessment

#	Author (year)	Cutoff point (µg/g)	S	E	LR+	LR-	LR+	LR-
1	Kennedy (2019)	115	0,70	0,50	1,4	0,60	Poor	Poor
2	Costa (2005)	UC 150 and CD 220	UC 0.89 and CD 0.87	UC 0.82 and CD 0.43	UC 5.55 and CD 1.75	UC 0.13 and CD 0.30	UC good and CD poor	UC good and CD poor
3	Chen (2021)	164	0.854	0.736	3.23	0.19	Fair	Good
4	Dolwani (2004)	78.4	1.00	1.00	0	0.0	Highly relevant	Highly relevant
5	García-Sánchez (2010)	150	0.75	0.68	2.34	0.36	Fair	Fair
6	Chang (2014)	48.5	0.90	0.95	18	0.11	Highly relevant	Highly relevant
7	Walker (2018)	107	0.86	0.90	8.68	0.15	Good	Good
8	Gaya (2005)	100	0.80	0.67	2.42	0.29	Fair	Fair
9	D'Haenz (2012)	250	0.77	0.50	1.54	0.46	Poor	Fair
10	Kostas (2017)	261	0.87	0.85	5.8	0.15	Good	Good
11	Mooiweer (2014)	140	0.86	0.72	3.07	0.19	Fair	Good
12	Urushikubo (2018)	175	0.68	0.61	1.74	0.52	Poor	Poor
13	Kwapisz (2015)	140	0.77	0.73	2.85	0.315	Fair	Poor
14	Onisor (2018)	540	0.71	0.96	17.75	0.302	Highly relevant	Poor
15	Lee (2018)	201	0.81	1.00	0	0.000	Highly relevant	Highly relevant
16	Smith (2014)	240	0.8	0.74	3.07	0.270	Fair	Fair
17	Dong Ju Kim (2018)	350.7	0.88	0.62	2.31	0.194	Fair	Good
18	Un Dhaliwal (2014)	100	0.97	0.76	4.04	0.039	Fair	Highly relevant

Table prepared by the authors.

could introduce), there are four studies with high risk, and in Domain 3, all articles have low risk for bias. In short, eight studies have heightened concern about introducing biases; however, the vast majority show little concern. Applicability, for its part, is only found with high concern in one study concerning the index test, and the remaining 94.7% with low concern.

For clarification, this evaluation should not be used for "quality scoring" since it is a methodology focused on the risk of bias and applicability[7]. If a study is considered "high" or "low" in one or more domains, then it may be regarded as "at risk of bias" or with "concerns regarding applicability"[8]. As a recommendation, a methodology yielding a summary quality score was not used because the interpretation of the score could be problematic and potentially misleading[9].

DISCUSSION

This research was an SLR that evaluated the quality of scientific evidence regarding the diagnostic efficacy of FC in adult patients with IBD and its ability to distinguish between functional and organic intestinal disorders, such as IBS and IBD, and its respective clinical activity to define relapse or remission.

Previous studies have pointed out the importance of conducting a rigorous and extensive literature search to ensure the reliability of the SLR. An SLR was completed in 2007 by Gisbert et al., whose bibliographic search was carried out only in Medline[10]. It is estimated that approximately only 60% of the available literature is found in this database, compared to our study, in which an exhaustive search was performed in multiple databases (Cochrane Library,

Table 3. Assessment of risk of bias of studies

#	Domain 1		Domain 2		Domain 3		Domain 4
	Patient selection	Applicability	Index test	Applicability	Reference standard	Applicability	Flow and timing
1	High	Low	High	Low	Low	Low	High
2	Low	Low	High	Low	Low	Low	High
3	High	Low	High	Low	Low	Low	High
4	High	Low	Low	Low	Low	Low	Low
5	Low	Low	High	Low	Low	Low	Low
6	High	Low	High	Low	Low	Low	Low
7	Low	Low	Low	Low	Low	Low	Low
8	Low	Low	Low	Low	Low	Low	Low
9	High	Low	Low	Low	Low	Low	Low
10	Low	Low	Low	Low	Low	Low	Low
11	Low	Low	Low	Low	Low	Low	Low
12	Low	Low	High	High	Low	Low	High
13	Low	Low	Low	Low	Low	Low	Low
14	Low	Low	Low	Low	Low	Low	Low
15	Low	Low	Low	Low	Low	Low	Low
16	Low	Low	Low	Low	Low	Low	Low
17	Low	Low	Low	Low	Low	Low	Low
18	Low	Low	Low	Low	Low	Low	Low

Table prepared by the authors.

PubMed, Scopus, Science Direct, OVID, Scielo, Web of Science, and Virtual Health Library), thus guaranteeing the greatest possible coverage of the subject matter.

Moreover, most articles included in this review have a low risk of bias. The study by Orcajo-Castelán, in which several methodologies were used to evaluate diagnostic accuracy, concluded that no scientific publications are free of biases, but there are procedures to reduce them[11].

In a diagnostic test accuracy SLR by Hosseini et al. in 2022, QUADAS-2, an exclusive tool for diagnostic accuracy studies, was also used. Both in our research and in the review by Hosseini et al., this method was operated independently by the authors, with the difference that a third author, who evaluated the discrepancies between the two principal authors, was included in such SLR. It should be noted that they also classified the biases as low, moderate, and high risk. In contrast, only high and low risk were included in our review, according to the domains and their applicability[12].

Notably, the majority of articles found were prepared in 2018. Despite not having clarity about this phenomenon, it is inferred that this responded to the increase in the incidence of IBD and its recognition, as in previous years, this pathology was misclassified or underdiagnosed.

In 1992, Roseth et al. developed the first method for determining FC using an enzymatic adsorption assay (ELISA)[13]. Since then, the method has been extensively improved and validated, and tiny stool samples have been used[14]. However, literature that meets the validity requirements for diagnostic accuracy has been found only since 2004, possibly due to the diagnostic method's technological advances and dissemination for routine clinical practice.

The main epidemiological design used in diagnostic accuracy studies is prospective, followed by retrospective. Research conducted in 2010 by pediatric gastroenterologists showed that all the studies evaluated had a prospective epidemiological design and included consecutive outpatients with suspected IBD[15]. In such an SLR, a smaller sample than the one in this work was analyzed, with the difference being that they included six articles with adults and six with a pediatric population[15].

FC is an indirect indicator of the state of the intestinal mucosa. To date, several meta-analyses have shown that it is helpful to discriminate IBD from other diseases, mainly organic, and predict the relapse of IBD patients in remission by evaluating clinical activity with various indices[16], which is also evident in the results of this research.

This SLR, together with information found in the literature, confirms that the level of FC is directly associated with the indices of clinical and endoscopic activity of IBD, with high sensitivity and specificity. Therefore, it is a valuable tool in clinical practice with benefits such as a reduction in invasive procedures, early diagnosis of relapse, and follow-up in remission because it is easy to perform, non-invasive, and relatively low-cost compared to colonoscopy. However, there has been no consensus to establish an optimal cutoff point for identifying organic versus functional disease or relapse[15,17,18]. The current data are still inconclusive regarding a cutoff level of FC as a predictor of clinical activity or remission, as values vary from 48.5 to 710 μg/g[18,19].

An SLR in 2013 showed that most studies evaluating FC used ELISA mechanisms, and most manufacturers recommended 50 μg/g as a cutoff point[17], as in the present study. Colonoscopy continues to be the primary reference standard[18], considered the gold standard for evaluating inflammation of the intestinal mucosa, although it is an expensive and invasive procedure; hence, there is an interest in biomarkers such as FC, which can perform comparably to colonoscopy.

CONCLUSION

FC is a reliable surrogate marker of endoscopic activity in IBD and is especially useful in predicting endoscopic activity to aid the differentiation of functional from organic disease. Thus, it has the potential to be used as a diagnostic and monitoring biomarker in patients with IBD without ignoring the lack of consensus to delimit a cutoff point and improve applicability and diagnostic accuracy. Colonoscopy remains the gold standard in all studies.

So far, the evidence is based on prospective design studies with a low risk of bias and insufficient concern about their applicability. However, more studies are necessary to reach a consensus for decision-making in the clinical setting.

REFERENCES

1. Aguirre D, Archila PE, Carrera J, Castaño R, Escobar CM, García Duperly R, et al. Consenso Colombiano de Enfermedad Inflamatoria Intestinal. Rev Col Gastroenterol. 2012;27(3 supl):s1-s44.
2. Juliao-Baños F, Puentes F, López R, Saffon MA, Reyes G, Parra V, et al. Caracterización de la enfermedad inflamatoria intestinal en Colombia: resultados de un registro nacional. Rev Gastroenterol Méx. 2021;86(2):153-62. https://doi.org/10.1016/j.rgmx.2020.05.005
3. Guardiola J, Lobatón T, Cerrillo E, Ferreiro-Iglesias R, Gisbert JP, Domènech E, et al. Recomendaciones del Grupo Español de Trabajo en Enfermedad de Crohn y Colitis Ulcerosa (GETECCU) sobre la utilidad de la determinación de calprotectina fecal en la enfermedad inflamatoria intestinal. Gastroenterol Hepatol. 2018;41(8):514-29. https://doi.org/10.1016/j.gastrohep.2018.05.029
4. Spiceland CM, Lodhia N. Endoscopy in inflammatory bowel disease: Role in diagnosis, management, and treatment. World J Gastroenterol. 2018;24(35):4014-20. https://doi.org/10.3748/wjg.v24.i35.4014
5. Juliao-Baños F, Arrubla M, Osorio L, Camargo J, Londoño J, Cáceres C, et al. Caracterización y prevalencia de manifestaciones extraintestinales en una cohorte de pacientes con enfermedad inflamatoria intestinal en Medellín (Colombia). Gastroenterol Hepatol. 2021;44(6):398-404. https://doi.org/10.1016/j.gastrohep.2020.07.012
6. Seyedian SS, Nokhostin F, Malamir MD. A review of the diagnosis, prevention, and treatment methods of inflammatory bowel disease. J Med Life. 2019;12(2):113-22. https://doi.org/10.25122/jml-2018-0075
7. Frolkis A, Dieleman LA, Barkema HW, Panaccione R, Ghosh S, Fedorak RN, et al. Environment and the inflammatory bowel diseases. Can J Gastroenterol. 2013;27(3):e18-24. https://doi.org/10.1155/2013/102859
8. Bernstein CN, Blanchard JF, Rawsthorne P, Wajda A. Epidemiology of Crohn's Disease and Ulcerative Colitis in a Central Canadian Province: A Population-based Study. Am J Epidemiol. 1999;149(10):916-24. https://doi.org/10.1093/oxfordjournals.aje.a009735
9. Ng SC, Shi HY, Hamidi N, Underwood FE, Tang W, Benchimol EI, et al. Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. Lancet.

2017;390(10114):2769-78.
https://doi.org/10.1016/S0140-6736(17)32448-0
10. Kotze PG, Underwood FE, Damião AOMC, Ferraz JGP, Saad-Hossne R, Toro M, et al. Progression of Inflammatory Bowel Diseases Throughout Latin America and the Caribbean: A Systematic Review. Clin Gastroenterol Hepatol. 2020;18(2):304-12.
https://doi.org/10.1016/j.cgh.2019.06.030
11. Orcajo-Castelán R, Sidonio-Aguayo B, Alcacio-Mendoza JA, López-Díaz GL. Análisis comparativo de pruebas de tamiz para la detección de problemas en el desarrollo diseñadas y validadas en México. Boletín Médico del Hospital Infantil de México. 2015;72(6):364-75.
https://doi.org/10.1016/j.bmhimx.2015.11.004
12. Hosseini P, Whincup R, Devan K, Ghanem DA, Fanshawe JB, Saini A, et al. The role of the electroencephalogram (EEG) in determining the aetiology of catatonia: a systematic review and meta-analysis of diagnostic test accuracy. EClinicalMedicine. 2023;56:101808.
https://doi.org/10.1016/j.eclinm.2022.101808
13. Røseth AG, Fagerhol MK, Aadland E, Schjønsby H. Assessment of the neutrophil dominating protein calprotectin in feces. A methodologic study. Scand J Gastroenterol. 1992;27(9):793-8.
https://doi.org/10.3109/00365529209011186
14. Rodrigo L. Calprotectina fecal. Rev Esp Enferm Dig. 2007;99(12):683-8.
https://doi.org/10.4321/S1130-01082007001200001
15. van Rheenen PF, Van de Vijver E, Fidler V. Faecal calprotectin for screening of patients with suspected inflammatory bowel disease: diagnostic meta-analysis. BMJ. 2010;341:c3369.
https://doi.org/10.1136/bmj.c3369
16. Lin J-F, Chen J-M, Zuo J-H, Yu A, Xiao Z-J, Deng F-H, et al. Meta-analysis: Fecal Calprotectin for Assessment of Inflammatory Bowel Disease Activity. Inflamm Bowel Dis. 2014;20(8):1407-15.
https://doi.org/10.1097/MIB.0000000000000057
17. Waugh N, Cummins E, Royle P, Kandala NB, Shyangdan D, Arasaradnam R, et al. Faecal calprotectin testing for differentiating amongst inflammatory and non-inflammatory bowel diseases: systematic review and economic evaluation. Health Technol Assess. 2013;17(55):xv-xix, 1-211.
https://doi.org/10.3310/hta17550
18. Rokkas T, Portincasa P, Koutroubakis IE. Fecal calprotectin in assessing inflammatory bowel disease endoscopic activity: a diagnostic accuracy meta-analysis. J Gastrointestin Liver Dis. 2018;27(3):299-306.
https://doi.org/10.15403/jgld.2014.1121.273.pti
19. Boube M, Laharie D, Nancey S, Hebuterne X, Fumery M, Pariente B, et al. Variation of faecal calprotectin level within the first three months after bowel resection is predictive of endoscopic postoperative recurrence in Crohn's disease. Dig Liver Dis. 2020;52(7):740-4.
https://doi.org/10.1016/j.dld.2020.03.020

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Original article

Quality of Life and Sexual Function in Women with Liver Cirrhosis in Colombia

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Abstract

Introduction: The female sex has been systematically identified as one of the predictors of poor quality of life in patients with cirrhosis. However, the relationship between quality of life and sexual function in women with cirrhosis has not been widely studied. **Aim:** To determine the relationship between quality of life and sexual function in women with cirrhosis. **Materials and methods:** A cross-sectional observational study. Female patients aged 18 to 69 years were included. The SF-36-V2 survey assessed health-related quality of life, and the IFSF-6 evaluated sexual function. Univariate and multivariate linear regression was used to identify the relationship between quality of life and sexual function. Statistical significance was set at a *p*-value < 0.05. **Results:** 36 patients were available for analysis. The average age was 61 years. In the SF36-V2 survey, the physical component summary mean was 58, and the mental component summary mean was 56. The IFSF-6 had an average of 10. Sexual dysfunction occurred in 80% of patients. The IFSF-6 score was positively related to health-related quality of life. Factors associated with the deterioration of sexual function were age and menopause. The Child-Pugh score and body mass index were the main determinants of health-related quality of life. **Conclusions:** Sexual function could be a determinant of quality of life in women with cirrhosis.

Keywords

Quality of life, cirrhosis, sexual health, women, psychological sexual dysfunctions.

INTRODUCTION

The most accepted definition of *quality of life* in the academic and scientific community is established by the World Health Organization (WHO), which refers to an individual's well-being[(1)]. Physical and mental health have a marked effect on the quality of life, which is why the concept of *health-related quality of life* (HRQoL) has been introduced[(2)]. It has been estimated in patients with cirrhosis and other chronic diseases using generic and specific scales[(3–9)], observing good reproducibility and consistency.

Sexual dysfunction is frequent in people with cirrhosis; the most probable cause is suppression of the hypothalamic-pituitary-gonadal axis[(10)]. The characterization of the sexual function of patients with chronic diseases through proper tools allows for assessing the global impact of the disease on these subjects[(11–17)].

Female sex has been identified as a predictor of worse quality of life in patients with chronic liver disease in various studies[(18,19)]. The determinants of this difference between the sexes have not been evaluated in detail. The relationship between sexual function and quality of life has been described

in other chronic diseases[16,17], so it would be plausible to speculate that the former could explain part of the differences in HRQoL between men and women with liver cirrhosis.

The objective of this study is to determine the relationship between quality of life and sexual function in women with liver cirrhosis treated at a hepatology center in Cartagena.

MATERIALS AND METHODS

A cross-sectional analytical observational study was carried out. The inclusion criteria were female, unequivocal cirrhosis diagnosis by clinical, imaging, analytical, or elastographic criteria, and aged between 18 and 69. A trained interviewer administered the SF-36 V2 and the FSFI-6 surveys during the same interview. Complementary information was collected from medical records. Laboratory test values were only considered if performed in the last three months.

Exclusion criteria

Limitations in answering the instruments verified by the researchers during the clinical evaluation. Patients with a previous diagnosis of diseases that limit physical or mental capacity, such as disability, sequelae of neurological disease, or moderate to severe cognitive impairment at the discretion of the researchers.

Instruments

The SF-36 V2 is a 36-item questionnaire that evaluates eight areas of HRQoL and generates two indicators that summarize the physical (PCS) and mental (MCS) components of the scale, namely, physical functioning (PF), role-physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role-emotional (RE), mental health (MH); with scores per dimension ranging from 0 to 100. The higher the score, the better the quality of life[20]. Qualitimetric Inc. granted permission to use the SF-36 V2 survey in Spanish, endorsed by the International Quality of Life Assessment Project Approach (IQOLA) for administration in Colombia[21].

The 6-item Female Sexual Function Index (FSFI-6) is a tool developed to assess female sexual function; it comprises six domains: desire, arousal, lubrication, orgasm, satisfaction, and pain. Its score ranges from 2 to 30; lower scores indicate poor sexual function. A score ≤ 19 reports a sensitivity of 93% and specificity of 94% for sexual dysfunction[22].

Statistical analysis

Quantitative and categorical variables were described through means (SD) and percentages as appropriate for numerical and categorical variables. To estimate the relationship between quality of life and sexual function, we used a simple linear regression analysis in which the PCS score of the SF36-V2 scale was the dependent variable, and the global score of the FSFI-6 scale was the independent variable. The same analysis was performed using the MCS score as the dependent variable. The factors associated with female sexual function were identified using a linear regression analysis. The dependent variable was the FSFI-6 scale score, and the independent variables were the sociodemographic and clinical variables. To identify factors related to quality of life, a simple linear regression analysis was performed in which the PCS and MCS score of the SF36-V2 scale were the dependent variables and the sociodemographic and clinical variables (etiology, Child-Pugh score, history of decompensation, type of decompensation, presence of esophageal varices, comorbidities, age at menopause, albumin value, total bilirubin, aminotransferases, platelets, international normalized ratio [INR], creatinine) the independent ones. Those variables with a statistically significant association in the simple linear regression were included in a multivariate analysis. A *p*-value less than 0.05 is the criterion for statistical significance in all cases. The software used was SPSS version 15.

Sample size calculation

Supposing a relationship between quality of life estimated by the SF36 scale and sexual function by the FSFI-6 scale of 10%, a power of the study of 80%, and an alpha error of 5%, a sample of 32 subjects is required for the analysis.

RESULTS

Thirty-six patients were available for analysis. **Figure 1** shows the flow of patient inclusion into the study. The mean age was 61 years (95% confidence interval [CI]: 58–64; standard deviation [SD]: 7.7). The mean PCS value was 58 (95% CI: 49–66; SD: 23), and the mean MCS value was 56 (95% CI: 49–63; SD: 18). The mean FSFI-6 score was 10 (95% CI: 6.8–13; SD: 8.5). 80.5% of the patients had sexual dysfunction using a cut-off point in the FSFI-6 ≤ 19, and 83.3% of the women were postmenopausal. The mean menopausal age was 44 years (95% CI: 39–48; SD: 12.35). 69.4% of the sample was classified in Category A of the Child-Pugh score, while 30.6% was in Category B.

The most common cause of liver cirrhosis in this group of women was non-alcoholic steatohepatitis (41.7%), followed by autoimmune etiology (19.4%), viral etiology (16.7%), and other causes (primary sclerosing cholangitis, alcoholic liver disease, cryptogenic, among others), which represented 22.2%. There were esophageal varices

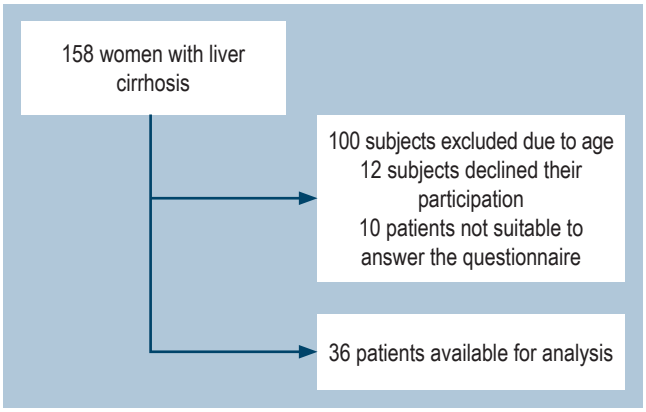

Figure 1. Patient selection flow chart. Figure prepared by the authors.

in 61.1% (small: 19.4%, medium: 16.7%, and large: 25%) and a history of variceal bleeding in 27.8%. The history of decompensation had a frequency of 44.4%, and a history of ascites was found in 19.4% of the total sample. Obesity was present in 19% of the women in the study; the mean body mass index (BMI) was 27.54 kg/m^2 (CI: 25.8–29.2; SD: 4.72). A more detailed description of the patient's baseline characteristics can be found in **Table 1**.

Factors associated with sexual function in cirrhotic women

When estimating the relationship between quality of life and sexual function through a linear regression analysis, the FSFI-6 score positively relates to PCS (B coefficient: 0.365; p = 0.029). As the FSFI-6 values increase, so will the PCS values. This relationship was not observed with the MCS (B coefficient: 0.219; p = 0.199) (**Table 2**).

The linear regression analysis of the factors associated with sexual function point to age (B coefficient: -0.525; p = 0.001) and menopause (B coefficient: -0.387; CI: 0.020) as predictors of deterioration in sexual function of this population. However, this relationship was not found in some variables that could have been relevant, such as the Child-Pugh score (B coefficient: -0.291; p = 0.085), the history of decompensations (B coefficient: -0.276; p = 0.103), BMI (B coefficient: -0.203; p = 0.235), obesity (B coefficient: -0.148; p = 0.389), or diabetes (B coefficient: -0.091; p = 0.596) (**Table 3**).

Factors affecting health-related quality of life

The simple linear regression analysis identified that the factors associated with HRQoL, taking PCS as the dependent variable, were BMI (B coefficient: -0.388; p = 0.019), creatinine (B coefficient: -0.376; p = 0.026), the Child-Pugh score (B coefficient: -0.733; p = 0.000), and other variables associated with this scale, such as decompensations (B coefficient: -2.7, p = 0.009), ascites (B coefficient: - 0.412, p = 0.012), and albumin (B coefficient: 0.437, p = 0.008); sexual function through the FSFI-6 scale showed an association with HRQoL (B coefficient: -0.365; p = 0.029). In the multivariate analysis, only BMI (B coefficient: -0.291; p = 0.008) and the Child-Pugh score were identified as factors associated with HRQoL. Other variables such as diabetes (B coefficient: -0.0004; p = 0.98), esophageal varices (B coefficient: 0.053; p = 0.75), history of variceal bleeding (B coefficient: -0.13; p = 0.45), and menopause (B coefficient: -0.101; p = 0.55) did not have a relationship in the simple linear regression.

The factors related to HRQoL in the simple linear regression analysis taking MCS as the dependent variable were the Child-Pugh score (B coefficient: -0.559; p = 0.00), as well as related variables (decompensation, albumin, ascites) and BMI (B coefficient: -0.396; p = 0.017). In the multivariate analysis, the relationship with the Child-Pugh score (B coefficient: -0.49; p = 0.0001) and BMI (B coefficient: -0.49; p = 0.045) was maintained. Diabetes (B coefficient: -0.113; p = 0.513), esophageal varices (B coefficient: 0.132; p = 0.442), history of variceal bleeding (B coefficient: -0.051; p = 0.76), creatinine (B coefficient: -0.209; p = 0.229), and menopause (B coefficient: 0.068; p = 0.694) showed no relationship with MCS (**Tables 4** and **5**).

DISCUSSION

A linear relationship between sexual function and HRQoL was observed in women with liver cirrhosis. The PCS values increased as those of the FSFI-6 scale also increased, and this association was statistically significant in the univariate analysis. This relationship has also been noted in women with cervical cancer and chronic kidney disease[16,23].

The average FSFI-6 was low (10.8 points) in this population; in fact, 80% of the patients presented with sexual dysfunction (FSFI-6 ≤ 19) according to the cut-off points reported in the literature[22]. Although this finding could be explained by the old age of the patients (61 years) and the high percentage of menopause in this cohort (83%), the FSFI-6 scores were low in pre- and postmenopausal women (19 vs. 9.3 points). From a biological point of view, the impairment of sexual function in cirrhosis is multifactorial. The autonomic dysfunction and changes in the female genital tissue caused by ovarian atrophy and premature menopause in these patients can affect desire and orgasmic response, not to mention psychiatric and affective disorders such as depression, which can also play an essential role in female sexual function[10].

Table 1. Demographic and clinical characteristics

Variable	n = 36		
SEL	**n (%)**	**Treatment**	**n (%)**
- I	1 (2.8)	- Other	9 (25)
- II	6 (16.7)	- BB	21 (58.3)
- III	22 (61.1)	- MRA	0 (0)
- IV	3 (8.3)	- Loop diuretics	0 (0)
- V	4 (11.1)	- BB. MRA and diuretic	3 (8.3)
- VI	0 (0)	- MRA and loop diuretic	3 (8.3)
Marital status	**n (%)**	**Obesity**	**n (%)**
- Single	1 (2.8)	- Yes	7 (19.4)
- Married	18 (52.8)	- No	29 (80.6)
- Domestic partnership	7 (19.4)	**Dyslipidemia**	**n (%)**
- Divorced	0 (0)	- Yes	11 (30.6)
- Separated	7 (19.4)	- No	25 (69.4)
- Widow	3 (8.3)	**HBP**	**n (%)**
Etiology	**n (%)**	- Yes	12 (33.3)
- Other	8 (22.2)	- No	24 (66.7)
- NASH	15 (41.7)	**Hepatocellular carcinoma**	**n (%)**
- Viral	6 (16.7)	- No	35 (97.2)
- Autoimmune	7 (19.4)	- Yes	1 (2.8)
- Alcoholic	0 (0)	**Child-Pugh score**	**n (%)**
		- A	25 (69.4)
		- B	11 (30.6)
	Mean (SD)	- C	0 (0)
Age	61.3 (7.7)	**Esophageal varices**	**n (%)**
Weight	70.0 (14.0)	- No	14 (38.9)
Size	1.57 (0.04)	- Small	7 (19.4)
BMI	27.5 (4.7)	- Medium	6 (16.7)
Menopause age	44.0 (12.35)	- Large	9 (25.0)
Menopause	**n (%)**	**Decompensation**	**n (%)**
- Yes	30 (83.3)	- Yes	16 (44.4)
- No	6 (16.7)	- No	20 (55.6)
Variceal bleeding	**n (%)**	**SF-36 V2**	**Mean (SD)**
- Yes	10 (27.8)	- PF	63.2 (27.0)
- No	26 (72.2)	- RP	60.5 (32.9)
Ascites	**n (%)**	- BP	63.2 (26.5)
- Yes	7 (19.4%)	- GH	45.1 (24.8)
- No	29 (80.6%)	- VT	51.6 (21.7)

Table 1. Demographic and clinical characteristics (*continued*)

Variable	n = 36		
Laboratory tests	**Mean (SD)**	- SF	60.3 (24.03)
- Total bilirubin	1.38 (1.36)	- RE	56.1 (25.08)
- AST	47.8 (22.8)	- MH	57.4 (19.7)
- ALT	40.0 (20.8)	- PCS	58.03 (23.6)
- Albumin	3.57 (0.54)	- MCS	56.3 (18.6)
- Platelets	153 838 (53 513)	**FSFI-6**	**Mean (SD)**
- INR	1.15 (0.16)	- Desire	2.25 (1.03)
- Creatinine	0.91 (0.37)	- Arousal	1.64 (1.62)
		- Lubrication	1.45 (1.56)
		- Orgasm	1.38 (1.52)
		- Satisfaction	1.41 (1.54)
		- Pain	1.83 (1.82)
		- Total score	10.8 (8.51)

ALT: alanine aminotransferase; AST: aspartate aminotransferase; BB: β-blocker; BO: bodily pain; BMI: body mass index; FSFI-6: 6-item female sexual function index; GH: general health; HBP: high blood pressure; INR: international normalized ratio; MH: mental health; MCS: mental component summary; MRA: mineralocorticoid receptor antagonist; NASH: non-alcoholic steatohepatitis; PF: physical functioning; PCS: physical component summary; RE: role-emotional; RP: role-physical; SF: social functioning; VT: vitality. Prepared by the authors.

Table 2. Relationship of quality of life with sexual function. Univariate linear regression analysis. Dependent variable, physical component summary, and mental component summary of the SF36v2 scale

	Variable	B	95% CI	*p*
Physical component summary	FSFI-6	0.36	0.10-1.8	0.029
Mental component summary	FSFI-6	0.219	(-0.246) - (1.13)	0.199

FSFI-6: 6-item female sexual function index. Prepared by the authors.

Age and menopause were independent predictors of sexual function in patients with cirrhosis. Other studies conducted in different geographic regions in the general population consistently support these results. Research carried out in Istanbul on 1009 women found that menopause increased the risk of sexual dysfunction by 84% (p = 0.046), and this risk could be up to 60% higher when comparing women aged 60–64 years versus those aged 20–29 (p = 0.000)[24].

The relationship between menopause and sexual dysfunction has been widely described, and this can be explained by multiple factors such as pain during sexual intercourse, genitourinary syndrome, and vaginal dryness, among others. A study published in 2017, which included 405 postmenopausal women, described a positive relationship between the FSFI score and quality of life questionnaires in all its domains[25], and this subgroup of patients was identified as susceptible to additional interventions that specifically improve their sexual function and quality of life.

A study conducted in Turkey, which included 282 healthy women, of which about 40% were over 40 years of age, found a prevalence of sexual dysfunction of 53.2% using the FSFI scale, and the risk was higher in older patients with urinary problems[26]. In our cohort, the prevalence of dysfunction was 80%, suggesting a possible role of cirrhosis as a determining factor in female sexual function.

Chronic liver disease and not necessarily cirrhosis also influences female sexual function. A case-control study

Table 3. Factors related to sexual function (FSFI-6). Univariate linear regression analysis. Dependent variable, FSFI-6 scale

Variable	B	95% CI	*p*
Age	-0.525	(-0.75) - (-0.209)	0.001
SEL	0.258	(-0.751) - (5.70)	0.128
Weight	-0.234	(-0.356) - (0.065)	0.17
BMI	-0.203	(-0.983) - (0.249)	0.235
Obesity	-0.148	(-10.6) - (4.25)	0.389
Dyslipidemia	-0.073	(-7.83) - (5.10)	0.67
HBP	-0.096	(-8.0) - (4.55)	0.57
Diabetes	-0.091	(-10.0) - (5.8)	0.59
Child-Pugh score	-0.291	(-11.6) - (0.78)	0.085
Decompensation	-0.276	(-10.5) - (1.01)	0.103
Variceal bleeding	-0.028	(-7.19) - (6.13)	0.872
Ascites	-0.271	(-13.1) - (1.39)	0.11
Total bilirubin	-0.9	(-3.0) - (1.7)	0.6
AST	-0.183	(-0.144) - (0.043)	0.284
ALT	-0.03	(-0.07) - (0.064)	0.861
Albumin	0.189	(-2.60) - (9.0)	0.268
Creatinine	-0.089	(-10.6) - (6.35)	0.613
Menopause	-0.387	(-16.2) - (-1.50)	0.02

ALT: alanine aminotransferase; AST: aspartate aminotransferase; BMI: body mass index; HBP: high blood pressure; SEL: socio-economic level. Prepared by the authors.

published in 2014, which included 337 women, compared a group of sexually active women with chronic hepatitis C without liver cirrhosis with another group of sexually active healthy women. In the chronic hepatitis C group, the scores of FSFI were significantly lower, and sexual dysfunction was more frequent (79% vs 21%, $p < 0.05$)[27].

There are few studies about sexual dysfunction in women with liver cirrhosis. A study published in 1989 found that of 150 women with non-alcoholic liver disease, sexual desire decreased in 33%, difficulty achieving arousal was observed in 18%, orgasm was not experienced in 25%, the frequency of sexual intercourse decreased since the onset of the disease by 27%, and dyspareunia occurred in 21%[28].

Only the Child-Pugh score and BMI were identified as independent predictors of HRQoL in the multivariate analysis in both the PCS and the MCS, which is consistent with previous studies in Colombia in which the Child-Pugh score, female sex, viral etiology, and albumin were identified as determinants[18]. Similarly, in a prospective cohort of 92 cirrhotic men and women, the Child-Pugh score and BMI were identified as factors associated with HRQoL[29].

The association of BMI with HRQoL is not limited to patients with cirrhosis. In a work published in 2018, which included 10,133 subjects, of which 71.7% were women, there was a significant association between BMI and HRQoL for the physical and mental components[30]. Additionally, an investigation of obese subjects published in 2014 in which 25 men and 70 women participated revealed the association between BMI and sexual function, with an inverse relationship between sexual function and BMI/waist circumference[31].

In 2013, Morotti published a study that included 90 women and found less vascularization of the clitoris in obese women compared to overweight or slim women; sexuality surveys reported higher scores in thin women compared to overweight and obese women. The percentage of anorgasmic women was higher in obese patients than in thin patients (23% versus 6%), and in the questionnaires that evaluated depressive symptoms, higher scores were found in obese patients. Furthermore, there was greater dissatisfaction with their figure and body[32]. These data indicate that weight has an essential association with quality of life and sexual function in women, and this effect remains and could even be more significant in women with chronic diseases such as cirrhosis. Still, in our study, BMI was a predictor of HRQoL but not of sexual function.

History of decompensation, ascites, and albumin were related to HRQoL for PCS and MCS. These findings likely occur because they are variables associated with the severity of cirrhosis and, therefore, it is common for patients with more significant alterations to have more advanced disease.

Despite the sample size, the consistency of our findings with those reported in other cohorts of patients with cirrhosis worldwide supports the robustness of our results. The inclusion of patients in the study was limited by the age range in which the FSFI survey was validated for Colombia (18–69 years)[33], the silent nature of the disease, and the lack of specific screening programs for chronic liver disease in our country, which has caused patients to be diagnosed at late ages.

Female sexual dysfunction is not actively evaluated in the consultation of patients with liver cirrhosis despite its high prevalence in this population. A comprehensive approach to the treatment of these patients should include the evaluation of the sexual sphere and BMI to identify patients who would benefit from an assessment by specialists in the

area to make interventions that improve HRQoL in this population.

CONCLUSIONS

In women with liver cirrhosis, sexual function is a determinant of HRQoL, and the factors that were associated with sexual dysfunction were age and history of menopause. The progression of the disease and weight are related to the deterioration of HRQoL. The conduct of new studies and the implementation of multidisciplinary programs that affect these determinants of quality of life and sexual function are necessary for the comprehensive management of women with this pathology.

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Conflicts of interest

None.

Table 4. Factors associated with quality of life (PCS). Univariate linear regression analysis. Dependent variable, physical component summary of the SF36v2 scale

Variable	B	95% CI	*p*
Age	-0.778	(-0.778) - (0.442)	0.442
BMI	-0.388	(-3.4) - (-0.321)	0.019
SEL	-0.134	(-12.2) - (5.38)	0.436
Obesity	-0.315	(-37.1) - (0.921)	0.061
Dyslipidemia	0.222	(-5.82) - (27.7)	0.193
HBP	0.67	(-13.5) - (20.0)	0.698
Diabetes	-0.004	(-21.5) - (21.0)	0.98
Child-Pugh score	-0.733	(-47.9) - (-24.5)	0.000
Esophageal varices	0.053	(-5.52) - (7.51)	0.758
Decompensation	-0.431	(-34.1) - (-5.34)	0.009
Variceal bleeding	-0.13	(-24.1) - (10.9)	0.451
Ascites	-0.412	(-41.9) - (-5.45)	0.012
Menopause	-0.101	(-27.3) - (15.0)	0.557
Albumin	0.437	(5.61) - (33.9)	0.008
AST	-0.209	(-0.399) - (0.096)	0.221
ALT	-0.153	(-0.268) - (0.103)	0.373
Total bilirubin	-0.245	(-10.5) - (1.76)	0.157
Creatinine	-0.376	(-44.4) - (-2.98)	0.026
Multivariate linear regression. Dependent variable PCS (SF36-V2)			
- Child-Pugh score	-0.841	(-54.4) - (-27.6)	0.000
- BMI	-0.29	(-2.91) - (-0.386)	0.008
- Creatinine	-0.219	(-2.91) - (30.5)	0.102

ALT: alanine aminotransferase. AST: aspartate aminotransferase; BMI: body mass index; HBP: high blood pressure; SEL: socio-economic level. Prepared by the authors.

Table 5. Factors associated with quality of life (MCS). Univariate linear regression analysis. Dependent variable, mental component summary of the SF36v2 scale

Variable	B	95% CI	*p*
Age	0.11	(-0.42) - (0.86)	0.49
BMI	-0.39	(-2.6) - (-0.27)	0.017
SEL	-0.075	(-8.25) - (5.31)	0.662
Obesity	-0.242	(-25.5) - (4.23)	0.155
Dyslipidemia	0.145	(-7.56) - (18.5)	0.399
HBP	0.237	(-3.72) - (21.3)	0.163
Diabetes	-0.113	(-21.4) - (10.9)	0.513
Child-Pugh score	-0.559	(-32.1) - (-10.2)	0.000
Esophageal varices	0.132	(-3.05) - (6.85)	0.442
Decompensation	-0.351	(-23.7) - (-0.84)	0.036
Variceal bleeding	-0.051	(-15.5) - (11.5)	0.767
Ascites	-0.372	(-30.6) - (-2.15)	0.025
Total bilirubin	-0.02	(-5.16) - (4.60)	0.908
AST	-0.108	(-0.253) - (0.132)	0.52
ALT	-0.086	(-0.179) - (0.108)	0.617
Albumin	0.377	(1.86) - (24.2)	0.024
Creatinine	-0.209	(-27.1) - (6.7)	0.229
Menopause	0.068	(-13.0) - (19.4)	0.694
Multivariate regression. Dependent variable MCS (SF36-V2)			
- Child-Pugh score	-0.49	(-29.5) - (-8.1)	0.001
- BMI	-0.29	(-2.10) - (-0.026)	0.045

ALT: alanine aminotransferase. AST: aspartate aminotransferase; BMI: body mass index; HBP: high blood pressure; SEL: socio-economic level. Prepared by the authors.

REFERENCES

1. The WHOQOL Group. The Development of the World Health Organization Quality of Life Assessment Instrument (the WHOQOL). En: Orley J, Kuyken W (editores). Quality of Life Assessment: International Perspectives. Springer Berlin Heidelberg; 1994. p. 41-57. https://doi.org/10.1007/978-3-642-79123-9_4
2. Urzúa MA. Calidad de vida relacionada con la salud: elementos conceptuales. Rev Med Chil. 2010;138(3):358-65. https://doi.org/10.4067/S0034-98872010000300017
3. Loria A, Escheik C, Gerber NL, Younossi ZM. Quality of life in cirrhosis. Curr Gastroenterol Rep. 2013;15(1):301. https://doi.org/10.1007/s11894-012-0301-5
4. North CS, Devereaux R, Pollio DE, Hong BA, Jain MK. Patient perspectives on hepatitis C and its treatment. Eur J Gastroenterol Hepatol. 2014;26(1):74-81. https://doi.org/10.1097/MEG.0b013e32836382b5
5. Orr JG, Homer T, Ternent L, Newton J, McNeil CJ, Hudson M, et al. Health related quality of life in people with advanced chronic liver disease. J Hepatol. 2014;61(5):1158-65. https://doi.org/10.1016/j.jhep.2014.06.034
6. Afendy A, Kallman JB, Stepanova M, Younoszai Z, Aquino RD, Bianchi G, et al. Predictors of health-related quality of life in patients with chronic liver disease. Aliment Pharmacol Ther. 2009;30(5):469-76. https://doi.org/10.1111/j.1365-2036.2009.04061.x
7. Mejía G, Gómez MT, Moreno-Medina K. Evaluación de la calidad de vida relacionada con la salud pre y post trasplante hepático, en pacientes de un hospital de alta complejidad. Psychologia. 2019;13(1):65-72. https://doi.org/10.21500/19002386.3721
8. Hamer J, McDonald R, Zhang L, Verma S, Leahey A, Ecclestone C, et al. Quality of life (QOL) and symptom burden (SB) in patients with breast cancer. Support Care Cancer. 2017;25(2):409-19. https://doi.org/10.1007/s00520-016-3417-6
9. Amodio P, Salari L, Montagnese S, Schiff S, Neri D, Bianco T, et al. Hepatitis C virus infection and health-related quality of life. World J Gastroenterol. 2012;18(19):2295-9. https://doi.org/10.3748/wjg.v18.i19.2295
10. Neong SF, Billington EO, Congly SE. Sexual Dysfunction and Sex Hormone Abnormalities in Patients With Cirrhosis: Review of Pathogenesis and Management. Hepatology. 2019;69(6):2683-95. https://doi.org/10.1002/hep.30359
11. Blümel JE, Binfa EL, Cataldo AP, Carrasco VA, Izaguirre LH, Sarrá CS. Índice de función sexual femenina: un test para evaluar la sexualidad de la mujer. Rev Chil Obstet Ginecol. 2004;69(2):118-25. https://doi.org/10.4067/S0717-75262004000200006
12. Faubion SS, Rullo JE. Sexual dysfunction in women: A practical approach. Am Fam Physician. 2015;92(4):281-8.
13. Fliegner M, Richter-Appelt H, Krupp K, Brunner F. Sexual Function and Socio-Sexual Difficulties in Women with Polycystic Ovary Syndrome (PCOS). Geburtshilfe Frauenheilkd. 2019;79(5):498-509. https://doi.org/10.1055/a-0828-7901
14. Pozzo MJ, Mociulsky J, Martinez ET, Senatore G, Farias JM, Sapetti A, et al. Diabetes and Quality of Life: Initial Approach to Depression, Physical Activity, and Sexual Dysfunction. Am J Ther. 2016;23(1):e159-71. https://doi.org/10.1097/01.mjt.0000433949.24277.19
15. Chang SR, Yang CF, Chen KH. Relationships between body image, sexual dysfunction, and health-related quality of life among middle-aged women: A cross-sectional study. Maturitas. 2019;126:45-50. https://doi.org/10.1016/j.maturitas.2019.04.218
16. Abozead SE, Abdelrahman G, Hassan A, Ibrahim WH. Sexual Dysfunction and Health Related Quality of Life among Female Patients Undergoing Hemodialysis. American Journal of Nursing Research. 2018;6(6):547-52. https://doi.org/10.12691/ajnr-6-6-24
17. Sun V, Grant M, Wendel CS, McMullen CK, Bulkley JE, Herrinton LJ, et al. Sexual Function and Health-Related Quality of Life in Long-Term Rectal Cancer Survivors. J Sex Med. 2016;13(7):1071-9. https://doi.org/10.1016/j.jsxm.2016.05.005
18. Yepes Barreto I, Lepesqueur Guillen L, Cadavid Asis S. Predictores de calidad de vida en pacientes con enfermedad hepática crónica en Colombia. Rev Col Gastroenterol. 2015;30(4):390-8. https://doi.org/10.22516/25007440.2
19. Yepes Barreto IDJ, Meza ZC, Contreras MNM. Calidad de vida en pacientes con hepatitis C crónica en Colombia. Rev Col Gastroenterol. 2017;32(2):112-9. https://doi.org/10.22516/25007440.139
20. Vilagut G, Ferrer M, Rajmil L, Rebollo P, Permanyer M, Quintana JM. et al. El Cuestionario de Salud SF-36 español: una década de experiencia y nuevos desarrollos. Gac Sanit. 2005;19(2):135-150. https://doi.org/10.1157/13074369
21. Alonso J, Ferrer M, Gandek B, Ware JE Jr, Aaronson NK, Mosconi P, et al. Health-related quality of life associated with chronic conditions in eight countries: results from the International Quality of Life Assessment (IQOLA) Project. Qual Life Res. 2004;13(2):283-298. https://doi.org/10.1023/B:QURE.0000018472.46236.05
22. Isidori AM, Pozza C, Esposito K, Giugliano D, Morano S, Vignozzi L, et al. Development and validation of a 6-item version of the female sexual function index (FSFI) as a diagnostic tool for female sexual dysfunction. J Sex Med. 2010;7(3):1139-46. https://doi.org/10.1111/j.1743-6109.2009.01635.x
23. Bae H, Park H. Sexual function, depression, and quality of life in patients with cervical cancer. Support Care Cancer. 2016;24(3):1277-83. https://doi.org/10.1007/s00520-015-2918-z

24. Aslan E, Beji NK, Gungor I, Kadioglu A, Dikencik BK. Prevalence and risk factors for low sexual function in women: a study of 1,009 women in an outpatient clinic of a university hospital in Istanbul. J Sex Med. 2008;5(9):2044-52. https://doi.org/10.1111/j.1743-6109.2008.00873.x
25. Nazarpour S, Simbar M, Ramezani Tehrani F, Alavi Majd H. Quality of life and sexual function in postmenopausal women. J Women Aging. 2018;30(4):299-309. https://doi.org/10.1080/08952841.2017.1395539
26. Kılıç M. Prevalence and risk factors of sexual dysfunction in healthy women in Turkey. Afr Health Sci. 2019;19(3):2623-33. https://doi.org/10.4314/ahs.v19i3.38
27. Elshimi E, Morad W, Mohamad NE, Shebl N, Waked I. Female Sexual Dysfunction Among Egyptian Patients with Chronic Hepatitis C. J Sex Med. 2014;11(3):768-75. https://doi.org/10.1111/jsm.12412
28. Bach N, Schaffner F, Kapelman B. Sexual behavior in women with nonalcoholic liver disease. Hepatology. 1989;9(5):698-703. https://doi.org/10.1002/hep.1840090507
29. Thiele M, Askgaard G, Timm HB, Hamberg O, Gluud LL. Predictors of health-related quality of life in outpatients with cirrhosis: results from a prospective cohort. Hepat Res Treat. 2013;2013:479639. https://doi.org/10.1155/2013/479639
30. Apple R, Samuels LR, Fonnesbeck C. Body mass index and health-related quality of life. Obes Sci Pract. 2018;4(5):417-426. https://doi.org/10.1002/osp4.292
31. Poggiogalle E, Di Lazzaro l, Pinto A. Health-related quality of life and quality of sexual life in obese subjects. Int J Endocrinol. 2014;2014:847871. https://doi.org/10.1155/2014/847871
32. Morotti E, Battaglia B. Body mass index, stunkard figure rating scale, and sexuality in young italian women: a pilot study. J Sexual Med. 2013;10(4):1034-1043. https://doi.org/10.1111/jsm.12045
33. Vallejo-Medina P, Pérez-Durán C, Saavedra-Roa A. Translation, Adaptation, and Preliminary Validation of the Female Sexual Function Index into Spanish (Colombia). Arch Sex Behav. 2018;47(3):797-810. https://doi.org/10.1007/s10508-017-0976-7

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Original article

Self-expanding Metal Stents in Malignant Obstruction of the Esophagus: A 25-Year Multicentric Study

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Abstract

Background: Self-expanding metal prostheses improve dysphagia in patients with incurable esophageal cancer (EC). New stents have been introduced, and chemoradiotherapy has been implemented for EC, changing patients' risk profiles. It is unknown whether this has affected palliation with stents. **Patients and methods:** Retrospective study in three centers in Medellín-Colombia; patients undergoing placement of palliative esophageal prostheses for malignant dysphagia (1997-2022). Major and minor complications after implantation, the influence of oncological therapies, and survival were evaluated for 1997-2009 (n = 289) and 2010-2022 (n = 318). **Results:** 607 patients underwent esophageal prostheses; 296 (48.8%) became complicated. It was higher in the second period (52.5% vs. 48.1%), as were major complications (20.8% vs. 14.2%, p = 0.033), with no differences in minor complications (33.9% vs 31.8%, p = 0.765). Also, 190 (31.3%) patients presented with recurrent dysphagia, stable in both periods. Migration increased over time (from 13.1% to 18.2%, p = 0.09). The most common minor adverse event was pain, increasing over time (from 24.9% to 33.95%, p < 0.01), and associated factors were chemoradiotherapy, absence of fistula, and squamous cell carcinoma. Acid reflux decreased in the second group (p = 0.038). Twelve percent of patients required another intervention for feeding. Survival was not impacted by time and use of stents. **Conclusions:** Stents are an alternative in non-surgical malignant dysphagia, although recurrent dysphagia has not decreased over time. Minor stent-related complications are increasing in association with the implementation of chemoradiotherapy.

Keywords

Esophageal cancer, metal stent, dysphagia, palliation.

INTRODUCTION

Annually, approximately 600,000 people are diagnosed with esophageal cancer worldwide[(1)]. More than half of patients present with inoperable disease at the time of diagnosis due to metastases or a poor medical condition. Dysphagia is a common symptom that dramatically impacts the patient's quality of life[(2)]. Although brachytherapy is superior in achieving long-term relief of dysphagia, esophageal stenting induces a more rapid resolution[(3)]. Therefore, it is currently accepted that the placement of an esophageal prosthesis is indicated mainly in patients with short-term survival[(4)].

The first description of the clinical use of esophageal prostheses is attributed to Celestin, who collected previous

experiences and results with the use of plastic esophageal prostheses to treat malignant dysphagia[5]. In Colombia, the first publication on the clinical use of plastic and rigid prostheses in the esophagus dates back 35 years by the group of the National Cancer Institute[6]. The first publication in the field using self-expanding metal prostheses is from 20 years ago, with the advantage of being locally built prostheses[7]. Currently, esophageal stenting is used for a wide variety of esophageal diseases. Various stent designs with different characteristics are available for clinical use. The attributes of esophageal stents vary depending on mechanical properties, such as the material (metal, plastic, or biodegradable), the radial and axial forces acting on the lumen of the esophagus, and the type and design of the cover (partial, total, or uncovered) surrounding the mesh of the prosthesis (silicone, polyurethane, among others). The implications of different stent characteristics on clinical outcomes have not been fully elucidated due to a lack of results from randomized, controlled clinical studies[8].

While esophageal prostheses can effectively restore luminal patency, they are not complication-free. Minor complications of esophageal stenting include chest pain, acid reflux, stent obstruction from tissue growth or poor diet, recurrent dysphagia, and stent migration. Moreover, the major adverse effects are bleeding, aspiration pneumonia, and perforation. These adverse effects may require repeating the endoscopy with possible stent removal[9]. Our experience with esophageal prostheses has been previously described, and we demonstrated that esophageal stents can improve dysphagia but do so imperfectly, with high complication rates (29.4% of patients experienced at least one minor complication)[10,11]. Several prostheses have been designed to minimize these risks in recent decades, with different materials, shapes, sizes, biodegradability, types, extent of coating, and anti-reflux, anti-migration, or even radioactive characteristics[12–16]. Still, whether these technical developments have positively impacted clinical outcomes remains uncertain.

The profile of patients selected for treatment with stents has changed with variations in the treatment of esophageal cancer (chemoradiotherapy). Patients who underwent esophageal stenting for the management of malignant dysphagia over the past 25 years were analyzed for dysphagia recurrence in two periods, describing other related adverse events with stents and survival in these two periods.

MATERIALS AND METHODS

Study population

We included patients who underwent placement of a self-expanding metal esophageal prosthesis between January 1997 and May 2022 with palliative intent for malignant dysphagia due to esophageal or cardia obstruction, treated in four quaternary care institutions in Medellín attending cancer cases. Patients with a malignant stricture at the anastomosis after partial esophagectomy or gastrectomy with or without concomitant fistula were also included.

Eligible subjects were identified from the institutions' database, reviewing endoscopy records and clinical studies from the four oncology institutions. Patients who received a self-expanding plastic stent were excluded.

Placement of the esophageal prosthesis

Different stents were placed during the study according to their historical evolution (steel, Z stents, nitinol). Still, the analysis was limited to evaluating whether the prosthesis was totally or partially covered due to inconsistencies in the description in the endoscopic report. The location, grade of stricture, and path were determined essentially by endoscopy and esophagram. The stent chosen depended on the center's availability and the doctor's discretion. Stenting was performed with the patient under conscious sedation. The lesion was inspected and explored with a standard endoscope when allowed by the diameter. If the stricture could not be crossed, the option was NOT to dilate and pass a guidewire. The esophageal location of the tumor was defined using the distance of the incisors from the upper margin of the tumor. It was subdivided into proximal (up to 22 cm), middle (22 to 28 cm), and distal (below 28 cm).

The stents were inserted over a guidewire and most frequently placed with no fluoroscopic but endoscopic control. The length of the esophageal prosthesis was determined considering the size of the stricture plus 4 cm, a minimum of 2 cm at each end above and below the tumor.

The fluoroscopy offers the option of having the path and length of the stricture better characterized to choose the size of the stent, but this choice was at the operator's discretion.

Generally, patients received a liquid diet the same day after the procedure. They also received detailed feeding instructions at the time of hospital discharge.

Objectives and data collection

The primary objective was to determine the clinical efficacy and safety of esophageal prosthesis placement regarding relief and recurrence of dysphagia and diachronically evaluate occurrence changes. The secondary objective was to identify risk factors for recurrent dysphagia and stent-related adverse events, clinical and technical success rate, dysphagia improvement, and survival.

The patient's medical records and endoscopy reports were reviewed, extracting the following data: age, sex,

dysphagia score, previous chemotherapy or radiotherapy, location of stricture, histology, date of stenting, type of stent (covered, uncovered, partial), and the use of dilation. Most data were retrospective, although data from prospective studies were also included from the institutions' electronic medical records and the online form (Drive).

Dysphagia was scored according to the Ogilvie scale[17]. The following outcome parameters were collected: technical success, complications, recurrent dysphagia, and survival. Technical success was defined as adequate deployment and placement of the stent in the intended position. Repositioning was allowed during the same procedure; however, if a second endoscopy with repositioning of the prosthesis was indicated, it was considered a technical failure.

Recurrent dysphagia was defined as stent migration, growth or overgrowth, occlusion of the alimentary canal, or other stent-related causes confirmed by endoscopy. Major complications involved severe or life-threatening complications, including perforation, hemorrhage, pneumonia, fever, fistula, or pressure necrosis. Minor complications included substernal pain and reflux symptoms. Time to major or minor complications was defined as the number of days from prosthesis placement to the first adverse event. Both complications were included if a minor and a major complication occurred in the same patient.

For evaluation purposes, the study was grouped into two 12-year periods, according to the date of stenting: Group 1 (January 1997 to December 2009) and Group 2 (January 2010 to May 2022). Data were collected until May 2022 to have a minimum follow-up of six months for the latest patients. The distribution into these two groups (first and second half of the series) considered the changes in the therapy approach (chemotherapy and neoadjuvant radiotherapy) given to esophageal cancer in the last ten years.

Statistical analysis

The occurrence of recurrent dysphagia, major and minor complications, and survival were evaluated using the Kaplan-Meier estimate and compared between the two consecutive periods using the log-rank test. Patients were censored at the time of death, after removal of the prosthesis, or at the end of follow-up. Univariate Cox regression analysis was performed to evaluate the association between multiple covariates, including time to prosthesis placement (in years) and the occurrence of recurrent dysphagia, subdivided into migration, tumor or tissue growth, and major and minor complications. Other covariates were age, sex, previous radiation or chemotherapies, fistula presence, stricture location, histology, extrinsic compression, and anterior dilation.

The statistical program SPSS version 22.0 (Chicago, Illinois, United States) was used for data analysis. *P*-values of 0.05 were considered the limit of statistical significance.

Ethical considerations

All procedures conformed to the ethical standards of the committee responsible for human experimentation (institutional and national) and to the 1964 Helsinki Declaration and later versions. The confidentiality of data was protected. The authors state that this article does not contain personal information that could identify patients. Data already analyzed from two studies were compared, which at the time were obtained from a secondary source without any intervention on the patients, so informed consent is not required.

RESULTS

Characteristics of the patients

A total of 668 patients who underwent self-expanding metal esophageal stenting for malignant dysphagia between September 1997 and April 2022 were identified. The flow diagram of the study with the excluded patients is presented in **Figure 1**.

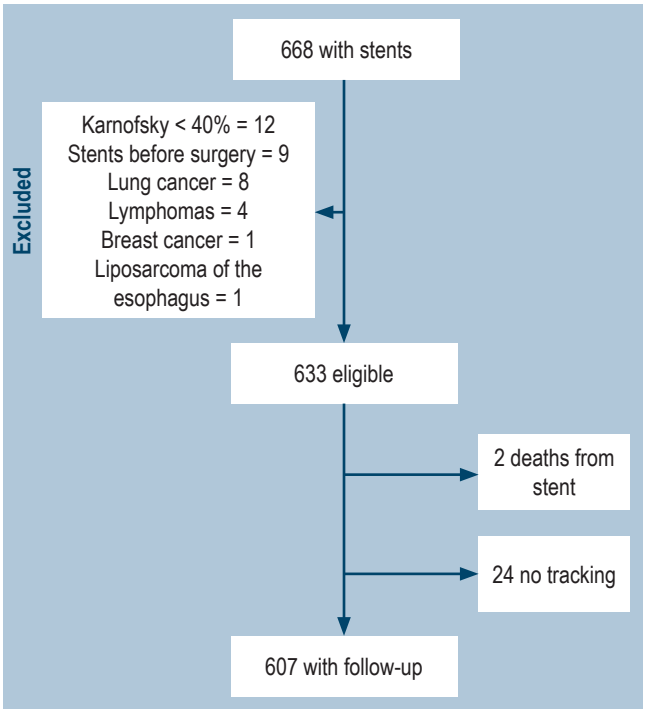

Figure 1. Flow chart with excluded patients. Prepared by the authors.

The calculations were based on 607 patients for whom the most information was available when reviewing the medical records. The clinical characteristics of the patients were discriminated into two temporary care groups: Group 1 (n = 289) with stents placed between September 1997 and December 2009, and Group 2 (n = 318) between January 2010 and May 2022. No differences were found in the median age or sex distribution in both groups (**Table 1**).

All patients had dysphagia ≥ 2 before prosthesis placement. In the second period (Group 2), 56.3% of patients had been pretreated with chemotherapy or radiotherapy, compared to 39.1% in the previous period ($p < 0.001$). In 49 patients, stenting was indicated for residual or recurrent malignant obstructive disease. The proportion of patients with the more distally located disease (distal esophagus/cardias) increased from 61.9% to 69.8%, with a significant difference ($p = 0.021$). A fully covered stent was inserted 73.1% of the time. The proportion of completely covered prostheses increased in the second period from 66.4% to 79.2% ($p = 0.01$).

Technical aspects and improvement of symptoms

Placement of endoscopic esophageal stents was technically successful in 310 of 318 patients (97%). Technical failure occurred due to incorrect stenting (n = 6) and insufficient stent deployment (n = 2). No differences in technical success between the two study periods were observed ($p = 0.95$). However, it is evident that in the second period of the study, fluoroscopy assistance was used in a lower proportion (24.6% vs. 15.1%, $p = 0.002$). Dysphagia scores improved from a median of Grade 3 to 0 ($p < 0.001$) four weeks after stenting.

Fistulas in the esophagus

We found an esophageal fistula before stenting in 51 patients (6.7%), an esophageal-respiratory fistula in 29 (4.8%), and a mediastinal fistula in 22 (3.6%) (**Table 1**). In all these patients, the dysphagia score improved (2.81 vs. 1.3, $p < 0.001$). Median survival after stenting of fistulas was 78.1 days (range: 41–232 days).

Recurrent dysphagia

Recurrence of dysphagia occurred in 190 of 607 patients (31.3%) and was related to stent migration (96 patients; 15.8%) with internal or excessive growth of tumor or hyperplastic tissue (75 patients; 12.3%), occlusion of the alimentary tract (14 patients; 2.3%), other stent-related causes (8 patients; 1.3%), and other non-stent-related causes (13 patients; 2.1%) (**Figure 2** and **Table 2**).

Recurrent dysphagia was diagnosed after a median of 44 days (range: 2–679 days). Univariable Cox regression analysis did not demonstrate a trend toward an increase in recurrent dysphagia over the two periods evaluated (hazard ratio [HR]: 1.01 per 1-year increase; 95% confidence interval [CI]: 0.92–1.05; $p = 0.5$). Furthermore, no association was found between previous chemotherapy and recurrent dysphagia (HR: 1.22; 95% CI: 0.91–1.81; $p = 0.4$).

Other adverse events

Almost half of the patients (296; 48.3%) had at least one complication. One hundred seven (17.6%) major complications occurred, including bleeding (n = 43), pneumonia (n = 26), perforation (n = 15), fistula (n = 14), and pressure necrosis (n = 7) (**Figure 3** and **Table 2**). Major complications developed in a median of 11 days after prosthesis insertion (range: 0–557 days). Univariable Cox regression analysis showed no change in major complications over time (HR: 0.99 per 1-year increase; 95% CI: 0.96–1.01; $p = 0.21$). Trends were noted for major complications with radiotherapy (HR: 1.60; 95% CI: 1.00–2.55; $p = 0.05$), adenocarcinoma (HR: 0.69; 95% CI: 0.64–1.12; $p = 0.07$), and younger age (HR: 0.99; 95% CI: 0.97–1.00; $p = 0.09$).

Pneumonia was the second most common major complication, with 18 of the 28 patients developing pneumonia within four days of stenting, suggesting aspiration during or immediately after the procedure. Pneumonia occurred more frequently in patients who had received prior chemoradiotherapy (18.1%) than in those who had received no initial therapy, chemotherapy alone, or radiation therapy alone (4.2%, 6.3%, and 5.4%, respectively; $p = 0.01$). The risk was also increased in patients with proximally located stenosis (8.0% vs. 3.2%; $p = 0.001$).

The risk of developing perforation was significantly higher after pre-prosthesis dilation (13.8% vs. 2.3%; $p = 0.04$). Dilation was performed to a median of 12 mm. There was a trend toward more frequent bleeding in distal strictures (9.4% vs. 6.0%; $p = 0.06$). There were 199 (32.8%) minor complications, most related to substernal pain (n = 280, 46.1%) (**Figure 4**).

The median time to minor complications was two days after stenting (range: 0–267). Cox regression analysis did not reveal an increase in minor complications over time. Other non-significant pain-related associations were younger age, squamous cell histology, previous distal location, and absence of fistula.

Regarding substernal pain, the univariate logistic regression analysis showed a significant increase in the second period (odds ratio [OR]: 1.07; 95% CI: 1.05–1.95; $p = 0.014$). Therefore, an additional binary multivariable logistic regression analysis was performed, showing that prior

Table 1. Characteristics of patients with esophageal prosthesis due to malignant obstruction

Characteristic		Group 1 (1997–2009) n = 289 (%)	Group 2 (2010–2022) n = 318 (%)	Total n = 607 (%)	*p*
Age		65.6 ± 11.7	68.2 ± 11.1	66.8 ± 10.2	
Sex	Male	187 (64.7)	212 (66.7)	399 (65.7)	0.611
	Female	102 (35.3)	106 (33.3)	208 (34.3)	
Location	Upper-middle esophagus	87 (30.1)	70 (22.0)	157 (25.9)	0.021
	Distal esophagus-cardias	179 (61.9)	222 (69.8)	401 (66.0)	
	Relapse	23 (8.0)	26 (8.2)	49 (8.1)	
Fistula	Mediastinal	10 (3.5)	12 (3.8)	22 (3.6)	0.965
	Esophageal-respiratory	13 (4.5)	16 (5.0)	29 (4.8)	
	No fistula	266 (92.0)	290 (91.2)	566 (93.3)	
Histology	Squamous cell	116 (40.1)	118 (37.1)	234 (38.6)	0.323
	Adenocarcinoma	158 (54.7)	190 (59.7)	348 (57.3)	
	Other	6 (2.1)	10 (3.2)	16 (2.6)	
	Unknown	9 (3.1)	0	9 (1.5)	
Differentiation	Grade 2	15 (5.2)	18 (5.7)	33 (5.4)	0.268
	Grade 3	181 (62.6)	206 (64.8)	387 (63.8)	
	Grade 4	74 (25.6)	84 (26.4)	158 (27.0)	
	Unknown	19 (6.6)	10 (3.1)	29 (4.8)	
Neoadjuvant	None	167 (57.8)	134 (41.6)	301 (49.6)	< 0.001
	Chemotherapy	50 (17.3)	90 (28.3)	140 (23.1)	
	Radiotherapy	25 (8.7)	34 (10.7)	59 (9.7)	
	Chemo- + radiotherapy	38 (13.1)	52 (17.3)	90 (14.8)	
	Unknown	9 (3.1)	8 (1.1)	17 (2.8)	
Fluoroscopy	Yes	71 (24.6)	48 (15.1)	119 (19.6)	0.006
	No	218 (75.4)	270 (84.9)	488 (80.4)	
Dilatation	Yes	65 (22.5)	43 (13.5)	108 (17.9)	0.002
	No	224 (77.5)	275 (86.5)	499 (82.1)	
Stent type	Fully covered	192 (66.4)	252 (79.2)	444 (73.1)	0.001
	Partially covered	62 (21.5)	48 (15.1)	110 (18.2)	
	Unknown	35 (12.1)	18 (5.7)	53 (8.7)	
Success	Technical	234/246 (95.1)	280/286 (97.9)	514/532 (97.0)	0.95
	Clinical	209/246 (84.9)	252/286 (88.0)	461/532 (87.0)	
	Unknown	43 (14.9)	32 (10.1)	75 (12.0)	

Prepared by the authors.

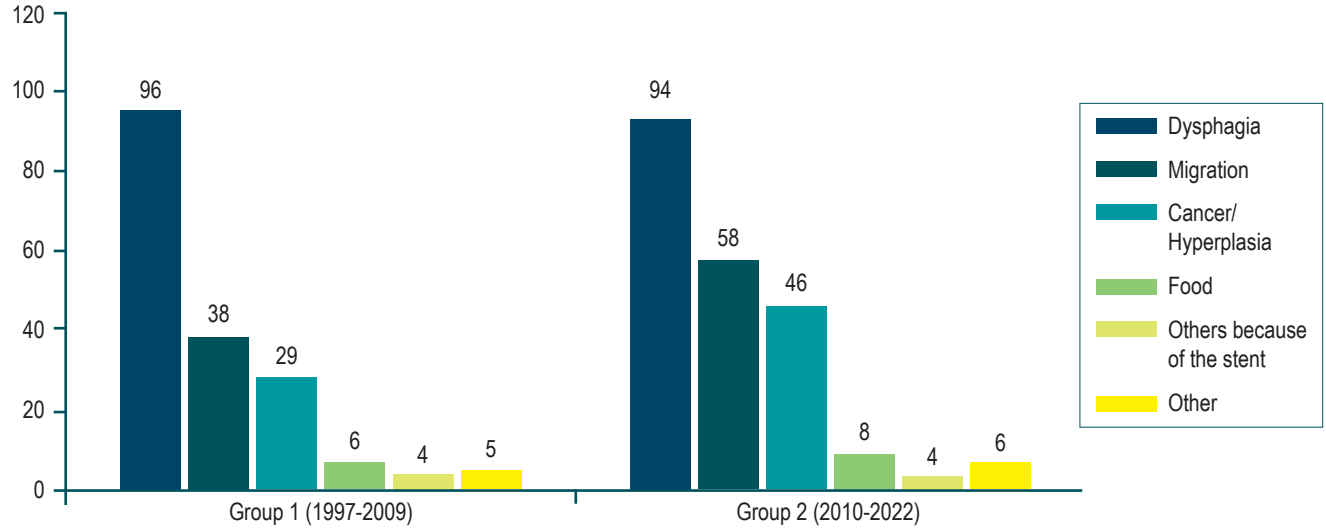

Figure 2. Causes of recurrent dysphagia in the two periods studied. Prepared by the authors.

Table 2. Summary of esophageal stent-related adverse events

Adverse events		Group 1 (1997–2009) n = 289 (%)	Group 2 (2010–2022) n = 318 (%)	Total n = 607 (%)	*p*
Recurrent dysphagia, in general		96 (33.2)	94 (29.6)	190 (31.3)	0.337
Types	Migration	38 (13.1)	58 (18.2)	96 (15.8)	
	Hyperplasia or cancer	29 (10.0)	46 (14.5)	75 (12.4)	
	Food	6 (2.1)	8 (2.5)	14 (2.3)	
	Other stent-related causes	4 (1.4)	4 (1.3)	8 (1.3)	
	Non-stent-related	5 (1.7)	6 (1.9)	13 (2.1)	
Patients with major complications		41 (14.2)	66 (20.8)	107 (17.6)	0.033
Types	Hemorrhage	21 (7.3)	22 (6.9)	43 (7.1)	
	Pneumonia	12 (4.2)	26 (8.2)	28 (4.6)	
	Perforation	13 (4.5)	2 (0.6)	15 (2.5)	
	Fistula	8 (2.7)	6 (1.9)	14 (2.3)	
	Pressure necrosis	4 (1.4)	3 (1.0)	7 (1.2)	
Patients with minor complications		98 (33.9)	101 (31.8)	199 (32.8)	0.765
Types	Pain	72 (24.9)	108 (33.9)	280 (46.1)	
	Gastroesophageal reflux	55 (19.0)	41 (12.9)	96 (15.8)	
	Fever	15 (5.2)	14 (4.4)	29 (4.8)	
Complicated patients, in general		139 (48.1)	167 (52.5)	296 (48.8)	0.183

Prepared by the authors.

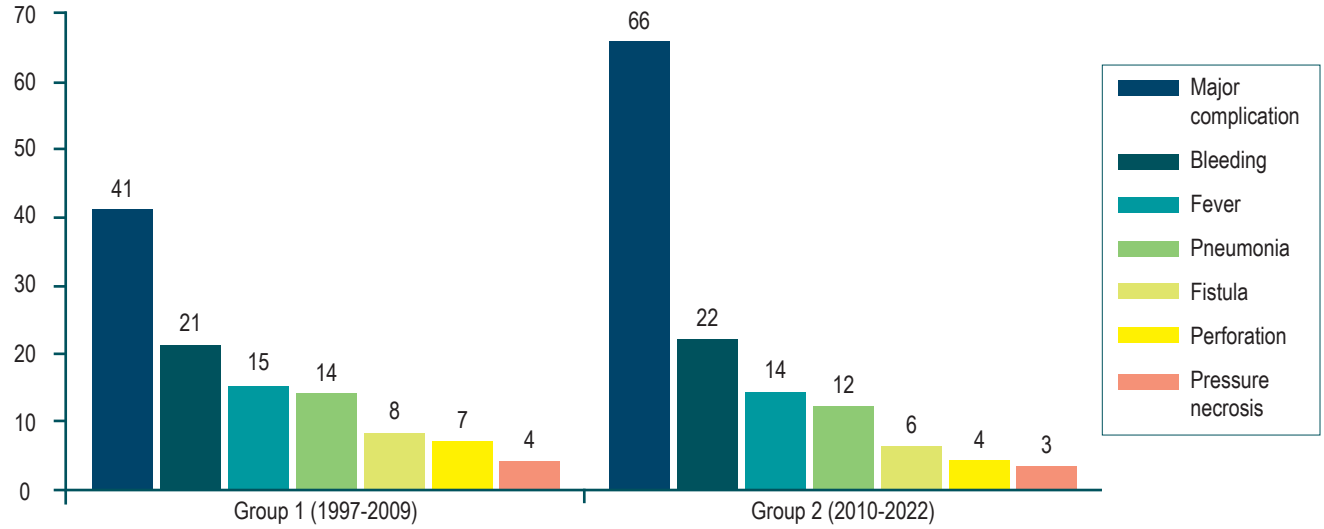

Figure 3. Major complications in the two study periods. Prepared by the authors.

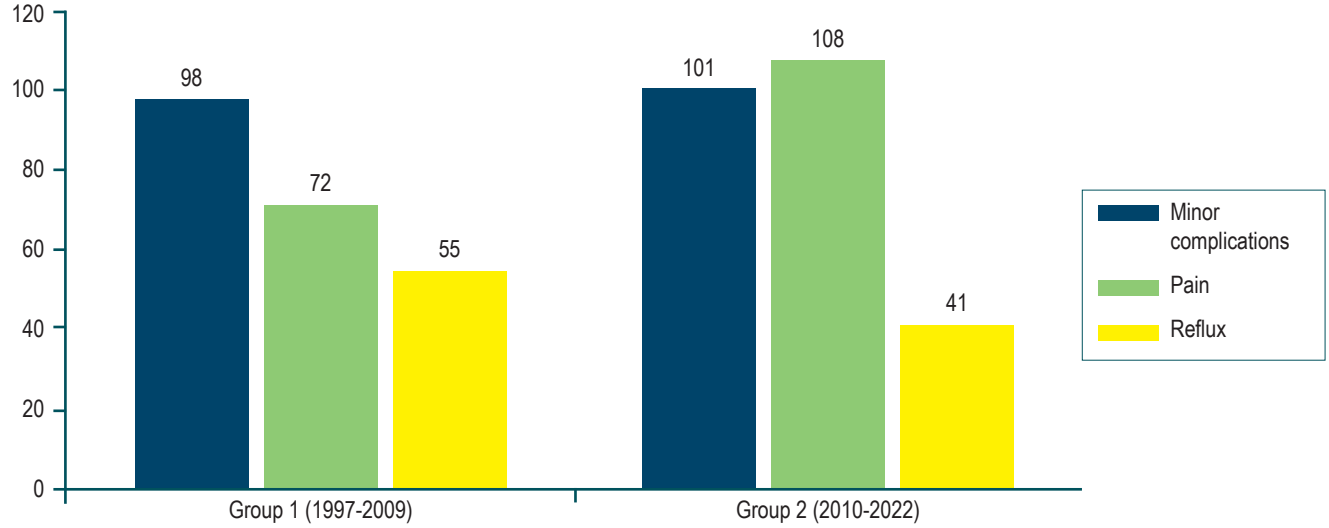

Figure 4. Minor complications in the two study periods. Prepared by the authors.

chemotherapy or radiotherapy and the absence of a fistula were factors significantly associated with pain. In contrast, adenocarcinoma was independently associated with a lower risk.

Reflux, as a minor complication, showed a significant decrease in its manifestation in the second group evaluated (from 19% to 12.9%, $p = 0.048$), which is explained by better patient orientation and formulation of acid blockers always on discharge.

Follow-up and survival

At follow-up, 65 patients (10.7%) needed another procedure to achieve enteral nutrition. This included an endoscopic gastrostomy tube in 44 patients (7.2%), a surgically placed gastrostomy tube in 14 patients (2.3%), and a feeding tube placed by interventional radiology in 7 patients (1.2%).

Median overall survival was 169 days (range: 1–1165). At the end of follow-up, 12 patients (2%) were still alive.

The majority of patients died as a result of tumor progression (n = 552; 91%), while 14 patients (2.3%) died due to a stent-related complication. No significant differences in survival were detected between the two groups ($p = 0.07$) (**Figure 5**).

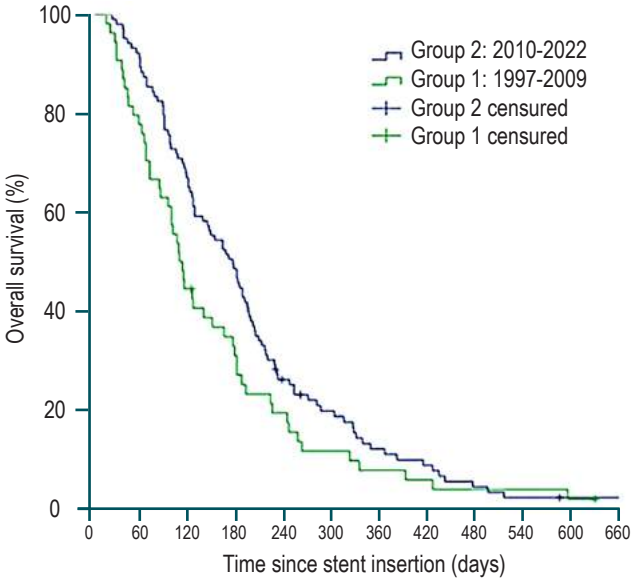

Figure 5. Kaplan-Meier estimate of the overall survival period from stenting. Prepared by the authors.

DISCUSSION

The incidence of esophageal cancer has increased in recent decades. At the same time, endoscopists place an increasing number of esophageal prostheses to palliate malignant obstruction of the esophagus, becoming an effective method to improve dysphagia and the patient's nutritional status and well-being[18]. The present study shows a growing increase in the use of esophageal prostheses in various cancer centers over 25 years, providing insight into temporal trends in stenting for malignant esophageal obstruction related to clinical efficacy and safety. A significant technical consideration in the study is the decreased use of fluoroscopy for placement over the years, with good technical and clinical results described in the literature[19]. However, with advances in endoprosthesis technology (anti-migration, anti-reflux systems, different coverage, diameters, among others), the rate of complications in their placement remains high, and lasting palliation is not achieved in a high proportion of patients[20].

The use of stents is highly effective in resolving dysphagia; still, recurrent dysphagia is common and occurs in 31.3% of patients, mainly due to migration or overgrowth of the tumor or hyperplastic tissue. The overall incidence of recurrent dysphagia has not decreased over the years. Indeed, there was a trend toward increasing risk over time, primarily due to a significantly increased risk of stent migration, likely related to the increasing use of fully covered prostheses. A wholly covered stent design substantially increases the risk of migration, which can be explained by less adhesion and fixation to the esophageal wall[8]. Furthermore, this fully covered design is more favorable to preventing tumor obstruction or excessive hyperplastic growth[21]. Importantly, our data suggest that the protective effect for tumor or tissue growth outweighs the migration risk because the fully covered design reduces the risk of overall recurrent dysphagia.

Not only recurrent dysphagia but also other adverse events related to prostheses harm patients with already incurable diseases. Complications were observed in almost half of the patients (48.8%), including major complications in 17.6%. We believe that the following findings regarding this topic deserve further attention:

- First, we saw a slight decrease in major complications during the second half of the study, with lower rates of bleeding and perforation. However, there was a gradual increase in the proportion of patients treated for more distally located diseases, and the risk of bleeding tends to be higher in these patients than in those with proximal esophageal obstruction.
- Second, perforation is another devastating iatrogenic complication. We found that the risk of perforation was significantly higher when dilation had been performed to facilitate stenting. This dilation was most commonly performed in the early days of the series and has now been largely abandoned. Current delivery systems are designed to traverse narrow strictures in a nontraumatic manner, avoiding the need for dilation.
- Third, the more significant number of patients treated with chemoradiotherapy before stenting is probably responsible for a greater risk of complications, such as pneumonia in this case, which was more frequent in the second group (4.2% vs. 8.2%, $p = 0.04$). Interestingly, no significant association could be established for chemotherapy or radiotherapy alone. This suggests a cumulative effect of both treatments. Possible mechanisms for increased susceptibility include pulmonary toxicity from chemoradiotherapy leading to decreased respiratory tract clearance, immunosuppressed state, decreased esophageal motility, and the presence of an esophageal-respiratory fistula[22]. It is likely that, at least in these cases, procedure-related aspiration has triggered lung infection, emphasizing the importance of close monitoring of the patient during stenting. Nonetheless, considering the lack of alternative palliative measures, we believe that stents can still be recommended to alleviate recurrent malignant dysphagia after chemoradio-

therapy, as supported in recent meta-analyses[23]. The relatively high risk of major complications should be discussed with patients as part of obtaining appropriate informed consent.

Migration is known to be a common and bothersome problem in esophageal stents. Migration rates have not improved over time, even with the introduction of new stents. Currently, anti-migration devices, such as endoscopic sutures, or endoclips, such as Stentfix, are alternatives that are emerging to impact migration rates[24]. Martins et al. point out that migration occurs in up to 36% of cases of esophageal stenting[25].

The migration rate increased in the second period evaluated (from 13.1% to 18.2%, $p = 0.113$) without being able to be related to a particular type of stent (fully covered, partially covered, or uncovered), as described in other series[26].

Retrosternal pain after stent deployment was the most frequently observed minor complication in our cohort in 29.7% of patients. Several explanations can be proposed: First, during the second period evaluated, a prospective study was carried out, which used a symptom diary to evaluate the experience of pain after esophageal stenting[27] extended to stents for malignancy. This triggered more accurate and reliable pain recording compared to assessments during previous years. In our practice, we routinely warn patients about the high likelihood of experiencing pain following esophageal stenting.

Second, more patients were pretreated with chemotherapy or radiotherapy, and this was marked as an independent risk factor for retrosternal pain. The exact mechanism to explain pain after pretreatment is unclear. It is conceivable that chemoradiotherapy-induced fibrosis results in lower esophageal wall compliance with relative overstretch and higher pressures after stent expansion compared with patients not treated with chemoradiotherapy.

During follow-up, 72 patients (11.9%) required other enteral nutrition modes. These results demonstrate that while esophageal stenting can be a valuable tool in alleviating dysphagia, it is not always practical, and patients may experience complications at high rates and may ultimately require an alternative to esophageal prostheses.

We must acknowledge several limitations of our study. Our results are based primarily on retrospectively collected data. Therefore, the occurrence of adverse events could have been underestimated. The sample size remains relatively small, which limits the ability to detect any differences that may exist. Additionally, data were missing on some potentially relevant variables; for example, it would have been interesting to evaluate whether the patient's functional status at follow-up or the stage of the disease has any influence on the clinical outcome and adverse events. Previous studies have denied such a relationship[28,29].

Esophageal stenting may allow the introduction of chemoradiotherapy. These therapies allow relief of dysphagia and complete oral nutrition, which is why the European Society of Gastrointestinal Endoscopy recommends their application. However, no clear statement exists on whether they should be introduced before or after stenting[30].

Since patients with incurable esophageal cancer have an extremely poor prognosis, the ideal palliative treatment for malignant esophageal strictures should provide rapid and long-lasting relief of symptoms, result in few complications, require a minimal hospital stay, and prolong survival. However, patients who underwent stenting did not often achieve lasting symptom relief due to stent malfunction and had to be readmitted for reoperation. Furthermore, palliation with stents only provides symptom relief but does not prolong survival. Stents with radioactive seed strands have recently been described as combining the advantages of stenting (i.e., faster relief of dysphagia) and brachytherapy (i.e., an advantage in stent patency and survival with a better quality of life)[31]. Zhu et al.[32] proved in a multicenter setting that the placement of esophageal prostheses loaded with I^{125} radioactive seed strands could produce a modest prolongation of survival in patients with incurable esophageal cancer (177 vs. 147 days; $p = 0.005$).

CONCLUSIONS

The present study demonstrates that esophageal prostheses are an alternative to improve the quality of life of cancer patients with symptoms of dysphagia. Still, they are an imperfect tool, which provides incomplete palliation to many patients, leading to thinking that improving the clinical outcome of stent therapy for malignant esophageal disease is challenging. Although new stent designs have been introduced over time, recurrent dysphagia remains a significant problem, occurring in approximately one-third of patients. Furthermore, changes in management strategies, with more patients pretreated with chemoradiotherapy, are associated with an increase in major complications, primarily pneumonia, but also with the development of substernal pain. Fully covered stents are the most popular option, allowing them to be removed if necessary. In this series, stents did not provide a durable source of enteral access in almost 12% of the cohort. Studies are needed to identify which patients will likely experience stent complications or poor palliation to accommodate technological advances better and enhance patient selection for this still-promising technique.

Conflicts of interest

The authors declare no conflict of interest.

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REFERENCES

1. WCRF International. Oesophageal Cancer Statistics | World Cancer Research Fund International [Internet]. WCRF International. 2022 [consultado el 16 de julio de 2022]. Disponible en: https://www.wcrf.org/cancer-trends/oesophageal-cancer-statistics/
2. Morgan E, Soerjomataram I, Rumgay H, Coleman HG, Thrift AP, Vignat J, et al. The global landscape of esophageal squamous cell carcinoma and esophageal adenocarcinoma incidence and mortality in 2020 and projections to 2040: New estimates from GLOBOCAN 2020. Gastroenterology. 2022;163(3):649-658.e2. https://doi.org/10.1053/j.gastro.2022.05.054
3. Homs MYV, Steyerberg EW, Eijkenboom WMH, Tilanus HW, Stalpers LJA, Bartelsman JFWM, et al. [Palliative treatment of esophageal cancer with dysphagia: more favourable outcome from single-dose internal brachytherapy than from the placement of a self-expanding stent; a multicenter randomised study]. Ned Tijdschr Geneeskd. 2005;149(50):2800-6.
4. Spaander MCW, Baron TH, Siersema PD, Fuccio L, Schumacher B, Escorsell À, et al. Esophageal stenting for benign and malignant disease: European Society of Gastrointestinal Endoscopy (ESGE) Clinical Guideline. Endoscopy. 2016;48(10):939-48. https://doi.org/10.1055/s-0042-114210
5. Celestin LR. Permanent intubation in inoperable cancer of the oesophagus and cardia: a new tube. Ann R Coll Surg Engl. 1959;25(2):165-70.
6. Valbuena JV, Olarte H. Prótesis per oral endoscópica en el tratamiento de cáncer de esófago y cardias. Rev Col Gastroenterol. 1987;2(1):17-22.
7. Castaño R, Sanín E, Ruiz MH. Stent esofágico de nitinol en el manejo de las fístulas esofagorrespiratorias malignas. Rev Col Gastroenterol. 2003;18(2):78-82.
8. Jackson CE, Johnson LS, Williams DA, Laasch HU, Edwards DW, Harvey AG, et al. A viewpoint on material and design considerations for oesophageal stents with extended lifetime Invited Viewpoint. J Mater Sci. 2022;57:3-26. https://doi.org/10.1007/s10853-021-06700-9
9. Castaño R. Técnicas en stents gastrointestinales endoscópicos: cómo, cuándo, manejo de complicaciones, selección del stent y costos. Rev Col Gastroenterol. 2012;27(1):32-44.
10. Castaño R, Ruiz Vélez MH, Juliao Baños F, Sanín Fonnegra E, Álvarez Barrera O, Lopera Bonilla J. Eficacia de un nuevo stent de nitinol fabricado localmente, en el tratamiento de la obstrucción maligna esofágica. Rev Col Gastroenterol. 2003;18(4):211-21.
11. Castaño R, Álvarez O, Lopera J, Ruiz MH, Juliao F, Sanín E, et al. Endoprótesis metálicas autoexpandibles en la obstrucción maligna esofágica y gastroduodenal. Rev Col Cirugía. 2005;20(1):33-48.
12. Castaño R, Álvarez O, Lopera J, Ruiz MH, Rojas A, Álvarez A, et al. Development and implementation of a new nitinol stent design for managing benign stenoses and fistulas of the digestive tract. Rev Col Gastroenterol. 2015;30(3):261-72. https://doi.org/10.22516/25007440.49
13. Yang Z, Wu Q, Wang F, Ye X, Qi X, Fan D. A Systematic Review and Meta-Analysis of Randomized Trials and Prospective Studies Comparing Covered and Bare Self-Expandable Metal Stents for the Treatment of Malignant Obstruction in the Digestive Tract. International Journal of Medical Sciences. 2013;10(7):825-35. https://doi.org/10.7150/ijms.5969
14. Hussain Z, Diamantopoulos A, Krokidis M, Katsanos K. Double-layered covered stent for the treatment of malignant oesophageal obstructions: Systematic review and meta-analysis. World J Gastroenterol. 2016;22(34):7841-50. https://doi.org/10.3748/wjg.v22.i34.7841
15. Law R, Prabhu A, Fujii-Lau L, Shannon C, Singh S. Stent migration following endoscopic suture fixation of esophageal self-expandable metal stents: a systematic review and meta-analysis. Surg Endosc. 2018;32(2):675-81. https://doi.org/10.1007/s00464-017-5720-9
16. Zhao CL, Gu B, Huo XB, Xia FF. I-125 seed-loaded versus normal stent insertion for obstructive esophageal cancer: a meta-analysis. Videosurgery and other Miniinvasive Techniques. 2021;16(4):633-40. https://doi.org/10.5114/wiitm.2021.104205
17. Ogilvie AL, Dronfield MW, Ferguson R, Atkinson M. Palliative intubation of oesophagogastric neoplasms at fibreoptic endoscopy. Gut. 1982;23(12):1060-7. https://doi.org/10.1136/gut.23.12.1060
18. Kumar S, Bahdi F, Emelogu IK, Yu AC, Coronel M, Ge PS, et al. How much progress have we made?: a 20-year experience regarding esophageal stents for the palliation of

malignant dysphagia. Dis Esophagus. 2022;35(6):doab085. https://doi.org/10.1093/dote/doab085
19. Chandan S, Mohan BP, Khan SR, Bhogal N, Canakis A, Bilal M, et al. Clinical efficacy and safety of palliative esophageal stenting without fluoroscopy: a systematic review and meta-analysis. Endosc Int Open [Internet]. 2020 [consultado el 6 de mayo de 2023];8(7):E944. Disponible en: /pmc/articles/PMC7297607/
20. Moutzoukis M, Argyriou K, Kapsoritakis A, Christodoulou D. Endoscopic luminal stenting: Current applications and future perspectives. World J Gastrointest Endosc [Internet]. 2023 [consultado el 6 de mayo de 2023];15(4):195–215. Disponible en: https://pubmed-ncbi-nlm-nih-gov.udea.lookproxy.com/37138934/
21. Johnson LA, Marino KA, Muesse J. Esophageal Stenting: Expert Techniques. CTSNet; 2022. https://doi.org/10.25373/ctsnet.19224678
22. Ivanov AI, Popov VA, Burmistrov MV. Complications of endoscopic esophageal stent implantation. Kazan Med J. 2021;102(1):74-84. https://doi.org/10.17816/KMJ2021-74
23. Tinusz B, Soós A, Hegyi P, Sarlós P, Szapáry L, Erős A, et al. Efficacy and safety of stenting and additional oncological treatment versus stenting alone in unresectable esophageal cancer: A meta-analysis and systematic review. Radiotherapy and Oncology. 2020;147:169-77. https://doi.org/10.1016/j.radonc.2020.05.015
24. Schiemer M, Bettinger D, Mueller J, Schultheiss M, Schwacha H, Hasselblatt P, et al. Reduction of esophageal stent migration rate with a novel over-the-scope fixation device (with video). Gastrointest Endosc. 2022;96(1):1-8. https://doi.org/10.1016/j.gie.2022.02.001
25. Martins B da C, Retes FA, Medrado BF, de Lima MS, Pennacchi CMPS, Kawaguti FS, et al. Endoscopic management and prevention of migrated esophageal stents. World J Gastrointest Endosc. 2014;6(2):49-54. https://doi.org/10.4253/wjge.v6.i2.49
26. Reijm AN, Didden P, Bruno MJ, Spaander MCW. Early pain detection and management after esophageal metal stent placement in incurable cancer patients: A prospective observational cohort study. Endosc Int Open. 2016;04(08):E890-4. https://doi.org/10.1055/s-0042-111202
27. Castaño R, Álvarez O, Lopera J, Ruiz MH, Rojas A, Álvarez A, et al. Desarrollo e implementación de un nuevo diseño de stent de nitinol para el manejo de estenosis y fístulas benignas del tracto digestivo. Rev Colomb Gastroenterol. 2015;30(3):261-72. https://doi.org/10.22516/25007440.49
28. Fuccio L, Scagliarini M, Frazzoni L, Battaglia G. Development of a prediction model of adverse events after stent placement for esophageal cancer. Gastrointest Endosc. 2016;83(4):746-52. https://doi.org/10.1016/j.gie.2015.08.047
29. Gao F, Xu YL, Liu YJ, Sun MH. Outcomes of self-expandable metal stent placement for malignant oesophageal strictures. Clin Radiol. 2020;75(2):156.e21-156.e27. https://doi.org/10.1016/j.crad.2019.10.008
30. Spaander MCW, van der Bogt RD, Baron TH, Albers D, Blero D, de Ceglie A, et al. Esophageal stenting for benign and malignant disease: European Society of Gastrointestinal Endoscopy (ESGE) Guideline - Update 2021. Endoscopy. 2021;53(7):751-762. https://doi.org/10.1055/a-1475-0063
31. Yang ZM, Geng HT, Wu H. Radioactive Stent for Malignant Esophageal Obstruction: A Meta-Analysis of Randomized Controlled Trials. J Laparoendosc Adv Surg Tech A [Internet]. 2021 [consultado el 14 de diciembre de 2023];31(7):783–9. Available from: https://pubmed.ncbi.nlm.nih.gov/32915105/
32. Zhu HD, Guo JH, Mao AW, Lv WF, Ji JS, Wang WH, et al. Conventional stents versus stents loaded with (125) iodine seeds for the treatment of unresectable oesophageal cancer: a multicentre, randomised phase 3 trial. Lancet Oncol [Internet]. 2014 [consultado el 14 de diciembre de 2023];15(6):612–9. Available from: https://pubmed.ncbi.nlm.nih.gov/24742740/

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Original article

Esophagogastric Junction Contractile Integral (EGJ-CI) in Various Phenotypes of Gastroesophageal Reflux Disease (GERD)

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Abstract

Introduction: Two parameters of high-resolution esophageal manometry are used to observe the function of the esophagogastric junction (EGJ): the anatomical morphology of the EGJ and contractile vigor, which is evaluated with the esophagogastric junction contractile integral (EGJ-CI). To date, how these parameters behave in different gastroesophageal reflux disease (GERD) phenotypes has not been evaluated. **Materials and methods:** An analytical observational study evaluated patients with GERD confirmed by pH-impedance testing and endoscopy undergoing high-resolution esophageal manometry. The anatomical morphology of the EGJ and EGJ-CI was assessed and compared between reflux phenotypes: acid, non-acid, erosive, and non-erosive. **Results:** 72 patients were included (63% women, mean age: 54.9 years), 81.9% with acid reflux and 25% with erosive esophagitis. In the latter, a decrease in EGJ-CI (median: 15.1 vs. 23, $p = 0.04$) and a more significant proportion of patients with type IIIa and IIIb EGJ (83.3% vs 37.1%, $p < 0.01$) were found. No significant differences existed in the manometric parameters of patients with and without acid and non-acid reflux. **Conclusion:** In our population, EGJ-CI significantly decreased in patients with erosive GERD, suggesting that it could be used to predict this condition in patients with GERD. This finding is also related to a higher proportion of type III EGJ and lower pressure at end-inspiration of the lower esophageal sphincter in this reflux type.

Keywords

Gastroesophageal reflux disease, esophagogastric junction, lower esophageal sphincter.

INTRODUCTION

The measurement and quantification of the functionality of the esophagogastric junction (EGJ) allow the establishment of adequate competence of this barrier mechanism. They can provide valuable information on conditions or pathologies in which it can be altered, such as gastroesophageal reflux disease (GERD)[1,2], postoperative states of myotomy in patients with achalasia, postoperative states of anti-reflux surgery, among others.

The Lyon Consensus proposes two parameters of esophageal high-resolution manometry (HRM) to observe the EGJ's function: the anatomical morphology of the EGJ and contractile vigor[3,4]. The morphology of the EGJ is defined by the relationship between the lower esophageal sphincter (LES) and the crura of the diaphragm (CD). Three types of

EGJ morphology are proposed: Type 1 when the LES and CD are superimposed, Type 2 when the LES and CD are separated by less than 2 cm, and Type 3 when the separation is greater than 2 cm[3–5]. The contractile vigor of the EGJ or esophagogastric junction contractile integral (EGJ-CI) is calculated using a similar method to that of the distal contractile integral (DCI). The DCI frame is placed over the EGJ to include three respiratory cycles; the average value recorded in mm Hg/cm/s is divided by the duration of the three respiratory cycles to obtain the EGJ-CI in mm Hg/cm (**Figure 1**)[3,6].

The study by Nicodeme et al. evaluated the severity of gastroesophageal reflux defined by pH impedance variables such as acid exposure time (AET), the number of reflux episodes in 24 hours, and a symptomatic index greater than 50%. They found that a greater EGJ-CI in the HRM was associated with fewer reflux episodes[6].

Although different GERD phenotypes have been described based on clinical, pH impedance, and endoscopic parameters, such as acid, non-acid, erosive, and non-erosive reflux, it has not been possible to define factors that can predict these phenotypes. Specifically, it has not been determined whether the assessment of the EGJ competence, especially the EGJ-CI, could be helpful in this context. Defining it would be clinically relevant since the treatment and prognosis of each phenotype differs significantly[7].

The present study aims to describe the function of the EGJ, including anatomical morphology and EGJ-CI in various GERD phenotypes, using pH-impedance testing and upper GI tract endoscopy as the gold standard.

MATERIALS AND METHODS

We conducted an analytical observational study, which included patients with a diagnosis of GERD confirmed by pH impedance or endoscopic findings that were taken for esophageal manometry in the gastroenterology unit of the Hospital Universitario San Ignacio, a referral hospital in Bogotá (Colombia), between June 2019 and June 2021. Patients over 18 with simultaneous HRM, pH-impedance

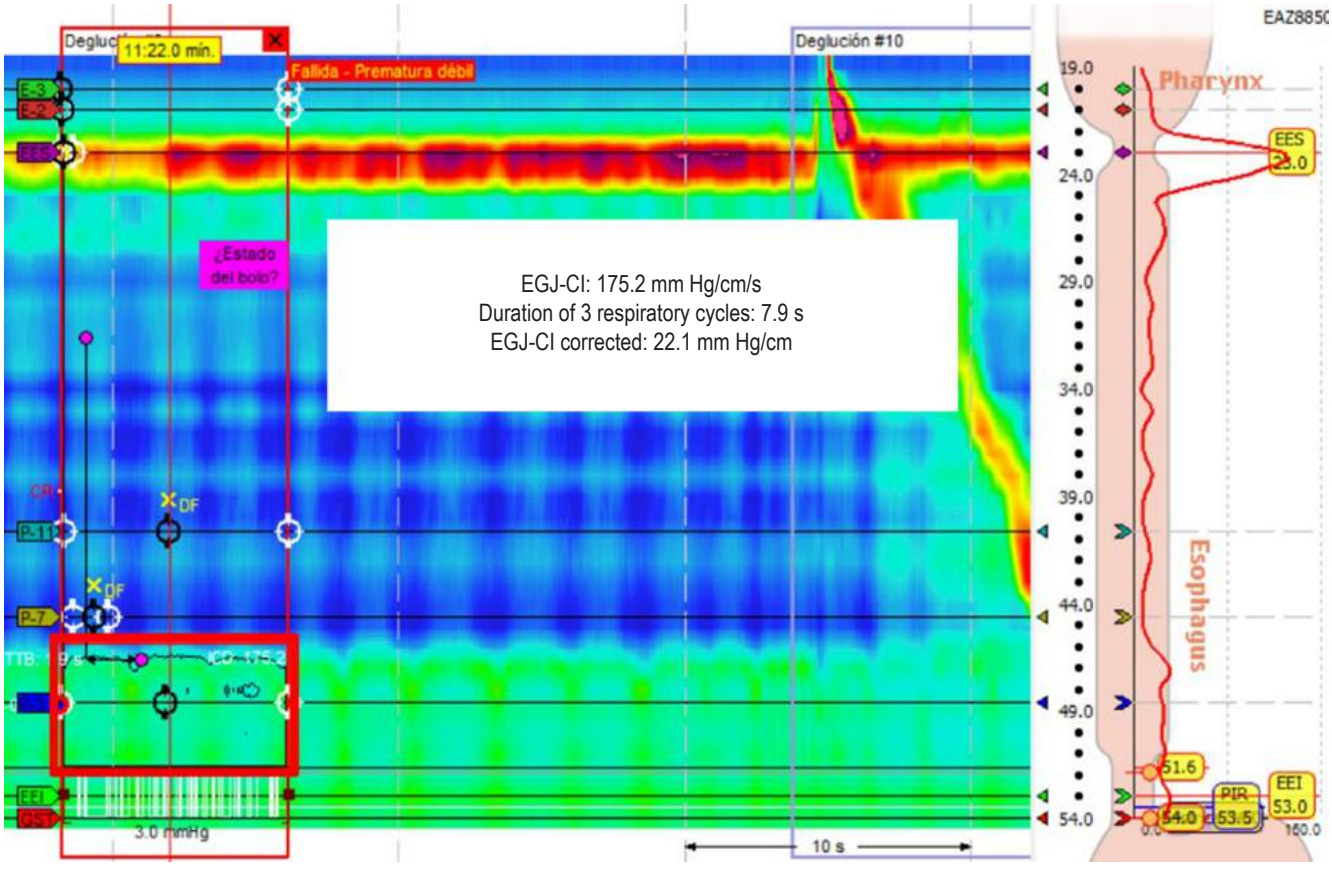

Figure 1. The distal contractile integral frame (red frame) is placed over the EGJ to include three respiratory cycles; the value recorded in mm Hg/cm/s is divided by the duration of the three respiratory cycles to obtain the EGJ-CI in mm Hg/cm. Authors' archives.

testing, and upper GI endoscopy were included. Patients with incomplete manometries for any reason, a history of upper GI surgery (total or partial gastrectomy), esophageal interventions, achalasia, outflow tract obstruction, Jackhammer, and hypercontractile esophagus, as well as patients who did not meet the GERD criteria, were excluded. The Hospital Universitario San Ignacio and the Pontificia Universidad Javeriana ethics committee approved the study under code FM-CIE-1992-21/246/2021.

The endoscopic procedures (esophagogastroduodenoscopy) were performed by gastroenterologists attached to the Hospital Universitario San Ignacio. The manometry and pH-impedance studies were conducted by duly trained nursing staff, and gastroenterology fellows analyzed them under the supervision and approval of certified gastroenterologist members of the digestive physiology group. The manometries were analyzed according to the parameters of the Chicago Classification v4.0 and the pH-impedance tests according to the guidelines of the Lyon Consensus[15,16]. Demographic data and the results of the different tests were obtained from the records systematically filled out in the unit and collected using a standardized form.

Non-acid reflux was defined as more than 27 reflux episodes when the patient came without treatment and more than 44 reflux episodes if the patient came with treatment. Acid reflux was determined as AET > 6%, or, in patients with AET in the gray zone (between 4% and 6%), as a number of acid refluxes greater than 80, a DeeMester score greater than 14.7, a post-reflux swallow-induced peristaltic wave index greater than 61% and the mean nocturnal baseline impedance less than 2,292 ohms. Non-erosive reflux was defined as those patients with routine endoscopy, and erosive reflux as the presence of Grade C and D esophagitis according to the Los Angeles Classification, Barrett's esophagus, or peptic stricture[16].

The EGJ-CI measurement used the DCI frame placed over the EGJ to include three respiratory cycles. The value recorded in mm Hg/cm/s is divided by the duration of the three respiratory cycles to obtain the EGJ-CI in mm Hg/cm (**Figure 1**).

Continuous variables were described using measures of central tendency and dispersion. A Shapiro-Wilk test was used to define whether the normality criterion in the data distribution was met. If met, the mean and standard deviation were described; otherwise, the median and interquartile range. Categorical variables were defined with absolute numbers and percentages. The groups generated according to the erosive, non-erosive, acid, and non-acid phenotypes were compared using a t-test or a Mann-Whitney U test. A Stata 16 statistical package was used for the analysis.

RESULTS

Seventy-two patients were included, with a mean age of 54.9 years (standard deviation [SD]: 14.1) and a predominance of the female sex (63%). Regurgitation and heartburn were the most frequent symptoms (66%), followed by cough and belching, with a frequency of 31% and 11%, respectively. The indication for performing pH-impedance testing in order of frequency was GERD, presurgery, typical symptoms, atypical symptoms, and patients with chest pain and dysphagia (**Table 1**). Of the patients included in the study, 34.7% did not receive any PPI, and 2% received alginate as a treatment strategy for GERD. The most frequently used PPI was esomeprazole, with 26%, followed by lansoprazole, dexlansoprazole, and pantoprazole (**Table 1**).

The comparison of manometric variables between patients with and without acid reflux and those with and without non-acid reflux is presented in **Table 2**; the mean LES pressure, the end-inspiratory LES pressure, the median IRP (integrated relaxation pressure), DCI, and EGJ-CI had no statistically significant differences between the groups.

The type of EGJ was different between patients with a positive versus negative pH impedance study for non-acid reflux ($p = 0.04$), with a more considerable proportion of patients with Type IIIa or IIIb EGJ among patients without that type of reflux (63.1% versus 31.3%). Among patients with acid reflux, no statistically significant differences were found in the variables studied (**Table 2**).

Lower end-inspiratory LES pressure was detected in patients with erosive reflux than those with non-erosive reflux (median: 6.1 vs. 11.9; $p < 0.01$). There was a similar when evaluating the EGJ-CI (median: 15.1 vs. 23, $p = 0.04$). The proportion of patients with Type IIIa and IIIb EGJ was higher in patients with erosive reflux (83.3% vs. 37.1%; $p < 0.01$) (**Table 3**).

DISCUSSION

The present study described the function of the EGJ in the different reflux phenotypes (acid, non-acid, erosive, and non-erosive) and found that Type IIIa and IIIb EGJs were more frequent in patients with erosive esophagitis and less common among patients with non-acid reflux. Additionally, EGJ-CI is significantly lower in patients with erosive reflux.

In our study, the symptoms that most frequently occurred in the population with GERD were regurgitation and heartburn, and the highest proportion of patients were women. These results correlate with what was documented by Paramo et al. in a published study of the prevalence of

Table 1. Clinical characteristics and treatment received by the included patients

Variable	Value
	n = 72
Female sex, n (%)	46 (63.9)
Age, mean (SD)	54.9 (14.1)
Symptoms	
- Regurgitation, n (%)	48 (66.7)
- Heartburn, n (%)	48 (66.7)
- Belching, n (%)	8 (11.1)
- Cough, n (%)	23 (31.9)
- Positive SI, n (%)	39 (54.2)
- SAP, n (%)	25 (34.7)
PPI use	
- Does not receive (%)	25 (34.7)
- One dose, n (%)	26 (36.1)
- Double dose, n (%)	21 (29.1)
pH impedance indication	
- GERD, n (%)	47 (65.28)
- Pre-surgical, n (%)	7 (9.7)
- Regurgitation, n (%)	4 (5.5)
- Heartburn, n (%)	7 (9.7)
- Cough, n (%)	3 (4.1)
- Belching, n (%)	2 (2.78)
- Chest pain, n (%)	1 (1.3)
- Dysphagia, n (%)	1 (1.3)
Proton pump inhibitor type	
- Esomeprazole, n (%)	19 (26.3)
- Omeprazole, n (%)	5 (6.94)
- Pantoprazole, n (%)	6 (8.33)
- Lansoprazole, n (%)	8 (11.1)
- Dexlansoprazole, n (%)	7 (9.7)
- No use of PPI, n (%)	25 (34.7)
- Alginate, n (%)	2 (2.78)

SD: standard deviation; n = number. Prepared by the authors.

symptoms of gastroesophageal reflux and associated factors in the Colombian population[11].

The PPI most frequently prescribed in our population was esomeprazole, followed by lansoprazole and dexlansoprazole, molecules with proven effectiveness in managing GERD according to different published studies[12].

When the manometric variables were evaluated in patients with and without acid reflux, we did not find significant differences in EGJ-CI, contrary to what was reported by Gor et al.[13], who found an inverse correlation between EGJ-CI and gastroesophageal reflux determined by AET. No statistically significant differences were found in the mentioned manometric parameters when the analysis was performed for the non-acid reflux subgroup. This finding could be because all of the patients in that study did not receive antisecretory therapy, while our study included patients with and without antisecretory treatment.

When evaluating the manometric variables between erosive and non-erosive reflux, our results were similar to those by Hyoju Ham et al., who reported that EGJ-CI is significantly correlated with the morphology of the EGJ, establishing the presence of GERD when the morphology of the EGJ is altered. For example, a Type 3 EGJ was associated with a more significant number of reflux episodes, a finding also correlated with EGJ-CI alteration[14]. Furthermore, our study demonstrated that the EGJ-CI is significantly decreased in patients with erosive GERD compared to non-erosive GERD ($p = 0.04$), representing a greater impairment of the barrier mechanism in the EGJ. Finally, we documented a significant decrease in end-inspiratory LES pressure among patients with erosive GERD compared to patients with non-erosive GERD ($p < 0.01$). The above shows us that the EGJ-CI is a new manometric parameter altered in patients with erosive and non-erosive GERD, significantly correlated with the alteration of end-inspiratory LES pressure and Type 3 EGJ. These results suggest that alteration of EGJ-CI could predict erosive reflux in our population and allow us to understand how the impairment of the anti-reflux barrier in patients with erosive GERD is more significant than in those with non-erosive GERD.

Wang et al. established a normal cut-off point for EGJ-CI with a mean of 34.7 mm Hg and a range between 26.2 and 58.3 mm Hg[15]; these results are compatible with ours, given that in our population with erosive GERD, the EGJ-CI had a median of 15.1 with a range between 7 and 25 mm Hg, decreased compared to this cut-off point established for healthy patients. In patients with non-erosive GERD, a decrease in EGJ-IC was also documented concerning these cut-off points, suggesting a dysfunction of the EGJ barrier mechanism in these patients. A recent

Table 2. Comparison of manometric variables in patients with or without acid and non-acid reflux

Manometric variable	Acid reflux			Non-acid reflux		
	Positive, n = 59	Negative, n = 13	p-value	Positive, n = 34	Negative, n = 38	p-value
Mean LES pressure (mm Hg), median (IQR)	10,4 (3,6 -21,9)	13,1 (11,6 -23,8)	0,08	12,1 (8,5-23,8)	10,1 (3,6 -15)	0,11
End-inspiratory LES pressure (mm Hg), median (IQR)	9,6 (5,9-15,4)	9,4 (5,9-12,9)	0,75	8,4 (5,2 -13,3)	9,85 (6,2 -15,4)	0,53
Median IRP (IQR)	3,9 (2,0-6,7)	4,4 (1,4-6,2)	0,80	4,3 (1,4-6,2)	3,9 (2,1-7,3)	0,48
DCI mm Hg, median (IQR)	1551 (910 -2412)	1476 (774-1862)	0,53	1660 (1021-2134)	1389 (783-2320)	0,52
EGJ-CI, median (IQR)	21 (14-44)	15 (11-28)	0,24	20,5 (12,7-30,0)	20 (14-44)	0,80
EGJ type, n (%)						
- I	8 (13,50)	2 (15, 38)	0,82	6 (17,65)	4 (10,53)	0,04
- II	21 (35,59)	6 (46, 15)		17(50,00)	10 (26,32)	
- IIIa	16 (27,12)	2 (15,38)		4 (11,7)	14 (36,84)	
- IIIb	14 (23,73)	3 (23,08)		7 (20,59)	10 (26,32)	

DCI: distal contractile integral; IQR: interquartile range; IRP: integrated relaxation pressure; LES: lower esophageal sphincter. Prepared by the authors.

Table 3. Comparison of manometric variables between erosive reflux and non-erosive reflux

Manometric variable	Erosive reflux		
	Positive, n = 18	Negative, n = 54	p-value
Mean LES pressure (mm Hg), median (IQR)	9,9 (4,0-11,6)	11,5 (5,0 -23,8)	0,09
End-inspiratory LES pressure (mm Hg), median (IQR)	6,1 (2,8-7,5)	11,9 (6,6-17,4)	< 0,01
Median IRP (IQR)	3,75 (2,3-6,6)	4,3 (2,8-6,3)	0,94
DCI (mm Hg), median (IQR)	1549 (783-2007)	1546 (991-2241)	0,41
EGJ-CI, median (IQR)	15,1 (7-25)	23 (14-42,0)	0,04
EGJ type, n (%)			
- I	2,0 (11,1)	8,0 (14,8)	< 0,01
- II	1,0 (5,6)	26,0 (48,2)	
- IIIa	9,0 (50,0)	9,0 (16,7)	
- IIIb	6,0 (33,3)	11,0 (20,4)	

DCI: distal contractility integral; IQR: interquartile range; IRP: integrated relaxation pressure; LES: lower esophageal sphincter. Prepared by the authors.

study published by Rogers et al., who evaluated the EGJ in healthy patients using the two manometric parameters described (EGJ type and EGJ-CI), established normal cut-off points for the EGJ-CI, very similar to those provided by Wang et al.[16] and Jasper et al.[17].

Tolone et al. explained that 50% of patients with decreased EGJ-CI present with GERD, and 14% have functional heartburn; data suggest that decreased EGJ-CI is associated with a longer AET, greater number of reflux episodes and esophageal mucosal damage documented on endos-

copy[18]. These findings were duly noted in our population for patients with erosive and non-erosive GERD.

We can conclude that in the Colombian population, the EGJ-CI objectively evaluates the barrier mechanism of the EGJ since it is decreased in all patients with GERD. Furthermore, as shown in our study, it allowed a characterization of patients with erosive esophagitis, given that the EGJ-CI in this group was found to be significantly decreased, which was correlated with the decrease in end-inspiratory LES pressure and Type IIIa and IIIb EGJ.

CONCLUSION

In our population, decreased EGJ-CI was significantly correlated with erosive GERD, suggesting that a reduction in EGJ-CI values could predict this condition in patients with GERD. This result is appropriately related to the type of EGJ morphology, with Type III being the most frequent, and lower end-inspiratory LES pressure, allowing us to characterize this reflux phenotype better to guarantee an appropriate diagnostic and therapeutic approach.

REFERENCES

1. Vakil N, van Zanten SV, Kahrilas P, Dent J, Jones R, Bianchi LK, et al. The Montreal definition and classification of gastroesophageal reflux disease: A global evidence-based consensus. Am J Gastroenterol. 2006;101(8):1900-20; quiz 1943. https://doi.org/10.1111/j.1572-0241.2006.00630.x
2. Prakash Gyawali C, Kahrilas PJ, Savarino E, Zerbib F, Mion F, Smout AJPM, et al. Modern diagnosis of GERD: The Lyon Consensus. Gut. 2018;67(7):1351-1362. https://doi.org/10.1136/gutjnl-2017-314722
3. Prakash Gyawali C, Kahrilas PJ, Savarino E, Zerbib F, Mion F, Smout AJPM, et al. Modern diagnosis of GERD: The Lyon Consensus. Gut. 2018;67(7):1351-1362. https://doi.org/10.1136/gutjnl-2017-314722
4. Hani A, Bernal W, Leguízamo AM, Zuluaga C, Vargas R, Vergara H, et al. Cómo realizar e interpretar una manometría esofágica de alta resolución usando la clasificación de Chicago 3.0. Rev Col Gastroenterol. 2017;32(4):369-78. https://doi.org/10.22516/25007440.181
5. Kahrilas PJ, Mittal RK, Bor S, Kohn GP, Lenglinger J, Mittal SK, et al. Chicago Classification update (v4.0): Technical review of high-resolution manometry metrics for EGJ barrier function. Neurogastroenterol Motil. 2021;33(10):e14113. https://doi.org/10.1111/nmo.14113
6. Nicodème F, Pipa-Muniz M, Khanna K, Kahrilas PJ, Pandolfino JE. Quantifying esophagogastric junction contractility with a novel HRM topographic metric, the EGJ-Contractile Integral: Normative values and preliminary evaluation in PPI non-responders. Neurogastroenterol Motil. 2014;26(3):353-60. https://doi.org/10.1111/nmo.12267
7. Katzka DA, Pandolfino JE, Kahrilas PJ. Phenotypes of gastroesophageal reflux disease: Where Rome, Lyon, and Montreal meet. Clin Gastroenterol Hepatol. 2020;18(4):767-76. https://doi.org/10.1016/j.cgh.2019.07.015
8. Costa VA, Pinto Saavedra OM, Hani Amador AC, Leguízamo Naranjo AM, Ardila Hani AF. Actualización en la interpretación de la medición del pH e impedanciometría. Rev Col Gastroenterol. 2021;36(1):73-80. https://doi.org/10.22516/25007440.608
9. Carlson DA, Gyawali CP, Khan A, Yadlapati R, Chen J, Chokshi RV, et al. Classifying esophageal motility by FLIP panometry: A study of 722 subjects with manometry. Am J Gastroenterol. 2021;116(12):2357-2366. https://doi.org/10.14309/ajg.0000000000001532
10. Yadlapati R, Kahrilas PJ, Fox MR, Bredenoord AJ, Prakash Gyawali C, Roman S, et al. Esophageal motility disorders on high-resolution manometry: Chicago classification version 4.0 ©. Neurogastroenterol Motil. 2021;33(1):e14058. https://doi.org/10.1111/nmo.14058.
11. Páramo-Hernández DB, Albis R, Galiano MT, de Molano B, Rincón R, Pineda-Ovalle LF, et al. Prevalencia de síntomas del reflujo gastroesofágico y factores asociados: una encuesta poblacional en las principales ciudades de Colombia. Rev Col Gastroenterol. 2016;31(4):337-46. https://doi.org/10.22516/25007440.108
12. Huerta-Iga F, Bielsa-Fernández MV, Remes-Troche JM, Valdovinos-Díaz MA, Tamayo-de la Cuesta JL, en representación del Grupo para el estudio de la ERGE 2015. Diagnóstico y tratamiento de la enfermedad por reflujo gastroesofágico: recomendaciones de la Asociación Mexicana de Gastroenterología. Rev Gastroenterol Mex. 2016;81(4):208-22. https://doi.org/10.1016/j.rgmx.2016.04.003
13. Gor P, Li Y, Munigala S, Patel A, Bolkhir A, Gyawali CP. Interrogation of esophagogastric junction barrier function using the esophagogastric junction contractile integral: an observational cohort study: EGJ barrier function on HRM. Dis Esophagus. 2016;29(7):820-8. https://doi.org/10.1111/dote.12389
14. Ham H, Cho YK, Lee HH, Yoon SB, Lim CH, Kim JS, et al. Esophagogastric junction contractile integral and morphology: Two high-resolution manometry metrics of the anti-reflux barrier. J Gastroenterol Hepatol (Australia). 2017;32(8):1443-9. https://doi.org/10.1111/jgh.13720
15. Wang D, Patel A, Mello M, Shriver A, Gyawali CP. Esophagogastric junction contractile integral (EGJ-CI)

quantifies changes in EGJ barrier function with surgical intervention. Neurogastroenterology and Motility. 2016;28(5):639-46. https://doi.org/10.1111/nmo.12757
16. Rogers BD, Rengarajan A, Abrahao L, Bhatia S, Bor S, Carlson DA, et al. Esophagogastric junction morphology and contractile integral on high-resolution manometry in asymptomatic healthy volunteers: An international multicenter study. Neurogastroenterol Motil. 2021;33(6):e14009. https://doi.org/10.1111/nmo.14009
17. Jasper D, Freitas-Queiroz N, Hollenstein M, Misselwitz B, Layer P, Navarro-Rodriguez T, et al. Prolonged measurement improves the assessment of the barrier function of the esophago-gastric junction by high-resolution manometry. Neurogastroenterol Motil. 2017;29(2). https://doi.org/10.1111/nmo.12925
18. Tolone S, de Bortoli N, Marabotto E, de Cassan C, Bodini G, Roman S, et al. Esophagogastric junction contractility for clinical assessment in patients with GERD: A real added value? Neurogastroenterol Motil. 2015;27(10):1423-31. https://doi.org/10.1111/nmo.12638

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Original article

Percutaneous Endoscopic Gastrostomy. Is It Truly Harmless?

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Abstract

Percutaneous endoscopic gastrostomy (PEG) is performed quite frequently in our environment. In general, its complications are few and mostly minor; however, there is a 2.4% incidence of significant complications, particularly abnormal displacement of the internal bumper of the gastrostomy, known as *buried bumper syndrome* (BBS). Serious infections, tears, and fistulas can also occur. This work illustrates five cases of severe complications of PEG.

Keywords

Gastrostomy, complications, buried bumper, infection.

INTRODUCTION

Percutaneous endoscopic gastrostomy (PEG) is a method to guarantee nutrition for patients with dysphagia of different etiologies and risk of broncho-aspiration, among others. Since its introduction by Gauderer and Ponsky in 1980[(1)], it has become one of the most used methods for this purpose. In the United States, nearly 250,000 procedures are performed yearly[(2)]. Still, despite their safety and technical ease, complications can occur in 0.4% to 22.5%[(3)], which, depending on their severity, can be classified as major and minor (**Table 1** and **Video 1**).

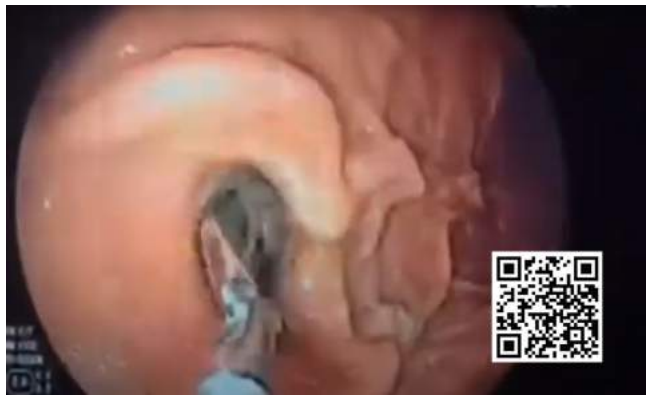
One of the most feared complications of gastrostomy is buried bumper syndrome (BBS), whose incidence is 1% (0.3%–2.4%)[(3)]. It is characterized by the following triad: inability to insert the tube, loss of permeability, and leakage through the tube's stoma[(4)], and occurs when the internal end of the gastrostomy migrates toward the stomach wall, even to the point of coming out of it. Therapy depends on migration related to the muscularis propria. In turn, BBS can cause other complications such as bleeding, perforation, peritonitis, and intra-abdominal or wall abscesses[(5)].

From the pathophysiological point of view, BBS occurs due to an increase in pressure between the internal and external fixation of the gastrostomy, resulting in ischemia and necrosis of the tissue, then inflammation and fibrosis, and finally, the displacement of the external fixation and thus the BBS[(5)]. The main risk factors depend on the

Table 1. Complications of percutaneous endoscopic gastrostomy[3]

Major complications	Minor complications
Necrotizing fasciitis	Skin infection
Buried bumper syndrome	Peristomal leakage
Colocutaneous fistula	Pneumoperitoneum
Gastrocolic fistula	Ileus
Gastric perforation	Bleeding
Massive broncho-aspiration	Tube site ulceration
	Blockage due to food sediment
	Tube deterioration
	Gastric outlet obstruction

Taken from: Itkin M, et al. Gastroenterology. 2011;141(2):742-765.



Video 1. Video of the main complications of endoscopic gastrostomy. Source: Unidad de Gastroenterología y Ecoendoscopia UGEC (2019, August 25th). Gastrostomía [video]. YouTube. https://n9.cl/fam1h

tube, the procedure, care with the device, and the patient (**Figure 1**).

From a diagnostic perspective, once the characteristic triad is suspected, an endoscopy of the upper GI tract and imaging should be performed to assess the relationship of the external fixation with the gastric wall. Then, the best available therapy, which can be medical, endoscopic, or surgical, will be given (**Table 2**)[1].

Below is a series of clinical cases illustrating serious complications after endoscopic gastrostomy[7,8]. We must be aware of such complications and evaluate the patient well before deciding whether the procedure is indicated, together with the patient and their family.

CASE 1

A 54-year-old female patient with a history of an extensive hemorrhagic stroke and severe compromise in the swallowing pattern without a good response to rehabilitation underwent a PEG. Ten days later, a call was received from the treatment group due to an obstruction to the nutrition passage of the gastrostomy. Due to suspicion of

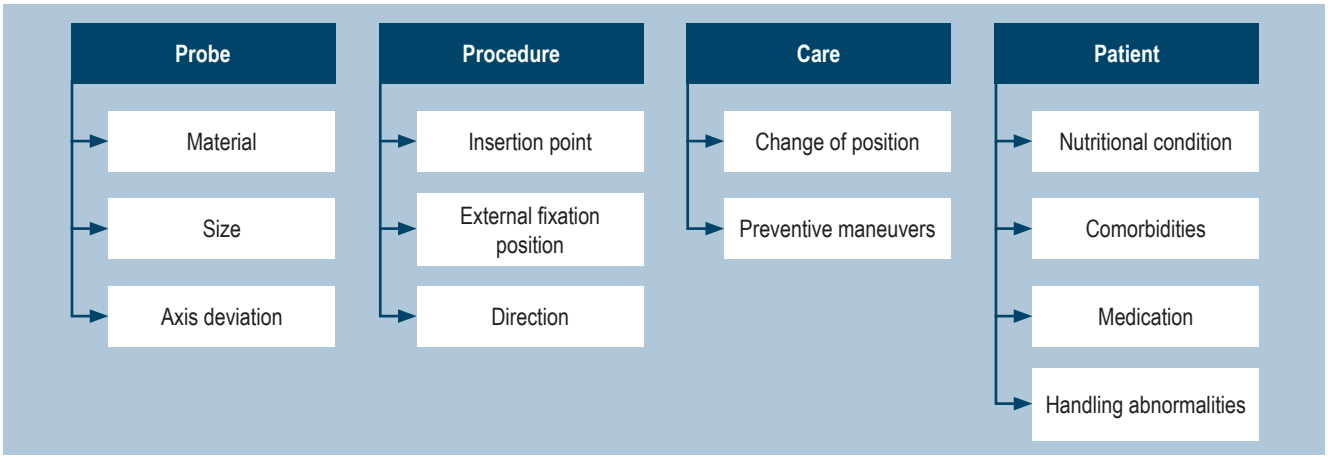


Figure 1. Risk factors for BBS[5]. Taken from: Schwartz HI et al. PEG feeding tube migration impaction in the abdominal wall. Gastrointest Endosc. 1989;35(2):134.

Table 2. BBS severity classification[6]

Grade	Clinical	Endoscopic	Radiological	Treatment
0	Movable	Normal	No	Prevention
1	Movable	Ulcer around the disc	No	Prevention
2	Fixed	>50% of the disk is visible	No	Endoscopy
3	Fixed	100% covered	Disc inside the stomach	Endoscopy, dissection
4	Fixed/Blocked	100% covered	Disc outside the stomach	Endoscopy, dissection
5	Subcutaneous disc	100% covered	No	Surgery/Extraction

Taken from: McClave SA, et al. Gastrointest Endosc Clin N Am. 2007;17(4):731-746.

BBS, we decided to perform an endoscopy, which showed the internal disc occluded by gastric tissue in more than 50% (**Figure 2**). An attempt was made to recover the foreign body with forceps unsuccessfully. So, a tube was cut before the external retention disc, and the guidewire was advanced through it. It was retrieved with a handle and attached to the gastrostomy tube, which was pulled using the push-pull technique. Once it came out through the abdominal wall, the tube was recovered, and the fistula was left patent with the new tube in a suitable position.

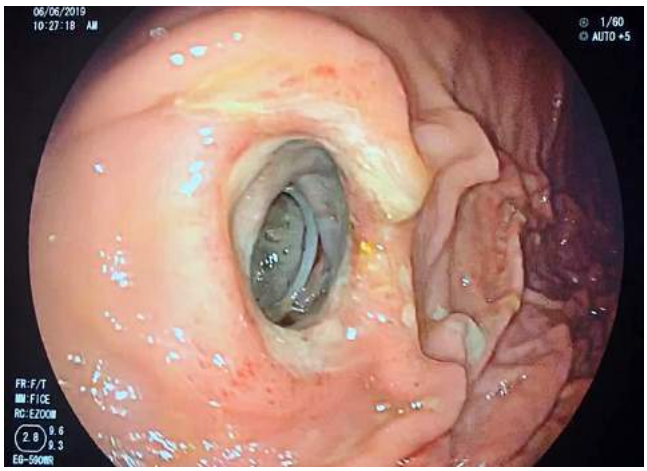


Figure 2. Type 2 buried bumper syndrome. The internal disc shows an occlusion of less than 50%. Authors' archive.

CASE 2

A 44-year-old female patient with a history of severe head trauma and severe swallowing disorder required a PEG. She was received through interconsultation for not having adequate mobility of the tube and a peristomal leak. We decided to take her to an endoscopy, showing an absence of the internal disc in the gastric cavity. Finally, she was diagnosed with Type 3 BBS (**Figure 3**). We performed a precut dissection in which the affected internal disc was found in the gastric wall. Once freed, it was successfully extracted.

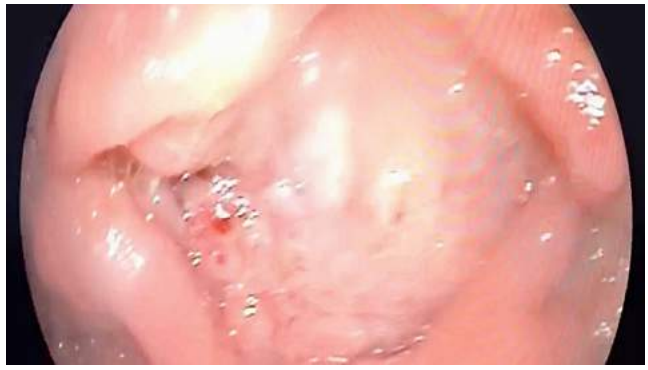


Figure 3. Type 3 buried bumper syndrome: gastrostomy disc completely covered by gastric mucosa. Authors' archive.

CASE 3

A 65-year-old male patient with sequelae of post-cardiac arrest hypoxic-ischemic encephalopathy required PEG due to a severe swallowing disorder. The attending group requested an evaluation (15 days after the gastrostomy) due to liquid stools with the same characteristics as the nutrition each time it was administered through a tube. He underwent an endoscopy, and the internal disc was not found. Given the clinical picture, displacement of the internal disc outside the stomach (gastrocolic fistula) was suspected (**Figure 4**). A total colonoscopy was performed, finding the internal retention disc of the gastrostomy at the transverse colon level. We decided to remove the tube and

leave him under observation for seven days, after which total closure of the fistula was observed on endoscopic follow-up.

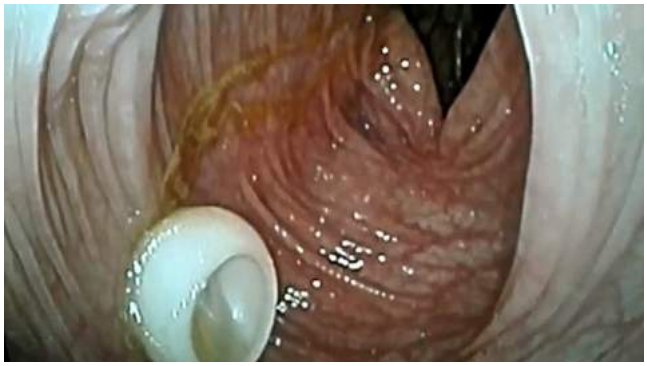


Figure 4. Gastrocolic fistula: internal disc outside the gastric cavity at the transverse colon level. Authors' archive.

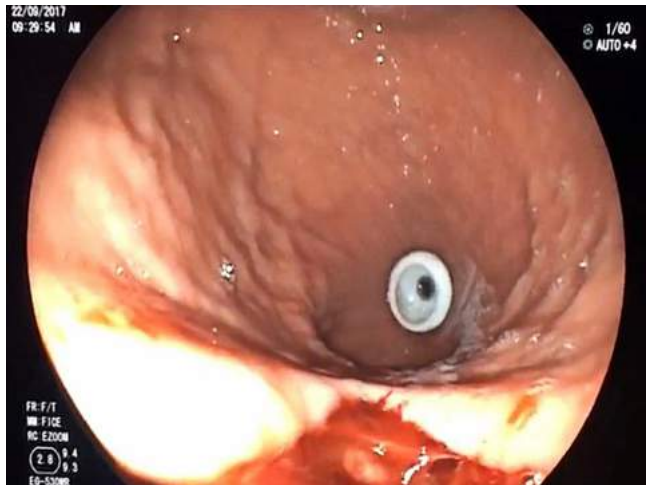


Figure 5. Tear of the gastric mucosa due to the passage of the internal disc. Authors' archive.

CASE 4

A 74-year-old male patient with sequelae of an ischemic stroke required endoscopic gastrostomy. Once the tube was pulled toward the wall and the external retention disc was fixed, an endoscopy was performed to assess the position, finding a severe tear of the gastric mucosa toward the greater curvature (**Figure 5**); no overt perforation was observed endoscopically. The patient did not have an acute abdomen on physical examination, so the gastrostomy was fixed and left under observation. A new endoscopy was performed seven days later, noting that the tear had healed.

CASE 5

A 50-year-old male patient with sequelae of an ischemic stroke underwent PEG for a swallowing disorder. Seventy-two hours after the procedure, edema and erythema were found in the peristomal area, rapidly progressing to the rest of the abdominal wall, forming fasciitis (**Figure 6**). A soft tissue ultrasound was performed without finding wall collections but fascia inflammation. With the diagnosis of surgical site infection, the tube was removed, and parenteral antibiotic therapy was started. The nasogastric nutrition tube was advanced to ensure enteral nutrition. Once the infection resolved, a new gastrostomy was performed without complications.

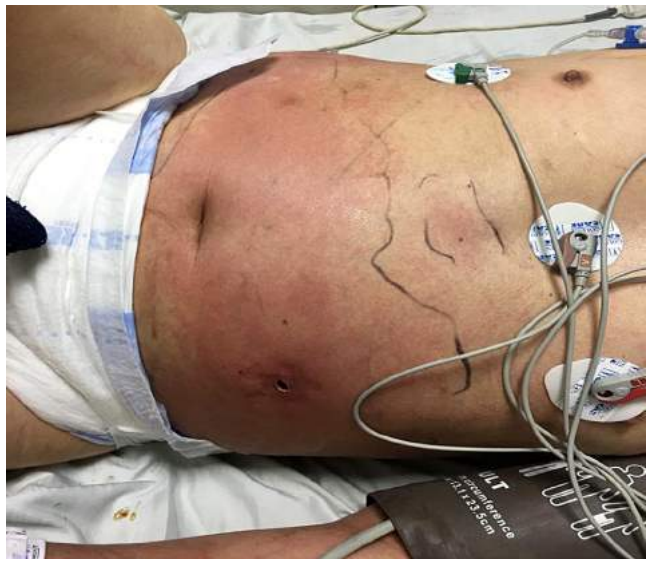


Figure 6. Infection of the abdominal wall. Authors' archive.

CONCLUSIONS

Endoscopic gastrostomy is a therapeutic procedure performed regularly in clinical practice, given the high incidence of diseases that result in swallowing disorders or oral tolerance. However, the frequent use of this procedure does not exempt it from mild or complex complications, such as those shown in this work.

Infection, bleeding, and diverse types of BBS are the most common complications. These depend on multiple factors, which must be controlled to prevent their occurrence. Once suspected, the physical examination is vital, and the tube seeks to assess the triad of BBS: absence of mobility, parastomal leak, and obstruction to fluid passage. The assessment must be complemented with an endoscopy and, if necessary, a radiological study to classify the complication and plan the best possible treatment, ranging from observation to endoscopic or surgical management.

REFERENCES

1. Gauderer MW, Ponsky JL, Izant RJ. Gastrostomy without laparotomy: a percutaneous endoscopic technique. J Pediatr Surg. 1980;15(6):872-875. https://doi.org/10.1016/S0022-3468(80)80296-X
2. Cyrany J, Rejchrt S, Kopacova M, Bures J. Buried bumper syndrome: complication of percutaneous endoscopic gastrostomy. World J Gastroenterol. 2016;22(2):618-627. https://doi.org/10.3748/wjg.v22.i2.618
3. Itkin M, DeLegge MH, Fang JC, McClave SA, Kundu S, d'Othee BJ, et al. Multidisciplinary practical guidelines for gastrointestinal access for enteral nutrition and decompression from the Society of Interventional Radiology and American Gastroenterological Association (AGA) Institute, with endorsement by Canadian Interventional Radiological Association (CIRA) and Cardiovascular and Interventional Radiological Society of Europe (CIRSE). Gastroenterology. 2011;141(2):742-765. https://doi.org/10.1053/j.gastro.2011.06.001
4. El AZ, Arvanitakis M, Ballarin A, Devière J, Le Moine O, Van Gossum A. Buried bumper syndrome: low incidence and safe endoscopic management. Acta Gastroenterol Belg. 2011;74(2):312-316.
5. Schwartz HI, Goldberg RI, Barkin JS, Phillips RS, Land A, Hecht M. PEG feeding tube migration impaction in the abdominal wall. Gastrointest Endosc. 1989;35(2):134. https://doi.org/10.1016/S0016-5107(89)72735-8
6. McClave SA, Jafri NS. Spectrum of morbidity related to bolster placement at time of percutaneous endoscopic gastrostomy: buried bumper syndrome to eakage and peritonitis. Gastrointest Endosc Clin N Am. 2007;17(4):731-746. https://doi.org/10.1016/j.giec.2007.07.011
7. Cyrany J, Repak R, Douda T, Rejchrt S, Kopacova M, Bures J. Buried bumper syndrome - management based of accurate staging. United European Gastroenterol J. 2014;2 Suppl 1:A170.
8. Boeykens K, Duysburgh I. Prevention and management of major complications in percutaneous endoscopic gastrostomy. BMJ Open Gastroenterol. 2021;8(1):e000628. https://doi.org/10.1136/bmjgast-2021-000628

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Original article

Gastrointestinal Foreign Bodies: 14 Years of Experience in a University Clinic

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Abstract

Introduction: Ingesting foreign bodies is a common medical problem, especially in the emergency department. Some small studies describe experiences in this regard. **Materials and methods:** A descriptive retrospective study included patients with suspected ingestion of foreign bodies admitted to the gastroenterology and GI endoscopy service of the Clínica Universitaria Colombia between January 2007 and August 2020. **Results:** The age of occurrence of the event was 18 to 95 years, and the average age was 45 years. The foreign bodies ingested and found were variable. The most frequent was fish bones, representing 64.11% of the cases, followed by chicken bones and dietary impaction. Thirty-eight percent of patients required foreign body removal; the most frequently used tool was the foreign body forceps. The primary location was the esophagus in 12.53% of cases, followed by the cricopharynx in 11.18% and the hypopharynx in 10%. **Conclusions:** The Clínica Universitaria Colombia is a referral site for many gastroenterology emergencies due to its high technological level and extensive human resources. This paper probably describes the largest number of patients with this reason for consultation, which is why this retrospective descriptive study was designed. It shows the demographic characteristics, foreign body types, radiological and endoscopic findings, and associated complications, which help to provide a more accurate knowledge of this pathology.

Keywords

Foreign bodies, endoscopy, radiology, complications.

INTRODUCTION

The ingestion of foreign bodies is a common medical problem, especially in the emergency department, which has greater relevance in three populations: pediatric patients, patients with some cognitive disability, and patients with psychiatric pathologies and a history of psychoactive substance use given the higher risk of complications and difficulties in extracting them[1]. Although these elements generally manage to pass spontaneously through the GI tract, in 20% of cases, endoscopic intervention will be required for their removal, and at least 1% of cases will require some surgical intervention[2,3].

International guidelines such as those proposed by the European Society of Gastrointestinal Endoscopy (ESGE) recommend emergent upper gastrointestinal endoscopy (EGD) (in the first 2 to 6 hours after ingestion) in three main scenarios: cases of complete esophageal obstruction, sharp-pointed foreign bodies given the high risk of perforation, and the ingestion of cells or batteries due to the risk of liquefactive necrosis and perforation, especially in sites of stricture (upper esophageal sphincter, aortic arch, lower esophageal

sphincter, pylorus, ileocecal valve, and anus). If these parameters are not met, it has been said that the endoscopic study can be performed urgently in the first 24 hours[4].

In Colombia, ingesting foreign bodies is a frequent reason for consultation; however, there is no data to establish the incidence of this problem in the country, nor to establish the type of foreign body ingested and its most common complications. This work aims to conduct a retrospective analysis of the experience of Clínica Universitaria Colombia gastroenterology and digestive endoscopy group in ingesting foreign bodies.

MATERIALS AND METHODS

This descriptive, retrospective study included patients with suspected ingestion of foreign bodies admitted to the gastroenterology and digestive endoscopy department of the Clínica Universitaria Colombia between January 2007 and August 2020. The cases were identified by reviewing the medical record, the reason for consultation, the reported symptoms, the reason for requesting EGD, and the report of endoscopic procedures. After excluding those patients with incomplete data and those under 18 years of age, 2,307 patients were included in the analysis.

The following demographic, clinical, and endoscopic data were collected: age, sex, time of onset of symptoms before consultation, primary symptoms, findings on neck X-ray, type of foreign body, location of the foreign body, extraction method, and associated complications.

RESULTS

Population characteristics

The age of occurrence was 18 to 95 years; the average age was 45 years, and the age range in which the event occurred the most was between 27 to 59 years. The female sex was predominant (62%).

Most patients consulted early within the first 24 hours of ingesting the foreign body (n = 1,786, 77.5%). The most common symptoms were feelings of discomfort (53.32%), foreign body sensation (17.21%), and dysphagia (13.4%). To a lesser extent, patients reported pain (12.8%), hypersalivation (2.56%), and dyspnea (0.5%).

Endoscopic features

The foreign bodies ingested and found were variable; the most frequent were fishbones, representing 64.11% of the cases, followed by the ingestion of chicken bones and food impaction with 17.43% and 9.19%, respectively. **Table 1** summarizes reported ingested foreign bodies. **Figures 1** to **4** correspond to some examples of ingested foreign bodies found during the endoscopic study.

Table 1. Reported ingested foreign bodies

Strange body	Number	Percentage
Fishbone	1479	64.11%
Chicken bone	402	17.43%
Food impaction	212	9.19%
Incomplete MR data	47	2.04%
Dental prosthesis	36	1.56%
Orthodontic wire	24	1.04%
Glass	22	0.95%
Plastic element (straw, piece of package)	19	0.82%
Fruit seed	16	0.69%
Tablets	15	0.65%
Toothpick	15	0.65%
Worm	7	0.30%
Pin	5	0.22%
Coin	3	0.13%
Eggshell	3	0.13%
Bezoar - hair	1	0.04%
Battery	1	0.04%
Total	2307	100%

MR: medical record.

Imaging studies were performed in 66% of the patients before endoscopy and neck X-ray, obtaining normal results in 55.5% of the patients. It was possible to detect the foreign body in only 10.6% of the cases, and, as an additional finding, there was soft tissue edema in 48% of the cases. **Figure 5** records the radiological findings.

Of note is that in more than half of the cases, the foreign body was not identified for extraction (62.3%), only 38% of the patients required foreign body extraction, and the most frequently used tool was the foreign body clamp in 34.89% of the cases. The primary location was the esophagus in 12.53% of cases, followed by the cricopharynx and hypopharynx in 11.18% and 10%, respectively. Only a small percentage of patients had to undergo surgery due to suspected complications associated with the ingestion of the foreign body (n = 20, 0–87%). **Figure 6** shows the location distribution of ingested foreign bodies.

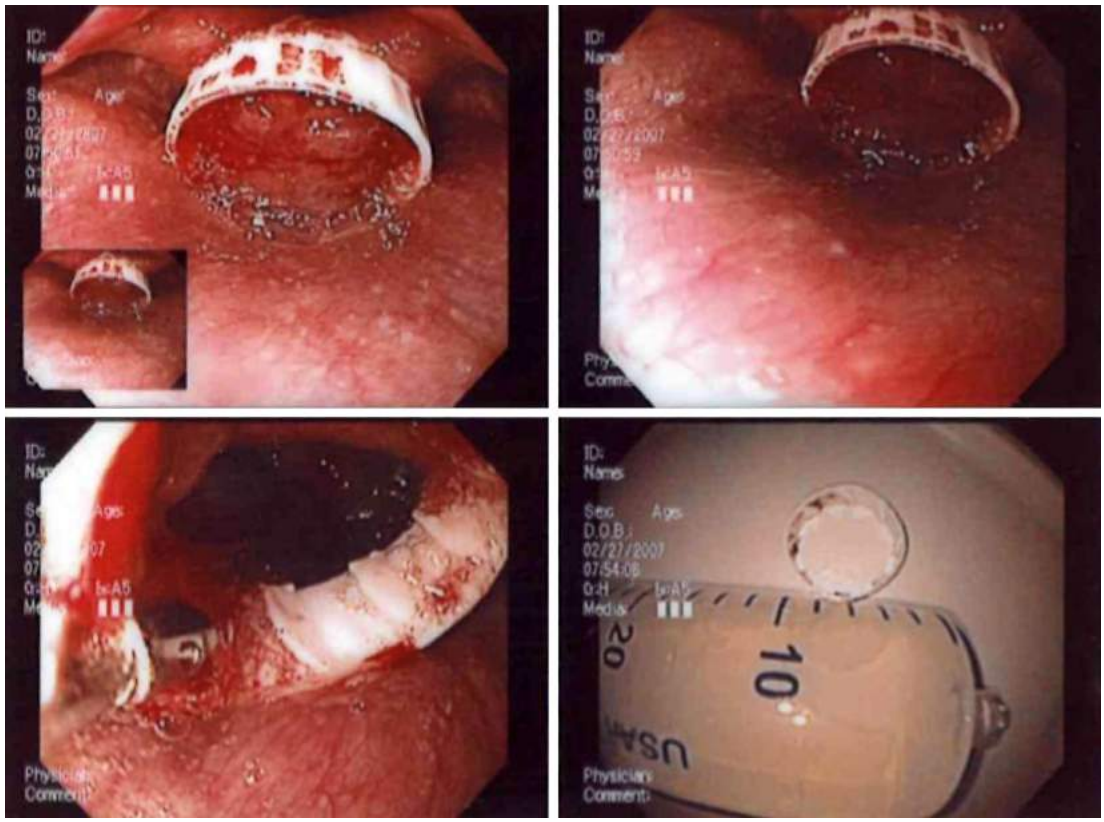

Figure 1. Plastic ring located in the hypopharynx; 2007. Taken from: Personal atlas of Dr. Diego Aponte.

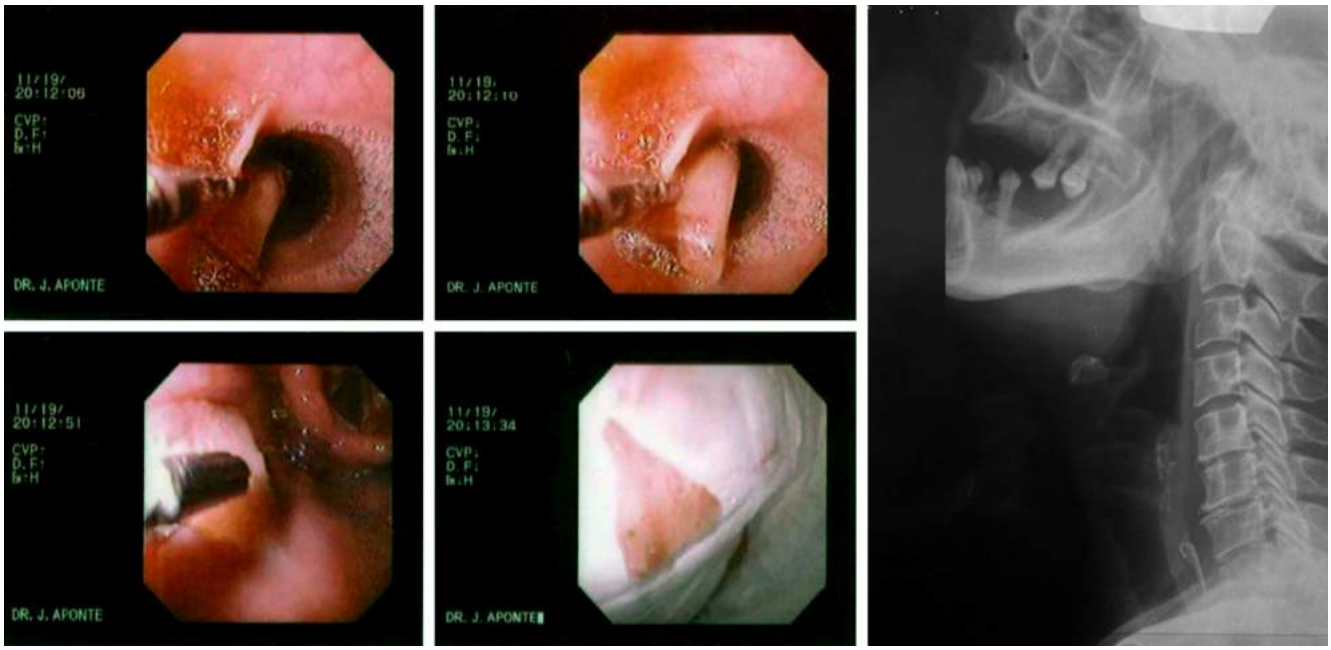

Figure 2. Chicken bone in the esophagus; 2008. Taken from: Personal atlas of Dr. Diego Aponte.

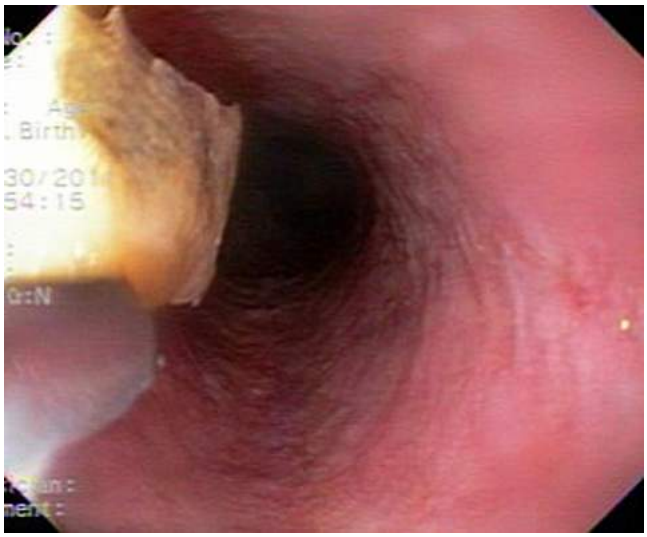

Figure 3. Fishbone in the esophagus; 2014. Taken from: Personal atlas of Dr. Diego Aponte.

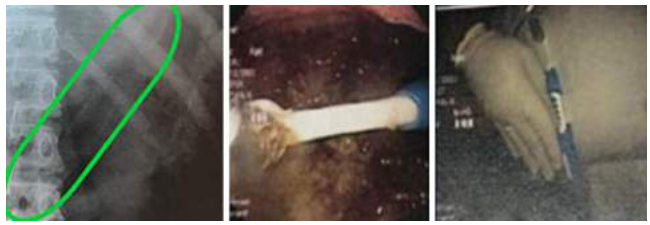

Figure 4. Toothbrush in the stomach; 2011. Taken from: Personal atlas of Dr. Diego Aponte.

In the endoscopic studies, the most frequent findings were lacerations at the pharynx level in 35%, followed by a typical endoscopic study in 31% of cases, and lacerations in the esophagus in 10.23% of patients. These findings are shown in **Table 2**.

We know that the ingested objects with the highest risk of perforation are those with sharp points, mainly fishbones and chicken bones, the most commonly ingested in the population studied. Of the 1,479 patients who ingested fishbones, 2% had findings suggestive of perforation, while of the 402 patients who ingested chicken bones, 3% showed findings suggestive of perforation (**Table 3**).

The predominant symptoms associated with foreign bodies identified in the endoscopic study were the sensation of discomfort in 28.9% and dysphagia in 25%, which occurred in the case of ingestion of fishbones in 64%, chicken bones in 16%, and food impaction in 10.9%.

DISCUSSION

The ingestion of foreign bodies continues to be a frequent reason for consultation and, in some circumstances, is still considered an emergency in gastroenterology. EGD is the method of choice as it is diagnostic and therapeutic[3,5]. It has been described that the vast majority of ingested foreign bodies, approximately 80%, manage to reach the stomach and, once there, cross the digestive tract smoothly[1,2]. However, we see how, in our series, it was only possible to

Table 2. Endoscopic findings

Endoscopic findings	Number	Percentage
Laceration in the pharynx	809	35.07%
Normal	717	31.08%
Laceration in the esophagus	236	10.23%
Hematoma in the pharynx	215	9.32%
Laceration, tear, or edema in the tonsil	81	3.51%
Hematoma in the esophagus	46	1.99%
Not classified	44	1.91%
Laceration, tear in the vallecula	39	1.69%
Ulcer in the esophagus	37	1.60%
Suspected perforation in the esophagus	29	1.26%
Suspected perforation in the pharynx	23	1.00%
Ulcer in the pharynx	23	1.00%
Perforation in the palate	4	0.17%
Suspected perforation in the stomach	2	0.09%
Suspected perforation in the duodenum	2	0.09%

Table 3. Description of complications associated with ingestion of fishbones and chicken bones

Findings	Fishbone		Chicken bone	
	Number	Percentage	Number	Percentage
None	1403	94.8%	366	91%
Normal	44	2.9%	17	4.22%
Perforation	29	2%	12	3%
Wall edema	3	0.20%	7	1.74%

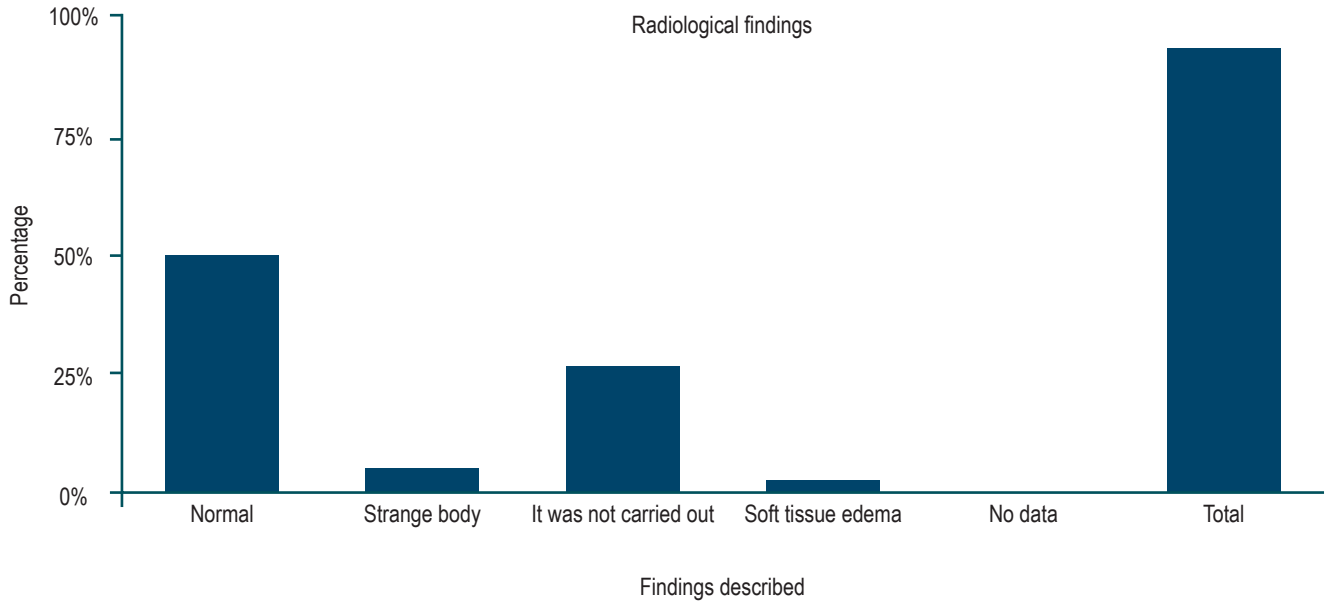

Figure 5. Radiological findings described.

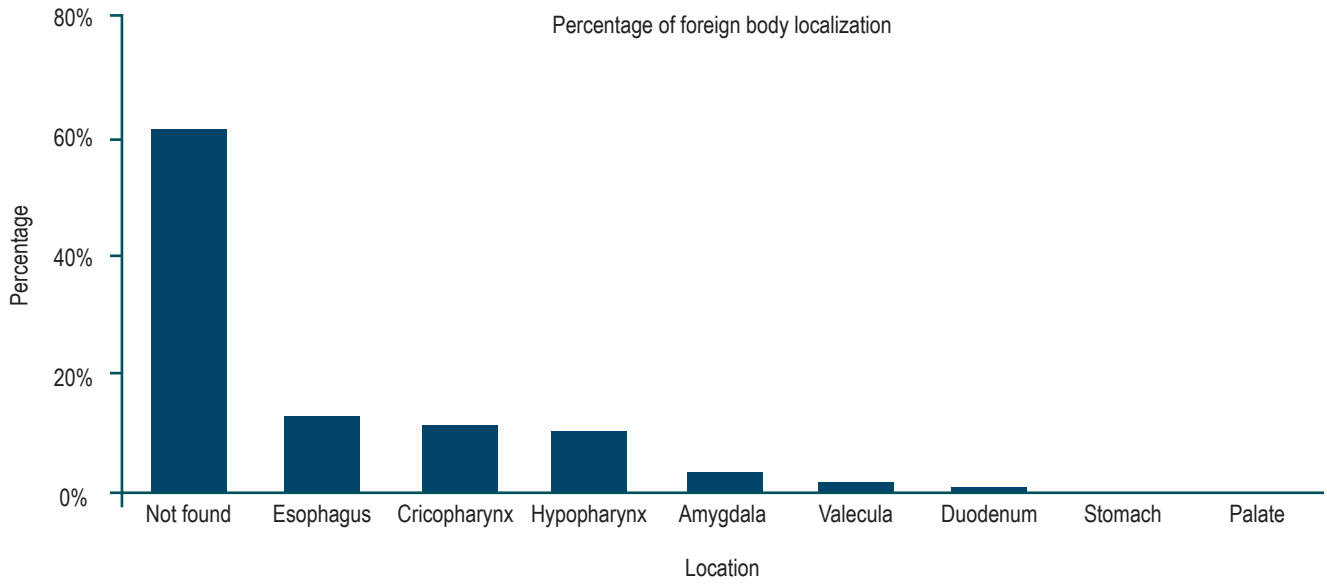

Figure 6. Location of foreign bodies.

find the ingested foreign body in 62.3% of the cases, possibly due to the early performance of endoscopic studies in our department.

Complications from foreign body ingestion are usually mild and include erosions, superficial lacerations, edema, and hematomas. However, serious complications such as perforation, mediastinitis, cardiac tamponade, and the development of fistulas may occur[6]. Among the risk factors for these complications, the presence of foreign bodies visible on cervical X-rays, impaction in the cricopharyngeus, and evolution of the impaction greater than 24 hours have been described[6,7]. The risk and severity of these complications go hand in hand with the ingested object's characteristics and impaction site[5,6]. Among the most frequent sites of foreign body impaction are the esophagus, in places of anatomical narrowness (at the level of the cricopharyn-

geal muscle, aortic arch, and gastroesophageal junction)[1], the stomach, the pharynx, and the duodenum[5,7]. Although imaging studies, such as cervical X-rays, are often used as part of the initial evaluation of these patients, it is known that they have a limited sensitivity in the scenario found, between 25% and 55%[8].

In this series, fishbones, which are recognized for the difficult visualization both in imaging studies and in endoscopy[7,8], were the most commonly ingested element and represented 64% of the cases, followed by chicken bones and food impaction, findings similar to those described in other series and reviews[3,9,10]. Still, radiological identification was achieved in only 10% of the cases, which speaks of the limited use of this diagnostic tool in this scenario, as described in other reports, and is of greater importance if there is suspicion of perforation[11,12].

Regarding location, these foreign bodies were found most frequently at the esophagus level, followed by the cricopharynx and hypopharynx, results consistent with previous studies[13–15]. The clinical manifestations associated with ingesting foreign bodies are related to the site of impaction and the duration of the condition[2]. In this series, it is clear that the most common symptoms were foreign body sensation and dysphagia concerning foreign body impaction in the hypopharynx and esophagus.

EGD continues to be the diagnostic and therapeutic tool of choice in these cases[2], which additionally has multiple tools with which the endoscopist must be familiar and achieves success rates of up to 95% for managing these patients[14,15]. In this series, in the patients with a foreign body, endoscopic removal was achieved, the impaction was resolved favorably in all cases, and foreign body forceps was the most used tool. Only a small percentage of patients required surgical management due to suspicion of perforation or other serious complications (0.84%), possibly related to the patients' early intervention, which could justify emergent EGD in this scenario.

CONCLUSIONS

The ingestion of foreign bodies continues to be a frequent reason for consultation and is considered one of the emergencies in gastroenterology. While simple X-ray studies are recommended to locate the ingested foreign body, this diagnostic aid has limited use in this scenario. EGD remains the procedure of choice for visualization and removal and is safe and highly effective.

This work is probably the most extensive series published worldwide, with findings very similar to those published in other series regarding the type of foreign body ingested, location, and associated complications.

REFERENCES

1. Bekkerman M, Sachdev AH, Andrade J, Twersky Y, Iqbal S. Endoscopic Management of Foreign Bodies in the Gastrointestinal Tract: A Review of the Literature. Gastroenterol Res Pract. 2016;2016:8520767. https://doi.org/10.1155/2016/8520767
2. Sugawa C, Ono H, Taleb M, Lucas CE. Endoscopic management of foreign bodies in the upper gastrointestinal tract: A review. World J Gastrointest Endosc. 2014;6(10):475-81. https://doi.org/10.4253/wjge.v6.i10.475
3. Lee CY, Kao BZ, Wu CS, Chen MY, Chien HY, Wu LW, et al. Retrospective analysis of endoscopic management of foreign bodies in the upper gastrointestinal tract of adults. J Chin Med Assoc. 2019;82(2):105-109. https://doi.org/10.1097/JCMA.0000000000000010
4. Birk M, Bauerfeind P, Deprez PH, Häfner M, Hartmann D, Hassan C, et al. Removal of foreign bodies in the upper gastrointestinal tract in adults: European Society of Gastrointestinal Endoscopy (ESGE) Clinical Guideline. Endoscopy. 2016;48(5):489-96. https://doi.org/10.1055/s-0042-100456
5. Jaan A, Mulita F. Gastrointestinal Foreign Body. [Actualizado el 28 de mayo de 2022]. En: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022. Disponible en: https://www.ncbi.nlm.nih.gov/books/NBK562203/
6. von Rahden BH, Feith M, Dittler HJ, Stein HJ. Cervical esophageal perforation with severe mediastinitis due to an impacted dental prosthesis. Dis Esophagus. 2002;15(4):340-4. https://doi.org/10.1046/j.1442-2050.2002.00290.x
7. Okan İ, Akbaş A, Küpeli M, Yeniova AÖ, Esen M, Özsoy Z, et al. Management of foreign body ingestion and food impaction in adults: A cross-sectional study. Ulus Travma Acil Cerrahi Derg. 2019;25(2):159-66. https://doi.org/10.5505/tjtes.2018.67240
8. González M, Gómez M, Otero W. Cuerpos extraños en esófago. Rev Col Gastroenterol. 2006;21(3):150-61.
9. Geng C, Li X, Luo R, Cai L, Lei X, Wang C. Endoscopic management of foreign bodies in the upper gastrointestinal tract: a retrospective study of 1294 cases. Scand J Gastroenterol. 2017;52(11):1286-291. https://doi.org/10.1080/00365521.2017.1350284
10. Magalhães-Costa P, Carvalho L, Rodrigues JP, Túlio MA, Marques S, Carmo J, et al. Endoscopic Management of Foreign Bodies in the Upper Gastrointestinal Tract: An Evidence-Based Review Article. GE Port J Gastroenterol.

2015;23(3):142-52.
https://doi.org/10.1016/j.jpge.2015.09.002
11. Guelfguat M, Kaplinskiy V, Reddy SH, DiPoce J. Clinical guidelines for imaging and reporting ingested foreign bodies. AJR Am J Roentgenol. 2014;203(1):37-53. Erratum in: AJR Am J Roentgenol. 2014;203(3):694. DiPoce, C Jason [corrected to DiPoce, Jason]. https://doi.org/10.2214/AJR.13.12185
12. Pinto A, Muzj C, Gagliardi N, Pinto F, Setola FR, Scaglione M, et al. Role of imaging in the assessment of impacted foreign bodies in the hypopharynx and cervical esophagus. Semin Ultrasound CT MR. 2012;33(5):463-70. https://doi.org/10.1053/j.sult.2012.06.009
13. Yao CC, Wu IT, Lu LS, Lin SC, Liang CM, Kuo YH, et al. Endoscopic Management of Foreign Bodies in the Upper Gastrointestinal Tract of Adults. Biomed Res Int. 2015;2015:658602. https://doi.org/10.1155/2015/658602
14. Li ZS, Sun ZX, Zou DW, Xu GM, Wu RP, Liao Z. Endoscopic management of foreign bodies in the upper-GI tract: experience with 1088 cases in China. Gastrointest Endosc. 2006;64(4):485-92. https://doi.org/10.1016/j.gie.2006.01.059
15. Mosca S, Manes G, Martino R, Amitrano L, Bottino V, Bove A, et al. Endoscopic management of foreign bodies in the upper gastrointestinal tract: report on a series of 414 adult patients. Endoscopy. 2001;33(8):692-6. https://doi.org/10.1055/s-2001-16212

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Review article

Hepatitis B and Celiac Disease: A Cause for Concern?

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Abstract

Some theories suggest that the development of the immune response to clear hepatitis B triggers the intestinal tissue damage seen in celiac disease in genetically predisposed individuals. Although the role of hepatitis B virus infection in the development of autoimmune diseases has been widely discussed in the literature, it remains a controversial topic. Our objective is to review whether there is an association between hepatitis B and celiac disease and the particularities of vaccination against hepatitis B in celiac patients.

Keywords

Hepatitis B, celiac disease, interferon alfa, vaccine.

INTRODUCTION

Celiac disease (CD) is a chronic immune-mediated disorder induced by gluten ingestion in genetically predisposed individuals[1]. Patients may present with classic clinical manifestations (diarrhea, anemia, weight loss) and involvement of other organic systems, such as the neurological, endocrinological, nephrological, and hepatic systems[2,3]. The diagnostic approach for CD in adults incorporates serological and histological data. Serologic testing for CD should consist of measurement of tissue transglutaminase (tTG) IgA antibodies while following a gluten-containing diet and simultaneous measurement of total IgA since the prevalence of IgA deficiency in patients with CD is 10 to 15 times higher than in healthy subjects[4,5]. A positive serological test supports the diagnosis, but no test is 100% specific for CD, and diagnostic accuracy varies considerably between laboratories[6]. The diagnosis of CD is definitively confirmed by lymphocytic infiltrate and villous atrophy in the small intestine biopsy according to the Marsh classification (**Figure 1**)[7].

Active screening for CD is recommended in patients with signs or symptoms suggestive of CD, including diarrhea, weight loss, abdominal pain, bloating, or laboratory abnormalities, such as unexplained elevated serum aminotransferase levels[4]. It is also recommended in some liver diseases, especially in those with autoimmune disorders, steatosis in the absence of metabolic syndrome, idiopathic

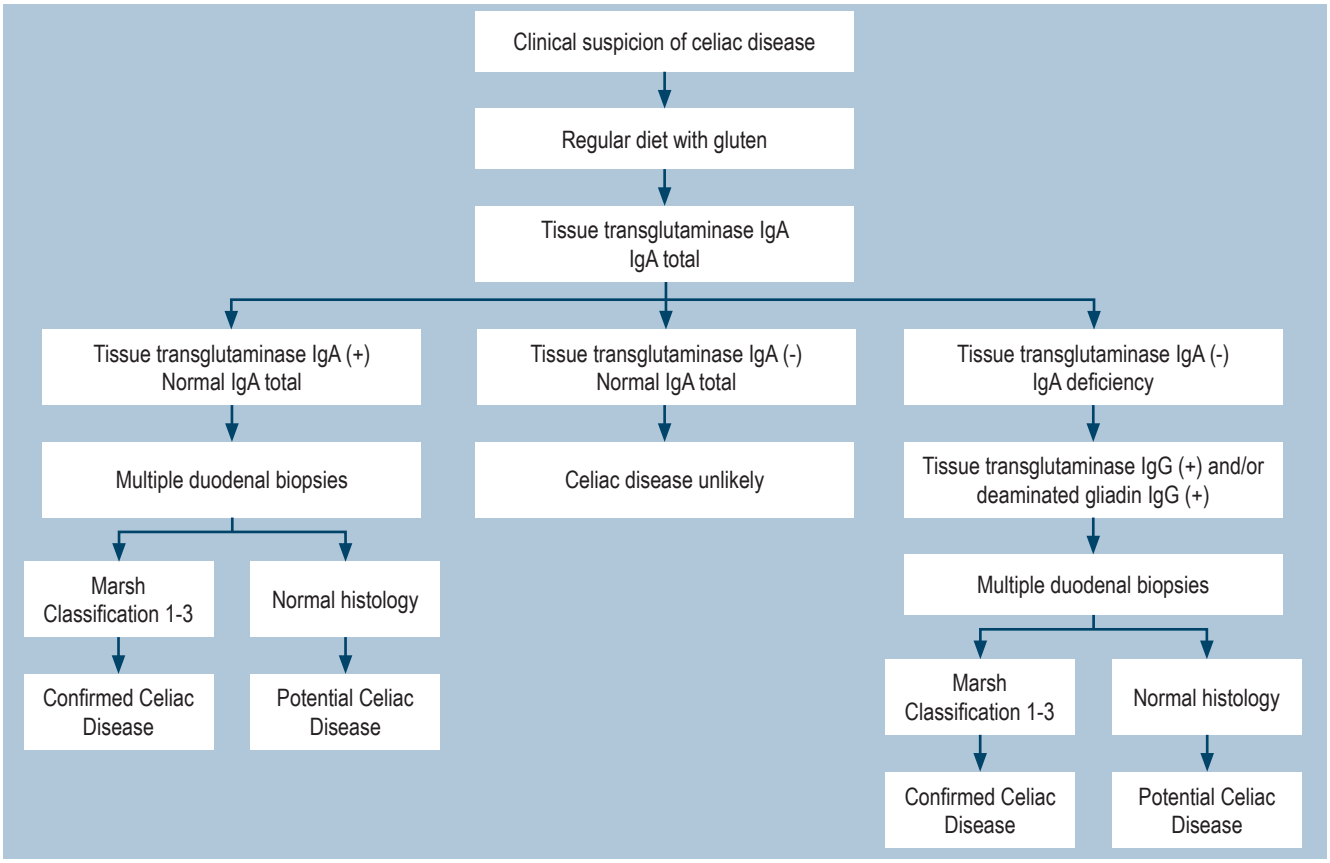

Figure 1. Diagnostic algorithm for celiac disease.

non-cirrhotic portal hypertension, cryptogenic cirrhosis, and in the context of liver transplant[8,9]. Apart from these scenarios, due to the high global prevalence of hepatitis B[10], this study aims to review articles in the literature that deal with a potential association between hepatitis B and CD and determine the particularities of the vaccination against hepatitis B in celiac patients.

MATERIALS AND METHODS

The PubMed database was searched in October 2022 to identify articles for this review using two search strategies. In the first strategy (Search A), the descriptor "CD + hepatitis B" was used, and in the second (Search B), "CD + HBV"; only English terms were employed. Additionally, manual searches were carried out in the articles' references. We included articles on CD and hepatitis B with a clearly described methodology, published in English-language journals without date restrictions, and selected by affinity with the objective. A full-text version of selected articles was obtained to confirm eligibility.

HEPATITIS B AND CD

Some authors have investigated the prevalence of CD in patients with hepatitis B; these findings are summarized in **Table 1**[11–14]. The prevalence of CD varied between 3.3% and 17.2%[6–8]. Leonardi et al.[11] demonstrated a high prevalence of CD in patients with hepatitis B. Although limited by the small size of the patients studied, this study is interesting because it may represent what has been observed in Italy[15]. The prevalence of hepatitis B virus (HBV) in Italy is higher than in the rest of Europe[16], and a high prevalence of CD is also estimated[17]. Concerning the study by Nau et al., southwest Brazil is also a region with a high prevalence of hepatitis B, where the majority of inhabitants are descendants of Portuguese, Italian, and German immigrants[18].

Despite the limited sample size of their hepatitis B cohorts, which requires conservative interpretation, the studies still provide intriguing data. Soto Iglesias et al.[19] presented two patients who developed CD after resolving an acute HBV infection. Reactive serological tests and the presence of typical histopathological findings confirmed

the diagnosis of CD. The same authors suggested that developing the immune response for clearance of HBV triggers the intestinal tissue damage observed in CD in genetically predisposed individuals. One hypothesis in the field of liver disorders is that a deregulated immune process would induce liver damage due to autoantibodies. Another hypothesis suggests that liver damage results from increased intestinal permeability, resulting in toxins or autoantigens from the liver through the portal vein[12]. Although the role of HBV infection in the development of autoimmune diseases has been widely discussed in the literature, it remains a controversial topic.

Bardela et al. found the opposite: The prevalence of HBV among 158 individuals with CD was 4.5%[20]. Other studies that evaluated the prevalence of HBV in celiac patients are summarized in **Table 1**[21–23]. After all these years, there is no clinical evidence of an association between CD and hepatitis infection, and the appearance of these two diseases in a patient may be a chance finding. Still, despite the findings described in this review, it is not possible to make a specific recommendation for CD screening in people with hepatitis B or vice versa[24].

INTERFERON α

Interferon α and its pegylated form have been used for more than thirty years to treat chronic hepatitis B with the advantages of a finite duration of treatment and a loss of hepatitis B surface antigen (HBsAg) with antibody seroconversion against the sustained hepatitis B virus surface antigen (anti-HBsAg); however, efficacy is limited since seroconversion is achieved in a small proportion of treated patients, and side effects are frequent[24]. Leonardi et al.[11] evaluated 15 of 60 patients who had used interferon α therapy for 12 months at a dose of 5 million units (5 MU). As mentioned above, it demonstrated a high prevalence of hepatitis B among celiac patients but did not compare the prevalence of hepatitis B according to interferon α use. Sima et al.[12] investigated 88 patients with chronic hepatitis B. They observed that 26 patients who had previously used interferon α had celiac antibodies compared to 6 patients without treatment with interferon α ($p < 0.05$). Some reports indicate autoimmune disorders such as insulin-dependent diabetes mellitus and CD that may develop during treatment with interferon α for viral hepatitis because this drug has immunomodulatory properties that can induce a silent autoimmune disorder such as CD[25–29].

Interferon α therapy may trigger CD in susceptible patients, and it has been hypothesized that the most likely pathogenesis of this process could be a dysregulation of the balance between the need to recognize antigens of pathogenic microorganisms and the need to prevent inappropriate immune responses to foods and normal flora[12]. These findings suggest that CD should be sought before interferon therapy for early diagnosis and prevention of CD complications. However, there is still insufficient evidence that interferon α can activate CD.

Table 1. Prevalence of celiac disease in patients with hepatitis B and vice versa

Author	Year	Country	Patients	Total	N	Prevalence
CD in patients with hepatitis B						
- Leonardi et al.[11]	2010	Italy	Patients with hepatitis B	35	6	17.2%
- Sima et al.[12]	2010	Iran	Patients with hepatitis B	88	8	9.1%
- Nau et al.[13]	2013	Brazil	Patients with hepatitis B	50	6	12%
- Sood et al.[14]	2017	India	Patients with hepatitis B	30	1	3.3%
Hepatitis B in patients with CD						
- Bardella et al.[20]	1995	Italy	Patients with CD and elevated aminotransferases	67	3	4.5%
- Novacek et al.[21]	1999	Austria	Patients with CD	178	1	0.6%
- Moghaddam et al.[22]	2013	United Kingdom	Patients with CD	98	1	1%
- Tanwar et al.[23]	2020	India	Patients with CD and portal hypertension	42	2	4.8%

HBV VACCINE

The success of a vaccination program depends on the availability of safe and highly effective vaccines and the implementation of appropriate vaccination strategies. After a complete vaccination cycle with the classic schedule of three vaccine doses administered at 0, 1, and 6 months, anti-HBsAg seroprotection rates at a concentration equal to or greater than 10 mIU/mL (the antibody threshold considered protective) are close to 100% in healthy children and almost 95% in healthy adults[30,31].

Along with host-related factors (i.e., age, sex, immunocompetence, genetics, and co-infections), vaccine and vaccination-related factors have also been found to affect the response to vaccination. Among these, the dose and vaccination schedule, the injection site, and the route of administration are critical factors in achieving an optimal immune response[32].

Addressing the issue of CD and hepatitis B is mainly related to immunization against hepatitis B in people with CD. The CD is more common in individuals with HLA-DQ2 and HLA-DQ8, and the literature has shown that these individuals have a lower response rate to HBV vaccination than the general population[33–36]. In particular, the immune response to the HBV vaccine is primarily determined by immunogenetic peptides through the HLA-DR and DQ molecules, and the DR3-DQ2 and DR7-DQ2 haplotypes generally have a lower response rate[37–39].

The correlation between CD activity (by measuring serum anti-transglutaminase titers) and the development of an antibody response to the HBV vaccine has been previously demonstrated[34]. Trovato et al.[40] evaluated 96 children with CD; 41.7% (n = 40) showed non-protective or absent antibody titers against HBV. Elevated tTG-IgA values ($p = 0.023$) and older age at diagnosis ($p < 0.001$) were associated with a lack of seroconversion to the HBV vaccine. They hypothesize that competition between gluten and the HBV surface antigen could explain this phenomenon. Therefore, we can speculate that in patients with CD, the immune system may focus on the non-self antigen that occurs most frequently in these patients (dietary gluten) and may polarize its activity in this direction rather than toward the antigen HBV surface antigen with massive production of tTG autoantibodies, but suboptimal production of antibodies against HBV surface antigens.

A lack of response has also been correlated with age, smoking, obesity, and male sex[39]. However, when children with CD follow a gluten-free diet, the immune response to the HBV vaccine is similar to that of the general population. This suggests that treatment adherence may improve the lack of response to the HBV vaccine in celiac children[41]. Lastly, the lack of response to the hepatitis B vaccine should be considered a sign of possible undiagnosed CD[33]. Nemes et al.[34] evaluated 128 children and adolescents with CD and 113 age-matched controls: 22 patients with CD were prospectively immunized after diagnosis during dietary treatment (Group 1) and a total of 106 celiac children, and the control subjects received vaccination by mass immunization regardless of diet status (Group 2). Diet compliance and CD activity were monitored by measuring tTG and anti-endomysial antibodies (EmA). The vaccine response rate for Group 1 was 95.5% compared to 50.9% for Group 2. The response rate among 27 undiagnosed and untreated CD patients was 25.9%, significantly lower than that in control subjects of 75.2% ($p < 0.001$).

Some strategies can be followed when vaccinating against hepatitis B in CD patients. One possibility would be administering the three usual doses, giving booster doses to non-responders, and performing serology to assess the response after each dose[42]. The intradermal route for the booster dose of the hepatitis B vaccine in celiac patients is a better option to obtain a higher titer of antibodies against HBV[43]. Furthermore, the intradermal route allows for a better cost-effectiveness ratio since the cost reduction exceeds 50% (2 µg per dose) compared to standard intramuscular vaccination (10 µg per dose)[44]. A third strategy would be to revaccinate celiac patients intramuscularly in treatment with a gluten-free diet after the decrease in celiac-specific antibodies[34]. The intradermal route is preferable for revaccination of these patients[45].

The prevalence of seroprotective levels of anti-HBsAg detected 11 years after primary immunization and the frequency of response to a booster dose of the vaccine are lower in celiac patients than in healthy controls[46]. Therefore, a booster dose of the vaccine should be administered every ten years to all celiac patients to protect non-responding celiacs from HBV infection[45].

CONCLUSION

Despite the coexistence of both diseases, a clear association between hepatitis B and CD has not been demonstrated, so routine screening for CD in HBV carriers cannot be recommended; however, hepatitis B should be investigated in the setting of elevated aminotransferases in celiac patients. Due to the poor response to vaccination against HBV, particular strategies should be implemented in celiac patients, such as the intradermal route and revaccination.

REFERENCES

1. Freeman HJ. Celiac disease: a disorder emerging from antiquity, its evolving classification and risk, and potential new treatment paradigms. Gut and liver. 2015;9(1):28-37. https://doi.org/10.5009/gnl14288
2. Green PH, Jabri B. Coeliac disease. Lancet. 2003;362(9381):383-91. https://doi.org/10.1016/S0140-6736(03)14027-5
3. Hadjivassiliou M, Sanders DS, Grunewald RA, Woodroofe N, Boscolo S, Aeschlimann D. Gluten sensitivity: from gut to brain. Lancet Neurol. 2010;9(3):318-30. https://doi.org/10.1016/S1474-4422(09)70290-X
4. Yoosuf S, Singh P, Khaitan A, Strand T, Ahuja V, Makharia GK. Prevalence of celiac disease in patients with liver diseases: a systematic review and meta-analyses. Am J Gastroenterol. 2023;118(5):820-32. https://doi.org/10.14309/ajg.0000000000002123
5. Kumar V, Jarzabek-Chorzelska M, Sulej J, Karnewska K, Farrell T, Jablonska S. Celiac disease and immunoglobulin a deficiency: how effective are the serological methods of diagnosis? Clin Diagn Lab Immunol. 2002;9(6):1295-300. https://doi.org/10.1128/CDLI.9.6.1295-1300.2002
6. Leffler DA, Schuppan D. Update on serologic testing in celiac disease. Am J Gastroenterol. 2010;105(12):2520-4. https://doi.org/10.1038/ajg.2010.276
7. Marsh MN. Gluten, major histocompatibility complex, and the small intestine. Gastroenterology. 1992;102(1):330-54. https://doi.org/10.1016/0016-5085(92)91819-P
8. Narciso-Schiavon JL, Schiavon LL. To screen or not to screen? Celiac antibodies in liver diseases. World J Gastroenterol. 2017;23(5):776-91. https://doi.org/10.3748/wjg.v23.i5.776
9. Narciso-Schiavon JL, Schiavon LL. Celiac disease screening in patients with cryptogenic cirrhosis. World J Gastroenterol. 2023;29(2):410-2. https://doi.org/10.3748/wjg.v29.i2.410
10. World Health Organization (WHO). Hepatitis B vaccines: WHO position paper; 2017. Wkly Epidemiol Rec. 2017;92(27):369-92.
11. Leonardi S, La Rosa M. Are hepatitis B virus and celiac disease linked? Hepat Mon. 2010;10(3):173-5.
12. Sima H, Hekmatdoost A, Ghaziani T, Alavian SM, Mashayekh A, Zali MR. The prevalence of celiac autoantibodies in hepatitis patients. Iran J Allergy Asthma Immunol. 2010;9(3):157-62.
13. Nau AL, Fayad L, Lazzarotto C, Shiozawa MB, Dantas-Corrêa EB, Schiavon LL, et al. Prevalence and clinical features of celiac disease in patients with hepatitis B virus infection in Southern Brazil. Rev Soc Bras Med Trop. 2013;46(4):397-402. https://doi.org/10.1590/0037-8682-0093-2013
14. Sood A, Khurana MS, Mahajan R, Midha V, Puri S, Kaur A, et al. Prevalence and clinical significance of IgA anti-tissue transglutaminase antibodies in patients with chronic liver disease. J Gastroenterol Hepatol. 2017;32(2):446-50. https://doi.org/10.1111/jgh.13474
15. Tursi A. Celiac disease and viral B hepatitis: lessons for clinical practice. Hepat Mon. 2010;10(4):311-2.
16. Stroffolini T, Almasio PL, Sagnelli E, Mele A, Gaeta GB. Evolving clinical landscape of chronic hepatitis B: A multicenter Italian study. J Med Virol. 2009;81(12):1999-2006. https://doi.org/10.1002/jmv.21643
17. Gasbarrini G, Miele L, Malandrino N, Grieco A, Addolorato G, Gasbarrini A, Cammarota G, Bonvicini F. Celiac disease in the 21st century: issues of under- and over-diagnosis. Int J Immunopathol Pharmacol. 2009;22(1):1-7. https://doi.org/10.1177/039463200902200101
18. Corrêa WK. Considerações sobre a formação territorial e econômica de Santa Catarina. Geosul. 1999;14(27):25-44.
19. Soto Iglesias S, Vazquez Rodriguez S, Ulla Rocha JL, Baltar Arias R, Diaz Saa W, Barrio Antoranz J, et al. [Onset of celiac disease after acute hepatitis B infection]. Gastroenterol Hepatol. 2010;33(1):17-20. https://doi.org/10.1016/j.gastrohep.2009.06.005
20. Bardella MT, Fraquelli M, Quatrini M, Molteni N, Bianchi P, Conte D. Prevalence of hypertransaminasemia in adult celiac patients and effect of gluten-free diet. Hepatology. 1995;22(3):833-6.
21. Novacek G, Miehsler W, Wrba F, Ferenci P, Penner E, Vogelsang H. Prevalence and clinical importance of hypertransaminasaemia in coeliac disease. Eur. J. Gastroenterol. Hepatol. 1999;11(3):283-8. https://doi.org/10.1097/00042737-199903000-00012
22. Moghaddam MA, Rostami Nejad M, Shalmani HM, Rostami K, Nazemalhosseini Mojarad E, Aldulaimi D, et al. The effects of gluten-free diet on hypertransaminasemia in patients with celiac disease. Int J Prev Med. 2013;4(6):700-4.
23. Tanwar A, Gupta GK, Chauhan V, Sharma D, Jain MK, Bhardwaj H, et al. Celiac Disease and Portal Hypertension: A Causal Association or Just a Coincidence? J Clin Exp Hepatol. 2020;10(4):290-5. https://doi.org/10.1016/j.jceh.2019.11.005
24. Ye J, Chen J. Interferon and Hepatitis B: Current and Future Perspectives. Front Immunol. 2021;12:733364. https://doi.org/10.3389/fimmu.2021.733364
25. Bardella MT, Marino R, Meroni PL. Celiac disease during interferon treatment. Ann Intern Med. 1999;131(2):157-8. https://doi.org/10.7326/0003-4819-131-2-199907200-00024
26. Cammarota G, Cuoco L, Cianci R, Pandolfi F, Gasbarrini G. Onset of celiac disease during treatment with Interferon for chronic hepatitis C. Lancet. 2000;356(9240):1494-5. https://doi.org/10.1016/S0140-6736(00)02880-4
27. Adinolfi LE, Durante Mangoni E, Andreana A. Interferon and Ribavirin treatment for chronic hepatitis C may activate celiac disease. Am J Gastroenterology. 2001;96(2):607-8. https://doi.org/10.1111/j.1572-0241.2001.03574.x
28. Monteleone G, Pender SL, Alstead E, Hauer AC, Lionetti P, McKenzie C, et al. Role of interferon α in promoting T

helper cell type 1 responses in the small intestine in celiac disease. Gut. 2001;48(3):425-9. https://doi.org/10.1136/gut.48.3.425
29. Narvaes I, Belen P, Mar Alcalde M, Jimenez C, Soria A. Chronic viral hepatitis, Interferon, diabetes mellitus, and celiac disease. Am J Gastroenterol. 2003;98(10):2336-7. https://doi.org/10.1111/j.1572-0241.2003.07652.x
30. Shaw Jr FE, Guess HA, Roets JM, Mohr FE, Coleman PJ, Mandel EJ, et al. Effect of anatomic injection site, age and smoking on the immune response to hepatitis B vaccination. Vaccine. 1989;7(5):425-30. https://doi.org/10.1016/0264-410X(89)90157-6
31. Treadwell TL, Keeffe EB, Lake J, Read A, Friedman LS, Goldman IS, et al. Immunogenicity of two recombinant hepatitis B vaccines in older individuals. Am J Med. 1993;95(6):584-8. https://doi.org/10.1016/0002-9343(93)90353-Q
32. Romano L, Zanetti AR. Hepatitis B Vaccination: A Historical Overview with a Focus on the Italian Achievements. Viruses. 2022;14(7):1515. https://doi.org/10.3390/v14071515
33. Leonardi S, Spina M, Spicuzza L, Rotolo N, La Rosa M. Hepatitis B vaccination failure in celiac disease: is there a need to reassess current immunization strategies? Vaccine. 2009;27(43):6030-3. https://doi.org/10.1016/j.vaccine.2009.07.099
34. Nemes E, Lefler E, Szegedi L, Kapitany A, Kovacs JB, Balogh M, et al. Gluten intake interferes with the humoral immune response to recombinant hepatitis B vaccine in patients with celiac disease. Pediatrics. 2008;121(6):e1570-6. https://doi.org/10.1542/peds.2007-2446
35. Ahishali E, Boztas G, Akyuz F, Ibrisim D, Poturoglu S, Pinarbasi B, et al. Response to hepatitis B vaccination in patients with celiac disease. Dig Dis Sci. 2008;53(8):2156-9. https://doi.org/10.1007/s10620-007-0128-3
36. Park SD, Markowitz J, Pettei M, Weinstein T, Sison CP, Swiss SR, et al. Failure to respond to hepatitis B vaccine in children with celiac disease. J Pediatr Gastroenterol Nutr. 2007;44(4):431-5. https://doi.org/10.1097/MPG.0b013e3180320654
37. Belloni C, Avanzini MA, De Silvestri A, Martinetti M, Pasi A, Coslovich E, et al. No evidence of autoimmunity in 6-year-old children immunized at birth with recombinant hepatitis B vaccine. Pediatrics. 2002;110(1 Pt 1):e4. https://doi.org/10.1542/peds.110.1.e4
38. Desombere I, Willems A, Leroux-Roels G. Response to hepatitis B vaccine: multiple HLA genes are involved. Tissue Antigens. 1998;51(6):593-604. https://doi.org/10.1111/j.1399-0039.1998.tb03001.x
39. Alper CA, Kruskall MS, Marcus-Bagley D, Craven DE, Katz AJ, Brink SJ, et al. Genetic prediction of nonresponse to hepatitis B vaccine. N Engl J Med. 1989;321(11):708-12. https://doi.org/10.1056/NEJM198909143211103
40. Trovato CM, Montuori M, Sansone A, Morelli A, Russo G, Pietropaoli N, et al. Association between Elevated TGA-IgA Titers and Older Age at Diagnosis with Absence of HBV Seroconversion in Celiac Children. Vaccines (Basel). 2021;9(2):101. https://doi.org/10.3390/vaccines9020101
41. Ertem D, Gonen I, Tanidir C, Ugras M, Yildiz A, Pehlivanoglu E, et al. The response to hepatitis B vaccine: does it differ in celiac disease? Eur J Gastroenterol Hepatol. 2010;22(7):787-93. https://doi.org/10.1097/MEG.0b013e32832e9d41
42. Rousseff T, Claeys T, Vande Vijver E, Moes N, Vande Velde S, Schelstraete P, et al. Hepatitis B virus vaccination and revaccination response in children diagnosed with coeliac disease: a multicentre prospective study. Acta Gastroenterol Belg. 2019;82(1):27-30.
43. Leonardi S, Praticò AD, Lionetti E, Spina M, Vitaliti G, Rosa ML. Intramuscular vs intradermal route for hepatitis B booster vaccine in celiac children. World J Gastroenterol. 2012;18(40):5729-33. https://doi.org/10.3748/wjg.v18.i40.5729
44. Sangfelt P, Uhnoo I, Reichard O, Weiland O. A low-dose intradermal hepatitis B vaccine programme in health-care workers and students is highly effective and cost saving: a retrospective follow-up survey in the clinical setting. Scand J Gastroenterol. 2008;43(4):465-72. https://doi.org/10.1080/00365520701733806
45. Vitaliti G, Praticò AD, Cimino C, Di Dio G, Lionetti E, La Rosa M, Leonardi S. Hepatitis B vaccine in celiac disease: yesterday, today and tomorrow. World J Gastroenterol 2013;19(6):838-45. https://doi.org/10.3748/wjg.v19.i6.838
46. Zingone F, Morisco F, Zanetti A, Romanò L, Portella G, Capone P, et al. Long-term antibody persistence and immune memory to hepatitis B virus in adult celiac patients vaccinated as adolescents. Vaccine. 2011;29(5):1005-8. https://doi.org/10.1016/j.vaccine.2010.11.060

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Case report

Intestinal Nonrotation, Imaging Findings in the Malrotation Spectrum: Case Report

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Abstract

Intestinal nonrotation is a rare embryonic developmental anomaly with a reported incidence of up to 0.5% in autopsies. Given the asymptomatic course, the diagnosis may be late, so it becomes an incidental finding. This study presents the most common imaging characteristics to familiarize readers with this pathology.

We describe the case of a 73-year-old patient who consulted for pain in the right inguinal region associated with the sensation of a mass. There were no significant findings on physical examination. An abdominal tomography with contrast was requested as a study method, identifying a reversal of the superior mesenteric artery/superior mesenteric vein relationship with the cecum, appendix, and ileocecal valve in the left flank and mesogastrium. A displacement of thin intestinal loops towards the right hemiabdomen was also noted.

Keywords

Diagnostic imaging, volvulus, congenital abnormalities.

INTRODUCTION

Intestinal nonrotation (INR) constitutes a part of the spectrum of intestinal malrotation abnormalities that occur in embryonic development[1,2]. The true incidence of the pathology is difficult to determine due to the asymptomatic or non-specific course in a significant group of patients[1].

INR occurs due to intestinal rotation failure and retroperitoneal fixation[2,3]. Although patients may remain asymptomatic throughout their lives, complications include intestinal obstruction, volvulus, venous congestion, and diagnostic errors in patients with appendicitis due to unconventional location[2].

CASE PRESENTATION

We present the case of a 73-year-old male patient who attended surgery due to pain in the right inguinal region associated with a sensation of an ipsilateral mass. He has no significant personal or family history. No positive findings were reported during the physical examination. A contrast-enhanced CT of the abdomen was indicated as a study method, identifying the transverse and ascending colon in the mesogastrium without crossing the midline and loss of the "C" shape of the duodenum located in the right hemiabdomen of the small intestine (**Figures 1A** and **B**).

The abnormal location of the cecum, ileocecal valve, and cecal appendix in the left flank and mesogastrium was observed (**Figures 1A** and **B**, **2A** and **B**).

There is an inversion of the relationship of the superior mesenteric vessels, where the superior mesenteric vein (SMV) was located to the left of the superior mesenteric artery (SMA), confirming the diagnosis (**Figure 3**).

Additionally, a globular deformity of the head of the pancreas was identified in the CT study (**Figures 4A** and **B**), later corroborated by additional MRI studies of the abdomen, with no evidence of dilation of the pancreatic duct (**Figures 5A** and **B**).

INR findings were considered in the context of an asymptomatic patient. Without symptoms or surgery criteria, expectant management of his condition and follow-up by the gastroenterology service were proposed. As a limitation, this study lacks additional endoscopic studies due to the absence of symptoms, the incidental nature of the finding, and the diagnosis confirmed by CT and MRI.

DISCUSSION

Intestinal rotation occurs during the fourth and twelfth weeks of gestation[2]. Intestinal embryonic development has been divided into three stages. In stages 1 and 2, the extrusion of the midgut towards the extraembryonic cavity occurs with a rotation of 90º and 270º counterclockwise[3]; this rotation brings the duodenal loop behind the SMA with the ascending colon on the right, the transverse colon on the upper side, and the descending colon on the left[4]. Stage 3 involves fusion and anchoring of the mesentery[3,4].

Intestinal malrotation mainly affects the midgut in stage 2, generating the spectrum of manifestation of INR, malrotation, and reverse rotation[3]. INR refers to a failure in the counterclockwise rotation of the midgut, resulting in the mispositioning of the duodenojejunal junction to the right of the midline[5]. Finally, the ligament of Treitz will be located on the right side of the abdomen, and the terminal ileum will cross the midline to meet the cecum in the left hemiabdomen instead of the right[6].

INR occurs in approximately 1 in every 500 live births and has been described in 0.5% of autopsies(4). A slight predominance has been reported in male patients with a wide age range at manifestation, from 18 to 97 years, according to the literature(7,8). Intestinal rotation abnormalities are usually asymptomatic; however, they can be combined with symptoms of intermittent or chronic abdominal pain(7,8). A study by Nehra and Goldstein reported nausea and diarrhea as the most common symptoms in patients with intestinal malrotation; other less frequent symptoms were emesis, abdominal pain and distension, dyspepsia, diarrhea, and constipation(6,7). Even if symptoms are pre-

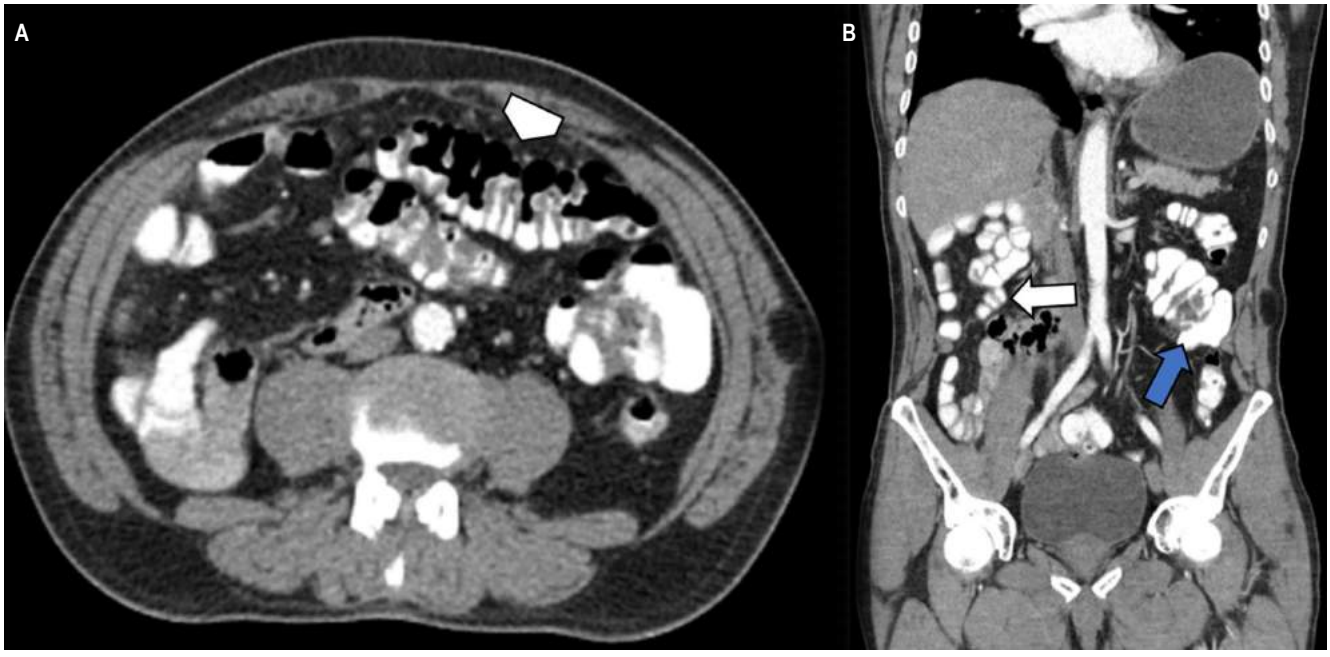

Figure 1. Contrast-enhanced CT of the abdomen in the axial section and coronal reconstruction. **A.** The transverse colon is located in the left hemiabdomen (arrowhead). **B.** Cecum and ileocecal valve on the left flank (blue arrow), thin intestinal loops in the right hemiabdomen (white arrow). Source: Authors' archive.

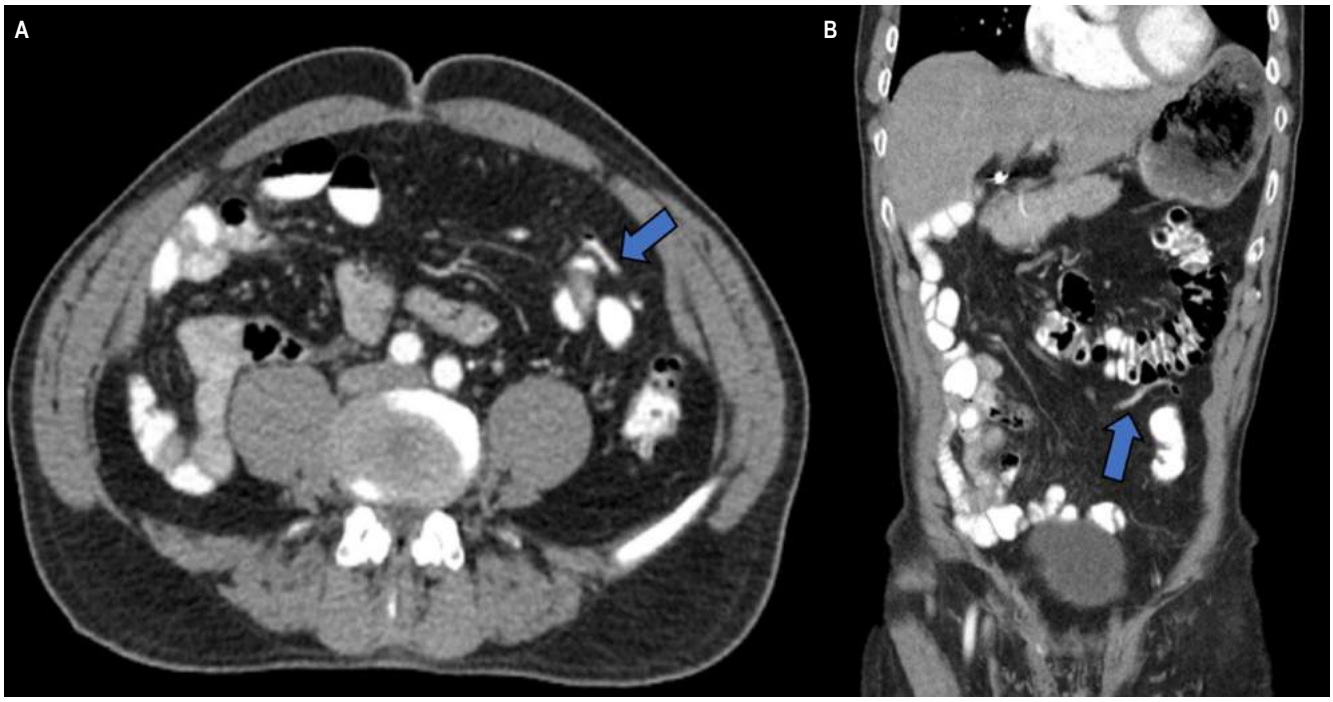

Figure 2. Abdominal CT scan in the axial plane (**A**) and coronal reconstruction (**B**). The cecal appendix with contrast medium and air inside on the left flank (blue arrow). Source: Authors' archive.

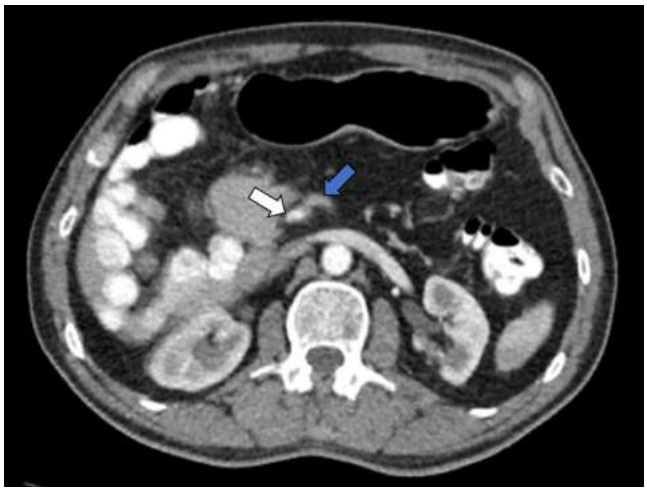

Figure 3. Abdominal CT scan in the axial plane. Inversion of the artery-vein relationship with the location of the SMV (blue arrow) to the left of the SMA (white arrow). Source: Authors' archive.

sent, it is difficult to attribute them to INR definitively; an abdominal CT study reported that up to 94% of patients with INR were asymptomatic(8,9). Other forms of manifestation include intestinal intussusception, although it is uncommon and often has a pathological starting point, such as a gastrointestinal malignancy or polyp(9,10).

Although INR in adult patients has a lower risk of volvulus since the base of the mesentery is wider than in malrotation, it may manifest as acute intestinal obstruction and intestinal ischemia[10–12] (**Table 1**).

Table 1. Symptoms reported in intestinal malrotation

Chronic (80% of patients)	Complications
Nausea and emesis	Intestinal obstruction
Intermittent abdominal pain	Intussusception
Early satiety	Volvulus
Dyspepsia, abdominal distension	Internal hernia
Diarrhea, constipation	Intestinal ischemia

Prepared by the authors.

Early diagnosis can prevent the complications of midgut volvulus and small bowel necrosis; however, it can be difficult radiologically; symptomatic patients may warrant laparoscopic or open exploration to confirm the diagnosis[9].

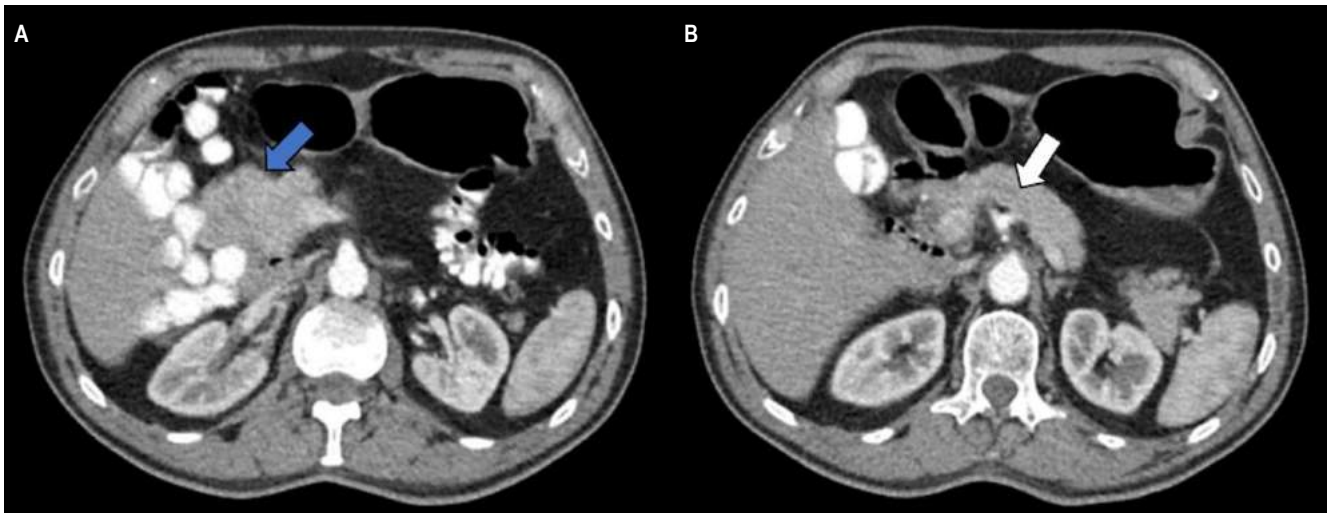

Figure 4A and **B.** Contrast-enhanced CT of the abdomen in axial sections. Globular deformity of the head of the pancreas (blue arrow) and absence of dilation of the pancreatic duct (white arrow). Source: Authors' archive.

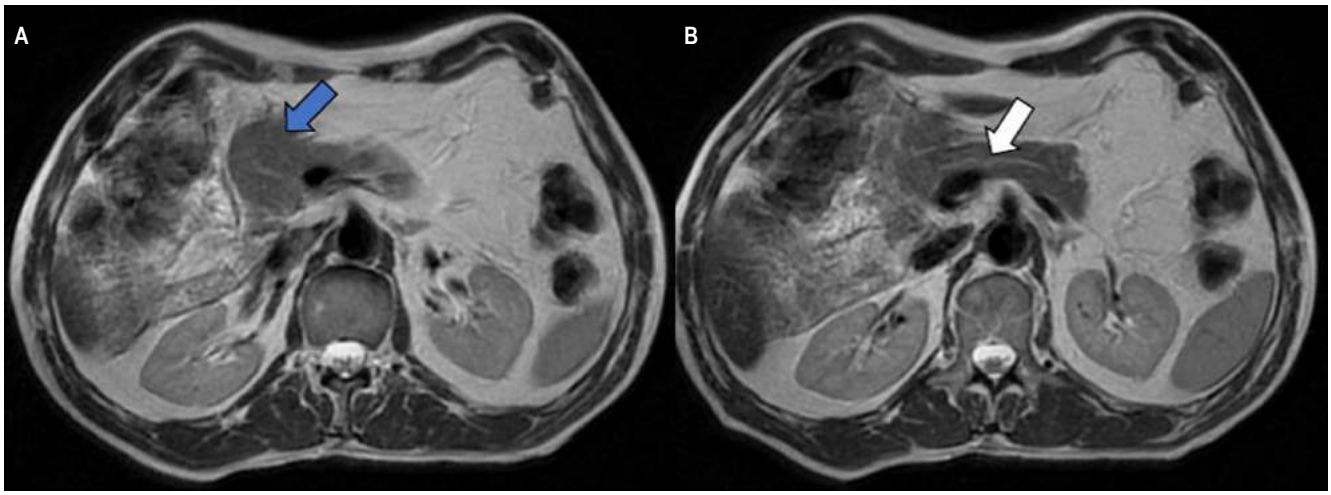

Figure 5A and **B.** MRI of the abdomen in axial sections. Globular deformity of the head of the pancreas (blue arrow) and absence of dilation of the pancreatic duct (white arrow). Source: Authors' archive.

Among the diagnostic imaging available are simple X-rays, the use of which is limited, although they may show some evidence of an abnormally located intestine[9]. For fluoroscopy studies, sensitivity and specificity of 93% and 77%, respectively, are reported for the diagnosis, showing the duodenojejunal junction that does not cross the midline and the mispositioning of the ascending colon and the cecum[6,9]. Ultrasound findings include inversion of the SMV and SMA[13].

CT reveals an inverse relationship between SMA and SMV, as observed in this clinical case[14]. Other findings include the location of the small intestine on the right side with the absence of a retroperitoneal segment of the duodenum and a cecum on the left side[14]. The "swirl" sign may be present, indicating twisting of the blood vessels around the mesenteric pedicle[7,14].

In the context of volvulus or obstruction, an abrupt transition in intestinal diameter may be visible[15]. Signs suggesting ischemia can be seen as increased attenuation or absence of enhancement of the intestinal wall, pneumatosis intestinalis, or thickening of the large intestine wall[15]. The pneumoperitoneum may be visible as a sign of perforation[15] (**Table 2**). Research by Xiong at Tongji Hospital concludes that using abdominal CT can improve reader

confidence in identifying asymptomatic cases of malrotation, reducing the proportion found in the configuration of volvulus and allowing classification into multiple potentially relevant subtypes[8].

Table 2. CT findings in intestinal nonrotation

Tomographic findings	Complications
Inversion of the SMA and SMV relationship	Pneumoperitoneum
Small intestine in the right hemiabdomen	Intestinal pneumatosis
Large intestine in the left hemiabdomen	Absence of enhancement of the intestinal wall
Absence of the retroperitoneal segment of the duodenum	Thickening of the intestinal wall
"Swirl" sign of mesenteric vessels	Findings of intestinal obstruction
Engorgement of mesenteric blood vessels	
Malformations of the head and uncinate process of the pancreas	

Prepared by the authors.

MRI is not commonly used in this context; however, if there is suspicion of inversion of the SMA and SMV relationship, it is usually helpful[16]. MRI and magnetic resonance cholangiography are better tools than CT to define the anatomy of the biliary tree and pancreatic duct. They are more capable of evaluating pancreatic and intrahepatic masses, making them diagnostic support for incidental findings, as in this clinical case[14,17].

A study by Chandra et al. described the frequency of normal variations in the contour of the head and the uncinate process of the pancreas in patients with intestinal malrotation, some of which can mimic a neoplasia[18]. The authors described the globular form as the most common variant, as in this clinical case, followed by the elongated form and a third mixed form (globular and elongated)[18]. Ninety percent of the patients in the study exhibited an inversion of the relationship between SMA and SMV[18]. Aplasia and hypoplasia of the uncinate process have been described in patients with INR[19]. Understanding the anatomical variants in the context of INR helps surgical planning, as in the case published by Pagkratis in a patient with pancreatic adenocarcinoma associated with INR[20].

Patients with acute symptoms and evidence of volvulus require immediate surgical intervention[18]. Treatment of people with rotational anomalies without volvulus is controversial and often dictated by symptoms[8]. The presence of vague abdominal discomfort in a patient with a known rotational anomaly justifies laparotomy[8]. Choosing a non-surgical treatment route requires extensive knowledge of subtle signs of complications by medical providers[8]. Appendectomy is recommended for all patients undergoing laparotomy[8,13]. A study by Brungard et al. showed that if an appendectomy is performed, it has a minimal impact on postoperative results and could be considered safe while the malrotation is surgically corrected[21].

CONCLUSIONS

INR is a rare pathology because patients can remain asymptomatic until adulthood, making it an incidental diagnosis in many cases. Knowing the characteristics of INR is relevant in the context of acute abdomen, taking into account the possibility of volvulus and intestinal obstruction inherent to this entity and in scenarios such as appendicitis, where its clinical manifestation may change depending on its location. Approaching the imaging findings of this pathology can help with early diagnosis and reduce the risk of complications.

Conflicts of interest

The authors declare no conflicts of interest.

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REFERENCES

1. Choi M, Borenstein SH, Hornberger L, Langer JC. Heterotaxia syndrome: the role of screening for intestinal rotation abnormalities. Arch Dis Child. 2005;90(8):813-5. https://doi.org/10.1136/adc.2004.067504
2. Langer JC. Intestinal Rotation Abnormalities and Midgut Volvulus. Surg Clin North Am. 2017;97(1):147-59. https://doi.org/10.1016/j.suc.2016.08.011
3. Sözen S, Güzel K. Intestinal malrotation in an adult: case report. Ulus Travma Acil Cerrahi Derg. 2012;18(3):280-2. https://doi.org/10.5505/tjtes.2012.60973
4. Appaji AC, Kulkarni R, Kadaba JS. Nonrotation of intestine: a case report. J Clin Diagn Res. 2013;7(11):2575-6. https://doi.org/10.7860/JCDR/2013/6177.3616

5. Mohan P, Ramamoorthy M, Venkataraman J. Clinical vistas: nonrotation of the intestine. CMAJ. 2008 Jul 1;179(1):49-50. https://doi.org/10.1503/cmaj.080038
6. Applegate KE, Anderson JM, Klatte EC. Intestinal malrotation in children: a problem-solving approach to the upper gastrointestinal series. Radiographics. 2006;26(5):1485-500. https://doi.org/10.1148/rg.265055167
7. Nehra D, Goldstein AM. Intestinal malrotation: varied clinical presentation from infancy through adulthood. Surgery. 201;149(3):386-93. https://doi.org/10.1016/j.surg.2010.07.004
8. Xiong Z, Shen Y, Morelli JN, Li Z, Hu X, Hu D. CT facilitates improved diagnosis of adult intestinal malrotation: a 7-year retrospective study based on 332 cases. Insights Imaging. 2021;12(1):58. https://doi.org/10.1186/s13244-021-00999-3
9. Diaz M, Reichard K, Taylor A. Intestinal nonrotation in an adolescent. Pediatr Emerg Care. 2009;25(4):249-51. https://doi.org/10.1097/PEC.0b013e31819e36aa
10. Gohl ML, DeMeester TR. Midgut nonrotation in adults. An aggressive approach. Am J Surg. 1975;129(3):319-23. https://doi.org/10.1016/0002-9610(75)90249-4
11. Strouse PJ. Disorders of intestinal rotation and fixation "malrotation". Pediatr Radiol. 2004;34(11):837-51. https://doi.org/10.1007/s00247-004-1279-4
12. Gandhi V, Pai N, Kashiva R, Mane D. Adult with intestinal malrotation and colocolic intussusception: an unusual combo. BMJ Case Rep. 2019;12(7):e226398. https://doi.org/10.1136/bcr-2018-226398
13. Pourmand A, Dimbil U, Drake A, Shokoohi H. The Accuracy of Point-of-Care Ultrasound in Detecting Small Bowel Obstruction in Emergency Department. Emerg Med Int. 2018;2018:3684081. https://doi.org/10.1155/2018/3684081
14. Kapfer SA, Rappold JF. Intestinal malrotation-not just the pediatric surgeon's problem. J Am Coll Surg. 2004;199(4):628-35. https://doi.org/10.1016/j.jamcollsurg.2004.04.024
15. Vandendries C, Jullès MC, Boulay-Coletta I, Loriau J, Zins M. Diagnosis of colonic volvulus: findings on multidetector CT with three-dimensional reconstructions. Br J Radiol. 2010;83(995):983-90. https://doi.org/10.1259/bjr/35714052
16. Etchevers J, Palermo M, Salvatore M, Tarsitano F,Villafañe V. Malrotación intestinal en adultos: causa infrecuente de abdomen agudo oclusivo. Rev Argentina de Radiol. 2008;72(4):435-38.
17. Tummala P, Junaidi O, Agarwal B. Imaging of pancreatic cancer: An overview. J Gastrointest Oncol. 2011;2(3):168-74. https://doi.org/10.3978/j.issn.2078-6891.2011.036
18. Chandra J, Grierson C, Bungay H. Normal variations in pancreatic contour are associated with intestinal malrotation and can mimic neoplasm. Clin Radiol. 2012;67(12):1187-92. https://doi.org/10.1016/j.crad.2011.11.021
19. Zissin R, Rathaus V, Oscadchy A, Kots E, Gayer G, Shapiro-Feinberg M. Intestinal malrotation as an incidental finding on CT in adults. Abdom Imaging. 1999;24(6):550-5. https://doi.org/10.1007/s002619900560
20. Pagkratis S, Kryeziu S, Lin M, Hoque S, Bucobo JC, Buscaglia JM, et al. Case report of intestinal non-rotation, heterotaxy, and polysplenia in a patient with pancreatic cancer. Medicine (Baltimore). 2017;96(49):e8599. https://doi.org/10.1097/MD.0000000000008599
21. Brungardt JG, Liebscher SC, Schropp KP. Malrotation Correction in the Adult Population. World J Surg. 2021;45(1):141-47. https://doi.org/10.1007/s00268-020-05790-x

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Case report

Thrombosis of the Superior Mesenteric Artery and Hepatic Artery Secondary to Acute Necrotizing Pancreatitis: Case Report and Literature Review

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Abstract

We describe the case of a female patient with severe acute pancreatitis of biliary origin who presented with clinical deterioration. A thrombosis of the superior mesenteric artery and hepatic artery was identified as the cause, thus creating a rare vascular complication. She was taken for pharmacological and mechanical thrombectomy, with the subsequent death of the patient. Arterial vascular complications are an entity little recognized in the medical literature; they have a high mortality rate and pose a significant diagnostic and therapeutic challenge.

Keywords

Acute pancreatitis, thrombosis, complication, biliary pancreatitis, thrombectomy.

INTRODUCTION

Acute pancreatitis is an inflammatory disease of the pancreas, which multiple etiologies can cause; the most common are alcohol consumption and gallstones[(1)]. Acute pancreatitis has variable severity and takes a mild course in most patients; however, it may cause local injury, systemic inflammation, multiple organ failure, and even death, which has been associated with severe acute pancreatitis. The most used severity classification of acute pancreatitis is the 2012 revision of the Atlanta Classification, which is divided into mild, moderately severe, or severe[(2)]. Consistently, more severe cases of acute pancreatitis are associated with a higher incidence of complications. Two phases of acute pancreatitis are known: early and late, which can overlap. The early phase comprises the first two weeks from the onset of the disease, while the late phase extends after two weeks from the onset and can last for months[(3)].

It has been reported that 10–20% of cases of acute pancreatitis are associated with pancreatic necrosis, necrosis of peripancreatic tissue, or both[(4)]. Vascular complications are rarer, occurring in 1.2% to 14% of cases. Among these, the most reported complications have been the formation of pseudoaneurysms, hemorrhage from pancreatic pseudo-

cysts, and venous thrombosis[5]. Arterial thrombosis is an infrequent complication with a high degree of mortality, for which there is limited information in the medical literature. The present study describes a case report of mesenteric and hepatic arterial thrombosis secondary to acute necrotizing pancreatitis and reviews the available literature.

CASE REPORT

A 59-year-old female patient, originally from Sasaima, Cundinamarca, Colombia, consulted for a clinical picture of high-intensity abdominal pain associated with emesis and abdominal distension.

She has a history of systemic arterial hypertension and grade II obesity and was under pharmacological management with losartan 50 mg per day.

During the abdominal pain study, the patient was assessed by the internal medicine service with a diagnosis of acute pancreatitis of probable biliary origin, and management with analgesia and intravenous fluids with crystalloids was indicated. The paraclinical parameters on admission were: total bilirubin of 3.05 mg/dL, direct bilirubin of 1.91 mg/dL, indirect bilirubin of 1.14 mg/dL, aspartate aminotransferase (AST) of 469 U/dL, alanine-aminotransferase (ALT) of 413 U/dL, complete blood count with absolute leukocyte count of 25,200, absolute neutrophil count of 22,700, hemoglobin of 18.9 g/dL, creatinine of 0.61 mg/dL, lipase of 224,200, and triglycerides of 185 mg/dL. An abdominal ultrasound was requested, showing cholelithiasis without acute cholecystitis, intra- and extrahepatic bile duct of standard caliber, and visualization of the head and part of the body of the pancreas with increased volume and echogenicity. She was evaluated by gastroenterology, ruling severe acute pancreatitis with a Marshall score of 2 points of probable biliary etiology. Medical management and surveillance were indicated.

The patient displayed a torpid evolution due to increased abdominal pain, tachycardia, respiratory deterioration due to dyspnea, a decrease in arterial oxygen pressure/inspired fraction of oxygen (PaO_2/FIO_2), an increase in total bilirubin levels to 8.17 mg/dL, with direct bilirubin of 5.59 mg/dL and indirect bilirubin of 2.58 mg/dL. Transfer to the intensive care unit (ICU) with control arterial blood gases with metabolic acidosis was indicated, and it was decided to request a contrast-enhanced computed tomography (CAT) scan of the abdomen. Subsequently, the patient had a hypoxemic ventilatory failure, requiring management with orotracheal intubation and invasive mechanical ventilation. She was re-evaluated by gastroenterology, who considered a possible Tokyo III cholangitis, so they requested an endoscopic retrograde cholangiopancreatography (ERCP). However, before performing the procedure, the CT result showed acute edematous interstitial pancreatitis with signs of pancreatic necrosis in the head and tail with an extension of 80% (**Figure 1**), no opacification of the lumen of the superior mesenteric artery at 60 mm from its origin and no opacification of the lumen of the hepatic artery compatible with arterial thrombosis.

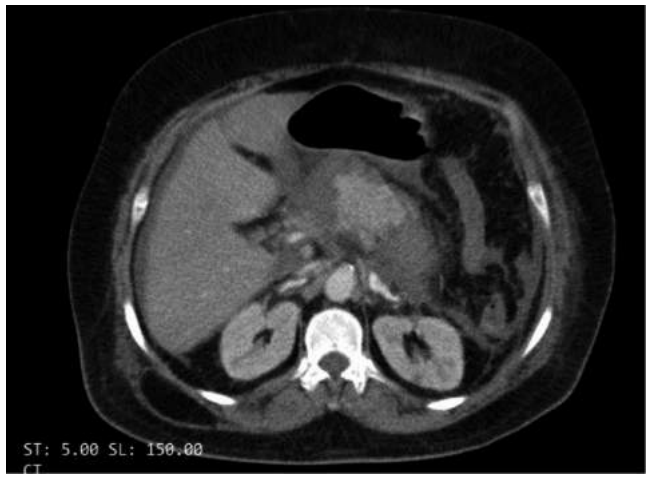

Figure 1. Computed tomography (CT) reveals acute necrotizing pancreatitis, primarily of the head and body of the pancreas. Source: Authors' archive.

The patient was immediately taken for an abdominal aortography, selective arteriography of the abdominal vessels, and thromboembolectomy by interventional radiology, finding occlusion of the common hepatic, superior mesenteric, and inferior mesenteric arteries (**Figure 2**). Using 6 Fr and 8 Fr indigo catheters, aspiration thrombectomy was performed on multiple occasions, and acute and subacute clots were obtained, with which it was only possible to revascularize the proximal third of this artery with outflow through the pancreatoduodenal arch that reperfused the hepatic artery proper and the first jejunal branch (**Figure 3**). The distal two-thirds of the superior mesenteric artery could not be revascularized due to poor outflow. Immediately after the procedure, the patient was taken to ERCP. In the second duodenal portion, marked edema that did not allow visualization of the papilla was observed, so the procedure was suspended.

The patient presented with clinical and paraclinical deterioration; multi-organ failure was considered due to cardiovascular, pulmonary, and renal involvement, and she subsequently died.

DISCUSSION

Acute pancreatitis is one of the most common gastroenterological pathologies for which patients consult the emer-

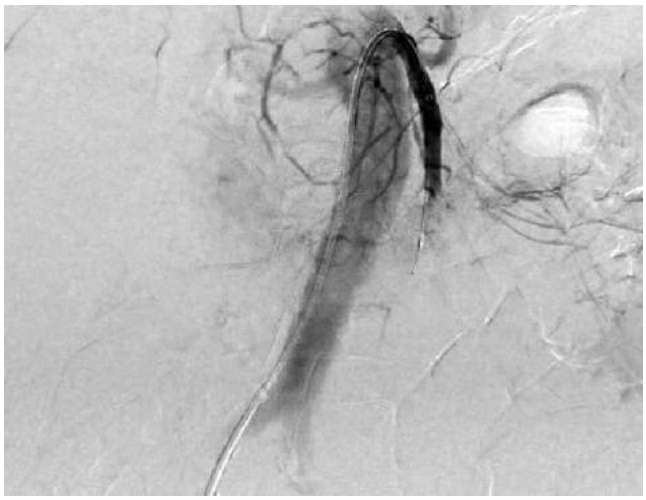

Figure 2. Selective arteriography of abdominal vessels denoting occlusion of the common hepatic, superior mesenteric, and inferior mesenteric arteries. Source: Authors' archive.

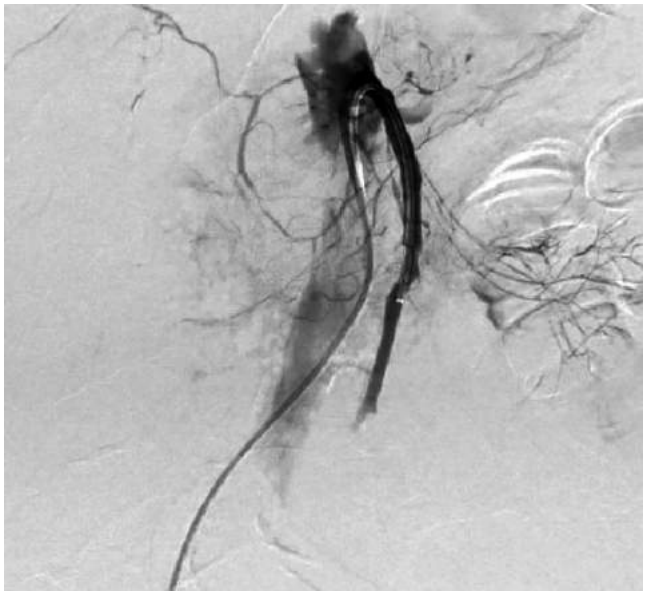

Figure 3. Reperfusion of the hepatic artery proper and first jejunal branch. Source: Authors' archive.

gency room. It involves significant morbidity and mortality and an economic burden on the health system since it represents high costs, particularly when associated with severe complications[3]. In Colombia, it has been reported that the most common cause of acute pancreatitis is of biliary origin; besides, most cases are classified as mild[6]. Mortality in Colombia has been reported around 2.5% and 4.1% in the general population[7,8]. However, in cases of severe acute pancreatitis, mortality rates of up to 8.25% have been reported[6].

Vascular complications of acute pancreatitis are rare but are highly feared due to their high mortality rate[9]. The most frequent vascular complications are venous thromboses, which are more associated with alcoholic etiologies. Among these, the most frequently involved veins are the splenic vein, the portal vein, and the superior mesenteric vein[9], and they are rarely associated with bleeding from necrotic tissue. Among the arterial complications, the most frequent is the formation of pseudoaneurysms, which have been reported in up to 10% of patients with acute necrotizing pancreatitis[5]. It may involve any pancreatic or peripancreatic artery, and involvement of the splenic artery, gastroduodenal artery, and left gastric artery is most common. Arterial pseudoaneurysm is the cause of 60% of massive hemorrhages related to acute necrotizing pancreatitis, with high mortality rates.

Arterial thromboses are the rarest vascular complication of pancreatitis; a prospective study that sought to evaluate arterial complications in 189 patients with acute pancreatitis did not find arterial thrombosis[10], and reports of these complications have been limited to case series. During the review of the literature, case reports of thrombosis of the superior mesenteric artery[11,12], renal arteries[13], aortic thrombosis[14], and the celiac trunk[15] were found. No reports of hepatic artery were identified. Moreover, no other apparent causes of mesenteric arterial thrombosis were detected in our patient.

In recent decades, the pathophysiology of arterial complications has moved away from the proposal of enzymatic autodigestion. It is currently considered that there is a cascade of microvascular events related to systemic and local inflammation that results in episodes of ischemia and reperfusion; these episodes produce acinar damage, release of pancreatin, recruitment of lymphocytes, and subsequent release of proinflammatory cytokines, which translates into proteolytic leak that, together with reactive oxygen species and cytokines, generate microvascular damage in the endothelium. This has been proposed as the pathophysiological mechanism of the *vasa vasorum* that would lead to thrombus formation[9]. The above has been related to the systemic inflammatory response and multi-organ failure[1].

The clinical manifestation of arterial thrombosis secondary to acute necrotizing pancreatitis is not well established due to the lack of high-quality information; however, its manifestation is associated with severe abdominal pain that does not modulate with analgesia or match the clinical status of patients. The diagnosis can be made through contrast-enhanced CT, contrast-enhanced magnetic resonance imaging of the abdomen, Doppler ultrasound, or angiography[5]. The treatment is poorly established; still, in previous case reports, mechanical thrombectomy,

pharmacological thrombectomy, and pharmacomechanical thrombectomy (a combination of both techniques) have been described as alternatives, especially in the context of the absence of intestinal ischemia, suggesting that management should be surgical[11]. The procedure should be strictly monitored, and surgical management should be considered in case of clinical deterioration. Adequate water management has also been described as paramount; in recent studies, it has been suggested that aggressive early management with intravenous fluids results in a higher incidence of fluid overload without improvement in clinical outcomes[16].

The mortality of arterial thrombosis is extremely high; in different series of cases, it has been reported to be greater than 90%[10,11]. The majority of cases were reported in women and patients with a history of obesity, high blood pressure, or diabetes, which constitute a metabolic syndrome. Nonetheless, information is too limited to establish apparent risk factors.

In conclusion, this article presents a case report of thrombosis of the superior mesenteric artery and hepatic artery secondary to acute necrotizing pancreatitis of biliary origin, a rare entity with high mortality rates. Early identification of this pathology is essential to determine early endovascular or surgical treatment. High-quality studies identifying risk factors, clinical manifestation, and better management strategies for this pathology are needed. For now, it requires timely multidisciplinary management due to the high complexity and unfavorable outcomes.

Conflict of interests

No financial or personal relationship with others or organizations has influenced this work.

REFERENCES

1. Leppäniemi A, Tolonen M, Tarasconi A, Segovia-Lohse H, Gamberini E, Kirkpatrick AW, et al. 2019 WSES guidelines for the management of severe acute pancreatitis. World J Emerg Surg. 2019;14:27. https://doi.org/10.1186/s13017-019-0247-0
2. Banks PA, Bollen TL, Dervenis C, Gooszen HG, Johnson CD, Sarr MG, et al. Classification of acute pancreatitis--2012: revision of the Atlanta classification and definitions by international consensus. Gut. 2013;62(1):102-11. https://doi.org/10.1136/gutjnl-2012-302779
3. Crockett SD, Wani S, Gardner TB, Falck-Ytter Y, Barkun AN; American Gastroenterological Association Institute Clinical Guidelines Committee. American Gastroenterological Association Institute Guideline on Initial Management of Acute Pancreatitis. Gastroenterology. 2018;154(4):1096-101. https://doi.org/10.1053/j.gastro.2018.01.032
4. Baron TH, DiMaio CJ, Wang AY, Morgan KA. American Gastroenterological Association Clinical Practice Update: Management of Pancreatic Necrosis. Gastroenterology. 2020;158(1):67-75.e1. https://doi.org/10.1053/j.gastro.2019.07.064
5. Barge JU, Lopera JE. Vascular complications of pancreatitis: role of interventional therapy. Korean J Radiol. 2012;13 Suppl 1(Suppl 1):S45-55. https://doi.org/10.3348/kjr.2012.13.S1.S45
6. Puerto LJ, Medina R, Núñez LR, Jiménez HC, Olaya JG, Sanjuán JF, et al. Outcomes of three years of experience managing acute pancreatitis at a fourth level hospital in Huila, Colombia. Rev Colomb Gastroenterol. 2019;34(1):10-6. https://doi.org/10.22516/25007440.243
7. Martínez Rodríguez EB. Caracterización de los pacientes con pancreatitis aguda que ingresaron al Hospital Universitario Nacional entre abril de 2016 y septiembre de 2017 [Internet] [Tesis]. Bogotá: Universidad Nacional de Colombia; 2018 [citado el falta la fecha]. Disponible en: https://repositorio.unal.edu.co/handle/unal/62919
8. Rojas C, Salazar N, Sepúlveda M, Maldonado C, Castro A, Gómez Y, et al. Clinical characteristics of patients with acute pancreatitis treated in a tertiary referral hospital in Cali. Rev Colomb Gastroenterol. 2021;36(3):341-48. https://doi.org/10.22516/25007440.682
9. Kalas MA, Leon M, Chavez LO, Canalizo E, Surani S. Vascular complications of pancreatitis. World J Clin Cases. 2022;10(22):7665-673. https://doi.org/10.12998/wjcc.v10.i22.7665
10. Dörffel Y, Wruck U, Rückert RI, Romaniuk P, Dörffel W, Wermke W. Vascular complications in acute pancreatitis assessed by color duplex ultrasonography. Pancreas. 2000;21(2):126-33. https://doi.org/10.1097/00006676-200008000-00004
11. Chait J, Duffy E, Marks N, Rajaee S, Hingorani A, Ascher E. Superior Mesenteric Artery Thrombosis after Necrotizing Pancreatitis. Ann Vasc Surg. 2019;59:307.e17-307.e20. https://doi.org/10.1016/j.avsg.2019.02.046
12. Garcia-Rodriguez V, Jacob R, daSilva-deAbreu A. A Rare Case of Pancreatitis-Induced Thrombosis of the Aorta and Superior Mesenteric Artery. Methodist Debakey Cardiovasc J. 2019;15(3):220-22. https://doi.org/10.14797/mdcj-15-3-220
13. Thajudeen B, Budhiraja P, Bracamonte ER. Bilateral renal artery thrombosis secondary to acute necrotizing pancrea-

titis. Clin Kidney J. 2013;6(5):503-6. https://doi.org/10.1093/ckj/sft106
14. Mishreki AP, Bowles MJ. A case of widespread aortic thrombosis secondary to acute severe pancreatitis. Ann R Coll Surg Engl. 2011;93(4):17-8. https://doi.org/10.1308/003588411X13008842578536
15. Kumaran C, Chung AYF, Ooi LLPJ, Chow PKH, Wong WK. Coeliac artery trunk thrombosis in acute pancreatitis causing total gastric necrosis. ANZ J Surg. 2006;76(4):273-74. https://doi.org/10.1111/j.1445-2197.2006.03701.x
16. de-Madaria E, Buxbaum JL, Maisonneuve P, García García de Paredes A, Zapater P, Guilabert L, et al. Aggressive or Moderate Fluid Resuscitation in Acute Pancreatitis. N Engl J Med. 2022;387(11):989-1000. https://doi.org/10.1056/NEJMoa2202884

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Case report

Endoscopic Ultrasound-Directed Transgastric Endoscopic Retrograde Cholangiopancreatography in a Patient with Gastric Bypass. Report of the First Local Case

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Abstract

We describe the first case in our environment of endoscopic ultrasound (EUS)-assisted transgastric endoscopic retrograde cholangiopancreatography in a patient with gastric bypass surgery. The procedure was performed with a side-viewing duodenoscope through a jejunogastrostomy using apposing stents, placed with EUS assistance, and a standard technique and instruments.

Keywords

Endoscopic retrograde cholangiopancreatography, altered anatomy, endoscopic ultrasound-directed transgastric endoscopic retrograde cholangiopancreatography.

INTRODUCTION

Obesity has been a public health problem for decades, which has caused the development of multiple treatments, including malabsorptive surgery, with increasing frequency since 1966 due to better results in terms of weight loss and metabolic control. However, changes secondary to bariatric procedures increase the frequency of calculous cholecystitis by up to 36%, with 15% of stones lodged in the bile duct. Endoscopic retrograde cholangiopancreatography (ERCP) is the procedure of choice for managing calculous pathology of the bile duct and for instrumentation of biliopancreatic obstructive diseases, including malignant disease; however, endoscopic access to the duodenal papilla in the altered anatomy of gastric bypass results in an enormous technical challenge, given the *sui generis* anatomical alteration that implies a long afferent loop.

In our setting, this very frequently translates into surgical management, either for bile duct exploration or laparoscopic transgastric ERCP.

This report describes a case of ERCP in a patient with gastric bypass, in which communication was created under endosonographic guidance between the gastric reservoir and the stomach left in the peritoneal cavity, allowing access to the papilla with a usual side-viewing instrument. The procedure was performed in the advanced endoscopy unit of Estudios Endoscopios SAS in Medellín without transferring the patient to the surgical unit with close out-

patient follow-up. This directly impacts hospitalization times, patient comfort, and associated costs.

CLINICAL CASE

We present the case of a 32-year-old female patient with a history of gastric bypass surgery for morbid obesity. After the associated weight loss, the patient had an episode of abdominal pain with an ultrasound diagnosis of cholelithiasis, which required a laparoscopic cholecystectomy one year before the current consultation. On admission, the patient reported abdominal pain in the upper quadrants, predominantly on the right, associated with mild jaundice and choluria without acholia. With suspected residual choledocholithiasis, the patient was taken for magnetic resonance cholangiography, which failed to identify the causes of pain associated with jaundice. A biliopancreatic endoscopic ultrasound (EUS) was requested, which showed a bile duct of standard diameter with an oval echogenic image of 3.8 mm in diameter, floating and with acoustic shadowing upon the alpha maneuver from the first scanning station (the other stations were not evaluable due to the history of bypass; **Figure 1**). This finding is compatible with choledocholithiasis, for which ERCP is indicated.

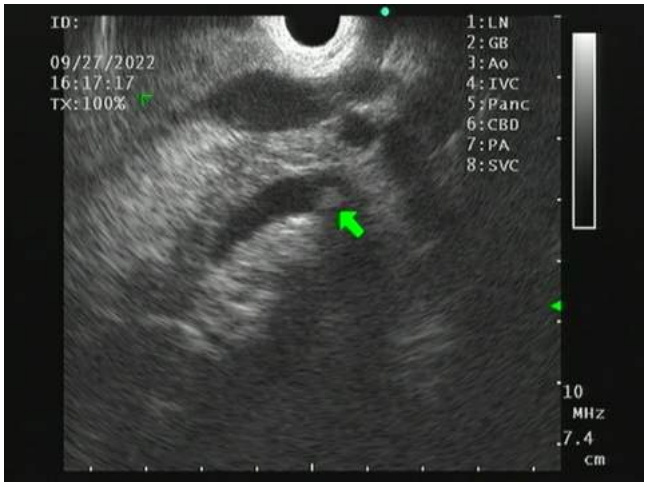

Figure 1. Initial diagnostic EUS. The cursor points to a small stone in the alpha maneuver from the first evaluation station. Source: Patient's medical record.

The possibility of ERCP by laparoscopic transgastric enteroscopy and EUS-directed transgastric ERCP (EDGE) is analyzed (**Figure 2**).

Given the background in the literature and our experience, which reveals a high risk of failed enteroscopy procedures associated with the length of the alimentary loop, we decided to rule out this option.

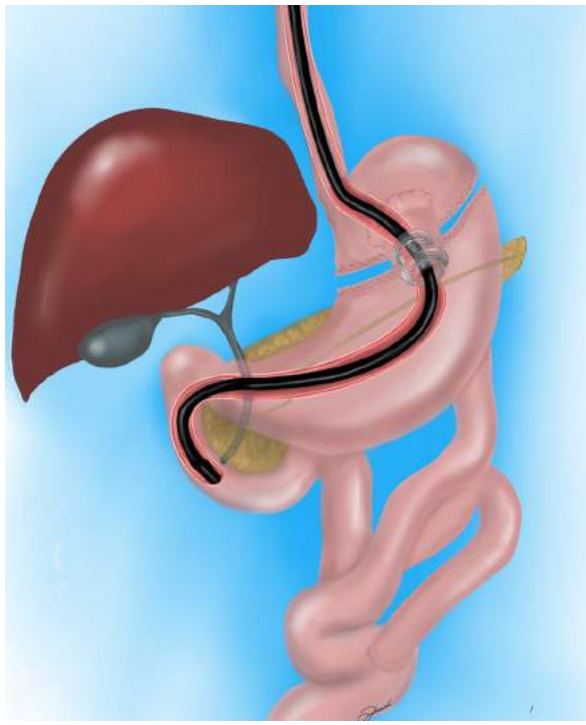

Figure 2. EDGE (representative drawing). Illustration by Dr. Andrés Ricardo.

The possibility of a laparoscopic approach is discussed, which is not imperative since the patient has had a cholecystectomy. It is also considered that the patient does not want new surgical interventions or their inherent risks. We then opted for EUS-directed management since, during the diagnostic EUS, the accessibility of the remnant stomach was verified in the proximity of the gastric reservoir and the afferent loop (**Figure 3**).

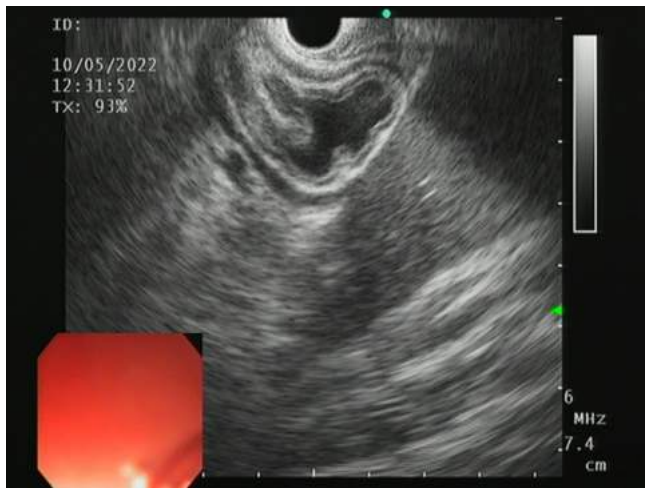

Figure 3. Visualization of gastric folds on EUS. Source: Patient's medical record.

At the time, the patient had no symptoms, so we decided to perform the procedure in two stages: in the first stage, an EUS-guided jejunogastrostomy with apposing stenting, which allowed the complete expansion of the stent and maturation of the tract. In the second stage, one week after stenting, consisting of the usual ERCP, the side-viewing duodenoscope was advanced.

The first stage was performed under sedation, with EUS and fluoroscopic guidance. The remnant stomach was traced near the distal jejunum 10 mm from the gastrojejunal anastomosis. EUS-guided puncture with a 19G needle, instillation of water-soluble contrast medium in distilled water, and a gastrogram were performed. A 0.035-inch hydrophilic guidewire was advanced through the puncture needle, deploying the 15-mm apposing stent with a hot-tip introducer (Hot Axios 15 mm, Boston) in four steps. The deployment of the proximal tab in the afferent loop required further advancement of the pusher for release, given the limited space in this segment, which prevents the tip from getting away from the intestinal wall. The location of the stent was verified endoscopically with a slim front-viewing gastroscope (**Figure 4**).

In-hospital follow-up was carried out for 24 hours, with the absence of symptoms and adequate tolerance to the oral route, so the patient was discharged with an outpatient appointment for ERCP.

The second stage was performed ten days later under sedation and after gastroscopy to verify adequate passage to the duodenum. The side-viewing duodenoscope was advanced through the apposing stent to the duodenal papilla, and the usual ERCP was performed with a sufficient papillotomy and stone extraction. There was no bleeding or complication during the procedure (**Figure 5**). Upon removal of the duodenoscope, the position of the apposing

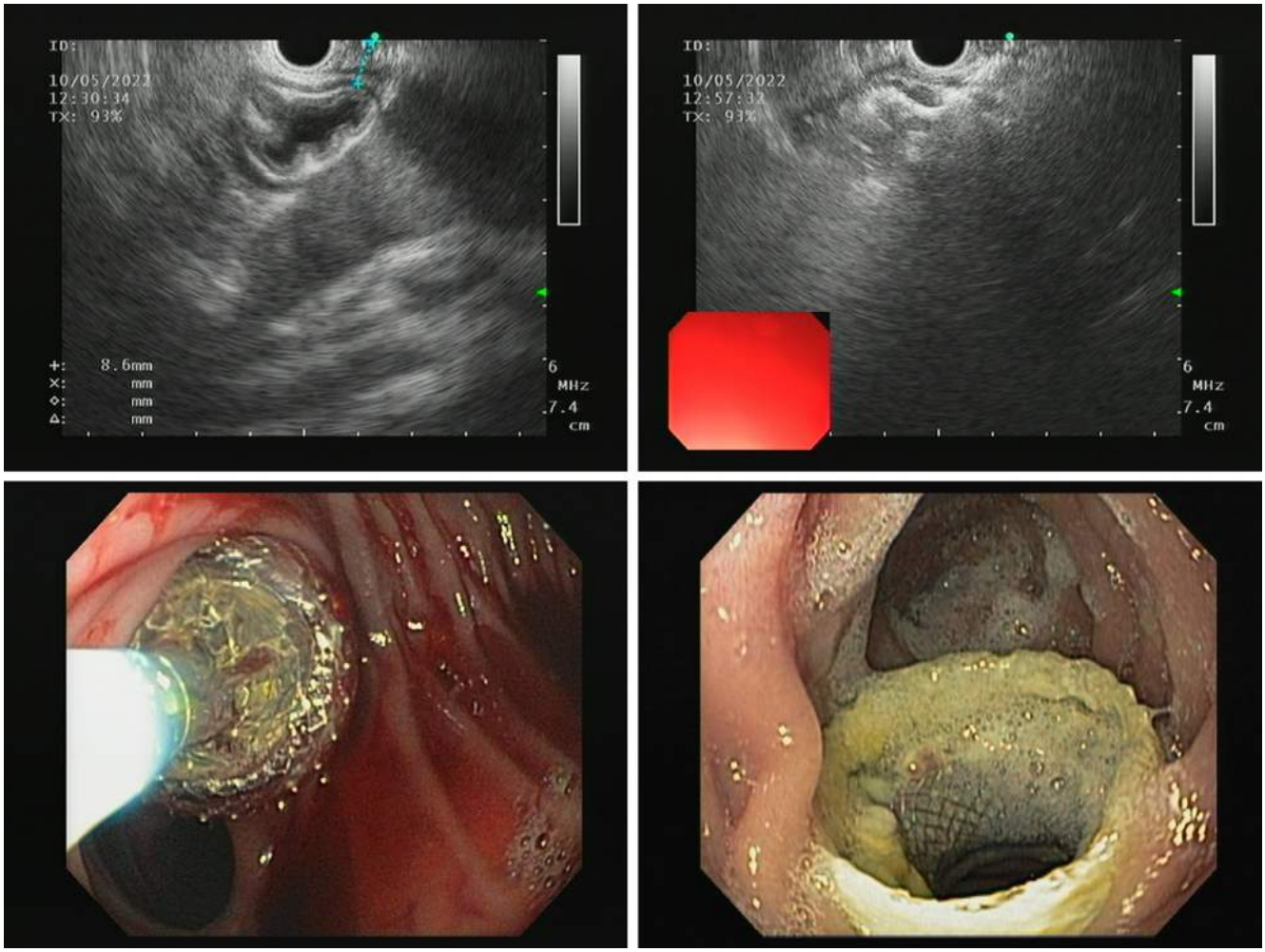

Figure 4. Step-by-step frames of the procedure until the mature jejunogastrostomy after one week. Source: Patient's medical record.

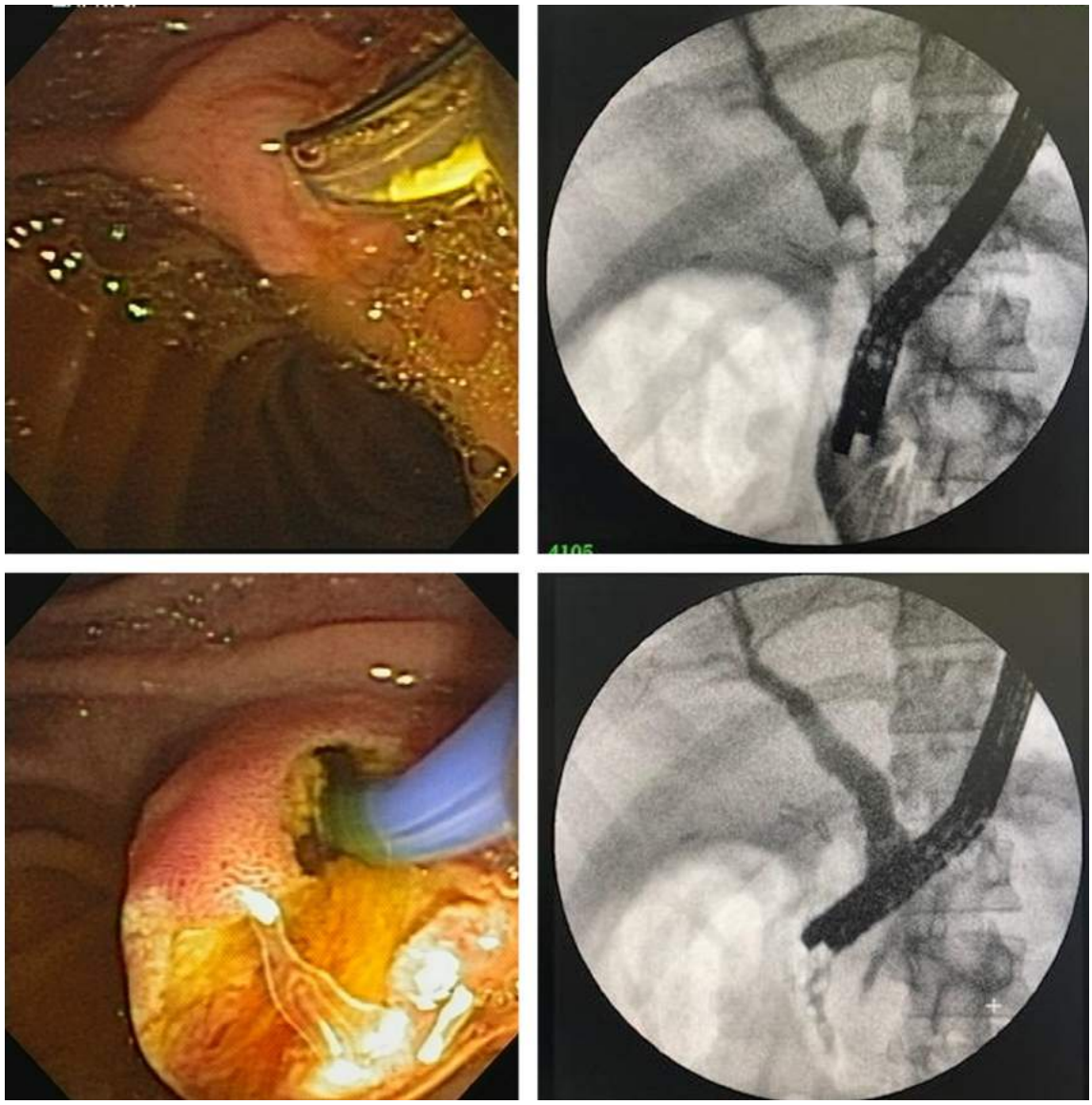

Figure 5. Access to the papilla through the apposing stent and cholangiogram with a side-viewing duodenoscope. Standard technique. Source: Patient's medical record.

stent was verified, and emptying of the gastric chamber was performed by aspiration.

The patient was managed on an outpatient basis through telephone follow-up; she did not exhibit alarm symptoms or abdominal pain and had adequate tolerance to the oral route.

The stent was left in position for two more weeks; it was removed endoscopically without difficulty, and the jejunogastric fistula was confirmed to be contracting.

DISCUSSION

In the second half of the 20th century and the first two decades of this century, the prevalence of obesity has resulted in a growing number of treatments to try to control its frequency and lethal consequences.

Medical treatments, including diet and lifestyle changes, have proven to have limited effectiveness, so surgical

therapies have been used with increasing frequency and variable success rates but are more satisfactory in the medium term. In our setting, bariatric surgical management has opted for gastric sleeve surgery and Roux-en-Y gastric bypass surgery (RYGB).

In the United States, RYGB accounts for 70–80% of bariatric procedures, and it has been estimated that between 29% and 36% of these patients will develop gallstone disease associated with rapid weight loss, primarily 12 to 18 months postoperative[1,2].

For more than 40 years, ERCP has been the standard for managing choledocholithiasis; however, post-surgical anatomical distortion in patients with RYGB significantly limits the endoscopic approach[3].

ERCP in patients with altered anatomy poses an enormous technical challenge and is associated with a significant number of failed procedures and adverse events when compared to the standard procedure. The most used approaches today can be classified as totally endoscopic, balloon or double-balloon enteroscopy-assisted (BEA-ERCP), EUS-assisted (EDGE), and mixed, endoscopic and laparoscopic techniques (laparoscopic-assisted transgastric ERCP)[4,5].

The endoscopic approach to the bile duct in these cases has several difficulties. The first is the endoscopic approach to the papilla. RYGB involves the creation of a bile loop of 80 to 150 cm, meaning maneuvering an endoscopic instrument requires very high skill and training. Even so, angulations of the loop generated by peritoneal adhesions or internal hernias can make it impossible to reach the duodenum in a retrograde manner.

Once the papilla is reached, the second difficulty level corresponds to selective bile duct cannulation, which must be performed inverted and with a front-viewing instrument. In addition, the usual accessories cannot be used on the enteroscopy because they lack the necessary length or diameter.

Lastly, successful permeabilization is difficult once the bile duct has been canalized. The lack of instruments specifically designed to deal with difficult stones, including the impossibility of implanting plastic or metal prostheses, can make the entire procedure fruitless[6].

The technical success of the enteroscopy approach in patients with RYGB is disappointing in statistical analyses, as it fluctuates between 69% and 74%; clinical success is even lower, between 60% and 65%[7].

Izawa et al., in a retrospective study with 91 patients with different types of gastroenteric reconstruction, report a success rate of 92.3% for the papilla approach, 90.5% for cannulation, but only 78% success for the complete procedure[8].

Baron and Vickers described the creation of a gastrostomy to access the gastric remnant through which double-balloon enteroscopy-assisted ERCP (DBE-ERCP) was performed. This technique is more effective in accessing the pancreaticobiliary tree, but it has difficulties regarding the maturation time of the gastrostomy and a high rate of complications associated with it[9].

Laparoscopic-assisted transgastric ERCP is a proven technique, initially described in 2002[10], which approaches the papilla in an antegrade manner with a side-viewing duodenoscope and standard endoscopic instruments; this increases the success of the procedure. It is necessary to access the excluded stomach by laparoscopy and create a gastrostomy through which the side-viewing duodenoscope is advanced, which must be guided by the laparoscopist for passage through the pylorus; subsequently, a technique similar to that performed in procedures with preserved anatomy must be followed.

A 2012 single-center retrospective study by Schreiner et al. found that laparoscopic-assisted ERCP was more effective than enteroscopy-assisted ERCP in patients with long-loop RYGB[11].

In 2014, Baron et al. performed percutaneous endoscopic gastrostomies and placed self-expanding metal stents to allow immediate transgastric ERCP[12].

Recently, with the emergence of apposing metal stents, communication of abdominal cavities has been achieved through EUS and fluoroscopy, allowing successful management of pancreatic necrosis and performance of gastroenteric bypasses in patients with obstruction of the gastric tract outlet. Performing EUS-guided gastrogastrostomy or jejunogastrostomy to access the remnant stomach in patients with RYGB is a technique proposed in 2014 in a series of cases published by Kedia et al.[13]; since then, the refinement of the method has allowed it to be performed more and more frequently and has multicenter experiences that support its feasibility and adoption.

In our country, no reports in the literature allow for evaluating the technique's performance, which is why the description of this clinical case is valuable.

A systematic review from 2022, conducted by Prakash et al. (14) with 169 patients, reported that the technique was successful in creating the gastrogastric or jejunogastric fistula in 99% of cases, and ERCP was completed in 98%.

Minor adverse events associated with stent migration or malposition during the procedure and mild abdominal pain afterward are described in 18% of cases. Moderate adverse events occurred in 5%, including bleeding, persistent fistula, and perforation. Only one serious event is listed, which was a gastric perforation that required surgery.

A common question is secondary weight gain. An American multicenter study of 13 groups on the East Coast collected data from 178 patients taken for EDGE and

mainly evaluated the persistence of fistula. It was objective in only nine cases, five of which were successfully managed with endoscopic closure. Three patients exhibited weight gain during the study, and this method found a success rate of 98% for the resolution of biliary pathology.

If these results are compared with those published in 2017 by Banerjee et al. regarding laparoscopic-assisted transgastric ERCP with a success rate in access to the papilla of 100% and ductal cannulation of 98.5%[15], it is not possible to sense apparent differences with the EDGE; however, comparative studies are required.

EDGE offers the possibility of using an utterly endoscopic technique under sedation on an outpatient basis, so, despite the high cost of apposing stents, it may find validity in future cost analyses.

CONCLUSION

EUS-directed ERCP is a procedure with an adequate safety profile in patients with biliary obstruction and a history of gastric bypass; it can be performed on an outpatient basis and in the comfort of the endoscopy room. There are limitations regarding the available studies; most have been published as case reports and systematic reviews. None describes the experience in our environment, so this initial report is valuable as an index case for implementing the method.

REFERENCES

1. Khara HS, Parvataneni S, Park S, Choi J, Kothari TH, Kothari ST. Review of ERCP Techniques in Roux-en-Y Gastric Bypass Patients: Highlight on the Novel EUS-Directed Transgastric ERCP (EGDE) Technique. Curr Gastroenterol Rep. 2021;23(7):10. https://doi.org/10.1007/s11894-021-00808-3
2. Caruana JA, McCabe MN, Smith AD, Camara DS, Mercer MA, Gillespie JA. Incidence of symptomatic gallstones after gastric bypass: is prophylactic treatment really necessary? Surg Obes Relat Dis. 2005;1(6):564-7; discussion 567-8. https://doi.org/10.1016/j.soard.2005.08.004
3. Tarantino I, Rizzo GEM. Biliopancreatic Endoscopy in Altered Anatomy. Medicina (Kaunas). 2021;57(10):1014. https://doi.org/10.3390/medicina57101014
4. Nakai Y, Kogure H, Yamada A, Isayama H, Koike K. Endoscopic management of bile duct stones in patients with surgically altered anatomy. Dig Endosc. 2018;30 Suppl 1:67-74. https://doi.org/10.1111/den.13022
5. Richardson JF, Lee JG, Smith BR, Nguyen B, Pham KP, Nguyen NT. Laparoscopic transgastric endoscopy after Roux-en-Y gastric bypass: case series and review of the literature. Am Surg. 2012;78(10):1182-6. https://doi.org/10.1177/000313481207801037
6. Krutsri C, Kida M, Yamauchi H, Iwai T, Imaizumi H, Koizumi W. Current status of endoscopic retrograde cholangiopancreatography in patients with surgically altered anatomy. World J Gastroenterol. 2019;25(26):3313-33. https://doi.org/10.3748/wjg.v25.i26.3313
7. Shah RJ, Smolkin M, Yen R, Ross A, Kozarek RA, Howell DA, et al. A multicenter, U.S. experience of single-balloon, double-balloon, and rotational overtube-assisted enteroscopy ERCP in patients with surgically altered pancreaticobiliary anatomy (with video). Gastrointest Endosc. 2013;77(4):593-600. https://doi.org/10.1016/j.gie.2012.10.015
8. Izawa N, Tsuchida K, Tominaga K, Fukushi K, Sakuma F, Kashima K, et al. Factors Affecting Technical Difficulty in Balloon Enteroscopy-Assisted Endoscopic Retrograde Cholangiopancreatography in Patients with Surgically Altered Anatomy. J Clin Med. 2021;10(5):1100. https://doi.org/10.3390/jcm10051100
9. Baron TH, Vickers SM. Surgical gastrostomy placement as access for diagnostic and therapeutic ERCP. Gastrointest Endosc. 1998;48(6):640-1. https://doi.org/10.1016/s0016-5107(98)70052-5
10. Peters M, Papasavas PK, Caushaj PF, Kania RJ, Gagné DJ. Laparoscopic transgastric endoscopic retrograde cholangiopancreatography for benign common bile duct stricture after Roux-en-Y gastric bypass. Surg Endosc. 2002;16(7):1106. https://doi.org/10.1007/s00464-001-4180-3
11. Schreiner MA, Chang L, Gluck M, Irani S, Gan SI, Brandabur JJ, et al. Laparoscopy-assisted versus balloon enteroscopy-assisted ERCP in bariatric post-Roux-en-Y gastric bypass patients. Gastrointest Endosc. 2012;75(4):748-56. https://doi.org/10.1016/j.gie.2011.11.019
12. Baron TH, Song LM, Ferreira LE, Smyrk TC. Novel approach to therapeutic ERCP after long-limb Roux-en-Y gastric bypass surgery using transgastric self-expandable metal stents: experimental outcomes and first human case study (with videos). Gastrointest Endosc. 2012;75(6):1258-63. https://doi.org/10.1016/j.gie.2012.02.026
13. Kedia P, Sharaiha RZ, Kumta NA, Kahaleh M. Internal EUS-directed transgastric ERCP (EDGE): game over. Gastroenterology. 2014;147(3):566-8. https://doi.org/10.1053/j.gastro.2014.05.045
14. Prakash S, Elmunzer BJ, Forster EM, Cote GA, Moran RA. Endoscopic ultrasound-directed transgastric ERCP (EDGE): a systematic review describing the outcomes, adverse events, and knowledge gaps. Endoscopy.

2022;54(1):52-61.
https://doi.org/10.1055/a-1376-2394
15. Banerjee N, Parepally M, Byrne TK, Pullatt RC, Coté GA, Elmunzer BJ. Systematic review of transgastric ERCP in Roux-en-Y gastric bypass patients. Surg Obes Relat Dis. 2017;13(7):1236-42.
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Case report

Primary Anorectal Melanoma: Case Report and Review of a Rare Neoplasm

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Abstract

Primary anorectal melanoma is a rare malignant melanocytic neoplasm; its principal manifestation is rectal bleeding. It has an ominous prognosis with a five-year survival rate of 10%. The case of a 56-year-old woman with rectal bleeding and the sensation of a rectal mass is presented. A polypoid lesion, resected transanally, was documented in the distal rectum during the colonoscopy. The histological study confirmed a primary anorectal melanoma.

Keywords

Malignant melanoma, anal neoplasms, rectal neoplasms, gastrointestinal bleeding, colonoscopy.

INTRODUCTION

Primary anorectal melanoma (PAM) is a rare pathology that represents less than 1% of all colorectal tumors[(1)]. The primary gastrointestinal mucosal location is the third most common after the skin and retina and mainly affects women between the fifth and sixth decade of life[(2)]. At the anorectal level, the lesion can appear anywhere melanocytes are found (perianal region, transitional zone, or rectal mucosa)[(3)]. The most frequently described clinical manifestations are rectal bleeding, the sensation of mass, and alterations in defecation. It is not uncommon for these lesions to be confused with complicated hemorrhoidal disease, which delays the diagnosis and negatively impacts the prognosis[(4)].

CLINICAL CASE

A 56-year-old woman with a history of rectal bleeding and hematochezia was referred with a diagnosis of thrombosed internal hemorrhoids. During the gastroenterology evaluation, a rectal examination and anoscopy were performed, identifying an indurated violaceous mass that protruded through the anal canal. The colonoscopy revealed a 3-cm violaceous polypoid lesion with ulcerated foci and stigmata of

recent bleeding (**Figure 1**). In the thoracoabdominal computed tomography (CT), no lesions suspicious of metastasis or lymph node involvement were found. Subsequently, a transanal surgical resection of the lesion was performed, and the pathology was reported as a semi-pedunculated polypoid formation covered by grayish mucosa, limited to the submucosa without vascular or perineural invasion. Histology describes a malignant cell tumor with hyperchromatic pleomorphic nuclei with nucleolus, abundant brown pigment in their cytoplasm, and extensive superficial ulceration (**Figure 2**). Finally, the patient was assessed by dermatology and ophthalmology, who found no skin or ocular lesions suggestive of melanoma. The patient continues to be followed up by gastroenterology and oncology; there is no evidence of local or imaging recurrence.

DISCUSSION

PAM was first described in 1857 by Moore; it is a rare pathology, with an incidence of 1.7 cases per million inhabitants[5]. Mucosal melanoma (MM) represents the third most common site of primary melanomas after the skin and eyes, and the incidence varies depending on its location[6] (**Table 1**). Compared to cutaneous melanoma (CM), primary gastrointestinal melanoma is sporadic; its most frequent location is the anorectum (more than 50%), followed by the stomach, small intestine, and colon. Rectal location is more frequent than anal[7]. Countries with a high incidence of CM have similar incidence rates of MM compared to other geographic regions[8]. It is more common in women than men (2:1 ratio), and the average age at diagnosis is 54.5 years[9], coin-

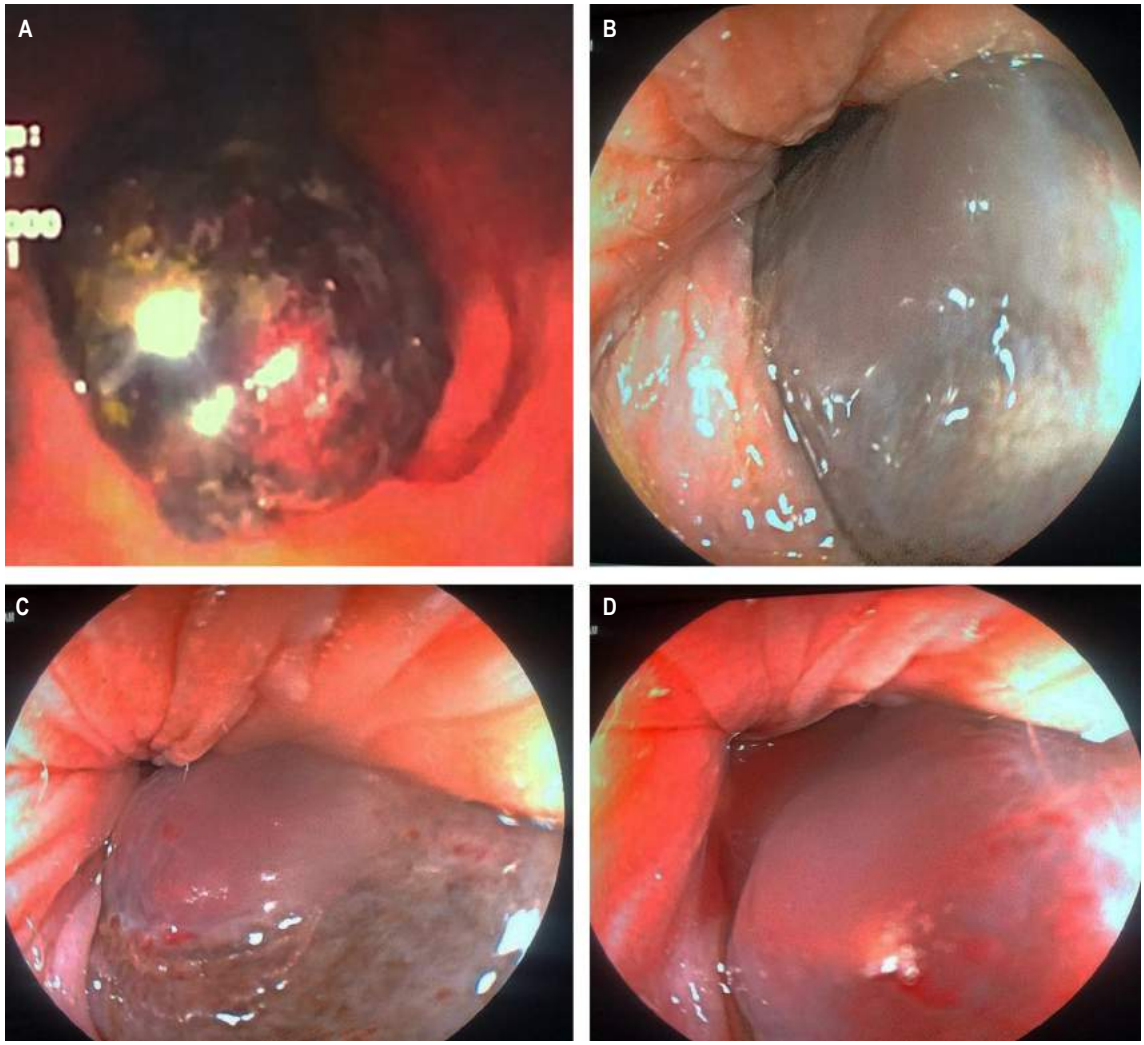

Figure 1. Colonoscopy imaging. **A.** In retroflexion, a hyperpigmented polyploid-looking lesion involving the distal rectum is observed. **B**, **C**, and **D.** A polyploid-looking lesion is observed that protrudes through the anal canal. Source: Case photos, authors' archive.

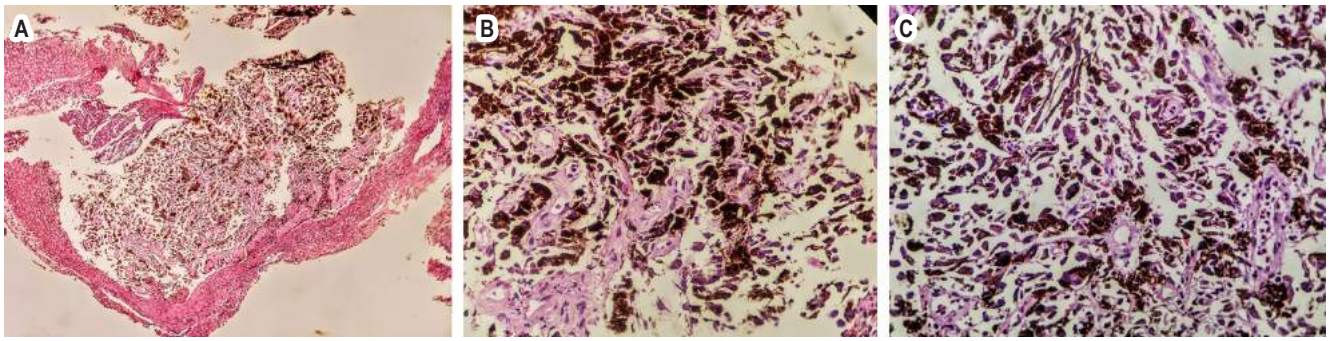

Figure 2. A, B and **C.** Histology demonstrates a malignant tumor of cells with pleomorphic and hyperchromatic nuclei with nucleoli and abundant brown pigment in their cytoplasm. Source: case photos, authors' archive.

Table 1. Epidemiology of primary mucosal melanoma

Primary mucosal melanoma	Cases/million/year
Conjunctival	0.5/million/year
Sinonasal	0.5/million/year
Anorectal	0.4/million/year
Oral	0.2/million/year

Taken and modified from Micu E. J Eur Acad Dermatol Venereol. 2011;25(12):1444–9.

ciding with the case presented. Overall survival is poor and ranges between 10% and 20% at five years, probably because of late diagnosis[10]. Most cases arise from the mucocutaneous junction; however, they can also arise from the skin of the anal verge, the transitional epithelium of the anal canal, or the rectal mucosa[11].

Solar radiation is the stimulus that causes the changes necessary for malignant transformation in the case of CM; in the case of anal melanoma, the causes are unknown. Melanin synthesis is the primary function of melanocytes; their role in mucosal areas is mainly characterized by antioxidant and adjuvant activity in the local immune response[12].

Malignant transformation in anorectal areas may be related to environmental and genetic factors, oxidative stress, immunosuppression, or viral infections[13], and human immunodeficiency virus (HIV) infection is considered an associated risk factor[14]. Another hypothesis is hormonal, possibly due to the participation of estrogens in the pathogenesis of melanoma, increasing the number of melanocytes and their melanin content[15]. These lesions may be an incidental finding during an endoscopic study or the result of histological analysis of a rectal polyp or hemorrhoidectomy[16].

Nodal involvement is found in approximately 60% of patients at diagnosis and distant metastases in 30% of cases[17]. The diagnosis should be suspected when observing a pigmented lesion in the anal canal, although 10% to 30% of these neoplasms are amelanotic[18]. An exhaustive search should be performed to identify malignant skin lesions with the potential to develop GI tract metastases to differentiate and clarify the diagnosis of the primary lesion[19].

The clinical manifestations can be very varied; the most frequent symptoms of this neoplasia are rectal bleeding, proctalgia, pruritus, tenesmus, sensation of anal mass, or alteration of intestinal habit; the lesion can protrude through the anal sphincter either during defecation or with the Valsalva maneuver, becoming a reason for consultation[20]. In a recent series, only 0.8% of patients manifested bleeding symptoms[21]. Regarding the endoscopic findings, the manifestation may be a melanotic polypoid lesion, as occurred in this case, or a mass that simulates colorectal cancer[22]. Histologically, the melanin pigment is characteristic, although immunohistochemistry with positivity for HMB-45 and S-100 protein is much more specific[23].

TREATMENT

Surgery is the most effective treatment for PAM if proper staging is performed. Contrast-enhanced magnetic resonance imaging (MRI) of the abdomen and pelvis allows us to clarify the degree of invasion[24]. PAM has an aggressive behavior; most patients have metastases at the time of diagnosis, mainly to the lungs[25]. Local resection (LR) has greater immediate benefits for the patient, such as early recovery, shorter hospital stays, and minimal

impact on intestinal function. Abdominoperineal resection (APR) offers better disease-free survival and greater locoregional control[26]. Neither of these two techniques is a definitive cure; APR has given fewer recurrences than LR (29% versus 58%)[27]. The role of lymphadenectomy in surgical treatment is controversial[26]. Bilateral inguinal lymphadenectomy in patients with PAM without palpable lymph nodes increases the risk of complications without improvement in survival[28]. Control of local primary disease can be achieved with adjuvant radiotherapy after surgical resection[29]. Non-surgical treatment of PAM includes the administration of chemotherapy and radiotherapy. Moozar et al. evaluated the usefulness of radiotherapy for palliative purposes in a series of patients with PAM, noting an improvement in survival (16 months versus five months) compared to patients who underwent surgery alone[30].

Regarding systemic therapies, there is currently no consensus on the most appropriate treatment for this type of melanoma. Some protocols, previously aimed at patients with CM, have been studied in the context of MM, including PAM[31]. A multicenter case-control study evaluating the effect of a four-drug combination known as the Dartmouth regimen (dacarbazine, cisplatin, carmustine, and tamoxifen) versus dacarbazine found a better response rate (19% vs. 10%)[32]. Singhal et al. reported on the efficacy of taxanes and showed a median overall survival of 11 months[33].

FOLLOW-UP

There is no clarity regarding how follow-up should be performed after treatment of melanoma with primary rectal involvement. Its approach is based on the extrapolation of patients with CM[34]. A retrospective study that included 81 patients described the most frequent locations of metastases, regardless of the primary site of the disease, and reported extension to the liver (57%), lungs (41%), lymph nodes (38%), soft tissues (22%), bone (12%), and the central nervous system (7%). With these data, the best follow-up option likely includes brain, chest, and abdominopelvic CT. Regarding endoscopic follow-up, the surveillance intervals are not defined; some referral centers recommend following closely (every three months) during the first year and then a colonoscopy every six months[35].

CONCLUSION

PAM is a rare malignant neoplasm that poses a diagnostic challenge. This tumor is characterized by aggressive behavior due to biological differences in the melanocytes in this anatomical area compared to other locations. Factors such as inadequate discernment of endoscopic findings, which are confused with benign pathologies such as hemorrhoidal disease, provide a poor short-term prognosis. Due to its low incidence, few studies report what the best therapeutic and surveillance strategy is; most data are extrapolations from CM. The survival of patients depends on the stage at the time of diagnosis. In this case, the patient underwent local resection and was referred to the oncology service. Therefore, it is deemed essential that gastroenterologists become familiar with this type of lesion, which will allow a timely diagnosis and adequate treatment.

Conflict of interest

The authors declare no conflict of interest.

REFERENCES

1. Hicks CW, Pappou EP, Magruder JT, Gazer B, Fang S, Wick EC, et al. Clinicopathologic presentation and natural history of anorectal melanoma: a case series of 18 patients. JAMA Surg. 2014;149(6):608-611. https://doi.org/10.1001/jamasurg.2013.4643
2. Callahan A, Anderson WF, Patel S, Barnholtz-Sloan JS, Bordeaux JS, Tucker MA, et al. Epidemiology of anorectal melanoma in the United States: 1992 to 2011. Dermatol Surg. 2016;42(1):94-9. https://doi.org/10.1097/DSS.0000000000000579
3. Seetharamu N, Ott PA, Pavlick AC. Mucosal melanomas: a review of the literature. Oncologist. 2010;15(7):772-781. https://doi.org/10.1634/theoncologist.2010-0067
4. Edelman A, Brown T, Gandhi R, Gandhi R. Anorectal Melanoma Misdiagnosed as Hemorrhoids: A Case Report and Review of the Literature. J Clin Aesthet Dermatol. 2021;14(4):32-35.
5. Parra RS, Almeida AL, Badiale BG, Moraes MM, Rocha JJ, Féres O. Melanoma of the anal canal. Clinics (Sao Paulo). 2010;65(10):1063-65. https://doi.org/10.1590/S1807-59322010001000026
6. Micu E, Juzeniene A, Moan J. Comparison of the time and latitude trends of melanoma incidence in anorectal region and perianal skin with those of cutaneous malignant melanoma in Norway. J Eur Acad Dermatol Venereol. 2011;25(12):1444-9. https://doi.org/10.1111/j.1468-3083.2011.04023.x

7. Ragnarsson-Olding BK, Nilsson PJ, Olding LB, Nilsson BR. Primary ano-rectal malignant melanomas within a population-based national patient series in Sweden during 40 years. Acta Oncol. 2009;48(1):125-31. https://doi.org/10.1080/02841860802120861
8. Miller BJ, Rutherford LF, McLeod GR, Cohen JR. Where the sun never shines: Anorectal melanoma. Aust N Z J Surg. 1997;67(12):846-8. https://doi.org/10.1111/j.1445-2197.1997.tb07609.x
9. Postow MA, Hamid O, Carvajal RD. Mucosal melanoma: Pathogenesis, clinical behavior, and management. Curr Oncol Rep. 2012;14(5):441-8. https://doi.org/10.1007/s11912-012-0244-x
10. Cagir B, Whiteford MH, Topham A, Rakinic J, Fry RD. Changing epidemiology of anorectal melanoma. Dis Colon Rectum. 1999;42(9):1203-08. https://doi.org/10.1007/BF02238576
11. Row D, Weiser MR. Anorectal melanoma. Clin Colon Rectal Surg. 2009;22(2):120-6. https://doi.org/10.1055/s-0029-1223844
12. Zecca L, Zucca FA, Wilms H, Sulzer D. Neuromelanin of the substantia nigra: A neuronal black hole with protective and toxic characteristics. Trends Neurosci. 2003;26(11):578-80. https://doi.org/10.1016/j.tins.2003.08.009
13. Curtin JA, Fridlyand J, Kageshita T, Patel HN, Busam KJ, Kutzner H, et al. Distinct sets of genetic alterations in melanoma. N Engl J Med. 2005;353(20):2135-47. https://doi.org/10.1056/NEJMoa050092
14. Jensen C, Kin C. Black is the new black: Prolapsing primary anorectal melanoma. Dig Dis Sci. 2017;62(11):2991-3. https://doi.org/10.1007/s10620-017-4527-9
15. Smith MA, Fine JA, Barnhill RL, Berwick M. Hormonal and reproductive influences and risk of melanoma in women. Int J Epidemiol. 1998;27(5):751-7. https://doi.org/10.1093/ije/27.5.751
16. Bullard KM, Tuttle TM, Rothenberger DA, Madoff RD, Baxter NN, Finne CO, et al. Surgical therapy for anorectal melanoma. J Am Coll Surg. 2003;196(2):206-11. https://doi.org/10.1016/S1072-7515(02)01538-7
17. Smith HG, Glen J, Turnbull N, Peach H, Board R, Payne M, et al. Less is more: A systematic review and meta-analysis of the outcomes of radical versus conservative primary resection in anorectal melanoma. Eur J Cancer. 2020;135:113-120. https://doi.org/10.1016/j.ejca.2020.04.041
18. Pessaux P, Pocard M, Elias D, Duvillard P, Avril MF, Zimmerman P, et al. Surgical management of primary anorectal melanoma. Br J Surg. 2004;91(9):1183-7. https://doi.org/10.1002/bjs.4592
19. Nam S, Kim CW, Baek SJ, Hur H, Min BS, Baik SH, et al. The clinical features and optimal treatment of anorectal malignant melanoma. Ann Surg Treat Res. 2014;87(3):113-17. https://doi.org/10.4174/astr.2014.87.3.113
20. Zhou HT, Zhou ZX, Zhang HZ, Bi JJ, Zhao P. Wide local excision could be considered as the initial treatment of primary anorectal malignant melanoma. Chin Med J (Engl). 2010;123(5):585-8.
21. David AW, Perakath B. Management of anorectal melanomas: a 10-year review. Trop Gastroenterol. 2007;28(2):76-8.
22. Slingluff CL Jr, Vollmer RT, Seigler HF. Anorectal melanoma: clinical characteristics and results of surgical management in twenty-four patients. Surgery. 1990;107(1):1-9.
23. Das G, Gupta S, Shukla PJ, Jagannath P. Anorectal melanoma: a large clinicopathologic study from India. Int Surg. 2003;88(1):21-4.
24. Chae WY, Lee JL, Cho D-H, Yu SK, Roh, J, Kim JC. Preliminary suggestion about staging of anorectal malignant melanoma may be used to predict prognosis. Cancer Res Treat. 2016;48(1):240-9. https://doi.org/10.4143/crt.2014.305
25. Podnos YD, Tsai NC, Smith D, Ellenhorn JD. Factors affecting survival in patients with anal melanoma. Am Surg. 2006;72(10):917-20. https://doi.org/10.1177/000313480607201017
26. Yeh JJ, Shia J, Hwu WJ, Busam KJ, Paty PB, Guillem JG, et al. The role of abdominoperineal resection as surgical therapy for anorectal melanoma. Ann Surg. 2006;244(6):1012-17. https://doi.org/10.1097/01.sla.0000225114.56565.f9
27. Falch C, Mueller S, Kirschniak A, Braun M, Koenigsrainer A, Klumpp B. Anorectal malignant melanoma: Curative abdominoperineal resection: patient selection with 18F-FDG-PET/CT. World J Surg Oncol. 2016;14(1):185. https://doi.org/10.1186/s12957-016-0938-x
28. Ceccopieri B, Marcomin AR, Vitagliano F. Primary anorectal malignant melanoma: report of two cases. Tumori. 2000;86(4):356-8. https://doi.org/10.1177/030089160008600430
29. Bujko K, Nowacki MP, Liszka-Deleck P. Radiation therapy for anorectal melanoma - a report of three cases. Acta Oncol. 1998;37(5):497-9. https://doi.org/10.1080/028418698430485
30. Moozar KL, Wong CS, Couture J. Anorectal malignant melanoma: treatment with surgery or radiation therapy, or both. Can J Surg. 2003;46(5):345-9.
31. Tacastacas JD, Bray J, Cohen YK, Arbesman J, Kim J, Koon HB, et al. Update on primary mucosal melanoma. J Am Acad Dermatol. 2014;71(2):366-753. https://doi.org/10.1016/j.jaad.2014.03.031
32. Chapman PB, Einhorn LH, Meyers ML, Saxman S, Destro AN, Panageas KS, et al. Phase III multicenter randomized trial of the Dartmouth regimen versus dacarbazine in patients with metastatic melanoma. J Clin Oncol. 1999;17(9):2745-51. https://doi.org/10.1200/JCO.1999.17.9.2745
33. Singhal NK, Ostwal VS, Shrikhande SV, Saklani A, Arya S, Ramadvar M. Systemic therapy in anorectal melanoma: Does choice of systemic therapy matter? ASCO. J Clin

Oncol. 2016;34(suppl 4S; abstr 731). https://doi.org/10.1200/jco.2016.34.4_suppl.731
34. Thibault C, Sagar P, Nivatvongs S, Ilstrup DM, Wolff BG. Anorectal melanoma--an incurable disease? Dis Colon Rectum. 1997;40(6):661-8. https://doi.org/10.1007/BF02140894
35. Shoushtari AN, Bluth MJ, Goldman DA, Bitas C, Lefkowitz RA, Postow MA, et al. Clinical features and response to systemic therapy in a historical cohort of advanced or unresectable mucosal melanoma. Melanoma Res. 2017;27(1):57-64. https://doi.org/10.1097/CMR.0000000000000306

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Case report

Manganese Associated with Non-Wilsonian Hepatolenticular Degeneration as a Rare Cause of Encephalopathy: Case Report

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Abstract

Aim: To describe the clinical picture, diagnosis, and treatment of a patient with encephalopathy as a manifestation of manganese-induced non-Wilsonian hepatolenticular degeneration (NWHD) in a high-complexity care center in a Latin American country. **Case description:** A 55-year-old male patient from the United States with a history of liver disease associated with alcohol consumption was admitted to the emergency department due to diarrhea, hematemesis, and psychomotor agitation. During his stay, his state of consciousness deteriorated, requiring orotracheal intubation. In his diagnostic study, cerebrospinal fluid tests were negative for infectious etiologies; the endoscopic examinations showed no marks of portal hypertension bleeding, while ammonium and tests for metabolic causes were normal. However, areas of hyperintensity in the basal ganglia were documented on brain MRI, with normal ceruloplasmin serum and urine copper levels, which ruled out Wilson's disease and determined the diagnosis of manganese-induced NWHD. **Conclusion:** NWHD is a rare cause of chronic encephalopathy with clinical manifestations of extrapyramidal symptoms secondary to basal ganglia dysfunction due to severe liver disease. Its diagnosis becomes a challenge, given that manganese deposits produce it, and no biomarkers can establish the level of exposure to this metal. Brain MRI is indispensable in reflecting these deposits in the basal ganglia.

Keywords

Hepatic encephalopathy, hepatolenticular degeneration, manganese, diagnostic imaging.

INTRODUCTION

Neurological disorders associated with liver diseases have attracted increasing interest. Acquired hepatolenticular degeneration (ADH) was described in 1919 by Woerkem[(1)] and was later called *acquired non-Wilsonian hepatolenticular degeneration* by Víctor et al.[(2)] in 1965. It is a neurodegenerative disorder that affects the basal nuclei and has mechanisms responsible for neuronal dysfunction and death other than Wilson's disease, which mainly generates extrapyramidal symptoms such as tremor and rigidity associated with cognitive impairment in patients with cirrhosis in the absence of Kayser-Fleischer rings characteristic of Wilson's disease[(3,4)]. Its origin depends on deposits formed by toxic substances not eliminated by the hepatobiliary system, which allows these agents, especially heavy metals such as manganese, to be released into the circulation and play an essential role in the pathogenesis of ADH[(5–8)].

We present the case of a man whose diagnosis of ADH was challenging, given that he had an established history of liver disease associated with alcohol consumption; however, the ammonium levels and the upper gastrointestinal endoscopy without stigmata of variceal bleeding led to thinking about different causes of encephalopathy, and magnetic resonance imaging (MRI) helped reach a definitive diagnostic approach.

CASE PRESENTATION

A 55-year-old man from the United States, where esophageal variceal ligation was performed in November 2021 related to the diagnosis at the time of liver cirrhosis secondary to alcohol intake since the age of 35, drank a bottle a day on average for ten years. He had no follow-up or outpatient treatment, nor did he suffer from other comorbidities or family history. He had a complete vaccination schedule against COVID-19.

He consulted the emergency service in July 2022 due to a three-day picture of watery stools without mucus, blood, melena, or temperature rises, two episodes of small hematemesis, temporal and spatial disorientation, and changes in behavior involving aggressiveness. In the first evaluation, he was alert, dyspraxic, disoriented in time and personal identity, uncooperative with the interview, and with no alteration in vital signs. Given the history of liver disease, it was classified as West Haven 2 hepatic encephalopathy (HE) during the first hours of care. He became agitated and aggressive, with tachycardia and tachypnea. After 24 hours, he had significant neurological deterioration (HE West Haven 4), requiring orotracheal intubation to protect the airway.

His initial studies showed normocytic anemia, mild electrolyte disorder due to hypernatremia and hyperchloremia, altered liver function with cirrhosis classified as Child-Pugh B, MELD of 14, preserved renal function, increased inflammatory markers, metabolic acidemia with elevated anion gap (17.3 mEq). /L), uncompensated (arterial gases: pH 7.3, partial pressure of carbon dioxide (PCO_2) of 21.8 mm Hg, partial pressure of oxygen (PO_2) of 97.8 mm Hg, oxygen saturation ($SatO_2$) of 98.1%, fraction inspired oxygen (FIO_2) of 21%, bicarbonate (HCO_3) of 16.6 mmol/L, Be of -5.3 mmol/L and lactic acid of 2.23 mmol/L) (**Table 1**).

Given the clinical and laboratory signs of a systemic inflammatory response and the probability of a systemic response, antibiotic management was indicated with ceftriaxone 1 g every 12 hours and intravenous vasoactive sup-

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

Laboratory	Patient value	Reference value	Laboratory	Patient value	Reference value
Leukocytes	8.04	4.8-11/mm^3	AST	47	8-33 U/L
Neutrophils	4.58	2.2-7.7/mm^3	ALT	18	4-36 U/L
Lymphocytes	2.66	1.3-2.9/mm^3	GGT	35	5-40 U/L
Hemoglobin	10.4	13-16 g/dL	Alkaline phosphatase	77	44-147 UI/L
Hematocrit	29.7	36 %-48 %	TB	1.97	0.1-1 mg/dL
MCV	93.4	80-100 fL	DB	1.33	<0.3 mg/dL
Platelets	151	150-450/mm^3	IB	0.64	0.1-0.5 mg/dL
Sodium	147	135-145 mEq/L	Albumin	3.3	3.8-5 g/dL
Potassium	3.9	3.9-5.5 mEq/L	PT	15.8	9.5-12.5 s
Chlorine	117	98-107 mEq/L	TPT	31.8	25-37 s
Magnesium	1.89	1.6-2.4 mEq/L	Creatinine	0.59	0.7-1.17 mg/dL
Phosphorus	2.5	2.5-4.5 mg/dL	Ureic nitrogen	19.1	20 mg/dL
Ionic calcium	1.18	4.8-5.6 mg/dL	CRP	12.5	<1 mg/dL
TSH	0.67	0.37-4.7 uU/mL	Procalcitonin	<0.05	<0.5 ng/mL

ALT: alanine aminotransferase; AST: aspartate aminotransferase; CRP: C-reactive protein; DB: direct bilirubin; GGT: gamma-glutamyl transferase; IB: indirect bilirubin; MCV: mean corpuscular volume; PT: prothrombin time; PTT: thromboplastin time; TB: total bilirubin; TSH: thyroid stimulating hormone. Prepared by the authors.

port with terlipressin 2 mg every 4 hours. Complementary paraclinical tests showed normal ammonium (48 µmol/L), normal liver infectious tests, normal ferrokinetic profile (ferritin 86.2 ng/mL, transferrin saturation percentage of 25%, normal vitamin B12 and folic acid, and negative hepatitis A IgM antibodies, hepatitis B surface antigen (AgSVHB), anti-AgSVHB antibodies, total hepatitis C antibodies, human immunodeficiency virus (HIV), rapid plasma reaginin (RPR), blood cultures, urine cultures, and PCR for SARS-CoV-2.

An upper GI endoscopy was performed, noting varicose cords with varicose veins smaller than 5 mm, without stigmata of recent bleeding (Paquet III) or gastric varices, which, added to the heterogeneous hepatic echogenicity documented in the abdominal ultrasound, led to the consideration of cirrhosis of alcoholic origin (risk consumption of 88 g of alcohol, 8.7 units of standard drink for ten years until November 2021), but there was no evidence of hypertensive portal bleeding. Therefore, it was necessary to rule out nonhepatic causes of encephalopathy.

A lumbar puncture showed no abnormalities in the cytochemistry, a microbiological study for molecular infectious panel turned out negative for neuroinfection, and cytology and an immunophenotype did not exhibit suspicion of tumor involvement. Finally, a nuclear MRI was performed to observe hyperintensities in basal ganglia, bilateral caudate predominance in T1 sequences, and fluid-attenuated inversion recovery (FLAIR) suggestive of hepatolenticular degeneration (**Figure 1**).

In the search for Wilson's disease, the ophthalmology area evaluated and ruled out the presence of Kayser-Fleischer rings. In addition, studies of serum ceruloplasmin (22 mg/dL) and urine copper (27.8 µg/24 hours) were normal.

After four days of intubation, extubation was achieved; 11 days later, he was discharged thanks to improved neurological condition, without recurrence of bleeding, stable hemoglobin, and an outpatient management plan with spironolactone, propranolol, and nutritional recommendations.

DISCUSSION

ADH is a rare entity; in a retrospective study with a population of more than 1,000 patients with liver cirrhosis, only 0.8% had this diagnosis, and in other reports, the prevalence is even lower (less than 0.5%)[5–9], while viral infectious etiology is the most common[10,11]. Manganese, which causes non-Wilsonian ADH, is the twelfth most crucial element and the fifth among metals[12].

Several enzymatic systems depend on and interact with manganese. It is helpful for the formation of cartilage and bone, the maintenance of mitochondria, and the production of glucose[13].

In *in vivo* and *in vitro* studies, both in animal models and in humans, it has been identified that SLC30A10 (Solute Carrier Family 30 Member 10), a carrier of manganese efflux from the cell, plays a vital role in the regulation of the levels of this metal. In predisposed individuals with environmental exposure due to a place of residence in industrial

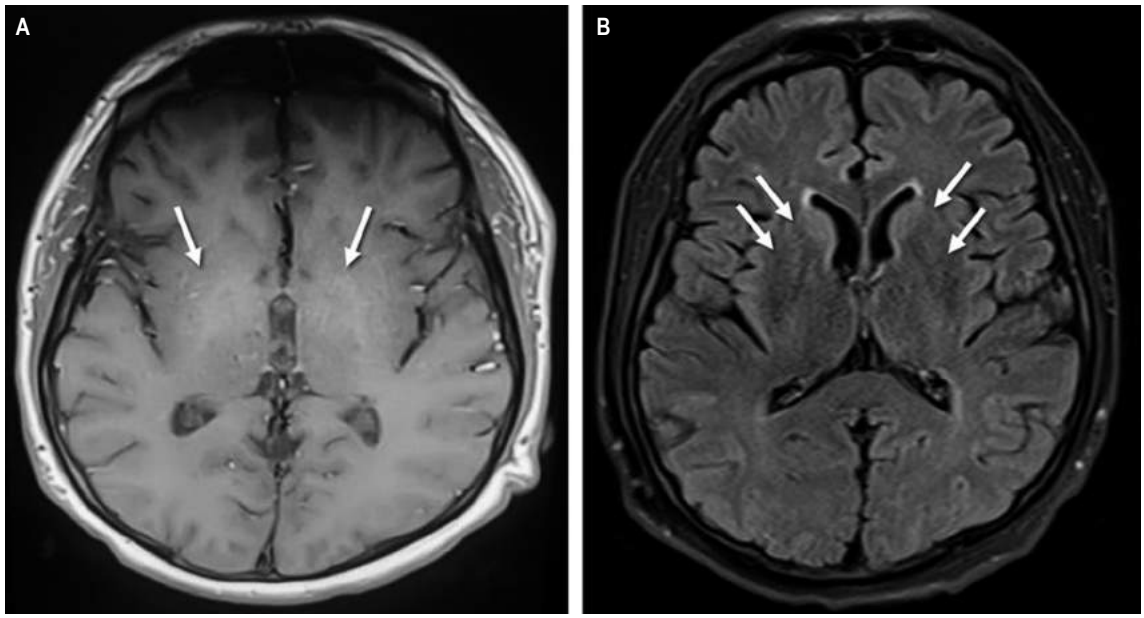

Figure 1. Brain nuclear MRI sequences T1 (**A**) FLAIR (**B**). Arrows show areas of hyperintensity in the bilateral basal ganglia. Source: Authors' archive.

or mining sectors or their occupation, mutations lead to loss of function of SLC20A10 and retention of manganese in the brain, particularly in the basal ganglia and liver, which causes neurotoxicity and liver damage, respectively[14]. Meanwhile, pre-existing diseases and the formation of portosystemic shunts promote the release of manganese into the systemic circulation and its deposition in the brain[15]. A series of five cases of ADH was recently reported; four of them had cirrhosis, one had chronic hepatitis due to the hepatitis C virus, and all had portosystemic shunts[16].

The clinical manifestations of the disease are very heterogeneous. Most patients have changes in behavior, Parkinsonian features, and dystonia with gait alteration[17]. In the case in question, the initial manifestation was a behavior change that alerted his family, then a phase of psychomotor agitation during the stay in the emergency room and subsequently a deterioration in the state of consciousness that required orotracheal intubation and invasive mechanical ventilation in the intensive care unit (ICU). These changes occur due to the increase in manganese in the systemic circulation and its underlying brain deposition, which can happen in the cortex, specifically in the basal ganglia. It entails oxidative stress and induces neurotoxicity through multiple mechanisms such as death of dopaminergic cells and alteration in γ-aminobutyric acid (GABA)-mediated transmission, both inhibitory stimuli; release of glutamate, the primary excitatory neurotransmitter, and a critical signaling molecule; choline deficiency, necessary for the synthesis of acetylcholine, and increase in acetylcholinesterase, the enzyme that degrades it[13,18]. Furthermore, deposits in the central nervous system lead to mitochondrial dysfunction of astrocytes at the level of benzodiazepine receptors[19]. This has been demonstrated in animals, in which manganese levels are observed to affect astrocytes, with a consequent decrease in high-affinity glutamate transport and stress-mediated neuronal death through the activation of the nitric oxide-cyclic guanosine monophosphate pathway[18].

The diagnosis to confirm or rule out ADH requires anamnesis, physical examination findings, blood analysis, and neuroimaging such as contrast-enhanced computed tomography, and, more usually, MRI, which allows the exclusion of other diagnoses such as brain hematomas, small vessel disease, and space-occupying lesions[8]. In ADH, MRI reveals changes in the basal ganglia with T1 hyperintensity, especially in the globus pallidus, a significant proportion in cirrhotic patients, related to the severity of the disease[20]. Laboratory tests can sometimes be helpful; however, it is worth mentioning that manganese levels in blood and urine indicate recent exposure (hours to days), but there are no biomarkers of cumulative exposure to manganese nor prognostic biomarkers of its neurotoxic effects. Therefore, they are not diagnostic.

In the case of suspected Wilson's disease, ceruloplasmin and ammonia levels can be requested to rule it out. In our patient, they were negative, which, in addition to the absence of Kayser-Fleischer rings on physical examination, allowed us to reinforce the diagnostic suspicion, which was complemented by MRI findings of manganese deposits as a causal agent of encephalopathy[19]. Anyway, there is a good correlation between blood manganese levels and T1 hyperintensity observed by MRI, not necessarily correlated with neurological function, so the diagnosis is ultimately based on clinical suspicion and exclusion of more frequent causes without a diagnostic test confirming another etiology[16,20].

Based on recent evidence in HE West Haven 4, finding normal ammonium levels with its high pretest probability is infrequent; still, regardless of the result, the priority in acute conditions is to manage potential contributors such as gastrointestinal bleeding, electrolyte alterations, and infections[21]. Once clinical stability is achieved, if ammonia is normal in HE, it is essential to evaluate the etiologies causing the systemic or neuronal inflammation that resulted in the activation of microglia and encephalopathy in the diagnostic algorithm[22].

For the case reported, the starting point was an already established liver cirrhosis with previous endoscopic management of esophageal varices, which required bleeding to be ruled out. Still, on this occasion, there were no stigmata of recent bleeding. Cultures to rule out systemic and central nervous system infectious causes were negative; however, we could not rule out culture-negative sepsis sensitive to ceftriaxone (community-acquired) due to metabolic acidosis, the possibility of bacterial translocation due to gastrointestinal bleeding, the clinical signs of clinical response, elevated acute inflammation reactants, and a leukocyte count of 8,040/mm3, which is higher than expected in portal hypertension and a prognostic marker for organ failure and mortality, as shown by the CANONIC study in acute-on-chronic liver failure. Therefore, antibiotics and supportive management were necessary in this patient.

Metabolic etiologies related to storage diseases were evaluated, obtaining a normal ferrokinetic profile. On the other hand, in the absence of standardized tests to measure manganese levels, normal ammonium and hyperintensities in the basal ganglia by brain MRI were vital in the differential diagnosis between Wilson's disease and non-Wilsonian ADH, in favor of the latter, taking into account normal levels of serum ceruloplasmin and serum and urinary copper. The distinguishing characteristics of the two diseases are listed in **Table 2**.

Regarding treatment, even if ADH is recognized, it is limited. The use of dopamine agonists may be considered given the symptoms similar to Parkinson's; however, a large proportion of patients do not have a good response. The

Table 2. The main differences between Wilson's disease and non-Wilsonian hepatolenticular degeneration

Wilson's disease	Non-Wilsonian hepatolenticular degeneration
Autosomal inheritance pattern	Acquired
Copper deposits in the liver and brain	Manganese deposits in the brain
The inability of ceruloplasmin and copper to bind	Association with liver failure, mainly of alcohol origin
ATP7B carrier mutation	Increased transport of manganese at the intestinal level and hepatocytes
Extrapyramidal signs of non-Parkinsonian predominance	Predominance of Parkinsonism and extrapyramidal syndrome
Multisystem condition	Histopathological findings similar to Wilson's disease

Adapted from: Rebolledo-García D, et al. Med Int Méx. 2015;31:478–84.

evidence for using rifaximin in managing HE in patients with ADH is poor and comes from case series. As occurred in the patient, the most relevant thing is the supportive treatment of the liver disease and nutritional measures for outpatient management.

A series of three cases of Wilsonian hepatolenticular degeneration was previously reported, and only one documented findings in the basal ganglia in the FLAIR sequence with various clinical manifestations. In contrast, in the case presented, MRI was fundamental for the final diagnosis of non-Wilsonian hepatolenticular degeneration[23]. This experience shows that the different ways this disease can manifest make necessary a comprehensive approach, including the clinical picture and the diagnostic studies available for each case.

CONCLUSION

ADH is a rare disease as a cause of encephalopathy in patients with liver disease, primarily associated with alcoholism, which produces debilitating neurological symptoms resulting from manganese deposits in the basal ganglia. For its diagnosis, it is necessary to rule out other more frequent causes and evaluate the brain image in search of the typical findings in the T1 sequence. While the etiology is defined, management should focus on supportive measures of the liver disease.

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REFERENCES

1. Woerkom W. La cirrhose hepatique avec alterations dan les centres nerveux evoluant chez des sujets dage moyen. Nouvelle Iconographie de la Salpetrie. Clinique Maladies Systeme Nerveux. 1914;7:41-51.
2. Victor M, Adams R, Cole M. The acquired (non-Wilsonian) type of chronic hepatocerebral degeneration. Medicine (Baltimore). 1965;44(5):345-96. https://doi.org/10.1097/00005792-196509000-00001
3. Weissenborn K Parkinsonism in patients with cirrhosis: coincidence or consequence? Liver Int. 2011;31(5):592-94. https://doi.org/10.1111/j.1478-3231.2011.02470.x
4. Butterworth RF. Parkinsonism in cirrhosis: pathogenesis and current therapeutic options. Metab Brain Dis. 2013;28(2):261-7. https://doi.org/10.1007/s11011-012-9341-7
5. Jog MS, Lang AE. Chronic acquired hepatocerebral degeneration: case reports and new insights. Mov Disord. 1995;10(6):714-22. https://doi.org/10.1002/mds.870100604
6. Basile A, Jones E. Ammonia and gabaergic neurotransmission: interrelated factors in the pathogenesis of hepatic encephalopathy. Hepatology. 1997;25(6):1303. https://doi.org/10.1002/hep.510250636

7. Rose C, Butterworth R, Zayed J, Normandin L, Todd K, Michalak A, et al. Manganese deposition in basal ganglia structures results from both portal- systemic shunting and liver dysfunction. Gastroenterology. 1999;117(3):640-44. https://doi.org/10.1016/S0016-5085(99)70457-9
8. Park N, Park J, Choi Y, Yoo CI, Lee CR, Lee H, et al. Whole blood manganese correlates with high signal intensities on T1-weighted MRI patients with liver cirrhosis. Neurotoxicology. 2003;24(6):909-15. https://doi.org/10.1016/S0161-813X(03)00111-6
9. Burkhard PR, Delavelle J, Du Pasquier R, Spahr L. Chronic parkinsonism associated with cirrhosis. A distinct subset of acquired hepatocerebral degeneration. Arch Neurol. 2003;60(4):521-28. https://doi.org/10.1001/archneur.60.4.521
10. Saporta M, Andre' C, Bahia P, Chimelli L, Pais PH, Silva TS, et al. Acquired hepatocerebral degeneration without overt liver disease. Neurology. 2004;63(10):1981-82. https://doi.org/10.1212/01.WNL.0000144193.62505.E6
11. Machado J, Gaspar S, Barbosa V, Bina J, Matos H. High intensity signal in basal ganglia on T1 weighted images: case report in Manson's schistosomiasis with portal systemic encephalopathy. Arq Neuropsiquiatr. 1999;57(2A):306-10. https://doi.org/10.1590/S0004-282X1999000200024
12. Nadaska G, Lesny J, Michalik I. Environmental aspect of manganese chemistry. HEJ. 2012. ENV-100702A:1-16.
13. Cowan DM, Fan Q, Zou Y, Shi X, Chen J, Aschner M, Rosenthal FS, et al. Manganese exposure among smelting workers: blood manganese-iron ratio as a novel tool for manganese exposure assessment. Biomarkers. 2009;14(1):3-16. https://doi.org/10.1080/13547500902730672
14. Balachandran RC, Mukhopadhyay S, McBride D, Veevers J, Harrison FE, Aschner M, et al. Brain manganese and the balance between essential roles and neurotoxicity. J Biol Chem. 2020;295(19):6312-29. https://doi.org/10.1074/jbc.REV119.009453
15. Rajoriya N, Brahmania M, Feld JJ. Implications of manganese in chronic acquired hepatocerebral degeneration. Ann Hepatol. 2019;18(1):274-78. https://doi.org/10.5604/01.3001.0012.7938
16. Kalisky I, Maor Y, Goldstein L, Inbar Y, Ben-Ari Z. Acquired hepatocerebral degeneration a case series of a rare condition. Isr Med Assoc J. 2023;25(1):8-12.
17. Ferrara J, Jankovic J. Acquired hepatocerebral degeneration. J Neurol. 2009;256(3):320-32. https://doi.org/10.1007/s00415-009-0144-7
18. Felipo V, Butterworth RF. Mitochondrial dysfunction in acute hyperammonemia. Neurochem Int. 2002;40(6):487-91. https://doi.org/10.1016/S0197-0186(01)00119-X
19. Yin Z, Aschner JL, dos Santos AP, Aschner M. Mitochondrial-dependent manganese neurotoxicity in rat primary astrocyte cultures. Brain Res. 2008;1203:1-11. https://doi.org/10.1016/j.brainres.2008.01.079
20. Pujol A, Pujol J, Graus F, Rimola A, Peri J, Mercader JM, et al. Hyperintense globus pallidus on T1- weighted MRI in cirrhotic patients is associated with severity of liver failure. Neurology. 1993;43(1):65-9. https://doi.org/10.1212/WNL.43.1_Part_1.65
21. Deutsch-Link S, Moon AM. The Ongoing Debate of Serum Ammonia Levels in Cirrhosis: the Good, the Bad, and the Ugly. Am J Gastroenterol. 2023;118(1):10-3. https://doi.org/10.14309/ajg.0000000000001966
22. Butterworth RF. The liver-brain axis in liver failure: neuroinflammation and encephalopathy. Nat Rev Gastroenterol Hepatol. 2013;10(9):522-8. https://doi.org/10.1038/nrgastro.2013.99
23. Castaño O, Gómez DM, Ocampo JM, Casanova ME. Degeneración hepatolenticular: a propósito de tres casos. 2017;30(4):436-42. https://doi.org/10.17533/udea.iatreia.v30n4a07

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Case report

Diagnosis of Celiac Disease after Starting Antitubercular Medication: A Case Report

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Abstract

We present the case of a young patient from Argentina living in a rural area without any relevant medical history. He consulted the emergency department after blunt chest trauma, and during trauma studies, images compatible with pulmonary tuberculosis were found, a diagnosis made incidentally.

After starting treatment, he exhibited gastrointestinal symptoms such as diarrhea, abdominal pain, and weight loss, which were initially considered an adverse effect of treatment with rifampin/isoniazid/pyrazinamide/ethambutol (RHZE). Upon completing the first phase of treatment and suspending the medication, the symptoms improved, and the bacilloscopies were negative.

Subsequently, the severity of the symptoms drew attention. Additional paraclinical tests were performed with malabsorptive diarrhea results, considering the patient's origin and the fact that his diet included products that he grew himself without prior exposure to gluten. Celiac disease is suspected, and antibodies and biopsy results compatible with this entity were obtained. When reviewing the association of symptom onset with the RHZE/pyridoxine treatment, we found these medications may have wheat-based excipients, which explains the worsening of symptoms, not due to the gastrointestinal adverse effects of the antibiotic but its excipients.

Finally, the case was analyzed, tuberculosis was ruled out, and treatment was suspended, refocusing the therapeutic effort on recovering the patient's nutritional status. Subsequently, no other hospital admissions were recorded, and he remained respiratorily asymptomatic, with weight gain and nutritional recovery.

Keywords

Celiac disease, wheat, tuberculosis, excipients, case report.

INTRODUCTION

Celiac disease (CD) is an autoimmune inflammatory disease that affects the small intestine's mucosa in genetically susceptible individuals; gluten ingestion is the triggering factor, and symptomatic improvement is observed with its withdrawal. A prevalence of 1% is described in the general population; in South America, a prevalence of 1.3% is estimated, and it is higher in countries with Caucasian ancestry, such as Brazil and Argentina. There are few population studies in Colombia, so its prevalence is unknown; its manifestation is variable, from a silent course to malabsorption syndromes. In the last century, there has been an increase in the use of gluten-based products, which could explain the rise in cases.

CASE DESCRIPTION

We present the case of a 41-year-old male patient from Argentina residing in a rural area; he has a domestic partnership, two children, and is a pedagogical advisor. He has no significant previous history.

The clinical picture began after chest trauma due to a traffic accident. A chest CT was performed, and the incidental finding was apical fibrosis suggestive of tuberculosis (TB). He had no respiratory symptoms, and due to the imaging findings, he was taken for bronchoalveolar lavage with XpertMTB/RIF detection for TB. We decided to start tetraconjugate treatment with rifampicin/isoniazid/pyrazinamide/ethambutol (RHZE), and the first phase was completed with control of negative smears (**Figure 1**).

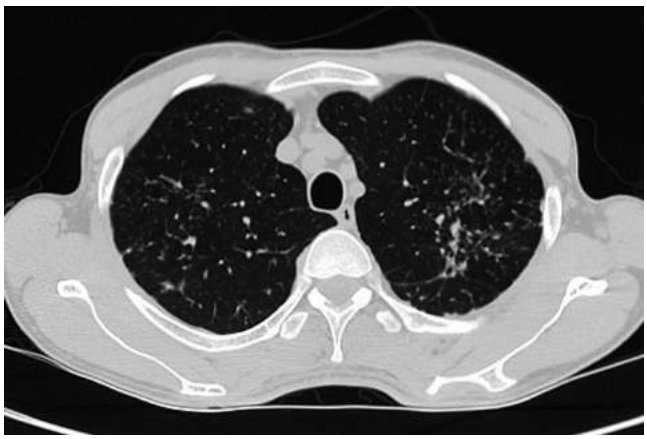

Figure 1. A chest CT shows fibrotic scarring changes in the left upper lobe with pleuroparenchymal tracts, traction bronchiectasis, and micronodules. Source: Authors' archive.

Since the beginning of treatment, the patient manifested gastrointestinal symptoms such as nausea, hyporexia, diarrhea, weight loss, and an increase in transaminases up to 5 times the upper normal limit, so the start of the second phase was suspended.

Once the transaminase values had normalized, the second phase of treatment with isoniazid and rifampin (HR) was initiated. Subsequently, the subject reported a reappearance of symptoms, so he consulted the emergency service. Given the severity, he was hospitalized for additional studies.

Liver and kidney tests and the hemoleukogram were normal, HIV was negative, and immunity studies with T lymphocyte subpopulation and immunoglobulins were normal. Stool, stool culture, and toxin *C. difficile* were negative; the colonoscopy and abdominal CT showed no abnormalities. In colon histopathology, eosinophils are slightly increased, with negative stains and no granulomas. A deficiency of vitamin B_{12}, folic acid, and low prealbumin levels pointed to a probable cause of malabsorption.

Given the patient's origin, we studied less frequent causes of chronic malabsorptive diarrhea, such as CD. The antibody profile turned out positive, so an endoscopy (EDS) was performed to take duodenal biopsies (**Table 1**, **Figures 2** and **3**).

Table 1. Paraclinical results

Paraclinical test	Result	Reference values for laboratory
Anti-transglutaminase IgG antibodies	27.3	Positive >10 IU/mL
Anti-tissue transglutaminase IgA (tTG IgA) antibodies	>200	Positive >10 IU/mL

IgA: immunoglobulin A; IgG: immunoglobulin G. Prepared by the authors.

Considering the clinical symptoms, the results of complementary studies, and that the patient comes from Argentina, where the disease is most prevalent, the diagnosis of CD was confirmed. The timing between the start of medication and the manifestation of symptoms was striking, as well as the suspension of the drug that led to their resolution. Analyzing the potential relationship between the consumption of RHZE/pyridoxine and the symptoms of CD, we found that these medications may contain wheat-based excipients, which explains the patient's symptoms not due to the adverse gastrointestinal effects of the antibiotic, but due to its excipients. Because of the patient's residence, he based his diet on cultivated products without regular exposure to gluten derivatives, which explains the absence of previous symptoms that would guide the diagnosis.

The case was discussed, and the diagnosis of pulmonary TB was questioned since positivity was demonstrated in the molecular test only. Cultures were negative, and the patient was respiratory asymptomatic. TB was ruled out, treatment was suspended, and therapeutic efforts were redirected toward recovering the patient's nutritional status. Subsequently, no other hospital admissions were recorded, and the patient remains respiratory asymptomatic, with weight gain and nutritional recovery.

DISCUSSION

CD, sometimes called *celiac sprue* or *gluten-sensitive enteropathy*, is an autoimmune condition triggered by dietary gluten that occurs in genetically predisposed individuals. Specifically, it is characterized by enteropathy at the small intestine level associated with systemic symptoms caused by secondary malabsorption and anti-transglutaminase antibodies.

Initially considered exclusive to countries with predominantly Caucasian populations, cases of CD have been reported worldwide over the years, but its exact prevalence is unknown. According to data extracted from a systematic review of the global prevalence of CD, a global prevalence of 1.4% (95% CI 1.1–1.7) was estimated based on the positive result for anti-transglutaminase antibodies, and

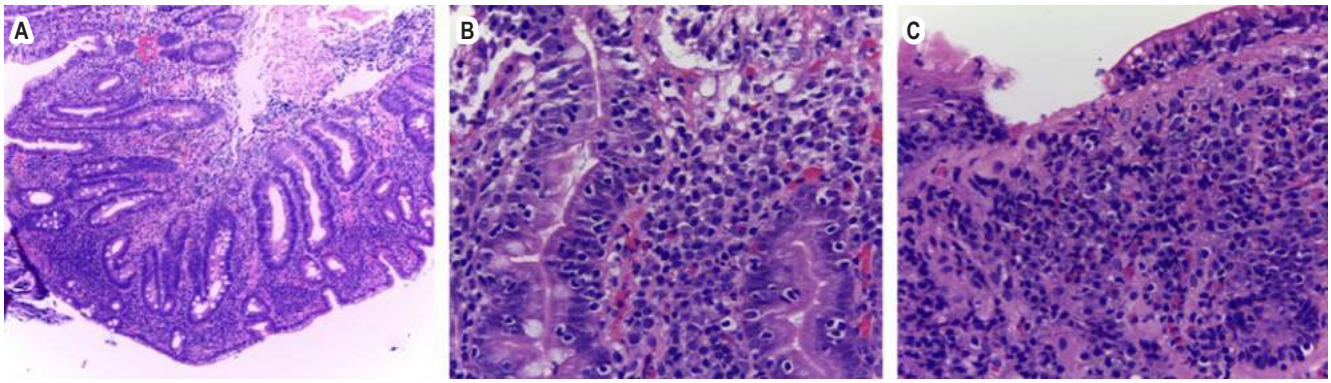

Figure 2. A. Intestinal mucosa with villous atrophy, crypt proliferation (Marsh 3b), large mononuclear inflammatory infiltrate, predominantly lymphocytic (H&E, X1000). **B.** Lymphocytic infiltrate with exocytosis to the adjacent mucosa; no epithelial dysplasia observed (H&E, X400). **C.** Erosion of the mucosa due to the severe inflammatory infiltrate (H&E, X4009). Source: Authors' archive.

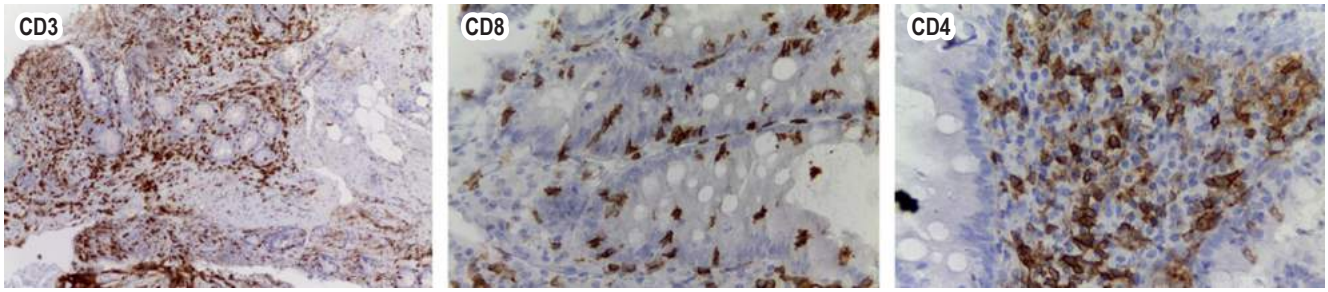

Figure 3. Immunohistochemistry: CD3 and CD8 positive in intraepithelial lymphocytes, CD4 negative in lymphoepithelial lymphocytes. Source: Authors' archive.

an overall prevalence of 0.7% (95% CI 0.5–0.9) when the diagnosis was confirmed by biopsy. Furthermore, its distribution in the continents was estimated; Asia had the highest prevalence with 1.8%, followed by Oceania and North America with 1.4%, Europe and South America with 1.3%, and Africa with 1.1%[1].

An annual increase of 7.5% in the disease has been reported, possibly due to greater recognition, the application of screening methods, and improvements in diagnostic techniques[2]. The estimated prevalence in Latin America is 0.46% to 0.64%. It is estimated that it affects 1 in every 100 people in Argentina. There are few studies for Colombia and no exact data[3,4].

We presented a patient from Argentina, where this pathology is common. Incidentally, the diagnosis of TB with tetraconjugate onset (RHZE) was made. Subsequently, the patient began with gastrointestinal symptoms and elevated transaminases. The clinical picture was assumed to be an adverse effect of the medication. Still, given the intensity of the symptoms, extension studies were initiated with evidence of malabsorption syndrome due to weight loss, hypoalbuminemia, and vitamin B12 deficiency.

With these suggestive symptoms, studies for CD were performed, initially with serological evaluation. Because of the positive TTG IgA result (>10 times the upper normal limit), an EDS was conducted with a duodenal biopsy showing villous atrophy and crypt proliferation, resulting in a Marsh 3b histological classification that confirmed the diagnosis.

Biopsy of the small intestine is of utmost importance. Microscopically, in CD, the villi are markedly atrophic or absent, but the mucosa's overall thickness is average due to crypt hyperplasia. There is an increase in lymphocytes and plasma cells containing immunoglobulin in the lamina propria and an accumulation of fat globules representing partially absorbed lipids on the surface of the epithelium. Although far from being pathognomonic, the increase in intraepithelial T lymphocytes is also a characteristic finding; in some cases, the villous architecture is only mildly atrophic or completely normal, and increased intraepithelial lymphocytes (IEL) may be the only evidence of the disease.

The most widely used grading system for CD in biopsies is a modification of the Marsh (Marsh-Oberhuber) criteria adopted by national institutes of health: Grade 0 = normal;

Grade 1 = IEL only; Grade 2 = IEL plus crypt proliferation; Grades 3 a, b, c = mild, moderate, and severe shortening of the villi, respectively; and Grade 4 = atrophic mucosa with flat villi[5].

The duodenal biopsy displays severe atrophy of the villi of the intestinal mucosa with a large lymphocytic infiltrate, and immunohistochemistry showed positivity for CD3 and CD8; the severity of atrophy and the presence of CD8+ cytotoxic lymphocytes are specific findings for CD over other entities.

In this case, the onset of symptoms after anti-TB treatment was established is striking because, in his usual diet, the patient did not include gluten-based products; after reviewing the excipients of the RHZE tablet, wheat starch was found within the components of pyrazinamide, which explains the appearance of symptoms at the start of treatment and their resolution when stopping it in both phases of treatment.

A case with similar characteristics was published by Cerezo-Lajas et al. in 2016 in which, as in this case, the tetraconjugate under the Rimstar® brand (the same one that our patient received) was supplied. A similar chain of events was observed: When the treatment was started, the symptoms began, and as soon as it was suspended, the symptoms resolved[6].

CONCLUSION

The CD is a rare pathology in Colombia, leading to doubts about its presence here. However, due to migration patterns and industrialization, an increase in cases is expected. Wheat derivatives are increasingly used in preparing foods and other products; for example, they are part of medication excipients, which was our patient's diagnostic key.

The index of suspicion should be increased in patients with symptoms of malabsorptive diarrhea, evaluating their response to a gluten-free diet.

Conflicts of interest

None.

REFERENCES

1. Singh P, Arora A, Strand TA, Leffler DA, Catassi C, Green PH, et al. Global Prevalence of Celiac Disease: Systematic Review and Meta-analysis. Clin Gastroenterol Hepatol. 2018;16(6):823-36.e2. https://doi.org/10.1016/j.cgh.2017.06.037
2. King JA, Jeong J, Underwood FE, Quan J, Panaccione N, Windsor JW, et al. Incidence of Celiac Disease Is Increasing over Time: A Systematic Review and Meta-analysis. Am J Gastroenterol. 2020;115(4):507-25. https://doi.org/10.14309/ajg.0000000000000523
3. Parra-Medina R, Molano-Gonzalez N, Rojas-Villarraga A, Agmon-Levin N, Arango MT, Shoenfeld Y, et al. Prevalence of celiac disease in Latin America: A systematic review and meta-regression. PLoS One. 2015;10(5):e0124040. https://doi.org/10.1371/journal.pone.0124040
4. Suarez-Correa J, López-Barreto JC, Mejía-Cardona AF, Paredes-Fernández AJ. Enfermedad celíaca: un reto diagnóstico en Colombia. Repert. Med. Cir. 2022;31(2):123-32. https://doi.org/10.31260/RepertMedCir.01217372.1159
5. Dickson BC, Streutker CJ, Chetty R. Coeliac disease: an update for pathologists. J Clin Pathol. 2006;59(10):1008-16. https://doi.org/10.1136/jcp.2005.035345
6. Cerezo-Lajas A, Caminero-Luna JA, Rodríguez-Guzmán MC, Miguel-Díez J. Tratamiento antituberculoso en un paciente con enfermedad celíaca. Archivos de Bronconeumologia. 2018;54(6):337-38. https://doi.org/10.1016/j.arbres.2017.12.009

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Case report

Immunoglobulin G4-Related Disease, A Diagnosis to Take into Account: About a Case

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Abstract

Immunoglobulin G4-related disease (IgG4-RD) is an immune-mediated and multisystemic condition associated with developing fibroinflammatory lesions in any organ. The diagnosis is made based on the sum of clinical, serological, radiological, and histopathological criteria; however, this is often difficult due to its similarity to neoplasms, infections, or other immune-mediated diseases. Treatment is based on corticosteroids, in a possible combination with immunomodulators. The present case concerns a 59-year-old man with a history of jaundice syndrome and weight loss, admitted for suspected malignant neoplasia of the bile duct. Imaging revealed stricture with dilation of the intrahepatic bile ducts, prominent pancreas, pancreatic duct stricture, and nodular renal lesions. Due to the history of left submandibulectomy two years before the current disease and histology compatible with Küttner's tumor, plus the high IgG4 serum values, the diagnosis of IgG4-RD was established. He started treatment with corticosteroids and was asymptomatic during follow-up.

Keywords

IgG4-related disease, autoimmune pancreatitis, immunoglobulin G4.

INTRODUCTION

Immunoglobulin G4-related disease (IgG4-RD) is a systemic and immune-mediated condition associated with fibroinflammatory lesions that can occur in any organ[1–4]. It generally manifests in patients between 50 and 60 with a male/female preponderance of 2:1[1,3,5,6]. The final diagnosis requires clinical and radiological evaluation, serum IgG4 levels, and characteristic histopathological findings; however, none of these approaches alone provide definitive evidence for accurate patient classification[7]. Treatment mainly involves systemic corticosteroids[8], and remission rates are reported to be up to 70%, with annual relapse rates of 11.5%[9]. Other regimens, such as immunosuppressants in combination with corticosteroids and, recently, the anti-CD20 monoclonal antibody (rituximab), have demonstrated efficacy[10,11].

CLINICAL CASE

We present the case of a 59-year-old male patient with a medical history of primary hypertension, heart failure, and diabetes *mellitus*, the latter appearing at 55 years of age. Ten months before hospital admission, he exhibited jaundice,

choluria, abdominal pain in the right hypochondrium, asthenia, and pruritus. The liver profile revealed cholestasis (**Table 1**); viral hepatitis A, B, and C studies were negative. Abdominal CT showed dilation of the intrahepatic bile ducts, and the common bile duct dilated up to 12 mm with diffuse thickening of its walls. Two weeks before admission, the patient presented with nausea, and the abdominal pain intensified, coupled with a weight loss of 17 kg during the disease, which resulted in his admission due to suspicion of malignant neoplasm of the bile duct.

On physical examination, he was awake, thin, and anicteric, and his abdomen showed no significant findings. Ancillary tests showed leukocytes at 3,920 cells/mm^3, hemoglobin of 12.7 gr/dL, platelets at 183,000/mm^3, and a liver profile with cholestasis (**Table 1**). Kidney function, tumor markers (CEA, CA125, alpha-fetoprotein), and rheumatologic markers (ANA and ANCA) were negative. The examinations were complemented by imaging studies, which showed chronic inflammatory changes in the right submandibular gland and the absence of the left submandibular gland (**Figure 1**).

Due to this last finding, the anamnesis was expanded; the patient reported that two years ago, he underwent a left submandibulectomy for suspected neoplasia whose pathological study was compatible with Küttner's tumor (**Figure 2**). The electrophoresis of proteins revealed an increase in total proteins and immunoglobulins, with an increase in IgG by 2,784 mg/dL (NV: 700–1690 mg/dL) and IgG4 by 556 (NV: 11–157 mg/dL). Proteinuria was 206.4 mg/24 hours, and the complement C3 level was decreased by 7 mg/dL (NV: 12.9–39.2).

Magnetic resonance cholangiopancreatography identified areas of stricture and dilation of the multifocal intrahepatic bile ducts and mural thickening of the common bile duct with stricture of its distal third, the prominent pancreas with a cephalic predominance, and the pancreatic duct with areas of stricture and nodular renal cortical lesions (**Figure 1**). The study was complemented by endoscopic ultrasonography demonstrating an 8 mm common bile duct with walls thickened by up to 3.5 mm, and the pancreas had a pseudotumoral appearance and scalloped edges.

Given the sum of the criteria, the diagnosis of IgG4-RD with multiorgan involvement (bile duct, pancreas, kidney, submandibular gland) was proposed. After a defocus study, treatment with prednisone 40 mg/day (0.8 mg/kg) was started. There were no complications during the first week of treatment, and he was discharged from the hospital. In the third week, the patient was asymptomatic with a reduction of prednisone to 30 mg/day, and leflunomide 20 mg/day was added to reduce the adverse effects of steroids and ensure remission of the disease.

DISCUSSION

IgG4-RD was first recognized as a distinct disease in 2003[12]: since then, it has been described more frequently by doctors from different specialties who participate in evaluating patients with this condition and, thus, a greater number of patients diagnosed worldwide[7,13,14]. It manifests as a multiorgan disease and can often be confused with diseases of infectious, autoimmune, or malignant origin[7], just like the diagnosis made on admission of this case.

Table 1. Biochemical monitoring

	Ten months before	Nine months before	Emergency admission	Before starting corticosteroids	Seven days posttherapy
TB mg/dL (NV: 0.2–1.3)	11.4	4.27	1.17	0.55	0.5
DB mg/dL (NV: 0–0.3)	5.36	2.14	0.6	0.3	0.3
IB mg/dL (NV: 0–1.1)	6.94	2.13	0.5	0.2	0.2
AP IU/L (NV: 38–126)	1001	1042	356	315	176
GGTP IU/L (NV: 15–73)	310	413	240	154	109
GOT IU/L (NV: 15–46)	86	177	54	49	38
GPT UI/L (VN: 15–35)	69	102	34	29	33

AP: alkaline phosphatase; DB: direct bilirubin; GGTP: gamma-glutamyl transpeptidase; GOT: glutamic-oxaloacetic transaminase; GPT: glutamic-pyruvic transaminase; IB: indirect bilirubin; TB: total bilirubin. Prepared by the authors.

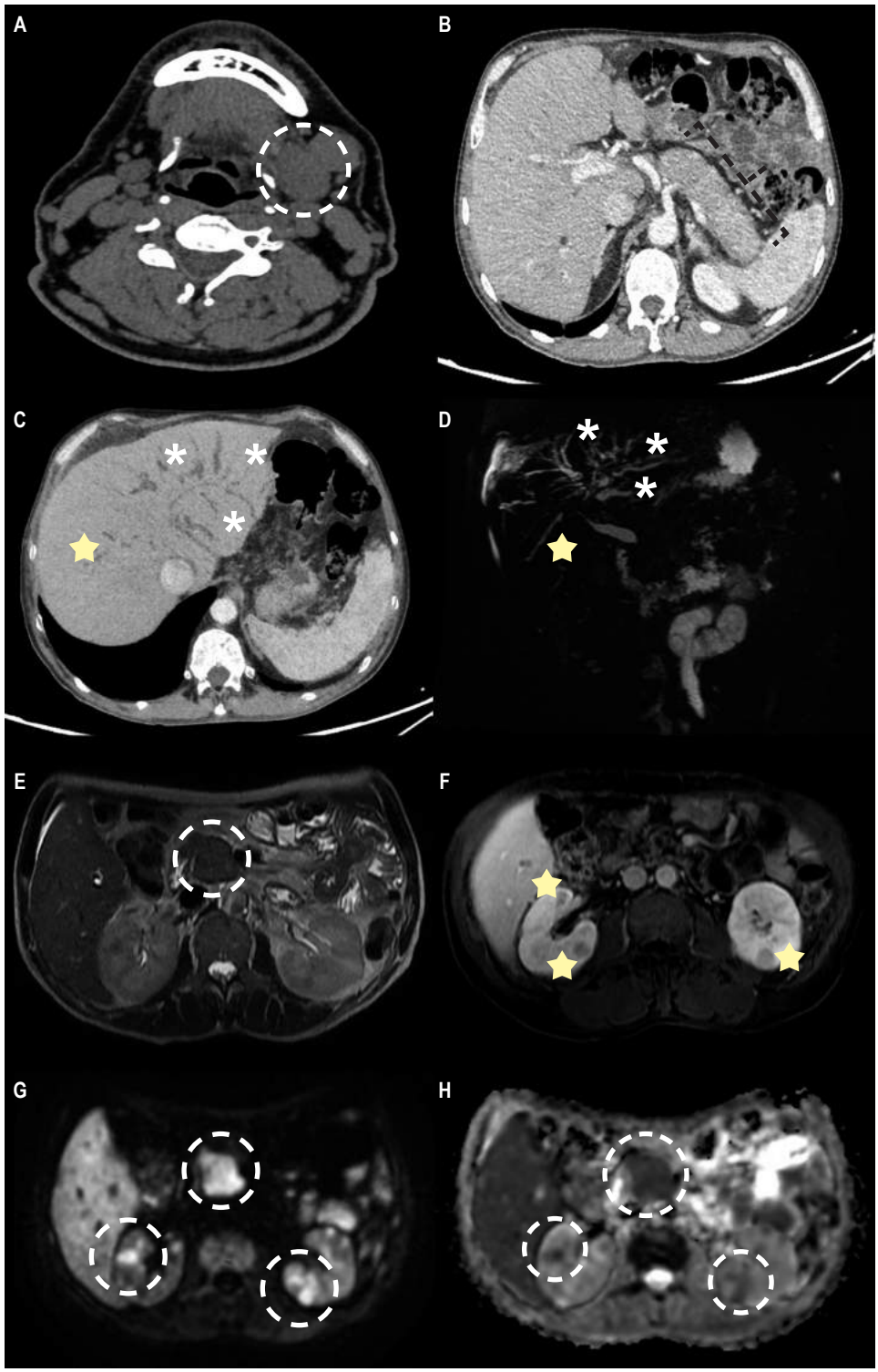

Figure 1. A. Non-contrast computed tomography (CT) two years before admission shows increased volume of the left submandibular gland, associated with some adjacent lymphadenopathy. **B.** Contrast-enhanced CT shows a characteristic hypoattenuating halo around the body and tail of the pancreas, a finding suggestive of diffuse autoimmune pancreatitis. **C** and **D.** MinIP reconstruction and magnetic resonance cholangiopancreatography show dilation of the intrahepatic bile duct (asterisk) and segmental stricture areas (star). **E.** Axial T2-weighted magnetic resonance image shows well-demarcated focal enlargement at the head level, which correlates with diffusion restriction (**G**). **F, G** and **H.** The contrast-enhanced T1-weighted axial magnetic resonance image shows multiple well-defined renal nodular lesions, with enhancement upon contrast administration and correlation with diffusion restriction (**G** and **H**). Source: Patient's medical record.

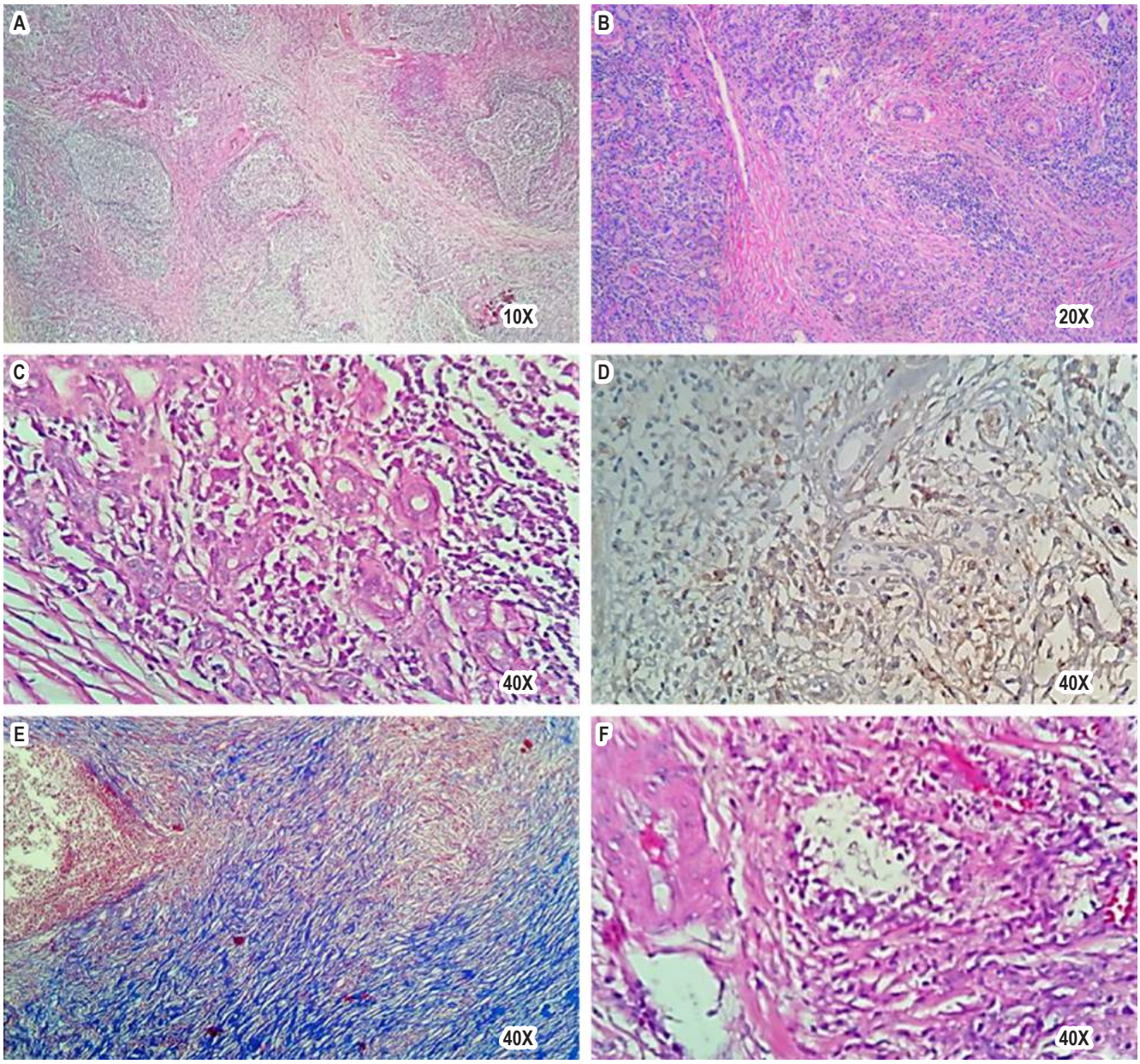

Figure 2. Histopathological findings of IgG4-RD in the submandibular gland. **A.** Panoramic view of submandibular gland with lymphoplasmacytic inflammation and interstitial fibrosis (H. E.). **B** and **C.** Chronic inflammation: lymphocytes and plasma cells surrounding excretory ducts (H. E.). **D.** CD138-positive plasma cells. **E.** Storiform fibrosis with Masson staining. **F.** Phlebitis obliterans (H. E.). Source: Patient's medical record.

The classic patient is a middle-aged man (58.8 years)[13], compared to the typical manifestation of predominantly female autoimmune diseases[3]. In autoimmune pancreatitis, the male/female ratio is 2:1[15]; however, if other organs, such as the head or neck, are affected, the proportion is comparable[16]. The reason for the differential expression according to the involvement of other organs between both sexes is unclear[3].

IgG4-RD follows a biphasic course[17]. In the inflammatory phase, polyclonal B and T cell subpopulations infiltrate affected tissues and undergo antigen-mediated interactions, releasing inflammatory and profibrotic cytokines[18]. T-follicular helper cells play an essential role in promoting the clonal expansion of IgG4-engaged B cells and enhancing the maturation of naïve B cells into mature plasma cells, with the production of IgG4[19]. In the second fibrotic phase, innate

immune cells, such as M2 macrophages, infiltrate IgG4-RD lesions and secrete profibrotic cytokines[20]. Activated fibroblasts deposit extracellular matrix, resulting in a dense stromal reaction that distorts tissue architecture, manifesting dysfunction and possibly organ failure[17].

Four IgG4-RD phenotypes have been described: pancreato-hepato-biliary disease (31%), retroperitoneal fibrosis with or without aortitis (24%), head and neck-limited disease (24%), and classic Mikulicz syndrome with systemic involvement (22%)[15].

In 2019. the American College of Rheumatology and the European Alliance of Associations for Rheumatology (ACR/EULAR) presented the IgG4-RD classification criteria. These were developed based on a three-step classification process: an entry criterion, a set of exclusion criteria, and weighted inclusion criteria[7,21].

The initial clinical manifestation of this case was the involvement of the submandibular gland. In this regard, one in five patients with IgG4-RD in the head and neck region has the disease that originates in one or more salivary glands[1]. In decreasing order of prevalence, the submandibular gland, parotid gland, sublingual gland, and minor salivary glands are included[1]. The most common salivary gland disease associated with IgG4-RD is chronic sclerosing sialadenitis or Küttner's tumor. This chronic benign inflammatory disorder most frequently affects the submandibular glands[22]. It appears as an increase in size or pseudotumor lesion in the region of the affected salivary gland and is usually unilateral; however, bilateral cases have been described[23]. The history and clinical findings are often highly suggestive of neoplasia and, as such, should always remain at the top of the list of differential diagnoses, considering IgG4-RD as a diagnosis of exclusion[4].

Meanwhile, during the evolution of his disease, the patient had biliary and pancreatic involvement. In this context, two subtypes of autoimmune pancreatitis (AIP) are known, of which only one (Type 1) is associated with IgG4-RD[24,25]. Type 1 AIP, the most common form, is characterized by the classic histopathological findings of lymphoplasmacytic sclerosing pancreatitis[24].

Clinically, it manifests as obstructive jaundice (generally painless) associated with weight loss and fatigue (simulating pancreatic neoplasia) or acute pancreatitis (generally benign without necrosis)[25]. CT features include diffuse pancreatic enlargement with late enhancement and a low-density capsule-like ring. Diffuse and irregular narrowing of the main pancreatic duct on magnetic resonance cholangiopancreatography is also definite for AIP[26,27].

IgG4-related sclerosing cholangitis (IgG4-SC) has a cholangiographic appearance similar to primary sclerosing cholangitis (PSC). Both IgG4-SC and AIP respond well to steroid therapy[28,29]. On the contrary, PSC is progressive, resistant to treatment, affects both the intrahepatic and extrahepatic bile ducts, and causes biliary cirrhosis[30]. Another differential diagnosis to consider in this context is hilar cholangiocarcinoma, which often requires a transpapillary endoscopic biopsy[30] because neither serum IgG4 concentrations nor cholangiographic or cholangioscopic findings differentiate these disorders clearly but may suggest a particular approach[31,32].

In this case, imaging studies revealed characteristic renal lesions indicating involvement of this organ. Tubulointerstitial nephritis has been described as the most common form of IgG4-RD in the kidneys[33]. The critical difference between kidney involvement and other solid organ involvement is the low complement concentrations. It is not well understood but is not believed to be related to IgG4 because this molecule does not bind to complement. This phenomenon is not replicated to a large extent in most other organs involving IgG4-RD[33]. Clinically, these patients may experience kidney failure and even end-stage renal disease. Although proteinuria may develop, it is often in the subnephrotic range. Imaging studies will indicate significantly enlarged kidneys and hypodense lesions evident on CT images and non-enhancing in post-contrast studies[34]. All these findings were apparent in this case.

A key point to consider is serum IgG4 concentrations, initially a critical characteristic for diagnosing IgG4-RD but described as neither necessary nor sufficient[26]. A cohort of patients with IgG4-RD demonstrated that high levels of IgG4 do not confirm the diagnosis, and low serum levels do not exclude it[35].

Regarding treating IgG4-RD, it will depend on the severity of the disease, the affected organs, and the individual factors of each patient[36].

Glucocorticoids are the cornerstone of treatment in patients with active IgG4-RD both at onset and at relapse. The goal is to resolve symptoms and normalize biochemistry and radiological findings. Generally, improvement should occur in days to several weeks, depending on the organs involved[37]; however, the lack of response to glucocorticoid therapy suggests that the diagnosis is incorrect and should be reconsidered[36]. The general practice is to start with a dose between 0.6-1 mg/kg/day[38]. Evidence suggests that the initial dose should be maintained for 2 to 4 weeks and then gradually reduced by 5 mg every two weeks throughout 4 to 6 weeks[6]. During this time, the patient should be monitored for common disease relapses, especially at lower doses and after discontinuation[39].

The role of immunomodulators in the induction of IgG4-RD remission has not been established[37]. Current guidelines indicate that some, but not all, patients require the combination of glucocorticoids and an immunosuppressant from the start of treatment; this is because monotherapy with

glucocorticoids will ultimately fail to control the disease, and long-term toxicity represents a high risk for patients[11]. Besides, biological agents such as rituximab (RTX) can be combined with corticosteroids to induce disease remission and allow early tapering of steroids[10]. It has also been used successfully in patients who showed resistance or side effects to classic treatments (steroids/immunomodulators)[11]. In maintenance therapy, RTX is superior to other regimens in reducing the relapse rate; however, dosing protocols are not established in this setting[40].

In this case, a new biopsy sample was rejected because there was previously a pathological finding within the IgG4-RD spectrum (Küttner's tumor). Previously, the diagnosis was obtained incidentally from extensive surgical specimens resected for suspected malignancy. Nonetheless, given the greater recognition of this condition, the current diagnosis is made using increasingly smaller biopsy samples and from accessible sites, even in selected cases, with the addition of classic non-invasive criteria and no anatomopathological study[7,41].

Conflict of interest

The authors declare no conflict of interest whatsoever.

REFERENCES

1. Stone JH, Zen Y, Deshpande V. Mechanisms of disease: IgG4-related disease. N Engl J Med. 2012;366(6):539-51. https://doi.org/10.1056/NEJMRA1104650
2. Ruiz-Rebollo ML, Álvarez-Quiñones-Sanz M, Fuertes-Alija JJ, Izquierdo-Santervás S. IgG4-related disease mimicking pancreatic tumour. Gastroenterología y Hepatología (English Edition). 2021;44(9):660–1. https://doi.org/10.1016/J.GASTRE.2020.07.026
3. Kamisawa T, Zen Y, Pillai S, Stone JH. IgG4-related disease. Lancet. 2015;385(9976):1460–71. https://doi.org/10.1016/S0140-6736(14)60720-0
4. Johnston J, Allen JE. IgG4-related disease in the head and neck. Curr Opin Otolaryngol Head Neck Surg. 2018;26(6):403–8. https://doi.org/10.1097/MOO.0000000000000487
5. Skillington SA, Ogden MA. IgG4-Related Disease and the Salivary Glands: A Review of Pathophysiology, Diagnosis, and Management. Otolaryngol Clin North Am. 2021;54(3):497–508. https://doi.org/10.1016/J.OTC.2021.02.002
6. Wallace ZS, Perugino C, Matza M, Deshpande V, Sharma A, Stone JH. IgG4-Related Disease. Clin Chest Med. 2019;40(3):583-97. https://doi.org/10.1016/J.CCM.2019.05.005
7. Wallace ZS, Naden RP, Chari S, Choi H, Della-Torre E, Dicaire JF, et al. The 2019 American College of Rheumatology/European League Against Rheumatism Classification Criteria for IgG4-Related Disease. Arthritis Rheumatol. 2020;72(1):7–19. https://doi.org/10.1002/ART.41120
8. Khosroshahi A, Wallace ZS, Crowe JL, Akamizu T, Azumi A, Carruthers MN, et al. International consensus guidance statement on the management and treatment of IgG4-related disease. Arthritis Rheumatol. 2015;67(7):1688–99. https://doi.org/10.1002/ART.39132
9. Yamamoto M, Yajima H, Takahashi H, Yokoyama Y, Ishigami K, Shimizu Y, et al. Everyday clinical practice in IgG4-related dacryoadenitis and/or sialadenitis: Results from the SMART database. Mod Rheumatol. 2015;25(2):199–204. https://doi.org/10.3109/14397595.2014.950036
10. Khosroshahi A, Carruthers MN, Deshpande V, Unizony S, Bloch DB, Stone JH. Rituximab for the treatment of IgG4-related disease: Lessons from 10 consecutive patients. Medicine. 2012;91(1):57–66. https://doi.org/10.1097/MD.0B013E3182431EF6
11. Carruthers MN, Topazian MD, Khosroshahi A, Witzig TE, Wallace ZS, Hart PA, et al. Rituximab for IgG4-related disease: a prospective, open-label trial. Ann Rheum Dis. 2015;74(6):1171–7. https://doi.org/10.1136/ANNRHEUMDIS-2014-206605
12. Kamisawa T, Funata N, Hayashi Y, Eishi Y, Koike M, Tsuruta K, et al. A new clinicopathological entity of IgG4-related autoimmune disease. J Gastroenterol. 2003;38(10):982-4. https://doi.org/10.1007/S00535-003-1175-Y
13. Uchida K, Masamune A, Shimosegawa T, Okazaki K. Prevalence of IgG4-Related Disease in Japan Based on Nationwide Survey in 2009. Int J Rheumatol. 2012;2012:358371. https://doi.org/10.1155/2012/358371
14. Masamune A, Kikuta K, Hamada S, Tsuji I, Takeyama Y, Shimosegawa T, et al. Nationwide epidemiological survey of autoimmune pancreatitis in Japan in 2016. J Gastroenterol. 2020;55(4):462-70. https://doi.org/10.1007/S00535-019-01658-7
15. Wallace ZS, Zhang Y, Perugino CA, Naden R, Choi HK, Stone JH. Clinical phenotypes of IgG4-related disease: an analysis of two international cross-sectional cohorts. Ann Rheum Dis. 2019;78(3):406–12. https://doi.org/10.1136/ANNRHEUMDIS-2018-214603
16. Zen Y, Nakanuma Y. IgG4-related disease: A cross-sectional study of 114 cases. Am J Surg Pathol, 2010;34(12):1812–9. https://doi.org/10.1097/PAS.0B013E3181F7266B

17. Pillai S, Perugino C, Kaneko N. Immune mechanisms of fibrosis and inflammation in IgG4-related disease. Curr Opin Rheumatol. 2020;32(2):146–51. https://doi.org/10.1097/BOR.0000000000000686
18. Della-Torre E, Feeney E, Deshpande V, Mattoo H, Mahajan V, Kulikova M, et al. B-cell depletion attenuates serological biomarkers of fibrosis and myofibroblast activation in IgG4-related disease. Ann Rheum Dis. 2015;74(12):2236. https://doi.org/10.1136/ANNRHEUMDIS-2014-205799
19. Chen Y, Lin W, Yang H, Wang M, Zhang P, Feng R, et al. Aberrant Expansion and Function of Follicular Helper T Cell Subsets in IgG4-Related Disease. Arthritis Rheumatol. 2018;70(11):1853–65. https://doi.org/10.1002/ART.40556
20. Furukawa S, Moriyama M, Tanaka A, Maehara T, Tsuboi H, Iizuka M, et al. Preferential M2 macrophages contribute to fibrosis in IgG4-related dacryoadenitis and sialoadenitis, so-called Mikulicz's disease. Clinical Immunology. 2015;156(1):9–18. https://doi.org/10.1016/J.CLIM.2014.10.008
21. Lanzillotta M, Lanzillotta M, Mancuso G, Mancuso G, Della-Torre E. Advances in the diagnosis and management of IgG4 related disease. BMJ. 2020;369:m1067. https://doi.org/10.1136/BMJ.M1067
22. Bhatti RM, Stelow EB. IgG4-related disease of the head and neck. Adv Anat Pathol. 2013;20(1):10–6. https://doi.org/10.1097/PAP.0B013E31827B619E
23. Mulholland GB, Jeffery CC, Satija P, Côté DWJ. Immunoglobulin G4-related diseases in the head and neck: a systematic review. J Otolaryngol Head Neck Surg.2015;44(1):24. https://doi.org/10.1186/S40463-015-0071-9
24. Chari ST, Kloeppel G, Zhang L, Notohara K, Lerch MM, Shimosegawa T. Histopathologic and clinical subtypes of autoimmune pancreatitis: The honolulu consensus document. Pancreas. 2010;39(5):549–54. https://doi.org/10.1097/MPA.0B013E3181E4D9E5
25. Sah RP, Chari ST, Pannala R, Sugumar A, Clain JE, Levy MJ, et al. Differences in Clinical Profile and Relapse Rate of Type 1 Versus Type 2 Autoimmune Pancreatitis. Gastroenterology. 2010;139(1):140–8. https://doi.org/10.1053/J.GASTRO.2010.03.054
26. Vashi B, Khosroshahi A. IgG4-Related Disease with Emphasis on Its Gastrointestinal Manifestation. Gastroenterol Clin North Am. 2019;48(2):291–305. https://doi.org/10.1016/j.gtc.2019.02.008
27. Zheng Y, Elsayes KM, Waranch C, Abdelaziz A, Menias CO, Sandrasegaran K, et al. IgG4-related disease in the abdomen and pelvis: atypical findings, pitfalls, and mimics. Abdominal Radiology. 2020;45(8):2485–99. https://doi.org/10.1007/S00261-020-02526-2
28. Erkelens GW, Vleggaar FP, Lesterhuis W, van Buuren HR, van der Werf SDJ. Sclerosing pancreato-cholangitis responsive to steroid therapy. Lancet. 1999;354(9172):43–4. https://doi.org/10.1016/S0140-6736(99)00603-0
29. Smal AJ, Loftus CG, Smyrk TC, Baron TH. A case of IgG4-associated cholangitis and autoimmune pancreatitis responsive to corticosteroids. Nat Clin Pract Gastroenterol Hepatol. 2008(12):707–12. https://doi.org/10.1038/NCPGASTHEP1296
30. Nakazawa T, Ando T, Hayashi K, Naitoh I, Ohara H, Joh T. Diagnostic procedures for IgG4-related sclerosing cholangitis. J Hepatobiliary Pancreat Sci. 2011;18(2):127–36. https://doi.org/10.1007/S00534-010-0320-2
31. Mendes FD, Jorgensen R, Keach J, Katzmann JA, Smyrk T, Donlinger J, et al. Elevated serum IgG4 concentration in patients with primary sclerosing cholangitis. Am J Gastroenterol. 2006;101(9):2070–5. https://doi.org/10.1111/J.1572-0241.2006.00772.X
32. Itoi T, Kamisawa T, Igarashi Y, Kawakami H, Yasuda I, Itokawa F, et al. The role of peroral video cholangioscopy in patients with IgG4-related sclerosing cholangitis. Journal of Gastroenterology. 2012;48(4):504–14. https://doi.org/10.1007/S00535-012-0652-6
33. Saeki T, Ito T, Yamazaki H, Imai N, Nishi S. Hypocomplementemia of unknown etiology: an opportunity to find cases of IgG4-positive multi-organ lymphoproliferative syndrome. Rheumatology International. 2009;30(1):99–103. https://doi.org/10.1007/S00296-009-0925-4
34. Saeki T, Kawano M, Mizushima I, Yamamoto M, Wada Y, Nakashima H, et al. The clinical course of patients with IgG4-related kidney disease. Kidney Int. 2013;84(4):826–33. https://doi.org/10.1038/KI.2013.191
35. Carruthers MN, Khosroshahi A, Augustin T, Deshpande V, Stone JH. The diagnostic utility of serum IgG4 concentrations in IgG4-related disease. Ann Rheum Dis. 2015;74(1):14–8. https://doi.org/10.1136/ANNRHEUMDIS-2013-204907
36. Zhang W, Stone JH. Management of IgG4-related disease. Lancet Rheumatol. 2019;1(1):e55–65. https://doi.org/10.1016/S2665-9913(19)30017-7
37. Lanzillotta M, Fernàndez-Codina A, Culver E, Ebbo M, Martinez-Valle F, Schleinitz N, et al. Emerging therapy options for IgG4-related disease. Emerging therapy options for IgG4-related disease. Expert Rev Clin Immunol. 2021;17(5):471-83. https://doi.org/10.1080/1744666X.2021.1902310
38. Okazaki K, Chari ST, Frulloni L, Lerch MM, Kamisawa T, Kawa S, et al. International consensus for the treatment of autoimmune pancreatitis. Pancreatology. 2017;17(1):1–6. https://doi.org/10.1016/J.PAN.2016.12.003
39. Hart PA, Kamisawa T, Brugge WR, Chung JB, Culver EL, Czakó L, et al. Original article: Long-term outcomes of autoimmune pancreatitis: a multicentre, international analysis. Gut. 2013;62(12):1771. https://doi.org/10.1136/GUTJNL-2012-303617
40. Omar D, Chen Y, Cong Y, Dong L. Glucocorticoids and steroid sparing medications monotherapies or in combination for IgG4-RD: a systematic review and network meta-

analysis. Rheumatology (Oxford). 2020;59(4):718–26. https://doi.org/10.1093/RHEUMATOLOGY/KEZ380
41. Deshpande V, Zen Y, Chan JKC, Yi EE, Sato Y, Yoshino T, et al. Consensus statement on the pathology of IgG4-related disease. Modern Pathology. 2012;25(9):1181–92. https://doi.org/10.1038/modpathol.2012.72

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Case report

Severe Hypocalcemia as an Atypical Manifestation of Seronegative Celiac Disease in a Patient with Systemic Lupus Erythematosus: Case Report

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Abstract

Aim: To describe the clinical picture and diagnosis of an episode of severe hypocalcemia in a patient with systemic lupus erythematosus (SLE) in remission, with chronic diarrhea that led to the diagnosis of celiac disease (CD). **Case presentation:** 22-year-old patient, diagnosed with SLE at age 10, in remission. He consulted for a two-month history of paresthesias, muscle spasms, myalgias, and episodes of tetany in the previous week, associated with malabsorptive postprandial diarrhea. His laboratory tests showed severe hypocalcemia, vitamin D deficiency, severe hypomagnesemia, and mild hypokalemia. In the study for CD, serology reported normal anti-tissue transglutaminase IgA, antigliadin IgA, and IgG and low total IgA levels. Enteroscopy revealed erosive bulbo-duodenitis, with villous atrophy and increased intraepithelial lymphocytes in the pathology, which, together with the immunohistochemical study, allowed the diagnosis of CD, Marsh 3a type. Management was initiated with a gluten-free diet, with a positive clinical response. **Conclusion:** CD should be suspected in patients with SLE who present with diarrhea, abdominal pain, nausea/vomiting, recurrent oral aphthosis, and anemia. In rare seronegative CD cases, other causes of villous atrophy, mainly infectious, toxic, and immunological, must be ruled out. There is an association between CD and SLE, so diagnosis must be early and timely with the best testing scheme available to achieve effective treatment before complications occur.

Keywords

Celiac disease, systemic lupus erythematosus, hypocalcemia, diarrhea, tetany.

INTRODUCTION

Celiac disease (CD) is a chronic enteropathy of the small intestine mediated by exposure to gluten in the diet. Worldwide, an annual increase of 7.5% has been reported due to greater recognition of the disease, screening methods, and improvement in diagnostic techniques[1]. Its manifestation is varied with both gastrointestinal and extra-intestinal signs and symptoms, and the non-classical form is the most common in more than half of the cases, which makes its exploration a challenge[2]. There is an association between CD and autoimmune diseases, the most common of which are type I diabetes *mellitus*, thyroiditis, and autoimmune hepatitis[3]. It has been noted that patients with systemic lupus erythematosus (SLE) have a prevalence four times higher than the general population and share a predisposition to certain specific genotypes (DQ2, DQ8, B8, and DR3) and environmental factors[4,5].

As stated, CD has various forms of clinical manifestation and can occur in coexistence with systemic autoimmune rheumatic diseases. In this case, we describe the condition of a patient with SLE in remission, in whom the study of

chronic diarrhea resulted in the diagnosis of CD, obtaining an excellent response to removing gluten from her diet.

CASE PRESENTATION

We present the case of a 22-year-old female patient from an urban area, a psychology student with a history of SLE diagnosis at the age of 10, who exhibited cutaneous, hematological, immunological, and neuropsychiatric signs; she was in clinical remission under outpatient rheumatology follow-up and was being managed with cyclosporine, rituximab, and oral methylprednisolone. Previously, she showed intolerance to hydroxychloroquine and adverse events with azathioprine. Besides, seven years ago, a case of diarrhea was attributed to the use of mycophenolate mofetil; a colonoscopy plus a biopsy was performed at that time, which reported ileitis and colitis with intraepithelial lymphocytosis. Although the medication was discontinued at the time, she continued to have diarrheal stools with malabsorption characteristics, which is why she was diagnosed with irritable bowel syndrome with a predominance of diarrhea and no response to conventional management.

Furthermore, vitamin B_{12} deficiency and iron deficiency anemia have been documented in recent years. The patient consulted the emergency department due to a two-month history of generalized paresthesias, muscle spasms, myalgias, and episodes of tetany in the previous week. Upon admission to the emergency department, postprandial diarrhea persisted, with 5 to 6 stools a day. At her initial evaluation, she was in poor general condition (hemodynamically stable, hydrated, anxious, with mucocutaneous paleness, generalized rigidity, positive Trousseau, and Chvostek sign). She was transferred to the intensive care unit (ICU) for monitoring and management.

The laboratory tests, upon admission, showed severe hypocalcemia: ionic calcium of 0.6 mmol/L (normal range (NR), 1.15–1.33 mmol/L), serum calcium of 5.4 mg/dL (NR, 8,6–10 mg/dL), albumin of 4 g/dL (NR, 3.5–5.2 g/dL), normal parathyroid hormone: 25 pg/mL (NR, 10–65 pg/mL), vitamin D deficiency: 18.8 ng/mL (NR, >30 ng/mL), severe hypomagnesemia: 0.59 mEq/L (NR, 1.59–2.56 mg/dL), and mild hypokalemia: 3.1 mmol/L (NR, 3.5–5.5 mmol/L). So, intravenous replacement of calcium, magnesium, and potassium was initiated.

Four months earlier, an upper GI endoscopy had been performed, which was reported as normal with negative *Helicobacter pylori*. The possibility that chronic diarrhea was a manifestation of SLE activity was considered, so a magnetic resonance enterography was performed to evaluate possible involvement, extension, and location; still, it was reported within normality. The laboratory tests did not show the consumption of serum complement (C3, C4), the anti-double-stranded DNA antibodies were negative, and no active urinary sediment was found. There were no findings other than the anemia in the blood count that suggested SLE activity given by calculators such as SLEDAI-2K and a usually high rate of complications such as vasculitis or lupus enteritis, which is why these latter diagnoses and the activity of the underlying disease were ruled out.

Exposure to toxins and infectious causes such as viral, bacterial, and parasitic, as well as the human immunodeficiency virus (HIV) and infection by *Clostridium difficile* and *Giardia lamblia*, among others, were ruled out. The differential diagnosis between CD and other causes of malabsorption, such as chronic pancreatitis and Crohn's disease, was then considered. Due to the suspected diagnosis, the following serological studies were requested: anti-tissue transglutaminase IgA antibodies (0.2 U/mL, NR <10 U/mL), antigliadin IgA (<0.1 U/mL, NR <20 U/mL) and IgG (<0.5 U/mL, NR <20 U/mL), with normal values and low levels of total IgA (0.02 g/Lm, NR: 0.7–4 g/L). Enteroscopy did not find pancreatic alterations but showed erosive bulboduodenitis, with villous atrophy and an increase in intraepithelial lymphocytes in the bulboduodenal and distal biopsy which, together with the immunohistochemical study, allowed us to conclude the diagnosis of Marsh 3a type CD (**Figures 1** and **2**).

This was reaffirmed with the positive clinical response to management with a gluten-free diet (GFD), and 15 days after discharge, control of gastrointestinal and muscular symptoms and correction of nutritional deficiencies was achieved. SLE, for its part, remained in continuous remission.

DISCUSSION

Patients with SLE may have gastrointestinal manifestations; nausea and vomiting are more common (53%), followed by anorexia (49%) and abdominal pain (19%)[6]. However, within the differential diagnosis of abdominal pain and diarrhea with malabsorption clinical characteristics, exocrine pancreatic insufficiency, bacterial overgrowth in the small intestine, liver disease, and CD should be considered[6]; the latter shares an autoimmune nature with SLE, but its coexistence remains rare[7].

In CD, intestinal malabsorption can manifest with weight loss, hypoproteinemia, early osteoporosis, fat-soluble vitamins and minerals, iron deficiency, and vitamin B_{12} deficiency, as in our patient's case[8]. Severe hypocalcemia and tetany may be found in around 10%[9]. The mechanism of hypocalcemia in CD is complex and multifactorial; it depends on the loss of villous surface resulting from villous atrophy, malabsorption of fatty acids, deterioration of intestinal calcium transport mechanisms due to calbindin deficiency in the enterocytes, deterioration in calcium

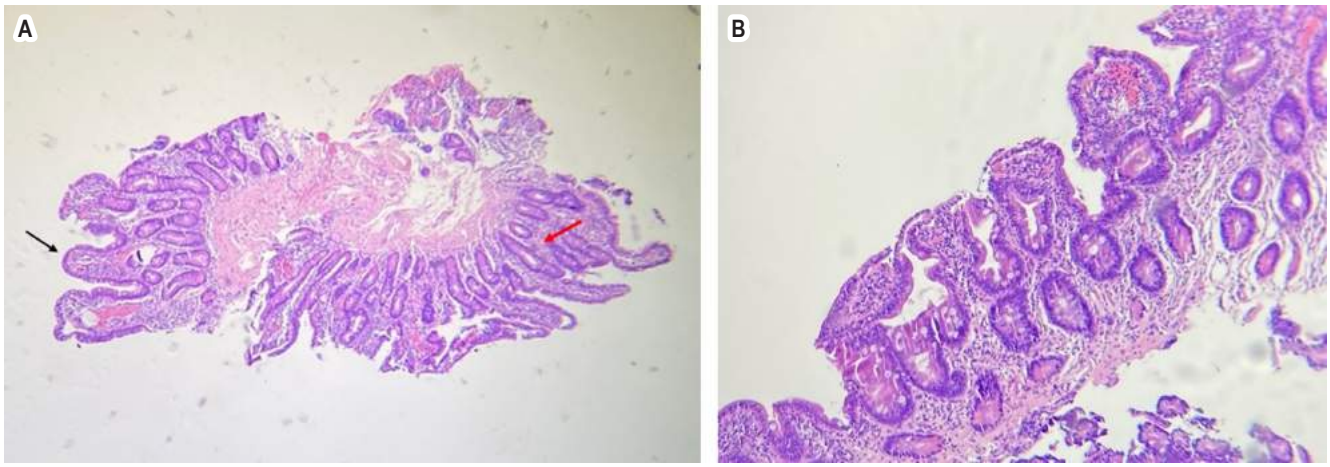

Figure 1. H-E x100. **A.** Moderate widening and flattening of some villi (black arrow). In other areas, it has preserved villi but with hyperplasia of the crypts (red arrow). **B.** Moderate villous atrophy. Source: authors' archive.

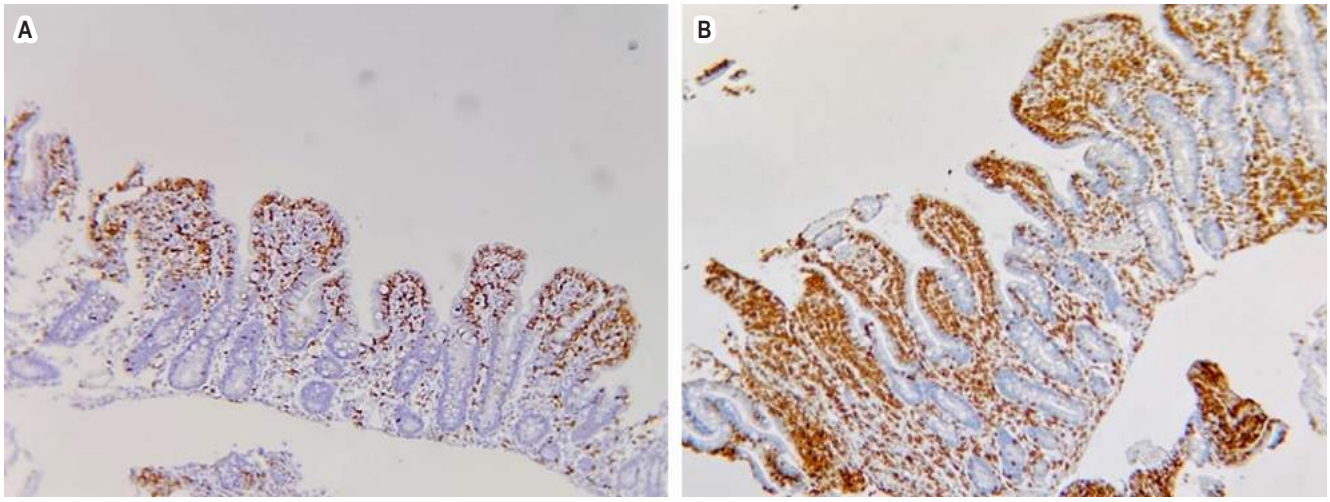

Figure 2. Immunohistochemical study with CD3 (**A**) and CD8 (**B**). An increase in intraepithelial lymphocytes with more than 40 x 100 cells. Source: Authors' archive.

absorption due to vitamin D deficiency, and hypomagnesemia secondary to malabsorption, with the consequent alteration of the parathyroid hormone both in its production and in its function, which further exacerbates the condition of hypocalcemia[10].

In diagnosing CD, serological tests should always be performed with gluten ingestion. They should include serum levels of total IgA, given that the deficiency of this immunoglobulin can give false negative results. If this occurs, anti-deamidated gliadin peptide IgG or anti-transglutaminase IgG antibodies could be helpful; however, they are usually negative[3]. Endoscopic findings in this context take on particular importance. Esophagogastroduodenoscopy can reveal changes in the mucosa: villous atrophy, areas of cracked mucosa, and mosaic pattern, among others, which can be so subtle as to go unnoticed. For this reason, its exploration is recommended even if the appearance of the mucosa is normal[2].

Despite being rare, seronegative CD is the most common cause of seronegative villous atrophy (SNVA), representing 31% to 45% in antibody-negative patient cohorts[2,11,12]. In this subtype of patients, it is necessary to consider other less frequent causes such as infections in up to 27%, usually *Giardia*, but also *Helicobacter pylori*, HIV, tuberculosis; autoimmune disorders such as Hashimoto's thyroiditis, Crohn's disease, Sjögren's syndrome, primary biliary cholangitis; enteropathy due to drugs, especially non-steroidal anti-inflammatory drugs (NSAIDs) and angiotensin II

inhibitors. There are particularities in this population; seronegative CD occurs in women later in life, around the age of 50, in white ethnic groups (in non-white races, up to two-thirds of villous atrophies are of infectious cause)[11,12]. Furthermore, in the immunohistochemistry of all patients with SNVA, there is positive staining for cytotoxic intraepithelial lymphocytes T-CD8; however, positive staining for T-CD4 is documented in patients with a non-CD cause of SNVA that can mimic refractory CD[11].

The SNVA presented here occurred in a woman much younger than what was reported in the seronegative CD and of mixed ethnicity; however, she had the typical pattern on immunohistochemistry, with positive staining for T-CD8 and negative staining for T-CD4. In the SNVA, the histopathological examination of the duodenal biopsy with multiple sampling currently emerges as the most conclusive test for CD and, together with the response to GFD, provides, as in the case of the patient, a reliable diagnosis[2]. Aziz et al. demonstrated that, in seronegative CD, survival is lower compared to seropositive CD in a 14-year follow-up, malabsorption is expected, and they are more related to other coexisting autoimmune diseases. Therefore, they require a more extensive study and closer follow-up[11]. In this specific group of patients, reports of severe hypocalcemia are not known, and it is a particularity of the case described.

In patients with SLE, it has been found that antigliadin antibodies are the most frequent, sensitive, and specific[13,14]. However, it must be considered that, as reported by Zidouni et al.[15], not all cases of SLE and CD are seropositive; conversely, Rensch et al.[13] studied 103 patients with SLE: 24 were positive for antigliadin antibodies, but no endoscopic or histological evidence of CD was found, which suggests that in SLE there is a hyperexpression of antigliadin antibodies, they are false positives in 23% and are not associated with CD. Considering that studies have estimated a prevalence of CD of 3% in patients with SLE, five times higher than in the general population, regardless of seropositivity, it is essential to use endoscopic and histological findings, HLA-DQ2/DQ8, and the response to gluten withdrawal to make a reliable diagnosis of CD. SLE can manifest before or after CD, with an average margin of five years, with diarrhea, abdominal pain, nausea/vomiting, recurrent oral aphthosis, and anemia, which should be taken as signs and symptoms to suspect this association[14].

CONCLUSION

Cases of seronegative CD are not typical and require a complete study of other entities that can generate SNVA in the non-white population, mainly infectious but also toxic and immune. Its lower survival, more significant association with other autoimmune diseases, and malabsorption make close follow-up imperative to avoid complications as severe as the reported hypocalcemia. CD should be suspected in patients with SLE who present with diarrhea, abdominal pain, nausea/vomiting, recurrent oral aphthosis, and anemia. Endoscopic and histological studies must be used, and the response to gluten suspension must be evaluated, given the probability of false positives and negatives with antibodies such as antigliadin. Due to the excellent prognosis with treatment, early diagnosis can improve quality of life and reduce morbidity.

Ethical considerations

This article was prepared after obtaining the patient's informed consent to process and disclose her medical record for scientific and academic purposes.

Conflict of interests

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REFERENCES

1. King JA, Jeong J, Underwood FE, Quan J, Panaccione N, Windsor JW, et al. Incidence of Celiac Disease Is Increasing Over Time: A Systematic Review and Meta-analysis. Am J Gastroenterol. 2020;115(4):507-25. https://doi.org/10.14309/ajg.0000000000000523
2. Caio G, Volta U, Sapone A, Leffler DA, De Giorgio R, Catassi C, et al. Celiac disease: a comprehensive current review. BMC Med. 2019;17(1):1-20. https://doi.org/10.1186/s12916-019-1380-z
3. Rubin JE, Crowe SE. Celiac disease. Ann Intern Med. 2020;172(1):ITC1-16. https://doi.org/10.7326/AITC202001070
4. Dahan S, Shor DBA, Comaneshter D, Tekes-Manova D, Shovman O, Amital H, et al. All disease begins in the gut:

Celiac disease co-existence with SLE. Autoimmun Rev. 2016;15(8):848-53. https://doi.org/10.1016/j.autrev.2016.06.003
5. Courtney PA, Patterson RN, Lee RJE, McMillan SA. Systemic lupus erythematosus and coeliac disease. Lupus. 2004;13(3):214. https://doi.org/10.1191/0961203304lu512xx
6. Ebert EC, Hagspiel KD. Gastrointestinal and hepatic manifestations of systemic lupus erythematosus. J Clin Gastroenterol. 2011;45(5):436-41. https://doi.org/10.1097/MCG.0b013e31820f81b8
7. Tian XP, Zhang X. Gastrointestinal involvement in systemic lupus erythematosus: insight into pathogenesis, diagnosis and treatment. World J Gastroenterol. 2010;16(24):2971-7. https://doi.org/10.3748/wjg.v16.i24.2971
8. Mooney PD, Hadjivassiliou M, Sanders DS. Coeliac disease. BMJ. 2014;348:g1561. https://doi.org/10.1136/bmj.g1561
9. Ross JR, Gibb SP, Hoffman DE, Clerkin EP, Dotter WE, Hurxthal LM. Gluten Enteropathy and Skeletal Disease. JAMA. 1966;196(3):270-4. https://doi.org/10.1001/jama.1966.03100160120035
10. Staun M, Jarnum S. Measurement of the 10,000-molecular weight calcium-binding protein in small-intestinal biopsy specimens from patients with malabsorption syndromes. Scand J Gastroenterol. 1988;23(7):827-32. https://doi.org/10.3109/00365528809090768
11. Aziz I, Peerally MF, Barnes JH, Kandasamy V, Whiteley JC, Partridge D, et al. The clinical and phenotypical assessment of seronegative villous atrophy; a prospective UK centre experience evaluating 200 adult cases over a 15-year period (2000-2015). Gut. 2017;66(9):1563-72. https://doi.org/10.1136/gutjnl-2016-312271
12. Volta U, Caio G, Boschetti E, Giancola F, Rhoden KJ, Ruggeri E, et al. Seronegative celiac disease: shedding light on an obscure clinical entity. Dig Liver Dis. 2017;48(9):1018-22. https://doi.org/10.1016/j.dld.2016.05.024
13. Rensch MJ, Szyjkowski R, Shaffer RT, Fink S, Kopecky C, Grissmer L, et al. The prevalence of celiac disease autoantibodies in patients with systemic lupus erythematosus. Am J Gastroenterol. 2001;96(4):1113-5. https://doi.org/10.1111/j.1572-0241.2001.03753.x
14. Soltani Z, Baghdadi A, Nejadhosseinian M, Faezi ST, Shahbazkhani B, Mousavi SA, et al. Celiac disease in patients with systemic lupus erythematosus. Reumatologia. 2021;59(2):85-9. https://doi.org/10.5114/reum.2021.105416
15. Zitouni M, Daoud W, Kallel M, Makni S. Association entre lupus érythémateux systémique et maladie coeliaque: cinq cas. Revue du rhumatisme. 2004;71(7):630-32. https://doi.org/10.1016/S1169-8330(03)00392-2

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Case report

Infiltrating Lobular Carcinoma of the Breast Metastatic to the Duodenum, about a Case

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Abstract

Introduction: Gastric outlet obstruction or pyloric syndrome can occur secondary to neoplastic involvement, and metastasis as an etiology is unusual. Breast neoplasms generally cause bone, liver, and lung metastases, rarely involving the gastrointestinal tract. **Case presentation:** A 69-year-old female patient with infiltrating lobular carcinoma of the right breast consulted for abdominal pain and postprandial emetic episodes with oral intolerance and dyspnea. Bilateral neoplastic breast involvement and dilation of the gastric chamber with thickening of the pylorus were recorded. She required antiemetic management and placement of a nasogastric tube. She was taken to an upper digestive tract endoscopy, which found an ulcerated lesion with an infiltrative appearance at the postpyloric level that circumferentially compromised the duodenal lumen. Then, a biopsy was taken, which was compatible with a breast carcinoma of a lobular type. This entity, called *pyloric syndrome due to neoplasia*, can be managed with gastrojejunostomy or an enteral prosthesis that improves the quality of life of patients with an ominous short-term prognosis. The patient in our case expressed advance directives not to receive invasive procedures, for which an uncovered metal prosthesis was placed for palliative purposes, achieving the re-establishment of the feeding route and resolution of dyspnea due to restriction. **Conclusions:** The metastatic involvement of neoplasms of the breast to the gastrointestinal tract is rare; however, it should be suspected in elderly patients with previously documented neoplasms.

Keywords

Breast neoplasms, metastasis of neoplasms, pylorus, case reports, duodenal obstruction.

INTRODUCTION

Pyloric syndrome or obstruction of the gastric outlet tract is an entity that can occur secondary to neoplastic involvement and adversely affect patients' quality of life[1,2]. Metastatic involvement as an etiology is unusual and even less frequently associated with a primary breast tumor[3,4], which makes it reasonable that in cases like the one described, various differential diagnoses should be suspected and explored.

CLINICAL CASE

A 69-year-old woman was diagnosed with infiltrating lobular carcinoma of the right breast one month before admission. She was admitted for a week of diffuse abdominal pain

associated with nausea, postprandial emesis, and dyspnea at rest. On admission, she was found to be in a fair general condition, tachycardic and tachypneic, with ambient saturation of 57%, and she had no other relevant history. Management was given with supplemental oxygen, and a study for dyspnea and emetic syndrome was initiated. Contrast-enhanced CT studies of the chest and abdomen were performed, and the results were negative for pulmonary thromboembolism, with findings of basal subsegmental atelectasis and pericardial effusion without hemodynamic compromise. Additionally, bilateral breast neoplastic involvement and dilation of the gastric chamber with thickening of the pylorus were evident (**Table 1**).

With these findings, the hypoxemia was attributed to atelectatic involvement. Regarding the gastrointestinal condition, it was considered compatible with a pyloric syndrome, and management was initiated with a nasogastric tube and antiemetic, resulting in partial improvement. The patient was taken for esophagogastroduodenoscopy, which showed changes in esophagitis due to food retention and content in the gastric chamber, which, in turn, revealed an infiltrative-looking lesion with an ulcerated surface and easy bleeding at the postpyloric level that circumferentially compromised the duodenal lumen (**Figure 1**).

Biopsies were taken from the lesion in the duodenum, which reported involvement by a group of atypical and discohesive cells with immunohistochemistry compatible with a lobular-type carcinoma of breast origin (negative for cytokeratin 20, CDX-2, and E-cadherin) (**Figure 2**). The findings were explained; however, the patient expressed advance directives not to receive invasive procedures, for which a 22 mm × 60 mm uncovered metal prosthesis was inserted to reestablish the feeding route and improve dyspnea and abdominal pain (**Figure 3**).

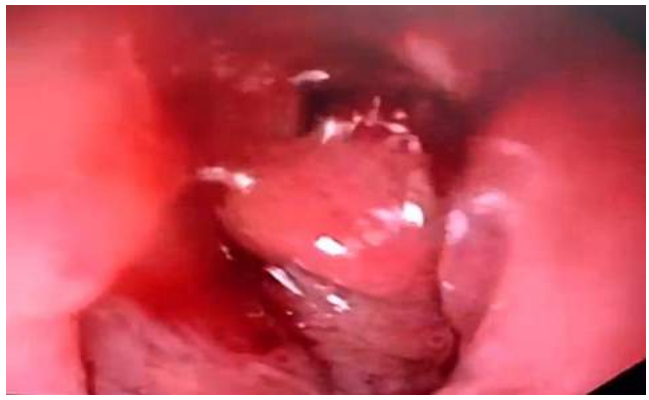

Figure 1. Prepyloric region with edematous, friable mucosa easily bleeding upon passage of the equipment with circumferential involvement. Source: Authors' archive.

DISCUSSION

Obstruction of the gastric outlet tract can be secondary to intrinsic or extrinsic causes that explain the mechanical blockage of gastric emptying; it can be located at the distal level of the stomach, pylorus, or duodenum and usually presents with nausea, vomiting, and abdominal pain[1].

The etiology is usually divided into malignant (62%) and benign (38%), including gastric neoplasms, duodenal adenocarcinoma, carcinomas of the ampulla of Vater, neoplasms of the gallbladder, lymphomas, and metastases, among the malignant causes[1,2]. Benign etiologies include peptic ulcers, acute and chronic pancreatitis, inflammatory entities (such as Crohn's disease), infiltrative entities (such as amyloidosis), and foreign bodies[2–5].

Regarding infiltrating lobular carcinoma of the breast, it is characterized by discohesive cells and mutations in genes

Table 1. Paraclinical studies

Study	Result
Transthoracic echocardiogram	Left ventricle of average size, concentric remodeling, preserved systolic function, EF of 60% without segmental disorders; moderate pericardial effusion with left pleural effusion and signs of collapsed or infiltrated lung segments; no significant valvular heart disease
Contrast-enhanced CT of the chest	Bilateral breast masses predominantly on the left concerning a known neoplastic history, with suspicious-looking lymph nodes in both axillary regions and mixed polyostotic involvement attributed to a secondary neoplastic disease; subsegmental atelectasis in the middle lobe and lingula
Contrast-enhanced CT of the abdomen	Moderate hepatic steatosis; dilation of the gastric chamber with apparent thickening of the pylorus walls; uncomplicated diverticular disease of the colon; polyostotic involvement concerning secondary neoplastic disease
Breast biopsy	Classic invasive lobular carcinoma

EF: ejection fraction. Prepared by the authors.

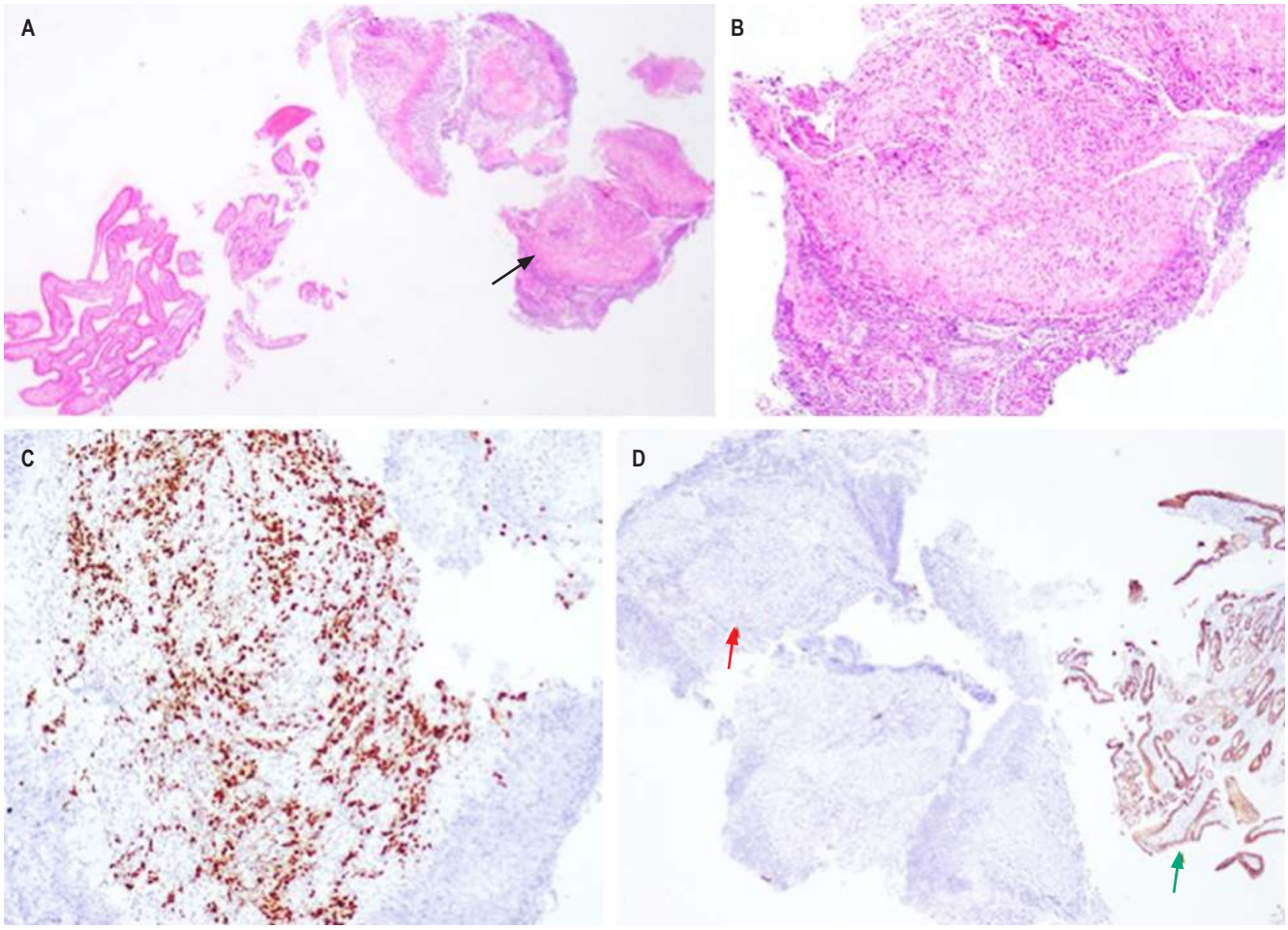

Figure 2. A. (Hematoxylin-eosin). Duodenal epithelium with preserved architecture and fragments of submucosa compromised by a tumor infiltrate (black arrow). **B.** (Hematoxylin-eosin). The tumor cells are discohesive, small to medium in size, with nuclear pleomorphism and hyperchromasia. **C.** (GATA-3). Positivity of tumor cells. **D.** (E-cadherin). Tumor cells are negative for E-cadherin (red arrow); there is adequate internal control in the intestinal epithelium (green arrow). Source: Authors' archive.

that code for E-cadherin since its absence supports the diagnosis[6–8]. However, there seems to be no association between this characteristic and the appearance of metastasis[7,9]. Multiple metastatic involvements of the bone, liver, and lung have been described but are rare in the peritoneum (14.6%) and the stomach (2.8%)[10].

In the case of the patient, duodenal metastatic involvement due to already-known breast carcinoma was documented. While metastases are not frequent within tumor lesions of the duodenum, there are case series that describe prevalences of 32%, of which up to 12% are metastases from squamous cell carcinoma, clear cell carcinoma (8%), melanoma (8%), and pleomorphic liposarcoma (4%)[3,11]. Yim et al., in a series of cases of patients with pyloric syndrome, reported a metastatic etiology close to 27.6%[12]. Unusual manifestations also include metastatic involvement due to adenocarcinoma of the cecum, squamous cell carcinoma of the cervix and anus[12–14], and pleomorphic lung carcinoma[15,16]. Regarding duodenal involvement due to breast carcinomas, episodes of gastric outlet obstruction secondary to or as the first manifestation of neoplasia are described, such as that reported by Khairy et al.[17].

Among the therapeutic alternatives for outlet obstructions of benign etiology, pharmacological therapy and some endoscopic procedures, such as balloon dilations, are listed, leaving surgical management as the last option. Regarding the management of malignant obstructions, the insertion of antroduodenal prostheses, gastrojejunostomies (GJ), and endoscopic ultrasound-guided gastroenterostomy (EUS-GE) are described[2,17–20].

Antroduodenal prostheses are metallic, whether or not covered by plastic or silicone membranes. The covered

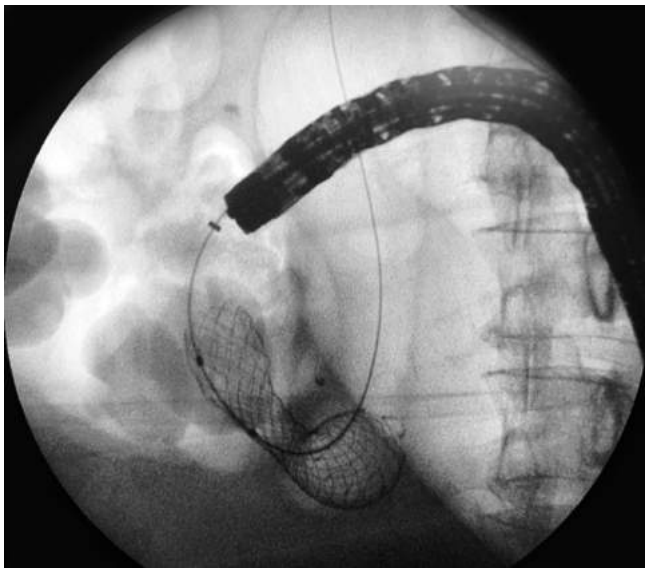

Figure 3. The duodenal prosthesis is positioned under fluoroscopy and takes the classic hourglass-shaped image. Source: Authors' archive.

ones have a higher risk of migration but a lower stricture rate. The leading cause of stricture is intra-stent tumor growth (8–25.4%), and argon plasma therapy or a new intraluminal stent is required. Prosthesis migration occurs in 0% to 19.4%, mainly in covered ones; they are rearranged or removed endoscopically or surgically. Bleeding associated with the insertion occurs in 1%, and conservative or endoscopic management is usually given. They have a limited useful life and an *in situ* duration of up to 85 days. They are generally employed in patients with a poor short-term prognosis to improve quality of life and bring the oral route back, which allows longer relief of symptoms and lower frequency of reintervention and costs[12,20].

GJ can be performed using the conventional approach or by laparoscopy in those patients with a life expectancy greater than or equal to two months[19,20].

EUS-GE is a safe and effective alternative, which uses metallic prostheses that oppose the lumen covered with a device that prevents migration. The insertion is carried out through the stomach, communicating with the distal duodenum or the proximal jejunum; a technical success of 87% to 96% and clinical success of 81% to 92% have been reported. Complications include pneumoperitoneum, gastric fistula, bleeding, peritonitis, or abdominal pain, which are usually infrequent. When comparing this technique with antroduodenal prostheses, both have similar technical success, hospital stay, and safety[19,20].

GJ has better technical success with symptom recurrence at a frequency similar to the endoscopic approach[20]. EUS-GE has a higher clinical success rate with greater obstruction and is a minimally invasive alternative with technical difficulty and less availability, which favors the other options[19,20].

In the case of our patient, who expressed her advance directive to refuse invasive maneuvers and, taking into account her clinical condition, the insertion of an uncovered duodenal prosthesis was considered as management.

CONCLUSION

The pyloric syndrome is a widely known entity with a significant percentage of malignant etiology. It can be suspected in patients like the one mentioned, taking into account their advanced age and previously known neoplastic involvement. Although metastatic involvement of breast neoplasms to the digestive tract is uncommon, and even less so for lobular carcinoma, immunohistochemical markers can help establish an etiological diagnosis.

Management will depend on the patient's context and clinical condition. Performing a GJ could be considered in patients with adequate functionality and medium-term prognosis. In those with an ominous prognosis, an enteral prosthesis could be inserted to improve the patient's quality of life.

REFERENCES

1. Koop AH, Palmer WC, Stancampiano FF. Gastric outlet obstruction: A red flag, potentially manageable. Cleve Clin J Med. 2019;86(5):345-53. https://doi.org/10.3949/ccjm.86a.18035
2. Storm AC, Ryou M. Advances in the endoscopic management of gastric outflow disorders. Curr Opin Gastroenterol. 2017;33(6):455-60. https://doi.org/10.1097/MOG.0000000000000403
3. Rosas-Marcos E, Frisancho-Velarde O, Yàbar-Berrocal A. Neoplasia maligna duodenal: pérfil clínico-patológico. Rev. gastroenterol. Perú. 2003;23(2):99-106.
4. Lambert LA. 3-27 Breast cancer: Presentation and intervention in women with gastrointestinal metastasis and carcinomatosis. Breast Dis. 2006;17(3):250-1. https://doi.org/10.1016/S1043-321X(06)80509-6
5. Santa-Botero DA, Luna-Meza Á, Castañeda-Cardona C, Rosselli D. Metástasis duodenogástrica por cáncer

de mama: reporte de caso. Rev. colomb. Gastroenterol. 2017;32(4):379-81. https://doi.org/10.22516/25007440.182
6. Dossus L, Benusiglio PR. Lobular breast cancer: incidence and genetic and non-genetic risk factors. Breast Cancer Res. 2015;17:37. https://doi.org/10.1186/s13058-015-0546-7
7. Ferlicot S, Vincent-Salomon A, Médioni J, Genin P, Rosty C, Sigal-Zafrani B, et al. Wide metastatic spreading in infiltrating lobular carcinoma of the breast. Eur J Cancer. 2004;40(3):336-41. https://doi.org/10.1016/j.ejca.2003.08.007
8. Desmedt C, Zoppoli G, Gundem G, Pruneri G, Larsimont D, Fornili M, et al. Genomic Characterization of Primary Invasive Lobular Breast Cancer. J Clin Oncol. 2016;34(16):1872-81. https://doi.org/10.1200/JCO.2015.64.0334
9. Engstrøm MJ, Opdahl S, Vatten LJ, Haugen OA, Bofin AM. Invasive lobular breast cancer: the prognostic impact of histopathological grade, E-cadherin and molecular subtypes. Histopathology. 2015;66(3):409-19. https://doi.org/10.1111/his.12572
10. Ovalle-Hernández AF, Vargas-Rubio RD. Experience in the management of neoplastic gastric outlet obstruction in patients at the Hospital Universitario San Ignacio in Bogotá, Colombia. Rev Gastroenterol Mex (Engl Ed). 2022;87(1):35-43. https://doi.org/10.1016/j.rgmxen.2021.10.002
11. Vargas-Rubio RD, Ovalle-Hernández AF, Ursida-Serrano V, Torres-Arciniegas SC, Hani de Ardila AC. Experiencia con los stents metálicos autoexpandibles para el manejo de cáncer gástrico distal. Rev. Gastroenterol. Peru. 2018;38(4):331-9.
12. Yim HB, Jacobson BC, Saltzman JR, Johannes RS, Bounds BC, Lee JH, et al. Clinical outcome of the use of enteral stents for palliation of patients with malignant upper GI obstruction. Gastrointest Endosc. 2001;53(3):329-32. https://doi.org/10.1016/S0016-5107(01)70407-5
13. Sebastián JJ, Zaragozano R, Vicente J, Gallego O, Trufero JM. Duodenal obstruction secondary to a metastasis from an adenocarcinoma of the cecum: a case report. Am J Gastroenterol. 1997;92(6):1051-2.
14. Marra E, Quassone P, Tammaro P, Cardalesi C, D'Avino R, Cipolletta F, et al. Malignant Gastric Outlet Obstruction Caused by Duodenal Cervix Metastasis in a Young Woman: Rendezvous Technique. Medicina (Kaunas). 2021;57(8):765. https://doi.org/10.3390/medicina57080765
15. Yuridullah R, Kaur P, Estifan E, Sanchez J, Nanavati S, Singhal M. Anal squamous cell carcinoma with metastasis to duodenum causing duodenal stricture and gastric outlet obstruction. AME Case Rep. 2019;3:33. https://doi.org/10.21037/acr.2019.07.12
16. Matsuda M, Kai Y, Harada S, Suzuki K, Hontsu S, Muro S. Duodenal Metastasis of Pulmonary Pleomorphic Carcinoma: A Case Report. Case Rep Oncol. 2021;14(3):1511-15. https://doi.org/10.1159/000519664
17. Khairy S, Azzam A, Mohammed S, Suleman K, Khawaji A, Amin T. Duodenal Obstruction as First Presentation of Metastatic Breast Cancer. Case Rep Surg. 2015;2015:605719. https://doi.org/10.1155/2015/605719
18. Kouanda A, Binmoeller K, Hamerski C, Nett A, Bernabe J, Watson R. Endoscopic ultrasound-guided gastroenterostomy versus open surgical gastrojejunostomy: clinical outcomes and cost effectiveness analysis. Surg Endosc. 2021;35(12):7058-67. https://doi.org/10.1007/s00464-020-08221-z
19. Ye BW, Lee KC, Hou MC. Endoscopic management of malignant gastric outlet obstruction. J Chin Med Assoc. 2021;84(4):346-53. https://doi.org/10.1097/JCMA.0000000000000502
20. Troncone E, Fugazza A, Cappello A, Del Vecchio Blanco G, Monteleone G, Repici A,et al. Malignant gastric outlet obstruction: Which is the best therapeutic option? World J Gastroenterol. 2020;26(16):1847-60. https://doi.org/10.3748/wjg.v26.i16.1847

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Case report

Giant Submucosal Lipoma of the Right Colon Spontaneously Expelled Rectally: Case Report

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Abstract

Colonic lipomas are benign tumors originating in mesenchymal tissue and are considered the second most common benign tumor in the colon after adenomatous polyps. They tend to affect women more; their most frequent location is the right colon. Generally, these lipomas do not exhibit symptoms, but when they reach a considerable size, they can cause manifestations. They can also result in complications such as obstruction, intussusception, and perforation.

Since their radiological characteristics are similar to fat, they can be visualized using computed tomography. Still, the final diagnosis is made through colonoscopy, where a fatty mass with an oval shape and elastic capacity is observed. Lesions can be removed endoscopically or surgically. Spontaneous expulsion of a lipoma rectally is rare, and its mechanism is not yet fully understood. Although the literature establishes a cut-off point of 2 cm to decide between endoscopic or laparoscopic resection, the former is increasing and can extend this limit. Surgical resection is recommended in cases such as the one in this article. This case is the biggest reported colonic lipoma (13 cm) expelled spontaneously.

Keywords

Lipoma, tumor, colon, intestine.

INTRODUCTION

Lipomas are soft tissue tumors derived from mature adipocytes, first described by Bauer in 1757, which are macroscopically and radiologically indistinguishable from normal adipose tissue; epidemiologically, they are the most frequent injuries derived from soft tissues in adult patients, with a slight predominance in male patients[(1)].

Location in the GI tract is infrequent and generally asymptomatic, which can be detected incidentally during surgery, colonoscopy, or autopsy[(2)]. Lipomas are often solitary lesions of submucosal origin found in the proximal colon and typically measure less than 2 cm in size, with a maximum diameter of 8.5 cm reported in the literature[(3).] Despite new techniques for radiological diagnosis, the gold standard continues to be a histopathological evaluation that leads to the precise diagnosis of this entity; the manner of removal depends on the manifestation of the case and could result in elective or emergent removal[(4)].

The article reports the case of a female patient who spontaneously expelled part of a giant submucosal lipoma via the rectum and required a secondary laparoscopic resection of the entire surgical specimen.

CASE DESCRIPTION

A 42-year-old female patient with no significant pathological history consulted for a clinical condition of one year of evolution that had worsened in the previous 12 hours. It was characterized by non-radiating colic-type pain in the mesogastrium, without mitigating or aggravating factors, whose intensity was 5/10 on the visual analog scale. It was accompanied by the expulsion of a soft, non-fouling, yellowish mass through the rectum (**Figure 1**).

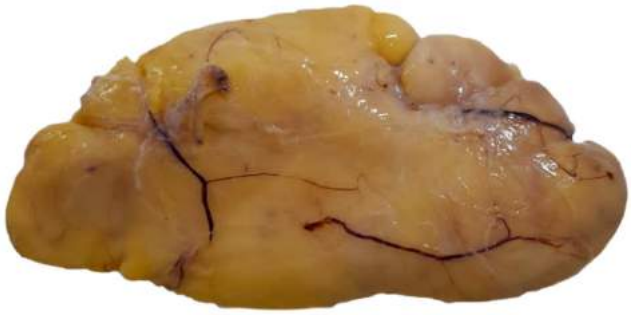

Figure 1. Lipoma expelled rectally with well-defined walls and no signs of bleeding. Source: Authors' archive.

Therefore, the patient attended the emergency department. During the interrogation, she reported a condition of intestinal intussusception ten months ago of unknown cause, which self-resolved and required hospitalization for three days. Considering this and the abdominal pain, a contrast-enhanced abdomen CT was requested, describing a lipomatous-type lesion at the ascending colon level (**Figure 2**).

In this context, the general surgery service evaluated the patient and suggested a total colonoscopy. It showed a raised, sessile, mamelonated, subepithelial lesion of approximately 6 cm in diameter at the right colon level near the cecum, which occupied one-third of the lumen of the colon (**Figure 3**).

The final pathological diagnosis of the spontaneously expelled specimen was a lipoma measuring 7 × 5 × 4 cm and weighing 117 g. A medical meeting was held with the gastroenterology and general surgery team, where they determined to perform a laparoscopic resection of the residual lesion, taking into account the history of intussusception less than one year ago and the reports in the literature, which will be addressed in the discussion of this article. A laparoscopic segmental colectomy-type procedure with end-to-end anastomosis was performed using mechanical staplers with negative margins. The patient remains asymptomatic one year after the procedure.

DISCUSSION

Colonic lipomas are benign tumors of mesenchymal origin whose manifestation is exceptional. They are consolidated as the most common benign colonic tumor, only preceded by adenomatous polyps[5]. Its incidence ranges between 0.2% and 4.4%, with a predominance in the female sex; the age of onset is, on average, between 40 and 50 years. Regarding its location, the most frequent location is the right colon, which represents 65% to 75% of all cases[6,7].

Other authors, such as Rogy et al., published a series of cases evaluated over ten years in referral centers and found that lipomas represented 0.3% of colorectal diseases in general and 1.8% of benign colon tumors, with a greater

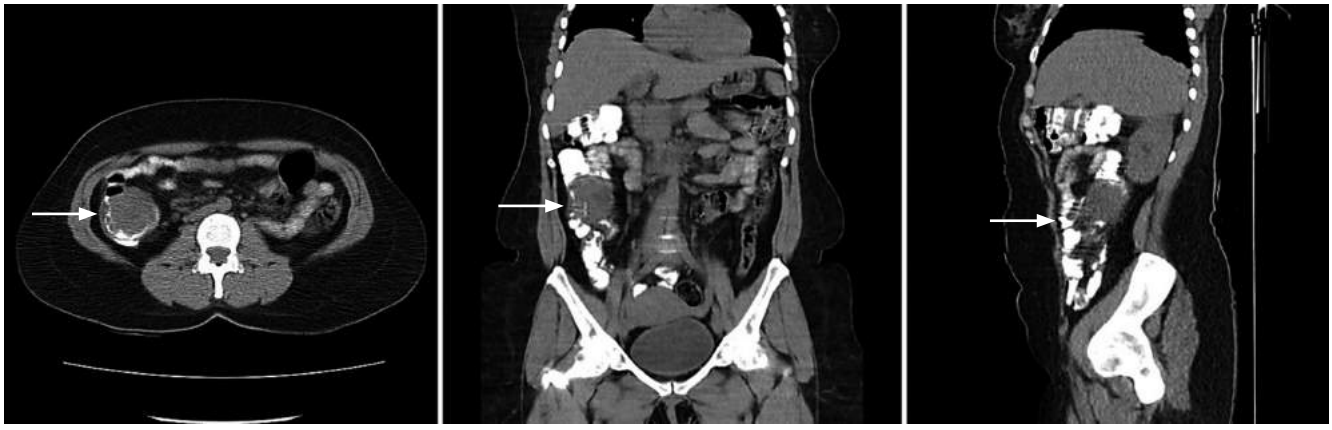

Figure 2. CT image showing, in different sections, a radiolucent tumor with well-defined edges in the right colon. Source: Authors' archive.

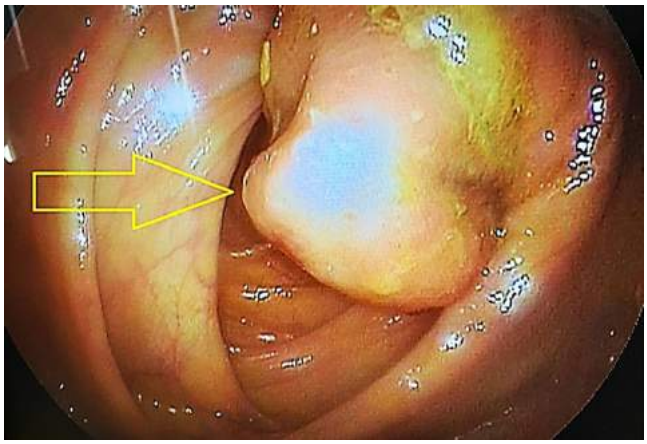

Figure 3. Endoscopic view of a subepithelial lesion occupying one-third of the colon's lumen. Source: Authors' archive.

frequency in women, in the right colon, and solitary in 90%; the remaining 10% corresponded to multiple manifestations[8].

Generally, these lesions are asymptomatic; however, 30% of large lesions will cause symptoms, especially when they measure more than 2 cm; the most common manifestations include abdominal pain, rectal bleeding, and changes in bowel movements[9,10]. It should be noted that abdominal pain may be secondary to permanent intestinal intussusception, and the lipoma serves as the head of the intussusception. At the same time, rectal bleeding could be explained by ulceration of the mucosa that covers the lipoma. Unusual complications of colonic lipoma include obstruction, intussusception, perforation, and severe bleeding[11].

The clinical significance of lipoma is the high probability of being confused with malignant neoplasms of the colon due to similar characteristics in clinical manifestations; however, no malignant changes associated with this type of lesion have been reported[12].

Concerning the diagnosis, the radiolucent characteristics of the fat mean that these tumors can be visualized by CT of the abdomen and barium enema, which makes it clear that it has a low sensitivity to tumors smaller than 1.5 cm; still, the diagnosis is fundamentally endoscopic, which can visualize a fatty, ovoid-looking mass with a specific elastic capacity to return to its initial shape after being pinched with a clamp (pillow sign)[8]. Since it is below the normal mucosa, a lesion biopsy is not recommended due to the low diagnostic yield. On the contrary, it increases the risks of bleeding and perforation. The gold standard for diagnosing colonic lipoma is based on histopathological diagnosis[13].

Treatment varies according to the lesion size; in lesions smaller than 2 cm, endoscopic en bloc resection can be considered; however, surgical resection is recommended in those with a diameter greater than 2 cm due to the risk of existing perforation since fatty tissue is a poor electrical conductor and can increase the risk of complications in endoscopic resection. Usually, lesions with complete resection do not recur, and the procedures are curative. This controversial analysis occurred between the gastroenterology and general surgery teams when choosing the surgical procedure for the patient. Lipomas are benign tumors with null degeneration, so resection is justified to prevent or treat complications[8,14,15].

The spontaneous expulsion of a lipoma rectally is rare and practically anecdotal; the mechanism of self-dissection of a lipoma is unknown. It is believed that in pedunculated lipomas, the pedicle could suffer strangulation and subsequent necrosis, causing its detachment. Another way would be the ulceration of the mucosa that covers the lipoma and its exit into the colonic lumen[16].

CONCLUSION

It is important to emphasize that, although the literature is emphatic in taking 2 cm as a cut-off point to choose between endoscopic versus laparoscopic resection, the endoscopic experience curve is currently increasing, which will undoubtedly lead to new consensuses that expand this diameter to attempt more advanced resections. However, in this case, considering that the lesion measured 6 cm, no one on the endoscopic team considered they had the expertise to perform it. If we add the 6 cm of the colonic lesion plus the spontaneously expelled 7 cm, it measures 13 cm, making this case the most giant colon lipoma reported to date.

REFERENCES

1. Liyen Cartelle A, Uy PP, Yap JEL. Giant Colonic Lipoma Presenting as Intermittent Colonic Obstruction with Hematochezia. Cureus. 2020;12(11):e11434. https://doi.org/10.7759/cureus.11434
2. Farfour AN, Abu Omar NA, Alsohaibani FI. Lipoma grande de colon ascendente: reporte de un caso y revisión de la literatura. J Surg Case Rep. 2020;2020(9):rjaa354. https://doi.org/10.1093/jscr/rjaa354

3. Sapalidis K, Laskou S, Kosmidis C, Passos I, Mantalobas S, Michalopoulos N, et al. Symptomatic colonic lipomas: Report of two cases and a review of the literature. SAGE Open Med Case Rep. 2019;7:2050313X19830477. https://doi.org/10.1177/2050313X19830477
4. Menegon Tasselli F, Urraro F, Sciaudone G, Bagaglini G, Pagliuca F, Reginelli A, et al. Colonic Lipoma Causing Bowel Intussusception: An Up-to-Date Systematic Review. J Clin Med. 2021;10(21):5149. https://doi.org/10.3390/jcm10215149
5. An HH, Duong TT, Van Truong N, Van Quoc L, Son VN, Thang NP, et al. A large lipoma of the descending colon: A rare case report. Radiol Case Rep. 2021;16(11):3396-99. https://doi.org/10.1016/j.radcr.2021.08.013
6. Ozen O, Guler Y, Yuksel Y. Giant colonic lipoma causing intussusception: CT scan and clinical findings. Pan Afr Med J. 2019;32:27. https://doi.org/10.11604/pamj.2019.32.27.18040
7. Chahri N, Querol V, Ballesta E. Expulsión espontánea de gran lipoma de colon izquierdo. Rev Esp Enferm Dig. 2013;105(8):502-3. https://doi.org/10.4321/S1130-01082013000800013
8. Pastor C, Valentí V, Poveda I, Martí P, Zozaya G, Baixauli J, et al. Lipomas submucosos de colon. Rev. esp. enferm. dig. 2007;99(5): 299-300.
9. Zenaidi H, Ismail IB, Rekik F, Aziz M, Rebii S, Zoghlami A. Large pedunculated colonic lipoma: a rare cause of colorectal intussusception in adults. Pan Afr Med J. 2020;36:200. https://doi.org/10.11604/pamj.2020.36.200.24606
10. Yeom JO, Kim SY, Jang EC, Yu JY, Chang ED, Cho YS. Colonic lipoma covered by hyperplastic epithelium: Case report. World J Clin Cases. 2013;1(3):124-7. https://doi.org/10.12998/wjcc.v1.i3.124
11. Presti ME, Flynn MF, Schuval DM, Vollmar TM, Zotos VD. Colonic Lipoma With Gastrointestinal Bleeding and Intussusception. ACG Case Rep J. 2015;2(3):135-6. https://doi.org/10.14309/crj.2015.32
12. Lee JM, Kim JH, Kim M, Kim JH, Lee YB, Lee JH, et al. Endoscopic submucosal dissection of a large colonic lipoma: Report of two cases. World J Gastroenterol. 2015;21(10):3127-31. https://doi.org/10.3748/wjg.v21.i10.3127
13. Zhou XC, Hu KQ, Jiang Y. A 4-cm lipoma of the transverse colon causing colonic intussusception: A case report and literature review. Oncol Lett. 2014;8(3):1090-92. https://doi.org/10.3892/ol.2014.2278
14. Meunier M, Limgba A, Schumacker I, Mehdi A. Intussusception related to transverse colonic lipoma: a case report and review of the literature. Acta Chir Belg. 2022;122(1):51-5. https://doi.org/10.1080/00015458.2020.1739843
15. Chase MP, Yarze JC. Giant lipoma-to attempt endoscopic resection or not? Am J Gastroenterol. 2000;95(8):2143-4. https://doi.org/10.1111/j.1572-0241.2000.02221.x
16. Allawati M, Logman T, Al Qubtan MT. Colonic Lipoma as a Leading Cause of Intussusception Resulting in Bowel Obstruction. Cureus. 2021;13(9):e18261. https://doi.org/10.7759/cureus.18261