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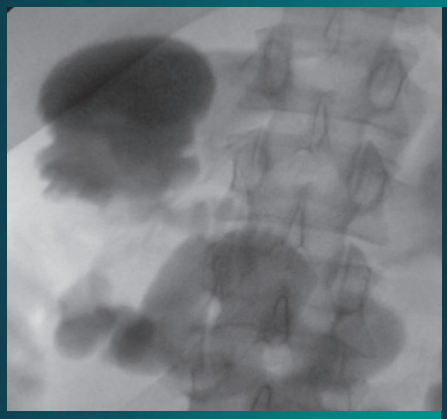

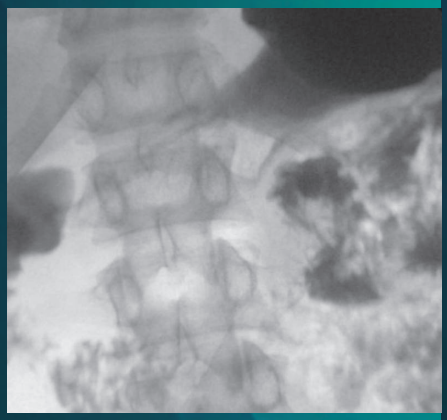



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Editorial

# Morphological subtypes of the duodenal papilla and their relationship with post-ERCP complications

Gustavo Adolfo Reyes.[1*]

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Endoscopic retrograde cholangiopancreatography (ERCP) is associated with a high rate of adverse effects within the group of endoscopic digestive procedures. Acute pancreatitis post-ERCP is the most common complication, occurring between 3.5% and 9.7% of the cases and leading to a 0.1% and a 0.7% mortality range. Other complications include perforation, bleeding, cholecystitis, and cholangitis[(1)]. Biliary cannulation is the limiting factor step for a successful ERCP. The European Society of Gastrointestinal Endoscopy (ESGE) has defined difficult biliary cannulation as the presence of more than 5 contacts with the papilla while attempting to cannulate, more than 5 minutes spent attempting to cannulate, or more than 1 unintended passage or contrast injection into the pancreatic duct[(2)]. Difficult cannulation can compromise ERCP success and increase the risk of complications.

Several factors associated with an increased risk of complications during an ERCP have been described. For example, female gender, acute pancreatitis post-ERCP history, a sphincter of Oddi dysfunction suspicion, being 40 years or younger, normal serum bilirubin, difficult cannulation, a medium contrast injection into the pancreatic duct, a passage of pancreatic guide wire to the pancreatic duct, pancreatic sphincterotomy, the presence of coagulopathy, the use of anticoagulant or antiplatelet drugs, among others[(1,3)]. The effect of duodenal papilla morphology on biliary cannulation outcomes has been recently studied[(4-6)], suggesting that some morphological subtypes of the papilla could be associated with difficulties in cannulation and an increased risk of post-ERCP complications.

In this issue of Revista Colombiana de Gastroenterología, the Hospital Nacional Guillermo Almenara Irigoyen group of Lima, Perú, describes a prospective and analytical study of 138 patients who were taken to ERCP, in which the relationship between the morphological type of the duodenal papilla and the risk of post-ERCP complications was determined. For this study, they used the Scandinavian study group classification of Haraldsson *et al*[(6)], which divides the duodenal papilla into 4 types: type 1, a regular, usual, "normal" papilla with no distinctive characteristics; type 2, a small, flat papilla, with a 3 mm diameter or smaller; type 3, similar to a bulky, pendular, prominent papilla with the papillary orifice oriented caudally; and type 4, defined as a "creased, ridged, extended distally" papilla.

In this study, acute pancreatitis occurred globally in 2.9% of patients, bleeding in 1.45%, and perforation in 0.7%. Flat papillae (type 2) were associated with higher complication rates: perforation (9.09%) and pancreatitis (9.09%). Other authors have also

 

found a higher rate of post-ERCP pancreatitis in papillae type 2[6,7]. As additional data, type 1 papilla (regular) was associated with a shorter cannulation time. Precut papillotomy was the procedure more frequently performed in patients with type 3 and type 4 papillae. Type 4 papilla required a longer cannulation time.

Consequently, some of the questions arising include: what to do with this information? How can we use these data to improve ERCP success and decrease the percentage rate of complications? These questions are relevant since there is currently no way for endoscopists to determine in advance the type of papilla they will deal with –except during ERCP. Furthermore, endoscopists cannot establish a relationship between the morphological type of duodenal papilla and a specific cannulation technique associated with a higher success rate or lower risk of complications. Some authors have suggested that in the presence of type 2 flat papilla, which entails a higher risk of complications, physicians with the least experience or personnel under ERCP training should refrain from continuing the procedure and let more experienced endoscopists perform it[8]. In addition, in the presence of a papilla susceptible to an increased risk of complications (such as acute pancreatitis), it is important to use all the prophylactic measures available to us to reduce the occurrence of such complications, for example, using diclofenac suppositories, pancreatic *stents,* and hydration with lactated Ringer's solution.

In the meantime, we continue working to find ways to reduce ERCP complications, which are the Achilles' heel of this procedure.

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Original article

# Association Between Body Mass Index and Liver Fibrosis Degree Measured Using Real-Time Elastography (Supersonic)

Diana Carolina Alfonso-Vergel,[1*] Jhon Edison Prieto-Ortiz.[2]

OPEN ACCESS

**Citation:**
Alfonso-Vergel DC, Prieto-Ortiz JE. Asociación entre el índice de masa corporal y el grado de fibrosis hepática medida por elastografía en tiempo real (Supersonic). Rev Colomb Gastroenterol. 2022;37(3):269-275. https://doi.org/10.22516/25007440.769

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## Abstract

**Introduction:** Non-alcoholic fatty liver disease (NAFLD) or fatty liver, is characterized by an excessive accumulation of fat in the liver, is a metabolic disorder with a worldwide prevalence close to 25%, with a spectrum of liver damage that covers the steatosis without fibrosis, steatohepatitis with variable fibrosis and cirrhosis or maximum degree of fibrosis, this fibrosis determines prognosis and outcomes in the disease. **Objective:** To evaluate the association between body mass index and the degree of liver fibrosis in patients diagnosed with fatty liver in a hepatology center in the city of Bogotá, Colombia. **Patients and methods:** A case-control study is carried out with patients diagnosed with fatty liver, who have undergone real-time elastography (Supersonic). Information was taken from patients diagnosed with fatty liver who met the inclusion criteria. Continuous variables were described using measures of central tendency and standard deviation. Categorical variables were described with numbers and percentages. A 95% confidence interval was considered statistically significant. **Results:** 361 patients were included, of which 95.2% (n=344) presented some degree of alteration (12% minimal fibrosis, 33% moderate fibrosis, 34% severe fibrosis and 16% cirrhosis) and only 5% showed a liver normal. Not having an adequate weight is related to severe fibrosis F3 OR 3.24 (1.03-10) and cirrhosis F4 OR 2.33 (2.33-42.99). No statistically significant differences were found between altered body mass index and any degree of fibrosis OR 2.74 (0.90-8.40). The presence of DM presents a 10-fold risk probability of ending in F4 cirrhosis, especially with poor disease control OR 5.16 (1.23-30.33). **Conclusion:** There is an association between abnormal body mass index and glycemic profile and the development of severe and advanced fibrosis. It is necessary in clinical practice, greater surveillance and evaluation of patients with fatty liver, in order to prevent the progression of fibrosis.

## Keywords

Non-alcoholic fatty liver, hepatic fibrosis, cirrhosis, real-time elastography, supersonic.

## INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) or fatty liver disease is characterized by excessive fat accumulation in the liver and is associated with insulin resistance[(1)]. A histological analysis defines it as the presence of steatosis in 5% or more of the hepatocytes. Fatty liver disease is diagnosed through biopsy or imaging and radiology, usually after detecting fat through ultrasound and after ruling out secondary causes of hepatic steatosis such as alcohol consumption greater than 20 g/day for men and greater than 10 g/day for women, hepatotoxic drugs intake, hepatitis B and C virus, hemochromatosis, autoimmunity, and other chronic liver disease causes[(2)].

Fatty liver disease is associated with obesity, diabetes *mellitus* (DM), dyslipidemia, and high blood pressure and is considered the hepatic manifestation of metabolic syndrome (MS)[(3)]. Most patients with fatty liver disease have hepatic

steatosis without fibrosis in its initial phase and a good long-term prognosis[4]. Other patients have fibrosis and inflammation or steatohepatitis (intermediate phase) and may progress to the final stage of fibrosis or cirrhosis with an additional risk of developing hepatocellular carcinoma (HCC)[5].

It is important to identify patients with fatty liver during the disease's different stages and, according to findings, provide them with a treatment to prevent the progression of fibrosis. Given their poor prognosis, complications such as esophageal varicose veins, hepatic impairment, and HCC should be evaluated in patients with cirrhosis[6,7]. Currently, liver biopsy has remained the gold standard for assessing the degree of liver fibrosis[8]. However, since this is an invasive test, it can cause pain, bleeding, and even death[9]. Therefore, non-invasive methods to assess the degree of fibrosis in patients with fatty liver disease are becoming increasingly common due to the invasive nature of biopsy and its complications[10].

There are several clinical scoring systems and non-invasive methods in medical practice. Some of these methods include the aspartate aminotransferase index (AST)/platelet count[11], the relationship between AST/alanine aminotransferase (ALT)[12], transient elastography (FibroScan), magnetic resonance elastography (MRE), and real-time elastography (RTE)[13] or SuperSonic; the latter is a non-invasive test recently used in Colombia. The RTE test determines liver elasticity and calculates the grade of liver fibrosis. Sometimes, the RTE test supersedes liver biopsy and is useful for monitoring most patients with hepatopathies[14].

The objective of this study is to evaluate the association between body mass index (BMI) and the degree of liver fibrosis in patients diagnosed with fatty liver in a hepatology center in Bogotá, Colombia.

## PATIENTS AND METHODS

### Population

Between January 1 and December 30, 2017, a case-control study of patients diagnosed with fatty liver disease was conducted through ultrasound or other imaging methods during hepatology consultation check-ups that would have undergone real-time elastography (SuperSonic) at Centro de Enfermedades Hepáticas y Digestivas (CEHYD) in Bogotá. We considered cases of patients who showed some degree of fibrosis and performed controls on participants with fatty liver without fibrosis determined as F0. We excluded patients who reported alcohol consumption (> 10 g in women and > 20 g in men per day), positive markers for hepatitis B virus (HBV) and hepatitis C virus (HCV), autoimmunity, hemochromatosis confirmed through a genetic study, or hepatotoxic drugs intake.

### Variables

The variables included age, gender, metabolic syndrome condition, high blood pressure, BMI, transaminase level, AST/ALT ratio, dyslipidemia, glycemia, insulin, and degree of fibrosis.

Operational definitions were made according to the following criteria: the presence of metabolic syndrome and dyslipidemia, according to the Adult Treatment Panel III guidelines (ATP III)[15]; high blood pressure, according to the JNC8 guidelines; DM, according to the American Diabetes Association criteria (ADA)[16]; overweight and obesity, according to the World Health Organization criteria (WHO)[17]. Liver fibrosis determination was performed through real-time elastography (SuperSonic) using the Aixplorer ultrasound system (SuperSonic Imagine S. A. Aix-en-Provence, France) with a convex broadband probe (SC6-1). Values between 5.1 and 6.8 kPa, F2 between 7.2 and 8.3 kPa, F3 between 9.2 and 10.1, and F4 between 12.8 and 18.8 kPa were considered F0-F1.

### Source of information

Project format: we used patients' medical records as a secondary source in a consultation at a hepatology center in Bogotá.

### Data collection plan and analysis

We used a format proposed for the data collection study that included the variables. Data was tabulated using the Stata 12 program and the Excel program database, creating the tables with their statistics and graphs, respectively.

Information was taken from patients diagnosed with fatty liver disease who met inclusion criteria to establish the degree of fibrosis and its relationship with BMI.

Continuous variables were described using measures of central tendency and standard deviation. Categorical variables were described with numbers and percentages. A 95% confidence interval (CI) was considered statistically significant.

## RESULTS

We excluded 683 patients from a group of 1044 seen between January and December 2017 because they did not meet the inclusion criteria or their information was incomplete. Included in the study were 361 patients (**Figure 1**), from whom 58% were women, with an average age of 57 years, a minimum age of 16 years, and a maximum of 90 years.

The overweight prevalence in this study was 49.2% (n = 177), with a BMI average of 26 ± 3.9, while the obesity prevalence was 20.7% (n = 75). The mean abdominal peri-

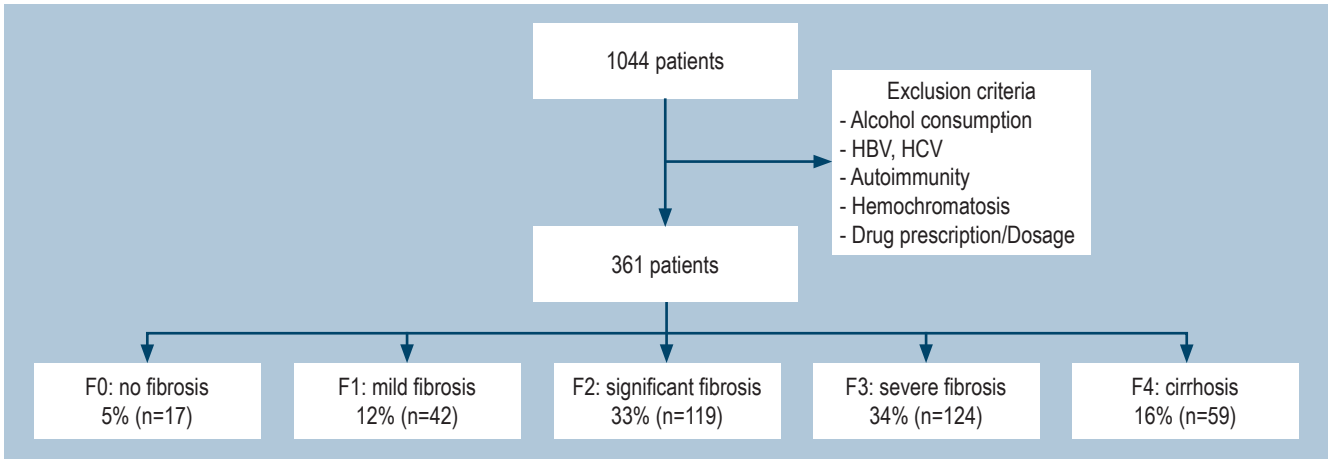


**Figure 1.** Patient flowchart.

meter was 94 ± 10 cm. Twenty-seven percent (n = 99) had a complete metabolic syndrome. High blood pressure was observed in 28% (n = 101), DM, 17.7% (n = 64); impaired fasting glycemia (IFG), 27.9% (n = 101), and hyperinsulinemia in 56.9% (n = 205) (**Table 1**).

We found 207 (57.3%) patients with a decreased HDL level and 160 (44%) of patients had > 150 mg/dL triglycerides levels. 81.5% (n = 294) of patients had a > 1 ALT/AST ratio, which is an indicator of liver fibrosis.

When measuring fibrosis with real-time elastography, 95.2% (n = 344) of the patients showed an alteration (11% mild fibrosis, 32% significant fibrosis, 34% severe fibrosis, and 16% cirrhosis), and only 4% of the patients showed a completely normal liver.

No statistically significant differences were found between the degree of fibrosis and gender (*odds ratio* (OR): 0.9; CI: 0.3–2.9). Unhealthy weight is associated with severe fibrosis F3 (OR: 3.24; CI: 1.03–10) and cirrhosis F4 (OR: 2.33; CI: 2.33–42.99) (**Figure 2**). No statistically significant differences were found between BMI impairment and any degree of fibrosis (OR: 2.74; CI: 0.90–8.40). Risk probability estimation between fibrosis and obesity was impossible because this group lacked fibrosis-free checks.

Women and men with larger abdominal circumference are 9.4-fold more likely to increase the risk of cirrhosis (CI: 2.41–39.64). High blood pressure was not associated with developing fibrosis to any degree, while the presence of DM has a 10-fold risk of ending in F4 cirrhosis, especially in patients with poor disease control (OR: 5.16; CI: 1.23–30.33). These values were unchanged with the logistic regression model (**Table 2**).

**Table 1.** Demographic, biochemical, metabolic, and diagnostic characteristics of liver fibrosis disease

| Variable | Men | Women |
|---|---|---|
| Age (years) | 41.3 (149) | 58.7 (212) |
| Mean BMI (kg/m$^2$) | 27 | 27 |
| MS (%/n) | 72.6 (262) | 27.4 (99) |
| HBP (%/n) | 72 (260) | 28 (101) |
| DM (%/n) | 82.2 (297) | 17.7 (64) |
| Glycemia > 100 mg/dL | 72 (260) | 28 (101) |
| HDL< 40 mg/dl (%/n) | 42.7 (154) | 57.3 (207) |
| TGs>150 mgs/dl (%/n) | 55.7 (201) | 44.3 (160) |
| **Degree of fibrosis** | | |
| F0 | 41.2 (7) | 58.8 (10) |
| F1 | 42.9 (18) | 57.1 (24) |
| F2 | 39.5 (47) | 60.5 (72) |
| F3 | 41.9 (52) | 58.1 (72) |
| F4 | 42.4 (25) | 57.6 (34) |
| **Total** | 146 | 212 |
| **BMI classification** | | |
| | **%** | **n** |
| Healthy weight | 30.1 | 109 |
| Overweight | 49.2 | 177 |
| Obesity | 20.7 | 75 |
| Total | 100 | 361 |

DM: diabetes mellitus; HDL: high-density lipoprotein; HBP: high blood pressure; BMI: body mass index; MS: metabolic syndrome; TGs: triglycerides.

**Table 2.** Association between degrees of liver fibrosis and BMI

| Dependent/independent variable | Adjusted OR | 95%CI |
|---|---|---|
| Fibrosis/Gender | 0.99 | 0.37-2.67 |
| Fibrosis/BMI | 2.74 | 1.02-7.31 |
| Fibrosis/overweight | 1.90 | 0.71-5.08 |
| Fibrosis/obesity | NA | |
| F1 fibrosis/BMI | 1.64 | 0.53-5.14 |
| F1 fibrosis/overweight | 1.32 | 0.61-4.11 |
| F1 fibrosis/obesity | NA | |
| F2 fibrosis/BMI | 1.85 | 0.66-5.14 |
| F2 fibrosis/overweight | 1.57 | 0.54-4.34 |
| F2 fibrosis /obesity | NA | |
| F3 fibrosis/BMI | 3.24 | 1.15-9.09 |
| F3 fibrosis/overweight | 2.03 | 0.71-5.80 |
| F3 fibrosis /obesity | NA | |
| F4 cirrhosis/BMI | 9.93 | 2.78-35.48 |
| F4 cirrhosis/overweight | 5.25 | 1.43-19.22 |
| F4 cirrhosis/obesity | NA | |
| Fibrosis/DM | 3.58 | 0.46-27.55 |
| F1 fibrosis/DM | 2.16 | 0.23-20.02 |
| F2 fibrosis/DM | 1.74 | 0.21-14.74 |
| F3 fibrosis/DM | 3.64 | 0.45-28.8 |
| F4 cirrhosis/DM | 10.22 | 1.26-82.3 |
| Fibrosis/Glyc > 100 mg/dL | 1.85 | 0.52-6.61 |
| F1 fibrosis/Glyc > 100 mg/dL | 1.09 | 0.25-4.75 |
| F2 fibrosis/Glyc > 100 mg/dL | 1.24 | 0.33-4.55 |
| F3 fibrosis/Glyc > 100 mg/dL | 1.76 | 0.47-6.51 |
| Cirrhosis F4/Glyc > 100 mg/dL | 5.16 | 1.26-2.39 |

## DISCUSSION

Fatty liver disease is a metabolic disorder with a 20%–40% prevalence in Western countries[18], 12%–30% in Asia[19], and an overall prevalence between 20% and 25%[20,21]. The disease severity increases with risk factors, which is found in 10%–20% of individuals with healthy weight, 50% overweight, and 80% with obesity[22].

Non-alcoholic fatty liver disease is a condition ranging across a spectrum of liver damage from steatosis to steatohepatitis with variable fibrosis and leading to cirrhosis with normal or elevated ALT values[23]. This disease is associated with some conditions, including metabolic syndrome, DM, obesity, high blood pressure, and dyslipidemia[24]. The metabolic syndrome is characterized by a group of risk factors that favor insulin resistance[25]; among these, BMI alteration is an important factor for developing NAFLD[26]. Additionally, we found that, among patients with fatty liver disease, 30.1% had a < 25 kg/m$^2$ BMI; 49.2%, had between a 25 and 30 kg/m$^2$ BMI, and 20.7%, had a > 30 kg/m$^2$ BMI. Furthermore, this study showed an association between BMI alteration and the development of severe and advanced fibrosis, which was statistically significant (**Table 2**).

Several studies showed the association between fatty liver disease and DM[27]. An Italian study with 458 patients found that DM was the most important marker for fatty liver disease and a higher degree of fibrosis (OR: 1.97; 95%CI: 1.2–3.7)[28]. This study shows that 82.2% of men and 17.7% of women had DM. When adjusting the data for the association between severe fibrosis F3 and cirrhosis, we found an association between DM (OR: 10.22; 95 % CI: 1.36–44.6) and impaired fasting glycemia (OR: 5.16; 95 % CI: 1.23–30.33).

This study confirmed that fatty liver could occur at any age, though it is not a risk factor[4] since no statistically significant association between age and sex was found in our patients.

In addition, 20% of patients with NAFLD develop cirrhosis[29]. In this study, cirrhosis was found in 16.3% of the entire series, with a slight predominance in women: 57.6% versus 42.4%.

However, this study is limited since it was a case-control study, and there was a selection bias in the check-ups group because all the participants were overweight or obese. In future studies, we can improve this aspect by increasing the number of participants. In summary, it was impossible to evaluate the association between abdominal perimeter and cirrhosis due to under-reporting in the medical histories.

## CONCLUSIONS

The study found a statistically significant association between an abnormal BMI and glycemic profile and severe and advanced fibrosis development. Therefore, further surveillance and evaluation of patients with fatty liver disease are necessary for clinical practice to prevent fibrosis progression.

### Authors' contribution

Content design for virtual environments: data and information conception, design, and acquisition; data analysis and interpretation; article planning and review of intellectual

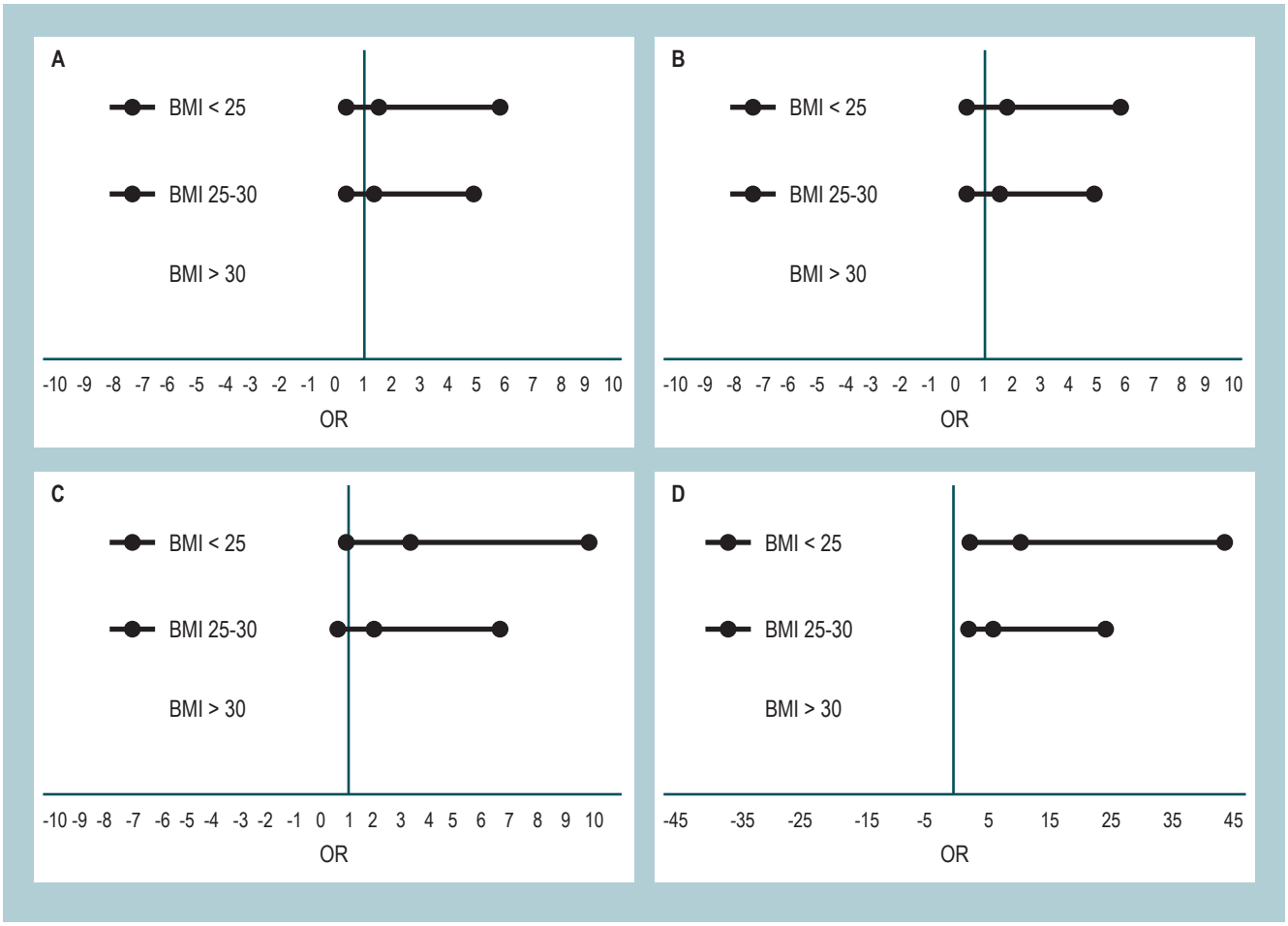


**Figure 2.** Association between liver fibrosis and BMI. **A.** Association between mild fibrosis and BMI. **B.** Association between significant fibrosis and BMI. **C.** Association between severe fibrosis and BMI. **D.** Association between cirrhosis and BMI.

content. JEPO: article preparation, important intellectual content review, and final approval before issue publication.


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## Conflict of interest

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


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Original article

# Sedation Administered by General Practitioners for Low Complexity Endoscopic Procedures: Experience in an Endoscopy Unit of a Tertiary Referral Hospital in Cali

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## Abstract

**Objectives:** in Colombia, sedation by non-anesthesiologists for endoscopic procedures outside the operating room has been implemented. A description of an experience in the gastroenterology unit of a tertiary referral hospital in Cali, Colombia, was conducted. **Materials and methods**: an analytical cohort observational study to describe the frequency and type of adverse events associated with sedation procedures performed by general practitioners and evaluate the factors related to their occurrence in patients who attended the endoscopy unit of Fundación Valle del Lili for endoscopic studies under intravenous sedation. Between November 2018 and June 2019, non-anesthesiologist physicians performed this procedure due to the minimal risk implied. A descriptive analysis was completed, and the median and interquartile range were calculated for numerical variables and frequencies for qualitative variables. **Results**: There were 1506 participants, 59.4% ASA I and 40.6% ASA II in this study. On average, the starting dose of propofol was 60 mg, and the total dose was 140 mg. Forty-six patients (3.05%) reported non-severe adverse events; the most common occurrence was transient desaturation (80.4%). No patients experienced severe adverse events. The average initial Aldrete scale score was 8, while at discharge, the average score was 10. **Conclusions:** sedation for endoscopic procedures performed by non-anesthesiologists is safe provided that it is performed by trained personnel conducting a correct assessment of the patient's (cardiovascular, gastrointestinal, and neurological) history and risk factors within the framework of the current institutional guidelines.

## Keywords

Endoscopy, colonoscopy, sedation, general practitioner, safety, experience.

## INTRODUCTION

Sedation is the level of consciousness decrease induced by drugs, intending to improve patients' tolerance to invasive and non-invasive medical procedures. Using sedation administered by trained general practitioners offers greater opportunity for procedures with a low risk of complication, either diagnostic or therapeutic.

Since 2015, low-risk patients at the endoscopy unit of Fundación Valle del Lili have been undergoing sedation by non-anesthesiologists. These general practitioners have previously received complete theoretical and practical training in sedation provided by the institution's anesthesiologists. We intend to share this experience to learn about procedural safety, describe drug regimens and doses used, and identify the incidence and type of adverse events and the risk factors for these events.

## MATERIALS AND METHODS

An observational, analytical cohort-type study was conducted to describe the frequency and type of adverse events related to sedation procedures performed by general practitioners and to assess the factors associated with their occurrence. Before data collection, pre-endoscopic assessment, intraprocedural adverse events reporting, and recovery formats were designed and implemented during the study. We prospectively included male and female patients over 18 who came to the unit to undergo an endoscopic study under intravenous sedation. Given its low risk, the sedation was performed by a non-anesthesiologist. However, the endoscopist did perform the procedure. Patients classified as ASA PS I and II were considered low-risk patients according to the American Society of Anesthesiologists criteria (ASA)[1].

Patient demographic variables such as gender, age, and medical history were recorded at the time of the procedure. We included information on difficult airway determinants: the Mallampati scale[2], dentures, cervical spine range of motion, thyromental distance, and a known difficult airway. The patient's vital signs were recorded before entering the procedure room (cannulation), at the beginning of the procedure, during the procedure, and upon admission to the recovery room.

Before the procedure, vital signs are monitored and the patient is pre-oxygenated with a nasal cannula. The institutional protocol regarding propofol use establishes the use of sedation with a single agent (monotherapy). The ideal agent for this procedure is propofol, and the instruction is to use it titrated, starting with a 0.5–1 mg/kg dose. Midazolam in low doses (< 0.05 mg/kg) may be used as an adjuvant medicinal product in the following cases: high doses of propofol and patients with high anxiety levels. Regarding non-anesthesiologists using propofol, the institutional guide and the Ministry of Health and Social Protection of Colombia established, according to Resolution 1441 of 2013, that trained non-anesthesiologists can perform sedation.

The initial and total doses of the drugs used to sedate the patient were recorded during the procedure. Likewise, adverse events are classified as follows: none, serious (admission to the intensive care unit [ICU], intubation, need for resuscitation, and death) or non-serious (paradoxical anxiety, oxygen saturation ($SaO_2$) < 90% for more than 10 seconds, more than 25% drop of systolic blood pressure, laryngospasm, heart rate (HR) drop exceeding 20% or HR greater than 100 beats per minute [bpm]). Two anesthesiologists are constantly offering support in the endoscopy unit.

Eventually, the patient's final destination after recovery was recorded (outpatient, hospitalization, ICU, morgue, other), and recovery from sedation was assessed with the Aldrete score[3] upon arrival at the recovery room and before discharge from the endoscopy unit. The work was approved and submitted by the ethics committee. Based on current legislation for procedures requiring sedation, we used the informed consent document from the institution.

A descriptive analysis of the data recorded in the recording formats was performed. Median and interquartile ranges (IQR) were calculated for numerical variables, while qualitative variables were described with frequencies. The Shapiro-Wilk statistical test was applied for quantitative data. Where relevant, bivariate and multivariate analyses were conducted to explore possible associations between exposure and outcome variables. Complications were measured for the frequency calculations obtained for all patients, so the estimates obtained are reliable. In addition, they are highly accurate due to the number of patients included and analyzed.

## RESULTS

Between November 2018 and June 2019, we included 1506 patients in this study. The patients' median age was 53 (95% IQR: 40–62), 63.6% were women, and 36.4% were men. The average body mass index (BMI) was 25.5 (95% IQR: 23.1–28), and the average weight was 68.7 kg (95% IQR: 61–78). The medical history and clinical characteristics of patients are summarized in **Table 1**. The most frequent indications for the procedures were dyspepsia (25.7%), regular check-ups or monitoring (14.4%), abdominal pain (13.7%), and gastroesophageal reflux (6%). Outpatients accounted for 88.4% and 11.6% were inpatient. Regarding the type of procedure, 51.2% were upper digestive endoscopies, 19.7% were colonoscopies, and 29.1% were upper endoscopy plus colonoscopy.

Patients classified as ASA I: 59.4% and 40.6% as ASA II. Seven (0.46%) patients had a history of difficult airways. On average, an initial dose of propofol of 60 mg (95% IQR: 40-80 mg) and a total dose of 140 mg (95% IQR: 100-200 mg) were used during endoscopic procedures. The average dose used for midazolam was 2 mg (95% IQR: 2-3 mg) (**Table 2**).

Regarding vital signs monitoring, the mean arterial pressure (MAP) at the beginning of the procedure averaged 89 mm Hg (IQR 95%: 80–98 mm Hg), HR was 71 bpm (IQR 95%: 64–80 bpm), and $SaO_2$ was 99% (95% IQR: 99–100). At the end of the procedure, the MAP was 83 mm Hg (95% IQR: 75–93 mm Hg) on average; HR, 69 bpm (IQR 95%: 62–77 bpm), and $SaO_2$, 99% (IQR 95%: 98–100). In the recovery room, the average MAP was 68 mm Hg (95% IQR: 61–77 mm Hg); HR, 67 bpm (IQR 95%: 59–75 bpm), and $SaO_2$, 98% (IQR 95%: 96–99). The initial average Aldrete score was 8, while at discharge, the average score was 10.

**Table 1.** Clinical characteristics of the population

| Characteristics | n = 1506 | % |
|---|---|---|
| Gender, n (%) | | |
| - Female | 958 | 63.6 |
| - Male | 548 | 36.4 |
| Origin, n (%) | | |
| - Outpatient | 1331 | 88.4 |
| - Inpatient | 175 | 11.6 |
| Past medical history, n (%) | | |
| - Neurological[a] | 41 | 2.7 |
| - Respiratory[b] | 35 | 2.3 |
| - Cardiovascular[c] | 335 | 22.2 |
| - Hematologic[d] | 52 | 3.5 |
| - Endocrine[e] | 299 | 19.9 |
| - Renal[f] | 43 | 2.9 |
| - Gastrointestinal[g] | 249 | 16.5 |
| - Allergies | 165 | 11.0 |
| - Total | 1219 | 80.9 |
| ASA PS classification, n (%) | | |
| - I (a normal healthy patient) | 896 | 59.4 |
| - II (mild systemic disease) | 610 | 40.6 |

Most commonly known past medical history reported:
[a] Psychiatric disorder (14), stroke (4), malignant hyperthermia (4), and migraine (4).
[b] Asthma (20), smoking (6), COPD (5), sleep apnea (3).
[c] High blood pressure (323), arrhythmias (10), heart attack (4), heart failure (2).
[d] Antiaggregation (23), anemia (12), anticoagulation (10).
[e] Thyroid diseases (192), diabetes mellitus (72), obesity (31), dyslipidemia (13).
[f] Chronic kidney disease (35), kidney stones (4).
[g] Dyspepsia (29), gastroesophageal reflux (21), neoplasia (17), peptic ulcer (8), inflammatory bowel disease (9), gastrointestinal bleeding (2).
COPD: chronic obstructive pulmonary disease

Non-serious adverse events were recorded in 46 patients (3.05%), of whom 80.4% had desaturation, 6.5% laryngospasm, 6.5% cough, and 4.3% bradycardia. No patients experienced serious adverse events. A relationship between the occurrence of adverse events in patients with a neurological ($p = 0.049$), cardiovascular ($p = 0.003$), and gastrointestinal ($p = 0.006$) medical history was found. Likewise, a

**Table 2.** Drug regimens used for sedation

| Drugs | Doses (IQR 95%)[a] |
|---|---|
| Propofol | |
| - Initial dose | 60 mg (40-80 mg) |
| - Total dose | 140 mg (100-200 mg) |
| Midazolam | |
| - Initial dose | 2 mg (1-3 mg) |
| - Total dose | 2 mg (2-3 mg) |
| Lidocaine | |
| - Single dose | 30 mg (20-40 mg) |

relationship was found in patients with ASA PS II anesthetic risk classification ($p = 0.002$) (**Table 3**). There was no statistically significant relationship between medication use and adverse events. The average time of endoscopy was 8 minutes, and 13 minutes for colonoscopy.

## DISCUSSION

The general practitioner model for sedation outside the operating room has been implemented in different countries worldwide with good results[4]. Since the publication of the Practice Guidelines for Sedation and Analgesia by Non-Anesthesiologists, first adopted by the ASA in 1995, the involvement of anesthesiologists in digestive endoscopy has been declining to allow trained physicians and nurses to take over. In the United States, although almost 100% of digestive endoscopies are performed under sedation[5], only 17.2% of colonoscopies involve an anesthesiologist's presence, which has reduced the costs of the procedures by approximately 20%[6,7]. Thus, the sedation process performed by general practitioners has similar safety and effectiveness levels to sedation administered by anesthesiologists in low-risk patients[4,8], as long as physicians are trained for this purpose[9]. The above mentioned per the institutional protocols, which emphasize that physicians must undergo a complete theoretical and practical training. On the other hand, patients with ASA PS classification between III and V are 5 and 7 times more at risk of complications than low-risk patients; therefore, they should be evaluated and treated by an anesthesiologist[10-12].

This system has been implemented in Colombia since 2012, as shown in the recommendations for sedation and analgesia by non-anesthesiologists and dentists of patients

**Table 3.** Relationship between adverse events and patients' characteristics

| Characteristics | Adverse events | | *p*[a] |
|---|---|---|---|
| | No (n = 1460) | Yes (n = 46) | |
| Age | 52 (39 - 62) | 64 (54 - 72) | 0 |
| Gender | | | |
| - Female | 927 | 31 | 0.39 |
| - Male | 533 | 15 | |
| BMI | 25.45 | 27.3 | 0.0011 |
| Procedure type | | | |
| - Endoscopy | 746 | 27 | |
| - Colonoscopy | 294 | 3 | 0.064 |
| - Endoscopy and colonoscopy | 420 | 16 | |
| Origin | | | |
| - Outpatient | 1292 | 39 | NC[b] |
| - Inpatient | 168 | 7 | NC[b] |
| Past medical history | | | |
| - Neurologic | 28 | 4 | 0.049 |
| - Respiratory | 20 | 1 | 0.609 |
| - Cardiovascular | 214 | 18 | 0.003 |
| - Hematologic | 32 | 2 | 0.654 |
| - Endocrine | 189 | 12 | 0.243 |
| - Renal | 26 | 0 | 0.625 |
| - Gastrointestinal | 154 | 15 | 0.006 |
| ASA PS classification | | | |
| - I | 882 | 15 | 0.002 |
| - II | 579 | 31 | |
| Mallampati score | | | |
| - I | 898 | 16 | |
| - II | 450 | 21 | 0.002 |
| - III | 105 | 8 | |
| - IV | 7 | 1 | |
| Dentures | | | |
| - Denies | 1347 | 42 | |
| - Fixed | 42 | 2 | 0.202 |
| - Removable | 71 | 2 | |
| Thyromental distance | | | |
| - Greater than 3 fingerbreadths | 1381 | 38 | 0.003 |
| - Less than 3 fingerbreadths | 79 | 8 | 0.234 |

[a]A $p < 0.05$ value was considered statistically significant. [b]CN: not calculated.

over 12 years, published by the Colombian Society of Anesthesiology and Resuscitation[11,13]. There was no report on the results of this practice in our country until recently. In 2019, Mullet-Vásquez *et al* published a study evaluating the evolution of colonoscopies in which propofol sedation was applied to low-risk patients. Even in our local context, they found that sedation performed by non-anesthesiologists is a safe procedure[14].

The use of intravenous (IV) sedation during endoscopic procedures ranges from 20% to 98%, depending on the country[5]. Using a benzodiazepine with an opioid is the most common method, although endoscopists reported better results using propofol for conscious sedation[15]. A recent meta-analysis showed that, overall, propofol had been associated with a 39% reduction in complications (hypoxemia, hypotension, or arrhythmias) during a low-complexity digestive endoscopy compared to other agents. However, this difference is not evident in patients undergoing advanced endoscopy[16]. Fortunately, preventing many sedation complications with proper staff training and standardization of associated processes is possible[11]. In addition, non-anesthesiologists administering propofol is associated with better sedation, increased patient cooperation, and shorter recovery discharge periods[8]. Propofol was used in our population because it is safe and we used it with average total doses of 140 mg and maximum doses of 200 mg. Propofol administration triggers pain at the puncture site, although chemical phlebitis is rare, and this uncomfortable effect can be controlled or avoided with the concomitant administration of lidocaine. The average dose of lidocaine used in our study was 30 mg.

Diagnostic digestive endoscopy has a 0.02% to 0.54% complication rate. In cases where sedation is applied, it accounts for 50% of complications[17]. In a prospective multicenter study documenting acute complications associated with endoscopy sedation between 2011 and 2014, the major complications rate (ICU admission, intubation, need for resuscitation, and death) accounted for 0.01%; mortality, 0.005%, and minor complication rate (paradoxical anxiety, $SaO_2$ < 90% for more than 10 seconds, more than 25% drop in systolic pressure, HR drop higher than 20%, or HR higher than 100 bpm) accounted for 0,3%, with a ratio directly proportional to the ASA PS class, the type and duration of the procedure[18]. Other less common complications include arrhythmias or bronchoaspiration.

In our study, the adverse event rate was 3.05 %, higher than the rate reported in the literature. In a paper by Sharma *et al,* reviewing data from 324,737 endoscopic procedures under sedation, cardiopulmonary adverse events were reported in 0.9% of procedures[19]. A higher rate in our study could be explained by a higher number of reported transient oxygen

desaturation episodes. The most common adverse event was desaturation, closely related to respiratory depression triggered by propofol or benzodiazepines, as appropriate. All desaturation cases were self-limiting or subsided with oxygen titration through a nasal cannula, routinely used in all procedures under sedation. The relationship of the ASA PS class with the occurrence of adverse events in our study was expected and consistent with the one reported in the literature. Notably, no relationship was found between predictors of difficult airways and the incidence of adverse events. However, in an event requiring securing the airway, it is advisable to inform the anesthesiologist of the presence of these factors and provide a rapid response system or code blue should major complications arise.

Monitoring should continue until the patient is wide awake, hemodynamically stable, has a permeable airway, and has adequate airway and respiratory reflexes during recovery[20,21]. The Aldrete scale has been used for more than 30 years to assess the clinical condition of patients after anesthesia and their gradual course towards recovery afterward. The scale assesses limb activity, respiratory function, circulatory status, oxygenation, and consciousness. Additionally, its modified version for outpatient surgery includes criteria for patient readiness to go home[3]. The average score of patients on admission to recovery was 8 and on discharge was 10, demonstrating satisfactory post-procedural recovery and probably indicative of close surveillance that could contribute to favorable outcomes.

## CONCLUSION

In recent years, the Clínica Fundación Valle del Lili's gastroenterology service has implemented sedation administered by non-anesthesiologists in the endoscopy unit with extensive experience. In this issue, we have summarized our experience on this topic. Therefore, this practice seems safe as long as it is performed by medical personnel trained within the current institutional guidelines. However, necessary resources and an anesthesiologist for the service where the procedure is to be performed should always be available should an event occur. Finally, more studies are required to verify the cost-effectiveness of this practice in Colombia.

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Original article

# Prevalence of Functional Dyspepsia in Cuban Adolescents

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## Abstract

**Introduction:** functional gastrointestinal disorders (FGID) are common in children. However, data on functional dyspepsia (FD) in Cuban adolescents is scarce. **Objective:** to determine the prevalence of FD in Cuban adolescents and their possible associations. **Methodology:** the questionnaire for pediatric digestive symptoms of Rome IV was used in Spanish to identify the presence of DF in adolescents from 3 schools in La Havana, Cuba. Sociodemographic, personal, family, clinical, and epidemiological variables were considered. **Results:** of the 318 adolescents who participated in the study, 11 (3.5%) aged 11.4 ± 1.2 years, 81.8% female, presented FD. Functional dyspepsia was more frequent in females (*odds ratio* [OR]: 5.33; 95% confidence interval [CI]: 1.06–51.45; $p = 0.019$). The postprandial distress syndrome (PDS) was higher than the epigastric pain syndrome (SDE) by a 1.8:1 ratio. There was an overlap between DF and functional constipation in 63.6% of the patients. There was an FD predominance in children with separated or divorced parents (OR: 4.74; 95% CI: 1.09–28.31; $p = 0.014$). **Conclusion:** functional dyspepsia is most common in female adolescents, PSD is the most frequent subtype, and its presence is associated with separated or divorced parents.

## Keywords

Functional dyspepsia, postprandial distress syndrome, epigastric pain syndrome, adolescents.

## INTRODUCTION

Functional dyspepsia (FD) is a common disorder in childhood. This disorder is associated with upper gastrointestinal symptoms, including epigastric pain or burning sensation, early satiety, and postprandial fullness, unrelated to bowel movements or other etiology to explain these symptoms. This disorder can cause a significant deterioration in the quality of life[1,2].

In recent years, FD's prevalence has increased (3%–27%), with a high demand for consultation of pediatric specialties. In many cases, FD may be associated with other gastrointestinal functional disorders, one of the most common after irritable bowel syndrome. Approximately 4.5% of children worldwide experience symptoms of FD at some point in their lives[2,3].

Patients with functional gastrointestinal disorders (FGIDs), which include FD, have higher rates of anxiety,

depression, poor coping skills, and somatization symptoms than children without FGIDs. Children with FD may be associated with significant morbidity, and symptoms may negatively impact the child's quality of life, adversely affecting school attendance[3].

Over time, FD diagnostic criteria have evolved. For the first time, the Rome IV criteria identified epigastric pain syndrome (EPS) and postprandial distress syndrome (PDS) as two subtypes of FD in children, as recognized in adults.[3-5]

According to the Rome IV Criteria, no studies have demonstrated the prevalence of FD in Cuban children. Understanding the associated factors would be extremely useful for diagnosing and managing this disorder. Thus, this study aims to determine the prevalence of FD in Cuban adolescents and their possible associations.

## METHODOLOGY

The study was conducted between March 2, 2020, and January 7, 2021, in 3 schools (2 primary schools and 1 basic secondary) in La Havana, Cuba. It was applied using the methodology in previous studies and those currently in progress by our group, *Functional International Digestive Epidemiological Research Survey* (FINDERS), an established international collaborative group that conducts epidemiological studies in Latin American children. Thus, parents or guardians of adolescents between fourth and ninth grades were invited and agreed to participate in the study after signing an informed consent/assent. We used the Questionnaire of Pediatric Gastrointestinal Symptoms-Rome IV Criteria (QPGS-IV) in Spanish, which has an appropriate criterion validity[6]. Sociodemographic (age, gender, race); personal (cesarean section, preterm birth); family (only child, firstborn, separated/divorced parents, intrafamily FGIDs); clinical (weight, height, body mass index [BMI], height-for-age, dengue history), and epidemiological (overlap, confinement) variables were obtained. The Hospital Dr. Luis Díaz Soto's Ethics Committee approved this study. Statistical analysis included the student's t-test two-sided, the Chi-Square test, and Fisher's exact test. To evaluate the possible risk factors for DF, a univariate and multivariate analysis was performed, calculating the *odds ratio* (OR) with its corresponding 95% confidence intervals (CI) and a $p$ significant < 0.05.

## RESULTS

From a group of 318 adolescents who answered the QPGS-IV in Spanish, 29.1% showed some FGID. We identified FD in 3.5% (2.2% postprandial distress syndrome – PDS, and 1.3% epigastric pain syndrome –EPS) (**Table 1**).

**Table 1.** Prevalence of FGIDs in Cuban schoolchildren

| n = 318 | |
|---|---|
| FGIDs | |
| - No | 225 (70,9) |
| - Yes | 93 (29,1) |
| Associated with nausea and vomiting | 5 (1,5) |
| Functional nausea and vomiting | 3 (0,9) |
| - Nausea | 1 (0,3) |
| - Vomiting | 2 (0,6) |
| Aerophagia | 1 (0,3) |
| Cyclic vomiting syndrome | 1 (0,3) |
| Associated with abdominal pain | 16 (5,0) |
| Functional dyspepsia | 11 (3,5) |
| - PDS | 7 (2,2) |
| - EPS | 4 (1,3) |
| Irritable bowel syndrome | 1 (0,3) |
| - With diarrhea and constipation | 1 (0,3) |
| Abdominal Migraine | 1 (0,3) |
| FAD not otherwise specified | 3 (0,9) |
| Associated with defecation | 72 (22,6) |
| - Functional constipation | 72 (22,6) |

FAD: functional abdominal distension.

The 11 children with FD were 11.4 ± 1.2 years, 81.8% were female and 54.4% mestizo, 54.5% were firstborn, 72.7% had separated/divorced parents, and 63.6% and 100.0%, respectively, were eutrophic for BMI and height-for-age according to the World Health Organization (WHO). There was an overlap of FD in 8 of the 11 children, primarily with functional constipation in 7 children. There were no significant differences between the sociodemographic (age, gender, race); personal (cesarean section, preterm birth); family (only child, firstborn, separated/divorced parents, intrafamily FGIDs); clinical (weight, height, BMI, height-for-age, dengue history), and epidemiological (overlap, confinement) variables (**Table 2**).

The prevalence of FD was higher in females (OR: 5.33; 95%CI: 1.06–51.45; $p = 0.019$). The same was the case for children whose parents were separated/divorced (OR: 4.74; 95%CI: 1.09–28.31; $p = 0.014$), predominantly in paternal absence (OR: 3.64; 95%CI: 0.88–17.42; $p = 0.033$) rather than maternal absence. The multivariate analysis did not show any variable contributing to FD overlap prevalence (**Table 3**).

## DISCUSSION

As far as we know, this is the first study that evaluated the prevalence and factors associated with FD in Cuban children according to the Rome IV criteria. Findings in this research showed that 29.1% of adolescents met the criteria for some FGID, FD was identified in 3.5%, and PDS is more frequent than EPS.

Our results are similar to those reported by Saps *et al*[7] in Colombian children, with a 3% FD prevalence, which is lower than the results reported by Robin *et al*[8] in North American children and by Baleeman *et al*[9] in Colombian children, between 7.2% and 16.1%, respectively, and higher than those reported by Zeevenhooven *et al*[10] in adolescents from Curacao, whose prevalence for FD was 1.9%. One of the possible explanations for these different figures, among others, is how these interviews were conducted. The data from North American children[8] were taken from the mothers' self-responses. Conversely, Colombian children[7,9] completed the questionnaires through self-

**Table 2.** General characteristics of children with functional dyspepsia

| n = 11 | | | | |
|---|---|---|---|---|
| | FD | Postprandial | Epigastric pain | *p* |
| | n = 11 | n = 7 | n = 4 | |
| **Sociodemographic variables** | | | | |
| Age | | | | |
| - Average ± standard deviation | 11.4 ± 1.2 | 11.4 ± 1.1 | 11.5 ± 1.7 | 0.9072 |
| - Range | 10 and 14 | 11 and 14 | 10 and 14 | |
| Age groups | | | | |
| - Schoolchildren (10–12 years) | 9 (81.8) | 6 (85.7) | 3 (75.0) | 0.618 |
| - Adolescents 13–18 years old | 2 (18.2) | 1 (14.3) | 1 (25.0) | |
| Gender | | | | |
| - Female | 9 (81.8) | 6 (85.7) | 3 (75.0) | 0.618 |
| - Male | 2 (18.2) | 1 (14.3) | 1 (25.0) | |
| Race | | | | |
| - Hispanic | 6 (54.5) | 5 (71.4) | 1 (25.0) | 0.197 |
| - White | 4 (36.4) | 2 (28.6) | 2 (50.0) | 0.470 |
| - Afro-descendant | 1 (9.1) | 0 (0.0) | 1 (25.0) | 0.364 |
| **Personal variables** | | | | |
| - C-Section | 4 (36.4) | 1 (14.3) | 3 (75.0) | 0.088 |
| - Preterm birth | 2 (18.2) | 0 (0.0) | 2 (50.0) | 0.109 |
| **Family variables** | | | | |
| - Only child | 3 (27.3) | 1 (14.3) | 2 (50.0) | 0.279 |
| - Firstborn | 6 (54.5) | 4 (57.1) | 2 (50.0) | 0.652 |
| - Separated/divorced parents | 8 (72.7) | 4 (57.1) | 4 (100.0) | 0.212 |
| - Intra-family FGIDs | 0 (0.0) | 0 (0.0) | 0 (0.0) | N/A |

**Table 2.** General characteristics of children with functional dyspepsia (*continued*)

| n = 11 | | | | |
|---|---|---|---|---|
| | FD | Postprandial | Epigastric pain | *p* |
| | n = 11 | n = 7 | n = 4 | |
| **Clinical variables** | | | | |
| Nutritional condition | | | | |
| - According to BMI | | | | |
| Eutrophic | 7 (63.6) | 5 (71.4) | 2 (50.0) | 0.470 |
| Malnourished | 4 (36.4) | 2 (28.6) | 2 (50.0) | 0.470 |
| Overweight/obese | 4 (36.4) | 2 (28.6) | 2 (50.0) | 0.470 |
| Overweight | 1 (9.1) | 1 (14.3) | 0 (0.0) | 0.636 |
| Obese | 3 (27.3) | 1 (14.3) | 2 (50.0) | 0.279 |
| - According to H/A | | | | |
| Eutrophic | 11 (100.0) | 7 (100.0) | 4 (100.0) | N/A |
| Altered height | 0 (0.0) | 0 (0.0) | 0 (0.0) | |
| History of dengue | 2 (18.2) | 1 (14.3) | 1 (25.0) | 0.618 |
| **Epidemiological variables** | | | | |
| Overlapping | **8 (72.7)** | **5 (71.4)** | 3 (75.0) | **0.721** |
| - Constipation | 6 (54.5) | 3 (42.9) | 3 (75.0) | 0.348 |
| - Constipation and nausea | 1 (9.1) | 1 (14.3) | 0 (0.0) | 0.636 |
| - Vomiting | 1 (9.1) | 1 (14.3) | 0 (0.0) | 0.636 |
| Confinement | 4 (36.4) | 1 (14.3) | 3 (75.0) | 0.088 |

N/A: not applicable; H/A: height-for-age.

response, and the QPGS-III was applied to the children in Curaçao[10], while the data interpretation to identify any FGID was conducted according to QPGS-IV.

On the other hand, other authors have only studied FD as part of FGIDs. Some of them[1,8,11], like us, have described a higher prevalence to present the PDS over the EPS subtype. Even Wei *et al*[11] found a 0.3% overlap between both FD subtypes, similar findings to ours with only 1 patient presenting such overlap, and different from the high prevalence reported by Turco *et al*[1]. The latter found a 36.0% overlap between both FD subtypes, which suggests a common pathophysiological mechanism. However, it is worth noting that Turco *et al*[1] classified FD subtypes according to the QPGS-III for adults.

Our results show that FD occurred more in female adolescents, as described by Kumagai *et al*[12], but different from Wei *et al*[11] and Turco *et al*[1], who did not find this association. Other authors have described some possible factors for presenting FD like Wei *et al*[11] that found age (OR: 1.112; 95%CI: 1.031–1.201; $p = 0.006$) and independent living from parents (OR: 1.677; 95%CI: 1.255–2.242; $p < 0.001$) as possible causes to develop FD. In their study with Japanese children, Kumagai *et al*[12] associated FD prevalence with sleeping habits. Although many patients with FD associate their dyspeptic symptoms with eating habits, few studies show that dietary factors may be involved in developing this FGID. For example, Wei *et al*[11] describe that delayed school meals (OR: 2.107; 95%CI: 1.447–

**Table 3.** Association between FD, overlapping, and variables

| n = 11 | | | | | | |
|---|---|---|---|---|---|---|
| | Functional dyspepsia | | | Overlapping | | |
| | OR | 95 % CI | *p* | OR | 95 % CI | *p* |
| Age groups | | | | | | |
| - Schoolchildren (10–12 years) | 1.00 | | | 1.00 | | |
| - Adolescents 13–18 years old | 0.51 | 0.05-2.57 | 0.3933 | 0.79 | 0.07-4.55 | 0.7806 |
| Gender | | | | | | |
| - Male | 1.00 | | | | N/A | |
| - Female | 5.33 | 1.06-51.45 | 0.0194 | | | |
| Race | | | | | | |
| - Hispanic | 1.80 | 0.44-7.67 | 0.3376 | 2.34 | 0.44-15.31 | 0.2362 |
| - White | 0.79 | 0.16-3.24 | 0.7220 | 0.49 | 0.04-2.82 | 0.3842 |
| - Afro-descendant | 0.44 | 0.01-3.32 | 0.4394 | 0.64 | 0.01-5.17 | 0.6799 |
| - Confinement | 0.36 | 0.07-1.49 | 0.1053 | 0.62 | 0.11-3.45 | 0.5152 |
| - C-section | 0.57 | 0.12-2.34 | 0.3849 | 0.64 | 0.09-3.40 | 0.5553 |
| - Preterm birth | 1.62 | 0.16-8.47 | 0.5420 | 2.6 | 0.24-15.21 | 0.2363 |
| - Only child | 2.18 | 0.35-9.68 | 0.2562 | 0.85 | 0.01-6.94 | 0.8865 |
| - Firstborn | 1.50 | 0.36-6.39 | 0.5108 | 1.23 | 0.22-6.73 | 0.7706 |
| - History of dengue | 1.39 | 0.13-7.17 | 0.6809 | 0.93 | 0.02-7.55 | 0.9468 |
| - Separated/divorced parents | 4.74 | 1.09-28.31 | 0.0141 | 2.87 | 0.54-18.79 | 0.1362 |
| Father | 3.64 | 0.88-17.42 | 0.0328 | 2.01 | 0.36-11.04 | 0.3180 |
| Mother | 1.63 | 0.03-13.16 | 0.650 | 2.30 | 0.04-19.52 | 0.4343 |
| - Intra-family FGIDs | | N/A | | | N/A | |
| Nutritional condition | | | | | | |
| - According to BMI | | | | | | |
| Eutrophic | 1.00 | | | 1.00 | | |
| Malnourished | 0.57 | 0.12-2.34 | 0.3849 | 0.14 | 0.003-1.15 | 0.0378 |
| Overweight/obese | 0.61 | 0.12-2.51 | 0.4505 | 0.15 | 0.03-1.23 | 0.0467 |
| Overweight | 0.20 | 0.004-1.46 | 0.0929 | | N/A | |
| Obese | 2.18 | 0.35-9.68 | 0.2562 | 0.81 | 0.01-6.58 | 0.8485 |
| - According to H/A | | | | | | |
| Eutrophic | | N/A | | | N/A | |
| Altered height | | | | | | |

3.068; $p < 0.001$), skipping breakfast (OR: 2.192; 95%CI: 1.103–3.688; $p = 0.003$), eating frequently (OR: 2.296; 95%CI: 1.347–3.912; $p = 0.002$), and eating cold foods daily (OR: 2.736; 95%CI: 1.263–5.927; $p = 0.011$) are possible food-related risk factors leading to FD. Likewise, Kumagai *et al*[12] found that impaired eating habits constitute a risk factor for developing FD.

Another risk factor we found leading to develop FD is children from separated parents. According to the biopsychosocial model, we cannot ignore that psychosocial factors play a crucial role in the pathogenesis of FGIDs. Stress has pathophysiological effects on the gastrointestinal tract, triggering or exacerbating abdominal pain through visceral hypersensitivity and changes in motility. Children with depressive or anxious symptoms are more likely to develop FGIDs[1,5,12]. Divorce is a major stressor at this age. Several Latin American studies associate the presence of separated/divorced parents with the prevalence of FGIDs [13,14], consistent with this study. Wei *et al*[11] also identified that children living independently from their parents were at higher risk of developing FD, comparable to the separated parents in this study. These two factors may trigger anxiety and stress in these patients.

Thus, the main strength of our study is that it is the first cross-sectional study conducted on Cuban adolescents that determined the prevalence of FD and its associated factors. However, this study also has limitations since, like other studies using the Questionnaires of Pediatric Gastrointestinal Symptoms, Rome IV version, it includes failure to ensure external validity of the results since the symptoms depend on the adolescent's report, which is based on the recollection of the event and its frequency, so there may be a memory bias. On the other hand, with the existing situation due to the 2019 coronavirus disease (COVID-19) and school closures, the series could not be larger and more representative.

In conclusion, functional dyspepsia is most common in female adolescents, PDS is the most frequent subtype, and its presence is associated with separated/divorced parents.

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Original article

# Prevalence and Gastric Location of *Helicobacter pylori* in Patients with Intestinal Atrophy and Metaplasia in a Tertiary Care Institution in Colombia

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## Abstract

**Introduction:** *Helicobacter pylori* infection plays a critical role in the carcinogenesis cascade of intestinal gastric cancer. However, its prevalence in preneoplastic conditions generating changes in the gastric mucosa is unclear. Currently, endoscopic surveillance using the Sydney protocol is suggested every 2 to 3 years, but the presence of *H. pylori* infection in the subcardial region and gastric fundus is ill-defined. **Objective:** to determine the prevalence and gastric location of *H. pylori* infection in patients with preneoplastic conditions. **Materials and methods:** a cross-sectional study in adults with a previous diagnosis of atrophy or intestinal metaplasia who entered control endoscopy and were antrum, body, incisura *angularis*, subcardial region, and gastric fundus biopsied. A descriptive analysis of the results by gastric regions was performed. **Results:** data from 160 patients with a prevalence of *H. pylori* of 37.5% were collected. It increased from proximal to distal, starting with a 12.5% prevalence in the subcardial region to a 30.6% prevalence in the antrum. In addition, there was a similar pattern in the prevalence of preneoplastic lesions. Furthermore, advanced lesions (dysplasia, carcinoma) were observed in the incisura. **Conclusions:** the prevalence of *H. pylori* in precancerous conditions showed a high presence in the distal regions compared to the proximal ones, and it is more frequent in the antrum and lower in the subcardial region. As for the gastric distribution of atrophy and metaplasia, more involvement was found in the antrum and angular notch and lower in the subcardial region and fundus.

## Keywords

*Helicobacter pylori*, gastric atrophy, intestinal metaplasia, gastric cancer, *Operative Link on Gastritis Assessment* (OLGA).

## INTRODUCTION

*Helicobacter pylorus* is a gram-negative bacterium that colonizes the gastrointestinal tract and has high implications, especially in the gastric tract, where it is considered a type I carcinogenic agent by the World Health Organization (WHO)[(1)]. Identifying it is critical for gastric carcinoma and public health-related issues since this cancer constitutes the fourth cause of morbidity and the second cause of mortality worldwide[(2)]. In Colombia, reports from the National Cancer Institute have flagged gastric cancer as the first cause of cancer mortality in men and the second in women[(3)]. *H. pylori* are characterized by their helical shape and flagella, crucial for its motility and successful colonization. The genes and proteins related to the microorganism's motility in the gastric environment are well documented in the literature[(4)].

As described by Dr. Pelayo Correa in his carcinogenesis model for intestinal-type gastric carcinoma, this pathogen activates in people genetically susceptible to the carcinogen cascade, beginning with an inflammatory response and

generating active chronic gastritis that can evolve to atrophic gastritis, intestinal metaplasia, and dysplasia –which will end up causing cellular changes to carcinoma[5]. It is recommended to monitor the patient in preneoplastic conditions (atrophic gastritis and intestinal metaplasia) and preneoplastic lesions (dysplasia) every 2 to 3 years, performing several biopsies on the antrum and gastric body. Additionally, if documented in the patient's histology, a treatment to eradicate *H. pylori* is recommended[6]. The Sydney system is currently the most widely used and recommended biopsy protocol. This system performs biopsies in the antrum (greater and lesser curvature, 2 cm from the pylorus), incisura *angularis,* and body (anterior and posterior wall, 8 cm from the cardia)[7].

The microorganism migration theory associated with changes in gastric distribution is proposed given the hypothesis of changes in the microenvironment in the gastric mucosa affected by *H. pylori*, as in intestinal atrophy and metaplasia, and considering the motility characteristics of this pathogen. Additionally, current protocols do not involve taking biopsies in the gastric fundus and cardia[8], which could lead to false negatives identifying *H. pylori* in these patients.

The objective of this study is to identify the distribution patterns of this pathogen in the presence of atrophy and intestinal metaplasia, which will establish a very close value to the actual prevalence and distribution of *H. pylori* in this context.

## MATERIALS AND METHODS

### Design and population

A descriptive observational cross-sectional study of adult patients diagnosed with intestinal atrophy or metaplasia in a tertiary care institution. Patients with proton pump inhibitor (PPI) use in the last six months, antibiotic use in the last 30 days, patients with a histological diagnosis of gastric cancer, patients with a history of gastric surgery, diagnosis of Zollinger-Ellison syndrome disease or gastric lymphoma, and patients who required emergency surgical management (bleeding, obstruction or perforation) were excluded.

### Sampling and sample size

The sample size was calculated based on an estimated prevalence of a 43.3% *H. pylori* presence[9], with an 8% absolute accuracy and a 95% confidence level for a minimum required sample size of 148 patients.

### Procedure

All patients with atrophy and intestinal metaplasia history who entered the gastroenterology unit to undergo upper gastrointestinal endoscopy (for their pathology check or any upper gastrointestinal symptomatology) were given informed consent. In addition, this study's objectives and the steps for its development were explained in detail in this consent. Likewise, each patient was given a questionnaire about PPI use and *H. pylori* eradication.

Once the clinical history of the previous diagnosis of intestinal atrophy or metaplasia was confirmed and, after ruling out gastrointestinal surgeries, or a history of gastric cancer –the upper endoscopy procedure and biopsy were performed as follows:

- Antrum: 2 and 3 cm from the pylorus in the major and lesser curvature (2 biopsies)
- Incisura *angularis* (1 biopsy)
- Body: 8 cm from the cardia in the anterior and posterior wall (2 biopsies)
- Stomach fundus
- Subcardial region

These biopsies were sent to pathology. Once the results were available, information on the questionnaires and pathologies was collected in a data extraction tool, typed by the same operator, and a double review of the information was made.

### Variables

Patient demographic and clinical information was collected, including pre-treatment information for underlying disease (atrophy or intestinal metaplasia) and current or previous use of PPIs. In addition, detailed information was collected on the histological diagnosis of the result of biopsies in the body and antrum, incisura *angularis*, subcardial region, and gastric fundus.

### Analysis

The final database was consolidated in the Stata 13 statistic software, and a descriptive analysis of the information was performed. Categorical variables were described as absolute; relative frequencies and quantitative variables were described as measures of central tendency and dispersion depending on the data distribution. The Shapiro-Wilk test evaluated a *p*-value less than 0.05 for statistical significance. An exploratory bivariate analysis was performed comparing the type of initial diagnosis and diagnosis according to the anatomical location.

## RESULTS

Of the potential patients in the study, 160 met the inclusion criteria, had no criteria for exclusion, and willingly agreed

to participate. Most of the patients were females (60%), and the median age was 61.5 years (interquartile range [IQR]: 54–71). At the initial patients' diagnosis, 90 (56.3%) were diagnosed with metaplasia and atrophy, 31 (19.4%) were diagnosed with atrophy, and 39 (24.3%) were exclusively diagnosed with metaplasia (**Table 1**).

The histological result highlights that 81.3% of the patients showed some lesion degree (atrophy, metaplasia, dysplasia, or carcinoma), whereas 13 patients (18.7%) did not show any lesion in the biopsies performed. Similarly, a 37.5% prevalence of *H. pylori* was observed in the study population, with a higher prevalence in patients without lesions in the histological results (43.3%) than in patients with lesions (36.2%) (**Table 1**).

Furthermore, among the differences found between patients with and without lesions, there was a striking gender difference. There was a higher proportion of females among patients without lesions (70%) than among patients with lesions (57%). A much subtler disparity in age was also found, with a greater median age in patients with some lesions (62 years) compared to patients without lesions (58.5 years) (**Table 1**).

Of the patients with premalignant lesions, two patients had dysplasia. The first patient was a 72-year-old male. His initial diagnosis included metaplasia and atrophy. During the pathology result, he was diagnosed with atrophy, metaplasia, and high-grade dysplasia in the incisura, with no evidence of *H. pylori* in any of the biopsies. The second patient was a 61- year-old male. His initial diagnosis was metaplasia and atrophy, showing pathology consistent with high-grade dysplasia in the body, incisura, and antrum. He had atrophy and metaplasia in the antrum with signs of *H. pylori* in the body and incisura.

The histological results also showed a single 60-year-old female patient with carcinoma and an initial diagnosis of metaplasia. Her pathology resulted in carcinoma in the incisura, atrophy, and metaplasia in the antrum with *H. pylori* in the body.

Based on the descriptive geographic analysis, it was possible to see that the prevalence of *H. pylori* increased from proximal to distal, starting with a 12.5% prevalence in the subcardial region and reaching a 30.6% prevalence in the antrum. A similar pattern was observed with the prevalence of preneoplastic lesions, starting with a low prevalence in the subcardial region (16.9%), decreasing at the fundus (11.9%), and with a progressive increase from that point to the antrum (66.2%) (**Figure 1**). In addition, there is a higher presence of advanced lesions (dysplasia, carcinoma) in the incisura (**Table 2**).

**Table 1.** Characteristics of patients undergoing endoscopic check for premalignant lesions

| | No injuries during check (n = 30) | | Injuries during check (n = 130) | | Total population (n = 160) | |
|---|---|---|---|---|---|---|
| | Frequency | % | Frequency | % | Frequency | % |
| Age (median/IQR) | 58.5 | (50-65) | 62 | (55-71) | 61.5 | (54-71) |
| Gender (female) | 21 | 70 | 75 | 57 | 96 | 60 |
| Initial diagnostic | | | | | | |
| - Atrophy | 23 | 76.7 | 98 | 75.3 | 121 | 75.6 |
| - Metaplasia | 23 | 76.7 | 106 | 81.5 | 129 | 80.6 |
| Endoscopic check diagnosis | | | | | | |
| - *H. pylori prevalence* | 13 | 43.3 | 47 | 36.2 | 60 | 37.5 |
| - Atrophy prevalence | 0 | 0 | 121 | 93.1 | 121 | 75.6 |
| - Metaplasia prevalence | 0 | 0 | 113 | 86.9 | 113 | 70.6 |
| - Premalignant lesions prevalence | | | | | 130 | 81.3 |
| Medical history of PPI treatment | 1 | 3.3 | 17 | 13.1 | 18 | 11.3 |
| History of antibiotic treatment | 12 | 40 | 32 | 24.6 | 44 | 27.5 |

**Table 2.** Diagnosis prevalence (%) by geographical location

| Diagnosis | Subcardial region | Fundus | Body | Incisura | Antrum | Total |
|---|---|---|---|---|---|---|
| H. pylori | 12.5 | 15.6 | 21.3 | 27.5 | 30.6 | 37.5 |
| Atrophy | 14.4 | 10.6 | 26.9 | 50 | 61.9 | 75.6 |
| Metaplasia | 14.4 | 8.13 | 22.5 | 46.9 | 55 | 70.6 |
| Dysplasia | 0 | 0 | 0.6 | 1.3 | 0.6 | 1.3 |
| Carcinoma | 0 | 0 | 0 | 0.6 | 0 | 0.6 |
| Neoplastic and pre-neoplastic lesions | 16.9 | 11.9 | 28.1 | 55.6 | 66.2 | 81.3 |

In the *H. pylori* intragastric distribution analysis with lesions, a higher prevalence of *H. pylori* was observed in all areas of the stomach in patients without lesions compared to patients with at least one lesion, showing a pattern of increasing prevalence from proximal to distal in both groups (**Figure 2**).

## DISCUSSION

The International Agency for Research on Cancer and the WHO classify *H. pylori* as a carcinogen type I[10]. Although the involvement of *H. pylori* in the carcinogenesis cascade of intestinal gastric cancer is accepted[11], its prevalence in preneoplastic conditions such as intestinal atrophy and metaplasia, causing changes in the mucosal microenvironment –which could alter the gastric distribution of this pathogen, is currently unclear[12]. Currently, many authors recommend surveillance in patients with premalignant conditions through endoscopic monitoring and biopsies of the antrum, body, and incisura (Sydney protocol) every 2 to 3 years[13]. However, it is unclear whether or not *H. pylori* infection occurs in other gastric regions, which can lead to false negatives in pathogen identification –considering that several authors support the regression theory of these conditions[8,14], pathogen identification would be critical to start an eradication treatment and, therefore, reduce the risk of gastric adenocarcinoma.

Approximately 50% of the world's population is infected with *H. pylori*, ranging between 40% and 73%, with some variation depending on latitude[9]. In the 2016 study conducted by Dr. Correa in Medellín in a population with dyspeptic symptoms taken to endoscopy, a prevalence of up to 36.4% was found, with male predominance (39.6%) versus female (34%), with an average age of 46.5[15]. There was a 36.2% prevalence of *H. pylori* in our population (patients with atrophy and metaplasia).

Although the global prevalence of *H. pylori* and its gastric distribution is known, its distribution in preneoplastic con-

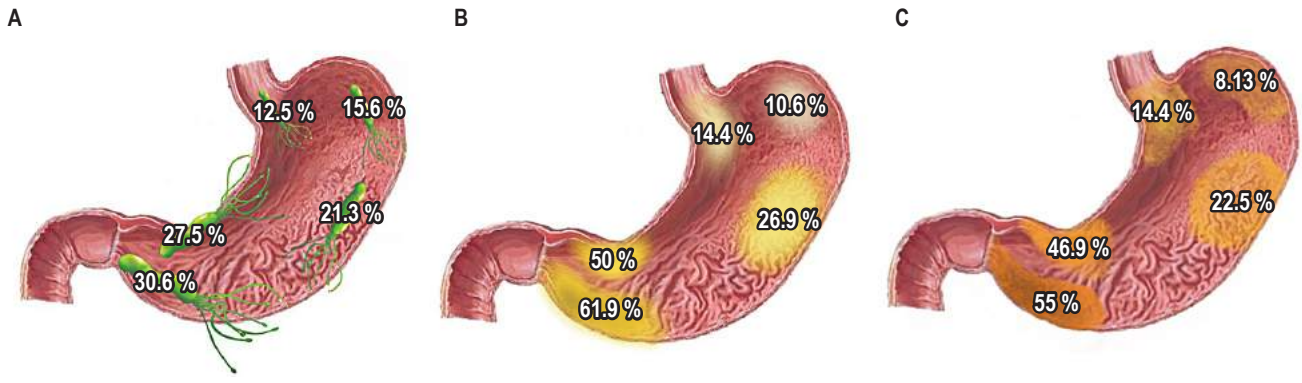


**Figure 1.** Prevalence and distribution of H. pylori (**A**), atrophy (**B**), and intestinal metaplasia (**C**) in patients with a previous diagnosis of preneoplastic conditions in Colombia.

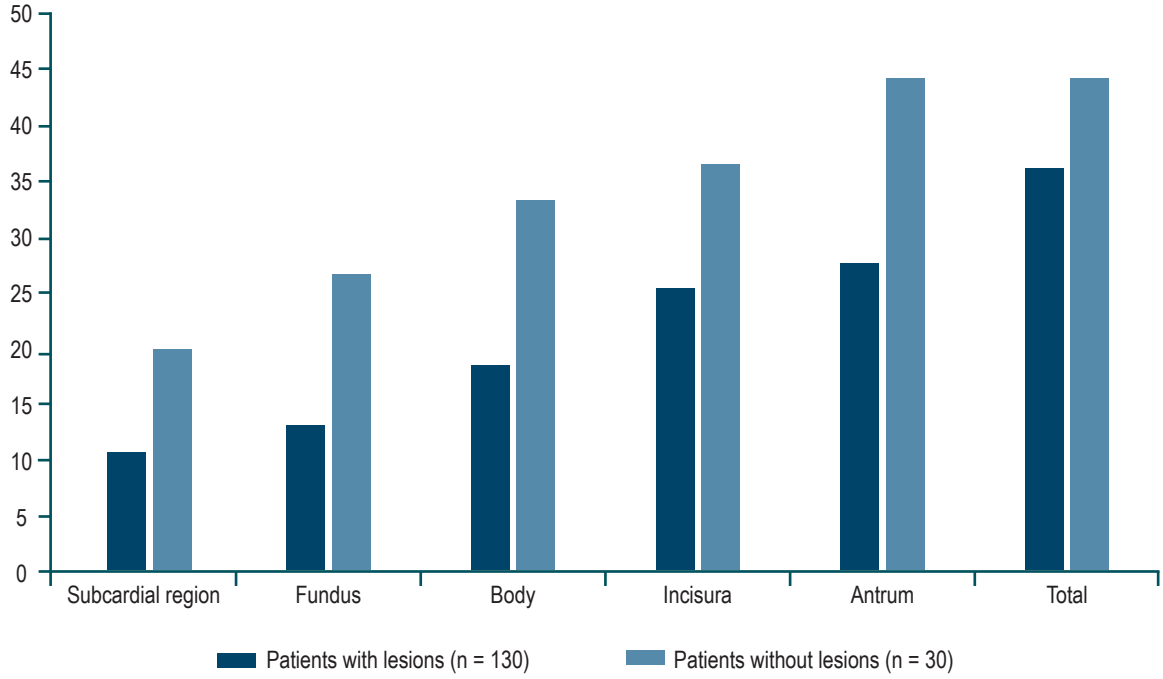


**Figure 2.** Prevalence (%) of H. pylori by presence or absence of lesions.

ditions such as atrophy and intestinal metaplasia is unclear. Therefore, the study was based on this pathogen's location in the different gastric regions and found a higher increase of *H. pylori* in distal regions, which is more frequent in the antral region (30.6%) and lower in the subcardial region, with a 12.5% prevalence. When comparing the distribution of *H. pylori* in patients with atrophy and metaplasia versus patients in whom no premalignant entity was found, the pathogen observed in the latter group had a higher prevalence of the pathogen.

Regarding gastric atrophy prevalence, ranges reported in the literature vary between 9.4% and 63%. On the other hand, for intestinal metaplasia, the ranges reported were between 7.1% and 42.5%[16-18]. Park and Kim's extensive review on premalignant entities in gastric cancer reported a 20.1% prevalence of gastric atrophy in the body and 42% in the antrum and a 21.2% prevalence of intestinal metaplasia in the body, and 28% in the antrum[19]. Our study found a similar distribution for atrophy and metaplasia in the gastric body (atrophy: 26%, intestinal metaplasia: 22%). However, a higher prevalence was observed in antral regions (atrophy: 61%, intestinal metaplasia: 55%). Notably, a lower prevalence of atrophy and metaplasia was also observed in proximal gastric areas, starting in the subcardial region (16.9%) and decreasing in the fundus (11.9 %) with a progressive increase up to the antrum (66.2 %).

Furthermore, the study conducted in Colombia in a high-risk population for gastric cancer reported a 39% intestinal metaplasia prevalence. Thus, showing a higher risk of gastric cancer in individuals with incomplete intestinal metaplasia and an extension of the metaplasia to the body and cardia[20]. Although this study's objective did not include evaluating the risk of adenocarcinoma according to the locations of the atrophy and metaplasia, two cases of patients diagnosed with dysplasia and one with adenocarcinoma were evidenced in the endoscopic check. They showed no *H. pylori* involvement due to atrophy or metaplasia in the gastric fundus or the subcardial region.

Our results suggest a low potential cost-benefit to performing control biopsies in the subcardial region and fundus, supporting the current suggested schemes. Nonetheless, this marginal benefit should be evaluated in longitudinal diagnostic studies to better assess the cost-effectiveness of biopsies in these two regions in patients with atrophy and metaplasia.

Among the strengths of this study is greater *H. pylori* diagnosis accuracy by covering all the anatomical areas of the stomach and a wide heterogeneity of the population as the study was conducted in a referral center in Colombia in a

contributory regime population. Some limitations include the cross-sectional nature of the evaluation, so the times of patients with the disease are not standardized. Likewise, this study's objective was to describe the *H. pylori* map in premalignant conditions, so making conclusions beyond the description of the population is not possible with the design.

Based on the evidence generated in this study, works of a longitudinal nature on a larger scale are recommended to measure *H. pylori* infection persistence or appearance impact in patients with preneoplastic entities more accurately. Moreover, studies should be conducted to evaluate the impact of biopsies in the fundus and subcardial region to establish control protocols in this population.

## CONCLUSIONS

*H. pylori* prevalence in premalignant conditions was 36.2%, with a higher presence in distal than proximal regions. It is more frequent in the antral region and less in the subcardial region, which does not support the upward migration theory of *H. pylori* in these premalignant conditions.

As for the gastric distribution of atrophy and metaplasia, more involvement was found in the antrum and incisura and lower in the subcardial region and the fundus.

In Colombia, this is the first study that shows a complete mapping of the prevalence of atrophy, metaplasia, and *H. pylori* in a population with gastric premalignant entities.

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Original article

# Morphological Characteristics of the Duodenal Papilla and its Association with Complications Post-Endoscopic Retrograde Cholangiopancreatography (ERCP) in a Peruvian Hospital

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## Abstract

**Introduction:** several risk factors exist for complications post-endoscopic retrograde cholangiopancreatography (ERCP), and the morphology of the duodenal papilla is among those recently studied. **Objectives:** to evaluate the association between the morphological characteristics of the duodenal papilla and post-ERCP complications in patients seen in the gastroenterology unit of a Peruvian referral hospital. **Methods:** a prospective and analytical study including 138 patients who underwent ERCP, establishing a relationship between the type of duodenal papilla according to the endoscopic classification proposed by Haraldsson *et al*. and post-ERCP complications for up to 1 month of follow-up. **Results:** one hundred thirty-eight patients were included, 93 were females (68.42%), and 45 were males (31.58%), with 51.46 years of mean age. Type 1 was associated with less difficulty in cannulation, with an *odds ratio* (OR): 0.42 (confidence interval [CI]: 0.20–0.88). Type 4 had a significantly longer cannulation time (6.83 minutes). The post-ERCP ratio for pancreatitis was 2.9%; bleeding, 1.45%, and perforation, 0.72%. The perforation showed a statistically significant association with papilla type ($p = 0.009$). Type 2 showed higher rates of pancreatitis (9.09%) and post-ERCP perforation (9.09%). **Conclusion:** the duodenal papilla type is significantly associated with post-ERCP perforation. Type 2 showed higher complication rates.

## Keywords

Endoscopic retrograde cholangiopancreatography, ampulla of Vater, adverse effects, endoscopy.

## INTRODUCTION

Since the late 1960s, endoscopic retrograde cholangiopancreatography (ERCP) has been described as a new technique for diagnosing biliopancreatic diseases[1]. A few years later, papillary sphincterotomy was described for bile tract lithotripsy removal[2,3], specifying this procedure's diagnostic and therapeutic nature.

Although this endoscopic procedure is currently widely used to treat multiple pathologies such as choledocholithiasis or benign and malignant biliary stenosis, complications are not excluded, occurring in up to 15% of the procedures[4] –post-ERCP pancreatitis is one of the most frequent complications.

There are multiple risk factors for each complication. However, a failed or difficult biliary cannulation is a com-

mon factor for these adverse events[5] and is also closely related to the anatomy of the duodenal papilla.

Several duodenal papilla classification systems have been proposed over the past decade. These systems have been used to predict cannulation success, complication rates, and the need for more advanced access techniques[6,7]. However, so far, only the Haraldsson *et al* classification system (**Figure 1**), which classifies the duodenal papilla into 4 types, has been subjected to an intra- and inter-observer discordance study[8], thanks to its simple classification scheme that admits within its types a wide variety of duodenal papilla presentation. Thus, any papilla can be categorized based on this classification. Additionally, this system is useful for predicting difficult biliary cannulation for experienced endoscopists and beginners, as it shows that types 2 and 3 papilla are the most difficult to cannulate[9].

The European Society of Gastrointestinal Endoscopy (ESGE) defines *difficult cannulation* when one or more of the following criteria is present: more than 5 contacts with the papilla while attempting to cannulate it, more than 5 minutes spent attempting to cannulate it after localizing the papilla, and more than one pancreatic duct involuntary cannulation or opacification[10].

This study aims to identify the relationship between the morphological characteristics of the duodenal papilla – according to the Haraldsson *et al* classification system and post-ERCP complications in patients treated in a gastroenterology unit of a referral hospital in Lima.

## MATERIALS AND METHODS

A prospective and analytical study that included 138 patients who underwent ERCP at Hospital Guillermo Almenara Irigoyen in Lima, Perú, a referral hospital where approximately 500 ERCPs are performed per year, according to the system registry. This was a convenience sam-

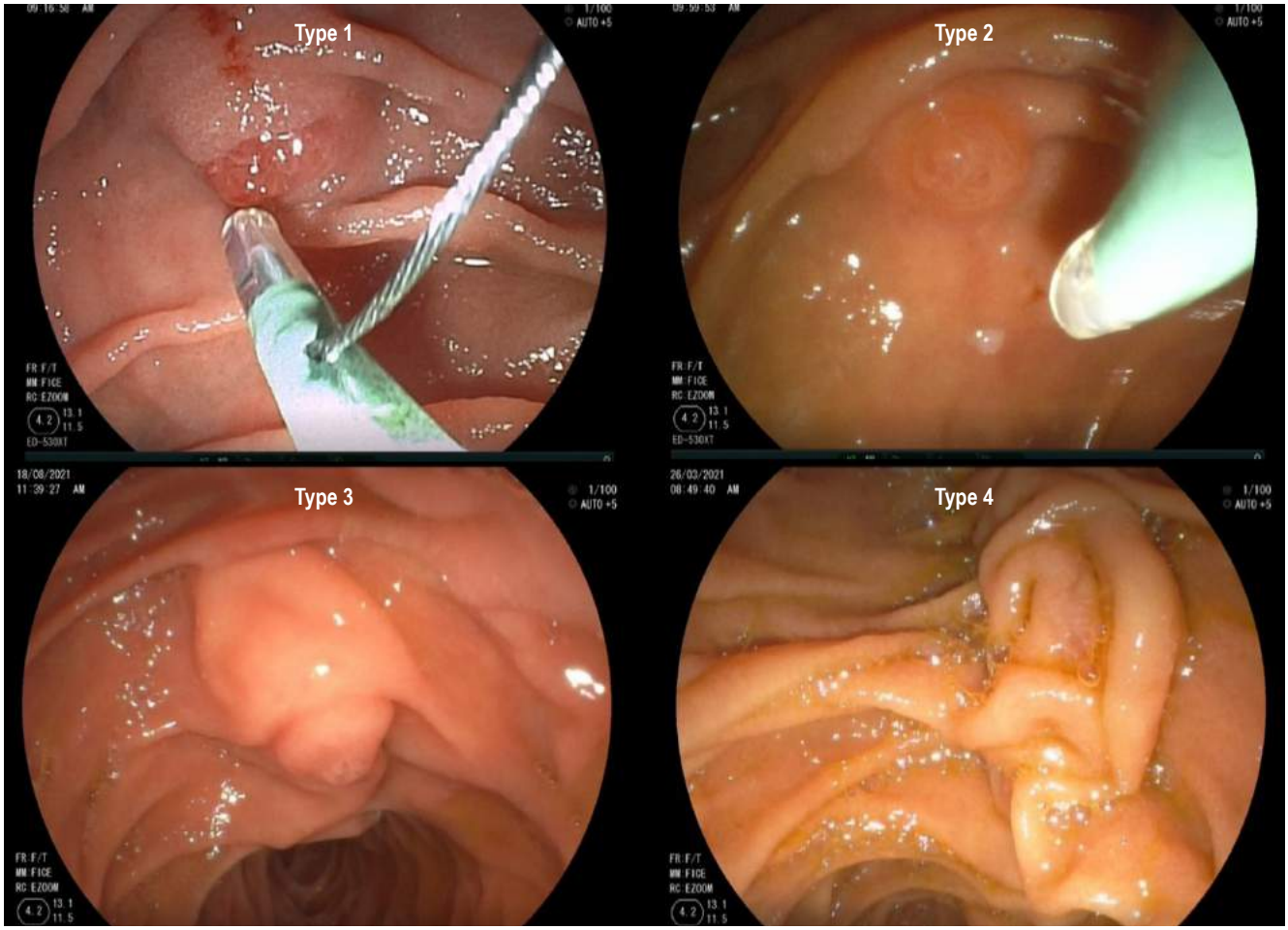


**Figure 1.** Types of duodenal papilla[8]. Type 1: "regular" appearance, without specific distinctive characteristics. Type 2: flat, with a diameter ≤ 3 mm. Type 3: protruded, pendulous, with prominent infundibulum. Type 4: ridged or "creased". Adapted from: Haraldsson et al. United Eur Gastroenterology J. 2017;5(4):504–10. Including images from the research group.

pling. Patients who signed informed consent and agreed to be part of the study were involved until the sample size was completed. On the other hand, patients with ERCP and previous sphincterotomy, with anatomy altered by previous gastroduodenal surgery, periampullary neoplasia, and pregnant women were excluded. Endoscopic and clinical data were collected for statistical analysis using central and association tendency measures such as odds ratio (OR), with a 95% confidence interval (CI). The association between the variables was measured with the Chi-square test, and a $p < 0.05$ value was considered statistically significant.

The equipment used was Olympus® and Pentax® video duodenoscopes. The materials for cannulation were Endo-flex® sphincterotomes, Endo-flex®, and Endo-med® balloons and extraction baskets. The x-ray equipment was a C-Arc from General Electric®, and the electrosurgical equipment was from ERBE®.

The patients signed an informed consent form in compliance with the ethical principle of autonomy. All procedures included clear therapeutic medical instructions in compliance with the non-maleficence principle. A local ethics committee approved the study.

## RESULTS

Of the 138 patients, 93 (68.42%) were females, and 45 (31.58%) were males. The mean age was 51.46 years (95%CI: 48.78–54.14). The most frequent type of papilla was type 1 with 81 patients (58.7%), followed by type 3 papilla in 40 patients (28.9%), and type 4 papilla was the least common, with 6 patients (4.35%). Type 4 papilla required, on average, a longer cannulation time (6.83 min), while type 1 papilla required a shorter cannulation time (2.93 min). Although these results were not statistically significant, no differences were found in cannulation attempts and unintended passage to the pancreatic duct between the different types of duodenal papillae.

A statistically significant relationship was found between papilla type and precut performance ($p = 0.0001$). Precutting was performed in 18 patients (13.04%) and was more frequent in type 4 papilla (33% of the cases of this type of papilla) and type 3 (30% of the cases). The analysis of each type of papilla showed that type 1 had an OR = 0.11 (CI: 0.03–0.39); type 2, an OR = 0.65 (CI: 0.08–5.38); type 3, an OR = 6.57 (CI: 2.26–19.11), and type 4, an OR = 3.63 (CI: 0.61–21.41) (**Table 1**).

Type 1 duodenal papilla was associated with less difficulty during cannulation (OR = 0.42; $p = 0.02$) compared to the other types and was statistically significant. The other types of papillae showed more difficulties during cannulation. Overall, no association was found between papilla type and difficult cannulation ($p = 0.123$) (**Table 2**).

The overall rate of post-ERCP pancreatitis in our study was 2.9%. In the analysis for each type of papilla, type 1 showed an OR = 0.23 (0.02–2.22); type 2, an OR = 4.43 (0.39–43.48), and type 3, an OR = 2.53 (0.34–18.59) for post-ERCP pancreatitis, although no statistical significance was obtained ($p = 0.376$).

The bleeding rate was 1.45%, and the perforation rate was 0.72%. Type 2 reported a higher complication rate with 9.09% of pancreatitis and 9.09% perforation. In the general analysis, perforation presented a statistically significant

**Table 1.** Characteristics of the population according to the type of duodenal papilla

| Characteristics | | Type of papilla | | | | *p* value |
|---|---|---|---|---|---|---|
| | | Type 1 | Type 2 | Type 3 | Type 4 | |
| Median age (years) (95% CI) | | 52,89 (49,42-56,36) | 53,68 (44,17-63,19) | 48,11 (43,04-53,18) | 50,5 (38,18-62,82) | 0,4615 |
| Gender | Female, n (%) | 53 (65,43 %) | 7 (63,64 %) | 30 (75 %) | 3 (50 %) | 0.554 |
| | Male, n (%) | 28 (34,57 %) | 4 (36,36 %) | 10 (25 %) | 3 (50 %) | |
| Average cannulation time (minutes) | | 2,93 | 3 | 3,67 | 6,83 | 0,1202 |
| Average cannulation attempts | | 2,94 | 3,18 | 3,33 | 3,83 | 0,3955 |
| More than 1 passage to the duct of Wirsung | | 9 (11,11 %) | 0 (0 %) | 5 (12,5 %) | 1 (16,67 %) | 0,645 |
| Precut, n (%) | | 3 (3,7 %) | 1 (9,09 %) | 12 (30 %) | 2 (33,33 %) | 0,0001 |
| Total, n (%) | | 81 (58,7 %) | 11 (8,05 %) | 40 (28,9 %) | 6 (4,35 %) | |

CI: confidence interval.

association with papilla type ($p$ = 0.009). Still, the risk for each type could not be determined due to the lack of events in some types of papillae (**Table 3**).

## DISCUSSION

Findings showed that the duodenal papilla type is significantly associated with post-ERCP perforation. Type 2 showed higher rates of pancreatitis (9.09%) and post-ERCP perforation (9.09%). There was an association between the type of duodenal papilla and precutting, and it is more likely to be performed in types 3 (OR = 6.57) and 4 (OR = 3.63).

Over the last few years, several studies have been published comparing different difficulty levels of biliary cannulation according to the duodenal papilla morphology[17,19,20]. However, these studies differ in the type of classification. They are based on different parameters such as the Viana classification, which divides the type of papilla according to the parameter combinations such as the papilla shape, the oral segment protrusion of the papilla, the number of transverse folds, and the presence of a diverticulum[7]. Other studies classify the type of papilla according to the oral protrusion and papilla pattern[11]. Moreover, other simpler and more classic studies, such as Canard's classification[12] and according to the primary characteristic of the duodenal papilla (large, small, and protruded)[6], are different from the classification proposed by Haraldsson *et al* which is the only one that has undergone a discordance intra- and inter-observatories study so far.

A retrospective study published in China in 2020 reveals that type 2 and 3 papillae require more time for cannulation and have a higher failed cannulation rate (12% and 11.1%, respectively) compared to type 1 and type 4 papillae (1.7% and 6.25%)[13]. Conversely, our results show that the types of papillae requiring more cannulation time were type 4 (6.83 minutes) and type 3 (3.67 minutes), although it was not statistically significant.

In 2019, Haraldsson *et al* found that type 2 and 3 papillae were more difficult to cannulate (OR = 1.89 and 1.61, respectively) compared to type 1 and 4 papillae. In addition, the median cannulation time was significantly longer for type 2 papilla (269 seconds) and type 3 papilla (245 seconds), both with a $p < 0.05$ value, compared to type 1 papilla (139 seconds)[9]. In Canada, a retrospective study was conducted using the Haraldsson classification and found that the OR for difficult cannulation was higher for type 2 (AOR = 3.73; 95%CI: 1.28–10.84) and type 3b (AOR = 3.97; 95%CI: 1.76 to 8.99). Additionally, these types were associated with post-ERCP pancreatitis (AOR = 7.28 and 4.25, respectively)[14], unlike our study, which found that only type 1 papilla was less difficult to cannulate (OR = 0.42). However, we found no association between the type of papilla and difficult cannulation. Meanwhile, the average cannulation times shown in our study were higher, especially for type 4. We found no association between the type of papilla and post-ERCP pancreatitis.

On the one hand, the overall post-ERCP adverse events rate was higher in type 2 papilla (18.18%), while no adverse events were observed in type 4 papilla in our study, contrary to what Balan *et al* presented, they obtained a significantly higher rate for patients with type 4 papilla[12]. Conversely, in his multicenter study, Canena concluded no significant difference in the adverse events rate between the different papilla types. However, they used a different classification system[7].

Pancreatitis was the most frequent adverse event, with a higher rate in type 2 papilla (9.09%). This finding was similar to what Chen *et al* found. Their study showed that type 2 papilla had the highest percentage of post-ERCP pancreatitis (20% compared to 6.78% for type 1; 1.59% for type 3, and 6.25% for type 4; $p$ = 0.020)[13]. In 2019, Haraldsson *et al* also reported a higher rate of pancreatitis for type 2 papilla (9.4%), but with no significant differences compared to the other papillae[9]. In turn, Mohamed *et al* used Haraldsson's classification with a modification: they divided type 3 papilla into 3a (protruding or bul-

**Table 2.** Papilla type and difficult cannulation

| Papilla Type | Difficult cannulation | | OR (95%CI) | p = 0,123 |
|---|---|---|---|---|
| | Yes | No | | |
| 1 | 19 (23,46 %) | 62 (76,54 %) | 0,42 (0,20-0,88) | 0,02 |
| 2 | 4 (36,36 %) | 7 (63,64 %) | 1,29 (0,36-4,66) | 0,698 |
| 3 | 17 (42,5 %) | 23 (57,5 %) | 2,05 (0,95-4,42) | 0,066 |
| 4 | 3 (50 %) | 3 (50 %) | 2,3 (0,44-11,89) | 0,308 |

CI: confidence interval; OR: odds ratio.

**Table 3.** Type of papilla and complications

| | Type 1 | Type 2 | Type 3 | Type 4 | Total | *p* value |
|---|---|---|---|---|---|---|
| Pancreatitis | 1,23 % | 9,09 % | 5 % | 0 % | 2,9 % | 0,376 |
| Bleeding | 2,47 % | 0 % | 0 % | 0 % | 1,45 % | 0,699 |
| Perforation | 0 % | 9,09 % | 0 % | 0 % | 0,72 % | 0,009 |
| Total | 81 | 11 | 40 | 5 | 138 | |

ging) and 3b (pendulous or redundant), and separated papillae associated with periampullary diverticula into type D. For them, pancreatitis was also the most frequent adverse event, it was significantly higher in type 2 and 3 papillae[14]. Another study conducted in Shanghai considered 5 types of papillae, where findings showed that pancreatitis was also the most frequent adverse event, showing the highest rate for papillae classified as flat, equivalent to type 2 (6.3%)[16].

Our study did not observe acute cholangitis as a complication, an adverse event reported in other studies with rates between 0.6% and 1.75%[9,13,15]. We found a statistically significant association between papilla type and fistulotomy-like precutting as a rescue technique in case of failed conventional cannulation, and it was more frequent in types 4 (33.33%) and 3 (30%). The cannulation success rate, including fistulotomy, was 100%, similar to that of Wen *et al*, who chose the precut according to the morphologic characteristics of the papilla and the entry into the pancreatic duct. They recommend the fistulotomy for a protruding papilla (type 3)[13]. Different studies found a 100% cannulation success rate for fistulotomy-type precut[18,21].

## CONCLUSIONS

The duodenal papilla morphology can be classified using the system proposed by Haraldsson *et al*. The duodenal papilla type is associated with post-ERCP perforation. Type 2 papilla has higher rates of pancreatitis and post-ERCP perforation than other types.

The type of papilla is associated with advanced cannulation techniques such as pre-cutting, and types 3 and 4 are more likely to be used. Although, due to the low number of type 4 papillae affecting statistical analysis, these results should be taken with caution.

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Case report

# Liver Abscess Caused by *Enterobius vermicularis* as a Differential Diagnosis for Liver Metastasis in Colorectal Cancer, Case Report

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## Abstract

**Introduction:** colorectal cancer is the fourth leading cause of cancer-related mortality worldwide. The identification of the metastases of this tumor in the preoperative stage is increasingly frequent due to the imaging studies currently available. We present the case of a patient with an infection caused by *Enterobius vermicularis* that simulates the presence of liver metastases. **Case presentation:** a female patient from a rural area showing a one-year abdominal pain evolution associated with lower gastrointestinal tract bleeding and weight loss. Endoscopic imaging and studies displayed a tumor lesion in the sigmoid colon, with biopsies reporting sigmoid colon adenocarcinoma and liver lesions suggesting malignancy. Anterior resection of the rectum and sigmoid was performed with high anastomosis and liver biopsies, which ruled out malignancy and reported the presence of liver infection by *E. vermicularis*. **Discussion:** in this case, the hepatic *E. vermicularis* infection was rare. This infection can simulate the presence of liver metastases; therefore, it should be considered a differential diagnosis of metastatic colorectal cancer.

## Keywords

Colon cancer, rectum cancer, liver abscess, *Enterobius*.

## INTRODUCTION

According to data from GLOBOCAN 2018[(1)], colorectal cancer ranks third in morbidity and fourth in cancer-associated mortality after lung and prostate cancer. Identifying advanced diseases (synchronous or metachronous) is becoming increasingly common with new, better-performing diagnostic methods. Intra-abdominal organs represent one of the greatest challenges in imaging suggestive of metastases from a primary colon lesion[(1)].

*Enterobius vermicularis*, also known as *Oxyurid vermicularis*, is a frequent helminthic infection in the United States and Eastern Europe. It predominantly affects the pediatric population[(2)]. The parasite lives and reproduces in the gastrointestinal tract. It usually lays eggs in the anal region with approximately 10,000-15,000 eggs overnight, causing

itching and discomfort[3]. This parasite has different ectopic locations in the human body, including the omentum, lungs, and liver, the latter, with very few cases reported in the literature[3].

The following is a patient's case with adenocarcinoma of the sigmoid colon with images suggesting liver metastases, with subsequent histological confirmation of *E. vermicularis* infection.

## CASE PRESENTATION

A 39-year-old Hispanic female patient from Villavicencio (Meta, Colombia) was admitted to the emergency room for a 1-year history of colicky abdominal pain on the left hemiabdomen, associated with a 20 kg weight loss in 4 months, self-limiting emesis, and rectal bleeding. She underwent a colonoscopy, in which an infiltrating mass with stenosis of 80% of the lumen of the sigmoid colon located 30 cm from the anal ridge was reported. Biopsies of the lesion reported moderately differentiated adenocarcinoma originating in tubulovillous adenoma.

Extension and staging studies were conducted, including a carcinoembryonic antigen quantified at 1.35 ng/mL, a computed axial tomography (CT) of the abdomen with contrast showing a polypoid mass dependent on the descending colon of roughly 45 mm in diameter, irregular, ulcerated, associated with stranding of the perilesional fat and adenopathies at the mesenteric edge. In addition, the liver showed a 98 mm focal lesion in segment VII and an approximately 10 mm focal lesion in segment IV (**Figure 1**). A magnetic resonance imaging (MRI) of the abdomen showed a 7 mm focal lesion in the IV liver segment and a 7.4 mm focal lesion in the right lobe, indicating liver metastases (**Figure 2**).

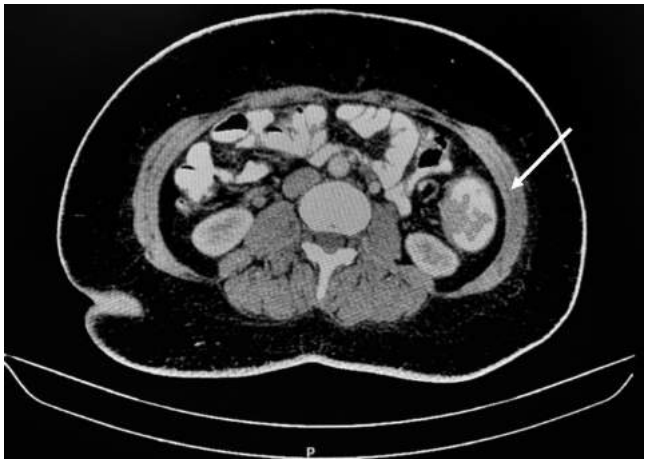

**Figure 1.** Abdomen CT scan using contrast, performed during admission, showing a sigmoid colon-dependent tumor with a large involvement of intestinal lumen.

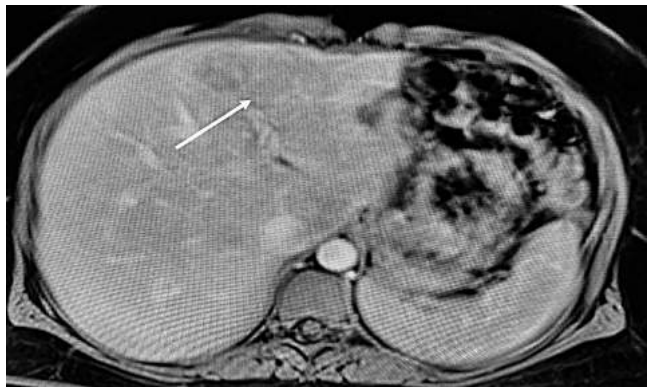

**Figure 2.** Abdomen MRI with contrast shows a liver lesion that does not rule out malignancy.

Based on these findings, anterior resection of the rectum and sigmoid was performed with high anastomosis and liver biopsy, as well as high ligation of the vascular pedicle. After a one-week hospital stay, the patient showed a good clinical evolution and was discharged for an outpatient check-up. Subsequently, after receiving the surgical pathology report, it showed a distinguishable adenocarcinoma of the sigmoid colon infiltrating up to the muscle layer, without lymphovascular or perineural invasion, as well as tumor-free resection edges and 0/16 positive nodes for a T2N0. As for the liver biopsy, a "necrosis and acute inflammation with *E. vermicularis* eggs, without evidence of malignancy in the material examined" report was obtained. Thus, the disease was classified as T2N0M0 for stage IB due to the absence of metastatic lung lesions. During outpatient follow-up, the patient received anthelmintic treatment; a check-up abdomen MRI was performed, showing a residual scar lesion in segment VII with scarring characteristics and another subcapsular lesion in segment IV.

## DISCUSSION

There are few cases described of liver infection caused by *E. vermicularis*. In developed countries, this nematode, also known as *Oxyurid vermicularis*, produces a frequent helminthic infection and predominantly affects the pediatric population[2]. The parasite lives and reproduces in the gastrointestinal tract. It usually lays eggs in the anal region overnight, causing itching and discomfort[3]. The entrance route is through the ingestion of pinworm eggs through the fecal-oral route. They enter the stomach and small intestine, and the larvae migrate to the ileum, cecum, and appendix. The adult female settles in the ileum, where she copulates. Around the fifth week, she begins laying eggs and migrates toward the colon and anus. Then, she releases thousands of eggs onto the perianal skin. The eggs survive in a humid

environment and a low temperature[4]. It is unclear how the nematode can reach the liver. However, it is believed that it cannot penetrate intact tissues, so the presence of non-intact or injured intestinal mucosa (as in colorectal cancer) can facilitate its migration[5].

Liver infection and abscess formation caused by *E. vermicularis* are extremely rare. Fewer than 10 cases have been reported in the literature, from which approximately 5 cases have been reported in patients with colorectal cancer and liver infection simulating liver metastases in imaging studies[2-4,6,7].

Colorectal cancer ranks third in cancer morbidity; 1.4 million patients with this disease are diagnosed each year globally. Patients with metastatic disease or stage IV have an overall 5-year survival[1,8]. Nonetheless, depending on the stage, up to 50% of patients will at some point develop liver metastases[8,9].

Abdominal ultrasound has a limited role in the complete characterization of liver lesions. Contrasting abdominal CT allows adequate identification and even volumetric calculations of liver lesions. Generally speaking, images suggesting metastasis describe a peripheral reinforcement in the arterial phase, and 11% may present calcifications[10]. Liver metastases are hypovascular in the arterial phase with hypervascular peripheral enhancement and heterogeneous hypoattenuation in the portal venous phase, with an 85% identification rate and a 96% positive predictive value (PPV).[10]

Several points help to discern between liver lesions suggestive of metastasis versus infectious liver lesions, such as margin in the portal venous phase, hepatic parenchyma enhancement, arterial border enhancement, dynamic change of arterial border enhancement, size discrepancy between arterial phase and portal venous phase, and perilesional hyperemia. Thus, according to Jae Gu Oh *et al* (**Table 1**)[11], abscesses, unlike metastases, have more defined margins in the portal venous phase, greater enhancement of the parenchyma, more peripheral (rim arterial) enhancement, and greater perilesional hyperemia. Regarding the dynamic changes of peripheral rim enhancement, abscesses report a higher enhancement persistence in the venous phase than metastases, which disappear in a higher percentage with the transition from the arterial to the venous phase[11].

A further important aspect to consider for liver lesions when comparing the arterial and portal venous phases is that there may be changes in size, as in liver abscesses, which may show changes in 45.2% compared to only 16.8% in cases of metastasis[11].

Another imaging study is MRI, which is more sensitive than CT in detecting metastatic liver lesions, particularly sub-centimeter size lesions, or for restaging lesions after neoadjuvant surgery, in which CT sensitivity drops to 77%[12]. Cases reporting liver infection by *E. vermicularis* suggest a predilection for the right hepatic lobe, close to the hepatic surface, with hypodense images in the CT between segments VII and VIII, similar to the findings in our patient[2,12].

**Table 1.** Differences between liver abscess and liver metastases on abdominal CT

| | Liver abscess | Liver metastases |
|---|---|---|
| Margins | Defined | Diffuse |
| Peripheral enhancement | Present in the arterial phase and persists in the venous phase | No peripheral enhancement in any phase |
| Size | Size change when comparing between phases | Constant size in all phases |
| Other | Higher bile duct dilation | Less parenchymal enhancement |

## CONCLUSIONS

Colorectal cancer metastases represent an important percentage of the spread of this primary cancer. However, an important differential diagnosis for comprehensive patient treatment is liver infections caused by bacteria or parasites. Cases in which the *E. vermicularis* parasite produces an infection of the liver parenchyma and simulates, in turn, a metastasis of a primary colon tumor are rare but have been described in the literature. Since multiple diagnostic imaging modalities have been introduced, more liver lesions have been detected in the pre-surgical setting. The correct characterization of these lesions through the study by the pathology group prevents patients from being taken to major surgeries that include liver resections.

### Conflicts of Interest

The authors have no conflicts of interest to declare.


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Case report

# Nutcracker Syndrome Combined with Wilkie Syndrome: Case Report

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## Abstract

**Objective:** to describe the clinical presentation, diagnosis, and surgical treatment of a patient with superior mesenteric artery syndrome or Wilkie syndrome combined with the nutcracker syndrome or left renal vein compression syndrome in a tertiary referral center in a Latin American country. **Case description:** a 25-year-old male patient from the United States who attended for a year of weight loss and intestinal obstruction episodes of unknown etiology after multiple imaging studies. Endoscopic studies were performed without findings. While in the recovery room, he developed abdominal pain requiring admission to the emergency service. The CT enterography showed dilation of the colon loops and small intestine with a decrease of the aortomesenteric (AOM) angle and the gastrointestinal series with the filiform passage of the contrast medium. Conservative management was attempted as initial therapy with intolerance to enteric nutritional support. Finally, we initially opted for surgical treatment, with a slow recovery process, but in the end, with a resolution of symptoms and weight gain. **Conclusion:** Wilkie syndrome is a rare disease and a diagnostic challenge in patients with weight loss and abdominal pain. We described a superior mesenteric artery compression case in which diagnosis was achieved with multiple diagnostic strategies and complete resolution after surgical treatment. The decreased aortomesenteric angle may compress the superior mesenteric artery and the left renal vein. In this case, it resulted in a combined Wilkie and nutcracker syndrome.

## Keywords

Superior mesenteric artery syndrome, Wilkie syndrome, superior mesenteric artery, syndrome/imaging, superior mesenteric artery syndrome/surgery, left renal vein syndrome, nutcracker syndrome, jejunum/surgery, intestinal obstruction/surgery.

## INTRODUCTION

Superior mesenteric artery (SMA) syndrome has been referred to by different names, *Wilkie's syndrome, aorto-mesenteric compass syndrome, cast syndrome, chronic duodenal ileus syndrome,* and *arteriomesenteric duodenal occlusion syndrome*. When the angle is < 25°, it is defined as the compression of the third portion of the duodenum between the abdominal aorta and the superior mesenteric artery (SMA)[1-9]. This syndrome is a rare cause of intestinal obstruction, with an estimated 0.1% to 0.3% incidence[1,2]. The abdominal aorta and SMA normally form an angle between 38° and 65°. Since the duodenum and left renal vein are located within the mesenteric angle, both types of compression may occur. Predisposing factors are associated with the decrease in the mesenteric fat pad between the aorta and the superior mesenteric artery, which reduces the angle and distance between the two. These conditions –congenital or

acquired, are associated with significant weight loss, including situations of hypermetabolism (trauma and burns), dietary conditions (anorexia nervosa and malabsorptive diseases), and conditions causing cachexia (AIDS, cancer, paraplegia)[1-13].

Because the clinical picture is variable, there is often a delay in diagnosis. The most typical clinical manifestations include reports of postprandial epigastric pain, nausea, vomiting, and early satiety with weight loss[1-11]. When SMA and Nutcracker syndrome coexists, hematuria, mainly microscopic, and proteinuria may appear when left renal vein stenosis is significant, which causes venous hypertension[10-14]. There are no currently validated clinical diagnostic criteria; thus, imaging studies may confirm a suspicion[5-10]. Conservative treatment has been proposed as the first line of action, in which nutritional support seeks to recover the mesenteric pad. Frequently, failure in therapy determines the need for surgical intervention, with high success rate reports in the literature[1-13].

## CASE PRESENTATION

A 25-year-old man from the United States. He repeatedly consulted for a clinical picture of a 1-year evolution of postprandial abdominal pain and distension, nausea, vomiting, and distension, contributing to a 30 kg weight loss. In several admissions to the hospital due to intestinal obstruction –which responded to medical treatment, laboratory tests were performed to rule out infectious, autoimmune, hematological, and neoplastic diseases. Additionally, upper and lower endoscopy, video capsule endoscopy, abdominal scan, abdominal magnetic resonance imaging (MRI), and diagnostic laparoscopy studies were performed without obtaining significant findings on a possible etiology. He received nutritional support and pharmacological treatment as part of his medical treatment. However, his symptoms did not improve.

In March 2020, he consulted our outpatient gastroenterology unit in Cali, Valle del Cauca. During anamnesis, the patient mentioned a history of infectious gastroenteritis 1 year before on a trip to San Andres, with subsequent weight loss. At admission, secondary cachexia to weight loss could be evidenced without alteration in the hemodynamic state. New endoscopic studies were performed that showed no evident alterations. While in the endoscopy recovery room, he required a transfer to the emergency department because he developed acute abdominal pain and oxygen desaturation. Within the examinations performed, the CT enterography showed dilation of the colon and small bowel loops. The sagittal reconstruction showed a decrease in the aortomesenteric angle and compression of the third portion of the duodenum and compression of the left renal vein (**Figure 1**). The upper digestive tract radiography showed a filiform passage of the contrast medium in the third portion of the duodenum toward the distal (**Figure 2**).

After confirming the diagnostic impression, enteral nutritional supplementation was started with poor response, persisting with nausea, vomiting, abdominal pain,

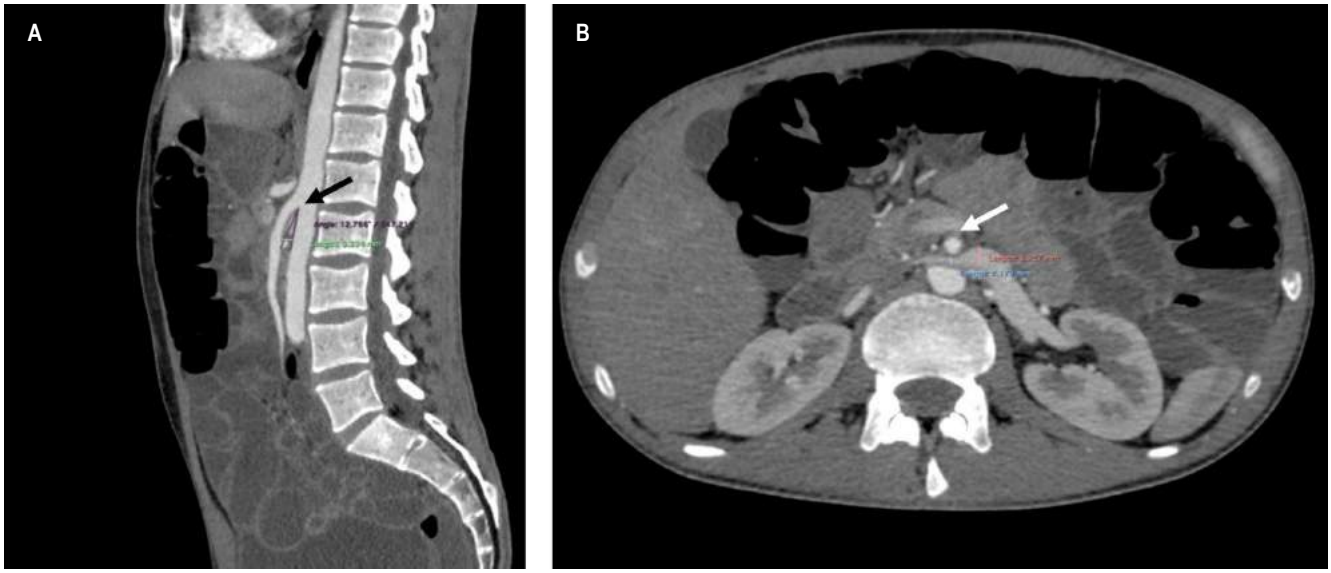


**Figure 1.** Abdominal CT scan. **A.** The reconstruction in the sagittal plane shows the narrowing of the aorto-mesenteric angle, 12,786°, with a reduced aorto-mesenteric length of 5334 mm (black arrow). **B.** The reconstruction in the axial plane shows the compression of the left renal vein with a ratio of the anteroposterior diameter of the compressed vein over the enlarged compressed vein (6927 mm/2179 mm = 1179) (white arrow).

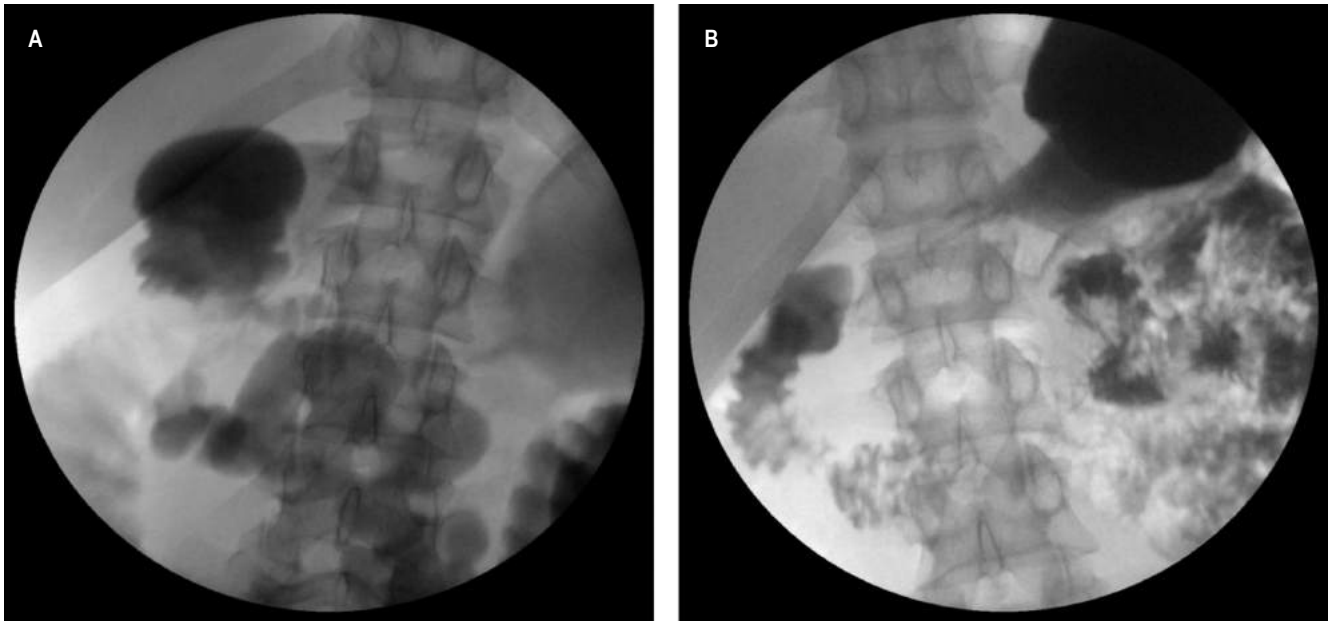


**Figure 2.** Gastroduodenal series. Radiographic imaging show proximal dilatation of the duodenum (**A**), with a significant compression in the midline of the third portion of the duodenum (**B**).

bloating and early fullness, and oral tolerance. The patient underwent surgery because he did not show any improvement signs. Thus, a transmesocolic duodenojejunostomy was performed 40 cm from the ligament of Treitz. There, large retroperitoneal lymph nodes found in the procedure were sampled, which in a subsequent pathological study showed reactive lymphadenopathy and follicular and sinus hyperplasia.

The patient's postoperative recovery was initially torpid, showing edema of the duodenojejunal anastomosis, which was treated with an endoscopic advancement of an enteral tube –distal to the anastomosis. Thus, the patient experienced a gradual symptom remission and gained 3 kg and progressive oral tolerance in the first month, resulting in the removal of the nasojejunal tube. As a result, the patient could return to the United States, and 9 months later, he has not reported any gastrointestinal symptoms. He is in good health condition and reported a 12 kg weight gain.

## DISCUSSION

Boerneus first described the SMA in 1752 through findings in a necropsy[11]. Around 1842, SMA was considered a cause of duodenal obstruction by Carl Freiherr von Rokitansky due to aorto-mesenteric compression[1]. Regarding its etiology, Soutclern associated lordosis with duodenal stasis; Kundrat asserted that incomplete duodenum obstruction was due to the compression of the mesentery root. In 1900, in *post-mortem* studies, Robinson found that the mesenteric vessels caused the compression of the duodenum, with dilation of its proximal portion[1,11]. It remained an unknown disease until 1927 when Wilkie reported 75 cases and would henceforth bear his name[1].

So far, SMA is known as a rare disease, and the bibliography corresponds to case reports. Different manifestations have been reported; however, patients typically report chronic gastrointestinal symptoms, abdominal pain, nausea, belching, excessive vomiting of bilious content or partial digestion, postprandial discomfort, and early satiety[1-13], as our patient showed in time. It also required treatment for multiple episodes of subacute intestinal obstruction and weight loss, characteristic of the disease as reported in the literature[2,6,8]. Studies have reported that SMA syndrome can be associated with compression of the left renal vein. When such cases show symptoms, hematuria is the most common one –not found in our patient[10-14].

In the first half of the twentieth century, there were no clear diagnostic criteria, and indications for treatment were limited, so the final results were not as desired. In the 1960s, aortic angiography combined with a contrasted gastroduodenal series began to take place in an attempt to determine the obstruction site[10]. It was until the 2000s that case studies began to define imaging in patients with a suggestive clinical picture[1-10]. Abdominal CT is currently considered

the gold standard for diagnosing SMA. It has a sensitivity and specificity rate close to 100%.[4-8]

The MSA is known to form an angle of approximately 45° with the abdominal aorta and the third portion of the duodenum[2,9]. Recent reports agree that factors that abruptly reduce the aorto-mesenteric angle to less than 25° can generate clamping of the third portion of the duodenum. This is the first diagnostic imaging criterion[1,2,6-8]. Other findings include an upper aortomesenteric distance less than or equal to 8 mm, the duodenum fixed by the ligament of Treitz, or an anatomical variant of the MSA syndrome[6]. The CT enterography of our reported case showed a 12.8° angle with a 5.33 mm distance –meeting these criteria (**Figure 1**).

Conservative treatment is the initial management option. Mobilization and positioning in the left lateral decubitus or the prone decubitus after meals to control postprandial symptoms, correcting hydro electrolytic alterations, and parenteral nutritional supplement focused on recovering the aortomesenteric fat pad[1]. Previous reports have shown that the likelihood of improvement with non-surgical therapy significantly decreases after the second unresponsive week[1-13]. Over the past year, the patient has received medical treatment for his symptoms and episodes of subacute bowel obstruction without full and lasting relief.

In 1908, Stavely performed the first successful surgery for Wilkie's syndrome at Johns Hopkins Hospital[11]. Since then, several procedures have been used, including Treitz ligament division (Strong's operation), gastrojejunostomy; subtotal gastrectomy and Billroth II gastrojejunostomy; duodenojejunostomy and anterior repositioning of the duodenum[1]. Nowadays, the preferred method is duodenojejunostomy, which in our case, resulted in a complete resolution of the symptoms and progressive weight gain[1-13]. Over the last 10 years, progress in the surgical technique has been made, and there are successful reports of short-duration laparoscopic duodenojejunostomy without complications[12,13].

Regarding the left renal vein compression, left renal vein transposition may be considered in cases of kidney failure, orthostatic proteinuria, persistent varicocele or hematuria, or non-response to conservative therapy. In asymptomatic cases –like our patients, conservative therapy is the first line of treatment.

## CONCLUSION

Wilkie's syndrome is a low-frequency disease that should be considered a differential diagnosis in patients with weight loss and subacute bowel obstruction presenting abdominal pain, nausea, belching, and bulky vomiting. Medical imaging confirms clinical suspicion, and abdominal tomography is the gold standard. Initially, conservative therapy may be considered, but most cases will require surgical therapy with laparoscopic duodenojejunostomy, which achieves recovery rates even greater than 80%.

### Ethical approval and consent to participate

No ethical approval was obtained for the publication of this clinical case, as it does not involve sharing the patient's personal data and photographs.

### Publication consent

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

### Conflict of interest

The authors state that they have no competing interests.

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Case report

# Esophageal and Pulmonary Involvement Caused by Paracoccidioidomycosis in Immunocompromised Patient: Case Report

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## Abstract

Paracoccidioidomycosis (PCM) is a fungal infection endemic to South America. It predominantly affects men, depending on their work field: farmers and agriculturists. Paracoccidioidomycosis is caused by the aspiration of the fungus in its micellar form and manifests in three conditions: acute, subacute, and chronic; the latter is more frequent in adults, whose treatment will depend on azoles, amphotericin B, and sulfonamides. This case concerns a 57-year-old Colombian man, a farmer with no pathological history who showed dysphagia for solids that progressed to liquids, sialorrhea, and weight loss for two months. He underwent upper GI endoscopy, and whitish lesions were observed; thus, he was biopsied, displaying yeasts in multiple gemmations compatible with paracoccidioidomycosis. In turn, a chest CT scan showed generalized interstitial parenchymal involvement. Subsequently, he was treated with itraconazole, showing improvement and resolution in his clinical picture. Since the pathology described is endemic in South America and can be disseminated in immunocompromised patients. Given the broad infection spectrum, consideration should be given to patients with risk factors, symptomatology, and findings in extension studies suggesting this disease to provide timely and specific treatment.

## Keywords

Paracoccidioidomycosis, blastomycosis, invasive fungal infections.

## INTRODUCTION

Paracoccidioidomycosis (PCM) is an infectious fungal disease endemic in South America with greater prevalence in Brazil, Venezuela, Colombia, and Argentina[1-3]. It is caused by two types of fungi that inhabit the soil in the mycelial form: *Paracoccidioides brasiliensis* and *Paracoccidioides lutzii*[4,5]. Upon inhalation, they enter the pulmonary alveoli, whose body temperature allows their conversion to yeast, which favors their asexual reproduction and generates acute infection of the disease, mainly in children, or chronic infection, primarily in adults[6], which sometimes progresses to its secular form and causes pulmonary fibrosis[7,8]. Since there are few reports in the literature of esophageal involvement caused by PCM, our objective is to bring the case of a farmer who debuts with constitutional syndrome associated with dysphagia, with biopsy findings of lesions evidenced in the upper gastrointestinal endoscopy (UGIE) which were compatible with PCM and confirmed esophageal and pulmonary involvement by chest CT findings.

## CASE PRESENTATION

A 57-year-old male Colombian farmer patient with no pathological history. He presented a clinical picture of two-month evolution, initially characterized by retrosternal foreign-body sensation. Subsequently, progressive dysphagia from solids to liquids, regurgitating 20 minutes after food intake, without nausea and without gagging, accompanied by sialorrhea in the last week of the clinical picture.

Upon admission, he reported occasional non-productive cough without dyspnea and a 10 kg weight loss in the last month. The patient showed a stable condition, systemic inflammatory response absence, vital signs unaltered, a 17 kg/m$^2$ body mass index (BMI), and signs of grade I dehydration. Constitutional syndrome secondary to neoplasia of gastrointestinal origin was initially suspected, so he was taken to UGIE (**Figure 1**), biopsies were taken, and extension studies such as chest tomography were requested (**Figure 2A**) showing lesions in the tree-in-bud and esophageal obstruction in the middle and distal third of the esophagus (**Figure 2B**). Tuberculosis infection was ruled out with 3 serial sputum smear tests and culture-negatives, a negative enzyme-linked immunosorbent assay (ELISA) test for human immunodeficiency virus (HIV), and blood count within normal limits. The histopathological study (**Figure 3**) of the esophageal biopsy showed a chronic non-necrotizing granulomatous inflammation disease secondary to fungal infection. The Grocott-Gomori's Methenamine Silver (GMS) stain confirmed extracellular yeasts with narrow-based gemmation and "steering wheels" appearance compatible with PCM. He underwent esophageal balloon dilatation and stent placement and was started on treatment with itraconazole capsules of 100 mg every 24 hours a day for 6 months, improving dysphagia and respiratory symptoms. However, there is no post-treatment imaging follow-up record.

## DISCUSSION

Paracoccidioidomycosis is a systemic disease endemic in South America, especially in Santander, Colombia. This disease predominantly affects men between 30-50 years old, but it most often affects farmers, whose primary infection is pulmonary, where the fungus is previously inhaled in mycelial form. The systemic involvement will depend on the host's immune response. This disease has three clinical presentations: acute, subacute (symptoms occur approximately 45 days after exposure), and chronic (more frequent in adults and characterized by a reactivation of the primary infection that could have been acquired months or even years earlier, and its symptoms depend on the affected organ). Disseminated manifestation, especially esophageal,

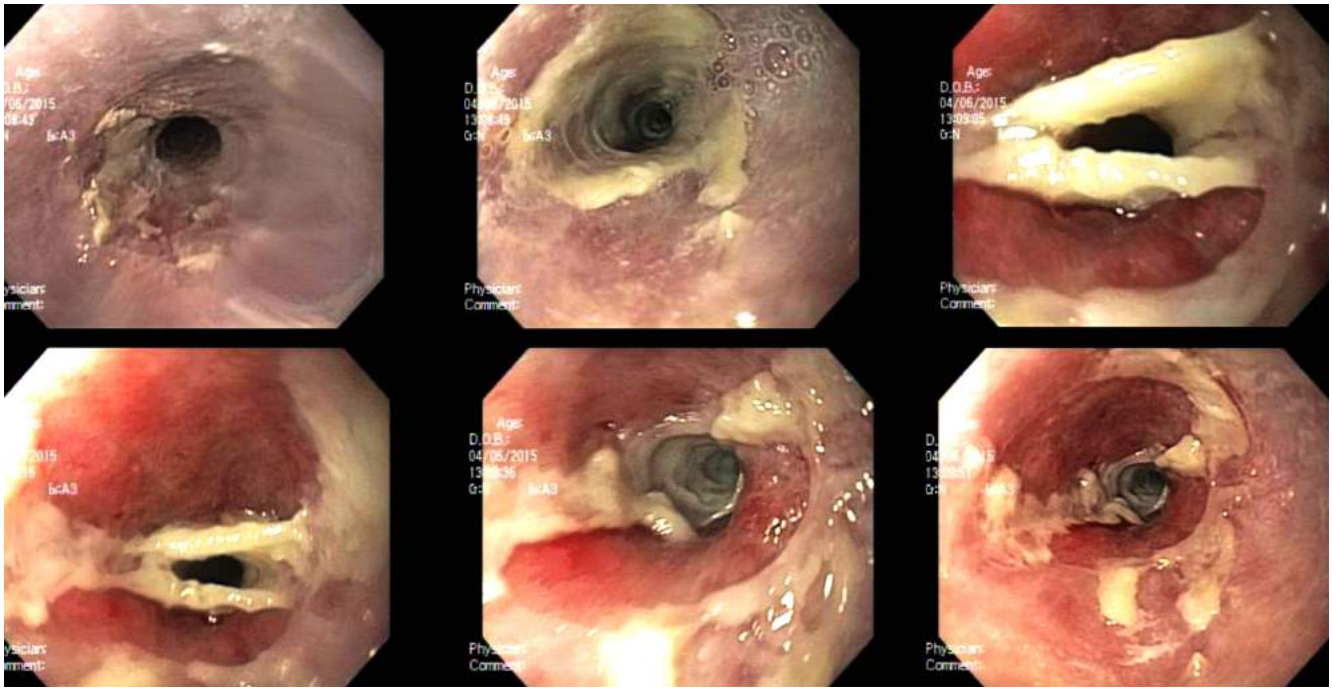

**Figure 1.** Endoscopic findings, esophageal stricture obstruction, and white endoluminal membranes without ulceration or bleeding.

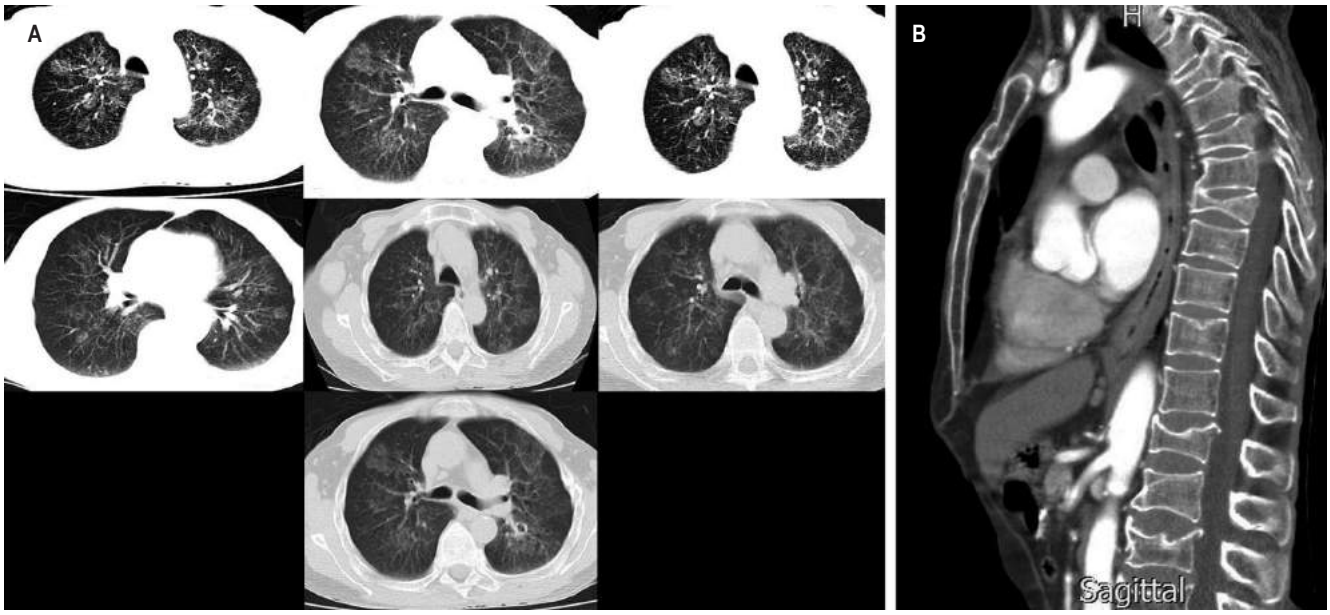


**Figure 2. A.** High-resolution chest tomography showing generalized interstitial parenchymal involvement with hyperdensities in the tree-in-bud. **B.** Sagittal chest tomography showing esophageal obstruction in the esophagus in the middle and distal third.

is rare in immunocompetent individuals. In these patients, the mucous membranes with greater involvement are found in the oral and the laryngeal cavity. However, very few reports exist in the literature[9-12]. Diagnosis methods range from histological studies and fungal culture to antibody detection[6,13-16].

Several risk factors for contracting the infectious agent were considered in this case, including the geographic area where the patient resides or works and gender. Its age group predisposed him to debut with reactivated chronic disease. In addition to the clinical evolution chronicity, he presented constitutional syndrome evidenced by involuntary weight loss; pulmonary involvement, manifested by cough without expectoration and occasional dyspnea, possibly explained by pulmonary parenchymal involvement (**Figure 2**), and esophageal involvement, characterized

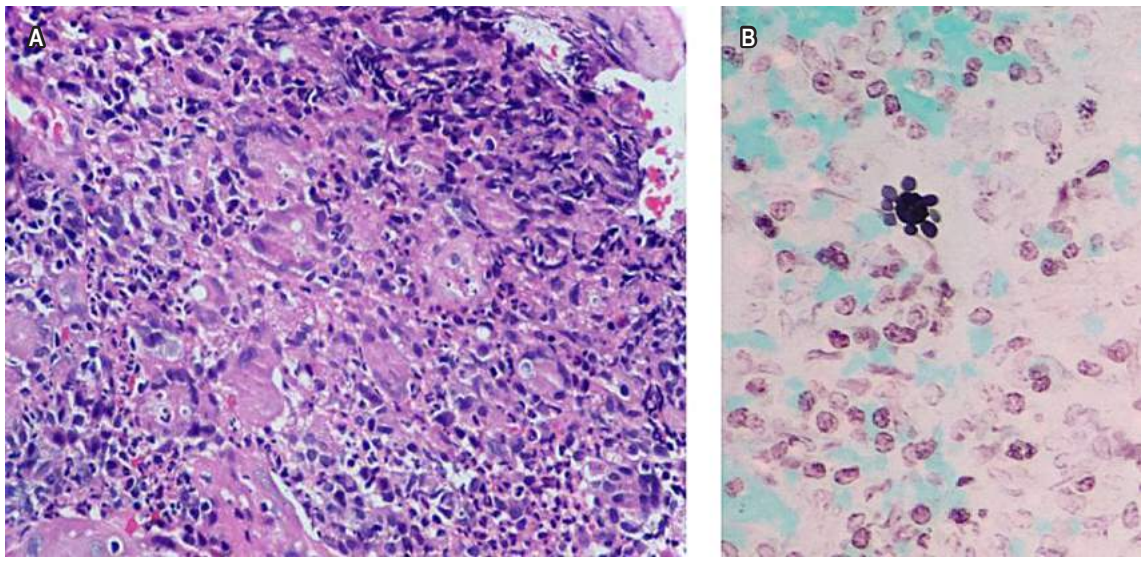


**Figure 3. A.** Esophageal biopsy, hematoxylin/eosin 40x. **B.** Esophageal biopsy, GMS stain, 40x. Microphotographs provided by Dr. Isabel Bolívar, Pathologist, FOSCAL.

by progressive dysphagia, which in turn was confirmed through imaging findings showing endoluminal involvement and endoluminal stenosis (**Figures 1** and **2B**). The treatment for this disease consists of azoles, especially itraconazole, which has better tolerance, absorption, and fewer adverse effects. This is the treatment that was administered to the patient, showing a subsequent clinical picture improvement. Sulfonamides and amphotericin B, the latter, may be prescribed for severe cases[17]. Studies have shown that the presence of comorbidities and pulmonary fibrosis is associated with high morbimortality due to exacerbation of the underlying disease and intrinsic complications of the infection, which is why the patient's prognosis is good since there is no pathological history and there is no evidence of pulmonary fibrosis in the requested lung tests[18,19].

## CONCLUSION

In conclusion, it is necessary to consider the geographic area, gender, occupation, and the time of evolution of the signs and symptoms of the patient's clinical picture must be considered for a PCM diagnostic approach. All of the above must be supported by imaging tests (in our case, chest tomography and UGIE with a histological biopsy study) and antifungal pharmacological management, which consists of azoles. Itraconazole is an excellent option due to its tolerance, absorption, and reduction of adverse drug effects. Sulfonamides and amphotericin B can improve the patient's clinical evolution. This entity must be considered within the differential diagnoses in people presenting the same symptomatology, whose final prognosis will depend on the degree of pulmonary fibrosis and associated pathological history.

### Conflicts of Interest

The authors have no conflicts of interest to declare.


### Acknowledgments

To the people who made possible the dissemination of this case report.


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Case report

# Retrorectal Cystic Hamartoma (Tailgut cyst): Case Report and Literature Review

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## Abstract

Retrorectal Cystic Hamartoma (*tailgut cyst* [TGC]) are uncommon, multiloculated congenital tumors derived from embryonic post-anal or tail gut remnants often undiagnosed due to their rare incidence, anatomical location, and non-specific clinical presentation.

We presented a 21-year-old patient with a perianal fistula history who underwent surgery. Nonetheless, she showed recurrence, and the cystic hamartoma was found in the resonance imaging. Therefore, the definitive treatment was complete resection of the lesion by posterior approach (Kraske-Mason).

## Keywords

Cystic hamartoma, retrorectal tumor, benign tumor.

## INTRODUCTION

Retrorectal cystic hamartomas (tailgut cysts) are uncommon, multiloculated congenital tumors derived from embryonic post-anal or tail gut remnants. In the presacral space is the junction of the hindgut and neuroectoderm, and the totipotent cells found there can cause several types of tumors[(1)]. Retrorectal tumors are rare and have an incidence of approximately 1:40 000[(2)]. Cystic hamartomas are a small proportion of these retrorectal tumors, and most publications include one or a few cases. The largest published report is a series of 53 cases collected over 35 years by Hjermstad and Helwig at the Armed Forces Institute of Pathology. This issue highlighted that only 2 out of 53 cases were accurately diagnosed from the outset[(3)]. Cystic hamartomas are located in the retrorectal space or anterior sacral space. The upper limit is the perianal skin fold; the lower limit is the levator ani and, laterally, the ureters and iliac vessels[(2)].

Although found at any age, most cystic hamartomas are more frequent in women between 40 and 60 (3:1 ratio). They are multicystic and frequently asymptomatic (26%-50%), but some patients present with symptoms including rectal prolapse, tenesmus, constipation, urinary symptoms, retrorectal abscess, and low abdominal pain[(4,5)]. If not removed early, the most common complications include

infection, fistula development, and malignant transformation. Congenital lesions are two-thirds of presacral tumors, including developmental cysts, sacral meningocele, cystic lymphangioma, sacral chordoma, and teratomas[1,6].

Surgical excision with negative margins is the definitive treatment. Due to its location, posterior surgery has been the most frequent, but laparoscopic and minimally invasive transanal surgeries have also been reported[7,8].

## CASE PRESENTATION

A 21-year-old male patient was evaluated in 2018 for a perineal abscess that drained to the skin and remained with an intermittent outflow of seropurulent material. A perianal fistula was found during the examination. He brought a colonoscopy in which a secondary anal fistula orifice was reported at the right anterolateral level and 3 cm from the anal margin, in addition to two rectal polyps resected with polypectomy loop and the rest colonoscopy up to the distal ileum was normal. The pathology showed that they were juvenile polyps in the rectum. Additionally, he brought a soft tissue ultrasound that showed a fistulous tract at the right lateral level. The patient was referred for surgery, but he was unable to do it at that time. He was assessed 3 months later, and two secondary orifices were found at the right anterolateral and posterolateral levels. When the surgery was performed a month later an abscess was also found which was drained during the procedure.

Postoperatively, the surgical wound failed to heal, and a mass was palpated 5 cm from the anal margin. Magnetic resonance of the pelvis showed a retrorectal multilobulated lesion extending to S-4 without involving the sacral bone in contact with the rectum, possibly a cystic hamartoma, and persistence of a fistulous tract at the right posterolateral level (**Figure 1**). In June 2019, he was taken to surgery, and the lesion was resected posteriorly (Kraske-Mason), and a fistulectomy was performed. Involvement of the rectal mucosa was found, so a colostomy was performed to protect it, which was closed 3 months later. Pathology indicated fragments of fibroconnective stroma with central cavitated lesion with extensive areas lined by epithelium alternating between squamous and columnar. In some areas devoid of epithelium, there was a dense inflammatory infiltrate, predominantly lymphohistiocytic (**Figures 2** and **3**). Currently, the patient has no evidence of relapse and has good continence.

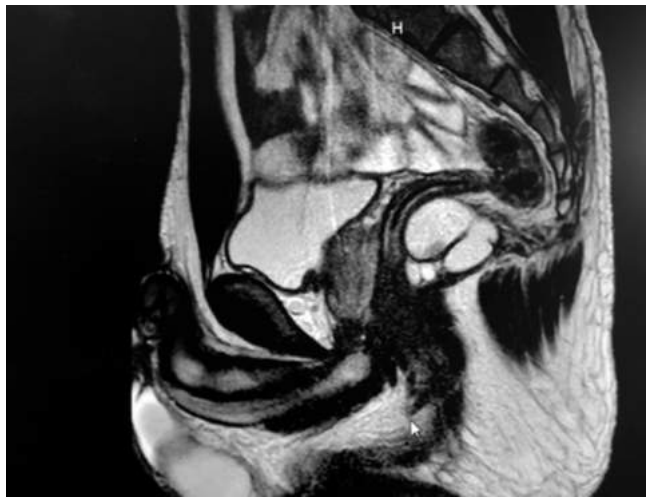

**Figure 1.** Retrorectal cystic lesion. The midline measures 5.7 cm anteroposterior x 3.6 cm x 4.2 cm, multiloculated with complete partitions and high signal intensity content in T1 sequences.

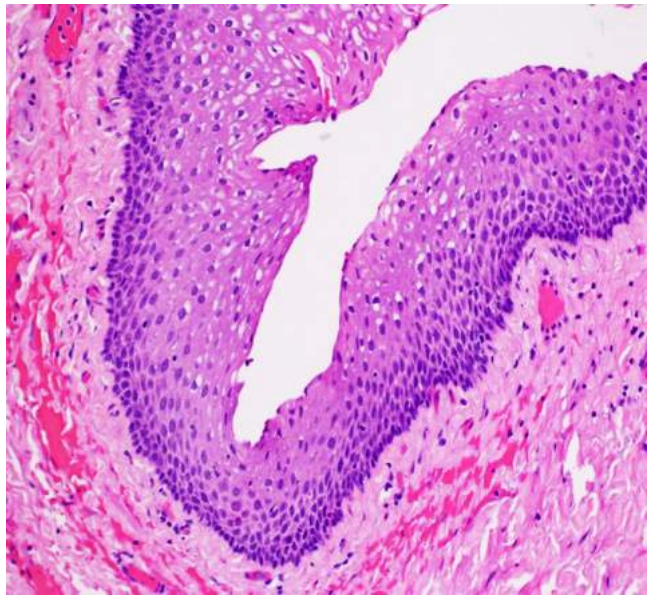

**Figure 2.** Retrorectal cystic hamartoma. The image shows the cyst wall area covered by stratified squamous epithelium resting on a fibroconnective stroma. Hematoxylin and eosin (H&E) stain. 20X magnification.

## DISCUSSION

Although the origin of the retrorectal cystic hamartoma is unknown, the lining cells and its location in the presacral space led to the hypothesis that it originates in the remnant of the tail of the hindgut. Between 28 and 35 days of embryogenesis, the embryo possesses a true tail, and the hindgut extends into this tail, hence the name tailgut for this entity. The intestine is distal to the future anus and normally undergoes involution later in embryogenesis. A remnant of this structure is thought to result in cystic hamartoma[9].

The differential diagnosis of cystic hamartoma includes epidermoid cysts, dermoid cysts, duplication cysts, and cys-

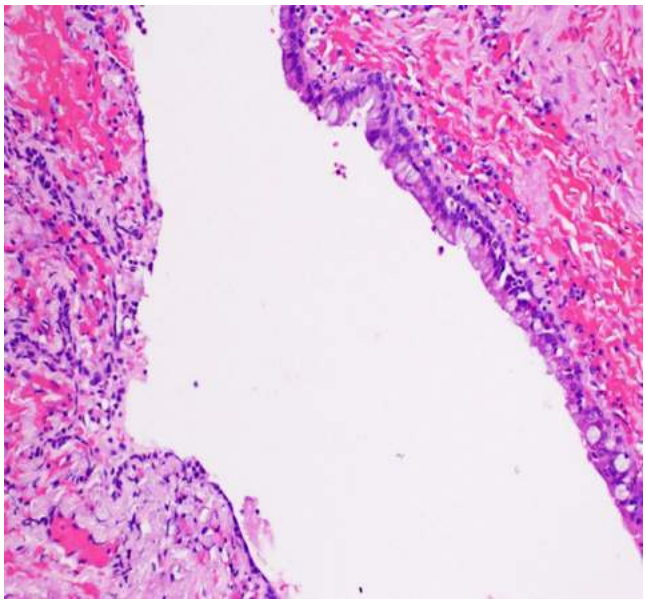

**Figure 3.** Retrorectal cystic hamartoma. In the upper right corner of the image is the cyst wall covered by the columnar epithelium with some goblet cells. In the lower and left portions of the image, the lining epithelium is a simple cubic type. H&E Coloring. 20X magnification.

tic teratomas. The underlying epithelium in the epidermoid cyst is a stratified squamous epithelium. Skin remnants on the cyst's wall are found in the dermoid cyst. In rectal duplication, the cysts are covered by the intestinal mucosa, there are crypts and villi, smooth muscle is found in their wall, and they are not multiloculated. Cystic hamartomas are multilocular; the underlying epithelium is cylindrical, transitional, squamous, or a combination thereof, with or without a stratified squamous component. Dispersed bundles of smooth muscle fibers are generally found on the wall of the cysts, but no submucosal or myenteric neural plexus is found[3,10,11].

Magnetic resonance imaging is the cornerstone for diagnosis and surgery planning. In magnetic resonance imaging, a cystic hamartoma shows a low-intensity signal in T1 and a high-intensity signal in T2, although this may vary if the content is proteinaceous, hemorrhagic, or mucinous. Magnetic resonance imaging is useful for differentiating retrorectal cystic lesions and predicting malignancy[4].

Complete surgical resection of retrorectal cystic hamartomas is recommended to decrease complications such as recurrence, infection, rectal fistula formation, bleeding, and malignant transformation. Malignant degeneration occurs between 2% and 13%, and the most frequently found tumors are adenocarcinomas, squamous carcinomas, neuroendocrine tumors, and sarcomas[7,12].

The surgery approach is based on the size of the tumor and the correlation with the pelvic floor (levator ani). The posterior approach is enough for infra-elevator tumors. For supralevator tumors, the above approach is necessary. The posterior approach is enough for cysts with infra- and supralevator extensions if they are small (< 5 cm). The anterior approach is advised when the cysts are between 5 and 10 cm. Cysts larger than 10 cm may be dumbbell-shaped multilocular, so a combined approach[13] is recommended. Laparoscopic[7] or robotic[14] resections have also been attempted, as well as endoscopic transanal microsurgery[15]. Surgery complications include delayed healing, pelvic floor, and sexual dysfunction. Complications are minor in the posterior approach[12].

## CONCLUSION

Retrorectal space tumors are rare and heterogeneous due to the diversity of tissues arising from embryonic remains in this topography. Given the lack of guidelines and paucity of information in the literature, this report aims to emphasize the importance of considering hindgut cyst as a differential diagnosis for presenting symptoms for earlier diagnosis and avoiding progression to carcinoma.

### Authors' contribution

All the authors contributed to writing the article, describing the case, discussing it, and verifying the bibliographic references.

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Case report

# Pyloric Exclusion with Ovesco (Over-the-scope-clip) Device for Jejunal Fistula in Duodenal Obstruction of Malignant Etiology

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## Abstract

A 25-year-old man diagnosed with a non-seminomatous germ cell tumor was admitted to the emergency department for diffuse abdominal pain associated with bloating and multiple emetic episodes. Due to the clinical suspicion of intestinal obstruction, a contrasted abdominal tomography was performed, showing an obstruction in the third duodenal portion resulting from extrinsic compression caused by multiple retroperitoneal conglomerates.

Surgical time was scheduled for a gastric bypass surgery where gastrojejunostomy was performed using conventional technique. On the fifth postoperative day, he presented clinical deterioration due to febrile episodes, abdominal pain, and tachycardia. A new abdominal tomography was performed, reporting an intra-abdominal collection of pus on the left flank of 12 x 12 x 5 cm secondary to the jejunal fistula process. Hence, percutaneous drainage management of the collection was performed by interventional radiology and drainage catheter placement. In addition, an EGD was performed to conduct a pyloric exclusion technique with an Ovesco (*over-the-scope-clip*) device for managing the jejunal fistula, which was technically successful.

A gastrointestinal tract X-ray was performed as a follow-up during the postoperative stage, showing no pyloric continuity with adequate patency of the gastrojejunostomy. In addition, a contrasted abdominal CT scan showed a decrease in the intra-abdominal collection without extravasation of the contrast medium.

This case outcome suggests the Ovesco device may be helpful in proximal GI fistulas cases, especially in patients with multiple comorbidities or poor general conditions who may benefit from minimally invasive procedures decreasing the risk of fatal outcomes.

## Keywords

Ovesco clips, GI fistula, GI perforation, endoscopic closure.

## INTRODUCTION

Ovesco (over-the-scope) clips, also known as *bear-claw*, are endoscopic clipping devices for endoscopic tissue approaches[(1)], originally used for fistula and perforation closure of the upper gastrointestinal tract and later used for bleeding cases, submucosal tumor resections, and esophageal stent fixations[(2)], thanks to its gripping, fixation, and easy application[(1,2)]. Given the small number of reports in the literature on its use in pyloric exclusion cases with this device, we share this patient's case with duodenal obstruction due to extrinsic compression concerning a retroperitoneal conglomerate. This patient underwent gastrojejunostomy with derivative purpose. Subsequently, a jejunal fistulous process and intra-abdominal collection required percutaneous drainage, so pyloric exclusion was performed

with the Ovesco device, resulting in a good evolution and closure of the fistulous process.

## CASE REPORT

A 25-year-old man with a nonseminomatous germ cell tumor diagnosis. He was admitted to the emergency room for intestinal obstruction due to diffuse abdominal pain associated with abdominal distension and multiple emetic episodes. A contrast abdominal tomography showed an obstruction of the third duodenal portion by extrinsic compression secondary to multiple retroperitoneal conglomerates (**Figure 1**).

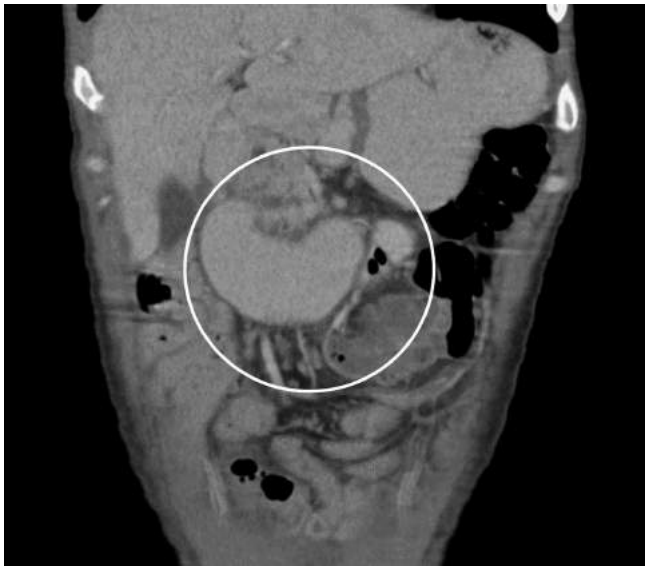

**Figure 1.** Compression of the third duodenal portion by retroperitoneal conglomerate.

The patient was taken for open gastric bypass surgery with intraoperative findings of a large multilobulated solid retroperitoneal mass of 25 x 20 cm that displaced the duodenum and pushed the jejunal loops down, the loop conglomerates to the right hypochondrium, involving the duodenum and the first jejunal loops, generating a mechanical obstruction by adhesions. In addition, the jejunal loop was 40 cm from the Treitz angle, infiltrated by a tumor with partial obstruction, so a laterolateral isoperistaltic gastrojejunostomy was performed with a 200 cm food loop measured from the ileocecal valve, and adhesions of involved jejunal loops release.

By the fifth postoperative day, there was clinical deterioration due to febrile episodes, abdominal pain, and tachycardia, so a new abdominal tomography was performed, reporting an intra-abdominal collection in the left flank of 12 x 12 x 5 cm secondary to the jejunal fistulous process (**Figure 2**).

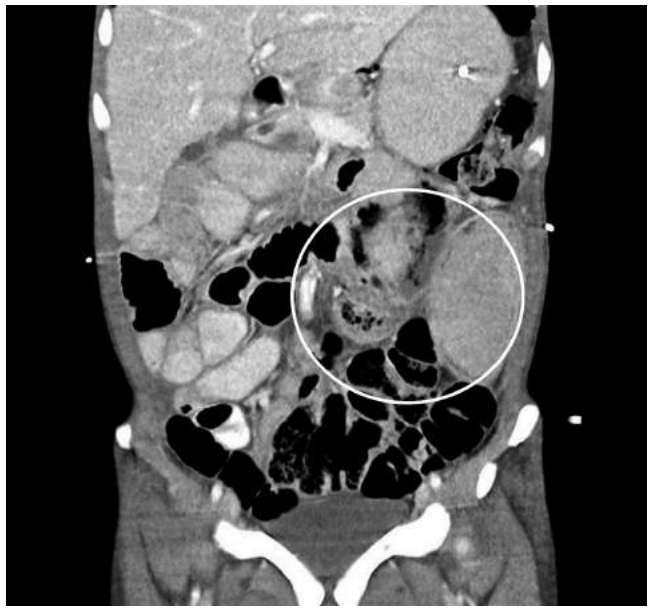

**Figure 2.** Jejunal fistula with collection on the left flank.

Percutaneous drainage of the collection was performed by interventional radiology and drainage catheter placement, in which 150 mL of purulent and intestinal contents were obtained, thus, controlling the infectious process and optimizing the patient's clinical condition. Based on the intraoperative findings and the laterolateral gastrojejunostomy, 3 days after the percutaneous drainage, the patient underwent endoscopic treatment of the proximal jejunal fistula through pyloric exclusion to reduce intraluminal content flow through the affected loop, concomitantly with multimodal pharmacological management with proton pump inhibitor (PPI), opioid, antidiarrheal, and parenteral nutrition. Given the patient's comorbidities and trying to find the least invasive procedure, the Ovesco device was used to perform the pyloric exclusion, considering an appropriate functionality of the gastrojejunostomy, which was technically successful (**Figure 3**).

On the fifth day after the endoscopic procedure, an imaging follow-up of the digestive tract confirmed no pyloric continuity with adequate patency of the gastrojejunostomy. A contrasted abdominal tomography showed a decrease in the intra-abdominal collection without contrast medium extravasation (**Figures 4** and **5**).

Given the patient's good clinical evolution, control of the infectious focus, and intestinal leakage evidenced through imaging, oral administration was started on the sixth postoperative day with adequate tolerance. Therefore discharge was advised on the tenth day of hospital stay. After 15 days, an outpatient follow-up was performed. The patient reported that he continued showing good oral tolerance and appropriate bowel transit, with no episodes of fever during his homestay.

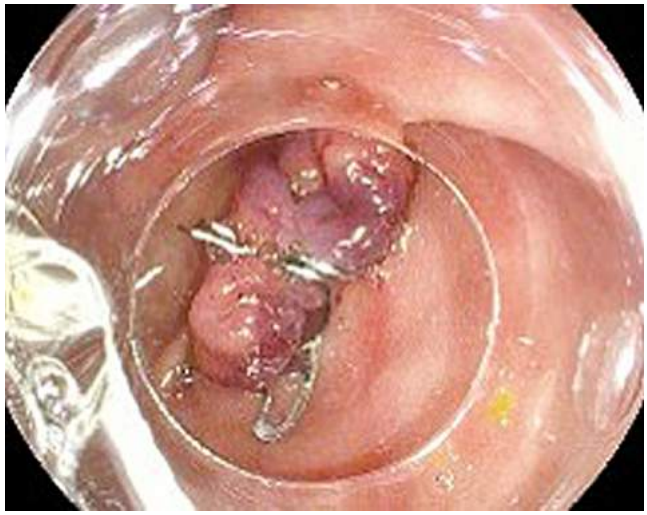

**Figure 3.** Pyloric exclusion with Ovesco 12/6 GC device.

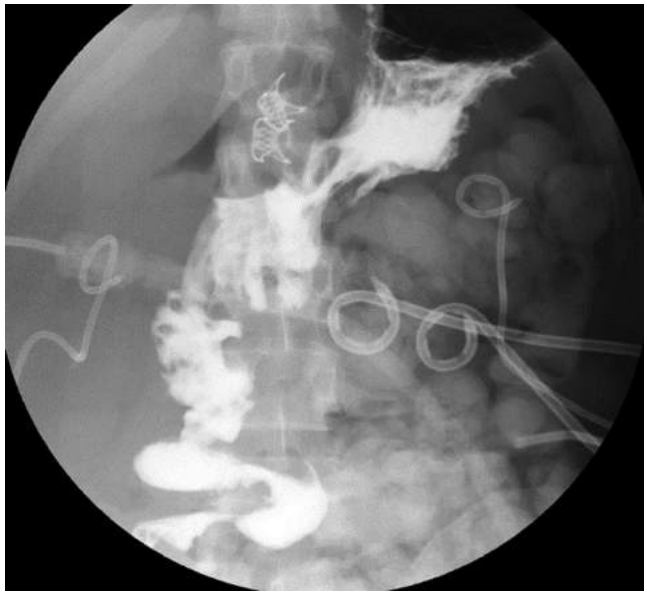

**Figure 4.** X-ray of digestive tract showing pyloric exclusion with adequate contrast passage through gastrojejunostomy.

## ENDOSCOPIC TECHNIQUE

In the endoscopy room, under anesthesiologist-assisted sedation, easy passage through the cricopharyngeus muscle was performed. Lumen, caliber, and normal mucosa were observed up to the distal third, and the cardia was passable at 38 cm.

The stomach was explored up to the pylorus, where an abundant gastric mucous lake and permeable gastrojejunostomy on the anterior wall were observed, the pylorus

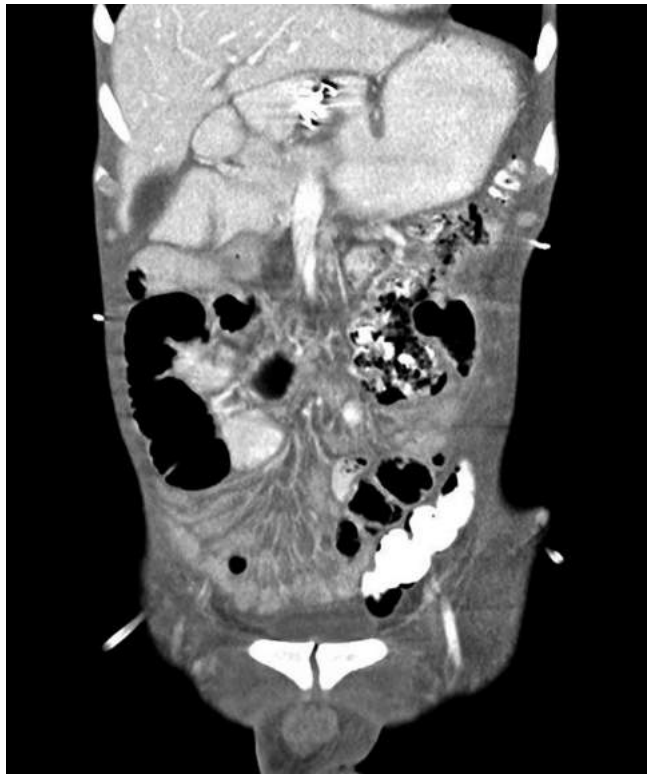

**Figure 5.** Contrast abdominal tomography with collection improvement without contrast extravasation in the gastrointestinal tract.

was identified, and using a suction technique, the edges of the pylorus were tackled with an Ovesco 12/6 GC clip. A permeable angle was observed during the examination, so the second Ovesco 12/6 GC clip was placed, occluding the pylorus in its entirety as part of the indicated pyloric exclusion.

## DISCUSSION

Ovesco clips are made of a nickel and titanium alloy called *nitinol*, which belongs to the so-called *shape memory alloy*, so they have had a great variability of uses since their discovery by the U.S. Navy around the 1950s[1,3].

The introduction of Ovesco devices for human use dates back to 2007, with approximately 10 case series published with about 79 patients treated for dehiscence of gastrointestinal anastomosis, fistulas, and gastrointestinal bleeding, and demonstrated up to 65% efficacy for fistula cases[4].

The evolution regarding the use of these clips has been so important that, nowadays, they are not only part of the armament of the digestive tract and gastroenterology medical equipment for the closure of fistulas and perforations, but also the literature has described cases in which much

more complex defects of the luminal gastrointestinal tract are treated, even during multimodal closure of defects of the abdominal wall. However, perhaps one of the most established uses today is controlling bleeding ulcers in difficult positions since its barrel-shaped design with a transparent lid can suction bleeding lesions. Furthermore, its advantages over other clips include a higher gripping force (8 to 9 Newtons) when released and a gripping capacity (defect closure, orifice closure, and edge facing) of up to 30 mm[1,4,5].

This wide range of uses makes it important for endoscopists to understand the scenario for monitoring the pathology requiring treatment with Ovesco clips. Hence, we have decided to present this case of pyloric exclusion with this device, even though duodenal perforation –whether iatrogenic or traumatic, remains the main indication for performing a pyloric exclusion, similar to duodenal diverticulization and pancreatoduodenectomy according to the lesion degree[6], particularly due to the good prognostic factors for the closure of the fistula in our case –a low output fistula and a previous gastrointestinal bypass (gastrojejunostomy), decreasing intestinal transit through the affected loop.

## CONCLUSION

As reported in the literature, although clinical experience is limited, Ovesco is a safe and effective device for closing perforations, anastomotic leaks, and bleeding from the gastrointestinal tract; however, its therapeutic efficacy in chronic fistulas due to associated fibrosis is lower[4,7]. Further studies are needed to determine the safety and efficacy of Ovesco clips in all scenarios in which they can be used and establishing a management algorithm that includes treatment with the Ovesco clips is also required.

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Case report

# Neuroendocrine Tumor Polypoid Presentation: Case Report and Literature Review

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## Abstract

Diagnosis of rectal neuroendocrine tumor (NET) has increased due to the implementation of colonoscopies as a screening method. Most rectal NETs are less than 1cm at diagnosis time, confined to the submucosa, and well differentiated. They generally have a benign course and are treated mainly using endoscopic methods. Metastases are rare and depend on tumor size and other factors such as submucosal invasion, lymphatic spread, and histologic classification, which will determine the prognosis and treatment. We present a case of a rectal neuroendocrine tumor as a polyp during routine endoscopic screening and a review of the current literature.

## Keywords

Neuroendocrine tumor, rectal neoplasia, polyp.

## INTRODUCTION

In the last decades, neuroendocrine tumors (NETs) have been diagnosed more frequently through the implementation of colonoscopy and complementary imaging studies in gastrointestinal diseases. They have distinctive histological, biological, and clinical characteristics[1]. These tumors originate in neuroendocrine cells from the endoderm along the mucosa and submucosa of the gastrointestinal tract[1]. They can synthesize and secrete monoamines, peptides, and hormones and transmit and receive nerve signals[2]. Lubarsch discovered these tumors in 1888. Later, Obendorfer named these tumors carcinoid (carcinoma-like). Nowadays, they are known as *neuroendocrine tumors* (NETs) according to their etiology, behavior, and location[3,4].

NETs constitute 0.5% of all malignant cancers and 2% of malignant tumors in the gastrointestinal tract[2]. They have an incidence of approximately 0.86 per 100,000 inhabitants, frequent in Black males and more prevalent in the Asian population[4-7]. Rectal NETs account for 18% of total NETs and 27% of gastrointestinal NETs[5].

Clinical presentation is nonspecific. Rectal bleeding, functional gastrointestinal disorders, abdominal pain, and carcinoid syndrome may be present in 10% of cases[6,7]. However, nearly half of the patients are asymptomatic and are diagnosed in screening colonoscopy or other colorectal

pathology studies[7-9]. They are usually found as single small polypoid tumors, metastatic disease is rare, and tumor size and invasion determine the prognosis of the disease[10-13].

In the latest digestive tumor classification edition (fifth edition, published in 2019) of the World Health Organization (WHO), the classification of well-differentiated NETs or poorly differentiated neuroendocrine tumors with small cell and large cell subtypes remains[14]. Histological classification is based on the mitotic and Ki-67 indexes recorded at tumor hot spots. During cell division, the Ki-67 protein is found in the cell nucleus. The proportion of Ki-67-positive tumor cells (Ki-67 index) correlates with cell proliferation, clinical course, and prognosis[2,14-16]. The 2019 WHO NET classification is described in **Table 1**.

**Table 1.** Classification of Neuroendocrine Tumors, WHO, 2019[16]

| | Ki-67 Index (%) | Mitotic index/10 HPF |
|---|---|---|
| Well-differentiated neuroendocrine neoplasms | | |
| - Grade 1 (Low) | < 3 | < 2 |
| - Grade 2 (Intermediate) | 3-20 | 2-20 |
| - Grade 3 (High) | > 20 | > 20 |
| Poorly differentiated neuroendocrine neoplasms | | |
| - N/A (no numerical assignment: high grade) | > 20 | > 20 |

HPF: high-power fields; N/A: not applicable. Taken and adapted from: Lloyd RV, Osamura RY, Kloppel G, Rosai J. WHO Classification of Tumors of Endocrine Organs. 5th edition. WHO; 2019.

In general, well-differentiated tumors are low or intermediate-grade tumors. Well-differentiated high-grade NETs are less frequent but have a better prognosis than poorly differentiated NETs, a fundamental classification to know the course of the disease and define the most appropriate treatment for the patient[1,12-14]. Below is a case of a neuroendocrine tumor as a polyp in the rectum.

## CASE PRESENTATION

This is an 88-year-old female patient with a medical history of hypertension, hyperlipidemia, type II diabetes *mellitus*, breast cancer in remission, and grade I internal hemorrhoids. She sought medical assistance for a long-standing clinical picture characterized by constipation with no other gastrointestinal symptoms. The patient underwent a colonoscopy where a polyp was evidenced in the upper third of the rectum, 12 cm from the anal edge of 2 cm in diameter (**Figure 1**). A polypectomy was performed, and a sample was sent for pathologic study, which reported morphologic findings compatible with a well-differentiated neuroendocrine tumor. Tumor size was 1 cm in greatest dimension, submucosal location, and lateral and deep negative resection margins for tumor involvement (**Figures 2** and **3**). Immunohistochemistry staining showed a well-differentiated neuroendocrine tumor with a low mitotic rate with Ki-67 < 1%. Outpatient follow-up with colonoscopy check-up in 1 year was indicated.

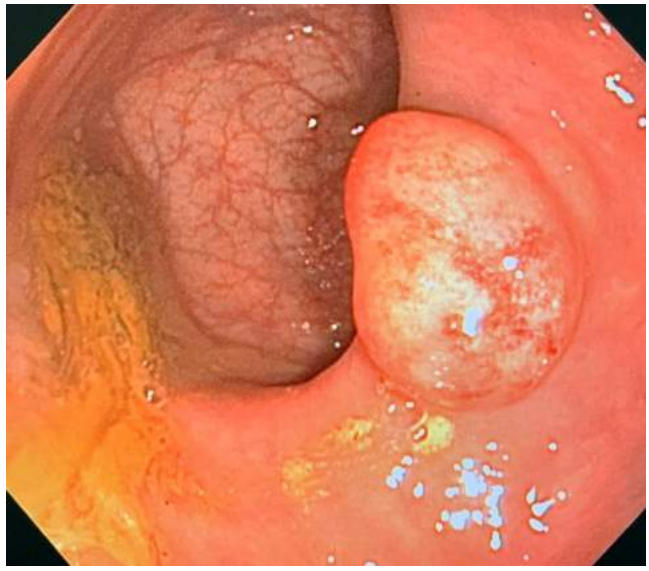

**Figure 1.** Colonoscopy image showing a neuroendocrine polyp in the upper third of the rectum, 2 cm in diameter.

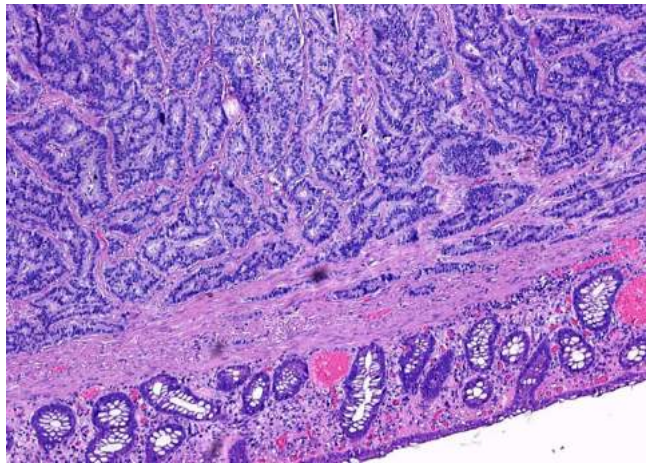

**Figure 2.** The colonic cut shows a submucosal lesion with an organoid pattern (4x). Hematoxylin and eosin (H&E) stain.

## DISCUSSION

In recent years, the diagnosis of rectal NETs has increased thanks to colonoscopy as a screening method for colon can-

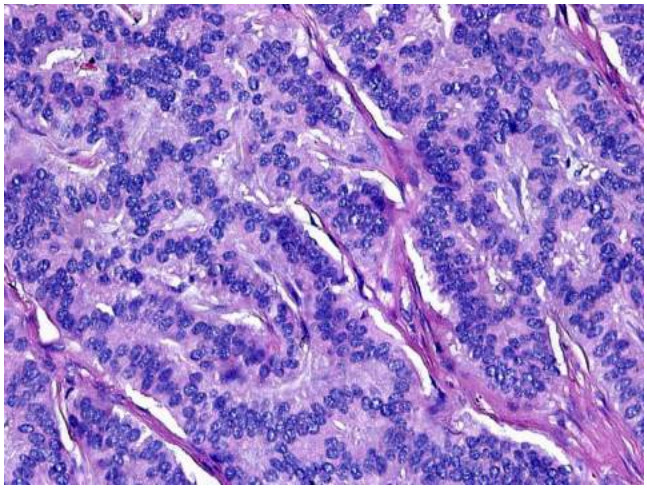

**Figure 3.** The cut reveals a submucosal lesion composed of monotonous cells with a salt and pepper chromatin appearance (40x). Hematoxylin and eosin (H&E) stain.

cer and the implementation of other imaging studies of the gastrointestinal tract[5]. In a British cohort of 13,061,716 patients who were screened with fecal occult blood, 259,765 of the participants obtained abnormal results, and 216,707 screening colonoscopies were performed; 146 patients were diagnosed with NETs, and it was evidenced that the diagnostic rates per 100,000 colonoscopies were 29 rectal, 18 colonic and 11 ileal NETs[17].

There is a tendency to delay the diagnosis of all types of NETs, which can take up to 5 years, related to their asymptomatic clinical presentation[17,18]. The vast majority (93%-100%) of rectal NETs are < 1 cm in size at diagnosis, limited to the submucosa, well-differentiated, and generally have a benign clinical course[14,19].

The risk of metastatic disease of NETs increases with tumor size, which is up to 60%–80% when the tumor is ≥ 2 cm[20]. Tumor size > 10 mm and muscle and lymphovascular invasion are independently associated with an increased risk of metastasis[20,21]. However, there is a higher detection of the disease in the early stages related to a lower risk of metastasis. A retrospective study that evaluated 48 patients showed that stage I tumors (TNM) accounted for 78.8% and were the most frequent. At the same time, distant metastases had a lower incidence[22], which is related to the findings of a recent systematic review in which it was evidenced that only 5% measured more than 20 mm at the time of diagnosis[20.21]. Endoscopic ultrasound and magnetic resonance imaging (MRI) are used to evaluate the tumor's exact size, extension into the rectal wall, and the condition of the perirectal lymph nodes, facilitating better treatment selection and improving the complete resection rate[10].

Various endoscopic procedures can be used in rectal NET resection, including conventional polypectomy, endoscopic mucosal resection, and endoscopic submucosal dissection[10,19]. According to the European Neuroendocrine Tumor Society consensus, well-differentiated rectal NETs below 1.5 cm without invasion of muscularis propria or lymph node involvement can initially be treated endoscopically[10,20]. Transanal excision should be considered when the margins of endoscopic resection are positive[19]. The distance between the tumor and the anal canal and the potential of the tumor to cause an obstruction should be considered when choosing the most appropriate treatment[19-21]. When there are positive locoregional lymph nodes or invasions of the muscularis propria, more radical methods such as excision with low anterior resection or abdominoperineal resection should be chosen[20,21].

According to the European Neuroendocrine Tumor Society (ENETS), patients should be monitored after the complete resection of rectal NETs, as described in **Table 2**.

**Table 2.** Follow-up and surveillance indications per tumor size and grade according to ENETS[6,10,14,21]

| Size | Grade | Follow-up |
|---|---|---|
| < 1 cm | 1-2 | No surveillance needed |
| < 1 cm | 3 | Annual colonoscopy for 5 years |
| 1-2 cm | N/A | Colonoscopy, ultrasound, and MRI at 12 months, then colonoscopy every 5 years |
| > 2 cm | 1-2 | Colonoscopy and annual MRI for 5 years |
| > 2 cm | 3 | Colonoscopy and MRI every 4 to 6 months for the first year, then annually for 5 years |

N/A: not applicable; MRI: magnetic resonance imaging; ENETS: European Neuroendocrine Tumor Society.

Rectal NETs have the best overall survival of all gastroenteropancreatic NETs, largely due to the high incidence of small rectal NETs with no evidence of invasion and an excellent long-term prognosis[21,23].

Localized rectal NETS (T1, N0, M0) have a 5-year survival of 98%-100%, while those with regional (N1) and distant (M1) metastases have a 54%–74% and 15%–37% survival, respectively[5,23,24].

We stress the importance of performing regular endoscopic screening in selected patients, detecting and diagnosing the presence of NETs early to avoid complications related to advanced stages of the disease and, thus, reducing morbimortality rates. When evaluating polyps of the gastrointestinal tract, the diagnosis of NETs should be considered a possibility, and its characteristics should be considered to define prognoses and follow-up.

## CONCLUSION

Thanks to the incursion of colonoscopy as a screening method for colorectal cancer, the diagnosis of rectal NETs has increased. The risk factors that may lead to their appearance are still unknown due to the lack of large epidemiological studies. In general, at the time of diagnosis, tumors are mostly less than 1 cm, well-differentiated, and can be found in polypoid form, as in our case, which gives patients a better long-term prognosis. Given their smaller size, they can be treated endoscopically without any risk. However, histological classification, size, and location must be considered to define the need for more radical treatments. Rectal NETs have better overall survival than all NETs. It is important to continue population screening through endoscopic studies for early detection and treatment of these tumors.

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Case report

# Intestinal Vasculitis and Endoscopic Video Capsule Findings: Case Report and Literature Review

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## Abstract

Systemic vasculitis can affect blood vessels of all sizes, causing necrosis and inflammation. Granulomatosis with polyangiitis (GPA) is a vasculitis of small and medium blood vessels. Clinical manifestations may be local or diffuse in the gastrointestinal tract. We present a patient's case with systemic vasculitis associated with anti-cytoplasmic antibodies (ANCA), myeloperoxidase (MPO) antibodies (microscopic polyangiitis) confirmed through renal biopsy, presenting a 15-day clinical picture consisting of asthenia, adynamia, subjective oliguria, edema of the upper and lower limbs, hyporexia, and melena. The digital rectal examination was positive for melena in the physical examination, later presenting melena with secondary anemization. An endoscopic video capsule was performed, showing findings compatible with enteric vasculitis. During his stay, he presented multisystemic involvement due to renal, pulmonary, neurological, and gastrointestinal involvement, managed in the intensive care unit (ICU), where systemic steroid pulses and hemodialysis started. **Conclusion:** although gastrointestinal vasculitis is a rare complication, it occurs and threats patients' lives. Differential diagnosis should cover other inflammatory diseases, especially Crohn's disease. Gastrointestinal vasculitis early diagnosis significantly influences prognosis, as prompt steroid therapy can change the course of the disease.

## Keywords

Vasculitis, small intestine, capsule endoscopic.

## INTRODUCTION

Granulomatosis with polyangiitis (GPA) is a small- and medium-vessel vasculitis with a preference for the airways and kidneys. It causes fibrinoid necrosis leading to organ dysfunction. Gastrointestinal (GI) involvement is observed in only 5% to 10% of cases and is a poor prognosis factor[(1)]. The small intestine and colon can be affected and cause life-threatening complications.

## CASE PRESENTATION

This is a 64-year-old male patient with a medical history of chronic kidney disease (CKD) diagnosed two months ago, with a 46.6 mL/min/1.73 $m^2$ glomerular filtration rate (GFR). He consulted for a 15-day clinical picture of asthenia, adynamia, subjective oliguria, upper and lower limbs edema, hyporexia, and melena. In his admission physical examination, he was found with a 113/73 mm Hg blood pressure

(BP), 88 beats per minute (bpm) heart rate (HR); during auscultation, decreased breath sounds in the lung bases and rhonchi bilaterally, limbs with grade II edema in the lower extremities and positive rectal examination for a mane.

Admission laboratory tests showed normocytic normochromic anemia (hemoglobin [Hb]: 7.7 g/dL, mean corpuscular volume [MCV]: 80.7 fL, mean corpuscular hemoglobin [MCH]: 25.8 pg), erythrocyte sedimentation rate (ESR): 15 mm/h, serum creatinine: 3.5 mg/dL, and non-nephrotic range proteinuria (1.05 g/24 hours). The urinalysis showed negative nitrites, negative proteins, blood hemoglobin 300 mg/dl, red blood cells 28 per field, leukocytes 10 per field, scarce squamous cells, and scarce bacteria.

Given the patient's clinical picture and his CKD exacerbation, he underwent a urinary tract ultrasound in which an increase in the echogenicity of the right and left renal parenchyma compatible with changes due to acute bilateral nephropathy was found. Thus, he underwent a renal biopsy with an anti-myeloperoxidase (anti-MPO) and anti-proteinase 3 (anti-PR3) antibodies, compatible with rapidly progressive glomerulonephritis crescent formation, positive for anti-MPO. Therefore, the patient was diagnosed with vasculitis associated with antineutrophil cytoplasmic antibodies (ANCA) microscopic polyangiitis (MPA), so treatment with steroids was started. During his hospital stay, he presented a complication of persistent melena with anemia, requiring a transfusion of 2 units of packed red blood cells (PRBCs), so gastrointestinal bleeding was suspected, and an upper and lower gastrointestinal tract endoscopy was performed without relevant findings. However, due to the persistence of overt bleeding originating in the small intestine, an endoscopic video capsule was performed, showing multiple deep, fibrin-covered, transverse ulcers in the distal duodenum and proximal jejunum, with circumferential margin involvement, predominantly on the folds, with evidence of scarce active bleeding, mucosa with congestion and severe edema, with no signs of necrosis (**Figure 1**). Given the previously described findings, the patient was diagnosed with enteric vasculitis. Due to his clinical condition, high surgical risk, and associated complications, continued systemic management was decided to control his disease and its gastrointestinal manifestation.

During the hospital stay, he presented a torpid evolution because of persisting multisystemic compromise due to renal, pulmonary, neurological, and gastrointestinal involvement, requiring intensive care unit (ICU) treatment, where systemic steroid pulses and hemodialysis were initiated. The patient did not respond to multidisciplinary management and died 28 days after admission.

## DISCUSSION

Systemic vasculitis can affect blood vessels of all sizes, causing necrosis and inflammation. The disease's extent and clinical course depend on the affected vessel's size and location. Intestinal manifestations are rare and may be indiscernible from those of mesenteric ischemia caused by emboli or thrombosis[2].

Clinical presentations may be local or diffuse in the gastrointestinal tract, resulting in nonspecific paralytic ileus, mesenteric ischemia, submucosal edema and hemorrhage or intestinal perforation, or stenosis. In addition, they may lead to anemia and hypoproteinemia, abdominal pain, and ulcers[3].

Radiological findings in various types of vasculitis often overlap, so the possibility of this pathological process should be considered whenever mesenteric ischemia occurs in young patients, is seen in unusual locations, tends

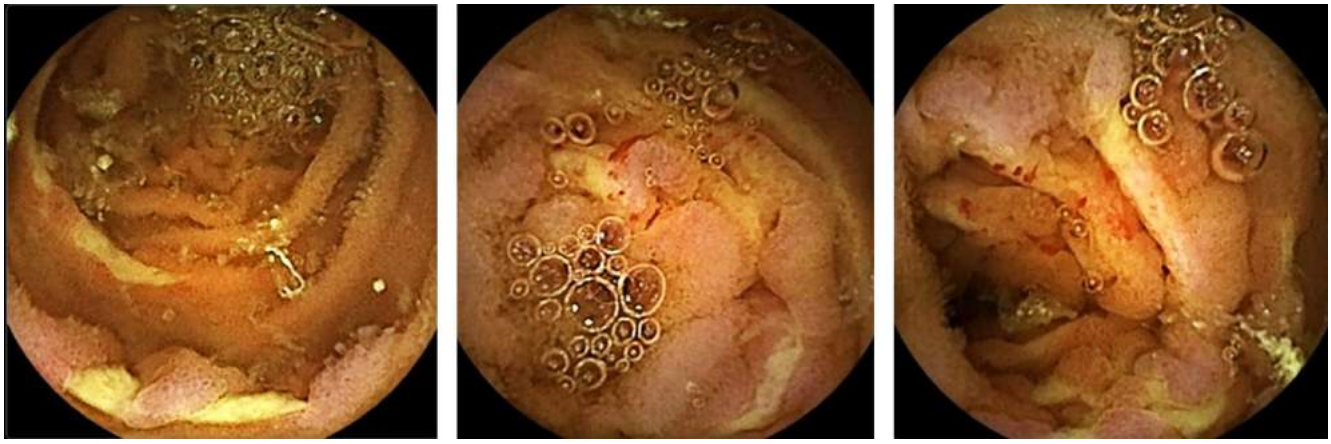

**Figure 1.** Multiple deep ulcers were observed, fibrin-coated with circumferential margin involvement and evidence of scarce active bleeding. Mucosal tissue with congestion and severe edema, without signs of necrosis.

to involve the small and large bowel concomitantly, and is associated with systemic clinical manifestations.

Capsule endoscopy has now been used to explore the entire small bowel. In addition, it is especially useful in treating occult and overt obscure gastrointestinal bleeding. Furthermore, it should be performed in all patients with this diagnosis after upper endoscopy and colonoscopy with ileonoscopy, performed by an expert examiner, do not find the cause of the bleeding.

This case is a female patient diagnosed with systemic vasculitis associated with ANCA MPO (microscopic polyangiitis) confirmed through renal biopsy. Understanding its systemic signs and symptoms may suggest that the result found in the endoscopic capsule at the distal duodenum and proximal jejunum as a first indication might be compatible with enteric vasculitis.

Common causes of small bowel bleeding (SBB) include vascular lesions, ulceration secondary to Crohn's disease (CD), non-steroidal anti-inflammatory drugs (NSAIDs), Meckel's diverticulum, Zollinger-Ellison syndrome, vasculitis, small intestinal tumors (gastrointestinal stromal tumors [GIST], neuroendocrine tumor, adenocarcinoma or small bowel lymphoma), aortoenteric fistula, or jejunal diverticulitis[4]. Reports have shown that the diagnostic sensitivity of capsule endoscopy for diagnosing the source of bleeding in SBB ranges from 38% to 93%[5]. Capsule endoscopy is significantly better than single-balloon enteroscopy[2,6], small bowel series[7,8], enteroclysis[9], and computed axial tomography (CT)[10] for identifying small intestine lesions in patients with SBB.

Small bowel ulcers are another common abnormality detected through capsule endoscopy. Although most small intestinal ulcers detected through capsule endoscopies are due to CD or NSAID enteropathy, other causes include infection, ischemia, trauma, or vasculitis[11].

GPA is a small- and medium-vessel vasculitis affecting the respiratory tract and kidneys. Necrotizing granulomatous inflammation characterizes the GPA clinical picture. Between 5% to 10% of cases have gastrointestinal involvement[1]. The clinical spectrum is highly variable, and vasculitis can be systemic or localized. Gastrointestinal tract involvement is often part of a systemic inflammatory process and is a well-recognized manifestation of small and medium-sized vessel vasculitis. Patients with gastrointestinal involvement often have abdominal pain, nausea, vomiting, diarrhea, or gastrointestinal bleeding. These gastrointestinal complications, when manifested, negatively affect the prognosis and indicate disease severity[12].

Although GPA occurs with the same frequency in men and women, gastrointestinal manifestations are most often seen in men. Lesions include ulcers, submucosal edema, hemorrhage, paralytic ileus, mesenteric ischemia, intestinal obstruction, and intestinal perforation[13].

The active inflammatory process located in the gastrointestinal tract in the course of GPA is a rare complication; however, it occurs and causes a serious threat to patients' lives. Differential diagnosis should cover other inflammatory diseases, especially CD. The type of vasculitis most commonly affecting mesenteric vessels includes systemic lupus erythematosus (SLE), Takayasu arteritis, polyarteritis nodosa, Wegner granulomatosis, and Kawasaki disease. When timely diagnosed, it significantly influences the prognosis, as the rapid initiation of steroid therapy can change the course of the disease[14]. Side effects of immunosuppressive therapy should also be considered a cause of intestinal complications. Therapeutic strategies widely accepted for treating GPA are effective in treating patients with gastrointestinal involvement in the course of the disease, although some complications require surgical intervention[13].

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Tribute

# *Helicobacter pylori*: the discovery that broke a dogma in medicine

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The online Merriam-Webster dictionary defines dogma as "something held as an established opinion, especially: a definite authoritative tenet." In other words, it is a concept or doctrine held by religion or other authorities which does not admit replication or doubt and, therefore, is exempt from being subjected to evidence of veracity[(1)]. Life, sciences, and medicine are full of these concepts. However, as Paul Valéry said, "That which has been believed by everyone, always and everywhere, has every chance of being false." The dogma to which we will refer in this article is the one that held for many years that the stomach was a sterile organ due to the action of hydrochloric acid and, consequently, bacteria cannot normally grow inside it. Over the millennia, as knowledge and science have progressed, evidence has shown that "[...] ignorance is less remote from the truth than prejudice.", as Denis Diderot put it. A prejudice or a belief makes an adequate and correct interpretation of reality impossible; it is like seeing through a colored lens: "[...] everything seems to be that color." Conversely, ignorance about something will cease once the problem is studied and the necessary knowledge is acquired.

On June 11, 1979, Professor Robin Warren, pathologist at the Royal Perth Hospital in Australia (**Figure 1**), described his first case of bacteria associated with chronic gastritis[(2)].

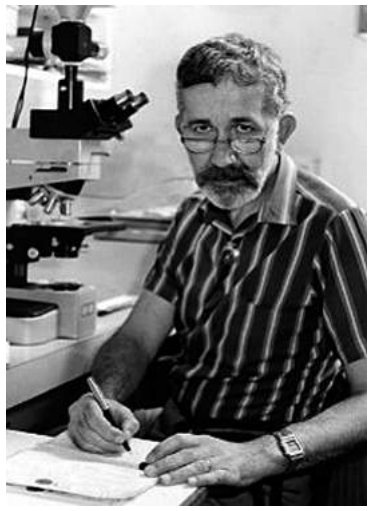


**Figure 1.** Dr. Robin Warren, Department of Pathology, Royal Perth Hospital Australia. Source: https://www.nobelprize.org/prizes/medicine/2005/warren/biographical/

After examining a gastric biopsy, he concluded that the specimen contained "[...] chronic gastritis with minor erosion and that the quality of the mucosal surface in many areas seemed slightly more inflamed than normal and contained numerous bacteria in close contact with the epithelium, which was *Campylobacter*-like and appeared to be actively growing and did not appear to be contaminants[2]."

Like every scientist, Dr. Warren was honest in admitting that not everything was clear to him and acknowledged that "[...] I did not know the meaning of these unusual findings but considered that they deserved further research regarding eating habits, gastrointestinal function, and microbiology." The finding and repeated reporting of such findings prompted two endless questions from attendees of the clinical-pathological meetings: 1) why do you insist it is the primary infection and not those considered secondary to inflammation, and 2) if they are there, why had they not been seen before? At that time, he did not have clear and correct answers to such questions. For the first question, it was necessary to wait for Barry Marshall to demonstrate the effects of antibiotics on these infections eventually. As such alterations were studied, findings progressively showed that there were reports from the previous century describing bacteria in the stomach, too. Still, such findings were considered incorrect and unimportant because the main concept was that "the stomach was sterile[2]." Nowadays, many scientific comments and interpretations can be made about these significant findings. Still, an in-depth reflection would also be what Winston Churchill once said: "Men occasionally stumble over the truth, but most of them pick themselves up and hurry off as if nothing had happened." No one believed Professor Warren's findings except Win, his wife –a psychiatrist. She encouraged him to continue his research and disregard the disqualification of public opinion. Thus, an obligatory question at this point is, who has not had the world against them, even over the most elementary ideas and concepts? Later, in 1981, Marshall, already an internal medicine resident, would come to his gastroenterology clerkship and be assigned to rotate with Dr. Warren, "a pathologist who was interested in following up on some bacteria that were in the stomach," although the actual words were "one of our pathologists who is trying to pin gastritis on a bacterial infection" (**Figure 2**).

Marshall initially doubted the importance of the project. Dr. Warren could not convince him and asked him to read the protocol and forget what the public thought about "gastritis" before continuing to question it. Barry Marshall read the document and finally agreed to start the investigation with 20 patients undergoing additional antral mucosa biopsies, apparently normal to endoscopy. What would a teacher of today think if a second-year resident of internal medicine, based on old prejudices, contradicts without any evidence

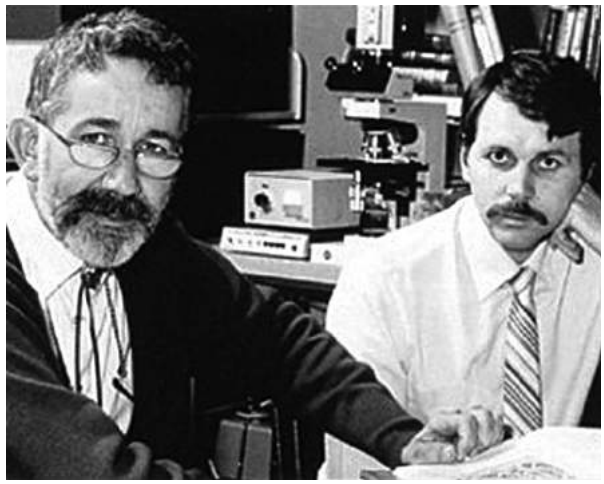


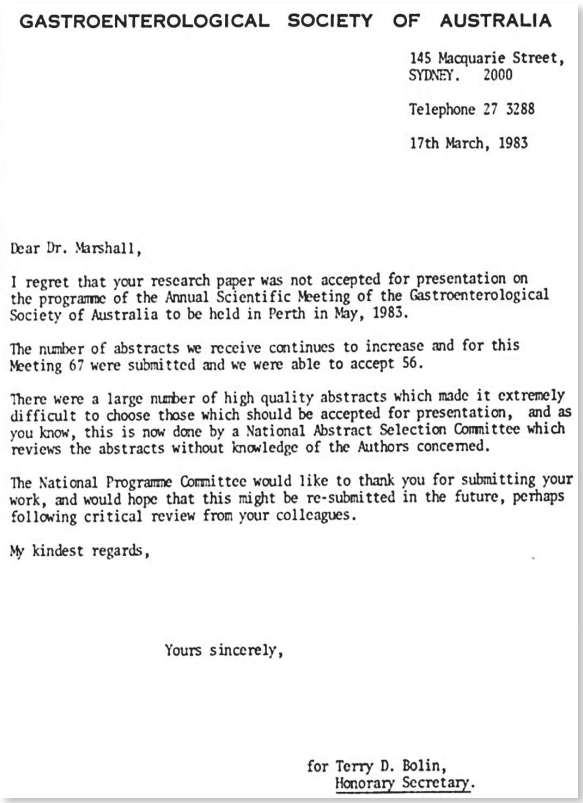
**Figure 2.** Robin Warren, on the left, Barry Marshall, on the right, July 1984. Source: https://www.nobelprize.org/prizes/medicine/2005/warren/biographical/

a protocol that was based on serious observations of an exemplary pathologist like Dr. Warren? That attitude reflects Bertrand Russel's claim: "The trouble with the world is that the stupid are cocksure and the intelligent full of doubt!"

Once this pair of "quixotes" agreed and decided to undertake the research, arguments appeared from the gastroenterologists who performed the endoscopies, who considered that "the idea of sending gastric biopsies for culture was ridiculous," "since the goal of gastroenterology and endoscopy was patient care and not esoteric research projects." Moreover, "no one in many centuries had cultivated stomach bacteria" and, therefore, "it did not make sense for a rational gastroenterologist to take biopsies to look for bacteria.[2]" Thanks to Marshall's constant insistence on the microbiology department and the high scientific qualities of the members of that great laboratory –who on multiple occasions modified the culture media and incubation temperatures, at last, the 35th culture was successful and showed bacteria! In fact, the department members had forgotten that culture and mistakenly left it incubating during the Easter festivities, which take five days in Australia. After the holidays, they returned to the laboratory, and on April 14, 1982, they found the typical colonies of *Helicobacter pylori* (*H. pylori*)[3]. Many skeptics and ill-intentioned critics initially considered this achievement as something fortuitous, by chance, and considered it *serendipity*, or as the jargon has it, "a sheer stroke of luck". However, if analyzed thoughtfully, the correct conclusion would probably be the one masterfully formulated by Louis Pasteur in his time: "Chance favors the trained mind."

Despite this interesting discovery, finding "bacteria that could cause chronic active gastritis," Marshall and Warren

–the authors, had not agreed on how they should communicate their findings to the scientific community, nor on the terms in which they should highlight them. They went to Professor Armstrong from the Electron Microscopy Unit of the Royal Perth. This magnificent scientist advised them to write two separate letters to the editor of the Lancet journal[4], and so they did[5,6]. The hardest battle against the world's disbelief would come from that moment on. In 1983, the Gastroenterological Society of Australia rejected the first work they did in which they demonstrated that *H. pylori* was more frequently associated with mucosa with chronic gastritis than with normal mucosa ($p = 0.001$), as well as with duodenal ulcers ($p = 0.01$), but not statistically significant with gastric ulcers ($p = 0.05$). Today, we have several explanations for these associations. That work was possible thanks to Dr. Warren's interest in calculators. However, it was quite an odyssey for him to manage an advanced calculator and interpret the statistical significance of the "*p*" in that rudimentary "gadget" for our times. Sixty-seven papers were submitted to the Australian congress, and the 56 best papers were selected. Warren and Marshall's work was in the bottom 11. At the end of the rejection letter were words of courtesy, "appreciating the effort and encouraging them to continue investigating and pursuing better quality research" (**Figure 3**).



GASTROENTEROLOGICAL SOCIETY OF AUSTRALIA

145 Macquarie Street,
SYDNEY. 2000

Telephone 27 3288

17th March, 1983

Dear Dr. Marshall,

I regret that your research paper was not accepted for presentation on the programme of the Annual Scientific Meeting of the Gastroenterological Society of Australia to be held in Perth in May, 1983.

The number of abstracts we receive continues to increase and for this Meeting 67 were submitted and we were able to accept 56.

There were a large number of high quality abstracts which made it extremely difficult to choose those which should be accepted for presentation, and as you know, this is now done by a National Abstract Selection Committee which reviews the abstracts without knowledge of the Authors concerned.

The National Programme Committee would like to thank you for submitting your work, and would hope that this might be re-submitted in the future, perhaps following critical review from your colleagues.

My kindest regards,

Yours sincerely,

for Terry D. Bolin,
Honorary Secretary.

**Figure 3.** Letter of rejection of Marshall and Warren's initial work. Source: taken from[2].

Then there would be multiple studies with interesting findings, such as the recurrence of duodenal ulcers, more frequently in those who had no cure for *H. pylori*[5], and the bactericidal activity of bismuth for *Campylobacter pyloridis*[7]. That initial name given to the microorganism was considered grammatically incorrect since, similarly, we do not say "*Escherichia colitis*" but "*Escherichia coli*." At a world congress, it was renamed as it is currently known[8]. Faced with the worldwide disbelief that a bacterium produced gastritis, Marshall ingested a supernatant with *H. pylori* to show that it did produce it and thus convince the world that it was not really "a tall tale[9]". Marshall continued to conduct multiple studies related to the diagnosis and treatment of the microorganism[10-16]. He developed the rapid urease test (RUT) and the urea breath test (UBT)[10,16]. He demonstrated that eradication in patients with peptic ulcers decreases the probability of recurrence[6]. Despite the high-quality evidence that *H. pylori* cure means ulcer cure, the scientific community remained skeptical until research by Dr. Graham, published in the Annals of Internal Medicine, confirmed Marshall and Warren's findings[17]. Such an important work, conducted by a scientist of Dr. Graham's stature, meant "a blessing". From that time on, the world was convinced about the story. Since then, this microorganism progressively became one of the most transcendental discoveries in gastroenterology, revolutionizing the concept of peptic ulcers and, finally, the etiology of gastric cancer. Thus, providing the possibility of preventing it if the infection is cured. In 2005, the Swedish Academy awarded the Nobel Prize in Physiology and Medicine to Warren and Marshall for discovering the causal relationship of *H. pylori* with chronic gastritis and peptic ulcers (**Figure 4**).

No one could have imagined that two clinical doctors with no master's or doctoral degrees or epidemiology studies would be awarded a Nobel Prize for clinical research. This should set an example for all researchers and our undergraduate and graduate students. They should also prompt reflection for many ethics committees in the underdeveloped world that eliminate research protocols and thereby annihilate the ambitions of many young researchers who are taking their first steps in research. This momentous discovery, in my opinion, was the prologue to an overwhelming story whose contemporary reach is absolutely shocking and fascinating.

Many researchers before Marshall and Warren had observed microorganisms in the stomach. They linked them to chronic gastritis, although the causal relationship could not be demonstrated due to the impossibility of culturing them. Dr. Steer was probably the closest to achieving this discovery[18-20]. However, the culture of his biopsies grew *Pseudomonas aeruginosa*. Manifold reflections might arise from this amazing story, but this com-

mentary would take too long. I believe that the strongest lessons might include: "absence of proof is not proof of absence" and "he who has faith in himself does not need others to believe in him." Besides, it is essential to work as a team because, as the letter to the Corinthians states, "the body is not made of one part but of many," or as Thomas Buxton said, "With ordinary talent and extraordinary perseverance, all things are attainable;" finally, "failures and difficulties should be reasons to keep trying." For instance, who is not aware of Abraham Lincoln's many failures, and who became President of the United States after multiple attempts and failures? Moreover, Steve Jobs founded Apple and was expelled from that company. Undoubtedly, "Man discovers himself when he measures himself against the obstacle!" Difficulties are the best stimulus for leaders and the bane of the fainthearted. Regarding leadership, scientific leaders are absolutely persevering and are not concerned about what public opinion thinks, which makes them completely different from politicians. Lastly, teachers are friends with students and can win a Nobel Prize together! (**Figures 5** and **6**).

**Figure 4. Left:** Barry Marshall received the Nobel Prize in Physiology and Medicine in 2005. **Right:** Robin Warren receiving the Nobel Prize in Physiology and Medicine in 2005. Source: https://www.nobelprize.org/prizes/medicine/2005/marshall/photo-gallery/ y https://www.nobelprize.org/prizes/medicine/2005/warren/photo-gallery/

**Figure 5.** Doctors Marshall and Warren today.


**Figure 6.** Doctors Marshall and Warren.

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