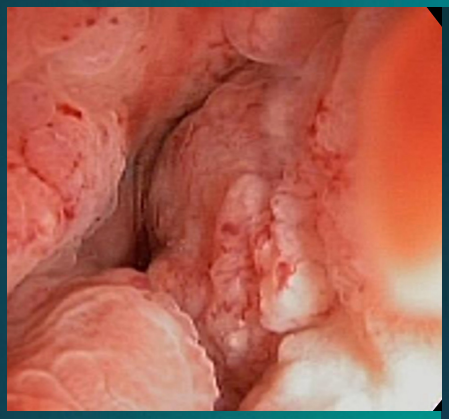
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Editorial

The prevalence of comorbidities in Irritable Bowel Syndrome requires a comprehensive clinical approach

David B. Páramo-Hernández.[1]

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Among functional digestive disorders—now known as *disorders of gut-brain interaction*—irritable bowel syndrome (IBS) is the most prevalent condition globally, estimated at 10% to 15%, with significant regional variations[1]. According to a global study conducted via online data collection in 24 countries and in-person interviews in 7 countries, a prevalence of 4.3% was reported in Colombia using the Rome IV diagnostic criteria in the adult population[2]. The study by Drs. Saade and Roselli[3] estimates a prevalence of 2.7% in the general Colombian population between 2018 and 2022. These two prevalence estimates are relatively low compared to what is commonly observed in clinical practice, likely influenced by the fact that the Ministry of Health's diagnostic records only include patients who seek medical consultation, as well as issues of underreporting, underdiagnosis, or cases where IBS is not the primary diagnosis. Similarly, since it is an online survey with more restrictive diagnostic criteria, such as those used by Rome IV, while sensitivity may improve, significant selection biases could also arise.

The findings of the Saade and Roselli study[3] further support the reality of the gut-brain axis, which is the bidirectional neurohumoral communication system between the brain and the gut. This system continuously sends signals about the homeostatic, physiological, or pathological state of the digestive system to the brain via afferent nerves (spinal and vagal) and humoral pathways of the enteric nervous system or "intestinal brain"[2,4,5]. The efferent response, after central processing—particularly by the insula, amygdala, and perigenual anterior cingulate cortex (areas that simultaneously process visceral sensitivity and our emotional responses)—is directed through descending projections from brainstem nuclei to the rostral ventrolateral medulla and the dorsal horn of the spinal cord, modulating afferent pain transmission at the first synapse[2,4,5]. It is important to note that these projections are primarily opioid-, noradrenergic-, and serotonergic in nature, a fact with significant therapeutic implications[2,4,5].

Within a biopsychosocial conceptual model, there is sufficient evidence regarding the contribution of genetic, epigenetic, and cultural factors. Stressful life events (including sexual abuse, physical maltreatment, and emotional abuse, particularly in childhood) have been proposed as the most influential compared to controls[6]. Precisely due to the bidirectional nature of the gut-brain axis, IBS patients report a higher prevalence of such adverse events, and this history is generally associated with anxiety and depressive disorders, greater severity of functional gastrointestinal disorders (FGIDs), worse clinical outcomes, increased stress, and impaired daily functioning and quality of life[2,4,5].

Among the most frequent comorbidities are affective disorders, particularly anxiety and depression. Systematic reviews indicate that 40% to 60% of IBS patients exhibit

clinically relevant psychiatric symptoms[7]. Additionally, IBS often coexists with other functional chronic pain conditions, such as fibromyalgia, chronic fatigue syndrome, functional dyspepsia, and migraines[8].

The presence of these comorbidities leads to increased healthcare utilization, higher direct and indirect healthcare costs, greater symptom burden, and a negative impact on patients' quality of life[9]. Furthermore, individuals with IBS and comorbidities tend to show poorer responses to conventional therapies, including antispasmodics, antidiarrheals, or laxatives[9]. This underscores the need for multimodal and comprehensive treatment strategies, incorporating psychological interventions (such as cognitive-behavioral therapy or hypnotherapy)[10], lifestyle modifications, and, in some cases, psychotropic medications—referred to here as *neuromodulators*[5].

The management of IBS should adopt an interdisciplinary, comprehensive, and individualized approach that addresses both intestinal symptoms and comorbid conditions. Identifying these associated disorders not only improves differential diagnosis but also optimizes treatment, reduces chronicity, and enhances patient prognosis. Recognizing the high prevalence of comorbidities in IBS presents a significant clinical challenge but also an opportunity to shift the care paradigm from a purely digestive focus to a broader, more effective biopsychosocial approach[11,12].

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Original article

Comorbidities of Irritable Bowel Syndrome in Colombia: Analysis of Data from the Ministry of Health

Natalia Saade-Cleves,[1*] Diego Rosselli.[2]

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Abstract

Irritable bowel syndrome (IBS) is the most common functional disorder of the gastrointestinal tract, characterized by altered bowel habits associated with chronic abdominal pain. In this context, a descriptive study was conducted using the Individual Health Service Provision Records (Registros Individuales de Prestación de Servicios de Salud – RIPS), the official healthcare services database from the Ministry of Health of Colombia. ICD-10 codes K580 (irritable bowel with diarrhea) and K589 (irritable bowel without diarrhea) were used to identify all registered patients between 2018 and 2022. Prevalence ratios of selected comorbidities described in the literature were calculated and compared to individuals without that diagnosis, stratified by age and sex. Our findings indicate a lower overall prevalence in Colombia (2.7%) compared to previously reported figures, with a female-to-male ratio of 2.2. Diagnoses such as fibromyalgia, depression, anxiety, polycystic ovary syndrome, migraine, schizophrenia, and post-traumatic stress disorder were found to be more prevalent in patients with IBS. Fibromyalgia had the highest prevalence ratio, with IBS patients being seven times more likely to receive this diagnosis, while schizophrenia had the lowest, with a 36% higher prevalence among IBS patients. The literature highlights shared pathophysiological pathways, including alterations in the gut microbiome, neurotransmitter metabolism, intestinal permeability, a pro-inflammatory gut environment, and neuronal sensitization. These findings underscore the increased risk of developing these comorbidities among individuals with IBS and highlight the need for further research in this area.

Keywords

Irritable bowel syndrome, comorbidity, fibromyalgia, mental disorders, gastrointestinal microbiome.

INTRODUCTION

Irritable bowel syndrome (IBS) is a functional gastrointestinal disorder characterized by altered bowel habits, often associated with chronic abdominal pain, diarrhea, constipation, or both, as well as abdominal bloating[1,2]. Diagnosis is based on the Rome IV criteria, which require recurrent abdominal pain at least one day per week for the past three months, associated with two or more of the following: changes in stool frequency or consistency. Symptoms must have been present for at least six months prior to diagnosis[2]. A literature review spanning articles from 1978 to 2013 reported a global prevalence of 10%–25%, with regional variations and a female-to-male ratio of 1.5–3:1, alongside lower diagnosis rates after age 50. The review also noted higher familial clustering of IBS (suggesting genetic and lifestyle components), no socioeconomic disparities, increased healthcare utilization among patients, and reduced quality of life due to disease chronicity, symptom exacerbations, and comorbidities such as fibromyalgia, depression, and anxiety[3]. Additionally, it highlighted inconsistencies in epidemiological data stemming from varying diagnostic criteria (e.g., Manning, Rome II, Rome III)[3].

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Colombian data vary by diagnostic criteria. A 2009 cross-sectional study using self-administered questionnaires in Bucaramanga reported a prevalence of 19.9% under Rome III criteria, with 62.4% of cases occurring in women. Logistic regression analysis revealed an association between depressive symptoms and female sex[4]. A global study combining online surveys (24 countries) and in-person interviews (7 countries) reported a Colombian prevalence of 4.3% using Rome IV criteria in adults[5]. The same authors noted that over 40% of people worldwide experience functional gastrointestinal disorders at some point, though diagnoses decline when using Rome IV versus Rome III criteria[5].

Due to its high frequency, IBS is considered a public health priority[6]. Beyond gastrointestinal symptoms, IBS is associated with conditions such as fibromyalgia[7], depression, anxiety[8], polycystic ovary syndrome[9], migraine[10], schizophrenia[11], and post-traumatic stress disorder[12]. Its pathophysiology involves genetic factors, chronic stress exposure, visceral hypersensitivity, immune dysregulation, intestinal permeability, gut-brain axis disruption, and microbiota alterations[6].

Colombia is the only country in the region with universal health coverage for its 50 million inhabitants. Its healthcare system operates under a single-payer model with two dozen public and private insurers reimbursing providers. This relatively complex scheme relies on a structured information system based on Individual Service Provision Records (RIPS). For each patient encounter, providers must complete RIPS forms with basic patient identifiers and one or more diagnoses coded per ICD-10 (International Classification of Diseases, Tenth Revision) to receive reimbursement. Over 500 million RIPS are collected annually[13]. These records have been used in research to estimate, for example, rheumatoid arthritis prevalence[14], disability-adjusted life years for gastric cancer[15], and demographic characteristics of Sjögren's syndrome[16].

MATERIALS AND METHODS

Access to the RIPS database was obtained through Excel 2016 using pivot tables, which connect via personal login credentials provided by the Ministry of Health for research purposes to one of the investigators (DR). The search was limited to patients treated during the five-year period from 2018 to 2022. Data were filtered by "unique patients" to ensure individuals with multiple contacts during this period were counted only once. Analysis was stratified by sex and age, with three age groups: 0–14 years, 15–64 years, and ≥65 years. ICD-10 codes K580 (irritable bowel syndrome with diarrhea) and K589 (irritable bowel syndrome without diarrhea) were used to identify IBS cases.

To evaluate comorbidities, the following ICD-10 codes were employed: anxiety: F411 (generalized anxiety disorder); depression: F320-F329 (encompassing mild, moderate, and severe depression); severe depression: F322-F323 and F332-F333; polycystic ovary syndrome: E282; migraine: G430-G439; fibromyalgia: M797; schizophrenia: F200-F209; and post-traumatic stress disorder: F431. Comorbidities were selected based on clinical relevance and documented associations with IBS. While conditions like depression and anxiety are well-established in IBS patients, less-studied psychiatric disorders (schizophrenia and PTSD) were included to explore potential associations. Clinically observed conditions frequently comorbid with IBS—such as fibromyalgia, polycystic ovary syndrome, and migraine—were also prioritized for analysis. Although other comorbidities are documented in literature, this study focused on a selected diagnostic group.

Patients with IBS were then compared to the general population to determine prevalence ratios (PR) for each condition. General population prevalence used the total treated population (stratified by age and sex) during the study period as the denominator.

Ethical Considerations

As this study involved secondary analysis of a consolidated, anonymized public database, ethics committee approval was not required.

RESULTS

From 2018 to 2022, 53,032,244 individuals received healthcare services nationwide. Of these, 1,423,175 patients (981,454 women; 68.9%) were documented with either ICD-10 code for IBS (K580 or K589), yielding an estimated general population prevalence of 2.7% in Colombia during this period. The study population (ages 0–100 years) demonstrated age-specific patterns (**Figure 1**), with most cases occurring among young adults. Prevalence was relatively low in children under 15 (3.38 per 1,000), slightly higher in girls (3.66) than boys (3.12). Among adults aged 15–64, prevalence rose to 32.2 per 1,000 (women: 41.7; men: 21.3 per 1,000), and was highest in those over 65 (40.0 per 1,000; women: 50.9; men: 26.9 per 1,000).

Table 1 presents case counts and prevalence rates per 1,000 for eight comorbid conditions.

Table 2 presents the number of individuals diagnosed with each of the eight conditions of interest, along with the number of patients having coexisting IBS diagnoses and their respective prevalence rates. The prevalence ratio indicates how much higher the prevalence is compared to the general population without IBS.

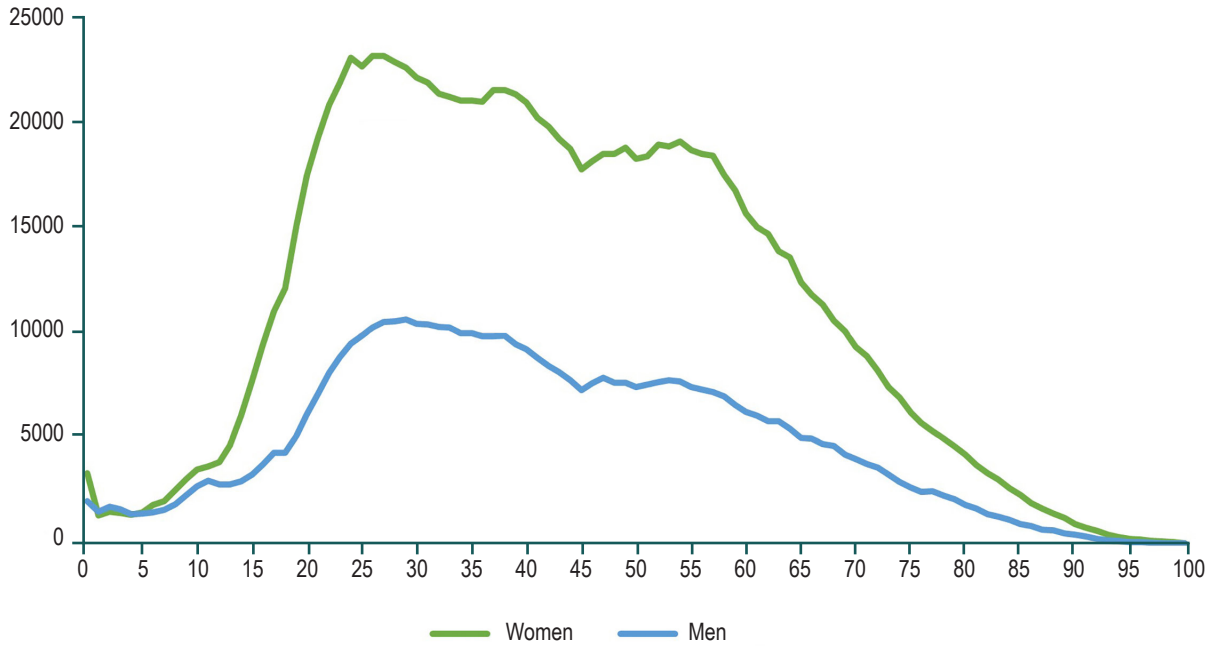


Figure 1. Age and sex distribution of 1,423,175 IBS-diagnosed individuals in Colombia (2018–2022). Image property of the authors.

Table 1. Sex-stratified diagnoses and prevalence (per 1,000) of comorbid conditions (2018–2022)

Condition	Women		Hombres	
	Cases	Prevalence	Cases	Prevalence
Anxiety	187,135	6.7	93,587	3.7
Depression	678,322	24.2	268,177	10.7
Severe depression	94,369	3.4	49,130	2.0
Polycystic ovary syndrome	429,497	15.4		
Migraine	1,639,853	58.6	444,270	17.7
Fibromyalgia	99,807	3.6	7573	0.3
Schizophrenia	96,707	3.5	120,634	4.8
PTSD	16,776	0.58	12,633	0.49

Table prepared by the authors.

Table 2. Total recorded cases for each diagnosis in Colombia (2018-2022), number of cases with coexisting irritable bowel syndrome (IBS) diagnosis, prevalence per 1000 IBS patients, and prevalence ratio (PR) compared to individuals without IBS

Comorbidity	Cases	With IBS	Prevalence	PR
Anxiety	280,722	27,792	19.5	3.98
Depression	946,499	73,182	51.4	3.04
Major Depression	143,499	10,176	7.2	2.77
Polycystic ovary syndrome	426,502	32,190	32.8	2.23
Migraine	2,084,123	170,757	120.0	3.24
Fibromyalgia	107,380	18,067	12.7	7.34
Schizophrenia	217,341	7772	5.5	1.34
PTSD	29,409	1738	1.2	2.28

Table prepared by the authors.

DISCUSSION

The global prevalence of IBS has been estimated at 11.2%, with significant regional variations. According to a systematic review and meta-analysis, the lowest prevalence occurs in Southeast Asia (7%), while the highest is found in South America (21%)[17]—similar to the 10%–25% global prevalence range reported in the previously mentioned literature review[3]. In Colombia, prevalence based on Rome III criteria was approximately 19.9% in a university study using electronic questionnaires with a random sample of adults in Bucaramanga[4]. A 2017 cross-sectional study at Pontificia Universidad Javeriana in Bogotá reported a 24% prevalence using Rome III criteria[18], contrasting with the 4.3% prevalence found using Rome IV criteria in the global study cited earlier[5]. Our study identified a general population prevalence of 2.7% in Colombia (2018–2022), lower than literature reports, likely due to underdiagnosis and underreporting.

Two-thirds of diagnoses occurred in women (female-to-male ratio: 2.2:1), consistent with existing literature[3,8,17]. While prior studies note decreased prevalence after age 50[3,17], we observed persistently high prevalence among older adults.

All analyzed comorbidities were more frequent in IBS patients than in the general population—from schizophrenia (34% higher prevalence) to fibromyalgia (7-fold higher). These conditions share potential underlying pathophysiologies: dysbiosis, nervous system sensitization, and adrenal axis activation[1,6,9,10–12,19].

Anxiety diagnoses were four times more common in IBS patients, while depression (aggregated mild/moderate/severe or major depression alone) was approximately three times more prevalent. Literature reports that 40%–90% of IBS patients meet criteria for mental health disorders, particularly depression and anxiety[19]. This reflects the gut-brain axis relationship, where bidirectional communication occurs between the enteric and central nervous systems[19].

One of the key shared mechanisms is intestinal microbiota dysregulation. Dysbiosis compromises the intestinal barrier, increasing permeability while simultaneously heightening pain sensitivity and altering motility (hallmarks of IBS). Elevated proinflammatory cytokine production may also exert cerebral effects linked to depression and anxiety[19,20]. This dysbiosis mechanism similarly connects to polycystic ovary syndrome (PCOS), which demonstrates immunoinflammatory responses alongside visceral hypersensitivity and motility alterations[9]. Our study found PCOS prevalence 2.23 times higher in IBS patients than in unaffected women. Sex hormones (testosterone, estrogen, progesterone) can modify gut microbiome composition, while conversely, altered microbiota may influence hormonal regulation[9,21]. The inflammation secondary to intestinal permeability in IBS has been implicated in migraine[22] and fibromyalgia—conditions sharing microbial dysbiosis patterns like reduced *Bifidobacterium* and *Ruminococcaceae*, and increased *Clostridium scindens*, though with distinct *Eubacterium* and *Rikenellaceae* profiles[7,23,24].

Serotonin plays a pivotal role in these pathophysiological interactions. Approximately 90% of serotonin resides in the gastrointestinal tract, regulating peristalsis and intestinal secretion. Altered serotonin metabolism may drive visceral hypersensitivity and is linked to anxiety/depression disorders[20]. Variants of the *5-HT* gene (encoding G protein-coupled serotonin receptors) associate with IBS symptoms—e.g., the *5-HT3* receptor subtype correlates with proalgesic effects, particularly in IBS-D[25]. In migraine, serotonin transporter polymorphisms relate to migraine with aura. Even in schizophrenia, serotonin metabolism alterations may connect both conditions, though evidence remains limited[26]. A 2015 review found 19% IBS prevalence among schizophrenia patients[11], whereas a cohort study showed no statistically significant schizophrenia incidence difference in IBS patients (relative risk [RR]: 1.8; 95% confidence interval [CI]: 0.9–3.6)[27].

Central nervous system sensitization is evident in fibromyalgia, which demonstrated the strongest IBS association in our study (7-fold higher diagnosis rate versus general population). Shared mechanisms include peripheral sensitization with enhanced ascending pain pathway activation and impaired descending inhibition in both conditions[28]. Both disorders also exhibit sympathetic nervous system and hypothalamic-pituitary-adrenal axis hyperactivity, impacting intestinal motility[28,29]. Neuroimaging in IBS and fibromyalgia patients suggests sensitization stems from dysfunctional anterior cingulate cortex inhibition, increasing insular activity to stimuli[30].

This central sensitization also manifests in PTSD, where IBS patients showed doubled risk (prevalence ratio: 2.28) following stressful events. Kearney et al. reported higher IBS prevalence among veterans with PTSD versus the general population[31]. PTSD and IBS share gut-brain axis dysregulation and central sensitization—an amplified response to repeated stimuli occurring at cellular and psychological levels, primarily mediated by the limbic system[30]. In IBS patients, exaggerated stress responses may alter motility, permeability, and visceral sensitivity, promoting gastrointestinal inflammation, microbiota disruption, and elevated risk for inflammatory digestive disorders like IBS[19].

When central sensitization increases responsiveness to stimuli in central nervous system nociceptors—where minor stimuli may trigger severe pain perception[32]—this mechanism also potentially underlies the IBS-migraine relationship, mediated by genetic factors, mitochondrial dysfunction,

and microbiota alterations[25]. Our study found IBS patients had triple the migraine risk versus the general population. Todorov et al.'s systematic review/meta-analysis reported an odds ratio (OR) of 2.09[25], suggesting migraine may share previously discussed mechanisms involving dysbiosis, central sensitization, and serotonin receptor genetics.

The corticotropin-releasing system also emerges as a shared pathway. This system induces gastrointestinal proinflammatory states via CRF1 receptor (corticotropin-releasing factor with urocortin 1) activation in enteric neurons, accelerating colonic transit[33]. Within the hypothalamic-pituitary-adrenal axis, physical or psychosocial stress elevates catecholamines, disrupting gut microbiota and exacerbating anxiety symptoms[19,34]. Concurrently, increased intestinal permeability, dorsolateral prefrontal cortex dysfunction, elevated interleukin-2 (IL-2), and B-cell activation—mechanisms also implicated in fibromyalgia—have been documented[20,28,35,36].

ETHICAL CONSIDERATIONS

As a secondary analysis of anonymized public data, informed consent was waived per Article 11 of Colombia's Ministry of Health Resolution 8430 (1993), classifying this as no-risk research. Ethics committee approval was therefore unnecessary.

This study received no funding and involved no conflicts of interest or artificial intelligence use.

CONCLUSIONS

Our study revealed lower IBS prevalence than literature reports, potentially reflecting underdiagnosis, underreporting, or diagnostic criteria variations. Crucially, it highlights elevated risks of mental health disorders (depression, major depression, anxiety, PTSD, schizophrenia) and somatic conditions (migraine, polycystic ovary syndrome (PCOS), fibromyalgia) in IBS patients. Fibromyalgia showed the strongest association (7-fold higher prevalence versus general population), while schizophrenia demonstrated the weakest (34% increased diagnosis rate).

Underlying mechanisms emphasize gut microbiota's role—particularly through neurotransmitter metabolism (especially serotonin), intestinal permeability changes, and proinflammatory environments—across all associated conditions, warranting further research. Central/peripheral sensitization also features prominently in these shared pathophysiological pathways.

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Original article

Prevalence of Achalasia in Colombia: Data from the Official Records of the Ministry of Health, 2017–2024

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Abstract

Introduction: The global prevalence of achalasia is low, estimated at between 7 and 32 cases per 100,000 inhabitants. Colombia is an endemic country for Chagas disease, and variants of the human leukocyte antigen DQ (HLA-DQ) have also been identified in the population. These factors may influence the disease's prevalence compared to global figures. **Methods:** This was a descriptive, cross-sectional study based on information from the database of Integrated Information System for Social Protection of Colombia (SISPRO). Prevalence was estimated based on healthcare encounters coded with ICD-10 diagnosis K22.0, corresponding to "achalasia of the cardia," during the period from 2017 to 2024. The analysis was stratified by department, sex, and age group. **Results:** A total of 9,621 cases of achalasia were recorded nationwide, with a prevalence of 21.8 cases per 100,000 inhabitants. Females accounted for 59.4% of the cases (95% CI: 58.4%–60.4%). The departments with the highest prevalence were Atlántico, Córdoba, Magdalena, and Bogotá, with 47, 39, 35, and 26 cases per 100,000 inhabitants, respectively. A progressively higher prevalence was observed with increasing age. **Conclusions:** The estimated prevalence of the disease in Colombia aligns with global reports. Further studies are needed to confirm geographic differences in prevalence and their possible underlying causes. These findings are useful for prioritizing resources and improving strategies for the detection and treatment of achalasia in Colombia.

Keywords

Esophageal achalasia, epidemiology, prevalence, Colombia.

INTRODUCTION

Achalasia is a rare chronic disorder characterized by impaired esophageal peristalsis and insufficient relaxation of the lower esophageal sphincter (LES), which hinders the passage of food into the stomach in the absence of structural obstruction in the esophagus or esophagogastric junction (EGJ)[(1)]. Its pathogenesis involves degeneration of ganglion cells in the myenteric plexus, primarily nitric oxide-producing inhibitory neurons, leading to compromised relaxation of esophageal smooth muscle[(2–4)]. It is proposed that achalasia types 1 and 2 result from a cytotoxic immune attack that causes progressive death of myenteric plexus neurons, while in type 3 achalasia, neuronal dysfunction occurs without cell death.

Possible causes include idiopathic and secondary etiologies, such as Chagas disease, herpes zoster, sarcoidosis, amyloidosis, eosinophilic esophagitis, and hereditary syndromes like Allgrove syndrome. Additionally, a potential genetic predisposition linked to human leukocyte antigen DQ (HLA-DQ) variants has been described[(5–7)]. This disease significantly impacts patients' quality of life and

generates high healthcare costs due to the complexity of required treatments, including Heller myotomy, peroral endoscopic myotomy (POEM), and esophageal dilations. In countries like the United States, annual costs per treated patient range between 3,000 and 14,000 USD[8].

A systematic review of the global epidemiology of achalasia from 1925 to 2021 described an increasing prevalence trend over the years, reaching 7.54 cases per 100,000 inhabitants between 1952 and 1999 and 16.9 cases per 100,000 inhabitants between 2018 and 2021. Most studies were conducted in Asia, Europe, and the United States and agree that this disease is more common in adults. However, some geographical differences exist, with Oceania having the highest prevalence at 16.9 cases per 100,000 people[9]. In South America, and particularly in Colombia, there are no epidemiological data on achalasia prevalence. Colombia is an endemic region for Chagas disease, and HLA-DQ variants have been reported in the population, which could influence disease prevalence compared to global records[4,9].

The Individual Health Service Provision Records (RIPS) are mandatory in Colombia's healthcare system and contain data from over 500 million medical encounters, making them a previously used resource for estimating the prevalence of various diseases[10–12]. Since they include information from all patients enrolled in the healthcare system (99.12% of the country's population), they represent an invaluable source for estimating disease prevalence in Colombia[13]. This study aims to determine the prevalence and geographical distribution of achalasia in Colombia by analyzing RIPS data.

METHODS

We conducted a cross-sectional descriptive study using data from the Integrated Social Protection Information System (SISPRO) database, which contains nationwide records of medical consultations and procedures. Data were extracted from the Individual Health Service Provision Records (RIPS) for patients diagnosed with "achalasia of cardia" (ICD-10 code K22.0) between 2017 and 2024. For each case, we collected additional information including sex, age, and geographic location (by department), with the exception of Guainía and Vaupés departments, which reported no data for this condition.

Disease prevalence was estimated using 2018 national census data from Colombia's National Administrative Department of Statistics (DANE) as the denominator[14]. Analysis was performed by groups according to: reporting department, sex, and age (in five-year intervals); with prevalence calculated per 100,000 inhabitants. Geographic distribution of prevalence was visualized using Tableau software[15].

Ethical Considerations

This research followed international ethical guidelines, including the Declaration of Helsinki and Colombian Ministry of Health Resolution 008430 of 1993, which classifies this study type as "no-risk research." Informed consent was not required as no personally identifiable patient information was published.

RESULTS

A total of 9,621 cases of achalasia were recorded nationwide between 2017 and 2024, with a prevalence of 21.8 cases per 100,000 inhabitants. Prevalence was higher among females, reaching 25.4 cases per 100,000 inhabitants, compared to 18.1 cases per 100,000 among males. Females accounted for 59.4% of cases (95% confidence interval [CI]: 58.4%-60.4%). Prevalence rates and case numbers by sex for each department are shown in **Table 1**. Geographic distribution of departmental prevalence is presented in **Figure 1**.

Nationally, the departments with the highest prevalence were Atlántico (47 cases per 100,000 inhabitants), Córdoba (39 per 100,000), Magdalena (35 per 100,000), Bogotá (26 per 100,000), and Valle del Cauca (25 per 100,000). Most departments showed higher prevalence among women; however, Chocó and Guaviare had higher prevalence in men (6 vs. 5 cases per 100,000 in Chocó, and 5 vs. 3 cases per 100,000 in Guaviare). These findings highlight greater disease prevalence in the country's northwestern region. National data are shown in **Figure 1**.

Age-group analysis revealed the highest prevalence in the 80+ years cohort (121 cases per 100,000). A progressive age-related increase was observed, with notably steeper incidence rises starting at age 55. Sex-stratified prevalence by five-year age groups is presented in **Table 2** and **Figure 2**.

DISCUSSION

This is the first study to estimate achalasia prevalence using comprehensive data from all regions of Colombia, as well as the first to characterize the disease in South America. The estimated prevalence in Colombia's general population aligns with global epidemiological records, which report approximately 7-32 cases per 100,000 inhabitants depending on geographic variation[1,16–18].

The correlation between increasing age and higher disease prevalence aligns with findings from other studies. Recent U.S. publications report rising incidence and prevalence rates, particularly among older adults, where prevalence can reach up to 162 cases per 100,000 people[19]. Notably, our analysis found a slightly higher prevalence in women, contrary to literature suggesting equal sex distri-

Table 1. Case numbers and prevalence of achalasia in Colombia per 100,000 inhabitants by sex and department

Department	Number of Cases		Prevalence per 100,000 inhabitants		Overall prevalence per 100,000 inhabitants
	Female	Male	Female	Male	
Amazonas	2	1	6.3	2.9	5
Antioquia	812	530	26.3	18.4	22
Arauca	9	9	7.6	7.4	8
San Andrés, Providencia and Santa Catalina	5	0	20.0	0	10
Atlántico	634	469	52.7	41.1	47
Bogotá, D.C.	1091	796	29.1	23.2	26
Bolívar	250	151	26.0	15.9	21
Boyacá	110	77	19.1	13.8	16
Caldas	127	74	26.7	16.5	22
Caquetá	39	30	22.0	16.4	19
Casanare	15	10	8.0	5.2	7
Cauca	85	47	13.5	7.6	11
Cesar	96	51	17.3	9.4	13
Chocó	12	15	5.2	6.6	6
Córdoba	370	230	47.4	29.7	39
Cundinamarca	316	202	22.4	14.6	19
Guaviare	1	2	2.9	5.1	4
Huila	60	45	11.9	8.9	10
La Guajira	62	15	14.7	3.7	9
Magdalena	243	200	38.5	31.6	35
Meta	72	55	15.9	11.8	14
Nariño	100	66	14.7	10.1	12
Norte de Santander	90	51	13.2	7.7	10
Putumayo	15	13	10.7	9.1	10
Quindío	71	37	26.9	15.1	21
Risaralda	128	63	29.2	15.7	23
Santander	267	201	26.0	20.4	23
Sucre	102	85	23.7	19.6	22
Tolima	63	63	10.2	10.3	10
Valle del Cauca	594	377	29.9	20.9	26
Vichada	4	2	11.1	4.9	8
Total	**5722**	**3899**	**25.4**	**18.1**	**22**

Table prepared by the authors.

bution. For instance, Van Hoeij et al.'s prevalence study in the Netherlands reported a 1:1 female-to-male ratio[20]. This discrepancy may be explained by Colombian women's higher utilization of healthcare services, as evidenced by their greater representation in RIPS records and the SISPRO platform compared to men[21]. However, similar studies also show higher female prevalence from age 25 onward[22], matching our findings.

The regional variation in prevalence rates may be partially attributable to healthcare access disparities. The geogra-

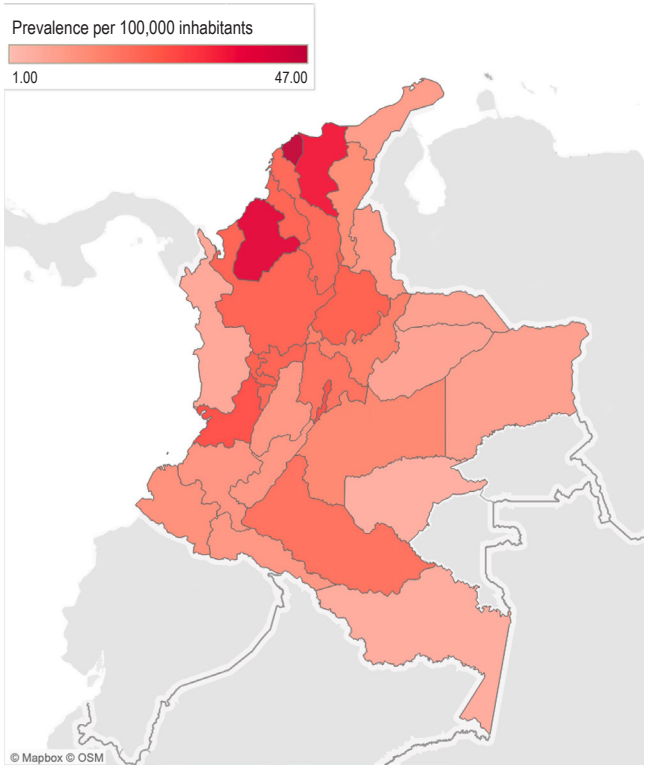


Figure 1. Prevalence map of achalasia in Colombia per 100,000 inhabitants. Image property of the authors.

Table 2. Prevalence of achalasia in Colombia per 100,000 inhabitants by sex and five-year age groups

Age	Female	Male	Total
0-4 years	1.4	2.1	1.7
5-9 years	7.4	9.5	8.5
10-14 years	10.6	11.8	11.2
15-19 years	11.5	9.8	10.7
20-24 years	12.0	10.1	11.1
25-29 years	13.4	8.5	10.9
30-34 years	18.0	10.1	14.1
35-39 years	18.9	14.7	16.9
40-44 years	27.2	18.3	23.0
45-49 years	29.4	17.7	23.9
50-54 years	28.8	19.9	24.6
55-59 years	41.4	26.6	34.5
60-64 years	57.7	36.5	48.0
65-69 years	61.3	43.9	53.3
70-74 years	71.5	59.6	66.1
75-79 years	78.7	67.6	73.8
80+ years	117.0	127.2	121.2
Total	25.3	18.1	21.8

Table prepared by the authors.

phic distribution of achalasia cases is particularly striking in the Caribbean Coast region. Atlántico department shows the nation's highest prevalence rates across most age groups, including children. This finding gains significance when compared to prevalence rates of achalasia-associated conditions like Chagas disease, which is linked not only to achalasia onset but also to complications such as megaesophagus[23]. While Chagas cases have been reported in Atlántico, the disease is more prevalent in northeastern departments like Boyacá, Norte de Santander, and Santander–areas that paradoxically show lower achalasia rates. Similarly, herpes zoster virus infection, another achalasia-associated condition, demonstrates a distinct pattern: while Atlántico reports considerable cases, departments like Córdoba, Amazonas, Valle del Cauca, Sucre, and the San Andrés Archipelago show higher incidence[24,25].

Although achalasia prevalence is not considered significantly influenced by ethnicity[1], the observed geographic differences in Colombia might relate to specific immune response genes, particularly those involved in antineural antibody production. These genes—including *HLA DQA1*01:03* and *DQB1*06:03* alleles—have been associated with up to 30% of achalasia cases[4,9]. In Latin American populations, alleles including *HLA-DRB1*14:54* and *DQB1*05:03* have been identified as potential risk factors in Mexican ancestry individuals[26]. In Colombia, Hernández-Mejía et. al. characterized the distribution of alleles and haplotypes for the HLA-A, HLA-B, HLA-C, HLA-DRB1, and HLA-DQB1 loci in a representative sample of donors registered with the National Bone Marrow Donor Registry. This analysis included data from eight departments (Bogotá, Cundinamarca, Antioquia, Valle del Cauca, Atlántico, Boyacá, Santander, and Tolima). When examining genes associated with achalasia, *DQA1*01:03* and *DRB114:54* were not represented in the study; however, *DQB105:03* was more frequent in Atlántico and Valle del Cauca[27].

STUDY LIMITATIONS

This analysis does not provide an actual prevalence rate but rather an estimate dependent on proper diagnosis

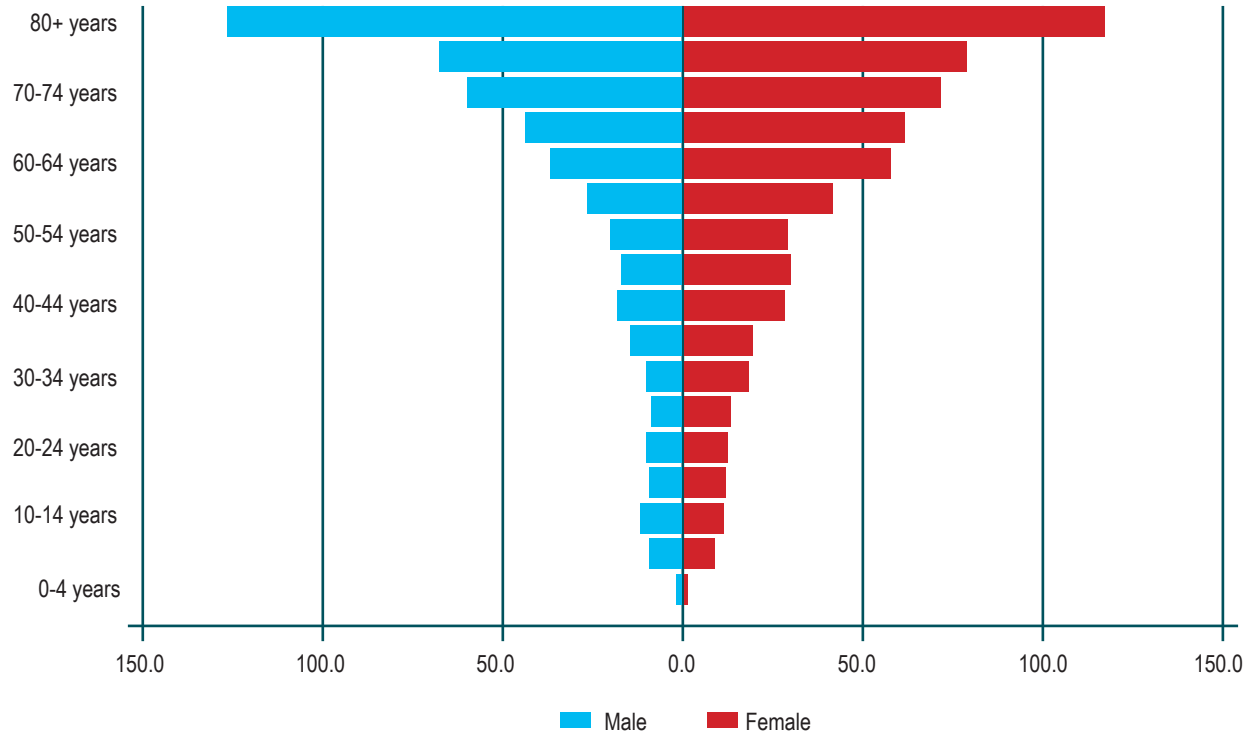


Figure 2. Prevalence of achalasia in Colombia per 100,000 inhabitants by sex and five-year age groups. Image property of the authors.

and accurate recording of data in the RIPS system by healthcare institutions in Colombia. The information platform only stores the primary diagnosis code, which may lead to prevalence underestimation when multiple diagnoses exist or overestimation if a diagnosis is recorded as confirmed without complete diagnostic documentation[28].

Comparisons with data from other countries are limited, and observed differences may be influenced by each study's diagnostic confirmation methods or varying strategies for estimating disease prevalence. Additional studies using standardized and complementary methodologies are needed to confirm not only prevalence rates but also geographic variations in disease presentation and potential associated causes.

CONCLUSION

The estimated prevalence of achalasia in Colombia aligns with global records, despite population differences influenced by genetic, cultural, and environmental factors. Further studies are required to validate these prevalence estimates, investigate geographic variations, and identify potential associated causes. This information is crucial for prioritizing resources and implementing improved detection and treatment strategies for achalasia in Colombia.

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Original article

Mortality and Futility in Patients Undergoing Gastrostomy Between 2020 and 2023

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Abstract

Gastrostomy is a common procedure in hospitals and clinics, typically associated with a low complication rate, and is performed in patients requiring long-term artificial feeding. In daily clinical practice, uncertainty often arises regarding the potential futility of some of these procedures, particularly given the poor vital and functional prognosis of many patients who require them. This study collected data on patients who underwent gastrostomy between 2020 and 2023 at a tertiary care institution, aiming to quantify in-hospital mortality and determine the proportion of procedures deemed futile. Futility in this context was defined as the performance of gastrostomy in patients with advanced dementia, a persistent vegetative state, or death within the first week following the procedure. Overall, in-hospital mortality was found to be 13.1%, and 10.4% of gastrostomies were considered futile. Additionally, higher rates of procedure-related complications and in-hospital deaths were observed during the COVID-19 pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). A downward trend in futile procedures was noted following the implementation of an institutional protocol on the subject during the study period.

Keywords

Gastrostomy, treatment futility, SARS-CoV-2, mortality, bioethics.

INTRODUCTION

Gastrostomy represents one of the artificial feeding options available for nutritional support in patients with swallowing difficulties. Alternative approaches include nasoenteric tubes or total parenteral nutrition. Given the nasal complications associated with the former and metabolic/vascular complications of the latter, gastrostomy remains the preferred long-term management strategy for eligible patients[(1)]. The procedure is typically performed endoscopically with low complication rates and allows for prolonged use by either the patient or caregivers after proper training.

A significant proportion of patients undergoing gastrostomy present with severe health conditions and comorbidities that reduce life expectancy. Many lack decision-making capacity, requiring caregivers or medical staff to authorize the procedure when no family representatives are available[(2)]. In some cases, the patient's clinical status may be so critical or their life expectancy so limited that the procedure could be considered *futile*, according to the accepted definition: "treatments that fail to improve patient physiology or provide any benefit to either the individual or their representatives"[(3)]. This phenomenon can be assessed by examining post-procedural survival, as deaths occurring shortly after gastrostomy (when excluding procedure-related complications) would indicate no clinical benefit was achieved. In more specific instances, the procedure was performed despite meeting standardized futility criteria, contradicting

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international medical deontology and Colombia's medical ethics code established in Law 23 of 1981[4].

This study aims to analyze in-hospital mortality among patients undergoing the procedure at a tertiary care institution during and immediately after the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic period, while also evaluating potential futility in selected cases. Additionally, it assesses the impact of an institutional patient selection protocol for gastrostomy candidates developed and implemented by the gastroenterology service in late 2020.

MATERIALS AND METHODS

We conducted a retrospective cohort study based on gastrostomy procedure requests performed using any technique between January 2020 and December 2023 at a tertiary care institution. This facility exclusively treats patients older than 16 years and does not provide care for pregnant women. From this patient list, we analyzed basic demographic variables, procedure indications, dates and techniques, patient location at time of request (hospital ward, intensive care unit [ICU], outpatient), discharge dates, and in-hospital mortality. We also collected nutritional variables, creatinine levels, and C-reactive protein values. We documented cases where life expectancy was recorded at procedure time, functional class, and whether cases were reviewed by the clinical ethics committee. We registered complications requiring endoscopic reintervention or gastroenterology evaluation. Finally, we excluded patients with existing gastrostomies (those undergoing device replacement).

Procedure indications were categorized as: SARS-CoV-2 infection, head and neck neoplasms, other gastrointestinal neoplasms, traumatic brain injury (TBI), cerebrovascular disease (CVD), advanced dementia (defined as a Clinical Dementia Rating score of 3[5]), and "other causes." This last category included patients with swallowing disorders from other morbidities or prolonged orotracheal intubation.

The institutional ethics committee of Clínica CES, in conjunction with Universidad CES, approved this study.

RESULTS

General Data and Procedure Indications

The medical records department provided a list of 962 gastrostomy requests during the study period. After excluding 217 patients undergoing device replacement (not their first gastrostomy), 56 device removal orders, 14 incorrectly processed orders or orders for other procedures, and duplicate electronic records, we included 519 patients in the final analysis (**Figure 1**).

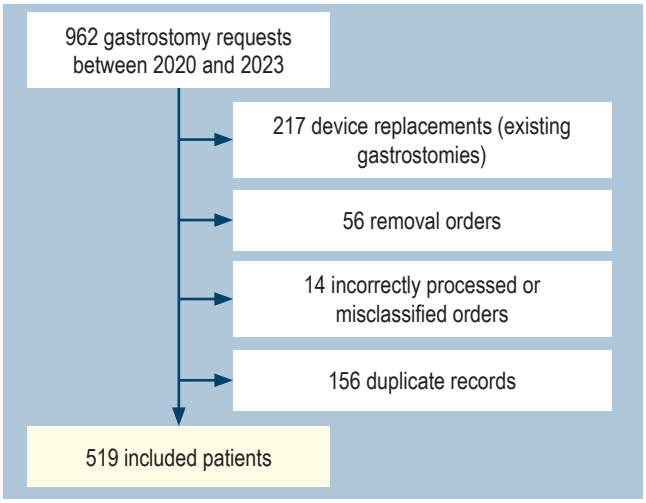


Figure 1. Patient selection flowchart. Image property of the authors.

Forty percent of patients were female. The mean age was 62 years, with 57% of procedures performed while patients were in the ICU. The most frequent indication was "other causes" (28.9%), predominantly comprising deconditioning associated with prolonged ICU stays, followed by SARS-CoV-2 infection (22%) and cerebrovascular disease (CVD) (21.2%). Complete data are presented in **Table 1** and **Figure 2**. Eleven gastrostomies (2.11%) were performed in patients with amyotrophic lateral sclerosis, while 29 patients (5.59%) underwent the procedure in outpatient settings. Endoscopic technique was used in 96% of cases, with surgical approach employed for the remainder. The radiologic gastrostomy technique described in literature was not performed at our institution during the study period. Most procedures (87%) were conducted in endoscopy suites, with the remainder performed in operating rooms due to anesthetic risk or technical contraindications for endoscopic approach.

Table 1. Patient Characteristics

Item	Variable	n (%)
Sex	Male	311 (59.90)
	Female	208 (40.10)
Mean age ± SD (years)	62.4 ± 16.4	
Procedure technique	Endoscopic	498 (95.95)
	Surgical	21 (4.05)
Patient location at procedure request	ICU	299 (57.61)
	Hospital ward/ER	191 (36.80)
	Endoscopy suite outpatient	3 (0.58)
	OR outpatient	26 (5.01)
Indication	SARS-CoV-2	117 (21.97)
	Non-SARS-CoV-2	402 (78.03)

SD: standard deviation; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; ICU: intensive care unit. Table prepared by the authors.

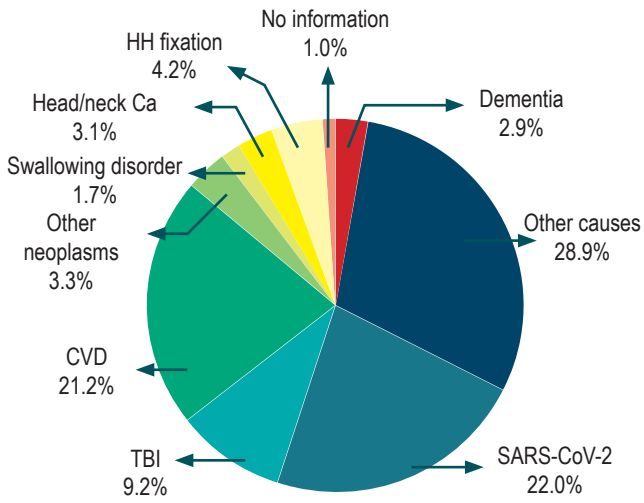


Figure 2. Medical indications for requested gastrostomies. Ca: cancer; CVD: cerebrovascular disease; HH: hiatal hernia; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; TBI: traumatic brain injury. Image property of the authors.

The unspecified smaller percentages correspond to patients who shared two or more of the aforementioned categories, including six patients with advanced dementia.

Among surviving patients, most were discharged home or with home healthcare services (82.1%). Others were transferred to other Healthcare Service Provider Institutions (IPS) specializing in chronic mechanical ventilation patients (11.5%), while the remainder were referred to other clinics or hospitals (5.9%). On average, 11 gastrostomies were requested monthly at the institution, with no increase observed during SARS-CoV-2 pandemic years, though it became the primary indication during this period. Twenty-two procedures (4.2%) were requested for gastric fixation following surgical hiatal hernia repair (CHH).

Procedure Complications

Procedure-related complications occurred in 7.32% of cases, most commonly accidental tube removal (36% of complications), followed by buried bumper syndrome (31%). Twenty-one percent of affected patients experienced multiple simultaneous complications. Complication rates averaged 2-3 cases per quarter, except during Q2-Q3 2021 (peak pandemic), with 8 and 6 cases respectively. No deaths resulted directly from gastrostomy complications. Complete complication frequencies are shown in **Table 2**.

In-Hospital Mortality

The overall cohort mortality was 13.1%. When excluding outpatients, this figure increased to 13.8%. After further excluding cases with CHH indications, the in-hospital mortality rate for nutrition-indicated gastrostomies reached 14%. Among deceased patients, the primary indications for gastrostomy were SARS-CoV-2 and "other causes" (30.9% each), followed by cerebrovascular disease (CVD) at 16.2%.

Table 2. Gastrostomy Complications

Complication	n (%)
Accidental removal	14 (2.69%)
Buried bumper syndrome	12 (2.31%)
Infection	8 (1.54%)
Bleeding	6 (1.15%)
Gastric/other organ perforation	6 (1.15%)
Multiple simultaneous complications	8 (1.54%)

Tabla elaborada por los autores.

Procedure-specific mortality analysis revealed: SARS-CoV-2 indication: 18.4% mortality; Traumatic brain injury (TBI): 16.6% mortality; "Other causes" category: 13% mortality. The overall mortality rate for non-SARS-CoV-2 cases (excluding CHH procedures) was 12%.

Most deaths (44%) occurred within seven days post-procedure (**Table 3**), with 67% of cohort deaths happening within the first two weeks. Mortality peaked during the first half of 2021, coinciding with the period of highest SARS-CoV-2-related hospital occupancy (**Figure 3**). Of the 68 deceased patients, 54 (78%) were in the intensive care unit (ICU) at the time of gastrostomy.

Table 3. Deaths by Days Post-Gastrostomy

Days	Deaths	Percentage
0-6	30	44.1
7-14	16	23.5
14-20	10	14.7
21-27	4	5.9
28-34	4	5.9
35-41	1	1.5
42-48	1	1.5
49-55	1	1.5
70-76	1	1.5
Total	68	100%

Tabla elaborada por los autores.

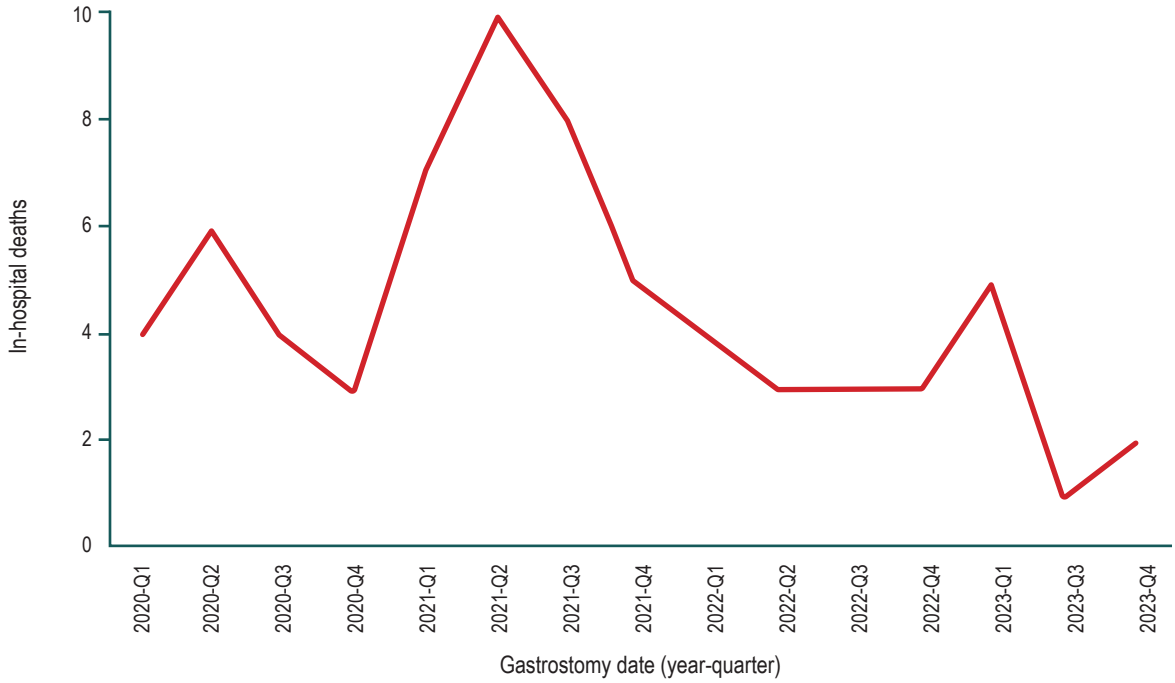


Figure 3. Quarterly mortality counts. Image property of the authors.

Procedure Futility

Documentation of patients' functional class prior to hospitalization and life expectancy in cases of neoplasms or terminal illnesses was notably absent in most medical records. No cases were presented to the ethics committee for procedure approval, as confirmed through separate review of institutional ethics committee minutes. Only three gastrostomies were performed on patients with established permanent vegetative state diagnoses, confirmed by neurology or neurosurgery specialists. Twenty-one gastrostomies (4.04%) were performed for advanced dementia indications—all before 2022, when this diagnosis became standardized as a futility criterion at the institution. Combining these two indications with patients who died within one week post-procedure suggests additional futile interventions.

The cohort included 54 futile procedures (10.4% of total), with a decreasing trend observed in later study quarters compared to initial periods (**Figure 4**).

Seventy-one point four percent of patients were unable to exercise autonomy regarding the procedure decision. In these cases, informed consent was obtained through patient caregivers or, in at least one documented case of social abandonment, through independent medical judgment. No gastrostomies were performed on unidentified patients.

DISCUSSION

This represents the largest study published to date in Colombia regarding gastrostomies and, more broadly, bioethical aspects of medical practice. The in-hospital mortality rate in our cohort aligns with the 2.4% to 23.5% 30-day mortality rates reported in other studies and systematic reviews[6-9]. A global downward trend in these figures has been documented, likely due to improved patient selection[10]. The quarterly number of gastrostomies remained stable throughout the four-year follow-up period, despite the shift in primary indications from SARS-CoV-2 to other causes during and after the pandemic, as hospital capacity did not increase during this time. However, procedure complications occurred more frequently in SARS-CoV-2 patients, potentially due to higher obesity rates in this population, which increased technical difficulty and likely multiorgan failure predisposition.

Most deaths occurred within two weeks post-procedure. This early mortality pattern was previously observed in Colombia by Dr. Atencio's study of patients over 60 years old, which reported 38% mortality within the first month after gastrostomy[11]. This phenomenon was also documented in a 2004 UK study that recommended implementing a one-week waiting period after gastrostomy request[11].

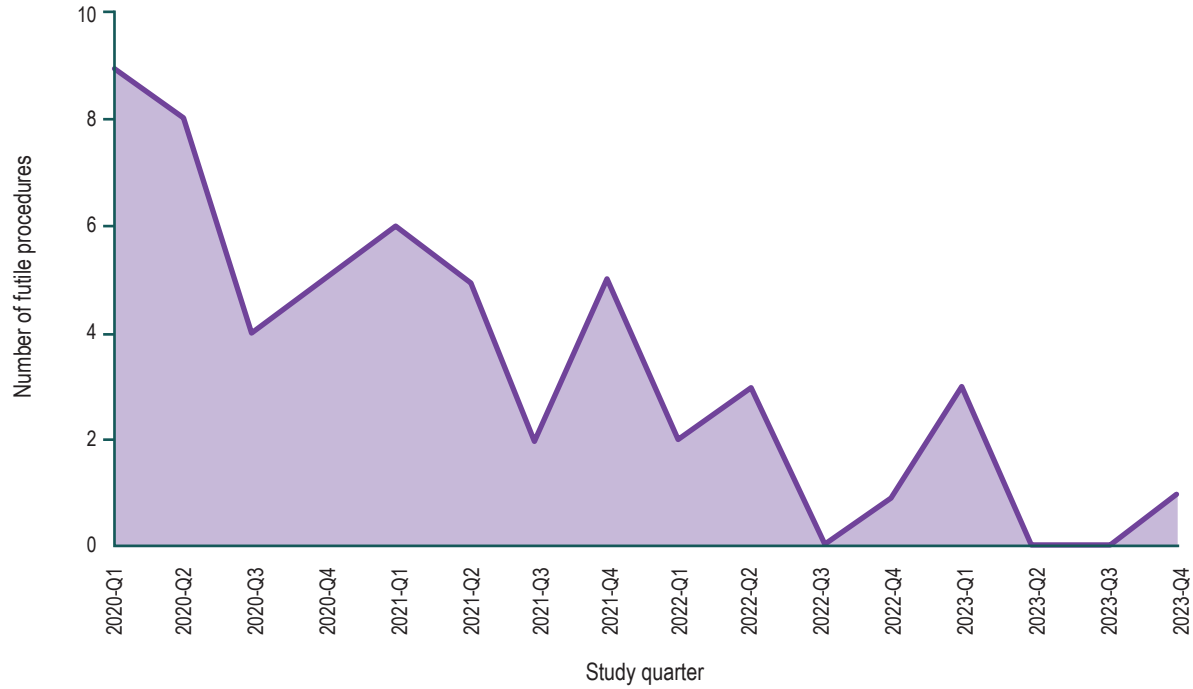


Figure 4. Futile procedures by study quarter. Image property of the authors.

This "reflection period" aims to better select patients who would genuinely benefit from the procedure and avoid potential futility. While challenging to implement in daily practice, clinicians are advised to prudently delay the procedure when patient conditions permit. Following this approach would allow gastrostomies to be performed on more stable patients with fewer coagulation disorders and less psychomotor agitation, thereby reducing complications. When procedure futility is uncertain, consultation with the institutional ethics committee is recommended. Furthermore, bioethical considerations, including potential futility, should be incorporated into institutional procedure protocols. For gastrostomies, procedures should be avoided when no benefit is expected–particularly in cases of advanced dementia, permanent vegetative state, or life expectancy under three months[12,13]. Unfortunately, gastrostomies for advanced dementia remain common practice in our setting, representing 30% of procedures in Dr. Atencio's study.

Our cohort demonstrated a progressive reduction in futile gastrostomies, most likely attributable to healthcare staff adherence to patient selection guidelines disseminated by the gastroenterology service in late 2020.

The 10.4% futile gastrostomy rate in this cohort may appear low or insignificant compared to research on new technologies or medications. For perspective, events such as post-ERCP pancreatitis (under 10%), herpes zoster in JAK inhibitor users, peroral endoscopic myotomy (POEM) failure for achalasia, and lifetime gastric cancer risk in untreated *Helicobacter pylori* patients all occur at rates below 10% yet warrant meta-analyses[14-17]. While gastrostomy represents a routine gastroenterology procedure, its ethical considerations often receive secondary attention. Preventing futile procedures simply requires careful consideration of short-term prognosis and clinical scenarios where no benefit is expected.

The study has several limitations. Its retrospective design resulted in scarce data regarding futility indicators such as patients' prior functional class and life expectancy, which are not routinely documented in medical records. Data on post-discharge mortality, subsequent hospitalizations, or home outcomes were also unavailable. While this study specifically evaluated in-hospital mortality, these additional data could help estimate short- to medium-term mortality. Gastrostomy site infection rates are likely underestimated, as complication data were obtained only from cases requiring endoscopic reintervention or gastroenterology consultation–services not always requested.

The study's strengths include its large patient cohort, comparison between SARS-CoV-2 pandemic and post-pandemic periods, and demonstration of the impact of an institutional gastrostomy indication protocol. Future

research could evaluate mortality prediction scales for various conditions requiring this procedure to help prevent futile interventions.

Notably, no medical records mentioned discussions with patients or caregivers about advance directives or prior informal expressions of treatment preferences. While institutional protocols required informed consent for all procedures, no documentation addressed patients' actual wishes regarding the procedure. This raises serious concerns about the ethical framework for obtaining medical intervention authorizations.

CONCLUSION

Approximately 10% of gastrostomies performed in the evaluated cohort met standardized futility criteria. Implementing a 1-2 week waiting period after procedure recommendation could reduce this percentage. Each institution should establish its own protocol regarding procedural futility or an ethics committee to provide guidance on this matter. **Table 4** presents recommendations for improved patient selection for gastrostomy, based on bioethical and legal considerations of this issue[18].

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Conflicts of Interest and Funding Sources

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Artificial Intelligence Use Statement

No artificial intelligence was used in the preparation of this study.

Table 4. Recommendations to Avoid Futility in Gastrostomy Requests

Step	Note
1. Confirm medical indication for procedure	- Avoid futile indications - Implement 1–2 week "reflection period"
2. Inquire about patient's concept of *quality of life*	- Remember, dignity interpretations are individual - Base decisions on patient's own quality of life standards
3. Obtain informed consent	- Ask about advance directives, prior informal expressions, or surrogate consent. In most cases, "medical best judgment" alone is unnecessary
4. Perform and re-evaluate indication	- Previous decisions can be reversed if the assessment changes

Table prepared by the authors.

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Original article

Low-Dose Ketamine in Combination with Midazolam for Diagnostic Upper Gastrointestinal Endoscopy: Case Report

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Abstract

Introduction and objectives: The number of outpatient endoscopic procedures in gastroenterology has increased in recent years. During the pandemic, due to drug shortages, alternative sedation techniques were explored. This study describes the sedation profile and adverse effects of combining low-dose ketamine with midazolam for sedation during diagnostic upper gastrointestinal endoscopy (UGIE). **Materials and methods:** A prospective, observational, descriptive case series study was conducted involving 30 patients aged 18 to 70 years with ASA physical status classification I or II, who underwent diagnostic UGIE. Sedation was induced with 0.03 mg/kg of midazolam and 0.3 mg/kg of ketamine prior to endoscopy. During and after endoscopy, the need for additional sedative medications and the occurrence of major adverse events (e.g., cardiorespiratory arrest or death) and minor events (e.g., desaturation, apnea, laryngospasm, hypertension, tachycardia, coughing, hypersalivation, dizziness, and recall of the procedure) were documented. Procedure duration, recovery time, and depth of sedation were also recorded. **Results:** Effective sedation was achieved in 27 ASA I and II patients without the need for additional sedatives to achieve the endoscopic procedure. The mean procedure time was 7.9 minutes, and the average recovery time was 26.1 minutes. Adverse events were observed in 66% of patients during the procedure (the most frequent being elevated blood pressure in 45.9%) and in 63.4% during recovery (most commonly dizziness in 50%). **Conclusions:** The combination of low-dose ketamine and midazolam appears to be a safe and effective sedation strategy for diagnostic UGIE, with minor adverse effects reported in more than 50% of patients.

Keywords

Gastrointestinal endoscopy, conscious sedation, ketamine, midazolam, safety.

INTRODUCTION

The pandemic caused by the emergence of the SARS-CoV-2 coronavirus (severe acute respiratory syndrome coronavirus 2) in 2020 has led to significant changes in healthcare delivery for patients worldwide. One of the challenges anesthesiologists have faced is the shortage of sedation medications due to the high demand for these drugs in intensive care units (ICUs) for sedating and providing analgesia to patients requiring invasive mechanical ventilation due to the coronavirus. Among the most commonly used medications at risk of shortage in various institutions in Colombia is the hypnotic agent propofol[1,2].

At Hospital Universitario San Ignacio, an average of 1,982 patients per year undergo gastroenterological procedures under sedation administered by anesthesiologists, and of these, approximately 13% (258) require diagnostic upper gastrointestinal endoscopies. Given that diagnos-

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tic procedures such as upper gastrointestinal endoscopy must continue to be performed, anesthesiologists have had to explore alternative pharmacological options[3].

Ketamine was first synthesized in 1962 and approved for human use by the Food and Drug Administration (FDA) in 1970. This drug exerts its effects through non-competitive antagonism of N-methyl-D-aspartate (NMDA) receptors, as well as through interactions with opioid, monoaminergic, cholinergic, and purinergic receptors, inhibition of non-NMDA glutamate receptors, and nitric oxide synthase[4]. Its administration induces a dose-dependent dissociative anesthetic state, along with psychodysleptic effects such as visual and auditory hallucinations, vivid dreams, altered time-space perception, and depersonalization.

In the cardiovascular system, ketamine has a stimulant effect mediated by the sympathetic nervous system, resulting in increased heart rate, cardiac output, and blood pressure. It has minimal impact on central respiratory drive, and at low doses, it preserves protective airway reflexes. Additionally, it induces smooth muscle relaxation, leading to bronchodilation and increased secretion production. Furthermore, due to its antagonism of NMDA receptors in the spinal cord, it has a potent analgesic effect that prevents central pain amplification. For these reasons, ketamine has been considered an alternative for anesthetic induction or sedation in patients with hemodynamic instability, airway hyperreactivity, or bronchospasm undergoing various procedures[5]. It has also been studied as part of multimodal analgesia regimens for acute or chronic pain management, asthma exacerbations, certain psychiatric conditions such as depression and substance addiction, and is even known for its recreational use[6].

Ketamine has been used over time, either alone or in combination with other medications, to achieve varying levels of sedation in adult and pediatric patients undergoing different procedures. Multiple studies in the literature describe the effectiveness and safety of various sedation regimens that include ketamine for gastroenterological procedures in children[7-10]. In contrast, evidence on the use of ketamine for sedation during gastroenterological procedures in adults is scarce. Due to the current situation of the SARS-CoV-2 pandemic and based on the limited evidence available in pediatric patients, this institution began using ketamine as a pharmacological alternative for sedating adult patients undergoing diagnostic upper gastrointestinal endoscopy. The goal was to find a drug combination with rapid recovery, comfort for the patient, anesthesiologist, and gastroenterologist, and a safety profile similar to or better than that of traditionally used medications, without serious adverse effects.

Therefore, the objective of this study is to describe the sedation profile, effectiveness (measured by whether the procedure could be performed and satisfaction with it), and safety provided by the use of low-dose ketamine in combination with midazolam for diagnostic upper gastrointestinal endoscopy in adult patients at Hospital Universitario San Ignacio. Based on the results of this study, we hope to conduct a subsequent randomized study comparing the commonly used medications or combinations (propofol and remifentanil) with the one used in this study (ketamine and midazolam).

MATERIALS AND METHODS

Data collection was conducted at Hospital Universitario San Ignacio between January and March 2022, involving a total of 30 patients for this prospective, descriptive, observational case series study, following the CARE checklist specific to this type of study.

Patients were included during pre-anesthetic evaluation prior to outpatient endoscopic procedures by two principal investigators based on the following inclusion criteria: patients aged 18–70 years, classified as ASA I or II by the American Society of Anesthesiologists, and scheduled for diagnostic upper gastrointestinal endoscopy. Exclusion criteria included pregnancy, active upper gastrointestinal bleeding, emergency procedures, psychiatric or neurocognitive disorders, additional interventions such as variceal ligation or polypectomy, and known allergies to ketamine or midazolam. Initial demographic data—age, sex, identification number, weight, medical history, and ASA classification—were recorded and verified using the hospital's electronic health record system (SAHI).

After obtaining informed consent, standard monitoring was implemented (blood pressure, electrocardiogram, peripheral oxygen saturation [SpO_2], and nasal capnography), alongside oxygenation via nasal cannula (target SpO_2 >90%) and peripheral venous access. Topical anesthesia (lidocaine aerosol) was applied to the oral cavity, followed by midazolam (0.03 mg/kg). After 2 minutes, ketamine (0.3 mg/kg) was administered. Sedation depth was assessed before proceeding with endoscopy. Intraprocedural data included: need for additional medications, major adverse events (e.g., cardiopulmonary arrest, death), and minor adverse events (e.g., desaturation, apnea, laryngospasm, agitation, excessive secretions requiring suctioning, hypertension, hemodynamic changes). Post-procedure monitoring in the recovery room included Aldrete scoring (10/10 for discharge) and documentation of minor adverse effects (e.g., hallucinations, unpleasant recall, dizziness, nausea/emesis). Patients rated sedation satisfaction on a 1–10 numeric scale (0: extremely poor experience; 10: pleasant, repeatable experience).

All procedural and post-procedural variables were recorded in a standardized RedCap (Research Electronic Data Capture) form, using only identification numbers for anonymization to comply with research ethics. Basic analysis was performed, with data presented in tables and figures.

Statistical Analysis

A descriptive analysis was conducted for event frequencies, including patient sedation states (ASA classification for sedation depth), adverse events during procedures/recovery, need for additional medications, and patient satisfaction.

Ethical Considerations

Recruited patients received a full study explanation, had questions addressed, and provided signed informed consent. Procedures adhered to the ethical standards of the 2005 Declaration of Helsinki. The study was approved by Hospital Universitario San Ignacio ethics committee (approval No.: FM-CIE-0753-21).

RESULTS

A total of 30 patients were enrolled, of whom 23 were female (76.6%) and 7 male (23.3%), with various comorbidities (**Table 1**). Ages ranged from 20 to 70 years (mean: 54). Based on comorbidities, patients were classified as ASA I (8 patients, 26.6%) or ASA II (22 patients, 73.3%). Sedation depth achieved with the drug combination was assessed using the ASA sedation scale (**Table 2**): 0% achieved Grade I (anxiolysis), 86.6% Grade II (conscious sedation), and 13.3% Grade III (deep sedation/analgesia). Procedure duration, recovery time (until achieving discharge-ready status per Aldrete score [10/10]), and effectiveness rates are detailed in **Table 3**. The procedure was successfully completed in 100% of patients, with additional medications required in 3 cases (10%). Cases requiring adjunct medications had endoscopic durations exceeding 10 minutes. Atropine was administered once for excessive salivation.

Table 1. Preoperative Characteristics

Characteristics	n (%)
Total patients	30
Age, years (mean, range)	54 (20-70)
Sex	
- Female	23 (77)
- Male	7 (23)
ASA	
- Grade I	8 (27)
- Grade II	22 (73)
Hypertension	8 (27)
Diabetes mellitus	5 (16)
Cardiac disease (ischemic, valvular, arrhythmic)	3 (10)
Hypothyroidism	7 (23)
Oncologic pathology	3 (10)
HIV	1 (3)
Pulmonary disease (OSAHS, COPD, asthma, PE)	9 (30)
Liver disease	1 (3)
Arthritis	1 (3)
Obesity	3 (10)
None	8 (27)

ASA: American Society of Anesthesiologists; COPD: chronic obstructive pulmonary disease; OSAHS: obstructive sleep apnea-hypopnea syndrome; PE: pulmonary embolism; HIV: human immunodeficiency virus. Table prepared by the authors.

Adverse events during the procedure and recovery are shown in **Figures 1** and **2**. The most frequent were hypertension (45.9% intraprocedural) and dizziness (50% during recovery). Adverse event incidence was 66% intraprocedural and 63.4% postprocedural, though no major events (cardiopulmonary arrest/death) occurred. Mean satisfaction score was 9.5 (range: 6–10), as shown in **Table 3**.

Table 2. ASA Classification of Sedation States

Characteristics	Grade I	Grade II	Grade III	Grade IV
Response	Normal response to verbal stimulus	Purposeful response to verbal/tactile stimulus	Purposeful response to repeated/ tactile/painful stimulus	Unresponsive to painful stimulus
Airway	Unaffected	No intervention needed	May require intervention	Usually requires intervention
Spontaneous ventilation	Unaffected	Adequate	May be inadequate	Frequently inadequate
Cardiovascular function	Unaffected	Maintained	Usually maintained	May be impaired

Table prepared by the authors.

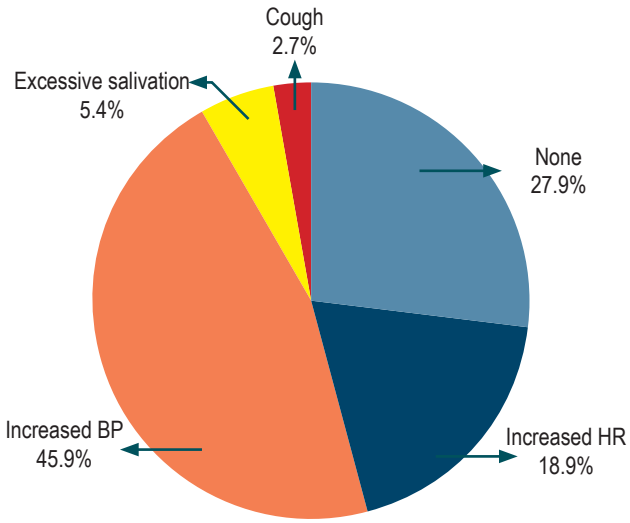


Figure 1. Adverse events during the procedure. Adverse events observed during surgery are shown, with the most frequent being increased blood pressure in 45.9% of cases (orange), followed by increased heart rate in 18.9% (blue), excessive salivation in 5.4%, and cough in 2.7%. All were minor adverse events, with no major events such as cardiopulmonary arrest or death reported. HR: heart rate; BP: blood pressure. Image property of the authors.

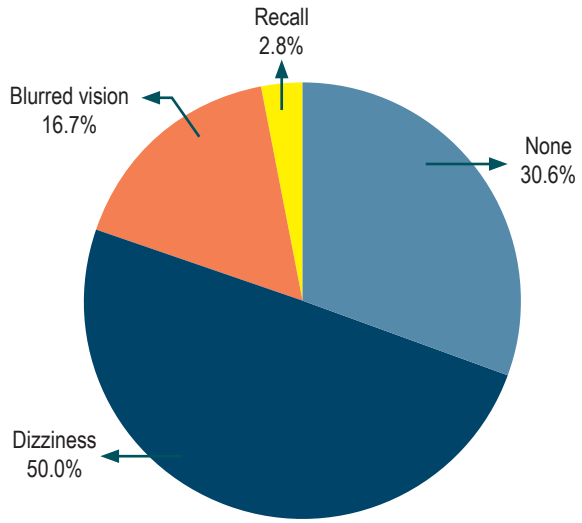


Figure 2. Adverse events during recovery. Adverse events observed during recovery are shown, with the most frequent being dizziness in 50% of cases (blue), followed by blurred vision in 16.7% (orange), and recall in 2.8% of patients. No major adverse events occurred. Image property of the authors.

Table 3. Outcomes

Item	
Mean procedure time, min (range)	7.9 (5-25)
Procedures without adjunct medications (%)	27 (90%)
Procedures with adjunct medications (%)	3 (10%)
Satisfaction score (1–10), mean (range)	9.5 (6-10)
Procedure completion rate (%)	100%
Recovery time, min (range)	26.1 (15-50)

Table prepared by the authors.

DISCUSSION

This study evaluated the feasibility of performing diagnostic upper gastrointestinal endoscopy in ASA I and II patients using low-dose ketamine and midazolam, with adequate patient satisfaction. The procedure was successfully completed using midazolam + ketamine in 90% of cases, while the remaining 10% required additional propofol doses–two of these cases were associated with endoscopic durations exceeding 10 minutes. ASA Grade I and II sedation levels were achieved, providing an adequate plane for successful low-complexity outpatient diagnostic procedures.

No major adverse events occurred during procedures or recovery. Minor intraprocedural adverse events occurred in 66% of cases, predominantly blood pressure increases >20% from baseline (without emergency criteria in any case), directly related to ketamine's catecholamine-mediated mechanism. Minor recovery-phase adverse events occurred in 63.4% of cases, with dizziness being most prevalent (50%). No patients experienced emesis. Despite >50% prevalence of minor events during and after procedures, mean patient satisfaction was 9.5, with a 100% procedural success rate by gastroenterologists. Average recovery time was <30 minutes–appropriate for outpatient procedures and comparable to other widely used sedation methods.

Several small descriptive studies have been published evaluating ketamine's use and safety, either alone or in combination with other medications, for inducing sedation in patients undergoing endoscopic procedures[7-9]. Most of these studies were conducted in pediatric populations, assessing various sedation protocols with ketamine doses ranging from 0.5 to 1 mg/kg. While the results are not definitive, these studies agree that ketamine–whether used alone or in combination–achieves adequate conditions for endoscopic procedures performed by gastroenterologists, with proper hemodynamic stability typically characterized by increased blood pressure and heart rate, and without major respiratory complications. Some cases reported minor procedural complications such as excessive

salivation, stridor, and laryngospasm, which were easily managed and did not lead to adverse outcomes[10]. Notably, this study used lower ketamine doses than those described in the literature, with similar effectiveness and no negative respiratory outcomes.

This study suggests that low-dose ketamine combined with midazolam is effective and provides an adequate safety profile compared to other commonly used combinations like propofol, remifentanil, and fentanyl. A key benefit of this technique is that none of the patients developed hypoxemia (defined as SpO_2 <90%), a complication reported with various combinations of the aforementioned medications, potentially offering a safer alternative during drug shortages.

Although this is not a randomized clinical trial, the findings may be generalizable to the broader population and represent an excellent option for ASA I and II patients when resources are limited, as during the SARS-CoV-2 pandemic. Beyond study design limitations, potential measurement bias may exist since the evaluating anesthesiologists were study participants. Additionally, the sample size was small. Finally, while procedures were successfully completed in 100% of cases, endoscopist satisfaction was not assessed.

Currently, no studies compare propofol versus ketamine for low-grade diagnostic outpatient endoscopic procedures in adults. This study, therefore, opens possibilities for future research, particularly randomized clinical trials comparing low-dose midazolam-ketamine combinations with standard medications like propofol to determine effectiveness, safety, and satisfaction among patients, gastroenterologists, and anesthesiologists across low- and high-risk populations.

CONCLUSIONS

Low-dose ketamine-midazolam sedation may be a reasonable alternative for low-complexity endoscopic procedures given its effectiveness and safety profile, particularly the low hypoxemia incidence. This makes it potentially suitable for high pulmonary-risk patients (e.g., morbid obesity, obstructive sleep apnea-hypopnea syndrome [OSAHS], difficult airway), while offering competitive recovery times and costs. However, optimal sedation duration proved insufficient for procedures exceeding 10 minutes.

Conflict of Interest Statement

The authors declare no conflicts of interest.

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Original article

Factors Associated with Complications in Sedation Administered by Non-Anesthesiologist Physicians During Outpatient Endoscopic Procedures

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Abstract

Objective: To identify clinical and sociodemographic factors associated with complications related to superficial sedation administered by non-anesthesiologist physicians during outpatient endoscopic procedures. **Materials and methods:** An analytical cross-sectional study was conducted, including 680 patients undergoing endoscopic procedures over a 32-day period. Clinical and demographic variables, type of procedure, sedative agents, need for additional dosing, and major and minor complications were evaluated. **Results:** The majority of patients were female (64%), with a mean age of 49.6 years. Esophagogastroduodenoscopy (EGD) was the most common procedure (62.6%). Most patients were classified as ASA I (58.2%), with hypertension and hypothyroidism being the most frequent chronic conditions. The average doses administered were 5.3 mg of midazolam and 83.9 µg of fentanyl; 36.3% of patients required additional doses. Minor complications occurred in 13% of patients, primarily hypotension and oxygen desaturation. No major complications were reported. In the bivariate analysis, minor complications were significantly associated with obesity (PR = 2.76; 95% CI: 1.333–5.739; p = 0.013), undergoing combined EGD and colonoscopy in a single session (PR = 1.53; 95% CI: 1.04–2.24; p = 0.028), colonoscopy alone (PR = 1.65; 95% CI: 1.05–2.58; p = 0.031), and fentanyl doses greater than 75 µg (PR = 2.13; 95% CI: 1.40–3.23; p < 0.001). **Conclusions:** A thorough medical history should be obtained prior to any procedure to identify relevant comorbidities. Sedative agents, particularly fentanyl, must be used with caution and appropriate dosing. Procedures of longer duration should be carefully planned to minimize the risk of complications.

Keywords

Conscious sedation, endoscopy, postoperative complications, endoscopic surgical procedures.

INTRODUCTION

Conscious sedation is characterized by a controlled reduction in alertness and pain perception while maintaining stable vital signs, airway protection, and spontaneous ventilation[1]. In Colombia, the Colombian Society of Anesthesiology and Resuscitation (SCARE) has issued recommendations for sedation and analgesia administered by non-anesthesiologist physicians, stating that outpatient endoscopic procedures under Grade I (anxiolysis) and Grade II (conscious sedation) sedation can be performed with a good safety profile[2]. This practice is permitted as long as patients are classified as ASA I or II and the personnel involved have the necessary academic training to carry out the procedure. The safety of this technique depends on careful patient selection, adequate staff training, and the implementation of appropriate safety policies and guidelines for the outpatient setting[3,4]. Although conscious sedation can be an effective, practical, and safe technique in outpatient care, it is important to consider the associated risks.

This study aims to identify potential complications related to conscious sedation and determine the factors

associated with their occurrence. The assessment seeks to guide the adoption of safe practices that help reduce the incidence of complications and adverse events related to sedation during endoscopic procedures.

MATERIALS AND METHODS

An analytical cross-sectional study was conducted on the clinical and sociodemographic factors associated with complications in sedation practices administered by non-anesthesiologist physicians in patients undergoing endoscopic procedures. The study was carried out at a specialized gastroenterology institute in Medellín from November 22 to December 23, 2023. Patients aged 13 to 75 scheduled primarily for upper and lower gastrointestinal endoscopy, classified as ASA I or II, and who provided informed consent for the procedure were included. These examinations were performed by a team of 11 gastroenterologists and 5 sedation physicians. Patients with predictors of difficult airways or those who did not receive sedative medications for the procedure were excluded. The variables analyzed included the patient's medical and demographic history, type of endoscopic procedure, sedative agents used, administered sedative doses, need for additional doses, and minor and major complications.

The following clinical conditions were considered minor complications: hypotension (a 30% decrease from baseline blood pressure), arrhythmias (heart rate >100 beats per minute [bpm] or a 20% drop from baseline heart rate), hypertension (systolic or diastolic blood pressure >180/110 mmHg), and desaturation (SpO_2 <90% for more than 15 seconds). Major complications were defined as those requiring orotracheal intubation, cardiopulmonary arrest, or death. The study was approved by the Institutional Ethics Committee and deemed risk-free since it did not involve any intentional intervention or modification of the biological, physiological, psychological, or social variables of the participants. The study also adheres to the fundamental principles of research ethics in accordance with the 2013 version of the Declaration of Helsinki[5] and Resolution 008430 of 1993 issued by the Colombian Ministry of Health[6].

Statistical Analysis

A database was created using clinical records in Excel 2013. Statistical analysis was performed using OpenEPI web and Jamovi version 2.2. Absolute and relative frequencies were calculated for qualitative variables, while measures of central tendency and dispersion were used for quantitative variables. Bivariate analysis was conducted using the chi-square test for dichotomous qualitative variables, with a *p*-value <0.05 considered statistically significant. The strength of the association was assessed using prevalence ratios.

RESULTS

Data were collected from 680 patients who underwent 924 endoscopic procedures. The results revealed a sex distribution of 64% female patients, with a mean age of 49.6 years.

Regarding procedures, esophagogastroduodenoscopy (EGD) was the most commonly performed, accounting for 62.6% of all procedures. ASA classification showed that 58.2% of patients were categorized as ASA I, while the remaining were ASA II. The most prevalent chronic conditions in the study population were hypertension (16.6%) and hypothyroidism (11.3%) (**Table 1**).

During the study, 13% of patients experienced sedation-related complications. Among these, hypotension (6.7%) and desaturation (3.4%) were the most common. Notably, all cases of arrhythmia (2.6%) were sinus-related, predominantly bradycardia (82.4%). No major complications were recorded. The distribution of complications is detailed in **Table 2**.

Regarding sedation medications, the average initial doses—regardless of the procedure—were as follows: midazolam 5.3 mg (range: 3–8 mg) and fentanyl 83.9 µg (range: 50–150 µg). A total of 36.3% of patients required additional medication during the procedure, either through titration of the initial drugs or the addition of ketamine.

Analysis of associations with medical history revealed that only obesity was significantly associated with complications (PR = 2.76, 95% CI: 1.333–5.739; *p*-value = 0.013). Additionally, a significant association was found between procedure type and complications: colonoscopy (PR = 1.65, 95% CI: 1.05–2.58; *p*-value = 0.031) and simultaneous EGD + colonoscopy (PR = 1.53, 95% CI: 1.04–2.24; *p*-value = 0.028). Conversely, patients undergoing EGD alone were less than half as likely (0.48 times) to experience sedation-related complications compared to those who did not undergo this procedure: PR = 0.48, 95% CI: 0.31-0.72, *p*-value <0.001.

No significant association was found between midazolam dose and minor complications, likely due to low variability in administered doses. In contrast, fentanyl doses >75 µg were associated with a higher risk of complications (PR = 2.13, 95% CI: 1.40–3.23; *p*-value < 0.001), whereas doses ≤75 µg had a protective effect (PR = 0.46, 95% CI: 0.30–0.70; *p*-value = 0.0003).

DISCUSSION

Over the past decade, there has been a notable increase in the use of non-anesthesiologist physicians to administer sedation during endoscopic procedures in gastroenterology,

Table 1. Summary of Demographic and Clinical Variables

Patient Characteristics	n = 680 (%)
Sex	
- Female	435 (64.0%)
- Male	245 (36.0%)
Age Group	
- 12 to 18	10 (1.5%)
- 19 to 26	36 (5.3%)
- 27 to 59	402 (59.1%)
- ≥60	232 (34.1%)
Procedure	
- Colonoscopy	343 (37.1%)
- Rectal echoendoscopy	2 (0.3%)
- Esophagogastroduodenoscopy	579 (62.6%)
ASA	
- I	396 (58.2%)
- II	284 (41.8%)
Medical History	**n = 680 (%)**
Hypertension	
- Yes	113 (16.6%)
- No	567 (83.4%)
Diabetes	
- Yes	40 (5.9%)
- No	640 (94.1%)
Obesity	
- Yes	14 (2.1%)
- No	666 (97.9%)
Respiratory Disease	
- Yes	13 (1.9%)
- No	667 (98.1%)
Hypothyroidism	
- Yes	77 (11.3%)
- No	603 (88.7%)
Psychiatric Disorders	
- Yes	34 (5.0%)
- No	646 (95.0%)

Table prepared by the authors.

Table 2. Frequency of Complications

Complications	n = 680 (%)
Presence of Complications	
- Yes	91 (13.4%)
- No	589 (86.6%)
Hypotension	
- Yes	46 (6.7%)
- No	634 (93.3%)
Hypertension	
- Yes	17 (2.5%)
- No	663 (97.5%)
Bronchospasm	
- No	680 (100.0%)
Laryngospasm	
- No	680 (100.0%)
Chest Rigidity	
- No	680 (100.0%)
Stridor	
- No	680 (100.0%)
Arrhythmia	
- Yes	18 (2.6%)
- No	662 (97.4%)
Desaturation	
- Yes	23 (3.4%)
- No	657 (96.6%)

Table prepared by the authors.

particularly in outpatient settings. This has sparked growing interest in understanding its impact on the safety, quality, and cost of such procedures. Internationally, various gastroenterology and anesthesiology societies—including the American Society for Gastrointestinal Endoscopy (ASGE), the European Society of Gastrointestinal Endoscopy (ESGE), the European Society of Anesthesiology, and the European Society of Gastroenterology—have published guidelines for procedures requiring sedation administered by non-anesthesiologists[7]. Questions have also arisen not only about who should administer sedation but also about the increasing use of medications previously restricted to deep sedation under an anesthesiologist's supervision, such as propofol[8-10].

In Colombia, the Colombian Society of Anesthesiology and Resuscitation (SCARE) recommends the use of medications for conscious sedation by non-anesthesiologist physicians, though some studies report the unregulated use of propofol[11,12]. This study did not include propofol due to the institution's adherence to current regulations regarding conscious sedation.

Complications associated with conscious sedation during endoscopic procedures include airway compromise (laryngospasm, bronchospasm) leading to desaturation or hypoxia, as well as hemodynamic events (hypotension, bradycardia), which in some cases may result in death[13]. This study recorded no major complications, consistent with findings from the multicenter *ProSed 2* study, which reported a major complication rate of 0.01% and a mortality rate of 0.005% in 368,206 procedures[14].

The incidence of minor complications varies in the literature, ranging from 5.3% in *ProSed 2* to 20% in a study conducted at Hospital San Martín in León, Argentina[15]. In the present study, it was 20%, aligning with previous research[16,17]. These complications were resolved with interventions such as Larson's maneuver, increased fraction of inspired oxygen (FiO_2), and anticholinergics like hyoscine for hypotension and bradycardia[18-20]. Obesity was identified as a significant risk factor for complications (p = 0.013; PR = 2.76; 95% CI: 1.333–5.739), highlighting the need for adjusted sedative dosing and close monitoring in these patients due to their higher risk of obstructive sleep apnea[21-24].

This study employed midazolam with fentanyl and, in some cases, ketamine as rescue medication for pain or anxiety. Doses exceeding 75 µg of fentanyl were associated with a significant increase in minor complications, underscoring the importance of careful administration (**Table 3**). No significant association was found between midazolam doses and complications, likely due to limited variability in its use.

Significant associations were observed between minor complications and combined procedures such as EGD/colonoscopy, while EGD alone showed lower risk, possibly due to its shorter duration and reduced sedative requirements[19].

CONCLUSIONS

Our study demonstrates that conscious sedation administered by non-anesthesiologist physicians during outpatient endoscopic procedures is safe, with a low incidence of minor complications and no major complications reported. Individualized planning of sedative medications—particularly fentanyl, which may affect respiratory and cardiovascular function depending on the dose—is crucial. Finally, prolonged procedures carry a higher risk of complications, emphasizing the need for effective time management during these interventions. These considerations are essential for classifying and preventing complications and determining whether patients should be referred for deep sedation under an anesthesiologist's care.

Table 3. Bivariate Analysis of Clinical and Demographic Factors in Patients Undergoing Conscious Sedation for Endoscopic Procedures

Characteristics	Complications		*p*-value
	Yes (%)	No (%)	
Sex			
- Female	58 (8.5%)	377 (55.4%)	0.96
- Male	33 (4.9%)	212 (31.2%)	
Age Group			
- 12 to 18	0 (0.0%)	10 (1.5%)	0.21
- 19 to 26	1 (0.1%)	35 (5.1%)	0.054
- 27 to 59	53 (7.8%)	349 (51.3%)	0.85
- ≥60	37 (5.4%)	195 (28.7%)	0.15
Procedure			
- Colonoscopy	20(2.9%)	79 (11.6%)	**0.031**
- EGD + COL	42 (6.2%)	202 (29.7%)	**0.028**
- Rectal echoendoscopy	0 (0.0%)	2 (0.3%)	0.57
- Esophagogastroduodenoscopy	29 (4.3%)	306 (45%)	**<0.001**
ASA			
- I	50 (7.4%)	346 (50.9%)	0.49
- II	41 (6%)	243 (35.7%)	
Medical History	**Complications**		***p*-value**
	Yes (%)	**No (%)**	
Hypertension			
- Yes	17 (2.5%)	96 (14%)	0.57
- No	74 (10.9%)	493 (72.5%)	
Diabetes			
- Yes	6 (0.9%)	34 (5%)	0.75
- No	85 (12.5%)	555 (81.6%)	
Obesity			
- Yes	5 (0.7%)	9 (1.3%)	**0.013**
- No	86 (12.6%)	580 (85.3%)	
Respiratory Disease			
- Yes	1 (0.1%)	12 (1.8%)	0.54
- No	90 (13.2%)	577 (84.9%)	
Hypothyroidism			
- Yes	6 (0.9%)	71 (10.4%)	0.12
- No	85 (12.5%)	518 (76.2%)	
Psychiatric Disorders			
- Yes	3 (0.4%)	31 (4.6%)	0.42
- No	88 (12.9%)	558 (82.1%)	
Midazolam Dose			
- ≤5 mg	71 (10.4%)	453 (66.6%)	0.81
- >5 mg	20(2.9%)	136 (20%)	
Fentanyl Dose			
- ≤75 µg	61 (9%)	275 (40.6%)	**<0.001**
- >75 µg	29 (4.3%)	312 (46.1%)	

ASA: American Society of Anesthesiologists classification; EGD + COL: Esophagogastroduodenoscopy and colonoscopy performed simultaneously. Table prepared by the authors.

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Review article

Research and Publication. Part 6. Key Aspects of the Discussion and Conclusions in a Scientific Article

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Abstract

Introduction: Publishing a manuscript in scientific journals allows for the dissemination of knowledge. However, for many researchers, writing the manuscript can be challenging, which delays the communication of their findings. The discussion section is arguably the most difficult part, as it involves interpreting the results, comparing them to existing knowledge, and recognizing the strengths and limitations of the study. **Objective:** To provide clear and practical recommendations for writing a strong discussion and conclusion section that enhances the overall quality of a scientific article. **Results and conclusions:** The discussion should clearly explain the main findings, compare them with those of previous studies, and address both the limitations and strengths of the research. It is essential to use clear, concise language and terminology that accurately conveys the implications of the results. The limitations section should detail the factors that may affect the generalizability of the findings, which in turn enhances the study's credibility. It can also be used to propose recommendations or new research questions to guide future investigations. The conclusions should be brief and straightforward, emphasizing the most important findings and their relevance. Ideally, the reader should come away with two or three key takeaways from the study.

Keywords

Research, journal article, epidemiological study design.

INTRODUCTION

Publishing articles in indexed scientific journals now enables broader and faster access to knowledge[(1)]. Writing a scientific article is an essential part of the research process; however, for many researchers, transforming findings into a clear and coherent text presents a challenge that may delay the dissemination of results[(1)].

After analyzing data and presenting results, the time comes to draft the discussion—one of the most demanding sections of the manuscript[(1,2)]. Here, authors interpret their findings in light of the proposed hypothesis and compare them with current evidence, conducting a critical analysis that requires clarity and depth[(1,2)]. For many authors, this section is the most complex, as it involves addressing multiple aspects: interpretation, comparison, argumentation, and acknowledgment of limitations, among others[(3,4)]. Many editors consider the discussion the core of the article, and its quality can determine whether the manuscript is accepted or rejected[(1,4)].

The discussion is closely linked to the introduction and results: it must answer the research questions posed at the outset[(3)]. Thus, along with the conclusions, it plays a key role in establishing the value of the study[(3)]. After the abstract, these sections receive the most attention from readers[(3)].

This article provides practical, clear recommendations for crafting a strong discussion and conclusions to enhance the quality of a scientific paper.

DISCUSSION: WHAT IS ITS PURPOSE?

The discussion aims to interpret study results clearly and comprehensibly[2]. It seeks to answer the research questions, assess whether findings support the proposed hypothesis, and suggest new avenues for investigation[2].

WHAT SHOULD THE DISCUSSION INCLUDE?

It should present key findings in accessible language, avoiding ambiguities that could lead to misinterpretation[2]. Additionally, authors must compare results with other studies, acknowledge limitations, and highlight strengths[3]. To guide writing, authors should ask: What are the most relevant findings? Do they confirm or contradict the hypothesis? What factors may have influenced them? How do they compare with other studies? What explanations justify differences? What new contributions do they make to knowledge?[5].

It is important to objectively relate results to other studies, recognizing biases and avoiding unfounded conclusions[2]. In cases of discrepancies or lack of evidence, authors should state whether results align with published data and how they might integrate to advance knowledge[1,3]. Another key point is acknowledging study limitations—from methodological aspects to factors affecting generalizability[3]; addressing them strengthens the work's credibility[2]. Finally, the discussion may conclude by proposing hypotheses for future research on the topic[5].

WHAT SHOULD BE AVOIDED?

Common mistakes must be avoided: misinterpreting results, introducing previously unreported data, making unsupported speculations, or drawing conclusions beyond the study's scope. All claims must be evidence-based and properly cited[2]. Unsubstantiated criticism should be avoided. Strengths and contributions should be highlighted without exaggeration to maintain a robust, credible discussion[2].

HOW TO WRITE THE DISCUSSION?

Writing the discussion section is often one of the most challenging tasks when preparing a scientific manuscript[1]. This section should be written in clear, direct, and accessible language, avoiding an authoritative tone, to help readers easily understand and interpret the study's findings[2,3]. During its preparation, it's helpful to use verbs that precisely communicate what the results show. Common examples include: demonstrate, indicate, reveal, suggest, confirm, illustrate, or imply[3]. These verbs can provide clarity and appropriate nuance based on the strength of the evidence presented.

Several valid strategies exist for beginning the discussion[2]. Some authors choose to start by directly answering the research question based on the obtained results. Others prefer to revisit the study's objective and relate it to the main findings, which helps build a solid foundation for the conclusions. Another approach is to list the most relevant results without repeating numerical data, giving readers an overview of the study without requiring them to constantly refer back to tables[2,4,6].

Below is an example of how the discussion section might begin[7]:

- Objective: The *MULTISTARS AMI* trial was designed to determine whether immediate multivessel percutaneous coronary intervention (PCI) during primary PCI was non-inferior to staged multivessel PCI in hemodynamically stable patients with multivessel coronary artery disease and ST-segment elevation myocardial infarction (STEMI).
- Discussion: Results from the *MULTISTARS AMI* trial showed that in patients with STEMI and multivessel coronary artery disease, immediate multivessel PCI was non-inferior to staged multivessel PCI regarding the risk of a composite of all-cause death, non-fatal myocardial infarction, stroke, unplanned ischemia-driven revascularization, or hospitalization for heart failure at one year. Several randomized controlled trials have demonstrated that complete revascularization is safe and reduces the risk of recurrent myocardial infarction and future revascularization in hemodynamically stable patients with STEMI and multivessel coronary artery disease.

The second part of the discussion should focus on interpreting the results, paying particular attention to comparing them with published findings from other authors. This critical comparison helps identify similarities, differences, and potential novel contributions of the study relative to existing literature[2]. To facilitate this, it's helpful to use expressions that appropriately qualify the degree of agreement or contrast with other studies. For instance, when results align with previous research, phrases like "similar to," "consistent with," "in line with," and "in agreement with" may be used. Conversely, when identifying differences or discrepancies, expressions such as "different from," "in contrast to," "contrary to," "in conflict with," or "differs from" are appropriate[3]. As an example, here's a model discussion opening that incorporates comparisons with other studies[8]:

- Objective: To characterize complications arising from sickle cell disease and transfusion therapy in patients treated at a tertiary care hospital in Medellín, Colombia.
- Discussion: This study described the main characteristics of transfusion therapy in the evaluated population.

We found that the primary indication for transfusion was symptomatic acute anemia, and that the vast majority of patients had undergone transfusion therapy during the course of their disease. Most patients had the homozygous SS phenotype, followed by double heterozygous SC, and finally heterozygous S-beta thalassemia–findings similar to those described in other populations from South America, Europe, and countries like Nigeria and Senegal. These latter countries are particularly relevant since hemoglobin S haplotypes in Colombia are predominantly of African origin, with significant associations between the SS phenotype and greater transfusion requirements in these populations. Most patients in our study were diagnosed with the disease within their first seven years of life. This contrasts with findings reported by Pinto et al. in 1991, who described that in a group of patients from Medellín, 50% of diagnoses were made after the age of ten.

Finally, it is essential to include a dedicated section outlining the study's limitations. These should be clearly and thoroughly described, considering aspects such as study design, participant inclusion/exclusion criteria, control of potential biases, and the scope or applicability of results[2,6]. Typically, these limitations are presented in a single paragraph placed immediately before the conclusion. Beyond acknowledging the study's weaknesses, this section provides an opportunity to propose new research questions or suggest future work addressing the identified challenges[3].

Below is an example of how to articulate limitations:

- Objective: To characterize the population with rapid ventricular response (RVR) atrial fibrillation (AF) presenting to an emergency department in Armenia, Quindío, during 2021-2022.
- Discussion, limitations section[9]: This study has several limitations. As a retrospective analysis, we had to exclude numerous patients due to incomplete medical records. Furthermore, being a single-center study, our findings cannot be generalized to other populations or healthcare settings with different resources. Future research should evaluate how different emergency department intervention strategies for AF management affect long-term clinical outcomes beyond success rates, including emergency department length of stay and RVR AF recurrence rates.

WRITING THE CONCLUSIONS

Depending on the target journal's format, conclusions may appear as a standalone section or be integrated at the discussion's end[3]. In either case, this section should be concise, clear, and direct, typically comprising 5-10% of the manuscript's total word count[10].

Conclusions should highlight the research's most relevant aspects, emphasizing contributions to existing knowledge and the implications of findings. This section also serves to propose specific recommendations for future research[3,10]. Effective conclusions directly address the study objectives. A helpful guiding question is: If readers remembered only two or three key ideas from the article, what should they be? These key points must be clearly articulated in the conclusion[3,10].

Example conclusion addressing study objectives[7]:

- Objective: The *MULTISTARS AMI* trial was designed to determine whether immediate multivessel percutaneous coronary intervention (PCI) during primary PCI was non-inferior to staged multivessel PCI in hemodynamically stable patients with multivessel coronary artery disease and ST-segment elevation myocardial infarction (STEMI).
- Conclusions: Among hemodynamically stable patients with STEMI and multivessel coronary artery disease, immediate multivessel PCI was non-inferior to staged multivessel PCI regarding the risk of all-cause death, nonfatal myocardial infarction, stroke, unplanned ischemia-driven revascularization, or hospitalization for heart failure at 1 year.

Below is a model conclusion highlighting key findings and their significance[8]:

- Objective: To characterize complications arising from sickle cell disease and transfusion therapy in patients treated at a tertiary care hospital in Medellín, Colombia.
- Conclusions: We observed high transfusion rates among sickle cell disease patients, with notably low utilization of red blood cell exchange for complications. While adverse transfusion reactions were infrequent, significant iron overload was apparent, underscoring the need for appropriate management strategies to mitigate this risk. These findings advance understanding of sickle cell disease clinical management and highlight the necessity for comprehensive approaches considering both benefits and risks associated with transfusion therapy.

CONCLUSIONS

This article provides practical guidance on essential elements for crafting a scientific manuscript's discussion section. This portion should be clear and concise, serving to integrate key findings, contrast them with existing evidence, and highlight both strengths and limitations. Furthermore, it should establish foundations for proposing new research questions based on obtained results, thereby contributing to continuous advancement of medical science knowledge.

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Review article

Association Between Polycystic Ovary Syndrome and Fatty Liver Disease in Women: A Literature Review

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Abstract

Introduction: Metabolic dysfunction-associated fatty liver disease (MAFLD) is a multisystem condition with a spectrum that begins with simple steatosis, followed by nonalcoholic steatohepatitis, and may progress to fibrosis. Its prevalence among women with polycystic ovary syndrome (PCOS) ranges from 34% to 70%, a relationship explained pathophysiologically by insulin resistance, obesity, hyperandrogenism, and other contributing factors. Currently, there is no approved treatment for either condition; therefore, management should focus on lifestyle modifications, including proper nutrition, weight loss, and physical activity—either as stand-alone strategies or in combination with pharmacological therapy. **Materials and methods:** This article reviews current evidence on the association between fatty liver disease and PCOS. A literature search was conducted using DeCS and MeSH terms in both Spanish and English, including studies published from 2014 to date. **Conclusion:** It is recommended that all women with PCOS undergo liver function testing and imaging studies (such as ultrasound and elastography) for the diagnosis of MAFLD.

Keywords

Nonalcoholic fatty liver disease, polycystic ovary syndrome, insulin resistance, obesity, hyperandrogenism.

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is a multisystem disorder encompassing various hepatic manifestations, including simple steatosis, nonalcoholic steatohepatitis (NASH), and progressive fibrosis. Its prevalence is rising and is characterized by hepatic steatosis affecting more than 5% of hepatocytes in the absence of other causes, such as excessive alcohol consumption, and may progress to cirrhosis[(1)]. Diagnosis is confirmed through histology or imaging studies[(1)]. NAFLD has been associated with obesity, insulin resistance, type 2 diabetes *mellitus* (T2DM), hypertension, and dyslipidemia[(2)].

A new terminology has been proposed for these conditions: metabolic dysfunction-associated steatotic liver disease (MASLD) instead of NAFLD, and metabolic dysfunction-associated steatohepatitis (MASH) instead of NASH. This updated nomenclature includes hepatic steatosis in the presence of at least one of five cardiometabolic criteria, such as overweight, hyperglycemia, hypertension, and dyslipidemia[(3)]. The diagnostic criteria for NAFLD/NASH remain valid for MASLD/MASH, particularly since studies show that up to 98% of NAFLD patients meet MASLD criteria[(4)]. This review uses the term MASLD instead of NAFLD and MASH for conditions related to NASH.

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Polycystic ovary syndrome (PCOS) is one of the most common endocrinopathies in reproductive-age women and the leading cause of oligoovulatory infertility. It is characterized by hyperandrogenemia, anovulation, elevated luteinizing hormone (LH) levels, and polycystic ovarian morphology on imaging[5]. Its prevalence varies depending on diagnostic criteria: 6%–10% using classic definitions[6], while the Rotterdam criteria identify 18%–20% of cases. The latter offers greater sensitivity and clinical utility by capturing a broader range of phenotypes beyond hyperandrogenism alone[7].

Multiple studies report a higher prevalence of NAFLD in women with PCOS (34%–70%) compared to the general population (14%–34%)[8]. Both conditions share common risk factors, including elevated serum androgens, obesity, and insulin resistance[9]. The liver-ovary axis theory suggests PCOS is an independent risk factor for NAFLD development and vice versa[10] (**Figure 1**).

METHODOLOGY

A narrative review was conducted, beginning with a literature search using the following DeCS (Health Sciences Descriptors) and MeSH (Medical Subject Headings) terms, as well as keywords in the search strategy: nonalcoholic fatty liver disease (NAFLD), polycystic ovary syndrome, insulin resistance, obesity, hyperandrogenism.

The search was limited to human studies published in Spanish and English from 2014 to the present. Animal studies and pediatric populations were excluded. Electronic databases including PubMed/Medline, Scopus, Embase, SciELO, and Science Direct were consulted. Additionally, manual searches were performed in gray literature databases and Google Scholar. All studies included in the review were thoroughly analyzed for scientific quality, considering their design and methodology. Ultimately, 21 articles were selected to complete the information presented in this text.

INSULIN RESISTANCE

Multiple studies have demonstrated an association between insulin resistance and fatty liver in women with PCOS[11]. Excess lipids lead to insulin resistance, which can result in cardiometabolic complications such as diabetes *mellitus*, cardiovascular disease, and fatty liver[9]. Similarly, increased insulin resistance has been observed in women with PCOS and hepatic steatosis[12].

Several associated mechanisms have been proposed. First, insulin resistance causes adipocyte dysfunction, disrupting lipolysis, increasing free fatty acids, reducing adiponectin secretion, and promoting the release of proinflammatory cytokines. These effects lead to lipid overload and accumulation in the liver, exacerbating hepatic steatosis and insulin resistance[13]. Decreased leptin and adiponec-

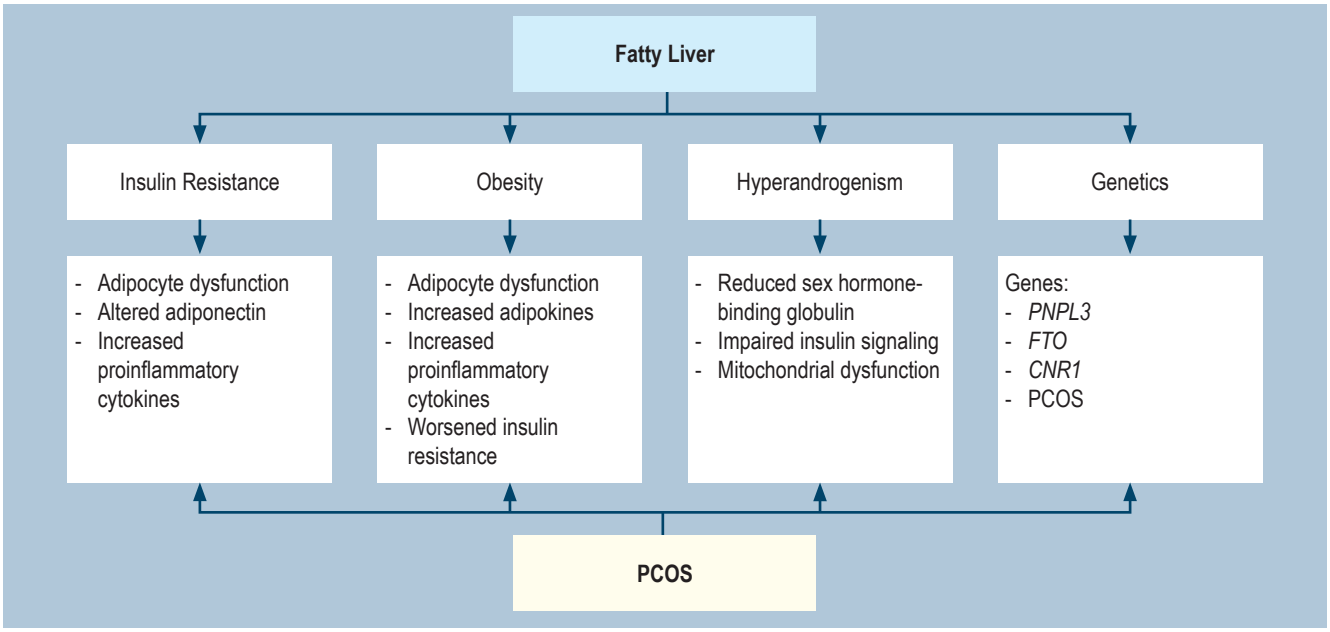


Figure 1. Pathophysiology of Fatty Liver and Polycystic Ovary Syndrome (PCOS). Image property of the authors.

tin levels are also associated with impaired insulin sensitivity[14]. Second, insulin resistance exerts both direct and indirect effects on the pituitary gland[15], stimulating androgen production, which reduces insulin clearance and leads to hyperinsulinemia[16]. Finally, MASLD and PCOS trigger a systemic inflammatory response involving nuclear factor kappa beta (NF-κB) activation and elevated proinflammatory cytokines. This activates stress-related protein kinases and induces phosphorylation of insulin receptor substrate 1 (IRS-1), impairing insulin signaling[17]. Proinflammatory cytokines and oxidative stress further inhibit signaling through IRS-1 and IRS-2[14].

When measuring insulin resistance, significantly higher values have been found in women with PCOS and hepatic steatosis compared to those with PCOS alone (HOMA-IR = 4.66 ± 2.78 vs. 2.26 ± 1.45; $p < 0.001$)[12]. A Chinese study found that NAFLD was significantly more prevalent in women with PCOS, and insulin resistance was also markedly more frequent[18]. Karoli et al. identified that women with PCOS had a higher prevalence of hepatic steatosis (67% vs. 25%; $p = 0.001$) and elevated transaminases (31% vs. 7%; $p = 0.03$), along with increased insulin resistance indices[19].

OBESITY

Obesity is a well-established risk factor for both hepatic steatosis and PCOS. Studies report that 50% of NAFLD patients and 80% of MASH patients are overweight or obese[20]. Among PCOS patients specifically, approximately 50% present with overweight or obesity[21]. Furthermore, excess weight has been linked to various cardiovascular risk factors shared by MASLD and PCOS patients[22].

Increased adipose tissue leads to elevated secretion of adipokines and cytokines—including leptin, adiponectin, tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), and interleukin-6 (IL-6)—resulting in higher circulating free fatty acids and leptin levels alongside reduced adiponectin. These changes promote insulin resistance and androgen production. Additionally, elevated follicular fluid insulin levels are observed, along with decreased sex hormone-binding globulin (SHBG), glucose transporter 4 (GLUT-4), and IRS-2 in granulosa and cumulus cells, exacerbating insulin resistance and fat accumulation. Ultimately, increased androgens and insulin resistance drive abdominal fat deposition, creating a self-perpetuating cycle[23].

A 2019 study found that abdominal obesity—defined as waist circumference >80 cm and BMI ≥25.0 kg/m^2—predicted fatty liver in PCOS patients versus healthy controls (p <0.001 for both parameters)[24]. Similar findings emerged in Petta et al.'s study, where PCOS patients had higher BMI (25.7 ± 2.9 vs. 23.9 ± 3.0 kg/m^2, p <0.001) and greater abdominal obesity prevalence (48.2% vs. 34.6%, p = 0.01) than controls. Steatosis independently correlated with waist circumference (OR: 1.04; 95% CI: 1.01–1.08; $p = 0.006$)[25].

HYPERANDROGENISM

SHBG is a sex steroid transporter with high affinity for testosterone in circulating plasma, regulating its bioavailability in target tissues[26]. PCOS patients characteristically demonstrate low SHBG levels–a hallmark feature associated with clinical manifestations of hyperandrogenism including hirsutism, alopecia, and acne[27]. Moreover, PCOS patients with reduced SHBG levels show increased risk of developing NAFLD[28].

Cellular studies demonstrate that decreased SHBG is associated with lower messenger RNA (mRNA) and protein levels of IRS-1, IRS-2, and PI3K, suggesting SHBG may be involved in insulin signaling pathways and insulin resistance[29]. Insulin resistance affects ovarian theca cells by increasing androgen production while decreasing hepatic SHBG synthesis, thereby elevating levels of free or biologically active testosterone[30]. Thus, reduced SHBG, hyperandrogenism, and insulin resistance form a vicious cycle that contributes to the increased prevalence and severity of both fatty liver disease and PCOS[10].

In Hong et al.'s study of 667 women diagnosed with PCOS and 289 controls with regular menstrual cycles, women with PCOS were 2.46 times more likely to have NAFLD (95% CI: 5.12-26.96). Total testosterone, free testosterone, and free androgen index showed the strongest correlation with this increased likelihood[31]. Another study in women with PCOS found that androgenicity, represented by free testosterone or free androgen index, was associated with nonalcoholic fatty liver disease (p <0.001) after adjusting for age, BMI, lipid profile, insulin resistance, and glycemic status[32].

OTHER FACTORS

Environmental factors have been linked to metabolic dysfunction, PCOS, and MASLD. A sedentary lifestyle and poor dietary habits can lead to overweight, obesity, and insulin resistance, resulting in cardiometabolic and reproductive disturbances[10]. Evidence suggests that diets high in sugar, particularly those rich in sucrose or high-fructose corn syrup, increase the risk of developing NAFLD and MASH[33].

Elevated thyroid-stimulating hormone (TSH) levels correlate with obesity, dyslipidemia, insulin resistance, fatty liver disease, and higher plasma total cholesterol concentrations[34]. Hypothyroidism frequently occurs in both MASLD patients and women with PCOS. Furthermore, elevated TSH levels may impair oocyte maturation and fer-

tilization in women with PCOS undergoing in vitro fertilization[35], and have been associated with increased all-cause and cardiovascular mortality in MASLD patients[36].

At the genetic level, mutations have been identified in the endocannabinoid receptor 1 gene (CNR1), patatin-like phospholipase domain-containing protein 3 (PNPLA3), and the fat mass and obesity-associated gene (FTO). Endocannabinoid system activity, influenced by the CNR1 gene, is significantly higher in overweight and obese patients with PCOS and metabolic dysfunction[37]. The *CNR1 rs12720071* variant has been associated with a threefold increased risk of PCOS (OR: 3.01), while the *CNR1 rs806368* variant correlates with an eightfold higher PCOS risk (OR: 8.81). Additionally, the *CNR1 rs12720071* variant has also been linked to a 3.6-fold increased risk of hyperandrogenism[38]. *CNR1* activation induces abdominal obesity, dyslipidemia, and insulin resistance in MASLD patients, whereas its blockade reduces transaminase levels and hepatic inflammation markers in women with PCOS[39].

DIAGNOSIS

PCOS should be suspected in women with irregular menstruation, acne, alopecia, and hirsutism[40]. Diagnosis is confirmed using Rotterdam criteria, requiring at least two of the following three criteria: oligo-anovulation, hyperandrogenism (clinical or biochemical), and polycystic ovarian morphology on ultrasound[41].

Hyperandrogenism is confirmed through the presence of hirsutism and biochemical assessment of circulating androgen levels, including free and total testosterone, as well as dehydroepiandrosterone sulfate. Ovulatory dysfunction is suspected in cases of polymenorrhea or oligomenorrhea and confirmed by measuring progesterone levels on days 22-24 of the menstrual cycle. Additionally, anti-Müllerian hormone (AMH) may be measured to assess increased antral follicle count. Transvaginal ultrasound helps identify polycystic ovarian morphology[42]. Following diagnosis confirmation, an oral glucose tolerance test and serum glucose measurements are recommended to evaluate insulin resistance[43]. Liver enzyme tests should also be performed to detect NAFLD-related abnormalities[6].

NAFLD diagnosis is based on histological, imaging, or serological evidence of hepatic steatosis, along with at least one of the following criteria: overweight/obesity, presence of type 2 diabetes, or at least two metabolic risk abnormalities[44]. Diagnostic evaluation includes liver function tests and hepatic imaging studies[45].

Liver biopsy remains the gold standard for NAFLD diagnosis and staging. However, due to its invasive nature, associated morbidity, and sampling error risk, noninvasive methods are preferred[46]. Ultrasound is the first-line imaging modality, though its sensitivity is limited (approximately 80% in cases with >30% fat infiltration) and performance decreases in subjects with BMI >40 or patients with mild steatosis (65% sensitivity)[47]. Transient elastography provides noninvasive measurement of liver stiffness and has been used to identify fibrosis. Similarly, magnetic resonance elastography is useful for assessing both hepatic steatosis and fibrosis[48].

We recommend the following algorithm for evaluating PCOS patients with suspected fatty liver disease (**Figure 2**).

MANAGEMENT STRATEGIES

The primary recommendations for managing PCOS and metabolic dysfunction-associated steatotic liver disease (MASLD) include lifestyle modifications, dietary adjustments, weight loss, and exercise—either alone or in combination with pharmacotherapy[49].

For women with PCOS, a 5%–10% weight loss over six months—particularly targeting abdominal fat—has been shown to: improve insulin sensitivity, restore ovulation, reduce testosterone levels, enhance conception rates, and lower miscarriage risk[50].

In NAFLD patients, a 3%–5% body weight loss correlates with improved hepatic steatosis, though a 10% reduction may be needed to ameliorate necroinflammation and fibrosis in some cases[51]. Notably, 90% of patients losing >10% of their weight achieved resolution of steatohepatitis, while 45% showed fibrosis regression[52].

The Mediterranean diet—characterized by reduced carbohydrate intake (especially sugars and refined carbs) and high monounsaturated fatty acid consumption—has demonstrated efficacy in reducing steatosis in fatty liver patients, even without significant weight loss[53]. However, evidence for dietary superiority in PCOS remains limited, with caloric restriction being the only universal recommendation[50].

Currently, no drugs are specifically approved for MASLD. Available pharmacologic options for PCOS aim to: reduce hepatic fat accumulation, improve insulin resistance, mitigate liver injury, and regulate ovulation and menstruation[49].

Pharmacological Therapy

- *Metformin*: This biguanide improves insulin sensitivity and helps control blood glucose by inhibiting gluconeogenesis. It activates AMP-activated protein kinase (AMPK) through a lysosomal pathway, suppresses gluconeogenic gene expression, and stimulates glucagon-like peptide-1 (GLP-1) release, thereby enhancing insulin secretion and GLUT-4 translocation in skeletal muscle[54,55]. While it has not proven effective for hepa-

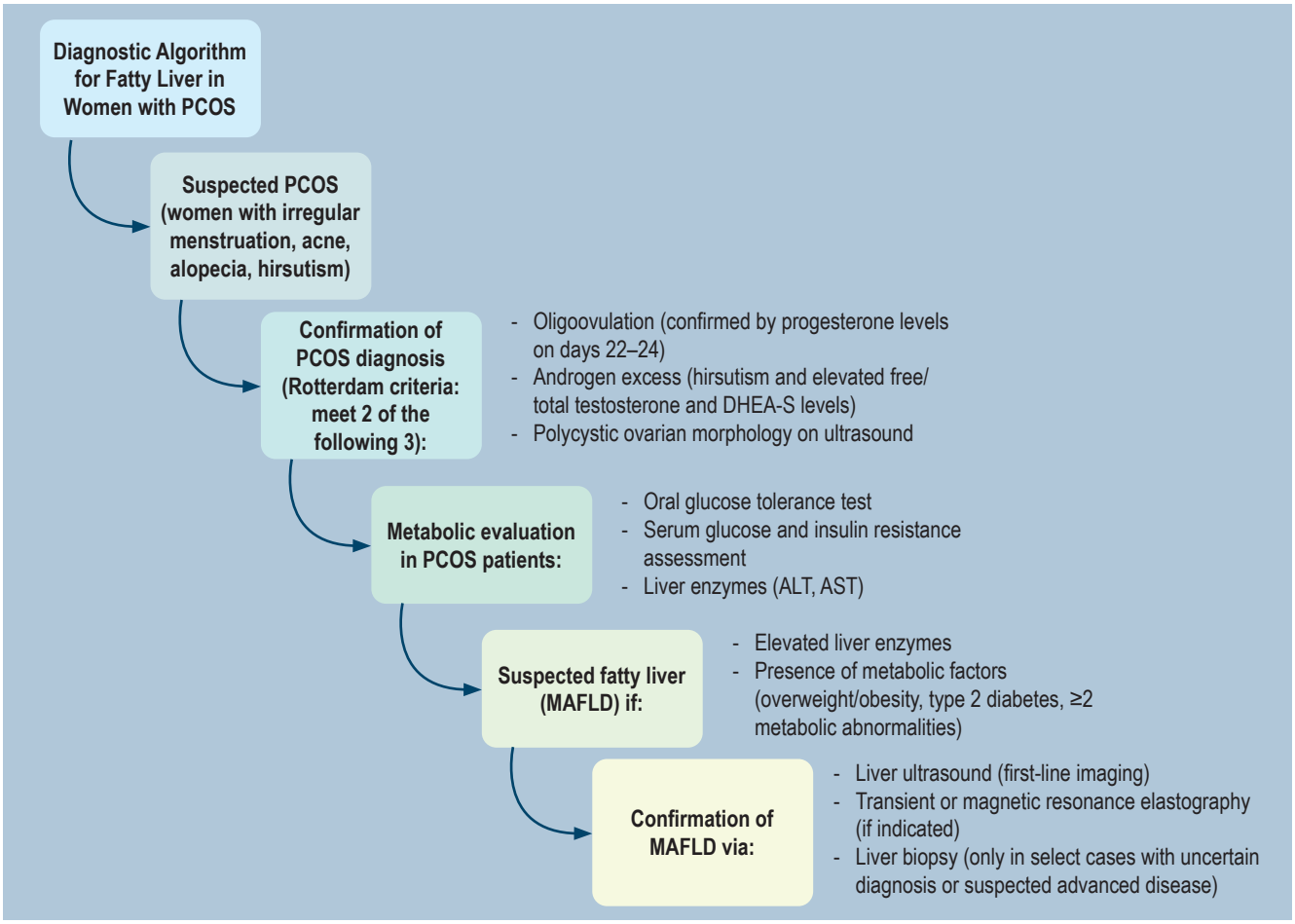


Figure 2. Diagnostic algorithm for nonalcoholic fatty liver disease in women with polycystic ovary syndrome. ALT: alanine aminotransferase; AST: aspartate aminotransferase; DHEA-S: dehydroepiandrosterone sulfate; MAFLD: metabolic dysfunction-associated fatty liver disease; PCOS: polycystic ovary syndrome. Image property of the authors.

tic steatosis—showing no superiority in histological or biochemical parameters for NAFLD patients[56]—it has demonstrated benefits in women with PCOS, including improved menstrual and ovulatory function, as well as potential advantages for insulin resistance and glucose control. Its use may be considered for women with metabolic abnormalities or those who fail to achieve therapeutic goals through lifestyle changes alone[50].

- *GLP-1 Receptor Agonists*: These agents may benefit both MASLD and PCOS, particularly in patients with insulin resistance, type 2 diabetes (T2DM), and dyslipidemia. They improve glycemic control, stimulate insulin secretion, protect pancreatic β-cells, and promote weight loss[57]. In MASH, they reduce steatosis, alleviate inflammation, and slow fibrosis progression[58]. Liraglutida has been associated with reduced liver enzyme levels[59], while semaglutida has shown decreases in alanine aminotransferase (ALT) and inflammatory markers[60]. For PCOS, these drugs may aid in weight and testosterone reduction[61]. One liraglutide study reported a 39% decrease in hepatic fat content and 5.6% body weight loss in PCOS patients after 26 weeks of treatment[62].
- *SGLT2 Inhibitors*: By inhibiting renal glucose reabsorption in the proximal tubule, these drugs lower serum glucose and promote urinary excretion of glucose and sodium. They also contribute to weight loss, improve diet-induced hepatic steatosis, and prevent MASH progression while reducing cardiovascular risk and improving blood pressure[63]. Though not specifically indicated for PCOS or MASLD, they show promise for these conditions. In a clinical trial with empagliflozin, significant reductions in anthropometric parameters (waist/hip circumference, BMI, lean mass) were observed in

women with PCOS, though hormonal and metabolic variables remained unchanged[64]. Caution is warranted for adverse effects, including urinary tract infection risk and euglycemic ketoacidosis in diabetic patients[65].

- *Vitamin E*: As an antioxidant, it may reduce inflammation and oxidative stress. While it has been shown to decrease steatosis, it lacks significant effects on liver fibrosis[48]. Its use may be considered for MASH in non-diabetic patients, but evidence is insufficient for T2DM or advanced fibrosis cases. The stroke risk associated with long-term use should be evaluated[66].
- *Hormonal Therapy for PCOS*: Combined oral contraceptives are recommended to regulate menstrual cycles, reduce hirsutism, and improve acne[67]. For contraindicated or intolerant patients, antiandrogens may be used[40]. Aromatase inhibitors (e.g., letrozole, clomiphene) are first-line for ovulation induction[68]. Infertility treatment-resistant cases may warrant laparoscopic ovarian surgery as second-line therapy, with *in vitro* fertilization as a last option[69,70].

CONCLUSIONS

A clear association exists between metabolic dysfunction-associated steatotic liver disease (MASLD) and PCOS. We therefore recommend that all women with PCOS undergo liver dysfunction screening via transaminase measurement and imaging—ultrasound as first-line, with elastography if fibrosis is suspected—for MASLD diagnosis.

Timely identification and treatment of this association enable a comprehensive approach centered on weight reduction, dietary modification, and regular exercise. Currently, no approved therapy specifically targets both conditions, underscoring the need for further research to develop future therapeutic strategies.

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Case report

Idiopathic Adult Ductopenia: Case report

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Abstract

Introduction: Intrahepatic cholestatic ductomas can be associated with an inflammatory process that leads to the destruction of small or medium caliber biliary canaliculi with their subsequent disappearance. Adult idiopathic ductopenia is a diagnosis of exclusion characterized by the destruction of at least 50% of the portal ducts and requires the exclusion of autoimmune and mechanical causes, among others. **Case Report:** 23-year-old patient with no pathologic history who presented with progressive jaundice and incoercible pruritus. Cholangioresonance was performed, which ruled out mechanical obstruction or images suggestive of primary sclerosing cholangitis. Studies of infectious etiology were negative and serum levels of antibodies associated with destruction of biliary canaliculi were within normal ranges. Given the persistence of jaundice of unclear cause, it was decided to perform a liver biopsy which reported loss of ducts in the portal triads with focal destruction. **Discussion:** After analyzing the requested studies, the presentation and course of the disease, the diagnosis of adult idiopathic ductopenia was considered, and management with ursodeoxycholic acid was started, achieving gradual improvement and a follow-up appointment was made. **Conclusion:** The diagnosis of ductopenia was made after having negative serological studies for infectious/inflammatory causes, through a negative cholangioresonance and a liver biopsy as as reported in the literature. Excluding secondary causes of ductopenia.

Keywords

Bile canaliculi, cholestasis, intrahepatic, biliary tract diseases, adult, jaundice.

INTRODUCTION

Idiopathic ductopenia (IAD) is a chronic condition classified within the spectrum of intrahepatic cholestatic diseases, characterized by the loss of septal and interlobular bile ductules in adulthood[(1)]. This disorder has the potential to progress to biliary cirrhosis and, in severe cases, may present as acute liver failure[(2)]. Since its first description in 1988 by Ludwig et al., the etiology remains unknown, though an inflammatory process leading to the destruction and eventual disappearance of bile ductules has been proposed. In recent years, few cases of idiopathic adult ductopenia have been reported in global literature, with even fewer in Latin American medical literature[(3)]. According to reviewed literature, two clinical presentations have been described: a mild, asymptomatic form and a more severe form in which the only effective treatment is liver transplantation. This report presents the case of a young patient from Cali, Colombia, who presented with jaundice and was ultimately diagnosed with ductopenia based on histopathological findings during diagnostic and therapeutic evaluation.

CASE REPORT

A previously healthy 23-year-old man, with no personal or family history of liver disease, no substance abuse, or

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use of herbal medications, sought care at Clínica Nueva Comfenalco in Cali due to a one-week history of progressive jaundice and intractable pruritus. Blood tests revealed the following: total bilirubin (TB): 16.6 mg/dL (0–1 mg/dL), alkaline phosphatase (ALP): 349 U/L (40–129 U/L), γ-glutamyltransferase (GGT): 73 U/L (8–61 U/L), aspartate aminotransferase (AST): 67 U/L (0–38 U/L), alanine aminotransferase (ALT): 120 U/L (0–41 U/L). The patient was screened for viral infections, including human immunodeficiency virus (HIV) and hepatitis A, B, and C, all of which returned negative.

Initial suspicion was primary sclerosing cholangitis, prompting further autoimmune testing. Serological identification samples were taken for autoimmune markers, including anti-smooth muscle antibodies, anti-mitochondrial antibodies, antinuclear antibodies, asthma antibodies, antinuclear antibodies (ANA), anti-mitochondrial antibodies (AMA), anti-microsomal antibodies, liver and kidney (LKM1), all of which yielded negative results. Immunoglobulin levels were measured as follows: immunoglobulin A (IgA): 193 mg/dL (63–484 mg/dL), immunoglobulin M (IgM): 85 mg/dL (22–240 mg/dL), immunoglobulin G (IgG): 978 mg/dL (540–1822 mg/dL). Further subclass quantification revealed: IgG1: 1.31 g/L, IgG2: 0.47 g/L, IgG3: 0.1 g/L e IgG4: 0.24 g/L. Protein electrophoresis showed an alpha-1 and alpha-2 peak with a decrease in gamma A.

Leptospira infection was ruled out (negative IgM), and blood smear testing excluded hemoparasite-related diseases. Endoscopic studies showed no significant findings except for antral hyperemic gastritis. An initial abdominal ultrasound detected hepatomegaly without other abnormalities. Subsequent magnetic resonance cholangiography ruled out choledocholithiasis or biliary duct dilation. Finally, a percutaneous liver biopsy revealed marked cholestasis and loss of bile ducts in portal triads. Immunohistochemical staining confirmed focal duct destruction in portal triads (**Figures 1**, **2**, and **3**).

The patient was diagnosed with idiopathic adulthood ductopenia. Initial management with corticosteroids was initiated, achieving slow progressive reduction of bilirubin levels. For symptomatic management, cholestyramine 4 g was administered orally every 12 hours without achieving symptom control. Subsequently, ursodeoxycholic acid 300 mg was added orally every 12 hours, resulting in notable improvement.

The patient was discharged with minimal residual symptoms, with plans for continued hepatology evaluation. However, due to clinical improvement, the patient voluntarily declined further testing.

DISCUSSION

Primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC) represent the most common causes of

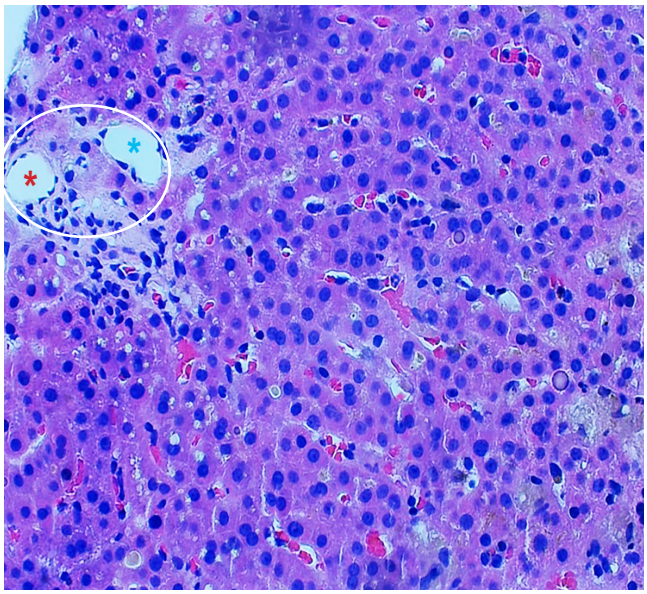


Figure 1. The histological section shows hepatic parenchyma with a portal space (circle), where portal vessels (artery and vein) are identified but no bile duct is observed (*red: artery, *blue: vein). Image property of the authors.

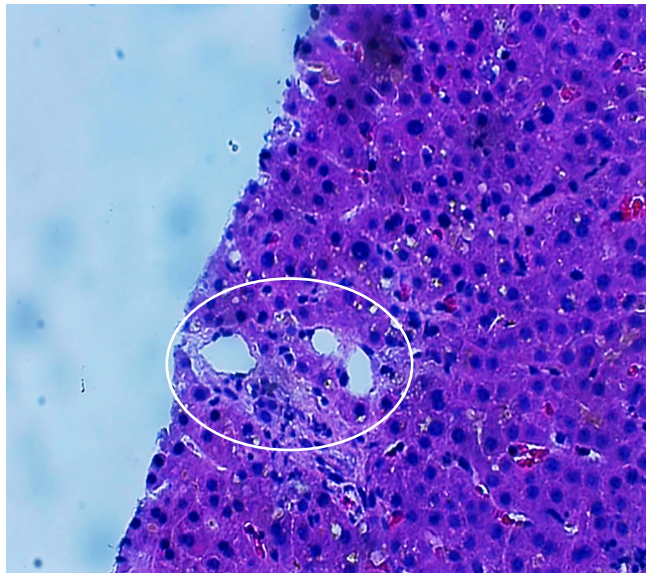


Figure 2. The section shows hepatic parenchyma with a portal space, where a normal portal triad was identified containing portal vessels (artery, vein) and bile duct. Image property of the authors.

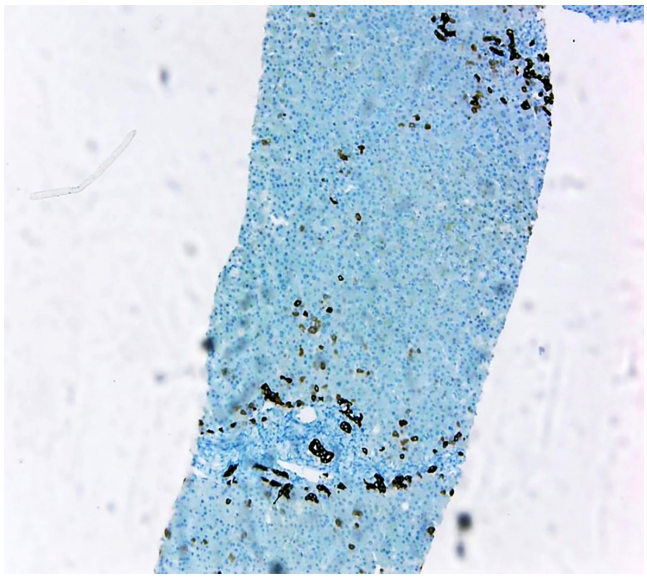


Figure 3. Immunohistochemical study with CK7 confirming the presence of ducts and adjacent hepatocytes with biliary metaplasia, demonstrating a cholangitic injury pattern. Image property of the authors.

chronic hepatic cholestasis in adults[4]. However, a small patient subset presents with chronic cholestasis lacking antimitochondrial antibodies (suggestive of PBC) or cholangiographic abnormalities (suggestive of PSC). These cases are frequently classified as AMA-negative PBC, small-duct PSC, or idiopathic adulthood ductopenia (IAD)[5].

IAD describes chronic hepatic cholestasis of unclear etiology, typically beginning in adulthood and associated with intrahepatic bile duct loss. Multiple pathogenic mechanisms for intrahepatic biliary destruction have been implicated, including biliary atresia development, immunological causes from aberrant MHC class II antigen expression, infections, ischemia, or chemical injury[1-3,6]. Several medications (chlorpromazine, prochlorperazine, organic arsenicals, tolbutamide) have also been associated with bile duct destruction. These were ruled out in our patient, as their identification would exclude IAD diagnosis.

Current diagnostic criteria require: biochemical cholestasis, normal endoscopic studies excluding inflammatory bowel disease, absent antimitochondrial antibodies, no granulomatous cholangitis, absent histiocytosis X, no suppurative neutrophilic cholangitis, no lymphoma or neoplasia on liver biopsy, and histopathological confirmation of ductopenia. The latter requires loss of ≥50% of septal/interlobular bile ducts in a sample containing ≥20 portal tracts, without granulomatous cholangitis or florid ductal injury[1,2,6-9] (**Figures 1** and **3**).

Clinical manifestations vary. Some patients remain asymptomatic, though the primary symptom is jaundice with typically intense pruritus. Biochemical analysis reveals a predominantly cholestatic pattern with direct hyperbilirubinemia and elevated alkaline phosphatase/γ-glutamyltransferase[1,10].

Literature describes two IAD presentations: Type 1 (often asymptomatic, may show chronic cholestasis symptoms, with less duct destruction on biopsy) and Type 2 (more severe, potentially progressing to biliary cirrhosis with extensive duct destruction histologically, where liver transplantation remains the only proven effective treatment)[2,8,10,11].

For mild cases, ursodeoxycholic acid has demonstrated symptomatic benefit in multiple reports, though without documented disease progression impact. Clinical outcomes depend on ductopenia severity. Reviewed literature agrees that IAD typically progresses to end-stage liver disease when >50% duct destruction exists, while lesser involvement usually follows a benign course[2,6,10]. Our patient showed <50% duct abnormality on biopsy with progressive jaundice improvement. Determining whether his course will remain benign remains unclear due to potential recent diagnosis and loss to follow-up.

CONCLUSION

Idiopathic adulthood ductopenia is a rare cholestatic liver disease diagnosed by excluding differential diagnoses while demonstrating biochemical cholestasis and biopsy-proven bile duct loss. While recognizing this entity is important, first excluding more common pathologies remains vital for survival. When biochemical-histopathological diagnosis is confirmed, prompt management of both cause and symptoms (when possible) impacts patient survival and quality of life.

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Conflicts of Interest

None reported.

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Case report

Refractory Very Early-Onset Inflammatory Bowel Disease to Anti-TNF Therapy

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Abstract

Background: Very early-onset inflammatory bowel disease (VEO-IBD), defined as symptom onset before the age of 6 years, presents a significant clinical challenge for healthcare teams. This case report aims to share clinical experience in managing a patient with VEO-IBD. **Case Report:** We present the case of a 3-year-old boy diagnosed with inflammatory bowel disease (IBD), Crohn's disease (CD) phenotype, with disease onset at four months of age. A comprehensive evaluation was conducted to rule out differential diagnoses such as food allergies, immunodeficiencies, and intestinal tuberculosis. Given the early onset, a genetic component was suspected, and genetic testing was performed. The patient presented with pancolitis and perianal involvement and was stratified as high-risk according to the ECCO-ESPGHAN guidelines. After therapeutic failure with infliximab and adalimumab, ustekinumab was initiated with successful clinical remission to date. This therapy has proven effective in refractory pediatric CD cases. **Conclusions:** To achieve an accurate diagnosis in suspected pediatric IBD, it is essential to follow clinical practice guidelines and apply individualized diagnostic approaches. Although most VEO-IBD cases have multifactorial etiology, genetic factors may play a significant role, particularly in children under 2 years of age. VEO-IBD is often associated with more severe disease in terms of extent and behavior.

Keywords

Inflammatory bowel diseases, pediatrics, Crohn's disease.

INTRODUCTION

Very early-onset inflammatory bowel disease (VEO-IBD), defined by symptom onset before 6 years of age, accounts for 6% to 15% of pediatric IBD cases[1,2]. VEO-IBD includes two subcategories: infant-onset IBD (IO-IBD), when disease onset occurs before 2 years of age, and neonatal-onset IBD, when symptoms appear within the first 28 days of life[3,4].

While most VEO-IBD cases result from multifactorial causes, genetic factors may play a significant role, particularly in children under 2 years (IO-IBD), where the likelihood of identifying a monogenic defect responsible for enteric inflammation is higher[1,2,5]. To date, over 70 genetic variants have been described, most commonly associated with inborn errors of immunity affecting B- and T-cell function or hyper-/autoinflammatory defects related to epithelial barrier dysfunction[1,6,7].

Selecting optimal therapy at such an early age poses a challenge for the treating team, given the nearly inevitable delay in confirming the diagnosis before initiating targeted treatment. To achieve an accurate diagnosis when pediatric IBD is suspected, the European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) established the Porto Criteria in 2014, con-

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solidating evidence-based recommendations for diagnostic methods and guiding a more individualized approach[8].

Key initial diagnostic tests include upper endoscopy, ileocolonoscopy with multiple biopsies from all evaluated segments, and complete small bowel evaluation. Advances in imaging modalities, serological and fecal biomarkers have improved detection and monitoring of these diseases[1,8]. This case report aims to share the clinical experience and challenges in managing a patient with this very early-onset condition.

CASE REPORT

A male infant, born to non-consanguineous parents, had no perinatal or neonatal risk factors or family history of atopy, immunodeficiencies, autoimmune diseases, or IBD. His clinical course began at 4 months of age with profuse watery diarrhea (3–30 stools per day), sometimes containing mucus but no blood, occurring day and night, accompanied by poor appetite. At 10 months, cow's milk protein allergy (CMPA) was suspected, leading to a diagnostic and therapeutic trial with extensively hydrolyzed formula (eHF) and maternal exclusion of cow's milk protein (CMP), without symptom improvement. From 12 to 16 months of age, diarrhea persisted despite multiple outpatient interventions, primarily antibiotics and antiparasitics, resulting in progressive weight loss and acute malnutrition. The diarrhea was later accompanied by oral aphthous ulcers, food refusal, intermittent fever, and lower limb edema.

At 17 months, during his first evaluation, the patient appeared in fair general condition: thin, pale, tachycardic, febrile, and hypoactive. Findings included asthenia, adynamia, brittle hair, bilateral eyelid edema, oral ulcers, and non-tender bilateral cervical, axillary, and inguinal lymphadenopathy (<1 cm in diameter). The abdomen was markedly distended, soft, depressible, and tender to palpation, without peritoneal irritation. The anus showed no lesions, but there was gluteal and lower limb hypotrophy, along with distal-predominant limb edema. Anthropometry revealed short stature and acute kwashiorkor-type malnutrition (weight: 7.84 kg, height: 74 cm, height/age: -2.7 standard deviations [SD], weight/height: -2.12 SD). Laboratory findings are presented in **Table 1**.

Table 1. Admission Laboratory Results

Hematologic	- Complete Blood Count: Hb: 7.7, Hct: 23.8, MCV: 93.9, MCHC: 32.5, RDW: 28%, RBC count: 2.53 (low), WBC: 15,700, Neutrophils: 3,600 (23%), Lymphocytes: 9,800 (62%), Monocytes: 1,800 (11%), Eosinophils: 300 (2.2%), Platelets: 516,000. - Reticulocyte Count (corrected): 2.8 (reticulocyte percentage: 5.2%).
Acute Phase Reactants	- CRP: 2.24 mg/dL (Ref.: 0.01–0.82) elevated - ESR: 97 (Ref.: 0–20) elevated
Liver Function Tests	- ALT: 11 - AST: 15 - Alkaline Phosphatase: 78 - GGT: 11.5 U/L - Total Bilirubin: 0.19 - Direct Bilirubin: 0.05 - PT: 11.9 (control: 11.4) - INR: 1.05 - Albumin: 2.3 g/dL (Ref.: 3.8–5.4) - Prealbumin: 8 (Ref.: 11–34)
Renal Function	- Creatinine: 0.15 mg/dL - BUN: 10.8
Gastrointestinal Infection	- Stool Analysis: No mucus/blood, pH 7, >5 WBC/hpf, no parasites observed. - Adenovirus/Rotavirus: Negative. - FilmArray GI Panel: Negative.
Other Infection Workup	- Urinalysis: Normal, urine culture negative. - Blood cultures (x2): Negative. - Chest X-ray: Normal.

ALT: alanine aminotransferase; AST: aspartate aminotransferase; BUN: blood urea nitrogen; GGT: γ-glutamyl transferase; GI: gastrointestinal; Hb: hemoglobin; Hct: hematocrit; INR: international normalized ratio; CRP: C-reactive protein; PT: prothrombin time; MCV: mean corpuscular volume; Ref.: reference range; ESR: erythrocyte sedimentation rate. Table prepared by the authors.

The patient presented with chronic diarrhea and severe nutritional compromise, requiring evaluation for multiple differential diagnoses. A multidisciplinary diagnostic workup was initiated, including an upper endoscopy (normal findings) and colonoscopy with the findings described in **Figure 1**.

Histopathology reported two completely ulcerated mucosae (cecum and transverse colon), increased eosinophils in descending colon, and scarce chronicity signs (occasional crypt branching). Findings were nonspecific but could represent either an infectious process or early-stage IBD (**Figure 2**). Special stains: Ziehl-Neelsen (ZN) and modified ZN were negative for acid-fast bacilli. Periodic acid-Schiff (PAS) and methenamine silver stains were negative for fungal structures (**Figures 3A**, **C** and **D**). CMV immunohistochemistry was negative (**Figure 3B**).

Initial management consisted of maintaining exclusive enteral nutrition with an elemental formula to ensure adequate caloric intake for nutritional recovery, while also serving as a management strategy for both cow's milk protein allergy (CMPA) and Crohn's disease (CD) induction therapy - two primary differential diagnoses. The patient additionally received multivitamin supplementation, folic acid, zinc, ferrous sulfate, albumin replacement, and packed red blood cell transfusion.

During hospitalization, the patient tolerated oral enteral formula well, with reduced diarrhea episodes, weight gain, improved abdominal distension, and resolution of

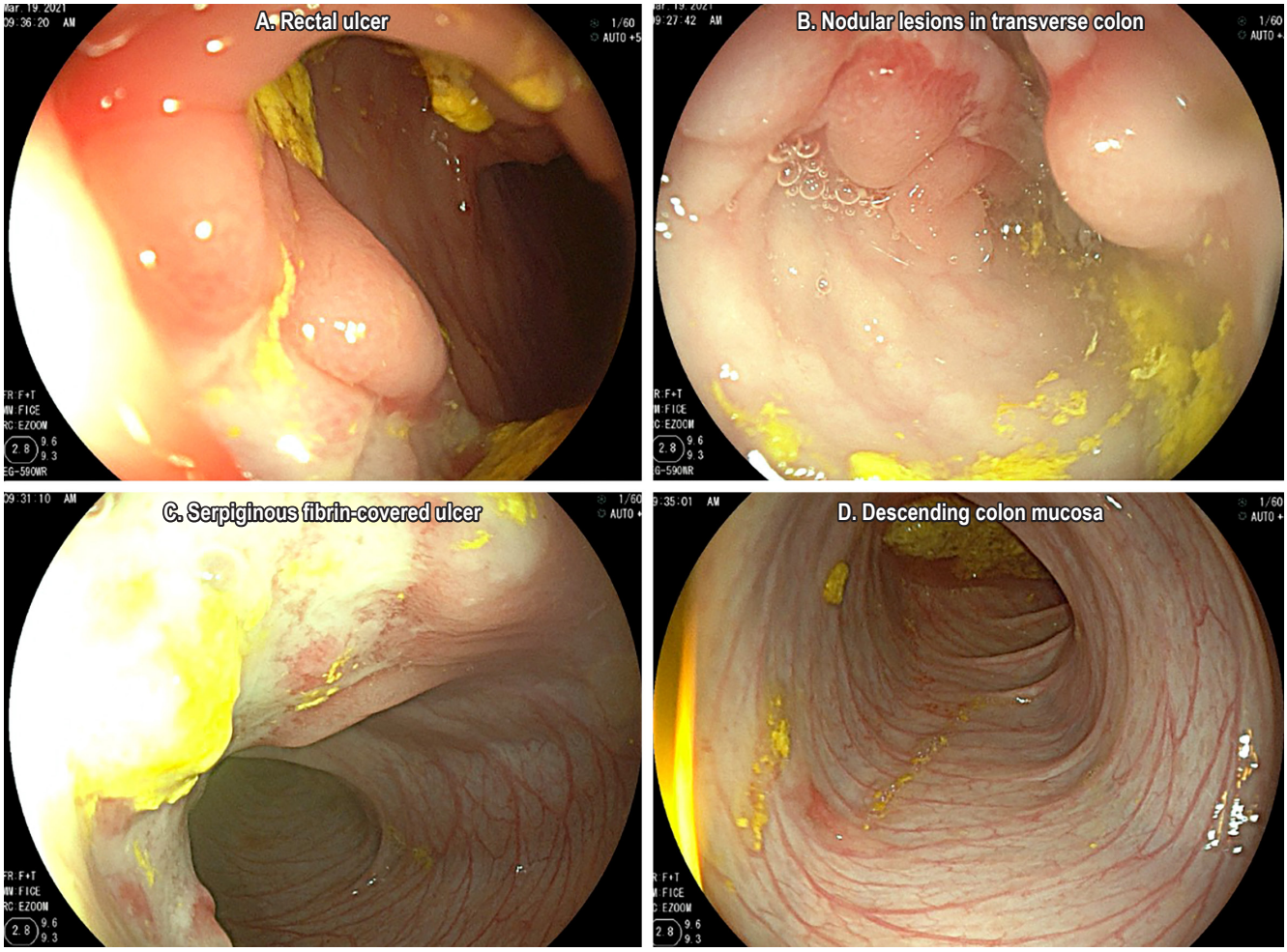


Figure 1. Initial colonoscopy. **A.** Anus and perianal region without lesions; poor preparation. At 5 cm from the anal margin, a large deep rectal ulcer covered with fibrin is observed. **B** and **C.** Rectosigmoid with edema and nodularity. The transverse colon shows multiple ulcerated nodular lesions forming a conglomerate causing partial circumferential stenosis. **D.** The remaining mucosa up to the cecum appears normal. Ileocecal valve could not be cannulated. Staged biopsies were taken, along with a transverse colon (nodular lesion) sample for mycobacterial PCR. Diagnosis: Inflammatory and ulcerated nodular lesions in rectosigmoid and transverse colon. Image property of the authors.

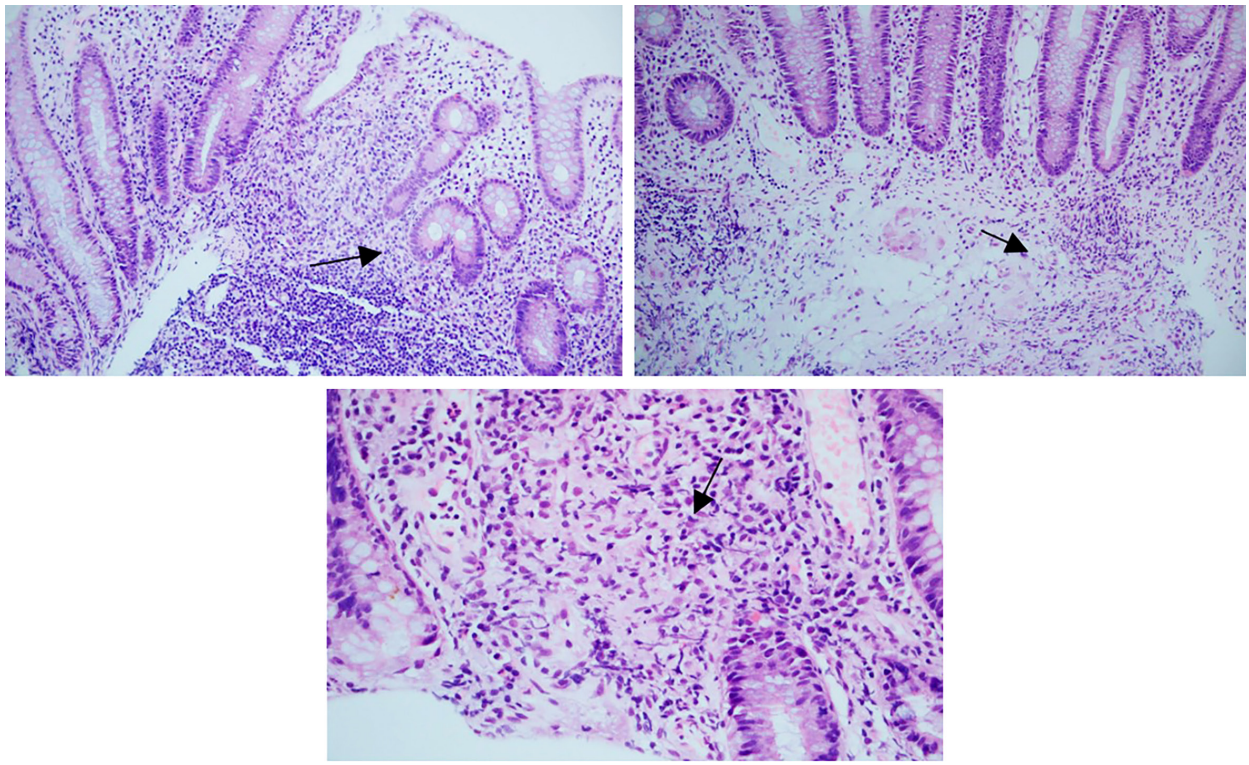


Figure 2. Conventional histology. Mixed inflammatory infiltrate with crypt architectural distortion (occasional branching indicating chronicity). Poorly defined granuloma present. Images property of the authors.

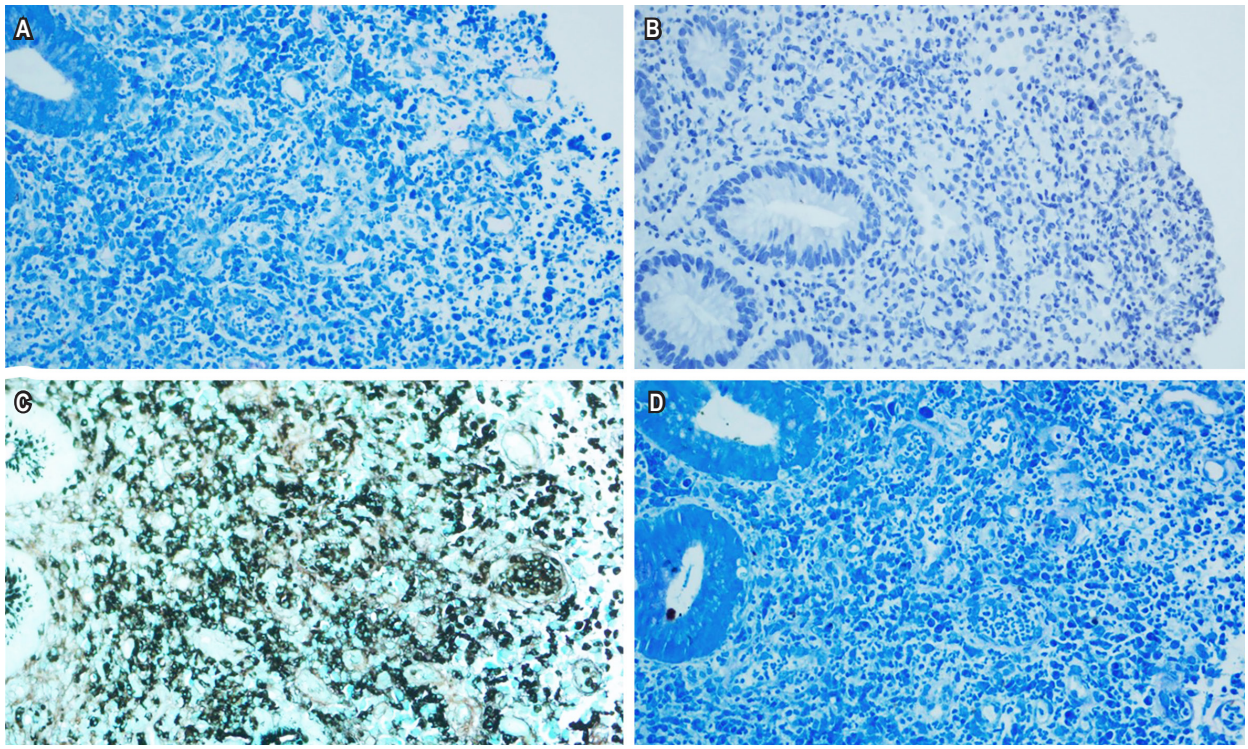


Figure 3. Special stains. **A.** Negative Ziehl-Neelsen (ZN) stain. **B.** Negative CMV immunohistochemistry. **C.** Negative periodic acid-Schiff (PAS) and methenamine silver stains. **D.** Negative modified ZN stain. Images property of the authors.

edema. However, isolated febrile spikes persisted. Given the endoscopic findings, comprehensive infectious workup was imperative - particularly for gastrointestinal tuberculosis (TB) and non-infectious causes of persistent fever (e.g., immune defects or intestinal barrier integrity disorders) - prompting whole exome sequencing.

Over the 27-day hospitalization, management followed a multidisciplinary approach (**Table 2**). Upon achieving clinical stability, gastrointestinal symptom improvement, and weight recovery (weight/height -0.95 SD), discharge was planned for outpatient follow-up and testing. Unfortunately, adequate adherence could not be maintained.

Follow-up evaluation during an IBD flare at 2 years of age (approximately 12 months after initial management) revealed persistent diarrhea (6-8 stools/day, some nocturnal) without mucus or blood, accompanied by abdominal pain/distension, food refusal, vomiting, left knee edema, bilateral conjunctival injection, oral aphthous ulcers, new perianal lesion, and intermittent fever. Physical examination showed the patient in fair general condition, febrile, with bilateral conjunctival injection, oral ulcers, distended abdomen tender to palpation (no masses or organomegaly), no peritoneal irritation, and perianal region demonstrating a skin tag with scant purulent discharge. Anthropometry confirmed persistent short stature with maintained weight-for-height adequacy.

Admission tests revealed severe anemia, elevated acute-phase reactants (erythrocyte sedimentation rate [ESR] and C-reactive protein [CRP]), hypoalbuminemia, thrombocytopenia, negative gastrointestinal FilmArray panel, and elevated fecal calprotectin. Given the presumptive diagnosis of early-onset IBD during a severe disease flare (PCDAI score: 60), a comprehensive workup was performed, including follow-up endoscopic studies (**Figure 4**), enterography to assess small bowel involvement, and pelvic MRI to evaluate perianal disease extent (**Figure 5**). A renewed

Table 2. Extended Workup

Test Category	Results
Infectious Profile	- PPD: 0 mm - COVID-19 RT-PCR: Negative - Mycoplasma pneumoniae IgM: Negative - PANFUNGAL PCR (colon biopsy): Negative - Mycobacterial PCR (colon biopsy): Negative (report received 04/06/2021)
Metabolic/Hormonal	- Venous blood gases: No acid-base imbalance - Ammonia: 22.3 (normal) - Glucose: 108 mg/dL - Iontophoresis: 33 (normal; previous Sept/2020: 31 - negative), ruling out cystic fibrosis - TSH: 4.23 (Ref.: 0.5-4.9) - normal - Fecal alpha-1 antitrypsin: 0.44 mg/g (normal ≤0.3) - elevated
Gastrointestinal	- Fecal calprotectin: 1251 µg/g - ASCA: IgA: 172.3 U, IgG: 64.6 U (Ref.: 0-20) - positive - ANCA: MPO: 1.8 (Ref.: 0-20), PR3: 2.6 (Ref.: 0-20) - negative - CT scan: Wall thickening in transverse/descending colon. No small bowel involvement.
Hematologic	- Serum iron: 40 (Ref.: 50-150) - low, Transferrin: 90 (Ref.: 186-388) - low - Ferritin: 90.8 (Ref.: 7-140) - normal, LDH: 160 U/L (Ref.: 145-345) - normal
Immunologic	- Protein electrophoresis: - Hypoalbuminemia, Alpha-1 region elevation, and Mild beta-1 region reduction. Faint nonspecific band in gamma region. IgA: 234 mg/dL (Ref.: 21-294) - normal IgG: IgG: 772 mg/dL (Ref.: 475-1210) - normal IgM: 319 mg/dL (Ref.: 41-183) - mildly elevated IgE: <25 (Ref.: 0-60) - normal

ANCA: Anti-neutrophil cytoplasmic antibody; ASCA: Anti-Saccharomyces cerevisiae antibody; COVID-19: Coronavirus disease 2019; IgA: Immunoglobulin A; IgE: Immunoglobulin E; IgG: Immunoglobulin G; IgM: Immunoglobulin M; LDH: Lactate dehydrogenase; PCR: Polymerase chain reaction; PPD: Purified protein derivative; PR3: Proteinase 3; RT-PCR: Reverse transcription polymerase chain reaction; CT: Computed tomography; TSH: Thyroid-stimulating hormone; Ref.: Reference range. Table prepared by the authors.

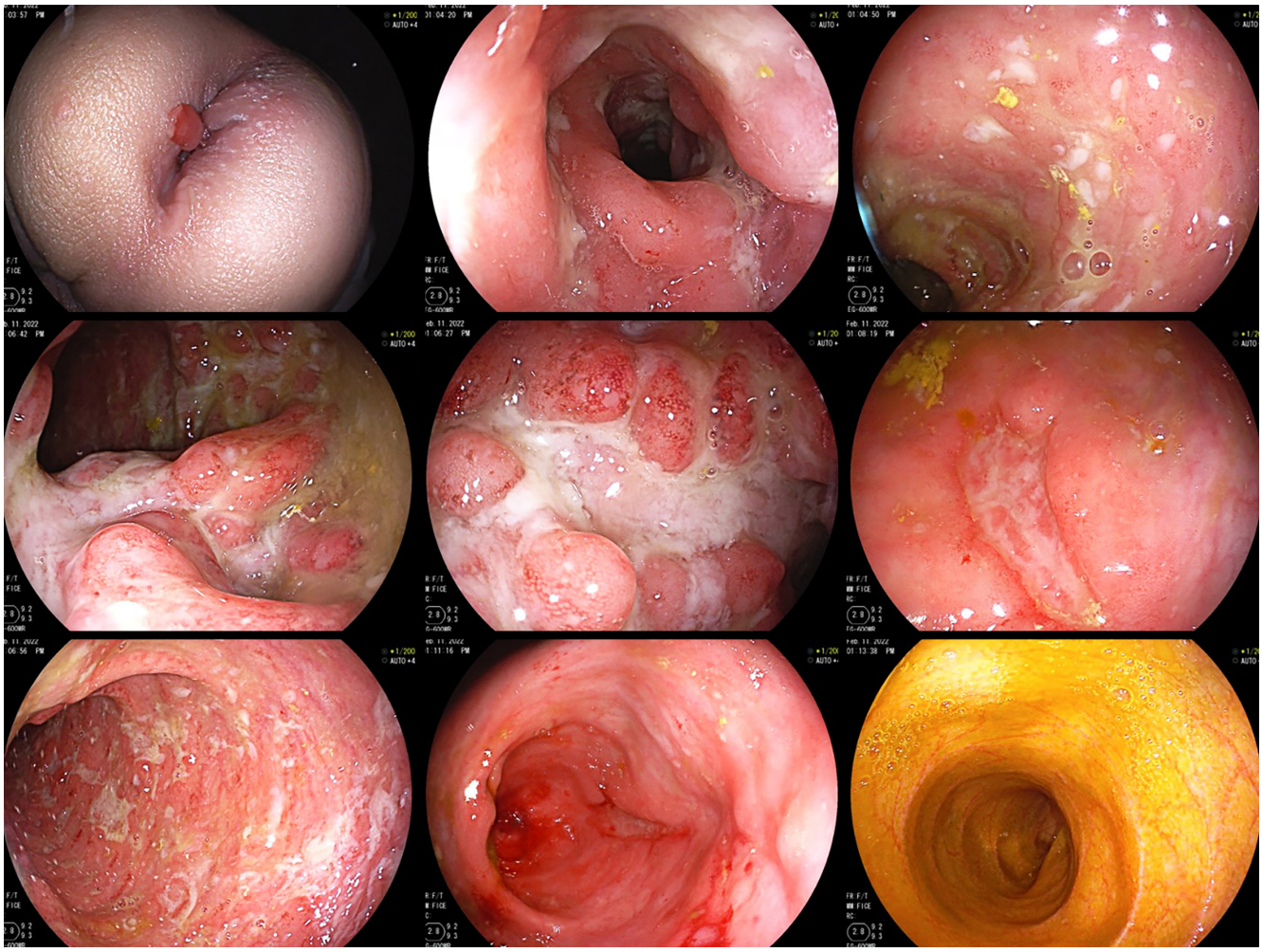


Figure 4. Follow-up ileocolonoscopy during disease flare. Images property of the authors.

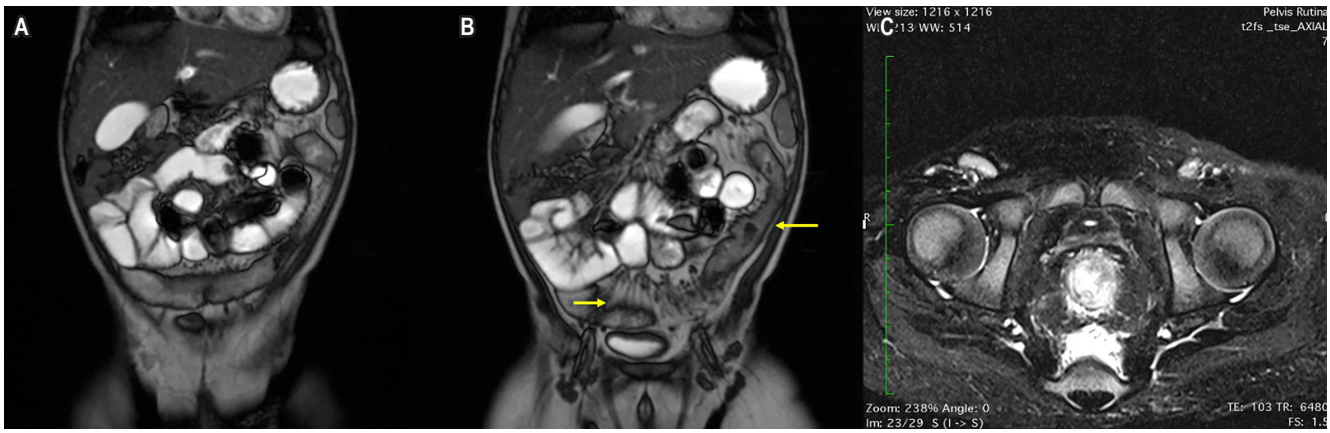


Figure 5. Enterography and pelvic MRI. **A.** Adequate small bowel distension with normal appearance - no pathological enhancement/wall thickening, stenosis, or dilatation. **B.** Pathological enhancement and wall thickening throughout the colon (predominantly left/transverse colon) consistent with colitis and vascular engorgement. **C.** Intersphincteric perianal fistula tract with associated right-quadrant abscess. Images property of the authors.

multidisciplinary approach was implemented with emphasis on addressing the patient's social context contributing to prior non-adherence.

After ruling out the most likely differential diagnoses through comprehensive clinical, endoscopic, histological, and radiological reevaluation, we classified our patient according to the Paris criteria as having very early-onset IBD of the Crohn's disease (CD) type in the infant subcategory (A1a), with colonic + perianal involvement (L2p), inflammatory and stenosing phenotype (B2), and growth failure (G1).

The patient exhibited multiple risk factors predicting a complicated disease course: Non-response to exclusive enteral nutrition induction therapy, Age <2 years at onset, Pancolonic involvement, Positive anti-Saccharomyces cerevisiae antibodies (ASCA), and Perianal disease requiring biologic therapy. Infliximab was selected as first-line treatment at 5 mg/kg/dose on an intensified frequency schedule (weeks 0-1-4), targeting serum trough levels >12.7 µg/mL before the fourth dose - the recommended pharmacological approach for perianal involvement. All management decisions followed ECCO/ESPGHAN pediatric CD guideline recommendations. This therapy was combined with azathioprine initiation (2 mg/kg/day) as an immunomodulator and dual therapy with salicylates.

For perianal disease management, in addition to intensified anti-TNF-α dosing, an antibiotic regimen (metronidazole + ciprofloxacin) was initiated along with surgical intervention consisting of fistulectomy with seton placement. This combined strategy achieved clinical improvement and partial endoscopic response.

Unfortunately, during infliximab therapy, the patient developed immunomediated loss of response manifested by anaphylaxis during infusion, necessitating biologic switching to adalimumab with induction dosing (80 mg) followed by maintenance (40 mg every two weeks).

Despite adherent maintenance therapy with adalimumab, the disease followed an unfavorable course with rapid progression and failure to achieve clinical/endoscopic remission. Subtherapeutic adalimumab levels (<0.2 µg/mL) with elevated antibodies (>200 ng/mL) confirmed secondary immunologic failure to this second-line anti-TNF. Having exhausted available pediatric therapeutic options for severe perianal CD, we transitioned to ustekinumab (anti-IL-12/IL-23 biologic) for induction (6 mg/kg) and maintenance (3 mg/kg every 8 weeks), which has been well-tolerated without adverse events to date.

Concurrently with ustekinumab initiation, due to high-risk perforating perianal disease, a multidisciplinary team recommended surgical management. Attempted seton placement for the perianal fistula failed due to anal stenosis and severe rectal inflammation, prompting concurrent diverting ileostomy creation.

Following ileostomy and ustekinumab induction, clinical improvement was evidenced by PCDAI=20 (from previous 55), representing a >20-point decrease indicating adequate treatment response, with restored appetite, pain reduction, sustained weight gain, normalized serum albumin, and decreased acute-phase reactants. Trio exome sequencing identified no pathogenic variants associated with very early-onset disease.

DISCUSSION

We present the case of a 3-year-old male patient who developed infant-onset IBD at 4 months of age, with a CD phenotype according to the Porto Criteria[8] and classified as A1aL2pB2G1 under the Paris Classification[9]. These VEO-IBD patients demonstrate significant differences compared to pediatric IBD occurring in children under 18 years or adults (**Figure 6**). The condition is notably distinct due to its predominantly colonic involvement, more severe disease course, reduced response to conventional therapy (59% vs 85%, p=0.003), higher need for surgical interventions (32% vs 14%, p<0.001), and association with monogenic defects[1,2,4].

When evaluating a patient with symptom onset at such an early age and presenting with the clinical conditions we observed at 17 months, it was crucial to conduct a comprehensive assessment to rule out differential diagnoses. In this case, given the initial endoscopic findings, it was particularly important to exclude immunodeficiency and intestinal tuberculosis (ITB)[3]. ITB can mimic Crohn's disease (CD) in several aspects, including clinical presentation, radiological features, endoscopic appearance, and histological findings[10]. For this patient, establishing an accurate diagnosis was essential to provide appropriate treatment.

Pediatric studies comparing ITB and CD remain limited; however, certain clinical and endoscopic features show significant associations with CD: chronic diarrhea (82% vs 40%, p=0.006), bloody stools (74% vs 10%, p<0.001), extraintestinal manifestations (21% vs 0%, p=0.02), and left-sided colonic involvement with deep longitudinal ulcers (87% vs 40%, p=0.003). In contrast, ITB cases predominantly present with intestinal obstruction (20% vs 0%, p=0.02), ascites (30% vs 0%, p=0.005), and isolated ileocecal involvement (40% vs 8.7%, p=0.03). Although evidence remains scarce, these findings align with adult-reported data[10]. Given our inability to isolate mycobacteria and the clinical, endoscopic, histological, and radiological features suggestive of CD, we proceeded with CD management.

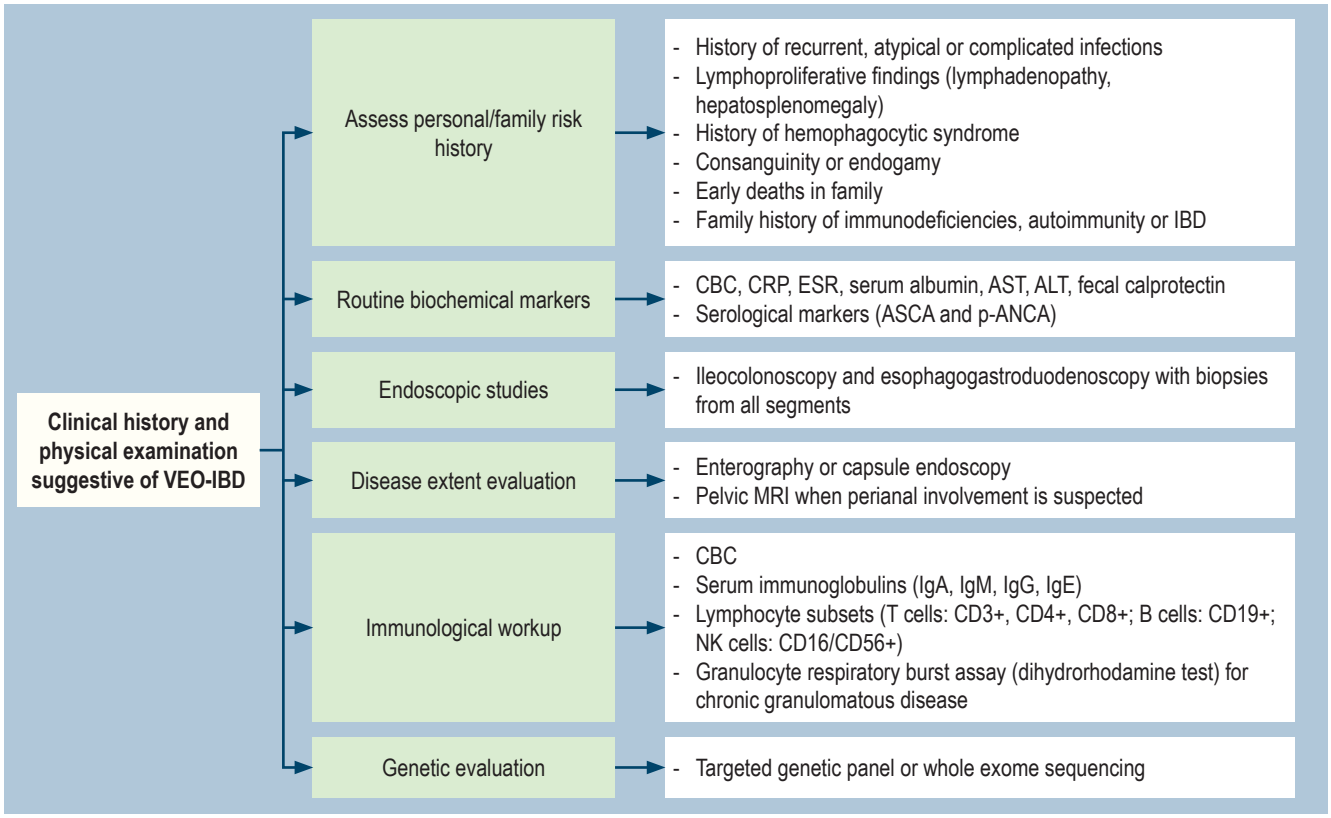


Figure 6. Diagnostic algorithm for suspected VEO-IBD. ALT: alanine aminotransferase; ASCA: anti-Saccharomyces cerevisiae antibodies; AST: aspartate aminotransferase; CD: cluster of differentiation; IBD: inflammatory bowel disease; IgA: immunoglobulin A; IgE: immunoglobulin E; IgG: immunoglobulin G; IgM: immunoglobulin M; CRP: C-reactive protein; p-ANCA: perinuclear anti-neutrophil cytoplasmic antibodies; ESR: erythrocyte sedimentation rate; VEO-IBD: very early-onset inflammatory bowel disease. Image property of the authors.

Accurate differentiation between phenotypes, particularly ulcerative colitis (UC) and CD, carries significant implications for defining disease natural history, induction/maintenance therapeutic strategies, and surgical considerations[8,11].

For disease monitoring, we employed the Pediatric Crohn's Disease Activity Index (PCDAI), where clinical remission is defined as a score <10 points and clinical response requires at least a 20-point reduction. Our patient's hospitalization scores >40 indicated severe disease activity[2,12]. Beyond clinical and endoscopic follow-up, we monitored inflammatory biomarkers (fecal calprotectin) and imaging (MRI)[12,13].

Our management strategy followed the 2020 ECCO-ESPGHAN guidelines[12], incorporating risk stratification - a critical step for identifying patients at high risk of complicated disease progression. Early pediatric stratification guides optimal therapy selection to minimize bowel damage. Our patient met high-risk criteria due to extensive stenosing colonic involvement, perianal disease, severe growth impairment, and lack of clinical/biochemical response after 12 weeks of exclusive enteral nutrition[12,14]. After excluding immunodeficiency[1,3] and considering the severe clinical course, we initiated anti-TNF biologic therapy with immunomodulator combination - a decision requiring evidence-based, systematic deliberation.

For perianal disease assessment, we performed detailed pelvic MRI (with/without contrast) and thorough examination under general anesthesia. Perianal CD complications (fistulae/abscesses) represent severe, treatment-resistant manifestations[15,16], occurring in 8-15% of pediatric patients. Risk factors include male sex (3-fold higher vs females) and systemic corticosteroid induction therapy (2-fold increased risk)[17].

Current recommendations for perianal CD advocate anti-TNF therapy as first-line induction/maintenance treatment, combined with antibiotics and surgical intervention[16,18]. Intensified infliximab regimens (dose/inter-

val optimization targeting pre-fourth-dose serum levels >12.7 μg/mL) significantly improve mucosal healing and fistula closure rates[15,19,20]. Additional criteria for intensified biologic therapy include low body weight (<30 kg), extensive disease, and hypoalbuminemia.

Regarding the surgical management of perianal disease, once the perianal involvement has been classified and characterized through pelvic magnetic resonance imaging, any identified abscess should be drained, typically through partial fistulectomy with seton placement[16,18]. When deep perianal ulcers, purulent discharge, and adjacent tissue inflammation accompany fistulae, diverting ostomy may be a recommended therapeutic option, particularly in cases refractory to medical therapy[15], as described in this case. Due to the refractory nature of the disease, surgical interventions are frequently required in the clinical course of VEO-IBD patients; studies have shown this group requires surgical procedures (diverting ostomies or colectomy) more frequently, with surgical intervention rates of 32% in VEO-IBD cases with symptom onset before one year of age compared to 14% when symptoms begin after one year ($p<0.001$)[1,2].

In our patient with severe, treatment-refractory disease and perianal involvement associated with significant rectal inflammation, a multidisciplinary team including pediatric surgery and coloproctology specialists decided to perform a diverting ileostomy to promote colonic rest and reduce inflammatory burden[1].

We combined infliximab with azathioprine as maintenance therapy to reduce immunogenicity risk[21]. Regarding infliximab maintenance dosing, adjustments should ideally be guided by proactive therapeutic drug monitoring. Unfortunately, during the fifth infliximab infusion, the patient developed an anaphylactic reaction with immunologic anti-TNF failure, prompting a switch to the second pediatric-approved biologic, adalimumab, whose effectiveness for perianal disease management has been validated in multiple clinical trials[13,22,23].

Our patient's clinical course highlights the concept of immunologic failure to first- and second-line anti-TNF therapy. Few studies evaluate anti-TNF use in VEO-IBD; however, available data suggest reduced durability of these biologics (90% anti-TNF persistence at 1 year, 75% at 3 years, and 55% at 5 years), with the most frequent reasons for discontinuation being loss of response (57% of cases) and adverse reactions (24%)[21,24,25].

Therapeutic drug monitoring is essential to guide treatment modifications rather than empirical anti-TNF dose adjustments. Optimal outcomes depend on close monitoring of treatment response with timely therapy adjustments when clinical and endoscopic targets are not met[12,26]. Unfortunately, this patient's sociodemographic circumstances and insurance status created barriers to adequate specialized follow-up.

During the most recent hospitalization, after multidisciplinary review, extensive literature analysis, and consultation with international referral centers, the decision was made to transition to ustekinumab (anti-IL-12/IL-23 biologic) for induction and maintenance therapy.

Ustekinumab is a monoclonal antibody targeting the p40 subunit shared by proinflammatory cytokines IL-12 and IL-23. Its mechanism of action involves blocking these cytokines' interaction with the IL-12 receptor on Th1 and Th17 lymphocytes - cells implicated in CD pathophysiology[27]. Ustekinumab has demonstrated efficacy in adults with anti-TNF refractory CD and UC[28].

Emerging evidence suggests ustekinumab may effectively induce and maintain remission in pediatric patients with anti-TNF failure, with documented improvements in clinical scores, biochemical parameters, and growth metrics[12,29,30].

A study of 50 children with IBD who discontinued anti-TNF therapy due to primary failure or adverse events showed 48% clinical response rate at 3 months in CD phenotype, increasing to 90% in biologic-naïve patients, with good tolerability and no serious adverse events reported[30].

Although emerging evidence supports ustekinumab use in pediatric populations, this medication is not yet approved for pediatric IBD in Colombia. Consequently, we lack local pediatric experience with this agent, making our patient the first pediatric VEO-IBD case receiving this treatment in Colombia. Selecting optimal therapy at such a young age presents both clinical and administrative challenges for the treatment team.

From a pediatric perspective, the significant nutritional impairment at disease onset warrants emphasis. Our patient presented with severe malnutrition that showed rapid weight recovery with appropriate enteral support; however, failure to thrive persisted throughout the disease course, reflecting greater systemic inflammatory burden in pediatric patients - a finding present in 46% of pediatric CD cases at diagnosis[31].

After two years of follow-up in this patient with very early-onset disease demonstrating aggressive progression and failure of multiple conventional therapies, genetic exome sequencing becomes crucial for early detection of monogenic defects[1] that may guide targeted therapy, as some patients may respond successfully to bone marrow transplantation[5,6]. Conversely, when no specific genetic or immunologic defect is identified (as in our case), treatment follows standard pediatric IBD protocols, recognizing these cases typically show poorer response to conventional therapies[1].

CONCLUSIONS

- VEO-IBD cases exhibit more severe disease in terms of extent and behavior.
- While most VEO-IBD cases are multifactorial, genetic factors play a significant role, particularly when symptom onset occurs before two years of age. Therefore, genetic exome sequencing is critical in the initial evaluation.
- Perianal involvement in pediatric IBD is a marker of more severe disease and a predictor of poor long-term outcomes.
- Intestinal tuberculosis (ITB) mimics Crohn's disease (CD) in clinical, radiological, endoscopic, and histological presentations.
- To achieve an accurate diagnosis in suspected pediatric IBD, adherence to clinical practice guidelines for diagnostic and individualized management is essential.
- Correct differentiation between IBD phenotypes has significant implications for defining disease natural history, therapeutic strategies, and surgical considerations.
- Selecting optimal therapy at such an early age presents a challenge for the treatment team. Thus, following management guidelines, expert recommendations, and a multidisciplinary approach is crucial.
- Therapeutic drug monitoring is fundamental to guide treatment adjustments rather than empirically modifying anti-TNF dosing.
- Ustekinumab represents a treatment alternative for CD patients who fail anti-TNF biologics.
- Patients with VEO-IBD frequently require more surgical interventions. In this population, diverting ostomies may promote colonic rest, reduce inflammatory burden, and improve quality of life when conventional therapy fails and severe colonic involvement progresses.

Author Contributions

All authors contributed to the design, development, and writing of the manuscript.

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Conflicts of Interest

None declared by the authors.

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Case report

Rendu-Osler-Weber Syndrome with Gastrointestinal, Hepatic, and Pancreatic Involvement

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Abstract

Rendu-Osler-Weber syndrome (ROWS) is characterized by the development of aberrant vascular structures such as dilated microvessels and arteriovenous malformations (AVMs) in the skin, gastrointestinal (GI) tract, lungs, liver, brain, and less commonly in the kidneys and pancreas. Complications include strokes, septic emboli, mesenteric ischemia, portal hypertension, and high-output cardiac failure. We report the case of a 52-year-old male patient with a history of recurrent epistaxis since adolescence and a family history of the same condition, who presented with symptoms of severe iron deficiency anemia. Endoscopic and radiologic studies confirmed the diagnosis of Rendu-Osler-Weber syndrome with hepatic and pancreatic involvement. The patient was referred for argon plasma coagulation therapy.

Keywords

Osler-Weber-Rendu syndrome, anemia, liver, pancreas.

INTRODUCTION

Rendu-Osler-Weber syndrome or hereditary hemorrhagic telangiectasia (HHT) is a rare autosomal dominant disorder with an estimated prevalence of 1/5,000-8,000 individuals. It results from mutations in the *ENG* and *ALK1* genes in approximately 85% of cases[(1)]. The most frequent clinical features include: epistaxis (95%), telangiectasias (95%), anemia (50%), hepatic arteriovenous malformations (AVMs) (47%-74%), pulmonary AVMs (15%-50%), gastrointestinal AVMs (13%-30%), pancreatic AVMs (up to 30%), cerebral AVMs (2%-20%), and pulmonary hypertension (1%-5%). While many patients may experience mild symptoms, others develop various complications from organ AVMs, leading to significant morbidity and mortality if not promptly detected and treated[(2)].

We present the case of a 52-year-old male with recurrent epistaxis hospitalized for severe anemia symptoms, found to have multiple cutaneous, mucosal, and gastrointestinal telangiectasias. Abdominal CT angiography further revealed hepatic and pancreatic AVMs. The patient was referred for argon plasma coagulation therapy.

CASE REPORT

A 52-year-old male presented with recurrent epistaxis since age 18 (1-2 monthly episodes lasting 4-5 days, resolving spontaneously) and monthly use of nonsteroidal anti-inflammatory drugs (NSAID) for mechanical low back pain. He denied significant weight loss or gastrointestinal symptoms. The patient reported multiple family members with recurrent epistaxis (**Figure 1**).

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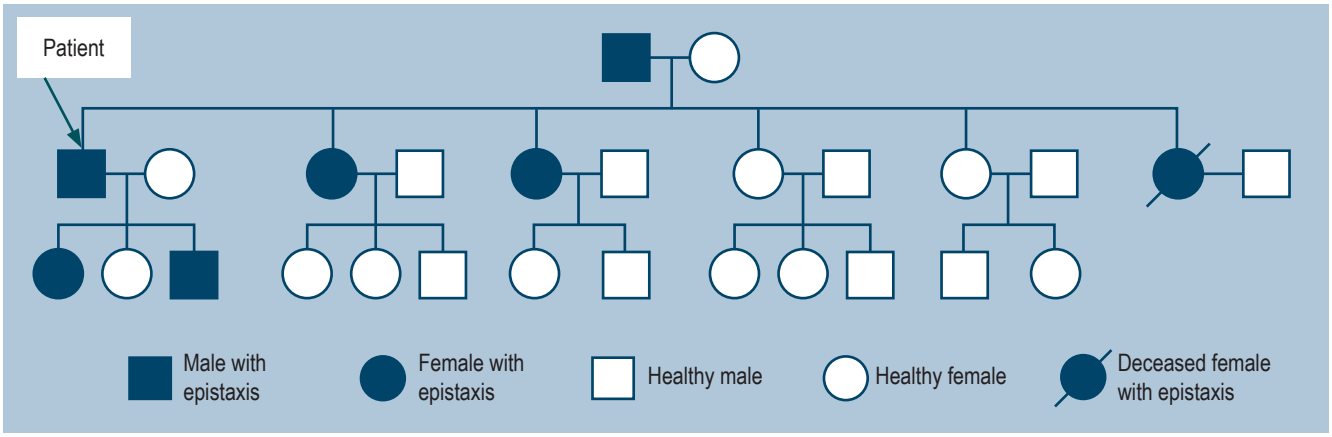


Figure 1. Family history of recurrent epistaxis, showing 6 affected relatives. Image property of the authors.

He was admitted for moderate exertional dyspnea, progressive fatigue, and new epistaxis episode two days prior. Physical examination revealed pallor and multiple telangiectasias on the face, tongue, lower lip, ears, neck, fingers, palms, and back (**Figure 2**). No hepatosplenomegaly or abdominal tenderness was noted.

Laboratory tests revealed the following results: hemoglobin: 4.8 g/dL, mean corpuscular volume (MCV): 64 fL, mean corpuscular hemoglobin (MCH): 16.4 pg, reticulocytes: 7.5%, normal folic acid and vitamin B_{12} levels, ferritin: 3 ng/mL, normal urinalysis and other laboratory values, and unremarkable chest X-ray findings.

Given the presentation of severe iron-deficiency anemia, cutaneous and mucosal telangiectasias, recurrent epistaxis, and positive family history, Rendu-Osler-Weber syndrome was suspected, prompting further evaluation. Upper endoscopy demonstrated multiple telangiectasias in the duodenum and stomach (**Figure 3**) without active bleeding stigmata. Colonoscopy showed no abnormalities.

As part of the diagnostic workup, portal Doppler ultrasound (**Figure 4**) showed multiple hepatic AVMs. Contrast-enhanced CT angiography (angio-CT) of abdomen and chest was performed to evaluate potential pulmonary involvement. Chest angio-CT was unremarkable, while abdominal imaging revealed multiple hepatic and pancreatic AVMs (**Figure 5**).

The patient remained asymptomatic during hospitalization. Management included intravenous iron supple-



Figure 2. Multiple telangiectasias on the tongue (**A**) and lower lip (**B**). Images property of the authors.

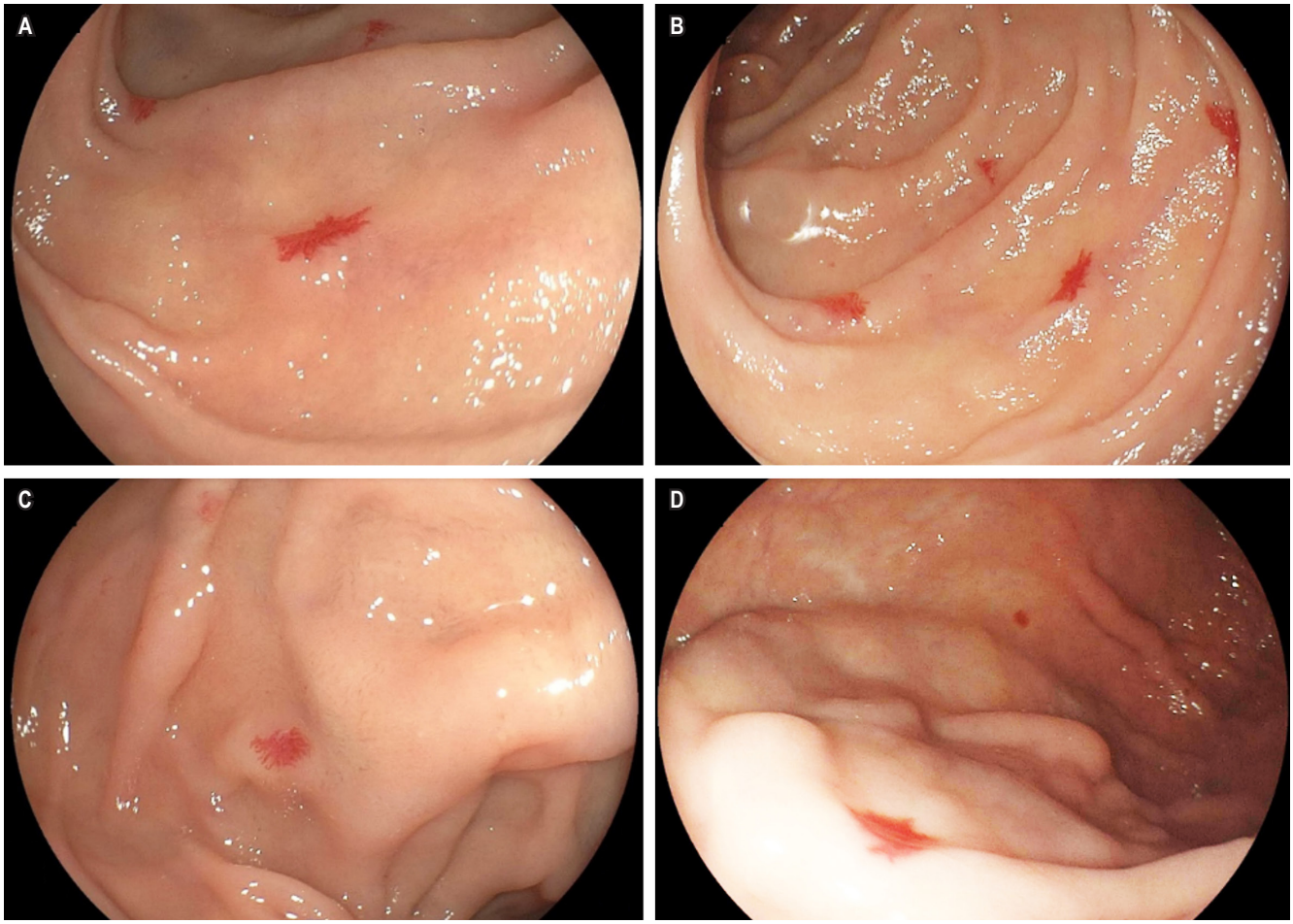


Figure 3. Upper endoscopy revealing multiple telangiectasias. **A and B.** 4-6 mm telangiectasias in the second portion of duodenum. **C and D.** 3-5 mm telangiectasias along the greater curvature of gastric body. Images property of the authors.

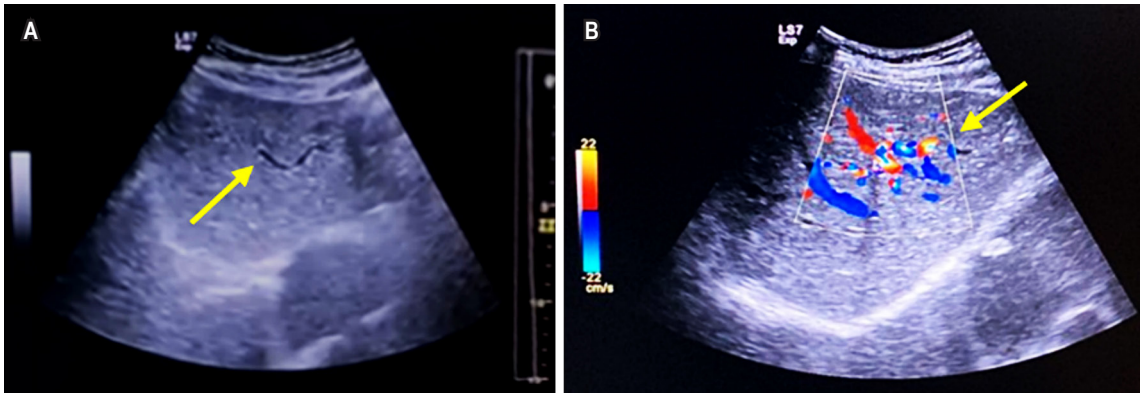


Figure 4. Portal Doppler ultrasound. **A.** Grayscale imaging showing serpentine-appearing vessels. **B.** Color Doppler enhancement of vascular structures. Images property of the authors.

mentation and otolaryngology evaluation with chemical cauterization of the right nasal fossa, resulting in no further epistaxis episodes. He was discharged asymptomatic on oral iron therapy, with comprehensive counseling regarding his diagnosis, potential complications, and warning signs. Referral was made to another institution for scheduled argon plasma coagulation therapy.

DISCUSSION

Rendu-Osler-Weber syndrome or HHT is a rare, multisystem disorder with variable clinical presentation and potential complications during its natural course[1]. This autosomal dominant condition results from mutations in the endoglin gene or activin receptor-like kinase 1 gene in 85% of cases, designated as HHT type 1 and HHT type 2, respectively[2]. These mutations cause endothelial migration and proliferation abnormalities, leading to vascular malformations, which carry an increased thrombosis risk and bleeding tendency[3,4].

The characteristic clinical features include epistaxis (95%), telangiectasias (75%), and anemia (50%) - all present in our patient. Notably, telangiectatic lesions typically appear during adolescence and increase with age[5].

Current diagnosis requires meeting three of four modified Curaçao criteria[6], as described in **Table 1**. Our patient fulfilled three criteria: spontaneous recurrent epistaxis since age 18; multiple telangiectasias on lips, oral cavity,

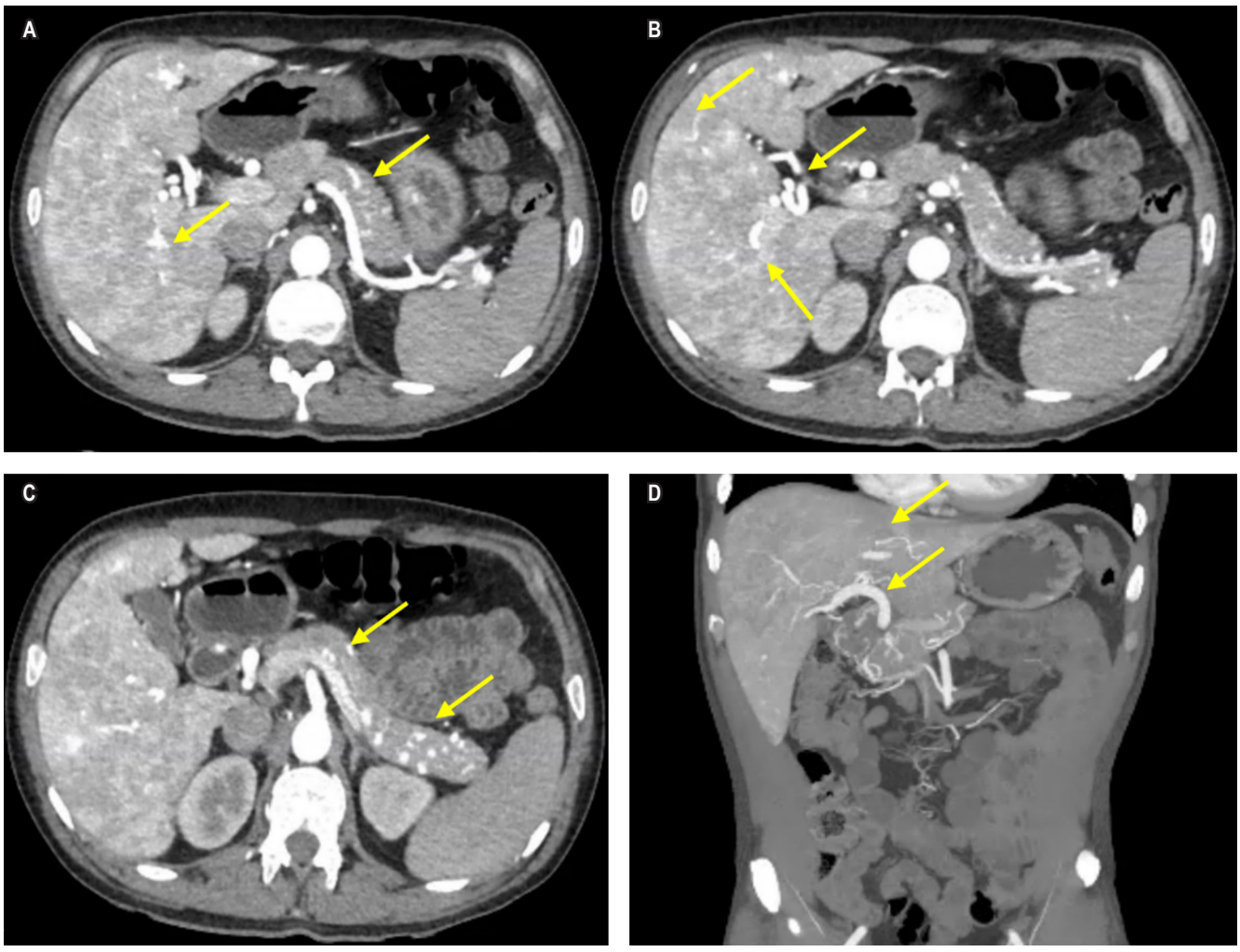


Figure 5. Abdominal angio-CT demonstrating multiple hepatic and pancreatic AVMs (arrows). Images property of the authors.

tongue, fingers and nose; and visceral telangiectatic lesions on upper endoscopy.

Table 1. Modified Curaçao criteria for clinical diagnosis of hereditary hemorrhagic telangiectasia (HHT)

Criteria	Description
Epistaxis	Spontaneous and recurrent
Telangiectasias	Multiple at characteristic sites: lips, oral cavity, fingers, nose
Visceral lesions	Gastrointestinal, pulmonary, hepatic, cerebral telangiectasias or spinal arteriovenous malformations
Family history	First-degree relative meeting these HHT criteria

Table prepared by the authors.

Patients may develop AVMs in hepatic, pulmonary, cerebral, and gastrointestinal systems. Gastrointestinal AVMs typically manifest during the 5th-6th decades, most commonly in stomach/proximal small bowel (colon involvement in 30%), causing slow chronic bleeding in 30% of cases[3]. Our patient demonstrated multiple gastric/duodenal telangiectasias without colonic involvement, consistent with literature.

Hepatic AVMs (47%-74%) create shunts between hepatic artery/portal vein, artery/hepatic veins, or portal/hepatic veins, potentially causing high-output heart failure, portal hypertension, hepatic encephalopathy, biliary/mesenteric ischemia, and cirrhosis. While usually asymptomatic, possible manifestations include abdominal pain, ascites, variceal bleeding, anicteric cholestasis, and encephalopathy. Our patient remained asymptomatic, but Doppler ultrasound detected hepatic AVMs later confirmed by abdominal CT.

Pulmonary AVMs (15%-50%) may complicate with embolic stroke and cerebral abscess. The first international HHT guidelines recommend screening and considering treatment/prophylactic antibiotics before certain procedures to prevent cerebral abscess[6]. Screening involves transthoracic bubble echocardiography or chest CT angiography. Our asymptomatic patient's chest CT showed no vascular lesions.

Cerebral AVMs (2%-20%) may cause intracranial hemorrhage and seizures. The utility of routine brain MRI screening remains controversial given adults' low complication risk[7].

This case uniquely demonstrated pancreatic AVMs - an uncommon finding with limited prevalence data in recent literature[8]. A 15-year study of 333 HHT patients reported pancreatic involvement in 18% versus hepatic involvement in 70%[9]. Potential complications include bleeding, pain, portal/splenic hypertension, and acute pancreatitis.

The treatment of HHT focuses on symptom management and complication prevention. For epistaxis, topical therapies or local ablative treatments such as laser therapy or sclerotherapy are recommended[10]. Iron deficiency anemia secondary to gastrointestinal bleeding is initially managed with oral iron supplementation, transitioning to intravenous iron if unresponsive. Based on three-month treatment response, cases are classified as: Mild HHT (hemoglobin targets achieved with oral iron), Moderate HHT (requires IV iron to reach hemoglobin targets), or Severe HHT (fails to reach targets with iron or requires transfusions)[11]. Our patient responded well to oral iron therapy.

For gastrointestinal telangiectasias, the Second International HHT Guidelines recommend argon plasma coagulation during endoscopy for both actively bleeding lesions and significant non-bleeding lesions (1-3 mm)[11]. Antifibrinolytics like oral tranexamic acid may be used for mild cases, while moderate-to-severe cases or those refractory to IV iron may require systemic antiangiogenic agents like bevacizumab[11]. Our patient had non-bleeding 3-5 mm telangiectasias requiring argon plasma coagulation, prompting referral to a specialized center.

Capsule endoscopy is recommended when upper endoscopy fails to identify significant telangiectasias in suspected HHT-related bleeding[11]—not indicated in our case given the diagnostic findings.

Genetic counseling is essential upon diagnosis to inform patients about the possible inheritance risk and the importance of early family screening to prevent complications.

CONCLUSIONS

Rendu-Osler-Weber syndrome should be suspected in patients with spontaneous recurrent epistaxis and cutaneous/mucosal telangiectasias. Multidisciplinary management is crucial given multisystem involvement. The condition carries high complication risks, necessitating timely diagnosis, ongoing monitoring, and genetic counseling.

Conflicts of Interest

The authors declare no conflicts of interest.

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Author Contributions

All authors contributed to study conception, design, manuscript preparation, and final approval.

Informed Consent

The patient provided consent for data and image publication.

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Case report

Type 3C Diabetes Mellitus Secondary to Chronic Pancreatitis: Case Report

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Abstract

Introduction: Type 3C diabetes mellitus (T3cDM), also known as pancreatogenic diabetes or diabetes of the exocrine pancreas, remains an underdiagnosed clinical entity. Acute pancreatitis is an inflammatory disease of the exocrine pancreas that accounts for over 300,000 hospitalizations annually, with a global incidence of 34 cases per 100,000 people and geographic variation. **Objective:** To present the case of a patient with pancreatogenic diabetes mellitus. **Case Report:** A 54-year-old male with a known history of insulin-requiring type 2 diabetes mellitus presented with marked hypoglycemia and a right gluteal abscess. Laboratory findings showed leukocytosis, anemia, and elevated acute-phase reactants. Imaging studies confirmed chronic pancreatitis and decreased C-peptide levels. **Conclusions:** This condition is often underdiagnosed and is associated with damage to pancreatic cells, leading to abnormal insulin release and an initial hypoglycemic state, which is frequently the presenting symptom, as seen in this case. A significant number of patients diagnosed with type 2 diabetes may present with poorly localized abdominal pain or signs of malabsorption. Therefore, it is important to inquire about alcohol and tobacco use, as both are risk factors for pancreatic injury. When clinical suspicion arises, imaging studies and pancreatic function tests are essential to evaluate pancreatic damage and dysfunction.

Keywords

Diabetes mellitus, pancreas, pancreatic diseases, pancreatitis.

INTRODUCTION

Type 3c diabetes *mellitus* (T3cDM), also known as *pancreatogenic diabetes,* remains an underdiagnosed pathological entity[(1)]. Etiologically, it develops in contexts of chronic pancreatitis, pancreatic cancer, cystic fibrosis, hemochromatosis, and prior pancreatic surgery[(2)]. Its pathophysiology is not fully understood but likely involves multiple factors including: islet cell mass loss, acute pancreatitis-induced autoimmunity, shared etiological risk factors, local/systemic inflammatory responses, and insulin-incretin axis dysfunction[(3-5)]. T3cDM affects all pancreatic islet cells, exhibiting both insulin resistance and production deficiency while also disrupting glucagon, pancreatic polypeptide, incretin, and adipokine secretion - making it a unique clinical entity[(6)].

Acute pancreatitis - an exocrine pancreatic inflammatory disease causing over 300,000 hospitalizations annually - has a global incidence of 34 cases per 100,000 people with geographic variation, and carries a 40% cumulative diabetes *mellitus* (DM) incidence rate[(7)]. Diagnostic criteria include major and minor components: major criteria require DM diagnosis plus pancreatic pathology on imaging (CT, endoscopic ultrasound, or MRI), while minor criteria

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include pancreatic polypeptide/incretin secretion defects, low basal C-peptide, or fat-soluble vitamin deficiencies[8,9]. This article presents a case of pancreatogenic DM.

CASE REPORT

A 54-year-old male with a heavy alcohol consumption history (weekly binge drinking) and insulin-dependent type 2 DM presented after self-administering 30 IU insulin glargine, with a home glucose reading of 28 mg/dL accompanied by neuroglycopenic symptoms. He reported a 15-day history of right gluteal abscess without discharge.

On admission, vital signs showed BP 95/67 mmHg, HR 54 bpm, RR 22 rpm, and temperature 36.0°C, with diaphoresis and mucocutaneous pallor. Initial labs revealed: WBC: 14,570/mm^3, neutrophils: 77.4%, hemoglobin: 9.8 g/dL, hematocrit: 29.2%, platelets: 472,000/mm^3, serum glucose: 30 mg/dL, sodium: 128 mmol/L, chloride: 108 mmol/L, potassium: 3.5 mmol/L, C-reactive protein (CRP): 24 mg/dL, prothrombin time (PT): 13.3, international normalized ratio (INR): 1.08), partial thromboplastin time (PTT): 35.1 sec, and creatinine: 0.74 mg/dL. Soft tissue ultrasound showed right gluteal inflammatory process without abscess.

By day 3, with worsening clinical course and new abdominal pain, contrast abdominal CT revealed chronic pancreatitis signs with anasarca (**Figure 1**), moderate free pleural effusion, moderate ascites, and diminished basal (0.1 ng/dL; reference range [Ref.]: 0.48-5.0 ng/mL) and postprandial (0.2 ng/dL; Ref.: 4.0-6.0 ng/mL) C-peptide levels. Despite treatment, the patient expired on day 4.

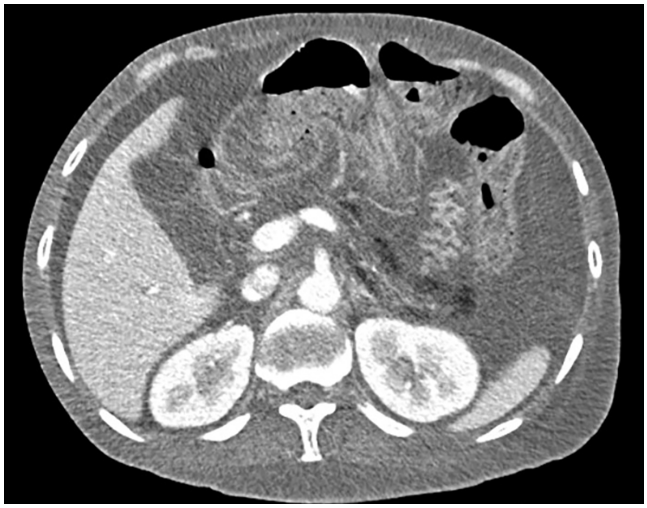


Figure 1. Axial CT scan showing atrophic pancreas with parenchymal microcalcifications suggestive of chronic pancreatitis. Image property of the authors.

The patient developed chronic pancreatitis likely secondary to chronic alcohol abuse, causing total pancreatic dysfunction that triggered admission hypoglycemia and subsequent clinical deterioration leading to fatal outcomes.

DISCUSSION

The diagnosis of pancreatogenic diabetes or type 3c diabetes *mellitus* (T3cDM) presents significant challenges due to the lack of standardized diagnostic tests and frequent misdiagnosis as type 2 diabetes. The American Diabetes Association (ADA) classifies this condition under "other specific types of diabetes," including diabetes secondary to exocrine pancreatic disease[10]. Our patient had been diagnosed with type 2 diabetes for 10 years and required high insulin doses during treatment. Approximately 78.3% of T3cDM cases are initially misdiagnosed as type 2 diabetes[5]. Several risk factors influence diabetes development in chronic pancreatitis patients, including smoking, alcohol consumption, and pancreatic fat accumulation, all identified as significant contributors[11]. Our patient had a history of early-onset alcohol use and occasional smoking.

The pathophysiology of type 3 diabetes characteristically involves destruction of pancreatic islet cells or acinar cells, leading to glucose dysregulation that manifests as hypoglycemic complications and increased mortality. Exocrine pancreatic dysfunction impairs nutrient absorption and incretin/glucagon secretion, with eventual alpha cell destruction. This glucagon deficiency likely explains our patient's severe hypoglycemic episodes, while his BMI of 17.6 kg/m^2 indicated malnutrition[12]. Islet cell destruction and cytokine production promote exocrine pancreatic insufficiency, causing pancreatic polypeptide (PP) cell loss and hepatic insulin resistance. The absence of PP response to mixed-nutrient ingestion helps differentiate T3cDM from type 2 diabetes pathogenesis[13]. Our patient's PP level of 0.1 ng/dL (normal range: 0.5-2.0) demonstrated complete exocrine pancreatic failure, with deficiency associated with reduced hepatic insulin receptors[14].

Premature beta cell destruction from inflammation leads to diabetes development in these patients. In our case, contrast-enhanced abdominal CT revealed chronic pancreatitis. Calcific pancreatitis represents one of the most common causes of secondary diabetes[15], though it may also follow acute pancreatitis.

Diagnostic criteria for our case included: exocrine pancreatic insufficiency, pathological pancreatic imaging, and absence of type 1 diabetes autoantibodies (unfortunately not assessed due to patient mortality)[16]. Early diagnostic imaging like ultrasound is recommended for suspected chronic pancreatitis cases[17].

Management requires oral pancreatic enzyme replacement and fat-soluble vitamin (A, D, E, K) supplementation alongside appropriate insulin therapy. Comprehensive preventive treatment addresses malnutrition and promotes healthy lifestyle modifications[18,19].

CONCLUSION

This underdiagnosed pathological entity results from pancreatic cell damage, causing abnormal insulin release and initial hypoglycemia - often the presenting symptom, as demonstrated in our case. Many patients diagnosed with type 2 diabetes may report nonspecific abdominal pain or show malabsorption signs. Clinicians should thoroughly assess alcohol and tobacco use, established pancreatic injury risk factors, and pursue pancreatic imaging/function tests when T3cDM is suspected to evaluate pancreatic damage.

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Conflicts of Interest

The authors declare no conflicts of interest.

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Case report

Rectal Mass as a Metastatic Manifestation of Prostate Cancer: Case Report

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Abstract

Prostate adenocarcinoma is the most common malignancy in men; however, its mortality does not rank among the top four causes of cancer-related death in this population. The most frequent metastatic sites are bone, liver, and lungs, while involvement of adjacent organs such as the colon or rectum is rare. Nevertheless, when local invasion into the gastrointestinal tract occurs, it is usually associated with a poorer prognosis. Therefore, it is essential to promptly recognize symptoms and consider this possibility as a differential diagnosis when encountering neoplastic-appearing lesions during procedures such as colonoscopy. We present the case of a 70-year-old man with a history of Gleason 4+4 prostate adenocarcinoma, initially treated with radiotherapy and hormone therapy. Years later, he presented with intestinal obstruction, and an infiltrative rectal mass was identified. Biopsy confirmed prostatic metastasis. Despite receiving targeted treatment, the patient died from infectious complications six years after the initial diagnosis.

Keywords

Prostatic intraepithelial neoplasia, neoplasm metastasis, neoplasms of the rectum.

INTRODUCTION

Prostate adenocarcinoma (PCa) ranks among the most prevalent neoplasms worldwide - the most common cancer in males and fifth leading cause of cancer-related mortality, with an incidence of approximately 29.4 cases per 100,000 men[(1)]. Its global significance continues growing alongside increasing cancer rates associated with extended life expectancy in developed and developing nations. While this malignancy frequently metastasizes to bone, lung, and liver, rectal metastasis remains relatively uncommon[(2)], resulting in limited evidence regarding its prognosis, management, and associated manifestations.

CASE PRESENTATION

We present the case of a 70-year-old male patient with a history of hypertension who was diagnosed with prostate adenocarcinoma in 2018, with a Gleason score of 4 + 4. Treatment was initiated with pelvic lymphadenectomy and 40 sessions of radiotherapy, combined with goserelin for one year. Follow-up was suspended due to the 2019 coronavirus (COVID-19) pandemic, so monitoring resumed in 2021. Laboratory tests revealed biochemical relapse, prompting treatment with abiraterone and leuprolide. However, the following year, imaging showed local progression, leading to bilateral orchiectomy and transurethral resection of the prostate.

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The patient was admitted to our institution the following year (2023) due to intestinal obstruction. Diagnostic workup included a gadolinium-enhanced pelvic magnetic resonance imaging (MRI), which revealed a necrotic-centered mass in the prostate that had invaded the bladder floor, seminal vesicles, and mid-to-lower rectum, causing partial obstruction of the large intestine (**Figures 1** and **2**). A colonoscopy was performed to assess the extent of involvement and obtain biopsy samples for histopathology. Endoscopic findings showed a friable, infiltrative lesion circumferentially involving the distal rectum, causing luminal stenosis that prevented passage of the scope (**Figure 3**). Histopathological examination confirmed prostate adenocarcinoma, ruling out the suspected diagnosis of a second primary tumor. The patient underwent a diverting colostomy and was placed on palliative systemic therapy. He died six years after the initial diagnosis due to infectious complications.

DISCUSSION

Prostate adenocarcinoma is the most common neoplasm in men, both in Colombia and worldwide; despite this,

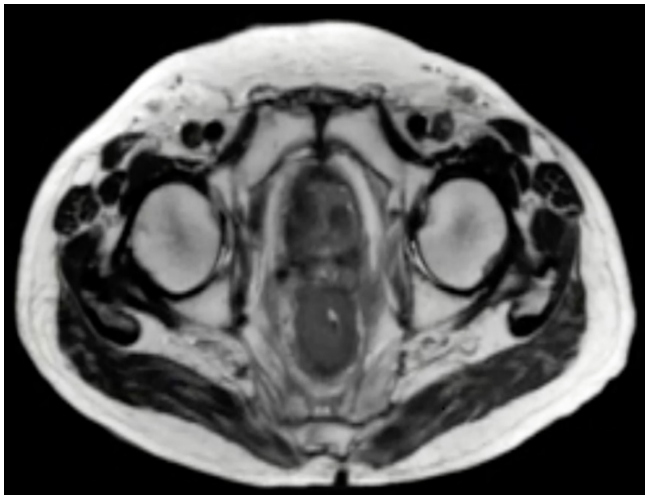


Figure 1. T2-weighted pelvic MRI showing concentric thickening of the rectal walls. Image property of the authors.



Figure 2. Gadolinium-enhanced MRI demonstrating concentric thickening of the rectal wall with involvement of the anterior serosa. Image property of the authors.

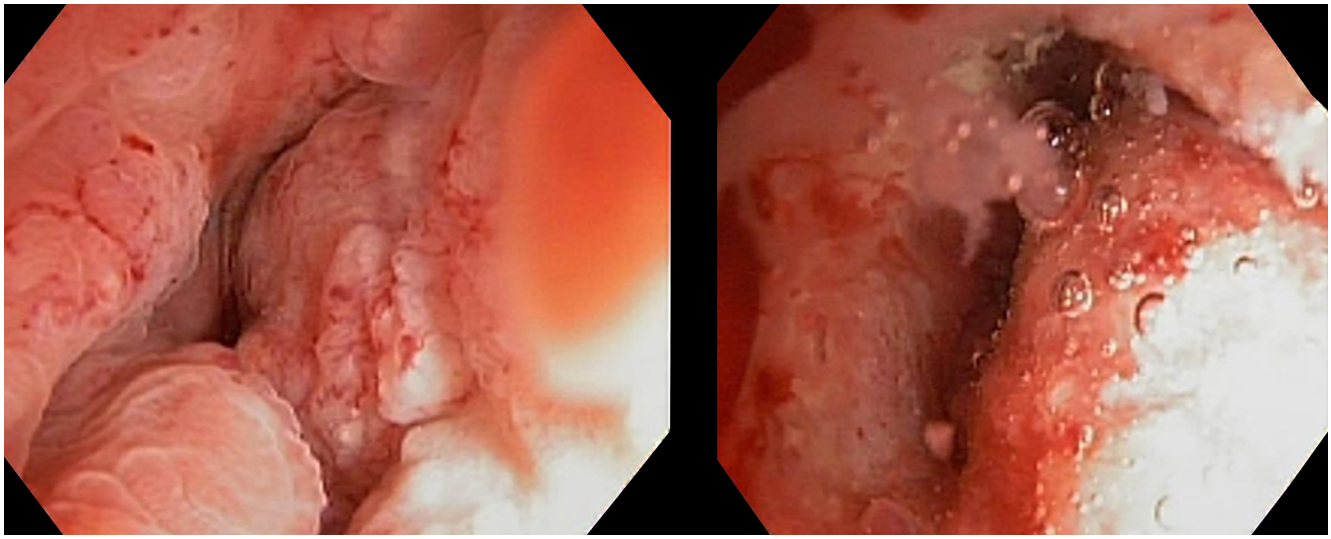


Figure 3. An infiltrative, friable lesion is observed in the rectum, causing luminal stenosis. Images property of the authors.

its mortality rate is not as high compared to other, less frequent neoplasms[1]. This cancer can cause local involvement of nearby organs, such as the bladder, ureters, adjacent lymph nodes, and bones. Globally reported cases have described rare metastatic involvement in organs such as the esophagus, stomach, liver, penis, and brain[3]. Like the aforementioned organs, rectal involvement in prostate adenocarcinoma is uncommon and, according to the literature, is a poor prognostic factor when it occurs[4]. Despite the proximity of the prostate to the rectum, tumor infiltration is rare due to the anatomical presence of the intraprostatic fascia (Denonvilliers' fascia), which acts as a barrier[5].

The proposed mechanisms can be explained by three main theories. The first is direct infiltration of the aforementioned fascia; the second involves drainage from pelvic lymph nodes that receive lymphatic flow from both the prostate gland and the rectum; and the third may be due to seeding of cancer cells in the perirectal tissue during prostate biopsy[5]. Symptoms are nonspecific, often leading to initial consideration of other conditions, such as rectal adenocarcinoma (hematochezia, intestinal obstruction) or radiation proctitis[6]. In our case, it presented as intestinal obstruction, evaluated through imaging, endoscopy, and histopathology.

It is important to note that the endoscopic findings of this condition are not typical and can be mistaken for a primary colon neoplasm, which would prompt immediate surgical management. Differentiating between these two entities is crucial, as their treatments are entirely different. The treatment for a rectal tumor involves chemoradiotherapy, in some cases with a total neoadjuvant therapy (TNT) regimen, whereas prostate tumors are managed with hormonal therapy, chemotherapy, or surgery, depending on disease presentation[7]. Additionally, this distinction may help identify secondary lesions and provide a more accurate prognosis for patients.

CONCLUSION

In patients with advanced prostate cancer, metastatic involvement of the rectum should be considered when rectal symptoms arise. If endoscopically visible lesions are detected, biopsies are essential to confirm the diagnosis or explore differential diagnoses. Confirmation of these metastases indicates a poor prognostic factor, which can help guide treatment decisions.

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Case report

Case Series: The Gastric Face of Lipid Deposits

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Abstract

Xanthoma is a benign lesion associated with lipid metabolism, commonly manifesting in various areas of the body. Gastric xanthomas, often incidentally identified during endoscopic procedures, are histopathologically characterized by the presence of foamy histiocytes in the gastric mucosa. Their prevalence ranges from 0.23% to 7%, with the antrum being the most frequently affected site and a clear association with increasing age.

This study presents 20 cases of patients diagnosed with gastric xanthoma between 2016 and early 2024. Chronic gastritis was observed in 90% of patients, intestinal metaplasia in 20%, mild atrophy in 25%, and low-grade dysplasia in only one case (5%). In addition, *Helicobacter pylori* infection was detected in 30% of the cases. The importance of conducting prospective research is emphasized to better understand the relationship between gastric mucosal alterations and gastric xanthomas, with a particular focus on early detection of gastric cancer.

Keywords

Xanthoma, *Helicobacter pylori*, atrophic gastritis, metaplasia.

INTRODUCTION

A *xanthoma* is defined as a benign, localized lesion of cholesterol deposits. First described in the early 20th century following histological studies in patients with these lesions in various body regions, it is associated with lipid metabolism[(1)]. These deposits frequently appear in periarticular areas, such as the trunk or extremities, as a result of hyperlipidemia (primary or secondary diabetes, hypothyroidism, myeloma, lymphoma, leukemia, and obstructive liver diseases)[(2)]. Xanthelasmas, also linked to hyperlipidemia, manifest subcutaneously, most commonly on the eyelids, presenting as yellowish plaques and papules[(3,4)].

The pathogenic mechanism of xanthoma formation begins with localized increased filtration of low-density lipoproteins (LDL) from the vascular network into underlying tissues. As these lipid aggregates accumulate, monocytes and macrophages phagocytize the lipoproteins, giving rise to foam cells[(5)]. Gastric xanthomas are incidentally found in the gastrointestinal tract during upper endoscopies[(6,7)]. The most significant histopathological finding is foam-laden histiocytes in the lamina propria of the gastric mucosa,

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occasionally accompanied by plasma cells, smooth muscle cells, and Schwann cells[5]. Their incidence ranges from 0.23% to 7%[6,8]). According to Gómez Martín et al., most are located in the antrum (53%), body (32%), antrum and body (10%), and fundus (5%). Additionally, xanthomas appeared as solitary lesions in 72% of cases[7].

In a study by Wei Na Shen et al. involving 47,736 patients who underwent endoscopy between January 2020 and December 2021, gastric xanthoma was detected in 2.85% (1,360 patients). Of these, 62.06% had a single lesion, while 37.94% had multiple lesions. The most common location was the antrum (52.50%), followed by the body (18.16%), with nonspecific locations accounting for 18.31%[9].

The etiology remains poorly defined, though two theories exist: the first focuses on hyperlipidemia (metabolic disorders such as type 2 diabetes and obesity), independent of gastric conditions; the second centers on prior gastric mucosal alterations, regardless of metabolic disorders. Key mucosal changes include chronic atrophic gastritis, complete intestinal metaplasia, gastric ulcer, *Helicobacter pylori* infection, bile reflux lesions, and partial Billroth gastrectomies[10]. Similarly, studies have established a significant association between gastric xanthomas and mucosal lesions such as chronic gastritis, atrophy, gastric cancer, and *H. pylori* infection[11-13].

METHODOLOGY

A retrospective search was conducted using endoscopic data and images from patients treated at Instituto de Gastroenterología y Hepatología del Oriente (IGHO S.A.S.) between 2016 and 2024, whose histopathological findings confirmed gastric xanthoma. Prior to inclusion, patients signed informed consent permitting the use of their anonymized data and images for research purposes.

RESULTS

A total of 20 cases of gastric xanthoma were identified, with detailed characteristics presented in **Table 1**. The mean age of these patients was 55.5 years (standard deviation: 13.3), with a minimum age of 37 and a maximum of 81. Sex distribution was equal, with 50% male and 50% female.

The most frequent relevant medical histories were hypertension (25%) and hypothyroidism (20%). Regarding lesion quantity, gastric xanthomas ranged from 1 to 4 lesions per case, with 75% of patients presenting multiple lesions. **Figure 1** illustrates their distribution across gastric regions: most were located in the gastric antrum (60%), followed by the gastric body (25%), fundus (5%), angular notch (5%), and pylorus (5%).

Table 1. Case Characterization

Variable	Category	n: 20	%
Sex	Male	10	50
	Female	10	50
Number of Lesions	1	5	25
	2	5	25
	3	5	25
	4	5	25
Location	Antrum	12	60
	Body	5	25
	Fundus	1	5
	Angular notch	1	5
	Pylorus	1	5
Metaplasia	No	16	80
	Yes	4	20
Atrophy	No	15	75
	Yes	5	25
H. pylori	No	14	70
	Yes	6	30
Dysplasia	No	19	95
	Yes	1	5
Metaplasia percentage	0%	16	80
	20%	1	5
	40%	2	10
	60%	1	5

Table prepared by the authors.

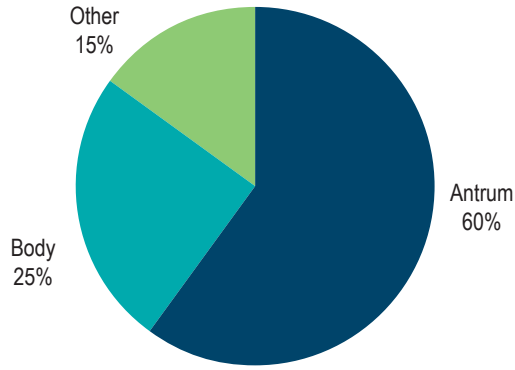


Figure 1. Distribution of gastric xanthomas by location. Image property of the authors.

Pathological analysis revealed chronic gastritis in 90% of cases. Moderately diffuse chronic gastritis was most prevalent (66.6%), followed by active follicular chronic gastritis (16%). Intestinal metaplasia was identified in four patients (20%, 40%, and 60% involvement in one, two, and one case(s), respectively). Mild gastric mucosal atrophy was observed in five patients, and low-grade dysplasia in

one case. *H. pylori* infection was detected in 30% of cases (6 patients), underscoring its relevance in gastrointestinal pathology.

Figures 2–6 provide morphological descriptions of endoscopic and histopathological findings, offering anatomical and microscopic details of the gastric xanthoma lesions.

DISCUSSION

Current literature demonstrates a significant increase in the incidence of these benign lesions among individuals over 60 years old, highlighting a correlation between advanced age and gastric xanthoma prevalence[12]. In the findings observed in the 20 patients diagnosed with this condition, the highest frequency was recorded in individuals in their fifth decade of life, accounting for 30% of cases.

Regarding sex distribution, the reviewed studies indicate that both men and women show similar incidence rates of these lesions. A study by Yi Chen et al.[15] identified 1,370 gastric xanthoma cases, distributed among 667 women and 703 men, but no significant difference in lesion incidence between sexes was demonstrated. In the cases reported in this article, we found an equal distribution between both sexes. However, it is relevant to consider that some studies postulate a higher prevalence of this lesion in men than in women[9].

Additionally, the most common location of these benign lesions tends to be predominantly in the gastric antrum[9,15,16], and these studies suggest a higher probability of finding a single gastric xanthoma lesion in the population. Regarding our case report findings, we observed agreement with the lesion location but not with the number of lesions, as 75% of cases presented with more than one lesion. This suggests the existence of particular characteristics in our population that warrant in-depth investigation.

It is crucial to note that chronic gastritis diagnosis is based on histopathological findings, with potential progression to atrophy and metaplasia over time[17]. When reviewing studies linking chronic gastritis to gastric xanthomas, we found limited evidence on this subject, with the few available studies suggesting a low incidence, representing a small percentage (2.29%) in patients with gastric xanthomas[9]. In our analysis, we found that 90% of the 20 cases presented with this condition, a discrepancy that may correspond to the coexistence of both conditions in our population.

Previous studies have demonstrated a strong association between gastric xanthomas and the presence of gastric mucosal atrophy[18,19]. In our case series, 30% presented with this association, similar to the findings of the study by Dinghong Xiao et al., where 30.1% of the studied population showed gastric mucosal atrophy[16]. Thus, this reinfor-

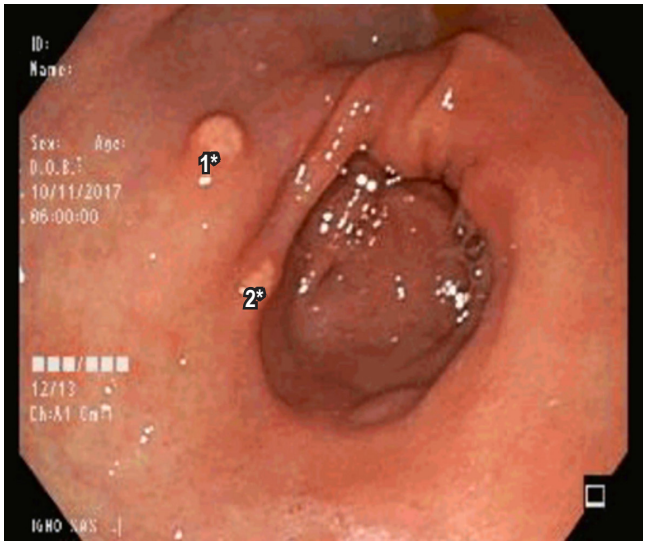


Figure 2. The gastric antrum is observed between the anterior wall and lesser curvature, classified as Paris 0-1s[14]. The lesion (1*) measures approximately 8 mm in diameter, with a yellowish, speckled, xanthomatous appearance and irregular borders. A second lesion (2*), approximately 5 mm, is located on the more proximal anterior wall near the pylorus, exhibiting similar yellowish speckling. Image property of the authors.

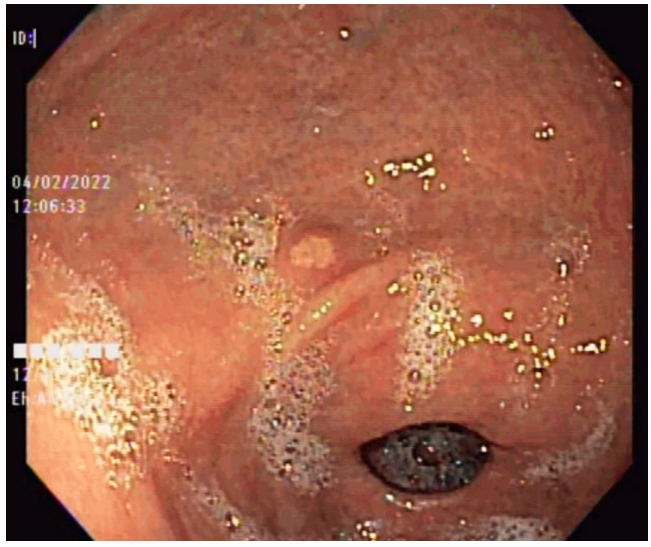


Figure 3. A yellowish, mottled lesion measuring ~4 mm in diameter (Paris 0-1s classification)[14] is observed in the antral region along the curvature and anterior wall. Image property of the authors.

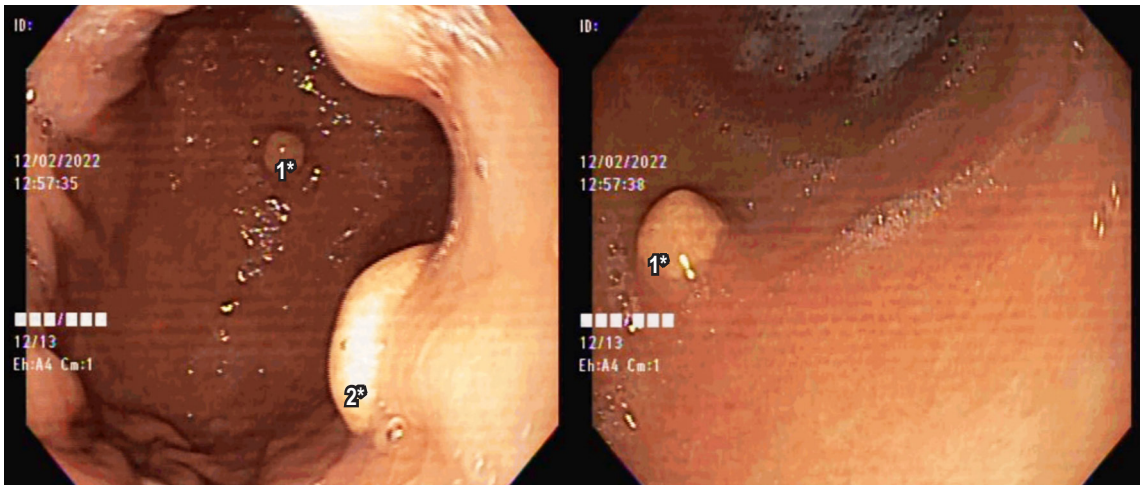


Figure 4. Endoscopic images of two lesions: The first (1*), located at the antral-body junction between the greater curvature and anterior wall, measures 7 mm with a yellowish surface (Paris 0-1s)[14]. The second (2*), ~10 mm in diameter, is positioned in the proximal body near the posterior wall along the lesser curvature. Images property of the authors.

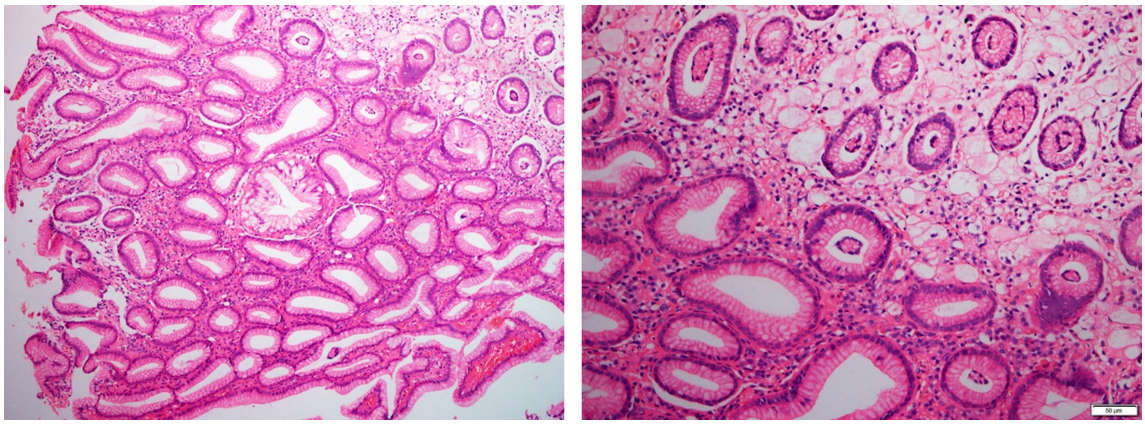


Figure 5. Histopathological images (20× and 40×, H&E staining). Gastric mucosa shows numerous foam-laden histiocytes in the lamina propria, with abundant globular, clear cytoplasm and round-to-oval, occasionally eccentric nuclei. Images property of the authors.

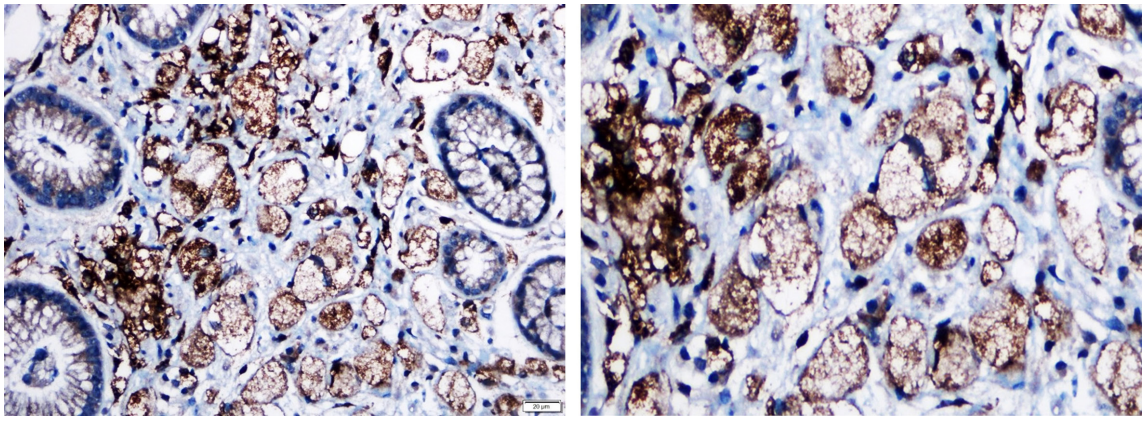


Figure 6. Immunohistochemistry was strongly positive for CD68 in all described cellular elements. Notably, these cells were negative for pan-cytokeratin and epithelial membrane antigen. Images property of the authors.

ces the idea that gastric xanthomas may be related to degenerative changes in the gastric mucosa.

A study conducted by Sekikawa et al. demonstrated that the presence of gastric xanthomas was associated with gastric cancer, with an odds ratio (OR) of 7.19 (95% confidence interval [CI]: 2.50-20.83) in the studied population[12]. Similarly, the study by Dinghong Xiao et al. revealed that gastric xanthoma was significantly associated with the presence of intestinal metaplasia (OR: 2.3; 95% CI: 1.6-3.2)[16]. In our results, no cases of gastric cancer were present, suggesting the need to expand the study sample size.

Regarding intestinal metaplasia and dysplasia in relation to gastric xanthomas, previous studies have reported a significant association with intestinal metaplasia ($p < 0.001$)[15] and a prevalence of approximately 49%[15,20]. Concerning dysplasia, the reviewed literature suggests a significant relationship ($p < 0.001$)[15]. In our study, intestinal metaplasia was evident in only 20% of cases, and intestinal dysplasia was identified in only one patient.

Regarding *H. pylori* infection, which has been the subject of numerous recent studies due to its association with gastric cancer, some research indicates a prevalence of about 94% in the relationship between the bacteria and gastric xanthomas[20]. The study conducted by Chen et al.[15] reports an *H. pylor*i prevalence of 30.8%. In our reported cases, we found that 30% of patients with gastric xanthoma had the bacteria. Finally, the immunohistochemistry results from our cases correlate exactly with what is described in the literature, highlighting intense positivity for CD68 with negativity in all cases for pan-keratins and epithelial membrane antigen[21].

CONCLUSION

Based on the above, there may be a relationship between the presence of gastric xanthomas and premalignant gastric lesions; therefore, additional studies are needed to confirm this hypothesis. Identifying this association could contribute to detecting new conditions or risk factors that facilitate the prevention and early diagnosis of malignant and premalignant gastric lesions. However, the information and data available to date are insufficient to make recommendations about modifications to clinical practice that could be included in current guidelines.

The study has certain limitations, as it is a retrospective study in which patient selection and data collection were based on existing reports. Additionally, the sample size limits the ability to establish robust associations and generalize the results. Prospective studies with more representative samples are needed to determine the relationship between premalignant gastric lesions and gastric xanthoma. This would facilitate the identification of additional predictive factors for gastric cancer prevention.

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Case report

Hepatic Hydatidosis with Abdominal Wall Invasion: Case Report and Literature Review

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Abstract

Introduction: Hepatic hydatidosis is a zoonotic disease caused by the parasite *Echinococcus granulosus*. It is often asymptomatic and carries a significant disease burden in developing countries. **Case Report:** We present the case of a 66-year-old woman with pain, a palpable mass, and inflammatory symptoms in the right hypochondrium. Initial laboratory tests were normal, and physical examinations revealed hepatomegaly. Subsequent ultrasound imaging showed cystic liver lesions, and CT scan confirmed collections in the liver and peritoneal cavity. Hepatic hydatidosis was suspected, and medical treatment was initiated. However, the clinical course was unfavorable due to cyst rupture into the peritoneal cavity. During surgery, multiple cysts involving the liver and abdominal wall were identified. The patient showed favorable postoperative progress and was discharged to continue oral antiparasitic therapy on an outpatient basis. Histopathological analysis revealed a germinal membrane, proliferative capsule, and ruptured *E. granulosus* scolices. **Discussion:** Echinococcosis is a zoonotic disease with public health impact in developing countries. It may form cysts in solid organs such as the liver. Clinical presentation varies depending on the location, ranging from asymptomatic cases to systemic involvement. Diagnosis relies on imaging studies, and treatment typically involves anthelmintic therapy and, in some cases, complex surgical procedures. **Conclusion:** Hepatic hydatidosis is a parasitic zoonosis that may become complicated by invasion of adjacent organs, requiring comprehensive management by appropriately trained medical personnel.

Keywords

Hepatic hydatidosis, *Echinococcus*, zoonosis, echinococcosis, hepatectomy, case reports.

INTRODUCTION

Hydatidosis is a zoonotic infection caused by parasites of the *Echinococcus* genus, most commonly *E. granulosus* and *E. multilocularis*, which are responsible for its two primary forms: hepatic echinococcosis (HE) and alveolar echinococcosis (AE), respectively[1]. In endemic regions for *E. granulosus*, such as South America, Eastern Europe, the Middle East, Russia, and China, incidence rates can reach up to 50 cases per 100,000 people per year, with prevalence ranging from 20% to 95%, varying in high-risk areas such as those where animals are slaughtered for human consumption[2]. Regarding mortality, untreated or inadequately treated HE has a rate of 2% to 4%, while AE can reach up to 90% within 10 years of diagnosis[1].

Imaging and serology are used for diagnosis, with ultrasound being the first-line choice as it allows for lesion characterization and staging[3,4]. Treatment involves an interdisciplinary approach—medical, surgical, or minimally invasive—including the administration of anthelmintics

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such as albendazole. Depending on the patient's symptoms and cyst characteristics, procedures like hepatectomy, cystopericystectomy, or capsulectomy may be performed[4,5].

CASE REPORT

A 66-year-old female patient with a history of type 2 diabetes *mellitus* and hypertension, residing in an urban area, presented to the emergency department with a one-month history of intermittent right hypochondrium pain and a palpable mass associated with erythema, edema, localized warmth, and unquantified febrile episodes. Physical examination revealed no abdominal distension or clinical signs of peritoneal irritation; however, hepatomegaly of 15 cm below the costal margin was noted. Initial blood biochemistry showed no significant abnormalities.

A full abdominal ultrasound revealed a hypoechoic area measuring 75 x 60 x 41 mm (95 mL in volume) in segment VI of the liver and another well-defined, heterogeneous subhepatic expansile lesion measuring 90 x 73 x 58 mm. Possible etiologies included a liquefying liver abscess, a neoproliferative expansile lesion, or a hydatid cyst. An abdominal computed tomography (CT) scan was subsequently performed, which confirmed an intraparenchymal collection in hepatic segment VI, an underlying intraperitoneal collection, and an intramuscular collection in the right flank (**Figure 1**). Tumor markers were assessed due to suspicion of a neoplastic lesion but showed no abnormalities. Consultations with Infectious Diseases and Hepatopancreatobiliary Surgery led to a diagnosis of hepatic hydatidosis, and empirical therapy with albendazole (400 mg every 12 hours for 30 days) was initiated, with outpatient follow-up scheduled.

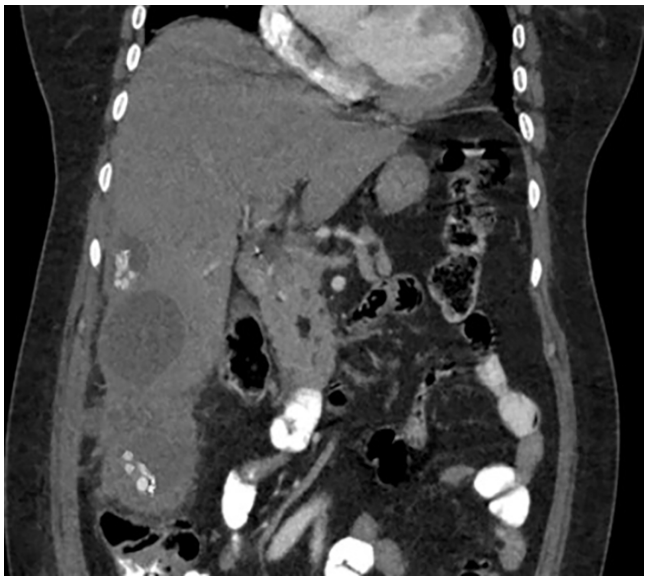


Figure 1. Coronal section of an abdominal CT scan showing hepatic and peritoneal involvement. Image property of the authors.

The patient experienced a poor clinical course due to persistent symptoms. Upon reevaluation by the treating team, spontaneous rupture of the hydatid cyst into the peritoneal cavity was suspected. Follow-up blood biochemistry studies revealed neutrophilic leukocytosis and elevated C-reactive protein (CRP). Subsequent serology for Echinococcus returned positive (enzyme-linked immunosorbent assay [ELISA] = 1/800). An abdominal magnetic resonance imaging (MRI) scan was performed, clearly demonstrating extensive hepatic involvement as well as abdominal wall invasion (**Figure 2**).

The patient underwent image-guided percutaneous drainage, yielding approximately 200 mL of frank purulent fluid. Gram staining revealed gram-positive cocci, though subsequent culture was negative. The case was discussed in a multidisciplinary medical meeting, and surgical management was decided. During the procedure, a large mass composed of multiple mixed-component (solid and liquid) cysts was found, involving hepatic segments V, VI, and part of VII, with spontaneous drainage into the abdominal wall. The cysts fully infiltrated the transverse abdominal muscle and 80% of the right internal oblique. A hepatic resection of the hydatid cysts and concurrent abdominal wall cyst excision were performed. Postoperatively, the patient recovered well and was discharged after 17 days to complete outpatient antiparasitic therapy. Histopathology confirmed the presence of a germinal membrane, a proliferative capsule, and protoscolices of *E. granulosus*, along with significant pericystic inflammatory reaction and marked infiltration of mononuclear and giant cells in the muscle tissue.

DISCUSSION

Hepatic hydatidosis, or echinococcosis, is a zoonotic infection with hepatic and alveolar presentations, caused primarily by *Echinococcus granulosus* and *E. multilocularis*[1]. Other species (*E. vogeli* and *E. oligarthra*) are associated with polycystic and rare unicystic forms, respectively[6]. It is a public health concern, particularly in developing countries, and the World Health Organization (WHO) has classified it among the 17 neglected tropical diseases targeted for control or elimination by 2050[1,3].

Endemic regions report incidence rates of up to 50 cases per 100,000 people/year, with prevalence ranging from 20% to 95% in high-risk areas. Although surgical cases are reasonably documented, they represent only a fraction of total infections. Low socioeconomic status, plant-based subsistence, regional climate, and livestock rearing with poor sanitary controls are established risk factors[2]. Humans are incidental hosts and do not participate in the parasite's life cycle, which requires a definitive host (typi-

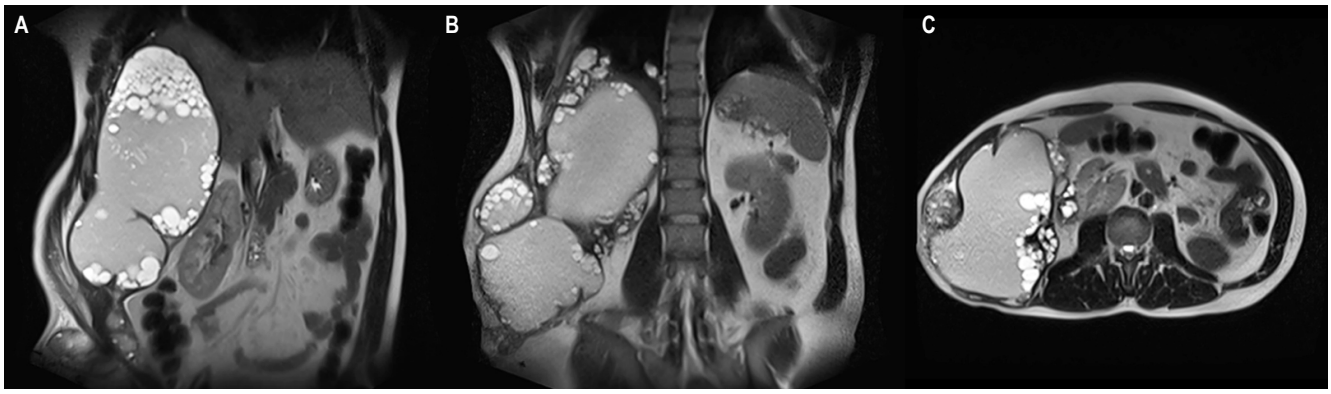


Figure 2. Follow-up abdominal MRI. **A.** Coronal view showing extensive hepatic involvement with multiple hydatid cysts. **B and C.** Coronal and axial views confirming hydatid cyst infiltration into the abdominal wall. Images property of the authors.

cally canines) for adult development and an intermediate host (e.g., pigs, sheep, or goats) for the larval stage. Humans ingest infectious eggs excreted by definitive hosts before larval development begins (**Figure 3**)[3,6,7]. Human-to-human transmission has not been reported[3].

The organs most frequently affected by echinococcosis are the liver (50–70% of cases) due to intestinal venous drainage, followed by the lungs (20–30%), and less commonly the spleen, heart, kidneys, bones, and central nervous system (CNS)[2,3]. Symptoms vary depending on the affected organ and are often absent in early stages. Hepatic symptoms typically emerge when the cyst(s) occupy more than 70% of the organ's volume or exceed 10 cm in diameter, compressing or destroying biliary ducts or vascular structures. In this case, the hepatic lesion measured 75 × 60 × 41 mm, while the extrahepatic lesion reached 90 × 93 × 58 mm.

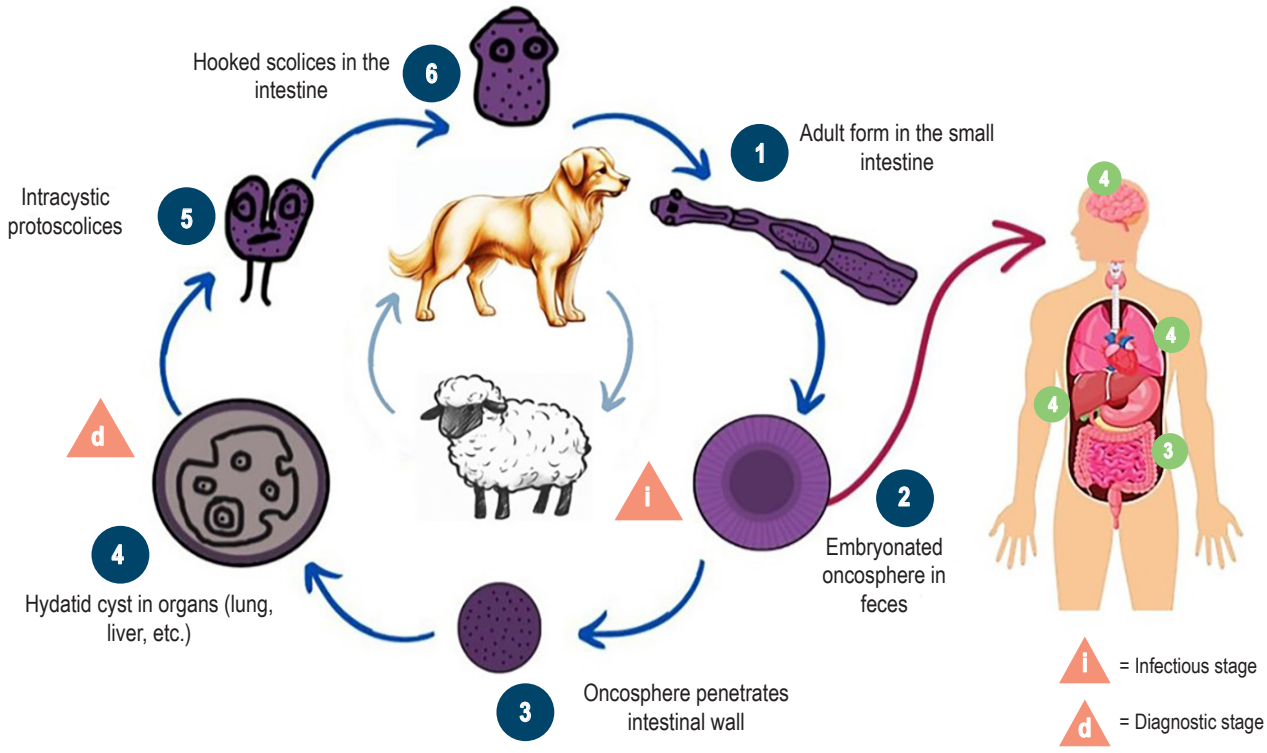


Figure 3. Life cycle of *Echinococcus granulosus*. Prepared by the authors based on information from the Centers for Disease Control and Prevention (CDC), Atlanta.

Clinical manifestations of hepatic hydatidosis often include abdominal discomfort/pain, decreased appetite, nausea/vomiting, and jaundice in cases of biliary obstruction. Physical exam may reveal a palpable upper abdominal mass, hepatomegaly (the most common sign), or abdominal distension. Cyst rupture can cause symptoms ranging from fever, urticaria, and eosinophilia to anaphylactic shock and death[1]. This patient's presentation aligned with the most frequently reported manifestations, including physical exam findings, though eosinophilia was absent on blood biochemistry.

Due to slow growth (approximately 1–5 cm/year)[8], most cases are incidentally detected on imaging during evaluation for nonspecific symptoms or unrelated conditions[3,5]. For symptomatic patients or incidental findings suggestive of the disease, diagnosis relies on combined imaging and serology. A detailed clinical history should identify risk factors (e.g., residence in/travel to endemic areas, contact with definitive hosts) alongside thorough physical examination[3].

The WHO Informal Working Group on Echinococcosis (WHO-IWGE) classifies cysts based on ultrasonographic findings and corresponding treatments (**Tables 1** and **2**)[4]. Liver ultrasound is the preferred diagnostic modality, with 95% sensitivity[9] for lesion identification, characterization, and staging, as well as post-treatment follow-up in endemic areas. It is also valuable for surveillance and screening[5] and is the most sensitive tool for detecting membranes, septations, and hydatid sand[2]. Here, ultrasound identified hepatic lesions and suggested the diagnosis, classifiable as CE1 based on sonographic features.

CT is typically the complementary imaging study of choice, providing more accurate assessment of cyst location, size, and hepatic parenchymal integrity. It is particu-

Table 1. WHO-IWGE Classification of Hydatid Cysts

Stage	Ultrasonographic Appearance (WHO-IWGE)
CL	Unilocular anechoic cyst, no internal echoes/septations
CE1	Cyst with fine internal echoes (hydatid sand): active cyst
CE2	Multiseptated cyst with "honeycomb" appearance (unilocular primary cyst): active cyst
CE3	Unilocular cyst with detached membranes ("water lily sign," CE3a) or daughter vesicles with hypo-/hyperechoic images (CE3b): transitional cyst
CE4	Mixed hypo-/hyperechoic content, no daughter vesicles ("ball of wool" appearance): degenerative cyst
CE5	Partially/fully calcified wall: inactive cyst

Table prepared by the authors.

Table 2. Hydatid Cyst Therapy Protocol

Stage	Size	First-Line Treatment	Alternative Therapy
Contraindication/invasive treatment refused		ABZ (6 months)	
CE1, CE3a	Small	ABZ alone (6 months)	PAIR + ABZ (1 month)
	Medium	Surgery + ABZ (1–6 months)	PAIR + ABZ (1 month)
	Large	Surgery + ABZ (1–6 months)	MoCaT + ABZ (1 month)
CE2, CE3b	Small	ABZ alone (6 months)	MoCaT + ABZ (1 month)
	Medium	Surgery + ABZ (1–6 months)	MoCaT + ABZ (1 month)
	Large	Surgery + ABZ (1–6 months)	MoCaT + ABZ (1 month)
CE4, CE5	Any	"Watch and wait"	"Watch and wait"
Complicated cysts (any stage)	Any	Surgery (± interventional endoscopy for biliary rupture) + ABZ (6 months)	Surgery (rupture) / percutaneous drainage (infection) + ABZ (1 month)

ABZ: albendazole; MoCaT: modified catheterization; PAIR: puncture, aspiration, injection, reaspiration. Table prepared by the authors.

larly useful for small cysts or when extrahepatic, vascular, or adjacent structure involvement (e.g., biliary tract) is suspected, with 95% sensitivity[9]. Additionally, it enables detailed surgical planning for complex or atypical cases like this one, where it clearly delineated the extensive abdominal wall involvement and guided surgical strategy. MRI is more valuable for CNS involvement[2,5].

Serologic testing for *Echinococcus* serves as another diagnostic tool, especially when imaging findings are suggestive but not pathognomonic. However, results require careful interpretation since specific antibodies may remain positive for years even after radical surgery, not necessarily indicating active infection. In this case, the patient's 1/800 titer suggested active infection. Several factors influence interpretation: WHO-IWGE stage (discussed earlier), size (>15 cm vs. <15 cm), hepatic/extrahepatic location, cyst multiplicity, and complications. One study found hepatic CE1 and CE4-5 cysts were seronegative in 30–58% and 50–87% of cases, respectively, whereas CE2/CE3 cysts had lower negativity rates (5–20%). Thus, diagnostic challenges arise with small CE1 cysts and inactive CE4-5 cysts exhibiting nonspecific imaging.

A positive correlation exists between active cyst size and serologic positivity, attributed to increased antigenic mass from cyst wall compromise (whether due to immune exposure or therapy)[10]. Fine-needle aspiration or biopsy may aid diagnosis when results remain inconclusive[5]. Other laboratory findings are nonspecific but may include leukopenia, thrombocytopenia, or liver profile abnormalities. Neutrophilia or eosinophilia may suggest secondary infection or cyst rupture—consistent with this patient's neutrophilia, supporting the suspected rupture during reevaluation for persistent symptoms[8].

Treatment options include medical, surgical, or minimally invasive approaches[11]. Medical management involves anthelmintics like albendazole (10–15 mg/kg/12h for 3–6 months) or mebendazole (if albendazole-intolerant). Adding praziquantel (25 mg/kg/24h) to benzimidazoles may enhance efficacy. After one year of medical therapy alone, ~30% of cysts resolve, 30–50% shrink, and 20–40% remain unchanged. Antiparasitics are also used adjunctively: preoperatively to reduce cyst viability and postoperatively to prevent intraoperative contamination and recurrence[4,5,8].

As previously described, the patient was initially treated with albendazole upon diagnosis and continued postoperatively to complete eradication therapy. For symptomatic, complicated, large, or active cysts, surgery remains the primary treatment. Surgical approaches include hepatectomy, pericystectomy, and capsulectomy, with technique selection depending on surgeon preference, patient characteristics, preoperative imaging planning, and intraoperative findings. Margin assessment and lymph node dissection have not proven beneficial. All procedures require peritoneal cavity protection—isolating the cyst to prevent content spillage and shielding the surgical field with hypertonic saline (typically 20%)-soaked gauze or anthelmintics. Laparoscopic intervention is preferred for anterior liver surface cysts (<3 cysts) without biliary involvement[4,8]. Cyst aspiration/injection carries complication rates of 1.4–13.7%, high therapeutic failure risk, and potential peritoneal dissemination[9].

Follow-up with imaging and serology is recommended every six months for the first two years, then annually based on clinical judgment and patient status[2].

CONCLUSION

Hepatic hydatidosis is a parasitic zoonosis that may complicate with adjacent organ invasion, requiring comprehensive management—often involving complex surgical interventions.

Ethical Considerations

The case and images are presented with patient representative consent. Patient privacy was protected by omitting personal data. Authors declare no conflicts of interest. Study funding was self-supported. The lead author participated in document conception/design; all authors contributed to data analysis/interpretation, manuscript drafting, and critical revision.

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Case report

Gastric Lymphoepithelioma-like Carcinoma: A Singular Case Challenging the Boundaries of Diagnosis and Treatment

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Abstract

Background: Lymphoepithelioma-like carcinoma is a rare presentation of gastric cancer, with an incidence of less than 4%. It has been associated with Epstein-Barr virus (EBV) in approximately 80% of cases. In the remaining cases, microsatellite instability has been documented, with loss of mismatch repair enzyme expression of the *hMLH-1* gene in 39% of cases. Chemotherapy is not standardized globally, and surgical management is considered first-line treatment. **Case Report:** We report the case of a 41-year-old male who presented with episodes of upper gastrointestinal bleeding, associated with a constitutional syndrome characterized by a 5-kg weight loss over the course of one month. An esophagogastroduodenoscopy revealed a Borrmann type III gastric adenocarcinoma. The patient underwent total gastrectomy, and the histological analysis revealed an infiltrating gastric carcinoma of the lymphoid stroma subtype, also known as lymphoepithelioma-like carcinoma. A notable finding was the reduced lymph node involvement, with only 2 of 25 lymph nodes affected. Immunohistochemistry was positive for CKAE1/AE3 and CAM5. The tumor was ultimately concluded to be a true lymphoepithelioma-like carcinoma, and Epstein-Barr virus positivity was confirmed using the EBER-ISH technique. **Conclusion:** Gastric lymphoepithelioma-like carcinoma is a rare entity with distinctive clinical and pathological features. Its strong association with Epstein-Barr virus highlights the need for a comprehensive diagnostic and therapeutic approach. This case underscores the importance of surgical management and immunohistochemical characterization to guide appropriate treatment.

Keywords

Epstein-Barr virus infections, gastric cancer, Epstein-Barr virus, microsatellite instability, immunohistochemistry.

INTRODUCTION

Gastric lymphoepithelioma-like carcinoma (LELC) is a rare subtype of gastric cancer characterized by undifferentiated carcinoma cells intermixed with a prominent lymphoplasmacytic infiltrate in the stroma. This type of cancer is strongly associated with Epstein-Barr virus (EBV) infection, though some cases test negative for EBV[(1)].

LELC accounts for approximately 1% to 4% of all gastric cancers. It is more frequently observed in men and often occurs in the upper regions of the stomach[(2)]. Clinically, it tends to exhibit less lymphatic spread and a better overall survival rate compared to other forms of gastric carcinoma, possibly due to the dense lymphoid stroma acting as an antimetastatic barrier[(1)].

Diagnosis is typically made via endoscopic biopsy and confirmed through histological examination, which reveals the characteristic lymphoid stroma and undifferentiated carcinoma cells[(1)]. Treatment approaches vary due to the disease's rarity, but successful outcomes have been reported with surgical resection and chemotherapy regimens such as tegafur, gimeracil, and oteracil plus oxaliplatin[(2)]. Despite

its aggressive histological appearance, the prognosis for gastric LELC patients is generally favorable, with many cases showing good outcomes post-treatment[3,4].

We present a clinical case of gastric lymphoepithelioma-like carcinoma (LELC). This diagnosis arose following a discrepancy in biopsy results and the patient's age, which fell outside the expected range for this tumor type. Additionally, multiple nodal involvement was identified, prompting exploration of further therapeutic options after surgical intervention. A pyrimidine inhibitor (capecitabine) was initiated as a chemotherapeutic agent in the context of adjuvant therapy.

CASE REPORT

A 41-year-old male patient presented with upper gastrointestinal bleeding in December 2019, accompanied by a 5 kg weight loss over one month, with no other associated symptoms. The patient underwent an upper gastrointestinal endoscopy (UGIE), which identified a gastric lesion described as a Borrmann type III fundic gastric adenocarcinoma. Initial pathological examination revealed a moderately differentiated infiltrating ulcerated adenocarcinoma. Staging studies via chest and abdominal computed tomography (CT) showed no metastatic lesions. Three months after symptom onset, a total gastrectomy was performed.

Pathological analysis of the gastric specimen described a lymphoepithelioma-like gastric carcinoma located in the gastric fundus, measuring 4 x 3 cm, with infiltration extending to the subserosa, along with lymphatic and perineural invasion but no vascular invasion (**Figure 1**). Surgical margins were tumor-free, and ectopic pancreatic tissue was noted as an incidental finding. Lymph node assessment revealed tumor involvement in 5 out of 25 lymph nodes without perinodal extension. The patient was evaluated by the clinical oncology service. Due to inconsistencies in the pathology results, a second review of both specimens was conducted. The final report confirmed that the gastric lesion identified in the UGIE was an infiltrating intestinal-type gastric adenocarcinoma with scant lymphocyte-rich stroma. The gastrectomy specimen confirmed an infiltrating gastric carcinoma of the lymphoepithelioma-like subtype, with the same size and infiltrative status as the previous report. The only difference was a reduction in nodal involvement, with 2 out of 25 lymph nodes affected by the neoplasm. Additional immunohistochemical studies

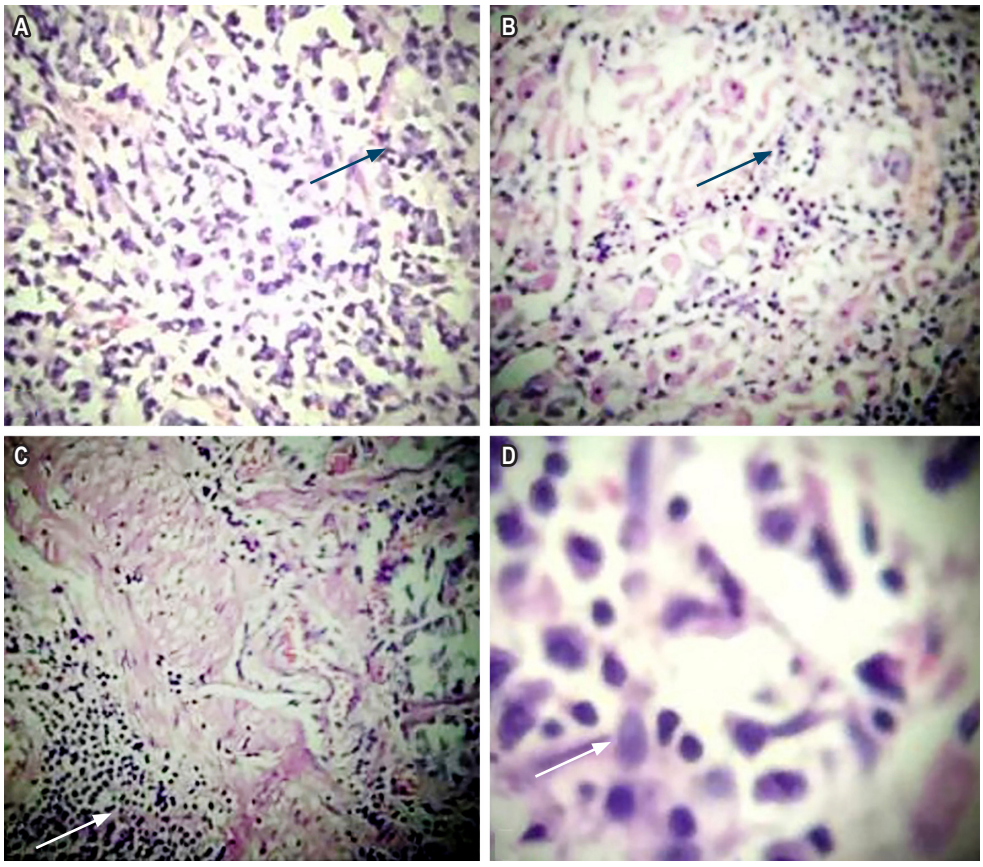


Figure 1. Gastrectomy specimen showing evidence of lymphoid infiltrate. Images property of the authors.

on one of the blocks showed positivity for CKAE1/AE3, CAM5.2, common leukocyte antigen, and CKAE1/AE (**Figure 2**). The pathology service corroborated these findings and concluded that the tumor was indeed a lymphoepithelioma-like carcinoma. EBV presence was confirmed via EBER-ISH testing.

The chemotherapy regimen consisted of six cycles of capecitabine. Over the next three years of imaging and endoscopic follow-up, the patient was considered to be in remission. However, in May 2022, the patient attended an oncology check-up reporting constitutional symptoms, including weight loss, night sweats, asthenia, and adynamia. Contrast-enhanced chest and abdominal CT scans revealed enlarged lymph nodes measuring 42 x 25 mm and 52 x 27 mm in the mesenteric root and retroperitoneum, suggesting metastatic involvement, along with hepatomegaly. A new biopsy and positron emission tomography (PET) scan were ordered to restage the disease.

DISCUSSION

Gastric cancer is one of the most frequent and deadliest neoplastic diseases worldwide, with an estimated annual prevalence of 934,000 cases. In the United States, approximately 27,600 stomach cancer cases are diagnosed each year (16,980 men and 10,620 women)[5], while in Colombia, it accounts for 9.5% of all diagnosed cancer cases[6].

The term *lymphoepithelioma-like gastric carcinoma*, also known as *lymphocyte-rich gastric carcinoma*, was introduced by Burke et al. upon observing this cellular distribution pattern in neoplastic gastric tissue[7]—a pattern previously described only in the nasopharynx by Regaud and Reverchon in 1921[8]. This tumor type is rare, constituting less than 4% of gastric cancers. Distinguishing this entity is clinically and prognostically significant, as it has distinct features affecting patient management and outcomes[9].

Chetty et al. describe lymphoepithelioma-like carcinoma as a neoplasm composed of small clusters of tumor cells with intratumoral lymphocyte infiltration[10]. In contrast, medullary carcinoma exhibits a syncytial histological pattern with peripheral lymphoid distribution, while conventional gastric carcinoma with lymphoid stroma is characterized by a glandular histological pattern and peripheral lymphoid distribution. This tumor type is more prevalent in males, suggesting a possible link to lifestyle and occupation. Although the average age of onset is around 60 years, it can occur in patients ranging from early adulthood to advanced age[11].

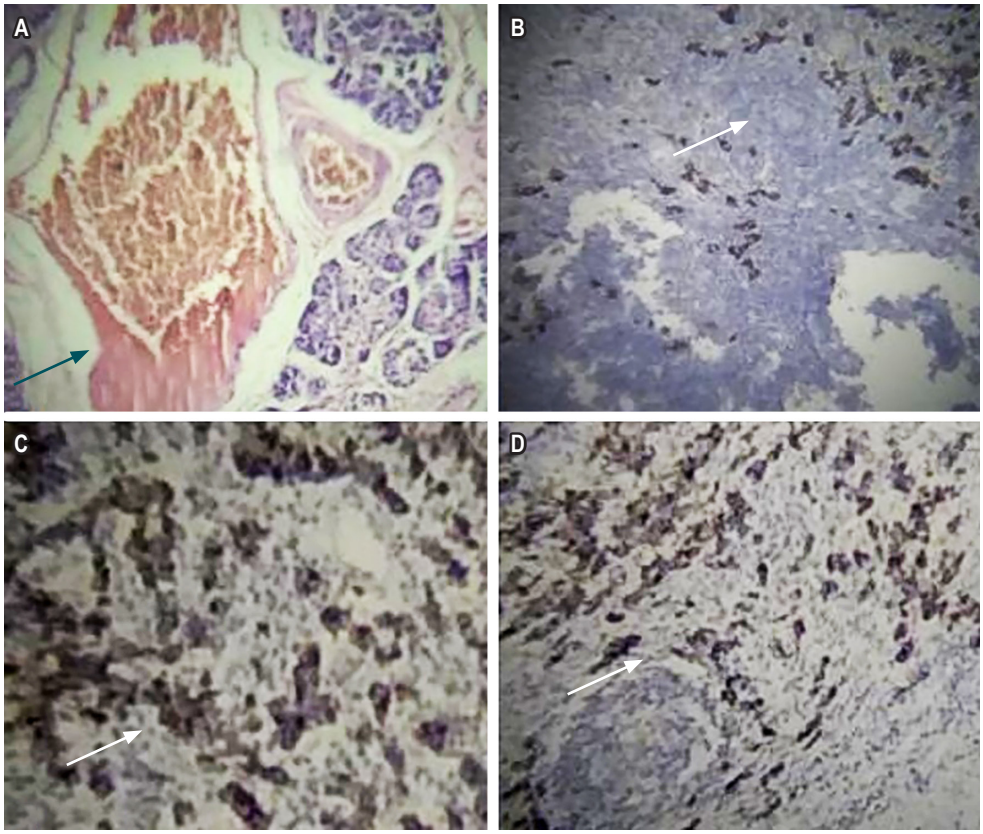


Figure 2. A. Subserosal involvement. **B.** Lymph node involvement. **C.** CAM5.2 immunohistochemistry. **D.** CKAE1/AE3 immunohistochemistry. Images property of the authors.

Several risk factors have been associated with this cancer, including consumption of salty or spicy foods, hot beverages, and exposure to wood dust or iron filings. However, these may be confounding factors, as the primary risk factor is its association with EBV[12–14]. *Helicobacter pylori* infection, a major risk factor for gastric adenocarcinoma, has also been studied but shows no correlation with this carcinoma type, suggesting distinct carcinogenic pathways[15].

Lymphoepithelioma-like carcinoma most frequently affects the proximal stomach but can occur in any gastric region or even elsewhere in the digestive tract[16]. It is characterized by dense, uniform stromal infiltration by T lymphocytes and plasma cells, alongside scattered adenocarcinoma cells. Two subtypes have been identified based on EBV presence (80%) and microsatellite instability (39%)[17].

Several hypotheses exist regarding EBV's oncogenic role. One widely accepted theory suggests that after primary infection, the virus remains latent in B lymphocytes via expression of the viral receptor CD21. EBV infection precedes clonal expansion of infected cells, inhibiting apoptosis and promoting cell proliferation, along with frequent chromosomal translocations. EBV detection in neoplastic tissue is typically performed using in situ hybridization (EBER-ISH) and polymerase chain reaction (PCR)[18].

Tumors with lymphoid stroma are generally smaller, exhibit less deep invasion, and have lower rates of nodal metastasis, contributing to a more favorable prognosis compared to typical gastric adenocarcinoma. The 5-year survival rate for lymphoepithelioma-like carcinoma is 83%–86% versus 46%–48% for conventional adenocarcinoma[19].

For diagnosis, UGIE is essential, particularly when identifying superficial depressed or ulcerated lesions in the upper stomach. The most sensitive diagnostic method is EBER1-2 in situ hybridization (EBER1-2 ISH) on biopsy specimens to confirm EBV[20].

Regarding therapeutic management, aggressive surgery can achieve radical cure, improving patient prognosis. Early-stage treatment—defined as cancer confined to the gastric mucosa or submucosa—has a 5-year survival rate exceeding 90%. Endoscopic mucosal resection and submucosal dissection are effective strategies at this stage. For advanced stages, though evidence is limited, DNA methylation inhibitors and immunotherapies (e.g., PD-1/PD-L1 blockade) have shown promising results in some studies[21].

This case underscores the importance of precise diagnosis and comprehensive management in lymphoepithelioma-like gastric carcinoma, highlighting the role of thorough pathological review and advanced techniques for accurate assessment.

CONCLUSION

This case emphasizes the need for rigorous diagnostic precision and multidisciplinary management in treating lymphoepithelioma-like gastric carcinoma. Exhaustive pathological specimen review and advanced techniques such as immunohistochemistry and EBER-ISH were crucial for confirming the diagnosis, which is vital for appropriate therapeutic intervention and patient prognosis.

Continuous follow-up and personalized treatment are essential to improving clinical outcomes in these patients. Early detection of recurrence and adaptive therapeutic strategies based on clinical progression and imaging findings enable better management of this rare and aggressive entity. This highlights the necessity for ongoing surveillance and an individualized therapeutic approach.

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Case report

Pancreatic Ascites in a Patient with Severe Acute Pancreatitis: An Unusual Case

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Abstract

Background: Pancreatic ascites is an uncommon clinical entity resulting from the accumulation of pancreatic fluid in the peritoneal cavity. It is caused by the leakage from a pancreatic pseudocyst or injury to the pancreatic duct. Diagnosis is based on elevated amylase levels in ascitic fluid (greater than 1000 U/L) and protein levels above 2.5 g/dL. Chronic pancreatitis (83%), acute pancreatitis (8.6%), and trauma (3.6%) are the most common causes of pancreatic duct disruption. **Case Summary:** We report the case of a 59-year-old male patient referred to our institution for severe acute pancreatitis of biliary etiology, complicated by infected encapsulated necrosis. Necrosis extended through the left paracolic gutter to the pelvis and left inguinal region, with additional subcapsular hepatic fluid collections involving segments VI and VIII, requiring both endoscopic and percutaneous management. During clinical follow-up, the patient developed grade 3 ascites, for which he underwent two diagnostic and therapeutic paracenteses. Analysis of the fluid was consistent with pancreatic ascites. **Conclusions:** Patients with pancreatic ascites represent a small and heterogeneous population. Early detection is crucial due to the prognostic and therapeutic implications of this finding. Mild cases typically respond to medical management, while more severe cases require endoscopic treatment, with surgical intervention being rarely necessary.

Keywords

Pancreatitis, ascites, biliary tract, pancreatic duct, surgery.

INTRODUCTION

Pancreatic ascites is an uncommon clinical complication caused by persistent leakage of pancreatic secretions into the peritoneum due to pancreatic duct injury. The epidemiology of this condition remains poorly understood and has primarily been reported in retrospective studies and case series[(1)]. Males account for the majority of cases (75%-85%), with the mean age of onset in the fifth decade of life[(2)].

The presence of ascitic fluid is characterized through imaging, and its volume has been associated with clinical outcomes[(3)]. Analysis of ascitic fluid—measuring amylase, protein, and albumin gradient—is indicated for diagnosing pancreatic ascites[(4)]. Gram stain and culture are also essential to detect superimposed infection. While peritoneal fluid lipase measurement has been described in some cases, there is no standardized protocol or sufficient evidence to support its routine use[(5-7)].

The severity of this condition varies widely depending on the location and extent of ductal injury, as well as the presence of infected fluid. Most mild cases resolve spontaneously; however, persistent pancreatic ascites—with or without infected fluid—is associated with significant morbidity[(8)].

Treatment for mild disease without visible pancreatic duct abnormalities on pancreatogram may involve medical management, including total parenteral or nasojejunal nutrition and octreotide or somatostatin. More severe cases with visible ductal abnormalities require endoscopic intervention with transpapillary stent placement. Surgical pancreatectomy is rarely needed as rescue therapy. However, due to the low incidence, comparative studies between available treatment modalities are lacking[9,10].

We present the case of a 59-year-old male admitted to our institution with clinical findings consistent with severe acute biliary pancreatitis. Local complications included walled-off necrosis with dissecting pancreatic collections showing signs of infection, as well as paracolic gutter, pelvic, and subhepatic collections. Initial management involved endoscopic cystogastrostomy and percutaneous drainage by interventional radiology. During hospitalization, he developed grade 3 ascites, requiring two therapeutic paracenteses with cytochemical analysis confirming pancreatic ascites.

CASE REPORT

A 59-year-old male patient, initially treated at an outside facility for severe biliary pancreatitis with documented local complications including walled-off necrosis and extraperitoneal dissecting collections, was referred to our institution for interdisciplinary evaluation due to case complexity. Repeat imaging revealed a pancreatic collection measuring 123 × 119 × 163 mm (L × AP × T) with a volume of 1240 cm^3, consistent with infected encapsulated necrosis extending through the left paracolic gutter to the pelvis and left inguinal region, along with subcapsular hepatic fluid collections in segments VII and VIII (**Figure 1**). The patient underwent cystogastrostomy, which identified a giant infected pancreatic cystic lesion. A metal stent was placed, yielding copious purulent drainage filling the entire gastric fundus. Cultures confirmed penicillinase-hyperproducing *Escherichia coli*. Subsequent intraperitoneal collection drainage was performed by interventional radiology.

During hospitalization, the patient developed grade 3 ascites requiring diagnostic and therapeutic paracentesis with 4000 cc drainage. Ascitic fluid analysis showed amylase 9579 U/L, total protein 2.69 g/dL, and albumin gradient <1.1 g/dL (**Table 1**), confirming pancreatic ascites. Given high suspicion for pancreatic duct injury based on ascitic findings, total parenteral nutrition was initiated followed by magnetic resonance cholangiopancreatography (MRCP).

This revealed a poorly defined peripancreatic collection adjacent to the body and tail with partial cystic components. T1/T2 hypointense areas suggested necrotic foci (55 cm volume, increased from prior imaging) without identifiable leak. Due to persistent ascites requiring repeat paracentesis and absence of endoscopically treatable duct disruption, video-assisted retroperitoneal debridement was performed. The procedure removed walled-off necrotic tissue involving 30% of proximal pancreas, with laparoscopic drainage of 2000 cc retroperitoneal fluid. Postoperatively, the patient showed marked clinical improvement without ascites recurrence and tolerated oral intake well with absent abdominal pain.

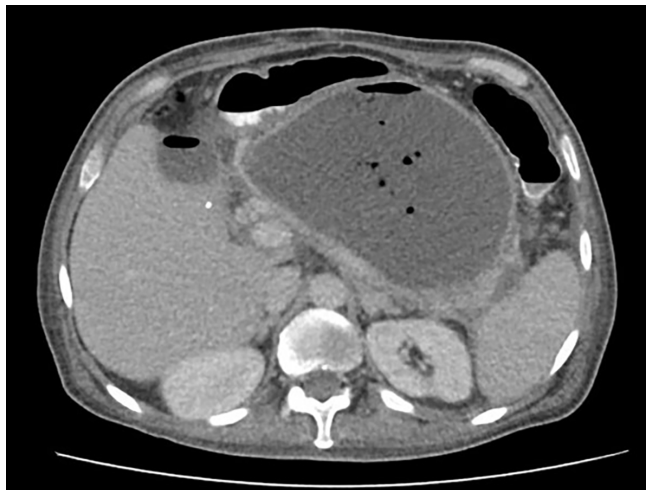


Figure 1. Initial CT scan showing pancreatic collection measuring 123 × 119 × 163 mm (L × AP × T). Image property of the authors.

Table 1. Initial Peritoneal Fluid Analysis

Peritoneal Fluid Study
Appearance: Slightly turbid Color: Yellow
WBC: 224 cells/mm^3 *Differential* - Lymphocytes: 78% - Monocytes: 4% - Neutrophils: 18%
Macrophages: 117 per 100 WBC Mesothelial cells: 2 per 100 WBC RBC: 244 cells/mm^3
Biochemical
Method: Colorimetric Glucose: 79.32 mg/dL Protein: 2.69 g/dL
Amylase
Amylase: 9579 U/L
Microbiology
Gram stain: No organisms Culture: ESBL-producing *E. coli*

Table prepared by the authors.

DISCUSSION

Pancreatic ascites is an uncommon complication of pancreatitis, most frequently occurring in the context of pseudocysts or walled-off necrosis, as seen in our patient. In chronic pancreatitis, pseudocysts typically develop less robust fibrin walls, allowing pancreatic secretions to leak from ruptured ducts into the pseudocyst and peritoneal cavity. Alternatively, pancreatic duct rupture without pseudocyst formation may create fistulous tracts.

The clinical manifestations vary depending on fistula location: anterior pancreatic duct disruptions permit direct pancreatic secretion drainage into the peritoneum, causing ascites, whereas posterior duct injuries often form fistulas through the aortic or esophageal hiatus or diaphragmatic dome, leading to pleural effusions. In both scenarios, the ascitic fluid is typically exudative with elevated amylase levels. Some attribute this exudative quality to pancreatic fluid triggering an inflammatory process that increases vascular permeability[11].

Diagnosis requires ascitic fluid analysis demonstrating amylase >1000 U/L, protein >2.5 g/dL (in our patient: 9579 U/L and 2.96 g/dL, respectively), and serum-ascites albumin gradient <1.1 g/dL.

Given the high suspicion for pancreatic duct disruption in this pathophysiology, pancreatography is recommended. Treatment approaches include medical, endoscopic, and surgical interventions, often used in combination, with no clear mortality superiority established for any single modality[12].

Mild cases may resolve with medical management alone (30%-50% of patients), though endoscopic therapy remains first-line due to lower morbidity. Transpapillary pancreatic duct stenting reduces intraductal pressure and diverts secretions to the small intestine. Other endoscopic options—such as injectable glues or fibrinogen sealants for fistula occlusion—lack robust evidence for routine use. Overall, endoscopic approaches show promising outcomes with lower mortality and morbidity than surgery[13].

EUS-guided endoscopic therapy may be indicated for pancreatic duct disruption syndrome when imaging confirms the lesion and anatomy suggests treatment responsiveness[14-16]. Our patient's anatomy precluded this approach, prompting surgical intervention.

Notably, while repeated endoscopic therapy appears inferior to surgery for long-term abdominal pain control (typically assessed after two years)[17,18], our patient fortunately reported no such complaints. Following inconclusive pancreatography and failed endoscopic control, we proceeded with video-assisted retroperitoneal debridement.

The overall prognosis for patients with pancreatic ascites has improved with the availability of endoscopic interventions. Endoscopic transpapillary stent placement demonstrates success rates ranging from 82% to 100%. For cases refractory to medical and endoscopic management, surgical intervention is pursued, with reported mortality rates between 15% and 25%. Recent studies indicate that endoscopic treatment has reduced mortality, hospital stay duration, recurrence rates, and hospitalization costs compared to standalone medical or surgical interventions[8].

Additional strategies—such as long-term pancreatic enzyme replacement—are indicated for severe exocrine pancreatic insufficiency and chronic pancreatitis with malabsorption symptoms or abdominal pain. Exocrine pancreatic insufficiency typically occurs when >90% of pancreatic parenchyma is compromised. In our case, only 30% of proximal pancreas required resection, preserving functionality and preventing malabsorptive symptoms[19,20].

CONCLUSION

Pancreatic ascites represents an uncommon complication of acute pancreatitis, resulting from peritoneal accumulation of pancreatic fluid due to ductal injury. It occurs most frequently in necrotizing pancreatitis with pancreatic duct involvement, with chronic pancreatitis being the primary risk factor.

Mild cases without visible duct disruption respond to medical management, while severe cases with main pancreatic duct injuries require endoscopic stenting. Surgical intervention is rarely needed as rescue therapy.

Although high-quality evidence remains limited, some studies suggest endoscopic approaches reduce hospitalization duration, morbidity, and mortality compared to medical or surgical management alone.

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Case report

Inverted-Growth Buschke-Löwenstein Tumor: A Case Report with Therapeutic Proposal

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Abstract

The Buschke-Löwenstein tumor (BLT) is a type of giant epithelial tumor typically characterized by a broad base, infiltrative potential, and local tissue destruction. As a result, recurrences are common, which confers a certain degree of malignant potential. From a histopathological standpoint, it is composed of hyperplastic epithelium, minimal atypia, and well-differentiated tissue with hyperkeratosis, parakeratosis, and the presence of koilocytes. This finding is a hallmark of human papillomavirus (HPV) infection at the cellular level, along with granular changes and mitotic activity in the basal layer. This article describes a rare variant with inverted growth and infiltration of the anal and perianal tissues, associated with a clinical presentation of anal fissures and fistulas. A therapeutic proposal is also discussed. The case involves a 35-year-old male from Bello, Antioquia, who presented to our institution with a 4-year history of perianal openings with purulent discharge, pain, and bleeding. A contrast-enhanced pelvic MRI revealed infiltration of the anal, perianal, and adipose tissues by condylomatous lesions with displacement of adjacent structures. A medical management protocol developed at the Instituto de Coloproctología (ICO) in Medellín, Colombia, was implemented and complemented with surgical treatment.

Keywords

Condyloma acuminatum, human papillomavirus, verrucous carcinoma, anoscopy, anal cancer, anal neoplasms.

INTRODUCTION

Approximately 80% of sexually active individuals, regardless of sexual preference, will come into contact with human papillomavirus (HPV) at some point in their lives, though not all will develop secondary lesions[1,2]. Anal and perianal lesions have become increasingly common in heterosexual individuals of all ages due to the growing prevalence of anal sex. It is well-established that HPV causes 98% of genital cancers (anus, cervix, vagina, penis) as well as laryngeal cancers, and there is emerging speculation that it may even play a role in the development of esophageal and lung cancers[3,4].

It is estimated that out of the world's population of over 7 billion, approximately one million people are newly infected with HPV daily. According to the World Health Organization (WHO), around 290 million women were infected by 2018, making HPV the leading cause of sexua-

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lly transmitted infections (STIs) worldwide and, consequently, a major public health concern.

Certain factors increase the risk of anal cancer associated with higher morbidity from HPV infection. Typically, the specific cellular and molecular damage caused by this virus is linked to the overproduction of genetic material and disruptions in the regulatory factors of cellular replication and apoptotic mechanisms. This leads to increased cell replication and the development of cellular dysplasia. Histopathology reveals enlarged nuclei, chromatin overproduction, or simply hypercellularity, while phenotypically, large warts with varied morphological formations develop. When these exceed 3 cm in diameter, they are classified as Buschke-Löwenstein tumors (BLT).

This case report describes an atypical growth pattern of BLT. Due to the loss of squamous epithelial continuity in the anal canal, verrucous infiltration into deep tissues occurred, with the potential to replace gluteal muscle. This infiltration colonized fistulous tracts, resulting in an inverted-growth BLT. A systematic review was conducted using five medical literature search engines (NCBI, BVS, Ovid, Trip Database, Google Scholar), which confirmed that no similar scientific records exist in the literature.

CASE REPORT

A 35-year-old male patient from Bello, Antioquia, who is HIV-positive (diagnosed in 2015), presented with a four-year clinical history of perianal orifices discharging mucopurulent fluid, bleeding, and pain. Initial conventional anoscopy identified a complex horseshoe perianal fistula with three secondary openings located in the right anterolateral, right lateral, and right posterolateral quadrants. The primary orifice could not be determined. Additionally, condylomatous lesions were observed, involving the entire length and 100% of the anal canal circumference. A biopsy of the lesions revealed a "low-grade squamous intraepithelial lesion (LSIL)."

The fistula and condylomas were surgically managed by a general surgery specialist at Clínica Las Américas in Medellín, Colombia. The patient returned in August 2020 due to the reappearance of new lesions and was subsequently evaluated at Instituto de Coloproctología (ICO). Physical examination identified five active fistulous tracts lined with condylomas, a non-mobile induration in the right gluteal region, and anal sphincter involvement with functional impairment (**Figure 1**).

A contrast-enhanced pelvic MRI was performed, reporting "gluteal infiltration by condylomas, with greater involvement on the right side and possible ipsilateral sphincter compromise" (**Figure 2**).

High-resolution anoscopy was also performed, confirming high-volume HPV-related disease. HPV genotyping tested positive for high-risk strains: 39, 52, and 68 (**Figure 3**).

Medical management was initiated using "*ICO seguro*" (ICO's Safe Protocol), which consisted of: Topical 5% 5-fluorouracil cream applied to perianal condylomatous lesions and inside the anal canal every 12 hours (5 consecutive days followed by 9 days of rest). Subcutaneous methotrexate (25 mg weekly) for 16 weeks. One month after completing therapy, a 50% reduction in disease burden was confirmed. However, subsequent follow-ups showed a plateau in response. Thus, in May 2021, surgical resection of the anal canal tumor was scheduled, with sphincter preser-



Figure 1. Macroscopic appearance of the inverted Buschke-Löwenstein tumor. Images property of Instituto de Coloproctología (ICO) S.A.S.

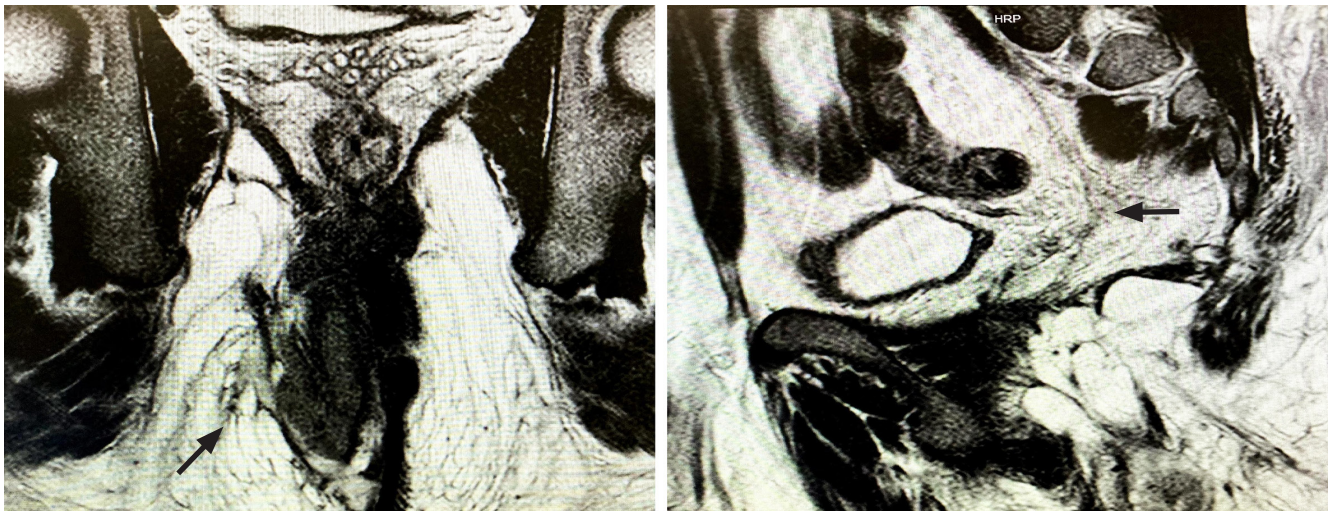


Figure 2. MRI of the inverted Buschke-Löwenstein tumor. Arrows indicate gluteal infiltration with predominant right-sided condyloma involvement and possible ipsilateral sphincter compromise. Images property of Instituto de Coloproctología (ICO) S.A.S.

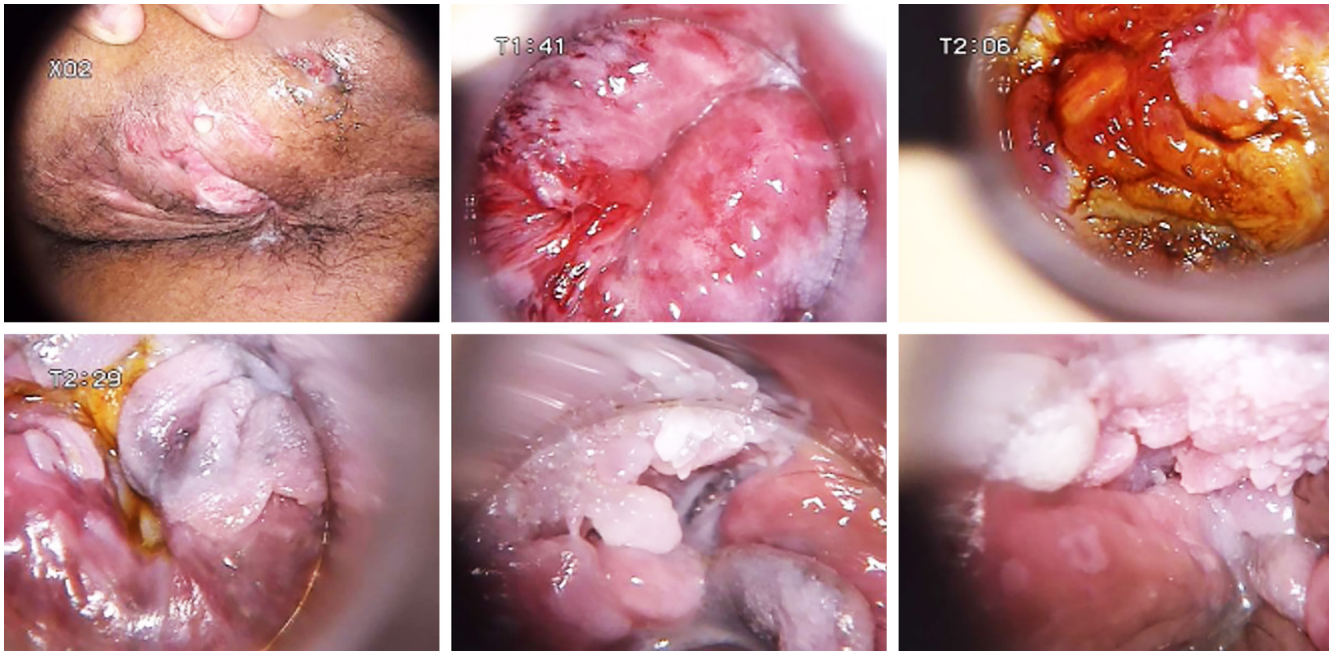


Figure 3. High-resolution anoscopy of the inverted Buschke-Löwenstein tumor. Images property of Instituto de Coloproctología (ICO) S.A.S.

vation and gluteal flap rotation to cover the defect (**Figure 4**). Histopathological analysis of the samples confirmed "condylomas with high-grade dysplasia."

One month postoperatively, follow-up examination showed 90% healing with no evidence of fistulas. A year later, on May 10, 2022, a control high-resolution anoscopy revealed HPV recurrence with high-volume disease involving 100% of the anal canal (**Figure 5**).

Medical therapy with 5-fluorouracil and methotrexate was reintroduced per the previous protocol. However, due to poor patient adherence, serial ablative therapy was initiated instead, achieving lesion resolution.

By July 2023, high-resolution anoscopy showed recurrent lesions affecting 50% of the anal canal. Repeat serial ablative therapy was performed, resolving active lesions (**Figure 6**) while preserving continence.



Figure 4. Surgical resection of the inverted Buschke-Löwenstein tumor with gluteal flap rotation and sphincter preservation. Images property of Instituto de Coloproctología (ICO) S.A.S.

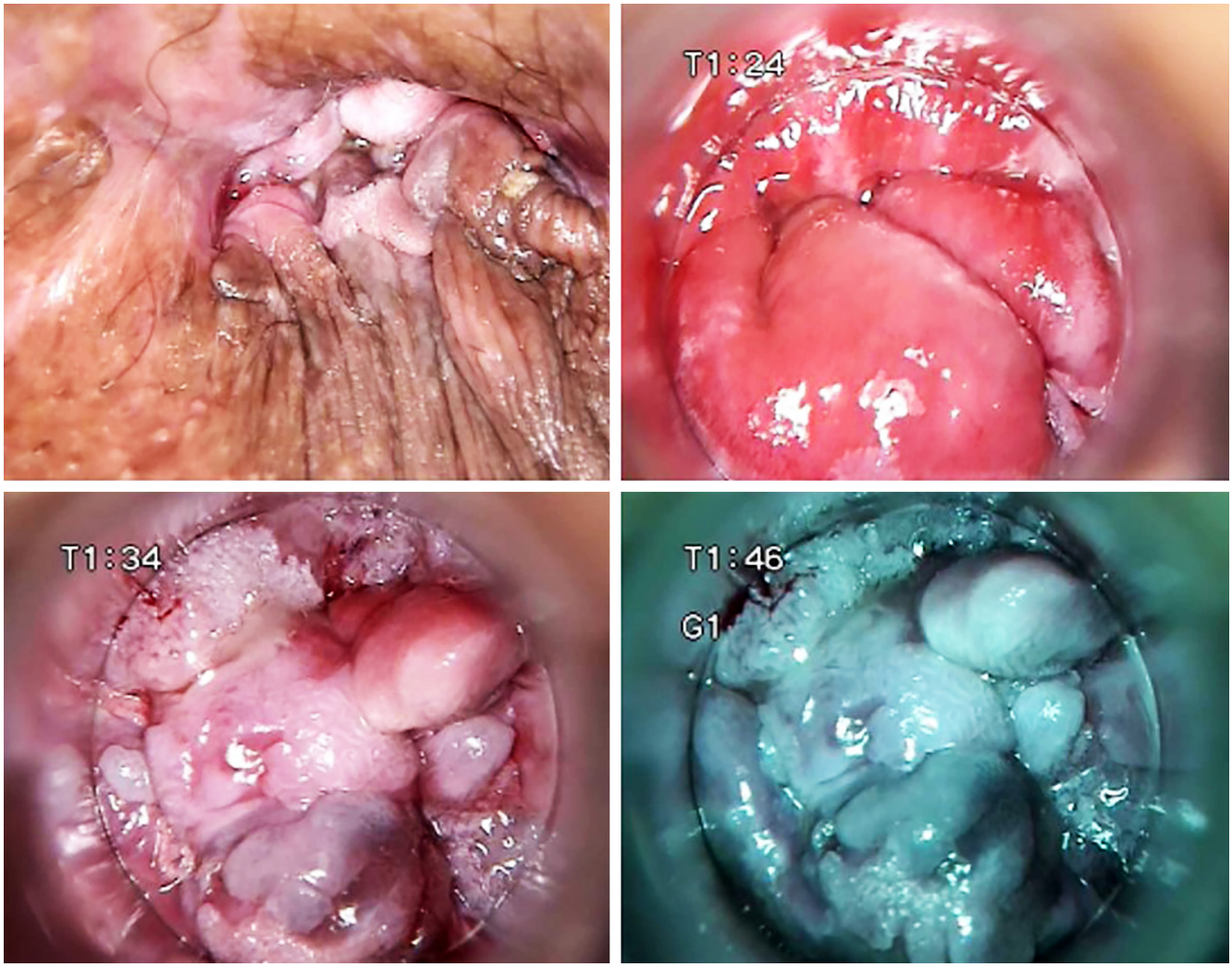


Figure 5. Recurrence of the inverted Buschke-Löwenstein tumor on high-resolution anoscopy one year after surgical resection. Images property of Instituto de Coloproctología (ICO) S.A.S.



Figure 6. Serial ablative therapy with resolution of active lesions in the inverted Buschke-Löwenstein tumor. Images property of Instituto de Coloproctología (ICO) S.A.S.

Currently, the patient's social circumstances have limited adherence to scheduled follow-ups. Nevertheless, he reports no recurrence of prior symptoms and feels confident about his current condition.

DISCUSSION

HPV is a small, non-enveloped, double-stranded DNA papovavirus, and its sexually transmitted infection is the most common human pathogen infection[5]. The main risk factors for HPV infection include sex with uncircumcised men, promiscuity, and early age of first sexual contact. Additionally, patients who have undergone solid organ transplantation (kidney, liver, etc.), those undergoing chemotherapy or radiotherapy (leukemia, lymphomas), or those on immunosuppressive treatment (biologic agents, chronic steroid use, diabetes, etc.) are at higher risk. Some studies, such as that by Nyitray et al., have reported anal carcinoma rates up to 10 times higher in kidney transplant patients compared to the general population[6].

Anal squamous cell carcinoma (ASCC) is a rare neoplasm, accounting for less than 5% of all gastrointestinal cancers. The current global incidence is estimated at 1.8 cases per 100,000 individuals, and both incidence and mortality rates have been increasing. Ninety percent of cases are associated with HPV infection. In fact, few physicians are aware that anal cancer is more common in women than in men. When analyzing high-risk groups—such as HIV-infected patients or men who have sex with men (MSM)—it is notable that anal cancer rates are exponentially higher in these populations than in the general population (1.8/100,000). Specifically, the incidence of anal cancer in HIV-negative MSM is 35/100,000, while in HIV-positive MSM, it rises to 131/100,000[7].

Currently, HPV infection is recognized as responsible for nearly all cervical cancers, 95% of anal cancers, 65% of vaginal cancers, 50% of vulvar cancers, 35% of penile cancers, and a significant proportion of head and neck cancers[8].

To date, nearly 450 HPV genotypes have been isolated and sequenced[9]. Of these, 40 subtypes infect through mucosal epithelial contact. Among high-risk types, strains 16, 18, 31, 33, 35, 52, and 45 stand out as the most significant carcinogenic agents, isolated in 91% of these tumors. However, types 16 and 18 alone account for 79% of anal canal cancers[10].

Giant condyloma acuminatum is also known as Buschke-Löwenstein tumor (BLT). It is a rare, locally invasive tumor arising from a preexisting wart-like lesion, often described as an exophytic, cauliflower-like growth. BLT was first reported in 1896 by Abraham Buschke in Neisser's *Atlas Stereoskopischer der Hautkrankheiten*. Later, in 1925, Abraham Buschke and his assistant Ludwig Löwenstein described BLT as a penile lesion clinically resembling both common condylomas and squamous cell carcinoma (SCC), but with distinct histological features and biological behavior[11,12].

Some authors consider BLT an intermediate condition between condyloma and squamous cell carcinoma[13]. Histologically, the tumor appears benign, with papillomatosis, epithelial hyperplasia, and koilocytosis; however, clinically, it can behave aggressively with extensive infiltration. Other distinguishing clinical features include extensive fistulation, abscess formation, and high local recurrence rates after surgical resection[14].

Focally, these tumors may also transform into invasive squamous cell carcinoma in approximately 30% to 50% of patients, with an overall mortality rate of 20%[15]. Metastasis is rare, and growth rates typically range from two to 10 years in immunocompetent individuals[15], though rapid progression may occur in immunocompromised patients.

This condition is more prevalent in men than women, with a ratio of 2.7:1[16]. Commonly affected sites include the penis, perianal region, vulva, vagina, rectum, scrotum, perineum, and bladder[17].

BLTs contain low-risk HPV, particularly strains 6 and 11, which appear central to the pathogenesis of this neoplasm. However, the cause of the transformation from benign condylomas to locally invasive BLT remains unknown[14,18]. Highly active antiretroviral therapy (HAART) does not affect concomitant HPV-related disease and has no efficacy against BLT[14].

Routine imaging studies—such as contrast-enhanced pelvic CT and MRI—are recommended to assess local and

regional extension, which is crucial for determining optimal treatment[19].

Traditionally, wide-margin surgical resection, with or without reconstructive surgery, has been the gold standard for treatment[12]. However, the high recurrence rates (66%) associated with this approach suggest the need to shift current paradigms, as mutilating surgery—which often sacrifices sphincter function while offering such low cure rates—does not represent the optimal solution.

In 2019, the authors developed an innovative medical treatment called *ICO-Seguro*—a low-morbidity, non-invasive approach with higher response rates compared to surgical resection for managing HPV-related anal pathology. This method significantly improves quality of life. However, it is crucial to acknowledge that the proposed therapy is still far from curative.

Among the 7,100 patients evaluated to date using high-resolution anoscopy and trained specialists, 17% (n=1,207) were found to have high-volume disease (i.e., prominent perianal tumors). The remaining cohort included 30% (n=2,130) healthy patients and 53% (n=3,763) with minor lesions. The latter group underwent outpatient cauterization under local anesthesia and anoscopic guidance. This procedure required no bowel prep, enemas, fasting, surgical intervention, or accompaniment, and caused no significant pain, tissue damage, or bleeding.

For high-volume disease, treatment combined 5-fluorouracil (5-FU) and methotrexate: Topical 5-FU acts as a local chemotherapeutic agent, disrupting DNA synthesis and mildly inhibiting RNA formation, inducing metabolic imbalance that triggers cell death. It targets rapidly proliferating and abnormal cells in actinic keratoses and basal cell carcinoma. Methotrexate slows disordered cellular growth.

Post-treatment follow-up under the *ICO-Seguro* protocol includes: (1) High-resolution anoscopy at 6 months. (2) If no lesions are detected, annual monitoring for two consecutive years, transitioning to anal cytology screenings thereafter.

Lastly, quadrivalent and nonavalent HPV vaccines (Gardasil) significantly reduce genital warts incidence. While no studies have measured their impact on BLT rates, these vaccines likely lower BLT risk since they target HPV strains 6 and 11—the primary drivers of BLT growth. Some authors also suggest therapeutic potential, citing cases of giant condyloma acuminatum regression post-vaccination[12].

CONCLUSION

The Buschke-Löwenstein tumor (BLT) in the anal and perianal region is a rare but dramatic lesion, presenting significant management challenges. With evolving sexual behaviors and preferences, cultural openness, and the growing number of immunocompromised yet sexually active individuals, the incidence of this condition is expected to rise—particularly as the anus becomes an increasingly explored erogenous zone.

The prognosis of BLT likely depends on its size, local recurrence, transformation to squamous cell carcinoma (SCC), secondary infections, and associated immunodeficiencies.

The traditional management approach has been surgical resection. However, the primary issue lies in the fact that this intervention often leads to varying degrees of scarring, which may result in fibrosis, anal stenosis, or even fecal incontinence—all without guaranteeing complete cure.

Instituto de Coloproctología (ICO) is the only institution in the region dedicated to early detection and comprehensive management of anal HPV infection. Since 2019, it has evaluated over 7,000 patients, establishing itself as the national leader in case registries and research in this field. ICO has developed an innovative, non-invasive, low-morbidity medical treatment program that demonstrates better response rates than surgical resection. While promising, it is important to acknowledge that these treatments are not yet curative.

Early diagnosis and appropriate aggressive treatment can reduce both medical and surgical morbidity, as well as overall mortality.

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Letter to the editor

Methodological Considerations for Assessing the Impact of Gastrointestinal Symptoms in Patients with COVID-19

Johan Azañero-Haro.[1*]

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To the Editor:

I would like to extend my greetings to both the journal and the authors of the recent article titled "Morbidity and Mortality in COVID-19 Patients With and Without Gastrointestinal Symptoms." This observational cohort study of hospitalized patients at the Fundación Santa Fe de Bogotá evaluates whether gastrointestinal symptoms influence adverse outcomes in COVID-19, including mortality, ICU admission, mechanical ventilation, and bacterial coinfection. The authors conclude that gastrointestinal symptoms do not represent a progression risk but recommend including liver function markers in initial assessments due to their potential prognostic value.

However, analyzing gastrointestinal symptoms as a homogeneous group may limit the accuracy of conclusions regarding their impact on COVID-19 progression. Studies suggest that specific symptoms—such as diarrhea and abdominal pain—could have differential effects on disease course due to distinct pathophysiological mechanisms. Some research links both abdominal pain and diarrhea to an increased risk of severe COVID-19, while other studies associate diarrhea with better clinical outcomes[1-3]. These variations suggest that the relationship between gastrointestinal symptoms and COVID-19 severity may be complex and mediated by additional factors. Evaluating each symptom individually could identify specific associations with disease progression and improve risk stratification in patients—a key consideration for multisystemic infections like COVID-19.

Another relevant aspect is controlling for confounders in the relationship between liver markers and COVID-19 severity. The article suggests that elevated alanine aminotransferase (ALT), aspartate aminotransferase (AST), and direct bilirubin levels are associated with higher rates of mechanical ventilation and ICU admission. However, liver dysfunction in COVID-19 patients may result not only from SARS-CoV-2 infection but also from potentially hepatotoxic medications such as lopinavir/ritonavir, remdesivir, or corticosteroids[4,5]. This warrants careful attention, as without proper adjustment for these confounders, it would be difficult to determine whether observed liver dysfunction is directly attributable to COVID-19 or to treatment side effects.

While the sample size of 414 patients is substantial, the subgroup with gastrointestinal symptoms (105 patients) may be insufficient to assess less frequent outcomes such as bacterial coinfection or mortality. This could limit the statistical power of the analyses and yield inconclusive results. Ensuring adequate sample sizes for each specific outcome

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would produce more robust findings and prevent potentially relevant associations from being dismissed as insignificant.

Regarding mortality, the study concludes that it is not associated with gastrointestinal symptoms or liver markers. However, existing literature suggests a possible link between liver injury and adverse COVID-19 outcomes[4], particularly in patients with severe disease. Further exploration of discrepancies between this study's findings and others could help identify additional variables influencing mortality and clarify the role of liver function in COVID-19 prognosis.

Finally, while the study appropriately recommends using ALT, AST, and direct bilirubin levels in initial COVID-19 assessments, more specific guidance on how these markers could stratify clinical risk would benefit practice. A cutoff-based approach would facilitate interpretation and improve decision-making regarding ICU management, ventilation needs, and intensive monitoring.

I appreciate the opportunity to share these observations, which I hope may contribute to strengthening future research on COVID-19 and its multisystemic manifestations.

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Letter to the editor

Response to "Methodological Considerations for Assessing the Impact of Gastrointestinal Symptoms in Patients with COVID-19"

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Dear Editor,

Regarding Dr. Azañero-Haro's comments on our article "Morbidity and Mortality in COVID-19 Patients With and Without Gastrointestinal Symptoms," we, the authors, believe his analysis provides valuable considerations that enrich the scientific discussion on this topic.

Concerning the study period, it is important to clarify that our data were collected between March 2020 and September 2021—a time when understanding of COVID-19 and its multisystemic impact was still emerging. Although our article was published in 2024, the analysis was based on the information and management guidelines available during that earlier period. As we all know, the pandemic represented a dynamic clinical scenario in which evidence and therapeutic strategies evolved progressively as new studies and recommendations emerged[1,2].

We understand the author's concerns about liver function and its potential relationship with COVID-19 severity. At the time, altered liver markers were considered potentially relevant for prognosis[3,4]. However, the scientific community has since refined this interpretation, and it is now recognized that elevated alanine aminotransferase (ALT), aspartate aminotransferase (AST), and bilirubin levels may reflect a patient's clinical status without necessarily predicting outcomes.

Furthermore, COVID-19 management has changed substantially since the pandemic's onset[2]. During our cohort's data collection period, various therapeutic strategies were employed—some of which, such as certain antivirals or immunomodulators, are no longer part of standard treatment. This may have influenced the interpretation of results related to liver function. Current management has been simplified and focuses primarily on corticosteroids in selected cases, reinforcing the need to interpret our findings within their original temporal context[5].

Regarding sample size and statistical power, as is common in scientific research, our initial calculations were based on certain epidemiological and statistical assumptions whose validity could only be confirmed after data collection. Therefore, for outcomes with lower-than-expected frequency (such as mortality and bacterial coinfection), the analytical capacity—particularly statistical power—may have been affected. The knowledge-building process inherently involves refining such assumptions, and our study provides a valuable starting point for future research.

We appreciate this opportunity for academic exchange and reiterate the importance of continued investigation into COVID-19's multisystemic effects. Evidence in this field

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continues to evolve, and future studies may address these questions with updated information and optimized methodological designs.

We thank Dr. Azañero-Haro for his comments and the editorial committee for allowing us to participate in this valuable discussion.

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