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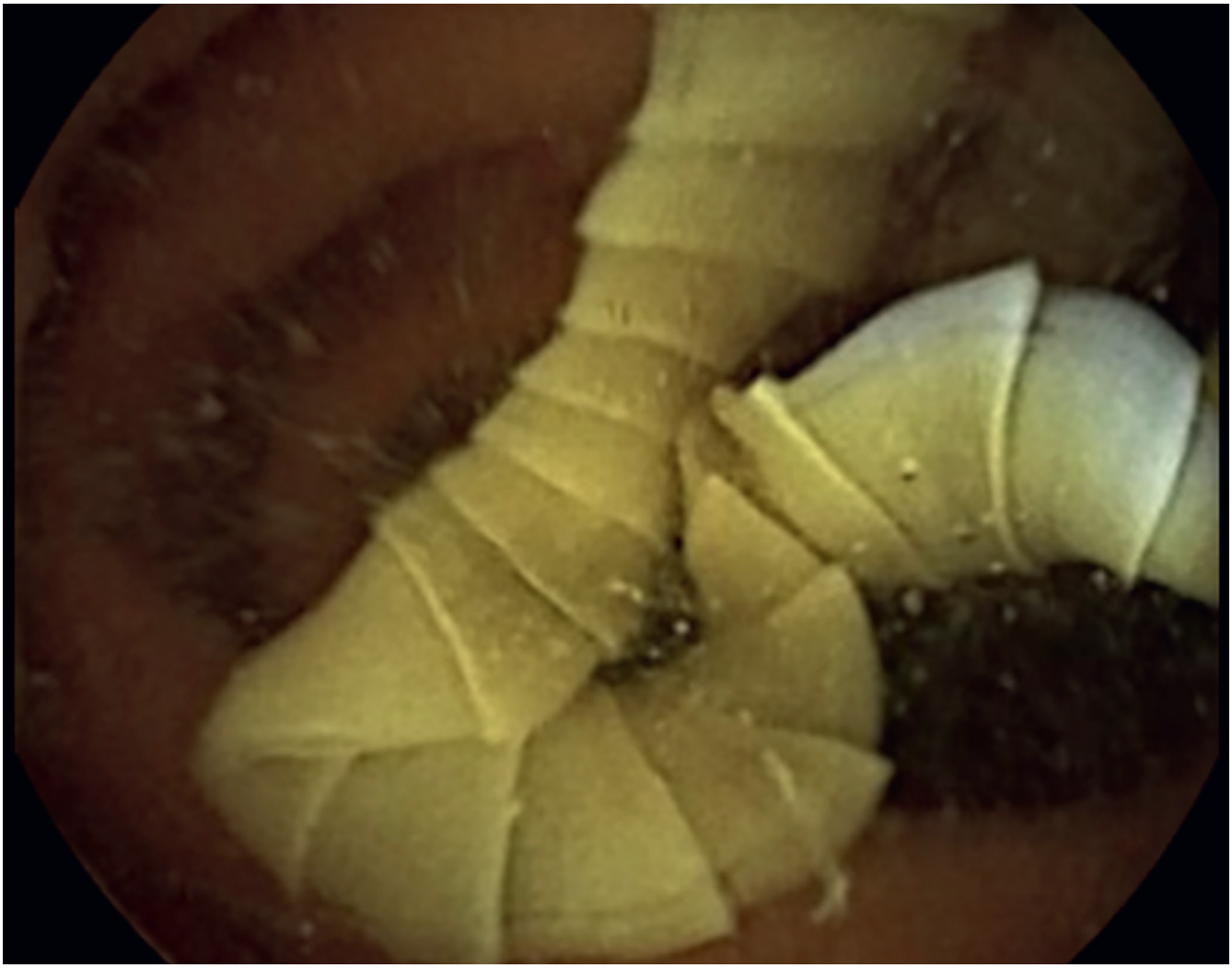

Highlights in this issue:

Research article: Safety of endoscopy units during the COVID-19 pandemic

Case reports: Diagnostic challenges in the diagnosis of eosinophilic gastrointestinal disorders

Case report: Autoimmune liver disease in HIV-infected patients

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Aims and Scope

The *GE Portuguese Journal of Gastroenterology* (formerly *Jornal Português de Gastrenterologia*), founded in 1994, is the official publication of Sociedade Portuguesa de Gastrenterologia (Portuguese Society of Gastroenterology), Sociedade Portuguesa de Endoscopia Digestiva (Portuguese Society of Digestive Endoscopy) and Associação Portuguesa para o Estudo do Fígado (Portuguese Association for the Study of the Liver).
The journal publishes clinical and basic research articles on Gastroenterology, Digestive Endoscopy, Hepatology and related topics. Review articles, clinical case studies, images, letters to the editor and other articles such as recommendations or papers on gastroenterology clinical practice are also considered. Only articles written in English are accepted.

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Cover illustration
Tapeworm in the small bowel, without mucosal lesions. From Freitas et al., pp. 69-70.

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Editorial

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Do Not Miss the Diagnosis: Not All Pink Findings Mean the Same in the Gastrointestinal Tract!

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Keywords
Infection · Gastrointestinal tract · Eosinophilic gastrointestinal diseases

Os diagnósticos que não devem ser esquecidos – nem todos os achados cor de rosa significam o mesmo no tubo digestivo

Palavras Chave
Infeções · Gastrointestinal · Doenças eosinófilicas gastrointestinais

The diagnosis of some gastrointestinal (GI) diseases, such as GI infections or immune-mediated disorders, can be challenging not only due to the diverse array of GI (and extra-GI) symptoms they may manifest with, but also due to the nonspecific endoscopic and sometimes even histological findings. In this supplementary issue of *GE – Portuguese Journal of Gastroenterology*, we present a compilation of articles concerning GI infections and eosinophilic GI diseases (EGIDs). Indeed, GI infections pose a significant burden in patients, health systems, and gastroenterologists and the diagnosis of EGIDs is also increasing. Of note, the national thematic meeting of the Portuguese Society of Gastroenterology (Sociedade Portuguesa de Gastrenterologia [SPG]) in 2023 was also dedicated to GI infections and this supplementary issue reinforces the importance of this problem in our beloved specialty.

GI infections can be caused by either virus, bacteria, fungi, and parasites, showcasing a wide range of clinical manifestations, and potentially leading to long-term morbidity or even mortality. In low-income countries, GI infections particularly gastroenteritis are a main cause of mortality, especially among children [1]. In high-income countries, even if mortality is lower, GI infections are also prevalent, namely, infections such as *Helicobacter pylori* (*H. pylori*) or hepatotropic virus, which still entail a considerable burden of disease. Indeed, in 2019 it was estimated that approximately 296 million people worldwide were living with chronic hepatitis B infection, and 58 million with chronic hepatitis C infection, with viral hepatitis being estimated to be the cause of roughly 1.1 million deaths per year, the majority due to both chronic liver disease and liver cancer [2]. On the other hand, *H. pylori* infects 40–50% of the world population and is one of the most common bacterial infections globally. Typically, infection occurs during childhood and becomes persistent if left untreated, with possible long-term consequences, including peptic ulcer disease and gastric cancer [3].

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Although there are disparities in GI infections across different countries, the current trend of migration is altering this landscape, posing challenges for physicians in identifying, diagnosing, and treating these diseases [4]. Similarly, immune-mediated disorders like EGIDs can also pose significant clinical dilemmas [5, 6]. The best known EGID is eosinophilic esophagitis (EoE), but the non-EoE EGIDs are now the subject of new research due to increased clinical awareness of these conditions [5, 6]. Non-EoE EGIDs can involve the stomach, small bowel, and colon, either individually or in any combination of segments, and can also vary in the depth of involvement of the GI wall layers, making the clinical presentation of EGIDs widely variable – to nonspecific symptoms such as abdominal pain to ascites if the serosa is involved [6, 7].

Laboratory tests should be performed, and peripheral eosinophilia, iron deficiency, or hypoalbuminemia can contribute to the suspicion of EGIDs. Even so, it is essential to consider and rule out alternative causes of peripheral eosinophilia, such as drug reactions, infections, malignancy, connective tissue diseases, vasculitis, Crohn's disease, hypereosinophilic syndrome, among others, to ensure an accurate diagnosis of non-EoE EGIDs [6].

Endoscopic evaluation is often performed, but the majority of endoscopic findings are nonspecific and sometimes are patchy. Biopsies play a crucial role in the diagnosis of EGIDs, and due to their patchy nature, multiple biopsies should be taken from both normal and abnormal mucosae. In some cases, full-thickness biopsies may be necessary to evaluate deeper wall involvement. However, even histology may be nondiagnostic due to suboptimal sensitivity and suboptimal specificity – indeed, the definition of GI tract eosinophilia has specific thresholds for documentation of abnormal eosinophil count that differ depending on the area of the GI tract involved but a fully consensus is not yet established [5–7]. Management can also be problematic because almost all the current therapies are from retrospective studies – either case reports and small case series. Dietary therapy for highly motivated patients can be an option, but the most used class of medications is corticosteroids [5, 6].

In this issue of *GE – Portuguese Journal of Gastroenterology*, several case reports are published reporting interesting non-EoE EGIDs and two case reports of GI parasite infections in immigrants, increasing awareness of heterogenous prevalence of these diseases and the clinical challenge we may encounter in diagnosing them. Freitas et al. [8] describe a case of an young patient with white cords in stools and mild lower GI symptoms in whom initial investigation revealed 3 negative stool samples and normal upper and lower GI endoscopy. A small bowel capsule endoscopy (SBCE) was decisive for the diagnosis since it showed a tapeworm infection in the small bowel without mucosal lesions. Despite this observation in SBCE, proglottids can be present in different cestodes species, and without direct observation, the specific type is difficult to determine. However, treatment is independent of the cestode species, and in this case, a single dose of praziquantel 10 mg/kg allowed full clinical response [9]. This case highlights the remarkable diagnostic value of SBCE in patients' high clinical suspicion of parasite infection with negative stool results.

In another case, reported by Franco et al. [10], a young immigrant patient with upper GI symptoms and peripheral eosinophilia was found to have a duodenal stricture on upper GI endoscopy. Histopathology later confirmed *Strongyloides stercoralis* duodenitis inducing duodenal obstruction. Following appropriate treatment, the patient showed complete resolution of symptoms and laboratory abnormalities. This case underlines not only the importance of recognizing the global spread of infectious diseases that can be silent for several years, but also the need to always keep an open mind toward the different clinical presentations possible for the same infectious agent.

Tarrio et al. [11] describe the case of a 40-year-old male with nonspecific GI symptoms and unintended weight loss. Laboratory findings such as anemia, peripheral eosinophilia, and elevated calprotectin were observed, and CT scan revealed bilateral pleural effusion, low-volume ascites, and thickening of the terminal ileum. Endoscopic evaluation including ileocolonoscopy did not show significant abnormalities, but random ileal biopsies collected using antegrade motorized spiral enteroscopy demonstrated mucosal inflammation characterized by eosinophilic infiltration, approximately 35 eosinophils per high-power field, and altered eosinophil distribution within the ileal wall. After thorough exclusion of other possible causes, a diagnosis of eosinophilic ileitis was established and the patient was started on oral prednisolone with resolution of the case. This study illustrates not only the clinical diverse spectrum that patients can appear with, but also the difficulty that physicians may encounter in their diagnosis sometimes needing persistent efforts and invasive methods to establish a correct diagnosis allowing proper treatment. After ruling out more prevalent etiologies (including infectious ones), the histological samples obtained through enteroscopy were vital for the diagnosis and treatment of this patient.

In this era of globalization, a more recent infection, SARS-CoV-2, has also been a central player in daily clinical practice in the last years. Gonçalves et al. [12] share in this issue their experience about safety in endoscopy units

during the SARS-CoV-2 pandemic. In a retrospective analysis of 2,166 patients proposed to GI endoscopy who underwent either PCR screening for SARS-CoV-2 (n = 1,521) or a specific questionnaire (n = 645) up to 72 h before the procedure, only 1.4% (n = 21) tested positive pre-endoscopy. Follow-up until 14 days after endoscopy identified only 9 positive patients (0.42%) for SARS-CoV-2, concluding that by implementing symptom and risk contact screening measures along with the use of individual protective equipment, the possibility of infection in endoscopy units can be reduced to a negligible level. This study draws attention to the crucial role of preventive measures in the propagation of infectious diseases, as adherence to these measures can significantly reduce the transmission of pathogens.

Although very distant apart in terms of pathogenesis and treatment options, several GI infections and EGIDs share some common ground including the variability in clinical manifestations – from asymptomatic to serious complications (protein-losing enteropathy, for example) – and the (very real) struggle in reaching a definitive diagnosis that often requires a combination of laboratory, endoscopic, imagological, and histological findings.

Statement of Ethics

Not applicable.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Jéssica Chaves performed the literature search and wrote the manuscript. Diogo Libânio was involved in the conception of this editorial, reviewed the manuscript, and made critical corrections.

Data Availability Statement

Not applicable.

References

1 Liang J, Du Y, Qu X, Ke C, Yi G, Liu M, et al. The causes of death and their influence in life expectancy of children aged 5–14 years in low-and middle-income countries from 1990 to 2019. Front Pediatr. 2022;10:829201.
2 World Health Organization. Global progress report on HIV, viral hepatitis and sexually transmitted infections, 2021: accountability for the global health sector strategies 2016–2021: actions for impact. World Health Organization; 2021.
3 Zamani M, Ebrahimtabar F, Zamani V, Miller WH, Alizadeh-Navaei R, Shokri-Shirvani J, et al. Systematic review with meta-analysis: the worldwide prevalence of Helicobacter pylori infection. Aliment Pharmacol Ther. 2018;47(7):868–76.
4 Gushulak BD, MacPherson DW. Globalization of infectious diseases: the impact of migration. Clin Infect Dis. 2004;38(12):1742–8.
5 Dellon ES, Gonsalves N, Abonia JP, Alexander JA, Arva NC, Atkins D, et al. International consensus recommendations for eosinophilic gastrointestinal disease nomenclature. Clin Gastroenterol Hepatol. 2022;20(11):2474–84.e3.
6 Redd WD, Dellon ES. Eosinophilic gastrointestinal diseases beyond the esophagus: an evolving field and nomenclature. Gastroenterol Hepatol. 2022;18(9):522–8.
7 Kinoshita Y, Oouchi S, Fujisawa T. Eosinophilic gastrointestinal diseases – pathogenesis, diagnosis, and treatment. Allergol Int. 2019;68(4):420–9.
8 Freitas M, Macedo Silva V, Boal Carvalho P, Rosa B, Cotter J. An unexpected guest in capsule endoscopy: tapeworm infection. GE Port J Gastroenterol. 2022:1–2.
9 Chai JY. Praziquantel treatment in trematode and cestode infections: an update. Infect Chemother. 2013;45(1):32–43.
10 Franco AR, Mendo R, Figueiredo P, Albuquerque AC. An unusual cause of duodenal obstruction: watch your feet! GE Port J Gastroenterol. 2022:1–3.
11 Tarrio I, Moreira M, Araújo T, Guerreiro E, Rodrigues C, Lopes L. A rare case of eosinophilic ileitis and the role of motorized spiral enteroscopy in its diagnosis. GE Port J Gastroenterol. 2022:1–6.
12 Gonçalves M, Guimarães A, Carvalho T, Antunes P, Mendes S, Soares J, et al. Safety of endoscopy units during the COVID-19 pandemic. GE Port J Gastroenterol. 2022:1–7.

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Research Article

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Safety of Endoscopy Units during the COVID-19 Pandemic

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Keywords
COVID-19 · SARS-CoV-2 screening · Endoscopy

Abstract

Introduction: The COVID-19 pandemic drastically changed the daily routine of all healthcare systems worldwide, and endoscopy units were no exception. Endoscopic exams were considered to have a high risk of transmission, and therefore, the safety of endoscopy units and the consequent need for pre-endoscopy SARS-CoV-2 screening were questioned early on. The aim of our study was to assess the safety of endoscopy units during the COVID-19 pandemic, as well as the effectiveness/necessity for SARS-CoV-2 screening prior to endoscopies. ***Material and Methods:*** This is a retrospective and single-center study carried out in a Portuguese tertiary hospital. All patients who underwent endoscopic procedures between September 1, 2020 and February 28, 2021 were included. The pre-endoscopy screening consisted of a specific questionnaire or a RT-PCR test for SARS-CoV-2 (nasal and oropharyngeal swab). Data were obtained through patient's clinical records and the Trace COVID platform. ***Results:*** A total of 2,166 patients were included. Patients had a mean age of 61.8 years and were predominantly male (56.2%, n = 1,218). Eighty-one (3.7%) patients had previous SARS-CoV-2 infection, with a median difference of 74 days (IQ 40.5:160.5) between infection and endoscopy. Most patients (70.2%, n = 1,521) underwent PCR screening for SARS-CoV-2 up to 72 h before the procedure, with the remaining patients (29.8%, n = 645) answering a questionnaire of symptoms and risk contacts up to 3 days before endoscopy. Of the patients who underwent RT-PCR screening for SARS-CoV-2, 21 (1.4%) tested positive, and all were asymptomatic at the time of the screening. The evaluation for SARS-CoV-2 infection up to 14 days after the endoscopic exams identified 9 positive patients (0.42%) for SARS-CoV-2. The median difference in days between endoscopy and the diagnosis of infection was 10 days. ***Discussion/Conclusion:*** Pre-endoscopy screening with RT-PCR test for SARS-CoV-2 identified a very small number of patients with COVID-19 infection as well as patients with COVID-19 infection in the following 14 days. Therefore, the risk of infection in endoscopy units is negligible if screening of symptoms and risk contacts is applied and individual protective equipment is used.

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A segurança das unidades de endoscopia durante a pandemia COVID-19

Palavras Chave
COVID-19 · Rastreio de SARS-CoV-2 · Endoscopia

Resumo
Introdução: A pandemia COVID-19 mudou drasticamente o dia-a-dia de todos os sistemas de saúde a nível mundial e as unidades de endoscopia não foram exceção. Os exames endoscópicos foram considerados exames com alto risco de transmissão pelo que desde cedo se questionou a segurança das unidades de endoscopia e a consequente necessidade de rastreio SARS-CoV-2 pré-endoscopia. O objetivo do estudo foi avaliar a segurança das unidades de endoscopia durante a pandemia por COVID-19 bem como a eficácia/necessidade de rastreio SARS-CoV-2 prévio aos exames endoscópicos. ***Material e métodos:*** Foi desenvolvido um estudo retrospetivo e unicêntrico, no qual todos os doentes submetidos a exames endoscópicos entre 1 de setembro de 2020 e 28 de fevereiro de 2021 foram incluídos. Como estratégia de rastreio pré endoscopia foram aplicados questionários específicos de sintomas e contactos de risco, ou teste PCR de SARS-CoV-2 (zaragatoa nasal e orofaríngea). Os dados clínicos foram obtidos através do processo clínico do doente e da plataforma Trace COVID-19. ***Resultados:*** Foram incluídos um total de 2,166 doentes submetidos a exames endoscópicos durante o período de estudo. Os doentes incluídos apresentaram uma média de idades de 61.8 anos e eram maioritariamente do sexo masculino (56.2%, *n* = 1,218). 3.7% (*n* = 81) dos doentes já tinha tido infeção por COVID-19 no passado, sendo a mediana da diferença de dias entre a infeção e a data do exame de 74 dias. A maioria dos doentes (70.2%, *n* = 1,521) foi submetido a rastreio por PCR de SARS-CoV-2 até 72 horas antes do procedimento, sendo os restantes doentes (29.8%, *n* = 645) submetidos a um questionário de sintomas e contactos de risco realizado até 3 dias antes do procedimento. Dos doentes que realizaram rastreio por PCR de SARS-CoV-2, 21 (1.4%) apresentaram teste positivo, estando todos assintomáticos à data do teste. Aquando da verificação de infeção por SARS-CoV-2 até 14 dias após a realização dos exames endoscópicos apurou-se que apenas 9 doentes (0.42%) testaram positivo para SARS-CoV-2, sendo a mediana da diferença de dias entre a data do exame e o diagnóstico de infeção de 10 dias. ***Discussão/Conclusão:*** O rastreio pré-endoscopia com teste PCR de SARS-CoV-2 identificou um número reduzido de doentes infetados com COVID-19 e o número de doentes com infeção por COVID-19, nos 14 dias seguintes aos exames endoscópicos, foi muito baixo. Assim, se aplicado o rastreio de sintomas e contactos de risco, usados os equipamentos de proteção individual adequados, o risco de infeção nas unidades de endoscopia torna-se negligenciável.

Introduction

In December 2019, Wuhan city of Hubei province, China, reported a cluster outbreak of viral pneumonia that was subsequently confirmed to be caused by a new coronavirus named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and the disease caused by it was termed coronavirus disease 2019 (COVID-19) by the World Health Organization (WHO) [1, 2].

COVID-19 was considered a pandemic by WHO in March 2020. In Portugal, the first documented cases were confirmed on March 3, and after that, the number of infected people increased steadily, leading to the declaration by local authorities of a state of emergency since March 18, 2020.

The most common symptoms of COVID-19 are fever, fatigue, and respiratory tract symptoms such as cough and shortness of breath. Gastrointestinal symptoms, mainly diarrhea and vomiting, have also been reported [2–5].

The current available evidence suggests that SARS-CoV-2 is primarily transmitted through respiratory droplets and contact routes [1, 3, 5–9]. Airborne transmission may also be possible during procedures that generate aerosols such as gastrointestinal or respiratory tract endoscopies [1, 10, 11].

The transmission of SARS-CoV-2 in asymptomatic patients is one of the key factors responsible for its rapid dissemination across the world [1, 12]. There are several routes of transmission of COVID-19 in endoscopy units, which include person-to-person via direct contact (as endoscopy involves close contact with the patients or respiratory droplets), generation of infected aerosols during endoscopy, and contact with contaminated endoscopic equipment, accessories, and body fluids [13]. Theoretically, a patient with high-viral load in the respiratory secretions can contaminate the air of the endoscopy room. Fomites loaded with virus can remain viable for a longer

duration, thus putting uninfected patients as well as endoscopy staff at risk [10].

Early on during the course of the pandemic, in order to limit the spread of COVID-19 and to protect both patients and healthcare workers (HCWs), multiple scientific societies around the world recommended that only urgent and high-priority endoscopic procedures should be done. In contrast to the severe acute respiratory syndrome outbreak in 2003 which was contained within 8 months [14], the COVID-19 pandemic has been exhibiting a vastly different epidemic trajectory. Maintaining a suitable balance between protecting HCWs and patients on the one hand and providing a timely and effective clinical service on the other hand have become more and more important as this pandemic persists [15].

Different pre-endoscopy screening strategies have been adopted around the world since the beginning of pandemic. Currently, as a screening strategy, questionnaires (symptoms and risky contacts) and RT-PCR testing for SARS-CoV-2 are used throughout several different endoscopy units globally prior to endoscopies.

According to the National Health Institute [16], all patients proposed for endoscopic exams, as an outpatient, must be screened and classified, using telephone questionnaires or equivalent, regarding the risk of COVID-19 in two moments: on the eve of the exam, by telephone, and on the day of the exam, before admission to the endoscopic unit. Despite not being recommended by the National Health Institute, the National Anesthesiology Society [17] recommends performing RT-PCR testing for SARS-CoV-2 in all patients before surgical or similar procedures in which it may be necessary to manage the airway (procedures under general anesthesia or anesthetic sedation).

And so, altogether, emerging evidence suggests that gastrointestinal endoscopy appears to be safe both for patients and HCWs if strict infection prevention and control measures are taken. Hence, our study aimed to assess the safety of endoscopy units during the COVID-19 pandemic, as well as the effectiveness and the need for SARS-CoV-2 screening prior to endoscopic exams.

Material and Methods

Study Design and Patients

We performed a retrospective, observational, and single-center study at the gastroenterology department of a Portuguese tertiary hospital. We included individuals who underwent elective endoscopic exams between September 1, 2020 and February 28, 2021. Patients with confirmed SARS-CoV-2 infection within 20 days prior to endoscopy were excluded. This study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the local Ethics Committee.

Data Collection

Medical records and the Trace COVID-19 platform were reviewed. Trace COVID-19 is a Portuguese software, developed during the pandemic, which registers data from patients infected with SARS-CoV-2, including the date of diagnosis and all the other clinical and demographic data.

The following clinical and demographics parameters were considered for analysis: age, gender, previous SARS-CoV-2 infection, endoscopic procedure, SARS-CoV-2 screening, infection by SARS-CoV-2 within 14 days after endoscopic exam. In order to investigate post-endoscopy SARS-CoV-2 infection, all patients were checked on the Trace COVID-19 platform, and the presence of a diagnosis of SARS-CoV-2 infection was verified within 14 days of the endoscopy procedure. All the parameters were analyzed and described for purposes of population's characterization.

SARS-CoV-2 Screening Strategy

The SARS-CoV-2 screening performed was based on a specific questionnaire of symptoms related to COVID-19 and assessment of risk contacts with people infected with COVID-19 during the days prior to endoscopy or RT-PCR test for SARS-CoV-2 (nasal and oropharyngeal swab). The questionnaire was carried out up to 3 days before the endoscopy, and the RT-PCR test for SARS-CoV-2 was done within the previous 72 h.

All the patients who underwent endoscopic procedure under anesthetic sedation did only a RT-PCR test for SARS-CoV-2, and all other patients were asked the specific questionnaire. All patients who answered "yes" to any of the questionnaire topics did not undergo the scheduled endoscopic examinations, which were, then, postponed for at least 14 days.

On the day of endoscopy, all patients, before entering in the endoscopy unit, answered a brief symptom questionnaire, and the tympanic temperature was measured. In addition to the tests and questionnaires, all patients and professionals always wore adequate masks, regular hand disinfection was carried out, and body temperature was determined on entry into the endoscopy unit. The access of family members and caregivers to the endoscopy unit was also limited in accordance with local and national health authority recommendations. It is also worth noting that during the study period, it was no longer recommended to postpone non-urgent elective activity, and therefore, all exams were being resumed.

Statistical Analysis

Statistical analysis was performed with Statistical Package for the Social Sciences® (SPSS), version 24.0. For categorical variables, the authors present frequencies (*n*) and percentages (%). For continuous variables with symmetric distribution, we determined means and standard deviations. Intervals between prior SARS-CoV-2 infection and the endoscopic procedure and between endoscopy and the SARS-CoV-2 infection, the median, and interquartile range (IQ) were used. The assumption of normality was verified by the Kolmogorov-Smirnov test, through the values of asymmetry and kurtosis, as well as by the analysis of histogram graphs.

Table 1. Characterization of endoscopic procedures

Total endoscopic procedures, *n*	2,371
Upper gastrointestinal endoscopy, *n* (%)	939 (39.6)
Colonoscopy, *n* (%)	828 (34.9)
Endoscopic ultrasonography, *n* (%)	205 (8.6)
Rectosigmoidoscopy, *n* (%)	168 (7.1)
Endoscopic retrograde cholangiopancreatography, *n* (%)	72 (3)
Anoscopy, *n* (%)	63 (2.7)
Endoscopic submucosal dissection, *n* (%)	46 (1.9)
Percutaneous endoscopic gastrostomy, *n* (%)	28 (1.2)

Table 2. Indications for endoscopic procedures of patients with SARS-CoV-2 infection after endoscopic procedure

Total of patients, *n*	9
Total of endoscopic procedure, *n*	11
Gastric dysplasia, *n* (%)	3 (27.3)
Anemia, *n* (%)	3 (27.3)
Dysphagia, *n* (%)	1 (9.1)
Barrett's esophagus, *n* (%)	1 (9.1)
Dyspepsia, *n* (%)	1 (9.1)
Colorectal cancer screening, *n* (%)	1 (9.1)
Colorectal polyp, *n* (%)	1 (9.1)

Results

Over the study period, a total of 2,166 patients underwent endoscopic exams. Patients had a mean age of 61.8 ± 14.7 years and were mostly male (56.2%, *n* = 1,218). None of the patients were vaccinated.

The exams were mostly performed in an outpatient setting, with only 118 (5.4%) patients requiring hospitalization after the endoscopic exam, namely, those undergoing endoscopic retrograde cholangiopancreatography and endoscopic submucosal dissection. Upper gastrointestinal endoscopy was the most common procedure (43.4%, *n* = 940). A description of the endoscopic procedures performed can be found in Table 1.

The main reasons for referral were extraction of colonic polyps (17.4%, *n* = 377), assessment of gastric dysplasia (7.5%, *n* = 162), diagnosis/follow-up of patients with inflammatory bowel disease (7.2%, *n* = 155), surveillance after colorectal cancer resection (5%, *n* = 109), and study of anemia (4%, *n* = 87). Gastric dysplasia represented an important part of the indication for performing endoscopic exams since it was considered a priority indication for upper gastrointestinal endoscopy during the COVID-19 pandemic and, also, because the study center is considered a reference center for endoscopic submucosal dissection, leading to an increase in the number of patients with this premalignant condition.

Eighty-one (3.7%) patients had previous SARS-CoV-2 infection, with a median difference of 74 days (IQ 40.5:160.5) between infection and endoscopy. Most patients (70.2%, *n* = 1,521) did an RT-PCR screening for SARS-CoV-2 up to 72 h before the procedure, with the remaining patients (29.8%, *n* = 645) answering a questionnaire of symptoms and positive risk contacts the day before the procedure; all of them presented a "negative" questionnaire.

Of the patients who underwent RT-PCR screening for SARS-CoV-2, 21 (1.4%) tested positive, and all were asymptomatic at the time of the screening. Endoscopic procedures for these patients were postponed at least 14 days.

Nine patients (0.42%) with an initial negative RT-PCR screening test developed SARS-CoV-2 infection within 14 days after visiting our department. The median difference between the procedure and diagnosis of infection was 10 days (IQ 6.5–13). All these patients were confirmed to have a negative RT-PCR test before endoscopy. Their endoscopic procedures were performed in an outpatient setting: upper gastrointestinal endoscopy in 5 patients, colonoscopy in 2 patients, and upper gastrointestinal endoscopy plus colonoscopy in the remaining 2 patients. Table 2 summarizes clinical indication for endoscopies in these patients.

None of the patients submitted to the questionnaire had a SARS-CoV2 infection within 14 days after the endoscopic exam. It should also be noted that during the study period, none of the HCWs of the endoscopy unit became infected with SARS-CoV-2.

Discussion

The pre-endoscopy SARS-CoV-2 screening strategy should carefully analyzed. The two main concerns with this pretesting strategy are the false-positive and the false-

negative tests. An infected individual with a negative RT-PCR test (false negative) using a surgical mask entering an endoscopy unit may be hazardous for staff and other patients. On the other hand, a patient with a false-positive test will have their exams called off and enter a 10-day quarantine period with absenteeism and consequent increase in anxiety and apprehension [18].

In our study, the prevalence of SARS-CoV-2 infection in patients undergoing pre-endoscopy screening was 1%, all of them asymptomatic and detected by RT-PCR test for SARS-CoV-2, which is in agreement with the few recent available studies [19–22]. These studies showed that asymptomatic SARS-CoV-2 among patients referred for endoscopic procedures had a prevalence ranging from 0.0% to 1.5%, but most studies reported a range from 0% to 0.5% regardless of local surges of COVID-19 cases. In all of these studies, the importance of symptom screening in endoscopy units is emphasized.

Regarding the prevalence of SARS-CoV-2 infection after endoscopic exams, we identified a prevalence of 0.42% of SARS-CoV-2 infection within 14 days after endoscopic exam. Once again, these findings are consistent with published literature. Several studies [23–30] show that post-endoscopy rates of infection ranged from 0% to 0.4%. The cases of COVID-19 were attributed to endoscopy exposure if there was no other reasonable justification. However, this assumption may be a bias, overestimating infection and transmission. Of these studies, 5 were in the context of a pre-procedure testing strategy, and 3 did not have an explicit pre-procedure testing strategy.

Several studies have already been carried out and demonstrated the effectiveness of vaccination in reducing the transmission of SARS-CoV-2. In a study carried out in Israel [31], the viral load present in the nasal mucosa of a sample of HCWs was evaluated on a weekly basis. The conclusion of the study showed that in vaccinated persons with COVID-19 infection, the viral load was 2–4 times lower than in unvaccinated persons. Also, another study performed in the USA [32] conducted on a sample of 3,950 HCWs showed that vaccines had an efficacy in preventing infection of 90% in the 14 days after the second dose and 80% in the 14 days after the first dose.

Recent guidelines published by the American Gastroenterological Association, concerning SARS-CoV-2 testing and endoscopy postvaccination [33], acknowledged the small potential benefit of pre-procedure testing (using RT-PCR test for SARS-CoV-2) with respect to patient and staff reassurance. However, there was no apparent benefit from preventing infections. The panel also evaluated the yield of testing and significant delays in care as well as decreased number of diagnoses of gastrointestinal cancers. Therefore, more value should be given to avoid delays in care, leading to a downstream impact on cancer diagnoses and other important diseases. Multiple visits to clinical units are also a factor also to be taken into consideration, and yet, avoiding all these unnecessary tests could lead to a great saving of time, money, and resources, with a major impact on our healthcare system.

Some limitations need to be mentioned: a causal relationship between an endoscopic procedures and subsequent SARS-CoV-2 infection could not be fully proved, and therefore, our results may be overrated. Furthermore, our investigation was single-centered, and data collected retrospectively; and therefore, some data may have been lost. These data may include patients with a positive symptom screening which, consequently, were no longer included in the list of endoscopies to which the authors had access. For this reason, patients who underwent symptom screening were not included in the rate of positive screening since this probably would lead to an underestimate value.

In Portugal, different hospitals followed different strategies with many clinical facilities performing only symptom screening. Hence, large prospective and multicenter trials could play an important role to validate our findings and defining the best pre-endoscopic screening approach in the future, for this or another pandemic scenario.

This was a pioneering study on the safety of endoscopic units during the COVID-19 pandemic in Portugal. There are no other Portuguese records assessing the incidence of SARS-CoV-2 infection after endoscopic procedures.

In conclusion, pre-endoscopy screening with RT-PCR test for SARS-CoV-2 identified a very small number of patients with SARS-CoV-2 infection, all of them asymptomatic and therefore with low risk of transmission [34]. Moreover, the number of patients with SARS-Cov-2 infection in the 14 days following endoscopy was very low, and this number may be even lower since it is not possible to fully associate these infections with the hospital visit. Given the current high vaccination rate (90%), we assume that screening of symptoms and identifying risk contacts is important and may be sufficient to prevent infection with SARS-CoV-2, if protective equipment is adequately used. That said, our study allows us to conclude that endoscopy units were safe, both for patients and HCWs during the COVID-19 pandemic and that, according to the most recent literature, pre-endoscopy SARS-CoV-2 screening should be rethought and standardization of actions should be applied across the country.

Statement of Ethics

Informed consent was not requested as this was an observational and retrospective study with no therapeutic intervention. The study protocol was authorized by the Braga Hospital Ethics Committee. The authors declare that the procedures followed were in accordance with the World Medical Association Declaration of Helsinki.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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None.

Author Contributions

M.G. was responsible for the design of the study, data analysis, data collection, and drafting of the manuscript. A.G., T.C., P.A., and S.M. were responsible for the collection and analysis of the data and helped drafting the manuscript. R.C., J.S., B.A., and A.R. were responsible for the design of the study, data collection and interpretation, and critical revision of the work for important intellectual content. All authors approved the final version to be published and agreed to be accountable for all aspects of the work.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author, Margarida Gonçalves. The data are not publicly available since they can contain information that could compromise the privacy of research participants.

References

1 WHO. Pneumonia of unknown cause. China; 2020. Available from: http://www.who.int/csr/don/05-january-2020-pneumoniaof-unkown-cause-china/en/ (accessed April 14, 2020).
2 Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med. 2020;382(8):727–33.
3 Chatterjee P, Nagi N, Agarwal A, Das B, Banerjee S, Sarkar S, et al. The 2019 novel coronavirus disease (COVID-19) pandemic: a review of the current evidence. Indian J Med Res. 2020;151(2):147.
4 Li LY, Wu W, Chen S, Gu JW, Li XL, Song HJ, et al. Digestive system involvement of novel coronavirus infection: prevention and control infection from a gastroenterology perspective. J Dig Dis. 2020;21(4):199–204.
5 Wong SCY, Kwong RTS, Wu TC, Chan JWM, Chu MY, Lee SY, et al. Risk of nosocomial transmission of coronavirus disease 2019: an experience in a general ward setting in Hong Kong. J Hosp Infect. 2020;105(2):119–27.
6 Repici A, Maselli R, Colombo M, Gabbiadini R, Spadaccini M, Anderloni A, et al. Coronavirus (COVID-19) outbreak: what the department of endoscopy should know. Gastrointest Endosc. 2020;92(1):192–7.
7 Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y, et al. Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia. N Engl J Med. 2020;382(13):1199–207.
8 Marchese M, Capannolo A, Lombardi L, Di Carlo M, Marinangeli F, Fusco P. Use of a modified ventilation mask to avoid aerosolizing spread of droplets for short endoscopic procedures during coronavirus covid-19 outbreak. Gastrointest Endosc. 2020;92(2):439–40.
9 Lei Y, Cao H, Jie Y, Huang Z, Guo X, Chen J, et al. A cross-sectional comparison of epidemiological and clinical features of patients with coronavirus disease (COVID-19) in Wuhan and outside Wuhan, China. Travel Med Infect Dis. 2020;35:101664.
10 Rana SS. Risk of COVID-19 transmission during gastrointestinal endoscopy. J Digestive Endosc. 2020;11(1):27–30.
11 Tran K, Cimon K, Severn M, Pessoa-Silva CL, Conly J. Aerosol generating procedures and risk of transmission of acute respiratory infections to healthcare workers: a systematic review. PLoS One. 2012;7(4):e35797.
12 Bai Y, Yao L, Wei T, Tian F, Jin DY, Chen L, et al. Presumed asymptomatic carrier transmission of COVID-19. JAMA. 2020;323(14):1406–7.
13 Soetikno R, Teoh AYB, Kaltenbach T, Lau JYW, Asokkumar R, Cabral-Prodigalidad P, et al. Considerations in performing endoscopy during the COVID-19 pandemic. Gastrointest Endosc. 2020;92(1):176–83.
14 Wilder-Smith A, Chiew CJ, Lee VJ. Can we contain the COVID-19 outbreak with the same measures as for SARS? Lancet Infect Dis. 2020;20(5):e102–7.
15 Lui RN. Safety in endoscopy for patients and healthcare workers during the COVID-19 pandemic. Tech Innov Gastrointest Endosc. 2021;23(2):170–8.
16 DGS. Norma 012/2020 – COVID-19: exames endoscópicos digestivos. Maio 2020.
17 Sociedade Portuguesa de Anestesiologia. Gestão dos procedimentos anestésicos em contexto de pandemia COVID-19; Maio 2020.
18 Sultan S, Siddique SM, Altayar O, Caliendo AM, Davitkov P, Feuerstein JD, et al. AGA institute rapid review and recommendations on the role of pre-procedure SARS-CoV2 testing and endoscopy. Gastroenterology. 2020;159(5):1935–48.e5.
19 Bowyer B, Thukral C, Patel S, Dovalovsky K, Bowyer SG, Ford J, et al. Outcomes of symptom screening and universal COVID-19 reverse transcriptase polymerase chain reaction testing before endoscopy in a community-based ambulatory surgery center. Gastrointest Endosc. 2021;93(5):1060–4.e1.
20 Forde JJ, Goldberg D, Sussman D, Soriano F, Barkin JA, Amin S. Yield and Implications of pre-procedural COVID-19 polymerase chain reaction testing on routine endoscopic practice. Gastroenterology. 2020;159(4):1538–40.
21 Hernández Camba A, Marcelino Reyes R, Hernández-Guerra M, Blasco Amato ÓA, Bennemann P, De La Riva N, et al. Pre-procedural antibody testing for SARS-CoV-2 in the routine endoscopic practice. Rev Esp Enferm Dig. 2021;113(2):116–8.
22 Lewis SS, Smith BA, Akinboyo IC, Seidelman J, Wolfe C, Kirk AB, et al. Early experience with universal preprocedural testing for SARS-CoV-2 in a relatively low-prevalence area. Infect Control Hosp Epidemiol. 2021;42(3):341–3.
23 Casper M, Reichert MC, Rissland J, Smola S, Lammert F, Krawczyk M. Pre-endoscopy SARS-CoV-2 testing strategy during COVID-19 pandemic: the care must go on. Eur J Med Res. 2022;27(1):41.
24 Hayee B, SCOTS II Project group, Bhandari P, Rees CJ, Penman I. COVID-19 transmission following outpatient endoscopy during pandemic acceleration phase involving SARS-CoV-2 VOC 202012/01 variant in UK. Gut. 2021;70(12):2227–9.

25 Hayee B, SCOTS project group, East J, Rees CJ, Penman I. Multicentre prospective study of COVID-19 transmission following outpatient GI endoscopy in the UK. Gut. 2021; 70(5):825–8.
26 Peña-Rey I, Almazán R, Rodríguez-Camacho E, Cubiella J. Resumption of endoscopy in the Galician colorectal cancer screening programme after the COVID-19 lock down: patient safety results. Rev Esp Enferm Dig. 2021; 113(2):119–21.
27 Huang Q, Liu G, Wang J, Duan T, Feng Y, Lin X, et al. Control measures to prevent coronavirus disease 2019 pandemic in endoscopy centers: multi-center study. Dig Endosc. 2020;32(6):914–20.
28 Repici A, Aragona G, Cengia G, Cantù P, Spadaccini M, Maselli R, et al. Low risk of COVID-19 transmission in GI endoscopy. Gut. 2020;69(11):1925–7.
29 Jagannath S, Agarwal A, Gunjan D, Mohindra S, Sharma V, Chowdhury SD, et al. Mandatory pre-procedure testing for SARS-CoV-2 for all-comers may not be required for resuming endoscopic services amidst the ongoing COVID-19 pandemic. Gut. 2021;70(9):1805–6.
30 D'Ovidio V, Lucidi C, Bruno G, Lisi D, Miglioresi L, Bazuro ME. Impact of COVID-19 pandemic on colorectal cancer screening program. Clin Colorectal Cancer. 2021;20(1):e5–11.
31 Callaway E. Delta coronavirus variant: scientists brace for impact. Nature. 2021;595(7865): 17–8.
32 Krause PR, Fleming TR, Longini IM, Peto R, Briand S, Heymann DL, et al. SARS-CoV-2 variants and vaccines. N Engl J Med. 2021; 385(2):179–86.
33 Sultan S, Siddique SM, Singh S, Altayar O, Caliendo AM, Davitkov P, et al. AGA rapid review and guideline for SARS-CoV2 testing and endoscopy post-vaccination: 2021 update. Gastroenterology. 2021;161(3):1011–29.e11.
34 Muller CP. Do asymptomatic carriers of SARS-CoV-2 transmit the virus? Lancet Reg Health Eur. 2021;4:100082.

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Secondary Sclerosing Cholangitis in a Critically Ill Patient with Severe SARS-CoV-2 Infection: A Possibly Emergent Entity during the Current Global Pandemic

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Keywords
Secondary sclerosing cholangitis · Critical care · Cholestasis · Biliary casts · SARS-CoV-2 · COVID-19

Summary
A 46-year-old woman without previous history of hepatobiliary disease was admitted to the intensive care unit due to SARS-CoV-2 infection. Admission blood tests revealed impending hyperinflammation in the context of systemic inflammatory response syndrome. She required 12 days of mechanical ventilation and vasopressor support. After admission, liver function tests became deranged in a cholestatic pattern and continued to worsen despite overall clinical improvement. Magnetic resonance cholangiopancreatography revealed liver abscesses, intrahepatic bile duct dilation with multiple strictures and some linear repletion defects at the bifurcation of the common hepatic duct. During endoscopic retrograde cholangiopancreatography, biliary casts were retrieved confirming the diagnosis of secondary sclerosing cholangitis in the critically ill patient triggered by a severe SARS-CoV-2 infection. Other causes of cholestasis and secondary sclerosing cholangitis were properly excluded. We present an illustrative case and discuss the current literature, focusing on SARS-CoV-2 infection contribution to the development of this potentially underdiagnosed and severe condition.

Colangite esclerosante secundária num doente crítico com infeção grave por SARS-CoV-2: uma possível entidade emergente no contexto pandémico atual

Palavras Chave
Colangite esclerosante secundária · Doente crítico · Colestase · Cilindros biliares · SARS-CoV-2 · COVID-19

Resumo
Uma mulher de 46 anos sem antecedentes de patologia hepatobiliar foi admitida na unidade de cuidados intensivos no contexto de infeção por SARS-CoV-2. Apresentava alterações analíticas interpretadas no contexto de síndrome de resposta inflamatória sistémica. Houve necessidade de suporte vasopressor e ventilação mecânica invasiva durante 12 dias. Após a admissão, verificou-se

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uma alteração das provas hepáticas com padrão colestático, com agravamento contínuo apesar da melhoria do quadro infecioso. A colangiografia por ressonância magnética revelou a presença de abcessos hepáticos, dilatação das vias biliares intrahepáticas com múltiplas estenoses e com alguns defeitos de repleção lineares na bifurcação do ducto hepático comum. Na colangiopancreatografia endoscópica retrógrada foram removidos cilindros bilares da via biliar, confirmando o diagnóstico de colangite esclerosante secundária associada aos cuidados intensivos, no contexto de uma infeção grave por SARS-CoV-2. Foram excluídas outras causas de colestase e colangite esclerosante secundária de forma exaustiva. Apresentamos um caso clínico ilustrativo com respetiva iconografia e revisão da literatura, com especial enfoque na contribuição da infeção por SARS-CoV-2 no desenvolvimento desta entidade clínica, potencialmente grave e subdiagnosticada.

Background

Secondary sclerosing cholangitis (SSC) is a severe disease characterized by progressive injury to bile ducts inflicted by autoimmune mechanisms, infections, drugs, ischemia, or obstruction [1]. SSC in critically ill patients (SSC-CIP) is a rare form of SSC first described in 2001 [2]. It is frequently underdiagnosed, since half of the patients die before a diagnosis can be made [1].

SSC-CIP manifests as cholestasis in critically ill patients with no prior history of hepatobiliary disease and no known pathologic process of injury responsible for bile duct obstruction [3]. The feature that distinguishes this entity in the intensive care unit (ICU) setting is the persistence of cholestasis beyond clinical recovery, reflecting irreversible anatomical damage. As such, prognosis is poor, and patients end up developing acute liver failure during ICU stay or progressive cholestasis rapidly progressing to biliary cirrhosis [1].

There has been a greater awareness of this underdiagnosed condition in the last years, reflected in the number of published literature case reports. We present a case of SSC-CIP precipitated by a severe SARS-CoV-2 infection during the current global pandemic, thereby creating an excellent learning opportunity about these two entities and promoting SSC-CIP early recognition in the critically ill patient.

Case Presentation

A previously healthy 46-year-old woman was admitted to the ICU with a 1-week history of progressively worse cough and breathlessness in the context of known SARS-CoV-2 infection. She had a medical history of hypertension and class III obesity (BMI 44 kg/m^2). Admission blood tests revealed lymphopenia 920/L, d-dimers >32.50 mg/L, ferritin 2,371 μg/L, C-reactive protein 15.72 mg/dL, procalcitonin 0.87 ng/mL, troponin 2.08 μg/L, aspartate aminotransferase (AST) 54 UI/L, and lactate dehydrogenase 797 UI/L. The remaining liver function tests (LFTs) were normal. Chest computed tomography suggested SARS-CoV2 pneumonia with extensive lung involvement. Due to severe and refractory hypoxemia, the patient was sedated with propofol and ketamine and subsequently intubated and ventilated on the same day of admission. She was treated with dexamethasone and anticoagulated with enoxaparin.

During ICU stay, she had a period of hypotension that required vasopressor support for a period of less than 24 h. She was treated with a course of piperacillin-tazobactam that was later deescalated to amoxicillin-clavulanate for ventilator-associated pneumonia and bacteremia to *Klebsiella pneumoniae*. Prone ventilation was performed in four occasions and low volumes with high positive end-expiratory pressure were used. After weaning from sedation, she was successfully extubated after 12 days.

While in ICU, it was noted that the patient's LFTs were becoming deranged with a predominantly cholestatic pattern. Prothrombin time remained within normal range (Fig. 1).

The patient was discharged to the medical ward after clinical improvement. She was further treated with meropenem due to nosocomial urinary tract infection due to multidrug-resistant *Klebsiella pneumoniae*. Blood and urine cultures were later repeated and were negative. However, blood tests revealed continuous worsening of LFTs.

Investigations

An abdominal ultrasonography was performed after ICU discharge and revealed liver steatosis and hypoechoic hepatic nodules suggestive of non-pure cystic nature, suspicious for hepatic abscesses.

Abdominal computed tomography and magnetic resonance imaging with cholangiopancreatography (MRCP) revealed several nodules in the liver suggestive of abscesses and mild dilation of the intrahepatic bile ducts with multiple strictures and beaded appearance, suggestive of sclerosing cholangitis. At the bifurcation of the common hepatic duct (CHD), there was a linear and trilaminar repletion defect, raising the suspicion of sludge or parasite (Fig. 2). There was no involvement of the common bile duct.

An endoscopic retrograde cholangiopancreatography (ERCP) was performed, revealing irregular intrahepatic bile ducts along with an ill-defined lacunar image at the bifurcation of the CHD (Fig. 3).

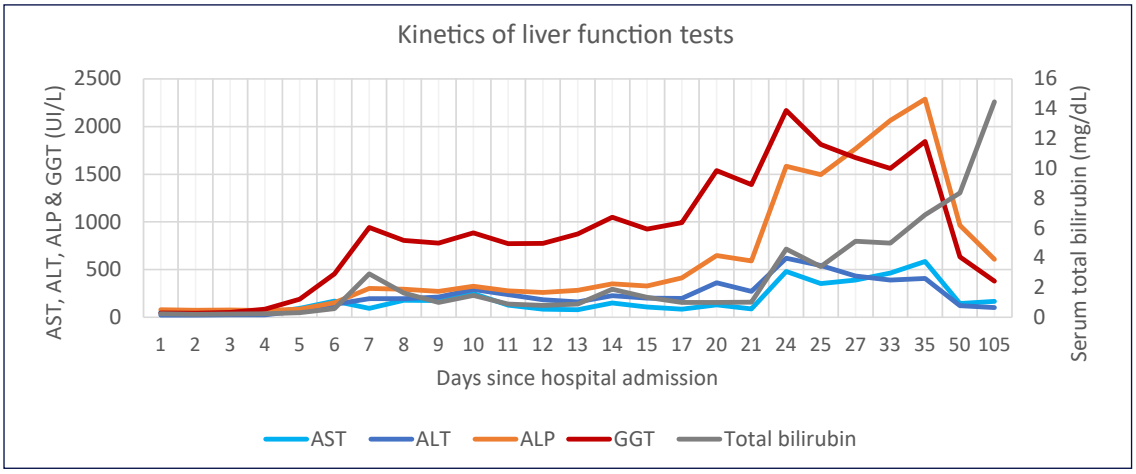

Fig. 1. Kinetics of liver function tests since hospital admission. AST, aspartate aminotransferase; ALT alanine aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyl transpeptidase.

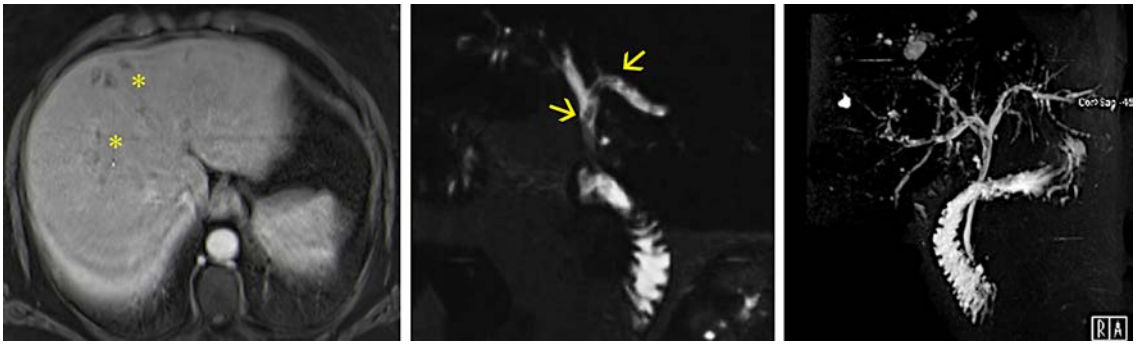

Fig. 2. Magnetic resonance imaging with cholangiopancreatography. Left – T1 portal venous phase with subcapsular clustered hypointense lesions with peripheral enhancement (*). These lesions had a hyperintense signal in the T2 sequence, suspected of microabscesses. Middle – cholangiographic T2 sequence, showing linear repletion defects at the bifurcation of the common hepatic duct (arrows). Right – cholangiographic 3D sequence showing dilation of intrahepatic bile ducts, with parietal irregularity, strictures, and post-stenotic dilations, suggesting sclerosing cholangitis.

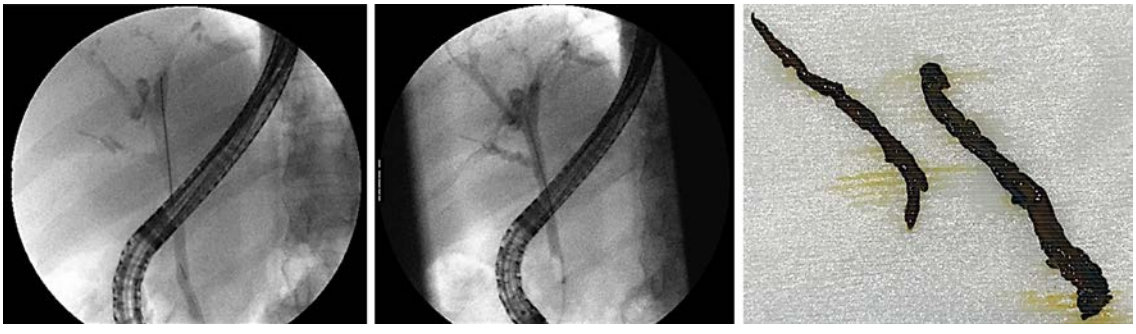

Fig. 3. Endoscopic retrograde cholangiopancreatography. Left – ERCP X-ray images after injection of contrast media, showing an ill-defined filling defect at the common hepatic duct bifurcation and irregular filling of intrahepatic bile ducts. Right – biliary casts that were retrieved from the common hepatic duct and left and right hepatic ducts, using an extraction balloon and a Dormia basket.

Serologies for human immunodeficiency virus, hepatitis B and C virus were negative. A panel of autoimmunity (including antinuclear, antimitochondrial, anti-smooth muscle, anti-liver-kidney microsomal and anti-neutrophilic cytoplasmic autoantibodies), immunoglobulin levels (including IgG-4 subclass), α1-antitrypsin and serum caeruloplasmin levels was within the normal range. The 24-h urinary copper was high, indicating cholestasis. Ferritin levels peaked at 11,924 μg/L, but transferrin saturation remained within normal values.

Serologies for Epstein-Barr, cytomegalovirus, *Entamoeba histolytica*, *Echinococcus granulosus* and *Fasciola hepatica* were negative.

Differential Diagnosis

During ICU stay, altered LFTs were thought to be the result of a combination of pathophysiological factors including SARS-CoV-2-induced systemic inflammatory response injury and drug-induced liver injury (DILI) associated with anesthetics and antibiotics. A conservative approach was taken at this point. However, despite respiratory insufficiency recovering, LFTs continued to deteriorate, and a pronounced worsening with a predominantly cholestatic pattern was seen 3 days after ICU discharge. There was no history of prior hepatobiliary disease that could have been decompensated by the current SARS-CoV-2 infection. DILI associated with anesthetics or antibiotics was a potential cause; however, it could not explain the magnitude of the cholestatic pattern and the lack of improvement upon discontinuation of potential causative drugs. Imaging played a decisive role, since MRCP revealed the presence of liver abscesses and irregularities in the intrahepatic bile ducts with beaded appearance, while excluding dilation of the main bile duct. Looking at the whole picture, a diagnosis of SSC-CIP was strongly suspected and later confirmed during ERCP after biliary cast removal.

Treatment

Patient was kept on meropenem once the radiological exams revealed liver abscesses; blood cultures were repeated on three occasions and were all negative, so no adjustments were made.

During ERCP, sphincterotomy was performed and biliary casts were retrieved from the left and right hepatic ducts using the extraction balloon and Dormia basket (Fig. 3). Histopathologic analysis supported the finding of biliary casts.

Outcome and Follow-Up

The patient was discharged 2 days after ERCP, after clinical improvement. Antibiotic therapy was continued with amoxicillin-clavulanate for another week, and the patient was started on ursodeoxycholic acid (UDCA).

Nine months after hospital discharge, LFTs revealed a decrease in cytocholestasis, while total bilirubin continues to rise (24 mg/dL). The patient has jaundice and pruritus that is amenable to medical therapy. MRCP was repeated at 3 and 8 months after discharge: there was complete resolution of liver abscesses and persistence of irregularity of intrahepatic bile ducts compatible with sclerosing cholangitis; however, signs of impending liver cirrhosis ensue with hepatosplenomegaly and caudate lobe hypertrophy. The patient is currently referred to the regional liver transplant center.

Discussion

SSC-CIP is a rare form of SSC first described in 2001 [2]. Since then, 250 cases have been reported and most of them in the last 6 years, reflecting increasing awareness of this condition [1].

The diagnosis of SSC-CIP is made when a cause for progressive bile duct damage and obstruction is identified in a critically ill patient admitted to the ICU with no prior history of hepatobiliary disease. While most patients with SARS-Cov-2 infection develop mild-to-moderate disease, our patient became critically ill and developed a systemic inflammatory response syndrome (SIRS), respiratory failure and acute respiratory distress syndrome (ARDS). These features are suggestive of a cytokine storm syndrome, in which hyperinflammation and multiorgan disease can arise through excessive cytokine release from uncontrolled immune activation [4].

Two major concepts are thought to be the underlying pathophysiological mechanisms of SSC-CIP: the "ischemic cholangiopathy" and the "toxic bile."

Ischemic Cholangiopathy

The biliary epithelium is prone to ischemic injury as a result of the blood irrigation supplied exclusively by branches of the hepatic artery, originating the peribiliary plexus. As such, disturbances of blood supply either at the level of the macro-circulation or microcirculation can trigger ischemic necrosis [5].

Hemodynamic instability with a decrease in mean arterial pressure <65 mm Hg was reported in 60–100% of patients with SSC-CIP [1], with a temporal relation be-

tween the onset of severe hypotension and development of cholestasis [5]. Epinephrine and norepinephrine frequently used in this context have a further dose-dependent negative effect on the perfusion of visceral organs [5]. Contrary to what was previously thought, even low doses of catecholamines and duration of catecholamines use or mechanical ventilation as short as only one day can trigger the development of SSC-CIP [5, 6].

Mechanical ventilation was reported in all patients with SSC-CIP [1]. High positive end-expiratory pressure (>10 cm H_2O), low tidal volumes and prone position have demonstrated negative effects on the microcirculation of the gastrointestinal tract in animal models [1, 5]. This strategy of ventilation was adopted in our patient since it is the one recommended to treat the SARS-CoV-2 associated ARDS [7]. Furthermore, obesity and prone ventilation appear to increase the risk of SSC-CIP in influenza A associated ARDS [8]. Therefore, both mechanical ventilation strategy and obesity have probably played a role for SSC-CIP development in our patient. Increased blood viscosity and hypercoagulable states can also compromise the microcirculation in the peribiliary plexus [5]. SIRS is a major contributor to SARS-Cov-2 associated coagulopathy, supporting the concept of thromboinflammation [9]. Such hypercoagulable state was clearly evident in our case (through a marked elevation in d-dimers), and that could also have contributed to biliary ischemic injury [5].

Toxic Bile

The lipid cellular membrane of cholangiocytes is protected from the detergent properties of hydrophobic bile acids by the hepatocellular secretion of phospholipids and the biliary secretion of HCO_3^- [5]. These cellular transport mechanisms can be compromised by proinflammatory cytokines, released in several clinical conditions such as SIRS/sepsis, trauma, burns, and major surgery [5]. Our patient was admitted with signs of impending hyperinflammation such as lymphopenia, elevated d-dimer, tissue damage/hepatitis (elevated lactate dehydrogenase, AST, and alanine aminotransferase), and macrophage/hepatocyte activation (elevated ferritin) [4]. Such SARS-CoV-2 induced SIRS, together with the period of severe hypotension (that can further induce SIRS via tissue ischemia), have probably contributed to the disruption of these protective mechanisms. Ischemia can also directly downregulate hepatobiliary transporters [5].

Bile duct damage in SSC-CIP can be a very early event, manifesting within the first 5 days of ICU admission through a rise in cholestatic enzymes [10]. Gamma-glutamyl transpeptidase is the first enzyme to become elevated peaking at 20–50 times the upper limit of normal (ULN), followed by alkaline phosphatase peaking at 5–21 times the ULN and later by bilirubin; AST and alanine aminotransferase can be moderately elevated (up to 20 and 9 times the ULN, respectively, in one case series) [10]. This pattern of abnormal LFTs was seen in our patient (Fig. 1). Of note, liver impairment has been reported in up to 53% of patients with SARS-CoV-2 infection reflecting hepatic involvement by a severe systemic inflammatory disease, although direct viral injury to hepatocytes cannot be excluded [11, 12]. However, SARS-CoV-2-associated LFT elevation occur predominantly in a hepatocellular pattern [11, 13, 14].

The differential diagnosis for cholestasis in the ICU setting is extensive, including sepsis, total parenteral nutrition, choledocholithiasis/cholangitis, DILI, and hypoxic liver injury [1]. A final diagnosis of SSC-CIP can only be established by imaging. Typical MRCP findings include filling defects in the intrahepatic biliary tree with diffuse strictures with beaded appearance appearing in later stages. ERCP remains the gold-standard method, allowing for biliary casts removal [1]. Importantly, the distal common bile duct is preserved in SSC-CIP, due to its dual blood supply (originating from the hepatic artery and gastroduodenal artery), differentiating it from other potential causes of SSC. Furthermore, biliary casts are exclusively seen in SSC-CIP and ischemia-induced SSC. These two entities can be distinguished from each other by the presence of extrahepatic bile duct involvement and a predominantly hepatocellular pattern in LFTs, which are only seen in ischemia-induced SSC [1].

SSC-CIP has a dismal prognosis, with mortality rates as high as 50% during ICU stay [1]. In a reported series, 38% of patients who survived rapidly progressed to cirrhosis in 18 months [15].

Antibiotic and endoscopic therapy with endoscopic dilation, sphincterotomy and sludge extraction were performed in most reported patients [15]. The addition of UDCA to endoscopic therapy seems to contribute to LFT normalization [16]. Once cirrhosis develops, orthotopic liver transplant (OLT) is the only curative treatment and outcomes seem comparable to other indications of OLT, with 1-, 3-, and 5-year survival rate of 85–100%, 83–86%, and 76%, respectively [10].

Learning Points

- SSC-CIP is a rare form of SSC that must be considered in critically ill patients with no previous history of hepatobiliary disease that develop persistent cholestasis

- Hemodynamic instability, mechanical ventilation and SIRS are among the most important triggers for its development
- Severe SARS-CoV-2 infection alone can cause a derangement in LFTs in a predominantly hepatocellular pattern and tend to follow the disease course
- Typical findings in MRCP are required for the diagnosis of SSC-CIP, including the presence of filling defects in the intrahepatic biliary tree and diffuse strictures with beaded appearance in later stages;
- Removal of biliary casts during ERCP further supports the diagnosis of SSC-CIP, although they can also be seen in ischemia-induced SSC (which can be distinguished by the involvement of extrahepatic bile ducts and by a predominantly hepatocellular pattern in LFTs).

Statement of Ethics

Patient's written informed consent to publish her case (including publication of images) was obtained.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

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Author Contributions

All authors participated in the management of the patient, with R.L. undertaking the ERCP specifically; B.M. reviewed the literature and drafted the manuscript; C.P. revised the final manuscript. All authors reviewed and approved the final version of the manuscript.

References

1 Martins P, Verdelho Machado M. Secondary sclerosing cholangitis in critically ill patients: an underdiagnosed entity. GE Port J Gastroenterol. 2020;27(2):103–14.
2 Scheppach W, Druge G, Wittenberg G, Mueller JG, Gassel AM, Gassel HJ, et al. Sclerosing cholangitis and liver cirrhosis after extrabiliary infections: report on three cases. Crit Care Med. 2001;29(2):438–41.
3 Gudnason HO, Björnsson SE. Secondary sclerosing cholangitis in critically ill patients: current perspectives. Clin Exp Gastroenterol. 2017;23(10):105–11.
4 Henderson LA, Canna SW, Schulert GS, Volpi S, Lee PY, Kernan KF, et al. On the alert for cytokine storm: immunopathology in COVID-19. Arthritis Rheumatol. 2020;72(7):1059–63.
5 Leonhardt S, Veltzke-Schlieker W, Adler A, Schott E, Hetzer R, Schaffartzik W, et al. Trigger mechanisms of secondary sclerosing cholangitis in critically ill patients. Crit Care. 2015;19(1):131.
6 Laurent L, Lemaitre C, Minello A, Plessier A, Lamblin G, Poujol-Robert A, et al. Cholangiopathy in critically ill patients surviving beyond the intensive care period: a multicentre survey in liver units. Aliment Pharmacol Ther. 2017;46(11–12):1070–6.
7 Parasher A. COVID-19: current understanding of its pathophysiology, clinical presentation and treatment. Postgrad Med J. 2021 May;97(1147):312–320.
8 Weig T, Schubert MI, Gruener N, Dolch ME, Frey L, Miller J, et al. Abdominal obesity and prolonged prone positioning increase risk of developing sclerosing cholangitis in critically ill patients with influenza A-associated ARDS. Eur J Med Res. 2012;17(1):30.
9 Masi P, Hékimian G, Lejeune M, Chommeloux J, Desnos C, De Chambrun MP, et al. Systemic inflammatory response syndrome is a major contributor to COVID-19-associated coagulopathy: insights from a prospective, single-center cohort study. Circulation. 2020;142(6):611–4.
10 Leonhardt S, Veltzke-Schlieker W, Adler A, Schott E, Eurich D, Faber W, et al. Secondary sclerosing cholangitis in critically ill patients: clinical presentation, cholangiographic features, natural history, and outcome: a series of 16 cases. Medicine. 2015;94(49):e2188.
11 Zhang C, Shi L, Wang F-S. Liver injury in COVID-19: management and challenges. Lancet Gastroenterol Hepatol. 2020;5(5):428–30.
12 Philips CA, Ahamed R, Augustine P. SARS-CoV-2 related liver impairment: perception may not be the reality. J Hepatol. 2020;73(4):991–2.
13 Kumar A, Kumar P, Dungdung A, Kumar Gupta A, Anurag A, Kumar A. Pattern of liver function and clinical profile in COVID-19: a cross-sectional study of 91 patients. Diabetes Metab Syndr Clin Res Rev. 2020;14(6):1951–4.
14 Da BL, Mitchell RA, Lee BT, Perumalswami P, Im GY, Agarwal R, et al. Kinetic patterns of liver enzyme elevation with COVID-19 in the USA. Eur J Gastroenterol Hepatol. 2020;32(11):1466–9.
15 Katsinelos P, Kountouras J, Chatzimavroudis G, Zavos C, Pilpilidis I, Paroutoglou G. Combined endoscopic and ursodeoxycholic acid treatment of biliary cast syndrome in a non-transplant patient. World J Gastroenterol. 2008;14(33):5223–5.
16 Voigtländer T, Jaeckel E, Lehner F, Manns MP, Lankisch TO. Liver transplantation for critically ill patients with secondary sclerosing cholangitis: outcome and complications. Liver Transpl. 2015;21(10):1295–9.

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Mediastinal Abscess Formation after EUS-Guided Sampling in a Young Patient with Sarcoidosis: Be Aware of the Increased Risk!

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Keywords
Endoscopic ultrasound-guided sampling · Mediastinal abscess · Mediastinitis · Sarcoidosis

Abstract
International guidelines establish EUS-guided sampling as safe and accurate for the evaluation of mediastinal solid lesions, such as lymphadenopathies of unknown origin, and point out an increased risk of severe infectious complications induced by needle puncture in mediastinal cystic lesions. A retrospective case series and a systematic review documented an increased risk of mediastinal abscess formation after EUS-guided lymph nodes sampling in patients with sarcoidosis. The authors describe a case of a 38-year-old male patient with a final diagnosis of sarcoidosis, who developed a large mediastinal abscess after EUS-guided fine-needle biopsy of mediastinal lymphadenopathies. Endoscopists should be aware of the potential increased risk of severe infectious complications when sampling mediastinal lymph nodes in suspected sarcoidosis, and a strategy to minimize such risk should be pursued.

Abcesso mediastínico após biopsia guiada por ecoendoscopia num doente jovem com sarcoidose: atenção ao risco acrescido!

Palavras Chave
Abcesso mediastínico · Biopsia guiada por ecoendoscopia · Mediastinite · Sarcoidose

Resumo
As normas de consenso internacionais estabelecem a biopsia guiada por ecoendoscopia como segura e precisa no diagnóstico de lesões sólidas do mediastino, tais como adenopatias de origem indeterminada, e sublinham o risco significativo de complicações infecciosas graves associado à punção de lesões mediastínicas quísticas. Uma série retrospectiva e uma revisão sistemática apontaram para um risco aumentado de abcesso mediastínico após punção guiada por ecoendoscopia de gânglios linfáticos em doentes com sarcoidose. Os autores descrevem o caso cínico de um jovem de 38 anos, com o diagnóstico final de sarcoidose, que desenvolveu um volumoso abcesso mediastínico após biopsia guiada por ecoendoscopia de adenopatias mediastínicas. Os endoscopistas deverão reconhecer o risco aumentado de complicações infeciosas graves aquando da punção de adenopatias mediastínicas na suspeita de sarcoidose e procurar definir uma estratégia preventiva para minimizar o referido risco.

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Introduction

Endoscopic ultrasound (EUS)-guided sampling is regarded as a safe and accurate diagnostic tool for the evaluation of mediastinal lymphadenopathies and masses of unknown origin [1]. The overall incidence of adverse events associated to EUS-guided puncture is very low, and the most common adverse event is infection (pooled infection rate, 0.4–1.7%), which is significantly higher for cystic lesions compared to solid ones [2, 3]. Limited evidence is available regarding patient-related risk factors of adverse events associated to EUS-guided sampling [2]. Awareness of such risk factors is crucial in the decision-making process of sampling (when and how to puncture), in the definition of preventive strategies, and in the optimization of the informed consent process. The only well-established risk factor for infection associated to EUS-guided sampling is the puncture of cystic lesions (specifically, pancreatic cysts or mediastinal cysts) [2]. Data from a large retrospective series, including 252 patients with sarcoidosis, documented an increased risk for mediastinal abscess formation and mediastinitis after EUS-guided sampling in patients with sarcoidosis (30-fold higher than for other indications for EUS-guided nodal sampling in the mediastinum) [4]. The authors describe a case of a young patient with a final diagnosis of sarcoidosis, who developed a large mediastinal abscess after EUS-guided fine-needle biopsy (FNB) and discuss potential preventive measures to avoid such severe complication.

Case Report

A 38-year-old man with a past history of a surgically removed duodenal GIST (AJCC stage 1, R0) was referred for EUS-guided sampling for characterization of several enlarged mediastinal lymph nodes, documented on computed tomography (CT). The patient was asymptomatic and had no lung lesions or abdominal lymphadenopathies on CT. EUS documented several coalescent, crescent-shaped lymph nodes in the posterior mediastinum, with a hypoechogenic homogeneous pattern, the largest with 35 × 17 mm in the subcarinal station (Fig. 1). FNB was performed using a 22-gauge fork-tip needle (SharkCore; Medtronic, Sunnyvale, CA), with three dedicated passes (until obtaining a macroscopic visible whitish core), using the fanning and stylet retraction techniques. Polymerase chain reaction for *Mycobacterium tuberculosis* and assessment of clonal B cell populations by flow cytometry were negative, and noncaseating granulomas with multinucleated giant cells, compatible with sarcoidosis, were documented on pathology (Fig. 2). Two weeks after EUS-FNB, the patient was admitted due to increasing retrosternal pain, fever (39°C), and progressive dysphagia. Serum inflammatory markers were elevated, and chest CT revealed a large subcarinal mass (54 × 45 mm) with heterogeneous liquefactive areas, consistent with a mediastinal abscess, in continuity with a thickened esophageal wall (Fig. 3). The patient was treated with intravenous meropenem for 7 days, followed by prolonged (4 week) oral treatment with ciprofloxacin (750 mg b.i.d.) and metronidazole (500 mg t.i.d.), with progressive clinical improvement and recovering completely. Treatment duration was based on previously reported cases, where noninvasively treated patients required prolonged (at least 4-week course) antibiotic therapy [4, 5].

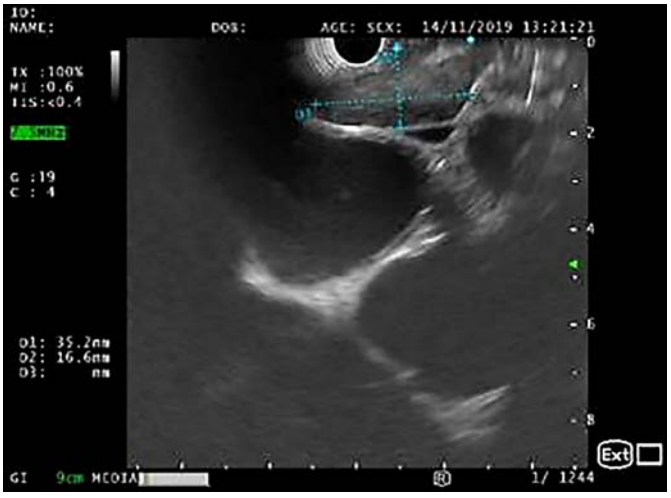

Fig. 1. EUS (linear array, transesophageal view – station 7): crescent-shaped lymph node, with 35 × 17 mm and a hypoechogenic homogeneous echo pattern.

Discussion

Current guidelines point out a higher risk of infection after EUS-guided sampling of mediastinal cystic lesions rather than of solid lesions [1–3]. As mediastinal abscess and mediastinitis are associated to high morbidity and potential mortality, EUS-guided sampling of mediastinal cysts is globally discouraged and should be restricted to carefully selected cases [1–3]. In patients undergoing EUS-guided sampling of any cystic lesion, prophylactic antibiotic administration is recommended [1–3]. Although infection prophylaxis is not advocated for EUS-guided sampling of solid lesions (as the pooled infection rate is very low) [1–3], a retrospective case series [4] and a systematic review [5] documented an increased risk of infection, with mediastinal abscess formation, after EUS-guided puncture of lymph nodes in patients with sarcoidosis.

Sarcoidosis is a granulomatous disease affecting mostly young adults and presenting with mediastinal or hilar lymphadenopathies in 85% of cases [4]. In suspected sarcoidosis, EUS-guided sampling of mediastinal nodes is increasingly being used as it demonstrated to have higher diagnostic yield when compared to con-

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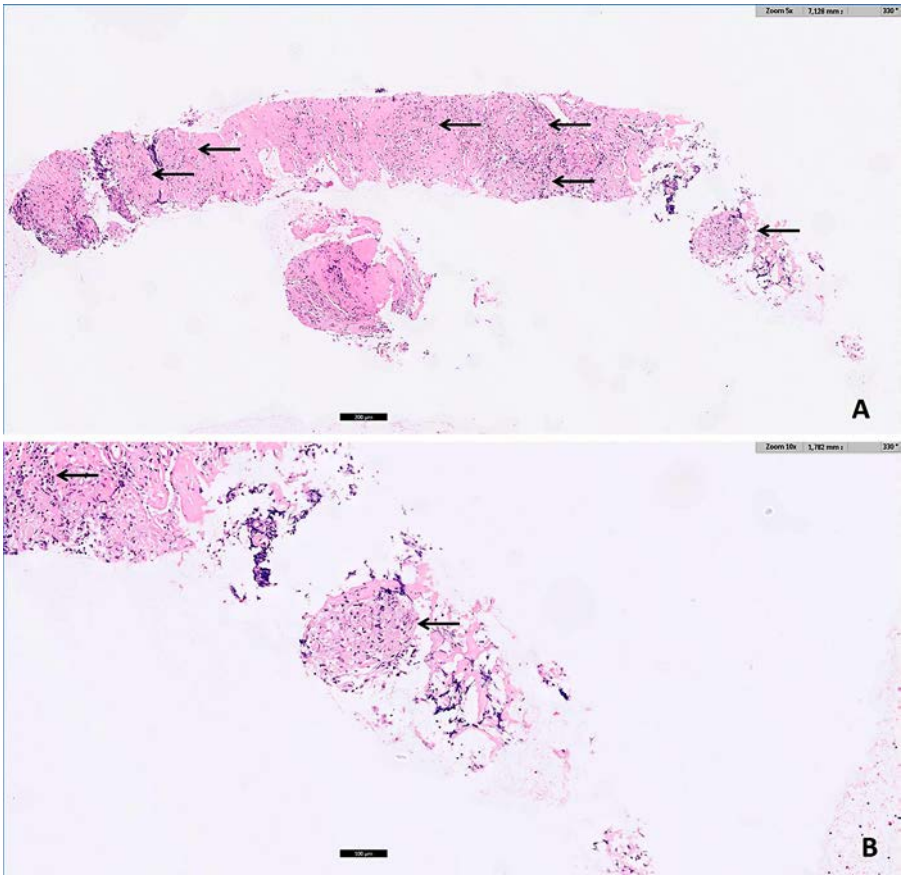

Fig. 2. Pathology (**A** H&E, ×5; **B** H&E, ×10): noncaseating epithelioid granulomas (arrows) with multinucleated giant cells, in a fibrotic stroma, compatible with sarcoidosis.

ventional bronchoscopy with transbronchial and endobronchial biopsies in the so-called Granuloma trial [6] and a similar diagnostic yield when compared to endobronchial ultrasound-guided sampling in the multicenter International Sarcoidosis Assessment (ISA) trial [7] (even though only first- and second-generation FNB needles were used in the EUS arm [7]). In a large series of 252 patients with the final diagnosis of sarcoidosis undergoing EUS-guided sampling, 5 patients developed mediastinal abscesses and 4 of those patients required surgical drainage [4]. This corresponded to a 30-fold higher incidence of nodal infection after EUS-guided puncture in patients with sarcoidosis compared to patients submitted to mediastinal node sampling for other indications (mostly for lung cancer staging) in the same institution [4]. An increased risk for infection after lymph node puncture in patients with sarcoidosis (caused by iatrogenic inoculation of commensal flora by the needle) may be related to the distribution of regulatory T-cells at the periphery of sarcoid granulomas, which may account for the state of anergy (poor re-

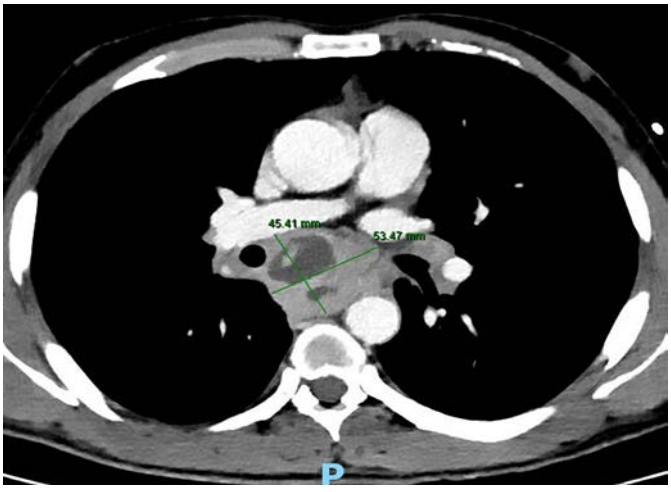

Fig. 3. Axial contrast-enhanced CT (mediastinal window): large subcarinal mass (54 × 45 mm) with heterogeneous liquefactive areas in continuity with a thickened esophageal wall.

sponse to antigens in vitro and in vivo) that characterizes sarcoidosis [8]. Endoscopists should be aware of the potentially increased risk of infection when sampling mediastinal lymph nodes in suspected sarcoidosis and a strategy to minimize such risk should be followed, although current guidelines do not yet consider this issue. An easy strategy to minimize the infection risk may be reducing the number of needle passes, by selecting a third-generation (frontal cutting) FNB needle (with a higher diagnostic yield per pass), and using on-site evaluation to confirm sample adequacy and the presence of granulomas, thus dismissing additional passes [9–11]. The use of prophylactic antibiotics for EUS-guided mediastinal lymph node puncture in suspected sarcoidosis should also be considered, and this approach is presently followed by the authors, using an antibiotic regimen similar to the one recommended for cystic lesions puncture [2, 3]. The low frequency of infection after lymph node sampling in the suspicion of sarcoidosis (~2% [4]) would require large numbers in trials to achieve adequate statistical power, and prospective studies validating the potential benefit of antibiotic prophylaxis in this setting are unlikely to be undertaken. Since endobronchial ultrasound-guided sampling seems to have a negligible risk of infection in sarcoidosis, which may be related to a lower contamination rate of commensal flora by the needle through the respiratory tract, this sampling route may be considered in this setting [5, 7].

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The authors would like to thank Dr. António Galzerano for providing histopathological images of this clinical case.

Statement of Ethics

Written informed consent was obtained from the patient for publication of this case report (including publication of images).

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Drafting of the manuscript: M.B. Literature review, critical revision of the manuscript, and approval of the final version to be published: all listed authors.

Data Availability Statement

All data analyzed during this study are included in the article. Further inquiries can be directed to the corresponding author.

References

1 Dumonceau JM, Deprez PH, Jenssen C, Iglesias-Garcia J, Larghi A, Vanbiervliet G, et al. Indications, results, and clinical impact of endoscopic ultrasound (EUS)-guided sampling in gastroenterology: European Society of Gastrointestinal Endoscopy (ESGE) clinical guideline – updated January 2017. Endoscopy. 2017;49(7):695–714.

2 ASGE Standards of Practice Committee, Forbes N, Coelho-Prabhu N, Al-Haddad MA, Kwon RS, Amateau SK, et al. Adverse events associated with EUS and EUS-guided procedures. Gastrointest Endosc. 2022;95(1):16–26.e2.

3 ASGE Standards of Practice Committee, Khashab MA, Chithadi KV, Acosta RD, Bruining DH, Chandrasekhara V, et al. Antibiotic prophylaxis for GI endoscopy. Gastrointest Endosc. 2015;81(1):81–9.

4 von Bartheld M, van der Heijden E, Annema J. Mediastinal abscess formation after EUS-guided FNA: are patients with sarcoidosis at increased risk? Gastrointest Endosc. 2012;75(5):1104–7.

5 von Bartheld MB, van Breda A, Annema JT. Complication rate of endosonography (endobronchial and endoscopic ultrasound): a systematic review. Respiration. 2014;87(4):343–51.

6 von Bartheld MB, Dekkers OM, Szlubowski A, Eberhardt R, Herth FJ, 't Veen JCCM, et al. Endosonography vs conventional bronchoscopy for the diagnosis of sarcoidosis: the GRANULOMA randomized clinical trial. JAMA. 2013;309(23):2457–64.

7 Crombag LMM, Mooij-Kalverda K, Szlubowski A, Gnass M, Tournoy KG, Sun J, et al. EBUS versus EUS-B for diagnosing sarcoidosis: the International Sarcoidosis Assessment (ISA) randomized clinical trial. Respirology. 2022;27(2):152–60.

8 Miyara M, Amoura Z, Parizot C, Badoual C, Dorgham K, Trad S, et al. The immune paradox of sarcoidosis and regulatory T cells. J Exp Med. 2006;203(2):359–70.

9 Bang JY, Kirtane S, Krall K, Navaneethan U, Hasan M, Hawes R, et al. In memoriam: fine-needle aspiration, birth – fine-needle biopsy – the changing trend in endoscopic ultrasound-guided tissue acquisition. Dig Endosc. 2019;31(2):197–202.

10 Tanisaka Y, Mizuide M, Fujita A, Ogawa T, Araki R, Suzuki M, et al. Comparison of endoscopic ultrasound-guided fine-needle aspiration and biopsy device for lymphadenopathy. Gastroenterol Res Pract. 2021;2021:6640862.

11 Chen YI, Chatterjee A, Berger R, Kanber Y, Wyse J, Lam E, et al. Endoscopic ultrasound (EUS)-guided fine needle biopsy alone vs. EUS-guided fine needle aspiration with rapid onsite evaluation in pancreatic lesions: a multicenter randomized trial. Endoscopy. 2022;54(1):4–12.

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Gastroduodenal and Colorectal Tuberculosis: Report of 2 Cases

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Keywords
Tuberculosis · Gastrointestinal tuberculosis · Gastroscopy · Stomach ulcer

Abstract
Introduction: Tuberculosis remains a public health concern in developing countries, as well as in developed countries as a result of immigration from endemic areas. Gastroduodenal and colorectal tuberculosis are rare manifestations of gastrointestinal infection. ***Case Presentation:*** We present 2 cases of gastric, duodenal, and colorectal tuberculosis. The first case, a 17-year-old male with no medical record, presented with chronic diarrhea and abdominal pain. At endoscopy, he had multiple ulcers in the stomach, colon, and rectum, which were positive to *Mycobacterium tuberculosis*. The second case was a 43-year-old HIV-positive male, with a history of intermittent fever, nausea, and vomiting. Upper gastrointestinal endoscopy revealed a deep ulcer on gastric fundus that tested positive to *M. tuberculosis* in the acid-fast bacilli staining. ***Discussion/Conclusion:*** Gastroduodenal and colorectal tuberculosis, although rare, should be considered in the differential diagnosis in both immunosuppressed and immunocompetent patients. An adequate tissue sample and appropriate diagnostic tests are essential for the diagnosis and prompt start of first-line antituberculosis agents.

Tuberculose gastroduodenal e retal: relato de 2 casos

Palavras·Chave
Tuberculose · Gastrointestinal · Gastroscopia · Úlcera estomacal

Resumo
Introdução: A tuberculose continua sendo um problema de saúde pública nos países em desenvolvimento, bem como nos países desenvolvidos, em decorrência da imigração. A tuberculose gastroduodenal e colorretalsão manifestações raras de infecção gastrointestinal. ***Apresentação do Caso:*** Apresentamos dois casos de tuberculose gástrica, duodenal ecolorretal. O primeiro caso, um jovem de 17 anos, apresentou diarreia crônica e dor abdominal. Na endoscopia, tinha múltiplas úlceras no estômago, cólon e reto que foram positivas para Mycobacterium Tuberculosis. O segundo caso foi um homem de 43 anos, HIV positivo, com relato de febre intermitente, náuseas e vômitos. A endoscopia digestiva alta revelou úlcera profunda do fundo gástrico positivo para *Mycobacterium tuberculosis* na coloração de bacilos álcool-ácido resistentes. ***Discussão/Conclusão:*** Tuberculosegastroduodenal e colorretal, embora raras, deve ser considerada como diagnóstico em pacientes imunossuprimidos e

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imunocompetentes. Uma amostra de tecido adequada e testes diagnósticos apropriados são essenciais para o diagnósticoe início imediato dos tuberculostáticos de primeira linha.

Introduction

Despite many advances in science in recent years, tuberculosis remains one of the leading causes of deaths worldwide, especially in developing countries [1]. Although pulmonary tuberculosis is the most common site of tuberculosis infection, abdominal tuberculosis is becoming more frequent, which includes involvement of the peritoneum, abdominal visceral organs, lymph nodes, and gastrointestinal tuberculosis [2]. In gastrointestinal tuberculosis, infection of the stomach and rectum is sparsely reported in the literature and has major limitations in its diagnosis [3]. We report 2 cases in immunocompetent and immunosuppressed patients who presented gastric, duodenal, and rectal ulcers due to *Mycobacterium tuberculosis* infection.

Case Report

Case1

We present the case of a 17-year-old male who presented to the emergency department with a 2-year history of cough, chronic abdominal pain, intermittent nausea and vomiting, non-bloody chronic diarrhea, and progressive weight loss up to 40 kg, equivalent to 45% of his body weight. On admission, vital signs were stable. On examination, the abdomen was tender to palpation with diffuse mild pain. No rebound was identified. Laboratory findings demonstrated hemoglobin of 8.7 g/dL (N = 13.2–16.6), mean corpuscular volume of 73 (N = 80–100), mean corpuscular hemoglobin of 22 (N = 27–32), and severe hypoalbuminemia of 2.3 g/dL (N ≥3.5). Biochemical and liver profiles were unremarkable. Human immunodeficiency virus and human T-cell lymphotropic virus 1 and 2 tests were negative. Functional stool test including presence of mucus, blood, polymorphonuclear leukocytes, lactoferrin, fat strains, and serial parasite analysis revealed no significant abnormalities; however, the plain chest X-ray showed apical infiltrates in both hemithorax (shown in Fig. 1). In the abdominal ultrasound, mild hepatomegaly was found without ascites. Endoscopic exams were mandatory for the patient. In the greater curvature of the gastric body, an irregular circumferential ulcer was identified with a diameter of 10 mm, elevated margins and a base with high-density fibrin (shown in Fig. 2). In the anterior wall of the duodenal bulb, a 0.5-mm orifice was present from which a scarce whitish discharge was obtained (shown in Fig. 3). In the colonoscopy evaluation, multiple irregular circumferential ulcers were seen, which involved the terminal ileum (shown in Fig. 4), ileocecal valve, cecum, colon (shown in Fig. 5, 6), and rectum (shown in Fig. 7). Biopsies obtained from the upper and lower lesions were positive to *M. tuberculosis* in the GeneXpert (MTB/RIF) assay, and no resistance to Rifampicin was detected. Histopathology revealed chronic granulomatous inflammation with multinucleated giant cells. First-line antituberculosis drugs were initiated with good clinical improvement. Positive culture results were obtained after 2 months. Informed consent was obtained from the patient for case and image publication.

Case 2

A 43-year-old male with a 2-month diagnosis of acquired immune deficiency syndrome without treatment (viral load of 280,000 copies/mL and a CD4 count of 67 cells/mm^3), presented with 6 months of intermittent fever, diffuse abdominal pain, progressive weight loss up to 10 kg (27% of his body weight), nausea,

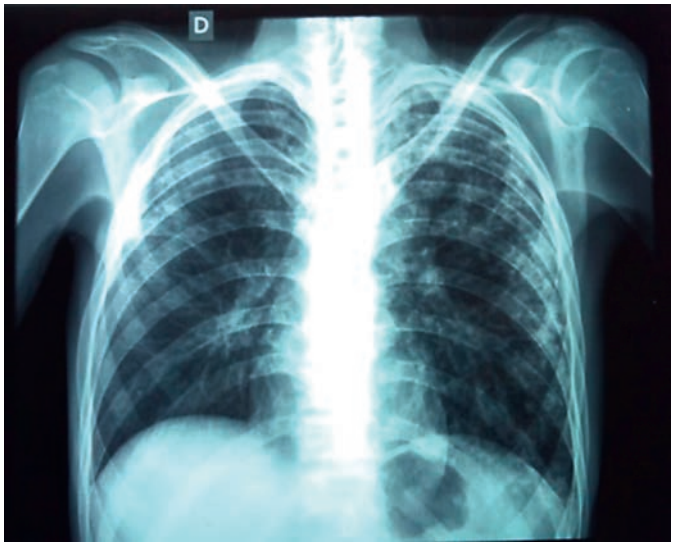

Fig. 1. Plain chest X-ray with apical infiltrates in both hemithorax.

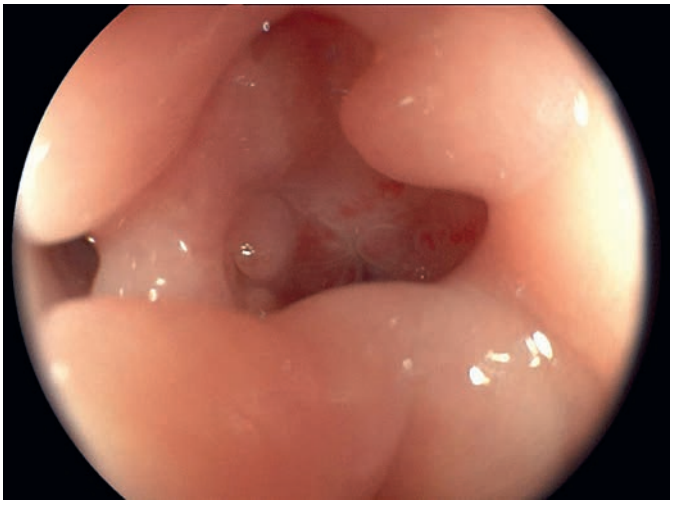

Fig. 2. Gastric irregular ulcer.

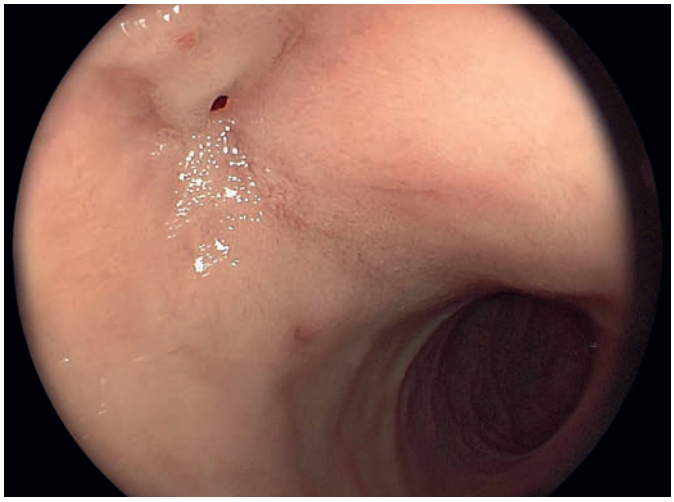

Fig. 3. Duodenal fistula with intermittent whitish discharge.

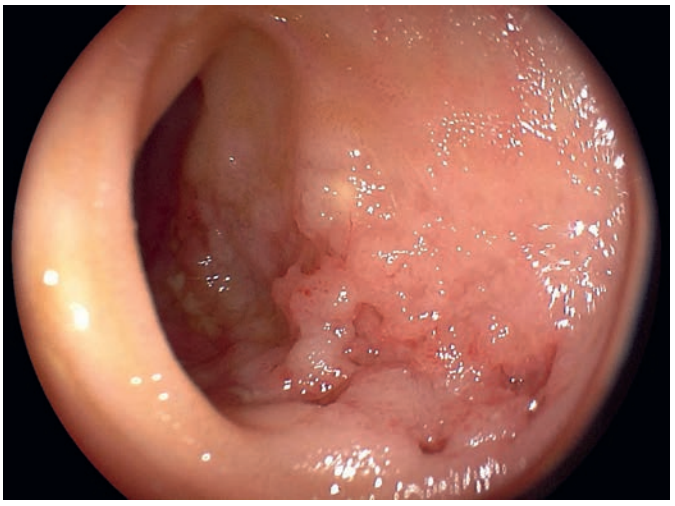

Fig. 4. Terminal ileum.

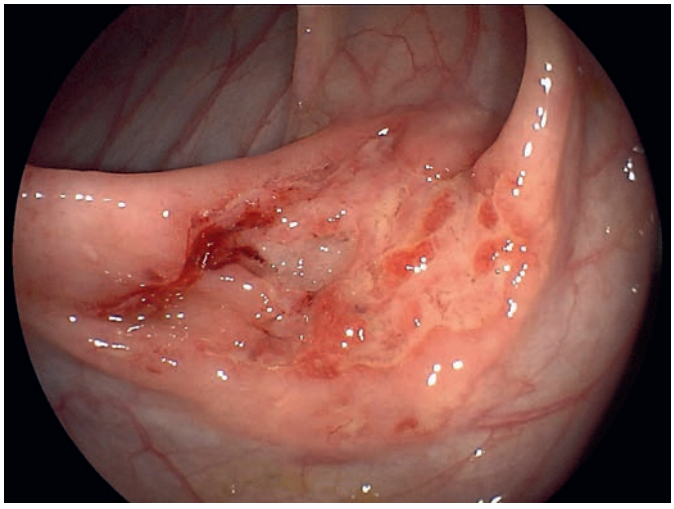

Fig. 5. Ascending colon ulcer.

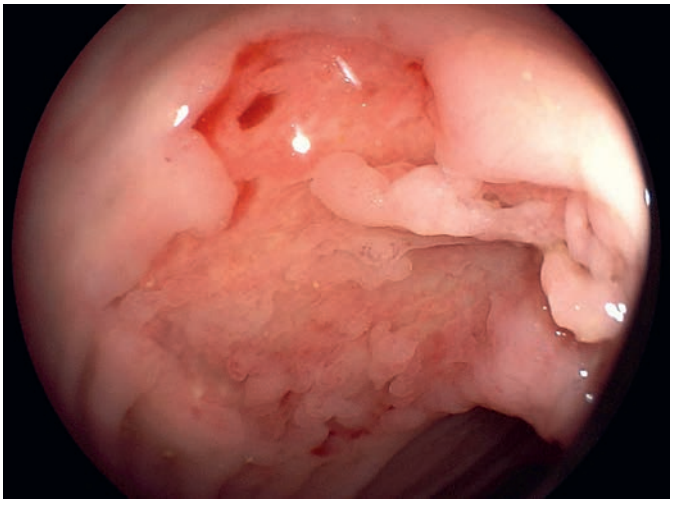

Fig. 6. Transverse colon ulcer.

and vomiting. On examination, the patient was febrile, pale, and emaciated. Hemoglobin of 9.4 g/dL (N = 13.2–16.6), mean corpuscular volume of 86 (N = 80–100), mean corpuscular hemoglobin of 29.2 (N = 27–32), and a non-pathogenic intestinal parasite, Entameba coli, in the parasitology exam were identified. The chest X-ray and sputum analysis were negative for tuberculosis. Abdominal computed tomography revealed retroperitoneal lymphadenopathy, splenomegaly, and a fluid collection in the psoas muscle of 2 cm with no need for drainage. Due to gastrointestinal symptoms such as nausea and vomiting, we decided to perform an upper gastrointestinal endoscopy. A deep irregular ulcer of 8 mm with a fibrin base was seen in the gastric fundus (shown in Fig. 8). Acid-fast bacilli staining in the biopsy was positive for *M. tuberculosis*. With the administration of first-line antituberculosis drugs, the patient had an optimal clinical recovery. Informed consent was obtained from the patient for case and image publication.

Discussion

Gastrointestinal tuberculosis is the most frequent site of affection in abdominal tuberculosis and can be a diagnostic challenge as it can mimic other illnesses as inflammatory bowel diseases, neoplasms, ischemic ulcers, and other infections [3, 4]. The most common affected sites are the ileum, cecum, and proximal colon. Gastric tuberculosis is an uncommon site of infection due to gastric acid that acts as a protective barrier against microorganisms; nevertheless, a high bacterial load can produce direct injury leading to infection. Other routes of contamination are hematogenous, retrograde lymphatic spread, and di-

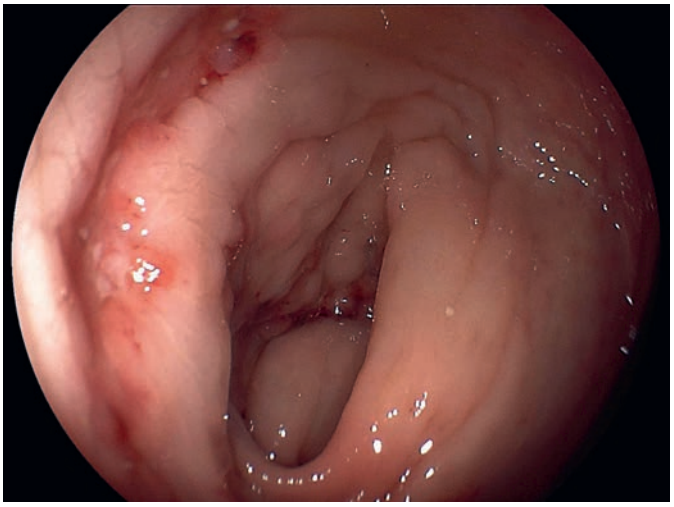

Fig. 7. Rectum ulcer.

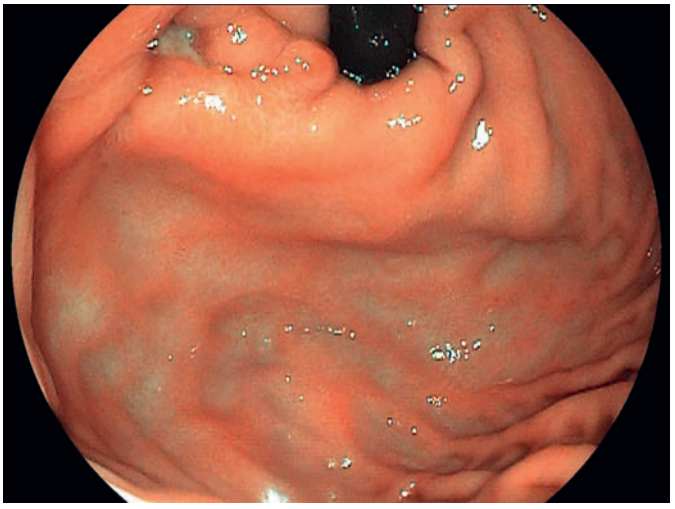

Fig. 8. Gastric fundus ulcer.

rect contact with affected adyacent organs [3, 5]. Symptoms are usually unspecific, ranging from non-specific abdominal pain, dyspepsia, weight loss, and anorexia [3]. Gastric tuberculosis can manifest endoscopically as multiple or single irregular ulcers, fistula formations, and hypertrophic-stenosing lesions, which can produce gastric outlet obstruction [6]. Ulcers are usually located in the lesser curve of the prepyloric region and antrum; however, fundic ulcers have also been described in the literature [7]. Our patients presented ulcers in the gastric corpus and fundus. These lesions were probably related to retrograde lymphatic spread that, although uncommon, has been reported before [3]. Duodenal tuberculosis should be suspected in areas with high endemicity of tuberculosis and can share some symptoms of gastric tuberculosis. In endoscopy or radiological exams, luminal narrowing, mucosal ulcerations, or extrinsic compressions might be seen. In some cases, patients require surgery due to stenosis of the duodenum, and the diagnosis is made postoperatively [8, 9]. Colonic tuberculosis involvement is being more frequently reported in the last years. It mainly affects the ascending colon and cecum, and symptoms can be unspecific as abdominal pain or present with hematochezia or diarrhea. In colonoscopy, lesions can present as ulcers, nodules, polypoid lesions, or luminal narrowing. These lesions usually respond satisfactorily to antituberculosis treatment [10]. On the other hand, rectal tuberculosis is rare and usually associated with immunosuppressive states [11]. Patients can present symptoms such as chronic diarrhea, rectal bleeding, tenesmus, and perineal fistulas, which can mimic an inflammatory bowel disease or cancer [12]. Our patient presented a linear ulcer in the rectum; however, nodular, stenotic, and hypertrophic lesions have been reported by authors before [11, 13].

Diagnosis is usually complicated due to the difficulty in getting an adequate tissue sample and the diagnostic test used. Different methods for diagnosis of gastrointestinal tuberculosis include acid-fast bacilli (AFB) staining, culture, GeneXpert MTB/RIF, and DNA-PCR. AFB is usually performed with the *Ziehl-Neelsen* method, is cost-effective, and has a specificity of 100%. However, the main disadvantage is its low sensitivity of around 31% [14]. Culture is the gold standard test; although it has a specificity of 100%, its sensitivity of only 9.3% can limit an accurate diagnosis [15]. GeneXpert MTB/RIF is a real-time PCR-based test that can also detect resistance to Rifampicin. Studies have shown high sensitivity values in biopsy samples ranging from 81.6 up to 95.7% and specificity from 78.9 to 100% [14, 16]. This test is considered one of the best for the diagnosis of gastrointestinal tuberculosis infection. Finally, DNA-PCR is also very effective with sensitivities up to 65% and specificity of 100% [14].

First-line treatment consists of isoniazid, rifampicin, ethambutol, and pyrazinamide. Administration of intravenous medication can be given in special situations as oral intolerance or adverse reactions [14]. Treatment length of 6 months has been suggested by most guidelines; however, some studies have suggested longer treatment might have better outcomes. In a systematic review published in 2016, no benefits were found in 9-month regimens versus the standard 6-month regimen. Until now, new recommendations cannot be made [17].

Gastrointestinal tuberculosis can manifest as a primary infection or in association with pulmonary tuberculosis in disseminated states. The coexistence between gastrointestinal and pulmonary tuberculosis ranges from 15 to 25%. The rest are reported to be isolated gastrointestinal tuberculosis; however, this number might be underestimated due to difficulties in diagnosing pulmonary tuberculosis. Treatment of pulmonary infection is adequate for gastrointestinal tuberculosis, and patients usually have a good prognosis [18, 19].

Gastroduodenal and colorectal tuberculosis, although rare, should be considered as a diagnosis in immunosuppressed and immunocompetent patients. An adequate tissue sample, which should be obtained from the edge and base of the ulcers, and appropriate diagnostic tests are essential for the diagnosis [20].

Statement of Ethics

Ethical approval was not required for this study in accordance with local/national guidelines. The subjects gave their informed consent for publication of their cases, including publication of images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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None to report.

Author Contributions

Claudia Alvizuri and Andrea Carlín wrote the manuscript and reviewed the literature. Víctor Aguilar and Vanessa Valenzuela edited the manuscript and approved the final manuscript.

Data Availability Statement

The data that support the findings of the two clinical case studies are available on request from the corresponding author (C. Alvizuri). No personal information was included to protect the participant's privacy.

References

1 Furin J, Cox H, Pai MM. Tuberculosis. Lancet. 2019 Apr 20;393(10181):1642–56.
2 Al-Zanbagi AB, Shariff MK. Gastrointestinal tuberculosis: a systematic review of epidemiology, presentation, diagnosis and treatment. Saudi J Gastroenterol. 2021 Sep–Oct;27(5):261–74.
3 Chaudhary P, Khan AQ, Lal R, Bhadana U. Gastric tuberculosis. Indian J Tuberc. 2019 Jul;66(3):411–7.
4 Eraksoy H. Gastrointestinal and abdominal tuberculosis. Gastroenterol Clin North Am. 2021 Jun;50(2):341–60.
5 Nayyar E, Torres JA, Malvestutto CD. Tuberculous gastric abscess in a patient with AIDS: a rare presentation. Case Rep Infect Dis. 2016;2016:5675036.
6 Manoria P, Gulwani HV. Gastric tuberculosis presenting as non healing ulcer: a case report. Indian J Tuberc. 2019 Oct;66(4):502–4.
7 Khan FY, AlAni A, Al-Rikabi A, Mizrakhshi A, Osman ME-M. Primary gastric fundus tuberculosis in immunocompetent patient: a case report and literature review. Braz J Infect Dis. 2008 Oct;12(5):453–5.
8 Chavhan GE, Ramakantan R. Duodenal tuberculosis: radiological features on barium studies and their clinical correlation in 28 cases. J Postgrad Med. 2003 Jul–Sep;49(3):214–7.
9 Flores HB, Zano F, Ang EL, Estanislao N. Duodenal tuberculosis presenting as gastric outlet obstruction: Aa case report. World J Gastrointest Endosc. 2011 Jan 16;3(1):16–9.
10 Mukewar S, Mukewar S, Ravi R, Prasad A, S Dua K. Colon tuberculosis: endoscopic features and prospective endoscopic follow-up after anti-tuberculosis treatment. Clin Transl Gastroenterol. 2012 Oct 11;3(10):e24.
11 Gompertz M, Carreño L, Gil La Rotta LC. Rectal tuberculosis: an uncommon clinical presentation and differential diagnosis with Crohn's disease. Rev Gastroenterol Mex. 2019 Oct–Dec;84(4):524–6.
12 Sachdeva S, Dahale AS, Dalal A. Isolated rectal tuberculosis with multiple fistulae. Clin Gastroenterol Hepatol. 2021 Sep;19(9):A22.
13 Manoria P, Singhai A, Gulwani HV. Isolated rectal tuberculosis in immunocompetent host. J Glob Infect Dis. 2021 Jul–Sep;13(3):148–50.
14 Lowbridge C, Fadhil SAM, Krishnan GD, Schimann E, Karuppan RM, Sriram N, et al. How can gastro-intestinal tuberculosis diagnosis be improved? A prospective cohort study. BMC Infect Dis. 2020 Mar 30;20(1):255.
15 Maulahela H, Simadibrata M, Nelwan EJ, Rahadiani N, Renesteen E, Suwarti SWT, et al. Recent advances in the diagnosis of intestinal tuberculosis. BMC Gastroenterol. 2022 Mar 1;22(1):89.
16 Elbrolosy AM, El Helbawy RH, Mansour OM, Latif RA. Diagnostic utility of GeneXpert MTB/RIF assay versus conventional methods for diagnosis of pulmonary and extra-pulmonary tuberculosis. BMC Microbiol. 2021 May 13;21(1):144.
17 Jullien S, Jain S, Ryan H, Ahuja V. Six-month therapy for abdominal tuberculosis. Cochrane Database Syst Rev. 2016 Nov 1;11(11):CD012163.
18 Malikowski T, Mahmood M, Smyrk T, Raffals L, Nehra V. Tuberculosis of the gastrointestinal tract and associated viscera. J Clin Tuberc Other Mycobact Dis. 2018 Sep 09;12:111–8. Erratum in: J Clin Tuberc Other Mycobact Dis. 2020 Sep 9;21:100177.
19 Debi U, Ravisankar V, Prasad KK, Sinha SK, Sharma AK. Abdominal tuberculosis of the gastrointestinal tract: revisited. World J Gastroenterol. 2014 Oct 28;20(40):14831–40.
20 Naga MI, Okasha HH, Ismail Z, El-Fatatry M, Hassan S, Monir BE. Endoscopic diagnosis of colonic tuberculosis. Gastrointest Endosc. 2001 Jun;53(7):789–93.

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Clinical Case Study

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Autoimmune Liver Disease in Human Immunodeficiency Virus-Infected Patients: 3 Case Series

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Keywords
Autoimmune hepatitis · Primary biliary cholangitis · Human immunodeficiency virus · Immune reconstitution syndrome

Abstract
We present 3 cases of autoimmune liver disease in human immunodeficiency virus (HIV)-infected patients and describe the different diagnostic and therapeutic approaches used in each case. The first patient was diagnosed with primary biliary cholangitis (PBC) with features of autoimmune hepatitis (AIH), requiring second-line therapy due to incomplete response to ursodeoxycholic acid. The second patient was diagnosed with AIH with features of PBC and had the particular challenges of presenting with advanced liver fibrosis and having a past history of disseminated cytomegalovirus infection. The last case concerns an AIH with acute liver injury, successfully treated with corticosteroids and azathioprine. Recently, the number of patients on antiretroviral therapy (ART) for HIV disease has increased significantly. Therefore, more patients with this chronic infection have been diagnosed with autoimmune diseases, leading to concerns regarding immunosuppressive therapies in this population. With these cases, we alert for these increasingly incident diseases and support the safety of immunosuppressive therapies, provided that HIV is suppressed with ART.

Doença hepatica autoimmune em doentes com infeção pelo VIH: 3 casos

Palavras Chave
Hepatite autoimmune · Colangite biliar primária · VIH · Síndrome de reconstituição imune

Resumo
Apresentamos três casos distintos de doença hepática autoimune em doentes com infeção pelo vírus da imunodeficiência humana (VIH), descrevendo as diferentes abordagens diagnósticas e terapêuticas. O primeiro doente foi diagnosticado com colangite biliar primária (CBP) com características de hepatite autoimune (HAI), necessitando de terapêutica de segunda linha por resposta incompleta ao

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ácido ursodesoxicólico (AUDC). O segundo doente foi diagnosticado com HAI com caraterísticas de CBP, com as particularidades de se apresentar com fibrose hepática avançada e de ter tido uma infeção disseminada pelo citomegalovírus. O terceiro caso apresentou-se como uma hepatite aguda grave, tratada com corticoterapia e azatioprina. Recentemente, o número de doentes sob terapêutica antirretroviral (TARV) para a infeção pelo VIH tem aumentado significativamente. Consequentemente, mais doentes com esta infeção crónica têm sido diagnosticados com doenças autoimunes, levando a receios na administração de terapêuticas imunossupressoras. Com esta série de casos pretendemos alertar para esta incidência crescente e para a segurança dos imunossupressores, desde que os doentes apresentem a sua infeção pelo VIH controlada com a TARV.

Introduction

In recent years, the number of patients on antiretroviral therapy (ART) for human immunodeficiency virus (HIV) infection has increased significantly [1]. Although antiretroviral drug-induced liver injury is the first hypothesis when elevation of liver enzymes occurs after starting these therapies, immune reconstitution-related autoimmune hepatitis (AIH) must be considered. In HIV-infected patients, HIV-associated cholangiopathy, co-infection with hepatitis B or C virus, opportunistic infections, alcohol abuse, and nonalcoholic fatty liver must also be excluded, among others.

About three dozen cases of AIH have been described in HIV-positive patients with no prior history of abnormal liver enzymes, who developed transaminase abnormalities months to years after starting ART [2–5]. These cases are mainly of AIH, with only two overlap syndromes with primary biliary cholangitis (PBC) and AIH being reported in the literature [6, 7]. The mechanism for this increasingly described entity of immune reconstitution syndrome is not fully understood, but probably involves the rapid increase in CD4+ lymphocyte number after starting ART. In AIH, cellular infiltrates in the liver are rich in CD4+. In particular, the pro-inflammatory Th17 subtype that releases IL-17 has been found to be elevated in AIH. Furthermore, these patients have decreased numbers of Treg cells, which suppress effector T cells and maintain tolerance to self-antigens. The rapid increase in CD4+ cells following ART may produce a larger proportion of Th17 cells without appropriate Treg cell numerical and functional reconstitution, thereby creating a "perfect storm" for AIH onset [2]. Additionally, other autoimmune disorders, such as vasculitis, systemic lupus erythematosus, psoriasis, and Graves' disease, have been described in HIV patients treated with ART [3].

It is challenging to start immunosuppressive therapy in patients with HIV infection, given the risk of worsening HIV status and increasing the risk of opportunistic infections or malignancies [5]. However, cases of AIH in HIV-infected patients have been described and successfully managed with either prednisolone alone or in combination with azathioprine, while on ART [3–5]. From the published data, only 4 cases of life-threatening infections occurred in HIV patients with AIH treated with immunosuppressors [8], although some reports have insufficient follow-ups. Current AIH guidelines recommend individualized immunosuppressive therapy in this population [9]. Particular attention is also needed for possible drug-drug interaction between immunosuppressive medications like azathioprine and antiretroviral medications, as they share common elimination and metabolism pathways such as cytochrome P450 enzyme system or P-glycoprotein and multidrug resistance-associated protein pathways [5].

Case Report

Case 1

This case concerns a 59-year-old Caucasian man with HIV (CDC Atlanta stage A1 [10]) infection controlled with abacavir, dolutegravir, and lamivudine (ABC/DTG/3TC) and hypercholesterolemia treated with simvastatin. He was otherwise healthy and fit, his body mass index (BMI) being 22.6 kg/m^2. Previously to ART, he already had pruritus and a slight elevation of liver enzymes, with an alkaline phosphatase (ALP) of 154 U/L, gamma-glutamyltransferase (GGT) of 201 U/L, and alanine transaminase (ALT) of 68 U/L. A significant increase in hepatic enzymes occurred 3 years after starting antiretrovirals: ALP 541 U/L (4 times the upper limit of normal [ULN]), GGT 1,025 U/L (17 times the ULN), and ALT 262 U/L (6 times the ULN), with normal bilirubin. The patient denied excessive alcohol consumption and intake of new drugs or herbal and dietary supplements (HDS). Viral and metabolic liver diseases were excluded. Positive antinuclear antibodies (ANA) (1:640), positive anti-mitochondrial antibodies (AMA) (1:160), elevated immunoglobulin G (1,824 mg/dL), and immunoglobulin M (478 mg/dL) were found. Abdominal ultrasound and computed tomography revealed a normal sized liver without bile duct alterations. Magnetic resonance cholangiopancreatography was not performed due to orthopedic metallic material. Liver biopsy revealed a mixed inflammatory infiltrate with lymphocytes, plasmocytes, neutrophils, and some eosinophils, with features of cholangitis, such as exuberant ductular proliferation and intraepithelial lymphocytes in bile ducts, without cholestasis or steatosis, with moderate interface hepatitis with bridg-

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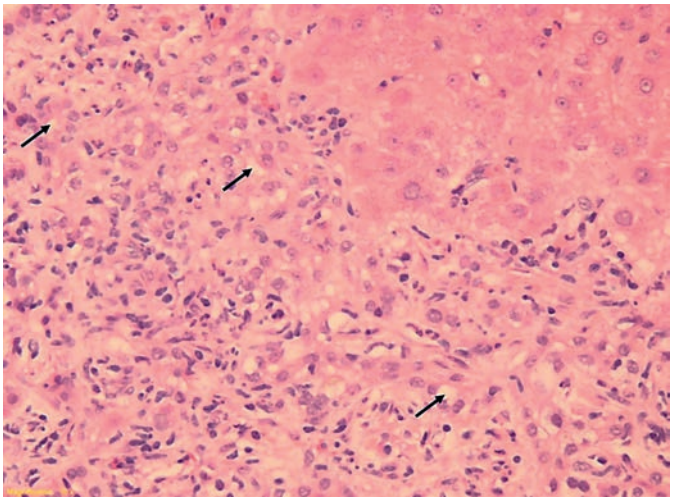

Fig. 1. Liver biopsy (9 portal spaces) revealed an intense inflammatory infiltrate with features of cholangitis (exuberant ductular proliferation (*arrows exampling some*) and intraepithelial lymphocytes in bile ducts) without cholestasis, with moderate interface hepatitis and bridging necrosis. Hematoxylin and eosin, ×20.

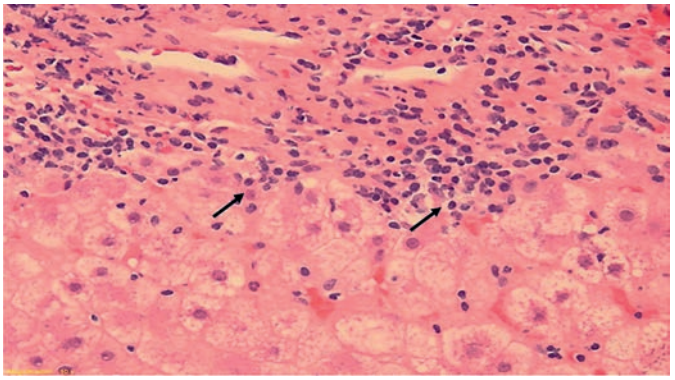

Fig. 2. Liver biopsy (6 portal spaces) revealing features of autoimmune hepatitis (moderate to severe lymphoplasmacytic infiltrate, interface hepatitis, and emperipolesis) with ductular proliferation without ductopenia. *Arrows showing inflammatory cells permeating through hepatocytes*. Hematoxylin and eosin, ×20.

ing necrosis and a chronicity index of 2/6 according to Ishak criteria (shown in Fig. 1).

A diagnosis of PBC with features of AIH, meeting Paris criteria for AIH-PBC overlap syndrome (ALP >2 times the ULN and GGT >5 times the ULN, positive AMA >1:40 and florid bile duct lesion on histology for PBC; ALT more than 5 times the ULN and histology with moderate interface hepatitis for AIH), was established, and ursodeoxycholic acid (UDCA) was started at 1,000 mg/day. According to Paris II criteria (ALP more than 1.5 times the ULN or aspartate transaminase [AST] more than 1.5 times the ULN or bilirubin more than 1 mg/dL), the patient had an incomplete response to UDCA at 12 months (ALP 541–261 U/L), despite ALT and AST improvement (from 150 U/L and 103 U/L to 51 U/L and 46 U/L, respectively). Although most recent guidelines suggest the association with obeticholic acid in these cases [11], data concerning its use with concomitant ART were lacking. Because the association of UDCA with bezafibrate has been shown to be promising as an alternative [12], bezafibrate 400 mg/day was added after confirming its safety in combination with ART. At this point, ALT and AST were at the ULN. A substantial improvement 6 months after starting bezafibrate was noted, with ALP normalization (91 U/L) and a significant reduction in GGT (318–140 U/L). One year after concomitant therapy with UDCA and bezafibrate, ALT, AST, and ALP are within the normal range, with a slight GGT elevation (110 U/L). Transient elastography improved from 13.3 kPa to 9.1 kPa. Although this patient met Paris criteria for "PBC with secondary AIH," a normalization of ALT and immunoglobulin G was achieved with the treatment for PBC. Therefore, no immunosuppressive treatment was initiated.

Case 2

This case concerns a 49-year-old Caucasian man with HIV infection diagnosed in the context of disseminated cytomegalovirus disease (esophagitis and proctitis) (CDC Atlanta stage C3 [10]), with complete remission and with recovery of immunological state (CD4 count> 500 cels/μL) and suppression of viral load with ABC/3TC/DTG since then. He was otherwise fit and had a BMI of 24.3 kg/m^2. An oscillating elevation of hepatic enzymes was noticed 2 years later, with maximum values of ALP 289 U/L, GGT 554 U/L, ALT 613 U/L, and AST 371 U/L, with normal bilirubin. He denied excessive alcohol intake, recently introduced drugs, or HDS. An extensive liver panel excluded viral and metabolic liver diseases. The patient had positive ANA (1:640), positive AMA (1:80), and elevated immunoglobulin G (2,536 mg/dL). Abdominal computed tomography revealed a cirrhotic liver. Liver biopsy, performed 6 months after starting UDCA 13 mg/kg/day (which had been initiated in the Infectious Diseases Clinic, previously to hepatology referral), confirmed fibrosis 5/6 according to Ishak criteria and features compatible with AIH (lymphoplasmacytic infiltrate, moderate to severe interface hepatitis, and emperipolesis) and biliary inflammation without duct destruction (shown in Fig. 2). Upper endoscopy excluded esophageal varices.

A diagnosis of AIH with features of PBC (meeting Paris criteria for overlap syndrome: ALP >2 times the ULN, GGT >5 times the ULN, and positive AMA >1:40 for PBC; histology with moderate to severe interface hepatitis and ALT >5 times the ULN for AIH) was established. Considering the severity of his initial HIV presentation and concerns regarding immunosuppression in this scenario, a decision was made to start prednisolone monotherapy, at an initial dose of 60 mg/day, without azathioprine. A significant analytical improvement was noted 1 month later (AST 244–42 U/L, ALT 326–69 U/L, ALP 170–104 U/L, GGT 276–45 U/L). Since interferon gamma release assay was positive, the patient was treated with isoniazide for latent tuberculosis for 9 months, while tapering prednisolone. However, the dose required to maintain a complete biochemical response was 15–17.5 mg. Recently, almost 2 years

Table 1. Comparison between the three cases of autoimmune liver disease in HIV-infected patients

	Case 1	Case 2	Case 3
Age, years	59	49	43
Gender	M	M	F
ART	ABC/3TC/DTG	ABC/3TC/DTG	DRV/FTC/TDF/RTV
CD4+ counts on HAART, cells/μL	587–1,056	227–1,189	454–1,108
Time between HAART and liver enzyme's abnormalities, years	3	2	7
ALP (min/max),* U/L	541	289	171
ALT (min/max),* U/L	262	613	158
Total bilirubin (min/max),* mg/dL	1.21	1.07	9.76
Immunoglobulin G,* mg/dL	1,824	2,536	5,100
Immunoglobulin M,* mg/dL	474	148	67
Positive autoantibodies	ANA (1:640) AMA	ANA (1:640) AMA	ANA (1:640) Anti-Sp100
Histology	Cholangitis with moderate interface hepatitis	Lymphoplasmacytic infiltrate, interface hepatitis, and emperipolesis	Lymphoplasmacytic infiltrate, interface hepatitis, emperipolesis, and hepatocellular rosette formation
Hepatic disease (presentation)	PBC with features of AIH (chronic, insidious)	AIH with features of PBC (chronic, insidious)	AIH type 1 (acute, severe)
Liver cirrhosis	No	Yes	Doubtful
Treatment	UDCA and bezafibrate	Prednisolone Azathioprine	Prednisolone Azathioprine
Follow-up since treatment initiation (months)	42	27	21

M, male; F, female; ART, highly active antiretroviral therapy; ABC, abacavir; 3TC, lamivudine; DTG, dolutegravir; DRV, darunavir; FTC, emtricitabine; TDF, tenofovir; RTV, ritonavir; ALP, alkaline phosphatase; ALT, alanine transaminase; PBC, primary biliary cholangitis; AIH, autoimmune hepatitis; UDCA, ursodeoxycholic acid. *Before UDCA or corticosteroids.

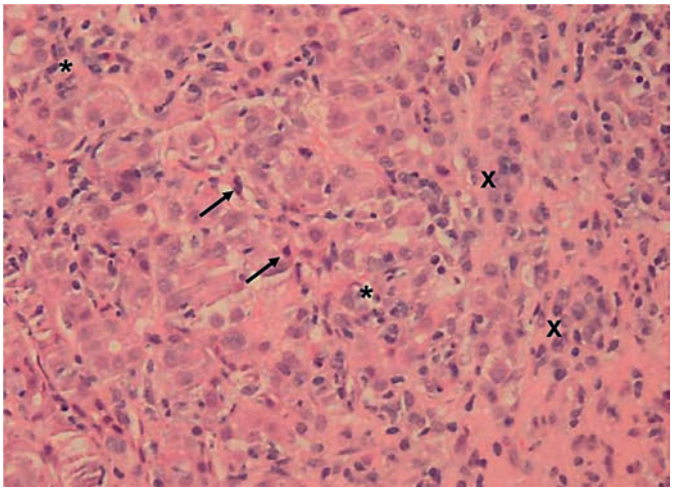

Fig. 3. Liver biopsy (10 portal spaces) revealing features of autoimmune hepatitis (lymphoplasmacytic infiltrate, with severe intralobular inflammatory activity (*stars evidencing inflammatory infiltrate and crosses evidencing plasma cells aggregates*) and necrosis (*arrows showing apoptotic bodies*). Hematoxylin and eosin, ×20.

after diagnosis and after completing SARS-CoV-2 vaccination, azathioprine was added at 50 mg/day (0.5 mg/kg) which allowed for prednisolone tapering to 10 mg, with sustained complete biochemical response.

Case 3

This case concerns a 53-year-old black overweight woman (BMI 28.4 kg/m^2) with long-term HIV infection (CDC Atlanta A2 stage [10]) treated with darunavir, emtricitabine, tenofovir, and ritonavir, with a good immunological state. She presented with acute abdominal pain, nausea, and new-onset jaundice, without fever or encephalopathy. Liver enzymes were increased (ALT 158 U/L, AST 395 U/L, ALP 171 U/L, GGT 328 U/L, and total bilirubin 9.76 mg/dL), and prothrombin time prolonged (20.9 s, with INR 1.8), hence meeting criteria of acute liver injury. She denied alcohol consumption, recently introduced drugs, or HDS. Abdominal Doppler ultrasound was normal. Viral hepatitis was excluded. Due to positive ANA (1:640) and significantly increased immunoglobulin G (5,100 mg/dL), liver biopsy was performed. Histology revealed features typical of AIH (lymphoplasmacytic infiltrate, interface hepatitis, emperipolesis, and hepatocellular rosette formation) with severe inflammatory activity, massive bridging necrosis, and parenchymal collapse, with an activity index of 13/18 and a chronicity index of 3/6 according to Ishak criteria (shown in Fig. 3).

Prednisolone was started (initial dose 50 mg/day), and the patient was safely discharged after 2 weeks. Azathioprine was added 1 week after discharge, when MELD-Na improved from 23 to 15 and with a total bilirubin of 4.75 mg/dL at this time, while tapering corticosteroids. The patient reached complete biochemical response almost 1 year after the initial presentation, while on 10 mg/day prednisolone and 50 mg azathioprine. Although liver biopsy during acute presentation showed a chronicity index of 3/6, more recent transient elastography values range from 20.2 to 15.1 kPa (1 month and 1 year after biochemical remission, respectively) and she presents fluctuating mild thrombocytopenia (with no varices on upper endoscopy), suggesting the development of compensated advanced chronic liver disease [13]. At the time of publication (2 years after the initial presentation), the patient remains in biochemical remission with 7.5 mg/day of prednisolone and 50 mg/day of azathioprine.

Conclusion

Our three reports (Table 1) are different manifestations from a same spectrum of autoimmune liver diseases, all arising in patients with HIV infection. The first case has the particularity of bezafibrate success after UDCA incomplete response in a patient with PBC with features of AIH, with the concern of unknown drug interactions between ART and the currently recommended second-line drug, obeticholic acid. The second case has additional immunosuppression concerns, since HIV diagnosis was made during a disseminated cytomegalovirus work-up and due to the advanced liver disease. Moreover, the use of isoniazid for latent tuberculosis adds further complexity to AIH management, since multiple potential causes for elevated liver enzymes can be present (AIH, azathioprine, or isoniazid-induced hepatotoxicity). The third case, which had a severe acute presentation with acute liver injury, occurred after our experience with the first 2 cases. This not only led to a more straightforward diagnosis, but also allowed for greater confidence when starting immunosuppression. The authors point out that the second patient maintained CD4+ lymphocyte counts >200 cells/μL and the first and third patient >400 cells/μL, with negative HIV viral load during immunosuppressive treatment, and no prophylactic treatment for opportunist infections was needed. No adverse events related to either UDCA, bezafibrate, prednisolone, or azathioprine were reported during follow-up, including infectious complications – Table 1.

With this case series, we also emphasize the importance of liver biopsy, given the extensive differential diagnosis in patients with liver function test abnormalities and an HIV infection, as previously mentioned. To conclude, in an era of generalization of ART therapy, it is important to remain alert to these increasingly incident autoimmune entities and their diagnostic and therapeutic challenges.

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The designated corresponding author of the above article submitted for consideration of publication to Portuguese Journal of Gastroenterology confirms that (i) all named authors agree to the submission of the paper to Portuguese Journal of Gastroenterology; (ii) all authors who contributed to the design and writing of the paper have been named on the paper; (iii) the paper is not currently under review by another journal; and (iv) the paper has not been accepted for publication elsewhere.

Statement of Ethics

This study was reviewed and approved by the Ethics Committee of Hospital Prof. Doutor Fernando Fonseca on March 16, 2022. Written informed consent was obtained from all participants for publication of the details of their medical case and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Maria Ana Rafael: manuscript writer and literature review. Filipa Bordalo Ferreira: patients' physician and literature review. Rita Theias Manso: histological diagnosis. Francesca Peruzzu: patients' physician and manuscript supervisor. Mariana Cardoso: patients' physician and manuscript supervisor.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

References

1 World Health Organization (WHO). AIDS fact sheet. 2021 Jul 14. Available from: https://www.who.int/news-room/fact-sheets/detail/hiv-aids.
2 Murunga E, Andersson M, Rensburg CV. Autoimmune hepatitis: a manifestation of immune reconstitution inflammatory syndrome in HIV infected patients? Scand J Gastroenterol. 2016 Jul;51(7):814–8.
3 Noreña I, Morantes-Caballero JA, Garcés A, Gómez BJ, Rodriguez G, Saavedra CC, et al. Autoimmune hepatitis in human immunodeficiency virus infection: case report and literature review. World J Clin Infect Dis. 2017 Nov 25;7(4):50–57.
4 Moura MC, Pereira E, Braz V, Eloy C, Lopes J, Carneiro F, et al. Autoimmune hepatitis in a patient infected by HIV-1 and under highly active antiretroviral treatment: case report and literature review. World J Immunol. 2014 Nov 27;4(3):194–8.
5 Mubder M, Azab M, Jayaraj M, Cross C, Lankarani D, Dhindsa B, et al. Autoimmune hepatitis in patients with human immunodeficiency virus infection: a systematic review of the published literature. Medicine. 2019 Sep; 98(37):e17094.
6 Caplan M, Trivedi A, McLaughlin M, Hebou A, Kleiner D, Heller T, et al. Primary biliary cirrhosis overlapping with autoimmune hepatitis in an HIV-infected patient on antiretroviral therapy. J Interdiscip Histopathol. 2013; 1(5):270–3.
7 Mathur J, Lhewa D, Sheikh MY. Autoimmune hepatitis overlap with primary biliary cirrhosis in an HIV infected patient. Am J Gastroenterol. 2016 Oct;111:S1350.
8 Wan DW, Marks K, Yantiss RK, Talal AH. Autoimmune hepatitis in the HIV-infected patient: a therapeutic dilemma. AIDS Patient Care STDS. 2009 Jun;23(6):407–13.
9 European Association for the Study of the Liver. EASL clinical practice guidelines: autoimmune hepatitis. J Hepatol. 2015;63(4):971–1004.
10 Centers for Disease Control and Prevention (CDC). 1993 revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. JAMA. 1993 Feb 10;269(6):729–30.
11 European Association for the Study of the Liver. EASL clinical practice guidelines: the diagnosis and management of patients with primary biliary cholangitis. J Hepatol. 2017 Jul;67(1):145–72.
12 Corpechot C, Chazouillères O, Rousseau A, Le Gruyer A, Habersetzer F, Mathurin P, et al. A placebo-controlled trial of bezafibrate in primary biliary cholangitis. N Engl J Med. 2018 Jun 7;378(23):2171–81.
13 Franchis R, Bosch J, Garcia-Tsao G, Reiberger T, Ripoll C; Baveno VII Faculty. Baveno VII: renewing consensus in portal hypertension. J Hepatol. 2022 Apr;76(4):959–74.

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Sequential Use of High-Volume Plasma Exchange and Continuous Renal Replacement Therapy in Hepatitis B Virus-Related Acute Liver Failure: A Case Report

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Keywords
Acute liver failure · High-volume plasma exchange · Continuous renal replacement therapy · Hepatitis · B virus

Abstract
Background: Acute liver failure (ALF) may represent an indication for liver transplantation (LT). However, in patients who do not meet the criteria or who have contraindications for LT, support measures remain indicated since they may improve survival. Continuous renal replacement therapy (CRRT) can be considered in the presence of hyperammonemia, 3 times above the upper normal limit, and hepatic encephalopathy (HE), even in the absence of the classic indications. High-volume plasma exchange (HVPE) is an artificial liver support system with proven benefits in ALF, allowing ammonia and inflammatory mediator clearance. Both techniques, HVPE and CRRT, are associated with an increase in transplant-free survival. ***Case Summary:*** We share a case of a 51-year-old male, without relevant personal history, diagnosed with severe acute hepatitis B which progressed to ALF, with grade IV HE (West-Haven criteria) and hyperammonemia (423 µg/dL). Due to the simultaneously diagnosed malignant neoplasm, he was not a candidate for LT. After refractory to medical therapy, HVPE was started, followed by CRRT. There was a significant improvement in liver tests, allowing surgical treatment of malignancy. After recovery, the patient returned to his everyday life. ***Conclusion:*** The authors present a successful case in which an early and invasive approach to ALF was revealed to be a game changer. The lack of response to the measures instituted, as well as the contraindication for LT, motivated the institution of HVPE and CRRT. Both techniques proved to be an asset, allowing complete clinical recovery, reaffirming their role in ALF.

Uso sequencial de plasmaferese de alto volume e técnica continua de substituição da função renal na insuficiência hepática aguda causada pelo vírus da hepatite B – caso clínico

Palavras Chave
Insuficiência hepática aguda · Plasmaferese de alto volume · Terapêutica de substituição da função renal contínua · Vírus da hepatite B

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Resumo

Background: A insuficiência hepática aguda (IHA) pode constituir uma indicação para transplante hepático (TH). Contudo, nos doentes que não cumprem os critérios ou que apresentam contraindicação para TH, as medidas de suporte continuam indicadas dado que podem ter benefício na sobrevivência. A terapêutica de substituição da função renal (TSFR) pode ser considerada na presença de hiperamonémia, superior a três vezes do limite superior do normal, e encefalopatia hepática (EH), mesmo na ausência das indicações clássicas. A plasmaferese de alto volume (PFAV) é um sistema de suporte artificial ao fígado (SSAF) com benefícios comprovados na IHA, permitindo a *clearance* de amónia bem como de mediadores inflamatórios. Ambas as técnicas, PFAV e TSFR, estão associadas ao aumento da sobrevivência livre de transplante. ***Resumo do caso:*** Apresentamos o caso de um homem de 51 anos, sem antecedentes pessoais de relevo, com o diagnóstico de hepatite B aguda grave que progrediu para IHA, com EH grau IV (critérios de West-Haven) e hiperamonémia (423 µg/dL). Devido ao diagnóstico simultâneo de neoplasia maligna, o doente não foi candidato a TH. Após refratariedade ao tratamento médico instituído, iniciou-se PFAV, seguida de TSFR. Verificou-se melhoria significativa das provas hepáticas, permitindo o tratamento cirúrgico da neoplasia. Após recuperação, o doente regressou ao seu quotidiano. ***Conclusão:*** Os autores apresentam um caso de sucesso em que uma abordagem precoce e invasiva revelou-se *game-changer*. A refratariedade às medidas instituídas, bem como a contraindicação ao TH, motivaram a instituição de HVPE e CRRT. Ambas as técnicas revelaram-se uma mais-valia permitindo a recuperação clínica total, reafirmando o seu papel na IHA.

Introduction

Acute liver failure (ALF) is defined by acute liver injury with hepatic encephalopathy (HE) and an elevated international normalized ratio (INR above 1.5). Normally, HE presents on the first 8–28 days of jaundice. Drug-induced and viruses, with high prevalence of hepatitis B virus (HBV), are currently the main causes [1]. Severe HBV-related ALF has a spontaneous survival rate of 25% [2]. Pathophysiology includes the accumulation of various metabolites and toxins, namely, ammonia, that lead to cerebral edema and herniation. Additionally, a systemic inflammatory response (SIRS) occurs and is responsible for multiorgan failure (MOF), namely, acute kidney injury (AKI), which happens in 40–80% of the cases [1, 3, 4].

ALF should be managed in an intensive care unit (ICU) at a liver transplant center. The approach involves treating the cause of the hepatitis as well as organ support measures. Early consideration should be given to the indication for liver transplantation (LT) as well as the artificial liver support system (ALSS). The presence of hyperammonemia and HE in ALF could be an indication for continuous renal replacement therapy (CRRT) [1]. CRRT, continuous veno-venous hemodiafiltration (cvvHDF) included, allows the clearance of ammonia and improves 21-day transplant-free survival, as found by Cardoso FS et al. (2018) [5]. In the ALSS group, high-volume plasma exchange (HVPE) has demonstrated benefit in increasing transplant-free survival at 3 months, as found by Larsen FS et al. (2016) [6]. HVPE is considered a rescue therapy when initial measures fail, allowing ammonia and inflammatory mediator clearance, which are responsible for MOF and, consequently, mortality [7].

Therefore, both are promising therapeutic weapons for patients who are not candidates for LT, allowing an opportunity for liver recovery and mitigating the need for LT. We share a case of fulminant acute hepatitis B virus with LT contraindication in which the institution of sequential HVPE and CRRT allowed noticeable clinical and hepatic improvement.

Clinical Case

A 51-year-old male was admitted in the emergency department for jaundice with 7 days of evolution. Personal history of sporadic consumption of alcohol was identified. At physical examination, mucocutaneous jaundice was found. Blood samples revealed elevation of liver cytocholestasis markers (aspartate transaminase 6,688 U/L; alanine transaminase 6,223 U/L; gamma-glutamyltransferase 243 U/L; and alkaline phosphatase 188 U/L), liver dysfunction (INR 2.6; total hyperbilirubinemia [TB] 27.12 mg/dL; and direct bilirubin 19.53 mg/dL; factor V 46.6%; ammonia 219 µg/dL), and mixed alkalemia (pH 7,47; $PaCO_2$ 32.5 mm Hg; HCO_3 23.7 mEq/L; lactate 1.7 mmol/L). An abdominal-pelvic computed tomography scan showed an expansive lesion in the left kidney, grade IV of the Bosniak classification. No changes related to the liver, bile ducts, spleen, or pancreas were described. In the etiological study performed, positive AgHBs, AcHBc IgM, and AcHBe with low viral load (VL) HBV of 41,100

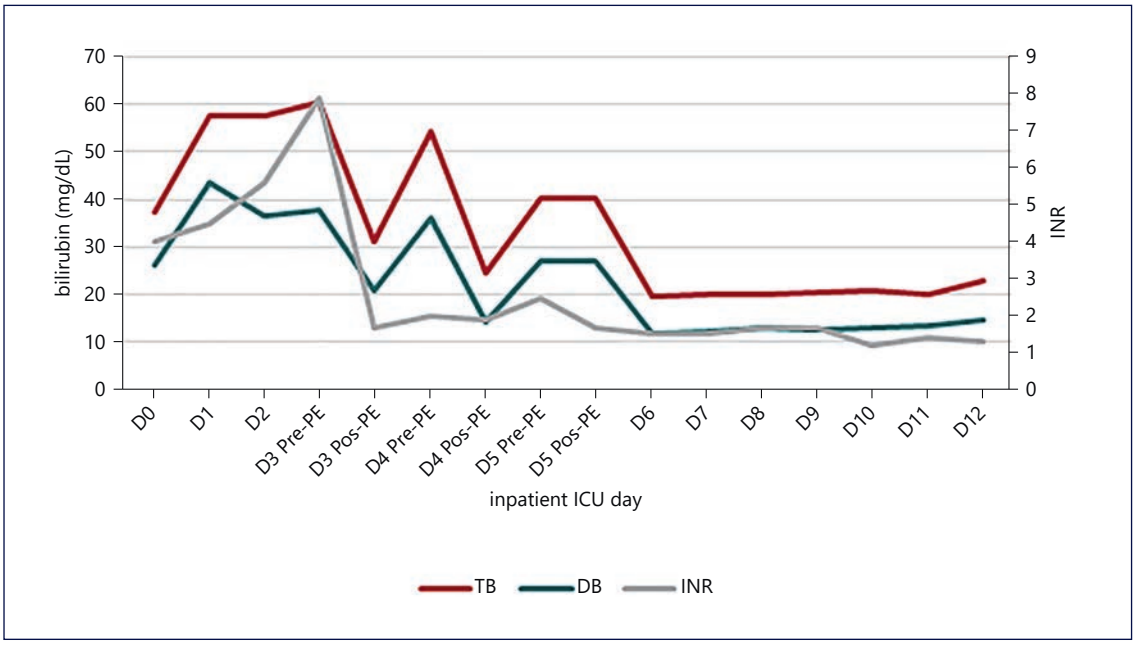


Fig. 1. Evolution of INR and bilirubin with the institution of HVPE and cvvHDF. A decrease in liver function markers was notice, which was maintained after discontinuation of the techniques. The stabilization of the INR value occurred earlier than that of bilirubin.

IU/mL were found. Serology for hepatitis D virus was negative.

A diagnosis of severe acute hepatitis B and probable solid neoplasm were assumed. The patient was transferred to the ICU and started on N-acetylcysteine and entecavir at a dose of 1 mg/day. After 48 h in the ICU, ALF criteria were met. Progression for grade IV HE motivated orotracheal intubation. Preventive measures of cerebral edema were instituted, and monitorization of intracranial hypertension was initiated with the measurement of the optic nerve sheath. Concomitantly, liver tests worsened, with a maximum TB of 60.59 mg/dL and direct bilirubin of 37.78 mg/dL; INR of 7.9; hyperammonemia of 423 μg/dL; and hyperlactacidemia of 2.3 mmol/L. No other organ failure was identified.

Although the Kings College and Clichy criteria for LT had been met, the probable malignant neoplasm represented a contraindication. Due to the persistent neurological dysfunction and worsening of liver tests, the team decided to start HVPE. A filter membrane was chosen and 8 L of plasma was infused in each of the 3 sessions. The median duration of each session was 8 h. The replacement volume was equal to the treated volume. To reduce the risk of bleeding and infection, the replacement volume consisted of 5% human albumin and fresh frozen plasma (FFP) in a ratio of 1:1. During HVPE, AKI was identified, with creatine 1.51 mg/dL, and terlipressin was started.

At the end of the third HVPE session, worsened AKI (maximum creatinine 3.26 mg/dL and urea 74 mg/dL) and hyperammonemia (325 μg/dL) led to the initiation of cvvHDF. An effluent dose (ED) of 50 mL/kg/h was programmed, without losses. There were no identified any classic indications for CRRT. After 4 days of cvvHDF, the ammonia level was under 100 μg/dL, and CRRT was suspended.

Figures 1–3 show the evolution of liver tests, ammonia, lactate, and sequential organ failure assessment (SOFA) score. After three HVPE sessions and 4 days of cvvHDF, ammonia levels and liver tests achieved sustained improvement. FFP administration is a confounding factor for the factor V elevation.

The mortality predicted by the SOFA score achieved the maximum value of 95.2% on the 5th day in the ICU, as shown in Figure 3. After discontinuing cvvHDF, the predicted mortality decreased, following the evolution of liver tests and ammonia, as shown in Figures 1–3.

On the 10th day in the ICU, a ventilator-associated pneumonia was diagnosed, and a second maximum value of predicted mortality was achieved. Concomitantly, hy-

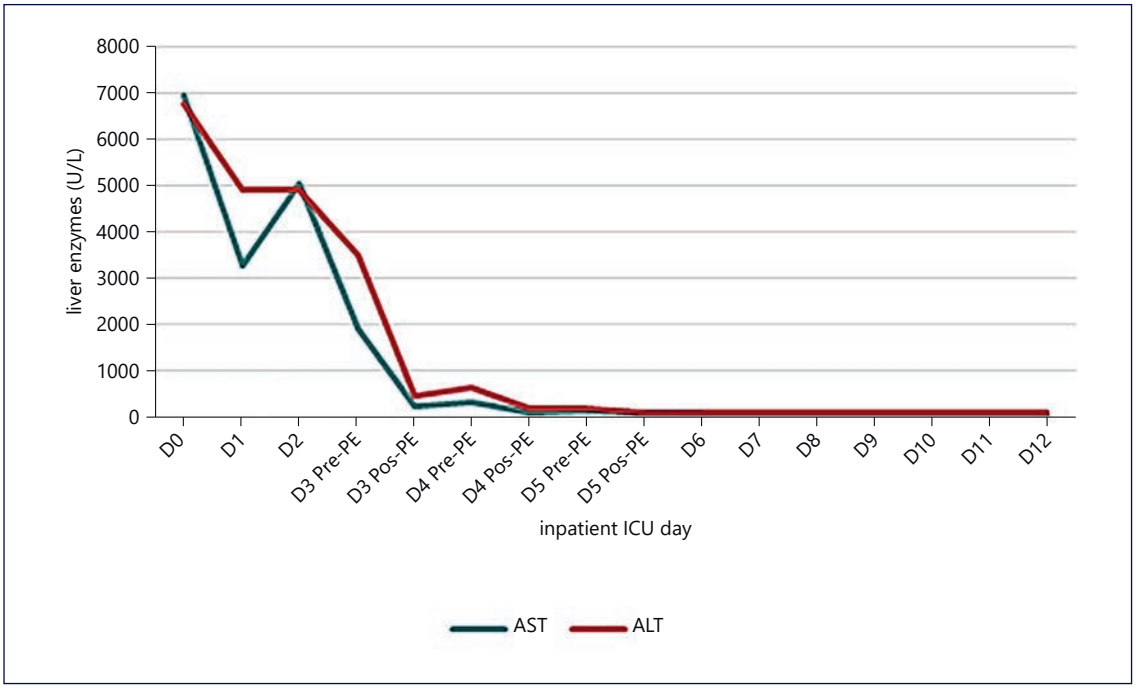
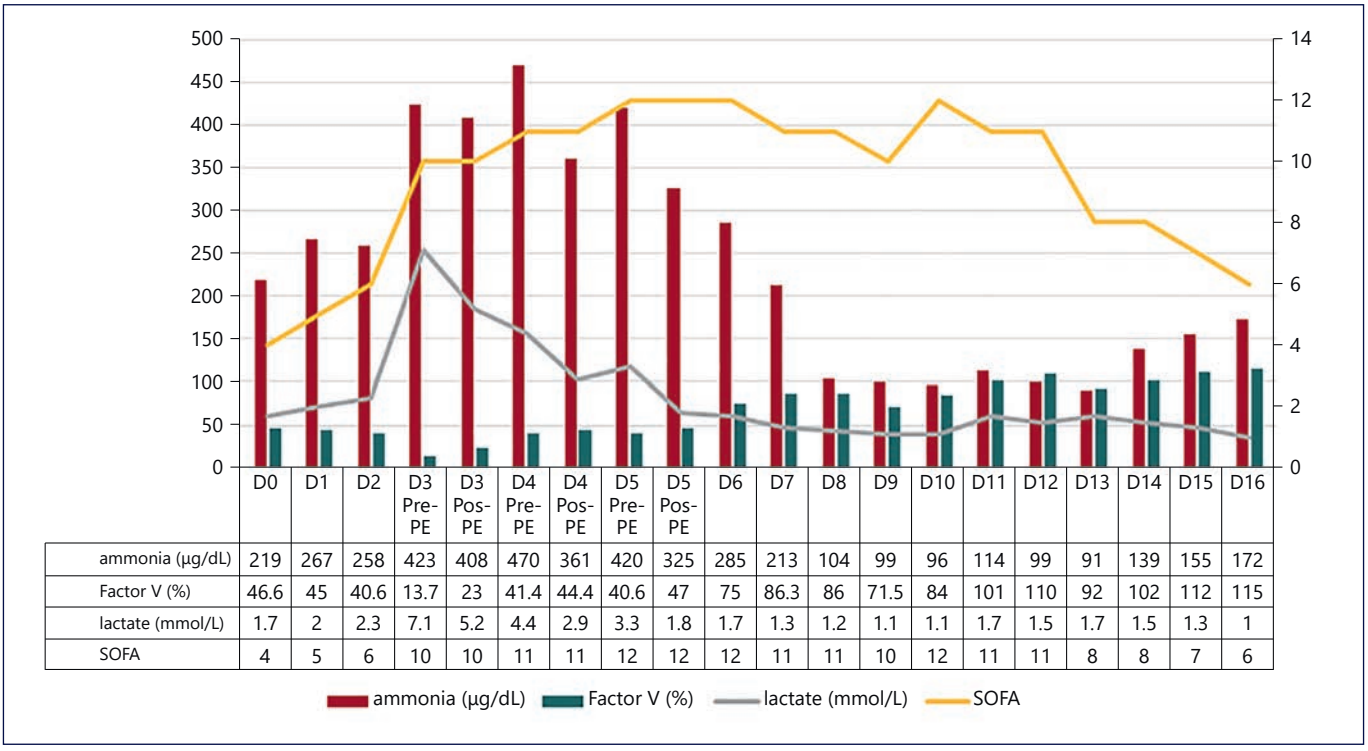


Fig. 2. Evolution of transaminases with the institution of HVPE and cvvHDF. A significant and early drop in transaminases was identified, which was maintained.



	D0	D1	D2	D3 Pre-PE	D3 Pos-PE	D4 Pre-PE	D4 Pos-PE	D5 Pre-PE	D5 Pos-PE	D6	D7	D8	D9	D10	D11	D12	D13	D14	D15	D16
ammonia (µg/dL)	219	267	258	423	408	470	361	420	325	285	213	104	99	96	114	99	91	139	155	172
Factor V (%)	46.6	45	40.6	13.7	23	41.4	44.4	40.6	47	75	86.3	86	71.5	84	101	110	92	102	112	115
lactate (mmol/L)	1.7	2	2.3	7.1	5.2	4.4	2.9	3.3	1.8	1.7	1.3	1.2	1.1	1.1	1.7	1.5	1.7	1.5	1.3	1
SOFA	4	5	6	10	10	11	11	12	12	12	11	11	10	12	11	11	8	8	7	6

Fig. 3. Evolution of SOFA score, serum lactate, ammonia, and FV with the established techniques. The SOFA score and ammonia followed the evolution of the previously described markers, until the infectious intercurrence. PE, plasma exchange; SOFA, Sequential Organ Failure Assessment; FV, factor V.

perammonemia occurred, but ammonia level normalization was observed without invasive measures.

After 3 days without cvvHDF, the patient was extubated. Clinical and analytical improvement was noticed. The patient was submitted to robot-assisted left radical nephrectomy on the 22nd day in the ICU. The histology of specimen revealed a clear cell renal carcinoma, grade 2 of grading system ISUP/OMS.

The patient was transferred to an internal medicine ward for continuity of care on the 31st day in the ICU. At that time, he had a Glasgow coma scale score of 15 points without sequels beyond ICU-associated myopathy. Analytically, he had cytocholestasis markers within reference values; TB 5.75 mg/dL; INR 1.4; lactate 0.7 mmol/L; creatinine 1.66 mg/dL; urea 30 mg/dL; and a HBV VL 51 IU/mL. Four months after hospital admission and a complete program of physical rehabilitation, the patient has fully recovered his autonomy.

Discussion

This case illustrates a new approach to HBV-related ALF with sequential use of HVPE and cvvHDF, with a significant improvement in liver tests without LT. The absence of immunosuppressive therapy or recent risk factors for HBV transmission suggests that ALF was caused by spontaneous HBV reactivation. Most reactivations are related with immunosuppression. Since kidney cell cancer is associated with immunosuppressive phenotype by upregulation of transforming growth factor β, its possible contribution was considered. However, scientific evidence regarding this association is scarce [1, 7–10].

Among the therapeutic measures instituted, antiviral therapy should be highlighted. The purpose of entecavir in acute hepatitis B is to prevent progression for ALF, but its role when ALF is already established is questionable [11]. Entecavir was the drug of choice since it is highly effective in reducing HBV VL [2, 11–13]. About 13% of the circulating entecavir molecule is bound to albumin; however, information on the effect of HVPE and CRRT in entecavir bioavailability is limited [13]. Even with HVPE and cvvHDF sessions, suppression of HBV viral replication was verified, with a reduction in 99% of HBV VL, on the 20th day of entecavir.

ALF criteria were met in the ICU, and despite having an indication for LT, the existence of an untreated extrahepatic cancer represented a formal contraindication [9]. Non-indication for LT did not imply nonadmission in the ICU. Therapeutic and support measures instituted, namely, neurological and respiratory, are associated with improved survival. Various indicators of poor prognosis were identified in this case. HE reflects a severe alteration of hepatic function, with hyperammonemia being a reliable marker of HE and is also associated with intracranial hypertension and brain herniation if above 150–200 μg/dL [1, 14–16].

Additionally, AKI developed; serum lactate elevation and hyperbilirubinemia suggested an unfavorable outcome [1, 9, 14, 15]. That, in the presence of a persistent neurological dysfunction and a contraindication for LT, led the team to institute other invasive measures, such as HVPE and cvvHDF. The tandem cvvHDF-HVPE has been used in immune-mediated AKI, without hemodynamic or ionic complications described, although it has not been used in ALF. In that setting, the authors decided to use a sequential approach [17, 18].

Due to the persistent neurological dysfunction and worsening liver tests, it was decided to start HVPE in the first place. It was chosen as the first option because of its effect, allowing not only ammonia clearance as well as bilirubin and others inflammatory mediators, the latest related with MOF and mortality. Among therapeutic plasma exchange techniques, HVPE is the 1st option in ALF treatment [2–4, 19, 20]. Compared to other ALSS, namely, molecular adsorbent recirculating system or Prometheus, HVPE has an advantage in transplant-free survival, as demonstrated in the prospective multicenter study of Larsen et al. (2016) [1, 6, 7, 19–21]. HVPE consists of separation of plasma from other blood components, then its removal, followed by the administration of a replacement solution. The difference from other therapeutic plasma exchange is related to the volume of total plasma treated. In HVPE, 8–12 L of plasma volume are removed, which corresponds to 15% of the ideal body weight. The removal rate is 1–2 L per hour, instead of 1–1.5x of the total plasma volume [1, 4, 9, 19, 22].

The replacement solution may consist of albumin and/or FFP [22]. The difference between the biochemical effect of albumin and FFP is still not fully understood, nevertheless the risk of infection and bleeding associated with each of the solutions are well defined. FFP allows the replacement of all plasma components. Nevertheless, FFP is expensive, requires blood type compatibility, and has the risk of viral infection and citrate toxicity. On the contrary, albumin has no infectious risk but leads to a decline in other plasma components, such as coagulation factors, and more prolonged depletion of all antibodies, especially IgG antibodies. Immunoglobulins replacement after HVPE was not considered as it is expensive and in FFP

composition, there are immunoglobulins and complement components [7, 23]. To equilibrate the risks of both solutions and reduce the costs, the authors decided to use a replacement solution composed of 50% albumin and 50% FFP. In Larsen et al. [6] study, patients with active malignancy were excluded, and the replacement volume used only consisted in FFP. The alternative replacement solution used in this case allowed achieving a good result. The HVPE duration was limited to 3 consecutive days due to the infectious risk, with intervals of 24 h, allowing regeneration of clotting factors and reducing the bleeding risk [5, 6, 19, 22].

Despite the improvement seen after the third HVPE session, worsening of AKI and hyperammonemia (3 times above the UNL), led the team to start CRRT, which is an ammonia-lowering strategy. Early CRRT use could be indicated in ALF in the presence of persistent hyperammonemia and hyponatraemia and for temperature control, even in the absence of classic indications for RRT [1, 5, 16, 24, 25]. The choice of cvvHDF over the intermittent technique is related with his minimal rebound effect, contributing to persistent improvement of ammonia levels [16, 26]. The authors chose an ED of 50 mL/kg/h because ammonia is a large molecule and needs higher ED to allow its clearance [16, 27]. cvvHDF was stopped when ammonia levels were under 100 μg/dL, although some authors recommend to stop when values are under 70 μg/dL [16]. Most patients with ALF and AKI achieved fully renal function recover upon discharge [1]. Kidney cancer can contribute to AKI; however, the mechanism is due to glomerulopathy, which is rare, being systematic inflammatory response-ALF the main contributor in this case [1, 9, 25, 28].

Besides the bleeding risk, hypocoagulation with citrate was used in HVPE and in cvvHDF. The goal was to reduce the risk of filter clotting which is associated to lower filter performance and clearance commitment. Hypocalcaemia is an adverse effect of citrate, so monitorization with arterial blood gas analysis is required. Compared to citrate, heparins have an increased risk of bleeding and required close monitorization for dose adjustment [29, 30].

The sequential use of HVPE and CRRT represented a game changer. Despite the poor prognostic and higher predicted mortality, an impressive liver recovery without LT was achieved. In a period when demand exceeds organic supply, the combination of both techniques appears as a good option, especially in patients with contraindication to LT.

Statement of Ethics

Written informed consent was obtained from the patient for publication of this case report and any accompanying images, according to the Helsinki Declaration. The authors have no ethical conflicts to disclose.

Conflict of Interest Statement

The authors have no conflict of interests to declare.

Funding Sources

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Author Contributions

Sofia Bragança, medical doctor at intensive care unit 7 at Hospital Curry Cabral (ICU7-HCC), assisted the patient during his stay; reviewed of scientific literature on the subject and cases already described in the literature; and wrote the present article. Mário Ferraz, medical doctor at ICU7-HCC, assisted the patient during his stay and reviewed the present article until the final version. Nuno Germano, responsible for ICU7-HCC, assisted the patient and was involved in decision-making in relation to the therapeutic attitude performed.

Data Availability Statement

The data that support this case report are not published anywhere because they contain information that may compromise the privacy of the patient, but they may be available if requested to Sofia Bragança.

References

1 Wendon J, Cordoba J, Dhawan A, Larsen FS, Manns M, Nevens F, et al. EASL clinical practical guidelines on the management of acute (fulminant) liver failure. J Hepatol. 2017 May 1;66(5):1047–81.
2 Ichai P, Samuel D. Management of fulminant Hepatitis B. Curr Infect Dis Rep. 2019;21(7):25.
3 Karvellas CJ, Stravitz RT. High volume plasma exchange in acute liver failure: dampening the inflammatory cascade? J Hepatol. 2016;64(1):10–2.
4 Rolando N, Wade J, Davalos M, Wendon J, Philpott-Howard J, Williams R. The systemic inflammatory response syndrome in acute liver failure. Hepatology. 2000;32(4):734–9.
5 Cardoso FS, Gottfried M, Tujios S, Olson JC, Karvellas CJ. Continuous renal replacement therapy is associated with reduced serum ammonia levels and mortality in acute liver failure. Hepatology. 2018;67(2):711–20.

6 Larsen FS, Schmidt LE, Bernsmeier C, Rasmussen A, Isoniemi H, Patel VC, et al. High-volume plasma exchange in patients with acute liver failure: an open randomised controlled trial. J Hepatol. 2016;64(1):69–78.
7 Tam L, Karvellas C, Sy E. The use of high volume plasmapheresis in acute liver failure. Cureus. 2020 Jun 20. ;12(6):e8721.
8 Hoofnagle JH. Reactivation of hepatitis B. Hepatology. 2009 May;49(Suppl 5):S156–65.
9 European Association for the Study of the Liver Electronic address easloffice@easloffliceeu, EASL clinical practice guidelines: liver transplantation. J Hepatol. 2016 Feb 1;64(2): 433–85.
10 Jian Y, Yang K, Sun X, Zhao J, Huang K, Aldanakh A, et al. Current advance of immune evasion mechanisms and emerging immunotherapies in renal cell carcinoma. Front Immunol. 2021;12:639636.
11 European Association for the Study of the Liver; EASL 2017 clinical practice guidelines on the management of hepatitis B virus infection. J Hepatol. 2017;67(2):370–98.
12 Mtisi TJ, Ndhlovu CE, Maponga CC, Morse GD. Tenofovir-associated kidney disease in Africans: a systematic review. AIDS Res Ther. 2019;16(1):12.
13 Yue-Meng W, Yang LH, Yang JH, Xu Y, Yang J, Song GB. The effect of plasma exchange on entecavir-treated chronic hepatitis B patients with hepatic de-compensation and acute-on-chronic liver failure. Hepatol Int. 2016;10(3): 462–9.
14 Samuel D, Ichai P. Prognosis indicator in acute liver failure: is there a place for cell death markers? J Hepatol. 2010;53(4):593–5.
15 Cardoso FS, Pereira R, Moreno R, Karvellas CJ, Germano N. Optic nerve sheath diameter in acute liver failure: a prospective cohort study. GE Port J Gastroenterol. 2021;28(3): 170–8.
16 Gupta S, Fenves AZ, Hootkins R The role of RRT in hyperammonemic patients. Clin J Am Soc Nephrol. 2016 Oct 7;11(10):1872–8.
17 Pérez-Sáez MJ, Toledo K, Ojeda R, Crespo R, Soriano S, Álvarez De Lara MA, et al. Tandem plasmapheresis and hemodialysis: efficacy and safety. Ren Fail. 2011 Sep;33(8):765–9.
18 Kaushik M, Liew ZH, Sewa DW, Phua GC, Cao L, Krishnamoorthy TL, et al. Description of parallel and sequential configurations for concurrent therapeutic plasma exchange and continuous kidney replacement therapy in adults. J Clin Apher. 2021 Feb 1;36(1):211–8.
19 Gerth HU, Pohlen M, Thölking G, Pavenstädt H, Brand M, Wilms C, et al. Molecular adsorbent recirculating system (MARS) in acute liver injury and graft dysfunction: results from a case-control study. PLoS One. 2017 Apr 1;12(4):e0175529.
20 Cisneros-Garza LE, Muñoz-Ramírez MdelR, Muñoz-Espinoza LE, Ruiz Velasco JAVR, Moreno-Alcántar R, Marín-López E. The molecular adsorbent recirculating system as a liver support system: summary of Mexican experience. Ann Hepatol. 2014;13(2):240–7.
21 Rifai K, Ernst T, Kretschmer U, Bahr MJ, Schneider A, Hafer C, et al. Prometheus: a new extracorporeal system for the treatment of liver failure. J Hepatol. 2003;39(6):984–90.
22 Padmanabhan A, Connelly-Smith L, Aqui N, Balogun RA, Klingel R, Meyer E, et al. Guidelines on the use of therapeutic apheresis in clinical practice: evidence-based approach from the writing committee of the American Society for Apheresis – the eighth special issue. J Clin Apher. 2019 Jun 1;34(3):171–354.
23 World Health Organization. Blood transfusion safety team. The clinical use of blood [Internet]. 2001 [cited 2022 Aug 4]. Available from: https://apps.who.int/iris/bitstream/handle/10665/42397/a72894.pdf.
24 Warrillow SJ, Bellomo R. Preventing cerebral oedema in acute liver failure: the case for quadruple-H therapy. Anaesth Intensive Care. 2014;42(1):78–88.
25 Davenport A. Is there a role for continuous renal replacement therapies in patients with liver and renal failure? Kid Int Suppl. 1999; (72):S62–6.
26 Saudan P, Niederberger M, de Seigneux S, Romand J, Pugin J, Perneger T, et al. Adding a dialysis dose to continuous hemofiltration increases survival in patients with acute renal failure. Kid Int. 2006 Oct 9;70(7):1312–7.
27 Slack AJ, Auzinger G, Willars C, Dew T, Musto R, Corsilli D, et al. Ammonia clearance with haemofiltration in adults with liver disease. Liver Int. 2014 Jan;34(1):42–8.
28 Stengel B. Chronic kidney disease and cancer: a troubling connection. J Nephrol. 2010; 23(3):253–62.
29 Lee G, Arepally GM. Anticoagulation techniques in apheresis: from heparin to citrate and beyond. J Clin Apher. 2012;27(3):117–25.
30 Bouchard J, Madore F. Role of citrate and other methods of anticoagulation in patients with severe liver failure requiring continuous renal replacement therapy. NDT Plus. 2009;2(1): 11–9.

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Severe Acute Liver Injury due to Secondary Hemophagocytic Lymphohistiocytosis: A Case Report

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Keywords
Hemophagocytic lymphohistiocytosis · Acute liver injury · Hepatitis

Abstract
Severe acute liver injury (ALI) is mostly triggered by viral infections and hepatotoxic drugs; however, it can also be seen in systemic diseases. Hemophagocytic lymphohistiocytosis (HLH) is a rare, immune-mediated syndrome that presents as a life-threatening inflammatory disorder affecting multiple organs. Secondary causes occur mainly in the set of malignancy, infection, and autoimmune disease, and are seldom triggered by vaccination. Although liver involvement is common, presentation as severe ALI is rare. We describe a case of a 65-year-old male with history of low-risk chronic lymphocytic leukemia and rheumatoid arthritis treated with prednisolone who presented with persistent fever and jaundice 1 week after COVID-19 vaccination. The diagnosis was challenging given the predominant liver impairment, characterized by hyperbilirubinemia, transaminases over 1,000 U/L, and prolonged INR, which prompted an extensive investigation and exclusion of autoimmune, toxic, and viral causes of hepatitis. Laboratory workup revealed bicytopenia, hyperferritinemia, which together with organ failure and evidence of hemophagocytosis in bone marrow suggested the diagnosis of HLH. After excluding infectious etiologies, flare of rheumatological disease, and the progression of hematological disease, HLH was diagnosed. He was successfully treated with etoposide and corticosteroids, with dramatic improvement of liver tests. After exclusion of other causes of secondary HLH, the recent vaccination for COVID-19 was the likely trigger. We report a case of double rarity of HLH, as it presented with severe liver dysfunction which was probably triggered by vaccination. In this case, the predominant liver involvement urged extensive investigation of liver disease, so a high index of suspicion was required to make an early diagnosis. Clinicians should consider HLH in patients with unexplained signs and symptoms of systemic inflammatory response and multiorgan involvement, including severe liver involvement as the first presentation.

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Lesão Hepática Aguda Grave Devido a Linfohistiocitose Hemofagocítica Secundária: Caso Clínico

Palavras Chave
Linfohistiocitose hemafagocítica · Lesão hepatica aguda · Hepatite

Resumo
A lesão hepática aguda (LHA) grave é desencadeada principalmente por infeções virais e hepatotóxicos; contudo, pode ocorrer em condições com envolvimento sistémico. A linfohistiocitose hemofagocítica (LHH) é uma síndrome inflamatória, rara, imunomediada, potencialmente fatal, que pode afetar múltiplos órgãos. A LHH secundária ocorre em contexto de neoplasias, infeções e doenças autoimunes, podendo raramente ser precipitada pela vacinação. Embora seja frequente o envolvimento hepático na LHH, a apresentação como LHA grave é rara. Os autores descrevem o caso de um homem de 65 anos com história de leucemia linfocítica crónica de baixo risco e artrite reumatóide sob prednisolona de 65 anos, que se apresentou com febre persistente e icterícia uma semana após a primeira dose da vacina COVID-19. O diagnóstico constituiu um desafio dado o envolvimento hepático predominante, caracterizado por hiperbilirrubinemia, transaminases acima de 1000 U/L e INR prolongado, o que condicionou uma extensa investigação e exclusão das causas autoimunes, tóxicas, e virais de doença hepática. A presença de bicitopenia e hiperferritinemia, conjuntamente com o desenvolvimento de falências de órgão e evidência de hemofagocitose na medula óssea sugeriram o diagnóstico de LHH. Após exclusão infeções, agudização da doença reumatológica e progressão da doença hematológica, foi feito o diagnóstico de LHH.O doente foi tratado com etoposido e corticosteróides com sucesso, verificando-se uma melhoria dramática das provas hepáticas. Após a exclusão de outras causas de LHH secundária, a recente vacinação foi assumida como provável fator desencadeante. Relatamos um caso raro de LHH, quer pela apresentação com lesão hepática grave, quer pela vacinação como presumível desencadeante. Neste caso, o envolvimento hepático predominante promoveu a uma investigação extensa da doença hepática, tendo sido necessário um elevado índice de suspeição para um diagnóstico atempado. Os médicos devem considerar o diagnóstico de LHH em doentes com sinais e sintomas de resposta inflamatória sistémica, inexplicados que se acompanham por disfunção multiorgânica, nomeadamente disfunção hepática grave como apresentação clínica.

Introduction

Acute liver injury (ALI) is characterized by an acute abnormality of liver blood tests in patients without underlying chronic liver disease, who develop liver-associated coagulopathy, but as opposed to acute liver failure (ALF), without any change in level of consciousness [1]. Viral infections and hepatotoxic drugs are the most common causes of severe ALI [2]; however, these features can be seen in various systemic disease processes [1].

Hemophagocytic lymphohistiocytosis (HLH) is a rare, potentially life-threatening hyperinflammatory syndrome associated with signs and symptoms consequent to extreme and ineffective immune activation [3–5]. HLH may be due to primary or secondary causes. Secondary causes result from acquired immune dysfunction in response to infections, malignancies, autoimmune diseases, and toxics; few case reports described HLH following administration of vaccines [3].

The clinical presentation is heterogeneous and nonspecific and may even course with multiorgan failure [4]. Cardinal features are continuous high fever, cytopenias, and hepatosplenomegaly [1]. Liver involvement is common; however, presentation with severe ALI/ALF is rare [3], which can lead to delays in diagnosis and therapy initiation, with consequent fatal outcome. Since there is no single diagnostic test, it is essential high index of suspicion and the application of the HLH-2004 criteria [3].

Case Presentation

A 65-year-old Caucasian man presented with persistent high fever (>39°C), myalgias, and jaundice 1 week after the first dose of COVID-19 vaccine. His medical history was remarkable for a low-risk chronic lymphocytic leukemia (CLL) (Rai 0, Binet A) with no symptoms under active monitoring, rheumatoid arthritis previously on prednisolone (10 mg/day), and traumatic splenectomy. There was no relevant epidemiological background.

Upon admission, on physical examination the patient was hemodynamically stable, febrile (40°C), frankly jaundiced and a non-painful hepatomegaly was detected; the remaining examination was unremarkable, with no signs of encephalopathy, ascites, chronic liver disease, active arthritis, mucocutaneous bleeding, cutaneous purpura, or enlarged lymph node. Initial blood investigations revealed bicytopenia, severe liver injury, and increased INR with normal remaining coagulation (shown in Table 1). Periph-

Table 1. Laboratory workup

Hemoglobin (g/dL) [13–17]	13.7
White blood cells (10^3/μL) [4.5–11.4]	8.0
Neutrophil (10^3/μL)	0.7 (3 months before: 5.8)
Lymphocytes (10^3/μL)	7.1 (3 months before: 8.3)
Platelets (10^3/μL) [150–350]	29
Peripheral blood smear	Predominance of mature lymphocytes No schistocyte
Coagulation tests	
INR [0.8–1.2]	1.7
aPTT (sec) [25.1–36.5]	27.5
Fibrinogen (g/L) [2–4]	1.2
D-Dimers (ng/mL) [<500]	478
Creatinine (mg/dL) [0.7-1.25]	0.89
Urea (mg/dL) [18–55]	50
AST (U/L) [5–34]	2,698
ALT (U/L) [<55]	1,962
GGT (U/L) [12–64]	542
ALP (U/L) [40–150]	338
TBil (mg/dL) [<1.2]/CBil (mg/dL) [<0.5]	6.42/5.78
LDH (U/L) [125–230]	996
Albumin (g/dL) [3.4–4.8]	2.7
C-reactive protein (mg/dL) [<0.5]	4.55
Procalcitonin (ng/mL)	0.5 (low probability for systemic infection)
Ferritin (ng/mL) [30–100]	>40,000.0
Erythrocyte sedimentation rate (mm/h) [<30]	2
Haptoglobin (mg/dL) [30–200]	146
Triglycerides (mg/dL) [<150]	360

AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma glutamyltransferase; ALP, alkaline phosphatase; TBil, total bilirubin; CBil, conjugated bilirubin.

eral blood smear showed predominance of mature lymphocytes. Computed tomography chest-abdomen-pelvis excluded signs of malignancy, enlarged lymph nodes, chronic liver disease, or biliary obstruction.

Initial septic workup (urine examination and imaging tests) ruled out infection; however pending the results of cultures, the patient was on antibiotic therapy. After 72 h, he remained febrile and developed organ failure: cardiovascular (systolic arterial pressure <90 mm Hg requiring inotropic support) and respiratory (PaO_2/FiO_2: 200–300 mm Hg requiring supplementary O_2), so he was admitted to the intermediate care unit. Cultures have proven sterile, and extensive workup for liver disease was normal (shown in Table 2). Further workup revealed high ferritin, LDH, and triglycerides and low fibrinogen (shown in Table 1).

After excluding malignancy (normal computed tomography), infections (negative cultures and normal wide virus panel), and rheumatic disorder flare (no arthritis and normal complement, autoimmunity, and erythrocyte sediment rate), we considered HLH diagnosis attending to the cytopenias, hyperferritinemia, and persistent fever. An HLH score of 277 supported the diagnosis. Attending to organ failure, while we were waiting for the results of the bone marrow aspirate, we started dexamethasone (10 mg/m^2 daily) and first dosage of etoposide (150 mg/m^2). Meanwhile, the bone marrow aspirate showed hemophagocytosis, predominance of mature clonal lymphocytes, and no signs of progression nor transformation to aggressive lymphoma. The patient continued treatment with etoposide (150 mg/m^2 biweekly for 2 weeks, then weekly) and dexamethasone (10 mg/m^2 daily for 2 weeks with progressive tapering).

Rapid clinical (apyrexia and reversal of all organ failures) and liver improvement was observed (shown in Fig. 1), as well as neutrophil count and INR normalization. However, after 6 weeks of therapy, the patient developed febrile neutropenia related to immunomodulatory therapy, so we discontinued etoposide and started granulocyte colony-stimulating factor and broad-spectrum antibiotic therapy. The patient remained neutropenic and acquired a healthcare-associated pneumonia requiring intensive care admission, there was a progressive worsening, and he died 8 weeks after admission.

Discussion

HLH results from uncontrolled activation of macrophages, natural killer cells, and T cells due to enhanced antigen presentation [3, 4]. This activation produces massive secretion of proinflammatory cytokines, a so-called cytokine storm, that directly contributes to end-organ

Table 2. Additional workup

A. Workup for liver disease	
Infectious	A, B, C, and E hepatitis virus negative (including RNA-HEV non-detectable) Microorganisms with liver tropism: anti-*Leptospira interrogans, Borrelia burgdorferi, Ricketsia* spp., *Mycoplasma pneumoniae*, and *Coxiella burnetii* IgG and IgM negative; Huddleston reaction and Rose bengal negative
Autoimmune	IgG 94 (700–1,600), IgM 30 (40–230) mg/dL *ANA, AMA, LKM1, SMA, SLA, LC-1* negative
Metabolic/genetic	Alpha-1-antitrypsin: 300 (200–400) mg/dL Ceruloplasmin: 27.8 (20–60) mg/dL, normal urinary copper
B. Workup for secondary causes of HLH	
Infectious	Epstein-Barr virus, cytomegalovirus, herpes simplex virus 1/2, and herpes varicella-zoster: negative Influenza, coxsackievirus, parvovirus, enterovirus, and SARS-CoV: negative HIV 1,2: negative Blood, urine, and sputum cultures: negative *Legionella pneumophila* and *Streptococcus pneumoniae* urinary antigen test: negative Other: IGRA, treponemic, and non-treponemic tests: negative
Autoimmune	Complement component: C3 and C4 – normal Erythrocyte sedimentation rate (mm/h) [<30]: 2 Rheumatoid factor: positive ENAs, ANCA, anti-double-strand DNA: negative
Neoplasia	Whole body CT scan without signs of malignancy or enlarged lymph nodes Bone marrow aspirate/bone biopsy: predominance of mature lymphocytes and hemophagocytosis, no signs of leukemia progression or lymphoma transformation

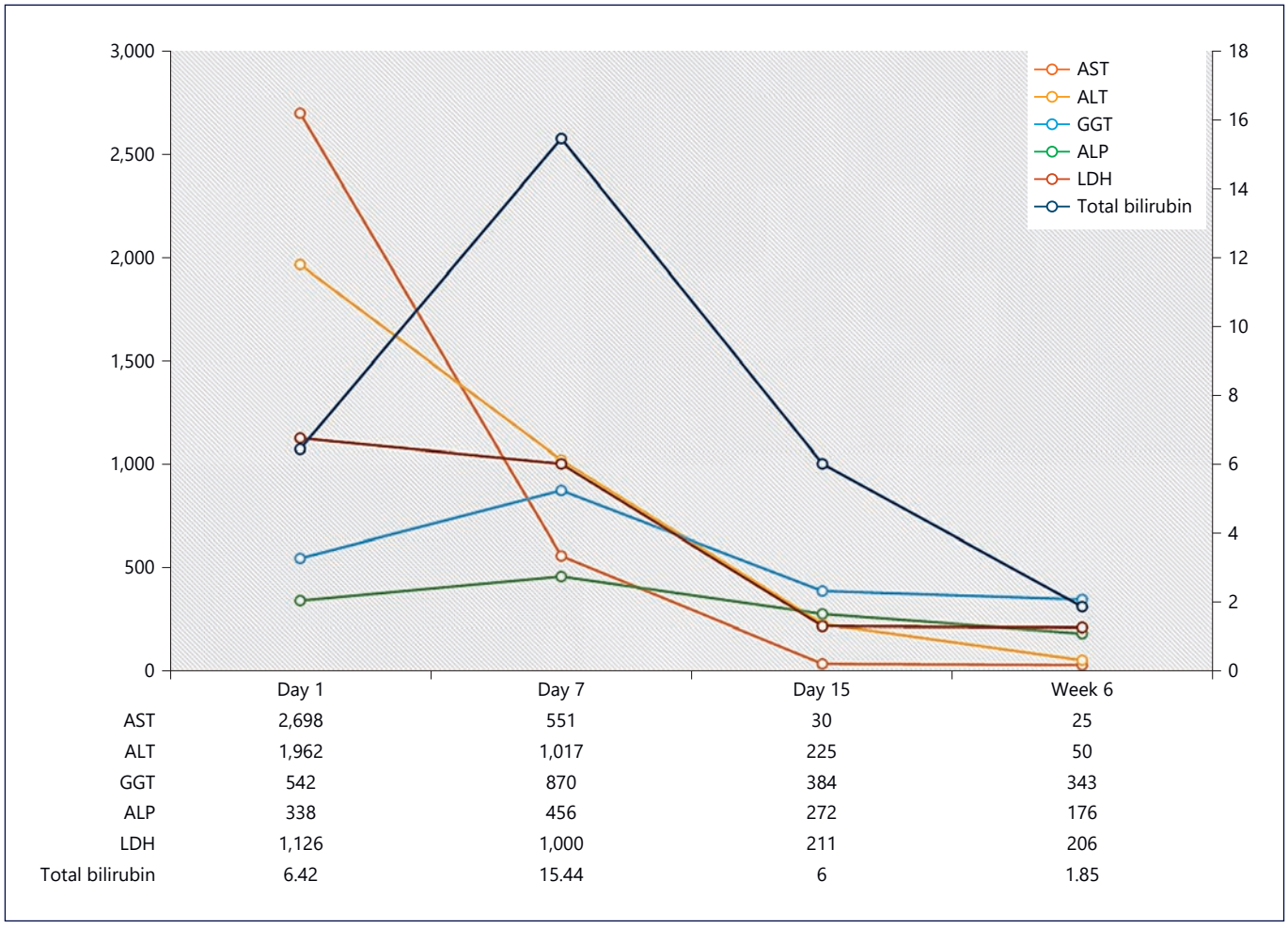
RNA, ribonucleic acid; HEV, hepatitis E virus; ANA, antinuclear antibodies; AMA, antimitochondrial antibodies; LKM1, liver kidney microsome type-1; SMA, smooth-muscle antibody; SLA, soluble liver antigen; LC-1, liver cytosolic antigen; HIV, human immunodeficiency virus; IGRA, interferon-gamma release assay; ENAs, extractable nuclear antigens; ANCAs, antineutrophil cytoplasmic antibodies; DNA, deoxyribonucleic acid; CT, computed tomography.

damage and rapidly progressive multiorgan dysfunction [4].

The etiology of HLH is classified into primary (genetic) and secondary (reactive). In children, congenital defects in cytotoxic T cell and natural killer cell function and inflammasome dysregulation are described. Secondary causes result from acquired immune dysfunction in response to infections, malignancies, autoimmune diseases, or other causes (e.g., drugs, vaccination, organ/stem cell transplantation) [3, 6]. The underlying cause cannot be identified in 20% of cases [6, 7].

CLL is a monoclonal lymphoproliferative disease that results from the proliferation and accumulation of morphologically mature but immunologically dysfunctional B-cell lymphocytes [8]. HLH in the context of CLL has rarely been reported, mostly due to chemotherapy and CLL progression/transformation [9]. We emphasize that our patient had no evidence of progression of CLL or transformation into a more aggressive lymphoma. In CLL, there is a continuous crosstalk between dysfunctional B and T lymphocytes [10, 11]. Disturbances in apoptosis of T cells, altered patterns of surface molecules of T cells, and unbalanced cytokine environment (IL-10, IL-6, IL-4) were described in CLL [10], which might contribute to uncontrolled activation of the immune system. Secondary HLH may be induced by autoimmune disorders, known as macrophage activation syndrome. Although our patient had rheumatoid arthritis, there were no arthritis nor analytical alteration suggesting flare.

Few case reports have described HLH following administration of vaccines [7, 12–14] including after COVID-19 vaccination [15–17], mostly in children with inherited variants of HLH-associated genes or immunosuppressed adults. We postulated that the uncontrolled activation of the immune system resulted from an immune response triggered by vaccination (time frame) and an underlying immune defect (immunosuppression, malignancy). Dramatic proinflammatory responses have been identified in some individuals following immunization [18].



	Day 1	Day 7	Day 15	Week 6
AST	2,698	551	30	25
ALT	1,962	1,017	225	50
GGT	542	870	384	343
ALP	338	456	272	176
LDH	1,126	1,000	211	206
Total bilirubin	6.42	15.44	6	1.85

Fig. 1. Analytical evolution.

The clinical presentation of HLH is mostly non-specific with an acute or subacute course [3]. The liver is one of the most affected organs. ALT and AST elevations are seen in ~85% of adult, mostly mild, and half of patients have hyperbilirubinemia [6, 7]. ALI/ALF as presentation is rare and usually occurs with concomitant organ failure [19]. Liver histopathological features include sinusoidal dilatation and hepatocellular necrosis [20]. Underlying liver disease, infiltration of activated histiocytes and overproduction of cytokines are the putative mechanisms of liver injury [21].

Pulmonary (42%), cutaneous (25%), and neurological (25%) involvement are also frequent [3, 22]. To make the diagnosis of HLH, the patient should meet five of the eight diagnostic HLH-2004 criteria (shown in Table 3) [23].

Table 3. HLH-2004 diagnostic criteria

HLH-2004 diagnostic criteria (5 of the 8 criteria below)
1. Fever
2. Splenomegaly
3. Cytopenias (affecting ≥2 of 3 lineages in the peripheral blood) Hemoglobin <90 g/L Platelets <100 × 10^9/L Neutrophils 1.0 × 10^9/L
4. Hypertriglyceridemia and/or hypofibrinogenemia Fasting triglycerides ≥3.0 mmol/L (≥265 mg/dL) Fibrinogen ≤1.5 g/L
5. Hemophagocytosis in bone marrow or spleen or lymph nodes. No evidence of malignancy
6. Low or no NK cell activity
7. Ferritin ≥500 µg/L
8. sCD25 ≥2,400 U/mL

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Cytopenias are the key laboratory markers of HLH. Hyperferritinemia is the finding that most often (90%) leads to suspicion of LHH [3, 23]. Hypertriglyceridemia or hypofibrinogenemia is easily determined. Although determination of soluble CD25 is helpful for diagnosis, it is rarely available [23]. Finally, the demonstration of hemophagocytosis in bone marrow is helpful for diagnosis, being also mandatory to exclude underlying malignant disorders [23]. In our patient, beyond the signs of hemophagocytosis in the bone marrow, there was no evidence of CLL progression nor transformation to aggressive lymphoma, so five criteria were met.

The HScore [24], which includes clinical and laboratory parameters, supports the diagnosis. Our patient predicted HLH with 99% of probability, so we started therapy immediately, given the presence of organ failure. The diagnosis of severe liver dysfunction induced by HLH is challenging, particularly in the early phase of the disease, as the presentation is non-specific, making it difficult to distinguish it other causes of ALI [3].

The prognosis of adult HLH is poor, with mortality rates ranging from 41 to 75% [3, 6, 19]. A delayed diagnosis is the limiting step toward a successful outcome, including hyperinflammation control (corticosteroids and etoposide) and treatment of the underlying cause, based on HLH-2004 protocols [3]. Early suspicion supported by a high HScore allowed the timely institution of successful treatment. The patient's outcome was consequence of neutropenia and respiratory infection. Some authors recommend prophylactic antibiotic and antifungal therapy and granulocyte colony-stimulating factor in patients treated with T-cell depleting therapy [25], which was not started as early as desirable in our patient. Additionally, there is growing evidence of polyvalent immunoglobulin in HLH treatment [23], specially in our patient, as CLL is associated with lower humoral immunity and hypogammaglobulinemia.

HLH requires a high index of suspicion and should be considered in patients with unknown cause of severe liver dysfunction accompanied by sudden unexplained onset of systemic inflammatory response and multiple organ involvement. We alert to the need to monitor suspicious symptoms after vaccination (e.g., high fever) in patients with underlying pathology. The diagnosis of HLH should not be based on the fulfilment of criteria alone, and it is of utmost importance that an experienced hematologist judges the clinical aspects and weighs up the risks and benefits of treatment.

Statement of Ethics

Ethical approval was not required for this study, in accordance with local/national guidelines. Written informed consent was obtained from the patient's next-of-kin for publication of this case report and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Material preparation, data collection, and first draft of the manuscript were performed by Cristiana Sequeira. Cristiana Sequeira, Sara Ramos Lopes, Anabela Neves, Inês Costa Santos, Cláudio Martins, and Ana Paula Oliveira read and approved the final manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

References

1 European Association for the Study of the Liver Electronic address easloffice@easloffice.eu; Clinical practice guidelines panel; Wendon J; Panel Members; Cordoba J, Dhawan A, et al. EASL Clinical Practical Guidelines on the management of acute (fulminant) liver failure. J Hepatol. 2017 May;66(5):1047–81.

2 Breu AC, Patwardhan VR, Nayor J, Ringwala JN, Devore ZG, Ganatra RB, et al. A multicenter study into causes of severe acute liver injury. Clin Gastroenterol Hepatol. 2019 May;17(6):1201–3.

3 Ramos-Casals M, Brito-Zerón P, López-Guillermo A, Khamashta MA, Bosch X. Adult haemophagocytic syndrome. Lancet. 2014 Apr;383(9927):1503–16.

4 Aricò M, Danesino C, Pende D, Moretta L. Pathogenesis of haemophagocytic lymphohistiocytosis: review. Br J Haematol. 2001 Sep;114(4):761–9.

5 Allen CE, McClain KL. Pathophysiology and epidemiology of hemophagocytic lymphohistiocytosis. Hematology. 2015 Dec 5;2015(1):177–82.

6 Li J, Wang Q, Zheng W, Ma J, Zhang W, Wang W, et al. Hemophagocytic lymphohistiocytosis: clinical analysis of 103 adult patients. Medicine. 2014 Mar;93(2):100–5.
7 Otrock ZK, Eby CS. Clinical characteristics, prognostic factors, and outcomes of adult patients with hemophagocytic lymphohistiocytosis: hemophagocytic lymphohistiocytosis of Adults. Am J Hematol. 2015 Mar;90(3):220–4.
8 Eichhorst B, Robak T, Montserrat E, Ghia P, Niemann CU, Kater AP, et al. Chronic lymphocytic leukaemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2021 Jan;32(1):23–33.
9 Kilari D, Venci N, Friedberg J, Bennett JM. Hemophagocytic lymphohistiocytosis masquerading as progressive chronic lymphocytic leukemia. Leuk Res Rep. 2013;2(1):4–6.
10 Vlachonikola E, Stamatopoulos K, Chatzidimitriou A. T cells in chronic lymphocytic leukemia: a two-edged sword. Front Immunol. 2020;11:612244.
11 Riches JC, Ramsay AG, Gribben JG. T-cell function in chronic lymphocytic leukaemia. Semin Cancer Biol. 2010 Dec;20(6):431–8.
12 Yahya AM, Al-Hammadi S, AlHashaykeh NO, Alkaabi SS, Elomami AS, AlMulla AA, et al. Case report: reactive lymphohistiocytic proliferation in infant with a novel nonsense variant of IL2RG who received BCG vaccine. Front Pediatr. 2021 Nov 2;9:713924.
13 Ikebe T, Takata H, Sasaki H, Miyazaki Y, Ohtsuka E, Saburi Y, et al. Hemophagocytic lymphohistiocytosis following influenza vaccination in a patient with aplastic anemia undergoing allogeneic bone marrow stem cell transplantation. Int J Hematol. 2017 Apr;105(4):389–91.
14 Lagousi T, Korovessi P, Panagouli E, Tsagris V, Kostaridou S. A rare case of measles-associated hemophagocytic lymphohistiocytosis in an infant. Cureus. 2020 May 23;12(5):e8246.
15 Ai S, Awford A, Roncolato F. Hemophagocytic lymphohistiocytosis following ChAdOx1 nCov-19 vaccination. J Med Virol. 2022 Jan;94(1):14–6.
16 Attwell L, Zaw T, McCormick J, Marks J, McCarthy H. Haemophagocytic lymphohistiocytosis after ChAdOx1 nCoV-19 vaccination. J Clin Pathol. 2022;75(4):282–4.
17 Tang LV, Hu Y. Hemophagocytic lymphohistiocytosis after COVID-19 vaccination. J Hematol Oncol. 2021 Dec;14(1):87.
18 Scully M, Singh D, Lown R, Poles A, Solomon T, Levi M, et al. Pathologic antibodies to platelet factor 4 after ChAdOx1 nCoV-19 vaccination. N Engl J Med. 2021 Jun 10;384(23):2202–11.
19 Lin S, Li Y, Long J, Liu Q, Yang F, He Y. Acute liver failure caused by hemophagocytic lymphohistiocytosis in adults: a case report and review of the literature. Medicine. 2016 Nov;95(47):e5431.
20 Favara BE. Histopathology of the liver in histiocytosis syndromes. Pediatr Pathol Lab Med. 1996 Jan;16(3):413–33.
21 Chen JH, Fleming MD, Pinkus GS, Pinkus JL, Nichols KE, Mo JQ, et al. Pathology of the liver in familial hemophagocytic lymphohistiocytosis. Am J Surg Pathol. 2010 Jun;34(6):852–67.
22 Tseng YT, Sheng WH, Lin BH, Lin CW, Wang JT, Chen YC, et al. Causes, clinical symptoms, and outcomes of infectious diseases associated with hemophagocytic lymphohistiocytosis in Taiwanese adults. J Microbiol Immunol Infect. 2011 Jun;44(3):191–7.
23 La Rosée P, Horne A, Hines M, von Bahr Greenwood T, Machowicz R, Berliner N, et al. Recommendations for the management of hemophagocytic lymphohistiocytosis in adults. Blood. 2019 Jun 6;133(23):2465–77.
24 Fardet L, Galicier L, Lambotte O, Marzac C, Aumont C, Chahwan D, et al. Development and validation of the HScore, a score for the diagnosis of reactive hemophagocytic syndrome: score for reactive hemophagocytic syndrome. Arthritis Rheumatol. 2014 Sep;66(9):2613–20.
25 Kim YR, Kim DY. Current status of the diagnosis and treatment of hemophagocytic lymphohistiocytosis in adults. Blood Res. 2021 Apr 30;56(S1):S17–25.

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A Rare Case of Eosinophilic Ileitis and the Role of Motorized Spiral Enteroscopy in Its Diagnosis

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Keywords
Eosinophilic gastrointestinal disorders · Eosinophilic ileitis · Eosinophilic ascites · Motorized spiral enteroscopy

Abstract
Introduction: Eosinophilic gastrointestinal disorders are rare idiopathic conditions characterized by eosinophilic infiltration of any area of the gastrointestinal tract. The clinical presentation is variable and depends on the location and depth of the eosinophilia. Peripheral eosinophilia or elevated serum IgE levels may be present and histological analysis is necessary to a definite diagnosis. ***Presentation:*** A 40-year-old male presented with generalized abdominal pain, nausea, vomiting, diarrhea and anorexia for 1 month and unintended weight loss for 2 months. He had anemia, peripheral eosinophilia, slight hypokalemia, an elevated fecal calprotectin and "a thin sheet of bilateral pleural effusion, reduced-volume ascites and parietal thickening of the entire ileum" in the thoracoabdominal CT scan. An elevated serum IgE was absent and stool for parasites or bacteria, viral serologies, mycobacteria direct exam and culture, and celiac disease screening were negative. The endoscopic exams showed no significant alterations; random ileal biopsies were collected by antegrade motorized spiral enteroscopy and revealed a very fragmented mucosa with inflammatory infiltrate with about 35 eosinophils per high-power field and an altered eosinophil distribution in the ileal wall. The patient initiated oral prednisolone for eosinophilic ileitis, with clinical, analytical, and imagiological improvement. ***Conclusion:*** Eosinophilic ileitis is a rare condition but should be considered in the differential diagnosis of unexplained gastrointestinal symptoms and ascites, particularly in the presence of peripheral eosinophilia. Motorized spiral enteroscopy can be helpful in the diagnosis, allowing the collection of biopsy specimens effectively and safely.

Um caso raro de ileíte eosinofílica e o papel da enteroscopia monitorizada espiral no seu diagnóstico

Palavras Chave
Doenças gastrointestinais eosinofílicas · Ileíte eosinofílica · Ascite eosinofílica · Enteroscopia monitorizada espiral

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Resumo

Introdução: As doenças gastrointestinais eosinofílicas são patologias idiopáticas e raras, caracterizadas pela infiltração eosinofílica de qualquer região do trato gastrointestinal. A apresentação clínica é variável e depende da localização e profundidade da invasão eosinofílica. Pode estar presente eosinofilia periférica ou elevação da IgE sérica; a análise histológica é necessária para um diagnóstico definitivo. ***Apresentação:*** Homem de 40 anos com dor abdominal generalizada, náuseas, vómitos e anorexia desde há um mês e perda involuntária de peso há dois meses. Apresentava anemia aguda, eosinofilia periférica, hipocalémia ligeira, elevação da calprotectina fecal e «uma pequena lâmina de derrame pleural, ascite de pequeno volume e espessamento parietal de todo o íleo». Não apresentava elevação da IgE sérica, o exame bacteriológico e parasitológico de fezes foi negativo, tal como o exame direto e cultural de micobactérias e o rastreio de doença celíaca. Os exames endoscópicos não apresentaram alterações significativas; realizaram-se biópsias ileais aleatórias através de enteroscopia motorizada espiral, que revelaram uma mucosa fragmentada com infiltrado inflamatório com cerca de 35 eosinófilos por campo de grande aumento e alteração da sua distribuição na parede ileal. O doente iniciou prednisolona oral, com melhoria clínica, analítica e imagiológica. ***Conclusão:*** A íleite eosinofílica é uma condição rara mas deverá ser considerada no diagnóstico diferencial de sintomas gastrointestinais inexplicados e de ascite, particularmente quando presente eosinofilia periférica. A endoscopia espiral motorizada pode ser útil para o diagnóstico, permitindo a biópsia do delgado de forma efectiva e segura.

Introduction

Eosinophilic gastrointestinal disorders (EGID) are rare conditions characterized by infiltration of the gastrointestinal tract (GIT) by eosinophils, in the absence of known causes for eosinophilia (e.g., parasitic infection, malignancy, drug reactions, …) [1].

Although idiopathic in nature, an allergic mechanism has been suggested in at least a subset of these patients. In fact, a personal or family history of food allergies, asthma, and atopic disorders is present in about 50% to 70% of cases [2]. The pathogenesis of the disease is not well defined, but it is thought to be a polygenic allergic disorder on the spectrum between IgE-mediated and delayed Th2 responses, in which an alteration of the mucosal integrity allows the direct contact of antigens with the gut wall, triggering an eosinophilic inflammatory response [3].

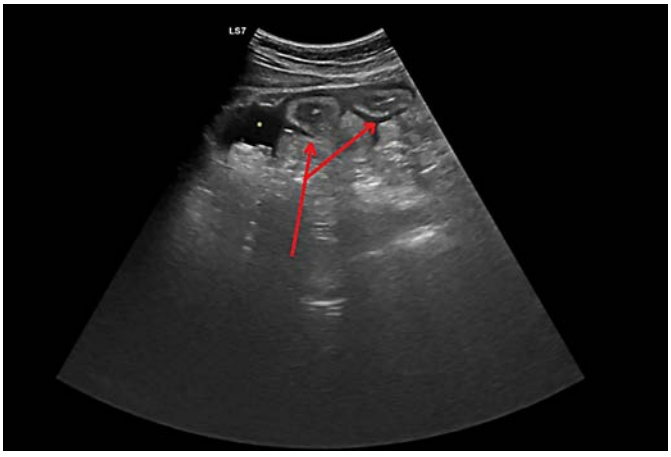

Fig. 1. Radial EUS demonstrating two small bowel loops with a thickened wall (red solid arrow), surrounded by free peritoneal fluid (asterisk).

This eosinophilic infiltration can occur in any area of the GIT – the antrum and proximal small bowel being the most frequently affected segments – and throughout the different layers of the GIT: mucosal (the most frequent), muscular, or serosal, so that the area and depth of the eosinophilia determine the clinical presentation [4–6]. Thus, patients with mucosal disease may present with abdominal pain, diarrhea, bleeding, iron-deficiency anemia, malabsorption symptoms, protein-losing enteropathy, or failure to thrive; the muscularis involvement can cause bowel thickening, leading to obstruction, and predominantly serosal pattern, which occurs in a minority of patients, presents with exudative ascites [1, 7].

EGID may or may not be accompanied by peripheral eosinophilia or elevated serum IgE levels and has unspecific radiologic findings, so that, together with clinical, laboratory, and endoscopic findings, the histologic confirmation of eosinophilic infiltration is necessary for a definite diagnosis [1, 8].

We describe the case of a patient with eosinophilic ileitis (EI) with transmural inflammation.

Case Presentation

A 40-year-old male presented in the emergency department, complaining of generalized abdominal pain, almost every day for 1 month, with no relation with meals. He also presented with nausea and vomiting, diarrhea (3–4 liquid stools), anorexia, and an

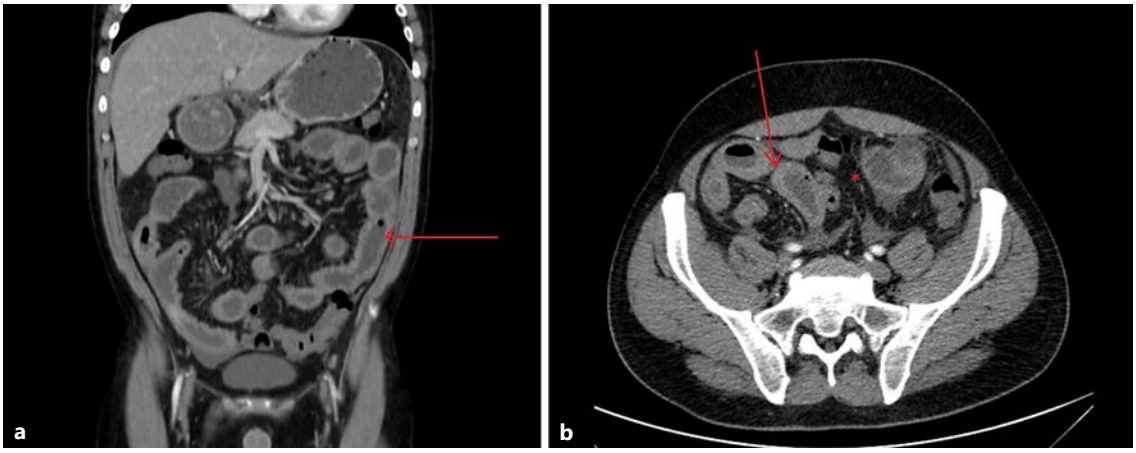

Fig. 2. CT enterography revealing a thickening of different layers of the ileal wall. The asterisk indicates a small amount of ascites.

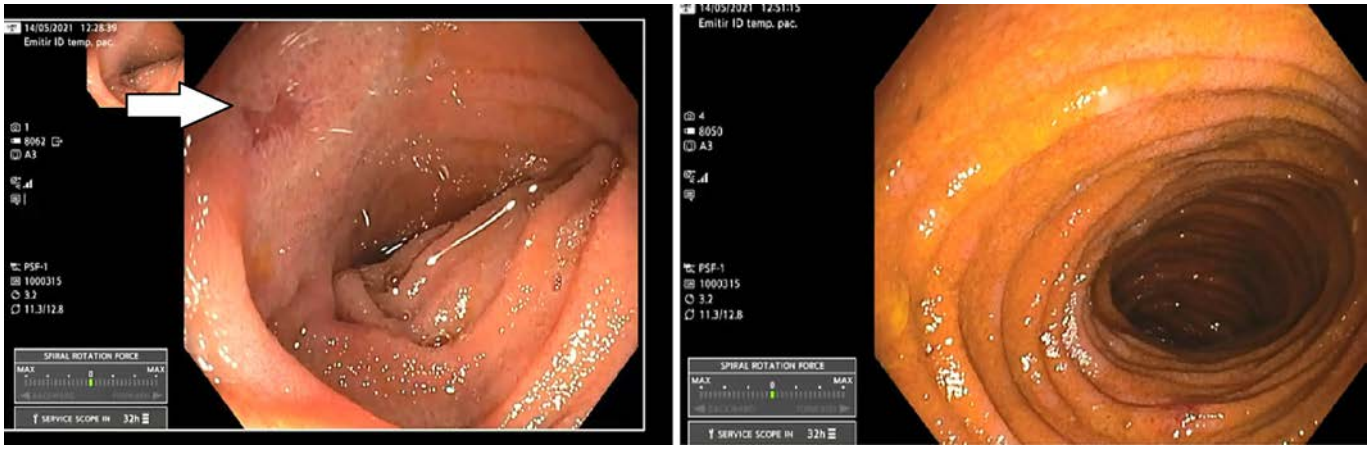

Fig. 3. A single small erosion detected in the distal jejunum (left) and the normal appearing ileal mucosa, observed by the antegrade motorized spiral enteroscopy.

unintended 10-kg weight loss in 2 months. He denied fever, dysphagia, fecal mucus, or bleeding. He was previously medicated with paracetamol, ibuprofen, scopolamine, and omeprazole, without a favorable response.

He worked as a brickworker, was an active smoker, and his only antecedents were dyslipidemia, removal of a sacrococcygeal cyst and an anal fistulotomy. He denied chronic medication, consumption of non-piped water, or contact with non-dewormed animals. He had no personal or family history of allergic or gastrointestinal pathologies.

His only significant finding on physical examination was mucosal pallor. Analytically, he had acute anemia (hemoglobin concentration of 12.5 g/dL, with a normal level from 2 days earlier), peripheral eosinophilia (1,600 eosinophils/L), and slight hypokalemia (3.4 mEq/L). The remaining results were normal, including C-reactive protein, renal, liver, thyroid, and pancreatic functions. He performed an abdominal ultrasound that showed a "small amount of free intraperitoneal liquid" and "several bowel loops demonstrating parietal thickening" (shown in Fig. 1) that was clarified with a thoracoabdominal CT scan that revealed a "thin sheet of bilateral pleural effusion, reduced-volume ascites and extensive regular parietal thickening of the entire ileum."

He was then hospitalized for symptomatic therapy, correction of hypokalemia, and diagnostic investigation. Analytically he had an elevated fecal calprotectin (974 μg/g); elevated serum IgE was absent and stool for parasites or bacteria were negative, such as viral serologies, mycobacteria direct exam and culture, and celiac disease screening.

He performed an upper endoscopy and colonoscopy, both of which showed no macroscopic lesions, including 5 cm of visualized ileum. Histopathological analysis revealed gastritis with *Helicobacter pylori* and "lympho-plasmocytic infiltrate, including eo-

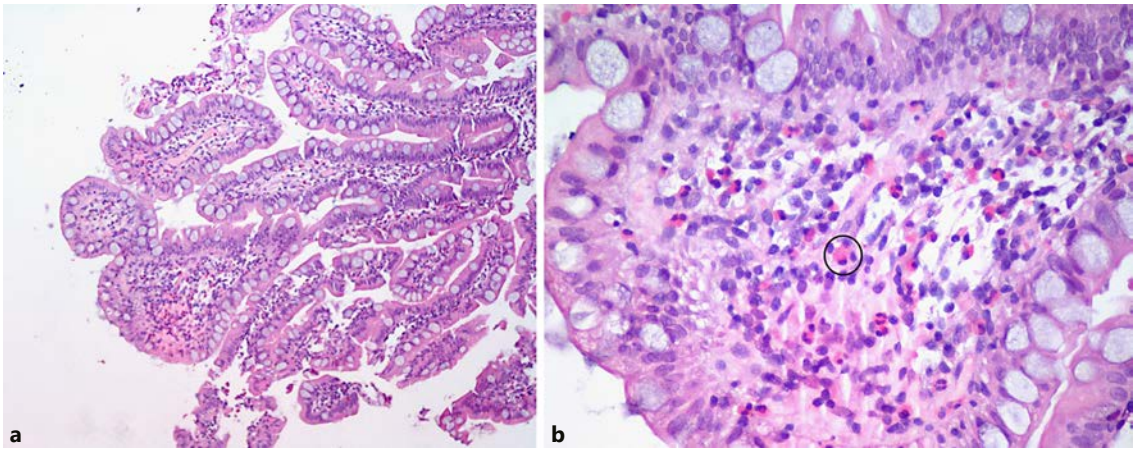

Fig. 4. a Ileal wall showing a fragmented mucosa, with inflammatory infiltrate. Hematoxylin-eosin. Original magnification, ×10. **b** Amplification of intestinal villi, showing the presence of eosinophils (one example surrounded by a black circle). Hematoxylin-eosin. Original magnification, ×40.

sinophils (fewer than 10 per high-power field HPF]), with signs of mild activity" in the ileal specimens. Then a CT enterography revealed similar results, namely "moderate edema of the ileum walls and small volume ascites, with no appreciable changes in the colon," as shown in Figure 2.

After 13 days of supportive treatment, the patient maintained 3–6 daily stools and peripheral eosinophilia (1,300 eosinophils/L), even though there was a resolution of the anemia and hypokalemia.

An antegrade motorized spiral enteroscopy (MSE) was performed, where the only macroscopic alteration was a single erosion in the distal jejunum (shown in Fig. 3). Despite the normal appearing mucosa, shown in Figure 3, ileal random biopsies were collected and histological analysis revealed a "very fragmented small bowel mucosa, with inflammatory infiltrate with about 35 eosinophils per HPF (and about 10 eosinophils per HPF in crypt epithelium), without epithelial permeation, microabscesses or erosion, being compatible with eosinophilic enteritis" (shown in Fig. 4).

The patient initiated on treatment with oral prednisolone and was discharged after 17 days, with clinical improvement (absence of abdominal pain and 1–2 daily stools) and a normal analytic study. He completed a course of 4 weeks of corticotherapy, which has proven to be successful at 1-month clinical and imagiological re-evaluation.

Discussion/Conclusion

The most common cause of ileitis is Crohn's disease; however, it can be caused by a wide variety of other conditions, such as infectious diseases, vasculitis, neoplasms, drug-induced and others, including eosinophilic enteritis [1]. The latter belongs to EGID and should be considered in the differential diagnosis of unexplained GI symptoms. Among EGID, EI is a particularly rare entity, so there have been few epidemiological studies, most of them addressing the prevalence of EI along with eosinophilic gastritis. Thus, in a retrospective study that included over 35 million individuals between 2012 and 2017, the prevalence of eosinophilic gastroenteritis (EoGE) was 5.1/100,000 people, which was similar to the results of Reed et al., in which the overall prevalence of EoGE along with eosinophilic colitis was 2–28/100,000 people (including adults and children), and did not differ much from those of a large retrospective analysis of a database with over 11 million individuals, in which 8.2/100,000 people met criteria for EoGE [9–11]. Even though epidemiologic data are limited, there has been an increasing prevalence and incidence of EGID for unknown reasons, being hypothesized that this trend may reflect the development of new and better diagnostic methods – increasing the detection rate –, along with the growth of allergic pathologies in developed countries, as explained by the hygiene hypothesis [11].

Our patient had particular features, as most of studies verify that EoGE is more prevalent in females and that prevalence gradually decreases with age, being higher in patients younger than 5 years [10]. In addition, several case series and single center studies have identified allergic comorbidities in patients with EoGE, ranging from 30 to 45.6% in adults and going up to 80% in children [12, 13]. As referred, a personal/family history of atopy was absent in this patient, which has concealed the suspicion of an eosinophilic pathology.

Clinically, the symptoms presented by our patient were consistent with those described in literature. According to Jensen et al., when the upper GIT is involved, abdominal pain, diarrhea, nausea, and vomiting are the most frequent symptoms, in descending order [10]. In this case, there was also ascites, which implies an involvement of the serosa, being therefore compatible with a transmural eosinophilic infiltration. Differently of eosinophilic pleural effusion – defined as containing at least 10% eosinophils in the white cell differential count –, there are no defined criteria for eosinophilic ascites [14]. Even so, an elevated eosinophilic count in ascitic fluid would have been a valuable diagnostic indicator; however, because of the small volume ascites, performing a paracentesis was technically impossible.

Besides, our patient had ileal wall thickness, which is in agreement with other cases described in the literature, such as Zhang et al. and Zheng et al. [5, 15]. Similarly, endoscopy did not contribute to clarify the diagnosis, such as in Reed et al.'s study, in which 47% of endoscopic examinations were normal, so that it was essential to study the ileal region [16]. With this in mind, methods such as endoscopic videocapsule would be useless and time-consuming since not only the probability of finding results was low, but also it would not allow performing biopsies. Therefore, to allow direct endoscopic access to the ileus, we performed an MSE. The alternative – balloon-assisted enteroscopy (single or double) – is currently the method of choice in most centers, since its efficacy and safety has been extensively studied. The MSE presents a different principle, where the bowel is pulled onto the scope rather than traversed by pushing the scope forward. In a recent systematic review with meta-analyses, the two methods were compared and it was found that despite the fact that there were no significant differences in diagnostic and therapeutic success rates, the procedure time was significantly shorter for the MSE group, with comparable safety [17, 18]. Until this day, we have performed in our center 10 of these procedures, with a high level of efficacy and safety.

To our knowledge this is the first reported case in which the use of MSE allowed the diagnostic of EI, enabling the observation of the entire small bowel and the collection of multiple biopsies from the ileum in about 70 minutes, without complications.

Regarding histopathology, since eosinophils can be detected in normal ileal mucosa, the concept of "abnormally increased eosinophils" is not well defined. According to Collins criteria, up to 28 eosinophils per HPF can be found in lamina propria of normal ileum, with a minimum of 56 eosinophils per HPF necessary for an EI diagnosis. Nonetheless, more recent evidence suggests that counting mucosal eosinophils is of little practical value when compared to the analysis of their distribution; eosinophils are normally solely dispersed in the lamina propria so that even a few cells in other locations should raise EI suspicion. Therefore, more than the 35 eosinophils per HPF, we valued the presence of epithelial cell damage along with the altered eosinophil distribution – with more than 4 eosinophils per HPF in crypt epithelium – and the absence of acute inflammatory cells [19, 20].

Although there are no consensus recommendations regarding the diagnosis, we supported it on orientations described in the literature, namely the conjugation of clinical manifestations with peripheral eosinophilia, an altered eosinophil distribution in ileal wall, the lack of involvement of other organs, and ultimately the favorable response to corticotherapy. Since the patient presented with peripheral eosinophilia (>1,500/L on admission) and organ disfunction, we consider of uttermost importance his surveillance with regard to the development of extragastrointestinal symptoms that may suggest that this is an initial manifestation of a hypereosinophilic syndrome, which implies a distinctive therapeutic approach and prognosis [21, 22].

In conclusion, EI is a rare condition that should be considered in the differential diagnosis of unexplained GI symptoms and ascites, particularly in the presence of peripheral eosinophilia. We report an unusual case of EI with transmural eosinophilic inflammation, in which MSE had an essential role for a less time-consuming diagnosis.

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Statement of Ethics

Written informed consent was obtained. This study did not require review or approval by the appropriate ethics committee.

Conflict of Interest Statement

The authors have no conflict of interests to declare.

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None.

Author Contributions

I.T. was part of the assistant medical team, designed and wrote the article. M.M., E.G., and C.R. were part of the assistant medical team. T.A. and L.L. reviewed the manuscript. All authors approved the final version to be published.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

References

1 DiLauro S, Crum-Cianflone NF. Ileitis: when it is not Crohn's disease. Curr Gastroenterol Rep. 2010 Aug;12(4):249–58.
2 Daneshjoo R, Talley NJ. Eosinophilic gastroenteritis. Curr Gastroenterol Rep. 2002;4:366–72.
3 Rothenberg ME. Eosinophilic gastrointestinal disorders (EGID). J Allergy Clin Immunol. 2004 Jan;113(1):11–28.
4 Talley NJ, Shorter RG, Phillips SF, Zinsmeister AR. Eosinophilic gastroenteritis: a clinicopathological study of patients with disease of the mucosa, muscle layer, and subserosal tissues. Gut. 1990 Jan;31(1):54–8.
5 Zhang L, Duan L, Ding S, Lu J, Jin Z, Cui R, et al. Eosinophilic gastroenteritis: clinical manifestations and morphological characteristics, a retrospective study of 42 patients. Scand J Gastroenterol. 2011 May;46(9):1074–80.
6 Feldman M, Friedman LS, Brandt LJ, Chung RT, Rubin DT, Wilcox CM. Sleisenger and Fordtran's gastrointestinal and liver disease. Elsevier; 2021. Vol. 30; p. 424–34.
7 Talley NJ, Shorter RG, Phillips SF, Zinsmeister AR. Eosinophilic gastroenteritis: a clinicopathological study of patients with disease of the mucosa, muscle layer, and subserosal tissues. Gut. 1990 Jan;31(1):54–8.
8 Zhang M, Li Y. Eosinophilic gastroenteritis: a state-of-the-art review. J Gastroenterol Hepatol. 2016 Jun;32(1):64–72.
9 Mansoor E, Saleh MA, Cooper GS. Prevalence of eosinophilic gastroenteritis and colitis in a population-based study, from 2012 to 2017. Clin Gastroenterol Hepatol. 2017 Nov;15(11):1733–41.
10 Jensen ET, Martin CF, Kappelman MD, Dellon ES. Prevalence of eosinophilic gastritis, gastroenteritis, and colitis: estimates from a national administrative database. J Pediatr Gastroenterol Nutr. 2016 Jan;62(1):36–42.
11 Spergel JM, Book WM, Mays E, Song L, Shah SS, Talley NJ, et al. Variation in prevalence, diagnostic criteria, and initial management options for eosinophilic gastrointestinal diseases in the United States. J Pediatr Gastroenterol Nutr. 2011 Mar;52(3):300–6.
12 Zhang L, Duan L, Ding S, Lu J, Jin Z, Cui R, et al. Eosinophilic gastroenteritis: clinical manifestations and morphological characteristics, a retrospective study of 42 patients. Scand J Gastroenterol. 2011 Sep;46(9):1074–80.
13 Guajardo JR, Plotnick LM, Fende JM, Collins MH, Putnam PE, Rothenberg ME. Eosinophil-associated gastrointestinal disorders: a world-wide-web based registry. J Pediatr. 2002 Oct;141(4):576–81.
14 Adelman M, Albelda SM, Gottlieb J, Haponik EF. Diagnostic utility of pleural fluid eosinophilia. Am J Med. 1984 Nov;77(5):915–20.
15 Zheng X, Cheng J, Pan K, Yang K, Wang H, Wu E. Eosinophilic gastroenteritis: CT features. Abdom Imaging. 2008 Mar–Apr;33(2):191–5.
16 Reed C, Woosley JT, Dellon ES. Clinical characteristics, treatment outcomes, and resource utilization in children and adults with eosinophilic gastroenteritis. Dig Liver Dis. 2015 Mar;47(3):197–201.
17 Beyna T, Aryanitakis M, Schneider M, Gerges C, Böing D, Devière J, et al. Motorised spiral enteroscopy: first prospective clinical feasibility study. Gut. 2021 Feb;70(2):261–7.
18 Baniva R, Upadhava S, Subedi SC, Khan J, Sharma P, Mohammed TS, et al. Balloon enteroscopy versus spiral enteroscopy for small-bowel disorders: a systematic review and meta-analysis. Gastrointest Endosc. 2017 Dec;86(6):997–1005.
19 Collins MH. Histopathologic features of eosinophilic esophagitis and eosinophilic gastrointestinal diseases. Gastroenterol Clin North Am. 2014 Mar;43(2):257–68.
20 Yantiss RK. Eosinophils in the GI tract: how many is too many and what do they mean? Mod Pathol. 2015 Jan;28 Suppl 1(1):S7–21.
21 Rached AA, Hajj WE. Eosinophilic gastroenteritis: approach to diagnosis and management. World J Gastrointest Pharmacol Ther. 2016 Nov 6;7(4):513–23.
22 Leru PM. Eosinophilic disorders: evaluation of current classification and diagnostic criteria, proposal of a practical diagnostic algorithm. Clin Transl Allergy. 2019 Jul;9(1):36–9.

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Clinical Case Study

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Eosinophilic Gastroenteritis: Still a Diagnostic Challenge

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Keywords
Eosinophilic enteropathy · Eosinophilia · Ascites

Abstract
Introduction: Eosinophilic gastroenteritis (EoG) is a rare condition with a yet poorly understood pathophysiology. ***Case Presentation:*** We report on a case of a 36-year-old woman with a history of atopy presenting with nausea, abdominal discomfort, weight loss, and ascites. Laboratorial analysis revealed peripheral eosinophilia and a slight elevation of inflammatory markers. The patient pursued medical assistance several times with a delay in the diagnosis. The pathway to the diagnosis of EoG with serosal infiltration and further management is presented. ***Discussion:*** Despite being diagnosed by exclusion, it is important to suspect EoG with subserosa involvement in patients presenting with the uncommon association of peripheral eosinophilia and ascites, particularly if there is a history of atopy.

Gastroenterite eosinofílica: os desafios do diagnóstico

Palavras chave
Gastroenterite eosinofílica · Eosinofilia · Ascite

Resumo
Introdução: A gastroenterite eosinofílica é uma condição rara, com uma etiologia ainda pouco compreendida. ***Caso Clínico:*** Uma mulher de 36 anos, com antecedentes de atopia, que se apresenta com náuseas, desconforto abdominal difuso, perda ponderal e ascite de novo. As análises laboratoriais revelaram eosinofilia periférica e ligeira elevação dos parâmetros inflamatórios. A doente recorreu a cuidados de saúde repetidamente sem um diagnóstico. É apresentado o percurso até ao diagnóstico de gastroenterite eosinofílica com infiltração serosa e tratamento subsequente. ***Discussão:*** Apesar de ser um diagnóstico de exclusão, é importante suspeitar de gastroenterite eosinofílica com envolvimento subseroso perante a associação de ascite a sintomas gastrointestinais inespecíficos particularmente em doentes com história de atopia.

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Introduction

Eosinophilic gastroenteritis (EoG) results from excessive infiltration by eosinophils in the mucosa, submucosa, or muscularis of the stomach and small bowel [1, 2]. It is a rare condition with an estimated prevalence of 5.1 per 100,000 people in the USA [3]. Pathophysiology is poorly understood, but atopy is a known risk factor [1, 3, 4]. Here, we report a case of a young patient with a history of atopy presenting with ascites, constitutional symptoms, and peripheral eosinophilia with a delayed diagnosis of EoG.

Case Report

A 36-year-old woman with a medical history of asthma and urticaria under treatment with levocetirizine and a combined oral contraceptive was admitted to the hospital for the study of acute diarrhea (1-2 liquid stools per day with no blood or mucus), associated with abdominal discomfort, abdominal swelling, early satiety, and asthenia with onset 2 weeks before. The patient also reported wheezing episodes on the previous week. During this period, she looked for medical assistance three times being discharged with symptomatic treatment and cotrimoxazole with no improvement. Physical examination revealed normal blood pressure (122/64 mm Hg) and heart rate (77 bpm), no fever (auricular temperature 36.5°C), 98% peripheral oxygen saturation, no mucocutaneous alterations, and cardiac and pulmonary auscultation without alterations, with moderate volume ascites as the only remarkable finding.

Laboratory results (Table 1) showed peripheral eosinophilia (7,000 eosinophils/μL, 45% of the leucocytes, ref. range <500/μL) and increased seric immunoglobulin E (1,083 IU/mL, ref. range <129 IU/mL). An abdominal ultrasound revealed diffuse small bowel wall thickening and moderate volume ascites. The cell count of the ascitic fluid revealed 89% of eosinophils (8,337/μL, Table 2). Serum ascites albumin gradient was inferior to 1.1, suggesting a peritoneal cause for the ascites. A thoraco-abdominopelvic computerized tomography presented no lung findings (Fig. 1a), yet it was identified a slight thickening of the distal esophagus (Fig. 1b), and diffuse jejunal and ileal wall thickening (Fig. 1c), without lymph node enlargement. An upper and lower endoscopy with segmental biopsies was performed, revealing a normal endoscopic appearance of the mucosa (Fig. 2). At this point, the considered differential diagnosis was EoG, eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome), hypereosinophilic syndrome, and, less likely, parasitosis, infectious gastroenteritis, food or drug hypersensitivity, celiac disease, connective tissue diseases, inflammatory bowel disease, and hematologic neoplasia [1, 2].

An exhaustive screening for systemic eosinophilia causes was carried out. The peripheral blood smear did not reveal cellular atypia. Serum levels of vitamin B12 were normal – 441 pg/mL (ref. range 211–911 pg/mL), such as folate 7.2 ng/mL (ref. range 3.5–17.5 ng/mL); serum iron was slightly below normal – 31 μg/dL (ref. range 50–170 μg/dL). Serum ferritine, total iron-binding capacity (TIBC), and transferrin saturation presented normal values. Microbiologic and parasitological stool examinations were negative for pathogenic strains. Serum antibodies *anti-toxocara canis*, *anti-echinococcus*, and *anti-fasciola* were also negative. The immunological study revealed negative antinuclear antibodies and antineutrophil cytoplasm antibodies. There was a slight elevation of the inflammatory marker C-reactive protein (12.9 mg/L; ref. range <3) with normal erythrocyte sedimentation rate. Anti-VIH I/II antibodies were negative. Total serum immunoglobulin E was increased (1,083 UI/mL; ref. <129). Immunoglobulin subtypes other than IgE and serum protein electrophoresis were within the normal range. The inhalatory allergen panel (Rast IgE) was positive, yet the food allergen panel was negative. Skin prick tests were neg-

Table 1. Blood tests results at admission

Variable	Reference range	Result
Hemoglobin	11.9–15.6 g/L	13.8
White-cell count	4.0–11.0 × 10^3/μL	**15.6**
Neutrophils	1.8–7.1 × 10^3/μL	5.1 (33%)
Lymphocytes	1.2–3.4 × 10^3/μL	2.8 (18%)
Eosinophils	0.0–0.5 × 10^3/μL	**7.0 (45%)**
Basophils	0.0–0.1 × 10^3/μL	0.0 (0%)
Monocytes	0.2–0.9 × 10^3/μL	0.6 (4%)
Platelet count	150–400 × 10^3/μL	176.0
Ureia	15–39 mg/dL	33.0
Creatinine	0.7–1.2 mg/dL	0.7
Sodium	135–145 mmol/L	139.0
Potassium	3.5–5 mmol/L	3.6
Cloride	98–107 mmol/L	106
AST	15–37 U/L	37
ALT	12–78 U/L	102
Total bilirubin	0.1–1.0 mg/dL	0.41
Alkaline phosphatase	45–117 U/L	57
Amilase	25–115 U/L	33
Total proteins	6.4–8.2 g/dL	6.6
Albumin	3.5–4 mg/L	3.5
C-reactive protein	<3 mg/L	**12.9**

Table 2. Ascitic fluid analysis at admission

Variable	Result
Eritrócitos	17,000/μL
Cell count	9,368/μL
Lymphocytes	374/μL (4%)
Eosinophils	**8,337/μL (89%)**
Monocytes	468/μL (5%)
Mesotelial cells	187/μL (2%)
Neutrophils	0/μL (0%)
Glucose	108.0 mg/dL
Protein	5.4 g/dL
Albumine	3.1 g/dL
Lactate dehydrogenase	138 UI/L
Amilase	13 UI/L

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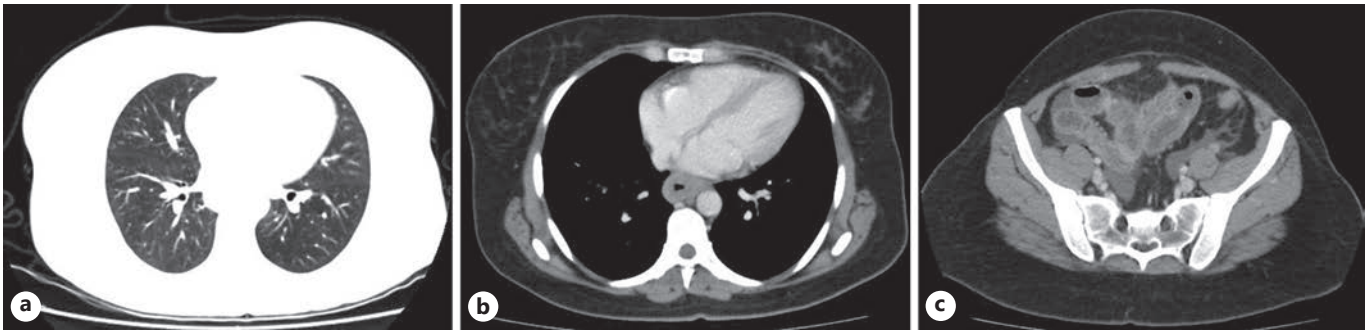

Fig. 1. Thoracoabdominopelvic computerized tomography (CT) without lung alterations (**a**); distal esophagus wall thickening (**b**); and diffuse jejunal and ileal wall thickening (**c**).

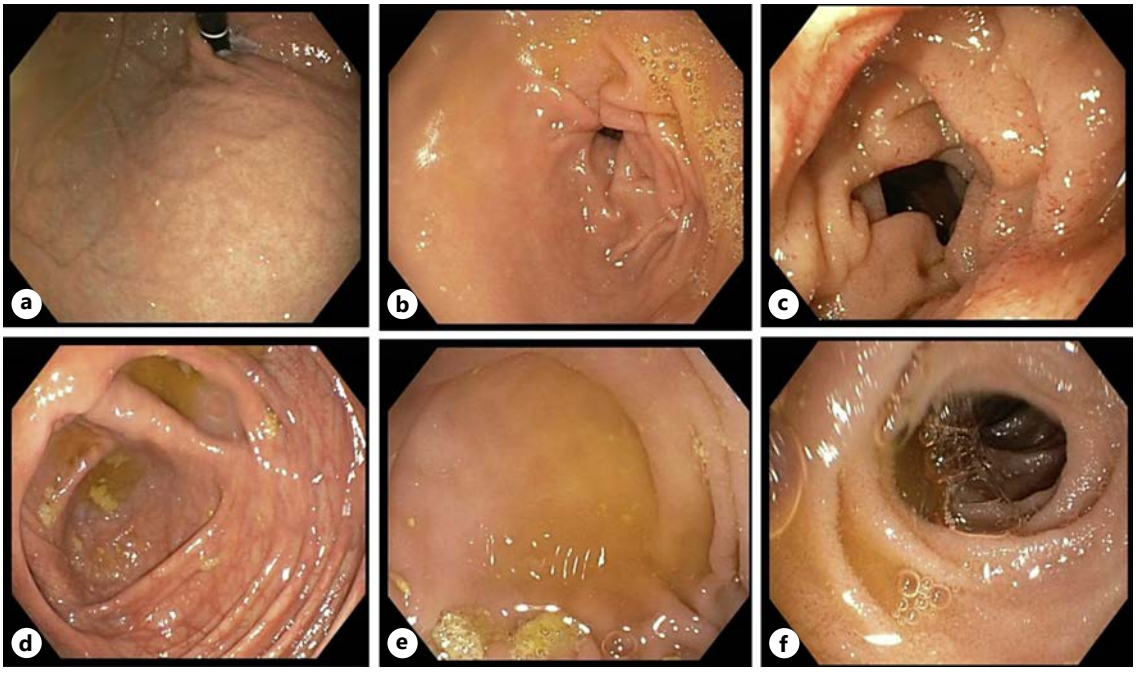

Fig. 2. Upper GI endoscopy with normal endoscopic appearance of gastric cardia and fundus (**a**), gastric antrum (**b**), and duodenum (**c**). Colonoscopy with ileoscopy with normal mucosa of the cecum (**d**, **e**) and terminal ileus (**f**).

ative for food allergens and positive for dust mites, dog and grass allergens. Electrocardiogram presented a sinusal rhythm without alterations. Troponin I and CK-MB seric levels were normal. Spirometry presented a mild restrictive ventilatory pattern. Liver tests were normal except for slightly elevated ALT levels at admission, which normalized 3 days later. Renal dysfunction markers and urinary sediment were within the normal range. In sum, an extensive investigation of the alternative causes of peripheral eosinophilia and infiltration of other organs by eosinophils was negative.

Empirical treatment for EoG with oral prednisolone 40 mg per day and the six-food elimination diet (eggs, milk, soy, nuts, seafood, wheat) was initiated with the support of a dedicated nutritionist. A rapid clinical improvement was observed with normalization of bowel habits and a reduction of abdominal volume. Additionally, a rapid reduction in peripheral eosinophilia with normalization at 3 weeks was observed.

Posteriorly, results of the endoscopic biopsies confirmed eosinophilic infiltration of the duodenum and ileum (>50 eosinophils per high-power field [HPF]), less expressive on esophageal and colonic biopsies (10 eosinophils/HPF; Fig. 3), which sustains the diagnosis of EoG. Gastric biopsies were negative for *Helicobacter pylori*.

Three months after the initial episode and upon the terminus of the oral steroid course, the patient was in clinical and laboratorial remission and so a progressive reintroduction of eliminated foods was conducted with close monitoring. It was observed a re-

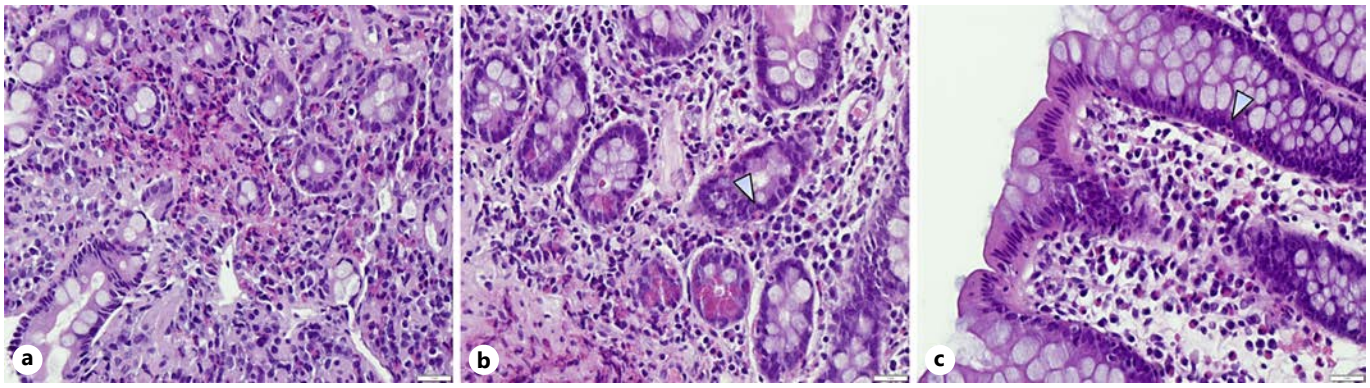

Fig. 3. Histopathologic images of endoscopic biopsies of duodenum (**a**) and ileum (**b**), HE. ×400, with infiltration of the lamina propria with eosinophils (>52 per HPF). Esophageal and colonic (**c**) biopsies with >10 eosinophils/HPF. HE, hematoxylin and eosin coloration.

surgence of diarrhea and abdominal pain with seafood ingestion ceased with subsequent restriction of these foods in the patient's diet. Two years after the diagnosis, the patient repeated upper endoscopy and colonoscopy with ileal and colonic biopsies, which revealed no eosinophilic infiltration. Three years after the initial episode, the patient is asymptomatic on a diet with a restriction of seafood without relapses or the need for any treatments.

Discussion

EoG is a rare condition with a yet poorly understood pathophysiology [1–3]. Clinical presentation depends on the site, extent, and depth of disease in the gastrointestinal (GI) tract [5]. Patients often present with nonspecific GI symptoms that may be accompanied with peripheral eosinophilia [1]. When there is serosal infiltration, patients often present with ascites associated with nonspecific GI symptoms such as abdominal pain, nausea, or vomiting [1]. Diagnosis is made by infiltration of the GI tract by excessive numbers of eosinophils in the absence of alternative causes [6]. The number of eosinophils necessary for diagnosis is not well defined, yet recent reviews suggest the values of >30 eosinophils per HPF for eosinophilic gastritis, >52 eosinophils per HPF for enteritis, and for eosinophilic colitis, >50 per HPF in the right colon, >35 per HPF in the transverse colon, and >25 per HPF in the left colon [1, 7]. The most relevant differential diagnosis is hypereosinophilic syndrome with GI involvement and secondary eosinophilic infiltration, which may occur in GI infections, hypersensitivity reactions, or connective tissue diseases [1, 2].

First-line treatments are short courses of systemic corticosteroids and food elimination diets with good efficacy [8]. Prognosis is generally favorable for patients who respond to first-line treatments, yet a minority of patients can exhibit a relapsing and remitting course and, therefore, EoG patients should receive long-term monitoring [8, 9]. The optimal follow-up is still a matter of debate with limited supporting data [1, 8]. The authors propose a close monitoring (every 4 weeks) until remission is achieved, followed by a further spaced follow-up (e.g., every 6 months). Remission can be assessed by the absence of symptoms and peripheral eosinophilia that can be complemented with repeated endoscopic biopsies when there are doubts. Despite being diagnosed by exclusion, it is important to suspect EoG with subserosa involvement in patients presenting with the uncommon association of peripheral eosinophilia and ascites, particularly if there is a history of allergies.

Statement of Ethics

Written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

S.S.M. drafted the manuscript; B.G. and J.B.S. were involved in the management of the patient and critically revised the manuscript; A.C.C. and R.G. critically revised and finished the manuscript.

Data Availability Statement

The data that support the findings of this study are not publicly available due to their containing information that could compromise the privacy of research participants but are available from the corresponding author (S.S.M.) upon reasonable request.

References

1 Walker MM, Potter M, Talley NJ. Eosinophilic gastroenteritis and other eosinophilic gut diseases distal to the oesophagus. Lancet Gastroenterol Hepatol. 2018;3(4):271–80.
2 Abou Rached A, El Hajj W. Eosinophilic gastroenteritis: approach to diagnosis and management. World J Gastrointest Pharmacol Ther. 2016;7(4):513–23.
3 Mansoor E, Saleh MA, Cooper GS. Prevalence of eosinophilic gastroenteritis and colitis in a population-based study, from 2012 to 2017. Clin Gastroenterol Hepatol. 2017;15(11):1733–41.
4 Guajardo JR, Plotnick LM, Fende JM, Collins MH, Putnam PE, Rothenberg ME. Eosinophil-associated gastrointestinal disorders: a world-wide-web based registry. J Pediatr. 2002;141(4):576–81.
5 Uppal V, Kreiger P, Kutsch E. Eosinophilic Gastroenteritis and colitis: a comprehensive review. Clin Rev Allerg Immunol. 2016;50(2):175–88.
6 Valent P, Klion AD, Horny HP, Roufosse F, Gotlib J, Weller PF, et al. Contemporary consensus proposal on criteria and classification of eosinophilic disorders and related syndromes. J Allergy Clin Immunol. 2012;130(3):607–12.e9.
7 Turner KO, Sinkre RA, Neumann WL, Genta RM. primary colonic eosinophilia and eosinophilic colitis in adults. Am J Surg Pathol. 2017;41(2):225–33.
8 Pineton de Chambrun G, Gonzalez F, Canva JY, Gonzalez S, Houssin L, Desreumaux P, et al. Natural history of eosinophilic gastroenteritis. Clin Gastroenterol Hepatol. 2011;9(11):950–6.e1.
9 Khan S, Orenstein SR. Eosinophilic gastroenteritis. Gastroenterol Clin North Am. 2008;37(2):333–48, v.

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Clinical Case Study

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Eosinophilic Colitis, an Uncommon Cause of Diarrhea: Case Report and Literature Review

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Keywords
Eosinophilic colitis · Hypereosinophilic syndrome · Chronic diarrhea · Hypereosinophilia

Abstract
Eosinophilic colitis and hypereosinophilic syndrome with colic involvement are rare diagnosis that are characterized by wide-ranging gastrointestinal symptoms and idiopathic infiltration of eosinophils in the colon. The diagnostic workup is challenging since there are no standardized criteria. We report a case of a man admitted to the hospital with a history of nonbloody chronic diarrhea. The detailed workup demonstrated blood eosinophilia, and the colonic biopsies revealed extensive eosinophilic infiltration. He was treated with steroids with clinical and analytical improvement. Due to relapsing colitis after therapy withdrawal, he was chronically medicated with 10 mg of prednisolone with ultimate symptom control. This case report describes the diagnostic workup and highlights the most important features of this often underdiagnosed entity.

Colite Eosinofílica, uma causa incomum de diarreia – caso clínico e revisão da literatura

Palavras Chave
Colite eosinofílica · Síndrome hipereosinofílico · Diarreia crónica · Hipereosinofilia

Resumo
A colite eosinofílica e síndrome hipereosinofílico com atingimento gastrointestinal é um diagnóstico raro caracterizado por uma grande variedade de sintomas gastrointestinais e pela evidência de infiltração por eosinófilos na mucosa cólica. A marcha diagnóstica é desafiante dado não haver até à data critérios de diagnóstico. Os autores apresentam um caso de um homem hospitalizado com história de diarreia crónica não sanguinolenta. Durante a investigação etiológica foi identificada eosinofilia periférica e as biópsias cólicas realizadas evidenciaram predominante infiltração eosinofílica. Foi iniciado tratamento com corticoterapia tendo-se verificado normalização da contagem de eosinófilos e resolução do quadro clínico. Dado o carácter recidivante da colite que pode ocorrer

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com o desmame de corticoterapia, o doente ficou medicado cronicamente com 10 mg de prednisolona. Destaca-se este caso pela sua raridade na literatura de forma a realçar aspetos particulares desta entidade incomum.

Introduction

Chronic diarrhea is a gastrointestinal symptom that often requires a dedicated and thorough diagnostic workup to correctly identify the underlying pathologic etiology. The pathophysiologic background of both eosinophilic colitis (EC) and hypereosinophilic syndrome (HES) with colic involvement is the tissue infiltration by eosinophils and consequent organ dysfunction. In fact, both are very rare clinical entities that can manifest with diarrhea and other general gastrointestinal symptoms. Due to the nonspecific nature of the symptoms, the diagnosis is often challenging and a high level of clinical suspicion is needed, especially when other more frequent causes have been excluded. We report an uncommon case of EC of a patient presenting with chronic diarrhea with discussion of the workup and etiologic investigation to highlight the diagnostic challenges and therapeutic possibilities.

Case Report

We present a case of a Portuguese 82-year-old male, ex-immigrant from Venezuela, with a past medical history of type 2 diabetes mellitus, chronic normocytic normochromic anemia, and chronic kidney disease stage IIIa (KDIGO classification). The patient was medicated with atorvastatin, perindopril, amlodipine, furosemide, metformin/sitagliptin, mirtazapine. He presented to the emergency department with a 1-month history of diarrhea. He complained of intermittent episodes of watery diarrhea up to 4–5 bowel movements a day with concomitant abdominal pain. The patient denied bloody stools, fever, weight loss or other constitutional symptom, recent antibiotic therapy, family history of inflammatory bowel disease, pulmonary or allergic symptoms. Physical examination revealed signs of dehydration, and gastrointestinal examination was unremarkable.

Laboratory workup showed a hemoglobin of 10 g/dL, normocytic and normochromic, hypereosinophilia of 1,900/μL, acute kidney injury with increased serum creatinine of 9.64 mg/dL (baseline value 1.21 mg/dL) with metabolic acidosis with pH 7.26, blood urea nitrogen of 277 mg/dL, and hyperkalemia of 6 mEq/L, without increased inflammatory parameters. He was admitted to the intermediate care unit and started intensive fluid administration with significant clinical and analytic improvement in the first 24 h, and then transferred to the general ward for further etiologic investigation. At admission, the problem addressed was essentially the chronic diarrhea and the documented blood hypereosinophilia. Peripheric blood smear and a protein electrophoresis revealed no abnormalities, and the immunoglobulin-level analysis revealed an isolated rise in the IgE fraction (1,106 kU/L).

Celiac disease antibodies and broad autoimmunity antibodies (such as ANAs, ANCAs, anti-dsDNA, anti-ENAs, and rheumatoid factor) were within normal range. Stool microbiologic evaluation (bacteriological, including *T. whipplei*, virological and parasitological, including *Giardia* antigens) was unremarkable (3 distinct samples). Fecal calprotectin was elevated (246 μg/g).

From stool observation under the microscope, it was reported the presence of Charcot-Leyden crystals which, according to the literature, might be indicative of a disease involving eosinophilic inflammation or proliferation, such as that found in allergic reactions and parasitic infections [1]. During the hospital course, his daily laboratory tests were remarkable for constant eosinophil predominance, with a maximum value of absolute eosinophil count above 4,000/μL.

Upper gastrointestinal endoscopy revealed no macroscopic or histopathologic findings (duodenal biopsies were not performed). An ileocolonoscopy was then performed, and no macroscopic changes were found (shown in Fig. 1); multiple biopsies were taken along the various colonic segments to exclude microscopic and EC. The histopathological examination of the colonic biopsies reported moderate to marked polymorphic inflammatory infiltrate rich in eosinophils, focal erosion of the lining epithelium, and focal cryptitis lesions with a predominance of eosinophils (shown in Fig. 2a–c). The patient also underwent video capsule endoscopy that revealed no pathologic findings.

Therefore, with these histological findings of colonic mucosa with chronic inflammatory lesions and marked polymorphic inflammatory infiltrate rich in eosinophils in a patient with chronic diarrhea and peripheral eosinophilia, we considered the diagnostic hypothesis of EC or a HES with colic involvement that are two overlapping disorders. The case was discussed in a multidisciplinary setting. Immunoallergology experts considered that given the age and the absence of possible allergic culprits, an allergic contribution for the eosinophilic involvement seemed unlikely. From the perspective of the hematology-oncology team, after revision of the patient clinical data and the performance of medullar biopsy, the possibility of a neoplasic process was discarded. After discussion with the gastroenterology team, a trial of corticosteroid therapy with prednisolone was recommended.

Regarding the potential involvement of other organs, a chest CT and echocardiogram were performed, which excluded involvement and dysfunction of those organs. In fact, a patient with considerable peripheral eosinophilia and a histological result showing infiltration and chronic inflammation by eosinophils met the diagnostic criteria for EC and therefore we established the diagnosis.

Due to the need of immunosuppressive therapy, the risk of exposure to *Strongyloides stercoralis* (patient lived in an endemic area – Venezuela) was considered and empirical ivermectin 15 mg daily for 2 days was administered. The patient then started prednisolone 40 mg daily, with analytical improvement and complete resolution of peripheral eosinophilia and clinical improvement of diarrhea after 5 days.

At discharge, he was instructed to take prednisolone 40 mg daily with slow tapering (2 months) and was referred for outpatient

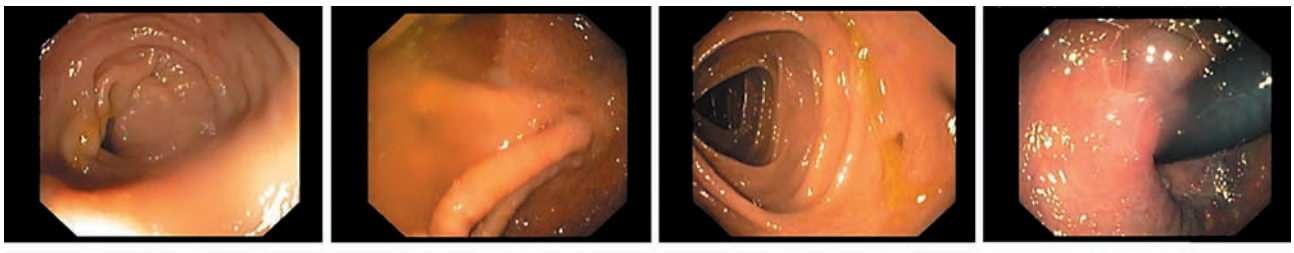

Fig. 1. Normal bowel mucosa with no evidence of erythema or ulceration.

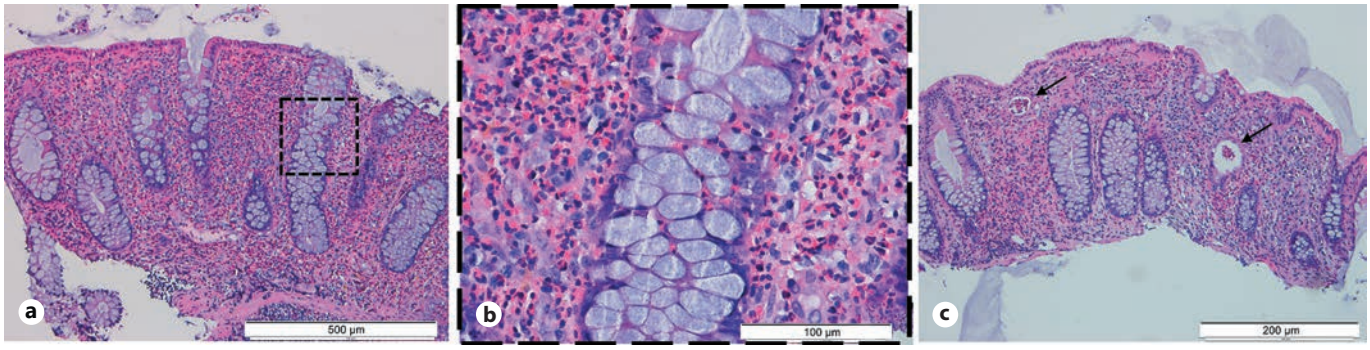

Fig. 2. a Colon biopsy that shows a high number of eosinophils per HPF. *Hematoxylin and eosin.* **b** Colon biopsy. Close-up of (**a**) that shows eosinophilic infiltration of lamina propria suggesting eosinophilic colitis. *Hematoxylin and eosin.* **c** The arrows in the panel show crypt abscesses that consists almost entirely of eosinophils. There are also an increased number of eosinophils in the lamina propria. *Hematoxylin and eosin.*

clinic of internal medicine and gastroenterology. No other changes were introduced to the patient's usual medication.

After stopping prednisolone, the patient had recurrence of peripheric eosinophilia and gastrointestinal symptoms with diarrhea leading to acute-on-chronic kidney injury requiring re-hospitalization. After reintroduction of prednisolone and slower tapering strategy, he presented clinical and analytical normalization, demanding at least 10 mg of prednisolone to avoid recurrence of symptoms.

Discussion

In this article, we presented a case of EC which is virtually indistinguishable from HES with colic involvement. HES is a group of disorders characterized by a permanent overproduction of eosinophils, associated with impairment of one or more organs due to eosinophilic involvement. The diagnosis should be considered in patients with sustained blood eosinophilia (>1.5 × 10^9/L) with eosinophil-mediated organ damage [2]. The HES has many subgroups and an organized and systematic diagnostic workup. We focused on the gastrointestinal involvement of the syndrome which corresponds only to 14% of the cases of HES. When isolated, it refers to a variant of the syndrome called organ-restricted hypereosinophilic condition that applies to blood eosinophilia with a single organ involvement. In fact, this entity can also be characterized by lower levels of peripheral eosinophilia with clear-cut organ involvement. Therefore, plenty of eosinophilic conditions such as eosinophilic gastrointestinal disorders can be difficult or impossible to distinguish from HES when hypereosinophilia is present. Overlapping diseases comprise a broad range of single organ-restricted eosinophilic disorders, such as considering the exclusive involvement of the colon is the case of EC.

EC is a rare gastrointestinal disease and the least frequent manifestation of primary eosinophilic gastrointestinal disorders [3, 4]. Its incidence is difficult to estimate owing to the rarity of the disease; a review article of 2010 defines it as "exceptionally rare" mentioning a few cases

being reported since 1979 [5, 6]. It can affect both adults and children. The pathophysiology of primary EC seems to be related to atopic processes, presenting mainly as a food allergy in infants and T lymphocyte-mediated (i.e., non-IgE related) in older patients [3, 7].

It is a heterogeneous entity characterized by focal or diffuse infiltration of eosinophils in the colon in the absence of secondary causes. The secondary forms are related to infections (manly parasitic infections), inflammatory bowel disease, celiac disease, drug-induced reactions (identified drugs are clozapine, carbamazepine, rifampicin, gold, naproxen, among others), neoplasia, connective tissue diseases, HES, and other causes [2, 8, 9]. By definition, EC might or not be associated with peripheral eosinophilia and so the differential diagnosis between the two is in clinical practice of no significance [2, 5, 7].

Clinical presentation may vary depending on location as well as depth and extent of bowel wall eosinophilic infiltration. The patients might report crampy generalized abdominal pain, diarrhea (bloody or nonbloody), and/or weight loss [5, 10]. It usually runs a chronic relapsing course.

In patients with EC, endoscopic changes are rather modest and not characteristic and so endoscopy might reveal edematous mucosa with a loss of the normal vascular pattern, patchy erythematous changes, and even superficial ulcerations [5, 11]. Colonic biopsies should be obtained and analyzed, but there is no established consensus for the histological diagnosis of EC; indeed, there is no defined cut-off for the number of eosinophils/high-power field (HPF) in the colonic mucosa in order to make a definitive diagnosis of this entity [5]. In fact, small amounts of eosinophils are normally present in the mucosa as a host defense mechanism. Therefore, the diagnosis should be confirmed by an experienced gastrointestinal pathologist to assess if the number of eosinophils is more than expected for a particular area [7].

Normal values for tissue eosinophils vary widely between different segments of the colon, and we found conflicting data on the literature. Some authors advocate a cut-off of 15–25 eosinophils per HPF without specifying the segment [3]. Other researchers claim that they are usually more numerous in the cecum and ascending colon than elsewhere and therefore the cut-off should have this evidence into account [8]. Other group of investigators had suggested other cut-off values [12], for example: right colon >100/HPF, transverse and descending colon >84/HPF, rectosigmoid colon >64/HPF. Regardless of the absence of diagnostic criteria, it is well accepted that clinical background is important as well as the location of the biopsy for interpretation of findings. In our case, even though the number of eosinophils/HPF was not reported, the abnormal high abundance of these cells was highlighted.

In the histopathology analysis, eosinophils infiltrating the crypts or focal collections of 10 or more eosinophils/HPF can be expected, in the absence of other identifiable abnormalities. Some histopathological similarities to chronic inflammatory bowel disease can also be found [8, 9].

There is no standard treatment regime for EC. The treatment choice for EC is based on the severity of symptoms. Dietary therapy with an empiric eviction diet is reasonable in patients with malabsorption and works best for those who have a stronger allergenic background (specially children).

Pharmacologic treatment for both HES (nonmyeloid variants) and EC is a trial of corticosteroid therapy with prednisolone (20–40 mg/day) with subsequent rapid tapering [11, 13]. The goal is to control the symptoms with the minimum dose possible. Some individuals might need more prolonged therapy or might even need long-term, low-dose maintenance therapy (for example, prednisolone 5–10 mg per day) [14]. Alternatively, budesonide is also listed as a possible treatment weapon [5, 11]. In severe, refractory, or steroid-dependent EC immunomodulatory drugs like those indicated for inflammatory bowel disease such as azathioprine or 6-mercaptopurine might be used [11]. The possibility of using montelukast, a leukotriene receptor antagonist, as a steroid-sparing therapy was also raised, and there are some studies and case reports that support its efficacy [15, 16]. Other drugs can also be used in the treatment of EC, namely, antihistamines such as ketotifen; mast cell stabilizers such as sodium cromoglycate; biological agents such as omalizumab and mepolizumab, all with varying proved efficacy [11].

The presentation of this case demonstrates that, although EC and HES with colic involvement are rare diseases, we should always pursue the underlying pathologic process. In this clinical setting, the peripheral eosinophilia gave us some guidance and supported the diagnosis, but it is not always the case and we should maintain a high level of clinical suspicion. It is essential that we perform a detailed clinical history to identify or exclude an atopic background and dismiss other possible causes of hypereosinophilia. The histopathological examination is essential, despite the lack of diagnostic criteria and clear cut-offs. The treatment decision should always be discussed, and the clinical response must be monitored

closely to promptly identify refractory patients that may need subsequent treatment with other pharmacological targets.

In conclusion, EC is a rare disorder that it is not easy to diagnose and has no standard treatment. In this case report, we describe the diagnosis workup and a treatment approach that allowed clinical improvement of this patient (online suppl. Table 1; for all online suppl. material, see www.karger.com/doi/10.1159/000526853).

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Statement of Ethics

All rules of the local Ethics Committee ("Comissão de Ética para a Saúde do Centro Hospitalar de São João/Faculdade de Medicina da Universidade do Porto, Portugal") were followed, preserving patient identity and confidentiality. Written informed consent was obtained from the patient for publication of this case report and any accompanying images. This retrospective review of patient data did not require ethical approval in accordance with local guidelines.

Conflict of Interest Statement

The authors have no conflicts of interest to report.

Funding Sources

The authors have no financial disclosures to report.

Author Contributions

Pedro Cardoso wrote the manuscript; Renato Medas provided the endoscopic images and reviewed the manuscript; Catarina Elias contributed to the manuscript; Leila Cardoso reviewed and edited the manuscript; Armando Peixoto and Guilherme Macedo did a critical expert review of the manuscript. The authors would like to thank Francisco Moreira for providing the pathology images.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material. Further inquiries can be directed to the corresponding author.

References

1 Siddique SM, Gilotra NA. Crystal clear: a unique clue to diagnosis in a patient with recurrent nausea and vomiting. Gastroenterology. 2014;147(2):e1–2.
2 Roufosse F. Hypereosinophilic syndromes: clinical manifestations, pathophysiology, and diagnosis. In: Post TW, editor. UpToDate. Retrieved December, 2021 Dec from: https://www.uptodate.com/contents/hypereosinophilic-syndromes-clinical-manifestations-pathophysiology-and-diagnosis?search=hypereosinophilic%20syndrome& source=search_result& selectedTitle=1~71& usage_type=default&display_rank=1)2021.
3 Yan BM, Shaffer EA. Primary eosinophilic disorders of the gastrointestinal tract. Gut. 2009;58(5):721–32.
4 Impellizzeri G, Marasco G, Eusebi LH, Salfi N, Bazzoli F, Zagari RM. Eosinophilic colitis: a clinical review. Dig Liver Dis. 2019;51(6):769–73.
5 Alfadda AA, Storr MA, Shaffer EA. Eosinophilic colitis: epidemiology, clinical features, and current management. Therap Adv Gastroenterol. 2011;4(5):301–9.
6 Fernández Salazar LI, Borrego Pintado H, Velayos Jiménez B, González Hernández JM. Differential diagnosis and management of histologic eosinophilic colitis. J Crohns Colitis. 2013;7(1):e20–1.
7 Gonsalves N. Eosinophilic gastrointestinal diseases. In: Post TW, editor. UpToDate. Retrieved December 2021 Dec from: https://www.uptodate.com/contents/eosinophilic-gastrointestinal-diseases2021.
8 Katsanos KH, Zinovieva E, Lambri E, Tsianos EV. Eosinophilic-Crohn overlap colitis and review of the literature. J Crohn's Colitis. 2011;5(3):256–61.
9 Walker MM, Potter MD, Talley NJ. Eosinophilic colitis and colonic eosinophilia. Curr Opin Gastroenterol. 2019;35(1):42–50.
10 Mori A, Enweluzo C, Grier D, Badireddy M. Eosinophilic gastroenteritis: review of a rare and treatable disease of the gastrointestinal tract. Case Rep Gastroenterol. 2013;7(2):293–8.
11 Alfadda AA, Storr MA, Shaffer EA. Eosinophilic colitis: an update on pathophysiology and treatment. British Medical Bulletin. 2011;100(1):59–72.
12 Collins MH. Histopathologic features of eosinophilic esophagitis and eosinophilic gastrointestinal diseases. Gastroenterol Clin North Am. 2014;43(2):257–68.
13 Roufosse F. Hypereosinophilic syndromes: treatment. In: Post TW, editor. UpToDate. Retrieved 2021 December 2021. from: https://www.uptodate.com/contents/hypereosinophilic-syndromes-treatment?csi=35f2ad05-2336-4c17-85e2-09ea586dc8a1&source=contentShare.
14 Chen MJ, Chu CH, Lin SC, Shih SC, Wang TE. Eosinophilic gastroenteritis: clinical experience with 15 patients. World J Gastroenterol. 2003;9(12):2813–6.
15 Ibis M, Beyazit Y, Sayilir A, Suvak B, Torun S, Kekilli M. Successful treatment of eosinophilic colitis by montelukast sodium plus budesonide in a patient with Waldenstrom macroglobulinemia. J Crohn's Colitis. 2011;5(3):277–8.
16 Wang NW, Hsieh H, Yang YJ. Successful Montelukast treatment in an infant with steroid-resistant eosinophilic colitis. Case Rep Gastroenterol. 2021;15(1):389–94.

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Endoscopic Snapshot

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Eosinophilic Esophagitis on and off Proton Pump Inhibitor

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Keywords
Esophageal stricture · Dysphagia · Diagnostic esophago-gastro-duodenoscopy · Proton pump inhibitor · Eosinophilic esophagitis

Esofagite eosinofílica com e sem inibidor da bomba de protões

Palavras Chave
Estenose esofágica · Disfagia · Endoscopia diagnóstica · Inibidor da bomba de protões · Esofagite eosinofílica

Pre-endoscopy empirical PPI usage has become standard in many countries, albeit there are significant concerns in terms of masking relevant endoscopy findings, which may, among others, include eosinophilic esophagitis (EoE), thus clearly calling for a change in practice pattern [1, 2]. A 28-year-old male patient with birch pollen allergy and dysphagia for solids and reflux-like symptoms for several months with incomplete response to proton pump inhibitors (PPIs) was referred for endoscopic stricture treatment due to a presumed reflux-related stricture. Outside office-based index esophago-gastro-duodenoscopy (EGD), while on empiric standard-dose PPI treatment, indicated a small hiatal hernia along with a discrete short stricture. At the time, biopsies from the distal esophagus remained non-contributory.

The recent EGD indicated questionable linear furrows with minor reduction in submucosal vessel visibility in the proximal esophagus (Fig. 1a). The short distal stricture was well reproduced (Fig. 1b), and a bougienage up to 20 mm using Savary-Gilliard bougies was performed (Fig. 1c; note fully preserved vascular markings in the distal esophagus). Given the lack of relevant mucosal tears after maximal bougienage (Fig. 1d), an additional radial electroincision using an IT knife was conducted (not shown). Esophageal biopsies with an adequate biopsy protocol (> two heights, >6 biopsies) yielded no evidence for potentially underlying EoE. Since the patient only benefitted transiently from the procedure and presented again after only 2 weeks with reflux-like symptoms and dysphagia, ancillary esophageal manometry did not demonstrate dysmotility. The patient consented to withdraw PPI treatment for 2 weeks with alginate bridging, causing

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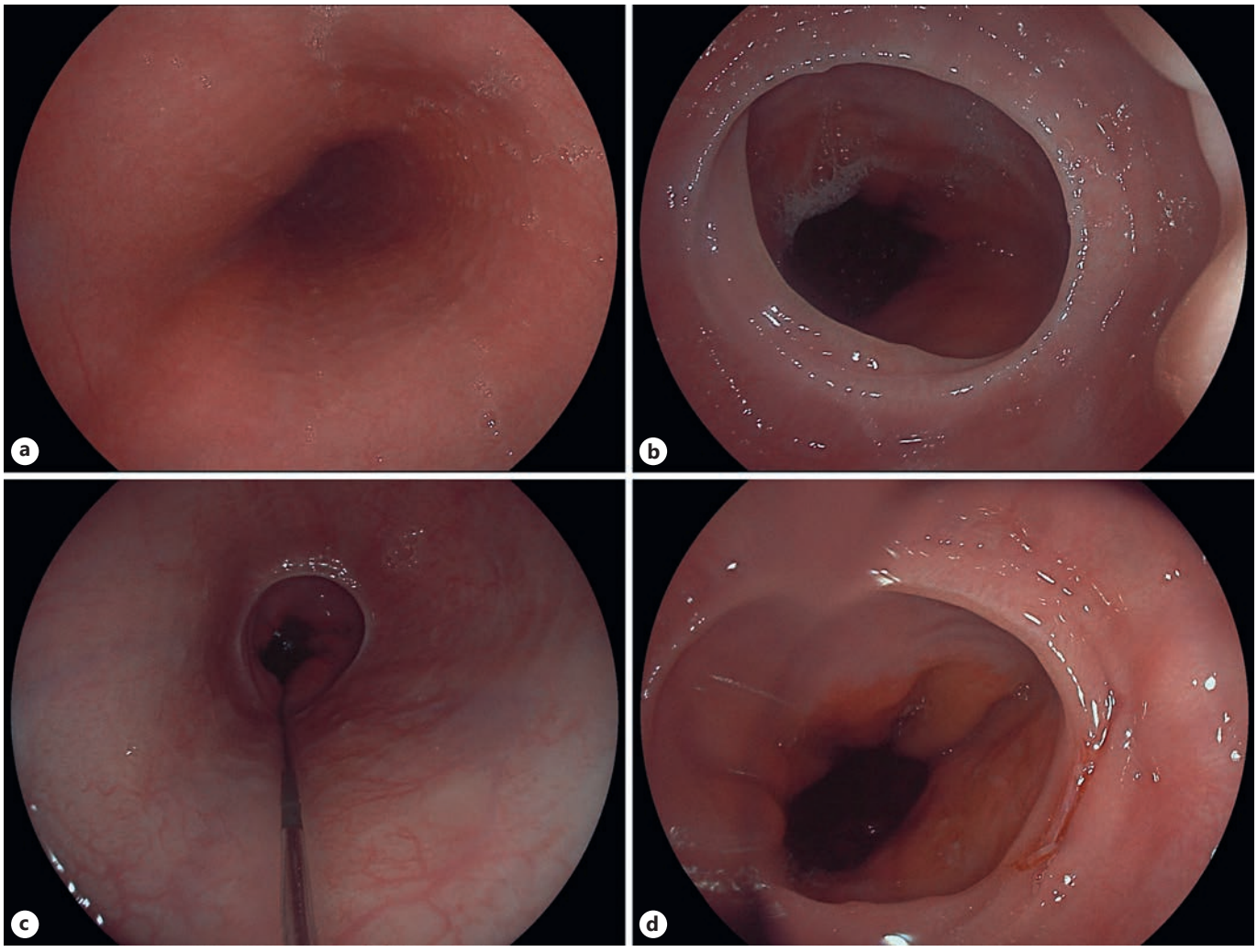

Fig. 1. a Discrete linear furrows with moderately reduced vascular markings restricted to the upper third of the esophagus. **b** Short distal esophageal stricture and small hiatal hernia. **c** Guidewire in situ prior to maximum bougienage to 20 mm; note fully preserved submucosal vessels in the distal esophagus. **d** Endoscopy after bougienage to 20 mm with only a minor tear at 4 o'clock.

significant clinical deterioration, i.e. worsening reflux and dysphagia. Repeat EGD provided clear-cut endoscopic EoE evidence with diffuse furrowing, diffuse lack of submucosal vessels reflecting significant edema (Fig. 2a) as well as recurrence of the distal stricture (Fig. 2b). In addition, coarse exudates were noted at the level of linear furrows, which were specifically targeted for histopathology [3, 4] (Fig. 2c – EREFS score 5). Repeat biopsies off PPI confirmed presence of EoE in this patient with a maximum infiltration of >32/HPF in the proximal esophagus. The patient was successfully treated by 2 × 1 mg orodispersible budesonide.

Empiric PPI treatment is oftentimes implemented prior to diagnostic EGD in clinical practice [5]. Unlike PPI-responsive EoE, this case of a patient falling behind endoscopic and/or pathology appreciation of EoE, while remaining highly symptomatic, should remind us to critically reconsider such practice, given that not only EoE may become masked. Beyond the need to strictly adhere to biopsy protocol recommendations even in patients without clear endoscopic EoE stigmata, this unique clinical report illustrates the potential divergence between clinical and endoscopic response in EoE.

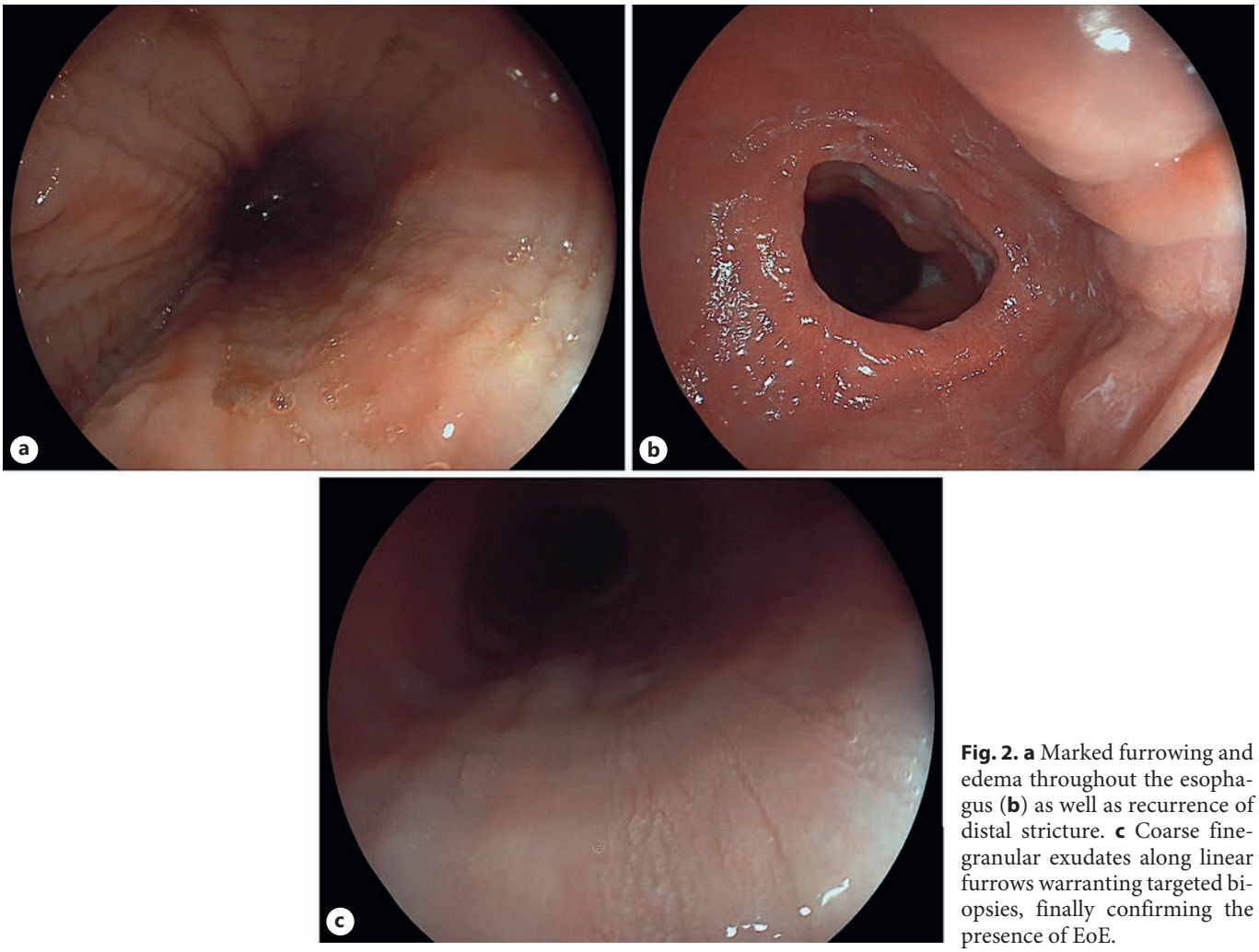

Fig. 2. a Marked furrowing and edema throughout the esophagus (**b**) as well as recurrence of distal stricture. **c** Coarse fine-granular exudates along linear furrows warranting targeted biopsies, finally confirming the presence of EoE.

Statement of Ethics

Ethical approval was not required for this study due to the retrospective design of the study, in accordance with local/national guidelines. The patient has given written informed consent for publication (including publication of images). The authors have no conflicts of interest to declare.

Funding Sources

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Author Contributions

Vincent Zimmer – clinical care and drafting and finalization of manuscript. Kai Emrich – pathology care and revision and finalization of manuscript.

Data Availability Statement

The data included in this study are not publicly accessible.

References

1 Attwood S, Epstein J. Eosinophilic oesophagitis: recent advances and practical management. Frontline Gastroenterol. 2021;12(7): 644–9.

2 Hillman L, Donohue S, Broman AT, Hoversten P, Gaumnitz E, Lomeli L. Empiric proton pump inhibitor therapy after esophageal food impaction may mask eosinophilic esophagitis diagnosis at follow-up. Dis Esophagus. 2021; 34(11):doab030.

3 Dellon ES, Liacouras CA, Molina-Infante J, Furuta GT, Spergel JM, Zevit N, et al. Updated international consensus diagnostic criteria for eosinophilic esophagitis: proceedings of the AGREE conference. Gastroenterology. 2018; 155(4): 1022–33. e10.

4 Hirano I, Chan ES, Rank MA, Sharaf RN, Stollman NH, Stukus DR, et al. AGA institute and the joint task force on allergy-immunology practice parameters clinical guidelines for the management of eosinophilic esophagitis. Ann Allergy Asthma Immunol. 2020;124(5): 416–23.

5 Odiase E, Schwartz A, Souza RF, Martin J, Konda V, Spechler SJ. New eosinophilic esophagitis concepts call for change in proton pump inhibitor management before diagnostic endoscopy. Gastroenterology. 2018; 154(5):1217–21.e3.

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An Unusual Cause of Duodenal Obstruction: Watch Your Feet!

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Keywords
Duodenal obstruction · Strongyloides stercoralis · Strongyloidiasis

Uma causa incomum de obstrução duodenal: cuidado onde pões os pés!

Palavras Chave
Obstrução duodenal · Strongyloides stercoralis · Estrongiloidíase

A 28-year-old female from Guinea-Bissau living in Portugal for 6 years presented with a 2-week history of intense epigastric pain with postprandial worsening, which was relieved by self-induced vomiting. Her past medical history was unremarkable. Laboratory investigation revealed eosinophilia (1.04×10^9/L; normal: 0.02–0.5 $\times 10^9$/L; 15.5%, normal: 0–6%), without anemia (Hb 13.2 g/dL, normal; 12–15 g/dL; MCV 80 fL, normal: 80–96.1 fL) or raised CRP (0.17 mg/dL, normal: 0–0.5 mg/dL).

Esophagogastroduodenoscopy was performed, showing gastric dilation with food residue, an easily traversable circumferential narrowing at the duodenal bulb, and a small phytobezoar in the second duodenal portion (Fig. 1). Upon its removal, a linear ulcer was found which extended to the third duodenal portion, ending in a pinhole ulcerated stricture (Fig. 2). Biopsies were taken for histopathological, microbiological, and mycobacterial analysis. She underwent enteral-MRI, revealing a circumferential narrowing of the third portion of the duodenum (Fig. 3).

Fecal calprotectin was normal (46 mg/kg; normal: <80 mg/kg). Duodenal mucosa's direct and cultural exams for mycobacteria were negative.

Histopathology showed expansion of the lamina propria at the expense of a mixed inflammatory infiltrate with eosinophils, as well as eggs and larvae of *Strongyloides stercoralis* (Fig. 4). Stool examination also revealed this finding. The diagnosis of duodenal obstruction due to *S. stercoralis* infectious duodenitis was made.

HIV infection was later excluded. The patient was treated with ivermectin 2 mg/kg for 2 consecutive days. Clinical, laboratory, and stool revaluation were scheduled at 1-month follow-up. On revaluation, she was asymptomatic, laboratory analysis showed normalization of eosinophils, and parasitological stool examination was negative. Due to loss of follow-up, endoscopic reassessment was not performed.

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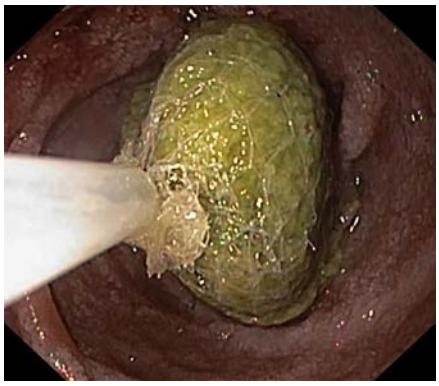

Fig. 1. Small phytobezoar in the second duodenal portion.

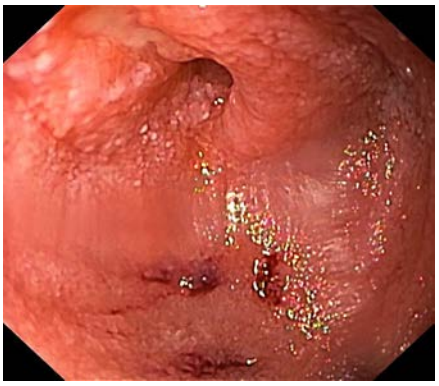

Fig. 2. Pinhole ulcerated stricture.

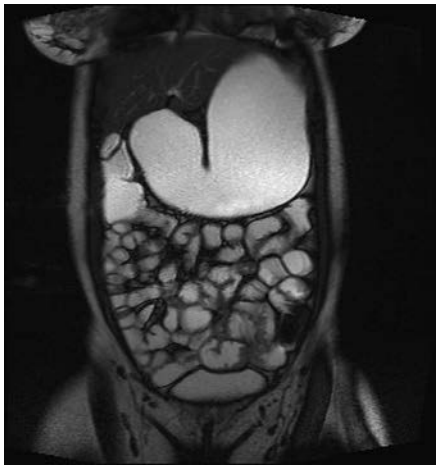

Fig. 3. Circumferential narrowing of the third portion of the duodenum and upstream dilatation.

S. stercoralis is a parasitic nematode that infects the gastrointestinal tract through skin contact with contaminated soil [1]. It is more prevalent in tropical and subtropical regions [1]. It has the ability of completing its life cycle entirely within the human host to establish an autoinfection cycle.

Chronic infection by *S. stercoralis* is often asymptomatic and clinical manifestations can occur long after initial infection, including nonspecific gastrointestinal, dermatological, and respiratory symptoms [2]. Small bowel obstruction is a poorly recognized and probably underreported complication of *S. stercoralis* infection, with only a few cases reported in the literature [1]. Severe mucosal edema is suggested to be the cause of bowel obstruction in these cases [1].

Laboratory tools for diagnosis of strongyloidiasis include stool testing and serology. Due to the intermittent shedding of larvae, stool examination has a low sensitivity (<50%) [3]. Serologic testing using ELISA is nowadays the gold standard, presenting high sensitivity (89%) and specificity (97%) [4].

The prognosis of duodenal obstruction due to *S. stercoralis* infection is not well established. Nevertheless, late diagnosis seems to add to its dismal prognosis, mostly due to bacterial translocation and sepsis [1].

We herein present a case of strongyloidiasis in an immunocompetent patient who had been in a non-endemic area for years and whose only clinical manifestation was epigastric pain. The key point is that strongyloidiasis should be considered in the differential diagnosis of gastrointestinal symptoms, especially in patients from endemic areas, because diagnosis may be challenging, and immunosuppression can have dire consequences by inducing hyperinfection [2].

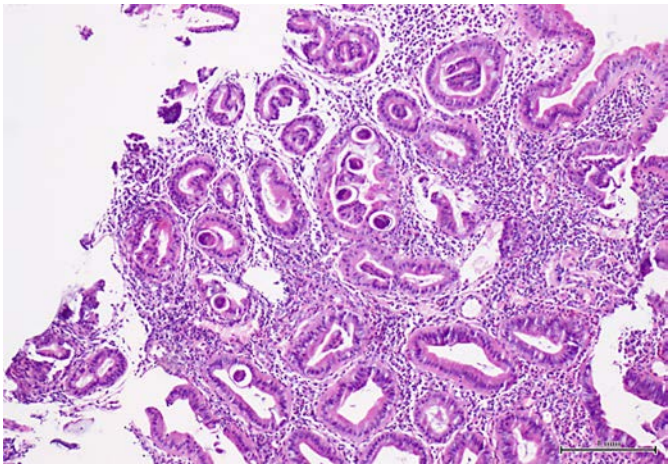

Fig. 4. Eggs and larvae of *Strongyloides stercoralis* in the duodenal mucosa.

Statement of Ethics

The authors have no ethical conflicts to disclose. Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Conflict of Interest Statement

The authors declare that they have no conflicts of interest to disclose.

Author Contributions

Ana Rita Franco, Pedro C. Figueiredo, and Ana Catarina Albuquerque contributed in the manuscript concept and design. Ana Rita Franco and Rui Mendo drafted the manuscript. Pedro C. Figueiredo performed a critical revision of the manuscript for important intellectual content.

References

1 Baqir AW, Alawad M, Loukeris K. A fatal cause of small bowel obstruction. Gastroenterology. 2019;156(8):e14–5.
2 Hindy P, Parvin R, Hanna K, Gress F. Strongyloidiasis presenting as duodenal obstruction in a patient infected with human T-cell lymphotropic virus type 1. Gastrointest Endosc. 2011;74(2):439–41.
3 Naidu P, Yanow SK, Kowalewska-Grochowska KT. Eosinophilia: a poor predictor of strongyloides infection in refugees. Can J Infect Dis Med Microbiol. 2013;24(2):93–6.
4 La Hoz RM, Morris MI. Intestinal parasites including cryptosporidium, cyclospora, giardia, and microsporidia, entamoeba histolytica, strongyloides, schistosomiasis, and echinococcus: guidelines from the American Society of Transplantation Infectious Diseases Community of Pract. Clin Transpl. 2019; 33(9):1–16.

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An Unexpected Guest in Capsule Endoscopy: Tapeworm Infection

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Keywords
Capsule endoscopy · Tapeworm infection · Taeniasis

Um achado inesperado na enteroscopia por cápsula: infeção por ténia

Palavras Chave
Enteroscopia por cápsula · Infeção por ténia · Teníase

Taeniasis is a parasitic infection caused by tapeworm species (*Taenia saginata*, *Taenia solium*, and *Taenia asiatica*), affecting about 50 million people globally. It occurs mainly in developing countries, by consumption of undercooked infected meat [1]. Its diagnosis is challenging as most patients remain asymptomatic or have mild nonspecific symptoms [2, 3]. Although microscopic stool examination remains the gold standard for its diagnosis, it has a low diagnostic yield [4]. Small bowel capsule endoscopy (SBCE) is an essential diagnostic tool for small intestine diseases. SBCE may help in stool-negative tapeworm infection cases, allowing a definitive diagnosis [3, 5].

We report a case of an 18-year-old young female patient, from a developed country, living in an urban area with sanitary conditions, with no past medical history and chronic medication, that was referenced to gastroenterology consultation for bloating, abdominal pain, and intermittent white cords in her stools during approximately 6 months, not seen by physicians. The patient did not report a previous consumption of undercooked meat and has no recent out-of-country travel. There were no relevant findings in the physical examination or the biochemical analysis. The microbiological stool examination, collected on three different days, was negative. Upper and lower gastrointestinal endoscopy had no relevant findings. Therefore, an SBCE was performed. Throughout the small intestine, a continuous segment of white, flat, and segmented structures (proglottids) without mucosal lesions were observed, compatible with intestinal tapeworm infection (shown in Fig. 1). The patient was treated with a single dose of praziquantel 10 mg/kg with full clinical resolution and was advised to properly cook meat. We performed additional stool testing 4 months after the treatment, and it was negative. Currently, with approximately 2 years of follow-up, the patient remains asymptomatic, without reporting white cords (proglottids) in her stools.

We emphasize that, although SBCE allows direct visualization of the tapeworm, and it was decisive for estab-

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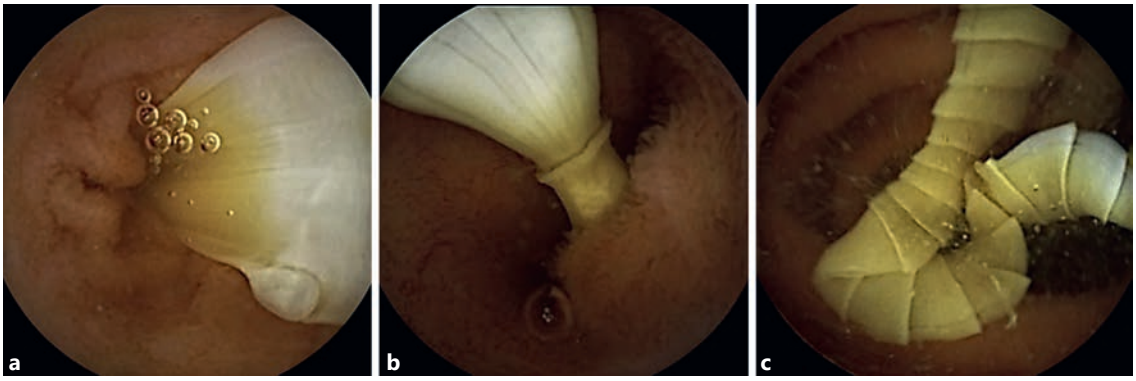

Fig. 1. SBCE findings. **a–c** Tapeworm in the small bowel. **c** A continuous segment of white, flat, and segmented structures without mucosal lesions.

lishing the diagnosis in this case, it has the drawback of not giving information of the type of *Taenia* species. This information is important in cases of *Taenia solium* infection, given the potential risk of neurocysticercosis. Nevertheless, this case illustrates a very rare diagnosis in developed countries, highlights the diagnostic challenges of some cases of tapeworm infection, and reveals that SBCE may play a crucial role in the diagnosis of taeniasis in suspected cases with negative microscopic stool examination and nonspecific symptoms.

Statement of Ethics

The patient received the current standard of care, without experimental intervention. All of the collected images and data were anonymized. All of the methods were performed in accordance with relevant guidelines and regulations, i.e., the ethical guidelines of the 1975 Declaration of Helsinki. The study was approved by an appropriate institution (the Ethical Committee of Gastroenterology of Hospital Senhora da Oliveira, Guimarães). Informed consent was obtained from the patient to perform capsule endoscopy and for publication of the details of their medical case and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

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Author Contributions

Marta Freitas did the literature research and drafted the manuscript. Vítor Macedo Silva, Pedro Boal Carvalho, and Bruno Rosa performed the capsule endoscopy, read and critically revised the manuscript. José Cotter critically revised the manuscript and approved the final version to be submitted.

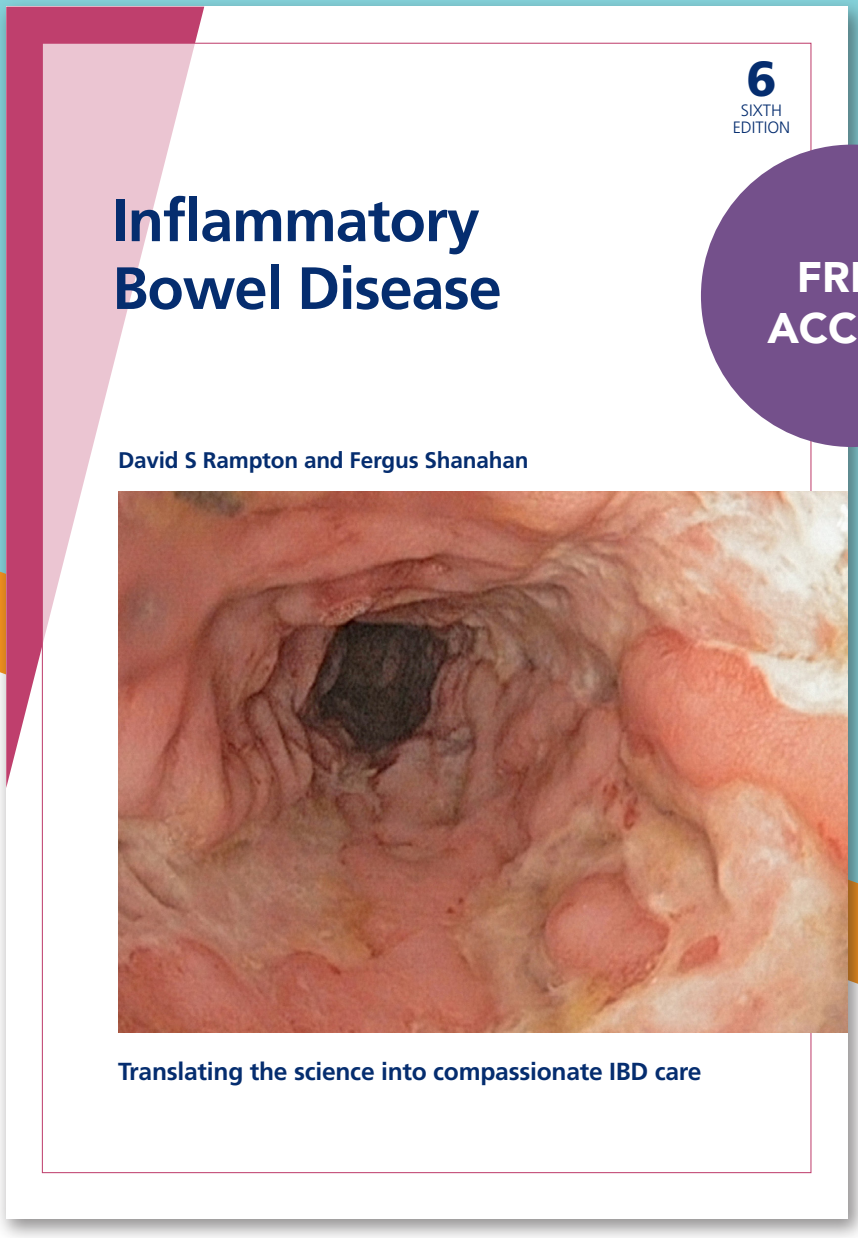
Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

References

1 Griffiths J, Maguire JH, Heggenhougen K, Quah SR. Public health and infectious diseases. Elsevier; 2010. p. 216.
2 López-Caleya JF, Contreras SN, Martín-Rodrigo L. Taenia saginata: an imported case. Rev Esp Enferm Dig. 2015;107(7):440–1.
3 Ucar LA, González AE, Sainz IF. Capsule endoscopy, a useful tool for the diagnosis of a tapeworm infection. Rev Esp Enferm Dig. 2020;112(1):71–2.
4 Okello AL, Thomas LF. Human taeniasis: current insights into prevention and management strategies in endemic countries. Risk Manag Healthc Policy. 2017;10:107–16.
5 Pezzoli A, Fusetti N, Pizzo E. Capsule endoscopy diagnosis of intestinal Taenia. Gastrointest Endosc. 2016;83(1):261–2.

Fast Facts:
Inflammatory Bowel Disease



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