Portuguese Journal of Gastroenterology

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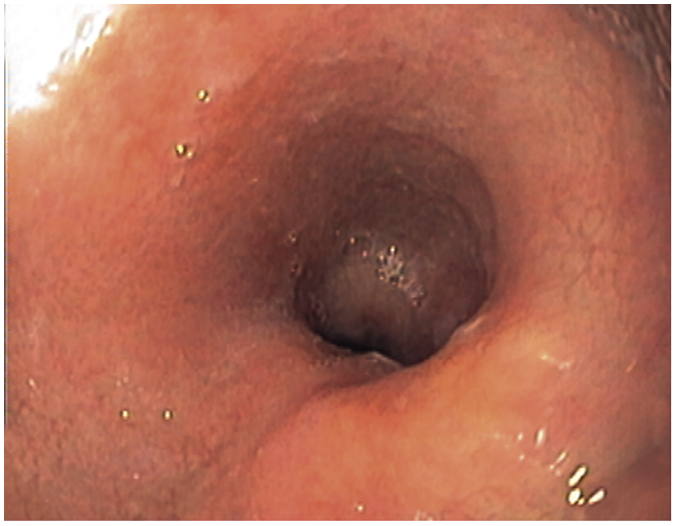

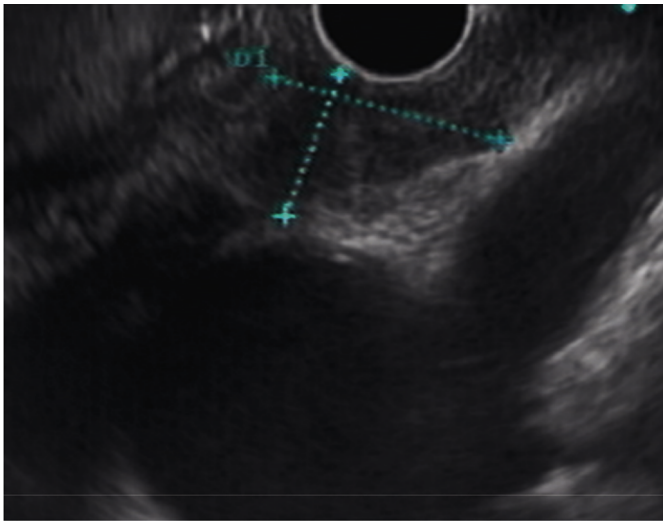

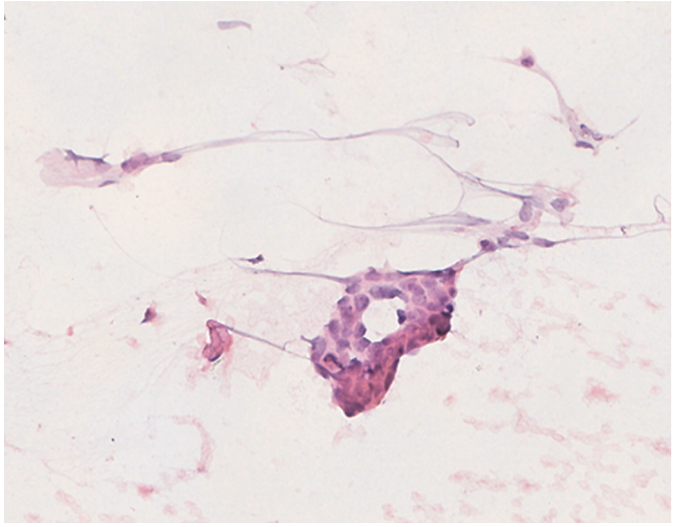

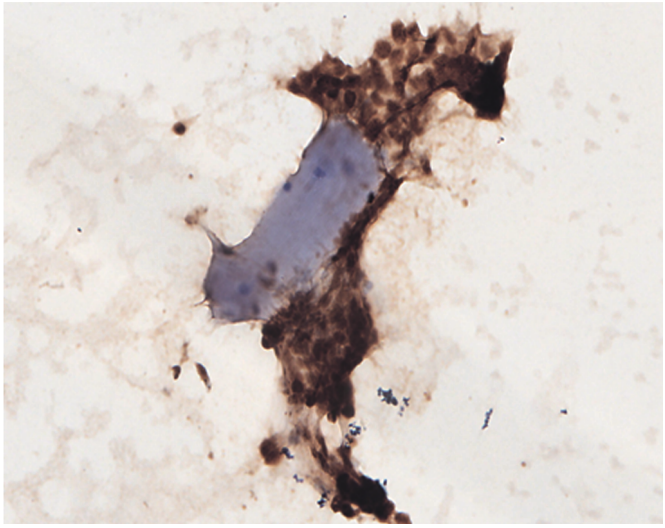

Highlights in this issue:

Review article: Portuguese Pancreatic Club Perspectives on Pancreatic Neuroendocrine Neoplasms: Diagnosis, Staging and Associated Genetic Syndromes

Research article: Clinical Characteristics of Genuine Acute Autoimmune Hepatitis

Research article: Prognostic Markers in Pediatric Acute Liver Failure

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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.

Price per printed issue: Free of charge
ERC-No.: 117866
Editor address: Rua Abranches Ferrão, nº 10–14º, PT–1600-001 Lisbon (Portugal)

ISSN Online Edition: 2387–1954

Journal Homepage: www.karger.com/pjg
Bibliographic Indices: This journal is regularly listed in bibliographic services, including PMC, PubMed, Web of Science, SciELO Citation Index, Google Scholar, DOAJ, Scopus, and WorldCat.

Publication Data: *GE Port J Gastroenterol* is published 6 times a year. Volume 31 with 6 issues appears in 2024.

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GE – Portuguese Journal of Gastroenterology

Vol. 31, No. 3, 2024

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Cover illustration
Yellowish subepithelial lesion in the proximal esophagus corresponding to a esophageal metastasis of breast cancer. From Medas et.al., pp. 221–223

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Letter to the Editor

GE Port J Gastroenterol 2024;31:151–152
DOI: 10.1159/000536536

Received: December 25, 2023
Accepted: January 18, 2024
Published online: March 1, 2024

Comments on "Percutaneous Endoscopic Sigmoidopexy: Still a Way to Go"

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Department of General Surgery, Faculty of Medicine, Ataturk University, Erzurum, Turkey

Keywords
Sigmoid volvulus · Endoscopic detorsion · Percutaneous endoscopic sigmoidopexy

Comentário: 'Sigmoidopexia Endoscópica Percutânea: um caminho ainda a percorrer'

Palavras Chave
Vólvulo do sigmóids · Destorção endoscópica · Sigmoidopexia endoscópica percutânea

I read the paper written by Garrido et al. [1] on a patient with recurrent sigmoid volvulus (SV) treated with percutaneous endoscopic sigmoidopexy (PES) following second endoscopic detorsion (ED). Although ED is successful in approximately four-fifths of patients, SV tends to recur in approximately one-third of patients, and approximately one-seventh of patients are diagnosed with short- or medium-term recurrences, which generally occur during the index admission period [2, 3]. Most probably due to the relatively low incidence of the early recurrence, the treatment algorithm is not clearly identified [4]. My comments relate to the management of the early SV recurrence based on our 57-year and 1,071-case experience, which is the most comprehensive single-centre SV data over the world [5].

The treatment of primary SV is well defined. ED followed by elective surgery is preferred in uncomplicated and non-gangrenous patients, while urgent surgery is required in complicated and gangrenous cases or in whom endoscopy is unsuccessful [5]. However, there are some controversies in the management of recurrent SV, particularly in patients with early recurrence [4]. A few-hour or day interval between ED and early recurrence provides an empty colon or allows for bowel preparation, or even antibiotic prophylaxis [3]. Although these advantages lead up to perform semi-elective surgery, second endoscopic decompression allows for minimally invasive procedures such as elective laparoscopic sigmoidectomy or PES [5]. For these reasons, some practitioners prefer surgery, while some others favour second endoscopy. Among limited availability of studies, Johansson et al. [6] and Mulas et al. [7] used surgery in 4 and 3 patients, respectively, while Iida et al. [8] and Maddah et al. [9] preferred second endoscopy in six and four cases, respectively. On the other hand, Bruzzi et al. [4] reported a 22-patient series including second endoscopy in 11 cases, while surgery in the remained 11 patients.

In our series, early recurrence was determined in 33 (5.3%) of 617 cases with successful nonoperative detorsion. All patients were treated with surgery, in whom bowels were viable. Sigmoidectomy with primary anastomosis was used in 17 patients (51.5%), while other operations were mesopexy in 11 (33.3%), sigmoidectomy with stoma in four (12.1%), and detorsion in one (3.0%). Mortality and morbidity rates

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were 3.0% (1 case) and 12.1% (4 patients), respectively. Although there is no case treated with second endoscopy and minimally invasive procedures in our series, in my opinion, second ED followed by elective laparoscopic sigmoidectomy is the optimal choice in well-conditioned and nonelderly patients, while PES is an alternative way in bad-conditioned and elderly cases, as was demonstrated by the authors. It is clear that an unsuccessful second endoscopy requires semi-elective open surgery including sigmoid colectomy in well-conditioned and nonelderly patients, while sigmoidopexy, mesopexy, extraperitonealization, or detorsion alone are main alternatives in bad-conditioned and elderly cases. I congratulate the authors and wait for their reply on my comments.

Statement of Ethics

Written informed consent was obtained from the participants of this paper.

Conflict of Interest Statement

The author declares that he has no conflict of interests.

Funding Sources

The author has no funding sources to declare.

Author Contributions

Sabri Selcuk Atamanalp collected and analysed the data, reviewed the literature, and wrote the text. He approved the final version of the manuscript.

Data Availability Statement

Data can be obtained from corresponding author.

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Review Article

GE Port J Gastroenterol 2024;31:153–164
DOI: 10.1159/000534641

Received: May 21, 2023
Accepted: September 25, 2023
Published online: December 27, 2023

Portuguese Pancreatic Club Perspectives on Pancreatic Neuroendocrine Neoplasms: Diagnosis and Staging, Associated Genetic Syndromes and Particularities of Their Clinical Approach

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Alexandra Fernandes[f] Filipe Vilas-Boas[a, b] Miguel Bispo[g]
Ricardo Rio-Tinto[g] Eduardo Rodrigues-Pinto[a, b]
on behalf of the Portuguese Pancreatic Club, specialized section of the Portuguese Society of Gastroenterology

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Keywords
Pancreatic neuroendocrine neoplasm · Diagnosis · Staging · Multiple neuroendocrine neoplasia type 1 · Von Hippel-Lindau disease

Abstract
Pancreatic neuroendocrine neoplasms (panNENs) have been historically regarded as rare, but their incidence has raised more than 6-fold over the last 3 decades, mostly owing to improvement in the detection of small asymptomatic tumours with imaging. Early detection and proper classification and staging are essential for the prognosis and management of panNENs. Histological evaluation is mandatory in all patients for the diagnosis of panNEN. Regarding localization and staging, multiphasic contrast-enhanced computer tomography is considered the imaging study of choice. Nevertheless, several other diagnostic modalities might present complementary information that can help in diagnosis and staging optimization: magnetic resonance imaging, somatostatin receptor imaging using positron emission tomography in combination with computed tomography (PET/CT), PET/CT with fluorodeoxyglucose (^{18}F-FDG), and endoscopic ultrasound. Approximately 10% of panNENs are due to an inherited syndrome, which includes multiple endocrine neoplasia type 1, von Hippel-Lindau disease, neurofibromatosis type 1 (NF-1), tuberous sclerosis complex, and Mahvash disease. In this review, the Portuguese Pancreatic Club summarizes the classification, diagnosis, and staging of panNENs, with a focus on imaging studies. It also summarizes the characteristics and particularities of panNENs associated with inherited syndromes.

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Perspetivas do Clube Português do Pâncreas sobre Neoplasias Neuroendócrinas Pancreáticas: Diagnóstico e Estadiamento, Síndromes Genéticos Associados e Particularidades da sua Abordagem Clínica

Palavras Chave
Neoplasia neuroendocrina pancreática · Diagnóstico · Estadiamento · Neoplasia neuroendócrina múltipla tipo 1 · Doença de Von Hippel-Lindau

Resumo
As neoplasias neuroendócrinas pancreáticas (panNENs) são historicamente consideradas raras, embora a sua incidência tenha aumentado mais de 6 vezes nas últimas três décadas, principalmente devido à otimização do diagnóstico de tumores pequenos e assintomáticos em exames de imagem. A deteção precoce, a classificação e o estadiamento adequados são essenciais para o prognóstico e abordagem dos panNENs. A avaliação histológica é obrigatória em todos os doentes para o diagnóstico de panNENs. Para a localização e estadiamento, a TC multifásica com contraste é considerada o estudo de imagem de eleição. Contudo, várias outras modalidades diagnósticas podem apresentar informações complementares que podem auxiliar no diagnóstico e na otimização do estadiamento: ressonância magnética, PET/CT dos receptores da somatostatina, PET/CT [^{18}F]FDG e ecoendoscopia. Aproximadamente 10% dos panNENs estão relacionados com síndromes hereditários, que incluem neoplasia endócrina múltipla tipo 1 (MEN1), doença de von Hippel-Lindau (VHL), neurofibromatose tipo 1 (NF1), complexo de esclerose tuberosa (TSC) e doença de Mahvash. Neste artigo, o Clube Português de Pâncreas aborda a classificação, diagnóstico e estadiamento de panNENs, com foco nos estudos de imagem, bem como resume as características e particularidades dos panNENs associados aos síndromes hereditários.

Introduction

Neuroendocrine neoplasms (NENs) can arise from different organs, even though the lungs, gastrointestinal (GI) tract, and pancreas are the most common sites. GI and pancreatic NENs (panNENs) are histologically classified under the same category; however, panNENs have particular clinical features from GI NENs and, thus, should be considered separately. PanNENs have been historically regarded as rare, but the reported prevalence in autopsy series (0.8–10%) is much higher than in population-based studies and their incidence has raised more than 6-fold over the last 3 decades [1]. This growth occurred across all disease stages and tumour grades, but it was particularly pronounced for localized low-grade tumours due to the widespread use of advanced imaging tests [1].

PanNENs are divided into functional and non-functional tumours. About 70–90% of panNENs are classified as non-functional [2]. Functional tumours secrete particular hormones or peptides, such as insulin, gastrin, vasoactive intestinal peptide, glucagon, and somatostatin.

Inherited syndromes are important to recognize in the setting of panNENs, as they have significant implications for patient's medical management, representing an opportunity for early detection of subsequent manifestations. Although most panNENs are sporadic, approximately 10% are due to an inherited syndrome, most commonly multiple endocrine neoplasia type 1 (MEN1) and, less commonly, von Hippel-Lindau disease (VHL), neurofibromatosis type 1 (NF-1), or tuberous sclerosis complex (TSC) [3]. Mahvash disease, a recently described inherited disease, has also been associated with panNENs.

In this review, the Portuguese Pancreatic Club summarizes the classification, diagnosis, and staging of panNENs, with a focus on imaging studies. It also summarizes the characteristics and particularities of the diagnosis and treatment of panNENs associated with inherited syndromes.

PanNEN Diagnosis

In accordance with World Health Organization (WHO) criteria, panNEN definitive diagnosis requires histological confirmation [4]. For appropriate pathological diagnosis, morphology, grading and immunohistochemical staining for chromogranin A (CgA) and synaptophysin should be reported. The neuroendocrine phenotype is confirmed by the immunohistochemical detection of one of the two neuroendocrine markers commonly used: synaptophysin and CgA. Other neuroendocrine markers, such as neuron-specific enolase and CD56, can be positive in panNEN, but lack specificity [5].

According to WHO 2019 classification, NENs are classified according to morphology and proliferation (Ki67 index and mitotic count) into well-differentiated

Table 1. WHO 2019 classification for gastroenteropancreatic NENs [4]

Morphology	Grade	Mitotic count, 2 mm^2	Ki67 index, %
Well-differentiated NETs	G1	<2	<3
Well-differentiated NETs	G2	2–20	3–20
Well-differentiated NETs	G3	>20	>20
Poorly differentiated NECs	G3	>20	>20
Small-cell			
Large-cell			

NEC, neuroendocrine carcinoma; NEN, neuroendocrine neoplasm; NET, neuroendocrine tumour; WHO, World Health Organization.

NENs (G1 to G3) and poorly differentiated neuroendocrine carcinomas (NEC) (always G3) (Table 1) [4]. If Ki67 index and mitotic count are discordant, the higher grade is attributed [6]. Well-differentiated NENs and NEC are biologically and genetically two different diseases. Furthermore, clear prognostic differences can be seen between these two conditions, even in grade 3 NEN. Therefore, the most recent WHO classification split the heterogeneous G3 NEN into well-differentiated NEN G3 and poorly differentiated NEC G3 [4, 6].

Clinical suspicion of functional panNENs can be confirmed by the measurement of specific hormones secreted by functional tumours (i.e., insulin, proinsulin, glucagon, gastrin, vasoactive intestinal polypeptide) and its correlation with hormonal symptoms [5]. Hormone levels also correspond to changes in tumour burden and can therefore serve as specific tumour markers during follow-up. If insulinoma is suspected, serum level of insulin and C-peptide along with glucose during prolonged fasting (72 h) is useful for the diagnosis [7]. Patients with insulinoma present abnormally elevated levels of insulin and C-peptide during hypoglycemia. Proinsulin levels are also elevated in insulinoma. When gastrinoma is suspected, fasting serum gastrin levels should be evaluated. A fasting serum gastrin level that is 10 times greater than the upper limit of the normal range along with a gastric pH <2 is diagnostic of gastrinoma [8]. Demonstration of gastric acid hypersecretion by means of gastric fluid pH evaluation in particular can be obtained through nasogastric tube or upper endoscopy using electrode, filter paper, or biochemical evaluation of aspirate [9]. However, given the advent of highly sensitive imaging-techniques and problems with the classical diagnosis of gastrinomas (intermediate levels of fasting serum gastrin and widespread use of proton pump inhibitors) most expert centres have adopted an alternative diagnostic work-up that include upper endoscopy, endoscopic ultrasonography, magnetic resonance imaging (MRI), and somatostatin receptor (STTR) imaging [9]. Serologic CgA has a limited specificity for the diagnosis of panNEN; however, it might be useful in follow-up [10]. Immunohistochemistry staining for peptide hormones such as gastrin, insulin and glucagon can also help confirm the source of a clinical symptomatology, but there is no complete agreement between immunohistochemistry and symptomatology [11]. Approximately 10% of non-functional panNENs are multiple (multifocal) [10].

PanNEN Staging

Disease stage and tumour grade are the two major independent prognostic parameters and should always be assessed to select the best therapeutic strategy. Tumour size >2 cm and Ki67 index >3% are predictors of metastatic disease, which is associated to decreased survival. Regarding panNENs staging, the tumour, node, and metastasis staging system proposed by the European Neuroendocrine Tumour Society (ENETS) and adopted in the eighth edition of the American Joint Committee on Cancer (AJCC) is recommended (Table 2) [12]. For NECs, however, the staging system of adenocarcinomas should be applied [12]. Furthermore, the primary tumour site has also an impact on the prognosis in advanced disease and should be detected in the presence of metastatic NEN. In fact, data show that patients with metastatic panNENs have a less favourable prognosis than patients with metastatic small intestinal NENs [13].

Computed tomography (CT) is the most widely used method for NEN imaging because of its availability and high diagnostic yield [14]. The ENETS, North American Neuroendocrine Tumour Society (NANETS), and European Society for Medical Oncology (ESMO) consensus guidelines recommend pancreatic protocol CT (three-phase CT) as the best imaging modality for staging, primarily due to the characterization of vascular

Table 2. Neuroendocrine tumours of the pancreas, TNM staging AJCC UICC 8th edition [11]

Primary tumour (T)	
T category	T criteria
Tx	Tumour cannot be assessed
T1	Tumour limited to the pancreas, <2 cm
T2	Tumour limited to the pancreas, 2–4 cm
T3	Tumour limited to the pancreas, >4 cm; or tumour invading the duodenum or common bile duct
T4	Tumour invading adjacent organs (stomach, spleen, colon, adrenal gland) or the wall of large vessels (celiac axis or the superior mesenteric artery)

Regional lymph nodes (N)	
N category	N criteria
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node involvement
N1	Regional lymph node involvement

Distant metastasis (M)	
M category	M criteria
M0	No distant metastasis
M1	Distant metastases
M1a	Metastasis confined to liver
M1b	Metastases in at least one extrahepatic site (e.g., lung, ovary, nonregional lymph node, peritoneum, bone)
M1c	Both hepatic and extrahepatic metastases

Prognostic stage groups			
when T is...	and N is...	and M is...	then the stage group is...
T1	N0	M0	I
T2	N0	M0	II
T3	N0	M0	II
T4	N0	M0	III
Any T	N1	M0	III
Any T	Any N	M1	IV

TNM, tumour node metastasis; AJCC, American Joint Committee on Cancer; UICC, Union for International Cancer Control.

involvement of the primary tumour. The sensitivity of CT to detect panNENs is 61–93% and the specificity is 71–100% [14–16]. The detection rate for liver metastases (LMs) is 79% [17, 18], and for extra-abdominal soft tissue metastases is 70% [19]. However, despite the good diagnostic performance of CT, this radiological method shows lower than desired sensitivity for the detection of small metastatic lymph nodes (<1 cm), bone metastases, and small peritoneal metastases [20].

MRI is a relevant complementary imaging test in the staging of patients with panNENs. In fact, abdominopelvic MRI protocol is advantageous for examination of the liver and the pancreas, when compared with CT, and is also recommended in the initial staging, as it outperforms CT for imaging small LMs [11]. Currently, diffusion-weighted imaging with MRI as well as magnetic resonance cholangiopancreatography is routinely applied, facilitating lesion detection. The MRI sensitivity to detect panNENs is described as 54–100%. The sensitivity of MRI for detection of LMs is 82–98% [21]. MRI is also superior to CT for imaging of the bones and the brain. However, MRI may miss small lung metastases, and CT is preferred for imaging of the lungs [14]. Despite this, MRI protocols, similar to CT

protocols, are usually restricted to images from the 11th vertebra body through the iliac crest in the staging of panNENs.

Endoscopic ultrasound (EUS) is the current optimal imaging method to diagnose small panNENs, being able to detect lesions as small as 2–3 mm in diameter. EUS is reported as having 82–93% sensitivity and 86–95% specificity for the detection of panNENs [22]. When compared with CT, EUS appears to have a better diagnostic performance, being able to detect lesions not apparent in other diagnostic modalities [23]. In the ENETS consensus guidelines, EUS is the imaging study of choice when other non-invasive imaging studies are negative, allowing screening the entire pancreas and a detailed evaluation of the tumour [5]. EUS has been shown to be superior to CT in the detection and localization of panNENs in patients with MEN1 syndrome, where the tumours are usually small and multifocal [24]. Furthermore, contrast-enhanced EUS (CE-EUS) is helpful in characterizing small panNENs, which are incidentally found on other imaging modalities [25]. Over 90% of panNENs showed hypoechogenicity in B-mode and hyperenhancement after the injection of contrast agent in contrast-enhanced EUS and up to 75% of hypervascular lesions on CE-EUS were NENs in a recent study [26]. Another benefit of EUS is that it allows for tissue acquisition, using fine-needle aspiration for cytology or, fine-needle biopsy (FNB) with a cutting needle for histopathological diagnosis. Several studies have documented better diagnostic performance with end-cutting FNB needles, particularly for Ki67 index determination (tumour grading), which may be underestimated in fine-needle aspiration samples [27, 28]. Preoperative knowledge of tumour grading is relevant for treatment decision, particularly in small (<2 cm) panNENs, for which tumour grading should be considered in the choice between surgery and surveillance [10, 26].

When diagnosing most NENs, STTRs imaging with positron emission tomography in combination with CT (PET/CT) using radiolabelled somatostatin analogues (e.g., [^{68}Ga]DOTATOC, [^{68}Ga]DOTANOC, [^{68}Ga]DOTATATE) is highly sensitive and should be included in the tumour staging process [14]. It offers a high detection rate of lymph node, bone, and peritoneal lesions, as well as a high detection rate of primary lesions in patients with unknown primary tumours [11]. In the past, when PET/CT was not as accessible, STTR scintigraphy (OctreoScan™) was used, with significantly less sensitivity [11]. The sensitivity to detect panNEN by STTR-PET/CT is 70.5–87.0%, and the specificity is 75–100% [29]. For the detection of bone metastases, STTR-PET/CT shows a sensitivity of 97–100% and a specificity of 92–100% [30]. Notwithstanding, the potential for false-positive uptakes must be considered, particularly within the uncinate process and the pancreatic head [28]. STTR-PET/CT should also not be used in the differential diagnosis between panNENs and other hypervascular nodules, such as ectopic spleen – for characterizing pancreatic nodules detected on MRI or CT, EUS with biopsy is superior [10].

[^{18}F]FDG-PET/CT is an additional diagnostic tool for patients with panNENs, particularly those equal to or higher than G2, characterized by higher glucose metabolism and lower STTR expression than low-grade NENs [31]. Furthermore, it provides prognostic value since FDG-positive NEN lesions associate with a worse prognosis [31, 32]. Combined STTR and FDG-PET/CT imaging (dual tracer PET/CT) have shown complementary lesion detection [31]. However, the benefits of this combination are not validated and should only be adopted on an individual basis, balancing the potential advantages with the increasing costs [11]. Regarding diagnosis and staging of NECs, FDG-PET/CT is of central importance, since STTR-PET/CT has low sensitivity.

Other diagnostic techniques such as contrast-enhanced ultrasound (US) and intraoperative US might be useful in the localization and staging of panNENs [11]. In fact, intraoperative US has an excellent diagnostic performance for the detection of lesions located in the pancreas and liver and is mandatory before pancreatic resection in MEN1 syndrome patients [11].

In summary, disease staging is a major independent prognostic parameter and should always be assessed. CT or MRI protocols with abdominopelvic imaging should be performed with additional anatomical segments evaluation in case of findings suggestive of metastatic disease. Based on current evidence, MRI should be preferred for the detection of the liver, pancreas, brain, and bone lesions, while CT is preferred for imaging of the lungs. Whole-body STTR-PET/CT imaging is complementary to CT or MRI and should also be part of the tumour staging. A summary of the imaging staging recommendations from different international societies can be found in Table 3.

Genetic Syndromes Associated with panNENs and Particularities of Their Clinical Approach

Five different inherited syndromes are associated with the development of panNENs: MEN1, VHL, NF-1, also known as Von Recklinghausen disease, TSC (Table 4), and the more recently described Mahvash disease. Mahvash disease (the rarest among the five known hereditary panNEN syndromes) is the only recessively inherited PNET syndrome (associated with a mutation in

Table 3. Imaging staging recommendations from international societies

	ESMO	ENETS	NANETS	JNETS
CT/MRI	• MRI is preferred to CT for the detection of the liver, pancreas, brain, and bone lesions • CT is preferred for imaging of the lungs	• CT/MRI (including MRCP) is recommended • The decision between CT or MRI may depend on the expertise of the institution	• CT/MRI are excellent tools for evaluating primary tumours and nodal metastases • MRI is better than CT for imaging hepatic metastases	• CT/MRI is recommended
PET/CT	• 68Ga/64Cu PET/CT imaging should be part of the tumour staging • FDG-PET/CT is optional in NENs	• 68 Ga PET/CT using is recommended for extrahepatic disease manifestation	• 68Ga/68Ga PET/CT is recommended for identifying primary tumours and the extent of metastatic disease	• 68Ga/68Ga PET/CT is recommended as it offers high specificity
EUS	• Not referred	• Small NF pancreatic NETs may be better assessed using EUS • EUS-FNB has good results in confirming a diagnosis	• EUS-FNB should be performed when histologic diagnosis of a panNEN would be helpful or when there is a question about tumour grade	• EUS-FNB is recommended when performing histology is recommended

ESMO, European Society for Medical Oncology; ENETS, European Neuroendocrine Tumour Society; NANETS, North American Neuroendocrine Tumour Society; JNETS, Japan Neuroendocrine Tumour Society; CT, computed tomography; MRI, magnetic resonance imaging; PET/CT, positron emission tomography in combination with CT; EUS, endoscopic ultrasound; FDG, fluorodeoxyglucose; MRCP, magnetic resonance cholangiopancreatography; FNB, fine-needle biopsy; panNEN, pancreatic neuroendocrine neoplasia.

Table 4. Characterization of geNENic syndromes associated with panNEN

Syndrome	Prevalence (per/100,000 population)	Frequency of panNENs	Type of panNEN
MEN1	1–10	20–80%	NF-panNENs Gastrinoma insulinoma Glucagonoma vipoma GRFoma Somatostatinoma
VHL	2–3	10–17%	NF-panNENs
NF-1	20–25,000	0–10%	Duodenal somatostatinoma
TSC	10	Uncommon	Gastrinoma, insulinoma NF-panNENs
MD	11 cases described	100%	NF-panNENs

MEN1, multiple endocrine neoplasia type 1; VHL, Von Hippel-Lindau Disease; NF-1, neurofibromatosis 1; TSC, tuberous sclerosis complex; MD, Mahvash disease; panNEN, pancreatic neuroendocrine neoplasia; NF-panNEN, non-functional panNEN; GRF, growth hormone-releasing factor.

the glucagon receptor gene), has a penetrance of 100% and appears to be exclusively associated with the development of non-functional panNENs. So far, only 11 cases have been describe in the literature, however, the clinical impact of Mahvash disease on panNENs is likely higher than that of NF-1 and TSC, which have very low panNEN penetrance [33]. The first four hereditary panNEN syndromes will be further discussed below.

Multiple Endocrine Neoplasia Type 1

MEN1 is a rare, autosomal-dominant, syndrome secondary to mutations in the *MEN1* gene on chromosome 11q13, which encodes the protein menin. Menin has an important role in regulating cell growth, cell cycle progression, and various other cellular processes [34]. Classically, MEN1 is characterized by the development of tumours/hyperplasia in multiple endocrine tissues (parathyroid, pancreas, and pituitary); however, other tumours can also be associated with MEN1, including the adrenal, skin, thyroid, CNS, smooth muscles as well as carcinoid (lung and thymus) tumours and gastric NENs [34–38].

As much as 20–80% of all patients with MEN1 will develop clinically relevant panNENs (Table 4) [34]. MEN1 occurs in 20–30% of all patients with gastrinomas and Zollinger-Ellison syndrome (ZES), 5% of patients with insulinomas, and <3% with non-functional panNENs [34]. In other types of functional panNENs, known as rare functioning tumours, MEN1 is the most frequent familial condition associated, with glucagonomas occurring in 3% of MEN1 patients, VIPomas in 3%, and GRHomas and somatostatinomas in <1% [39].

Non-functional panNENs are among the most common tumours of the pancreaticoduodenal region in patients with MEN1, with a penetrance as high as 35% at 50 years of age. In most patients, non-functional panNENs are ≤2 cm and therefore the risk of metastasis and death is very low [34]. However, average life expectancy for patients with non-functional panNENs is similar to that for patients with gastrinomas and shorter than that for patients without panNENs.

The best way to diagnose and stage non-functional panNENs in patients with MEN1 is unclear. Assays for tumour markers like CgA have low value [40]. Similar to panNENs not associated with MEN1, imaging modalities appear to be ideal for the diagnostic work-up of these patients as well as for the screening of panNENs in patients with MEN1. Current guidelines recommend annual imaging with CT, MRI, or EUS for the screening of panNENs in patients with MEN1 starting at the age of 18 years old [41]. However, given the low growth rate of these lesions, 2–3 years intervals may be considered in patients with previously negative surveillance. Recent data suggest that EUS outperforms CT scanning in this setting, and a combination of MRI plus EUS has been recommended [42]. Furthermore, STTR-PET/CT scanning has been reported to have high sensitivity for panNEN in MEN1, often leading to a change in management [43]. However, high radiation dose has been reported during surveillance program in patients with MEN1 [44]. As such, multimodality imaging strategies designed to minimize radiation exposure should be considered.

The management of non-functional panNENs in MEN1 is controversial [45]. Many experienced centres have been using a tumour size threshold of 2 cm in the decision to surgically resect non-functional panNEN [46], with subsequent yearly surveillance [47]. Generally speaking, tumours under 1 cm have a low risk for substantial growth and metastasis and avoiding surgery with continued surveillance is reasonable. Available data for tumours between 1 and 2 cm are less clear. Triponez et al. demonstrated that the risk of death was low for patients with panNEN <2 cm and proposed a conservative attitude for these patients in the absence of aggressive features such as rapid progression on imaging studies [48].

In patients with MEN1, panNENs are responsible for 30% of the ZES, with duodenal NENs being responsible for the remainder. Most gastrinomas are well differentiated, with a low proliferative activity (Ki67 index), usually close to 2%. Immunohistochemically, almost all gastrinomas stain for gastrin [49]. Patients with ZES and MEN1 present at an earlier age (mean 32–35 years) than patients with sporadic disease [34]. Of all MEN1/ZES patients, 25% lack a family history of MEN1, supporting the need to suspect of MEN1 in all patients with ZES [34]. In up to 45% of MEN1 patients, the symptoms of ZES precede those of hyperparathyroidism and can be the initial symptoms [50]. However, almost all MEN1 patients have hyperparathyroidism at the time of ZES diagnosis, although in many patients it can be asymptomatic [34, 50]. Regarding insulinomas, approximately 5% are associated with MEN1 syndrome. Comparative studies between patients with insulinomas, with or without MEN1 are lacking. Finally, the association between MEN1 and rare functioning tumours is less clear.

Because of the frequent association between MEN1 and ZES, and in similarity to patients with a clinical diagnose of MEN1 (Table 5), all patients with ZES should have biochemical studies for MEN1. Similarly, all patients with insulinoma or rare functioning tumours with suspicion of MEN1 (Table 5) should have the same evaluation. Serum parathormone levels, ionized calcium levels and prolactin levels should be performed at initial evaluation and during yearly follow-up in patients with ZES [34, 50]. Furthermore, all patients suspected of MEN1 (Table 5) need to be assessed for the other tumours, which are generally non-functional [49]. Specific parathyroid studies are required if hyperparathyroidism is found (US, CT/MRI, 99m Tc-sestamibi scan) [51]. All patients require MRI of the *sella turcica* region and, after 20 years of age, require CT of the chest/abdomen [52]. If MEN1/ZES is

Table 5. MEN1 genetic testing criteria

Individuals meeting any one of the following should be referred for genetic counselling and gene testing
• Patient meeting MEN1 clinical diagnostic criteria:
1) Two or more classic MEN1-associated tumours (parathyroid adenoma, pituitary adenomas, or GEP-NEN)
2) Single MEN1-associated tumour and a first-degree relative with MEN1
• First-degree relative of a patient with MEN1 syndrome
• Parathyroid adenoma diagnosed before age 30
• Multiple parathyroid adenomas
• Gastrinoma or multiple panNEN at any age
• Single panNEN diagnosed before age 20
• Female with thymic NEN
• One classic MEN1-associated tumour and one nonclassic feature (carcinoid tumour, dermatologic features, or adrenal tumour)

MEN1, multiple endocrine neoplasm type 1; NEN, neuroendocrine neoplasia.

present, UGI endoscopy for gastric NEN is recommended [53]. Routine SRS is not recommended if other imaging studies for NEN are negative. EUS is more sensitive than cross sectional imaging studies (CT, MRI, US) for the detection and characterization of small non-functional panNENs. However, since routine surgical resection of small panNENs (<2 cm) is not recommended and the EUS criteria on when to operate these patients are not established the added benefit of EUS is controversial [54].

Regarding genetic testing, it should be performed in patients meeting criteria for MEN1 (≥2 tumours associated with MEN1), patients with gastrinomas or patients meeting further criteria described in Table 5. If genetic testing is considered, genetic counselling should be offered, prior to testing [51, 55].

In MEN1/ZES patients, surgery without a Whipple resection is associated with >90% of recurrence [34, 49, 56]. Therefore, routine surgical exploration is controversial in patients with MEN1/ZES. Indeed, these patients usually have multiple gastrinomas, frequently with lymph node metastases, with concomitant panNENs (non-functional primarily), are rarely cured and have an excellent life expectancy if only small tumours (<2 cm) are present [34, 49, 57]. However, surgery is the only treatment approach with curative intent [56]. As such, it has been generally recommended that surgery should be performed in patients with MEN1 and panNENs >2 cm [48]. In patients with MEN1 and insulinoma, in which multiple tumours are frequently present, the aim of surgery is to control inappropriate insulin secretion by excising all insulinomas. As such, preoperative localization of which pancreatic tumours are the insulinomas is mandatory because these patients frequently have other panNENs (usually non-functional) [58].

The prognostic significance of MEN1 in patients with panNENs is not entirely clear. Some studies in patients with gastrinomas suggest these patients have a better prognosis, even though the gastrinomas are almost always multiple [59]. With the ability to treat both the ZES and the hyperparathyroidism, recent studies show that in patients with MEN1, the natural history of the panNEN is increasingly becoming a determinant of survival [34]. Finally, patients with MEN1 frequently have multiple insulinomas, however, these are usually cured surgically [60]. There are no comparative studies on survival in MEN1 patients with insulinomas compared to sporadic cases.

Von Hippel-Lindau Disease

VHL is a rare autosomal-dominant disease caused by mutations in the *VHL* gene, on chromosome 3p25, that encodes the peptide pVHL, important in the regulation of angiogenic growth and the activity of several mitotic factors (VEGF, PDGF, TGFα, erythropoietin) [34]. VHL is characterized by hemangioblastomas of the retina and craniospinal region, endolymphatic sac tumours, renal cell carcinomas or cysts, pheochromocytomas, and epididymal cystadenomas (Table 6). Furthermore, pancreatic tumours or cysts can be present in 35–77% of patients [46, 59]. Specifically, panNENs develop in 10–17% of patients with VHL, and in almost all cases they are non-functional panNENs, and usually are asymptomatic (Table 4) [61]. In contrast to MEN1 patients, most VHL patients have a single panNEN, although patients might also present with multifocal lesions [34]. The majority of panNENs in VHL are well differentiated (grade 1 or 2), small (<2 cm) and present a slow growth when compared with sporadic tumours. As a result of its clinical indolence, many of these lesions are diagnosed incidentally during routine VHL surveillance for renal lesions [62]. However, in 8–50% of VHL patients, panNENs are metastatic and LMs occur in 9–37% [63]. In patients with VHL, panNENs are more likely to metastasize when present with size >3 cm in diameter, rapid tumour doubling time (<500 days), and VHL missense and/or exon 3 pathogenic variants [64]. Based on these 3 risk factors, risk stratification of panNENs in the context of VHL has been suggested for management optimization [64]. As such, in the presence of a panNEN, if clinical features suggest VHL (Table 6), appropriate gene testing should be considered after genetic counseling [34], and molecular imaging, typically with STTR-PET/CT should be offered [65].

Table 6. Von Hippel-Lindau disease (VHL) diagnostic criteria

Simplex case (no family history), individual with ≥2 of the following
• Two or more hemangioblastomas of the retina, spine, or brain or a single hemangioblastoma in association with a visceral manifestation (e.g., multiple kidney or pancreatic cysts) • Renal cell carcinoma • Paraganglioma or pheochromocytoma • Less commonly, endolymphatic sac tumours, papillary cystadenomas of the epididymis or broad ligament, or neuroendocrine tumours of the pancreas
Familial case (known relative with VHL), individual with ≥1 of the following
• Retinal angioma • Spinal or cerebellar hemangioblastoma • Paraganglioma or pheochromocytoma • Renal cell carcinoma • Multiple renal and pancreatic cysts

Management of panNENs is primarily surgical, although the criteria for surgical resection differ from those of patients with sporadic panNENs. Surgical resection should be reserved for patients with potentially resectable lesions greater than 3 cm in diameter in the body or tail of the pancreas, or greater than 2 cm in diameter in the head of the pancreas [65]. The hypoxia-inducible factor-2alpha (HIF-2alpha) inhibitor Belzutifan, rather than other systemic therapies, is considered the best approach if surgery is not feasible, or the tumour is considered unresectable [65]. Nonoperative approaches (e.g., surveillance, Belzutifan) are appropriate for small primary lesions (≤3 cm), incorporating other clinical factors such as type and location of the VHL pathogenic variant, and rate of tumour growth [63]. Regarding prognosis, VHL-associated panNENs tend to be associated with a more indolent course and, similarly, long-term outcomes of resected VHL-associated panNENs appear to be generally better than those of sporadic [66].

Neurofibromatosis Type 1

NF-1 is an autosomal-dominant syndrome with a population frequency of 1 in 3,000 births, with half of cases due to a de novo mutation [67]. NF-1 is due to mutations in the *NF-1* gene on chromosome 17q11.2, which encodes the protein neurofibromin, which affects cell growth, through Ras protein activation and mammalian target of rapamycin (mTOR) cascade regulation [46, 62]. This condition is characterized by the development of several tumours, including neurofibroma, pheochromocytoma, and GI stromal tumour (Table 1) [46, 62]. CNS abnormalities are frequent with learning disorders (30–60%), attention deficit hyperactivity disorder, and epilepsy [46, 62]. Furthermore, panNENs occur only in a minority of NF-1 patients (10%) and are almost exclusively duodenal somatostatinomas (Table 4) [46, 63, 64]. However, NF-1 patients have been reported with NF-panNENs, ZES and insulinomas [34]. Duodenal somatostatinomas characteristically occur in the periampullary region, have a mean size of 2.8 cm (range 1–5), comprise 23% of all ampullary NENs in several series, metastasize in 30% of cases, and are rarely associated with the clinical somatostatinoma syndrome (1–2%) [46]. To this date, there are no data to allow specific management recommendations of panNENs in the context of NF-1 and patients with NF-1 with panNENs are usually treated as sporadic panNENs. However, it is important to remember that in patients with panNENs, if clinical features suggest NF-1, appropriate gene testing should be considered after genetic counseling [34].

Tuberous Sclerosis Complex

TSC is an autosomal-dominant disease caused by a mutation in one of two genes: the *TSC1* gene (which encodes hamartin) or the *TSC2* gene (which encodes tuberin). Both hamartin and tuberin are codependent and play a role in mTOR cascade regulation, protein translation, protein synthesis, and cell proliferation [34]. This condition is characterized by the development of hamartomas in multiple organs, neurological features (autism, mental retardation, epilepsy), and dermatological features (hypomelanotic macules, shagreen patches, ungual fibromas, facial angiofibromas) [68]. A small percentage of TSC patients (1%) have been reported to have panNENs, including gastrinomas, insulinomas, and non-functional panNENs, some of which are metastatic (Table 4) [69]. As such, in patients with panNENs, if clinical features suggest TSC, appropriate gene testing should be considered after genetic counselling [34]. However, to this date, specific management recommendations of panNENs in the context of tuberous sclerosis are lacking and patients are usually treated as sporadic ones.

Conclusion

Among pancreatic neoplasms, panNENs are rare tumours. However, their incidence is increasing with the advancement of imaging technology and increased

opportunities for checking pancreatic diseases. Early detection and proper staging are paramount for prognostication and for treatment decision. Histological evaluation is mandatory in all patients for the diagnosis of panNENs and plays a central role in grading these tumours, essential for proper prognostic information.

Regarding localization and staging, multiphasic contrast-enhanced CT is considered the imaging study of choice. MRI has been suggested to be more sensitive in detecting small tumours and LM than other modalities. STTR-PET/CT has been approved for the diagnosis and staging of panNENs and has improved sensitivity when compared with the more traditional STTR scintigraphy. EUS can detect tumours as small as 2–3 mm. Its sensitivity is equal or superior to multidetector CT or MRI for their detection. Other benefits of EUS include the detection of lymph node involvement and vascular invasion and the possibility of tissue acquisition through FNB, which is crucial for tumour grading. EUS-FNB is the best modality for the differential diagnosis between panNENs and other hypervascular nodules detected on CT or MRI.

In the presence of inherited syndromes, panNENs may present with additional challenges. A thoughtful approach to the diagnosis and management is required, as these syndromes often involve multi-organ disease with a lifelong risk for tumour development. Additionally, the natural history of tumours in the setting of a hereditary condition may be different than it would be expected in a sporadic form of the disease. The unique aspects to management, challenges in hereditary disease recognition and accurate diagnosis, and rarity of these syndromes should be kept present during the evaluation of patients with panNENs.

Acknowledgment

The authors would like to thank Dr. Ana Oliveira (Nuclear Medicine Specialist at Centro Hospitalar São João) for revising the document regarding functional imaging data.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

The authors have no funding to declare.

Author Contributions

Joel Ferreira-Silva, Sara Meireles, Massimo Falconi, and Eduardo Rodrigues-Pinto were responsible for literature review and manuscript writing. Results were discussed in two meetings of Clube Português do Pâncreas and approved by all members. All authors critically reviewed and approved the final manuscript.

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GE – Portuguese Journal of Gastroenterology

Research Article

GE Port J Gastroenterol 2024;31:165–172
DOI: 10.1159/000531269

Received: July 15, 2022
Accepted: March 12, 2023
Published online: July 11, 2023

Prognostic Markers in Pediatric Acute Liver Failure

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Keywords
Pediatric acute liver failure · Acute liver failure · Prognosis · Liver transplant · Lactate

Abstract
Introduction: Acute liver failure (ALF), although rare in children, is a complex progressive pathology, with multisystem involvement and high mortality. Isolated variables or those included in prognostic scores have been studied, to optimize organ allocation. However, its validation is challenging. This study aimed to assess the accuracy of several biomarkers and scores as predictors of prognosis in pediatric ALF (PALF). ***Methods:*** An observational study with retrospective data collection, including all cases of ALF, was defined according to the criteria of the Pediatric Acute Liver Failure Study Group, admitted to a pediatric intensive care unit (PICU) for 28 years. Two groups were defined: spontaneous recovery (SR) and non-SR (NSR) – submitted to liver transplantation (LT) or death at PICU discharge. ***Results:*** Fifty-nine patients were included, with a median age of 24 months, and 54% were female. The most frequent etiologies were metabolic (25.4%) and infectious (18.6%); 32.2% were undetermined. SR occurred in 21 patients (35.6%). In NSR group ($N = 38$, 64.4%), 25 required LT (42.4%) and 19 died (32.2%), 6 (15.7%) of whom after LT. The accuracy to predict NSR was acceptable for lactate at admission (AUC 0.72; 95% CI: 0.57–0.86; $p = 0.006$), ammonia peak (AUC 0.72; 95% CI: 0.58–0.86; $p = 0.006$), and INR peak (AUC 0.70; 95% CI: 0.56–0.85; $p = 0.01$). The cut-off value for lactate at admission was 1.95 mmol/L (sensitivity 78.4% and specificity 61.9%), ammonia peak was 64 µmol/L (sensitivity 100% and specificity 38.1%), and INR peak was 4.8 (sensitivity 61.1% and specificity 76.2%). Lactate on admission was shown to be an independent predictor of NSR on logistic regression model. Two prognostic scores had acceptable discrimination for NSR, LIU (AUC 0.73; 95% CI: 0.59–0.87; $p = 0.004$) and PRISM (AUC 0.71; 95% CI: 0.56–0.86; $p = 0.03$). In our study, the PALF delta score (PALF-ds) had lower discrimination capacity (AUC 0.63; 95% CI: 0.47–0.78; $p = 0.11$). ***Conclusions:*** The lactate at admission, an easily obtained parameter, had a similar capacity than the more complex scores, LIU and PRISM, to predict NSR. The prognostic value in our population of the promising dynamic score, PALF-ds, was lower than expected.

Marcadores de Prognóstico na Falência Hepática Aguda Pediátrica

Palavras Chave
Falência hepática aguda · Lactato · Pediatria · Prognóstico · Transplante hepático

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Resumo

Introdução: A falência hepática aguda (FHA), apesar de rara em pediatria, é uma patologia complexa, com envolvimento multissistémico e elevada mortalidade. Têm sido estudadas variáveis isoladas ou incluídas em scores de prognóstico, com o objetivo de otimizar a alocação de órgãos. No entanto, a sua validação apresenta alguns desafios. O presente estudo tem como objetivo avaliar a precisão de vários biomarcadores e scores, como preditores de prognóstico na FHA. ***Métodos:*** Estudo observacional com método de colheita de dados retrospetivo, tendo como critérios de inclusão os casos de FHA, definida de acordo com os critérios da *Pediatric Acute Liver Failure Study Group*, admitidos numa Unidade de Cuidados Intensivos Pediátricos (UCIP) num período de 28 anos. Definiram-se 2 grupos: recuperação espontânea (RE) e sem recuperação espontânea (SRE) – doentes submetidos a transplante hepático (TRH) ou morte na alta da UCIP. ***Resultados:*** Incluíram-se 59 doentes, com mediana de idade de 24 meses, 54% do sexo feminino. As etiologias mais frequentes foram a metabólica (25.4%) e a infeciosa (18.6%); em 32.2% foi indeterminada. Apresentaram RE 21 doentes (35.6%). No grupo SRE (N = 38, 64.4%), 25 necessitaram de TRH (42.4%) e 19 faleceram (32.2%), dos quais 6 (15.7%) tinham sido submetidos a TRH. A precisão prognóstica para a ausência de recuperação espontânea foi aceitável para o lactato na admissão (AUC 0.72; IC 95%: 0.57–0.86; p = 0.006), amónia máxima (AUC 0.72; IC 95%: 0.58–0.86; p = 0.006) e INR máximo (AUC 0.70; IC 95%: 0.56–0.85; p = 0.01). O valor de *cut-off* do lactato na admissão foi de 1.95 mmol/L (sensibilidade 78.4% e especificidade 61.9%) e da amónia máxima foi de 64 umol/L (sensibilidade 100% e especificidade 38.1%). O lactato à admissão mostrou ser um fator independente para NSR, no modelo de regressão logística. Os scores LIU e PRISM apresentaram curvas ROC com aceitável capacidade de discriminação para a ausência de recuperação espontânea, com AUC de 0.73 (IC 95%: 0.59–0.87; p = 0.004) e 0.71 (IC 95%: 0.56–0.86; p = 0.03), respetivamente. No nosso estudo, o score PALF-Delta (PALF-ds) teve uma menor capacidade de discriminação (AUC 0.63; IC 95%: 0.47–0.78; p = 0.11). ***Conclusões:*** O lactato na admissão, um parâmetro de fácil obtenção, teve uma capacidade semelhante aos scores mais complexos, LIU e PRISM, para predizer a ausência de recuperação espontânea. O valor prognóstico nesta série, do promissor score dinâmico PALF-ds, foi inferior ao esperado.

Introduction

Pediatric acute liver failure (PALF) is a rare and life-threatening multisystem and dynamic disorder that progresses to multiorgan failure within days or weeks in children with no pre-existing chronic liver disease [1]. Although the actual incidence of PALF is unknown, it is estimated to be the cause of liver transplantation (LT) in 10–15% of pediatric population undergoing LT [2, 3].

Etiology depends on age and epidemiology, and includes viral hepatitis, metabolic disorders, autoimmune hepatitis, ischemia, neoplastic disease, and toxins [4]. However, there are still many cases in which etiology remains indeterminate (40–50%) [1, 5]. Although its presence is not strictly necessary, unlike adults, most children develop hepatic encephalopathy with varying degrees of impairment [1], and its signs can be subtle.

Despite the advances in supportive measures and target treatment for specific etiologies in intensive care units [6], ALF carries a high mortality risk or requires LT in 70% of cases [2, 7]. Since that a critical factor in the prognosis of PALF is the early referral to a LT center [8], in January 2008, a multidisciplinary national meeting was held in Portugal on PALF, which involved the Societies of Gastroenterology, Hepatology and Nutrition and Pediatric Intensive Care of the Portuguese Society of Pediatrics, resulting in a consensus on action reinforcing the importance of its differentiated approach and early referral to the only one pediatric LT national center. Therefore, when patients have a PALF diagnosis in any hospital in our country, contact should be made with the LT center, in order to optimize its management and, eventually, provide an early hospital transfer [8].

Several prognostic factors have been studied, including age, etiology, encephalopathy, serum bilirubin levels, coagulation factors (international normalized ratio [INR], factor V), ammonia, and serum lactate [9]. Scoring systems have also been developed to help predict the risk of death or the need for LT, trying to improve organ allocation decisions. The pediatric end-stage liver disease (PELD) for children aged less than 12 years has been used to predict mortality in children with a chronic liver disease listed for LT. However, its validity as a prognostic score in PALF is questionable, due to the limited use and non-consensual results [10]. Another one, the liver injury unit (LIU) scoring system, appears to predict the likelihood of receiving a LT better than the risk of death [11, 12].

Most of these scoring models use static clinical parameters assessed within the first hour or the first day, so they do not reliably predict mortality as the disease may

rapidly deteriorate in hours or days [13, 14]. A new, non-yet validated prognostic score, the PALF delta score (PALF-ds), based on changes in serial laboratory values in the first week after admission, seems to have a higher predictive mortality accuracy, despite the complexity of its calculating formula [15].

The pediatric intensive care unit (PICU) scoring systems like pediatric risk of mortality (PRISM) and pediatric index of mortality (PIM) have been developed to assess the severity of illness and mortality risk, irrespective of the diagnosis but they have been scarcely studied in PALF [6, 16]. Currently, unlike adults, there are no validated PALF prognostic scores that clearly distinguish between patients who will recover spontaneously from those who will need LT to survive [3]. So, it is essential to establish more versatile, accurate, and straightforward prognostic tools. Our study aimed to investigate the accuracy of several biomarkers and scores as prognostic tools in PALF in a PICU of a national referral center for pediatric LT.

Materials and Methods

An observational study with retrospective data collection was performed.

Eligibility criteria were children and adolescents (aged between 0 and 17 years) admitted to a PICU of a national referral center for pediatric LT between January 1994 and January 2022 with PALF diagnosis from the PICU database. Patients with PALF due to secondary liver injury related to multiple organ failure were excluded.

The sample was divided based on patient outcomes into two groups: spontaneous recovery (SR) which included patients benefiting from eventual etiologic treatments such as N-acetylcysteine therapy and non-SR (NSR – transplantation or death at PICU discharge). All patients benefitted from standard supportive care.

PALF was defined according to Pediatric Acute Liver Failure working group criteria as biochemical evidence of liver injury and coagulopathy not corrected by vitamin K in the presence of an INR greater than 1.5 in patients with hepatic encephalopathy, or an INR greater than 2, regardless of hepatic encephalopathy, in patients with no known evidence of chronic liver disease [4, 6]. To assess the presence and grade of hepatic encephalopathy, it used a scale adapted to pediatric age [17].

Data collection was obtained by consulting the computer records from the PICU and hospital general databases (B-ICU Care, SClinico) and, in older cases, from paper medical charts. The variables analyzed were age, gender, etiology, presence and grade of encephalopathy; biomarkers at admission, and peak values (alanine aminotransferase, aspartate aminotransferase, total bilirubin [TB], serum ammonia, serum lactate, INR, serum albumin, creatinine, sodium); and PICU support therapies (mechanical invasive ventilation, cardiovascular support, and continuous renal replacement therapy). The following prognostic scores were calculated (Table 1):

1. PELD/MELD scores. The PELD score was applied in patients aged less than 12 years, and the MELD score was applied in patients aged 12 years or older [10, 18] at the time of PICU admission using available internet calculator (peld-score-pediatric-end-stage-liver-disease-younger-12 and meld-score-model-end-stage-liver-disease-12-older).
2. LIU score at PICU admission according to the formula described in Table 1 [12].
3. PALF-ds was obtained from the laboratory values at PICU admission and its evolution over the following 7 days [14].

The PICU mortality prediction model, PRISM and PIM, scores were also considered. The PRISM score uses fourteen physiologic variables (blood pressure, heart rate, respiratory rate, PaO_2/FiO_2, $PaCO_2$, Glasgow coma score, pupillary reactions, coagulation study, TB, potassium, calcium, glucose, and bicarbonate) and is automatically calculated by completing a patient's clinical situation form in the first 24 h of PICU admission. Similarly, PIM score uses ten variables (systolic blood pressure, pupillary reaction, PaO_2, FiO_2, mechanical ventilation, base excess, elective/urgent ICU admission, reason for ICU admission, and risk diagnosis) that were obtained by filling the clinical form with clinical admission data.

Statistical analysis was performed with the Statistical Package for the Social Science, version 27. Nominal variables were expressed as numbers and percentages. Numeric variables were reported with mean and standard deviation or median and interquartile range (P25 to P75), depending on its distribution.

The χ^2 test or Fisher's exact test, according to Cochran rules, was used to compare nominal variables. Regarding quantitative variables, comparisons between groups were made, using the parametric test, independent sample *T* test and the nonparametric Mann-Whitney U test, as appropriate. The threshold for significance was defined as $p < 0.05$.

The receiver operating characteristic curve of all the prognostic scores and biomarkers considered was analyzed. We used the area under the receiver operating characteristic curves (AUC) as an effective way to evaluate the overall diagnostic accuracy of the score/biomarker [19]. So, an AUC of 0.5 suggests no discrimination capacity of the model; 0.7 to 0.8 is considered acceptable; 0.8–0.9 is considered excellent, and more than 0.9 is considered outstanding [19].

We performed a multivariate analysis through a logistic regression model to evaluate the influence of some variables on lactate capacity to predict NSR. Omnibus Test of Model Coefficients and Nagel R Square statistic was applied to assess good fit. The good fit quality of the model was classified according to Nagelkerke R^2: poor quality <10%, moderate quality 10–50%, good to very good quality >50%. Results of the logistic regression analysis were reported as adjusted odds ratios with 95% confidence intervals (CIs).

Results

The study included 59 patients with a median age of 24 months (interquartile range 4–68), 54% of the female gender. According to admission year, 35 patients were admitted between 1994 and 2007 and 24 between 2008 and 2022.

There were 53 children transferred from other hospitals. The median time between the onset of symptoms and PICU admission was 5 days (2–14).

Table 1. LIU and PALF-ds formula

Score	Formula
LIU [12]	[3.507 × peak TB (mg/dL)] + [45.51 × peak INR] + [0.254 × peak ammonia, mmol/L]
PALF delta [13]	[0.232 × Δpeak TB (mg/dL)] + [2.263 × Δdaily INR] + [0.013 × peak ammonia, mmol/L] – 4.498

Δdaily INR, maximum change in serial INR level; Δpeak TB, difference between the peak TB and TB at enrollment; INR, international normalized ratio; peak ammonia, maximum value of ammonia; peak INR, maximum value of INR; peak TB, maximum value of total bilirubin; TB, total bilirubin.

Table 2. Demographic and clinical characteristics of the two groups of patients

Variable	SR (*N* = 21)	NSR (*N* = 38)	*p* value
Female gender, *N* (%)	11 (52.4)	21 (55.3)	0.8*
Median age (IQR), months*	12.3 (2.0–70.0)	31.5 (4.5–68.3)	0.7[a]
Etiology, *N* (%)			
Indeterminate	7 (33.3)	12 (31.6)	
Metabolic	8 (38.1)	7 (18.4)	
Infectious	2 (9.5)	9 (23.8)	0.4*
Autoimmune	–	4 (10.5)	
Toxin	2 (9.5)	3 (7.9)	
Toxic	1 (4.8)	1 (2.6)	
Infiltrative	–	1 (2.6)	
Ischemic/vascular	1 (4.8)	1 (2.6)	
Encephalopathy on admission, *N* (%)	9 (42.9)	24 (63.2)	0.2*
Encephalopathy grade, median (IQR)	1 (1–3)	2 (1–4)	**0.02[a]**
Mechanical invasive ventilation, *N* (%)	6 (28.6)	31 (81.6)	**<0.001***
Cardiovascular support, *N* (%)	7 (33.3)	24 (63.2)	0.08*
CRRT, *N* (%)	0 (0)	6 (15.8)	0.2[b]

CRRT, continuous renal replacement therapy; IQR, interquartile range; SR, spontaneous recovery; NSR, non-spontaneous recovery. *χ^2 of Pearson test. [a]Mann-Whitney U test. [b]Fisher's exact test.

The most frequent etiologies were metabolic (*N* = 15; 25.4%) and infectious (*N* = 11; 18.6%); in 32.2% (*N* = 19) of the patients, it was not possible to determine an ethology. SR occurred in 21 (35.6%), and NSR occurred in 38 patients (64.4%).

In the group of NSR, 25 children underwent LT (42.4%) and 19 died, of whom six after LT. From the remaining 13 that died, two were considered for LT. Table 2 shows the demographic and clinical characteristics of the two groups.

More than half (*N* = 33; 55.9%) had encephalopathy on admission, with the highest grades in the group of NSR ($p = 0.02$). Patients in the NSR group often required mechanical invasive ventilation ($p < 0.001$), cardiovascular support, and continuous renal replacement therapy.

Biomarkers and scores were compared between the two groups (Table 3). Lactate and TB on admission, ammonia peak, TB peak, and INR peak were significantly higher in the NSR group than in the SR group.

The NSR group had higher values in all prognostic scores analyzed. However, these differences were only statistically significant in LIU and PRISM scores.

The accuracy of the biomarkers and scores to predict NSR can be observed in Table 4. NSR was acceptable for lactate at admission (AUC 0.72; 95% CI: 0.57–0.86; $p = 0.006$), ammonia peak (AUC 0.72; 95% CI: 0.58–0.86; $p = 0.006$), and INR peak (AUC 0.70; 95% CI: 0.56–0.85; $p = 0.01$).

Additionally, two prognostic scores had acceptable discrimination performance for NSR with AUC 0.73 for LIU and 0.71 for PRISM, both statistically significant. The multivariate analysis with a logistic regression model was statistically significant (X^2 [3] = 11.8, $p < 0.001$). The model correctly classifies 88.7% of the cases and has a

moderate quality of good fit (Nagelkerke R^2 24.1%) (Table 5). The lactate on admission was an independent factor for NSR.

Discussion

PALF treatment involves the challenging decision whether to maintain only supportive medical therapy or to advance to an urgent LT. LT is the only proven treatment for PALF and has allowed, in recent decades, a significant improvement in its prognosis, increasing survival to about 60–85% [8].

Despite these encouraging results, optimal prognostic criteria are lacking. An effective prognostic model for PALF is essential for clinical practice to accurately differentiate between patients who may recover spontaneously from those who probably will die without LT [3]. This process would help with appropriate organ allocation, avoiding unnecessary LT in patients with a good chance of SR [3].

Another critical factor in the prognosis of PALF is the early referral to a LT center [8]. The multidisciplinary and differentiated approach allows optimization of support measures, undergoing LT in better conditions, identifying situations in which LT is contraindicated and eventually enhancing the probability of SR. An early referral to the LT center is associated with higher survival than a late referral [8].

Developing prognostic models or scores for PALF encompasses numerous challenges. In particular, the heterogeneity of age and etiology in PALF, and a lack of universal understanding of the natural history of the disease, poses additional difficulties, not permitting the application of adult criteria.

Several laboratory variables have been identified, and their incorporation into scoring systems has been attempted, but no optimal validated model for PALF has yet been established. A suitable model should reflect the dynamic nature of PALF and simultaneously include easily accessible variables, making it easy to apply in clinical practice.

In the present study, the authors evaluated the prognostic accuracy of several biomarkers and scores at admission and during the first week in children with PALF admitted in a PICU to predict the outcome, namely, death or need for LT (NSR). Regarding the etiology of PALF, metabolic disorders were the most frequent (25.4%), possibly because our hospital is a reference for this type of disease. Metabolic conditions account for approximately 10% of all cases of PALF and 18% of PALF cases among children younger than 3 years [8].

The proportion of patients with indeterminate etiology (32.2%) is lower than described in most studies [1, 2, 7]. These numbers may be related to a large diagnosis effort based on an exhaustive investigation, even after patients' death.

This center is the Portuguese reference in pediatric LT and PALF since 1994 and 2008, respectively, with a reduction in referral time and severity of cases upon admission since 2008 and a trend to mortality decline [20]. Thus, our results are in line with the noteworthy mortality associated with PALF (32.2%) and LT survival rate (76%), as described in the literature [1, 2, 4].

The majority of our patients had encephalopathy, which was more severe at admission in the NSR group. The presence of encephalopathy is widely associated with poor outcome [1, 3, 20] in particular in adult ALF. However, encephalopathy is challenging to incorporate into a prognostic model as it can be subtle and difficult to evaluate in younger children [17].

Several prognostic and scoring systems for adult ALF have been suggested, but there is a limitation to the applicability of these prognostic scores to PALF, as pointed above [3, 14]. Given the severity and dynamic of this condition, robust prognostic tools with reasonable accuracy to early identify patients with a poor prognosis to include them in the urgent transplant list are needed [1]. As most of the decisions to LT listing occur within the first few days of admission, the evolution of biomarkers, highlighting the peak values, in the first week of hospitalization was considered.

These data indicate that lactate and TB on admission, peak values of ammonia, TB, and INR were significantly associated with NSR. All these values presented an acceptable predictive accuracy with AUC ranging from 0.67 to 0.72, emphasizing the good discrimination power of lactate on admission and peak ammonia (both had an AUC value of 0.72).

Our study is one of the few studies that analyzed the accuracy of serum lactate as an isolated biomarker related to the evolution of PALF. The lactate value on admission had higher predictive power than the described scores, particularly the PALF-ds, characterized by high complexity in its calculation. Serum lactate as a prognostic tool has been studied in various situations of critically ill pediatric patients, such as septic shock [21] and has been included in PICU mortality scores [22, 23]. In some studies, a high blood lactate level at admission has been considered independently associated with and predictive of in-hospital mortality in the general population of critically ill children

Table 3. Comparison of biomarkers and scores between groups

Variable	SR (*N* = 21)	NSR (*N* = 38)	*p* value
ALT on admission (U/L)	1,511 (438.5–3,153.5)	1,258 (324.3–2,445.5)	0.8[a]
ALT peak (U/L)	2,054 (438.5–5,891.5)	1,793 (664–3,147)	0.4[a]
Lactate on admission, mmol/L	1.7 (1.2–3.1)	2.8 (2.2–4.6)	**0.006**[a]
Lactate peak, mmol/L	3.5 (2.1–5.1)	4.5 (2.2–4.6)	0.11[a]
Ammonia on admission, µmol/L	63 (27.5–100)	76 (48.8–136)	0.16[a]
Ammonia peak, µmol/L	93 (38–153)	147.5 (89–232.8)	**0.006**[a]
TB on admission, mg/dL	3.7 (1.6–12.)	12.1 (3.8–20.2)	**0.03**[a]
TB peak, mg/dL	7.6 (2.1–19.8)	18.4 (8.6–25)	**0.03**[a]
INR on admission (s)	2.5 (2.1–3.6)	3.1 (2.3–4)	0.46[a]
INR peak (s)	3.4 (2.4–5.3)	5.5 (3.4–7.3)	**0.01**[a]
PALF-ds	0.1 (−2.3–5.2)	2.4 (1.8–6.1)	0.11[a]
LIU	216.9 (144.7–336.7)	324.3 (250–472.6)	**0.004**[a]
PELDL/MELD, mean (SD)	24.1 (12.2)	26.1 (11.2)	0.54**
PRISM	5 (1.8–12.1)	13.4 (4.9–25.3)	**0.03**
PIM	6 (4.6–9.6)	8 (5.8–18.2)	0.17

Values are median (IQR) unless otherwise indicated. ALT, alanine aminotransferase; INR, international normalized ratio; IQR, interquartile range; LIU, liver injury unit scoring system; PALF-ds, PALF delta score; PELD, pediatric end-stage liver disease; NSR, non-spontaneous recovery; PIM, pediatric index of mortality; PRISM, pediatric risk of mortality; SD, standard deviation; SR, spontaneous recovery; TB, total bilirubin. **Dependent sample *T* test. [a]Mann-Whitney U test.

[22–24]. These results described in the literature support the relation between lactate and mortality that can be eventually applied in PALF. Therefore, the cut-off value for lactate of 1.95 mmol/L (with a sensitivity of 78.4% and specificity of 61.9%) seems relevant and helps identifying the patients that will not recover spontaneously. Additionally, lactate on admission was independently correlated with NSR when included in a logistic regression model with possible confounding factors, such as metabolic etiology.

Moreover, these results show that blood ammonia levels, especially peak values, could predict outcomes in PALF. Several studies found a significant difference on admission and peak biomarker values with definitely higher values in the group with organ loss, particularly for ammonia [1, 3, 15]. Liu, et al. observed in their cohort of 81 children with PALF that high ammonia levels were significantly associated with death or need for LT [11, 12]. Furthermore, compared with adult ALF, ammonia seems to be a far better prognostic parameter for children than for adults [1, 3, 15].

From the prognostic scores, LIU was the one that best predicted the evolution of both the need for LT and mortality in our study. This score is a tool that includes TB, INR, and ammonia peak values, significantly associated with death/LT in previous studies [11, 12]. Nevertheless, the predictive capacity (AUC 0.73) observed by us was lower than that found by other authors, which may be explained by the small sample size performed at a single institution.

The promising new dynamic, PALF-ds score based on changes in serial laboratory data using the variations of TB/INR to predict NSR had AUC of 0.63 (sensitivity of 71.1% and specificity of 61.9%), lower than some laboratory isolated variables. Moreover, it had lower predictive performance than described by its authors (AUC 0.918; sensitivity 81%, specificity 91% to predict death) [14]. This discrepancy may be explained by the lack of external validation of the score, which was only applied to two populations of South Korea different from ours (lower proportion of metabolic etiology and a higher percentage of undetermined etiology). Furthermore, the authors considered different outcomes compared with our study, analyzing three groups: LT, death, and SR. Another contributing factor may be the influence of the score's complexity, including several evolutive values, which increase the probability of missing data on a retrospective study.

The PELD/MELD score had poor prognostic accuracy in PALF outcome, according to what is described in the literature. King's College Hospital Criteria (KCH criteria) and Clichy-Villejuif Criteria, two adult most recognized prognostic models, do not adequately discriminate the patients who would die without LT, have low sensitivity, and do not reliably predict death in PALF [2, 25]. However,

Table 4. Discriminative capacity of biomarkers and scores to predict non-SR

Variable	AUC	*p* value	95% CI	Cut-off	Sensitivity, %	Specificity, %
Lactate on admission, mmol/L	0.72	**0.06**	0.57 to 0.86	1.95	78.4	61.9
Lactate peak, mmol/L	0.63	0.11	0.47 to 0.78	2.45	91.7	38.1
Ammonia on admission, µmol/L	0.61	0.16	0.46 to 0.76	64.5	62.2	57.1
Ammonia peak, µmol/L	0.72	**0.006**	0.58 to 0.86	64	100	38.1
TB on admission, mg/dL	0.68	**0.03**	0.53 to 0.83	10.2	63.2	71.4
TB peak, mg/dL	0.67	**0.03**	0.52 to 0.83	8.5	78.9	57.1
INR peak, s	0.70	**0.01**	0.56 to 0.85	4.8	61.1	76.2
PALF-ds	0.63	0.11	0.47 to 0.78	1.1	71.1	61.9
LIU	0.73	**0.004**	0.59 to 0.87	246.2	78.9	61.9
PELD/MELD	0.57	0.4	0.41 to 0.73	21.0	67.6	52.4
PRISM	0.71	**0.03**	0.56 to 0.86	15.3	47.1	100
PIM	0.66	0.2	0.44 to 0.87	12.84	45	90

95% CI, 95% confidence interval; INR, international normalized ratio; LIU, liver injury unit scoring system; PALF-ds, PALF delta score; PELD, pediatric end-stage liver disease; PIM, pediatric index of mortality; PRISM, pediatric risk of mortality; TB, total bilirubin.

Table 5. Logistic regression to identify independent explanatory factors associated with NSR

Variables	β ± SD	OR	95% CI	*p* value
Admission year	−0.03 ± 0.04	0.97	0.89–1.05	0.46
Metabolic etiology, presence	1.1 ± 0.68	3.0	0.79–11.4	0.11
Lactate on admission, mmol/L	**0.42** ± **0.2**	1.5	1.04–2.2	0.03

95% CI, 95% confidence interval; OR, odds ratio; SD, standard deviation.

it is well established that a significant increase in INR/decrease in factor V level such as higher degrees of encephalopathy are associated with worse prognosis in PALF.

This study also has an innovative aspect regarding commonly used pediatric intensive care scores applied to the PALF setting. In this work, we observed that PRISM, a score based on age-related physiological parameters collected during the first 24 h after admission, had a good diagnostic accuracy with AUC 0.71 ($p = 0.03$). As mentioned in some studies, the PIM score had a lower predictive power in PALF [22, 23, 26].

The limitations of our study include its retrospective nature, the small sample size, and the specific population analysis, which differs from the other studies. The extended study period increased the probability of bias and missing data since we could not account for undocumented data in the paper support since the beginning of LT in Portugal. Moreover, a referral bias may exist as our institution is a LT and PALF referral center.

In conclusion, PALF is a rare, highly heterogeneous, and progressive disease. To date, no optimal PALF prognostic model exists. Prognostic variables in PALF are determinants for emergency LT allocation, so they must be dynamic but at the same time easy to measure and unbiased to interpretation [25]. Although more research is needed, especially through the construction and analysis of multicenter international databases, our study highlights that the blood lactate level upon admission and peak ammonia is robust, simple, direct, and accurate predictors of poor outcomes in PALF. Furthermore, these results lead to the possibility of considering the inclusion of lactate in the prognostic scores, particularly in LIU score.

Statement of Ethics

This study did not require informed consent, and the authors declare that the procedures followed were in accordance with the World Medical Association Declaration of Helsinki. This study was approved by the Ethics Committee of Centro Hospitalar e Universitário de Coimbra (Reference: OBS.SF.218/2022).

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

Our study does not have any funding associated.

Author Contributions

Andreia Nogueira and Catarina Teixeira acquired and analyzed the data and drafted the manuscript; Carla Fernandes and Rita Moinho acquired the data and revised the manuscript; Isabel Gonçalves and Leonor Carvalho acquired the data, interpreted the findings, and revised the manuscript; Carla Regina Pinto conceptualized the study, acquired and analyzed the data, interpreted the findings, and revised the manuscript. All authors approved the final version to be published.

Data Availability Statement

The datasets generated during the current study are available from the corresponding author on reasonable request.

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GE – Portuguese Journal of Gastroenterology

Research Article

GE Port J Gastroenterol 2024;31:173–181
DOI: 10.1159/000531018

Received: November 23, 2022
Accepted: April 17, 2023
Published online: July 12, 2023

Clinical Characteristics of Genuine Acute Autoimmune Hepatitis

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Keywords
Autoimmune hepatitis · Symptom flare up · Prognosis · Treatment outcome · Alanine transaminase · Serum albumin · Prothrombin

Abstract
Introduction: Autoimmune hepatitis (AIH) has a spectrum of symptoms ranging from asymptomatic disease to acute severe hepatitis, chronic hepatitis, and decompensated cirrhosis. The acute presentation is not rare and could represent genuine acute AIH (GAAIH) or acute exacerbation of chronic autoimmune hepatitis. We aimed to identify the prevalence, clinical features, and prognostic factors associated with GAAIH and compare these cases with acute exacerbation of chronic AIH. ***Methods:*** This cross-sectional observational study evaluated patients with acute AIH presentation, defined as total bilirubin >5 times the upper limit of normality (xULN) and/or alanine aminotransferase >10 xULN, and no prior history of liver disease. Histology findings of acute disease defined GAAIH. Bivariate analyses were performed to identify factors associated with the GAAIH, when compared with acute exacerbation of chronic AIH. ***Results:*** Seventy-two patients with acute presentation of AIH were included and six (8.3%) of them presented GAAIH. Comparative analysis between patients with GAAIH and patients with acute exacerbation of chronic AIH revealed that prothrombin activity (96% [74–100] vs. 61% [10–100]; $p = 0.003$) and albumin levels (3.9 ± 0.2 g/dL vs. 3.4 ± 0.5 g/dL; $p < 0.001$) were higher in patients with GAAIH. The International Autoimmune Hepatitis Group score was higher in patients with acute exacerbation of chronic AIH (18.5 [8–23] vs. 16.5 [15–17]; $p = 0.010$). Compared to 15.2% of acute exacerbation of chronic AIH, complete therapeutic response to treatment was achieved in 67.7% of cases with GAAIH ($p = 0.018$). ***Conclusions:*** GAAIH was rare (8.3%), and patients with this presentation exhibited more preserved liver function tests, suggesting that most cases presenting with loss of function are acute exacerbation of chronic AIH. Additionally, patients with GAAIH had a better complete therapeutic response, suggesting a more preserved liver function at presentation, and early diagnosis has a positive therapeutic implication.

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Características Clínicas da Hepatite Autoimune Aguda Genuína

Palavras Chave
Hepatite autoimune · Exacerbação dos sintomas · Prognóstico · Tratamento · Alanina transaminase · Albumina sérica · Protrombina

Resumo
Introdução: A hepatite autoimune (HAI) apresenta um espectro de sintomas que varia de doença assintomática a hepatite aguda grave, hepatite crónica e cirrose descompensada. A apresentação aguda não é rara e pode representar hepatite autoimune aguda genuína (HAIAG) ou exacerbação aguda de hepatite autoimune crónica (EAHAIC). O nosso objetivo foi identificar a prevalência, caraterísticas clínicas e fatores prognósticos associados à HAIAG, e comparar esses casos com EAHAIC. ***Métodos:*** Estudo observacional, transversal, incluindo doentes com apresentação aguda de HAI, definida como bilirrubina total > 5 vezes o limite superior da normalidade (xLSN) e/ou ALT > 10 xLSN, e sem história prévia de doença hepática. HAIAG foi definida pela presença de achados histológicos de doença aguda. Análises bivariadas foram realizadas para identificar fatores associados à HAIAG, quando comparado com o EAHAIC. ***Resultados:*** Foram incluídos setenta e dois doentes com apresentação aguda de HAI, dos quais seis (8.3%) com HAIAG. A análise comparativa entre doentes com HAIAG e doentes com EAHAIC mostrou que a atividade de protrombina (96% (74-100) versus 61% (10-100; p=0.003) e os níveis de albumina (3,9 ± 0,2 g/dL vs. 3,4 ± 0,5 g/dL; p < 0,001) foram significativamente mais elevados em pacientes com HAIAG. O score do Grupo Internacional de Hepatite Autoimune foi mais elevado em doentes com EAHAIC (18.5 (8-23) versus 16.5 (15-17); p=0.010). A resposta terapêutica completa ao tratamento foi alcançada em 66.7% dos casos de HAIAG (vs. 15,2% na EAHAIC, p=0,018). ***Conclusões:*** A HAIAG é rara (8.3%), e os doentes com esta apresentação mostraram testes de função hepática mais preservados, sugerindo que a maioria dos casos com perda de função são EAHAIC. Além disso, os doentes com HAIAG tiveram maior taxa de resposta terapêutica completa, sugerindo que uma função hepática mais preservada na apresentação e o diagnóstico precoce tem uma implicação terapêutica positiva.

Introduction

Autoimmune hepatitis (AIH) is an inflammatory liver disease of unknown etiology. This condition primarily affects women and is characterized by autoantibodies, hypergammaglobulinemia, interface hepatitis, and plasma cell infiltration. AIH responds well to immunosuppressive therapy, mainly azathioprine and corticosteroids [1, 2].

Patients with AIH frequently exhibit characteristics of a chronic disease, including nonspecific symptoms such as fatigue, nausea, and arthralgias [1, 2]. However, acute-onset AIH has a clinical spectrum ranging from asymptomatic forms to an acute presentation simulating viral or toxic hepatitis or even a fulminant acute presentation [3–6]. Interestingly, most patients with acute-onset AIH exhibit histological features of chronic hepatitis or cirrhosis.

There is no consensus definition of acute presentation of AIH. Yamamoto et al. [7] proposed as definition of this form of presentation a duration of symptoms ≤26 weeks, aminotransferases higher than 10 times the upper limit of normality (xULN), and/or bilirubin higher than 5 mg/dL. In 2019, Rahim et al. [8] proposed that acute presentation of AIH should correspond to acute hepatitis (jaundice ≤26 weeks, without coagulopathy or encephalopathy), severe acute hepatitis (jaundice ≤26 weeks, with coagulopathy and without encephalopathy), and fulminant acute hepatitis (jaundice ≤26 weeks, with coagulopathy and with encephalopathy).

Independently of the definition, acute presentation of AIH corresponds to two different situations: acute exacerbation of chronic AIH, in which patients show clinical and laboratory findings of acute hepatitis and histology of chronic disease, and genuine acute AIH (GAAIH), in which patients exhibit clinical, laboratory, and histological features of acute hepatitis [9, 10]. Since these individuals frequently have low IgG levels, absence or low titers of autoantibodies, and unusual histological characteristics such as centrilobular necrosis in zone 3, diagnosing GAAIH might be difficult [4, 11–15]. Centrilobular necrosis in zone 3 is a common finding in patients with drug-induced acute liver injury [16], acute post-transplant rejection [17, 18], hepatic congestion or ischemia [19, 20], or even acute viral hepatitis. These factors hamper the diagnosis of autoimmune etiology due to low International Autoimmune Hepatitis Group (IAIHG) scores [21]. Furthermore, histological criteria for AIH are not completely clear. The previous published criteria aimed

mainly the findings of chronic AIH with abnormalities in portal and periportal regions that cannot always be applied to acute presentation of AIH. More recently, the paper by Lohse et al. [22] defined probable AIH if there is predominance of lobular hepatitis with or without centrilobular necroinflammation associated to at least one of these characteristics: portal lymphoplasmocytic hepatitis, interface hepatitis, or portal fibrosis. These histological criteria include both acute and chronic presentation of AIH, however, without establishing clear histological criteria for genuine acute hepatitis. The present study aimed to identify the prevalence, clinical features, and biochemical and histological response to treatment in patients with GAAIH and compare these cases with patients with acute exacerbation of chronic AIH.

Materials and Methods

Study Population and Data Collection

This hospital-based descriptive study evaluated a prospectively maintained database of patients referred to a tertiary outpatient clinic between 1997 and 2014. It involved patients with acute presentation of AIH. The diagnosis of AIH was based on the criteria of the IAIHG for all patients [21]. Acute presentation of AIH was defined as acute onset of symptoms (≤26 weeks), total bilirubin levels higher than 5 mg/dL, and/or alanine aminotransferase (ALT) levels higher than 10 xULN as well as no prior history of liver disease [7]. GAAIH was distinguished from the acute presentation of chronic AIH based on histological findings of mainly lobular hepatitis, with or without centrilobular necrosis, portal and lobular lymphoplasmacytic inflammatory infiltrate, and no degree of fibrosis.

Exclusion criteria were alcohol consumption of more than 20 g/day and evidence of liver disease of other causes (drugs, viral or metabolic causes). Patients presenting with acute liver failure and overlapping syndromes were also excluded.

Initial Assessment and Follow-Up

The patients were submitted to clinical and laboratory evaluation at the disease presentation and during each visit. The visits were scheduled fortnightly at the beginning of follow-up, then monthly, and after that for 3 months. The laboratory tests included measurement of the liver enzymes ALT, aspartate aminotransferase (AST), γ-glutamyltransferase (GGT), alkaline phosphatase (ALP), total bilirubin and fractions, prothrombin time, and protein electrophoresis. ALT, AST, GGT, and ALP are expressed as an index: value obtained/xULN.

Detection of Autoantibodies

Antibodies to the smooth muscle (SMA), antibodies to liver/kidney microsome type 1 and anti-mitochondrial antibodies were identified by indirect immunofluorescence on rat liver, kidney, and stomach tissue sections. Antinuclear antibodies (ANA) were determined by standard indirect immunofluorescence on the imprint and HEp-2 cells. A titer higher than 1:40 was considered to be significant for ANA imprint and 1:80 for HEp-2 cells.

In addition, the other autoantibodies were investigated by immunoblotting: antibodies against soluble liver antigen/liver-pancreas, liver cytosol-specific antibody type 1 (LC1), antibodies to Ro 52 (anti-Ro52), anti-Sp100, and anti-gp210 (Euroimmun, Lübeck, Germany) according to the manufacturer's instructions. Patients positive for anti-LC1 were also tested by indirect immunofluorescence in rodent tissue.

Treatment Regimen

Patients with AIH were treated with prednisone at an initial daily dose of 50 mg, which was reduced to a daily maintenance dose of 10 mg, in combination with azathioprine at doses of 50–150 mg (mean dose of 100 mg). Either prednisone or azathioprine alone was used in case of contraindication of the combined therapy. Patients non-responsive to conventional therapy regimens were given alternative drugs, such as mycophenolate mofetil, tacrolimus, and cyclosporine.

Biochemical Response

The biochemical response was defined as the normalization of ALT, AST, bilirubin, and gamma-globulins evaluated at 6 months of treatment [23].

Statistical Analysis

Exploratory data analysis included mean, median, standard deviation, and range for continuous variables and number and proportion for categorical variables. Descriptive statistics, graphs, and the specific test for theoretical assumption of normality Shapiro-Wilk were considered to analyze the behavior of continuous variables. In accordance with the variable distribution, the Student's *t* test or Mann-Whitney test was used to compare continuous variables between two independent groups; when appropriate, the Pearson χ^2 test or Fisher's exact test was used to compare categorical variables between two independent groups. Statistical analysis was performed using IBM-SPSS Statistics software version 28 (IBM Corporation, NY, USA) and R software. The tests were two tailed, and p values < 0.05 were considered significant.

Results

Over 17 years, 131 patients with AIH diagnoses were evaluated for inclusion in the study. Fifty-one patients with chronic AIH presentation and eight others for not having been submitted to a liver biopsy were excluded from the analysis. Thus, 72 patients with acute AIH symptoms were included (Fig. 1). Most patients (93.7%) were females, and the mean age was 32 (6–70) years; 59% of the patients were Caucasian. Only 6 patients (8.3%) presented histological criteria compatible with GAAIH; these patients' clinical features are shown in Table 1. Sixty-six patients (92%) had a histological diagnosis of chronic hepatitis and 32 presented with liver cirrhosis.

All cases with GAAIH had elevated levels of gamma-globulins. ANA were detected in 5 of the 6 cases, associated to SMA in 3 cases and with anti-Ro52 in 1 case. The

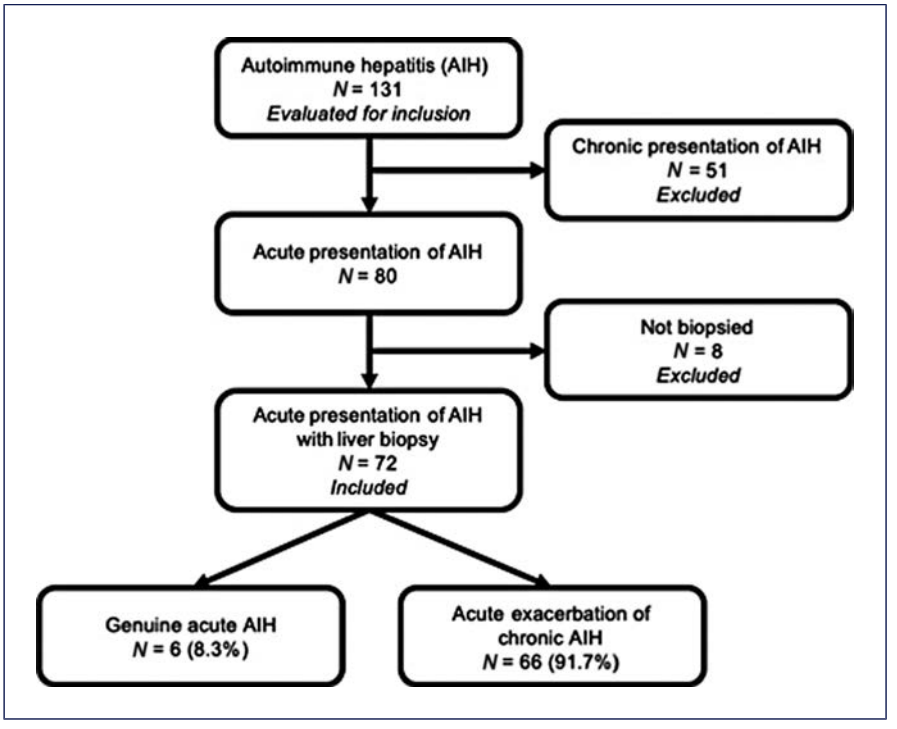

Fig. 1. Flow diagram of the potential candidates for participation in the study, reasons for exclusion, and subjects enrolled.

only patient who did not exhibit ANA or SMA was positive for antibodies to soluble liver antigen/liver-pancreas and anti-Ro52. Concerning the histological findings in patients with GAAIH, we observed the presence of predominantly lobular lymphoplasmacytic infiltrate in all the cases, multiacinar necrosis in 3 cases, and confluent zone 3 necrosis in 2 cases (Fig. 2). A definitive and probable diagnosis of AIH according to the IAIHG score was observed in 2 and 4 patients with GAAIH, respectively.

Comparative analysis between patients with GAAIH and acute presentation of chronic disease (Table 2) revealed a trend toward higher ALT levels in GAAIH (24.9 vs. 16.6 xULN; $p = 0.057$). There were no differences in AST, bilirubin, ALP, GGT, and gammaglobulin levels or ANA and SMA titers. Prothrombin activity (96.0 vs. 61.0%; $p = 0.003$) and albumin levels (3.95 ± 0.18 g/dL vs. 3.45 ± 0.53 g/dL; $p < 0.001$) were higher in patients with GAAIH. The IAIHG score was higher in patients with acute exacerbation of chronic AIH (18.5 vs. 16.5; $p = 0.010$). Sixty-six percent of patients with true GAAIH and 15.2% with acute exacerbations of chronic AIH experienced full treatment response ($p = 0.018$; Table 3).

After a mean follow-up of 9 ± 4.7 years, all 6 patients with GAAIH underwent a new biopsy; two of them had progressive liver disease, while the other four showed recovery and had little histological changes (reactional liver). During follow-up, 2 of these patients relapsed after discontinuation of treatment and 2 remained in clinical and biochemical remission to date. After reintroduction of immunosuppression, the 2 relapsed patients normalized aminotransferases and IgG levels and are in remission of the disease to date. During the follow-up, the survival in the group with GAAIH was 100%, while among the patients with acute exacerbation of chronic hepatitis, it was 42%.

Discussion

The diagnosis of acute presentation of AIH is challenging. Since the first report of acute AIH in 1984 by Lefkowich [24], some groups have been studying this condition. Still, many aspects, such as the correct diagnosis and prognosis of this particular form of presentation, remain unclear. The clinical spectrum of acute presentation is broad, ranging from asymptomatic conditions [24] to severe acute disease and fulminant hepatic failure [4–6].

Acute presentation of AIH is reported as infrequent, varying from 20% to 55% [4, 7, 25–28]. A difference in the frequency of acute-onset AIH may be due to differences in the population of patients and in the criteria used to

Table 1. Characteristics of 6 patients with GAAIH

Case	Gender	Age, years	Autoantibodies	Gamma-globulins, g/dL	Histopathological findings	IAIHG score	HLA
1	F	11	ANA, SMA	2.3	Multiacinar necrosis accompanied by predominantly lymphoplasmacytic inflammatory infiltrate and ductular proliferation. No interface hepatitis and/or fibrosis	15	–
2	F	52	ANA, anti-Ro52	2.4	Multiacinar necrosis accompanied by predominantly lobular lymphoplasmacytic inflammatory infiltrate and ductular proliferation. Presence of discrete portal lymphoplasmacytic inflammatory infiltrate. No interface hepatitis and/or fibrosis	15	–
3	F	22	SLA/LP, anti-Ro52	2.3	Disarray of the plate architecture, swollen hepatocytes, acidophilic bodies, and spotty necrosis, especially near the terminal hepatic venules. Lobular clusters of predominantly lymphoplasmacytic inflammatory infiltrate marking sites of hepatocyte necrosis. Slight portal lymphoplasmacytic inflammatory infiltrate, no interface hepatitis, and/or fibrosis	14	DRB1*03 DRB1*04
4	F	23	ANA	3.3	Swollen hepatocytes, spotty necrosis, and areas of confluent necrosis in zone 3. Predominant lobular lymphoplasmacytic inflammatory infiltrate. Presence of discrete portal lymphoplasmacytic inflammatory infiltrate, no interface hepatitis, and/or fibrosis	18	DRB1*03 DRB1*12
5	F	52	ANA, SMA	3.8	Confluent necrosis mainly in the centrilobular localization, sometimes with bridging, accompanied by lobular mononuclear inflammatory infiltrate. Presence of discrete portal predominantly lymphoplasmacytic inflammatory infiltrate, no interface hepatitis, or fibrosis	17	–
6	F	30	ANA, SMA	2.4	Multiacinar necrosis accompanied by predominantly lobular lymphoplasmacytic inflammatory infiltrate and ductular proliferation. Presence of discrete portal lymphoplasmacytic inflammatory infiltrate, no interface hepatitis, or fibrosis	15	DRB1*03 DRB1*15

F, female; IAIHG, International Autoimmune Hepatitis Group; HLA, human leukocyte antigen; ANA, antibodies against nuclear antigen; SMA, smooth muscle antibodies; SLA/LP, antibodies to soluble liver antigen/liver-pancreas; anti-Ro52, antibodies to Ro 52.

define acute onset. Interestingly, the percentage of patients with acute presentation in our study (61%) was much higher than the cited references (20–55%). Comparing our data with those from Yamamoto, who used the same definition criteria as ours, our proportion of acute presentation was higher (61% vs. 38.5%) [7], perhaps due to ethnic differences. Certain ethnicities may be prone to developing a complicated AIH course [29, 30]. However, despite the high acute-onset AIH in this study, most patients exhibited histological characteristics of chronic disease, in agreement with other studies. Overall, we found a small number of patients with GAAIH, reflecting the rarity of this form of presentation of AIH.

Comparative analysis of the two groups showed higher levels of ALT in patients with GAAIH, a finding also described in other case series reported in the literature [3, 4, 12, 29, 31]. Patients with GAAIH often have low levels of gamma-globulins and IgG [3, 4, 8, 28] and absence or low titers of autoantibodies [4, 12]. Our study found no difference in gamma-globulin levels or ANA and SMA titers.

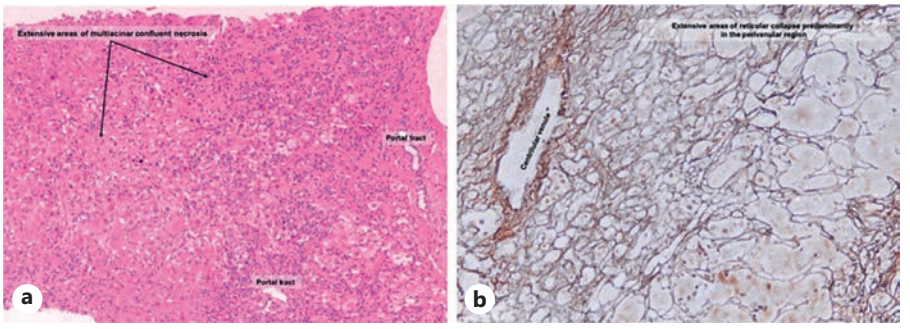

Fig. 2. a, **b** Liver biopsy of a patient with GAAIH exhibiting confluent necrosis mainly in the centrilobular localization, sometimes with bridging, accompanied by lobular mononuclear inflammatory infiltrate. Presence of discrete portal predominantly lymphoplasmacytic inflammatory infiltrate. Absence of interface hepatitis or fibrosis.

Table 2. Comparative analysis between GAAIH and acute exacerbation of chronic AIH

	All patients *N* = 72	Acute exacerbation of chronic AIH *N* = 66	GAAIH *N* = 6	*p* value
Age, years	30 (6–70)	30 (6–70)	26.5 (11–52)	0.911
Gender, *n* (%)				
Male	6 (8.3)	6 (9.1)	0 (0.0)	1.000
Female	66 (91.7)	60 (90.9)	6 (100.0)	
Ethnicity, *n* (%)				
White	42/71 (59.2)	41/66 (62.1)	1/5 (20.0)	0.199
African American	27/71 (38.0)	23/66 (34.8)	4/5 (80.0)	
Asian	2/71 (2.8)	2/66 (3.0)	0 (0.0)	
Other autoimmune diseases, *n* (%)	18 (25.0)	17 (25.8)	1 (16.7)	1.000
ALT (xULN)	17.8 (1.3–52.9)	16.6 (1.3–52.9)	24.9 (18.0–49.6)	0.057
AST (xULN)	18.4 (2.5–67.5)	18.0 (2.5–67.5)	24.0 (10.5–32.6)	0.244
ALP (xULN)	1.25 (0.3–20.0)	1.30 (0.3–20.0)	1.0 (0.5–1.8)	0.215
GGT (xULN)	5.9 (0.5–38.4)	5.9 (0.5–38.4)	7.5 (1.6–20.0)	0.769
Bilirubin, mg/dL	6.35 (0.5–35.0)	6.0 (0.5–35.0)	8.8 (1.2–17.7)	0.313
Prothrombin activity (%)	65.5 (10–100)	61.0 (10–100)	96.0 (74–100)	**0.003**
Albumin, g/dL	3.45±0.53	3.40±0.53	3.95±0.18	< **0.001**
Gamma-globulin, g/dL	2.93±1.08	2.95±1.11	2.75±0.64	0.658
ANA positive, *n* (%)	56 (77.8)	51 (77.3)	5 (83.3)	1.000
ANA titer, *n* (%)				
1/80	2/56 (3.6)	2/51 (3.9)	0/5 (0.0)	0.239
1/160–1/320	22/56 (39.3)	18/51 (35.3)	4/5 (80.0)	
≥1/640	32/56 (57.1)	31/51 (60.8)	1/5 (20.0)	
SMA positive, *n* (%)	39 (54.2)	36 (54.5)	3 (50.0)	1.000
SMA titer, *n* (%)				
1/40–1/80	7/38 (18.4)	5/35 (14.3)	2/3 (66.7)	0.060
1/160–1/320	19/38 (50.0)	19/35 (54.3)	0 (0.0)	
≥1/640	12/38 (31.6)	11/35 (31.4)	1/3 (33.3)	
Anti-Ro52 positive, *n* (%)	19/65 (29.2)	17/61 (27.9)	2/4 (50.0)	0.574
SLA, *n* (%)	15/68 (22.1)	14/63 (22.2)	1/5 (20.0)	1.000
IAIHG score	18.0 (8.0–23.0)	18.5 (8.0–23.0)	16.5 (15.0–17.0)	**0.010**

Continuous variables are expressed as median (minimum - maximum) or mean±standard deviation; categorical variables are described as number (percentage). AIH, autoimmune hepatitis; ALT, alanine aminotransferase; xULN, times the upper limit of normal; AST, aspartate aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyl transferase; ANA, antinuclear antibody; SMA, smooth muscle antibody; IAIHG, international autoimmune hepatitis group.

Our results showed higher levels of albumin and higher prothrombin activity in the group with GAAIH, in contrast to the findings of Yamamoto et al. [7]. The explanation for this finding may be the fact that the present study has included only patients from an outpatient clinic, without having patients with fulminant or severe forms of acute presentation. These data suggest that genuine acute hepatitis is associated with fewer functional impacts

Table 3. Comparative analysis of response to treatment between groups

	Acute exacerbation of chronic AIH *N* = 66	GAAIH *N* = 6	*p* value
Biochemical response, *n* (%)	47 (71.2)	6 (100.0)	0.331
Therapeutic response, *n* (%)			
Complete (biochemical + histological)	10 (15.2)	4 (66.7)	**0.018**
Partial (biochemical)	52 (78.8)	2 (33.3)	
Failure	4 (6.1)	0 (0.0)	

Categorical variables are described in number (percentage).

due to a better hepatic residual liver function, except for fulminant liver failure patients. It has been reported in the literature that patients with acute severe autoimmune hepatitis may benefit from corticosteroids [32–34].

Five of 6 patients in this study had multiacinar or confluent zone 3 necrosis on liver biopsy and all had predominant lymphoplasmacytic infiltrates. The findings support the need for liver biopsy in cases with a clinical suspicion of autoimmune etiology if these histological characteristics are present.

We found predominantly lymphoplasmacytic infiltrates in all patients, even though we did not find all classical histological characteristics of AIH in our cases. This finding, along with the observation of positive autoantibodies and elevated gamma-globulin levels, resulted in IAIHG scores compatible with definite (2 cases) and probable (4 cases) AIH. These results show that, although higher in patients with acute exacerbation of chronic AIH, this score is helpful for the diagnosis of patients with GAAIH.

Four out of the 6 patients with GAAIH had a complete response to treatment (biochemical plus histological). However, total bilirubin levels were above 10 mg/dL on presentation in 3 of the 5 patients of this group (*data not shown*), a poor prognostic factor of response to treatment [4]. These results may suggest that the degree of functional reserve has a positive impact on the therapeutic response. Insignificant fibrosis has previously been related to biochemical response to treatment [29]. The fact that none of the patients presented prothrombin activity <40% (*data not shown*), a factor related to poor prognosis [7], may have contributed to the good clinical response observed in this study. Nonetheless, liver dysfunction has been reported as a predictor of biochemical response to treatment [29]; a study with fewer patients evidenced no difference regarding treatment failure and clinical presentation [26]. At long-term follow-up, 2 patients presented progressive liver disease with classical AIH periportal activity, as seen in other studies [11, 15].

There are some possible limitations to the present study. Although the total number of patients included in the study was representative of the overall population, we examined feasible associations between certain factors and GAAIH, noticeably reducing the number of subjects presenting particular variable combinations and, consequently, the power of statistical tests. Although it is not a strict rule, maintaining a minimum of ten events per variable is advised for logistic regression analysis. This recommendation is based on studies that showed increasing bias and variability, unreliable coverage of confidence intervals, and problems with model convergence as the events per variable declined below ten [35–37]. Another limitation of this study is its retrospective design, which was minimized by using a standardized protocol and the absence of severe or fulminant cases.

In summary, this study showed that acute biochemical presentation of AIH was frequent (61%), while GAAIH was uncommon (8.3%). The autoimmune etiology of acute hepatitis should, therefore, always be considered. The IAIHG score contributes to the diagnosis. A biopsy should be performed whenever possible, as it is very useful for identifying these cases, permitting the early institution of treatment before a significant functional loss occurs and thus improving the prognosis of these patients. Patients with GAAIH had a better complete therapeutic response, suggesting a more preserved liver function at presentation, and early diagnosis has a positive therapeutic implication.

Acknowledgments

The partial results of this study were presented at "The 65th Annual Meeting of the American Association for the Study of Liver Diseases: The Liver Meeting 2014."

Statement of Ethics

Subjects have given their written informed consent and this study protocol conforms to the ethics recommendations of the Helsinki Declaration of 1975 and has been approved by the Ethics and Human Research Committee of the Federal University of Sao Paulo number 1.093.866.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

This study was funded by the Coordination for the Improvement of Higher Education Personnel (CAPES) research support agency, Brazil.

Author Contributions

Elze Maria Gomes-Oliveira and Maria Lucia Cardoso Gomes Ferraz designed the study. Elze Maria Gomes-Oliveira, Ana Cristina de Castro Amaral, Patricia Marinho Costa Oliveira, Valéria Pereira Lanzoni, Renata Mello Perez, Janaína Luz Narciso-Schiavon, Raul Carlos Whale, and Roberto José Carvalho-Filho participated in the acquisition, analysis, and interpretation of the data and drafted the initial manuscript. Antonio Eduardo Benedito Silva and Maria Lucia Cardoso Gomes Ferraz revised the article critically for important intellectual content. All authors have read and approved the final version of the article.

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.

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GE – Portuguese Journal of Gastroenterology

Research Article

GE Port J Gastroenterol 2024;31:182–190
DOI: 10.1159/000531135

Received: October 28, 2022
Accepted: April 25, 2023
Published online: July 19, 2023

Influence of COVID-19 on Patients with Esophageal Varices under Prophylactic Endoscopic Band Ligation Therapy

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Keywords
COVID-19 · Endoscopic band ligation · Liver cirrhosis · Variceal eradication

Abstract
Background and Objectives: Endoscopic band ligation (EBL) plays a critical role in patients with clinically significant portal hypertension, as variceal eradication (VE) is essential to prevent further variceal upper gastrointestinal bleeding (GI). The emergence of COVID-19 has led to a dramatic reduction in endoscopic activity. Our study aimed to evaluate the effect of COVID-19 on VE, GI, and 6-month mortality of patients treated with prophylactic EBL therapy. In addition, our goal was to identify the risk factors for our proposed outcomes. ***Methods:*** A single-center retrospective cohort study included patients with esophageal varices treated with prophylactic EBL therapy between 2017 and 2021. To demonstrate the impact of COVID-19 on two independent groups on prophylactic EBL therapy with 1 year of follow-up, March 2019 was selected as the cut-off date. Clinical, laboratory, and endoscopic data were recovered from electronic reports. ***Results:*** Ninety-seven patients underwent 398 prophylactic EBL sessions, 75 men (77.3%) with mean age 59 ± 12 years. Most achieved VE (60.8%), 14.4% had GI bleeding post-therapy, and 15.5% died at 6 months. The rate of variceal obliteration was significantly lower in the pandemic group (40.9% vs. 77.4% in the pre-pandemic group, $p = 0.001$). Mean number of EBL sessions and pandemic group were independently associated with incomplete VE, while MELD-Na, portal vein thrombosis and failed VE were identified as risk factors associated with mortality at 6 months. ***Conclusions:*** Almost 60% of patients in the pandemic group failed to eradicate esophageal varices. Failure to achieve this result conferred a higher risk of GI bleeding and death at 6 months, the latter also significantly associated with the MELD-Na score and portal vein thrombosis. Our study is among the first to demonstrate the impact of COVID-19 in patients receiving prophylactic EBL therapy.

Influência da COVID-19 nos doentes com varizes esofágicas submetidos a laqueação elástica profilática

Palavras Chave
Cirrose hepática · COVID-19 · Erradicação de varizes esofágicas · Laqueação elástica endoscópica

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Resumo

Introdução e objetivos: A laqueação elástica endoscópica (LEE) é crucial nos doentes com hipertensão portal clinicamente significativa, uma vez que permite a erradicação das varizes esofágicas (EVE) que, por sua vez, previne a hemorragia digestiva varicosa. Com o início da pandemia COVID-19, a atividade endoscópica foi drasticamente reduzida. Com este estudo pretendemos avaliar a influência da COVID-19 na EVE, hemorragia gastrointestinal (GI) e mortalidade aos 6 meses dos doentes sob LEE profilática, assim como identificar os seus fatores de risco. ***Métodos:*** Estudo de coorte monocêntrico e retrospetivo que incluiu doentes com varizes esofágicas sob LEE profilática entre 2017 e 2021. Para demonstrar o impacto da pandemia COVID-19 em dois grupos independentes sob LEE profilática durante um ano de follow-up, a escolha da data-limite foi Março de 2019. Os dados clínicos, laboratoriais e endoscópicos foram obtidos a partir dos relatórios eletrónicos. ***Resultados:*** Noventa e sete doentes cumpriram 398 sessões de LEE, 75 homens (77,3%), com idade média de 59 ± 12 anos. A maioria dos doentes obteve EVE (60,8%), 14,4% desenvolveu hemorragia GI e 15,5% faleceu nos primeiros 6 meses pós-terapêutica. A taxa de EVE foi significativamente inferior no grupo pandémico (40,9% vs. 77,4% no grupo pré-pandémico, $p = 0.001$). O número médio de sessões de LEE e o grupo pandémico foram independentemente associados à EVE incompleta; enquanto MELD-NA, trombose da veia porta e falha na EVE foram identificados como fatores de risco associados à mortalidade aos 6 meses. ***Conclusão:*** Cerca de 60% dos doentes no grupo pandémico não conseguiu erradicar as varizes esofágicas. A EVE incompleta aumenta o risco de hemorragia GI e mortalidade aos 6 meses, esta última também associada de forma significativa ao score MELD-Na e TVP. O nosso estudo foi pioneiro na demonstração do impacto da pandemia COVID-19 nos doentes sob LEE profilática.

Introduction

Patients with compensated cirrhosis or compensated advanced chronic liver disease and clinically significant portal hypertension have guided diagnostic and therapeutic orientations in variceal bleeding prophylaxis, as they are at increased risk of decompensation. Accordingly, nonselective beta-blocker (NSBB) treatment should be considered in primary prophylaxis, preferably carvedilol, as it is more effective in decreasing the hepatic venous pressure gradient and improves survival. Child-Pugh C patients or patients with high-risk varices (large varices [≥5 mm]) or signs of red spots), who have intolerance or contraindications to NSBB, should undergo endoscopic band ligation (EBL) to prevent first variceal bleeding [1].

Regarding the prevention of recurrent variceal bleeding (secondary prophylaxis), first-line therapy is the combination of NSBBs and EBL. In patients without access or who cannot tolerate NSBBs or EBL, any of these therapies can be maintained alone [1–3]. A recent individual patient meta-analysis has shown that pharmacological therapy with NSBB is the most important part of combination therapy and should be used as monotherapy in patients who are unable or unwilling to be treated with EBL [4]. EBL is performed every 3–4 weeks until eradication is achieved. Varices are eradicated usually after a mean of 2–3 sessions, but there is high variability ranging from 1 to more than 10 sessions [2]. The American Association for the Study of Liver Disease recommends esophagogastroduodenoscopy (EGD) 3–6 months after eradication and every 6–12 months thereafter. Variceal recurrence occurs frequently, with 20–75% of patients requiring repeated EBL sessions [5].

Taking into account the importance of variceal eradication (VE) as a preventive measure for further decompensation in cirrhosis, the emergence of COVID-19 as a global pandemic in March 2020 led to the cessation of endoscopic activity and liver cancer management throughout the world [6–9]. Most guidelines during the pandemic recommended the decision to perform EBL therapy on a case-by-case basis [10]. Our department delayed EBL therapy during 3 months after lockdown. The restart of endoscopic activity required negative polymerase chain reaction test 72 h before procedure. All this led to endoscopic activity reduction from 4,725 gastroscopies in 2018 to 2,651 procedures in 2020. In United Kingdom, COVID-19 pandemic reflected in a 58% reduction in missing cancer cases per week, ranging from 19% (biliopancreatic) to 72% (colorectal) [9]. An European multinational cross-sectional survey of patients with neoplastic GI lesions and feasible endoscopic resection revealed that in 2020, 55% of scheduled procedures were postponed, with 3% of cases requiring surgery [8]. Concerning liver cancer, an international survey from March to June 2020 showed that 87% of the centers modified their clinical practice, 80.9% in the screening program, 50% cancelled curative and/or palliative treatments, and 41.7% modified the liver transplantation program [6]. Our study aimed to evaluate the effect of COVID-19 on the outcomes of

patients with esophageal varices under prophylactic EBL therapy in a tertiary hospital, namely VE and bleeding after the first EBL therapy during a year of follow-up, and death at 6 months after the last session.

Materials and Methods

Study Design and Patient Selection

We conducted a single-center retrospective cohort study between 2017 and 2021. All patients with esophageal varices under primary or secondary prophylactic EBL therapy were consecutively included based on the endoscopic reports extracted from our data between March 2018 and March 2021. However, in case patients started EBL therapy before March 2018, the total number of EBL sessions was recorded since the first procedure, with some of them having started in 2017. In order to demonstrate the impact of COVID-19 on two independent groups on prophylactic EBL therapy with 1 year of follow-up, March 2019 was selected as the cut-off date. The exclusion criteria were previous placement of a transjugular intrahepatic portosystemic shunt, liver transplantation, and patients with acute variceal gastric bleeding.

Definitions

EBL therapy was performed under sedation using Multiband Ligator® (Wilson-Cook Medical), starting with the first band from the gastroesophageal junction. The mean number of ligation bands applied per session was six. In our institution, EBL session was performed each 4 weeks, until the varices were obliterated at the discretion of the endoscopist. Prophylactic EBL was defined as therapy for prophylaxis of variceal bleeding in patients without active bleeding at the time of EGD. Primary prophylaxis referred to the prevention of the first variceal bleed, while secondary referred to the prevention of its recurrence. The medium-large varices were defined as not collapsing with insufflation at EGD, in contrast to the small ones [3]. The diagnosis of portal hypertensive gastropathy (PHG) was made endoscopically by showing a snake-skin mosaic pattern (mild subtype), which could have superimposed red signs (severe PHG), usually located in the proximal stomach (fundus and body) [2].

Liver cirrhosis was defined based on the diagnosis of electronic reports, laboratory and radiological findings, liver transient elastography values, and histological reports, if available. Portal vein thrombosis (PVT) was diagnosed based on computed tomography scanning and/or magnetic resonance.

Etiological factor suppression was defined as the elimination of liver cirrhosis cause at least 1 year before the first EBL session, such as alcohol abstinence, sustained virological response in HCV, or undetectable viral load in HBV. Post-EBL bleeding was defined according to EGD reports as bleeding related to gastroesophageal varices or ligation ulcers, or even as blood detected in the upper GI tract without other evident cause.

Demographic, Clinical, and Endoscopic Variables

The characteristics of the patients, the relevant medical history, the laboratory data, and the date of death were recovered from the electronic reports. Endoscopic data: indication; type of varices; presence of PHG; total number of EBL sessions per patient as its first and last registered date; endoscopic report of VE achievement and bleeding after EBL therapy. National electronic health records were assessed to detect EBL therapy in other institutions and all post-EBL bleeding admissions. The access was restricted in case patients deceived in other institution.

Outcomes

Our primary endpoint was to compare the two groups (pre-pandemic and pandemic) regarding the outcomes defined as VE and bleeding after the first EBL therapy during 1 year of follow-up, and death at 6 months after the last session. In case patient lost follow-up and VE was unknown, we assumed as incomplete VE for our outcomes. Our secondary objectives were to evaluate the influence of other variables on our results, including sex, age, eradication of cirrhosis etiology, liver reserve defined by Child-Pugh classification and MELD-Na score, hepatocellular carcinoma, PVT, as well as the role of INR, platelets, use of anticoagulants, periprocedural proton pump inhibitors (PPIs), and NSBB on GI bleeding after EBL therapy.

Data and Statistical Analysis

Continuous variables were reported as mean ± standard deviation or median ± range, according to their distribution. Categorical variables were reported as absolute and relative frequencies. Continuous variables were compared between 2 groups using Student's t test if normal variance distribution and homogeneity were verified, or Mann-Whitney U test in the absence of these conditions. Categorical variables were compared using Pearson's χ^2 test or Fisher's exact test. Univariate and multivariate analysis using a logistic regression model was performed to determine factors associated with our defined outcomes. Covariates with a p value <0.1 in the univariate analysis were included in the multivariate analysis. All hypotheses were 2-tailed and a p value <0.05 was considered statistically significant. Statistical analysis was performed using SPSS v27 (SPSS Inc., Chicago, IL, USA).

Results

We included 97 patients with 398 prophylactic EBL sessions, 75 men (77.3%) with mean age 59 ± 12 years. Cirrhosis was the predominant cause of portal hypertension in 85 cases (87.6%), with alcohol and virus as the main etiologies (76.5%). Etiology eradication was observed in 54 of 78 cases (55.7%). The majority were Child-Pugh A (63.9%) with a median MELD-Na score of 11 (9.0–14.0). Twenty-two patients presented PVT (22.7%) and 9 hepatocellular carcinoma (9.3%). Regarding their medication, most were using periprocedural PPI (68.0%) and NSBB (63.9%): carvedilol (43.3%) and propranolol (20.6%). Fourteen patients (14.4%) were on anticoagulation: warfarin 7.2%, direct oral anticoagulants (DOACs) 4.1%, and enoxaparin 3.1%. Only a minority were on antiplatelet therapy (4.1%). The median results of the laboratory tests were INR 1.2 (1.1–1.4), platelets 85.0 10^9/L (58.5–138.5), and bilirubin 0.9 mg/dL (0.7–1.7).

Regarding the total number of 389 prophylactic EBL sessions in 97 patients, most of them underwent EBL as a secondary prophylaxis (68.0%). At the first session of EBL,

almost all esophageal varices were medium-large, with only 3.1% small varices with red signs. Additionally, PHG was present in 87.6% of the cases, 47.4% mild and 40.2% severe. The mean EBL sessions per patient were 4.1 ± 2.0. Considering our results, most patients managed to eradicate esophageal varices (60.8%), 20.6% lost follow-up, and 18.6% did not eradicate it. Fourteen patients (14.4%) had GI bleeding after EBL therapy. We observed 15 cases (15.5%) of death at 6 months after the last session, with 5 cases occurring at 6-week mortality.

Taking into account our main endpoint (Table 1), 53 patients underwent 223 sessions (56%) in the prepandemic group and 44 underwent 175 (44%) in the latter, with no statistical significance in the mean number of sessions between them ($p = 0.577$). VE was the only outcome with significant difference between the two groups ($p = 0.001$). In fact, 40.9% of the pandemic group reached variceal obliteration, in contrast to the prepandemic, whose patients were almost double (77.4%) (Fig. 1).

Regarding our secondary objectives, the variables associated with incomplete VE (Table 2) in univariate analysis were PVT, EBL therapy as secondary prophylaxis, mean number of EBL sessions and pandemic group. In multivariate analysis, the last two remained independently associated with incomplete variceal obliteration: EBL sessions (odds ratio [OR] 0.8; 95% confidence interval [CI] 0.6–0.9) and pandemic group (OR: 4.9; 95% CI: 1.8–13.2). Mean number of EBL sessions and incomplete VE were associated with bleeding after EBL therapy (Table 3) in univariate analysis. However, male gender (OR: 5.0; 95% CI: 1.2–21.3), EBL sessions (OR: 1.4; 95% CI: 1.1–2.0), and incomplete VE (OR: 4.9; 95% CI: 1.1–21.4) were independently associated in multivariate analysis. There was no statistically significant association of peri-interventional use of PPIs, NSBBs, anticoagulants, and coagulation test results with bleeding incidence after EBL. Univariate analysis found that Child-Pugh B/C, MELD-Na score, PVT, and incomplete VE were associated with 6-month mortality (Table 4). After multivariate adjustment, the association remained significant with all except Child-Pugh B/C: MELD-Na (OR: 1.3; 95% CI: 1.1–1.6); PVT (OR: 10.5; 95% CI: 1.4–79.4); and incomplete VE (OR: 23.4; 95% CI: 2.6–211.9).

Discussion

Our study showed that our prepandemic group achieved VE in almost 80% of cases, consistent with published data rates between 58% and 100% [11]. However, the pandemic COVID-19 reduced the total number of EBL prophylactic sessions by 12 percentage points, therefore variceal obliteration was significantly affected. Almost 60% of the patients lost follow-up or did not eradicate the varices, in particular the secondary prophylaxis group, where EBL plays a crucial role in combination with NSBB in preventing recurrent GI bleeding [4]. Several meta-analyses have demonstrated that combination therapy (EBL and NSBB) is significantly more effective than either alone in preventing a new episode of GI hemorrhage, although pharmacological therapy with NSBB is the fundamental part [1, 12]. Regarding the complication rates of GI bleeding after EBL therapy and mortality at 6 months, there were no significant differences between the two groups ($p = 0.760$ and $p = 0.500$, respectively).

Incomplete VE was associated with PVT, secondary prophylaxis indication, mean number of EBL sessions, and pandemic group. In multivariate analysis, only the last two remained independently associated. There is little evidence on risk factors for incomplete variceal obliteration, with the majority focusing on bleeding and death complications. A plausible explanation for the association between the identified variables (except the pandemic group) and incomplete VE is the continued increase in portal hypertension by PVT, which was not measured by splenic elastography, nor invasively. A retrospective Italian study evaluated the role of PVT in EBL efficacy, concluding that it is a predictor of longer time to achieve VE, with no difference in eradication rates or in median sessions of EBL between cirrhotic patients with or without PVT [13].

The bleeding rate after EBL therapy was 14.4% at 1 year of follow-up, consistent with the results of several studies [11, 12, 14], where the mean rates were 9% (0–25%) for primary prophylaxis and 14% (6–26%) for secondary prophylaxis, partly explained by the significant heterogeneity regarding variceal treatment, definitions of recurrent bleeding, follow-up time, and presence of risk factors [11]. As such, several causes have been associated with the occurrence of variceal bleeding, including the severity of portal hypertension, poor liver reserve, variceal sizes, endoscopic treatment modality of acute bleeding, infection, and PVT [15, 16]. In our study, the mean number of EBL sessions and incomplete VE were associated with bleeding complication in the univariate analysis. However, in multivariate analysis, besides these two variables, male gender was also independently associated to the outcome (OR: 5.0; 95% CI: 1.2–21.3). EBL sessions (OR: 1.4; 95% CI: 1.1–2.0) and incomplete VE (OR: 4.9; 95% CI:

Table 1. Patients characterization

Variables	Pre-pandemic (n = 53)	Pandemic (n = 44)	p value
Sex male (%)	39 (73.6)	36 (81.8)	0.466
Age, years	57.3±12.6	61.9±11.8	0.068
Cirrhosis (%)	47 (88.7)	38 (86.4)	0.765
Child-Pugh A	37 (69.8)	25 (56.8)	
Child-Pugh B	8 (15.1)	10 (22.7)	0.404
Child-Pugh C	2 (3.8)	3 (6.8)	
Etiology (%)			
Alcohol	19 (40.4)	21 (55.3)	0.054
Viral	10 (21.3)	5 (13.2)	
Alcohol + viral	6 (12.8)	4 (10.5)	
Other	12 (25.5)	8 (21.1)	
Etiology eradication (%)	31/43 (72.1)	23/35 (65.7)	0.544
Portal vein thrombosis (%)	9 (17.0)	13 (29.5)	0.141
HCC (%)	7 (13.2)	2 (4.5)	0.143
NSBBs (%)	32 (60.4)	30 (69.8)	0.339
MELD-Na score, median (IQR)	11.0 (8.8–14.0)	11.0 (9.00–14.0)	0.966
Platelets 10^9/L, median (IQR)	96.0 (60.0–150.0)	74.5 (55.8–128.0)	0.264
INR, median (IQR)	1.2 (1.1–1.4)	1.3 (1.1–1.4)	0.377
Primary prophylaxis (%)	21 (39.6)	10 (22.7)	0.076
Secondary prophylaxis (%)	32 (60.4)	34 (77.3)	0.076
Total EBL sessions (%)	223 (56)	175 (44)	0.577
Mean EBL sessions	4.2±1.7	4.0±2.3	
Variceal eradication (%)	41 (77.4)	18 (40.9)	**0.001**
GI bleeding (%)	7 (13.2)	7 (15.9)	0.706
6-month mortality (%)	7 (13.2)	8 (18.2)	0.500

HCC, hepatocellular carcinoma; NSBBs, nonselective β-blockers; MELD, model of end-stage liver disease; IQR, interquartile range; INR, international normalized ratio; EBL, endoscopic band ligation; GI, gastrointestinal.

1.1–21.4) might be related to more severe portal hypertension and therefore the necessity for more EBL sessions.

As secondary objectives, there was no statistically significant association of coagulation test results with bleeding incidence following EBL. As changes are common in advanced liver disease, several studies have already shown that standard coagulation tests are a poor indicator of bleeding [16]. Moreover, administration of blood products or factor concentrates in patients with stable cirrhosis did not reduce the frequency of these episodes or procedure-associated mortality [16, 17]; therefore, it is not recommended [18]. Also, we did not observe an association between anticoagulants, the use of periprocedural PPIs, and bleeding complications. In cirrhotic patients, anticoagulant therapy can confer a higher risk of bleeding due to their susceptible rebalanced hemostasis [18]. However, its use in two studies did not increase secondary GI bleeding [19, 20]. Regarding PPI use, our findings were consistent with a recent study that also did not identify it as a risk factor [16]. Nonetheless, there are several data [21–23], including a meta-analysis study, suggesting that short-term acid suppression may be considered in patients undergoing prophylactic EBL, as it significantly decreases bleeding incidence [23].

The 6-month mortality rate of our study (15.5%) was within the values of published studies [12], a reflection of end-stage liver disease [11]. In this regard, we identified an association between our outcome and Child-Pugh B or C, median MELD-Na score, PVT, and incomplete VE in the univariate analysis. After multivariate adjustment, the association remained independent with all except Child-Pugh B/C. A study by Ray G. also showed that Child-Pugh class C and alcohol consumption were independent risk factors that affected mortality [11].

Regarding the interpretation of our results, we need to consider several limitations of the present study. First, this is a single-center retrospective study with a small sample size, whose design implies some limitations as well as potential selection and recall biases. Second, the percentage of follow-up loss in pandemic group was significantly higher compared to pre-pandemic (29.5% vs. 13.2%, respectively).

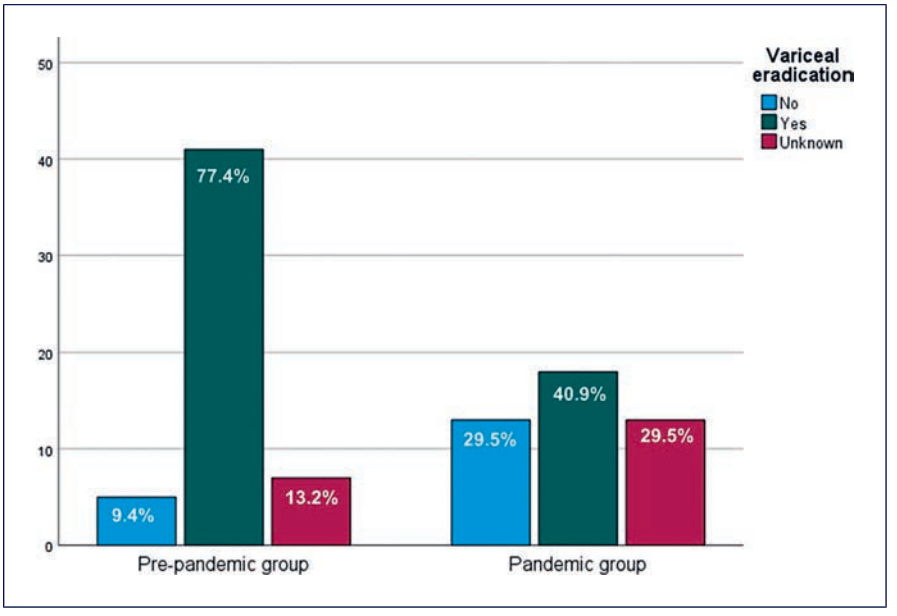

Fig. 1. Variceal eradication.

Table 2. Analysis of risk factors associated with variceal eradication

Risk factors	Variceal eradication complete (*n* = 59)	Variceal eradication incomplete (*n* = 38)	Univariate analysis			Multivariate analysis		
			OR	95% CI	*p* value	OR	95% CI	*p* value
Male gender (%)	47 (79.7)	28 (73.7)	0.7	0.3–1.9	0.493			
Age (mean±SD), years	58.7±11.5	60.5±13.8			0.491			
Etiology eradication (%)	33/49 (67.3)	21/29 (72.4)	1.3	0.5–3.5	0.639			
Child-Pugh B/C (%)	14/53 (26.4)	9/32 (28.1)	1.1	0.4–2.9	0.863			
MELD-Na, median (IQR)	11.0 (8.3–14.0)	11.0 (9.75–15.0)			0.348			
PVT (%)	9 (15.2)	13 (34.2)	0.3	0.1–0.9	**0.030**	2.9	0.9–9.4	0.077
HCC (%)	5 (8.5)	4 (10.5)	0.8	0.2–3.1	0.734			
NSBBs (%)	35 (59.3)	27/37 (73.0)	0.5	0.2–1.3	0.173			
Platelets 10^9/L, median (IQR)	82.0 (57.0–144.0)	90.5 (66.0–133.5)			0.779			
Nr.EBL sessions (mean±SD)	3.7±1.4	4.7±2.6			**0.028**	0.8	0.6–0.9	**0.048**
Secondary prophylaxis (%)	34 (57.6)	32 (84.2)	0.3	0.1–0.7	**0.006**	3.0	0.9–9.7	0.068
Severe PHG (%)	25 (42.4)	14 (36.8)	1.3	0.5–2.9	0.588			
Pandemic group (%)	18 (30.5)	26 (68.4)	0.2	0.08–0.5	<**0.001**	4.9	1.8–13.3	**0.002**

SD, standard deviation; MELD, model of end-stage liver disease; PVT, portal vein thrombosis; HCC, hepatocellular carcinoma; NSBBs, nonselective β-blockers; EBL, endoscopic band ligation; IQR, interquartile range; PHG, portal hypertensive gastropathy.

Several reasons may explain this increase, namely endoscopic activity reduction during pandemic period, requirement for SARS-CoV-2 swab before procedure, as patients' denial to perform gastroscopy due to fear of enhanced risk of COVID-19 infection in hospitals [24]. Third, VE at the discretion of the endoscopist enabled a high interobserver variability. Also, post-EBL bleeding definition englobed all possible causes, as varices, ligation ulcers, or even as blood

Table 3. Analysis of risk factors associated with gastrointestinal (GI) bleeding

Risk factors	Control (n = 83)	GI bleeding (n = 14)	Univariate analysis			Multivariate analysis		
			OR	95% CI	p value	OR	95% CI	p value
Male gender (%)	67 (80.7)	8 (57.1)	3.1	0.9–10.3	**0.080**	5.0	1.2–21.3	**0.030**
Age (mean±SD), years	59.5±11.5	58.5±17.1			0.780			
Etiology eradication (%)	50/69 (72.5)	4/9 (44.4)	3.3	0.8–13.6	0.124			
Child-Pugh B/C (%)	21/74 (28.4)	2/11 (18.2)	1.7	0.4–8.9	0.719			
MELD-Na, median (IQR)	11.0 (9.0–14.0)	12.0 (10.0–14.0)			0.516			
PVT (%)	20 (24.1)	2 (14.3)	0.5	0.1–2.5	0.513			
HCC (%)	8 (9.7)	1 (7.1)	0.7	0.8–6.3	1.000			
NSBBs (%)	53/82 (64.6)	9 (64.3)	0.9	0.3–3.2	0.980			
PPIs (%)	56/82 (68.3)	10 (71.4)	1.2	0.3–4.0	1.000			
Anticoagulants (%)	11 (13.3)	3 (21.4)	1.8	0.4–7.4	0.420			
Platelets 10^9/L, median (IQR)	82.0 (58.0–138.0)	108.0 (72.5–184.5)			0.257			
INR, median (IQR)	1.3 (1.1–1.4)	1.2 (1.1–1.4)			0.383			
Nr.EBL sessions (mean±SD)	3.9±1.9	5.6±2.3			**0.003**	1.4	1.1–2.0	**0.025**
Incomplete VE (%)	27 (32.5)	11 (78.6)	0.1	0.03–0.5	**0.001**	4.9	1.1–21.4	**0.036**
Severe PHG (%)	33 (39.8)	6 (42.9)	1.1	0.4–3.6	0.827			
Pandemic group (%)	37 (44.6)	7 (50.0)	1.2	0.4–3.9	0.706			

SD, standard deviation; MELD, Model of End-Stage Liver Disease; IQR, interquartile range; PVT, portal vein thrombosis; HCC, hepatocellular carcinoma; NSBBs, nonselective β-blockers; PPIs, proton pump inhibitors; INR, international normalized ratio; EBL, endoscopic band ligation; PHG, portal hypertensive gastropathy.

Table 4. Analysis of risk factors associated with mortality at 6 months

Risk factors	Control (n = 82)	Death at 6 months (n = 15)	Univariate analysis			Multivariate analysis		
			OR	95% CI	p value	OR	95% CI	p value
Male gender (%)	65 (79.3)	10 (66.7)	1.9	0.6–6.3	0.319			
Age (mean±SD), years	58.8±11.8	62.6±15.1			0.273			
Etiology eradication (%)	47/67 (70.1)	7/11 (63.6)	1.3	0.4–5.1	0.729			
Child-Pugh B/C (%)	16/72 (22.2)	7/13 (53.8)	4.1	1.2–13.9	**0.037**	2.7	0.4–20.3	0.336
MELD-Na, median (IQR)	11.0 (8.5–14.0)	15.0 (10.0–22.0)			**0.016**	1.3	1.1–1.6	**0.016**
PVT (%)	15 (18.3)	7 (46.7)	3.9	1.2–12.4	**0.038**	10.5	1.4–79.4	**0.023**
HCC (%)	6 (7.3)	3 (20.0)	3.2	0.7–14.4	0.142			
NSBBs (%)	52 (63.4)	10/14 (71.4)	1.4	0.4–5.0	0.764			
Nr.EBL sessions (mean±SD)	4.2±2.0	3.7±1.9			0.363			
Incomplete VE (%)	26 (31.7)	12 (80.0)	0.1	0.03–0.5	< **0.001**	23.4	2.6–211.9	**0.005**
Severe PHG (%)	32 (39.0)	7 (46.7)	1.4	0.5–4.1	0.579			
Pandemic group (%)	36 (43.9)	8 (53.3)	1.5	0.5–4.4	0.500			

SD, standard deviation; MELD, model of end-stage liver disease; IQR, interquartile range; PVT, portal vein thrombosis; HCC, hepatocellular carcinoma; NSBBs, nonselective β-blockers; INR, EBL, endoscopic band ligation; VE, variceal eradication; PHG, portal hypertensive gastropathy.

detected without other evident cause. Thus, its rate might have been underestimated, as national electronic health records could not be accessed in 7 patients (7.2%) who deceased in other institutions. Fourth, regarding the risk factors for our outcomes, even though almost all varices were large (96.9%), we did not register the risk factors for esophageal varices, in particular presence of red marks or spots, nor the number of bands applied. However, in several studies, there was no significant association between them and the risk of bleeding [14, 25]. Finally, no portal hypertension measurement was performed in our patients. Therefore, our explanations related to variceal obliteration are

hypothetical and need further investigation. Nevertheless, despite these limitations, the present study reflects the importance of EBL therapy in these patients, for whom no data are available about the impact of pandemic COVID-19 on gastroesophageal varices treatment.

In conclusion, our study is among the first to demonstrate the impact of pandemic COVID-19 on patients receiving prophylactic EBL therapy, namely in achieving VE during this period. Our results also showed that patients with incomplete VE were at higher risk for GI bleeding and death at 6 months. Incomplete VE was associated with PVT, secondary prophylaxis indication, mean number of EBL sessions, and pandemic group, perhaps explained by a further increase in portal hypertension and therefore the need for more EBL sessions. However, we need to consider the limitations mentioned above in order to interpret our conclusions with caution. Thus, the impact of COVID-19 on the management of these patients requires further validation by multicentric studies.

Statement of Ethics

This study was approved by the Ethical Review Board of the Medical Academic Center of Lisbon on March 17, 2022 (reference number 02/22). The study protocol conformed to the ethical guidelines of the Declaration of Helsinki of 1975, as reflected in a priori approval by the institution's human research committee. Considering the retrospective observational character of the study, the Local Ethics Committee waived the need for individual informed consent.

Conflict of Interest Statement

The authors declare that there is no conflict of interest.

Funding Sources

This research did not receive specific grants from any funding agency in the public, commercial, or non-profit sectors.

Author Contributions

Data gathering, literature review, and manuscript writing: Ana Craciun and Inês Botto. Manuscript revision for important intellectual content: João Lopes, Miguel Moura, Sofia Carvalhana, Helena Cortez-Pinto, and Rui Tato Marinho.

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.

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GE – Portuguese Journal of Gastroenterology

Clinical Case Study

GE Port J Gastroenterol 2024;31:191–195
DOI: 10.1159/000531380

Received: February 12, 2023
Accepted: May 11, 2023
Published online: July 26, 2023

Primary Gastric Tuberculosis in an Immunocompetent Patient: The Truth Lying beneath the Surface

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Keywords
Mycobacterium tuberculosis · Gastric tuberculosis · Bite-on-bite biopsies

Abstract
Gastrointestinal tuberculosis is an uncommon entity, in which clinical presentation can be widely variable, from mild and nonspecific symptoms to an acute abdomen and gastrointestinal bleeding. Gastric involvement by *Mycobacterium tuberculosis* is rare, especially when it occurs without other recognized infectious foci – primary gastric tuberculosis – with only a few reported cases. Endoscopic findings can be very heterogeneous, from areas of hyperemia to pseudotumor lesions. We present a case of primary gastric tuberculosis in an immunocompetent patient, in which the absence of an epidemiological context and nonspecific endoscopic findings led to a delay in the diagnosis. Bite-on-bite biopsies proved to be essential, allowing to obtain samples from deeper layers of the submucosa where *M. tuberculosis* was identified. This case aimed to increase awareness for this entity, especially in endemic countries or regions with a high prevalence of tuberculosis since the diagnosis is based mainly on a high index of suspicion.

Tuberculose gástrica primária num doente imunocompetente: A verdade escondida sob a superfície

Palavras Chave
Mycobacterium tuberculosis · Tuberculose gástrica · Biópsia em túnel

Resumo
A tuberculose gastrointestinal é uma entidade pouco comum, com uma apresentação clínica amplamente variável, desde sintomas ligeiros e inespecíficos até quadros de abdómen agudo e hemorragia digestiva. O envolvimento gástrico pelo *Mycobacterium tuberculosis* é raro, especialmente quando ocorre sem outros focos infeciosos reconhecidos – tuberculose gástrica primária –, havendo apenas alguns casos descritos na literatura. Os achados endoscópicos podem ser muito heterogéneos, variando desde áreas de mucosa hiperemiada até lesões pseudo-tumorais. Apresentamos o caso de uma doente imunocompetente com diagnóstico de tuberculose gástrica primária, em que a ausência de um contexto

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epidemiológico e achados endoscópicos inespecíficos conduziram a um atraso no diagnóstico. As biópsias sobre biópsias mostraram ser essenciais para o diagnóstico, pois permitiram obter amostras de camadas mais profundas da submucosa do antro gástrico onde foi identificado o agente infecioso. Este caso pretende sensibilizar para existência desta entidade, especialmente em países endémicos ou regiões com alta prevalência de tuberculose, uma vez que o seu diagnóstico implica um elevado grau de suspeição.

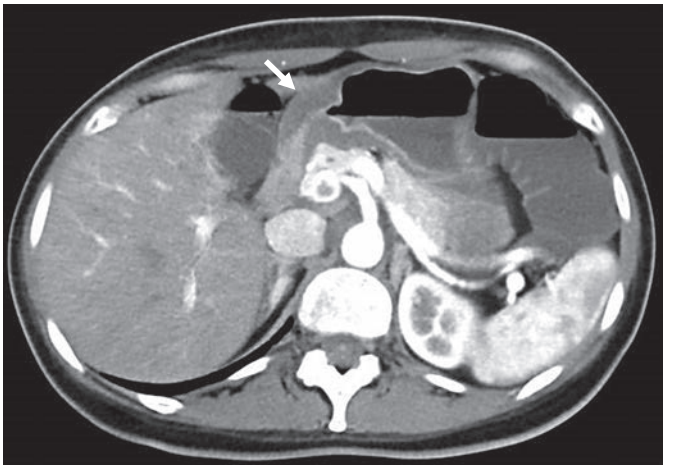

Fig. 1. Abdominal CT scan. Concentric parietal thickening (13 mm) of the gastric antrum.

Introduction

Tuberculosis is an infectious disease caused by the bacillus *Mycobacterium tuberculosis*, and until the COVID-19 pandemic, it was the leading cause of death from a single infectious agent [1]. About 25% of the world's population is infected with *M. tuberculosis*; however, only a small proportion will develop disease during their lifetime, with immunocompromised individuals being the most susceptible group. Although pulmonary tuberculosis is the most frequent manifestation, the involvement of other organs (extrapulmonary tuberculosis) is not negligible, and recent data show that, in some countries, extrapulmonary tuberculosis constitutes up to 30% of all active tuberculosis [2].

Gastrointestinal (GI) tuberculosis is an unusual form of extrapulmonary tuberculosis, although its prevalence may be underestimated due to its nonspecific clinical presentation. The ileocecal region is the most frequently affected site, followed by the colon and small intestine, while the stomach and esophagus are rarely involved [3]. We present a rare case of primary gastric tuberculosis with nonspecific clinical presentation and unsuspected endoscopic appearance, which made this diagnosis challenging.

Case Report

We present a case of a 46-year-old Portuguese woman, who was referred to the Gastroenterology Outpatient Clinic due to epigastric pain, early satiety at meals, and loss of >25% patient's total weight for 3 months. Her past medical and family histories were irrelevant. The patient denied any other symptoms, and physical examination showed no changes. Laboratory tests (including blood count, coagulation, electrolytes, renal function, liver tests, and C-reactive protein) were normal. An upper GI endoscopy revealed diffusely hyperemic gastric mucosa, which was biopsied (antrum and gastric body). The patient was treated with pantoprazole 40 mg bid and domperidone 10 mg tid but without effect. Gastric biopsies revealed chronic gastritis with some atrophy and marked inflammatory activity with rare non-necrotizing epithelioid granulomas. No acid-fast bacilli (AFB) (Ziehl-Neelsen staining) were observed, and immunohistochemical for *Helicobacter pylori* was negative.

For investigation of granulomatous gastritis, a careful clinical history (without epidemiological context for tuberculosis) and additional laboratory tests were carried out: interferon gamma release assay negative; angiotensin-converting enzyme 45 U/L (reference range, 8–52 U/L); anti-*Saccharomyces cerevisiae* and antineutrophil cytoplasmic antibodies negatives, fecal calprotectin 502 mg/kg (reference value: <50 mg/kg), and negative stool culture and ova and parasite analysis; HIV and VDRL negatives; erythrocyte sedimentation rate 10 mm/h (reference range: 0–20 mm/h); β2-microglobulin 1.3 mg/L (reference value: <2 mg/L); and normal peripheral blood smear. Chest and abdominopelvic CT scan did not reveal pulmonary nodules, lymph nodes, or digestive tract thickening. Colonoscopy with terminal ileoscopy and biopsies was performed – with no changes.

Six months later, after an extensive workup that was inconclusive, an upper GI endoscopy with biopsies was repeated. Once again, endoscopic findings were nonspecific, and the biopsies showed non-necrotizing epithelioid granulomas. Culture (Löwenstein-Jensen medium), immunohistochemistry (MPT64), and polymerase chain reaction (PCR) (GeneFinder TB) for *M. tuberculosis* were negatives. *H. pylori* was detected and treated with bismuth subcitrate potassium 140 mg qid, metronidazole 125 mg qid, and tetracycline 125 mg qid for 10 days.

The patient had worsening epigastric abdominal pain and persistent vomiting, unable to tolerate an adequate oral intake, so she was admitted to the Gastroenterology Department. At that time, an abdominopelvic CT was repeated revealing slight (13 mm) concentric parietal thickening of the gastric antrum (shown in Fig. 1). An upper GI endoscopy showed some gastric erosions

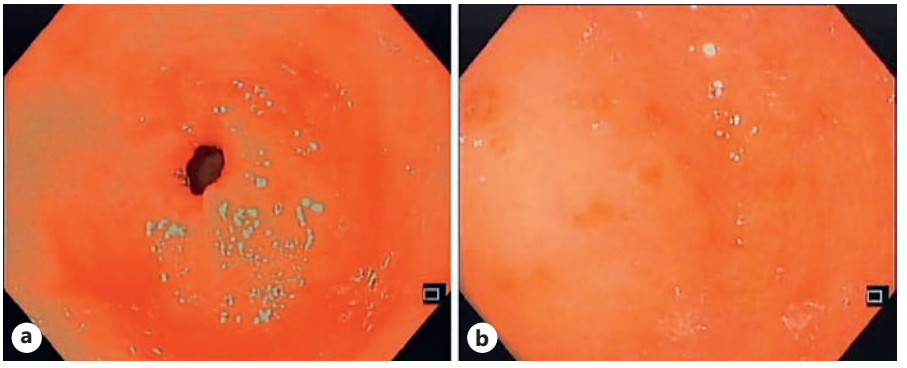

Fig. 2. a, **b** Upper GI endoscopy. Hyperemic mucosa and gastric erosions.

(shown in Fig. 2), and biopsies were taken from body and antrum of the stomach. Bite-on-bite biopsies were performed in the antrum, and gastric juice was also collected for microbiological study.

Given the suspect of tuberculosis, a bronchoscopy was performed. Bronchial secretions and bronchoalveolar lavage were negative for *M. tuberculosis* in AFB staining (Ziehl-Neelsen), culture (Löwenstein-Jensen medium and BACTEC MGIT 960), and PCR (GeneXpert MTB/RIF). Capsule endoscopy excluded lesions in the small intestine.

Deep biopsies of the gastric antrum would reveal numerous epithelioid granulomas with central necrosis in the lamina propria (shown in Fig. 3, 4). AFB stain (Ziehl-Neelsen) and *M. tuberculosis* culture (Löwenstein-Jensen medium and BACTEC MGIT 960) were negative in both gastric juice and biopsies. PCR for *M. tuberculosis* in fresh samples of the antrum were negative, but positive in paraffin-embedded tissue (GeneFinder TB), thus making the diagnosis of gastric tuberculosis.

The patient was referred to Infectious Diseases and started treatment with isoniazid, rifampin, pyrazinamide, and ethambutol for 2 months, followed by 7 months of isoniazid and rifampin. There was a slow but complete clinical response at the end of treatment. Endoscopic reassessment with biopsies 3 months later was unremarkable, and fecal calprotectin was 95 mg/kg.

Discussion

Gastric tuberculosis is a rare entity, accounting for 0.5–3% of GI tuberculosis cases [4]. Several factors have been described that seem to be responsible for the rare gastric involvement, namely, (1) low pH in the gastric lumen, which has a bactericidal role; (2) the absence of lymphatic follicles; (3) the local immunity induced by the integrity of gastric mucosa; and (4) fast gastric emptying [3–5]. Most cases of gastric tuberculosis occur in patients with active pulmonary tuberculosis [6, 7], due to swallowing infected sputum, but it may also be secondary to hematogenous or lymphatic spread and contiguous spread from the adjacent organ. When no other tuberculosis foci are identified after an extensive workup, it is called primary gastric tuberculosis. The latest is a rare form of gastric tuberculosis, sometimes occurring in the context of ingestion of infected milk products and meat [3–5]. Interestingly, our patient did not have an epidemiological context nor a state of immunosuppression that would increase the risk of infection, which makes the case even more particular.

The few reported cases of gastric tuberculosis show that the clinical presentation is nonspecific and variable, from dyspeptic symptoms to acute GI bleeding and gastric perforation [4]. This characteristic along with the low index of suspicion for this entity, especially in non-endemic regions, is responsible for delayed diagnosis. Abdominal pain and vomiting were the main symptoms in this case, and according to a recent systematic review [8], they are present at diagnosis in 43.5% and 64.4% of cases, respectively. Constitutional symptoms associated with tuberculosis such as anorexia, weight loss, night sweats, fever, and fatigue may also be present. More rarely, presentation with an acute condition like upper GI bleeding or perforation has been described [4].

With regard to endoscopic findings, in our case, there were no specific lesions, only small erosions. However, ulcerated or hypertrophic gastric lesions, often causing strictures and mimicking gastric neoplasms, are consistently described in the literature [4, 5, 7, 8]. Lesions are more frequent in the lesser curvature of the gastric antrum, next to the pylorus, due to the presence of lymphoid follicles in this location and the high incidence of gastric ulcers in this topography, which break the integrity of the mucosa [8].

M. tuberculosis isolation proved to be the most challenging step in this case. Published data regarding the diagnostic sensitivity of the different methods in GI tuberculosis are mostly based on cases of intestinal tuberculosis. Interferon gamma release assay has a

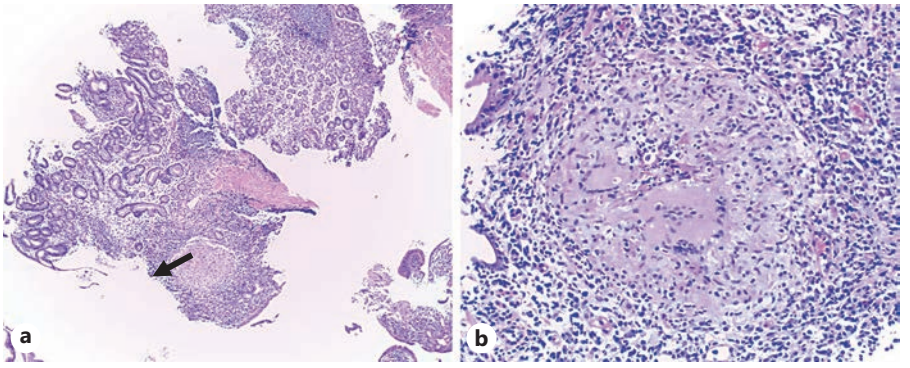

Fig. 3. a Hematoxylin-eosin stain (×4). Antrum-type gastric mucosa with moderate to severe chronic gastritis, with moderate activity, mild atrophy, and expansion of the lamina propria by inflammatory infiltrate, reactive lymphoid aggregates, and an epithelioid granuloma (arrow). **b** Hematoxylin-eosin stain (×20). Epithelioid granuloma with central necrosis, some neutrophils, and Langhans-type multinucleated giant cells.

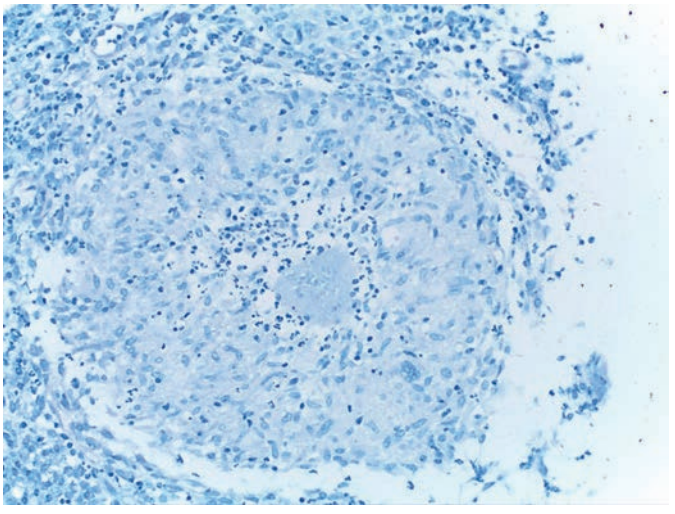

Fig. 4. Ziehl-Neelsen stain (×20). Granuloma. No acid-alcohol-resistant bacilli were identified.

diagnostic sensitivity of 77–84%, failing to distinguish between latent and active infection. AFB staining, such as Ziehl-Neelsen, has a low diagnostic sensitivity (17–31%). *M. tuberculosis* culture has a high specificity, but a very variable sensitivity (usually less than 50%), being considered the gold standard for the diagnosis of intestinal tuberculosis. Disadvantages of the culture are the prolonged incubation time (6 weeks) and allowing only qualitative analysis [9, 10]. Histologically, the most typical findings are granulomas and caseous necrosis. Histopathological examination has a sensitivity of around 68%, and these findings are highly influenced by factors such as the number and quality of biopsies [9]. PCR examination has a very high specificity and a sensitivity ranging from 22 to 65%. Currently, there are fully automated real-time PCR methods (e.g., GeneXpert) that have a higher sensitivity (81–95.7%) and allow simultaneous detection of mutations related to the resistance of *M. tuberculosis* to rifampicin [9]. In summary, if diagnostic suspicion is high, several diagnostic methods should be explored. The PCR test is one of the most sensitive tests and should be used early.

The diagnostic yield of these methods may be compromised in cases of gastric tuberculosis since the pathological findings may be present only in the submucosa [8, 11]. Bite-on-bite biopsies (bites are taken sequentially at the same location to expose the submucosa), as well as endoscopic ultrasound-guided biopsies, may be particularly useful in allowing the acquisition of histological material from deeper layers [12]. Although the bite-on-bite biopsy technique has a low diagnostic yield (23.3%) compared to endoscopic ultrasound-guided biopsy, it should be considered as an initial approach as it is cheaper, safer, and universally available [13, 14].

From the study carried out, it should be noted the elevation of fecal calprotectin around 10 times the upper limit of normality. Fecal calprotectin, a protein released by neutrophils, is a sensitive marker of inflammation of the GI tract, being elevated not only in inflammatory bowel disease (IBD) but also in infectious diseases. The usefulness of this marker in the differential diagnosis of IBD and tuberculosis is limited since both entities show high values of the biomarker, although very high values (>1,000 mg/kg) are suggestive of IBD. Studies have shown that a decrease in the fecal calprotectin level after antituberculosis therapy is an important indicator of therapeutic response in GI tuberculosis [15–18].

Antituberculosis drugs are the cornerstone of gastric tuberculosis treatment [7, 19]. Regarding the duration of treatment, although many physicians still consider a longer therapy (9–12 months) to be safer in terms of cure and risk of recurrence compared to the standard

duration for pulmonary tuberculosis, there are several recent studies showing that 6-month regimens have been shown to have similar efficacy to 9-month regimens in recent studies [2, 3, 12]. Endoscopic and surgical approach should be reserved for more complex situations, such as cases of obstruction of the gastric tract outlet, GI bleeding, or perforation [4, 19].

In conclusion, primary gastric tuberculosis is a rare entity, whose clinical and endoscopic presentation can be very nonspecific. It is essential to have a high index of suspicion for this pathology, particularly in patients with an epidemiological context, to avoid delay in diagnosis and treatment. Bite-on-bite biopsies showed to be a cost-effective method in obtaining material for histological diagnosis.

Statement of Ethics

This study was reviewed and approved by Hospital Prof. Dr. Fernando Fonseca Ethics Committee. Written informed consent was obtained from the participant 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

The authors declare that no funds, grants, or other support was received during the preparation of this manuscript.

Author Contributions

All the authors managed the patient; Fábio Pereira Correia and Luísa Martins Figueiredo drafted the paper; Sofia Santos, Rita Theias Manso, Luís Carvalho Lourenço, and David Horta critically revised the final version of the manuscript; all the authors approved the final version of the 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.

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GE – Portuguese Journal of Gastroenterology

Clinical Case Study

GE Port J Gastroenterol 2024;31:196–202
DOI: 10.1159/000531396

Received: January 12, 2023
Accepted: March 16, 2023
Published online: August 10, 2023

Small Bowel Villous Atrophy in a Young Patient: A Challenging Diagnosis

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Keywords
Celiac disease · Common variable immunodeficiency · Small bowel

Abstract
Common variable immunodeficiency enteropathy is a sprue-like disease, which may manifest as a severe malabsorption syndrome with nutritional deficits and cachexia. The authors report a case of a 33-year-old Afghan man, who presented to the emergency department due to chronic watery diarrhea and severe malnourishment. He had been previously misdiagnosed with celiac disease in his early adulthood; however, this was based on inconclusive findings. After a thorough diagnostic workup, the final diagnosis of common variable immunodeficiency enteropathy with symptomatic *norovirus* infection of the gut was obtained during his prolonged hospitalization. A slow but progressive improvement was observed with immunoglobulin replacement therapy, corticotherapy, and ribavirin treatment. This is a noteworthy case of a rare malabsorption disorder, and it reviews important aspects concerning the differential diagnosis of small bowel villous atrophy of unknown etiology, as well as gastrointestinal manifestations of common variable immunodeficiency disorder.

Atrofia vilositária do intestino delgado: um caso desafiante

Palavras Chave
Doença celíaca · Imunodeficiência comum variável · Intestino delgado

Resumo
A Enteropatia associada à Imunodeficiência Comum Variável é uma entidade com características clínicas e endoscópicas semelhantes à doença celíaca. Por vezes apresenta-se como um síndrome de malabsorção, levando a défices nutricionais e caquexia severa. Os autores relatam o caso de um homem de 33 anos de idade de naturalidade afegã, que recorreu ao serviço de urgência por um quadro de diarreia aquosa crónica e desnutrição severa. O doente teria sido diagnosticado erroneamente com doença celíaca no início da vida adulta, com bases em dados clínicos inconclusivos. Após um estudo exaustivo durante um internamento prolongado, o doente foi diagnosticado com uma Enteropatia associada à Imunodeficiência Comum Variável com sobreinfeção por *Norovirus*. Foi observada uma melhoria lenta e progressiva com instituição de terapêutica substitutiva com

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imunoglobulina, corticoterapia e ribavirina. Este caso retrata uma causa rara de malabsorção, abordando pontos essenciais no diagnóstico diferencial da atrofia vilositária do intestinal delgado, bem como das manifestações gastrointestinais da Imunodeficiência Comum Variável.

Introduction

Common variable immunodeficiency disorder (CVID) is a heterogeneous condition characterized by impairment on B-cell differentiation and antibody production. Patients with CVID present a wide range of clinical manifestations, including recurrent bacterial infections, autoimmune disorders, and lymphoproliferative disorders [1, 2]. The prevalence of CVID ranges from 1 per 50,000 to 1 per 25,000 and is the most frequently diagnosed symptomatic primary immunodeficiency in adulthood [3]. According to the diagnostic criteria from the International Consensus Document on CVID, the diagnosis of this disease requires low serum IgG levels, low serum IgA and/or IgM levels, impairment of vaccine response to at least 1 antigen, and exclusion of secondary causes of hypogammaglobulinemia [4].

Gastrointestinal manifestations in CVID are common, caused by infectious agents (such as *Giardia lamblia*, *Campylobacter jejuni*, and *Salmonella*) and also in the setting of a noninfectious gastrointestinal inflammatory disorder characterized by chronic watery diarrhea and small bowel sprue-like histological changes – CVID enteropathy. A small subset of patients exhibit a rare and severe form of this former condition, leading in some cases to a severe state of cachexia [3].

Case Presentation

A 33-year-old refugee Afghan man was admitted to the emergency department due to chronic watery diarrhea (5–7 non-bloody liquid stools per day) and weight loss (loss of 30% of body weight) in the previous 6 months, associated with marked fatigue that limited the performance of his daily activities. The patient denied having abdominal pain, fever, anorexia, arthralgia, or similar symptoms among his cohabitants.

Past medical conditions included a presumptive diagnosis of celiac disease (CD) 10 years before his admission, when he presented a 6-month clinical condition of watery diarrhea, abdominal pain, and bloating, with no other symptoms. The patient underwent esophagogastroduodenoscopy, which revealed macroscopic alterations compatible with CD; however, neither biopsies nor other diagnostic exams were performed at the time. He has been on a gluten-free diet ever since.

Table 1. Laboratory studies of the patient at the time of the admission

Parameter	Value	Reference range
Complete blood count		
Hemoglobin, g/dL	11.0	13.0–18.0
Leucocytes count, ×10E3/μL	9.3	3.8–10.6
Neutrophils, ×10E3/μL	6.48	1.3–8.8
Eosinophils, ×10E3/μL	0.15	0.0–0.7
Lymphocytes, ×10E3/μL	1.98	1.0–4.8
Monocytes, ×10E3/μL	0.6	0.1–0.8
Basophiles, ×10E3/μL	0.03	1.0–4.8
Platelet count, ×10E3/μL	274	150–440
Blood chemistry		
Glucose, mg/dL	83	80–100
Creatinine, mg/dL	0.63	0.67–1.17
Blood urea nitrogen, mg/dL	32	13–43
Sodium, mmol/L	134	136–145
Potassium, mmol/L	**2.6**	3.5–5.0
Chloride, mmol/L	105	98–107
Calcium, mg/dL	**6.5**	8.8–10.2
Magnesium, mmol/L	**0.26**	1.3–2.1
Total bilirubin, mg/dL	0.36	0.1–1.1
Aspartate aminotransferase, U/L	25	4–33
Alanine transaminase, U/L	21	4–33
Alkaline phosphatase, U/L	58	4–50
C-reactive protein, g/dL	**1.3**	0–0.5
Sediment velocity, mm/Hr	**2**	0–0.5
Albumin, g/dL	**2.8**	3.5–5.0
Total proteins, g/dL	**5.3**	6.4–8.3

The patient had not taken any medications (including over-the-counter drugs and supplements) or antibiotics in the previous 3 months. He had moved to Portugal 4 months prior to the admission, as a war refugee, after staying for a short period in a refugee camp. He also denied prior gastrointestinal surgeries and family history of gastrointestinal disorders.

Physical examination revealed a poor nutritional status, with a body mass index of 12.9 kg/m^2 (weight 35 kg), and marked skin pallor. The remainder of the physical examination was unremarkable, and there were no signs of peripheral edema or ascites. At the emergency department, laboratory studies revealed severe electrolyte imbalances (hypomagnesemia and hypokalemia) and hypoalbuminemia (Table 1). An abdominal ultrasound was also performed, and no signs of chronic liver disease, ascites, or bowel wall thickening were present. Due to severe cachexia and electrolyte imbalances, the patient was admitted to the medical ward.

Initial workup included exclusion of infectious gastrointestinal agents (bacterial stool cultures and microscopic stool examination/stool antigen detection for parasites) and HIV serology (Table 2), which were all negative. Extended laboratory data (Table 3) also revealed low serum levels of several proteins, including severe hypogammaglobulinemia, and low urinary protein excretion. Due

Table 2. Infectious agents tested, grouped by biological sample

Infectious agent	Microbiological method	Result
Blood		
HIV	Serology	Negative
Stools		
Salmonella spp.	Bacterial culture	Negative
Shigella spp.	Bacterial culture	Negative
Yersinia spp.	Bacterial culture	Negative
Campylobacter spp.	Bacterial culture	Negative
Vibrio spp.	Bacterial culture	Negative
Clostridium difficile	Antigen-based test	Negative
Giardia Lamblia	Stool microscopy Antigen-based test	Negative
Entamoeba histolytica	Stool microscopy Antigen-based test	Negative
Cryptosporidium	Stool microscopy Antigen-based test	Negative
Norovirus	PCR	Positive
Rotavirus	PCR	Negative
Adenovirus	PCR	Negative
Duodenal biopsies		
Mycobacterium spp.	PCR*	Negative
	Culture	Negative
Tropheryma whipplei	PCR	Negative

PCR, polymerase chain reaction. *Only for *Mycobacterium tuberculosis*.

to the absence of signs of impaired liver function (normal abdominal ultrasound, normal liver enzymes, and no signs of altered mental status) or proteinuria in a patient with chronic diarrhea, the diagnosis of a protein-losing enteropathy (PLE) was made.

Given the past medical history of CD, the exclusion of refractory CD and intestinal lymphoma was imperative in this case scenario [5]. Despite a negative result of CD antibodies, the patient presented severe hypogammaglobulinemia, so negative serologies could not exclude CD-related complications. Therefore, the patient initially underwent esophagogastroduodenoscopy, which demonstrated loss of duodenal folds and a granular appearance of the mucosa (Fig. 1). Duodenal biopsies were collected, revealing distortion of the glandular architecture, with atrophy and flattening of villi associated with an increase in intraepithelial lymphocytes (IEL) (>40 IEL/100 cells), and no evidence of granulomas, no thickening of the subepithelial collagen layer, or any signs of dysplasia/malignancy of enterocytes. Small bowel capsule endoscopy was later performed, revealing diffuse duodenal and jejunal villous atrophy, with no ulceration or other lesions (Fig. 2).

At this point, the physicians were standing before a non-ulcerative PLE, with small bowel villous atrophy and increased IEL, of unknown etiology, with multiple possible differential diagnoses (Table 4). Given his past medical history, refractory CD was initially the most likely diagnosis [5]. Nevertheless, HLA-DQ typing excluded HLA-DQ2 and HLA-DQ8 haplotypes, ruling out the initial diagnosis of CD [6].

Concerning other potential differential diagnosis, HIV, bacterial, and parasitic infections were previously excluded. Duodenal biopsies allowed the exclusion of intestinal tuberculosis and Whipple disease. As for intestinal lymphoma, T-cell receptor rearrangement analysis of intestinal lymphocytes did not identify a monoclonal pattern, excluding this condition.

Given that the patient exhibited nonselective hypogammaglobulinemia, an undiagnosed CVID could explain this clinical scenario. Lymphocyte immunophenotyping revealed absence of isotype-switched B memory cells (IgM-/IgD-/CD27), transitional B cells, and plasmablasts. An impairment of B-cell differentiation was evident, establishing the diagnosis of CVID in this clinical setting. This was also corroborated with functional antibody tests, denoting poor immune response to tetanus and pneumococcal immunization.

Later on, due to the fact that patients with CVID and severe hypogammaglobulinemia may develop a PLE related to chronic *norovirus* infection, PCR testing in stool samples for this agent was carried out, and a positive result was obtained. The final diagnosis of CVID enteropathy with symptomatic *norovirus* infection of the gut was established.

The patient went through a prolonged hospitalization, with a slow improvement of his gastrointestinal symptoms and body weight. Before the final diagnosis was established, he had initiated oral prednisolone (1 mg/kg/day) and parenteral nutrition. However, due to the scarce clinical improvement and after obtaining the final diagnosis, he was started on intravenous prednisolone (1 mg/kg/day) combined with immunoglobulin replacement therapy (IRT), targeting IgG levels above 1,200 mg/dL (40 g every 4 weeks), and ribavirin treatment (200 mg every 12 h). Concerning nutritional support, the patient initiated parenteral nutrition combined with oligomeric enteral nutrition, followed by a transitory period of polymeric enteral nutrition, and finally a personalized dietary plan with food fortification. After a 3-month hospital stay with an exhaustive investigation, the patient was discharged with clinical and nutritional follow-up in the outpatient clinic, monthly IRT, ribavirin (in order to complete 6 months of antiviral therapy), and weaning of prednisolone.

Discussion

Small bowel villous atrophy is the histopathological hallmark of many chronic enteropathies, which can manifest clinically with a malabsorption syndrome. CD is the most prevalent condition in this context, especially in Western countries. However, differential diagnosis and clinical management of non-celiac enteropathies are still challenging because of their rarity and overlapping clinical and histopathological features [7].

Despite the fact that the patient did not report a personal history of recurrent infections, severe hypogammaglobulinemia on laboratory studies was the first feature that raised the suspicion of CVID [2]. This was corroborated by the demonstration of a poor response

Table 3. Laboratory studies conducted during diagnostic workup

Serum protein electrophoresis		
parameter	value	reference range
Albumin	2.8	3.5–5.0
Gama globulin	0.27	0.6–1.3
Alpha-1 globulin	0.17	0.1–0.2
Alpha-2 globulin	0.59	0.4–0.8
Beta globulin	0.43	0.5–1.1
Other serum proteins, mg/dL		
Cholesterol	105	120–200
Transferrin	82	200–360
Ceruloplasmin	11	15–30
Immunoglobulins		
IgG, mg/dL	309.0	680–1,450
IgG1	275.0	422–1,292
IgG3	22.2	117–747
IgG3	11.3	41–129
IgG4	2.3	0–291
IgA, mg/dL	19	83–47
IgM, mg/dL	28	34–214
CD antibodies		
IgA anti-deamidated gliadin peptide, U/mL	<0.1	<7
IgG anti-deamidated gliadin peptide, U/mL	<0.4	<7
IgA anti-transglutaminase, U/mL	<0.1	<7
IgG anti-transglutaminase, U/mL	<0.4	<7
Urinary protein excretion		
Proteins, mg/dL	13.5	
Creatinine, mg/dL	53.0	
Protein-to-creatinine ratio, mg/mg	0.25	<0.2
Lymphocyte immunophenotyping		
T CD3, /mm^3	1,143	1,100–1,700
T CD4, /mm^3	631	100–1,100
T CD8, /mm^3	501	500–900
Ratio T CD4/CD8	1.259	
NK cells, /mm^3	73	200–400
B CD19, /mm^3	215	200–400
B-cell subpopulations, %		
Naive B Cells	68.27	51.3–66.2
Marginal zone B cells	20.12	9.0–17.7
"Unswitched" memory B cell	11.5	8.22–14.05
"Switched" memory B cell	0	8.12-14-72
CD21 low B cell	26.98	6.1–12.6
Transitional B cell	0.02	1.37–4.41
Plasmablasts	0	0.02–14.13

PCP, pneumococcal capsular polysaccharide; NK, natural killer.

to immunization and absence of switched memory B cells, transitional B cells, and plasmablasts [1]. Furthermore, other secondary causes of immunodeficiency were not evident, namely, HIV infection, medications, and hematological malignancies. However, a PLE might, per se, cause immunoglobulin depletion, which made the clinicians seek other possible conditions [8].

The previous misdiagnosis of CD in this patient was a confounding factor and caused a delay in the diagnostic workup, given that a CD-related complication had been primarily assumed [9]. Unfortunately, the lack of standardized endoscopic protocols, availability of diagnostic procedures, and awareness of rare diseases in developing countries had led to the initial misdiagnosis [10, 11].

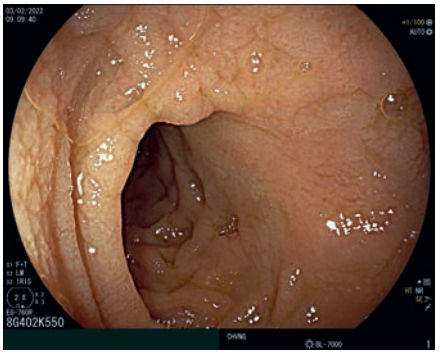

Fig. 1. Esophagogastroduodenoscopy, revealing loss of duodenal folds and a granular appearance of the duodenal mucosa. EGD, esophagogastroduodenoscopy.

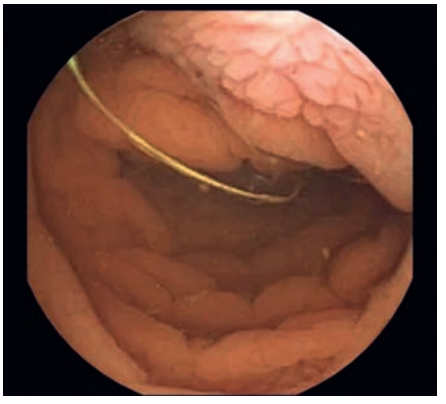

Fig. 2. Capsule endoscopy frame, revealing diffuse villous atrophy throughout the small bowel.

Even though gastrointestinal manifestations occur in 20–60% of CVID patients, these rarely lead to severe nutritional deficits [12]. In contrast, the authors present a severe case of PLE caused by CVID enteropathy. In fact, a small subset of CVID patients present a malabsorption syndrome, requiring hospitalization and nutritional support [3].

Regarding medical treatment, due to the difficulty of gathering a large number of patients to conduct randomized controlled trials and heterogeneity within the CVID enteropathy, the optimal induction of remission strategy in severe cases is yet to be defined. Medical treatment involves not only IRT but also an immunosuppressive strategy, given that mucosal damage and inflammation are caused by an immunoregulatory dysfunction similar to inflammatory bowel disease [13]. Corticosteroids have shown to induce a positive clinical response in these patients [9, 13], as well as some corticosteroid-sparing agents, namely azathioprine [14], infliximab [15], and vedolizumab [12]. Nevertheless, histological improvement seems to be inconsistent [16].

As described by some authors, these patients exhibit a very slow improvement of clinical manifestations and nutritional status, requiring a prolonged hospitalization [9]. Refractoriness to oral therapy, due to the extensive involvement of the small bowel, demanded a change to the intravenous route. Combined with IRT and antiviral therapy, this immunosuppressive strategy led to a positive clinical response.

Severe intestinal malabsorption in CVID demands the exclusion of *norovirus*. CVID patients present a cytotoxic aberrant immune response to the chronic infection caused by *norovirus*, leading to epithelial damage and mucosal villous atrophy [16]. The pathogenicity of *norovirus* has been further associated with symptomatic and histological improvements observed after viral clearance in several case reports [17, 18]. Unfortunately, for this particular scenario, there are no approved antiviral agents. The decision to start this patient on ribavirin came from the fact that previous authors had reported viral clearance in the norovirus enteropathy associated with CVID after its introduction [3, 19, 20].

Concerning nutritional strategy, after a course of parenteral nutrition, the patient received oligomeric enteral nutrition. Severely ill patients with malabsorption syndromes may benefit from formulas containing peptides and medium-chain triglycerides, as stated by the European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines [21]. Furthermore, polymeric formulas may worsen gastrointestinal symptoms, as opposed to formulas with amino acids [22].

As noted throughout the case description, several other differential diagnoses were considered in this context (Table 4). Infectious causes had to be excluded, namely, Whipple disease, giardiasis, HIV infection, and *Mycobacterium* species. Additionally, gastrointestinal infections are common in refugee camps due to overcrowding and poor hygiene conditions [23]. Tropical sprue could also fit in this clinical context, given that the patient was from an Asian country, where this condition is highly prevalent [24].

Crohn's disease and autoimmune enteropathy were also two possible differential diagnoses, requiring further diagnostic procedures (colonoscopy and anti-enterocyte antibodies, respectively). However, given the diagnosis of CVID, these procedures were not performed during the patient's hospital admission [7].

Table 4. Differential diagnosis of villous atrophy with increased IEL

Infection (tropical sprue, Giardia, Whipple disease, *Mycobacterium avium* complex, AIDS enteropathy)
Collagenous sprue
Autoimmune enteropathy; common variable immunodeficiency
Graft versus host disease
Crohn's disease
Drugs (mycophenolate mofetil, colchicine, olmesartan, losartan)
Chemoradiation therapy
Immunomodulatory therapy (anti-CTLA-4 antibody)
Eosinophilic gastroenteritis
Bacterial overgrowth
Enteropathy-associated T-cell lymphoma
Nutritional deficiency
Amyloidosis

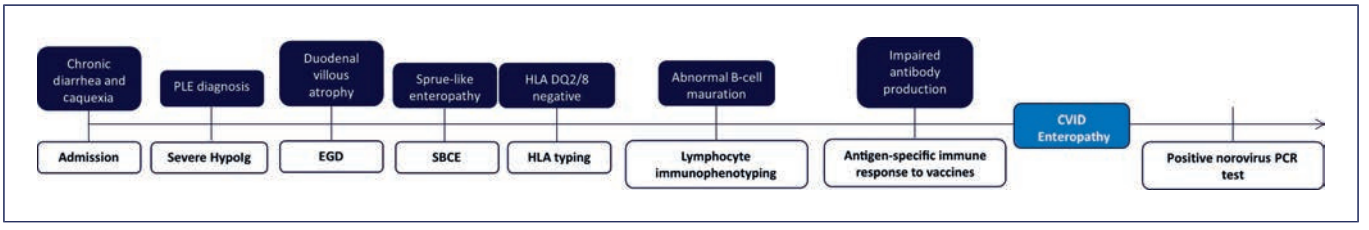

Fig. 3. Longitudinal course of the diagnostic workup. HypoIg, hypogammaglobulinemia; EGD, esophagogastroduodenoscopy; SBCE, small bowel capsule endoscopy; CVID, common variable immunodeficiency disorder; PCR, polymerase chain reaction.

Conclusions

The authors report an exceptional case of a rare non-ulcerative enteropathy in a severely malnourished patient. As previously stated, a PLE with small bowel villous atrophy has a wide range of differential diagnosis, demanding a thorough and exhaustive investigation (Fig. 3). Fortunately, despite the delay in the final diagnosis, the patient had a positive outcome. Clinicians should always keep in mind CVID as an alternative diagnosis in a patient with a PLE. Although IRT is the mainstay of CVID treatment, immunosuppressive therapy is frequently needed to improve mucosal absorption and nutritional status of these patients.

Statement of Ethics

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

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

This work was not funded.

Author Contributions

João Correia was responsible for writing the original draft; Andreia Freitas and António Marinho were responsible for data curation; Ana Ponte, Edgar Afecto, and Manuela Estevinho were responsible for writing, review, and editing.

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.

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GE – Portuguese Journal of Gastroenterology

Clinical Case Study

GE Port J Gastroenterol 2024;31:203–208
DOI: 10.1159/000531773

Received: December 12, 2022
Accepted: June 15, 2023
Published online: August 16, 2023

Autoimmune Hepatitis Induced by Hepatitis Delta Virus: A Conundrum

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Keywords
Autoimmune hepatitis · Hepatitis delta · Immunosuppression

Abstract
Introduction: The association of hepatitis delta virus (HDV) infection with positive autoantibodies and autoimmune features has been known for decades. However, to date, very few cases of clinical autoimmune hepatitis (AIH) have been reported in association with HDV infection, most of them being in the context of treatment with peginterferon. ***Case Report:*** This case refers to a 46-year-old woman born in Guinea-Bissau who moved to Portugal in 2018 to investigate complaints of diffuse abdominal discomfort and nausea. Her initial work-up, including laboratory and liver histology, was consistent with type 1 AIH. She had HBe antigen-negative chronic hepatitis B virus infection with negative DNA and also a positive total anti-HDV antibody, with negative IgM and undetectable RNA. Therefore, after initiating prophylactic tenofovir difumarate, she was started on prednisolone followed by azathioprine, which was later stopped due to presumed hepatotoxicity. Repeated histology showed signs of viral superinfection, and she was treated with acyclovir due to a positive herpes simplex IgM, with HDV RNA remaining negative. A third flare in transaminases prompted the introduction of mycophenolate mofetil (MMF) after a thorough exclusion of additional causes of liver disease. About 6 months later, during another bout of hepatitis, HDV RNA was finally positive and classified as genotype 5. MMF was stopped, and, considering a contraindication to interferon, the patient was offered therapy with bulevirtide, which she refused for personal reasons as she is currently living in her home country. ***Discussion:*** This is a challenging case of autoimmune or "autoimmune-like" hepatitis, probably induced by chronic HDV infection. High suspicion of HDV was essential because, had the case been interpreted as refractory AIH, with escalation of immunosuppression, a more severe course of the viral infection might have ensued. Recently, HDV suppression with bulevirtide was shown to reverse autoimmune liver disease. We hypothesize that the same could have happened to our patient, had she accepted this treatment.

Hepatite autoimune induzida pelo vírus da hepatite delta: um quebra-cabeças

Palavras Chave
Hepatite autoimune · Hepatite delta · Imunossupressão

Resumo
Introdução: A associação da infeção pelo vírus da hepatite delta (VHD) com a presença de autoanticorpos e outros aspetos de autoimunidade é conhecida desde há

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várias décadas. Contudo, até à data, muito poucos casos de hepatite autoimune (HAI) clínica foram reportados em relação com a infeção VHD, sendo a maioria destes no contexto de terapêutica com interferão peguilado. ***Caso clínico:*** O caso refere-se a uma mulher de 46 anos natural da Guiné-Bissau, que se mudou para Portugal em 2018 para investigação de queixas de desconforto abdominal difuso e náuseas. A avaliação laboratorial inicial e a histologia hepática foram compatíveis com HAI tipo 1. A doente apresentava também infeção crónica a VHB (vírus da hepatite B) antigénio HBe negativa, com DNA negativo, e anti-VHD (vírus da hepatite delta) total positivo, com IgM negativo e RNA indetetável. Assim, após início de tenofovir difumarato profilático, foi iniciada terapêutica com prednisolona seguida de azatioprina, que posteriormente se interrompeu por presumível hepatotoxicidade. Uma segunda biópsia mostrou aspetos de superinfeção viral e como tal a doente foi tratada com aciclovir, tendo em conta IgM positivo para Herpes Simplex, mantendo-se o RNA VHD negativo. Um terceiro *flare* de transaminases motivou o início de micofenolato de mofetil, após extensa investigação e exclusão de outras causas de doença hepática. Cerca de 6 meses mais tarde, durante novo episódio de hepatite, o RNA VHD revelou-se finalmente positivo e este foi classificado como genotipo 5. O MMF foi suspenso e, considerando a contra-indicação para interferão, foi proposto à doente tratamento com bulevirtide, que esta recusou, alegando motivos pessoais, visto estar atualmente a residir no seu país de origem. ***Discussão:*** Este é um caso desafiante de hepatite autoimune, ou autoimune-*like*, provavelmente induzida pela infeção crónica pelo VHD. Um elevado índice de suspeição para VHD foi essencial porque, se o caso tivesse sido interpretado como HAI refratária, com incremento de imunossupressão, poderia ter-se verificado um agravamento da hepatite viral. Recentemente, foi reportado que a supressão do VHD pelo bulevirtide pode reverter a doença hepática autoimune. Questionamo-nos se o mesmo poderia ter sucedido com a nossa doente, caso esta tivesse aceite este tratamento.

Introduction

Chronic hepatitis delta is the most aggressive form of viral hepatitis [1–3]. Although universal testing of patients with positive hepatitis B virus (HBV) surface antigen has been proposed by European recommendations for more than 10 years [4], diagnosis can sometimes be hindered by laboratorial shortcomings, especially when considering less frequent genotypes [5].

The association of hepatitis delta virus (HDV) infection with positive autoantibodies and autoimmune features has been known for decades [6, 7]. However, to date, very few cases of clinical autoimmune hepatitis (AIH) have been reported in association with HDV infection, most of them being in the context of treatment with peginterferon [8, 9]. In this clinical case study, we describe the challenges faced in the diagnosis and treatment of a patient with autoimmune hepatitis that we believe was induced by HDV.

Case Report

The case refers to a 46-year-old woman born in Guinea-Bissau, where she worked as a teacher. Her past medical history was positive for hypertension, treated with losartan 50 mg since 2016, and a cholecystectomy. The patient moved to Portugal in 2018 to investigate complaints of diffuse nonspecific abdominal discomfort and nausea with 2-month duration. She denied alcohol intake or exposure to hepatotoxic drugs. She had no known family history of liver disease, viral infections, or cancer.

Physical examination was unremarkable. The patient's weight was 45 kg and height was 1.60 m, corresponding to a body mass index of 17.5 kg/m^2. Initial blood work-up showed elevated liver enzymes, namely, aspartate aminotransferase (AST) 540, alanine aminotransferase (ALT) 686, alkaline phosphatase 111, and gamma-glutamyl transferase 198 U/L, with INR 1.2 and normal bilirubin and platelet count. Abdominal ultrasound revealed a normal liver, slight main biliary duct dilatation due to previous cholecystectomy, and no splenomegaly, ascites, or venous thrombosis. She was admitted in the Internal Medicine Department for investigation. Further testing showed positive HBsAg, HBcAb, and HBeAb, with negative HBeAg and HBsAb and undetectable HBV DNA. Total anti-HDV was positive, with negative IgM and undetectable RNA. Other hepatotropic viruses were excluded, with negative anti-hepatitis C virus (HCV), anti-hepatitis E virus IgG and IgM, and anti-human immunodeficiency virus; positive anti-hepatitis A virus IgG with negative IgM; positive anti-CMV (cytomegalovirus) IgG with negative IgM; positive Epstein-Barr virus VCA IgG and IgM and EBNA IgG, with negative DNA. *Rickettsia*, *Coxiella*, and *Plasmodium falciparum* were also excluded. The patient had mild peripheral eosinophilia and a positive IgG antibody for *Strongyloides stercoralis* (12.59 [<1.00]), which was also identified in stool. Autoimmune panel was positive for antinuclear antibodies (ANA), fine-speckled, and with a titer of 1/320, but negative for anti-smooth muscle, anti-liver kidney microsomal type 1 (anti-LKM1), anti-liver cytosol type 1 (anti-LC1), and anti-soluble liver antigen (anti-SLA) antibodies, as well as anti-mitochondrial antibodies. Serum protein electrophoresis showed a polyclonal hypergammaglobulinemia. Serum immunoglobulin G (IgG) was elevated at 2,570 mg/dL, while immunoglobulin M was normal. Alpha-1 antitrypsin, ceruloplasmin, urinary copper, serum iron, and serum ferritin levels were within normal range.

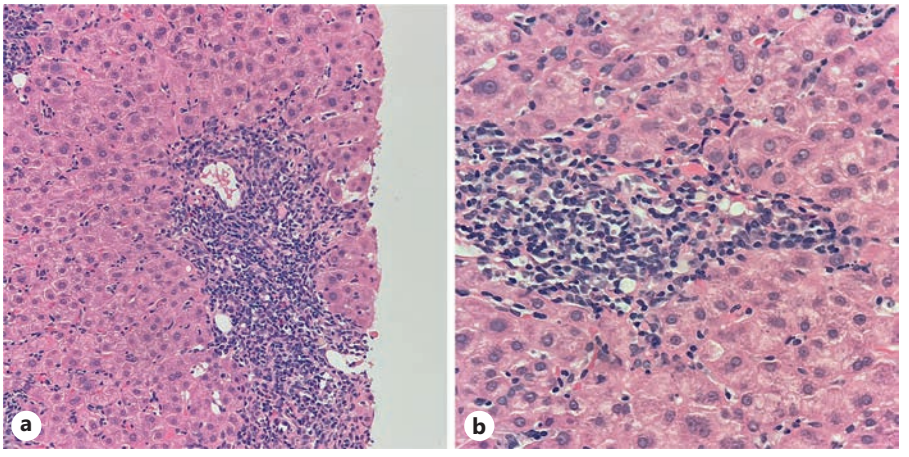

Fig. 1. Portal tracts showing intense inflammatory infiltrates with lymphocytic predominance, rich in plasmocytes and with rare eosinophils, with interface hepatitis and hepatocyte ballooning. **a** H&E ×200. **b** H&E ×400.

The patient was treated with ivermectin for *Strongyloides stercoralis* infection. Following treatment, the eosinophilia resolved in 4 days, and repeat stool testing was negative for parasites. There was a decrease in transaminases (AST 100, ALT 141 U/L), and the patient was discharged.

Around 6 months later, the patient was readmitted due to persistent abdominal discomfort. At this time, she presented AST 323, ALT 331 U/L, and IgG 3,101 mg/dL. After Hepatology consultation, a liver biopsy was performed, showing intense lymphoplasmocytic infiltrates, interface hepatitis, emperipolesis, and no cytopathic viral effect, as shown in Figure 1a, b. These findings were compatible with autoimmune hepatitis with mild fibrosis (Ishak fibrosis score 1/6).

When applying the revised original AIH diagnostic score, the diagnosis was classified as probable (13 points, pretreatment) [10]. Therefore, the patient was started on prednisolone 1 mg/kg/day while commencing prophylactic tenofovir disoproxil fumarate. Transaminases had spontaneously decreased in the previous 4 weeks (AST 152, ALT 181 U/L) and had a further reduction after 7 days of therapy (AST 59, ALT 108 U/L). Upon azathioprine (AZT) 50 mg introduction 2 weeks later, however, there was again a steep rise in transaminases (AST 544 and ALT 1496 U/L), with IgG reduction to 1,962 mg/dL (Fig. 2). AZT was stopped due to presumed toxicity, and PDN was increased to 1 mg/kg/day. A second liver biopsy showed less pronounced inflammatory infiltrates and features suggesting possible viral superinfection (shown in Fig. 3, 4). An extensive viral search was again conducted, including negative HBV and HDV viral loads, positive Epstein-Barr virus DNA in serum (556 copies/mL) but negative in liver tissue, and positive herpes simplex IgM. After discussing with the Infectious Diseases team, the patient was treated with acyclovir for 21 days, and steroids were tapered, resulting in a decrease in transaminases.

She was kept on low-dose PDN (7.5 mg) for several months, maintaining a normal IgG and transaminases around 2–3 times the upper limit of normal. However, there was a new disease flare (AST 166, ALT 286 U/L, IgG 2,417 mg/dL), with repeated negative viral screening and histology revealing only features of AIH. Therefore, PDN was increased to 20 mg and mycophenolate mofetil (MMF) 1.5 g/day was added, with no response in transaminases.

About 6 months later, despite normalization of IgG, transaminases peaked again (AST 490, ALT 1,000 U/L). HBV DNA and HDV IgM remained negative. Serum hepatitis E RNA was also negative. Histology showed active AIH, including moderate lymphoplasmocytic infiltrates, interface hepatitis, and emperipolesis, with no cytopathic viral effect. Surprisingly, HDV viral load, which had been repeatedly undetectable in the past, now came back positive at 103,100 UI/mL. Further testing in an external laboratory classified the virus as genotype 5 (GT5).

Having diagnosed chronic hepatitis delta, MMF was stopped. Therapy with pegylated interferon was contraindicated due to the autoimmune disease. More recently, almost 1 year later, bulevirtide became available in our country. However, the patient refused this treatment for personal reasons because she is currently spending most of her time in her home country, Guinea-Bissau, where she has both her family and her job. She is being kept on steroid monotherapy (prednisolone 20 mg), with persisting hepatitis (AST 127 and ALT 350 U/L). There were concerns about progression of fibrosis, as platelet count has progressively dropped to $78{,}000 \times 10^9$/L. However, her liver stiffness (FibroScan®) value is currently at 9.0 kPa.

Discussion

This is a complex and challenging case of chronic hepatitis delta presenting with autoimmune features. It is our belief that HDV acted as a trigger for autoimmunity in our patient.

In fact, viral infections have long been described as possible triggers of autoimmune liver diseases in genetically predisposed individuals. One of the few known autoantigens in AIH, specifically AIH type 2, is CYP2D6, which shares an amino acid sequence with HCV proteins and is the target of anti-LKM1 autoantibodies, suggesting molecular mimicry [11]. In fact, 10% of patients infected with HCV present detectable anti-LKM1 antibodies [12]. Autoantibodies associated with AIH are also common in HBV infection, particularly in HBV/HDV patients [7] (with up to two-thirds of patients presenting ANA, anti-smooth muscle, or anti-LKM3) [13]. Although these are generally considered part of the course of the viral infection [14], cases of concurrent HBV and AIH have been described, with viral

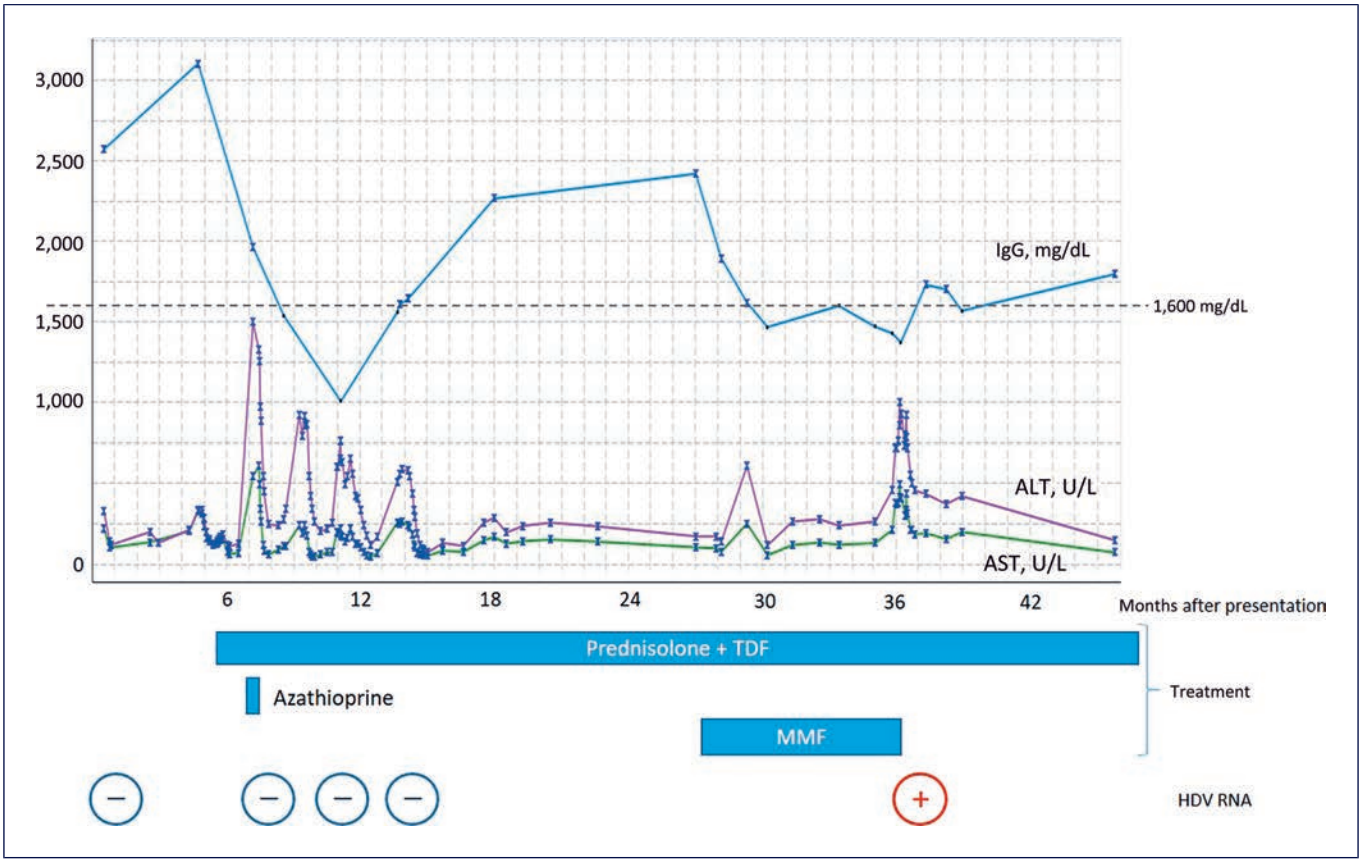

Fig. 2. Graphic showing the evolution of transaminases and immunoglobulin G (IgG) throughout time and the moment of introduction of different treatments. Broadly speaking, there is an inverse correlation between transaminases and IgG levels. ALT, alanine aminotransferase; AST, aspartate aminotransferase; HDV, hepatitis delta virus; MMF, mycophenolate mofetil; TDF, tenofovir disoproxil fumarate.

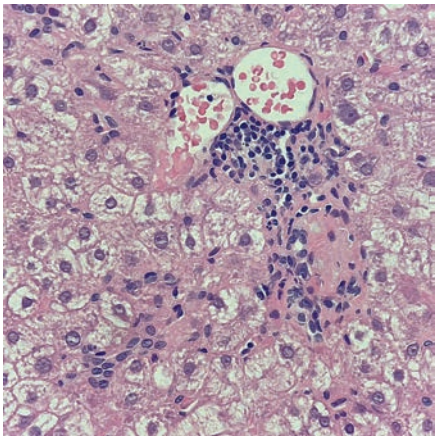

Fig. 3. Portal tract with mild-to-moderate inflammatory infiltrates with lymphocytic predominance and rare plasmocytes (H&E ×400).

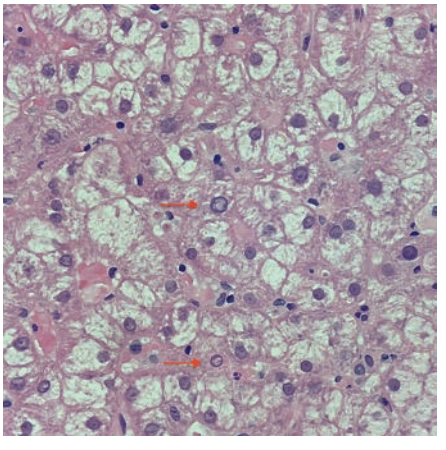

Fig. 4. Hepatocytes showing nuclei with peripheral condensation of chromatin (arrows) and hyaline and amorphous cytoplasm suggesting viral cytopathic effect, in a background of intralobular inflammatory activity (H&E ×400).

infection preceding AIH by many years and possibly having worked as a trigger [8]. Furthermore, occult HBV infection has been described in higher proportions of AIH patients when compared to the general population [15–17], suggesting an etiologic role for HBV in AIH. Regarding HDV specifically, very few cases have been described in association with AIH, most of them being during or after treatment with interferon-alpha-based regimens [8, 9].

Establishing the diagnosis of AIH in the context of concomitant viral hepatitis is challenging and controversial. In fact, diagnostic scoring systems deduct points when there is evidence of viral hepatitis [10, 18] and are therefore not adequate in this setting [8]. In the case of our patient, all the classical hallmarks of autoimmune hepatitis were in fact present. It could be argued, though, that if HDV cure led to reversal of autoimmunity, then the disease would not be self-perpetuating and would therefore be fundamentally distinct from classical, or "idiopathic," AIH. A similar rationale has recently been used to propose the designation of "drug-induced autoimmune-like hepatitis" to liver disease with laboratory and histological features that may be indistinguishable from AIH but that resolve upon removal of the trigger (in this case, a drug), therefore not requiring long-term immunosuppression [19]. Similarly, in our patient, "autoimmune-like hepatitis" could potentially be used to describe the autoimmune liver features. Very recently, a case report was published where bulevirtide was used to treat chronic hepatitis delta in a patient with autoimmune hepatitis. Differently from our patient, this patient had cirrhosis with portal hypertension and was negative for ANA. Following viral suppression, IgG normalized, and there was regression of autoimmune features on histology [20].

In the case of our patient, the diagnosis of HDV required a very high index of suspicion. This was driven by factors such as the dissociation between transaminases and IgG, a somehow erratic response to immunosuppressive treatment and ALT being always above AST (Fig. 2), as well as the patient's origin (Western Africa, endemic for HBV/HDV) [21].

It is not clear though why the HDV viral load was only positive at the fourth determination. The method for extraction (MagNA Pure®, Roche) and amplification (RealStar® HDV RT-PCR, Altona Diagnostics) did not change throughout time. Automated extraction methods, including the one used in this case, were shown to underestimate HDV RNA by about 10-fold when compared to a manual method [22]. As an alternative to serum HDV RNA, HDV antigen search in liver biopsy by immunohistochemistry could have been performed. In fact, this request was placed but then canceled, as serum HDV RNA came back positive in the meantime.

It is possible that the RNA PCR test that was used could only detect the virus when it reached a certain threshold. This leads to the question of whether immunosuppression could have unveiled a chronic HDV infection. It is possible that the peak in transaminases that followed AZT's introduction was actually an undetected HDV flare rather than hepatotoxicity. In addition, it was only months after the introduction of MMF, with IgG being in the normal range and probably the patient being most immunosuppressed, that HDV was finally detected (Fig. 2). Differently from HBV monoinfection, there is a paucity of data regarding reactivation of HDV in the context of immunosuppression, with only case reports mentioning HDV flairs in patients treated with sunitinib [23] and chemotherapy for lymphoma [24].

Another key aspect of this case is the fact that the patient was infected with HDV GT5, which probably hindered the diagnosis. In fact, most laboratories underestimate or fail to detect GT5 and other African genotypes [5]. Furthermore, when compared to GT1, patients infected with GT5 were shown to less frequently express IgM antibodies [25] (such was the case of our patient, who was persistently negative for anti-HDV IgM). The issue of HDV genotype is of crucial importance in our center since the majority of our HDV patients come from Guinea-Bissau and are infected with GT5 [26]. This subject has become increasingly relevant in Europe in recent years as domestic infection, mostly related to intravenous drug use, are being replaced by cases introduced by immigration from endemic areas [3]. Also, the difficulties that we faced in bringing our patient to clinic and starting treatment are in line with reports from the French cohort, where migrant populations were shown to have suboptimal adherence and commitment to care, driven by socioeconomic insecurity [27].

In conclusion, we present a challenging case of autoimmune or "autoimmune-like" hepatitis, probably induced by chronic HDV infection. High suspicion of HDV was essential because, had the case been interpreted as refractory AIH, with escalation of immunosuppression, a more severe course of the viral infection might have ensued. Recently, HDV suppression with bulevirtide was shown to reverse autoimmune liver disease. We hypothesize that the same could have happened to our patient, had she accepted this treatment.

Acknowledgments

We would like to acknowledge the contribution of Dr. Joaquim Tinoco and Dr. Rita Theias (Pathology Department) for the discussion of liver biopsy features and preparation of histology

slides and legends, Dr. Bárbara Flor-de-Lima (Infectious Diseases) for specialist infectious diseases input, Dr. Elizabeth Pádua (Instituto Nacional de Saúde Dr. Ricardo Jorge) for developing a new method for hepatitis delta genotyping following this clinical case, and Prof. Heiner Wedemeyer (Hannover Medical School, Germany) for his enthusiasm in discussing this case.

Statement of Ethics

This patient gave her written informed consent to publish the case (including publication of images).

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

The authors have no funding sources to declare.

Author Contributions

Mariana F. Cardoso drafted the article. Rita Carvalho is the main healthcare provider of the patient. All authors were actively involved in the discussion of the clinical case and reviewed the final version of the article.

Data Availability Statement

All data generated or analyzed during this study are included in this article.

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GE – Portuguese Journal of Gastroenterology

Endoscopic Snapshot

GE Port J Gastroenterol 2024;31:209–211
DOI: 10.1159/000533498

Received: April 6, 2023
Accepted: July 21, 2023
Published online: September 19, 2023

Cholangioscopy with Laser Lithotripsy in the Treatment of a Patient with Type II Mirizzi Syndrome

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Keywords
Endoscopic retrograde cholangiopancreatography · Colangioscopy · Mirizzi syndrome

Colangioscopia com Litotrícia Laser no tratamento de doente com Síndrome de Mirizzi tipo II

Palavras Chave
CPRE · Colangioscopia · Síndrome de Mirizzi

Eighty-Seven-year-old woman, without relevant medical past history, was referred to ERCP for treatment of acute cholangitis. Abdominal CT scan revealed dilatation of intra and extrahepatic bile ducts with hyperdense content in the cystic duct and in the common bile duct, suggestive of Mirizzi syndrome and choledocholithiasis. An abdominal MRI was performed revealing a large 4 cm stone in the infundibulum-cystic duct, a 2 cm stone in the hepatic duct (Fig. 1).

During the initial ERCP, cholangiography revealed a large stone in the cystic causing a stenosis of the hepatic duct with upstream dilation of the biliary tree, confirming the Mirizzi syndrome (Fig. 2). A plastic double pigtail stent (7 Fr × 4 cm) was inserted, after sphincterotomy. After multidisciplinary evaluation of the patient conditions, given the patient frailty it was decided to treat the condition using an endoscopic approach – laser lithotripsy assisted by cholangioscopy.

SpyGlass cholangioscopy revealed two impacted large stones, one in the cystic duct and unexpectedly, another in the hepatic duct. Lithotripsy with laser Holmium was successfully performed in both stones; after both lithotripsies, a fistula between the cystic and the hepatic duct was noticed, involving less than one-third of the circumference of the hepatic duct (Mirizzi type II). The patient presented a favourable clinical evolution and was discharged 4 days after the procedure.

Discussion

Mirizzi syndrome is an uncommon cause of acute cholangitis [1]. ERCP allows the resolution of jaundice through the placement of stents and, in some cases, the removal of the cystic duct stone, although most patients

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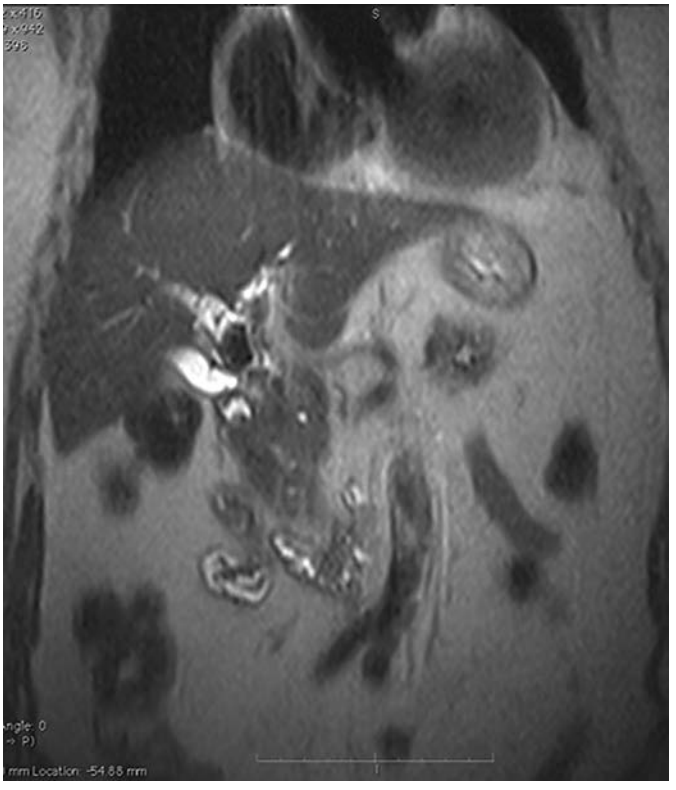

Fig. 1. MRI showing a large stone in the infundibulum-cystic duct, with about 4 cm.

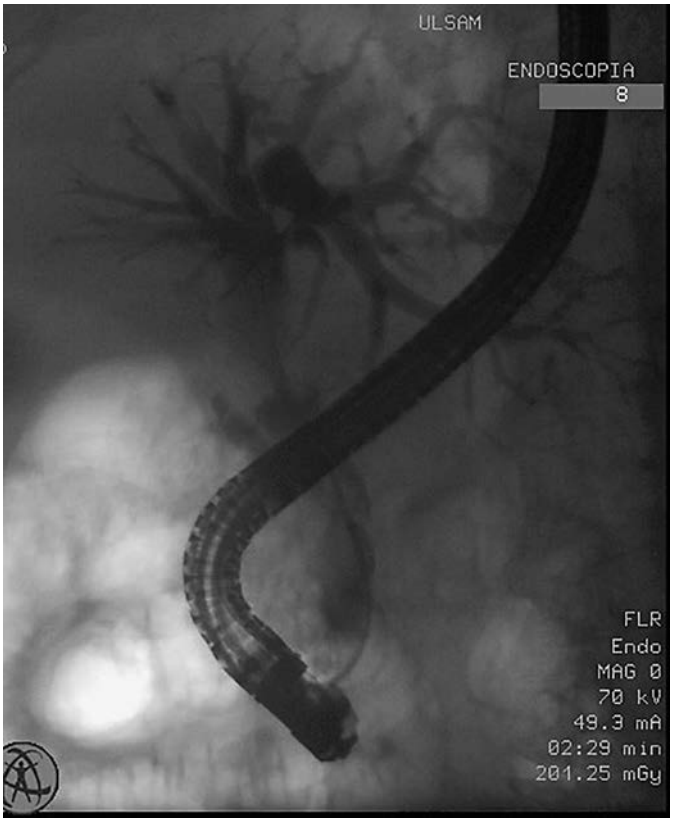

Fig. 2. Cholangiography showing a large stone causing compression of the common hepatic duct.

are treated surgically [1–3]. The use of cholangioscopy-guided lithotripsy with the Spyglass platform was already described in the treatment of patients with Mirizzi syndrome in some case reports [3–5].

Statement of Ethics

The subject has given her written informed consent to publish their case (including publication of images) that is stored in the archives of the department. This article is exempted from ethical approval due to local guidelines. The data regarding this case are not publicly available due to containing information that could compromise the privacy of the patient but are available from M.M. (corresponding author e-mail) upon reasonable request.

Conflict of Interest Statement

Authors declare no conflict of interests for this article.

Funding Sources

This study did not require any funding.

Author Contributions

Marta Moreira, Ana Catarina Carvalho wrote the manuscript. Isabel Tarrio and Alda João Andrade helped in the video edition. Tarcísio Araújo and Luis Lopes were responsible for the revision of its contents.

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GE – Portuguese Journal of Gastroenterology

Endoscopic Snapshot

GE Port J Gastroenterol 2024;31:212–214
DOI: 10.1159/000533931

Received: May 21, 2023
Accepted: July 31, 2023
Published online: September 29, 2023

Endoscopic Extraction of Two Giant Stone Bezoars Using Mechanical and Laser Lithotripsy

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Keywords
Stone bezoars · Lithotripsy · Laser · Endoscopy

Remoção endoscópica de dois bezoares gigantes petrificados com recurso a litotrícia mecânica e por laser

Palavras Chave
Bezoares petrificados · Litotrícia · Laser · Endoscopia

An 80-year-old woman with iron-deficiency anaemia underwent an outpatient upper gastrointestinal endoscopy, presenting two large petrified bodies with 60 mm and 90 mm length in the gastric lumen, associated with a 12 mm ulcer in the incisura (Fig. 1). Past medical history was relevant for type 2 diabetes mellitus and ruled out previous gastric surgeries.

The patient was referred to our hospital and although liver tests and abdominal ultrasound were normal, she performed a magnetic resonance cholangiopancreatography that excluded a cholecystogastric fistula or any fistulous tract between the biliary tree and the stomach. In spite of being asymptomatic, considering the advanced age and high surgery risk, endoscopic extraction was scheduled. A double-channel gastroscope was used for the procedure, which was performed in two sessions (online suppl. video 1; for all online suppl. material, see https://doi.org/10.1159/000533931). Endoscopic reassessment confirmed the presence of two bulky, hard, and rounded stones with smooth surface impossible to be removed directly using standard retrieval devices. The 60 mm stone was fragmented from the periphery using the LithoCrush V™ mechanical lithotriptor (Fig. 2a, b), and all fragments were extracted with a RothNet® during approximately 30 min. However, the 90 mm stone was too thick and round and could not be grasped with any of the available commercially baskets. Fulguration using bipolar and argon plasma coagulation probes at high potencies (120 W) was unsuccessful, with rapid loss of the endoscopic field of view due to smoke. Thus, laser lithotripsy was programed for a second intervention after 3 weeks. Using Auriga™ XL holmium laser and LightTrail™ fibre (600 μm; 120 W) from Boston Scientific, usually applied in urologic surgery, the stone was dissolved,

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producing smaller fragments that could be further fragmented with the lithotriptor basket and safely removed (Fig. 2c). The procedure was performed in an outpatient setting, under deep sedation and has taken almost 3 h. No associated complications were observed and the patient was further discharged. Pathological analysis was suggestive of phytobezoar. Low-fibre diet was recommended and proton-pump inhibitor prescribed for ulcer healing. One month later, the control endoscopy presented no residual stones or mucosa ulceration (Fig. 3).

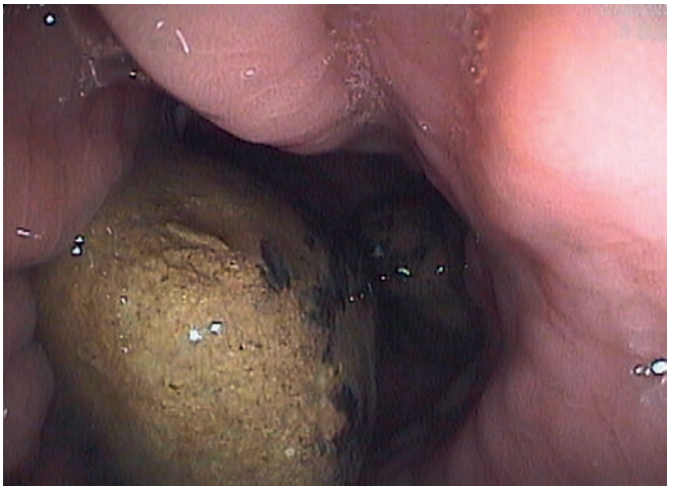

Fig. 1. Two petrified bodies with 60 mm and 90 mm length in the gastric lumen.

Gastric bezoars are foreign bodies resulting from accumulation of undigested material, most commonly vegetable fibres, being rarely associated with severe gastrointestinal complications. Treatment includes chemical dissolution with agents like CocaCola® or acetylcysteine, prokinetics, endoscopic removal, and surgery. Endoscopic therapy involves fragmenting the bezoar using different mechanisms, most commonly forceps, snares, baskets, and argon plasma coagulation [1]. Although endoscopic treatment is not standardized, a minority of cases managed using laser lithotripsy were reported [2–5]. The authors describe a unique case of two giant gastric bezoars successfully treated through laser and mechanic lithotripsy.

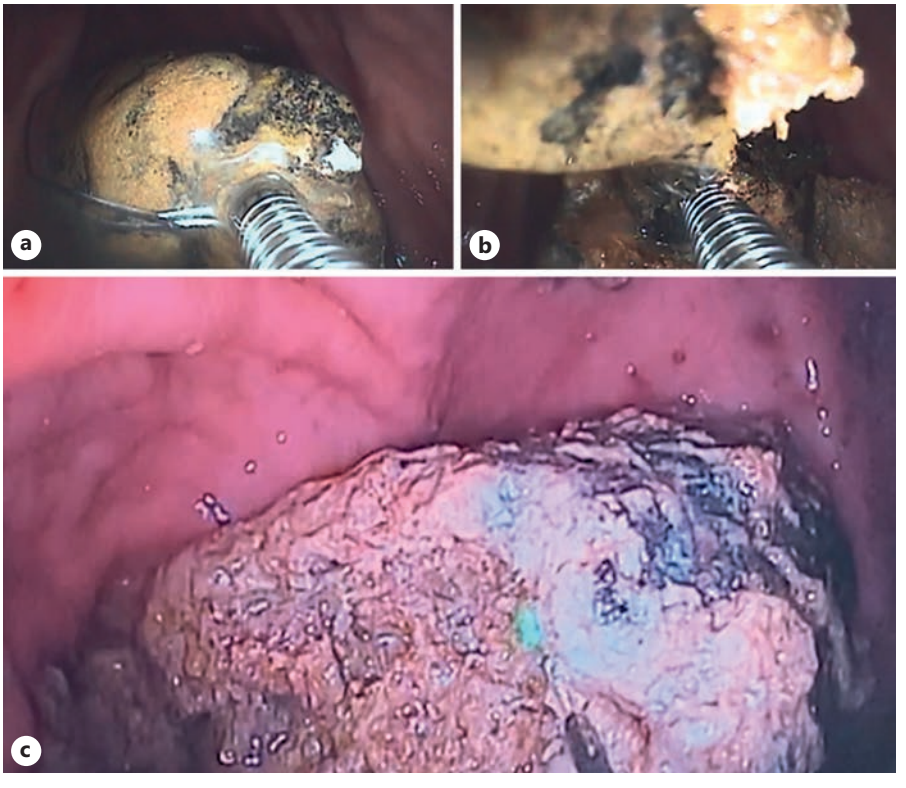

Fig. 2. a–c Mechanical lithotripsy using a Dormia basket and laser lithotripsy using holmium laser.

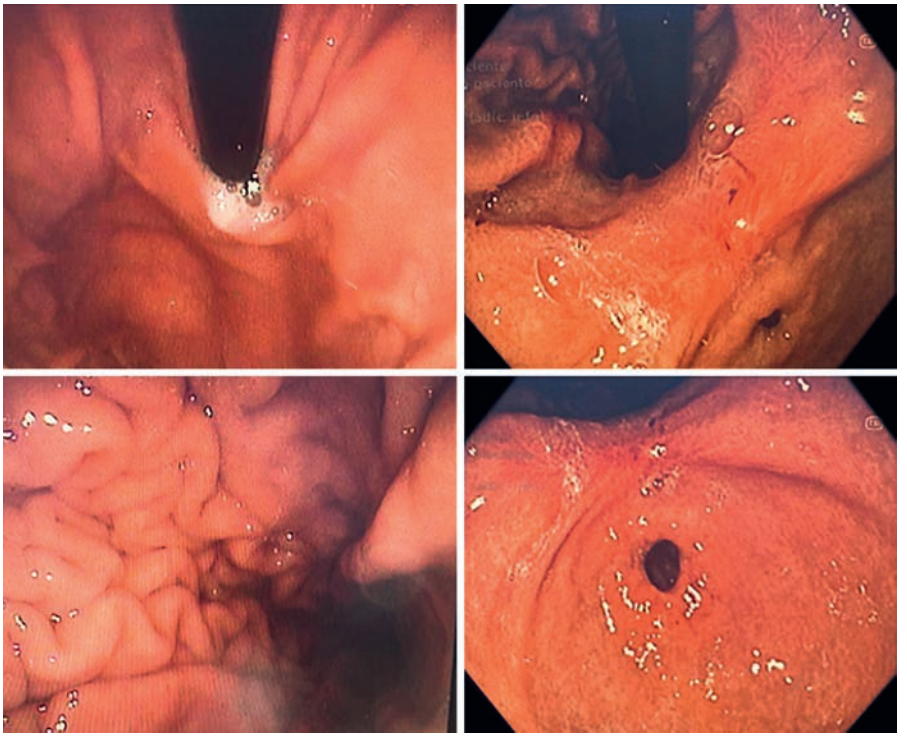

Fig. 3. Gastric lumen with no residual lesions after the endoscopic procedure.

Statement of Ethics

The authors have no ethical conflicts to disclose. Ethical approval was not required for this study, in accordance with local/national guidelines. The patient has given the informed consent for publication of the present case.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

The authors have no funding sources to disclose.

Author Contributions

Carla Oliveira was responsible for material preparation, data collection, and the first draft of the manuscript. Gonçalo Nunes performed the endoscopic procedure, read, and approved the final manuscript. Francisco Vara-Luiz, Gabriel Oliveira, Ana Nunes, and Jorge Fonseca read and approved the final manuscript.

Data Availability Statement

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

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GE – Portuguese Journal of Gastroenterology

Endoscopic Snapshot

GE Port J Gastroenterol 2024;31:215–216
DOI: 10.1159/000534801

Received: August 4, 2023
Accepted: October 9, 2023
Published online: November 16, 2023

Percutaneous Endoscopic Sigmoidopexy: Still a Way to Go

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Keywords
Percutaneous endoscopic sigmoidopexy · Sigmoid volvulus · Colonoscopy

Sigmoidopexia endoscópica percutânea: um caminho ainda a percorrer

Palavras Chave
Sigmoidopexia endoscópica percutânea · Vólvulo do simgoide · Colonoscopia

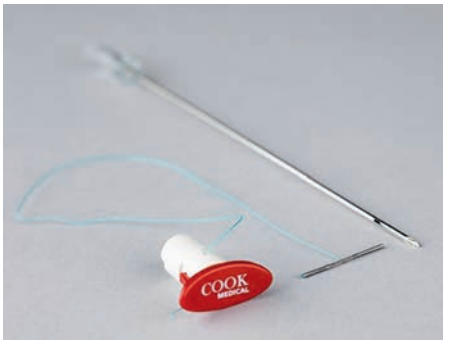

Fig. 1. Entuit Scure system (Cook Medical®).

An 85-year-old man with a past medical history of Parkinson's disease, ischemic cardiomyopathy, and osteoarticular pathology presented to the emergency department with acute colonic obstruction. Plain abdominal radiograph showed a sigmoid volvulus, and endoscopic decompression was performed. Ten days later, the patient presented a new episode of sigmoid volvulus. Endoscopic detorsion was repeated. Given the poor performance status and advanced dementia, the patient was considered unfit of surgery. After a multidisciplinary team discussion, it was decided to perform a percutaneous endoscopic sigmoidopexy (PES), and bowel preparation was initiated.

Cefazolin was administered 30 min before the procedure. A complete colonoscopy was performed under sedation with midazolam. The patient was then mobilized into supine position, so that it was possible to identify the transillumination through the abdominal wall in the site of the sigmoid colon. The abdominal operator performed digital compression to assure that the bowel wall was in contact with the abdominal wall. Following lidocaine injection, the abdominal operator punctured the distal sigmoid colon wall under endoscopic guidance, using three Entuit Scure systems, Cook Medical® (Fig. 1) with a 1-cm distance between each other in a triangular disposition (online suppl. Video 1; for all online suppl. material, see https://doi.org/10.1159/000534801). Another fixation was made in the proximal sigmoid colon using the same technique (Fig. 2a, b).

An abdominal radiograph was performed on the day of the procedure, with no evidence of complications besides mild pneumoperitoneum (Fig. 2c). The patient completed

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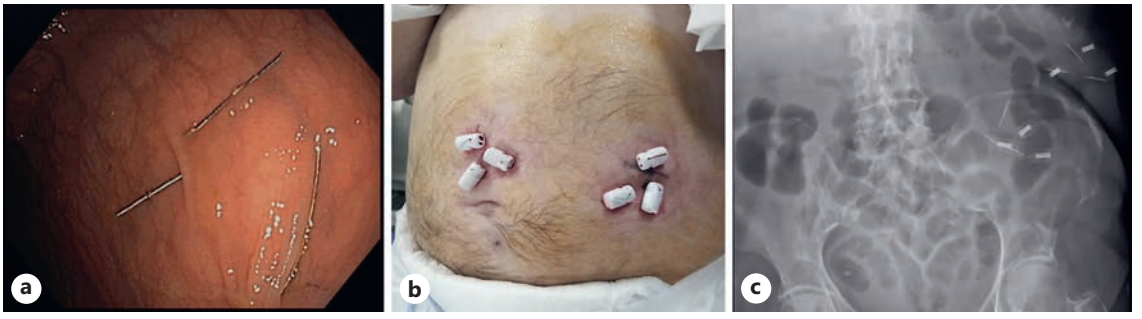

Fig. 2. Fixation of sigmoid colon to the abdominal wall in a triangular disposition. **a** Endoscopic view. **b** External view. **c** Radiological view.

5 days of prophylactic antibiotic therapy (ciprofloxacin and metronidazole). Except for mild abdominal pain, there were no complications. After 4 months of follow-up, there was no further recurrence of the sigmoid volvulus.

The treatment of recurrent sigmoid volvulus typically involves endoscopic decompression followed by surgical resection due to the high risk of recurrence [1]. However, most cases occur in elderly patients with multiple comorbidities who are not suitable candidates for surgery. PES has been seldom described as an effective and safe procedure to prevent the recurrence of sigmoid volvulus in selected patients who are non-surgical candidates [2, 3]. We present a successful case of PES as an alternative in the treatment of recurrent sigmoid volvulus, using a new device, that is, equally effective but more accessible and practical.

Statement of Ethics

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

Conflict of Interest Statement

The authors have no disclosures to report.

Funding Sources

The authors have no funding sources to declare.

Authors contributions

Isabel Garrido did literature review and drafted the manuscript. Isabel Garrido, Armando Peixoto, and Guilherme Macedo have critically revised and finalized the manuscript. All authors have approved the final version of the 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.

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GE – Portuguese Journal of Gastroenterology

Images in Gastroenterology and Hepatology

GE Port J Gastroenterol 2024;31:217–220
DOI: 10.1159/000534081

Received: March 24, 2023
Accepted: July 25, 2023
Published online: October 20, 2023

Chondroepithelial Choristoma: A Rare Cause of Congenital Esophageal Stenosis

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Keywords
Choristoma · Ectopic tissue · Esophageal stenosis

Coristoma condroepitelial: uma causa rara de estenose esofágica congénita

Palavras Chave
Coristoma · Tecido ectópico · Estenose esofágica

A female patient, aged 3 years, was referred to our hospital on account of a persistent history of food impaction dating back to when she was 9 months old. This condition was alleviated through induced emesis, and the patient exhibited limited tolerance for solid foods, exclusively consuming liquids, leading to inadequate weight gain and falling below the third percentile. Notably, there were no reported instances of regurgitation.

A barium swallow test was conducted, revealing a posterior indentation on the upper thoracic esophagus, with a regular progression of the contrast material. This finding suggested the presence of an aberrant right subclavian artery, also known as *arteria lusoria*. Additionally, stenosis of the distal esophagus was observed, above the phrenic ampulla, characterized by delayed progression of the contrast agent (Fig. 1).

Esophagogastroduodenoscopy was performed, uncovering, in the upper third of the esophagus, a pulsatile protrusion of the posterior wall. In the distal esophagus, a stenosis was observed, measuring 4 mm in diameter and 2–3 mm in length (Fig. 2). However, passage of an ultraslim upper endoscope after inflation (5.9 mm) was possible without encountering resistance. The stenosis was found to be untransposable with an 8.8 mm device. Biopsies taken during the procedure did not reveal any pathological findings.

A CT scan was conducted, confirming the presence of an aberrant right subclavian artery causing esophageal compression (Fig. 3). Two millimetric hyperdense images were observed in the distal esophagus, lacking specific characteristics, without significant stenosis (Fig. 3).

Surgeons performed a distal esophagectomy with anastomosis. Histological examination of the resected esophageal wall revealed nodules of respiratory-type cartilage and seromucous glands, compatible with tracheobronchial remnant (TBR) (Fig. 4). The patient has been asymptomatic for almost 2 years after surgery.

Congenital esophageal stenosis (CES) is a constriction of the esophagus present at birth, which may not cause any symptoms in the neonatal period. It is a rare condition. It can be attributed to factors such as TBR, segmental fibromuscular hypertrophy, and membranous diaphragm/stenosis [1]. TBR, also known as choristoma or heterotopy, represents one of the most common causes of lower CES [1].

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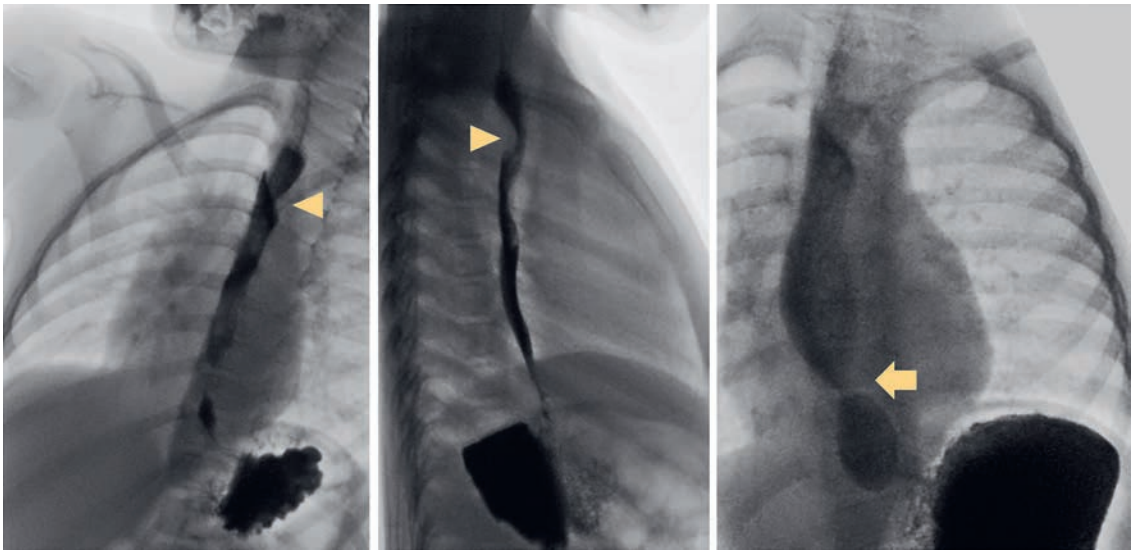

Fig. 1. Barium swallow test with posterior indentation on the upper thoracic esophagus (arrowhead), suggesting the presence of an aberrant right subclavian artery (arteria lusoria) and stenosis of the distal esophagus, above the phrenic ampulla (arrow), with delayed progression of the contrast agent but without complete occlusion.

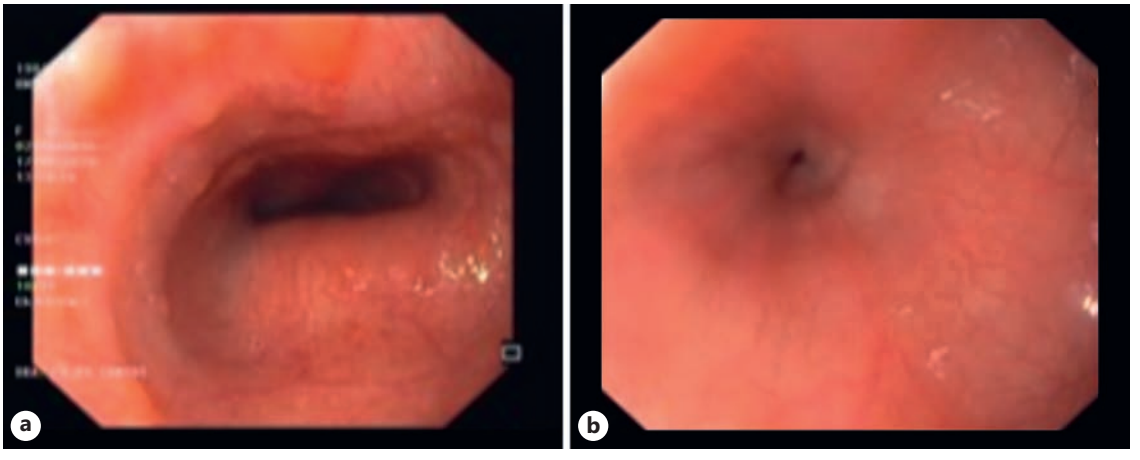

Fig. 2. Esophagoscopy revealing, on the upper third of the esophagus, a protrusion of the posterior wall, pulsatile (**a**), and, on the distal esophagus, a reduction in esophageal diameter (**b**).

The etiology is unknown, although an embryologic origin has been suggested. Failure to separate the esophagus from the respiratory tract on day 25 of gestation can halt cartilage growth, typically near the cardia, within 3 cm [2]. CES is frequently associated with esophageal atresia [3].

Symptoms start during the transition from liquid to solid diets and include dysphagia, regurgitation, and vomiting. The severity of these symptoms correlates with the degree of involvement of the esophageal wall [3].

The diagnosis is suspected from clinical, endoscopic, and esophagographic correlation. These exams enable the evaluation of stenosis severity and associated dilation upstream, while ruling out alternative causes of stenosis [1].

A definitive diagnosis is only achieved through histopathological examination of the resected esophageal segment, which includes the presence of cartilage, seromucous glands, and pseudostratified ciliated columnar epithelium [4]. Surgical excision, either by resection of the stenotic region or by enucleation of the cartilaginous remnants, is the recommended treatment approach [1, 5]. In cases of CES, diagnostic differentiation is essential, to identify the best treatment.

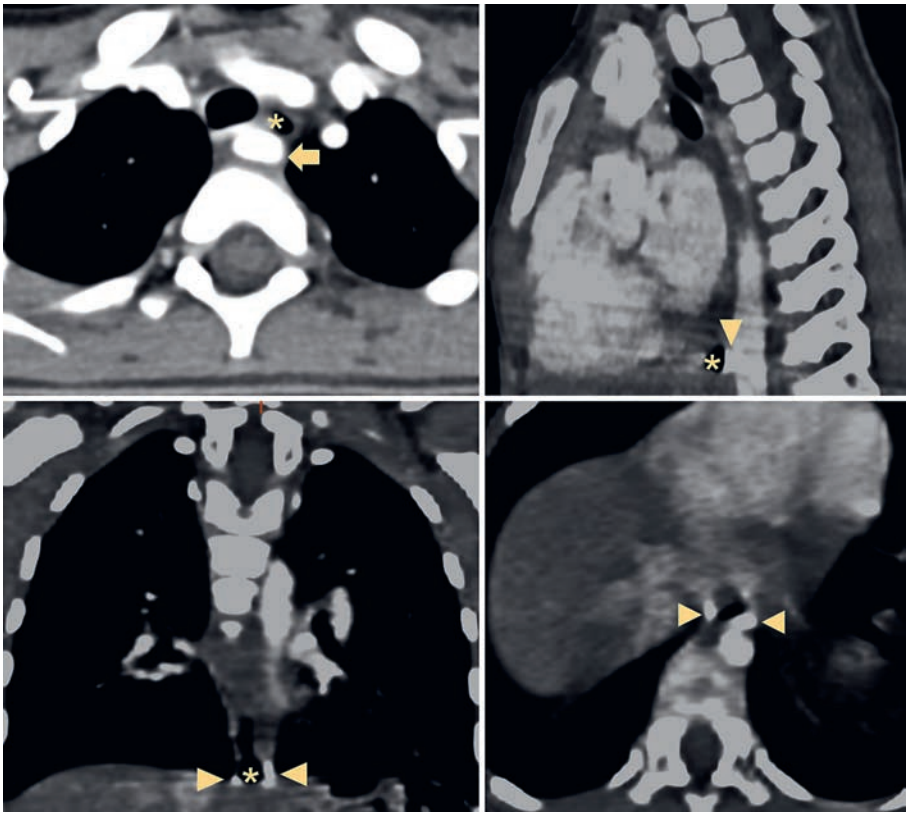

Fig. 3. Chest CT scan shows an aberrant right subclavian artery (arrow), passing around the esophagus (asterisk), with esophageal compression. On the distal esophagus (asterisk), the exam reveals two millimetric hyperdense images (arrowheads), nonspecific, without significant stenosis.

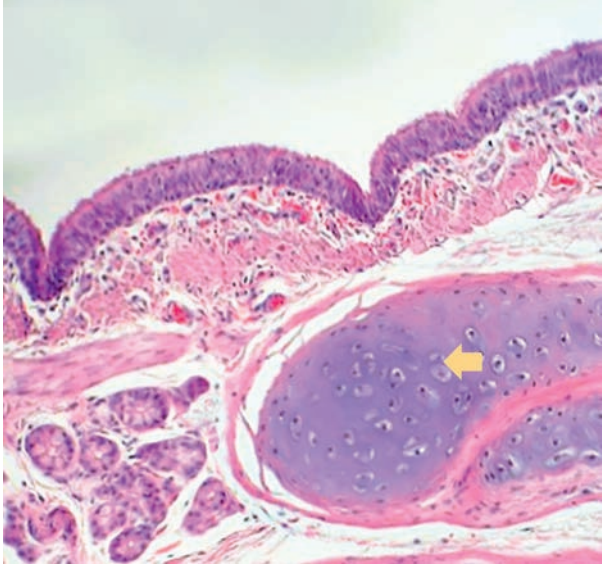

Fig. 4. Histopathology of distal esophagectomy. Ciliated respiratory-type epithelium with a layer of connective tissue, glands, sparse smooth muscle, and a well-defined nodule of cartilage (arrow) (HE, ×200).

Statement of Ethics

Written informed consent was obtained from the parents for publication of the case and accompanying iconography. This type of publication does not need ethical board approval according to national laws.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

No funding was received for this study.

Author Contributions

Data collection was performed by Eugénia Soares, Filipa Marques dos Santos, and Rita Carneiro. Isabel Afonso performed the endoscopy. The draft of the article was made by Filipa Marques dos Santos. Rita Carneiro reviewed the article.

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.

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GE – Portuguese Journal of Gastroenterology

Images in Gastroenterology and Hepatology

GE Port J Gastroenterol 2024;31:221–223
DOI: 10.1159/000534263

Received: August 10, 2023
Accepted: September 11, 2023
Published online: October 25, 2023

Middle-Age New-Onset Dysphagia

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Keywords
Esophageal metastasis · Breast cancer · Endoscopic ultrasonography · Fine-needle biopsy

Disfagia de início recente na meia-idade

Palavras Chave
Metástase esofágica · Cancro da mama · Ultrassonografia endoscópica · Biópsia aspirativa com agulha fina

A 59-year-old woman who underwent radical mastectomy due to multifocal mixed invasive ductal and micropapillary breast carcinoma presented with a 3-month history of progressive dysphagia for solids. After surgery, she underwent adjuvant chemoradiotherapy and hormone therapy, without clinical or radiological signs of recurrence during an 18-year follow-up period.

Gastroscopy and computed tomography were unremarkable. The contrast esophagogram revealed a slight narrowing of the proximal esophagus (besides the physiological aortic arch compression), persistent throughout the examination, but with normal contrast progression. Due to the progressive dysphagia worsening, she was referred to gastroenterology.

Gastroscopy with peri-procedural fluoroscopy was repeated and showed a protruded yellowish area, between 25 and 27 cm from the incisors, suggestive of a submucosal lesion or extrinsic compression (Fig. 1a, b). Fluoroscopic findings were similar to the previous evaluation (Fig. 1c). Endoscopic ultrasound (EUS) revealed a hypoechogenic lesion with well-defined contours and limits, measuring 15.8 × 7.8 mm, originating in the muscle layer and with intimal contact with the aortic arch, without local invasion (Fig. 1d, e). Despite resistance, the scope was able to traverse de stenosis. Then, an EUS-guided 19-gauge fine-needle biopsy (FNB) was performed.

Histopathological examination revealed nuclear overlapping and hyperchromatic aggregates of epithelial cells infiltrating the striated muscle. Strong nuclear staining of estrogen receptors was present in 100% of the neoplastic cells (Fig. 2a, b). These findings were compatible with esophageal metastasis from breast cancer. Palliative treatment with letrozole and ribociclib was initiated, and the patient reported symptomatic improvement.

Esophageal metastasis from breast cancer is rare, with a prevalence of 4.2–5.9% in autopsy studies, despite only 0.59% of patients having dysphagia [1]. A large case series (n = 2,246) reported a 0.4% prevalence of breast cancer esophageal metastases over an 18-year period [2]. The middle third of the esophagus is the

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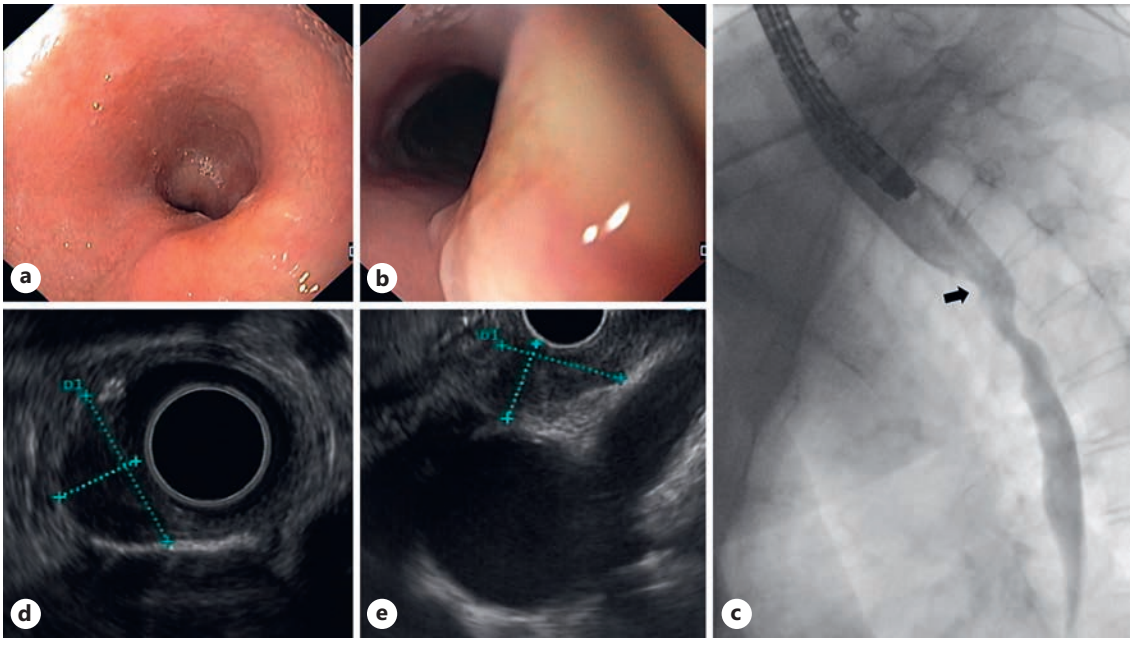

Fig. 1. a, **b** Endoscopic view of an elevated yellowish area covered with normal-appearing mucosa. **c** Normal contrast progression, despite the presence of a 15 mm narrowing of the proximal esophageal lumen (arrow). EUS revealed a hypoechogenic mass with well-defined contours and limits, centered in the muscle layer and with intimal contact with the aortic arch, maintaining the cleavage plane (**d**: radial probe, **e**: linear probe).

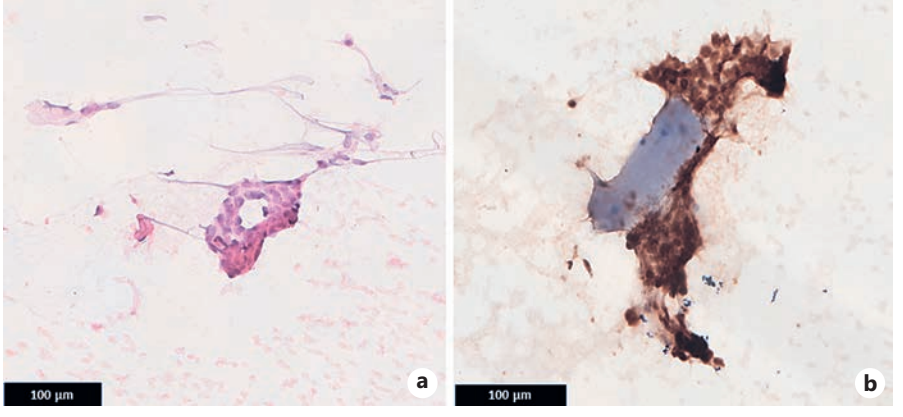

Fig. 2. a Nuclear overlapping and hyperchromatic aggregates of epithelial cells. **b** Neoplastic cells showed strong nuclear staining of estrogen receptors and infiltrate the striated muscle.

most frequently affected site, probably due to the involvement of tracheobronchial lymph nodes and lymphatic drainage into the mediastinum [3]. The average time between the onset of dysphagia and diagnosis is 8 months. Diagnosis may be difficult since esophageal metastatic lesions are almost always located below the mucosal plane, originating from the outside layers to inwards [4]. Thus, standard mucosal biopsy specimens are often not diagnostic. In turn, EUS-FNB can improve diagnostic accuracy [5]. When EUS-FNB is not feasible, mucosal-incision-assisted biopsy or single-incision needle-knife biopsy are valid alternatives. Diagnosis of esophageal metastasis from breast cancer is challenging and should be considered in every patient with a clinical history of this neoplasia, regardless of the follow-up period.

Statement of Ethics

Informed consent was obtained from the patient for publication of the medical case and any accompanying images. Ethical approval by the Ethical Committee was not required due to local laws.

Conflict of Interest Statement

None of the authors acted as reviewer or editor of this article. None of the authors disclosed personal conflicts of interest or financial relationships relevant to this publication.

Funding Sources

The authors have no funding sources to declare.

Author Contributions

Renato Medas and Gany Mussagi prepared the manuscript, did the literature review, and created the first draft. Pedro Moutinho-Ribeiro performed the procedure and supervised the manuscript preparation. Joanne Lopes identified the pathology, prepared histopathology images, and reviewed the manuscript. Guilherme Macedo performed the critical expert review 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.

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GE – Portuguese Journal of Gastroenterology

Retraction Statement

GE Port J Gastroenterol 2024;31:224
DOI: 10.1159/000538229

Published online: March 8, 2024

Retraction Statement

Paper by Chee Yik Chang and Bryan Tan entitled "Splenic Abscess Caused by *Clostridium difficile*" [GE Port J Gastroenterol 2023; https://doi.org/10.1159/000533163]

The article "Splenic Abscess Caused by *Clostridium difficile*" [GE Port J Gastroenterol 2023; https://doi.org/10.1159/000533163] by Chee Yik Chang and Bryan Tan has been retracted by the Publisher and the Editors on behalf of the authors. After publication of the article, the corresponding author contacted the journal and requested retraction of their article due to the absence of ethics committee or review board approval for the publication. While written informed consent was obtained from the patient for the publication of the article, the authors stated that they did not request nor obtain institutional approval for the study prior to submission of their manuscript. The article has therefore been retracted.

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