Portuguese Journal of Gastroenterology

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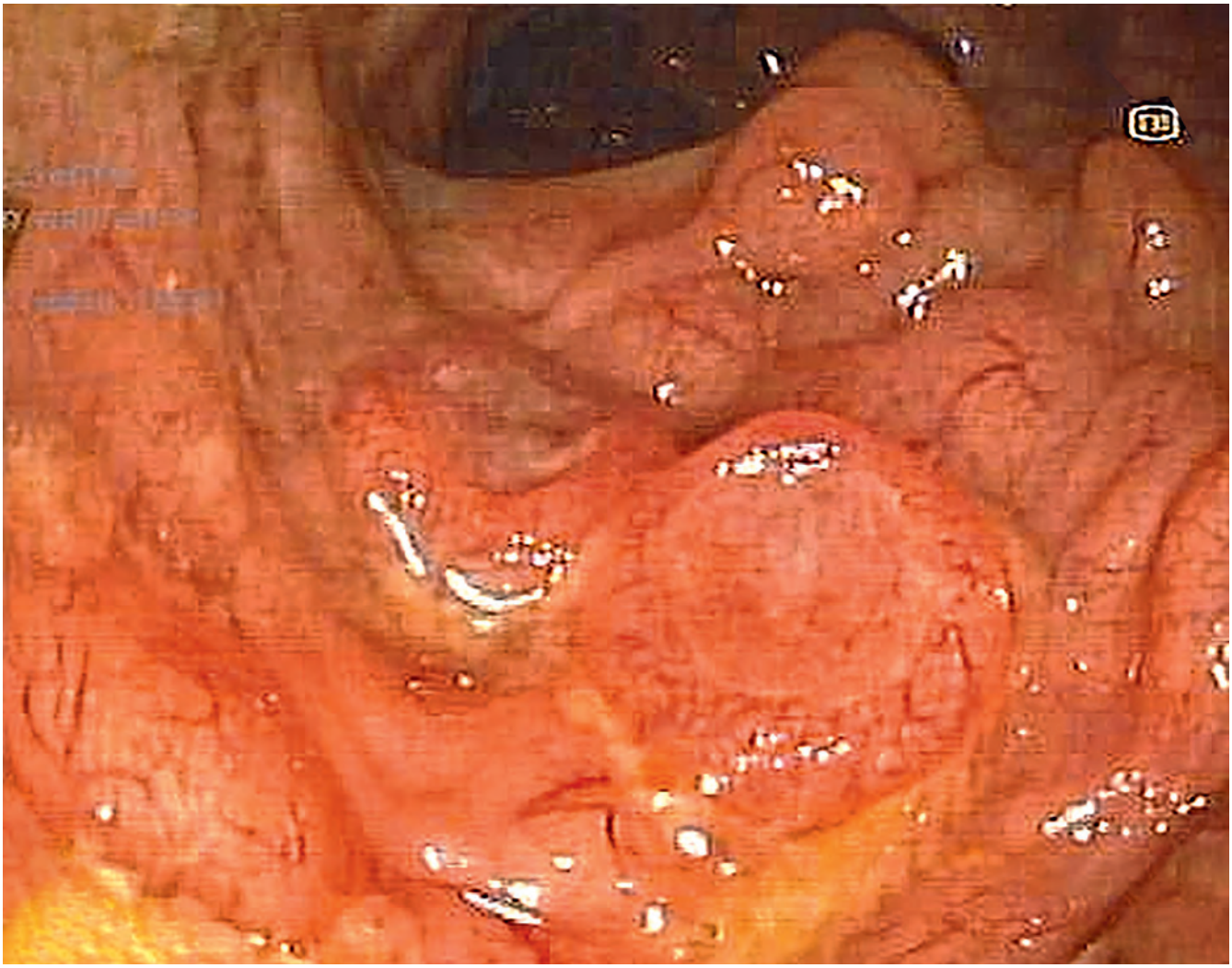

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Aims and Scope

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Review Article

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Current Approach to Dysphagia: A Review Focusing on Esophageal Motility Disorders and Their Treatment

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Keywords
Dysphagia · Esophageal motility · Patient-reported outcomes

Abstract
Background: Dysphagia is a prevalent condition which may severely impact the patient's quality of life. However, there are still lacking standardized therapeutic options for esophageal motility disorders. ***Summary:*** Dysphagia is defined as a subjective sensation of difficulty swallowing which can result from oropharyngeal or esophageal etiologies. Regarding esophageal dysphagia, after excluding structural causes and esophageal mucosal lesions, high-resolution manometry (HRM) is the gold standard for the diagnosis of esophageal motility disorders. HRM has not only improved the sensitivity for detecting achalasia but has also expanded our understanding of spastic and hypomotility disorders of the esophageal body. The Chicago Classification v4.0 uses a hierarchical approach and provides a standardized diagnosis of esophageal motility disorders, allowing a tailored therapeutic approach. Dysphagia is often a long-term health problem that broadly impacts health and well-being and leads to physical and psychosocial disability, namely, malnutrition and aspiration pneumonia, as well as social isolation, depression, and anxiety. Apart from achalasia, most esophageal motility disorders tend to have a benign long-term course with symptoms of dysphagia and noncardiac chest pain that can improve significantly over time. Patient-reported outcomes (PROs) are self-assessment tools that capture the patients' illness experience and help providers better understand symptoms from the patients' perspective. Therefore, PROs have a critical role in providing patient-centered care. ***Key Messages:*** Motility disorders should be ruled out in the presence of nonobstructive esophageal dysphagia, and treatment options should be considered according to the severity of symptoms reported by the patient.

Abordagem atual à disfagia: Uma revisão dos distúrbios da motilidade esofágica e respetivo tratamento

Palavras Chave
Disfagia · Motilidade esofágica · Outcomes reportados pelos doentes

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Resumo

Contexto: A disfagia é uma condição prevalente que poderá ter impacto negativo na qualidade de vida dos doentes. No entanto, a abordagem terapêutica dos distúrbios da motilidade esofágica não está ainda padronizada. ***Sumário:*** A disfagia define-se como uma sensação subjetiva de dificuldade de deglutição que pode resultar de uma etiologia orofaríngea ou esofágica. Na disfagia esofágica, após exclusão de causas estruturais e lesões da mucosa esofágica, o estudo por manometria de alta resolução (MAR) está indicado como avaliação por excelência para o diagnóstico de distúrbios da motilidade esofágica. A implementação da MAR aumentou a sensibilidade para o diagnóstico de acalásia, como também melhorou a nossa compreensão dos distúrbios espásticos e de hipomotilidade do corpo esofágico. A Classificação de Chicago v4.0 utiliza uma abordagem hierárquica fornecendo um diagnóstico padronizado dos distúrbios da motilidade esofágica, o que permite uma abordagem terapêutica adaptada às diferentes condições. Frequentemente manifesta-se como uma condição clínica crónica com amplo impacto na saúde e bem-estar dos afetados, dada as suas consequências físicas e psicossociais. Pode estar associada a complicações graves, incluindo desnutrição e pneumonia por aspiração, bem como isolamento social, depressão e ansiedade, com redução acentuada da qualidade de vida. A maioria dos distúrbios da motilidade esofágica, à exceção da acalásia, tende a ter um curso benigno a longo prazo com sintomas de disfagia e de dor torácica não cardíaca que podem melhorar significativamente ao longo do tempo. Os *outcomes* reportados pelo doente (PRO) são ferramentas de autoavaliação que captam a experiência da doença dos afetados e ajudam os profissionais a entender melhor os sintomas na perspetiva dos doentes. Portanto, os PROs têm um papel crítico na prestação de cuidados centrados no doente. ***Mensagens-Chave:*** Doenças motoras deverão ser excluídas na presença de disfagia esofágica não obstrutiva. A terapêutica instituída deverá ser definida mediante a gravidade dos sintomas reportados pelo doente.

Dysphagia: Epidemiology, Characterization, and Clinical Relevance

Dysphagia is defined as a subjective sensation of difficulty or abnormality of swallowing [1]. It is a common symptom in the general population, with a prevalence of 20% and affecting up to 50% of people over 60 years [2]. From an anatomical point of view, it can result from oropharyngeal or esophageal etiologies, whereas from a pathophysiological perspective, esophageal dysphagia can be caused by organic diseases (benign or malignant) and functional diseases causing impaired physiology (mainly motility) or perception disorders [3].

A focused anamnesis and knowledge of potential diagnoses will help identify the location and type of dysphagia. To distinguish oropharyngeal from esophageal dysphagia, the site at which the patient experiences the symptom is of limited use since dysphagia felt in the throat can also be referred from the esophagus [2]. There are, however, four aspects that predict oropharyngeal dysphagia with an 80% accuracy: delay in initiating swallowing, deglutitive postnasal regurgitation, deglutitive cough, and the need for repetitive swallowing to achieve satisfactory clearance [2]. Oropharyngeal dysphagia can be associated with neurodegenerative conditions, such as Parkinson's disease or dementia, as well as with structural causes, namely, Zenker's diverticulum or osteophytes [3].

Esophageal dysphagia should be characterized according to the types of food that produce symptoms, time course, and associated symptoms. For example, dysphagia to both solids and liquids from the onset of symptoms is probably due to a motility disorder, while dysphagia starting only to solids is usually related to an organic disease leading to a narrowed esophageal lumen. In this last scenario, a progressive evolution of symptoms points out to causes like peptic stricture or esophageal cancer, while an intermittent evolution suggests eosinophilic esophagitis or esophageal ring. On the other hand, patients with motility disorders such as achalasia or distal esophageal spasm (DES) may also exhibit progressive or intermittent dysphagia, respectively (Fig. 1) [2].

Dysphagia is often a life-changing health problem that broadly impacts well-being since it can have both physical and psychosocial health consequences. It is associated with many serious complications including malnutrition, dehydration, aspiration pneumonia, and choking, as well as social isolation, depression, and anxiety which also severely reduce quality of life. For patients with dysphagia, mealtimes are often long, exhausting, and difficult and they might feel they cannot eat in the presence of others. This often leads to diminished motivation to eat, sense of social isolation, increased depression, and poverty in overall nutritional intake [4, 5].

Recognition of the clinical relevance and complications of dysphagia is growing among healthcare professionals in several fields. Furthermore, the emergence of new methods to screen and assess swallow function and

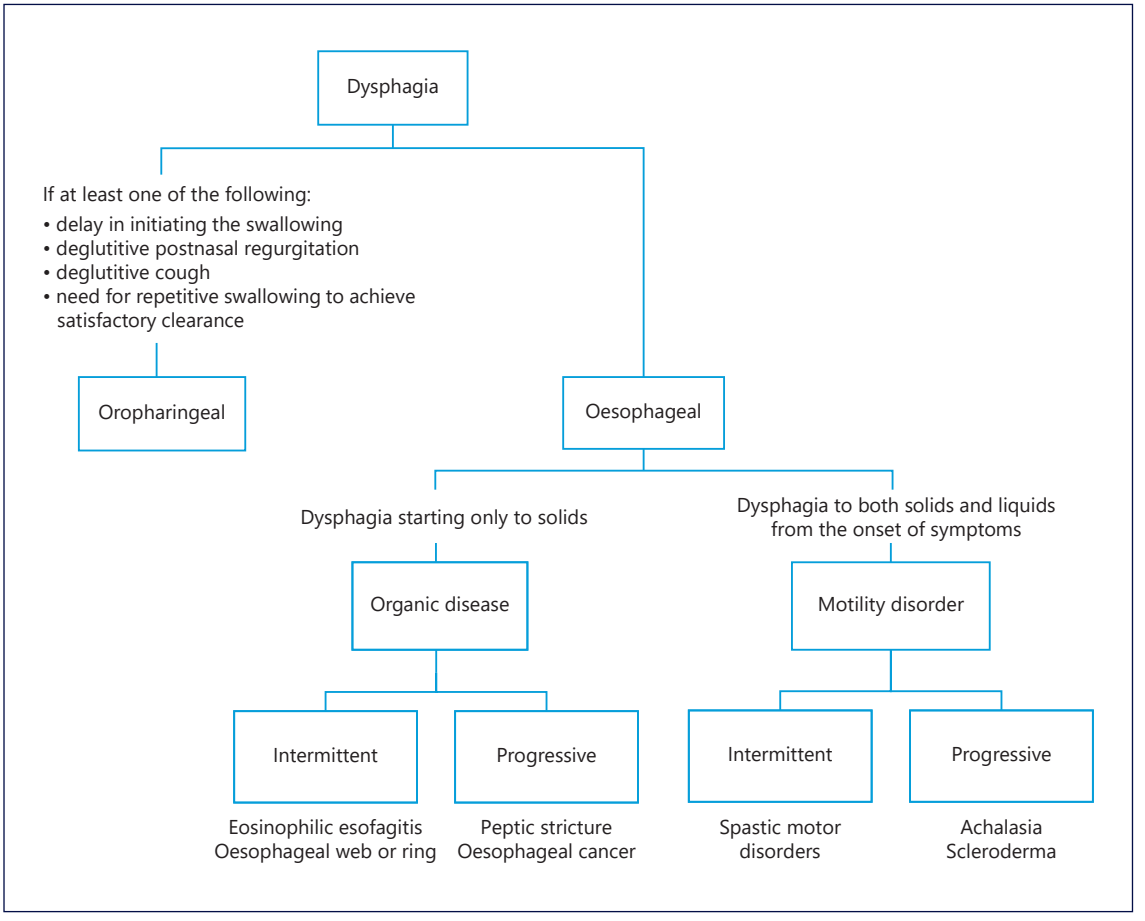

Fig. 1. Clinical approach to dysphagia.

marked advances in understanding the pathophysiology of these conditions are paving the way for a new era of intensive research and active therapeutic strategies for affected patients [3].

Diagnostic Evaluation of Esophageal Dysphagia

Esophageal dysphagia is considered an alarm symptom, with esophagogastroduodenoscopy (EGD) recommended as the first-line diagnostic test, after a detailed clinical history and physical examination [2, 6]. After excluding structural causes and esophageal mucosal lesions, high-resolution manometry (HRM) is indicated [7].

When both EGD with esophageal biopsies and HRM are normal, a barium esophagogram should be performed to exclude subtle strictures not identified by EGD before considering functional dysphagia [2]. Functional lumen imaging probe (FLIP) has been recently recommended as a complementary tool to HRM in the presence of esophagogastric junction outlet obstruction (EGJOO) or other inconclusive patterns [6, 8]. A cardiac cause should obviously be excluded in a patient presenting with retrosternal chest pain [6]. However, acute dysphagia during a meal, normally associated with retrosternal chest pain, can be due to food impaction, often requiring an urgent EGD [2].

Endoscopy

EGD is mandatory and the first diagnostic tool to be performed in the workup of a patient with esophageal dysphagia, excluding conditions that can lead to secondary esophageal motor dysfunction [6, 9]. Certain findings during endoscopy can also be suggestive of motility disorders, such as increased esophageal diameter and difficulty passing the esophagogastric junction (EGJ) [6]. In

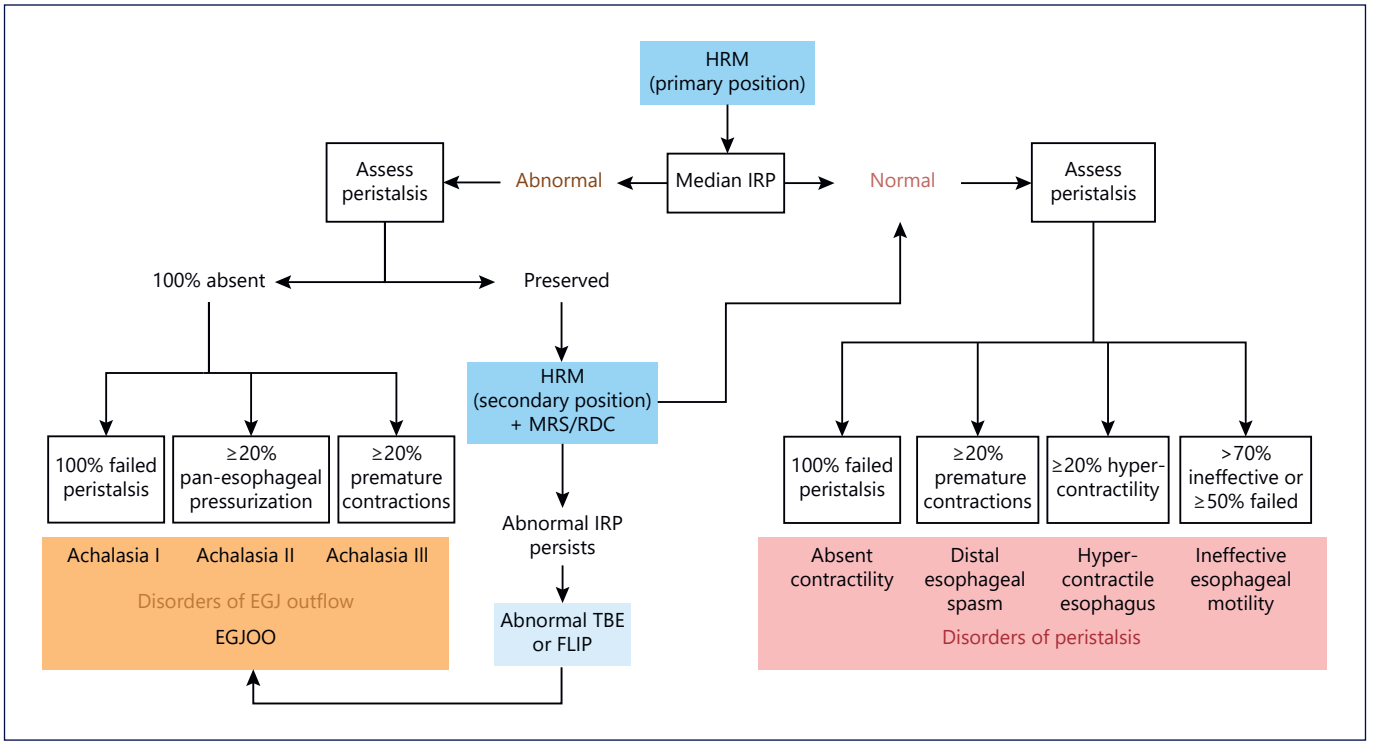

Fig. 2. CC v4.0 for esophageal motility disorders. HRM, high-resolution manometry; IRP, integrated relaxation pressure; MRS, multiple rapid swallow; RDC, rapid drink challenge; EGJ, esophagogastric junction; EGJOO, esophagogastric junction outlet obstruction; TBE, timed barium esophagogram; FLIP, functional lumen imaging probe.

the absence of structural lesions, at least six biopsies from the distal and proximal esophagus, in separate containers, should be performed [8, 10].

High-Resolution Esophageal Manometry

HRM is currently the gold standard for the evaluation of esophageal motor dysfunction [7]. HRM combined with impedance sensors is recommended to assess intrabolus pressure and bolus transit in relation to manometric pressures [7].

HRM Protocol

The recent Chicago Classification (CC) v4.0 introduced a recommended HRM protocol to standardize the procedure across motility laboratories, in order to optimize generalizability and reliability of HRM interpretation (Fig. 2) [11]. According to the CC v4.0, after HRM catheter placement, the study can begin in either the supine or upright position [8]. A minimum of 60 s of rest after catheter placement allows for an adaptation period, followed by a minimum of three deep inspirations to confirm adequate placement, and subsequently a baseline period of at least 30 s to enable identification of anatomic landmarks including the upper esophageal sphincter, lower esophageal sphincter (LES), respiratory inversion point, basal EGJ pressure, and crural diaphragm [8]. A series of ten 5-mL single wet swallows are then performed with a 30-s interval between swallows [8]. In equivocal cases, the patient is then transitioned from supine to upright or vice versa, again with a 60-s adaptation period, three deep inspirations, and a 30-s baseline period, followed by a series of five 5-mL single wet swallows [8]. Data acquisition in both supine and upright positions has been shown to increase diagnostic yield of esophageal motility disorders [12, 13]. Unless the diagnosis is straightforward, positional changes and provocative maneuvers are recommended, such as multiple rapid swallow (MRS) sequences and a rapid drink challenge (RDC) [6, 7, 11].

HRM Metrics

The key metrics assessed by HRM include evaluation of deglutitive relaxation across the LES (integrated re-

laxation pressure) and metrics of esophageal body peristalsis based on contraction (distal contractile integral) and latency of deglutitive inhibition (distal latency) [11].

MRS Sequences

MRS is a simple provocative maneuver that consists in the ingestion of five 2-mL swallows in rapid sequence (<10 s) [6]. This test augments central and peripheral deglutitive inhibition, hence suppressing contractions in the esophageal body and inducing relaxation of the LES [6]. The last swallow of the MRS series is followed by a powerful peristaltic sequence in the esophageal body together with a contraction in the LES and reflects the contraction reserve in the esophageal body [6, 7]. An intact response to MRS is defined as the absence of esophageal body contractility with complete deglutitive relaxation of the LES during the repetitive swallows, with an augmented post-MRS contraction [6]. Abnormal results include incomplete inhibition of the EGJ, peristaltic contractility during MRS, or an abnormal contraction after MRS [6, 7]. The failure of post-MRS peristaltic augmentation, as seen in ineffective esophageal motility (IEM), is associated with higher acid exposure time in non-erosive gastroesophageal reflux disease (GERD), late postoperative dysphagia following antireflux surgery (ARS), presence or development of IEM after ARS, and possibly failure of promotility agents [6, 7].

Rapid Drink Challenge

RDC consists in the administration of 200 mL of water and is performed in the upright position and mainly applied for evaluation of EGJ resistance [7]. As with MRS, RDC is not necessary in the majority of cases but is a complementary tool in patients with suspected EGJOO and in achalasia with inconclusive or discordant findings with single wet swallows [7].

Functional Lumen Imaging Probe

FLIP is an assessment tool used for measuring the mechanical properties of the gastrointestinal wall within a specific area, mostly used in the esophagus as a diagnostic device to assess its physiology [6]. FLIP catheter uses high-resolution impedance planimetry during volume-controlled distension to measure esophageal cross-sectional area and distensibility [6]. It is nowadays recommended as a complementary tool to HRM in the presence of suspected EGJOO or other inconclusive manometric patterns [6, 8]. The most recent FLIP v2.0 converts the readings to color-coded lumina diameter in real-time plots, enabling evaluation of distensibility index (DI) across the EGJ (measuring the relationship between the cross-sectional area over the distensive pressure to generate luminal distensibility) as well as contractile response to distension in the esophageal body [6, 14]. Studies in healthy volunteers suggest that a normal EGJ distensibility index (EGJ-DI) is >2.8 mm^2/mm Hg and normal EGJ diameter is >13 mm [15]. The presence of repetitive antegrade contractions is considered as a normal response to distension [16]. A reduction in EGJ-DI and/or diameter is often seen in patients with EGJOO. EGJ-DI of <2 mm^2/mm Hg is considered definitely abnormal, whereas EGJ diameter of <13 mm is likely abnormal and can serve as a supportive measure when EGJ-DI is indeterminate (2–3 mm^2/mm Hg) [15]. FLIP has been demonstrated to predict treatment outcomes and to have a guiding role in therapeutic interventions [17, 18]. Intraoperative use of FLIP in patients undergoing peroral endoscopic myotomy (POEM) resulted in additional real-time myotomy in 65% of cases and improved clinical outcomes [19]. FLIP has also performed superiorly to HRM in the evaluation of bolus emptying [20]. The DI on FLIP has been demonstrated to be a useful measure of EGJ opening in achalasia-treated patients [20]. While the role of FLIP as a first-line tool for evaluation of esophageal motility is still evolving, its role as a supportive test as well as monitoring post-treatment outcomes is increasingly appreciated.

Barium Esophagram

Barium esophagogram consists of the radiographic imaging evaluation of bolus transport through the esophagus into the gastric lumen after ingesting barium contrast, providing information regarding upper esophageal sphincter function, esophageal peristalsis, and bolus clearance through the EGJ [6]. It remains as an important diagnostic test in patients with dysphagia since it can identify structural lesions such as strictures and help identify major esophageal motility disorders [6]. However, the overall sensitivity for the diagnosis of esophageal motility disorders is relatively low (56–69%) [21, 22]. Addition of 13-mm barium tablet to the esophagram protocol along with evaluation of esophageal emptying (timed barium esophagram) at 1, 2, and 5 min can increase sensitivity and also be used to monitor treatment response in disorders of EGJOO [23].

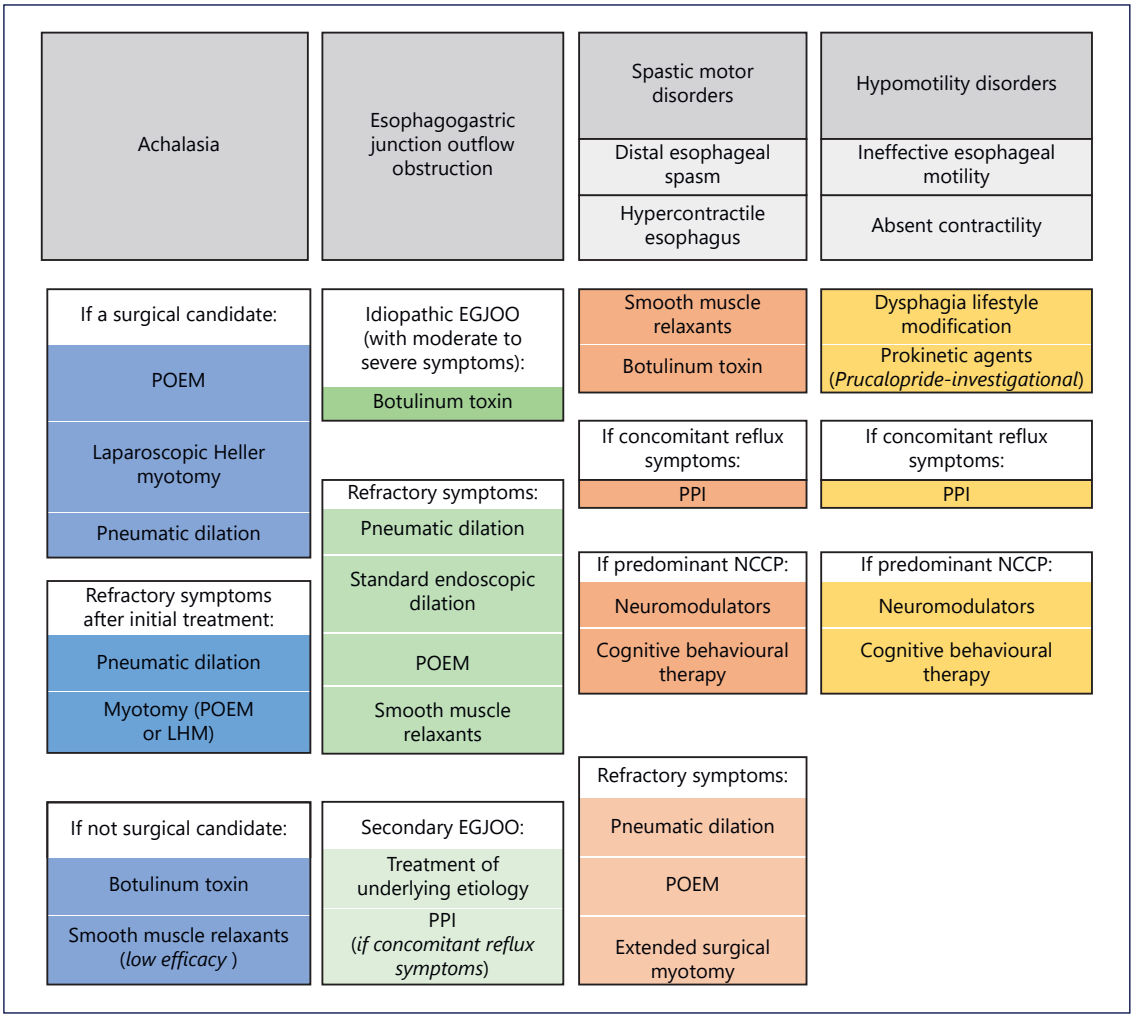

Fig. 3. Treatment options in patients with esophageal motility disorders. CCB, calcium channel blockers; EGJOO, esophagogastric junction outlet obstruction; LHM, laparoscopic Heller myotomy; NCCP, noncardiac chest pain; POEM, peroral endoscopic myotomy; PPI, proton pump inhibitor.

Treatment of Esophageal Motility Disorders

Achalasia and EGJ Outflow Obstruction

Achalasia management is aimed at decreasing the resting pressure of the LES and depends on achalasia type, institutional expertise, patient's surgical risk, and preferences (Fig. 3). For patients with acceptable surgical risk, pneumatic dilation (PD), POEM, and laparoscopic Heller myotomy (LHM) show similar initial success rates (approximately 90%) and are considered first-line options for type I and II achalasia. In general, type II achalasia responds better to all alternatives [6]. For type III achalasia, POEM is preferred compared to LHM (response rate 93% vs. 71%) as it enables a more precise and longer myotomy, extending above the LES and targeting areas of spasticity, tailored to the findings on HRM [24]. Moreover, POEM is proposed to be advantageous for patients with an anatomically abnormal esophagus (dilated or sigmoid) or refractory to previous conventional treatments [24, 25]. POEM can be performed on both the anterior and posterior sides of the esophagus, with similar efficacy and rate of post-procedural reflux [26, 27]. When compared to POEM, LHM with partial fundoplication comprises higher serious adverse events rate (7 vs. 2%), except for lower reflux esophagitis (44 vs. 29%) [28]. In a recent meta-analysis, including nine randomized controlled trials comparing POEM, LHM, and PD, both POEM and LHM showed a lower rate of treatment failure, followed

Table 1. Pharmacological treatments for spastic motor disorders and hypomotility disorders

	Medication	Dosage	Studies
Smooth muscle relaxants	Nitrates	Isosorbide dinitrate 5 mg SL 15 min before meals Nitroglycerin 0.4 mg SL 15 min before meals	Small uncontrolled studies show symptomatic improvement in diffuse esophageal spasm [65]
	Calcium channel blockers	Diltiazem 60–90 mg four times a day Nifedipine 10 mg 30 min before meals	RCT: diltiazem significantly lowered distal esophageal peristaltic pressure and NCCP in nutcracker esophagus [66] RCT: nifedipine significantly reduced the frequency of dysphagia in achalasia [67]
TCA	Imipramine	10–25 mg id at night, titrating to 50–75 mg after 4 weeks if no response	RCT: statistically significant reduction in NCCP [45]
	Amitriptyline	10–25 mg once a day at night	RCT: in combination with PPI significant reduction in NCCP compared to PPI alone [68]
SNRI	Venlafaxine	75 mg once a day	RCT: statistically significant reduction in NCCP [45]
SSRI	Sertraline	50–200 mg once a day	RCT: statistically significant reduction in NCCP [45]
	Trazodone	100–150 mg once a day	RCT: no statistically significant reduction in NCCP [45]

TCA, tricyclic antidepressants; SNRI, serotonin and norepinephrine reuptake inhibitors; SSRI, selective serotonin reuptake inhibitors; SL, sublingual; NCCP, noncardiac chest pain; RCT, randomized controlled trial; PPI, proton pump inhibitor.

by LHM in comparison to PD, but neither POEM nor LHM was significantly more effective than the other. There was no significant difference in the rate of adverse events, need for re-intervention or surgery, or GERD. LHM showed the lower rate of GERD and PD the lower rate of erosive esophagitis, with no statistical significance [29]. Another meta-analysis showed that POEM had a significantly better intervention success than LHM but was associated with an increased risk of GERD [30]. To overcome post-POEM GERD, a pilot study including 21 patients was conducted in which an endoscopic fundoplication was added to the standard POEM procedure, demonstrating technical success in all cases without complications [31].

Patients' comorbidities should be considered when choosing an intervention. Indeed, if a medium to large hiatal hernia is present, LHM with partial fundoplication should be preferred in order to concomitantly correct the hiatus defect [6].

PD presents as the most cost-effective and less invasive procedure, with low rates of perforation (3%) and post-procedural reflux esophagitis (7%) [32–34]. However, its effect weakens over time, with a 90% success rate at 6 months decreasing to 44% at 6 years.

For refractory symptoms after initial treatment, if a myotomy (POEM or LHM) was performed, available options include PD or redo myotomy, using either the same or an alternative myotomy technique [35, 36]; if PD was performed, the patient may undergo repeated PD or myotomy.

The recently developed EsoFLIP integrates impedance planimetry into a dilator balloon and might prove to be a useful tool in the treatment toolbox of esophageal motility disorders. By providing real-time monitoring of therapeutic dilation as it is being performed, EsoFLIP can possibly enhance performance of dilation by confirming appropriate positioning, but further studies are needed [37].

If the patient is not a surgical candidate, botulinum toxin (BTX) injection should be considered. Injection of BTX into the LES is a simple procedure, inducing immediate symptomatic relief (79%). However, about half of patients need retreatment in less than a year [38]. Moreover, multiple treatment sessions may induce mucosal fibrosis and compromise subsequent interventions [39].

Regarding pharmacological treatment, options include calcium channel blockers (nifedipine) and nitrates (isosorbide dinitrate). However, efficacy is lower and the rate of adverse effects is not negligible, with loss of clinical response over time [6, 40]. Therefore, pharmacotherapy should be used only for patients with achalasia who are not candidates for definitive therapies and have failed BTX injection.

EGJOO comprises a heterogeneous group of diseases. For secondary EGJOO, treatment should target the underlying etiology. Concerning idiopathic EGJOO, it is es-

timated that most patients with mild symptoms will demonstrate spontaneous resolution [41]. Therefore, treatment is only considered for patients with moderate to severe symptoms and should focus on the dominant symptom.

BTX injection is an adequate initial treatment choice. The pooled response rate was 63.6% in six series using the CC v3.0. However, response durability may be limited [42]. Standard endoscopic dilation showed a response rate of 55.6–100% (pooled response rate 69.6%) and PD using a 30-mm balloon or larger showed a pooled response rate of 71.8% [42, 43]. POEM may also have a possible role. In a small retrospective study, POEM was associated with a clinical success rate of 93%, with normalization of integrated relaxation pressure on post-POEM HRM in 71% of the patients with EGJOO [44].

Pharmacological treatments such as smooth muscle relaxants are generally ineffective (pooled response rate 30%) [42]. If noncardiac chest pain is the predominant symptom, tricyclic antidepressants (amitriptyline or imipramine), venlafaxine, and sertraline may be considered [6, 45] (Table 1). Proton pump inhibitors (PPIs) should be used to treat concomitant reflux symptoms.

Spastic Motor Disorders

First-line therapies for spastic disorders (DES and hypercontractile esophagus) include pharmacological treatments such as smooth muscle relaxants and, if noncardiac chest pain is the dominant symptom, neuromodulators may also be effective [6, 45] (Table 1). Furthermore, due to the potential overlap between GERD and spastic disorders, for patients with concomitant reflux symptoms, a trial of PPI is recommended [6, 46] (Fig. 3).

For refractory symptoms, empirical PD directed to subtle strictures or luminal remodeling might be an option, with a reported response rate of 70% [47]. BTX injections at the level of the EGJ and at the distal esophagus in patients with spastic disorders have also demonstrated a 1-month response rate of 50% that fell for 30% after 1 year [48].

POEM and surgical myotomy have also been proposed for highly selected patients with spastic disorders with an obstructive physiology. In a meta-analysis, response rates as high as 88 and 72% have been proposed for POEM with extended myotomy in the context of DES and hypercontractile esophagus, respectively, with a low rate of adverse events (14%) [49]. The extended surgical myotomy also demonstrated high clinical efficacy in a subset of 20 patients with DES [50].

Hypomotility Disorders

There are no drugs capable of restoring esophageal smooth muscle contractility. Moreover, there is no clear indication when IEM needs management since the symptomatic correlation is inconsistent. Diet and lifestyle modification, such as chewing carefully, sitting upright in erect position, chasing solid bolus with liquids, and effective control of GERD, is the mainstay of treatment (Fig. 3). Besides PPI, newer prokinetic agents may prove beneficial. Prucalopride, a selective high-affinity serotonin receptor agonist, approved for chronic idiopathic constipation, increased primary peristaltic wave amplitude in reflux patients [51]. Mosapride, a 5HT-4 agonist, may facilitate secondary peristalsis induced by rapid air distension in patients with IEM, by augmenting sensitivity, but without improvement in primary and secondary esophageal contraction vigor [52]. Buspirone, a mixed dopamine D2 receptor antagonist and partial 5HT-1A agonist, was not more effective than placebo in patients with hypomotility disorders and dysphagia [53]. Metoclopramide and domperidone are not useful [54]. Coping strategies, cognitive and behavioral therapy, and hypnotherapy may be adjunctive therapies [55]. For patients with esophageal hypomotility and GERD symptoms undergoing ARS, except those with absent contractility, complete (Nissen) fundoplication showed similar outcomes compared to partial fundoplication [54].

How to Assess the Severity of Dysphagia (and Select Who to Treat)? The Importance of Patient-Reported Outcomes

When assessing dysphagia, the main goal is to understand the nature of this symptom and its impact on the patient's daily function [56]. These patients often experience decreased quality of life resulting from impaired social and psychological well-being [57–59]. The idea that patients are able to perceive and report their swallowing difficulty is valuable in the management of dysphagia. Accordingly, a major part of dysphagia assessment relies on subjective measures, collected through the application of validated surveys [56].

Evaluation of dysphagia is challenging. Occasionally, it may cause tremendous distress that patients are not able to effectively describe. On the contrary, they may be oblivious to any swallowing difficulty [56, 57, 60, 61]. Although there are many options available for swallowing assessment, including instrumental and noninstrumental tools, patient-reported outcomes (PROs) have a critical role by providing an accurate patient perception toward dysphagia [58, 60, 62, 63].

PROs are self-assessment tools that capture the patients' illness experience and help providers better understand symptoms from the patients' perspective [58, 62, 63]. Regarding dysphagia, PRO can improve clinical outcomes by ascertaining the true individual impact on quality of life. Therefore, these standardized measures are valuable tools for demonstrating treatment effectiveness, directing medical care, and enhancing patient-provider relationship [58, 62, 64].

A systematic review by Patel et al. [62] critically evaluated all dysphagia-related PRO scales for adults. Overall, the dysphagia-related PROs identified demonstrated significant variability in their developmental rigor. There was one general dysphagia PRO measure with exceptional characteristics – PROMIS-GI disrupted swallowing – developed with the goal of evaluating the individual impact of dysphagia independently of etiology or type of dysphagia [62, 64]. Several other high-quality PROs were rigorously developed in specific diseases, namely, FACT-E for esophageal cancer and DSQEoE for eosinophilic esophagitis. One of the most useful applications of PRO is monitoring change in dysphagia over time to compare efficacy of interventions or evaluate the natural history of the condition. However, only a minority of the identified PRO measures demonstrated adequate responsiveness [62].

The relationship between self-perception and objective findings remains to be completely elucidated in dysphagia. PROs complement swallowing assessment, potentially aiding to guide management decisions, also tailored to the underlying etiology [56, 57, 62]. Management of dysphagia is multidisciplinary and involves speech therapists, doctors, nurses, and dietitians. Most importantly, the individual patient should be involved in decision-making throughout assessment and treatment [57, 60, 61]. Naturally, the use of tests cannot replace clinical judgment, which is based on a comprehensive assessment and multidimensional evaluation of dysphagia in a particular individual [57, 63].

Conclusion

Nonobstructive esophageal dysphagia is best characterized by HRM using the hierarchical CC v4.0. Therapeutic approach should be tailored to the underlying condition and considering the impact on patient quality of life. Therefore, PRO may have a critical role by providing an accurate patient perception toward the symptom.

Statement of Ethics

Not applicable to a review article.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

André Mascarenhas, Rui Mendo, Catarina O'Neill, Ana Rita Franco, Raquel Mendes, Inês Simão, and José Pedro Rodrigues wrote the manuscript. José Pedro Rodrigues supervised and coordinated the review.

Data Availability Statement

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

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Technical and Clinical Outcomes of Using a Single Wide-Caliber Double-Pigtail Stent for Endoscopic Ultrasound-Guided Pancreatic Pseudocyst Drainage: A Multicenter Prospective Study

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Keywords

Endoscopic ultrasound · Pancreatic pseudocyst · Pancreatitis · Cystogastrostomy · Single double-pigtail

Abstract

Introduction: Endoscopic ultrasound (EUS)-guided pancreatic cysto-gastrostomy/duodenostomy is the current accepted practice for management of symptomatic pancreatic pseudocysts with insertion of two or more double-pigtail (DP) stents. There is no much work on the efficacy of using a single wide-caliber DP stent, aiming to decrease the time, complications, and accessories used in the procedure. ***Aim of the Work:*** The aim of this study was to assess technical and clinical outcomes of using a single wide-caliber DP stent in EUSguided pancreatic pseudocyst drainage. ***Methodology:*** This multicenter prospective study included 57 patients, from which the 35 patients with symptomatic pancreatic pseudocysts enrolled. Patients with cysts with multiple septations (7 cases) or cyst with >30% necrosis (8 cases) of the cyst content and patients with generalized ascites (4 cases) or patients with major comorbidities (3 cases) were excluded. Patients were followed up within 1 month and 6 months after stent placement to assess complete resolution or a decrease in the sizes of cysts with clinical symptomatic improvement. ***Results:*** From 57 patients, 35 patients (19 females/16 males, median age 40 years) with a symptomatic pancreatic pseudocyst were referred for EUS-guided drainage. All used stents were 10 Fr DP plastic stents. The median duration of the whole procedure was 16 min. Technical success was achieved in all cases. Clinical success was encountered in 32 patients (91.4%) without re-accumulation on follow-up. Minor adverse events were encountered in 3 patients (8.6%) including post-procedure abdominal pain (1 case) and fever (2 cases). ***Conclusion:*** We suggest that using a wide-caliber single-pigtail stent for EUS-guided cystogastrostomy is safe and effective with short procedure time, with reduced risks from the insertion of another stent(s).

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Resultados Técnicos e Clínicos da Utilização de Stent Duplo Pigtail de Grande Calibre para Drenagem Endoscópica de Pseudoquistos Pancreáticos: Estudo Prospetivo Multicêntrico

Palavras Chave
Ecoendoscopia · Pseudoquisto pancreático · Pancreatite · Cistogastrostomia · Stent plástico

Resumo
Introdução: A cistogastrostomia/duodenostomia pancreática guiada por ecoendoscopia (EUS) é atualmente aceite para a abordagem dos pseudoquistos pancreáticos sintomáticos através da inserção de dois ou mais stents duplo pigtail (DP). A evidência é escassa relativamente à eficácia da utilização de apenas um stent duplo pigtail de grande calibre, com o objetivo de diminuir o tempo, as complicações e os dispositivos utilizados no procedimento. ***Objetivo:*** Avaliar os resultados técnicos e clínicos do uso de stent duplo pigtail único de grande calibre na drenagem de pseudoquistos pancreáticos guiada por ecoendoscopia. ***Metodologia:*** Estudo prospetivo multicêntrico incluindo 57 doentes (dos quais 35 com pseudoquistos pancreáticos sintomáticos). Foram excluídos pacientes com quistos multiseptados (7 casos), com necrose >30% (8 casos), com ascite (4 casos) e comorbidades major (3 casos). O follow-up foi ao 1 mês e 6 meses após a colocação do stent para avaliar a resolução completa ou diminuição no tamanhos dos pseudoquistos com melhoria sintomática. ***Resultados:*** Dos 57 doentes, 35 (19 mulheres/16 homens, idade média 40 anos) com pseudoquistos pancreáticos sintomáticos foram submetidos a drenagem guiada por EUS. Todos os stents utilizados foram stents DP plásticos com 10 Fr. A duração mediana do procedimento foi de 16 minutos. O sucesso técnico foi alcançado em todos os casos. Ocorreu sucesso clínico em 32 doentes (91,4%), sem reacumulação no seguimento. Eventos adversos menores ocorreram em 3 doentes (8,6%), incluindo dor abdominal pós-procedimento (1) e febre (2). ***Conclusão:*** Os resultados sugerem que a utilização de stent pigtail único de grande calibre para cistogastrostomia guiada por EUS é segura e eficaz, com tempo de procedimento curto e reduzindo o risco da inserção de outro(s) stent(s).

Introduction

Pancreatic and peripancreatic collection (PPC) is a common complication of acute and chronic pancreatitis. The incidence of PPC in acute pancreatitis is 5–16%; however, in chronic pancreatitis, it may reach 20–40% [1–4]. The majority of peripancreatic fluid collections complicating acute pancreatitis usually resolve spontaneously within 4–6 weeks of the onset of the attack [5]. Nevertheless, PPC associated with chronic pancreatitis might resolve spontaneously only in a minority of cases [6].

According to duration and amount of necrosis, PPC is categorized into four types: acute peripancreatic fluid collection, pseudocyst, acute necrotic collection, and walled-off necrosis (WON) [7]. The unresolved PPC may be asymptomatic or present with epigastric pain, dyspepsia, fever, gastric outlet obstructive symptoms, or biliary obstruction [8]. Symptomatic and long-term unresolved PPC are the common indications for drainage [9].

Unresolved symptomatic PPC management has evolved dramatically over recent years from surgical or percutaneous drainage into minimal-invasive endoscopic approaches [10]. EUS-guided drainage is the favored approach in current management algorithms, having better outcomes compared to non-guided endoscopic, percutaneous, or surgical drainage approaches [11].

For evaluation of PPC, EUS is the preferred method since it can accurately measure the distance between the GI lumen and the pseudocyst with delineation of a safe nonvascular window for drainage using Doppler US [12, 13]. Likewise, the choice of the stent type used for drainage can be directly influenced by the nature of the fluid content detected by EUS. EUS evaluation of the wall might also affect management decision with the necessity to pre-drainage clarification of diagnosis using EUS-FNA when suspecting cystic neoplasms with focally enlarged/thickened wall [14].

Regarding that EUS-guided transmural drainage needs multiple steps and lots of resources, it would be more wise and efficient if the number of steps is to be minimized, providing shorter time for the procedure as well as using fewer resources while maintaining the efficacy and patient safety of the procedure. A systematic review by Bang et al. [15] concluded that current evidence does not favor routine placement of metal stents over conventional plastic stents for transmural drainage of PPC. Additionally, there is a conflict in current practice about the number and caliber of the plastic stents for EUS-guided drainage of PPC [16]. We tried in this study to alleviate this conflict about the sufficient number of

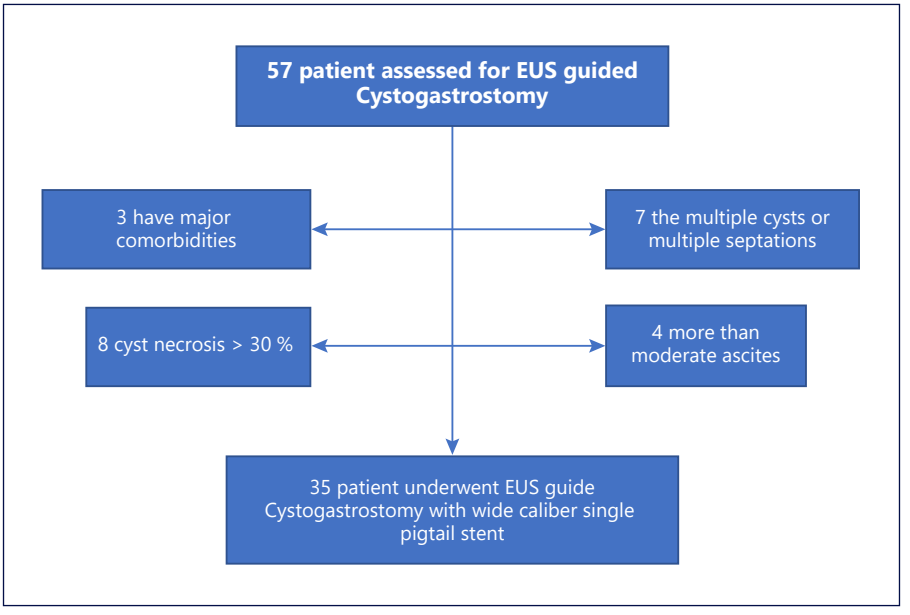

Fig. 1. Flowchart summarizing study population.

plastic stents needed for pancreatic pseudocyst drainage and evaluate the efficacy of using only one wide-diameter double-pigtail (DP) plastic stent.

Methods

This is a multicenter prospective study for cases of EUS-guided PPC drainage in the endoscopy units of four tertiary centers between January 2017 and February 2020. Patients with symptomatic pancreatic pseudocyst that unresolved for at least 6 weeks after the last episode of pancreatitis were included in this study (Fig. 1). We excluded patients with major comorbidities being unfit for general anesthesia (3 cases), those with multiple cyst septation (7 cases), or >30% necrosis of the cyst content (8 cases) and patients with moderate to marked abdominal free fluid (4 cases). Patients' medical data were recruited including detailed history for symptoms of pancreatitis (epigastric pain radiating to the back), onset, duration, severity, and possible etiology of pancreatitis (alcoholic, biliary, etc.), basic laboratory investigations, and radiological evaluation including abdominal ultrasound, contrast-enhanced CT and or MRCP. Before EUS-guided intervention, cyst fluid analysis (fluid amylase, CEA, and cytological examination) was achieved for confirmation of the diagnosis of PPC.

The procedure time was defined as the elapsed time from the first image of the lesion for the EUS procedure which was obtained to the confirmed image of placement of the pigtail stent into the cyst. Technical success was defined as successful and appropriate placement of the DP stent in the transmural tract. Follow-up examinations, including CT, were performed within 1 month after stent placement to assess complete resolution or a decrease in the sizes of cysts with clinical symptomatic improvement. Treatment success (or clinical success) was defined as a partial (reduction of >50% of the large axis) to complete resolution of the drained cysts with symptomatic improvement on follow-up CT at 4 weeks.

Endoscopic Procedure and Outcome Assessment

EUS-guided drainage was performed by three experienced endosonographers with long experience in the field of therapeutic EUS using linear-type echoendoscope (Pentax EG-3870UTK "PENTAX Medical, Tokyo, Japan, attached to a Hitachi – Aloka Avius processor "Hitachi, Tokyo, Japan" and Fujifilm EG-580UT "Fujifilm Global, Tokyo, Japan" with SU-1) in all cases with the deployment of one 10 Fr DP plastic stent either through the transgastric or transduodenal approach. Technical success was defined as successful transmural stent placement into the PPC, while clinical success was an improvement of symptoms and resolution of the fluid collection or decrease for more than 50% as determined by contrast-enhanced CT performed 1 month after the procedure without recurrence after stent removal within the follow-up period (6 months from the procedure). The detailed technique, duration of the procedure, related complications, and intraoperative complications (bleeding, perforation, leak, stent mal-deployment, or migration) were assessed. Also, early postoperative complications like pain, fever, nausea, vomiting, peritonitis, or pneumoperitoneum and late complication like stent migration, recurrence, pancreatitis were reported. The procedure technique involved EUS characterization of the PPC regarding size, wall thickness, distance from the GI lumen, percent of solid components, exclusion of mural nodules, and choosing the shortest vascular free tract for possible drainage. Subsequently, puncturing of the pancreatic pseudocyst wall was achieved in all cases using a 19-gauge FNA needle under the guidance of the Doppler US, followed by confirmatory aspiration of the content. Afterward, a 0.035-inch guidewire was inserted through the needle into the pseudocyst lumen, forming 2–3 coils under both EUS and fluoroscopy guidance to prevent any potential dislodgment. Furthermore, graded dilatation of the needle tract was achieved using electrocautery (6 or 10 Fr cystotome or needle knife) followed by dilatation using either a 10 Fr Soehendra dilator (Soehendra® Biliary Dilation Catheter) or dilatation balloon of different sizes, 10-11-12 or 12-13.5-15 (Cook® Hercules Dilation Balloon or Boston Scientific® CRE balloon). Finally, under the guid-

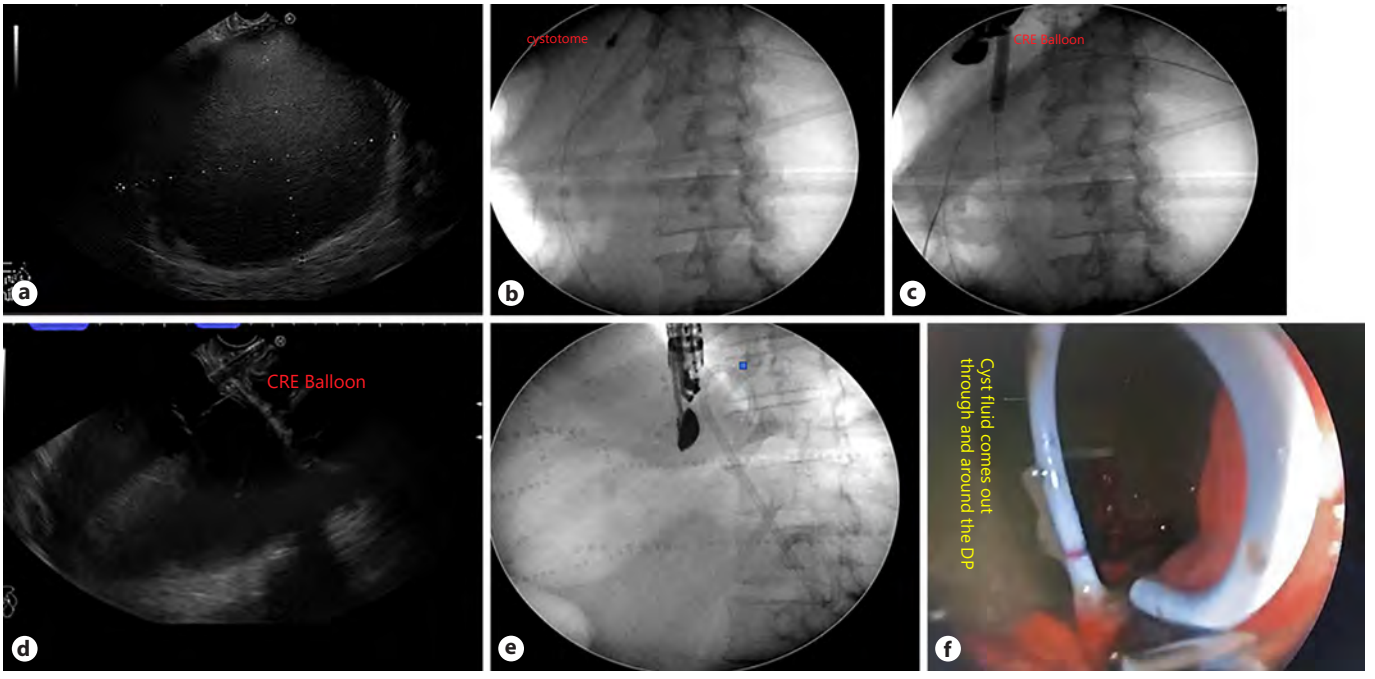

Fig. 2. a–f Steps for EUS-guided cystogastrostomy.

ance of EUS and fluoroscopy, a wide-caliber, 10 Fr DP plastic stent was deployed over the guidewire into the pancreatic pseudocyst with the consequent flow of the content into the GI lumen under an endoscopic view, confirming a successful technique (Fig. 2). All procedures were done under general anesthesia with endotracheal intubation, while the patient is in the left lateral position.

Statistical Analysis

Summary statistics were used to describe the characteristics of the study population (median, ranges for describing quantitative variables, frequency, and percentage for categorical variables). The Mann-Whitney U test was used to compare continuous variables, while χ^2 and Fisher's exact tests were used to compare categorical and dichotomous variables between study subgroups. Logistic regression was used to detect the independent factors affecting clinical outcomes. All statistical analyses were performed using IBM® SPSS software (version 23) for Windows. p value was evaluated as two-tailed, and significance was established at a $p < 0.05$ level.

Results

Study Population Baseline Characteristics

A total of 57 patients diagnosed with PPC were referred for EUS-guided pseudocyst drainage. Twenty-two patients were excluded (3 patients with major comorbidities, 7 had multiple cyst septation, eight cases had >30% necrosis of the cyst content, and 4 patients with moderate to marked abdominal free fluid). Thirty-five patients were enrolled (19 females/16 males, median age 40 years, range; 3–73), and patient and clinical characteristics are demonstrated in Table 1. While most of the patients were referred directly to EUS drainage, only 4 (11.4%) patients experienced a prior failed trial of percutaneous drainage approach. Idiopathic pancreatitis was the most common etiology (n = 19, 54.3%) followed by biliary (n = 5, 14.3%), post-traumatic (n = 4, 11.4), two post-chemotherapy for acute lymphocytic leukemia, and one case of alcoholic, post-distal pancreatectomy, postsplenectomy, post-ERCP, and primary hyperparathyroidism. All the patients were symptomatic with abdominal pain as the most common symptom (n = 24, 68.6%), early satiety, and dyspepsia in (n = 10, 28.6%) in addition to 1 patient who presented with a picture of gastric outlet obstruction and persistent vomiting.

Endoscopic Details and Outcomes

Most of the PPCs were located at the pancreatic body (n = 31, 88.6%). The median size of PPC was 10 cm (range; 5–20) with most of patients >10 cm (n = 20, 57.1%). Median percentage of necrosis within PPCs was 5% (range; 0–30) with 19 patients (54.3%) ≤5%, 16 (42.8%) between 5 and 25% and 1 patient with 30% necrotic area. All patients had a periprocedural antibiotic course of 3rd gen-

Table 1. Patient baseline characteristics and endoscopic therapy details

Subjects, *n*	35
Age, median (range), years	40 (3–73)
Gender, female, *n* (%)	19 (54.3)
Cause of pancreatitis, *n* (%)	
Idiopathic	19 (54.3)
Biliary	5 (14.3)
Post-traumatic	4 (11.4)
Others	7 (20)
Clinical symptoms, *n* (%)	
Abdominal pain	24 (68.6)
Early satiety and dyspepsia	10 (28.6)
GOO and persistent vomiting	1 (2.8)
Location of PPC, *n* (%)	
Body	31 (88.6)
Head	4 (11.4)
Size of PPC, median (range), cm	10 (5–20)
<10 cm, *n* (%)	15 (42.9)
≥10 cm, *n* (%)	20 (57.1)
Wall thickness of PPC, median (range), mm	5 (3–9)
Necrosis area within PPCs, median (range), *n* (%)	5 (0–30)
≤5%	19 (54.3)
5–25%	16 (42.8)
30%	1 (2.9)
Periprocedural antibiotic course, median (range), days	5 (3–20)
Drainage site, *n* (%)	
Transgastric route	33 (94.3)
Transduodenal	2 (5.7)
Stent length	
10 cm	16
7 cm	13
5 cm	6
Electrocautery method	
Electrocautery cystotome	33
6 Fr	24
10 Fr	9
Precut needle	2
Dilatation of the needle tract	33
Soehendra 10 Fr dilator	14
Dilation balloon	9
Both	10
Median duration of the whole procedure (range), min	
In 35 patients	16 (13.5–40)
In 34 patients	16 (13.5–27)
1 patient	40

eration cephalosporins or quinolones with a median period of 5 days (range; 3–20). EUS drainage through the transgastric route was the predominant procedure (*n* = 33, 94.3%). All stents used for the drainage were 10 Fr DP plastic stents with 10, 7, and 5 cm lengths. Electrocautery cystotome (6 or 10 Fr) were used for primary tract dilatation in 33 patients (94.3%) and precut needle in only 2 patients (5.7%). Subsequent dilatation of the needle tract was achieved in 33 patients using a Soehendra dilator 10 Fr alone in (*n* = 14, 40%), dilation balloon (median 8 mm, range; 4–15) in (*n* = 9, 25.7%), or subsequent dilatation by both in (*n* = 10 patients, 28.6%). The median duration of the whole procedure in 34 patients was 16 min (range; 13.5–27), and only one case with mal-deployment of the stent into the lumen of the cyst completed using another stent within 40 min.

Technical success was achieved in all the cases despite few difficulties encountered in 5 patients including difficult access in the duodenal bulb in 2 patients, small-sized stomach in one child case (3 years old), shearing of the wire with the need to re-puncture in one case, and a mal-deployed stent into the PPC lumen in 1 patient. Nonetheless, clinical success was encountered in 32 patients (91.4%) with the improvement of patient symptoms and resolution of the cyst without re-accumulation on follow-up. The three failed cases had a relapse of the cyst after an initial good response with the need for re-intervention in 1 patient with percutaneous drainage and repeated EUS-cystogastrostomy in another patient. The third patient of the failure group was misdiagnosed as pancreatic pseudocyst due to misleading laboratory data of cyst fluid analysis with re-accumulation after early good symptomatic response. The repeated analysis revealed a diagnosis of mucinous cystic neoplasm and ultimately the patient died with liver metastasis. In addition to the three cases with clinical failure, minor post-procedure adverse events were encountered in 3 patients (8.6%) including post-procedure abdominal pain in 1 patient which improved gradually and fever in 2 patients with resolution after conservative management including antipyretics and broad-spectrum antibiotics. No perforations or bleeding were encountered.

Comparison between clinical success and failure subgroups revealed no significant difference regarding patient clinical data and PPC characteristics (Table 2). Also, multivariable logistic regression showed no independent factors affecting clinical success (Table 3).

Discussion

This study showed that the management of symptomatic pancreatic pseudocyst by EUS-guided cystogastrostomy with the insertion of a wide-caliber single-pigtail plastic stent is technically feasible, safe, and effective and leads to shorter procedure time. As the general trend in most medical procedures nowadays is evolving toward

Table 2. Outcome in studied population

	Clinical failure	Clinical success	*p* value
Subjects, *n* (%)	3 (8.6)	32 (91.4)	0.859
Age, median (range), years	32 (30–66)	40 (3–73)	
Gender, female	3	16	0.234
Cause of pancreatitis			
Idiopathic	2	17	0.957
Biliary	0	6	
Post-traumatic	1	3	
Others	0	6	
Location of PPC			
Body	2	29	0.313
Head	1	3	
Size of PPC			
<10 cm	1	14	1.000
≥10 cm	2	18	
Wall thickness of PPC, median (range), mm	4 (4–5)	5 (3–9)	0.263
Necrosis area within PPCs, median (range), %	20 (0–25)	5 (0–30)	0.446
Drainage site			
Transgastric route	3	30	1.000
Transduodenal	0	2	
Stent length			
10 cm	1	15	0.732
7 cm	1	12	
5 cm	1	5	
Cutting incision			
Electrocautery cystotome	3	30	0.471
Precut needle	0	2	
Dilatation of the needle tract			
No	0	2	0.650
Soehendra 10 Fr dilator	2	12	
Dilation balloon	0	9	
Both	1	9	
Median duration of the procedure (range), min	16 (14–18)	16.5 (13.5–40)	0.767

Table 3. Multivariable logistic regression for clinical success

Variable	*p* value	OR
Pancreatitis etiology	0.343	0.726
Necrosis area	0.180	0.900
Duration of the procedure	0.313	1.302
PPC size >10 cm or <10 cm	0.821	0.576
Stent length	0.354	0.446

the easiest, short duration, minimally invasive, fewer resources consuming with the highest efficacy approaches, our study revealed that using one wide-diameter DP plastic stent for symptomatic pseudocyst drainage was safe and effective. In our patients, we had faced only minor adverse events in 3 patients (8.5%) including fever and post-procedure abdominal pain; both have resolved with conservative treatment.

Technical success was achieved in all cases (100%) of our cases with the insertion of a transmural pigtail stent despite the difficulties encountered in few cases (those with transduodenal route) which emphasize the easiness of the technique with decreasing the number of approach steps using only one stent. Clinical success was achieved in 91.4% of our patients with the resolution of patients' symptoms and no recurrence of a cyst with follow-up after 1 month, 6 months, and 12 months. Our study showed a recurrence rate of 5.7% after an initial good response which needs reintervention (one repeated endoscopic cystogastrostomy and the second underwent percutaneous drainage). This matched with the results of a systemic review that analyzed the mean clinical and technical success of 56 studies (each enrolled more than 10 patients

at least, most use more than one stent) which were 97% and 90%, respectively, with a recurrence rate of 8%.

Regarding data using a single-pigtail stent, our results go in line with data reported by retrospective studies showing that drainage of PPC and procedure-related adverse events are not affected by the number or size of used stents and that a single stent may be enough for safe effective drainage [16, 17]. Lin et al. [16] found that clinical success for using a single stent was 93.9% (46/49) versus 97.4% (37/38) for multiple stents ($p = 0.799$). Secondary infection for single-stent drainage was more than multiple stents (18.4% vs. 5.3%) ($p = 0.134$). Secondary infection also was more for stent diameter 10 F or more versus 8.5 F or less (17.2% vs. 3.4%; single or more stents) ($p = 0.138$). Bang et al. [17] also evaluated the number and size of the plastic stent with the treatment outcome in 122 patients, and they found that no relationship between the number or the size of the stent with the treatment success or number of re-intervention (overall success was 94.3%, 83.6% with one intervention and 10.7% with re-intervention and 5.7% failed endoscopic treatment).

Our study has included symptomatic patients with unresolved PPC for more than 6 weeks enabling the cyst wall to be well-defined. The main etiologies for acute pancreatitis and related complication worldwide are gallstones and alcoholism [18]. Most of our cases had idiopathic or biliary etiologies (68.6%). Alcoholism as a cause of pancreatitis is not so common in the Egyptian population due to the lower incidence of alcoholism in Egyptian society.

The transgastric drainage was regarded as the most common drainage site [19] which is consistent with our study with 94.3% of patients underwent transgastric PPC drainage. Regarding needle tract dilatation, a single-center retrospective study by Kitamura et al. [20] has shown that the use of electrocautery dilator for the needle tract during PPC drainage was shown to be safe and effective. These data have favored the use of cautery dilatation for all cases in our study which in turn has facilitated stent deployment without major related adverse events. Also, the use of electrocautery as the first dilatation device can fasten the procedure. This matched with Kitamura et al. [20] that showed a significant difference in procedure time between the electrocautery group (with mean time 30 ± 12 min) than non-electrocautery group (52 ± 20 min).

All included patients received periprocedural antibiotic course of 3rd generation cephalosporins or quinolones for a median period of 5 days. While broad-spectrum antibiotics are strongly recommended for patients with an infected pseudocyst either empirically or based on culture sensitivity [21], its prophylactic role for non-infected pseudocyst has not been studied [7].

The median duration of the procedure in most cases was 16 min (range; 13.5–27). This short procedure time is mostly related to the insertion of one stent rather than multiple stents. Multiple-stent placement is more difficult, takes a longer time, and has a higher risk of complications.

Regarding hospital stay, the median hospital stay was 3 days (2–7 days). However, in Lin et al.'s [16] work, the mean length of hospital stay was 9.9 ± 10.1 days (range 1–50 days). The short hospital stay in our study is due to exclusion of patients with WON and cyst with more than 30% necrosis, and this indicates the safety and less complication related to the procedure.

Despite our study was prospective and multicenter, we have some limitations including a relatively small number and single-armed protocol. A large number of randomized controlled studies are needed. In conclusion, management of symptomatic pancreatic pseudocyst by EUS-guided cystogastrostomy with the insertion of a wide-caliber single-pigtail plastic stent is technically feasible, safe, and effective with short procedure time.

Key Summary

- There is a conflict in current practice about the number and caliber of the plastic stents for EUS-guided drainage of PPC.
- Drainage using multiple plastic stents may be time-consuming with the consumption of more accessories through multiple dedicated steps with increased risk of complications and loss of access during the exchange procedures.
- The use of a single wide-caliber DP stent is technically feasible and effective with high clinical success and reduced procedure steps with less time, accessories, and complications.

Statement of Ethics

The study protocol was approved by the Research and Ethical Committee of Egyptian Liver Research Institute and Hospital (ELRIAH, IORG #0008819) IRB00010534. The protocol and conduct of the study complied with the International Ethical Guidelines for Biomedical Research Involving Human Subjects, with its amendments in 2008. Written informed consent was obtained from each patient.

Conflict of Interest Statement

The authors declare that they have no conflict of interest.

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Author Contributions

Protocol of the study, study design, methodology, follow-up of the patients, collecting data, data analysis, and writing – original draft preparation: Elsayed Ghoneem, Kalid Ragab, Hussein Okasha, Mohamed Fathi, Mohamed Hamouda, Reham Soliman, and Ramy Agwa. Statistical analysis, writing – review, and editing: Elsayed Ghoneem and Mohamed Hamouda. Supervision: Gamal Shiha, Hussein Okasha, and Ramy Agwa. The procedure (EUS-guided cystogastrostomy) was done by Hussein Okasha (Endoscopy Unit at Kasr Elini Cairo University), Khalid Ragab (Endoscopy Unit at Theodor Bilharz Research Institute), Elsayed Ghoneem (Endoscopy Unit at Specialized Medical Hospital, Mansoura University, and Egyptian Liver Hospital).

Data Availability Statement

All data generated or analyzed during this study are included in this published article and readily available for share.

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The New FibroScan-AST (FAST) Score: Enhancing Diabetes Mellitus Impact on Metabolic-Associated Fatty Liver Disease

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Keywords
Metabolic-associated fatty liver disease · Liver transient elastography · Hepatology

Abstract

Background: Metabolic-associated fatty liver disease (MAFLD) is an increasingly prevalent cause of chronic liver disease. In 2020, the FibroScan-AST (FAST) score was internationally validated as a new tool able to identify patients with steatohepatitis who benefit the most from further therapies, based on liver transient elastography (LTE) findings and serum levels of aspartate aminotransferase (AST). We aimed to identify, in MAFLD patients, which metabolic features may predict a higher FAST score. ***Methods:*** Retrospective study of consecutive patients with MAFLD submitted to LTE for two consecutive years. Patients without an AST sample collected within 6 months of the LTE were excluded. FAST score was calculated, stratifying the patient's risk as low (<0.35), medium (0.35–0.67), or high (>0.67). ***Results:*** The sample included 117 patients, 53.0% of the female gender, with a mean age of 53 years. On multivariate analysis, patients with type 2 diabetes (T2DM) ($p < 0.001$), dyslipidemia ($p = 0.046$), and smoking habits ($p = 0.037$) presented with significantly higher FAST score values. Furthermore, diabetic patients did not only present significantly higher FAST scores but were also more frequently assigned to the high-risk group according to FAST score criteria (OR = 9.2; 95% CI = 1.8–45.5; $p = 0.007$). ***Conclusions:*** Calculating the FAST score, patients with T2DM presented a significantly higher risk of having significant fibrosis and steatohepatitis. Physicians may rely on this validated instrument to more easily identify which patients with T2DM and MAFLD benefit the most from a specialized follow-up.

O Novo Fibroscan-AST (FAST) Score: Reforçando o Impacto da Diabetes Mellitus no Fígado Gordo Associado a Disfunção Metabólica

Palavras Chave
Fígado gordo associado a disfunção metabólica · Elastografia hepática · Hepatologia

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Resumo

Introdução: O fígado gordo associado a disfunção metabólica (FGADM) é uma causa crescente de doença hepática crónica. Em 2020, o score Fibroscan-AST (FAST) foi validado internacionalmente como uma nova ferramenta capaz de identificar pacientes com esteatohepatite que beneficiam de terapêuticas adicionais, baseado nos achados da elastografia hepática transitória (EHT) e níveis séricos de aspartato aminotransferase (AST). Os autores procuraram identificar, em pacientes com FGADM, que fatores metabólicos predizem um score-FAST maior. ***Métodos:*** Estudo retrospetivo de pacientes com FGADM submetidos a EHT durante 2 anos consecutivos. Pacientes sem uma amostra de AST colhida nos 6 meses prévios à EHT foram excluídos. O score-FAST foi calculado, estratificando o risco do paciente como baixo (<0,35), moderado (0,35-0,67) ou alto (>0,67). ***Resultados:*** A amostra incluiu 117 pacientes, 53% do sexo feminino, com uma idade média de 53 anos. Em análise multivariada, pacientes com Diabetes Mellitus tipo 2 (DMT2) ($p < 0,001$), dislipidemia ($p = 0,046$) e hábitos tabágicos ($p = 0,037$) apresentaram valores de score-FAST significativamente maiores. Além disso, os pacientes diabéticos apresentaram não só valores de score-FAST significativamente maiores, como também foram mais frequente classificados como pertencendo ao grupo de alto risco, de acordo com os critérios deste score (OR = 9,2; 95%IC = 1,8–45,5; $p = 0,007$). ***Conclusões:*** Calculando o score-FAST, pacientes com FGADM e DMT2 apresentaram um risco significativamente maior. Esta ferramenta validada poderá ser utilizada para selecionar os pacientes com DMT2 e FGADM que poderão beneficiar de seguimento especializado.

Introduction

Metabolic-associated fatty liver disease (MAFLD) has become one of the most prevalent causes of chronic liver disease worldwide, emerging as the next leading cause of end-stage liver disease, with a global prevalence around 25% [1]. This recent growth in MAFLD prevalence has paralleled the increasing frequency of people with obesity and other metabolic syndrome (MS) components such as arterial hypertension (AH), dyslipidemia, and type 2 diabetes mellitus (T2DM), which is not surprising since these represent the most commonly accepted risk factors for the development of MAFLD [2].

Despite this, there is a heterogeneous pathogenesis in metabolic fatty liver diseases, with inaccuracies in their terminology and definitions precluding clinical trial designs and drug developments. In 2020, a group of experts sought to integrate current understanding of patient heterogeneity captured under the previous acronym nonalcoholic fatty liver disease (NAFLD) and provide suggestions on terminology that more accurately reflects pathogenesis and can help in patient stratification for management [3]. Experts reached consensus that NAFLD does not reflect current knowledge, and "MAFLD" was suggested as a more appropriate overarching term.

The current burden of MAFLD has led to a consequently higher number of referrals to Hepatology Clinic [4]. Although most MAFLD patients do not progress to advanced fibrosis and cirrhosis, there are an increasing number of cases who do develop chronic liver disease and progress to unfavorable outcomes such as hepatocellular carcinoma or liver transplantation [5]. Therefore, a key aspect is to precociously identify patients with a greater risk of clinical progression by worsening liver fibrosis, which might benefit from a closer follow-up and additional treatment with new therapeutic options [6].

A significant turning point in MAFLD is the presence of steatohepatitis (SH), as a result of profound liver cell injury [7]. Liver biopsy remains the gold standard to identify SH, despite being limited by its invasiveness, complications, variability in interpretation, and lack of compliance for seriate monitoring [8]. Noninvasive biomarkers of steatosis and fibrosis such as algorithms, serum biomarkers, and imaging modalities are also widely available but do not measure the degree of inflammatory liver injury [9]. Many different algorithms have been studied in NAFLD; however, only NAFLD fibrosis score and Fib-4 index have been externally validated multiple times with consistent results among different populations and may be used as first-line screening tools to exclude severe fibrosis [10].

In 2020, Newsome et al. [11] proposed to validate a noninvasive score identifying patients simultaneously having SH, elevated NAFLD activity score (NAS ≥4), and advanced liver fibrosis ($F \geq 2$). The FibroScan-AST (FAST) score was constructed by combining liver transient elastography (LTE) parameters – both controlled attenuation parameter (CAP) and liver stiffness measurement (LSM) – and aspartate aminotransferase (AST) levels. This score showed good accuracy in reflecting histopathology, providing a novel and efficient way to noninvasively identify patients with MAFLD at risk of clinically relevant SH, with significant inflammatory ac-

tivity and fibrosis. In this study, our group aimed to identify which metabolic features led to higher values on this newly available score, by applying the FAST score in consecutive MAFLD patients submitted to LTE in our center.

Materials and Methods

Study Design and Data Collection

We conducted a retrospective study including consecutive adult patients with MAFLD scheduled to undergo surveillance LTE for two consecutive years. MAFLD was diagnosed based on the evidence of hepatic steatosis in adult patients (detected either by imaging, blood biomarkers/scores and/or liver biopsy) associated with one of three criteria: overweight or obesity (body mass index (BMI) ≥25 kg/m^2 in Caucasian individuals); T2DM; or the presence of at least 2 metabolic risk abnormalities (waist circumference ≥102/88 cm in men and women; blood pressure ≥130/85 mm Hg or specific drug treatment; plasma triglycerides ≥150 mg/dL or specific treatment; plasma high-density lipoprotein cholesterol <40 mg/dL in men or <50 mg/gL in women or specific treatment; prediabetes; homeostasis model assessment insulin resistance score ≥2.5; plasma high-sensitivity C-reactive protein >2 mg/L) [12].

Patients were excluded in case of cirrhosis, pregnancy, ascites, liver transplantation, or hepatic surgery. Age, gender, BMI, obesity (BMI ≥30 kg/m^2), current smoking habits, T2DM, AH, dyslipidemia data were collected for each patient. Platelet count, AST, ALT, and albumin levels were considered only when blood samples were collected within 6 months of the LTE performance, as validated by Newsome et al. [11].

LTE (FibroScanVR Compact 530®; Echosens, Paris, France) was performed with a minimum fasting of 2 h [13]. LSM and CAP were assessed and expressed in kilopascals (kPas) and decibels per square meter (db/m^2), respectively. Measurements were performed by placing the probe covered with ultrasound gel on the right lobe of the liver through 9th to 11th intercostal space on the middle axillary line with the patient lying in dorsal position with the right arm in maximal abduction. An LTE was considered valid if having 10 valid measurements with interquartile range (IQR)/median (M) for LSM below 30% [14]. LTE was initially performed with the M probe in every patient, except those with a skin-capsule distance greater than 25 mm, which was shown to be an independent predictive factor of M probe failure [15]. In those patients with M probe failure, measurements were repeated with the XL probe. Conditions which interfere with LSM measurements reliability, such as extrahepatic cholestasis, aminotransferases ≥5× upper limit of normal, and right heart failure or other causes of liver congestion, were considered to be exclusion criteria.

FAST score was calculated for each patient by inserting LSM, CAP, and AST levels in a formula provided by FibroScan®. FAST score varied on a scale from 0 to 1, with the patients being classified as having low (<0.35), intermediate (0.35–0.67), or high (>0.67) probability of having SH with significant inflammatory activity and fibrosis.

Statistical Analysis

Statistical analysis was performed using SPSS® software, version 23 (IBM, Armonk, NY, USA). Categorical variables are presented as frequencies and percentages and continuous variables as means and standard deviations or median (IQR), when appropriate. Reported p values are two tailed, with statistical significance being considered for p value <0.05.

For assessment of each metabolic factor impact on FAST score, univariate analysis was conducted with either student t test/Mann-Whitney test for categorical variables or simple linear regression for continuous variables. Variables with significant ($p < 0.05$) or nearly significant variables ($p < 0.10$) were then computed into multivariate analysis by means of a multiple linear regression, in order to identify important contributions in the variability of FAST score values when adjusted for possible confounders. To assess if the above reported variables would predict not only significantly different scores but also being assigned to the high-risk FAST score group, a multivariate analysis was performed by means of a binary logistic regression.

Results

From 128 patients submitted to LTE for MAFLD surveillance, 6 were excluded for not having an AST measurement within 6 months of the procedure and 5 were excluded for not having a valid LTE measurement, with a final sample of 117 individuals. The sample consisted of 62 women (53.0%), with a mean age of 53 ± 12 years. The most commonly found metabolic feature was dyslipidemia ($n = 96$; 82.1%), followed by obesity ($n = 67$; 57.3%), AH ($n = 55$; 47.0%), and T2DM ($n = 42$; 35.9%). The number of patients simultaneously having these 4 components was 22 (18.8%). Smoking habits were reported in 20 patients (17.1%). As of LTE, median CAP was 303 (IQR 50) dB/m^2 and median LSM was 5.5 (IQR 3.1) kPa. Median AST levels were 24 (IQR 17) UI/L (reference levels 15–37). Table 1 summarizes the characteristics of our sample.

FAST score median value was 0.140 (IQR 0.310). According to this score, 87 (74.4%), 19 (16.2%), and 11 (9.4%) patients were assigned to low-, intermediate-, and high-risk groups, respectively.

FAST score had significant moderate correlations to Fib-4 index ($r = 0.545$; $p < 0.01$) and NAFLD fibrosis score ($r = 0.400$; $p < 0.01$). A total of 8 and 37 patients on the "grey areas" of Fib-4 index and NAFLD fibrosis score would have been reclassified to FAST score high- and low-risk groups, respectively.

Liver biopsy was performed in 23 (19.7%) patients – 4 from the FAST score high-risk group and 19 from the low- or intermediate-risk groups. All of the high-risk patients had confirmed advanced fibrosis and significant SH on the histologic sample, which was significantly different from those in the other groups (100.0% vs. 15.8%; $p = 0.004$). This represented overall specificity of 100%,

Table 1. Patients' baseline characteristics

Variable	All patients (n = 117)
Demographics	
Female gender, *n* (%)	62 (53.0)
Age, years	53±12
Medical records	
Smoking habits, *n* (%)	20 (17.1)
BMI, kg/m^2	31.30±4.75
MS components, *n* (%)	
Dyslipidemia	96 (82.1)
Obesity	67 (57.3)
AH	55 (47.0)
T2DM	42 (35.9)
Coexistence of all 4 factors	22 (18.8)
Blood samples	
AST levels, U/L	24 (17)
ALT levels, U/L	44 (34)
Serum albumin, g/dL	4.10 (0.50)
Platelet count, UI × 10^3 per liter	237 (71)
LTE findings	
CAP, dB/m^2	303 (50)
LSM, kPa	5.5 (3.1)
Fib-4 index	
Median value (IQR)	0.83 (0.63)
Classification, *n* (%)	
Advanced fibrosis unlikely (F0–F2)	90 (76.9)
Intermediate group	18 (15.4)
Advanced fibrosis likely (F3–F4)	4 (3.4)
NAFLD fibrosis score	
Median value (IQR)	−1.55 (2.01)
Classification, *n* (%)	
Absence of significant fibrosis (F0–F2)	54 (46.2)
Intermediate group	44 (37.6)
Presence of significant fibrosis (F3–F4)	8 (6.8)
FAST score	
Median value (IQR)	0.140 (0.310)
Classification, *n* (%)	
Low-risk group (<0.35)	87 (74.4)
Medium-risk group (0.35–0.67)	19 (16.2)
High-risk group (<0.35)	11 (9.4)

Results are presented in *n* (%) for categorical variables and mean ± SD/median (IQR) for continuous variables. Dyslipidemia: plasma triglycerides ≥150 mg/dL or specific treatment, plasma high-density lipoprotein cholesterol <40 mg/dL in men or <50 mg/gL in women or specific treatment; obesity: BMI ≥30 kg/m^2; arterial hypertension: blood pressure ≥130/85 mm Hg or specific drug treatment; type 2 diabetes mellitus: HbA1c ≥6.5%; fasting plasma glucose levels ≥126 mg/dL, random plasma glucose levels ≥200 mg/dL or specific treatment. AST, aspartate aminotransferase; BMI, body mass index; CAP, controlled attenuation parameter; FAST, FibroScan-AST; IQR, interquartile range; LSM, liver stiffness measurement; LTE, liver transient elastography; SD, standard deviation.

Table 2. Multivariate analysis – multiple linear regression for impact on FAST score values

Variable	B (95% CI)	p value
Body mass index, kg/m^2	0.007 (−0.002 to 0.015)	0.109
T2DM	0.336 (0.082 to 0.247)	<0.001***
Dyslipidemia	0.175 (0.002 to 0.213)	0.046*
Smoking habits	0.180 (0.007 to 0.218)	0.037*

* p value <0.05; *** p value <0.001.

Table 3. Multivariate analysis – binary logistic regression for assignment to high-risk group according to FAST score values

Variable	Odds ratio	Wald 95% CI	p value
Body mass index, kg/m^2	1.07	0.94–1.21	0.297
T2DM	9.17	1.83–45.45	0.007*
Dyslipidemia	1.01	0.16–6.29	0.988
Smoking habits	2.42	0.56–10.42	0.413

* p value <0.05.

sensitivity of 57.1%, positive predictive value of 100%, and negative predictive value of 84.2%.

On univariate analysis, the presence of T2DM (0.235 IQR 0.480 vs. 0.100 IQR 0.200; $p < 0.001$), dyslipidemia (0.165 IQR 0.360 vs. 0.070 IQR 0.120; $p = 0.010$), and smoking habits (0.305 IQR 0.390 vs. 0.120 IQR 0.280; $p = 0.002$) resulted in a significantly higher FAST score result. It was additionally shown that patients simultaneously presenting with all four components of the MS presented with significantly higher values when compared to those with 3 or less of the components (0.420 IQR 0.570 vs. 0.120 IQR 0.220; $p = 0.001$). Male gender (0.170 IQR 0.280 vs. 0.095 IQR 0.300; $p = 0.182$), AH (0.15 IQR 0.430 vs. 0.125 IQR 0.220; $p = 0.512$), obesity (0.140 IQR 0.320 vs. 0.140 IQR 0.250; $p = 0.851$), age in years ($\beta = 0.081$; $p = 0.386$), and body mass index ($\beta = 0.094$; $p = 0.064$) did not show significant associations to FAST score values.

A multiple linear regression concluded that the presence of T2DM ($B = 0.165$; 95% CI = 0.082–0.247; $p < 0.001$), dyslipidemia ($B = 0.175$; 95% CI = 0.002–0.213; $p = 0.046$), and smoking habits ($B = 0.112$; 95% CI = 0.007–0.218; $p = 0.037$) led to significantly higher FAST score values when adjusted for other variables. The model results are described in Table 2.

In order to evaluate if these variables would predict not only significantly higher FAST score values but also higher odds of the patient being assigned to the high-risk group, a binary logistic regression was executed with the same predictive variables. After this analysis, only T2DM (OR = 9.2; 95% CI = 1.8–45.5; $p = 0.007$) was found to be a significant predictive factor of the patient being in the high-risk group. Binary logistic regression results are shown in Table 3.

Discussion/Conclusion

Identification of MAFLD patients with higher risk of progression is of the utmost importance, since a diverse range of therapeutic options, other than lifestyle interventions, is currently under development, particularly for SH [16]. Most MAFLD patients are followed up in primary care centers by general practitioners. Accurate fibrosis assessment in this setting is challenging, since it is limited by performance of liver blood tests, which correlate poorly with fibrosis, and limited access to discriminatory fibrosis tests [17]. Srivastava et al. [18] proposed a primary care referral pathway for patients with MAFLD, where performance of LTE is proposed in cases where Fib-4 index presents with an intermediate result, ultimately concluding which patients benefit the most from specialized hepatology consultation. FAST score gains a crucial role by identifying patients simultaneously having SH with significant inflammatory activity and fibrosis, consequently those who are most likely to benefit from follow-up in specialized centers and to eventually undergo under-development therapies.

FAST score values in our population had significant moderate correlations with indirect markers of fibrosis previously used in NAFLD, namely, Fib-4 index and NAFLD fibrosis score. A correlation was expected, since part of the outcome that the FAST score aims to identify is the presence of significant fibrosis, which is the same predicted outcome in the abovementioned clinical scores. The fact that it was only moderate may be explained as the remaining variability could be attributed to the second outcome in FAST score – the inflammatory activity. By adding this parameter, FAST score could pave its way into clinical practice, as it offers wider information on patients' disease staging by means of simple and noninvasive diagnostic tools.

Smoking habits represent a classical risk factor for chronic diseases such as cardiovascular diseases, neoplasms, and T2DM [19]. Although far less studied, associations with chronic liver disease have also been reported. Cigarette smoking induces liver disease progression by multiple pathways, the most flagrant one being the induction of hepatic fibrogenesis, to which contributes the systemic inflammation and oxidative stress promoted by heavy smoking [20]. MAFLD is no exception, as was recently shown in a meta-analysis by Akhavan Rezayat et al. [21], where smoking was significantly associated with development of this condition. A key aspect that may help explain this association is the substantial negative impact of smoking in insulin resistance, which is largely accepted to be the main pathophysiologic mechanism in MAFLD development and progression [22]. Moreover, cigarette smoking per se conduces to advanced liver fibrosis independently of T2DM, with nondiabetic patients reporting 10 or more pack-years smoking history having an odds ratio of 2.5 for presence of this adverse outcome [23]. Other than this, recent animal models demonstrated that cigarette exposure, in addition to Western diets, led to significantly higher elevations of biochemical parameters that were accompanied by an increase in hepatic damage shown as more severe fat accumulation, hepatocyte ballooning, and inflammation infiltrates, representing reliable models of MAFLD to SH progression [24]. Our study agreed with previous reports, since patients with cigarette smoking history presented significantly higher FAST scores when adjusted for other variables. In the light of these findings, it is our belief that MAFLD patients should strongly be encouraged to quit smoking, as this represents a modifiable risk factor that can potentially work as a co-factor for progression in addition to other underlying conditions.

Previous reports have already been published mentioning the relationship between dyslipidemia and adverse outcomes in MAFLD, with deranged lipid metabolism being associated with progression to SH [25]. In 2020, a multicentric retrospective cohort of Mexican patients with biopsy-proven SH concluded that high low-density lipoprotein and triglyceride serum levels were the variables with the biggest impact when predicting the presence of advanced liver fibrosis (F4), with an OR of 3.04 and 4.96, respectively [26]. In another cohort study of 260,950 patients, dyslipidemia was one of the significant independent predictive factors of MAFLD/SH progressing to cirrhosis [27]. In our population, similar results were found, as dyslipidemic patients presented with higher FAST score values, reinforcing the urge to implement preventive measures such as nutritional advisory or early statin use in order to achieve control of this component.

The impact on FAST score was rather greater for T2DM, as diabetic patients were also more frequently classified as being in the high-risk group (FAST score over 0.67; OR = 8.26; $p = 0.012$). A bidirectional association between MAFLD and T2DM has already been consistently described in literature [28]. First, MAFLD patients have higher insulin resistance rates than those without MAFLD, regardless of body mass index and whether already having T2DM or not [29]. For that reason, MAFLD patients present a 2-fold increased risk of developing T2DM [30]. On the other hand, patients diagnosed with T2DM present with 80% more liver fat than age-, weight-, and sex-matched nondiabetic patients [31]. This difference remains significant for any given body mass index or waist circumference, according to the authors' findings. Our results were in line with previous reports, as patients with TD2M presented with significantly higher FAST score values and therefore simultaneously higher inflammatory activity and significant fibrosis. The key aspect for T2DM is that in addition to having higher scores, these patients had a significant 8-fold increased risk of being assigned to the high-risk group, differently from the other mentioned conditions. These findings strengthen the important role of T2DM in MAFLD, with this causality already acknowledged in the European Association for the Study of the Liver guidelines, by recommendation of MAFLD screening in all T2DM patients regardless of transaminases levels, as these patients are expected to be at n higher risk of disease progression [32]. Our group believes that TE, with further application of the FAST score, may play a crucial role in this setting, by precociously identifying diabetic patients who are more likely to benefit from biopsy for trial enrollment or subsequent treatment. An investigation by Ciardullo et al. [33] has already shown that, in hypertense patients, T2DM was a factor that significantly increased referral for specialized hepatology consultation due to MAFLD . Therefore, these patients should be promptly referred to specialized hepatology consultation, so a rigorous follow-up program can be achieved. Nonetheless, nondiabetic patients with MAFLD must also be encouraged to maintain healthy lifestyles and advised on dietetic measures in order to evade T2DM development.

Classically, obesity has been accepted as the main risk factor for MAFLD development [32]. This association is explained not only by higher amounts of visceral fat, and therefore liver fat, in overweight and obese people, but also because these patients are more likely to have other MS compounds such as AH, dyslipidemia, and T2DM [34]. Additionally, obesity also increases the risk of having a more histologically severe disease, with the prevalence of SH rising from 2.7% in lean individuals to around 27% in morbidly obese patients undergoing bariatric surgery [35]. So, it may seem surprising that, in our sample, neither obesity nor body mass index values resulted in significant differences on FAST score values. However, this can be explained as most of the reported investigations did not adjust obesity impact for its comorbidities, which can result in bias since, as stated before, those patients more frequently have other risk factors such as dyslipidemia and T2DM. Supporting our findings is an investigation published in 2020 by Lum et al. [36]. From a population of 263 adults with biopsy-proven MAFLD, the development of SH and the presence of significant fibrosis was not significantly different between obese and nonobese patients. Knowing this, every clinician must be aware that lean MAFLD patients are as susceptible as the obese ones to present with important liver disease. Thus, comparable or even tighter caution must be taken when managing this subset of individuals.

A note must be made on the fact that a synergism effect was seen in our population, as patients with combined T2DM, obesity, AH, and dyslipidemia presented with significantly higher FAST scores when compared to those with 3 components or less. Caution must be taken when managing this set of patients, and therefore our group suggests their follow-up to be ideally kept at specialized consultation, as these patients are expected to benefit the most from additional treatments.

In conclusion, our study represents a groundbreaking evaluation of MAFLD in a Portuguese population. In the last years, few studies have addressed MAFLD in Portuguese patients. In 2020, Leitão et al. [37] have analyzed the prevalence and risk factors of fatty liver in a random sample of Portuguese adults, having found an overall prevalence of 17.0%, with MAFLD individuals being more frequently older and with increased probability of having obesity or diabetes. Nevertheless, fibrosis assessment and risk factors for significant fibrosis were not measured. More recently, in 2022, Rigor and associates have validated different noninvasive fibrosis tools in a Portuguese MAFLD sample, which presented an overall advanced fibrosis incidence of 21.5% [38]. However, the newly available FAST score was not yet applied in this population. Therefore, we believe our investigation represents a breakthrough evaluation, by not only being the first to apply the FAST score on a Portuguese population but also by evaluating the weighted influenced of each MS component on the assessed outcomes.

Our investigation has few limitations, namely, its retrospective design and the unavailability of gold standard

comparison with liver biopsy in every patient. Nevertheless, our conclusions pave the way for further validation with prospective multicenter studies with larger samples, which will allow a better comprehension of this newly reclassified definition of MAFLD.

Statement of Ethics

This study is an observational, retrospective, and anonymous study, not meeting the criteria for clinical trial. The manuscript includes anonymous data from 117 patients with MAFLD undergoing TE at our institution. This study conforms to the ethical guidelines of the 1975 Helsinki Declaration (6th revision, 2008), assuring patients' anonymity and data protection. The study has been approved by the institution's Human Research Committee (85/2022). Due to the retrospective nature of the study, informed consent was waived, as long as patients' anonymity was assured.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Nothing to declare.

Author Contributions

All authors contributed to and agreed on the content of the manuscript. Macedo Silva, V. designed the study, carried out data analysis, and drafted the manuscript. Freitas, M. carried out data collection and analysis. Xavier, S. and Magalhães, J. performed liver transient elastographies and critically revised the manuscript. Boal Carvalho, P. and Marinho, C. critically revised the manuscript. Cotter, J. critically revised and approved the final version of the manuscript.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Endoscopic Approach to Duodenal Adenomas in Familial Adenomatous Polyposis: A Retrospective Cohort

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Keywords

Familial adenomatous polyposis · Duodenum · Adenomas · Endoscopy · Endoscopic mucosal resection

Abstract

Introduction: Over 90% of the patients with familial adenomatous polyposis (FAP) will develop duodenal adenomas. ***Aim:*** The aim of this study was to evaluate the effectiveness and safety of endoscopic excision of large duodenal adenomas in FAP patients. ***Methods:*** All FAP patients from a familial risk clinic submitted to endoscopic therapy for duodenal adenomas ≥10 mm between January 2010 and February 2021 were included. ***Results:*** From 151 FAP families, 22 patients (50 lesions) were included: 54.5% female; median follow-up 8.5 (IQR: 5.8–12.3) years after the first endoscopy. First therapeutic endoscopy occurred at a median age of 41.0 years (IQR: 33.0–58.2). Repeat therapeutic endoscopy was required in 54.5% of patients. Median size of the largest adenoma was 15 mm (IQR: 10–18 mm); resection was piecemeal in 63.1% and en bloc in the remaining. In 2 cases, the resection was incomplete (fibrosis due to previous resection and difficult positioning). Complications occurred in 6.3% of the resected lesions (4 patients): 2 immediate (bleeding, perforation); 4 in the first week (1 bleeding, 2 mild pancreatitis, 1 perforation requiring surgery; the latter two after ampullectomy). Histology revealed low-grade dysplasia adenomas in 90.1%; no adenocarcinomas were found. One patient with Spigelman stage IV disease not amenable to endoscopic control underwent elective duodenopancreatectomy (without duodenal cancer). ***Conclusion:*** Endoscopic surveillance and treatment of duodenal adenomas in FAP patients was safe and effective in the prevention of duodenal cancer.

Abordagem endoscópica de adenomas duodenais na Polipose Adenomatosa Familiar: um coorte retrospetivo

Palavras Chave

Polipose adenomatosa familiar · Duodeno · Adenomas · Endoscopia · Mucosectomia

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Resumo

Introdução: Mais de 90% dos doentes com Polipose Adenomatosa Familiar (PAF) desenvolvem adenomas duodenais. ***Objetivo:*** Avaliar a eficácia e segurança da excisão endoscópica de adenomas duodenais em doentes com PAF. ***Métodos:*** Incluídos todos os doentes com PAF submetidos a terapêutica endoscópica de adenomas duodenais ≥10 mm entre janeiro/2010-fevereiro/2021. ***Resultados:*** Em 151 famílias com PAF, incluídos 22 doentes (50 lesões): 54.5% mulheres; mediana do follow-up 12.3 (IQR: 6.0–19.0) anos. Primeira endoscopia terapêutica (resseção de pólipos duodenais ≥10 mm) ocorreu numa mediana de idades 41.0 (IQR: 33.0–58.2) anos.Em 54.5% dos casos, foi necessária uma nova endoscopia terapêutica. Dimensão mediana do maior adenoma: 15 mm (IQR: 10–18 mm); resseção realizada em piecemeal em 63.1% e em bloco nos restantes. Em dois casos, a resseção endoscópica foi incompleta (fibrose em local de resseção prévia:1; posicionamento:1). Complicações em 6.3% das lesões ressecadas (4 doentes): 2 imediatas (hemorragia e perfuração, manejadas endoscopicamente); 4 na primeira semana (1 hemorragia controlada endoscopicamente, 2 pancreatites ligeiras tratadas conservadoramente, 1 perfuração com necessidade de cirurgia; as duas últimas após ampulectomia). A avaliação histológica revelou adenomas com displasia de baixo grau em 90.1%; nenhum adenocarcinoma. Um doente com doença Spigelman IV não controlável endoscopicamente realizou duodenopancreatectomia (sem cancro). ***Conclusão:*** A vigilância e tratamento endoscópicos de adenomas duodenais em doentes com PAF revelaram-se seguros e eficazes na prevenção de cancro duodenal.

Introduction

Familial adenomatous polyposis (FAP) is an inherited autosomal-dominant condition caused by a mutation of the *adenomatous polyposis coli (APC)* gene, on the long arm of chromosome 5 [1]. It is marked by a high incidence of colorectal adenomas and cancer. Nevertheless, with adequate screening and prophylactic measures regarding colorectal cancer, duodenal disease has emerged as one of the most important causes of morbidity and mortality in affected patients [2]. Duodenal adenomas (DAs) occur in more than 90% and duodenal cancer in 3–5% of FAP cases [3–6]. The adenoma-carcinoma progression in this location may take up to 15–20 years [7]. Specific regions of the *APC* gene may be associated with severe disease, due to clustering of somatic mutations, and loss of the wild-type allele [2, 8].

International guidelines advocate regular endoscopic surveillance of the duodenum. Risk stratification, follow-up intervals, and therapeutic approaches are determined according to the Spigelman classification [9], which considers polyp number, size, and histology [9–14]. Excision is recommended for non-ampullary (and some ampullary) adenomas ≥10 mm [14], considering the balance between the risk of endoscopic/surgical resections and the risk of developing duodenal carcinoma. The chosen method is often endoscopic mucosal resection (EMR), which has proven to be safe and effective [15–18]. Significant recurrence rates have been reported, although it is not always straightforward whether they are true recurrences or simply disease progression [16–21]. Furthermore, despite these recommendations, it remains unknown whether DA resection truly changes the natural history of cancer risk since there is an underlying field defect in the duodenum [22].

When invasive disease is suspected, surgical approaches should be considered [14]. These include pancreas-sparing duodenectomy and pancreatoduodenectomy, which offer definitive therapy in preventing duodenal carcinoma, or segmental duodenal resection, for patients with dominant or limited disease, where removing a short segment allows safe endoscopic surveillance/treatment of the remaining bowel. Nevertheless, adenomatous disease may recur in the remaining small bowel, and these patients must be kept under regular surveillance [23, 24].

Additionally, medical treatment using the cyclooxygenase inhibitors sulindac and celecoxib has been studied, yielding conflicting results – due also to significant side effects, their use is not recommended in Europe [25–30]. The aim of this study was to evaluate the effectiveness and safety of endoscopic excision of large DAs in patients with FAP and to assess results in light of the most recent guidelines.

Methods

A retrospective study was developed in the familial cancer clinic of an oncological centre, where 151 families with FAP are currently accompanied. FAP families' files from the familial cancer clinic were reviewed and all FAP patients submitted to endoscopic resection of DAs with at least 10 mm greatest axis, from January 2010 to February 2021, were included. These procedures were described as therapeutic endoscopies.

FAP patients undergo regular endoscopic surveillance according to international guidelines, having their first upper gastrointestinal endoscopy at the age of 20–25 or earlier in case of colec-

Table 1. Patient characteristics

Variable	Frequency
Male, *n* (%)	10 (45.5)
APC mutation, *n* (%)	
Exon 4	1 (4.5)
Exon 5	3 (13.6)
Exon 10	1 (4.5)
Exon 13	3 (13.6)
Exon 15	12 (54.5)
Not available	2 (9.0)
Colorectal surgery, *n* (%)	
Colectomy with rectal sparing	8 (36.4)
Protocolectomy with ileal pouch	14 (63.6)
Colorectal cancer, *n* (%)	4 (18.2)
Desmoid tumours, *n* (%)	4 (18.2)
Fundic gland polyps, *n* (%)	15 (68.2)
Gastric dysplasia, *n* (%)	5 (22.7)
Other tumours, *n* (%)	
Thyroid (papillary)	1 (4.5)
Small bowel (ileostomy adenocarcinoma)	1 (4.5)

APC, adenomatous polyposis coli gene.

tomy before 20 years old. Follow-up intervals are determined according to the Spigelman classification [9], which considers the number, size, and histological characteristics (architecture and dysplasia grade) of duodenal polyps. Spiegelman stage is then calculated by summing the points attributed to these criteria and patients with Spigelman stage 0/I, II, III undergo endoscopy every 5, 3, and 1 year, respectively; those with Spigelman stage IV must be considered individually, undergoing surgery or surveillance every 6 months. Surveillance intervals may be shortened after removal of polyps with higher risk of recurrence, such as those harbouring high-grade dysplasia or with a villous histology, especially if removed piecemeal. This is considered case by case.

Study Procedures

The exams were performed under propofol sedation by an Anaesthesiologist, in the Endoscopy Unit of the Gastroenterology Department of our institution in case of non-ampullary adenomas or in a tertiary hospital with expertise in endoscopic retrograde cholangiopancreatography in case of ampullary adenomas. Endoscopes and duodenoscopes belonged to Olympus series 190 and 180, respectively. EMR was usually performed after submucosal injection of a solution containing patent blue (25 mg/mL), adrenalin (1:100,000), and Gelafundin, but decision was made case by case, namely, in ampullary tumours, where submucosal injection was not always necessary. The choice of the snare varied according to endoscopist's preference (10–25 mm snares were available). Current settings were cutting and coagulation of 120 W – Pulse Cut Slow (ESG-100, Olympus Inc., Tokyo, Japan) for non-ampullary lesions or Endocut 2 60 W (ICC 200, Erbe, Tübingen, Germany) for ampullary tumours.

Statistical Analysis

SPSS Statistics 26 (IBM) was used for analysis. Demographic and clinical characteristics were presented as frequencies. Continuous variables were expressed as average and standard deviation or as median and interquartile range, according to data distribution, and were compared using t-Student or Wilcoxon tests, respectively. Qualitative variables were compared using χ^2 or Fisher exact tests. A p value lower than 0.05 was considered statistically significant.

Results

Study Population Characteristics

In a total of 151 FAP families, 22 patients from 21 families met the inclusion criteria (DAs with at least 10 mm greatest axis resected in the study period): 54.5% of the patients were female (Table 1), with a median follow-up time of 8.5 (IQR: 5.8–12.3) years after the first endoscopy and 3.7 (IQR: 1.0–5.3) years after the first therapeutic endoscopy. Most germline *APC* mutations occurred in exon 15 (54.5%). Eight (36.4%) patients had known family history of DAs. The highest Spigelman stage found in these relatives was I, II, III, and IV in 1, 2, 1, and 4 cases, respectively. Patient characteristics are summarized in Table 1. The first screening upper endoscopy happened at 38.0 years of age (median) (IQR: 28.8–52.3) in the study population and DAs were detected in the first exam in 18 (81.8%) of them – staged as Spiegelman I, II, and III in 3, 13, and 2 cases, respectively.

Endoscopic Therapeutic Procedures

First therapeutic endoscopy (resection of ≥10 mm duodenal polyps) occurred at a median age of 41.0 (IQR: 33.0–58.2) years, and 9.1% (n = 2), 40.9% (n = 9), 45.5% (n = 10), and 4.5% (n = 1) of the patients were staged as Spiegelman I, II, III, and IV, respectively. The median time interval between the first screening endoscopy and the first therapeutic endoscopy was 60.3 (±39.1) months, corresponding to a median number of three endoscopies (IQR: 1–5) during that period, in which smaller adenomas were resected in 15 patients (68.2%).

After the first therapeutic endoscopy, a new procedure was required in 12 (54.5%) patients, once in 5 cases, twice in 4, three times in 2, and five times in 1 (median number of therapeutic endoscopies = 2, IQR 1–3), corresponding to a total of 46 therapeutic endoscopies and 50 lesions removed. The median time interval between therapeutic procedures was 20 (IQR: 14–23) months.

Most therapeutic procedures (69.6% of the procedures) included resection of only one large (≥10 mm) adenoma. The largest adenomas had a median size of 15 mm (IQR: 10–18 mm). The most frequently used technique was

Table 2. Endoscopy-related outcomes

Events	Non-ampullary adenoma	Ampullary adenoma
Piecemeal EMR	25 (24 endoscopies)	5
Immediate complications	–	1 perforation*
Early complications	–	1 bleeding*
R0 resection	25	5
En bloc EMR	11 (8 endoscopies)	9
Immediate complications	1 bleeding	1 perforation#
Early complications	–	2 acute pancreatitis (mild: 1; moderate: 1#)
R0 resection	9	9
Total	36 resections (32 endoscopies)	14 resections (14 endoscopies)

Pancreatitis severity grading according to the Revised Atlanta Criteria. Two patients had both immediate and early complications (marked with * and#). EMR, endoscopic mucosal resection; R0, endoscopically complete resection.

Table 3. Procedure-related complications – statistical analysis

Variable	*p* value
Gender	0.571
Age	0.168
Technique (piecemeal vs. en bloc)	0.619
Type of adenoma (ampullary vs. non-ampullary)	0.078
Adenoma size	0.873

piecemeal and en bloc mucosectomy for non-ampullary and ampullary adenomas, respectively (Table 2). Prophylactic defect closure with clips was performed after resection of a 15 mm ampullary tumour and two non-ampullary lesions of 10 and 18 mm; visible vessels were coagulated with snare-tip soft coagulation after resection of a 30 mm non-ampullary adenoma. Illustrating pictures can be seen in Figure 1. In 2 cases, resection was considered endoscopically incomplete – one due to scarring in previous resection site and the other due to difficult positioning. These patients were re-evaluated 3 and 5 months later and what was thought to be the residual lesion was successfully removed with cold snare in one and with biopsy forceps in the other case. Further endoscopic follow-up was performed annually and none developed adenocarcinoma. Complications occurred in 8.0% ($n = 4$) of the resected lesions – 3 after ampullectomy and one after a flat lesion mucosectomy (Table 2). Two patients had both immediate (first 24 h) and early (first 7 days) complications; the others had early complications. Immediate complications consisted in intraprocedural bleeding after non-ampullary tumour resection, and perforation after ampullectomy, successfully managed endoscopically. Early (during the first week after the intervention) complications included 1 case of bleeding in a patient who had prophylactic defect closure with through-the-scope clips after ampullectomy, controlled in a repeat endoscopy; 2 cases of acute pancreatitis; one perforation after ampullary tumour resection that was undetected during the procedure. Both pancreatitis occurred after ampulloma resection, despite prophylactic pancreatic stent placement. According to the Revised Atlanta Criteria, one was mild and the other was moderate due to local complications. The latter happened in the same patient in whom a duodenal perforation was diagnosed more than 24 h after the procedure. This patient underwent surgery, with construction of a feeding jejunostomy and pancreatic necrosectomy. He did not require organ support and had a favourable outcome.

Occurrence of complications was not significantly associated with the technique (piecemeal vs. en bloc mucosectomy) ($p = 0.619$), type of adenoma (ampullary vs. non-ampullary) ($p = 0.078$), or adenoma size ($p = 0.873$) (Table 3). Histology revealed adenomas harbouring low-grade dysplasia in 89.1% (tubular adenomas 76.1%, tubulovillous 13.0%); high-grade dysplasia in 4.6% ($n = 2$) of cases; no adenocarcinomas were found.

One patient underwent elective duodenopancreatectomy, which did not harbour duodenal cancer. This patient had Spiegelman stage IV disease with three large (>30 mm) lesions that were considered to have a high risk of recurrence/treatment failure after endoscopic resection – one involving the bulbus with a bulky sessile component, one in the transition to the second portion of the duodenum, and the other adjacent to the papilla, close to a fibrotic area of previous resections. All other patients remain under active surveillance.

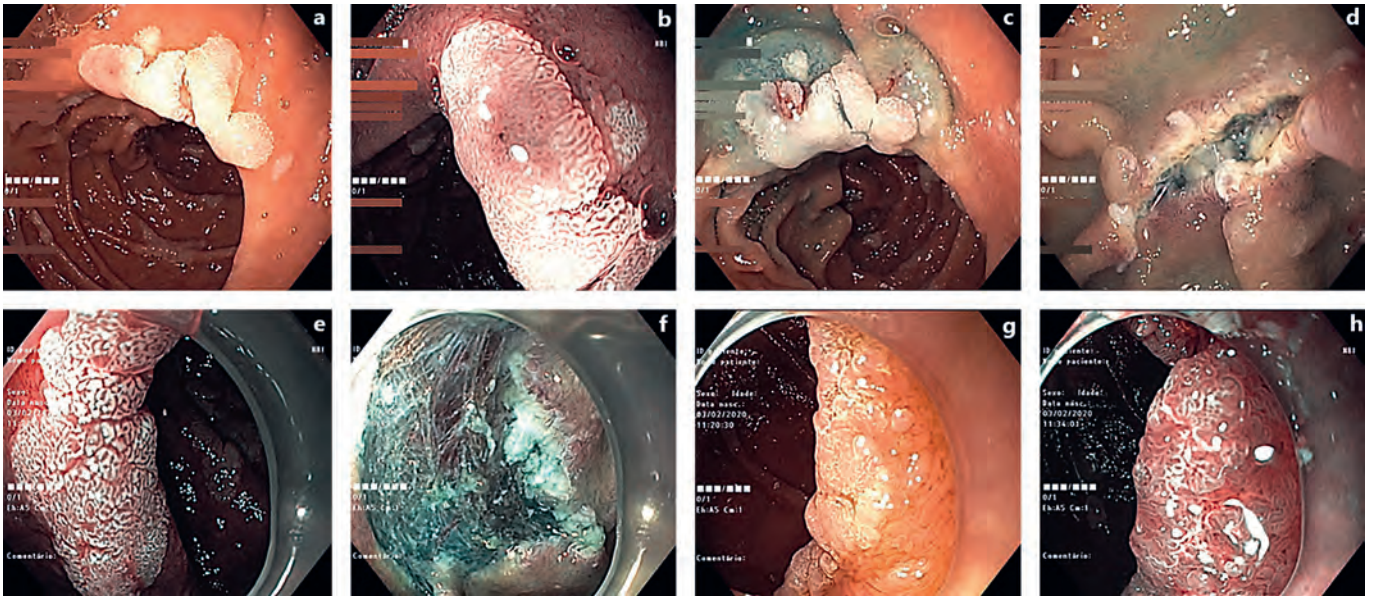

Fig. 1. Examples of resected DAs. **a** A 12-mm lesion (Paris 0–IIa) in white light examination (WLE). **b** Same lesion under narrow band imaging (NBI). **c** After submucosal injection. **d** During the resection procedure. **e** 15-mm DA (Paris 0–IIa) in WLE. **f** Post-polyp resection. **g** 12-mm lesion (Paris 0–IIa) in WLE. **h** Under NBI.

Discussion

Adenomatous duodenal disease is a known morbidity factor in FAP patients. Endoscopic resection of DAs has a high success rate, with reported complete resections in 86–100% of the cases [16, 21, 31–33]. Even though reported recurrence rates are 10–37% [18, 31–33], the natural history of DAs in FAP patients makes it difficult to distinguish disease progression from local recurrence. In our series, most patients required 2 therapeutic endoscopies during follow-up, reflecting this characteristic.

Endoscopic resection was a safe technique in our series, with an 8.0% complication rate, but with most cases amenable to conservative or endoscopic approaches. This rate is similar or even lower than that reported in other series, and it is also similar in terms of severity of the adverse events. As stated in the literature, most complications occurred after resection of ampullary adenomas, even though it did not reach statistical significance, probably due to our series' small numbers. Particularly, acute pancreatitis occurred in 2 of 14 ampullary tumour resections despite pancreatic stent placement, in line with previous reports [18, 34–36]. Notably, intraprocedural bleeding rates were lower than expected from literature review [31, 32, 37].

The duodenum remains a challenging location for endoscopic therapy and mucosal resection is the first-line endoscopic resection technique for non-malignant large DAs [38, 39]. However, when EMR is not feasible and considering the risks associated with the surgical alternatives, endoscopic submucosal dissection can be considered by experienced endoscopists [39, 40]. In our series, duodenal surveillance started later than recommended in international guidelines since a significant number of patients were referred to our clinic only in adult age after a CRC diagnosis in the patient or in a family member.

There were no cases of duodenal cancer during follow-up, reflecting the effectiveness of endoscopic surveillance according to the Spigelman stage. Therefore, this work further strengthens current recommendations of DAs surveillance in FAP patients and legitimates the choice of endoscopic resection as the first-line treatment.

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Statement of Ethics

All procedures were done in accordance with the Helsinki Declaration. Ethical approval was not required for this study in accordance with local/national guidelines, and retrospective observational studies do not require specific authorization by our institution's policy. All patients gave oral and written informed consent for every endoscopic procedure, and the research was carried out in accordance with the Helsinki Declaration.

Conflict of Interest Statement

The authors have no conflict of interest to declare.

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Author Contributions

Joana Lemos Garcia and Isadora Rosa wrote the paper; João Pereira da Silva was responsible for the endoscopic treatment and for the referral of ampullectomy patients; Pedro Lage and Isabel Claro reviewed the paper; and Isadora Rosa, Pedro Lage, and Isabel Claro were responsible for the follow-up of these patients in the Familial Risk Clinic.

Data Availability Statement

Research data are not shared due to confidentiality.

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Groove Pancreatitis: Clinical Cases and Review of the Literature

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Keywords
Groove pancreatitis · Pancreatoduodenectomy · Paraduodenal pancreatitis

Abstract
Introduction: Groove pancreatitis (GP) is a type of chronic segmental pancreatitis that affects the pancreatoduodenal groove area, and it is often misdiagnosed. Outflow obstruction of the minor papilla associated with alcohol consumption seems to be the main pathophysiological mechanism, and it affects mainly middle-aged males. Symptoms include nausea and postprandial vomiting from gastric outlet obstruction, weight loss, and abdominal pain. Despite modern advances, such as radiological and endoscopic methods, distinction between GP and pancreatic cancer remains a challenge, and histological examination is sometimes necessary. When a diagnosis can be obtained without a surgical specimen, management can be conservative in the absence of acute or chronic complications. ***Case Presentation:*** The authors present 2 clinical cases which portray the diagnostic workup and management decisions of this entity. ***Discussion/Conclusion:*** GP is a clinical entity, offering diagnostic and therapeutic challenges. Imaging exams are crucial in the diagnosis and follow-up, but surgery may be necessary in a significant number of cases due to the incapacity to rule out malignancy.

Pancreatite da goteira: Casos clínicos e revisão da literatura

Palavras Chave
Pancreatite da goteira · Pancreatoduodenectomia · Pancreatite paraduodenal

Resumo
Introdução: A pancreatite da goteira (PG) constitui uma forma de pancreatite crónica segmentar, que afeta a área da goteira pancreatoduodenal, sendo frequentemente subdiagnosticada. O mecanismo fisiopatológico principal parece ser a obstrução ao fluxo da papila *minor* relacionada com o consumo de álcool. Esta patologia ocorre mais frequentemente em homens entre a 4ª e 5ª décadas de vida. A maioria dos doentes apresenta sintomas como náuseas e vómitos pós-prandiais, perda ponderal e dor

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abdominal. Apesar do desenvolvimento atual dos métodos radiológicos e endoscópicos, a distinção entre PG e neoplasia pancreática constitui um desafio diagnóstico e a avaliação histológica pode ser necessária. Se for possível obter o diagnóstico sem intervenção cirúrgica, o tratamento pode ser conservador na ausência de complicações agudas e crónicas. ***Apresentação do caso:*** Apresentamos 2 casos clínicos que demonstram a abordagem diagnóstica e a gestão de decisões terapêuticas nesta entidade. ***Discussão/Conclusão:*** A PG é uma entidade clínica que oferece com diagnóstico e terapêutica desafiantes. Apesar da importância crucial dos exames imagiológicos no diagnóstico e seguimento, a incapacidade de excluir um processo maligno torna necessária a intervenção cirúrgica numa parte significativa dos casos.

Introduction

Groove pancreatitis (GP), also described as paraduodenal pancreatitis, is a rare form of segmental chronic pancreatitis characterized by fibrotic scarring of the pancreatoduodenal (PD) groove, an anatomical area bound by the pancreatic head, duodenum, and common biliary duct (CBD) [1]. There are two forms of GP: pure GP occurring solely within the pancreaticoduodenal groove and segmental GP also affecting the pancreatic head [2, 3]. Its pathophysiology remains unclear, but it is likely to be multifactorial with a common pathway being the obstruction of the minor papilla [4]. Imagiological findings include fibrotic changes of the pancreatic groove and the presence of duodenal wall cysts as well as the thickening of the duodenal wall, pancreatic head enlargement, CBD, and Wirsung duct stricture. Given the clinical and radiological resemblance to pancreatic cancer, the diagnosis is challenging and frequently requires surgical intervention [5, 6]. We report two cases of GP as well as a review of the literature. Both our patients were male with a history of alcohol consumption and had a similar clinical and imaging presentation. However, they were managed differently with one of them requiring pancreatoduodenectomy.

Case Report 1

A 52-year-old male patient, with a history of hypertension and dyslipidemia, active smoking habits (35 pack units/year), and alcohol consumption over 100 g of alcohol daily, presented to the emergency department with right quadrant abdominal pain for over 5 months, with irradiation to the back associated with vomiting and weight loss (6% of the total body weight in 1 year). On examination, tender right hypochondrium palpation was noted. No signs of peritoneal reaction, ascites, or organomegaly were observed. Liver function tests, bilirubin, and amylase were within the normal ranges. He was referred to an outpatient consultation for follow-up.

The patient was reevaluated 5 months later, and because of his persistent abdominal pain and vomiting, an upper endoscopy was performed and revealed a bulging of the duodenal bulb with irregular mucosa. Duodenal biopsies were negative for neoplastic cells. Abdominal CT scan revealed diffuse parietal thickening of the second duodenal portion and diffuse densification of the surrounding tissues with preserved pancreatic structure and no Wirsung duct dilation (shown in Fig. 1). Serum carcinogen antigen 19.9 (CA 19.9) and IgG4 were normal. An abdominal magnetic resonance imaging (MRI) revealed heterogeneity in the pancreatic-duodenal recess, thickening of the second duodenal portion with a central cystic image (8 mm), and maintained pancreatic morphology and dimension (shown in Fig. 1). An endoscopic ultrasonography (EUS) showed hyperechoic foci and parenchymal lobularity, aspects of chronic pancreatitis, without pancreatic head nodular lesions or Wirsung duct dilation. Despite alcohol withdrawal, tobacco reduction, and pain medication, intense abdominal pain persisted with a great impact on the patient's quality of life. An abdominal CT was performed 14 months after the initial presentation, showing the same findings as before. The case was discussed at an oncology multidisciplinary meeting, and after discussion with the patient, he was submitted to a cephalic pancreaticoduodenectomy with complete remission of the abdominal pain. The pathology result was compatible with GP (shown in Fig. 2). At 5 years of follow-up, the patient is asymptomatic.

Case Report 2

A 63-year-old male with active smoking habits (60 pack units/year) and alcohol consumption (25 g alcohol per day) presented with a 1-month history of unintentional weight loss (31% of previous weight, BMI 15 kg/m^2) associated with postprandial vomiting and abdominal pain for 2 weeks. On examination, epigastrium and right hypochondrium tenderness on palpation were noted. He had no jaundice, palpable masses, or lymph nodes. Liver function tests, pancreatic enzymes, IgG4, and CA 19.9 were normal. Abdominal CT scan (shown in Fig. 3a) showed increased volume of the pancreatic head with small calcifications and a CBD of 8-mm upstream from the intrapancreatic portion. Upper endoscopy revealed extrinsic duodenal bulb compression (shown in Fig. 3b). EUS showed a heterogeneous pancreatic head parenchyma with hyperechoic foci with shadowing, but without Wirsung duct dilatation and duodenal wall thickening (25 mm). There was no evidence of nodular lesions (shown in Fig. 3c). The patient was maintained with nasojejunal feeding during 15 days with weight gain and pain relief.

The case was discussed at a multidisciplinary meeting, and it was decided to maintain the patient under active surveillance with conservative treatment. The patient stopped alcohol and tobacco consumption. Three months after discharge, he gained 18 kg and had no abdominal pain or vomiting. The MRI showed thickening and cystic changes in the duodenal wall and delayed enhancement in the PD groove, with a nondilated CBD. At 5 years of follow-up, he was asymptomatic and had normal laboratory tests.

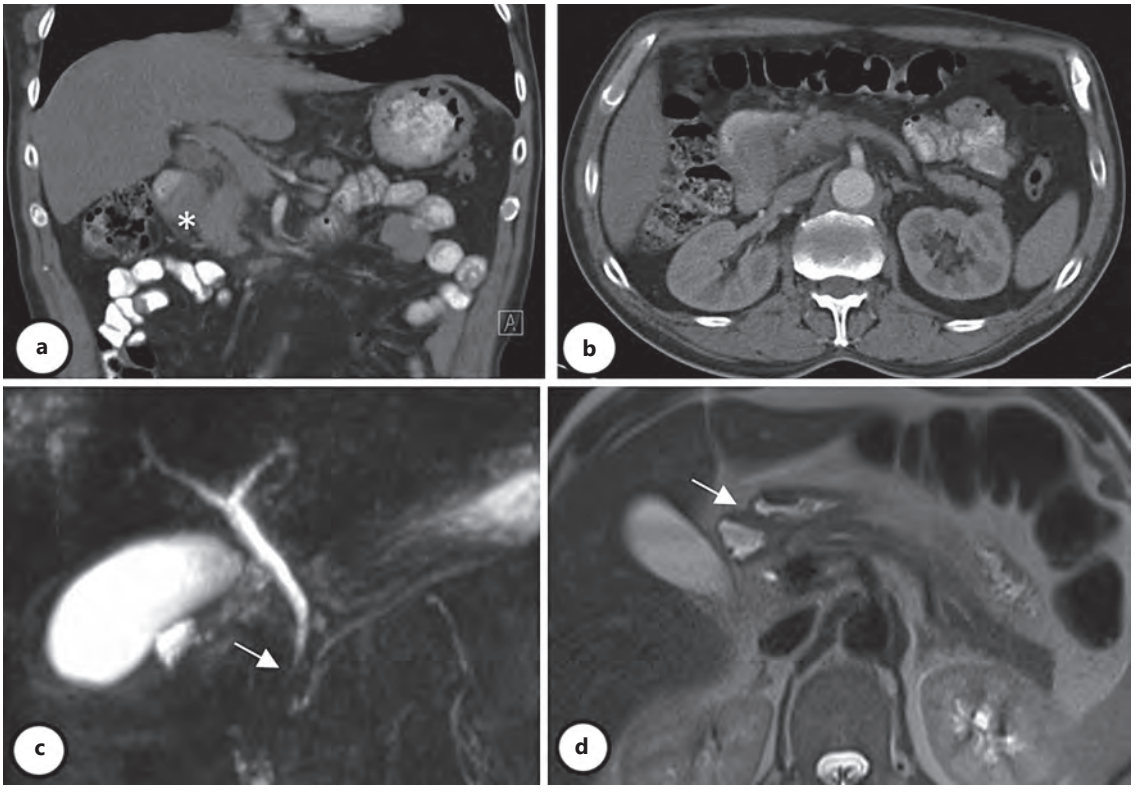

Fig. 1. Abdominal CT of case 1 showing a crescentic mass-like structure in the groove region (*) which causes duodenal stenosis (**a**) with a normal pancreas structure without Wirsung duct dilation (**b**) MRCP showing a smooth tapering of CBD (arrow) (**c**) and in a T2-weighted image (**d**) a cyst in the groove region. CT, computed tomography; MRCP, magnetic resonance cholangiopancreatography; CBD, common biliary duct.

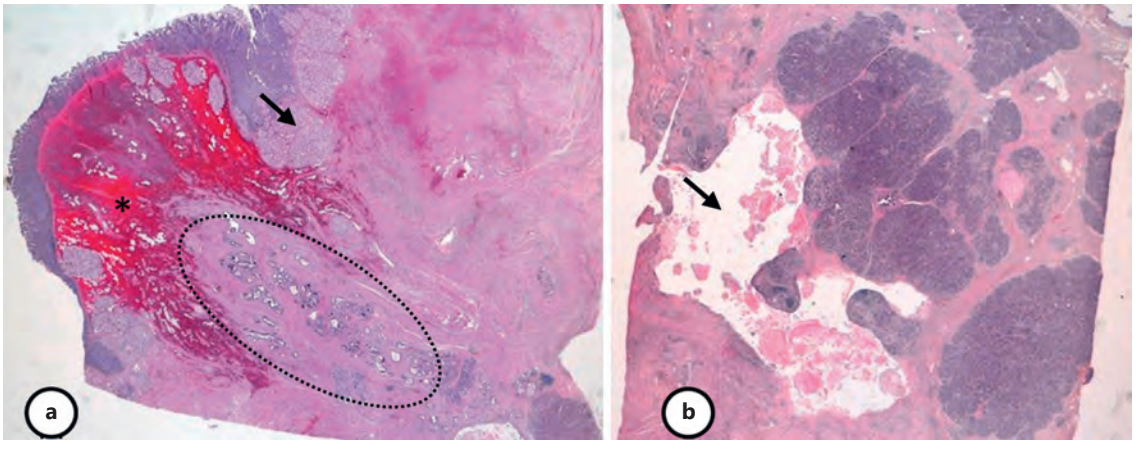

Fig. 2. Microscopic findings in case 1 showing (**a**). inflammatory changes with the presence of fibrosis and lymphoid infiltrate (circle), Brunner gland hyperplasia (arrow), and recent hemorrhage (*); (**b**) cystic spaces (arrow) and pancreatic acini with fibrosis.

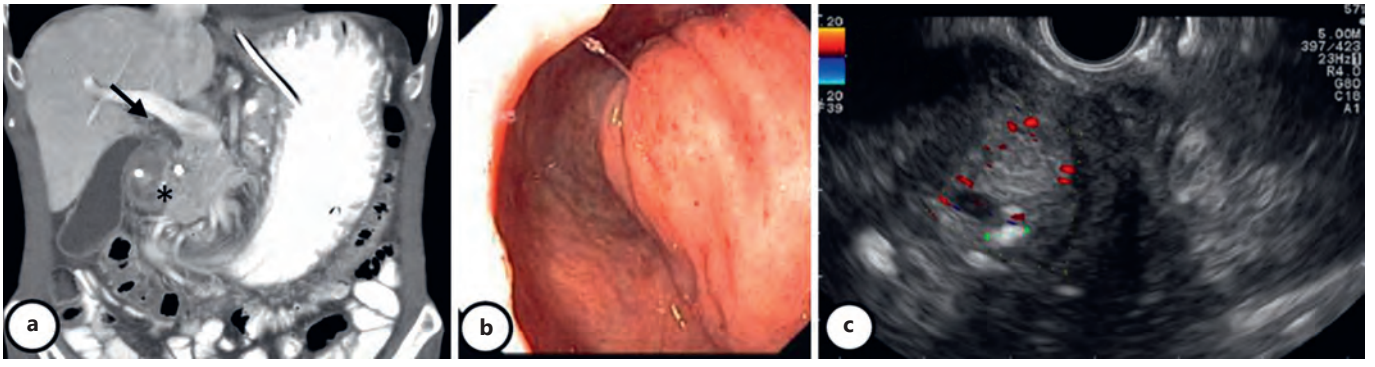

Fig. 3. a Abdominal computed tomography of case 2 showing enlargement of pancreas head with foci of cystic degeneration (*) and CBD dilation (8 mm) (arrow). **b** Upper endoscopy of case 2 showing duodenal stenosis (bulb represented) by extrinsic compression. **c** Endoscopic ultrasound of case 2 showing hypoechoic band-like thickening of the pancreaticoduodenal groove, as well as thickening of the adjacent duodenum and a hypoechoic heterogeneous pancreatic head. CDB, common biliary duct.

Discussion/Conclusion

GP – Pathophysiology

GP is a type of segmental chronic pancreatitis, first described in 1973 by Becker [2] with the German word Rinnenpankreatitis and translated into GP in 1982 by Stolte et al. [7]. The true incidence and its underlying etiology remain uncertain, but the central mechanism seems to be an anatomical or functional outflow obstruction of the minor papilla [1, 8–10]. The vast majority of patients have significant alcohol consumption, indicating that alcohol plays a major role in promoting pancreatic juice viscosity and exacerbating the inflammatory process [11]. Various factors contribute to outflow obstruction: pancreatic heterotopia in the duodenal wall with localized inflammation and duct dilation; Brunner gland hyperplasia, which can occur from chronic alcohol stimulation or from increased levels of cholecystokinin; or gastrin and pancreas *divisum* with subsequent increased pressure in the minor papilla [9, 12, 13].

Clinical Symptoms

GP manifests most commonly in men in their fourth to fifth decade of life with a history of chronic alcoholism, as occurred in our 2 cases [9]. The typical clinical symptoms are severe upper abdominal pain, nausea, recurrent postprandial vomiting, and weight loss [14]. Rarely, some patients can present with duodenal stenosis. Jaundice is rare and is often more suggestive of an underlying malignancy [10].

Diagnosis

The differential diagnosis includes pancreatic adenocarcinoma, periampullary cancers, pancreatic groove neuroendocrine tumor, autoimmune pancreatitis, and acute pancreatitis [3, 5]. Although in some patients, there are significant clinical and imaging features of GP, there is often overlap with other infiltrative processes involving the pancreatic groove, namely pancreatic cancer. Table 1 summarizes the clinical, laboratorial, and imagiological differences between GP and cancer.

Laboratory values and biochemical markers are often nonspecific. While liver function tests and bilirubin are generally within the normal range, alkaline phosphatase levels can be elevated even in the absence of biliary obstruction. Amylase and lipase may be slightly increased [4, 11]. Tumor marker's carcinoembryonic antigen and CA19.9 levels are generally normal. However, obstructive jaundice, if present, may cause an elevated level of CA 19.9, not related to an underlying malignancy [15]. IgG4 levels should be measured since autoimmune pancreatitis may mimic GP [16].

Imaging Features

Contrast-enhanced CT and MRI are the primary imaging modalities used when GP is suspected. The classic imaging features on CT scan consist of an ill-defined crescentic soft tissue mass seen in the PD groove with the pure form of GP. In its segmental form, there is a mass-like enlargement of the whole pancreatic head that can be indistinguishable from pancreatic cancer. The duodenal wall is involved in 92% of patients with luminal narrowing due to wall thickening. Smalls cysts are seen within

Table 1. Clinical, laboratory, and imaging features for distinguishing GP and pancreatic cancer arising in the groove region

	GP	Pancreatic cancer
Age	Younger patients (fourth–fifth decade)	Older patients
Ethanol abuse	Frequent	Uncertain association
Jaundice	Late event	Can occur early
Serum CA 19-9	Usually normal	Usually elevated
CT scan	Plate-like hypodense crescentic lesion and cysts in the PD groove	Round irregular pancreatic head mass
MRI	Sheet-like mass in the groove, hypointense on T1-weighted images, variable T2-weighted intensity. Cysts in the groove region	Round irregular pancreatic head mass
EUS	Duodenal wall thickening and luminal stenosis, long and smooth common bile duct stenosis, hypoechoic area and cysts in the groove region	Irregular and abrupt common bile duct stenosis, vascular encasement

CT, computed tomography; MRCP, magnetic resonance cholangiopancreatography; EUS, endoscopic ultrasound.

the duodenal wall or in the PD groove itself, in 81% and 75% of cases, respectively [17]. This common finding in GP contrasts with its rarity in pancreatic adenocarcinoma. CBD may be narrowed with a smooth, tapered, and regular stenosis [4, 11].The peripancreatic vessels are typically maintained, in contrast with the typical encasement in cases of adenocarcinoma. MRI shows a "sheet"-like mass of tissue, which is hypointense on T1-weighted images and variable in T2-weighted images, according to the time of disease onset [5]. Duodenal wall thickening is also seen, and T2-hyperintense cysts can be found in both the duodenal wall and PD groove [4, 9]. A study conducted by Kalb et al. [18] indicates that during focal thickening (>3 mm), abnormal increased enhancement of the second portion of the duodenum and cystic changes in the region of the pancreatic accessory duct are all present, the diagnostic accuracy is 87.2%, and a diagnosis of cancer can be excluded with a negative predictive value of 92.9%. Upper endoscopy typically shows mucosa edema, erosion, polypoid appearance of the descending duodenal part, and luminal stenosis [9]. EUS is considered by some authors the preferred imaging method as it provides high-resolution images of the head of the pancreas and PD groove, and it allows to obtain tissue sampling [5]. In GP, EUS can detect a hypoechoic band-like thickening of the PD groove and adjacent duodenum with intramural cysts, smooth stenosis of CBD and, in the segmental forms, a heterogeneous hypoechoic pancreatic head mass. Nonetheless, EUS is not able to differentiate inflammation and malignant infiltration in several cases [4, 11, 12].

Histopathology

Pathologic analysis of the pancreatic resection specimen is the only definitive way of diagnosing GP. Gross examination shows active and chronic inflammation of the PD groove, adjacent duodenal wall, and pancreatic head, as well as extensive scarring. Cystic spaces (0.2–2 cm) can be identified within the duodenal muscularis propria and submucosa and/or PD groove [9, 19].

The histological aspect of GP is characterized by thickening of the duodenal wall, inflammation of the Brunner gland and smooth muscle hyperplasia. Sometimes, heterotopic pancreatic tissue in the duodenal wall is identified, but this finding is not universal. Spindled stromal cells are the most common finding after fine needle aspiration (FNA). However, endoscopy-guided FNA biopsy presents great variability depending on the area sampled and the presence of cytological features associated with reactive cellular atypia resulting from pancreatitis may mimic neoplasia [4]. To our knowledge, there are no studies comparing EUS-guided FNA versus FNB, specifically in GP. However, recently, Wong et al. [20] compared the diagnostic performance of EUS-guided tissue acquisition by EUS-guided FNA versus EUS-guided FNB for solid pancreatic mass, and they found that the diagnostic yield of solid pancreatic mass was higher in FNB than in FNA (94.6 vs. 89.6%).

Treatment

Currently, there are no treatment guidelines on GP. When an accurate diagnosis of GP is possible, patients may be treated conservatively. Conservative therapy includes analgesia, alcohol and tobacco cessation, and parenteral nutrition when enteral nutrition is contraindicated, the patient does not meet the daily energy needs for more than 10 days, or in case of gastric or intestinal outlet obstruction [12]. There are also some reports of cases using somatostatin analogs, but the results appear to be temporary [21]. Endoscopic treatment may involve pseu-

docyst drainage, pancreatobiliary stent placement, or duodenal dilation. When cancer cannot be safely excluded, surgery is advised. Surgical treatment encompasses pancreatoduodenectomy, the most common procedure, and digestive or biliary bypass operations.

A recent systematic review evaluated clinical outcomes in GP after treatment [14]. The treatment was conservative in 29%, and half of the patients had complete symptom relief. Endoscopic and surgical treatment occurred in 12% and 59% of cases, respectively. Although surgery resulted in complete symptom relief in most of the patients (79%), it is associated with a high rate of complications (20%) [14]. Furthermore, in a large case series from Arvanitakis M et al., medical treatment associated with endoscopic approach (pancreatic ductal drainage, stricture dilation, and cyst drainage) allowed completed clinical success in 80% of the cases [22]. Thus, a stepwise approach, starting with conservative treatment, is recommended, unless malignancy cannot be ruled out.

In conclusion, we present the 2 cases of patients with classic risk factors, including alcohol and tobacco abuse, and symptoms of GP. Furthermore, they have similar clinical, laboratory, and imaging findings, namely, normal CA 19.9, parietal thickening of the descending part of the duodenum, and cystic changes without pancreatic duct dilation or vascular encasement. Thus, chronic abdominal pain and vomiting in a patient with history of alcohol abuse and no significant laboratory findings can point out to a chronic pancreatitis like GP. The treatment should be individualized, but a surgical approach may be necessary, as indicated in the first case.

Statement of Ethics

The authors have no conflicts of ethics. A written informed consent was obtained from participants for publication of the details of their medical case and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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There were no funding sources relevant to this case report.

Author Contributions

Catarina Nascimento – acquisition and interpretation of clinical data for the case report, drafting the case report, and corresponding author. Carolina Palmela and António Soares – conception and design of the case, data collection, critically revising the case report, and final approval of the version to be published. Maria Lobo Antunes and Luísa Glória – critically revising the case report and final approval of the version to be published. Catarina Fidalgo – conception and design of the case, critically revising the case report, and final approval of the version to be published.

Data Availability Statement

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

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Successful Endoscopic Closure of Esophageal Perforation in Boerhaave Syndrome Using the Over-the-Scope Clip

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Keywords
Endoscopy · Boerhaave syndrome · Esophageal perforation · Over-the-scope clip

Abstract
Boerhaave syndrome (BS) is a rare but potentially fatal condition. Although surgery is considered the standard treatment, endoscopic therapy has acquired an important role as a minimally invasive management approach. The authors describe 2 cases of middle-aged male patients, presenting with spontaneous esophageal perforation after severe straining and vomiting. In the first case, the patient presented with a bone impaction in the upper esophagus successfully removed by rigid esophagoscopy. After the procedure, a chest X-ray/cervicothoracic computerized tomography scan (CT) showed a left hydropneumothorax and pneumomediastinum with oral contrast leak at the lower esophagus. In the second case, the patient presented to the Emergency Department with severe chest pain after an episode of vomiting. The CT showed a massive pneumomediastinum, subcutaneous emphysema, and an oral contrast leak compatible with BS. The patient was initially submitted to surgical suture, but contrast extravasation persisted after 12 days. After multidisciplinary team discussion of both patients, an upper gastrointestinal endoscopy was performed, which revealed pericentimetric wall defects at the distal esophagus. These were successfully closed using an over-the-scope clip (OTSC). After at least a 9-month follow-up, patients have remained clinically well with no relapse. The authors highlight the severity of these clinical cases and the endoscopic option that proved to be decisive in addressing BS. The favorable outcomes suggest a role for the OTSC approach in closing spontaneous esophageal perforation both as first-line and as rescue therapy after a surgical failure.

Encerramento endoscópico de perfuração esofágica em síndrome de Boerhaave com "Over-the-Scope Clip"

Palavras Chave
Endoscopia · Síndrome de Boerhaave · Perfuração esofágica · Over-the-scope clip

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Resumo

A síndrome de Boerhaave (SB) é uma entidade rara, mas potencialmente fatal. Embora a cirurgia seja o tratamento padrão, o tratamento endoscópico tem adquirido um papel importante como opção minimamente invasiva. Os autores descrevem dois casos de doentes do sexo masculino de meia-idade, que apresentaram perfuração esofágica espontânea após esforço emético intenso e vómitos. No primeiro caso, o doente apresentou impactação de um osso no esófago superior, que foi removido com sucesso por esofagoscopia rígida. Após o procedimento, o doente realizou radiografia de tórax e tomografia computorizada (TC) cervico-torácica que evidenciou hidropneumotórax esquerdo e pneumomediastino com extravasamento de contraste oral ao nível do esófago inferior. No segundo caso, o doente apresentou-se no Serviço de Urgência com toracalgia intensa após episódio de vómito. A TC mostrou pneumomediastino exuberante, com enfisema subcutâneo e extravasamento de contraste oral compatível com SB. O doente foi inicialmente submetido a rafia cirúrgica, mas o esofagograma ao 12º dia mostrou persistência de extravasamento do contraste. Após discussão em reunião multidisciplinar, ambos os doentes realizaram endoscopia digestiva alta, com visualização de orifícios pericentimétricos no esófago distal, encerrados com sucesso com a aplicação de clip over-the-scope (OTSC). Após seguimento de pelo menos 9 meses, os doentes permaneceram clinicamente bem, sem evidência de recidiva. Os autores destacam a gravidade desses casos clínicos, bem como a opção endoscópica que se mostrou decisiva no tratamento da SB. Os resultados favoráveis sugerem um papel para a abordagem com OTSC no tratamento da perfuração esofágica espontânea, tanto como tratamento de primeira linha, como terapêutica de resgate após falência do tratamento cirúrgico.

Introduction

Spontaneous esophageal perforation, known as Boerhaave's syndrome (BS), is a predominantly longitudinal perforation of the distal esophagus due to forceful emesis. It is associated with a high mortality rate (20–40%) due to delay in recognition and treatment [1]. The classical triad of subxiphoid retrosternal pain, vomiting, and subcutaneous emphysema is present in only a few patients, posing a difficult diagnostic challenge. In fact, in a few patients, the injury occurs silently, without any relevant medical history [2]. The esophagogram may aid diagnosis, but it has a false-negative rate of 10%. In such cases, CT with orally administered water-soluble contrast provides the best diagnostic tool [3].

The BS management includes the resolution of the source of the infection, thoracic and mediastinal debridement, and surgical or nonsurgical closure of the defect. With the development of endoscopic procedures during the last decades, endoscopy represents a minimal or significantly lower burden in the diagnosis of BS and its treatment [4]. Endoscopic stenting and over-the-scope clip (OTSC) have been reported as an alternative to surgery in selected cases, with good results [5]. Here, we report 2 cases of successful endoscopic management of a spontaneous esophageal rupture using OTSC.

Case Reports

Case 1

A 49-year-old man was transferred from a peripheral hospital following an episode of meat bone impaction during lunch which could not be removed by upper gastrointestinal endoscopy (UGE) on that Unit. The impaction was associated with spontaneous and self-induced retching. The patient was submitted to a rigid esophagoscopy under deep sedation with successful removal of the bone located immediately below the superior esophageal sphincter, with no evidence of severe wall damage. During the first day of recovery, the patient developed left and anterior severe thoracic pain associated with respiratory failure. Initial chest radiography revealed a left-sided pleural effusion and pneumothorax (Fig. 1a). Broad-spectrum antibiotics and oxygen therapy were immediately started. A thoracic catheter was inserted, allowing the drainage of a cloudy serous fluid with increased amylase, and positivity to methylene blue challenge, suggestive of a gastrointestinal tract perforation. Oral contrast cervicothoracic CT confirmed pneumomediastinum and left empyema with contrast leak at the lower esophagus level (Fig. 1b). After a multidisciplinary meeting, a UGE was performed on the 4th day, showing superficial laceration at the proximal esophagus related to the recent impaction and a 10-mm recent esophageal perforation in the distal esophagus (Fig. 1c). An 11-mm t-type OTSC (Ovesco, Tübingen, Germany) was selected. The perforation edges were grasped and captured into the cap using a harpoon device (OTSC anchor®) (Fig. 1d). The clip was then released and the perforation hole was successfully closed (Fig. 1e). On the fourth day after clipping, an esophagogram showed no leak, and oral intake was started. The patient was discharged on the 15th day postendoscopic closure, clinically well with resolution of empyema. Three months later, revision UGE revealed OTSC in situ (Fig. 1f) with effortless passage into the stomach. The patient remains clinically well on a complete diet.

Case 2

A 50-year-old man with no relevant medical history was admitted to the Emergency Department with severe chest pain after an episode of vomiting. A cervicothoracic CT showed an exuberant pneumomediastinum, extending to the muscular planes of the neck

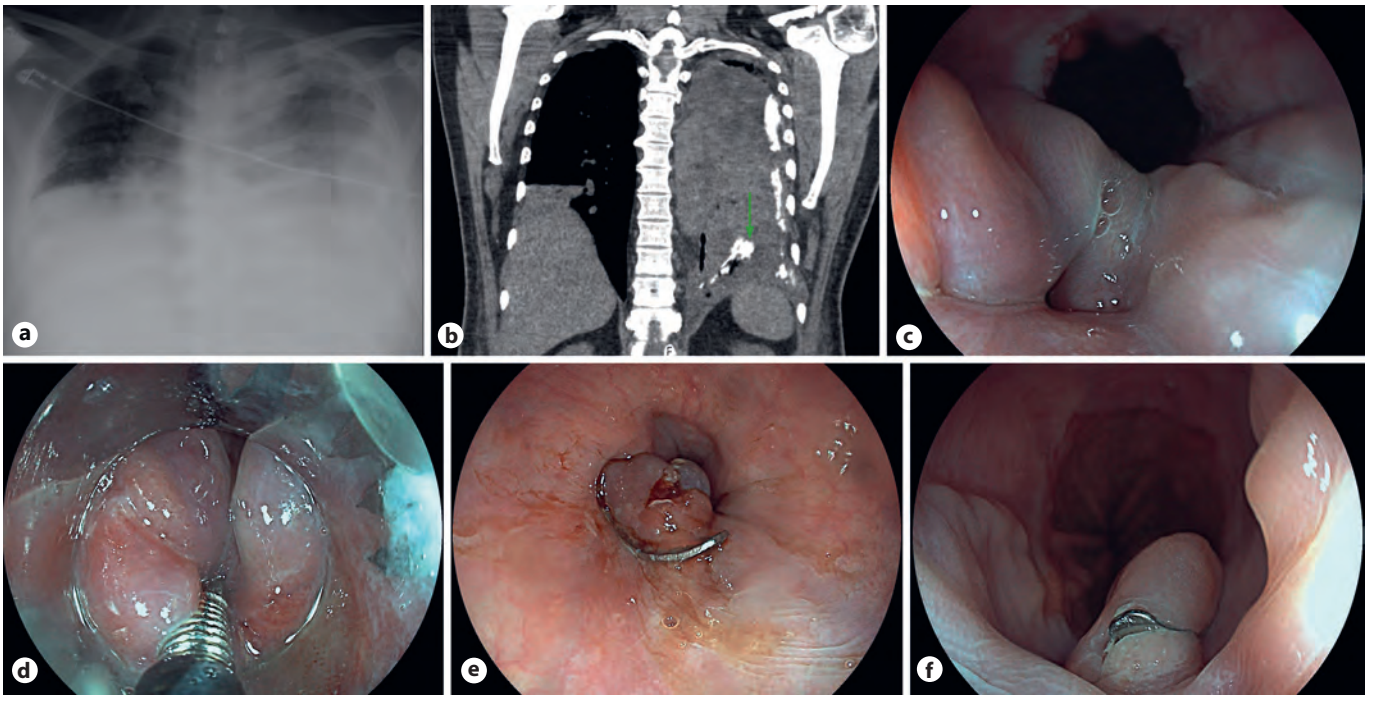

Fig. 1. a Chest radiography showing left pneumothorax and pleural effusion, with complete opacification of the left hemithorax and the trachea shifted to the right. **b** Cervicothoracic CT revealed an oral contrast leak at the distal esophagus (arrow). **c** Upper gastrointestinal endoscopy showing a hole in the distal esophagus. **d** Perforation's edges were captured with the OTSC anchor® into the cap, before clipping. **e** Perforation hole was successfully closed using OTSC. **f** Three months later, UGE revealed OTSC in situ, with no signs of esophagus obstruction.

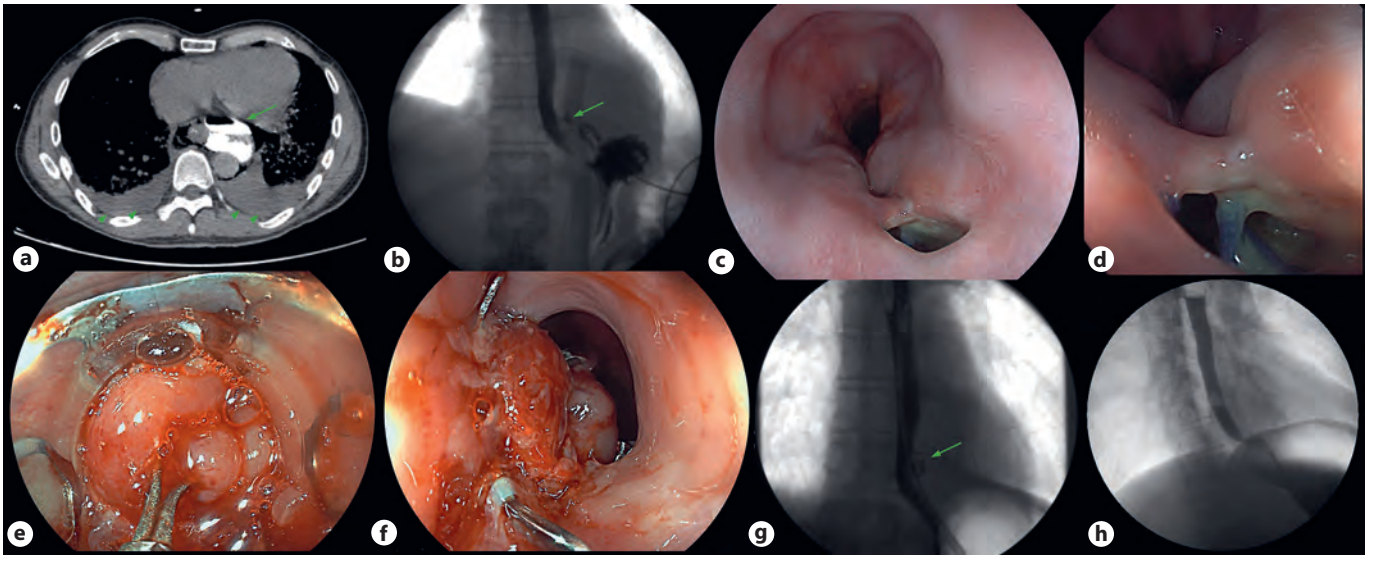

Fig. 2. a Cervicothoracic CT showing oral contrast extravasation from the esophagus into the mediastinum (arrow) and bilateral pleural effusion (arrowheads). **b** Esophagogram performed 12 days after surgery showing persistence of oral contrast extravasation (arrow) near the left distal esophagus wall. **c**, **d** Endoscopic view of two adjacent holes in the distal esophagus, being possible to look at some suture points. **e** Holes' edges being pulled by OTSC anchor® into the cap, before clipping. **f** Esophagus after OTSC application, encompassing both holes. **g** Ten days postprocedure esophagogram showing OTSC in situ (arrow) with no contrast extravasation or signs of esophagus obstruction. **h** Nine months postprocedure esophagogram with no signs of OTSC, esophageal leakage, or esophageal stricture.

Table 1. Baseline characteristics and individual outcomes of cases of patients with BS managed with OTSC

Authors (year), reference	Patient Sex, age (years)	Size of mucosal defect (mm)	Pleural/ Mediastinal collections	Management	Timing to defect closure	Technical success of endoscopic approach, %	Complications related to endoscopic procedure	Discharge (days)	Follow-up (months)
Ramhamadany et al. [13]	Male, 69	NR	Yes	Thoracic drains + OTSC	Several days	100	None	NR	6
Kobara et al. [14]	Male, 62	100	No	OTSC + endoscopic clips	NR	100	None	25	0.8
Bona et al. [15]	Male, 36	10	Yes	Thoracic drains + OTSC + thoracotomy with decortication	10 days	100	None	28	NR
Vinnamala et al. [16]	Male, 63	10	Yes	Thoracic drains + OTSC	<24 h	100	None	NR	3
Musala et al. [17]	Male, 50	7	No	OTSC	1 day	100	None	4	1.5
Ngo et al. [18]	Male, 82	15	No	OTSC	4 h	100	None	NR	NR
González et al. [19]	Male, 63	20–25	Yes	Thoracic drains + OTSC + FCSEMS + video-assisted thoracoscopic decortication	NR	100	None	NR	2
Barakat et al. [20]	Male, 62	10	Yes	Thoracic drains + OTSC + FCSEMS	Immediately	100	None	NR	1
Al-Zahir et al. [21]	Male, 43	15	Yes	Thoracic drains + OTSC + chemical pleurodesis	9 days	100	None	16	6
Núñez-Rodríguez et al. [22]	Male, 63	10	No	OTSC	12 h	100	None	3	4
Hayashi et al. [23]	Female, 68	10	Yes	Thoracic drains + OTSC	12 days	100	None	32	2

BS, Boerhaave syndrome; NR, no reference; OTSC, over-the-scope clip; FCSEMS, fully covered self-expanding metal stent.

and presenting subcutaneous emphysema. The passage of oral contrast to the mediastinum confirmed the diagnosis of BS (Fig. 2a).

The patient was initially submitted to surgical treatment, with esophageal suture and drainage of the mediastinum. Thereafter, he was admitted to the intensive care unit, under invasive mechanical ventilation, antibiotics, and prolonged need for aminergic support. On the 12th day, an esophagogram showed persisting contrast leakage from the left wall of the distal esophagus in close communication with the multicapillary drain placed in the mediastinum (Fig. 2b). A UEG was performed showing two adjacent holes at the level of the distal esophagus, the largest with 12 mm of diameter, through which it was possible to observe suture points and the multicapillary drain (Fig. 2c, d).

It was decided to close it with 11 mm t-type OTSC using the OTSC anchor® with complete closure encompassing both holes (Fig. 2e). At the end of the procedure, a mild reduction of the esophageal lumen at the OTSC level was observed (Fig. 2f).

There was a favorable clinical and analytical response in the following days, with the progressive withdrawal of all supportive measures. After 10 days, the esophagogram revealed the OTSC in place and no signs of contrast leakage (Fig. 2h). The patient was discharged after 15 days tolerating an oral diet. Nine months after the procedure, the patient was asymptomatic and repeated an esophagogram and cervicothoracic CT, showing no signs of esophageal leakage or OTSC presence.

Discussion

Although no consensus exists regarding the best strategy, the current treatment of BS should be fitted to the patient's presentation, the type and extent of the rupture, the delay to the diagnosis, and the consequent viability of the esophageal wall [4]. Conservative management includes intravenous broad-spectrum antibiotics, restriction of oral intake, derivation of nasogastric content, pain control, gastric acid suppression, and hemodynamic monitoring and support. However, due to the high mortality associated with BS, an exclusive conservative approach can only be considered plausible under the following conditions: perforation already 5 days old and absence of signs of severe sepsis, esophagogram showing a contained perforation that drains freely back into the esophagus, and absence of contamination in the pleural space [6]. Unfortunately, this is hardly the rule, frequently occurring a more severe presentation and a worse prognosis due to septic complications.

Classical surgical intervention consists on open primary esophageal repair (laparotomy and/or thoracotomy). General principles of this approach include excellent exposure, debridement of nonviable tissue, closure of the defect, use of buttress to reinforce esophageal sutures, and adequate tube drainage. Overall mortality after open surgery for esophageal perforation is around 20%; however, prompt surgical intervention can reduce that mortality by 50% [7].

Less invasive techniques in the setting of esophageal surgery, such as laparoscopy and left video-assisted thoracoscopy, may be beneficial in minimizing operative surgical trauma, reducing postoperative pain, improving ventilation, and facilitating early mobilization. Early presentation, stable vital signs, and expertise of the surgical team are required [4].

Given the increasing improvements in advanced imaging, diagnosis, and therapeutic techniques, endoscopic treatment has become an effective and valid alternative to surgery in many clinical conditions, including BS in selected patients. Most data about the endoscopic approach to esophageal perforation come from the endoscopic management of iatrogenic perforation during endoscopic procedures. The most decisive factor in the selection of endoscopic modality seems to be the size of the esophageal wall defect. Through-the-scope clips have shown to be effective for small defects (less than 10 mm), while OTSC can be applied in moderate-size perforations up to 20 mm. Larger perforations in the mid and lower esophagus can be managed with the temporary placement of self-expandable metal stents [8].

Endoscopic vacuum therapy (EVT) and more recently endoscopic suturing should also be considered in larger defects. EVT uses negative pressure to absorb secretions and promote wound healing by secondary intention, having proved to be especially useful in patients with postoperative anastomotic leaks. The evidence on endoscopic suturing is still scarce and there are technical difficulties in applying it to the esophagus [9, 10].

Early perforations (those diagnosed within 24 h) are described as having the best outcomes, as tissues have no edema, facilitating defect closure, and there is no active bacterial infection in the thoracic cavity or mediastinum. Therefore, apart from the perforation size, the timing of the intervention and the presence of inflammation or poor surrounding tissue quality with ischemic/necrotic wound edges may be relevant factors to take into account in the selection of the endoscopic approach. Even so, there are no comparative studies between different endoscopic modalities.

Concerning BS, case series also demonstrate that endoscopic management represents a valuable option [11, 12]. Table 1 summarizes the main characteristics and patients' outcome of several case reports of BS managed with OTSC published over the last decade, emphasizing the efficacy of the procedure with no reported direct complications [13–23].

In the 2 cases presented, the size of the perforations (and the complexity in case 2), the time elapsed since the

presumed occurrence and the associated thoracic manifestations, led to the choice of OTSC as the most adequate approach to secure an effective transmural closure. However, a self-expandable metal stent has also proven to be appropriate in this context, covering esophageal leaks and preventing fistula formation. Furthermore, with the possible exception of EVT, the endoscopic management of BS complicated with mediastinal or pleural collections should always be combined with percutaneous or surgical drainage of the extraesophageal contamination, as was the case [4]. In conclusion, the standard of care for patients with BS should be based on a multidisciplinary and case-to-case personalized approach including conservative, endoscopic, and/or surgical treatment. Our case report highlights that esophageal defect closure with OTSC may be a suitable minimally invasive option in a delayed scenario of BS, both as primary and rescue therapy, provided that it is technically feasible and mediastinal or pleural infection are sought and adequately drained.

Statement of Ethics

Ethical approval was not required for this study in accordance with local/national guidelines. The authors state that the patients provided written informed consents to publish their cases, including publication of images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

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Author Contributions

J.E.: literature research, manuscript preparation, and drafting; R.P., E.G-S., M.G.-S., and P.A.: critical revision of the manuscript for important intellectual content; and P.F.: manuscript final approval.

Data Availability Statement

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

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Pancreatic Insulinoma: When Surgery Is Not an Option

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Keywords
Insulinoma · Pancreatic neuroendocrine tumor · Endoscopic ultrasonography · Alcohol ablation

Insulinoma Pancreático: Quando a Cirurgia Não é Opção

Palavras Chave
Insulinoma · Tumor neuroendócrino pancreático · Ecoendoscopia · Ablação por álcool

A 74-year-old woman, with the history of obesity (body mass index: 38.05 kg/m^2), obesity-hypoventilation syndrome, and hypertension, was referred to endocrinology consultation due to symptomatic recurrent hypoglycemia for 15 years with worsening during the last 4 months. Computed tomography revealed a 2-cm hypervascular pancreatic isthmus mass compatible with a neuroendocrine tumor. Fasting insulin (53 μIU/mL, normal range: 3–25) and C-peptide (5.23 ng/mL, normal range: 0.93–3.73) were elevated during severe hypoglycemia, allowing the diagnosis of insulinoma. Endoscopic ultrasonography (EUS) was consistent with a neuroendocrine tumor adjacent to the main pancreatic duct (MPD; shown in Fig. 1). GaDOTA-NOC-PET was otherwise unremarkable. Diazoxide was started with inpatient dose titration to 150 mg three times daily (t.i.d.). However, she developed a hyperglycemic hyperosmolar syndrome. A lower dose was restarted (50 mg t.i.d.), but generalized edema developed. Considering these adverse events in a patient unfit for surgery, diazoxide was suspended and EUS-guided alcohol ablation (EUS-AA) was performed. Using a linear-array echoendoscope (EG-3270UK Slim Ultrasound Video Endoscope, Pentax, Tokyo, Japan; HI VISION Preirus Hitachi Medical Systems, Tokyo, Japan) and a 25-gauge needle (EchoTip, Wilson-Cook, Winston-Salem, NC, USA), a total of 0.9 mL of absolute alcohol (fractions of 0.1 mL, three passes) was injected with partial hyperechoic filling (shown in Fig. 2). Two small hypoechoic areas were left untreated to prevent MPD injury. She experienced incomplete response and underwent a second ablation, 3 months later, with equal injection volume (five passes). Two small MPD-adjacent hypoechoic areas persisted (shown in Fig. 3). Prophylactic rectal indomethacin and intravenous hydration were administered. Prophylactic antibiotics were not used. She

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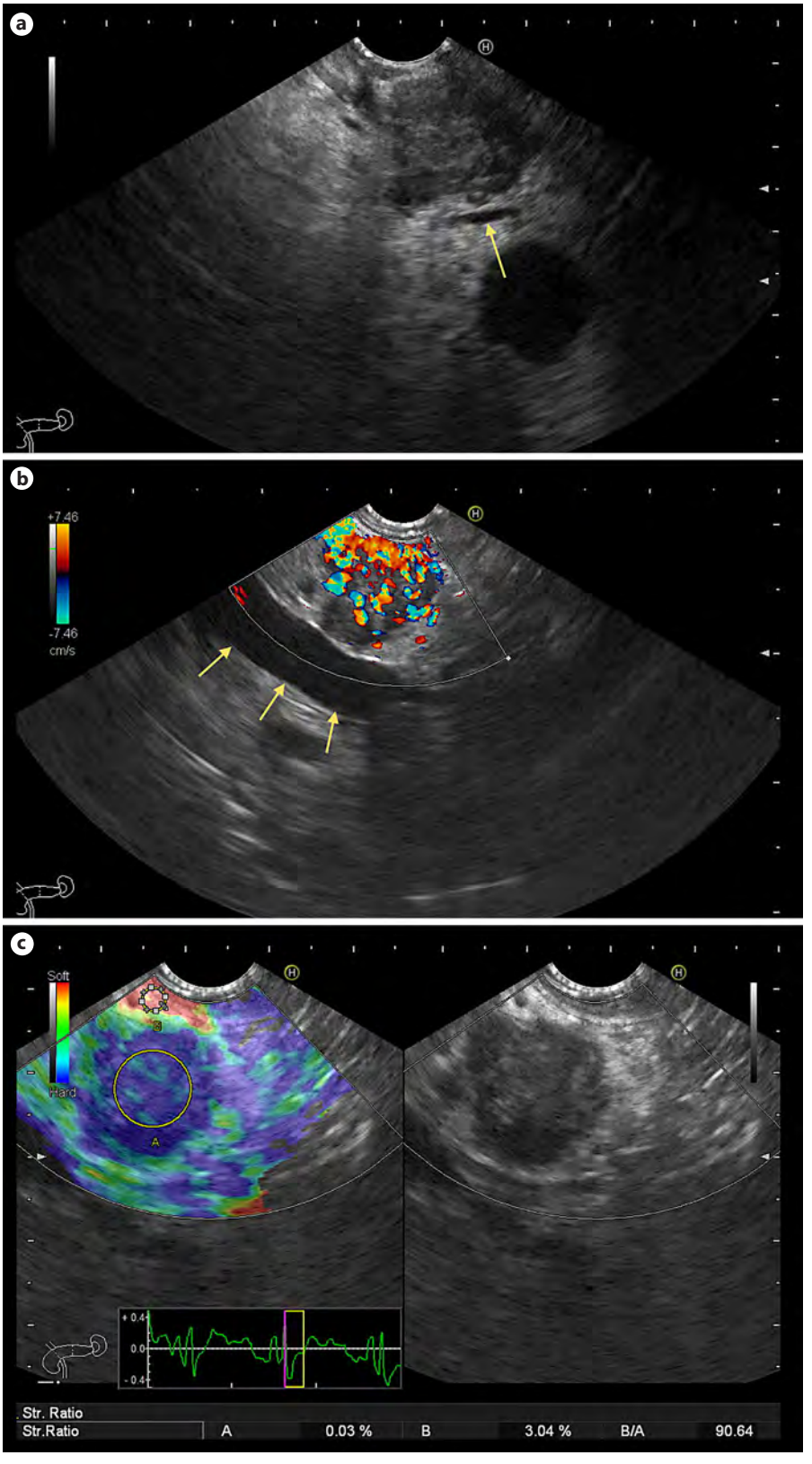

Fig. 1. Hypoechoic 18-mm lesion in the pancreatic isthmus, in close proximity to the MPD (arrow, **a**) and to the splenic-mesenteric confluence (arrows, **b**). The lesion is hypervascular (color Doppler, **b**) and reveals a predominantly blue elastography pattern (**c**). These features are compatible with a neuroendocrine tumor.

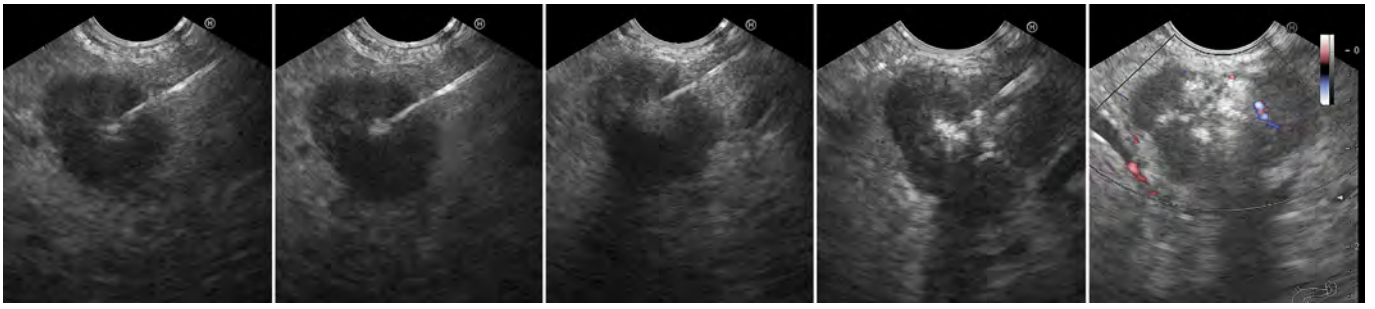

Fig. 2. First EUS-guided alcohol ablation session. A hyperechoic filling of the tumor is noticed from left to right with remaining hypoechoic areas (right).

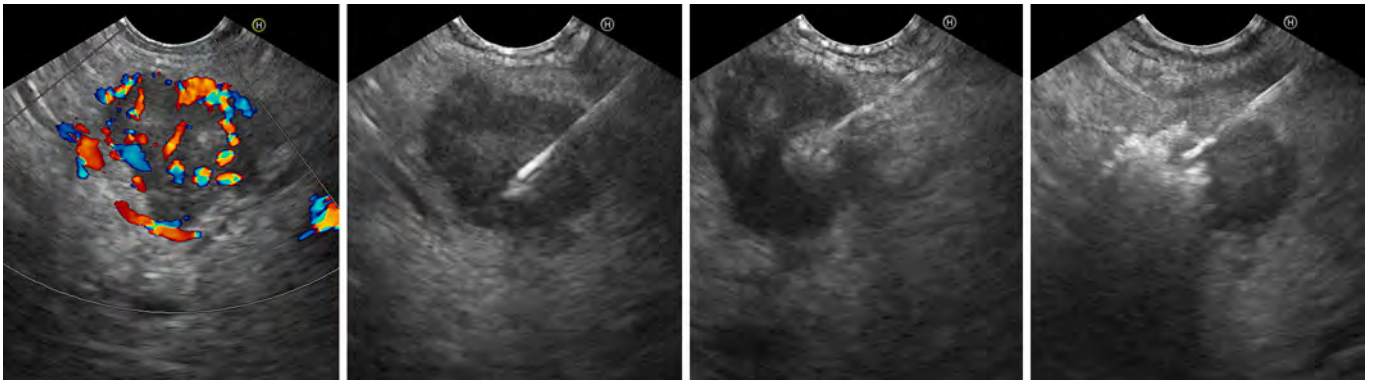

Fig. 3. Residual hypervascular lesion at the start of the second EUS-guided alcohol ablation session (color Doppler, left). Hyperechoic tumor filling is shown from left to right.

was discharged after glycemic profile stabilization, 8 and 3 days following the first and second sessions, respectively. No adverse events or further hypoglycemia occurred. Fasting insulin normalized. The patient remains asymptomatic after 6 months. Since symptom relief was the treatment goal and given the very low risk of malignant transformation, no further imaging was performed.

Pancreatic insulinomas are rare tumors with an incidence of 4 cases per million per year [1]. They are more frequent in the pancreatic head and often have indolent courses [2]. Surgery is the treatment of choice [3]. Medical therapy is considered in poor surgical candidates, diazoxide being the most used. However, side effects are frequent and the underlying cause is not addressed [4].

Insulinoma EUS-AA was described in 2006 [5]. Reported cases were systematically reviewed, with a total of five pancreatic neck insulinomas submitted to EUS-AA [2]. The median insulinoma size was lower than ours (13 vs. 18 mm), and still the median alcohol injection volume was larger (1.55 vs. 0.9 mL, per session). That may be justified by the absence of standardized recommendations and by the MPD proximity in our case, increasing the risk of pancreatitis and alcohol-induced duct stricture [2]. EUS-guided radiofrequency ablation is an alternative to EUS-AA with similar results. However, higher costs and lower availability limit its use. Our case supports previous evidence regarding the role of insulinoma EUS-AA in the absence of surgical indication. Small alcohol volumes with repeated sessions may be effective and safer for MPD-adjacent lesions.

Statement of Ethics

Ethical approval was not required for this study in accordance with local/national guidelines. Written informed consent was given by the patient authorizing publication of the case, including images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

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Author Contributions

M.A.S.: revision of the literature and drafting of the manuscript; A.R.: revision of the literature; N.V.: clinical care; A.F.: clinical care, endoscopic procedure, and critical revision of the article; E.P.: endoscopic procedure; and H.V.: final revision and approval of the article.

Data Availability Statement

All data generated and analyzed are included in this manuscript. Further enquiries can be directed to the corresponding author.

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Bile Duct Ulcer due to a Migrated Pancreatic Stent after Pancreatoduodenectomy

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Keywords
Bile duct ulcer · Pancreatic stent migration · Pancreatoduodenectomy

Úlcera da via Biliar Intrahepática Devido a Migração de Prótese Pancreática Após Pancreatoduodenectomia

Palavras Chave
Úlcera do ducto biliar · Migração da prótese pancreática · Pancreatoduodenectomia

A 71-year-old woman was referred to our department for epigastric fullness and discomfort lasting for a month. She underwent pancreatoduodenectomy (PD) with modified Child's reconstruction and internal stenting across a pancreaticojejunostomy (PJ) 15 months earlier for distal bile duct cancer and had no recurrence or problem associated with the surgery in her follow-up. On admission, she had no leukocytosis, and her liver tests and pancreatic enzymes were within the normal range. Contrast-enhanced computed tomography showed the migration of the pancreatic stent into the intrahepatic bile duct with pneumobilia (Fig. 1). Although her liver tests remained normal, endoscopic retrieval using a single balloon enteroscope (SIF-H290S; Olympus Medical Systems, Tokyo, Japan) was performed, considering that her symptoms may have been associated with the migrated stent. Single balloon enteroscopy showed the migrated stent lying across the hepaticojejunal anastomosis, and furthermore, a bile duct ulcer due to the migrated stent was found at the right hepatic duct (Fig. 2). Endoscopic retrieval of the migrated stent was successfully achieved by using a snare under fluoroscopy (Fig. 3). The patient was discharged uneventfully, and her epigastric fullness and discomfort gradually ceased after the stent retrieval.

Postoperative pancreatic fistula remains the leading cause of morbidity after PD. Various management strategies have been proposed to reduce postoperative pancreatic fistula; the use of an internal stent with the PJ is a commonly used tactic for PD [1]. Although the internal stent placed across the PJ usually passes spontaneously through the rectum, endoscopic stent retrieval should be considered when an internal stent migrates [2]. The incidence of internal stent migration into the bile ducts following PD was reported to range from 7 to 16.8%, and these migrations were mostly subclinical [2–4]. To date, stent-induced complications including bile duct stricture, hepatolithiasis, and liver abscess have been noted in

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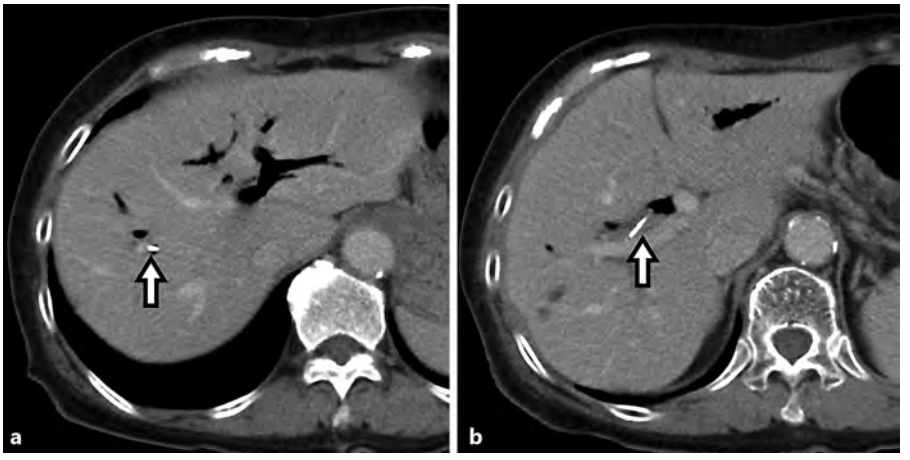

Fig. 1. a, **b** Contrast-enhanced computed tomography showed the migration of an internal pancreatic stent into the intrahepatic bile duct with pneumobilia (arrow).

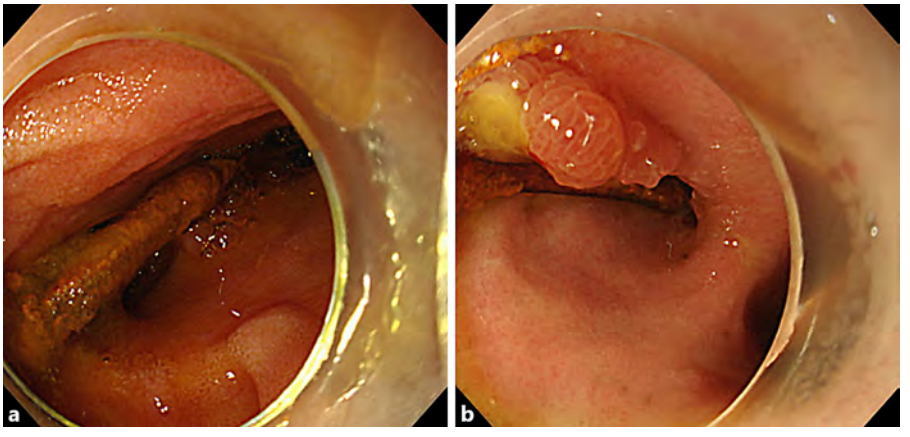

Fig. 2. Single balloon enteroscopy showed a migrated pancreatic stent lying across the hepaticojejunal anastomosis (**a**) and a bile duct ulcer at the right hepatic duct (**b**).

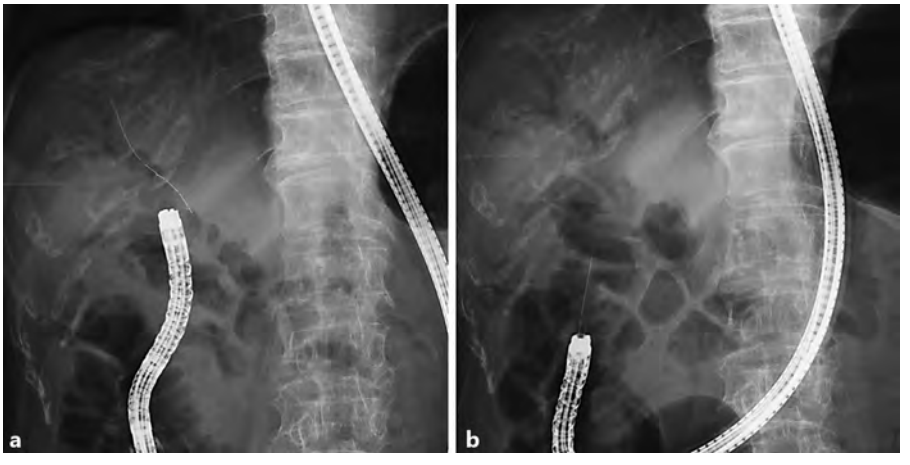

Fig. 3. a, **b** Endoscopic retrieval of the migrated stent was successfully achieved by using a snare under fluoroscopy.

previous reports, and they usually involve changes in computed tomography findings or liver tests. This case suggests that bile duct ulcer should be included in the differential diagnosis in patients presenting with stent migration into the bile ducts after PD, even if the patients have normal liver tests.

Statement of Ethics

Ethical approval was not required for this study in accordance with local/national guidelines. Written informed consent was given by the patient for the publication of this report, including images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

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Author Contributions

Sho Kitagawa is the article guarantor and wrote the manuscript. Keiya Okamura edited the final manuscripts.

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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Endoscopic Snapshots of a Sealed Metal Stent: An Unusual Complication after Novel Antireflux Covered Metal Stent Placement in the Hepaticogastrostomy

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Keywords
Antireflux covered metal stent · Hepaticogastrostomy · Endoscopic intervention

Stent selado: uma complicação invulgar após a colocação de um novo stent metálico totalmente coberto com válvula anti-refluxo na hepaticogastrostomia

Palavras Chave
Stent metálico com válvula anti-refluxo · Hepaticogastrostomia · Intervenção endoscópica

A 90-year-old woman, who underwent endoscopic ultrasound-guided hepaticogastrostomy for the B3 duct/segment by using a covered metal stent (CMS) (8 mm × 100 mm, Niti-S S-type stent; Taewoong Medical, Seoul, South Korea) 12 months earlier for extrahepatic bile duct cancer, was referred for the treatment of acute cholangitis. Food impaction into the CMS was found on endoscopy, and after the CMS removal, a 6-Fr nasobiliary drainage tube was then placed by hepaticogastrostomy. After 7 days of intravenous biapenem (0.3 g q12h), a novel antireflux CMS (10 mm × 60 mm, KAWASUMI Duckbill Biliary Stent; Kawasumi Laboratories, Tokyo, Japan), which has a duckbill-shaped antireflux valve (DARV), was placed across the hepaticogastrostomy tract. However, the patient developed shaking chills and fever followed by hypotension 21 h after the CMS placement. Urgent endoscopy revealed that the DARV remained closed with pus coming out through the hepaticogastrostomy, which indicated acute obstructive suppurative cholangitis due to the DARV dysfunction (Fig. 1). After puncturing the DARV with a catheter to reduce the bile duct pressure, the stent was retrieved by a snare and was successfully replaced with a CMS without an antireflux valve (10 mm × 60 mm, X-Suit NIR fully covered; Olympus Medical Systems, Tokyo, Japan) (Fig. 2). No problem related to the CMS was observed until she died from the acute myocardial infarction 5 months later.

Antireflux CMS has been developed to prevent the reflux of food or intestinal juice into the bile duct with the expectation of a longer time to recurrent biliary obstruction. To date, several types of antireflux valves have been applied to CMS: wineglass-shaped, nipple-shaped, long funnel-shaped, and windsock-shaped antireflux valve [1]. A meta-analysis of antireflux CMSs compared with conventional self-expandable metal stents concluded that antireflux CMS had a lower risk of stent occlusion [2]. In recent studies, CMS with DARV demonstrated a longer time to recurrent biliary obstruction than the conventional CMS [3, 4]. The DARV of the CMS is constituted by an expanded polytetrafluoroethylene membrane that

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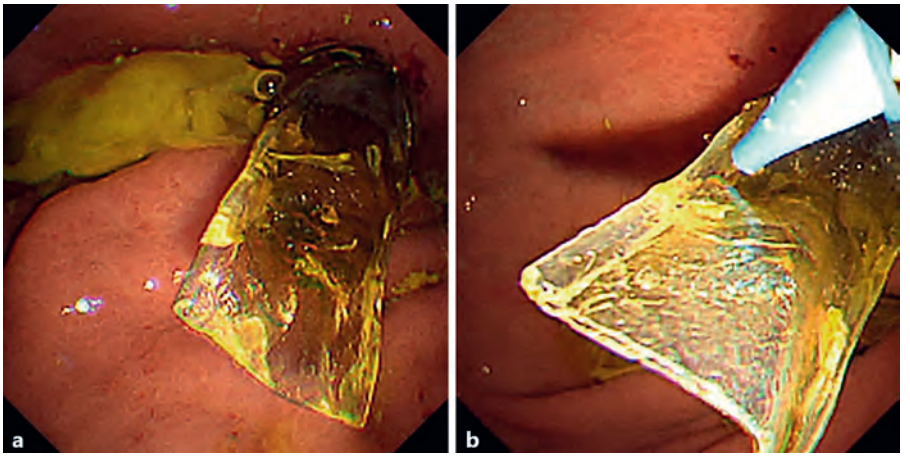

Fig. 1. Endoscopic images of an antireflux CMS placed across the hepaticogastrostomy tract showing pus coming out through the hepaticogastrostomy (**a**) and complete closure of the antireflux valve (**b**).

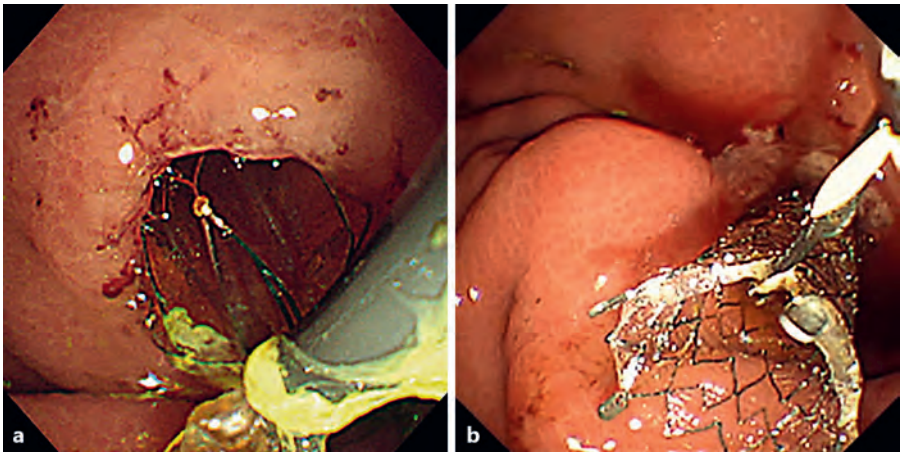

Fig. 2. Endoscopic images of hepaticogastrostomy stent replacement showing snare retrieval of an antireflux CMS (**a**) and a CMS without an antireflux valve placed across the hepaticogastrostomy tract (**b**).

extends beyond the distal end of the CMS. The DARV is usually closed to prevent the duodenobiliary reflux but opens when the bile duct pressure increases; however, in this case, even though the DARV was open when the CMS was deployed, the DARV remained closed as if sealed. Although to the best of our knowledge, antireflux CMS placement for other than distal malignant biliary obstruction has never been studied in much detail, the force of gravity may have prevented the biliary outflow from the DARV, and so clinicians should pay additional attention to the DARV dysfunction when placing the CMS with DARV across the hepaticogastrostomy.

Statement of Ethics

Ethical approval was not required for this study in accordance with local/national guidelines. Written informed consent was given by the patient for the publication of this report, including images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

There has been no financial support for this work.

Author Contributions

Sho Kitagawa is the article guarantor and wrote the manuscript. Keiya Okamura edited the final manuscripts.

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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Endoscopic Submucosal Dissection of Subepithelial Lesion in the Cecum: Granular Cell Tumor

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Keywords
Endoscopic submucosal dissection · Granular cell tumor · Cecum

Disseção endoscópica da submucosa de lesão subepitelial do cego: tumor de células granulares

Palavras Chave
Disseção endoscópica da submucosa · Tumor de células granulares · Cego

A 44-year-old female patient was subjected to total colonoscopy that revealed a 15 mm bulge in the cecum, covered by normal mucosa, compatible with subepithelial lesion, of hard consistency and no pillow sign (Fig. 1a). The lesion was evaluated by ultrasonography with miniprobe (Fig. 1b), which confirmed the presence of a subepithelial nodular hypoechoic lesion although it was not possible to safely distinguish between the second and third ultrasonographic wall layers.

Endoscopic submucosal dissection (ESD) was proposed. The endoscopist had extensive experience in colorectal ESD. A glycerol solution with indigo carmine and adrenaline (1:50,000) was injected (Fig. 2a). Mucosal incision was performed (Fig. 2b), followed by submucosal endoscopic dissection using DualKnife J™ (Olympus, Tokyo, Japan) and IT Knife nano™ (Olympus, Tokyo, Japan), with dry-cut current effect 2.5 and swift coagulation current effect 3 achieving total excision of the lesion at the end of the procedure (Fig. 2c–e). The scar was closed with Resolution 360™ ULTRA clips (Boston Scientific, Boston, USA) (Fig. 2f, g). The lesion was retrieved en bloc (Fig. 2h). No adverse events were observed.

Histological evaluation revealed a solid neoplasia of the submucosa consisting of epithelioid cells of vast granular citoplasma, centered by small, round, uniform nuclei (Fig. 3a, b). These cells were positive for S100 and inhibin – granular cell tumor (GCT) (Fig. 3c, d). The lesion was limited to the submucosa and was covered by normal colonic mucosa. The excision margins were free. A surveillance colonoscopy at 12 months is currently scheduled.

The authors present a case of a subepithelial lesion in the cecum evaluated by miniprobe ultrasonography and removed en bloc by ESD. GCT's are a rare entity, whose pathological behavior is not fully understood, and are most frequently found incidentally. Granular cells have neuronal origin, and Schwann cells are precursors [1, 2].

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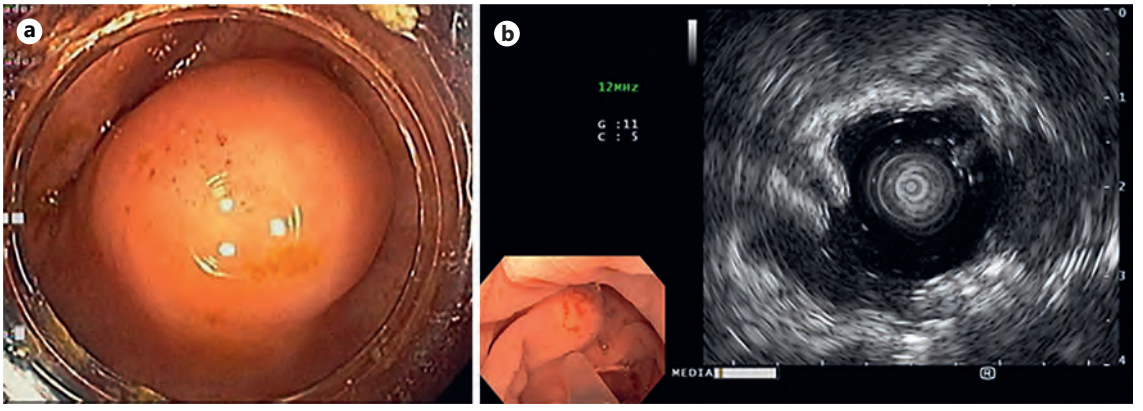

Fig. 1. Endoscopic findings. **a** In the cecum, a 15 mm bulge with normal mucosa was observed. **b** Ultrasonography – a subepithelial nodular lesion was confirmed, although it was not possible to safely distinguish between the second and third ultrasonographic wall layers.

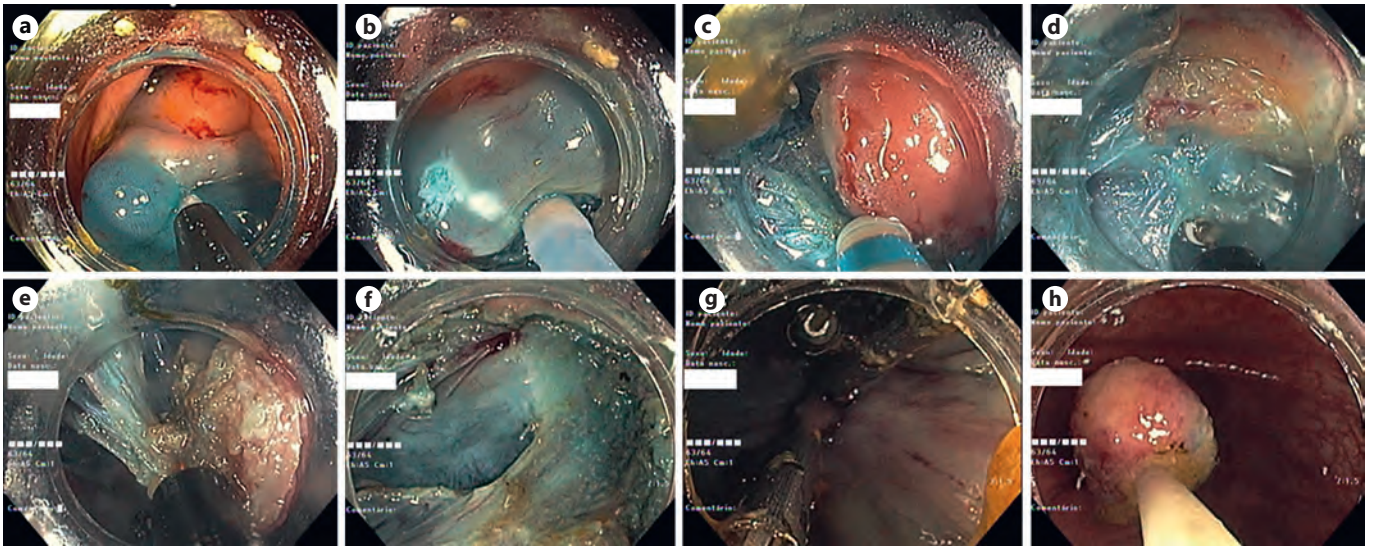

Fig. 2. Endoscopic submucosal dissection. **a** Submucosal injection. **b** Mucosal incision. **c–e** Submucosal dissection. **f** Dissection scar. **g** The scar was closed with clips. **h** En bloc lesion retrieval.

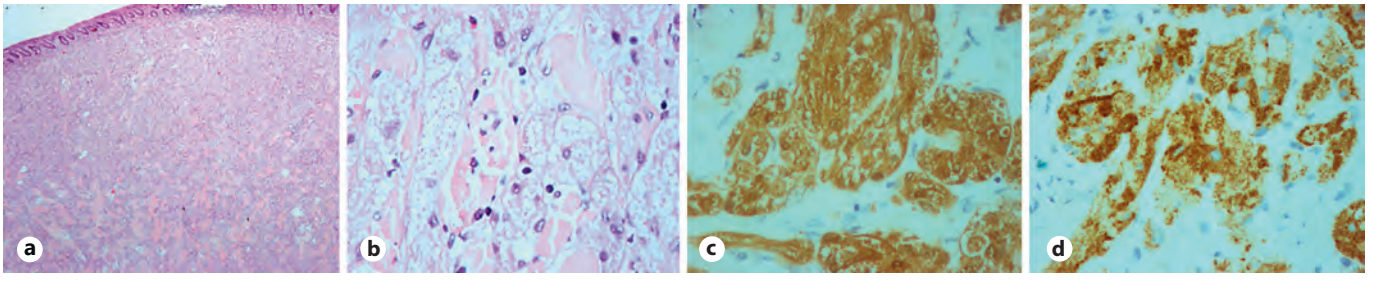

Fig. 3. Histological evaluation. **a** Submucosal expansion by epithelioid cells, covered by normal colonic mucosa (×20 magnification). **b** These cells have vast granular citoplasma, centered by small, round, uniform nuclei (×100 magnification). **c**, **d** Immunohistochemistry showing positivity for S100 (**c**) and inhibin (**d**) (×400 magnification).

The cases reported in the literature suggest a generally benign behavior but <2% have shown potential for malignancy, which is suggested by endoscopic features of ulceration or size >40 mm [3]. Histological proposed criteria for malignancy are the following: high number of mitosis, big nuclei, signs of lymphovascular invasion; evidence of metastization being the sole definitive criteria [2]. A case of local recurrence due to incomplete resection was reported [3]. ESD in the colon is a safe, technically demanding procedure that allows an en bloc resection and avoids surgery in the absence of features of malignancy. Endoscopic full-thickness resection using a full-thickness resection device is an alternative and developing method, with current evidence apparently showing a similar safety profile albeit with a lower complete resection rate [4]. To the best of our knowledge, this is the first case of GCT in the cecum treated by ESD in the West; all the other four cases were reported in China [5, 6].

Statement of Ethics

Ethical Approval Statement: ethical approval was not required for this study in accordance with local/national guidelines. Written informed consent was obtained from the patient for publication of this case report and any accompanying images, according to Helsinki declaration.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

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Author Contributions

Diogo Bernardo Moura: article concept, literature review, and drafting of the manuscript. Nuno Nunes: main endoscopist of the described procedure, literature review, and critical review of the manuscript. Carolina Chálim Rebelo, Francisca Côrte-Real, Ana Catarina Rego, and Maria Antónia Duarte: critical review of the manuscript.

Data Availability Statement

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

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Silent Multiple Lymphomatous Polyposis in Mantle Cell Lymphoma: From the Ileum to the Stoma

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Keywords
Colonoscopy · Multiple lymphomatous polyposis · Mantle cell lymphoma

Polipose Linfomatosa Múltipla Silenciosa No Linfoma de Células Do Manto: Desde o Íleon Até Ao Estoma

Palavras Chave
Colonoscopia · Polipose linfomatosa múltipla · Linfoma de células do manto

We present the case of a 79-year-old male with known history of sigmoid colon cancer, diagnosed in the context of bowel obstruction in 2018. In that setting, he was submitted to an emergent Hartmann procedure, maintaining the colostomy ever since. After staging (IIIB AJCC classification), the patient completed 6 months of adjuvant chemotherapy (CT). The first and last colonoscopy was 6 months after surgery. No relapse was noticed during the surveillance period. Three years later, he developed oropharyngeal dysphagia, without any other gastrointestinal symptoms. Physical examination showed an asymmetric tonsillar hypertrophy and multiple soft and painless cervical adenomegalies. He was referred to otorhinolaryngology and hematology at a cancer center. The tonsil biopsy showed a classic mantle cell lymphoma (MCL), and the chromosomal translocation t(11; 14) was identified by fluorescence in situ hybridization technique. The staging computerized tomography scan revealed adenopathies above and below the diaphragm, a large cecal mass (shown in Fig. 1c), and a heterogeneous appearance of the colic and ileal mucosa (shown in Fig. 1a, b). A total colonoscopy was performed, and, between the colostomy and the terminal ileum, multiple polyps were identified (shown in Fig. 2a–c and Fig. 2e), some of them with central umbilication. In addition, a vegetating mass measuring 55 mm in diameter was observed in the cecum (shown in Fig. 2d). Biopsies of the polyps in the ileum, ascending and descending colon, as well as cecal mass were performed, and, in all of them, pathology showed a monomorphic lymphoid cell infiltrate (shown in Fig. 3a). The lymphoid cells stained positive for CD20 and CD5 and negative for CD3 (shown in Fig. 3b). In addition, cyclin-D1 nuclear overexpression was observed (shown in Fig. 3c). The patient was diagnosed with an MCL stage IVA (Ann-Arbor classification), with a high-risk MIPIb score. After completing 2 cycles of R-bendamustine

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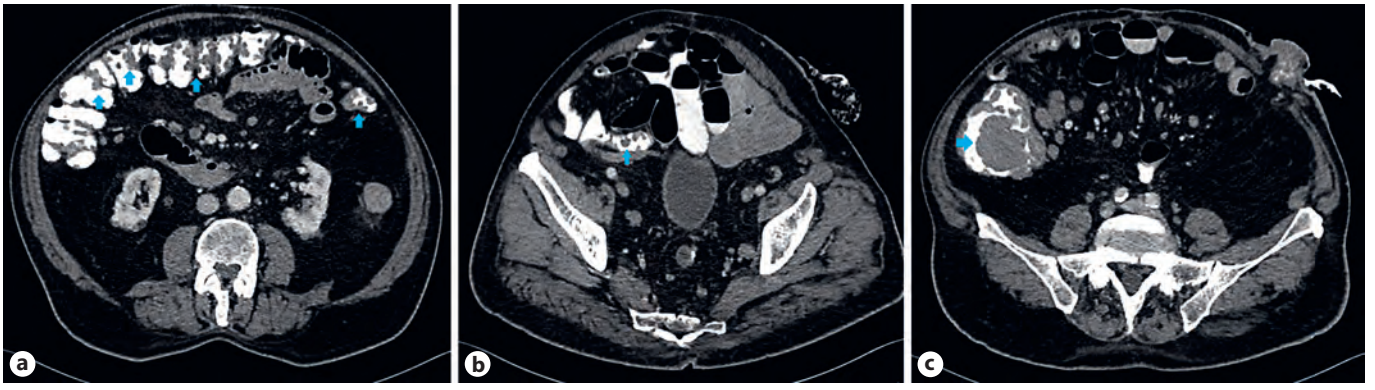

Fig. 1. Computerized tomography scan showing heterogeneous changes in colic mucosa (blue arrows) (**a**) and in terminal ileum (blue arrows) (**b**). **c** Cecal mass (blue arrows).

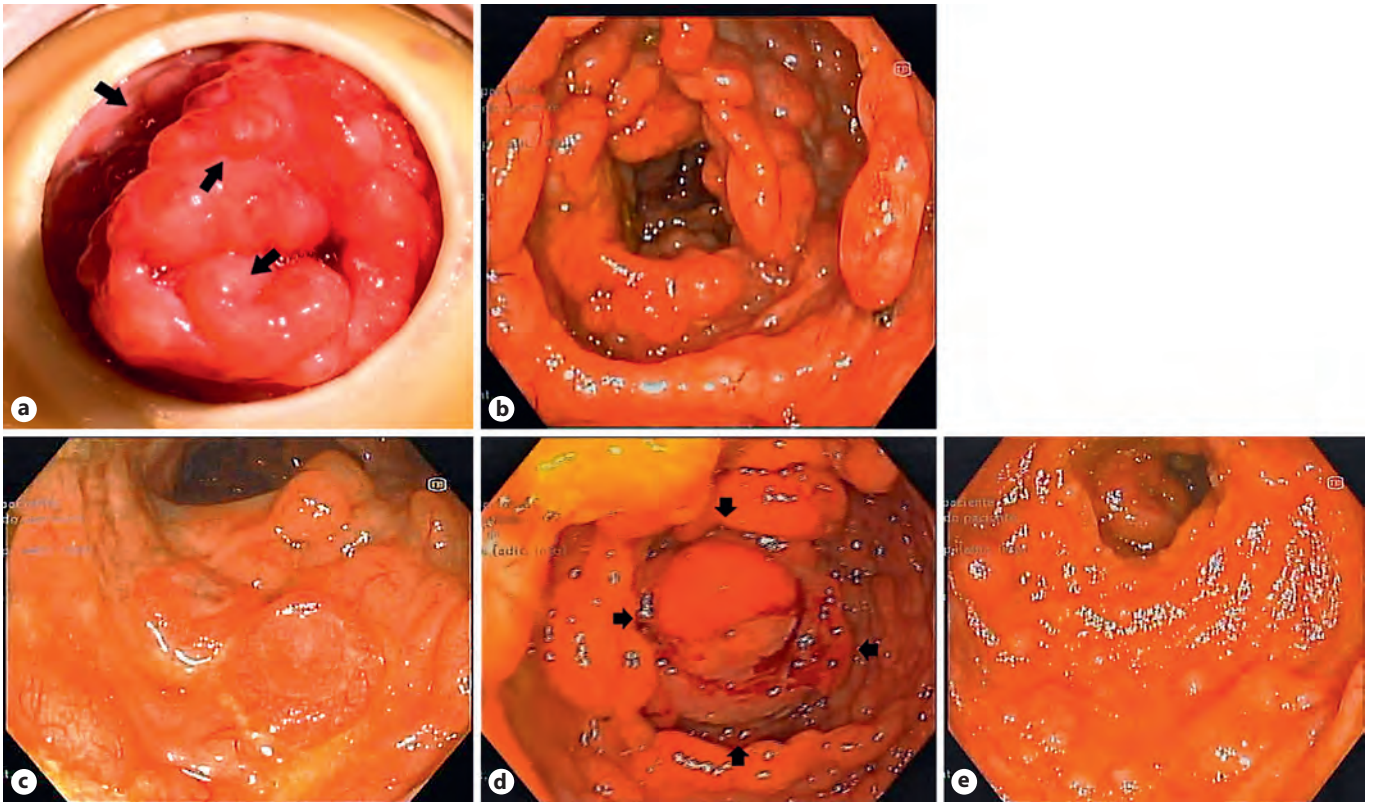

Fig. 2. Colonoscopy findings showing colostomy orifice with polyps on the surface (black arrows) (**a**); colon with multiple polyps (**b**); polyp with central umbilication (**c**); vegetating cecal mass – outlined by black arrows (**d**); terminal ileum with multiple polyps (**e**).

(rituximab and bendamustine), he was diagnosed with COVID-19, and CT was suspended. The MCL remained stable while waiting for virologic cure. The patient restarted CT with R-CVP (rituximab, cyclophosphamide, vincristine, prednisolone), and a reevaluation colonoscopy will be performed at the end of 6th CT cycle.

This case illustrates a silent presentation of an exuberant entity: multiple lymphomatous polyposis (MLP).

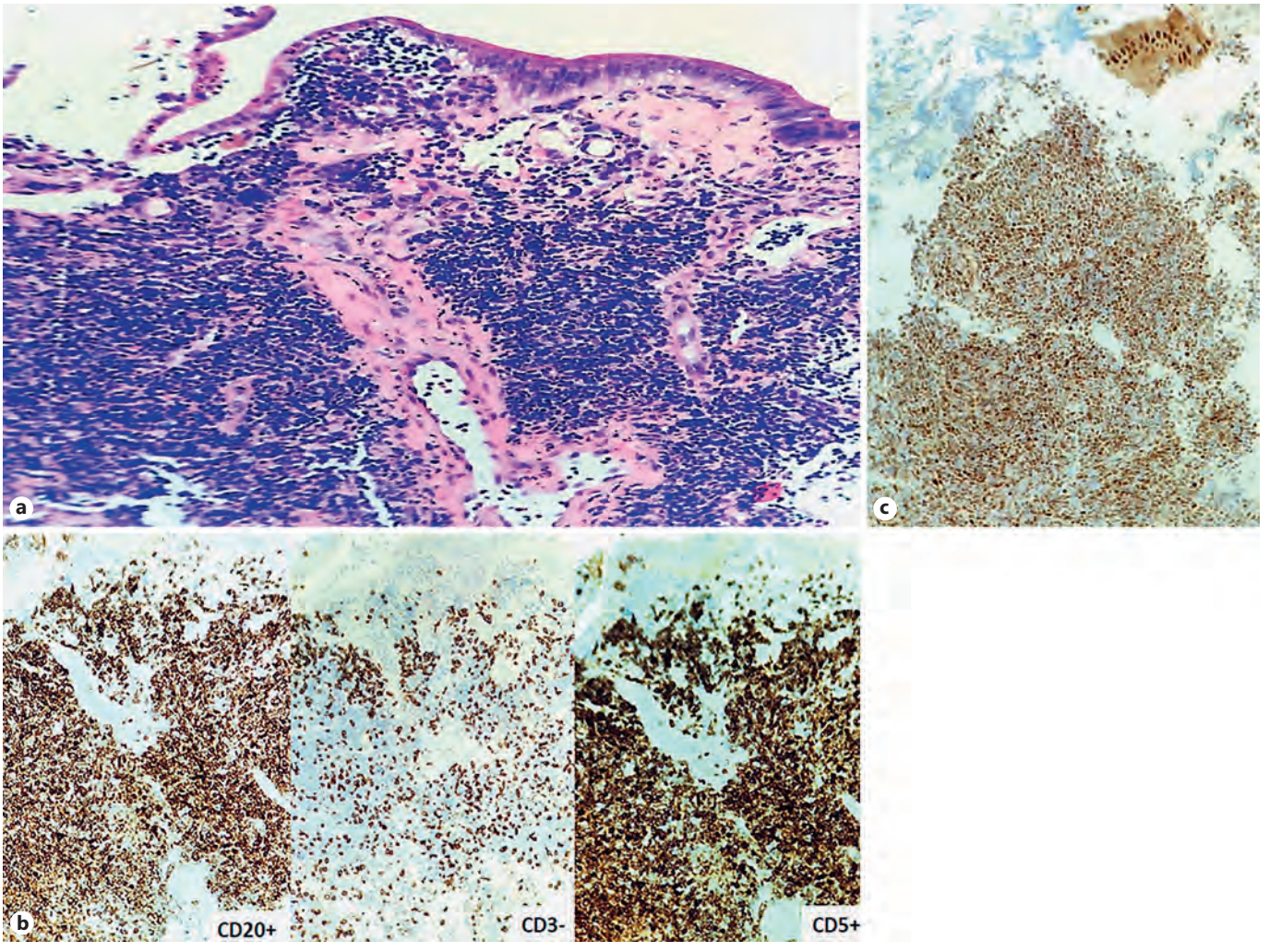

Fig. 3. Anatomopathological findings showing H&E ×100 showing a monomorphic lymphoid cells infiltrate (**a**); immunohistochemistry ×100 – staining positive for CD5 and CD20 and negative for CD3 (**b**); and overexpression of cyclin-D1 (×100) (**c**).

MCL represents 6% of all non-Hodgkin lymphomas and is characterized by the chromosomal t(11; 14) which results in cyclin-D1 overexpression. The MCL affects mostly males in their 60–70 years and usually presents with disseminated disease, as seen in our patient [1]. Previously, gastrointestinal involvement was described in about 30% of the cases; however, it may be underestimated given the evidence of only microscopic involvement of the colon in about 84% of patients [2]. MLP is the most frequent colonic endoscopic finding of MCL, although isolated polyps or masses can also be found [3]. Besides lymphoma, the main differential diagnosis of MLP is intestinal pneumatosis. In younger patients, polyposis syndromes and inflammatory bowel disease should also be considered [4]. Regarding MCL treatment, the R-bendamustine regimen has the higher 5-year progression-free survival (65.5% vs. 55.8%), but the R-CVP regimen confers less immunosuppression [5].

Statement of Ethics

Ethical approval was not required for this study in accordance with local/national guidelines. Written informed consent was obtained from the patient, authorizing the publication of the clinical case and images, according to the Declaration of Helsinki.

Conflict of Interest Statement

The authors have no conflict of interests to declare.

Funding Sources

The authors have no funding sources to declare.

Data Availability Statement

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

Author Contributions

Sofia Bragança obtained the data, wrote the manuscript, and reviewed the literature. André Pereira reviewed the histopathological findings and provided the histopathological images as well as explanation. Filipa Moita provided clinical data on the diagnosis and treatment of lymphoma as well critical revision of the manuscript. Gonçalo Alexandrino, Mariana Nuno Costa, and David Horta were responsible for critical revision of the manuscript. All authors approved the published version of the manuscript.

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Images in Gastroenterology and Hepatology

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Dysphagia Aortica: An Uncommon and Potentially Life-Threatening Condition

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Keywords
Dysphagia · Dysphagia aortica · Aortic aneurism · Esophageal external compression

Disfagia aórtica: uma situação clínica rara e potencialmente fatal

Palavras Chave
Disfagia · Disfagia aórtica · Aneurisma da aorta · Compressão extrínseca esofágica

A Caucasian 75-year-old male with a history of arterial hypertension, dyslipidemia, and aortic prosthesis for ascending aortic dissection in 2015 was admitted to the emergency room following an episode of syncope. There were no prodromal symptoms, lip smacking, or bladder or bowel incontinence. The patient referred a progressively worsening dysphagia, manifested by difficulty in swallowing solid food for the last 3 months, with a normal esophagogastroduodenoscopy (EGD) performed 4 weeks prior. He presented no history of cervical pain, weight loss, dysphonia, or previous radiotherapy. The physical examination, including neurologic exam, was unrevealing. The laboratory evaluation revealed D-Dimer elevation. An arterial phase thoracic computed tomography (CT) excluded pulmonary thromboembolism but revealed an aortic aneurysm throughout all its thoracic and abdominal segments. This dilation was causing compression and displacement of the esophagus, with anterolateral deviation of the organ and a significant reduction of its lumens' caliber in its distal third (Fig. 1). There was also an extrinsic compression of cardiovascular structures, namely the left atrium and the inferior vena cava (Fig. 2) which may explain the episode of syncope due to a compromise of the venous return. The patient was admitted for aneurysm repair surgery, which resulted in symptomatic improvement, and was then discharged.

A thoracic aortic aneurysm (TAA) is usually a silent disease, diagnosed as an incidental finding, which makes it difficult to assess its prevalence. Most of TAA are degenerative and associated with risk factors for atherosclerosis [1]. In case of a previous aortic dissection repair, reintervention is often required in 20–40 percent of them due to aneurysmal degeneration of the residual aorta [2], as may have happened in this patient. TAA can present initially

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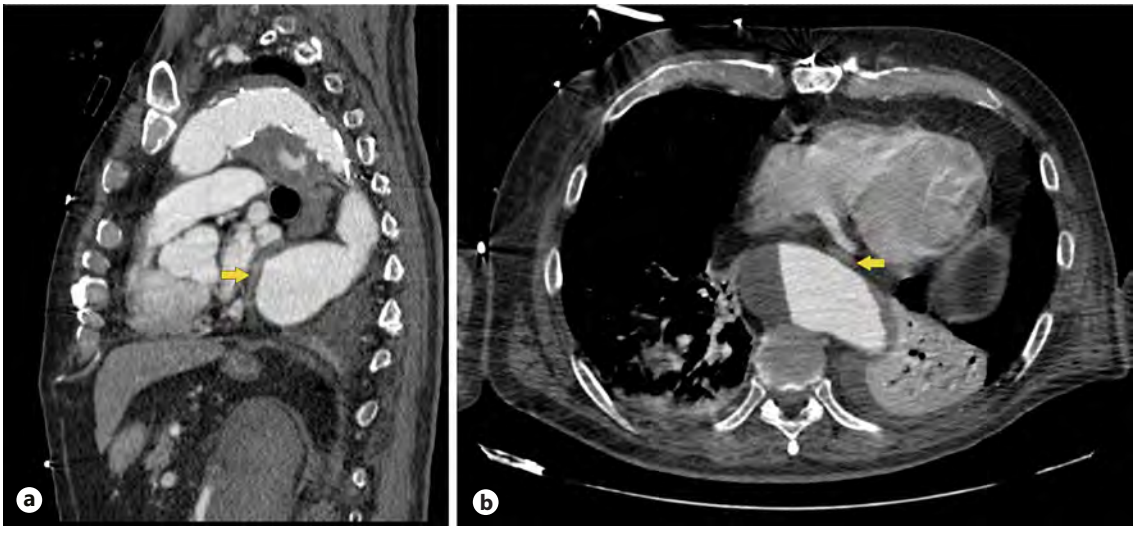

Fig. 1. Thoracic CT showing an aortic aneurysm, reaching a maximum caliber of 62 mm. This dilation causes compression and displacement of the esophagus (yellow arrow), with anterolateral deviation of the organ and a significant reduction of its lumens' caliber in its distal third, presenting with a maximum diameter of 4 mm in this topography. **a** Sagittal view. **b** Axial view.

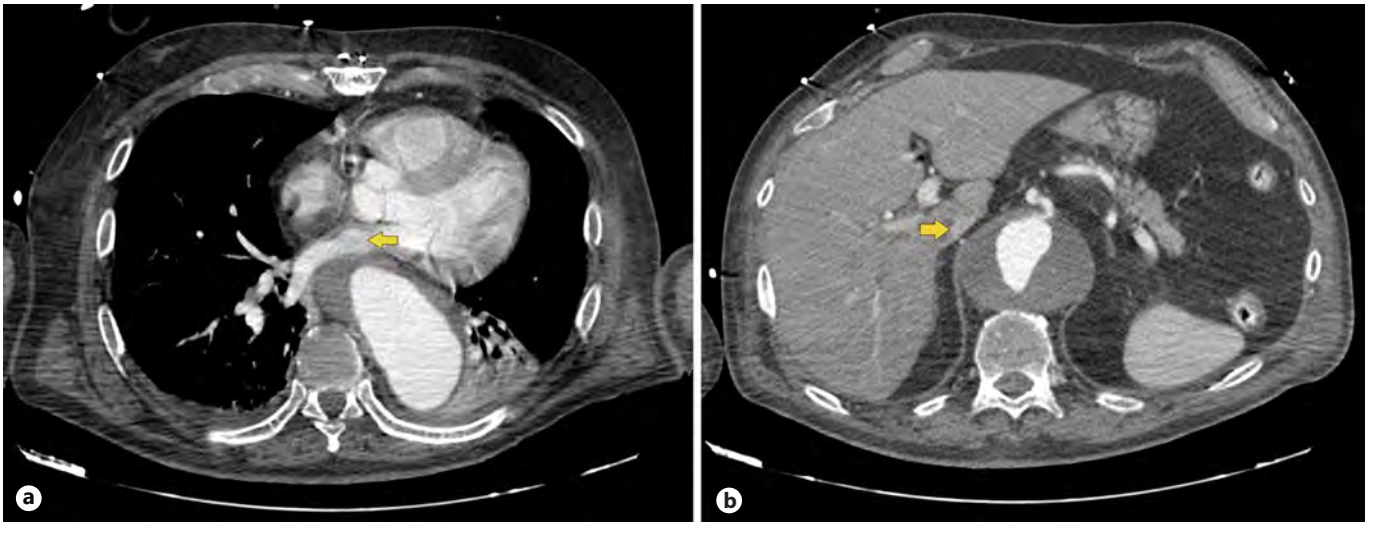

Fig. 2. Thoracic CT showing external compression of cardiovascular structures (yellow arrow), namely the left atrium (**a**) and the inferior vena cava in its retrohepatic portion, reaching a minimum caliber of 4 mm (**b**).

with symptoms related to rapid expansion and compression of adjacent structures, namely dysphagia from esophageal compression, a rare phenomenon called dysphagia aortica. This term, rarely mentioned in gastroenterological textbooks, arises when the aorta pushes the esophagus anterolaterally and against the crural diaphragm [3]. The most feared complication is primary aortoesophageal fistula, typically following untreated TAA [4]. However, other causes of aortic dysphagia need to be addressed, namely aortic dissection, tortuous aorta, double aortic arch, or aortic pseudoaneurysm. Also, there are other cardiovascular anomalies that may lead to dysphagia, including abnormal right subclavian artery (dysphagia lusoria) and abnormal dilated left atrium (dysphagia megalatriensis) [5].

Considering its rarity, there is no gold standard for diagnosis and therapy. The diagnostic workup should include EGD as the first-line investigation, followed, according to clinical suspicion, by barium or videofluoroscopic swallowing study, thoracic CT, or esophageal manometry, although no single method can definitively prove the diagnosis. The treatment of dysphagia aortica depends on the severity of symptoms, comorbidities, etiology, location in the aorta, and the expected survival, which impact the choice of approach to repair (open vs. endovascular) [3]. The authors highlight dysphagia aortica as a rare clinical entity, in which lack of awareness and symptom underestimation contribute to high-risk diagnostic delay. Thoracic CT may reveal rare causes of dysphagia when first-line investigations such as EGD are inconclusive.

Statement of Ethics

The patient has given written informed consent for publication (including the publication of images).

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

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Author Contributions

Francisco Vara-Luiz, Eduardo Fernandes, Fábio Pé D'Arca Barbosa, and Ana Albuquerque wrote the manuscript; Ana Valada Marques and Jorge Fonseca critically reviewed the manuscript; Eduardo Fernandes analyzed the CT images. All authors approved the final version of this paper.

Data Availability Statement

The complete data of this study are not publicly available due to the patient's privacy but are available from the corresponding author upon reasonable request.

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Letter to the Editor

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Acute-on-Chronic Liver Failure Remains a Minor Indication for Liver Transplant in Portugal

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Keywords
Cirrhosis · Liver failure · Transplantation

A ACLF continua a ser uma indicação menor para transplante hepático em Portugal

Palavras Chave
Cirrose · Falência hepática · Transplantação

Dear Editor,

Patients with acute-on-chronic liver failure (ACLF) have high short-term mortality [1]. Over the past few decades, better access to intensive care and liver transplant (LT) has improved these patients' outcomes [2]. However, concerns remain regarding futility of care, especially in patients with ACLF grade 3, the ones with the greatest severity of disease [3]. Not only their short-term survival following LT may be lower but they also frequently face several complications, namely, infection and different organ dysfunctions [4].

In the south LT region of Portugal, between 2013 and 2021, ACLF (defined as per the European Chronic Liver Failure Consortium) represented a median (interquartile range) of 3.1% (2.4–4.3%) of all indications for LT (Fig. 1: a maximum of 6.2% in 2013 and a minimum of 1.5% in 2016) [5]. Among a total of 186 patients with cirrhosis admitted for more than 24 h to the intensive care unit (ICU) at our center between 2013 and 2021, the ACLF grading on ICU day one was as follows: grade 0 in 7 (3.8%) patients, grade 1 in 46 (24.7%), grade 2 in 55 (29.6%) patients, and grade 3 in 78 (41.9%). Median (interquartile range) SOFA score on ICU day one was 12 (10–14). Overall, 35 (18.8%) patients received an LT (31 within the index hospital stay and 4 following hospital discharge). LT was significantly associated with lower 1-year all-cause mortality (Fig. 2: Kaplan-Meier curve with Breslow test $p = 0.001$). Moreover, patients transplanted during the index hospital stay (emergent LT) had significantly higher median hospital length-of-stay (48 vs. 21 days, $p < 0.001$). There was no association between year of enrollment and these outcomes.

Our 1-year posttransplant crude survival was lower than described elsewhere [6]. Several reasons may help explain such discrepancy, for example, (1) the relative number and severity of organ failures in ACLF 3 patients; (2) local evolving practices for selecting patients for transplant; (3) timely access to suitable organs in different regions; or (4) the quality of organs available across countries.

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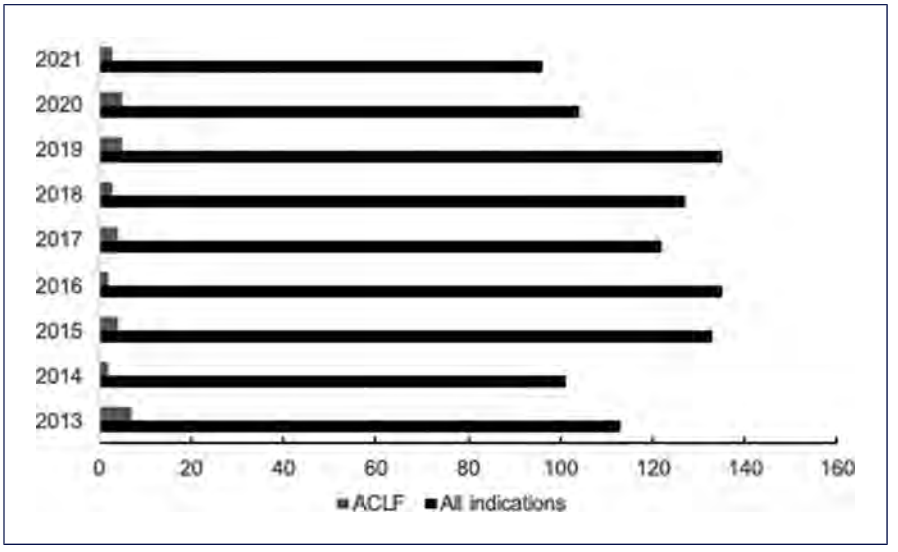

Fig. 1. ACLF among other indications for LT.

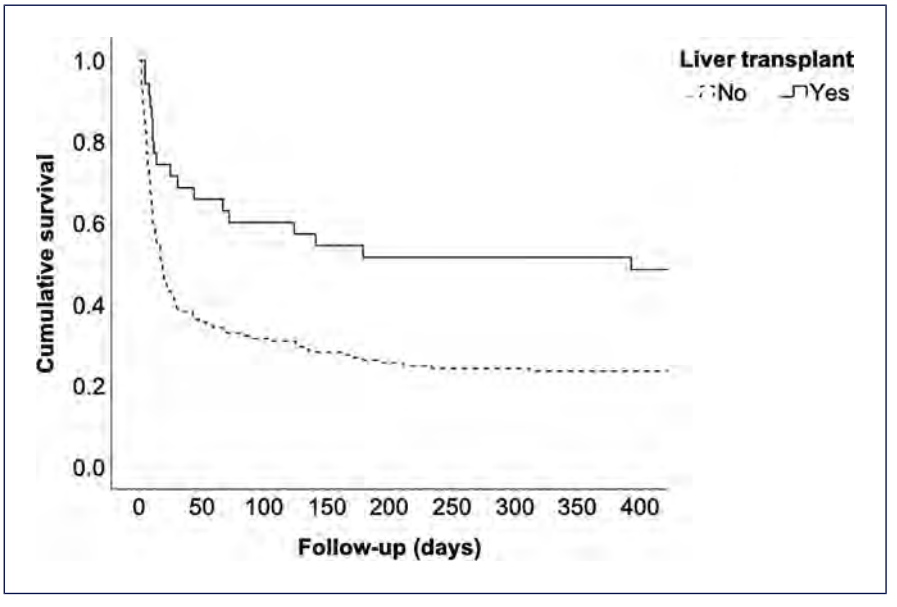

Fig. 2. Survival analysis for all patients stratified by LT status.

Nevertheless, our results add to the increasing evidence highlighting that patients with ACLF may derive a substantial survival benefit from LT. However, associated morbidity and costs need to be taken into account as well. Furthermore, ethical concerns remain regarding futility and the fair distribution of scarcely available organs among patients with different indications for LT. In the future, hospitals will probably be under pressure to admit more of these patients to higher levels of care, especially the ICU. Thus, the complex planning of systems to deliver high quality of care will need to include these patients. Furthermore, clinicians will likely be confronted with more difficult decisions regarding the selection of patients with ACLF for LT. Therefore, future studies will be needed to improve our ability to identify those patients with ACLF who have the highest chances of surviving the longest following LT.

Statement of Ethics

This study protocol was reviewed and approved by Central Lisbon University Hospital Center Ethics Committee, approval

number (#CES371_2016, December 16, 2016). The informed consent was waived by Central Lisbon University Hospital Center Ethics Committee.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Filipe S. Cardoso conceived the idea, collected data, performed analysis, and wrote the manuscript. Rui Perdigoto, Jorge Lamelas, João S. Coelho, Hugo P. Marques, and Luís Bagulho provided content expertise and approved the final version of the manuscript.

Data Availability Statement

Data may be available upon reasonable request directed to the corresponding author and after Central Lisbon University Hospital Center Ethics Committee authorization.

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GE – Portuguese Journal of Gastroenterology

Letter to the Editor

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"Hepatologia em Rede": A Portuguese Association for the Study of the Liver (APEF) Initiative for the Improvement of Research in Liver Disease in Portugal

Rui Caetano Oliveira[a] Susana Rodrigues[b] Joana Espírito Santo[c]
on behalf of Hepatologia em Rede

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"Hepatologia em Rede" — uma iniciativa da Associação Portuguesa para o Estudo do Fígado (APEF) para a investigação em hepatologia em Portugal

Introduction

Liver diseases represent an annual 2 million deaths worldwide [1]. Regarding mortality, cirrhosis is responsible for more than 1 million deaths worldwide, and liver cancer is responsible for almost 800,000 deaths/year [2, 3]. Furthermore, chronic liver disease leads to a high burden of disability and increased health care utilization, and its estimate is likely to be conservative and underestimated [4, 5].

Specifically, in Portugal, liver disease burden is still a major health problem [6, 7]. Liver diseases are the 7th cause of death, with an increase in chronic liver disease, as seen in Europe globally, mainly due to alcohol consumption and increasing cases of obesity and diabetes mellitus [7, 8].

During the past 3 decades, liver disease research has delivered significant breakthroughs. Promoting continuous cooperation between researchers, stimulating synergies between different research domains and boosting more high-quality research studies will lead to an improvement in management of many high-concern liver diseases more effectively. At present, most studies published in hepatology, in Portugal, are overwhelmingly single-centre and retrospective studies, with inherent biases. Furthermore, some areas of hepatology, such as alcohol-related liver disease have fewer studies supported by the pharmaceutical companies, although they represent a very heavy burden from a public health perspective [9].

Therefore, multicentre and prospective research projects will allow for data that are more accurate and the development of precise strategies for liver diseases. In Portugal, these studies have been very difficult to implement. Although there is a national patient registry platform,

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Liver.pt, that was successfully used to perform a Portuguese cohort study in primary biliary cholangitis [10], it has never used to its full potential due to lack of common projects or capacity to coordinate them.

"Hepatologia em Rede" Programme

It is in this context that the programme "Hepatologia em Rede" was born. This initiative from the Portuguese Association for the Study of the Liver (APEF) has a mission to improve national research in hepatology, in basic and clinical fields, support competitive research projects and thus, to amplify the Portuguese scientific position in the global hepatology research community.

The objectives of the network hepatology programme are:

1. To enhance and develop national research in the area of hepatology, in basic and clinical science;
2. To homogenize at a national level the scientific quality of the works produced;
3. To stimulate scientific dialogue and promote cooperation, as well as establishment of partnerships between different national and international hepatology research units, enhancing synergies and networking research projects;
4. To enlarge the scientific production and to promote the realization of research works with increasing quality and relevance;
5. To disseminate in the educational and scientific communities, nationally and internationally, the research carried out in hepatology;
6. To support the training of young researchers;
7. To encourage the submission of projects to specific national and international funding programmes, helping to create the conditions for their feasibility;
8. To centralize reference contacts in foreign institutions for research and specific scientific training;
9. To disseminate its work programme and its results.

Call to Action!

Since its establishment in 2021, "Hepatologia em Rede" has already received several collaborative national cohort projects. One example is a cross-sectional study on the prevalence of Wilson's disease in Portugal. This study will be merged with data from the Spanish cohort of Wilson's disease to produce robust data on an understudied and rare liver disease. Collaboration is an essential principle for scientific advancement, and for this reason, we strongly encourage *all* national centres which regularly treat liver patients to adhere to this programme.

Hepatologia em Rede Committee

José Presa, Helena Cortez-Pinto, Carlos Ferreira, Dalila Costa, Filipe Nery, Susana Gomes Rodrigues, Joana Espírito Santo, Mariana Cardoso, Mariana Machado, Mário Jorge Silva, Rui Caetano Oliveira, Sílvia Vilarinho.

Statement of Ethics

Not applicable.

Conflict of Interest Statement

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Author Contributions

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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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INFORMAÇÕES ESSENCIAIS COMPATIVEIS COM O RESUMO DAS CARACTERISTICAS DO MEDICAMENTO. DENOMINAÇÃO DO MEDICAMENTO: Dioralyte, pó para solução oral. **COMPOSIÇÃO QUALITATIVA E QUANTITATIVA: Substâncias activas** g/saqueta: Glicose 3,56; Cloreto de sódio 0,47; Cloreto de potássio 0,30; Citrato dissódico 0,53. **INDICAÇÕES TERAPÊUTICAS:** Correcção da perda de líquidos e electrólitos nos lactentes, crianças e adultos. Tratamento da diarreia aquosa de várias etiologias, incluindo as gastrenterites, em todos os grupos etários. **POSOLOGIA E MODO DE ADMINISTRAÇÃO:** Cada saqueta deve ser sempre dissolvida em 200 ml de água. O volume de Dioralyte reconstituído a tomar deve ser decidido pelo médico assistente, tendo em consideração o peso do doente e o estado e gravidade da situação. Um princípio básico no tratamento da diarreia é a substituição da perda de líquidos e a manutenção de uma ingestão de líquidos suficiente para repor a sua perda nas fezes. A ingestão diária deve ser baseada num volume de 150 ml/Kg de peso nos lactentes e 20–40 ml/Kg de peso nos adultos e crianças. Uma aproximação razoável é a seguinte: -lactentes – 1 a 1,5 vezes o volume alimentar habitual, - crianças – 1 ou 2 saquetas após cada dejecção diarreica, - adultos – 1 ou 2 saquetas após cada dejecção diarreica. Inicialmente, podem ser necessárias maiores quantidades de Dioralyte para assegurar uma reposição precoce do equilíbrio hidro-electrolítico. Nos estadios iniciais do tratamento da diarreia, todos os alimentos, incluindo o leite de vaca e o leite artificial, devem ser interrompidos. Não se deve no entanto interromper o aleitamento materno. Nas crianças amamentadas sugere-se que se dê à criança o mesmo volume de Dioralyte do que o da alimentação normal, seguindo-se o aleitamento. Pode ser necessário, durante este período, a expressão do leite residual da mama. Após 24-48 horas, quando os sintomas desaparecerem, a dieta normal deve ser retomada gradualmente para evitar o agravamento da situação. O regime sugerido para o tratamento da diarreia infantil grave baseado no peso corporal em Kg é apresentado no quadro anterior. Quando a diarreia é acompanhada de vómitos, sugere-se ingestão frequente de pequenas quantidades de Dioralyte. No entanto, é importante que seja tomado o volume total necessário de Dioralyte. Quando o funcionamento dos rins é normal torna-se difícil superhidratar por via oral e quando existem dúvidas acerca da dosagem correcta, mais vale tomar a mais do que a menos. **CONTRA-INDICAÇÕES:** Não se conhecem contra-indicações ao Dioralyte. No entanto, existem algumas situações em que o tratamento com Dioralyte é inapropriado, tais como por exemplo, situações de oclusão intestinal requerendo intervenção cirúrgica, ou em caso de vomitos persistentes e desidratação grave ou diarreia infantil grave em que será necessária uma terapêutica por via intravenosa. **ADVERTÊNCIAS E PRECAUÇÕES ESPECIAIS DE UTILIZAÇÃO:** O Dioralyte só deve ser reconstituído com água. Cada saqueta deve ser sempre reconstituída em 200 ml de água. Uma solução mais fraca do que a recomendada não contem a concentração óptima de glicose e electrólitos e uma solução mais forte do que a recomendada pode provocar desequilíbrio electrolítico. Se a diarreia não melhorar rapidamente, os doentes deverão ser reavaliados. Nos idosos, a administração de soluções contendo glucose e electrólitos deve ser cuidadosa em caso de alterações renais ou hepáticas graves ou em outras situações em que o balanço electrolítico normal se encontre alterado. Nos lactentes, deve interromper-se durante 24 horas a alimentação com leite de vaca ou leite artificial, que deverão ser reintroduzidos gradualmente quando a diarreia tiver diminuído. Não se deve interromper o aleitamento materno. **EFEITOS INDESEJÁVEIS:** Podem ocorrer náuseas ou vómitos após a administração da solução, em particular quando esta é ingerida com demasiada rapidez. Estão também descritos casos isolados de desconforto abdominal e de obstipação.Data da revisão do texto: Janeiro de 2004. **TITULAR DA AUTORIZAÇÃO DE INTRODUÇÃO NO MERCADO:** KORANGI - Produtos Farmacêuticos, Lda. Medicamento não sujeito a receita médica. **Para mais informações contactar o Titular da Autorização de Introdução no Mercado**

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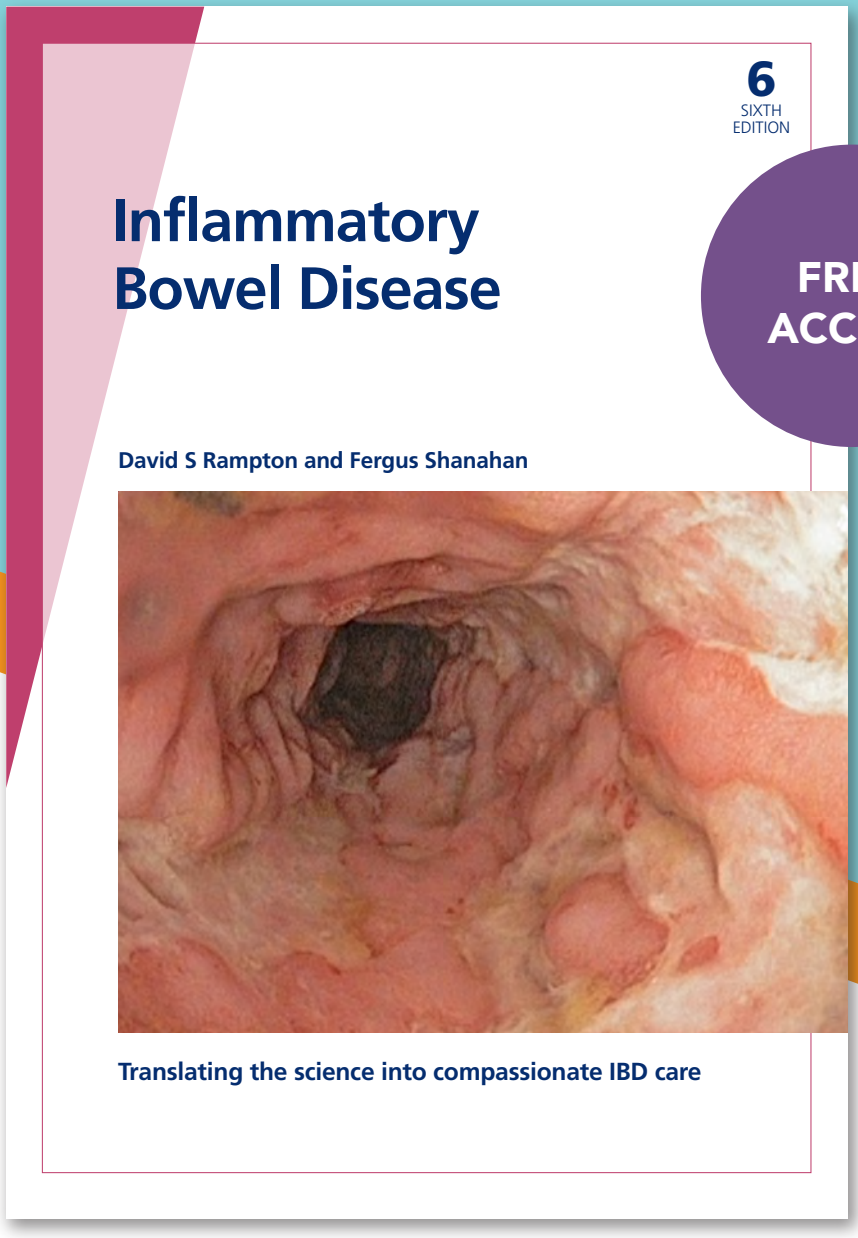

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