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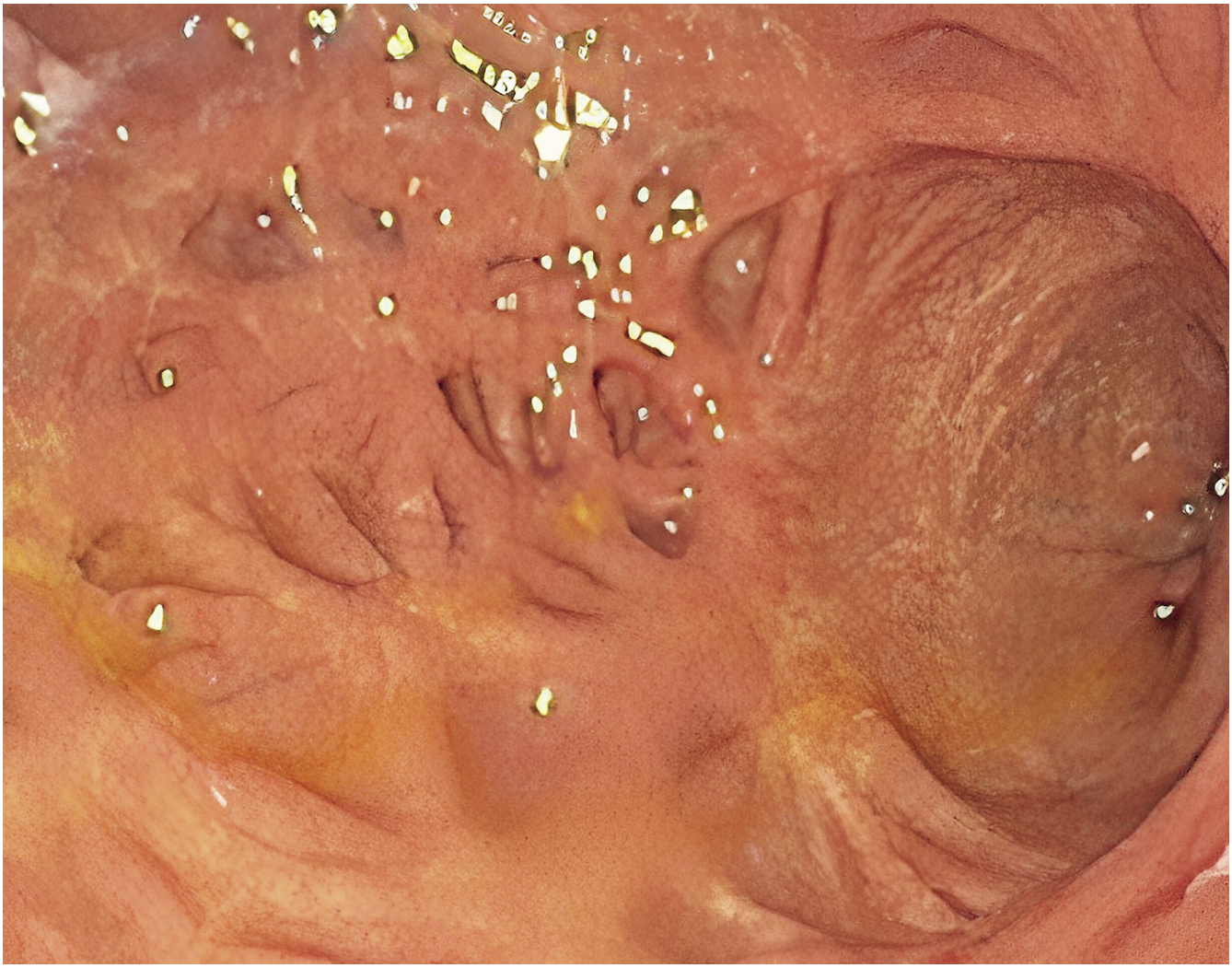

Highlights in this issue:

Review article: Pharmacological treatment of functional dyspepsia

Endoscopic resection of neuroendocrine tumors

Long-Term Intestinal Failure and Home Parenteral Support – a single-center experience

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Aims and Scope

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The journal publishes clinical and basic research articles on Gastroenterology, Digestive Endoscopy, Hepatology and related topics. Review articles, clinical case studies, images, letters to the editor and other articles such as recommendations or papers on gastroenterology clinical practice are also considered. Only articles written in English are accepted.

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Contents

Editorial

83 Endoscopic Resection of Gastrointestinal Neuroendocrine Tumors: Safe and Effective
Abreu, N.; Carvão, J. (Funchal)

Review Article

86 Pharmacological Treatment of Functional Dyspepsia: An Old Story Revisited or a New Story to Be Told? A Clinical Review
Chaves, J. (Porto); Pita, I. (Santa Maria da Feira); Libânio, D.; Pimentel-Nunes, P. (Porto)

Research Articles

98 Endoscopic Resection of Gastrointestinal Neuroendocrine Tumors: Long-Term Outcomes and Comparison of Endoscopic Techniques
Pimentel-Nunes, P.; Ortigão, R.; Afonso, L.P.; Bastos, R.P.; Libânio, D.; Dinis-Ribeiro, M. (Porto)

107 Cap-Assisted Endoscopic Mucosal Resection for Rectal Neuroendocrine Tumors: An Effective Option
João, M.; Alves, S.; Areia, M.; Elvas, L.; Brito, D.; Saraiva, S.; Martins, R.; Cadime, A.T. (Coimbra)

115 Endoscopic Submucosal Dissection for Subepithelial Tumor Treatment in the Upper Digestive Tract: A Western, Multicenter Study
Manta, R. (Perugia); Zito, F.P. (Naples); Pugliese, F. (Milan); Caruso, A.; Mangiafico, S. (Modena); D'Alessandro, A. (Caserta); Castellani, D.; Germani, U. (Perugia); Mutignani, M. (Milan); Conigliaro, R.L.; Bonetti, L.R. (Modena); Matsuda, T. (Tokyo); De Francesco, V. (Foggia); Zullo, A. (Rome); Galloro, G. (Naples)

121 Impact of COVID-19 in Pediatric Patients and Young Adults with Inflammatory Bowel Disease
Magalhães, T. (Porto); Granado, M.C. (Guimaraes); Manuel, A.R. (Lisbon); Espinheira, M.C.; Trindade, E. (Porto)

127 Long-Term Intestinal Failure and Home Parenteral Support: A Single Center Experience
Brito, M. (Almada/Monte da Caparica); Padinha, M. (Monte da Caparica/Almada); Carlos, S.; Oliveira, C.; Santos, A.P. (Almada); Nunes, G. (Almada/Monte da Caparica); Santos, C.A. (Almada); Fonseca, J. (Almada/Monte da Caparica)

134 Validation and Application of Predictive Models for Inadequate Bowel Preparation in Colonoscopies in a Tertiary Hospital Population
Afecto, E.; Ponte, A.; Fernandes, S.; Gomes, C.; Correia, J.P.; Carvalho, J. (Vila Nova de Gaia)

Cover illustration
Bamboo-joint-like appearance in a patient with gastric Crohn's disease.
From Garrido et al., pp. 166–168.

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GE – Portuguese Journal of Gastroenterology

Clinical Case Studies

141 Small Bowel Adenocarcinoma in a Patient with Crohn's Disease: The Role of Balloon-Assisted Enteroscopy
Dias, E.; Mascarenhas Saraiva, M.; Moreira, F.; Cardoso, H.; Macedo, G. (Porto)

147 Transvenous Obliteration Procedure in the Management of Parastomal Variceal Bleeding: A Case Report
Estorninho, J.; Patrão, P.; Temido, M.J.; Perdigoto, D.; Figueiredo, P.; Donato, P. (Coimbra)

Endoscopic Snapshots

153 Sodium-Polystyrene Sulfonate-Induced Colitis
dos Santos, F.S.; Aver, G.P.; Paim, T.V.; Riva, F. (Caxias do Sul); Brambilla, E.; Soldera, J. (Caxias do Sul/Porto Alegre); Soldera, J. (Caxias do Sul/Porto Alegre)

156 Solitary Peutz-Jeghers Type Hamartomatous Polyp Arising from the Appendix
Sant'Anna, M.; Gravito-Soares, E.; Gravito-Soares, M.; Mendes, S.; Figueiredo, P.N. (Coimbra)

159 Anorectal Endoscopic Hybrid Resection of an Uncommon Cause of Debilitating Diarrhoea: Polypoid Supra-Anal Mucosal Prolapse Syndrome
Zimmer, V. (Neunkirchen/Homburg); Heinrich, C. (Saarbrücken)

Images in Gastroenterology and Hepatology

162 SX-ELLA Danis-Stent for Refractory Acute Esophageal Variceal Bleeding
Currais, P. (Lisbon/Almada); Nunes, G. (Almada/Monte da Caparica); Patita, M. (Almada); Coimbra, É. (Lisbon); Fonseca, J. (Almada/Monte da Caparica)

166 An Unusual Endoscopic Finding of Gastric Crohn's Disease
Garrido, I.; Santos-Antunes, J.; Macedo, G. (Porto)

169 Errata

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GE – Portuguese Journal of Gastroenterology

Editorial

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Endoscopic Resection of Gastrointestinal Neuroendocrine Tumors: Safe and Effective

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Keywords
Neuroendocrine tumors · Endoscopic resection · Endoscopic mucosal resection · Endoscopic submucosal dissection

Ressecção endoscópica de tumores neuroendócrinos gastrointestinais: segura e eficaz

Palavras Chave
Tumores neuroendócrinos · Resseção endoscópica · resseção endoscópica da mucosa · Disseção endoscópica da submucosa

Gastrointestinal neuroendocrine tumors (GI-NETs) are being increasingly diagnosed, particularly at earlier stages of disease, where endoscopic resection (ER) is a well-known treatment alternative [1, 2]. The appropriate management of GI-NETs requires a complete understanding of tumor size, depth of invasion, lymph node metastasis status, and location within the gastrointestinal tract. In general, small superficial NETs can be managed by either standard endoscopic mucosal resection (EMR), modified EMR (cap or band assisted), or endoscopic submucosal dissection (ESD). Several studies have described ER as safe and effective alternative with favorable outcomes; however, most of the studies include a small number of patients, are retrospective in nature, and lack direct comparison of different ER techniques. In this issue of *GE – Portuguese Journal of Gastroenterology*, we will find 3 new studies that provide further evidence of the safety, feasibility, and favorable outcomes of different ER methods for GI-NETs.

First, João et al. [3] present a prospective cohort study evaluating the efficacy and safety of cap-assisted EMR (EMR-C) for small (≤10 mm) low-grade rectal NETs (r-NETs). In this single-center cohort study, 13 patients were included during a 4-year period (January 2017 until September 2021), with a 100% complete ER rate and a 92% complete pathological resection (CPR) rate (median lesion size of 6 mm). These results are consistent with the largest retrospective studies on the outcomes of EMR-C for small r-NETs. Yang et al. [4] and Lee et al. [5] report a 94% and 83% complete histological resection rate, respectively. These results are encouraging and, as stated by the authors, EMR-C had higher rates of CPR than conventional EMR (77%), and similar results with ESD, with the advantage of significant lower procedural times [4]. There was only one adverse event (7.6%) reported by the authors corresponding to a case of intraprocedural bleed-

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ing, similar to previously reported, rendering EMR-C a safe ER method [4, 5]. There was no evidence of residual or recurrent lesions during a median follow-up of 6 months, which was expected due to the excellent prognosis of small r-NETs. In fact, GI-NETs guidelines state that small, completely resected r-NETs do not warrant regular follow-up [2]. In 2 cases, EMR-C was used for recurrent r-NETs with endoscopic and histological success, reaffirming the benefit role of salvage EMR.

ESD is another minimally invasive technique that has been described for the treatment of GI-NETs, although it is still controversial which lesions benefit from this more demanding technique with also higher risk of adverse events. Manta et al. [6], in a multicenter retrospective study, evaluated the efficacy and safety of ESD in a cohort of 84 patients with esophageal (n = 13), gastric (n = 61), and duodenal (n = 10) gastrointestinal subepithelial tumors. Despite the 95.5% overall CPR rate, this rate was lower (75%) when applied specifically to GI-NETs. These results are similar to reported for overall ESD for foregut GI-NETs (69–96.6%) and the high variability of CPR rates most likely reflects the inclusion of all organs, grade, size, morphology, and depth of invasion of included lesions and merits careful interpretation [7, 8]. Regarding complications (8.3%), only one major bleeding was observed while no cases of perforations were reported, further emphasizing the safety of ER.

Even though CPR is the ultimate goal in every ER modality, in the specific case of GI-NETs, the true impact of incomplete pathological resections for both recurrence and overall survival remains unclear. Pimentel-Nunes et al. [7] present the first study that focused specifically on the long-term outcomes of different ER methods for the treatment of luminal GI-NETs. More specifically, the authors showed the short- and long-term outcomes after different ER methods of gastric, duodenum, and rectal GI-NETs, namely, standard endoscopic mucosal resection (sEMR), EMR-C, and ESD. In this single-center retrospective analysis, 53 patients with GI-NETs were included (25 gastric, 15 duodenal, and 13 rectal), with a complete ER in all cases (sEMR = 21; EMR-C = 19; ESD = 13) and a 68% overall CPR with no difference between ER techniques. The patients were followed for a mean of 45 months and during this period there were only 3 distant recurrences and 1 local recurrence. Distant recurrence occurred in 2 cases of gastric NETs (type 1 and type 3) and one duodenal NET. Only 1 patient had positive margins on the first resection. Endoscopic and histopathological lesion size of ≥12 mm and 20 mm, respectively, were considered as risk factor for distance recurrence in univariate analysis. Also, only one death was noted after the distance recurrence, due to surgical complications. These results demonstrate that, for small lesions (≤12 mm on endoscopy and ≤20 mm on histopathology), regardless of the ER technique and margins at histopathological examination, as long as the lesions are completely resected, local and distance recurrence is rare and the overall global prognosis is very favorable. For larger lesions, multidisciplinary decision is advised, and if ER is pursued, a more intensive follow-up may be required. Previous studies also highlighted the favorable outcome even with histological positive margins for GI-NETs. For example, in the retrospective study by Matsueda et al. [9] of ER (sEMR, band-ligation EMR, and ESD) of nonampullar duodenal NETs, 97% of the 34 lesions were completely resected, but CPR rate was only 59%. However, there was no local or distant recurrence after a median follow-up of 47.9 months. Sivandzadeh et al. [10] also showed an absence of distant recurrence during a mean follow-up of 64 months in 36 patients with endoscopically resected GI-NETs (sEMR, band-ligation EMR) where only 38.9% had a CPR. For small r-NETs, a meta-analysis also demonstrated no difference in long-term outcomes between different EMR techniques (modified EMR, ESD, and sEMR), with local and distant recurrences being exceedingly rare even after incomplete pathological resection [11]. Finally, in the study of Pimentel et al. [7] EMR-C was surprisingly associated with a significantly higher complication rate (EMR-C 32%, ESD 8%, and EMRs 0%, $p = 0.01$), with 3 cases of perforations (2 duodenal and 1 gastric), mostly managed endoscopically with surgery being needed in only 1 patient after duodenal ESD.

These new 3 studies provide new evidence and strengths that ER is a safe and highly effective therapy for small luminal GI-NETs and should be the first-line therapy for lesions <15–20 mm, depending on the location, and as recommended by the most current guidelines. For most small gastric, duodenal, and rectal lesions, EMR probably should be favored over ESD if lesion characteristics suggest that en bloc complete ER is feasible. ESD appears to be the best option for lesions that cannot be removed en bloc with EMR, and the comparable outcomes of EMR and ESD may also reflect the inclusion of more difficult lesions in the latter technique. To note, EMR-C and ESD are associated with higher risk of major complications, specifically in duodenum, even when performed by skilled operators. However, multicenter, prospective randomized trials are still warranted to confirm and support these results.

Statement of Ethics

Ethics approval was not required.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Joana Carvão and Nélia Abreu contributed equally to the conception, writing, and critical revision of the manuscript.

Data Availability Statement

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

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Review Article

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Pharmacological Treatment of Functional Dyspepsia: An Old Story Revisited or a New Story to Be Told? A Clinical Review

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Keywords
Functional dyspepsia · Treatment

Abstract
Dyspepsia incorporates a set of symptoms originating from the gastroduodenal region, frequently encountered in the adult population in the Western world. Most patients with symptoms compatible with dyspepsia eventually end up, in the absence of a potential organic cause, being diagnosed with functional dyspepsia. Many have been the new insights in the pathophysiology behind functional dyspeptic symptoms, namely, hypersensitivity to acid, duodenal eosinophilia, and altered gastric emptying, among others. Since these discoveries, new therapies have been proposed. Even so, an established mechanism for functional dyspepsia is not yet a reality, which makes its treatment a clinical challenge. In this paper, we review some of the possible approaches to treatment, both well established and some new therapeutic targets. Recommendations about dose and time of use are also made.

Tratamento farmacológico da dispepsia funcional: uma história antiga ou uma nova história a ser contada? uma revisão clínica

Palavras Chave
Dispepsia functional · Tratamento

Resumo
A dispepsia engloba um conjunto de sintomas provenientes do trato gastroduodenal, frequentes na população adulta ocidental. A maioria dos doentes com sintomas compatíveis com dispepsia, acaba eventualmente, na ausência de causa orgânica, por ser diagnosticado com dispepsia funcional. Novos conhecimentos sobre a fisiopatologia responsável pelos sintomas de dispepsia têm sido adquiridos, nomeadamente a hipersensibilidade ao ácido, eosinofilia duodenal e as alterações do esvaziamento gástrico, entre outros. Estas novas descobertas vieram proporcionar novos possíveis alvos terapêuticos. Ainda assim, um mecanismo exato ainda não é conhecido, o que torna o tratamento da dispepsia funcional tantas vezes um desafio clínico. Neste trabalho, algu-

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mas abordagens das possíveis terapêuticas são revisitadas, tanto aquelas que já são uma prática usual, bem como novos alvos terapêuticos. Recomendações sobre dose e duração do tratamento são também elaboradas.

Introduction

Dyspepsia represents multiple and heterogeneous symptoms originating in the gastroduodenal area, including pain or discomfort in the epigastric region, gastric fullness, early satiety, nausea, or belching [1, 2]. Using a broad definition, dyspepsia is common in the adult population, with an estimated prevalence of 10–21% worldwide and an annual incidence of 1–5%, being more frequent in women [1–3].

Dyspepsia can be associated with medication, infections, and several diseases, either systemic or locoregional [1, 4]. Given that symptoms are not a good differentiator between organic or functional dyspepsia (FD), an accurate diagnosis of FD requires exclusion of a structural disease in accordance with Rome IV criteria (Table 1) [2]. Also, in the latest Maastricht and Kyoto consensus [5, 6], infection with *Helicobacter pylori* (*H. pylori*) is considered a cause of dyspepsia (termed *H. pylori* associated dyspepsia) and so it should be included in the differential diagnosis [2, 5, 7, 8]. Even if dyspeptic symptoms can be caused by several etiologies, a majority of patients presenting with dyspepsia, after thorough search, will be diagnosed with FD [1, 4, 8, 9].

FD can be divided in two major subcategories: epigastric pain syndrome (EPS) – mostly related with pain and burning in the epigastric region – and postprandial distress syndrome (PDS) – associated with postprandial fullness and early satiety. It is estimated that PDS is more common than EPS (57–61% vs. 8–18%, respectively) and about 21–35% of patients will have an overlap of symptoms [3, 10]. The main objective in this subdivision is to differentiate the underlying pathophysiology and to adjust medical therapy, although there are conflicting data about the relevance of this subdivision in terms of treatment response and prognosis [11].

Several studies have highlighted multiple factors associated with and possibly causing FD, including environmental exposures, immunological mechanisms (duodenal inflammation, duodenal eosinophilia, and cytokines), impaired gastric emptying or accommodation, and visceral hypersensitivity or altered brain response to pain.

Table 1. Rome IV criteria for FD

Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis
Diagnostic criteria – one or more of the following:
Bothersome postprandial fullness
Bothersome early satiation
Bothersome epigastric pain
Bothersome epigastric burning
And no evidence of structural disease (including at upper endoscopy) that is likely to explain the symptoms

Even though the pathophysiology of FD has been a subject of recent discoveries, a multifactorial etiology is likely [1, 12, 13].

The heterogeneous and complex mechanisms behind FD make a targeted treatment difficult and a nonpharmacological approach with lifestyle recommendations is still the first-line treatment. Even so, an increased interest in drugs targeting FD's pathophysiology has been rising [4, 11, 12, 14–16].

Some of the older treatment options for FD are acid-suppressing drugs, neuromodulators and prokinetics [4, 7, 8, 11, 16]. But new treatment options are just around the corner, including new drugs targeting old pathways and old drugs aiming newly discovered pathways (e.g., with the use of immunosuppressive drugs or histamine-1 receptor antagonists) [17–19]. In this work, we aim to revisit some of the pharmacological treatment options for FD, both well stablished and new, highlighting the efficacy, dosage, duration of therapy, and possible adverse effects (AE).

Methods

A nonsystematic review was performed using a bibliographic search on MEDLINE using the keywords: "functional dyspepsia"; "non-ulcer dyspepsia"; and "treatment". Articles written in English, Spanish, or Portuguese were reviewed. Systematic reviews, meta-analyses, and guidelines published in the last 5 years were preferred.

Treatment of *H. pylori*-Associated Dyspepsia

H. pylori infection is an organic cause of dyspepsia and should not be considered as FD [5]. As such, eradication is the first-line treatment in dyspeptic patients

with *H. pylori*. Indeed, sustained symptomatic improvement is significantly increased after eradication (absolute difference of 10% when compared to placebo or acid suppression therapy; number needed to treat [NNT] 12.5–14), even if it can take up to 6–12 months to be reached [5, 6, 20]. Eradication therapy must have in account personal history (including previous attempts of eradication, recent prescription of antibiotics, and allergies) and local resistance to antibiotics. In settings where primary clarithromycin resistance exceeds 15%, quadruple therapy with or without bismuth is recommended [5].

In Europe, a recent study showed a high prevalence of clarithromycin and metronidazole resistance (21.4% and 38.9%, respectively) [21]. Portugal has also a high prevalence of clarithromycin and metronidazole resistance (42% and 25%, respectively), and thus quadruple therapy with bismuth and proton pump inhibitor (PPI) twice daily (BID) during 10 days is recommended [5, 22]. Most common AE include abdominal pain, diarrhea, and nausea, but they are usually mild and compliance is higher than 90% (need to discontinue of 2–3%) [23, 24]. It is important to alert patients to expected side effects: darker stools, metallic taste, diarrhea, and increased skin photosensitivity. Alcohol and dairy products should be avoided. Eradication rates >90% have been shown across Europe [23–25]. Assessment of the patient's symptoms after eradication will tell if there is any need to pursue further investigation since a substantial percentage of patients will remain symptomatic after successful eradication and will, in the absence of other disease, be ultimately classified as having FD [5, 16].

Current Treatment Options for FD

Acid-Suppressive Drugs

PPIs and Histamine-2 Receptor Antagonists

Although FD is not usually related to an increase in acid output, an increased sensitivity to acid is a potential mechanism in FD [16, 20]. Waters et al. [26] showed that a PPI course decreases duodenal eosinophil counts in a small group of FD patients, which is also a possible explanation for symptom improvement with PPIs in FD.

The two main types of acid-suppressive drugs are PPIs and histamine-2 receptor antagonists (H_2RAs). H_2RAs decrease acid output by inhibiting histamine H_2 receptors in parietal cells, and a 2006 Cochrane meta-analysis of randomized controlled trials (RCTs) reported a benefit in FD over placebo with a NNT of 7 [27]. The main issue with these trials is the inconsistent definition of FD (with inclusion of patients with GERD in older trials) [28].

PPIs act by an irreversible covalent ligation with the H^+/K^+-ATPase proton pump, and they have been one of the most used drugs in FD [17, 20, 26, 29]. A 2017 Cochrane meta-analysis showed that PPI therapy was statistically more effective than placebo with a NNT of 11 [29]. No difference was found between low and standard dose of PPIs and it is unlikely that higher doses have a superior effect [20, 29]. Differences among response in PDS or EPS have controversial results, but in this meta-analysis no difference was found. Comparison between PPIs and H_2RAs failed to show statistically significant differences between the two in ameliorating symptoms, but methodological classification of FD in older studies might be an issue [20, 29].

H_2RAs have some AE like diarrhea, headache, and cimetidine specifically has a weak anti-androgen effect. The development of tachyphylaxis is also a problem as the effectiveness of this class may decrease with continued use [16, 30].

PPIs, on other hand, are relatively safe in short courses but can also cause diarrhea and abdominal pain. The increased risk of some infections, for example, by *Clostridioides difficile* might be worrisome. In longer courses, PPI-induced hypochlorhydria interfere with the absorption of vitamins (B12), drugs, or ions (calcium, iron), but the majority of recommendations is against routine evaluation of these ions [16, 29, 31].

Treatment with a standard dose of H_2RA BID with a 4-week course is an option in FD [32]. With PPIs, the standard dose is usually employed, and esomeprazole and rabeprazole may be more appropriate where the prevalence of PPI extensive metabolizers is high, namely, in Europe and North America [5]. Most studies use a 2- to 8-week treatment duration, but therapy can be extended if needed [7, 16, 20, 29]. On-demand therapy (with a repeated course) in patients with intermittent symptoms is also an option after initial success. De-prescribing PPIs may be challenging and both dose tapering and abrupt discontinuation can be considered [33]. Due to their safety profile and higher acid-suppressing capacity, PPIs are indicated as the first-line therapy for all FD patients in recent guidelines, but more high-quality studies are needed [20, 34, 35].

Potassium-Competitive Acid Blocker

Vonoprazan is an established potassium-competitive acid blocker and competitively blocks the potassium-binding site of the H^+/K^+-ATPase proton pump [36]. It

Table 2. Current medical treatment options for FD regarding *H. pylori* eradication and acid-suppressive drugs

Intervention/efficacy (NNT)	Treatment option	Dosage/duration	AE	Our recommendation
H. pylori eradication NNT 12.5–14 [5, 20]	Bismuth subcitrate potassium 140 mg + metronidazole 125 mg + tetracycline hydrochloride 125 mg + PPI	3 capsules 4 times a day (6/6 h) of Pylera® + PPI standard dose 2 times a day (12/12 h) after meals 10–14 days [5]	Abdominal pain, diarrhea, nausea, alteration of stool color, metallic taste Avoid: exposure to sun, alcohol, or dairy products during treatment [5, 23, 24]	All patients with dyspepsia should be tested and treated if positive Eradication should be confirmed If still positive after quadruple therapy with bismuth, consider triple therapy with levofloxacin If no improvement after successful eradication, adjust other therapies or pursue further investigation if not done before
Acid-suppressive therapy H_2RAs NNT 7 [27] PPI NNT 11 [29]	H_2RAs	Famotidine 10 mg 12/12 h Ranitidine 150 mg 12/12 h 4 weeks [16, 28]	Diarrhea, headache, abdominal pain With cimetidine, possible reversible gynecomastia [16, 30]	PPIs are usually preferred Limited by tachyphylaxis [20, 33]
	PPIs	Standard dose of PPI ID in the morning (fasting), for example, esomeprazole 20 mg; pantoprazole 40 mg; or rabeprazole 20 mg 2–8 weeks [16, 20, 33]	Diarrhea, abdominal pain, constipation, headache With longer courses, possible interference with absorption of minerals/vitamins [16, 31]	First-line option in all FD patients, *H. pylori* negative/*H. pylori* eradicated still symptomatic If no response, consider further investigation (if not done previously) and stop PPI Discuss using PPI treatment on demand to manage symptoms in responders who relapse
	PCAB	Vonoprazan 10–20 mg ID 2–8 weeks	Similar to PPI	Needs further studies Not largely available

FD, functional dyspepsia; *H. pylori*, *Helicobacter pylori*; H_2RAs, histamine-2 receptor antagonists; ID, once daily; NNT, number needed to treat; PCAB, potassium-competitive acid blocker; PPIs, proton pump inhibitors.

appears to produce a stronger and more sustained acid suppression than PPIs, with a recent meta-analysis demonstrating that vonoprazan is more effective than PPIs in patients with severe erosive esophagitis [37]. It is given once daily (ID) in a dose of 10–20 mg and AE appear to be similar to PPIs, but they are not available in Western countries [38]. Regarding FD, clinical improvement was assessed in a small retrospective study with a 48.8% rate of symptomatic improvement, but further studies are needed [39, 40]. Table 2 summarizes medical treatment options for FD regarding *H. pylori* eradication and acid-suppressive drugs.

Prokinetics

Gastric dysmotility is a proposed mechanism for FD through impaired gastric accommodation (present in 15–50% of FD patients) and delayed gastric emptying. Thus, prokinetics are considered one of the treatment options, especially in PDS [7, 16, 34, 36]. Korean guidelines, for instance, assume that prokinetics can be useful as a first-line therapy in PDS [41].

In 2019, a meta-analysis showed that FD patients treated with prokinetics had a statistically significant reduction in global symptoms compared to placebo (NNT of 7; 12 when cisapride was removed from analysis) [42]. However, heterogeneity among pharmacological classes and older studies may limit generalizability [16, 36, 42, 43].

Most prokinetic drugs act either as a dopamine 2 (D_2) receptor antagonist, 5-hydroxytryptamine 4 (HT_4) receptor agonist, or motilin agonist. More recently, the acetylcholine pathway has been modulated [16, 41, 42]. Domperidone, metoclopramide, levosulpiride, clebopride, and itopride are some of the most prominent D_2 receptor antagonists.

Domperidone is one of the most frequently used prokinetics [42, 44, 45]. Older studies demonstrated its efficacy in FD, but the risk of bias may be an issue [41, 43].

One of the most feared AE is the potential for QT prolongation, estimated in up to 6–10% with a baseline electrocardiogram being recommended [46–48]. A normal dosage is 10 mg three times daily (TID) between 2 and 4 weeks [41]. Even so, longer periods (6–12 months) and higher doses (up to 20 mg TID) have been used in gastroparesis without major AE, but a follow-up electrocardiogram during treatment is advised [46–49].

Metoclopramide is a D_2 receptor antagonist and a 5-HT_4 agonist/5-HT_3 receptor antagonist that can pass the blood-brain barrier and cause extrapyramidal symptoms in 1–6% and hyperprolactinemia [4, 7, 16, 50, 51]. Studies propose a dosage of 10 mg three to four times daily and it should not be used for longer than 12 weeks [45, 50, 52].

Itopride and clebopride also belong to D_2 antagonist's class, with the second one passing the blood-brain barrier and possible causing extrapyramidal symptoms. Their use in FD is sparse, but few older studies show symptom improvement [11, 53, 54].

Cisapride facilitates the release of acetylcholine in the myenteric plexus via 5-HT_4 receptor agonism. There is evidence that cisapride improves FD symptoms, with an NNT as low as 4 [42]. Then again, heterogeneity among trials makes it difficult to reach a conclusion [36, 43]. Worrisome about potentially fatal AE makes this treatment not commercially available in several countries [11].

Mosapride, another 5-HT_4 receptor agonist, facilitates gastrointestinal motility and gastric emptying, but a 2018 meta-analysis did not show improvement of FD symptoms when compared to placebo [41, 43]. On the other hand, in a Bayesian network meta-analysis, mosapride was more effective than itopride and acotiamide in treating FD patients [55]. Mosapride has the advantage of no arrhythmia-related AE and recently a once-daily formulation was developed which can improve compliance [41]. A usual regime is 5 mg TID (the extended release 15 mg/daily), between 2 and 6 weeks [16, 41]. Given the current evidence, there is a chance for mosapride to be used in clinical practice, but more data are needed.

Prucalopride and Velusetrag are potent high specificity 5-HT_4 agonists theoretically leading to less cardiovascular risk. Studies in constipation and gastroparesis are ongoing. Further studies in FD may reveal a potential benefit [7, 16, 36, 56, 57].

Erythromycin, a motilin receptor agonist, has already been shown to improve gastric emptying [58]. Nowadays, its use is almost reserved in gastroparesis, but one study demonstrated its efficacy in bloating [59]. A usual dose between 125 and 500 mg TID for a few weeks may be employed. Tachyphylaxis may develop and decrease treatment efficacy [41, 58].

Trimebutine maleate is also a prokinetic drug with antimicrobial properties [60, 61]. An RCT comparing trimebutine 300 mg BID to placebo for 4 weeks in FD patients showed a statistically significant reduction in FD symptoms [62].

Acotiamide is a selective antagonist of acetylcholinesterase and M1/M2 muscarinic receptors in the presynaptic neuron, improving gastric emptying/accommodation, and appears to act in the gut-brain axis via vasovagal response [36, 63]. Several studies have demonstrated its efficacy in FD and a NNT of 20 was estimated in 2018 [36, 43]. Acotiamide appears to have particular benefit in PDS symptoms [16, 41]. It has a good safety profile and minimal dopaminergic receptor effects [36, 64]. Doses between 50 and 100 mg TID are suitable and improvement in symptoms may occur after 2 weeks [16, 64, 65]. However, acotiamide is not commercially available in Europe. Main prokinetics used in FD are summarized in Table 3.

Neuromodulators

Some of the multiple and varied mechanisms involved in FD are related to the gut-brain axis and for this reason it seems logical that targeting this pathway may be beneficial [8, 14, 66, 67]. A significant association between FD with depression and anxiety has already been proved, with the prevalence of depression and anxiety symptoms being 2.5–3 times higher in patients with refractory FD [68].

Neuromodulators seem, for this reason, a strategical treatment for FD. A 2017 systematic review showed the benefit of these drugs, with a NNT of 6, although on subgroup analysis improvement was limited to antipsychotics and tricyclic antidepressants (TCAs). Moreover, when only studies on individuals with no coexistent mood disorder were considered, this benefit was not proven [14]. As suggested by the Rome Foundation, augmentation therapy (combining a second neuromodulator) can also be considered if there is no success of single-agent therapy or if single-agent therapy produces side effects at higher doses [69].

Antidepressants

Selective serotonin reuptake inhibitors are one of the most used drugs for mood disorders, but trials have not shown significant improvement in FD symptoms and a meta-analysis concluded that selective serotonin reuptake inhibitors were not effective in the management of FD [70]. TCAs, such as amitriptyline and imipramine, act

Table 3. Current medical treatment options for FD regarding prokinetics

Intervention/efficacy (NNT)	Treatment option	Dosage/duration	AE	Our recommendation
Prokinetics NNT 12 (without cisapride) [42]	D_2 receptor antagonists	Domperidone 10 mg TID, 30 min before meals 1–6 weeks Metoclopramide 10 mg TID, 30 min before meals No more than 12 weeks Itopride 50–200 mg TID 4–8 weeks Clebopride 0.5 mg TID, 15–30 min before meals 4 weeks [16, 40, 49]	Abdominal pain, diarrhea, sedation, rash Except for itopride: elevation in prolactin levels Domperidone: QT prolongation Metoclopramide, clebopride: Parkinsonian-like symptoms and potentially irreversible tardive dyskinesia [16, 49, 50]	PPI failure and predominant PDS symptoms, consider a prokinetic Caution due to AE and avoid long periods of use
	5-HT_4 agonist receptor	Mosapride 5 mg TID (extended release 15 mg daily) 2–6 weeks [16, 40]	Abdominal pain, dizziness, headache, insomnia, malaise, nausea, diarrhea [16, 40]	Cisapride and tegaserod have serious AE and are unavailable in several countries For prucalopride and velusetrag, there is no evidence in FD yet Mosapride is not commercially available in several countries
	Others	Erythromycin 125–500 mg TID 4 weeks Trimebutine 300 mg BID 4 weeks Acotiamide 50–100 mg TID 2–48 weeks [16, 40, 59, 62]	All: abdominal pain, dry mouth, nausea, headache, diarrhea Attention to interactions with cytochrome P450 3A4 with erythromycin [16, 59, 62]	Reserve erythromycin for second line Trimebutine available in some countries in 200 mg so a dosage of 200 mg TID is suitable. Needs more studies in FD, however Acotiamide not available in Europe

AE, adverse effects; BID, twice daily; FD, functional dyspepsia; NNT, number needed to treat; PDS, postprandial distress syndrome; PPIs, proton pump inhibitors; TID, three times daily; 5-HT_4, 5-hydroxytryptamine 4.

on several neuronal pathways [7]. Amitriptyline is one of the most studied antidepressants in FD. Ford et al. [11] in a 2021 meta-analysis showed that amitriptyline was superior than placebo in FD. TCAs appear particularly interesting in EPS or in patients where pain is a major feature [11, 14, 41, 71]. Due to their mechanism of action, TCAs are more prone to cause AE than placebo, but withdrawal due to them was not increased [11]. Drowsiness, dry mouth, constipation, weight gain, sexual dysfunction, arrhythmias, and suicidal intention may be potential AE [16, 69]. Therapeutic dosage of amitriptyline is between 10 and 50 mg daily and periods of 10–12 weeks have been studied in the management of FD [16, 71, 72]. Even so, if clinical improvement is achieved most antidepressants must be given between 6 and 12 months [69, 73]. While more evidence is needed, amitriptyline can be a next first line for FD treatment, especially in EPS, but AE and contraindications must be taken seriously [14, 69].

Imipramine is another TCA studied in FD. An RCT with refractory FD patients showed that imipramine 50 mg for 12 weeks was associated with significant symptom relief compared to placebo, but discontinuation due to AE occurred in 18% [74].

Mirtazapine is a tetracyclic antidepressant and it is associated with weight gain [75]. Weight loss, considered an alarm symptom, may be present in up to 40% of tertiary care FD patients [75, 76] and so weight gain may be desirable. An RCT to assess the efficacy of 15 mg of mirtazapine for 8 weeks versus placebo observed that mirtazapine was associated with significant recovery of weight loss and quality of life. A trend was found for improvement in overall dyspepsia symptoms at week 4 but not at week 8 [75]. Besides this, mirtazapine's antagonism of the H_1 receptor requires further study [19]. Given this evidence, mirtazapine 15–30 mg during 8 weeks may be beneficial to those with FD and weight loss. AE, other than weight gain, may be increased liver enzymes, edema, rash, orthostatic hypotension, and tremor [34, 75].

Venlafaxine is a serotonin norepinephrine reuptake inhibitor that exhibits some peripheral gastric effects [7,

16, 77]. However, in an RCT venlafaxine was not more effective than placebo in FD, which may be explained by the lower dosage used (75–150 mg) [7, 77]. In the future, higher doses may be tried, but for now, venlafaxine is not an option in the treatment of FD.

Atypical Antipsychotics

Sulpiride and levosulpiride are atypical antipsychotic agents which block the presynaptic dopaminergic D_2 receptors and also have a potential 5-HT_4 agonism [69]. Due to this, they are also recognized as an antiemetic drug [78]. In a 2021 meta-analysis, levosulpiride was significantly more effective in treating FD than several other drugs, including some PPIs, prokinetics, and antidepressants, despite uncertainty around the results (small number of trials and patients) [79]. Levosulpiride dosage is 15–25 mg TID for a short period [41, 78]. AE may include sedation, dizziness, weight gain, diabetes, and Parkinsonism-like symptoms [41, 69].

Azapirones

Buspirone and tandospirone (azapirones) were developed as anxiolytics drugs [7, 69]. Peripherally, they promote relaxation of the proximal stomach, improving gastric accommodation [7, 16, 80]. In 2012, a study with 17 FD patients showed that buspirone significantly reduced the overall symptom severity compared to placebo [81]. Also, a study of tandospirone showed an improvement in upper abdominal pain and discomfort versus placebo [82]. Despite this, in meta-analysis, azapirones were unsuccessful in providing improvement in FD patients [14]. This negative result can be at least somewhat explained by the small number of trials and patients included [14]. Possible AE are sedation, headache, and vertigo. A dose of 30 mg daily in divided doses (TID) for 4 weeks has been used [7, 16, 34, 81, 82].

Anticonvulsants

Some anticonvulsants (e.g., gabapentin and pregabalin) are employed nowadays in controlling neuropathic pain and fibromyalgia [69, 83]. Reducing neurotransmission in overly active pain circuitry is likely the underlying mechanism behind their efficacy [69, 83, 84]. Gabapentin and pregabalin reduce excessive release of excitatory neurotransmitters such as glutamate and both have been recently studied in FD [69].

Gabapentin led to a significant improvement of dyspeptic symptoms such as abdominal pain and postprandial fullness in a retrospective study [85]. An RCT on 126 refractory FD patients, either taking omeprazole 20 mg ID plus placebo or omeprazole 20 mg ID plus gabapentin 300 mg BID, showed that both groups had a reduction in the severity of symptoms that was higher in the gabapentin group, although without statistical significance [86]. The studied treatment duration in gabapentin was 4 weeks and a dosage up to 900 mg daily (300 mg TID) may be used. Treatment should begin with a small dose, such as 300 mg at bed time, and increased after 3 days if tolerated [85, 86]. Main AE of these drugs are sedation, headache, vertigo, weight gain, and peripheral edema [69].

Pregabalin, a second-generation drug, appears to have a better profile in potency, pharmacokinetics, and less AE compared to gabapentin [69, 83, 86]. An RCT of 72 enrolled patients with FD, including PPI nonresponders, showed that pregabalin for 8 weeks led to significant improvement of dyspeptic symptoms compared to placebo, especially in patients with epigastric pain. No serious AE were reported [83]. The duration period was 8 weeks, with a dosage of 75 mg daily. Though this class may become a valid strategy particularly in those whom pain is a predominant feature, additional evidence is needed.

New Targets: Immune Response and Dysbiosis

New data about altered local immune response, mainly in duodenum, make it attractive to new treatment targets [12, 36]. Steroids are one of the most commonly used immunosuppressive drugs. Budesonide has a good pharmacokinetic and pharmacodynamic profile, and it is safely used in several gastrointestinal diseases which makes it appealing in FD [87–89]. Even so, most of the formulations available do not deliver budesonide in the upper gastrointestinal system [88].

Talley et al. [89] tried a budesonide 9 mg/day liquid form versus placebo in an RCT with 162 patients with FD for 8 weeks. There was no significant change in eosinophil count from baseline to post-treatment in either group, but a drop in duodenal eosinophil count was significantly correlated with a decrease in postprandial fullness severity and frequency as well as early satiety severity. These results show a lack of efficacy of this formulation but validate the theory that a decrease in duodenal eosinophil counts may be associated with FD symptom improvement [89].

Histamine and mast cell infiltration have likewise been linked with FD. For this reason, anti-allergic therapies may seem a good option for new studies. Antagonism of H_1 receptor was studied in visceral hypersensitivity in irritable bowel syndrome and appears to be effective in

Table 4. Current medical treatment options for FD regarding neuromodulators and new therapies [14–16, 69, 71–73, 76, 79, 84, 85, 87, 96]

Intervention/efficacy (NNT)	Treatment option	Dosage/duration	AE	Our recommendation
Neuromodulators NNT 6 [14]	Antidepressants	Amitriptyline 10–50 mg ID at bed time (starting dose between 10 and 25 mg ID and increase 25 mg every 2 weeks) 10–12 weeks Imipramine 50 mg ID 12 weeks Mirtazapine 15–30 ID at bed time 8 weeks [16, 69, 72, 96]	Drowsiness, dry mouth, constipation, and weight gain Mirtazapine: alteration in liver enzymes, edema, rash, orthostatic hypotension, and tremor [16, 69, 76]	Amitriptyline: good choice for PPI nonresponders in which epigastric pain is a major feature Caution with AE Mirtazapine may be a choice if weight loss is a major concern If clinical improvement is achieved, most antidepressants must be given between 6 and 12 months [69, 73]
	Atypical antipsychotics	Levosulpiride 15–25 mg TID 4–8 weeks [16, 79]	Sedation, dizziness, weight gain, diabetes, and Parkinsonism [16, 79]	These drugs also have anti-emetic effects that may be desired A new option with rabeprazole is already in the market in some countries More studies needed
	Azapirones	Buspirone/tandospirone 10 mg TID 4 weeks	Sedation, headache, vertigo	Consider if anxiety is present and if the FD subtype is PDS
	Anticonvulsants	Gabapentin 300 mg BID-TID (starting with 300 mg at bed time, increase after 3 days if well tolerated) 4 weeks Pregabalin 75 mg ID at bed time 8 weeks [84, 85, 87]	Sedation, headache, vertigo, weight gain, peripheral edema [71]	Could be an option in refractory patients particularly if pain is a predominant feature Pregabalin maybe more suitable (single-dose, second-generation medication)
Other potential treatments	Antibiotics	Rifaximin 400 mg TID 2 weeks [15]	Dizziness, headache, fatigue, abdominal pain [15]	A relatively safe option can be pondered in some FD patients, but more data are needed in whom or when should be used H_1-receptor antagonists and anti-leucotriene-1 receptor antagonist need studies in adult population before a statement can be addressed

AE, adverse effects; BID, twice daily; FD, functional dyspepsia; ID, once daily; NNT, number needed to treat; PDS, postprandial distress syndrome; PPIs, proton pump inhibitors; TID, three times daily.

children with FD [12, 90]. A combination of histamine-1 and histamine-2 receptor blockade was reported in a case series in Australia. Fourteen patients with FD received ranitidine 150–300 mg BID and loratadine 10–20 mg ID during 1–24 months (median 4 months). Treatment resulted in symptom improvement in 10 patients, and those who responded had significantly higher baseline duodenal eosinophil counts versus nonresponders [18].

Montelukast, an anti-leucotriene-1 receptor antagonist, was studied in children with FD, with a statistically significant symptom improvement [91]. On the other hand, RCTs to access the response to these drugs in the adult population are lacking. These drugs are generally well tolerated, with few AE, and may have potential to ameliorate FD symptoms [12].

The alteration in gut microbiota has been studied in both functional and inflammatory GI disorders [12]. Gastrointestinal infection can induce FD and an interest in modulating gut microbiota has emerged [92].

Rifaximin is a poorly absorbed oral antibiotic with a good safety profile. In FD, an RCT including 86 individuals examined the efficacy of 2 weeks 400 mg of rifaximin TID versus placebo. Patients were observed at week 2 (end of the treatment), 4, and 8. At week 8, a significantly difference was observed in symptom relief in the rifaximin's group. The effect was more pronounced in women and a similar incidence of AE was reported [15].

More RCTs are mandatory before a definitive role for immune and microbiota modulation in FD's treatment becomes a reality. Table 4 summarizes treatment options for FD regarding neuromodulators and new therapies.

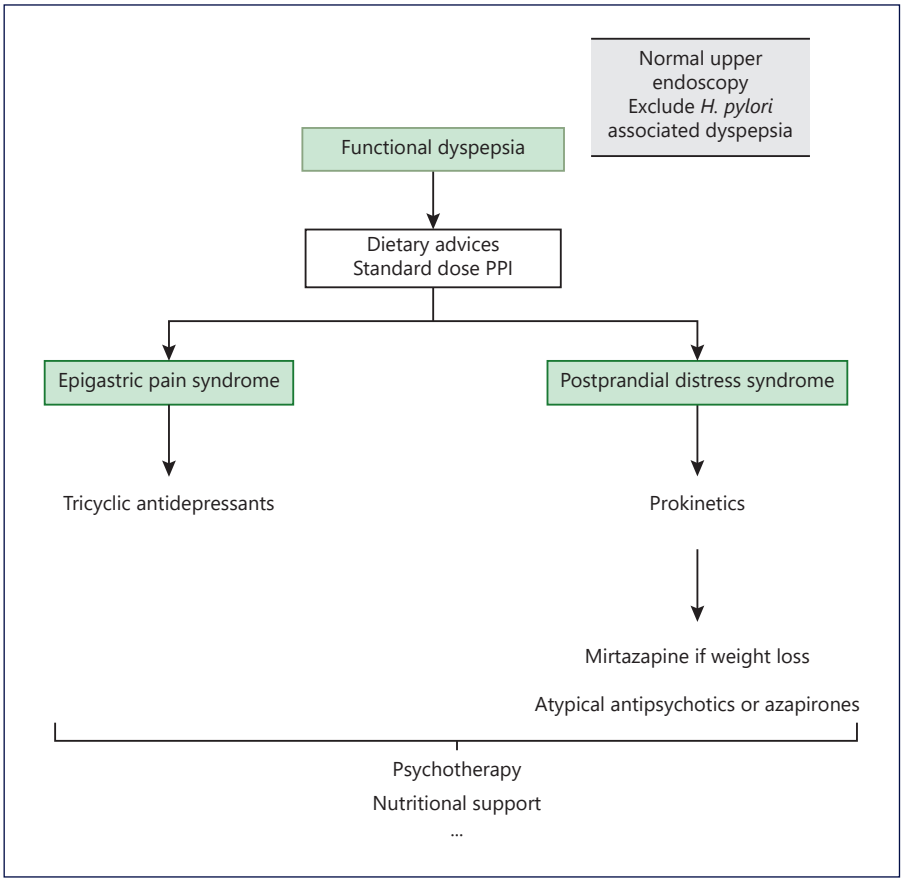

Fig. 1. Schematic representation of a proposed algorithm for the management of functional dyspepsia. *H. pylori, Helicobacter pylori;* PPIs, proton pump inhibitors. *Dietary advices may be eating slowly at regular intervals, decrease the lipid supply and reducing consumption of coffee- and carbonated drinks. **Standard dose PPI may include esomeprazole 20 mg, pantoprazole 40 mg; rabeprazole 20 mg and lansoprazole 30 mg.

Other Therapies

Bismuth salts can suppress *H. pylori* and so its use in eradication treatment. Role for bismuth salts in FD can also be present since it inhibits peptic activity. Even so, beneficial effect with bismuth salts in FD in older studies is difficult to validate nowadays, without newer studies not including *H. pylori*-infected patients [20, 93].

Simethicone is a defoaming agent. Older studies show overall improvement in FD with similar results to those achieved with cisapride and with faster relief. A clinical plausibility due to decrease in abdominal gas makes it appealing in those patients where bloating is a major complain. A dosage between 84 and 105 mg TID during 8 weeks has been used. AE are infrequent but nausea, diarrhea, and constipation may occur [94, 95].

Clinical Management: More Than a Disorder, a Patient!

As we all know, FD is a complex and heterogeneous entity. The most important step in treating these patients is to manage expectations. One treatment may not work and there may be a need to proceed to others. Clinical evaluation should be done between 4 and 12 weeks after a new therapy has been started. If failed, choosing the next target should take into account the patient's predominant complaints and previous comorbidities. Attention to contraindications of some of these therapies must be present and it is advisable to explain the potential AE of the new treatment. Figure 1 represents a schematic algorithm proposed for the management of FD.

Although treating FD is a hard task, do not give up! A tailored approach is probably the best option so far.

Conclusion

FD is a multifactorial disorder, with recent discoveries in some of the pathways involved, including the role of the immune system. Current treatment options are not ideal in terms of efficacy, but also regarding AE. Likewise, targeting the pathophysiology of FD still needs to be refined.

Future studies should focus on accurately defining FD, according to Rome IV criteria, and on analyzing FD subdivision according to predominant symptoms. Standardization of dose and duration of treatment is also a point to look for. Trials with new medications are missing and some of the old drugs should be revisited. Furthermore, management of symptom relapse after successful treatment is still a matter of doubt: should we use the same drug or try a different option? This is another question for future studies to answer. For now, treatment of FD remains an old story revisited, but a new story to be told is not so far away.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

J.C. performed the literature search and wrote the manuscript. I.P. reviewed the manuscript and made critical corrections. D.L. collaborated in the structure and critical corrections. P.P.N. revised and reviewed the manuscript.

Data Availability Statement

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

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Endoscopic Resection of Gastrointestinal Neuroendocrine Tumors: Long-Term Outcomes and Comparison of Endoscopic Techniques

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Keywords
Neuroendocrine tumours · Survival · Endoscopic mucosal resection · Endoscopic submucosal dissection

Abstract
Introduction: Gastrointestinal neuroendocrine tumors (GI-NETs) are being more frequently diagnosed and treated by endoscopic resection (ER) techniques. However, comparison studies of the different ER techniques or long-term outcomes are rarely reported. ***Methods:*** This was a single-center retrospective study analyzing short and long-term outcomes after ER of gastric, duodenum, and rectal GI-NETs. Comparison between standard EMR (sEMR), EMR with a cap (EMRc), and endoscopic submucosal dissection (ESD) was made. ***Results:*** Fifty-three patients with GI-NET (25 gastric, 15 duodenal, and 13 rectal; sEMR = 21; EMRc = 19; ESD = 13) were included in the analysis. Median tumor size was 11 mm (range 4–20), significantly larger in the ESD and EMRc groups compared to the sEMR group ($p < 0.05$). Complete ER was possible in all cases with 68% histological complete resection (no difference between the groups). Complication rate was significantly higher in the EMRc group (EMRc 32%, ESD 8%, and EMRs 0%, p = 0.01). Local recurrence occurred in only one patient, and systemic recurrence in 6%, with size ≥ 12 mm being a risk factor for systemic recurrence (p = 0.05). Specific disease-free survival after ER was 98%. ***Conclusion:*** ER is a safe and highly effective treatment particularly for less than 12 mm luminal GI-NETs. EMRc is associated with a high complication rate and should be avoided. sEMR is an easy and safe technique that is associated with long-term curability, and it is probably the best therapeutic option for most luminal GI-NETs. ESD appears to be the best option for lesions that cannot be resected en bloc with sEMR. Multicenter, prospective randomized trials should confirm these results.

Exérese endoscópica de tumores neuroendócrinos gastrointestinais: resultados a longo prazo e comparação de técnicas endoscópicas

Palavras Chave
Tumores neuroendócrinos · Sobrevida · Ressecção endoscópica da mucosa · Dissecção endoscópica da submucosa

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Resumo

Introdução: Os tumores neuroendócrinos gastrointestinais (GI-NET) são frequentemente diagnosticados e tratados por técnicas de resseção endoscópica (ER). Contudo, estudos comparativos das diferentes técnicas de ER ou resultados a longo prazo são raramente descritos. ***Métodos:*** Estudo unicêntrico retrospectivo que analisa resultados a curto e longo prazo após ER de NETs gástricos, duodenais e retais. Realizou-se uma análise comparativa entre as técnicas de mucosectomia convencional (sEMR), mucosectomia com cap (EMRc) e disseção endoscópica da submucosa (ESD) ***Resultados:*** Foram incluídos 53 doentes com GI-NET (25 gástricos, 15 duodenais e 13 rectais; sEMR=21; EMRc=19; ESD=13). A mediana do tamanho da lesão foi 11 mm (âmbito 4-20), sendo significativamente maiores nos grupos ESD e EMRc quando comparado com sEMR ($p < 0.05$). A ER completa foi possível em todos os casos com taxa de resseção histológica completa de 68% (sem diferença entre os grupos). A taxa de complicações foi significativamente superior no grupo EMRc (EMRc 32%, ESD 8% e EMRs 0%, $p = 0.01$). Recorrência local apenas ocorreu em 1 doente e recorrência sistémica em 6%, com o tamanho da lesão $\geq$ 12mm a ser um factor de risco para recorrência sistémica ($p = 0.05$). Sobrevida específica de doença após ER de 98%. ***Conclusão:*** ER é segura e altamente eficaz para o tratamento de GI-NETs principalmente com tamanho inferior a 12 mm. EMRc está associada a uma taxa de complicações elevada e deve ser evitada. sEMR é uma técnica segura e eficaz que se associa a curabilidade a longo prazo, sendo provavelmente a melhor opção terapêutica para a maioria dos GI-NETs luminais. ESD parece ser a melhor opção para as lesões que não podem ser removidas em bloco pela técnica de sEMR. Estudos randomizados, prospectivos e multicêntricos devem confirmar estes resultados.

Introduction

Neuroendocrine tumors (NET) are relatively uncommon gastrointestinal (GI) tract neoplasias, with a global annual age-adjusted incidence rate of 2/100,000 people per year [1]. However, the widespread use of endoscopy has led to increased detection of luminal GI, often at initial stages of disease. Not surprisingly, the majority of these initial stage GI-NETs are from the stomach, duodenum, and rectum, the most accessible areas to endoscopic exploration [2].

GI-NETs are classified as NET G1, NET G2 (both considered well-differentiated), and neuroendocrine carcinoma (NEC) G3 (poorly differentiated) based on the mitotic count and Ki-67 index [3]. Even though tumor grade is one of the most important prognostic factors (that is only correctly defined after resection), the size of the tumor is also an independent prognostic factor, increasing the risk of lymph node metastasis [4]. For this reason, most guidelines only recommend endoscopic resection (ER) as a treatment for small GI-NET, usually with less than 10–15 mm depending on the location, with every GI-NET larger than 2 cm being considered for surgery [4, 5].

Several studies and meta-analyses confirm the safety and effectiveness of ER for small GI-NETs. However, these studies include a small number of patients, and rarely long-term outcomes are reported [6–9]. Moreover, to our knowledge, no single study compared short- or long-term outcomes of the standard inject-and-cut endoscopic mucosal resection (sEMR) with more complex techniques such as EMR with a cap (EMRc) or endoscopic submucosal dissection (ESD).

In this retrospective study, we analyze long-term outcomes after ER of GI-NETs in the stomach, duodenum, and rectum. Moreover, we compare the short and long-term outcomes of the different ER methods.

Materials and Methods

Patients and Lesions

A retrospective observational study was performed. Pathological database of the Portuguese Oncology Institute of Porto was searched for GI-NETs diagnosed between 2010 and 2020. After evaluation of the pathological report, patients with non-GI NET, pancreatic, small bowel (with the exception of duodenum), appendix, or colonic (with the exception of rectum) NET were excluded from the analysis. The clinical records of all the other patients were analyzed. At this stage, additional exclusion criteria were non-endoscopic initial treatment (surgery or somatostatin analogs), GI-NET only present in biopsies, endoscopic diagnosis/treatment only with cold or hot-snare resection (without submucosal injection), endoscopic treatment at other hospital, or less than 12-month follow-up. At the end, only patients with GI-NET from stomach, duodenum, or rectum treated in our institute by sEMR, EMRc, or ESD with at least 1 year of follow-up were included in the analysis. In Figure 1, we can see the flowchart for patient enrolment.

ER Procedures

Standard EMR (EMRs) was defined as the conventional technique of tumor resection with hot snare technique after submucosal injection with normal saline and diluted adrenaline (1:10,000 to 1:50,000 dilution) (Fig. 2). EMRc was performed with a transparent cap (Olympus, reusable oblique cap) at the tip of conven-

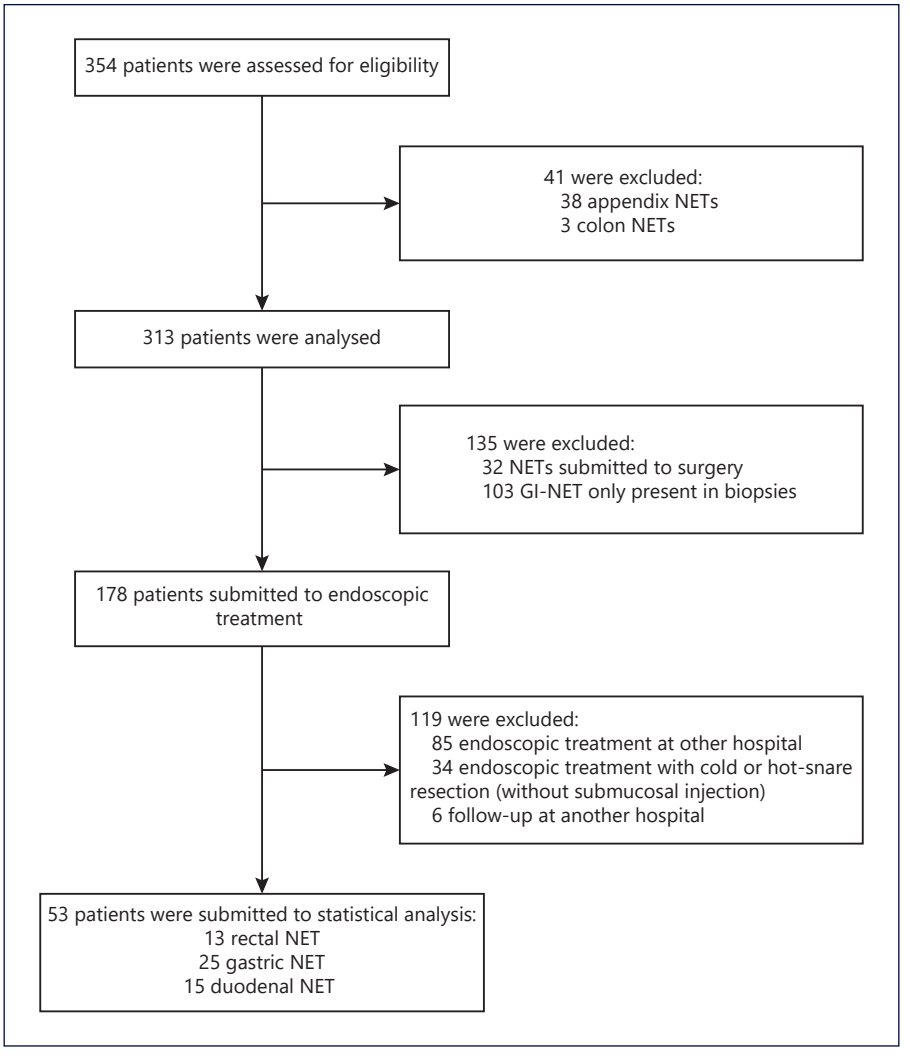

Fig. 1. Patient selection flowchart. NET, neuroendocrine tumor; GI-NET, gastrointestinal neuroendocrine tumor.

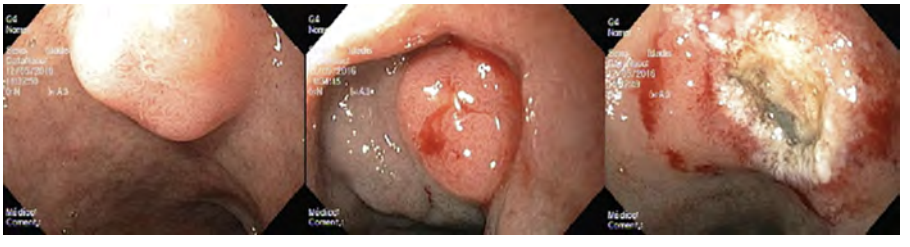

Fig. 2. Endoscopic mucosal resection of a 12-mm subepithelial lesion of the duodenal bulb.

tional upper GI endoscope and a crescent-type snare (EMR snare, Olympus). Hot-snare resection was done after submucosal injection with normal saline and diluted adrenaline (1:10,000 to 1:50,000 dilution) and suction of the lesion into the cap. ESD was performed as previously described (Fig. 3). Briefly, small coagulation marks were made around the lesion and then submucosal injection was performed with saline, diluted epinephrine (1:50-100,000), and methylene blue. After elevation, 3–4 incisions were made with a needle knife (Olympus®) to get access to the submucosal layer, and an insulated-tip knife (mainly IT-Knife™; Olympus®) was used to perform circumferential dissection using the Endo Cut mode (Olympus electrosurgical unit, 80/60 W). Complete dissection was then performed in the Endo Cut or swift coagulation mode, with additional submucosal injection whenever necessary. The procedures were performed mainly under general anesthesia (with orotracheal intubation); deep sedation was restricted to a minority of procedures.

Definitions and Follow-Up

En bloc ER was defined as ER in one single fragment versus piecemeal resection defined as two or more fragments ER. Complete ER was defined as no evidence of macroscopic disease after

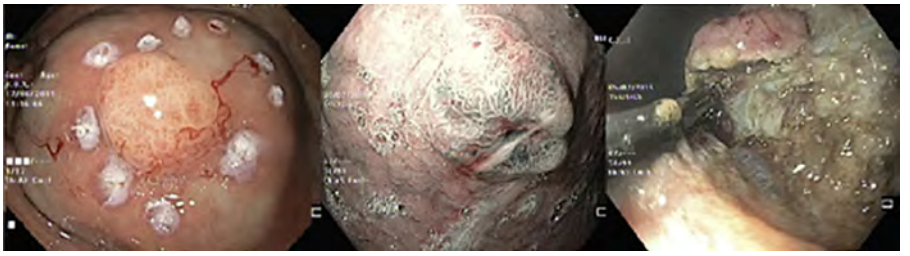

Fig. 3. Endoscopic submucosal dissection of a 12-mm gastric lesion.

Table 1. Patient characteristics

	Gastric lesions ($n = 25$)	Duodenal lesions ($n = 15$)	Rectal lesions ($n = 13$)	p	Total ($n = 53$)
Male, *n* (%)	12 (48)	9 (60)	5 (38)	ns	26 (49)
Age, median (range), years	60 (38-77)	58 (42-75)	55 (47-66)	ns	59 (38-77)
Tumor size, median (range), mm	12 (5-22)	10 (4-18)	9 (4-15)	0.1	11 (4-20)
WHO TNE type (after ER)				0.03	
Grade 1	12 (48)	12 (80)	11 (85)		35 (66)
Grade 2	13 (52)	3 (20)	2 (15)		18 (34)
Grade 3	0	0	0		0
Gastric TNE					
Type 1	21 (84)	–	–	–	21 (84)
Type 2	0				0
Type 3	4 (16)				4 (16)
ER procedure				0.005	
EMRs	5 (20)	5 (33)	11 (84)		21 (40)
EMRc	11 (44)	7 (47)	1 (7)		19 (36)
ESD	9 (36)	3 (20)	1 (7)		13 (24)

ER, independent of the type of ER (en bloc or piecemeal). Adverse events were defined as immediate (during procedure) or delayed complications (not apparent during the procedure). Bleeding as a complication was defined as intraprocedural bleeding requiring non-planned hemostasis (immediate bleeding) or as melena or hematochezia after the procedure (delayed bleeding), independently if additional interventions were required or not. Perforation was defined as a bowel wall penetration identified during the procedure (immediate perforation) or as symptoms compatible with perforation with imagiological (CT) confirmation of that (delayed perforation). Endoscopic size was defined as the estimated macroscopic size attributed by the gastroenterologist in the endoscopy report.

All the histological findings were evaluated by two pathologists, with at least one of them being experienced in GI-NET evaluation, with each specimen being graded according to the WHO classification [3]. Histological complete resection was defined as margins free of tumor, both lateral and vertical margins. Histological maximum size of the lesion was considered as the maximum diameter from one side to the other.

All patients were followed-up with periodic endoscopy (at least one per year), serum chromogranin A (at least one per year) and imagiological methods, generally PET-CT with somatostatin receptors markers (as needed). Local recurrence was defined as histologically confirmed diseased at the site of ER, and systemic recurrence as histologically confirmed ganglion, liver and/or another organ NET metastasis.

Statistical Analyses

Data were expressed as mean + standard deviation or as median and interquartile range (according to the dispersion) for continuous variables and as frequencies and/or proportions for categorical variables. Differences in outcomes were compared using independent *t* tests for numerical variables and χ^2 tests for categorical variables (p values were considered significant if they were <0.05). Multivariable logistic regression model was constructed to identify risk factors for systemic recurrence (including age, sex and variables with $p < 0.20$ at univariable analysis). All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) software (version 27.0; IBM Corp., Armonk, NY, USA).

Table 2. Clinical outcomes of the different ER procedures

	EMRs (*n* = 21)	EMRc (*n* = 19)	ESD (*n* = 13)	*p*	Total (*n* = 53)
Endoscopic tumor size, mm	8.7 (3.9)	11.1 (3.7)	12.3 (3.2)	**0.06** (EMRs vs. EMRc) **0.008** (EMRs vs. ESD) 0.3 (EMRc vs. ESD)	10.5 (3.9)
ER specimen, mm	9.7 (4.8)	15.2 (3.4)	21.9 (8.3)	**<0.001** (all comparisons)	14.6 (6.7)
Complete ER	21 (100)	19 (100)	13 (100)	0.4	53 (100)
En bloc	21 (100)	18 (95)	13 (100)		52 (98)
Piecemeal	0 (0)	1 (5)	0 (0)		1 (2)
Histological complete resection*	15 (71)	12 (63)	9 (69)	0.15	36 (68)
Vertical margins +	4 (19)	7 (37)	4 (31)	0.4	15 (28)
Horizontal margins +	4 (19)	1 (5)	1 (8)	0.3	6 (11)
Procedure time, min	7.8 (3)	21 (16)	57 (21.3)	**<0.001** (all comparisons)	24.7 (24.1)
Complications	0 (0)	6 (32)	1 (8)	0.01	7 (13)
Bleeding	0 (0)	3 (16)	0 (0)	0.03	3 (6)
Perforation	0 (0)	3 (16)	1 (8)	0.04	4 (8)
Surgery (because of)	0 (0)	0 (0)	1 (8)	0.4	1 (2)
TNE location				0.003	
Gastric	5 (24)	11 (58)	9 (69)		25 (47)
Duodenum	5 (24)	7 (37)	3 (23)		15 (28)
Rectal	11 (52)	1 (5)	1 (7)		13 (25)

Data presented as *N* (%) or as mean (SEM). * Histological complete resection implies both V and H margins negative – the number of V+ plus H+ might be higher than uncomplete histological resection since some specimens may be both V+ and H+.

Table 3. Distant recurrence cases

	Location (and type if gastric)	Endoscopic/ histological size, mm	NET grade	Vertical margin	Lymphovascular invasion
Case 1	Gastric type 1	12/25	G2	V1	LV1
Case 2	Gastric type 3	20/30	G1	V0	LV0
Case 3	Duodenum	12/20	G2	V0	LV0

Results

Patient and Lesion Baseline Characteristics

A total of 53 patients were included in the analysis (Table 1). The median age was 58 years old and 49% were male, with no differences between the groups. The median size of the lesions was 11 mm (4 minimum, 20 maximum) with a non-significant trend for larger lesions in the stomach group. Only NETs grade 1 on biopsies were considered for ER (with a histological upgrade in the resection specimen to grade 2 lesions in 34% of the lesions). Twenty per cent of gastric NETs were type 3 and both this feature and size translated into more advanced lesions in the stomach group (52% grade 2 lesions vs. 20% and 15% in the duodenum and rectum, respectively, p = 0.003). Endoscopic ultrasound (EUS) was performed in 51% of the patients, generally for lesions bigger than 10 mm.

Clinical Outcomes

The clinical outcomes of the different ER methods are summarized in Table 2. In general, EMRs was used for smaller lesions. There were no differences between the techniques regarding complete endoscopic and histological resection, with only one lesion being resected in piecemeal in the EMRc group. Even though complete ER was always achieved, histological complete resection rate was only of

Table 4. Risk factors for distant recurrence

	No recurrence ($n = 50$)	Recurrence ($n = 3$)	p	Multivariate
Age, mean (SD)	55.3 (12.9)	55.3 (12.8)	0.60	
Endoscopic size, median (range), mm	10.0 (4 – 20)	12 (12-20)	0.05	
Procedural time, min (mean, SD)	23.4 (24.1)	46.7 (15.3)	0.11	0.662
Maximum histological size, median (range), mm	14.5 (4.0-25.0)	25 (20-30)	0.004	
Sex			0.61*	
Male	24 (92.3%)	2 (7.7%)		
Female	26 (96.3%)	1 (3.7%)		
Technique			0.17#	0.852
EMR-std	21 (100%)	0 (0%)		
EMR-cap	18 (94.7%)	1 (5.3%)		
ESD	11 (84.6%)	2 (15.4%)		
Maximum histological size			0.004	0.997
<20 mm	39 (100%)	0 (0%)		
≥20 mm	11 (78.6%)	3 (21.4%)		
Location			0.56#	
Stomach	23 (92%)	2 (8%)		
Duodenum	14 (93.3%)	1 (6.7%)		
Rectum	13 (100%)	0 (0%)		
NET type (gastric)			0.31*	
Type I	19 (95%)	1 (5%)		
Type III	3 (75%)	1 (25%)		
Ulcer			0.51*	
No	40 (95.2%)	2 (4.8%)		
Yes	10 (90.9%)	1 (9.1%)		
En bloc			0.80	
No	1 (100%)	0 (0%)		
Yes	49 (94.2%)	3 (5.9%)		
Grade			0.26*	0.386
G1	34 (97.1%)	1 (2.9%)		
G2	16 (88.9%)	2 (11.8%)		
Invasion depth			0.785#	
Mucosa	4 (100%)	0 (0%)		
Submucosa	43 (93.5%)	3 (6.5%)		
Muscularis propria	3 (100%)	0 (0%)		
Horizontal margin			0.816#	
HM0	44 (93.6%)	3 (6.4%)		
HM1	3 (100%)	0		
HMx	3 (100%)	0		
Vertical margins			0.938#	
VM0	36 (94.7%)	2 (5.3%)		
VM1	13 (92.9%)	1 (7.1%)		
VMx	1 (100%)	0 (0%)		
Lymphovascular invasion			0.51*	0.826
LV0	40 (95.2%)	2 (4.8%)		
LV1	10 (90.9%)	1 (9.1%)		
R			0.89#	0.775
R0	34 (94.4%)	2 (5.6%)		
R1	13 (92.9%)	1 (7.1%)		
Rx	3 (100%)	0		

SD, standard deviation; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; std, standard/lift-and-cut; NET, neuroendocrine tumor. * Fisher's exact test. # χ^2 test.

68% (no differences between the groups). ESD was significantly longer than EMRc and EMRc significantly longer than EMRs (57, 21, and 8 min, respectively, $p < 0.001$). The complication rate was significantly higher in the EMRc group (2 duodenal and 1 gastric perforation) when compared to the other two groups (EMRc 32%, ESD 8% and EMRs 0%, $p = 0.01$). However, surgery because of complication was only needed in one patient, after duodenal ESD.

Follow-Up

The mean follow-up was 44.6 months (range 12-102 months, no differences between the ER groups), and in this period there was only one local recurrence (2%), which was treated by another ER. There were 6 new lesions identified and treated by ER, all type 1 lesions in the stomach. Systemic recurrence occurred in 3 patients (1 only nodal and 2 liver and nodal disease, one of this with carcinoid syndrome), one case of type 1 gastric, other case type 3 gastric, and one duodenal NET. The mean time between diagnosis and systemic recurrence was 9 months (range 6-12 months). Only the duodenal NET patient with systemic recurrence died because of NET (after surgical treatment). Three additional patients died during follow-up due to NET-unrelated causes (specific disease-free survival 98%, global survival 92%).

Risk Factors for Recurrence

There was only one local recurrence, a 4-mm recurrence 3 years after R1 resection of type 1 gastric TNE that was treated effectively by hot snare technique. There was no statistically significant risk factor for local recurrence. Only one out of 17 (6%) R1 resections locally recurred.

Distant recurrence occurred in 3 patients (Table 3). The only identified risk factors for distant recurrence (Table 4) were the ones related to the size of lesion. Median endoscopic size of the lesions that recurred was 12 mm ($p = 0.05$) with all the recurrent lesions having a maximum histological size larger or equal to 20 mm ($p = 0.004$). Histological maximum size was the strongest risk factor for distant recurrence ($p = 0.004$).

For metachronous lesions, the only risk factor was type 1 gastric NET ($p < 0.001$).

Discussion

GI-NETs are being more frequently diagnosed and treated by ER methods. Even though several studies show the effectiveness and safety of different ER methods for the treatment of GI NETs, long-term outcomes are rarely described. To our knowledge this is the first study that focuses on long-term outcomes after several ER methods for the treatment of luminal GI NETs. Our results confirm that ER should be a first-line therapy for small GI NETs providing curability in most cases.

There are some limitations to our study. First, we have a relatively small sample size of 53 patients. Secondly, by including all the organs we should be careful to interpret and generalize our results. Thirdly, even though similar, follow-up was not standardized between patients and so recurrence data should be interpreted with caution. Fourthly, band-EMR was not applied in any case, and so no conclusion can be made about this technique. Finally, the retrospective nature of the study should limit our conclusions regarding comparison of the several ER methods since selection bias is highly likely. Nevertheless, our study has several strengths. To our knowledge, it is the first study to focus on long-term outcomes after ER of luminal GI-NETs. We show that, independently of the organ, ER is a safe and highly effective therapy for small luminal GI-NETs. Moreover, we provide comparative data of 3 different ER methods that were rarely addressed in the literature. Our results show that EMRc should be avoided for the treatment of GI-NET since the risk of complications appears too high to justify this technique. Even though most complications can be handled endoscopically, they prolong hospitalization of our patients with greater costs, and if safer techniques are available, they should be preferred. Our results also demonstrate that, independently of the technique and margins, if ER is complete, local and distant recurrence is highly unlikely and does not seem to affect the global prognosis of these patients.

In a per-organ analysis for gastric NET, there are only few comparative studies of ER methods, all of them with a limited number of cases. Kim et al. [10] compared EMR and ESD in type I g-NETs and showed a higher complete resection and higher complication rate for ESD (both non-significant). Based on this, they concluded that ESD might be a better option for the treatment of gastric NET. However, no clinical advantage was seen in this study. In fact, other studies found no tumor recurrence after ER (EMR and ESD) during the follow-up of gastric NET G1/G2, even in patients with positive margins [11, 12]. This is in accordance with our results that showed that the importance of positive margins after complete ER regarding clinical and long-term outcomes is probably minimal since there was only one local recurrence after R1 resection (6% risk), and a small easily to treat recurrence. Regarding type 3

(sporadic) gastric NETs most guidelines still consider surgery as the best approach [3, 4]. However, Kwon et al. [13] suggested that ER can be safely performed in type 3 gastric NETs if <20 mm, G1 grading, confined to SM, and without lymphovascular invasion. In accordance, we were able to treat efficaciously 3 out of 4 type 3 gastric NET, with the only type 3 tumor that recurred systemically being a >15-mm tumor (the other 3 were 10- to 13-mm lesions). Even though these results should be interpreted cautiously, these 2 studies suggest that at least for <15-mm type 3 lesions, ER (particularly by ESD) may be a safe option.

For duodenal NETs, there are only some series, and they all include a small number of patients and a short long-term follow-up. Even though complete resection rates are high for both EMR and ESD, ESD perforation rates in the duodenum appear exceedingly high (>20%) [14–16]. In fact, our ESD duodenal perforation rate in our study was 1 in 3 (33%), and we now favor EMR-based techniques for duodenal NET ER.

For ER of rectal NET, the number of studies is considerable with evidence gathered in some meta-analyses (even though substantiated mostly on single-center studies with small groups of patients) [7, 8]. Based on significantly higher complete pathological rates both with modified EMR techniques and ESD compared to sEMR, with a similar safety profile, the authors concluded that modified EMR techniques and ESD should be preferred over sEMR. Despite this conclusion, long-term clinical outcomes were not different between the groups, with local recurrences being exceedingly rare (0.89%) even after incomplete pathological resection [7]. In fact, in our study most rectal NETs were treated by sEMR, and despite only 70% complete pathological resection rate, all patients were cured with no long-time local or systemic recurrence.

Taking all together, regarding short-term outcomes, all ER methods were highly efficacious in treating small luminal GI-NETs. Even though we did not find higher complete pathological rates, EMRc and ESD were selected for bigger and depressed lesions, particularly ESD, as they are associated with a significantly bigger specimen size. EMRc was associated with a significantly higher complication rate and, in our opinion, should be avoided in the treatment of luminal GI-NET. So, for most gastric, duodenal, and rectal lesions <10–12 mm in size, sEMR probably should be favored over ESD if lesion characteristics suggest that en bloc complete ER is feasible. If the lesion size is >12 mm or if the lesion shows depressed morphology, then ESD, even though more cumbersome, should be preferred over sEMR at least in the stomach and rectum, since in the duodenum the high perforation rates make it prohibitive.

Regarding long-term outcomes, our study suggests high curative rates after successful ER of small luminal GI-NETs. Local or systemic recurrences are an exception even after R1 resections. Thus, in our opinion, positive margins after a complete ER should not guide further treatments or significantly influence further management. However, lesion size >12 mm significantly increases the risk of systemic recurrence. So, in these cases, before considering ER, multidisciplinary evaluation is advised. Nevertheless, even for these lesions, ER should be an option, particularly if the location of the tumor may imply a more aggressive surgery and/or when the patient is not fit for surgery. Furthermore, since maximum histological size is the strongest risk factor for recurrence, if after ER maximum histological size is at least 20 mm, consideration should be given to additional treatments in a multidisciplinary discussion. If ER is decided for these lesions, frequent (annual/biannual or as clinical needed) imagiological (e.g., PET-CT) follow-up is advised since the risk of systemic recurrence is high. Regarding endoscopic surveillance, our results suggest that besides type 1 gastric NETs, there is no need for a strict endoscopic follow-up, since local recurrence or new lesions are exceedingly rare. We recommend endoscopy 1 year after ER and, if there is no evidence of local recurrence, there is probably no need for further endoscopic surveillance (if positive margins are present, endoscopy 3–5 years after resection might be considered).

In conclusion, ER is a safe and highly effective treatment particularly for <12-mm luminal GI-NETs and when the maximum histological size post-ER is <20 mm. sEMR is an easy and safe technique that is associated with long-term curability, even if there are positive margins, and it is probably the best therapeutic option for most luminal GI-NETs. ESD appears to be the best option for lesions that cannot be removed en bloc with sEMR. Multicenter, prospective randomized trials evaluating long-term outcomes should confirm these results before strict recommendations can be made.

Statement of Ethics

This study was approved by the ethical committee of the Portuguese Oncology Institute of Porto in 2020 (CES 44/021).

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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None.

Author Contributions

P.P.-N. is the guarantor of the article and participated in all aspects of the work; L.P.A. performed the pathological evaluation of all lesions and wrote the paper; R.O., R.P.B., D.L., and M.D.-R. designed and performed the research and wrote the paper

Data Availability Statement

Data available upon request.

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Cap-Assisted Endoscopic Mucosal Resection for Rectal Neuroendocrine Tumors: An Effective Option

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Keywords

Rectal neuroendocrine tumors · Endoscopy · Endoscopic mucosal resection

Abstract

Introduction: The incidence of rectal neuroendocrine tumors (r-NETs) is increasing, and most small r-NETs can be treated endoscopically. The optimal endoscopic approach is still debatable. Conventional endoscopic mucosal resection (EMR) leads to frequent incomplete resection. Endoscopic submucosal dissection (ESD) allows higher complete resection rates but is also associated with higher complication rates. According to some studies, cap-assisted EMR (EMR-C) is an effective and safe alternative for endoscopic resection of r-NETs. ***Aims:*** This study aimed to evaluate the efficacy and safety of EMR-C for r-NETs ≤10 mm without muscularis propria invasion or lymphovascular infiltration. ***Methods:*** Single-center prospective study including consecutive patients with r-NETs ≤10 mm without muscularis propria invasion or lymphovascular invasion confirmed by endoscopic ultrasound (EUS), submitted to EMR-C between January 2017 and September 2021. Demographic, endoscopic, histopathologic, and follow-up data were retrieved from medical records. ***Results:*** A total of 13 patients (male: 54%; $n = 7$) with a median age of 64 (interquartile range: 54–76) years were included. Most lesions were located at the lower rectum (69.2%, $n = 9$), and median lesion size was 6 (interquartile range: 4.5–7.5) mm. On EUS evaluation, 69.2% ($n = 9$) of tumors were limited to muscularis mucosa. EUS accuracy for the depth of invasion was 84.6%. We found a strong correlation between size measurements by histology and EUS ($r = 0.83$, $p < 0.01$). Overall, 15.4% ($n = 2$) were recurrent r-NETs and had been pretreated by conventional EMR. Resection was histologically complete in 92% (n = 12) of cases. Histologic analysis revealed grade 1 tumor in 76.9% ($n = 10$) of cases. Ki-67 index was inferior to 3% in 84.6% ($n = 11$) of cases. The median procedure time was 5 (interquartile range: 4–8) min. Only 1 case of intraprocedural bleeding was reported and was successfully controlled endoscopically. Follow-up was available in 92% ($n = 12$) of cases with a median follow-up of 6 (interquartile range: 12–24) months with no evidence of residual or recurrent lesion on endoscopic or EUS evaluation. ***Conclusion:*** EMR-C is fast, safe, and effective for resection of small r-NETs without high-risk features. EUS accurately assesses risk factors. Prospective comparative trials are needed to define the best endoscopic approach.

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Mucosectomia assistida por cap para tumores neuroendócrinos do reto: uma opção efetiva

Palavras Chave
Tumores neuroendócrinos do reto · Endoscopia · Resseção endoscópica da mucosa

Resumo

Introdução: Os tumores neuroendócrinos do reto (r-NETs) apresentam incidência crescente. A maioria dos tumores de pequenas dimensões pode ser excisada endoscopicamente, no entanto, a abordagem ótima é controversa. A mucosectomia convencional associa-se, frequentemente, a resseção endoscópica incompleta. A disseção endoscópica submucosa (ESD) permite elevadas taxas de resseção completa, mas é tecnicamente complexa e associa-se a maior número de complicações. Alguns estudos sugerem a mucosectomia assistida por cap (EMR-C) como uma alternativa eficaz e segura. ***Objetivo:*** Este estudo pretendeu avaliar a eficácia e segurança da mucosectomia com cap na resseção de r-NETs com dimensões ≤10 mm, sem invasão da muscularis própria nem infiltração linfovascular. ***Material e Métodos:*** Estudo prospetivo unicêntrico incluindo consecutivamente r-NETs com ≤10 mm, sem invasão da muscularis própria ou linfovascular confirmada em ultrassonografia endoscópica (EUS), submetidos a mucosectomia assistida cap entre janeiro de 2017 e setembro de 2021. Colheita de dados demográficos, clínicos e histopatológicos através de registos médicos eletrónicos. ***Resultados:*** Incluídos 13 doentes (género masculino: 54%; *n* = 7) com idade mediana de 64 (intervalo interquartil [IIQ]: 54–76) anos. A maioria das lesões localizava-se no reto inferior (69.2%; *n* = 9) e apresentava tamanho mediano de 6 (IIQ: 4.5–7.5) mm. Na avaliação por EUS, 69.2% (*n* = 9) encontravam-se limitados à muscularis mucosa. A acuidade da EUS na avaliação do envolvimento das camadas da parede retal foi de 84.6% e o tamanho avaliado por EUS correlacionou-se fortemente com o medido na histologia ($r = 0.83$, $p < 0.01$). Dois casos (15.4%) corresponderam a recorrências de mucosectomias convencionais prévias. A resseção foi macroscópica e histologicamente completa em 92% (*n* = 12) dos casos. A análise histológica revelou 76.9% (*n* = 10) tumores de grau 1. O índice Ki-67 foi inferior a 3% em 84.6% (*n* = 11) dos casos. O tempo mediano de procedimento foi 5 (IIQ: 4–8) minutos. Verificou-se apenas um caso de hemorragia intraprocedimento resolvida endoscopicamente. O seguimento de 92% dos casos (*n* = 12) com mediana de 6 (IIQ:12–24) meses não revelou lesão residual ou recorrência em avaliações endoscópica e ultrassonográfica. ***Discussão/Conclusão:*** A EMR-C é uma técnica endoscópica segura, rápida e efetiva para a resseção de r-TNEs pequenos sem fatores de alto risco. A EUS apresenta elevada acuidade na avaliação dos fatores de risco. Estudos comparativos prospetivos são necessários para estabelecimento da abordagem endoscópica mais profícua.

Introduction

Rectal neuroendocrine tumors (r-NETs) are rare tumors derived from the neuroendocrine cell system, mainly L-cells and are characterized by the production of glucagon-like peptide, pancreatic polypeptide, and peptide YY. r-NETs represent 27% of all gastrointestinal NETs and have an annual age adjusted incidence of 0.86/100,000 in the USA [1]. The incidence of r-NETs has increased over the past decades due to a heightened awareness of the disease process in conjunction with an enhancement in colorectal cancer screening and improved endoscopic diagnosis [2–4].

Clinically, most patients are asymptomatic, and the diagnosis is made during screening colonoscopy. On endoscopy, r-NETs are generally small, smooth, round, mobile, yellowish submucosal lesions with a reddish tinge, significant microvessel density, sometimes with a central punctum and found between 5 and 10 cm from the anal verge in 87% of the cases (Fig. 1) [1, 5]. The presence of atypical findings (central ulceration, flattening, or depression) seems to predict a more aggressive form of disease [1]. Biopsy should be taken for histological confirmation in suspected r-NETs over 5 mm and/or high-risk stigmata. Endoscopic mucosal resection (EMR) may be performed in small lesions at index colonoscopy, given the lesser risk of invasion and metastases. Also, a full colonoscopy is required at some point, as part of staging, and to exclude synchronous carcinoma. Endoscopic ultrasound (EUS) is recommended in all lesions with diameter superior to 5–10 mm or with atypical features to assess tumor size, depth of invasion, and the presence of lymph node metastasis (LNM). These r-NETs appear as well-demarcated, homogenous, isoechoic or hypoechoic lesions arising from superficial layers (Fig. 2) [5]. EUS accuracy in determining depth of invasion was reported to be between 92.5 and 100% [2]. In patients with lesions with diameter superior to 10 mm and/or when LNM are detected,

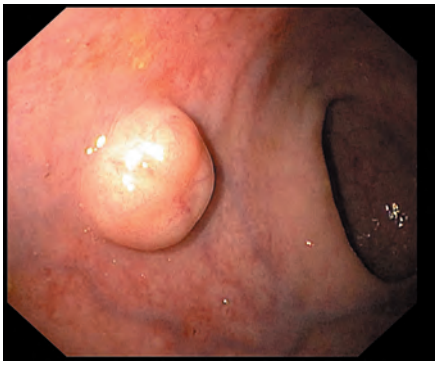

Fig. 1. Endoscopic typical appearance of a rectal neuroendocrine tumor (r-NET): a small, smooth, round, mobile, yellowish, subepithelial lesion.

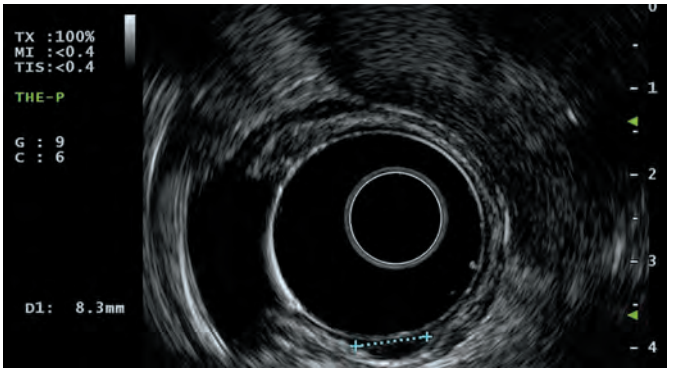

Fig. 2. EUS of a rectal neuroendocrine tumor (r-NET): round, well-demarcated, hypoechogenic nodule with a diameter of 8.3 mm arising from the submucosal layer.

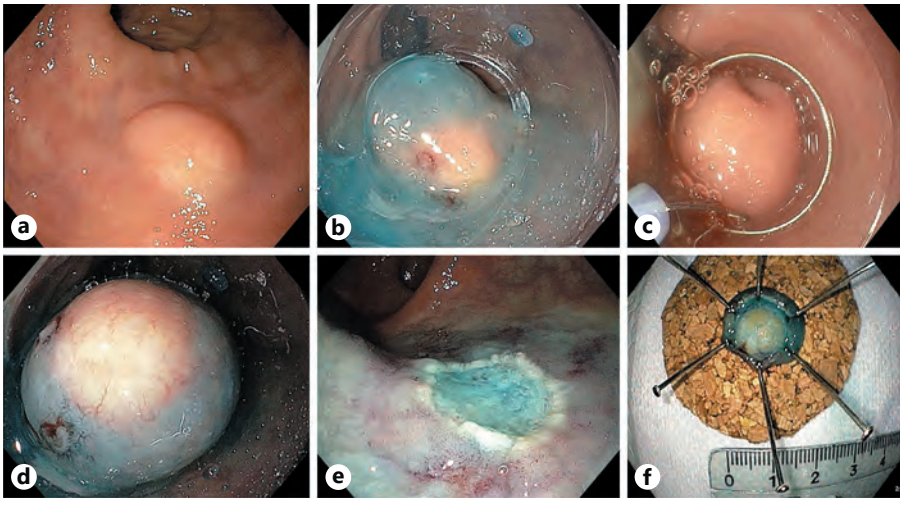

Fig. 3. a Small r-NET. **b** Submucosal injection with a mixture of diluted epinephrine (1:100,000) in 0.9% saline solution and methylene blue (1:500,000). **c** Crescent snare suction on the adjacent rectal wall and fitted along the inner rim of the transparent cap. **d** The r-NET snared with a snare-fitted cap while suctioning it. **e** The postresection defect. **f** The resected specimen fixed and measured.

additional imaging includes a thoracic, abdominal, and pelvic computed tomography scan to assess for distant metastasis. Magnetic resonance imaging of the pelvis is also indicated for r-NETs with size superior to 20 mm, muscularis propria invasion or beyond, LNM or after an incomplete resection. For well-differentiated r-NETs with diameter superior to 20 mm, muscularis propria invasion or LNM, somatostatin receptor positron emission tomography is useful for detecting metastatic lesions. Fluorodeoxyglucose-positron emission tomography is preferable in poorly differentiated r-NETs. Minimum laboratory studies include serum chromogranin A determination [1].

r-NET management depends on size, grade, and staging. Most r-NETs are smaller than 15 mm and do not invade the muscle layer nor have LNM. Considering these characteristics, most r-NETs can be endoscopically treated and cured.

Conventional EMR is safe and fast but often incomplete, as tumors arise from deeper layers than mucosa. Histological complete resection after conventional EMR is only 72–74% [6, 7]. Endoscopic submucosal dissection (ESD) allows for high rates of complete en bloc resection (90–100%) and excellent diagnostic yield; however, it is associated with higher complication rates and longer procedure times [8].

Device-assisted EMR, namely, EMR using a band-ligation device (EMR-B), cap-assisted (EMR-C) or EMR using a dual-channel endoscope can remove the deeper part of the submucosal layer. Compared with ESD, these techniques resulted in comparable or slightly lower histologically complete resection rate but with a quicker resection

Table 1. Baseline clinical, endoscopic, ultrasonographic, and pathologic characteristics of patients (n = 13)

Gender, male, *n* (%)	7 (54)
Age, median (minimum–maximum)	64 (44–86) years
Medication, *n* (%)	
Antiplatelet agents	2 (15.4)
Anticoagulants	1 (7.7)
Size, median (minimum–maximum)	6 (3.7–10) mm
Recurrent r-NET, *n* (%)	2 (15.4)
Colonoscopy indication, *n* (%)	
Screening for colorectal cancer	8 (62)
Postpolypectomy surveillance	5 (38)
Location, *n* (%)	
Lower rectum	9 (69.2)
Medium rectum	2 (15.4)
Upper rectum	2 (15.4)
EUS findings	
Wall layer involvement, *n* (%)	
Lamina propria	9 (69.2)
Submucosa	4 (30.8)
Complete en bloc resection, *n* (%)	13 (100)
Procedure complications, *n* (%)	
Bleeding	1 (7.6)
Perforation	0 (0)
Procedure time, median (minimum–maximum)	5 (3–10) min
Histologic characteristics, *n* (%)	
Ki67 index <3%	11 (84.6)
Grade 1	10 (76.9)
Lymphovascular invasion	0 (0)
Complete resection (R0)	12 (92)
Recurrence, *n* (%)	0 (0)
Follow-up time, median (minimum–maximum)	6 (6–36) months

time and fewer side effects [9–12]. Recent techniques such as clip-assisted endoscopic full-thickness resection revealed complete resection rates of 95% for r-NETs with 10–20 mm or G2 grading [13].

In conclusion, the optimal strategy for endoscopic resection in r-NETs still requires additional studies to provide strong evidence. Therefore, we aimed to evaluate our experience with the feasibility, efficacy, and safety of EMR-C for r-NETs.

Materials and Methods

Study Design

This was a single-center, prospective cohort study performed from January 2017 to September 2021.

Inclusion and Exclusion Criteria

Patients aged 18 years old or older with histologically confirmed r-NETs up to 10 mm of diameter, without muscularis propria invasion, and without lymphovascular invasion established by EUS. All patients were examined by endoscopy and EUS (Olympus GF-UE160 AL5 radial ultrasound endoscope, 5–10 MHz, with balloon) in our center before endoscopic resection. Patients without endoscopic biopsy confirming r-NET diagnosis or EUS evaluation in our center were excluded.

Definitions

An "en bloc" resection was defined as an excision of the tumor in one piece. A complete pathological resection was defined as an "en bloc" resection of the lesion with a tumor-free margins, that is, the distance from the horizontal and vertical margins to the borders of the tumor was superior to 1 mm. Procedure time was defined as time from the submucosal injection to complete removal of the lesion. Intraprocedural bleeding was defined as any bleeding that required endoscopic hemostasis during the procedure, and delayed bleeding was defined as any bleeding from the resection site that required endoscopic hemostasis or transfusion after the endoscopic resection. Perforation was defined according to deep mural injury classification [14]. Recurrence was defined by the presence of a histologically confirmed r-NET at the previous complete resection of r-NET at least 6 months after the initial resection. At the follow-up EUS, a hypoechoic nodule disrupting any wall layer was considered compatible with recurrence.

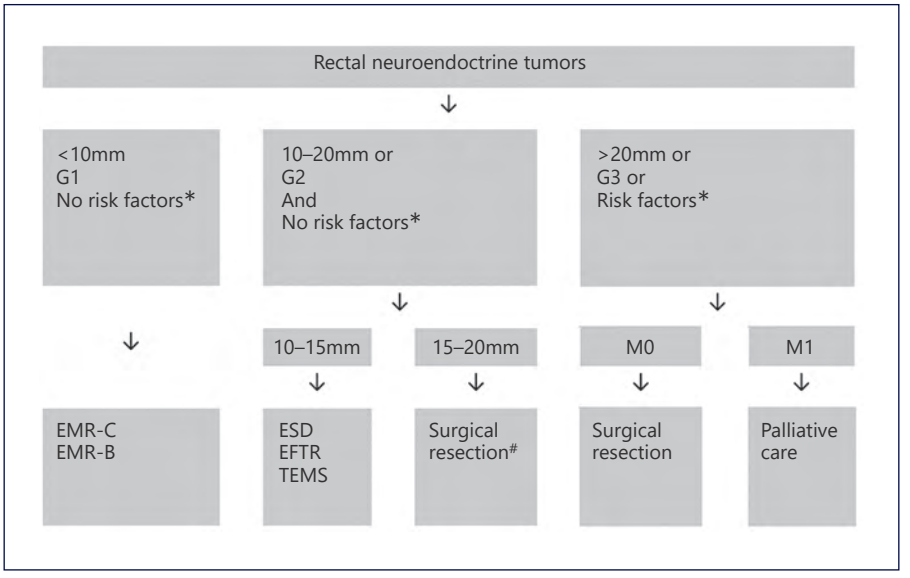

Fig. 4. Summarized management of rectal NETs. *Risk factors: invasion of muscularis propria or lymphovascular infiltration. #ESD, EFTR, or TEMS alternative if no muscular invasion and patient refuses major surgery. EMR, endoscopic mucosal resection; EMR-C, cap-assisted EMR; EMR-B, band-ligation device EMR; ESD, endoscopic submucosal dissection; EFTR, endoscopic full-thickness resection; TEMS, transanal endoscopic microsurgery.

Technique Description

A high-definition, single-channel gastroscope was used to perform EMR-C procedures. A mixture of diluted epinephrine (1:100,000) in 0.9% saline solution and methylene blue (1:500,000) was injected submucosally around and beneath the lesion to lift it apart from the muscle layer. A transparent cap for EMR-C was fitted to the scope, and a crescent-type snare was looped along the inner lip of the cap. The lesion was sequentially suctioned into the cap, grasped by the snare, and resected by using the Olympus electrosurgical generator PSD-60 until 2020, with Endocut forced mode 20W effect 2 settings (first 11 cases). From 2021 on, the Olympus electrosurgical generator ESG-300 was used, with Pulsedcut mode 60W effect 4 settings (last 2 cases) (Fig. 3a–f) [10].

Follow-Up

All patients submitted to complete en bloc resection of r-NETs were followed with standard endoscopy and EUS at 6 and 12 months and yearly thereafter. Biopsy of post-EMR-C scar was done only if recurrence was suspected.

Demographic, Clinical, Endoscopic, and Histologic Variables

Patients' characteristics: age, gender, antiplatelet and anticoagulant therapy were retrieved from electronic reports. Endoscopic data: tumor size, location, procedure time, macroscopic complete resection, and adverse events were collected from endoscopy report. Ultrasonographic data: tumor size, wall layers involved, and the presence of LNM were collected from EUS report. Histologic data: histopathologic type, Ki67 index, horizontal and vertical resection margins, and lymphovascular involvement were retrieved from the pathology report. In addition, the World Health Organization classification of tumors of the digestive system was used for histopathological evaluation.

Data and Statistical Analysis

Continuous variables were reported as mean and standard deviation or median and interquartile range, if they have a normal or skewed distribution, respectively; categorical variables as absolute and relative frequencies. The correlation between continuous variables with skewed distribution was evaluated by calculating Spearman correlation. Diagnostic accuracy was evaluated by using the Wilcoxon signed-rank test. Statistical analysis was performed using SPSS version 25 (SPSS Inc., Chicago, IL, USA).

Results

A total of 13 patients were included, 54% ($n = 7$) were male and median age was 64 (54–76) years. Antithrombotic agents' intake was reported in 23% patients ($n = 3$). All patients were asymptomatic. The indications for performing the diagnostic colonoscopy were screening for colorectal cancer (62%, $n = 8$) and postpolypectomy surveillance (38%, $n = 5$). Median lesion size on histology, endoscopy, and EUS was 6 (4.5–7.5) mm, 6 (5–7) mm, and 6 (5–7) mm, respectively. There was a strong correlation between size estimated by EUS and histology ($r = 0.83$, $p < 0.01$), and by endoscopy and histology ($r = 0.88$, $p < 0.01$). EUS accuracy for the depth of invasion was 84.6%. Nine (69.2%) r-NETs were in the lower, 2 (15.4%) in the medium, and 2 (15.4%) in the upper rectum. Overall, 2 (15.4%) were recurrent r-NETs and had been treated previously by conventional EMR. Submucosal involvement was documented in 4 (30.8%) patients. All the tumors were removed en bloc. The median procedure time was 5 (4–8) minutes. Only 1 case of intraprocedural bleeding was reported and was successfully controlled endoscopically with clips. There was no delayed bleeding or

perforation. According to histopathologic evaluation, 10 (76.9%) tumors were grade 1, and Ki 67 index was inferior to 3% in 11 (84.6%). No lymphovascular (L0, V0) infiltration was observed in any of the tumors. The histologic complete resection was obtained in 12 (92%). The patient with an r-NET incompletely resected (positive vertical margin) is under endoscopic and EUS follow-up. At 6 months, no evidence of residual or recurrent lesion was found in both exams.

Endoscopic and ultrasonographic follow-up was available in 12 cases (92%). The median follow-up time was 6 (12–24) months. No evidence of residual or recurrent lesion on endoscopic and EUS evaluation was found. There was no distant metastasis on follow-up. This information is summarized in Table 1.

Discussion/Conclusion

Recently, the detection of r-NETs is increasing with the widespread use of screening colonoscopy. Our findings are in accordance with this statement because most r-NETs were detected in screening colonoscopy in patients otherwise asymptomatic. As reported in previous studies, and also in our population, most patients were male, and the median age at the diagnosis was 64 (54–76) years [9, 10, 13, 15]. Current guidelines recommend endoscopic resection for r-NETs with diameter lower than 10 mm without risk factors, that is, grade 1, no lymphovascular infiltration nor muscularis propria invasion [1, 16–18]. For higher grade r-NETs (grade 3, Ki67 index superior to 20%), tumors with diameter superior to 20 mm in size or with high-risk factors, surgical resection is recommended. Intermediate grade r-NETs (grade 2, Ki67 3–20%) or lesions with 10–20 mm in size are best managed with surgery. However, if the patient refuses or is less fit for surgery, endoscopy resection, preferably with ESD, can be offered. Figure 4 summarizes the algorithm for treating r-NETs according to current guidelines. EUS was found to be useful for measuring the size and local staging of r-NETs, which is essential for determining appropriate treatment. In our study, tumor size estimation by EUS demonstrated a strong correlation with histologic assessment. Additionally, EUS showed a good accuracy for evaluation of wall layer involvement. Our results are slightly lower than previous studies reporting EUS accuracy in determining depth of invasion of 92.5–100%. Also, for size estimation, Park et al. [19] found a strong correlation between size measurements by histology and EUS ($r = 0.91$, $p < 0.01$). In summary, EUS can be applied to facilitate local staging and has been shown to correlate well with depth of invasion and histopathology specimens' size [19, 20].

The best method for endoscopic resection for r-NETs with diameter lower than 10 mm without risk factors remains controversial. Conventional EMR and polypectomy are fast but often incomplete [1]. Some studies advocate device-assisted EMR or ESD as better endoscopic resection methods.

In our study, including r-NETs with diameter lower than 10 mm without risk factors, EMR-C provided an overall complete resection rate of 92%. Our rate of complete histologic resection is in line with the rate of 94.1% reported in a study conducted by Yang et al. [10]. In our study, EMR-C yielded better results than previously reported for EMR-B (82.8%) [9]. Remarkably, our histologic complete resection rates were similar to those reported for ESD (89.5–94.1%) [8, 10, 21]. The procedure time was 5 (3–10) min. A slightly shorter procedure time was documented by Yang et al. [10] (3.9 ± 1.1 min). Their large experience with EMR-C can explain this difference. Nevertheless, we concluded that EMR-C is a fast procedure, even faster than another device-assisted EMR, such as EMR-B (6.4 ± 3.5 min) [9]. ESD reported times are longer (15–43 min) than those of device-assisted EMR and require a proficient endoscopist in this technique [10, 21]. In our study, only one intraprocedural bleeding, endoscopically treated, was reported, supporting the safety of EMR-C. A study comparing ESD versus EMR-C did not show any differences in adverse events' rate. A study comparing ESD versus EMR-C did not show differences in the rates of adverse events [10]. There are no complications described from EMR-B procedures for resection of r-NETs [9, 22].

The only patient with r-NET incompletely resected (positive vertical margin) is under endoscopic and EUS follow-up, after multidisciplinary decision. In contrast with colorectal carcinoma endoscopically removed, the true impact of incomplete resection for r-NETs on both recurrence-free survival and overall survival remains unclear. A previous study conducted by Park et al. [19] found residual tumor cells in only 10% of patients considered histologically incomplete but whose resection appeared to be complete endoscopically [23]. Furthermore, true incomplete resection of an r-NET has not yet been proved to be predictive of recurrence or survival [15, 24].

In our study, 2 (15.4%) patients had recurrent r-NETs pretreated with EMR. These recurrent r-NETs were adequately resected by EMR-C. Moreover, no local recurrence was observed during follow-up. Our results under-

line the efficacy of this technique as salvage treatment as previously demonstrated by Cha et al. [15]. During follow-up time, no evidence of residual or recurrent lesion on endoscopic and EUS evaluation was found, corroborating the favorable natural history of small r-NETs.

According to the European and North American Neuroendocrine Societies, completely resected tumors with a diameter inferior to 10 mm, grades 1 and 2, with no muscularis propria or lymphovascular invasion do not require regular surveillance. However, they postulate that EUS may be required if recurrence is suspected [16]. Unlike r-NETs initial staging, the role of EUS in the follow-up appears to be limited. In a study conducted by Stier et al. [25], EUS appears to have no benefit in the detection of residual r-NET. Until more data are available, we continue to include EUS in surveillance of r-NETs resected endoscopically.

Finally, our study intends to increase endoscopist awareness for the recognition of r-NETs. As reported in previous studies, the overwhelming majority of endoscopists do not suspect the correct diagnosis and perform inadequate endoscopic resection in half of the cases [26].

There are several limitations of this study. First, this was not a randomized control study and is based on the experience of a single tertiary referral center. Therefore, selection bias related to the study design is a major limitation and should be considered before interpreting the results. Second, due to rarity of r-NETs, the patient numbers were small, precluding outcome comparisons within tumor size, location, or grade. Third, the follow-up time was short to assess recurrence as an indicator of therapeutic outcome of r-NETs, which are slowly progressing tumors.

In summary, we demonstrate that EMR-C is a fast, safe, and effective option for r-NETs measuring less than 10 mm without risk factors. Owing to its safety and simplicity, EMR-C might be favored over ESD, and other device-assisted EMR for small r-NETs. However, prospective comparative trials and cost-efficacy studies are needed to better define the role of EMR-C for r-NETs.

Statement of Ethics

Protection of human and animal subjects: the authors declare that no experiments were performed on humans or animals for this study. Confidentiality of data: the authors declare that they have followed the protocols of their work center on the publication of patient data. Right to privacy: the authors declare that no patient data appear in this article. Ethical committee approval for this study was exempted due to the observational design.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

The authors have no funding sources to declare.

Author Contributions

Mafalda João: conception and design of the study; execution of the procedures; acquisition, analysis, and interpretation of data; and drafting the manuscript. Miguel Areia and Luís Elvas: conception and design of the study, analysis and interpretation of data, critical revision of the manuscript. Susana Alves, Daniel Brito, Sandra Saraiva, Raquel Martins, and Ana Teresa Cadime: acquisition of data and critical revision of the manuscript for important intellectual content. All authors approved the published version of the manuscript and agreed to be accountable for all aspects of the work ensuring questions related to the accuracy or integrity of any part of the work were appropriately evaluated and resolved.

Data Availablity Statement

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

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Endoscopic Submucosal Dissection for Subepithelial Tumor Treatment in the Upper Digestive Tract: A Western, Multicenter Study

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Keywords

Endoscopic submucosal dissection · Subepithelial tumors · Gastrointestinal stromal tumor · Neuroendocrine tumor · Upper GI

Abstract

Background/Aims: Endoscopic submucosal dissection (ESD) has been proposed for removal of gastrointestinal subepithelial tumors (GI-SETs), but data are still scanty. This study aimed to report a case series from a western country. ***Patients and Methods:*** Data of patients with upper GI-SETs suitable for ESD removal observed in 4 centers were retrospectively reviewed. Before endoscopic procedure, the lesion was characterized by endosonographic evaluation, histology, and CT scan. The *en bloc* resection and the R0 resection rates were calculated, as well as incidence of complications, and the 1-year follow-up was reported. ***Results:*** Data of 84 patients with esophageal ($N = 13$), gastric ($N = 61$), and duodenal ($N = 10$) GI-SETs were collected. The mean diameter of lesions was 26 mm (range: 12–110 mm). There were 17 gastrointestinal stromal tumors, 12 neuroendocrine tumors, 35 leiomyomas, 18 lipomas, and 2 hamartomas. *En bloc* and R0 resection were achieved in 83 (98.8%) and in 80 (95.2%) patients, respectively. Overall, a complication occurred in 11 (13.1%) patients, including bleeding ($N = 7$) and perforation ($N = 4$). Endoscopic approach was successful in all bleedings, but 1 patient who required radiological embolization, and in 2 perforations, while surgery was performed in the other patients. Overall, a surgical approach was eventually needed in 5 (5.9%), including 3 in whom R0 resection failed and 2 with perforation. ***Conclusions:*** Our study found that ESD may be an effective and safe alternative to surgical intervention for both benign and localized malignant GI-SETs.

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Disseção endoscópica da submucosa nas lesões subepiteliais do tubo digestivo superior: estudo multicêntrico ocidental

Palavras Chave
Disseção endoscópica da submucosa · Tumores subepiteliais · Tumor do estroma gastrointestinal · Tumor neuroendócrino · Tubo digestivo superior

Resumo
Introdução/objetivos: A dissecção endoscópica da submucosa (ESD) tem sido proposta para a exérese de tumores subepiteliais gastrointestinais (GI-SETs), embora a literatura seja escassa. Este estudo teve como objetivo reportar uma série de casos de um país ocidental. ***Métodos:*** Coorte retrospectiva incluindo doentes com SETs do tubo digestivo superior submetidos a ESD em 4 centros (1 ano de follow-up). Antes do procedimento, a lesão foi caracterizada por ecoendoscopia, histologia e tomografia computadorizada. Foram avaliadas as taxas de ressecção em bloco e R0, bem como a incidência de complicações. ***Resultados:*** Incluídos 84 doentes com GI-SETs esofágicos (*N* = 13), gástricos (*N* = 61) e duodenais (*N* = 10). O diâmetro médio das lesões foi de 26 mm (intervalo 12–110 mm) – 17 tumores do estroma gastrointestinal, 12 tumores neuroendócrinos, 35 leiomiomas, 18 lipomas e 2 hamartomas. A resseção foi em bloco e R0 em 83 (98.8%) e em 80 (95.2%) doentes, respectivamente. Globalmente, ocorreram complicações em 11 (13.1%) doentes, incluindo hemorragia (*N* = 7) e perfuração (*N* = 4). A terapêutica endoscópica foi eficaz em todas as hemorragias exceto em 1 doente que necessitou de embolização radiológica e em 2 perfurações (submetidas a cirurgia). No geral, a abordagem cirúrgica foi necessária em 5 (5.9%) – 3 doentes com resseção R1 e 2 com perfuração. ***Conclusões:*** A ESD pode ser uma alternativa eficaz e segura à intervenção cirúrgica para GI-SETs benignos e malignos localizados.

Introduction

Gastrointestinal subepithelial tumors (GI-SETs) include a wide range of submucosal lesions whose prognosis may vary from benign and indolent to malignant and potentially aggressive neoplasia, such as neuroendocrine (NET) and gastrointestinal stromal tumors (GIST) [1]. Usually asymptomatic, most GI-SETs are diagnosed as incidental findings during screening endoscopy or radiological examinations. Some studies revealed that less than 10% of these lesions exhibit a significant increase in size at follow-up [2]. Despite a wide range of different histopathologic lesions, endoscopic aspect of GI-SETs is similar as they appear like smooth bulges of the inner cavity of GI tract with normal or ulcerated overlying mucosa. For this reason, when a GI-SET is suspected, endoscopic ultrasonography (EUS) examination should be performed to rule out extraluminal compression and delineate the most likely histological layer of tumor origin [3–5]. Although histology is needed for a definite diagnosis, several sonographic features, such as size, borders, echogenic homogeneity, vascularization, presence of anechoic areas, or lymph node metastases may be helpful to predict the nature of the submucosal tumor [3, 6, 7]. The management of smaller, asymptomatic GI-SETs with malignant potential or large benign lesions presenting with GI bleeding includes endoscopic resection as alternative to surgical intervention [8, 9]. In this study, we report the efficacy and 1-year outcome of endoscopic submucosal dissection (ESD) for GI-SET treatment.

Patients and Methods

Patients

Data of patients with endoscopically treated upper GI-SETs in 4 third-level endoscopy centers (Modena, Napoli, Milano, Perugia) between July 2014 and January 2020 were retrospectively reviewed. All patients included underwent standard gastroscopy, and by bite-on-bite, biopsies were obtained on lesions. When histological diagnosis was inconclusive, both radial and linear EUS were performed for adequate endosonographic evaluation, and EUS-guided fine needle biopsy sampling was carried out. Before endoscopic resection, all patients underwent CT scan to exclude local infiltration or lymph node metastasis when a malignant lesion was detected. Endoscopic resection was proposed for bleeding or symptomatic benign lesions (leiomyoma and lipoma), as well as for superficial low-risk GIST exhibiting very narrow connection with the muscular layer (type I and II) and non-ampullary NET with diameter less than 10 mm [10]. Informed consent was obtained before procedure in all patients. Since no experimental drugs were administered, no additional costs or procedures for the patients were required, no identification of patients was allowed, and no funds were received; the Investigational Review Boards waived formal approval, deeming the study to be an extension of existing clinical practice. Patients were informed and signed their consent for the procedure and the anonymous use of their data for scientific purposes.

Endoscopic Procedures

All ESD procedures were performed in general anesthesia by skilled operators in submucosal dissection with at least 10 years of

practice in therapeutic endoscopy and experience of ESD training in Japan. A standard single-channel gastroscope with a water-jet system (GIF-H190; Olympus, Tokyo, Japan) was used, and transparent hood (ND-201-11802; Olympus) was applied to the distal tip of the endoscope. A high-frequency generator (VIO300D; ERBE, Tübingen, Germany) was used during mucosal incision and submucosal dissection. For mucosal incision, Endocut I mode (Effect 2) was set, while submucosal dissection was performed using Swift Coag mode (Effect 3, 40W). Carbon dioxide insufflation was used during all ESD procedures. ESD was performed after initial injection of solution (100 mL saline solution, 5 mL 0.8% indigo carmine, and 1 mL epinephrine) with a 23-gauge disposable needle into the submucosa and circumferential mucosal incision, at 1 cm from the mucosal bulge, was performed with Dual Knife (KD-650L, Olympus) or Dual Knife J (KD-655L, Olympus). Then, submucosal dissection was continued close to the muscular layer and below the subepithelial lesion. When the tumor originated from the muscularis propria, submucosal dissection was completed with IT-Knife 2 (KD-611L) or Hook Knife (KD-620RL, Olympus) to grasp and remove the muscularis propria fibers along the capsule of the tumor. Major blood vessels as well as any intraprocedural bleeding were managed with Coagrasper (FD-410LR, Olympus). A careful inspection of the resection site at the end of the procedure was performed to coagulate exposed blood vessel or identify and treat any microperforation with through-the-scope (TTS) endoclips. *En bloc* resection was defined as excision of the tumor in only one piece with no evidence of macroscopic tissue remnant. Post-ESD complications requiring therapeutic intervention, such as perforation or bleeding, were defined as early or late events according to the time of onset, namely, within or after 48 h following the endoscopic procedure, respectively. Post-ESD cutting sites were treated in all cases by TTS positioning as the first attempt, in order to prevent and reduce the risk of bleeding and late perforation. Following endoscopic procedure, proton pump inhibitor therapy was administered to all patients, intravenously for 5 days and then switched to oral for 4 weeks at discharge. Broad spectrum antibiotics were administered to all patients for 7 days. Oral feeding was reintroduced 48 h later if the patient was asymptomatic and no bleeding was suspected. Endoscopic control for local recurrence was scheduled 3 and 6 months after endoscopic resection and then yearly in malignant lesions.

Histological Examination

Removed lesions were fixed by using 10% formalin solution, embedded with paraffin, and sectioned for histological evaluation at 2 mm intervals. Experienced GI pathologists assessed the histological type, macroscopic appearance, tumor size, depth of invasion, lymphatic and vascular involvement, capsule integrity, and resection margins. R0 resection was defined as *en bloc* resection with intact capsule and/or at least 2-mm free margins were present at histology. Immunohistochemistry was performed on 3 microns of thickness section for NET, GIST, and mesenchymal tumors with uncertain histopathological diagnosis. In detail, chromogranin-A and synaptophysin stains were used to confirm the diagnosis of NETs, while Ki-67 and the mitotic index were applied to define the tumor's differentiation degree. Histological diagnosis of GIST included C-Kit, DOG1, and CD34 immunostains. Other immunohistochemical markers were used for the diagnosis of stromal tumors and included S100, smooth muscle actin, and desmin. The lesions removed from the duodenum and histologically defined as Brunner's hamartomas when proliferation of Brunner's glands, organized in lobules and with marked cystic dilatation lined by columnar cells, were detected. Glands were intermingled to stromal cells and vascular spaces without atypia. The lesion probably originated from the subepithelium but deepened to the submucosa layer, however, without having invasive characteristics. Preprocedure histopathological diagnosis was achieved in 63 (75%) out of 84 patients, and it was eventually confirmed in all these cases on the resected specimen.

Results

A total of 84 patients (56 males; mean age 63.5 years, range: 33–89) with upper GI-SETs were endoscopically treated, including 13 localized in esophagus (distal tract), 17 in proximal stomach (corpus/fundus/cardia), 44 distal stomach (antrum/angulus), and 10 in the duodenum (8 in the bulb and 2 in the second portion).

The mean diameter of the resected lesions was 26 mm, ranging from 12 to 110 mm. The mean ESD procedural time was 53 min (range: 30–160). The procedure was successful in all but 1 patient, in whom it was aborted for technical difficulty. *En bloc* and R0 resection were achieved in 83 (98.8%; 95% CI = 96.5–100) and in 80 (95.2%; 95% CI = 90.1–99.8) patients, respectively. At histological assessment, there were 17 GISTs, 12 NETs, 34 leiomyomas, 18 lipomas, and 3 hamartomas. In the 4 patients in whom R0 was not achieved, surgical laparoscopic-assisted gastric wedge resection was performed in 3 cases (1 gastric large, bleeding leiomyoma; 2 gastric NETs) and endoscopic full-thickness resection (EFTR) in the remaining patient (duodenal bulb NET) by using full-thickness resection device (FTRD® – Ovesco Endoscopy, Tubingen, Germany). A complete lesion removal was histologically confirmed in all these cases (Fig. 1).

Overall, a complication occurred in 11 (13.1%; 95% CI = 5.9–20.3) patients. In detail, major bleeding was observed in 7 (8.3%) patients, including 5 with gastric GISTs (3 fundus, 2 corpus), one with NET, and one with hamartoma of the duodenal bulb. Endoscopic hemostasis with adrenaline and TTS clips was successfully obtained in 4 out of 7 patients, while an 11-mm atraumatic with 6-mm cap (11/6) OTSC was necessary to control the bleeding in 2 patients, and radiologic embolization in a patient with a duodenal hamartoma. In this case and in a patient with a GIST of the gastric fundus, gastrointestinal hemorrhage presented with acute severe anemia and clinical feature of hypovolemic shock within 24 h after the procedure, while in the other 5 cases, the bleeding occurred during the endoscopic resection. A perforation

Table 1. Results according to site and lesions

Site	*N*	Histology	Mean size (range), mm	Technical success, *n* (%)	R0 resection, *n* (%)	Perforation, *n* (%)	Bleeding, *n* (%)	Recurrence at 12 months
Esophagus	13	13 leiomyomas	24 (21–52)	13 (100)	13 (100)	0	0	0
Proximal stomach (cardia, corpus, fundus)	17	6 lipomas; 5 GISTs; 3 NETs; 2 leiomyomas 1 hamartoma	30 (20–110)	16 (94.1)	14 (82.4)	1 (5.9) [1 GIST]	5 (29.4) [5 GISTs]	1 (5.9)
Distal stomach (angulus, antrum)	44	19 leiomyomas; 10 GISTs; 8 lipomas 6 NETs; 1 hamartoma	37 (25–60)	44 (100)	44 (100)	3/44 (6.7) [3 GISTs]	1 (2.2) [1 NET]	0
Duodenum	10	4 lipomas; 3 NETs 2 GISTs; 1 hamartoma	13 (12–20)	10 (100)	9 (90)	0	1 (10) [1 hamartoma]	0
Total	84	84	26 (12–110)	83 (98.8)	80 (85.2)	4 (4.8)	7/84 (8.3)	1 (1.2)

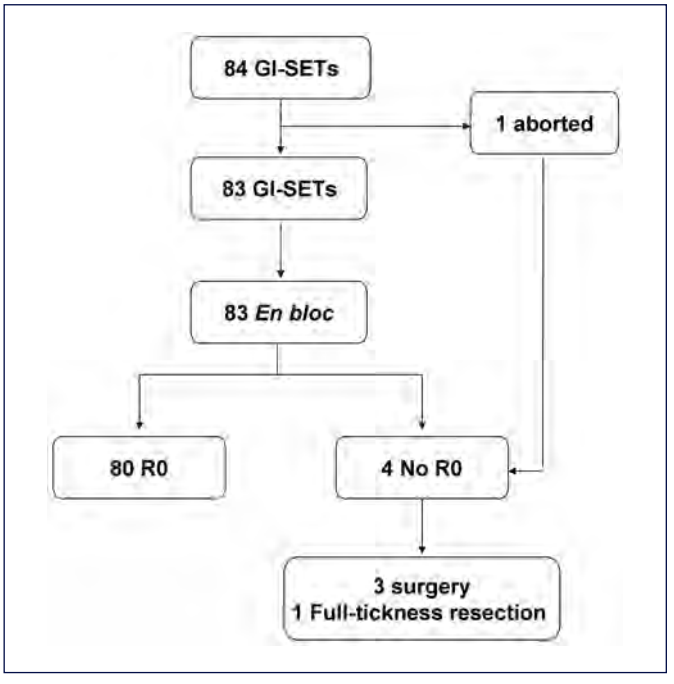

Fig. 1. Outcomes of ESD for gastrointestinal subepithelial tumor (GI-SET) removal.

occurred in 4 (3.6%) patients. In detail, the complications were immediately observed after removal of antral GIST in 3 cases, two successfully treated at endoscopy with 11/6 traumatic OTSC positioning, while the other patient underwent surgical intervention with subtotal gastrectomy. In the remaining case, a late perforation occurred on third day postresection of a gastric fundus GIST, and the patient was treated with surgical intervention of total gastrectomy. Overall, a surgical approach was eventually needed in 5 (5.9%; 95 CI = 0.9–11), including 3 in whom R0 resection failed and 2 with perforation. The mean hospital stay was 5.1 ± 1.3 days.

At 3 and 6 months of follow-up, no local recurrence was described, while at 12 months follow-up, relapse of 10-mm subepithelial tumor was observed in only 1 patient after resection of an ulcerated large lipoma of the gastric corpus so that a full-thickness resection was performed. No fatal events were registered at follow-up. All data were summarized in Table 1.

Discussion

ESD is a minimally invasive technique allowing to remove large GI lesions with low risk of recurrence, without resorting to a more invasive surgical approach [2, 9]. Notably, this procedure might be particularly useful for endoscopic treatment of symptomatic (bleeding, obstructive) GI-SETs, including benign masses, as well as GISTs or NETs within specific size limits and without suspicion of locoregional involvement. Indeed, these lesions generally exhibit a low malignant potential so that surgical treatment with lymph node dissection is not mandatory [10–12]. In detail, this endoscopic approach could be particularly useful for duodenal and cardia SETs, representing a valid alternative to demolitive surgery associated with a higher rate of morbidity and mortality [13, 14]. However, ESD is challenging when the lesion is localized in some GI sites, such as the duodenum or fundus, where the risk of complications increases even when performed by skilled operators [15, 16]. In addition, dissection may result particularly difficult for lesions originating from the muscle layer or when they are larger than 5 cm, increasing the risk of perforation up to 20% [17].

ESD feasibility for GIST treatment should be evaluated according to their location in the gastric wall and their connection with the muscularis propria [18]. Indeed, ESD appears to be a good option for lesions protruding into the luminal gastric side with very narrow contact with the muscle layer (type I) or for GI-SETs, still protruding into the stomach with an obtuse angle, showing a wider contact with muscle fibers (type II). On the contrary, GISTs located in the middle of the gastric wall (type III) or exhibiting extraluminal growth (type IV) should be evaluated for surgical intervention, EFTR technique or combination of both [10]. Indeed, the improvement of EFTR has provided a less invasive treatment alternative to surgery, allowing a deeper resection, compared to ESD, of large size submucosal tumors or lesions involving the muscularis propria [19].

Largely performed in Asian centers, data on ESD removal in western countries are still scanty. Data of our case series, including different GI-SETs, showed that ESD is a successful approach, with very high values of both *en bloc* and R0 resection rates. In detail, a complete lesion removal, with histological free margin resection, was achieved in more than 95% of cases, which is a value in agreement with the results reported in Asian series. Nevertheless, data of some studies found a lower (72%) R0 rate when ESD was performed for GIST or other lesions arising from the muscle layer, most likely due to a strict connection between the tumor and the muscularis propria that increases the difficulty of the procedure and the risk of complications [11, 15]. Of note, in our series, all the 4 perforations occurred in removing gastric GISTs as well as 5 (75%) out of the 7 major bleedings occurred after resection of this type of lesions. This result may depend on the huge vascularity typical of this subgroup of tumors and their origin from the muscle layer. Based on these observations, we would suggest paying particular attention during GIST removal. Overall, the rate of complications is acceptably low, and both bleeding and perforation were generally suitable for an endoscopic approach. Indeed, the surgical intervention was eventually needed in only 6% of cases, due to either complication or incomplete lesion removal, in agreement with data from previous studies [9, 14].

In our study, GI-SETs showing invasion deeper than muscularis propria at EUS were excluded because large repair of the gastrointestinal wall would be required after the standard procedure of ESD. However, recently, many other techniques have been described to provide a more conservative resection of submucosal lesions, including EFTR with endoscopic suturing of the wall defect, submucosal tunneling endoscopic resection, or laparoscopic endoscopic cooperative surgery procedures. With the EFTR approach, an endoscopic full-layer resection including the *serosa* is initially performed resulting in an intentional perforation. Then, the transmural wall defect is closed by using endoscopic suturing device (Apollo Endosurgery, Austin, TX, USA), OTSC, or combination of TTS endoclip and endoloop [20, 21]. On the other hand, the submucosal tunneling endoscopic resection procedure allows the resection of submucosal masses without transmural loss of integrity of the gastrointestinal wall. Indeed, starting a mucosal incision about 2–3 cm from the target lesion, a submucosal tunnel is created to approach the GI-SET and then dissect the tumor from the surrounding tissue and muscularis propria. Finally, laparoscopic endoscopic cooperative surgery procedures combine the technique of ESD to determine the precise cutting line around the gastric or duodenal SETs followed by laparoscopic wedge resection. Although scientific data are scanty, all these procedures have shown good results in terms of efficacy and safety, representing a valid alternative for GI-SETs requiring full-layer resection [22]. Some potential limitations of our study might be put forward. It was a retrospective evaluation of available data, and the 1-year follow-up may be inadequate to evaluate long-term outcome. Moreover, ESD was not compared to other endoscopic techniques. In conclusion, our experience demonstrated that ESD, performed by high-trained endoscopist, may be a valid and safe alternative to surgical intervention for both benign and localized malignant GI-SETs.

Statement of Ethics

The Investigational Review Boards waived formal approval, deeming the study to be an extension of existing clinical practice. Patients signed informed consent for both procedure and anonymous use of their data for scientific purposes.

Conflict of Interest Statement

All the authors declare no conflicts of interest.

Funding Sources

No found was received.

Author Contributions

Conception of the work: R.M. and G.G.; data acquisition: F.P.Z., F.P., A.C., S.M., A.D.A., D.C., U.G., M.M., R.L.C., and L.R.B.; data analysis and drafting: A.Z. and V.D.F.; critical revision: T.M. All the authors approved the final version.

Data Availability Statement

All analyzed data in this study are available following reasonable inquiries directed to the corresponding author.

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Impact of COVID-19 in Pediatric Patients and Young Adults with Inflammatory Bowel Disease

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Keywords
Crohn's disease · Ulcerative colitis · SARS-CoV-2 · COVID-19 · Pediatrics

Abstract
Introduction: Acute COVID-19 in pediatric and young adult patients tends to be milder in severity compared to adult infection. Recent studies seem to show that inflammatory bowel disease (IBD) patients are at no greater risk than the general population. We aim to describe our experience in the follow-up of pediatric and young adult patients with IBD followed in our center and determine possible risk factors of said population for severe COVID-19. ***Methods:*** We performed a retrospective study of all patients aged under 25 years followed for IBD at the Unit of Pediatric Gastroenterology in a tertiary center between December 2019 and April 2021 evaluating the incidence of COVID-19 and characterization of positive cases. ***Results:*** Of the 268 participants, 24 had COVID-19: the mean age was 19 years old and gender had an equal distribution; 75% ($n = 18$) had Crohn's disease, whereas only 25% ($n = 6$) had ulcerative colitis. Most patients were in clinical remission ($n = 21$). The majority of patients were under treatment with a tumor necrosis factor (TNF) antagonist (58%, $n = 14$), mainly infliximab, and most had no comorbidities other than IBD (83%). Regarding COVID-19, 17% of the patients were asymptomatic while the rest had only mild symptoms. There were no reported gastrointestinal complaints, no complications nor hospitalizations. Most patients did not require interruption of their IBD treatment. ***Conclusions:*** Our data suggest that pediatric and young adult IBD patients have a low risk for complications and hospitalization, regardless of IBD treatment. We believe that this experience is encouraging and allows for safe counseling regarding treatment options and school attendance in pediatric and young adult IBD patients.

Impacto da COVID-19 em Doentes Pediátricos e Jovens Adultos com Doença Inflamatória Intestinal

Palavras Chave
Doença de Crohn · Colite ulcerosa · SARS-CoV-2 · COVID-19 · Pediatria

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Resumo

Introdução: Na população pediátrica e de jovens adultos a gravidade da COVID-19 tende a ser moderada quando comparada com os doentes adultos. Os estudos mais recentes sugerem que os doentes com doença inflamatória intestinal (DII) não têm risco acrescido em relação à população geral. O objetivo do presente estudo é a descrição da nossa experiência no follow-up de crianças e jovens adultos com DII a COVID-19 e determinar a existência de possíveis fatores de risco para doença grave na referida população. ***Métodos:*** Foi realizado um estudo retrospetivo de todos os doentes com idade inferior a 25 anos, seguidos na Unidade de Gastrenterologia Pediátrico de um centro terciário por DII, com avaliação da incidência de COVID-19 entre dezembro de 2019 e abril de 2021, e caracterização dos casos postivos. ***Resultados:*** Entre os 268 participantes, 24 tiveram COVID-19. A idade média foi de 19 anos com uma distribuição por género equiparável. Destes, 75% (*n* = 18) tinham doença de Crohn, enquanto 25% (6) tinham colite ulcerosa. A maior parte dos doentes apresentavam-se em remissão clínica (*n* = 21) e, à data da doença COVID-19. A sua maioria, os doentes encontravam-se sob tratamento com antagonistas do fator de necrose tumoral (58%, *n* = 14), predominantemente o infliximab, e a generalidade dos doentes (83%) não apresentava outras comorbilidades além da DII. Relativamente à COVID-19, 17% eram assintomáticos enquanto os restantes apresentavam apenas sintomas ligeiros. Não houve relato de queixas gastrointestinais, complicações ou necessidade de hospitalização. Na maioria dos casos, não houve necessidade de interromper o tratamento da DII. ***Conclusão:*** Os nossos dados sugerem que doentes pediátricos e jovens adultos com DII apresentam um risco baixo de complicações ou hospitalização associados à COVID-19, independentemente do tratamento em curso para a DII. Este estudo apresenta resultados encorajadores e contribui para o aconselhamento adequado e fundamentado aos doentes e respetivos cuidadores, no que diz respeito às opções terapêuticas e frequência escolar dos doentes pediátricos e jovens adultos com DII.

Introduction

Since its emergence in December 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has spread into a global pandemic of a disease known as COVID-19, with significant public health implications around the globe [1].

The SARS-CoV-2, an enveloped RNA virus, is predominantly transmitted via respiratory droplets [2]. After contact with the virus, it enters the human cells via the angiotensin-converting enzyme 2 (ACE2) receptor using its spike protein S1 subunit. While primarily expressed in the lungs, the ACE2 receptor is also expressed in many extrapulmonary tissues, including the gastrointestinal (GI) tract. High levels of ACE2 receptors were found on the luminal surface of differentiated epithelial cells in the terminal ileum and colon [2–4].

Acute COVID-19 infections in pediatric patients have been milder in severity, with quicker recovery and fewer sequelae compared to adult infection [4, 5]. This difference is believed to be due to multiple factors such as variations in the distribution of ACE2 receptors, T-cell and B-cell responses, and the balance of modulating and pro-inflammatory cytokines [2].

Concerning the pediatric population, as of April 2021, the estimated incidence of COVID-19 in Portugal was almost 15% of all cases [6]. Yet, according to the Surveillance Epidemiology of Coronavirus Under Research Exclusion for Inflammatory Bowel Disease (SECURE-IBD), only 103 cases were reported [7].

Until the moment, the knowledge concerning the risk of COVID-19 in inflammatory bowel disease (IBD) patients, particularly pediatric IBD patients, is still scarce [8, 9]. Recent studies seem to show that IBD patients are at no greater risk than the general population [9].

This report aims to review the experience of our center and describe the disease course of COVID-19 in our sample of pediatric IBD patients.

Materials and Methods

This retrospective study included all patients under 25 years with IBD infected by SARS-CoV-2 between December 2019 and April 2021 and followed by the Unit of Pediatric Gastroenterology in Centro Hospitalar São João anytime during that period.

Telephone inquiries were performed, in addition to consultation of medical records, and the following variables were collected: demographic data (age, gender), clinical data at the time of COVID-19 (type of IBD, IBD extension according to Paris classification, medication for IBD, disease activity according to the PUCAI and PCDAI scores measured in the last visit previous to infection as well as fecal calprotectin measured within the same timeframe, and presence of comorbidities and COVID-19 data [vaccination status, severity and length of symptoms, presence of GI symptoms, whether medication for IBD was stopped during infection, complications, and need for hospitalization]). COVID-19 severity was determined as stated in the World Health Organization (WHO) definition, being mild when symptoms were present with no evidence of viral pneumonia or hypoxia and moderate when there were clinical signs of non-severe pneumonia [10].

Table 1. Demographics, disease characteristics, and clinical outcomes of pediatric and young adult IBD patients with COVID-19 infection

Characteristic	Pediatric cohort (*N* = 11)	Young adult cohort (*N* = 13)
Median age, years (min–max)	15 (7–18)	20 (18–24)
Female sex, *n* (%)	5 (45.5%)	7 (53%)
Diagnosis, *n* (%)		
Crohn's disease	7 (64%)	11 (85%)
Ulcerative colitis	4 (36%)	2 (15%)
Disease extension (Paris classification), *n* (%)		
Crohn's disease		
L1	1 (14%)	2 (18%)
L1 + L4a	0 (0%)	1 (9%)
L2 + L4a	2 (29%)	1 (9%)
L3	3 (43%)	5 (46%)
L3 + L4a	1 (14%)	1 (9%)
L4b	0 (0%)	1 (9%)
Ulcerative colitis		
E3	4 (100%)	2 (100%)
IBD disease activity (by GPA), *n* (%)		
Remission	8 (73%)	13 (100%)
Mild	1 (9%)	0 (0%)
Moderate	2 (18%)	0 (0%)
Mean fecal calprotectin*	286.2±463.6 µg/g	210.5±186.8 µg/g
Remission	119±133.6 µg/g	210.5±186.8 µg/g
Active disease	730±466 µg/g	N/A
IBD medication, *n* (%)*, #		
Sulfasalazine/mesalamine	5 (45%)	1 (8%)
Steroids (for IBD, not COVID-19)	1 (9%)	0 (0%)
TNF antagonist monotherapy	2 (18%)	5 (38%)
Infliximab	2 (100%)	5 (100%)
TNF antagonist + AZA	2 (18%)	5 (38%)
AZA monotherapy	2 (18%)	2 (15%)
Anti-integrin (vedolizumab)	1 (9%)	0 (0%)
Mean COVID-19 symptoms duration, days	4.1±2.9	6±4.2
Comorbidities, *n* (%)	2 (18%)	1 (9%)
Asthma	0 (0%)	1 (0%)
Hepatitis	1 (9%)	0 (0%)
Cardiac arrhythmia	1 (9%)	0 (0%)

AZA, azathioprine; COVID-19, coronavirus disease 2019; GPA, Global Physician Assessment; IBD, inflammatory bowel disease; MTX, methotrexate; N/A, non-applicable; TNF, tumor necrosis factor. * At the time of COVID-19 infection. # Medication categories are not mutually exclusive unless otherwise noted.

A descriptive analysis was performed. Continuous variables with asymmetrical distribution were presented as a median (minimum–maximum).

The study was approved by the ethical committee of our institution. All information is anonymous and confidential.

Results

Of the 338 patients with IBD included, only 268 were available to answer the telephone inquiry. Of these, 24 participants had COVID-19 (Table 1). Overall, the mean age was 19 years old (minimum seven and maximum 24 years old). Specifically, there were 11 (45%) pediatric patients under 18 years old (mean 15 years) and 13 (55%) young adults (mean 20 years). Both groups had an equal gender distribution (male-to-female ratio of 1:1).

Concerning the IBD classification, 75% (*n* = 18) had Crohn's disease, whereas only 25% (*n* = 6) had ulcerative colitis. Among patients with Crohn's disease, four had ileal disease, three had colonic disease, ten had ileocolonic disease, of which two had concomitant involvement of the distal esophagus, and one patient had exclusive up-

per disease distal to the ligament of Treitz. All patients with ulcerative colitis had extensive disease according to the Paris classification.

Most patients were in clinical remission (n = 21) with only one case of mild disease activity and two cases of moderate disease activity. All three patients with active disease had ileocolic Crohn's disease and a mean disease duration of almost 6 years at the time of COVID-19. Fecal calprotectin had a mean value of 730 ± 493 μg/g in the group of patients with active disease and of 158 ± 213 μg/g in the remission group.

The majority of patients were under treatment with a tumor necrosis factor (TNF) antagonist (58%, n = 14), most commonly infliximab. Of these, 50% were treated with anti-TNF monotherapy and the other 50% with an association of anti-TNF with azathioprine.

Most patients had no comorbidities other than IBD (83%).

Regarding the COVID-19 disease, 17% (n = 4) were asymptomatic, and the remaining patients had mild disease. Average symptom duration was 4 days. In one case, a 19-year-old patient, COVID-19 infection occurred after the first dose of vaccination against COVID-19 (the vaccine used is unknown). There were no reported gastrointestinal complaints. There were no reports of complications or hospitalizations due to COVID-19, and most patients (90%) did not require interruption of their IBD treatment. The three patients who did interrupt their treatment did so for mandatory quarantine, which prevented them from going to the hospital to receive their intravenous treatment.

Discussion/Conclusion

We analyzed a total of 24 patients with IBD, less than 25 years of age, infected with SARS-CoV-2.

Despite being commonly referred to as a respiratory illness, it is now clear that COVID-19 can also affect the GI system, particularly in the pediatric population, as evidenced by a prevalence of 6% of GI symptoms found in a metanalysis of 1,810 healthy pediatric patients [11]. In our study, however, no GI symptoms were observed. This might be explained by the median age in our sample, which was higher than the median age in the metanalysis by Badal et al., even when adjusted to include only the pediatric patients (15 years [7–18] compared to 8 years [6–10]).

We reported no hospitalizations and no complications from COVID-19. These findings are in line with other studies, such as the SECURE-IBD registry that found a rate of 7% hospitalization, a 2% ventilation support requirement, and no deaths in a pool of 209 COVID-19 cases with pediatric IBD [4]. In addition, an observational study of 522 IBD patients, including 59 children in an Italian tertiary referral center, reported no admissions for SARS-CoV-2 infection [12]. Our findings are also identical to reports on young adults who are generally described to have a milder disease with a good prognosis and low hospitalization rates [3]. In fact, our sample results showed a significant overlap between both age groups, which can be explained by the high mean age found in the pediatric group.

The reasons why IBD patients appear to be less affected and develop milder clinical pictures are still unknown. It has been suggested that the lower infection rate may be a consequence of improved adherence to shielding recommendations [13]. Among the possible risk factors for severe COVID-19 described in the literature are IBD treatments such as steroids and thiopurines, whereas the use of TNF-antagonists was reported as protective [4, 14, 15]. Of note, despite concerns shown by the patients and their parents of a higher risk of infection in patients under biologic treatment, it appears that the blockage of the cytokine storm by immunomodulators taken for IBD, which lead to the control of bowel inflammation, may assist in the prevention of COVID-19 severe symptoms [5, 16]. In fact, a study conducted during the first pandemic wave found that up to 23% of pediatric patients who delayed or temporarily discontinued their biologic therapy due to the lockdown experienced a disease exacerbation [17]. Moreover, Turner et al. showed that pediatric patients who interrupted their IBD treatment had a significant rate of developing flairs while those who continued treatment had no complications [18].

The cumulative experience of the last 2 years is in favor of continuing ongoing IBD therapy and not delaying the beginning of conventional immunomodulators or biological therapy because of the pandemic situation, in patients without COVID-19 [19, 20].

An open question is the need for treatment interruption in patients with COVID-19.

The ECCO-COVID Task Force and the IOIBD recommend the interruption of anti-TNF, thiopurines, and corticosteroids in patients with SARS-CoV-2, regardless of symptoms [15, 21, 22].

In our sample, three patients had to delay their intravenous treatment during COVID-19 infection due to mandatory quarantine. The expected half-life of anti-TNF such as infliximab is almost 10 days, but its effect is

largely potentiated by the use of thiopurines like azathioprine whose immunosuppressive effect goes beyond their half-life. Perhaps, while more evidence is awaited, a personalized approach should be considered according to severity and clinical course of the disease.

Additional risk factors found for hospitalization in pediatric IBD patients with COVID-19 included other comorbidities besides IBD, moderate or severe IBD disease activity, and presence of gastrointestinal symptoms [4]. In our sample, comorbidities were found in a rather small number of cases, and only two patients had moderate disease activity. Regardless, no complications nor hospitalizations were reported in this group.

This study has limitations. First, its retrospective nature might have led to the underestimation of the severity and length of the symptoms by the participants. Secondly, no statistical analysis was performed due to the sample size.

In conclusion, we present the reassuring experience of our center in the follow-up of pediatric and young adult patients with IBD who developed COVID-19. Our data suggest that pediatric IBD patients have a low risk for complications and hospitalization, regardless of the IBD treatment. A larger multicentric study with longer follow-up would be required to draw more conclusions, but we believe that this report is encouraging and allows for safe counseling regarding treatment options and school attendance in pediatric and young adult IBD patients.

Statement of Ethics

Informed consent was obtained from participants (or their parent/legal guardian/next of kin) to participate in the study.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Tiago Magalhães: conception of the work, analysis and interpretation of data for the work; drafting the work; final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Maria Cristina Granado: conception of the work, acquisition of data for the work; revising the work critically for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Ana Rute Manuel: conception of the work, acquisition of data for the work; revising the work critically for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Maria do Céu Espinheira: conception of the work, acquisition of data for the work; revising the work critically for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Eunice Trindade: conception of the work, acquisition of data for the work; revising the work critically for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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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Long-Term Intestinal Failure and Home Parenteral Support: A Single Center Experience

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Keywords
Intestinal failure · Home parenteral nutrition · Home parenteral hydration · Short bowel syndrome

Abstract
Introduction: Home parenteral nutrition (HPN) and/or home parenteral hydration (HPH) are the gold-standard treatment for patients with long-term intestinal failure (IF). The authors aimed to assess the impact of HPN/HPH on nutritional status and survival of long-term IF patients, as well as HPN/HPH-related complications. ***Methods:*** This was a retrospective study including IF patients under HPN/HPH followed in a single large tertiary Portuguese hospital. The data collected included demographics, underlying conditions, anatomical characteristics, type and duration of parenteral support, IF functional, pathophysiological, and clinical classifications, body mass index (BMI) at the beginning and end of follow-up, complications/hospitalizations, current patient status (deceased, alive with HPN/HPH, and alive without HPN/HPH), and cause of death. Survival after HPN/HPH beginning, until death or August 2021, was recorded in months. ***Results:*** Overall 13 patients were included (53.9% female, mean age 63.46 years), and 84.6% of patients presented type III IF and 15.4% type II. Short bowel syndrome caused 76.9% of IF. Nine patients received HPN and 4 HPH. Eight patients (61.5%) were underweight at the beginning of HPN/HPH. At the end of follow-up, 4 patients were alive without HPN/HPH, 4 maintained HPN/HPH, and 5 died. All patients improved their BMI (mean initial BMI 18.9 vs. 23.5 at the end, $p < 0.001$). Eight patients (61.5%) were hospitalized due to catheter-related complications, mainly infectious (mean hospitalization episodes 2.25, mean hospital stay of 24.5 days). No deaths were related to HPN/HPH. ***Conclusion:*** HPN/HPH significantly improved IF patients' BMI. HPN/HPH-related hospitalizations were common, however causing no deaths, reinforcing that HPN/HPH is an adequate and safe therapy for long-term IF patients.

Suporte nutricional parentérico domiciliário e falência intestinal crónica: a experiência de um único centro

Palavras Chave
Falência intestinal · Nutrição parentérica domiciliária · Hidratação parentérica domiciliária · Síndrome do intestino curto

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Resumo

Introdução: A nutrição parentérica domiciliária (NPD) e/ou a hidratação parentérica domiciliária (HPD) constituem o tratamento *gold-standard* para doentes com falência intestinal (FI) crónica. O objetivo do presente estudo foi avaliar o impacto da NPD/HPD no *status* nutricional e sobrevivência dos doentes com FI crónica, bem como as complicações relacionadas à NPD/HPD. ***Métodos:*** Estudo retrospetivo, incluindo doentes com FI sob NPD/HPD, seguidos num hospital terciário em Portugal. Informação recolhida para cada doente: dados demográficos, patologia de base, características anatómicas, tipo e duração do suporte parentérico, classificação funcional, fisiopatológica e clínica da FI, índice de massa corporal (IMC) no início e final do seguimento, complicações/hospitalizações, estado atual do doente (falecido, vivo sob NPD/HPD e vivo sem NPD/HPD) e causa de morte. A sobrevida após início da NPD/HPD foi calculada em meses, até à data da morte ou agosto de 2021. ***Resultados:*** Incluídos 13 doentes (53.9% do sexo feminino, idade média 63.46 anos), 84.6% com FI tipo III e 15.4% com FI tipo II. A síndrome do intestino curto foi causa de 76.9% das FI. Nove doentes foram tratados com NPD e 4 com HPD. Oito doentes (61.5%) apresentavam IMC baixo no início da NPD/HPD. No final do seguimento, 4 doentes estavam vivos sem NPD/HPD, 4 mantinham NPD/HPD e 5 faleceram. Todos os doentes melhoraram significativamente o seu IMC (IMC médio no início do seguimento 18.9kg/m^2 vs 23.5kg/m^2 no final, p<0.001). Oito doentes (61.5%) tiveram de ser hospitalizados devido a complicações relacionadas com o cateter, sobretudo de causa infeciosa (número médio de hospitalizações por doente 2.25, duração média de internamento 24.5 dias). Não houve mortes relacionadas com a NPD/HPD. ***Conclusão:*** A NPD/HPD melhorou significativamente o IMC dos doentes com FI. As hospitalizações relacionadas com a NPD/HPD foram comuns, contudo não causaram mortes, reforçando o facto que a NPD/HPD é uma terapêutica segura e adequada para doentes com FI crónica.

Introduction

According to the European Society for Clinical Nutrition and Metabolism (ESPEN), intestinal failure (IF) is defined as the reduction in gut function below the minimum necessary for the absorption of macronutrients and/or water and electrolytes, such that intravenous supplementation (IVS) is required to maintain health and/or growth [1]. IF can be classified according to functional, pathophysiological, and clinical features. From a functional perspective, IF can be classified into three types. In type I, short-term IF, IVS is usually required over a period of days to a few weeks. Type II is a long-term, subacute condition, where IVS is maintained for weeks/months, and type III is a chronic condition, with metabolically stable patients requiring IVS over years, sometimes during all their lives [1, 2]. Regarding pathophysiological classification, there are five major pathophysiological mechanisms for IF: short bowel, intestinal fistula, extensive small bowel mucosal disease, intestinal dysmotility, and mechanical obstruction. From a clinical perspective, classification is based on the weekly IVS energy and volume requirement. It can be categorized from A to D regarding the IVS energy supplied weekly, and from 1 to 4 for the volume of the IVS [1]. The clinical classification is illustrated in Table 1.

Table 1. Clinical classification of chronic IF

IV energy supplementation, kcal/kg body weight	Volume of the IV supplementation, mL			
	≤1,000	1,001–2,000	2,001–3,000	>3,000
A: 0	A1	A2	A3	A4
B: 1–10	B1	B2	B3	B4
C: 11–20	C1	C2	C3	C4
D: >20	D1	D2	D3	D4

IF, intestinal failure; IV, intravenous.

IF treatment aims to restore bowel function through nutrition, pharmacological, and/or surgical therapy [3]. In long-term IF, mainly in type III, although some oral nutrient intake is possible in most individuals, home parenteral nutrition (HPN) and/or home parenteral hydration (HPH) remain the foundation of treatment. This comprises the administration of macro- and micronutrients, fluids, and electrolytes via a central venous catheter at the patients' home [4]. Long-term IF patients require a multidisciplinary approach since treatment is complex and requires differentiated expertise.

Although type I IF is very common in surgical wards, type III chronic IF is rare and is, usually, considered the rarest of chronic organ failures [5, 6], and type II is even less frequent. Due to the rarity of long-term IF, comprehensive studies are scarce. To the best of our knowledge, there is minimal literature on the effect of HPN/HPH on nutritional status and survival in patients with IF. The authors here outline their experi-

ence of the use of HPN/HPH, amounting to 10 years of experience. The aim of this study was to assess the impact of HPN/HPH on nutritional status and survival of long-term IF patients, as well as HPN/HPH-related complications.

Materials and Methods

The authors performed a retrospective analysis of patients with IF who underwent, or were currently under HPN and/or HPH, followed in a single large tertiary Portuguese hospital. IF outpatients were managed in our hospital's Artificial Nutrition Outpatient Clinic, by a multidisciplinary nutrition support team (NST) including physicians (gastroenterologists and surgeons), a dietitian, and a nurse. After the outpatient appointment, the nutritional decisions were discussed with the team pharmacists and, whenever needed, with other physicians. The criteria for acceptance into the HPN/HPH program included the inability to maintain a normal nutritional status with oral/enteral support after hospital discharge, due to IF from underlying disease, as well as patient commitment to ensure compliance with treatment and adequate hospital follow-up. Some patients presented the competence and skills to achieve autonomy for self-administration of parenteral nutrition. For those patients where self-administration or administration by a relative or caregiver is impossible, the hospital nurses from home care provided daily home support.

Before entering the HPN/HPH program, all subjects and/or their legal caregivers were carefully informed in detail about the risks and benefits of this therapy and gave their informed consent. The present study is retrospective and the only initial exclusion criteria was an incomplete clinical file.

The following clinical data were collected for each patient: age, gender, underlying condition motivating IF, IF classifications (functional, pathophysiological, and clinical classification), anatomical characteristics, duration and characteristics of parenteral support during most of the HPN/HPH period (after initial stabilization and before the final withdrawal period before finishing parenteral support), body mass index (BMI) at the beginning and at the end of follow-up, HPN/HPH-related complications requiring hospitalization, and current patient status (deceased, alive with HPN/HPH, or alive without HPN/HPH). For the deceased patients, the date of death was recorded, and survival was calculated in months after the beginning of HPN/HPH. For the remaining patients, survival was calculated in months from the beginning of follow-up until August 2021. The cause of death was also assessed (HPN/HPH related, comorbidity related, or due to acute infection, other than catheter related).

Statistical analysis was performed using the Statistical Package for Social Sciences (IBM SPSS® Statistics, version 25.0). Categorical variables are presented as frequencies and percentages, and continuous variables as means and standard deviations. Normal distribution was checked using the Shapiro-Wilk test or skewness and kurtosis. A parametric independent *t*-test was used to compare variables normally distributed. All reported *p* values are two-tailed, with a *p* value below 0.05 indicating statistical significance.

Results

From the total HPN/HPH patients, 3 were excluded due to incomplete clinical files. A total of 13 adult patients with IF under HPN/HPH were included: 7 females (53.9%) and 6 males (46.1%), aged between 28 and 92 years (mean 63.46 ± 18.433 years), with a follow-up period ranging from 6 to 114 months (mean 28.8±29.207 months). The majority of patients (n = 11, 84.6%) presented type III IF, while the remaining 2 patients presented type II IF (15.4%), both with long-term type II IF, allowing sufficient metabolic stability to continue treatment at home with HPN. Most patients (n = 10, 76.9%) presented IF due to short bowel syndrome (SBS) of several causes: abdominal cancer surgery (n = 3), Crohn's disease (n = 2), familial adenomatous polyposis (n = 2), intestinal ischemia (n = 1), multiple bowel adhesions (n = 1), and incarcerated umbilical hernia (n = 1). Of the SBS patients: 6 presented terminal ileostomies, 3 presented terminal jejunostomies (all 3 with less than 100 cm of small bowel), and 1 patient presented ileostomy plus colostomy. In all patients, a subcutaneously tunneled central catheter (Hickman catheter) was placed. Nine patients (69.2%) were receiving HPN, and 4 patients (30.8%) were under HPH. No patient received glucagon-like peptide 2 (GLP-2) analogues. At the beginning of HPN/HPH, 8 patients (61.5%) were underweight (BMI <18.5) and 5 patients presented a normal BMI. The characteristics of the study population are described in Table 2.

The mean duration of HPN/HPH was 23 months. HPN was administered for a mean period of 6.2 days/week and HPH for a mean of 4.6 days/week. Table 3 summarizes HPH/HPH support characteristics and duration for each patient. All patients improved their BMI during the follow-up period (mean BMI at the beginning of follow-up 18.9 vs. 23.5 at the end, $p < 0.001$). Regarding clinical outcome at the end of follow-up, 4 patients (30.8%) were alive without IVS, 4 patients (30.8%) maintained IVS, and the other 5 patients (38.4%) died (Table 2).

Four patients were able to discontinue home parenteral support (2 presented type II IF and 2 type III IF). The 2 patients with type II IF could be treated and resumed oral feeding: one had severe Crohn's disease and required multiple surgical interventions, namely ileostomy, resulting in SBS, and required HPN for 8 months, but after reconstruction and medical therapy optimization he was able to resume exclusive oral intake; the other type II patient presented IF due to a jejunal fistula that resulted from a hernioplasty surgical complication and required 8 months of HPN. Once the fistula was surgically corrected,

Table 2. Characteristics of the study population ($n = 13$)

Gender	Age, years	Underlying condition	Functional classification	Pathophysiological classification	Clinical classification	HPN/HPH	Initial BMI	Final BMI	Outcome
Male	71	Colorectal cancer	Type III	Short bowel	D2	HPN	14.7	18.4	Deceased
Female	84	Intestinal ischemia	Type III	Short bowel	D2	HPN	20.0	26.7	Deceased
Male	65	Crohn's disease	Type II	Short bowel + intestinal fistula	D3	HPN	17.7	20.1	Alive without IVS
Male	68	Colorectal cancer	Type III	Short bowel	A2	HPH	26.2	27.5	Deceased
Male	69	Familial adenomatous polyposis	Type III	Short bowel	A2	HPH	16.4	27.9	Alive without IVS
Female	58	Malabsorption from rituximab	Type III	Extensive bowel mucosal disease	D2	HPN	16.0	22.9	Deceased
Female	63	Bowel adhesions	Type III	Short bowel + obstruction	A2	HPH	25.3	28.8	Alive with IVS
Female	92	Umbilical hernia	Type III	Short bowel	D2	HPN	18.1	21.6	Deceased
Female	83	Hernioplasty prosthesis fistula	Type II	Intestinal fistula	D3	HPN	24.6	29.6	Alive without IVS
Female	62	Intestinal dysmotility	Type III	Intestinal dysmotility	D3	HPN	16.5	19	Alive without IVS
Male	28	Crohn's disease	Type III	Short bowel	D3	HPN	14.7	19.7	Alive with IVS
Female	46	Gynecological cancer surgery	Type III	Short bowel	D3	HPN	15.3	21.8	Alive with IVS
Male	36	Familial adenomatous polyposis	Type III	Short bowel	A2	HPH	20.5	21.9	Alive with IVS

HPN, home parenteral nutrition; HPH, home parenteral hydration; BMI, body mass index; IVS, intravenous supplementation.

the patient resumed oral intake. Also, 2 type III IF patients resumed oral feeding: one underwent total proctocolectomy with terminal ileostomy due to familial adenomatous polyposis, and required 6 months of HPH until ileostomy output was stabilized. The fourth patient presented IF due to intestinal dysmotility and required 15 months of HPN. Afterwards, this fourth patient was able to maintain an adequate nutritional status with oral intake plus enteral supplementation. The 4 other non-deceased patients who maintained home parenteral support all presented type III IF.

Eight patients (61.5%) were hospitalized due to catheter-related complications, 3 of them with more than one hospital admission (mean hospitalization episodes of 2.25 per patient, with a mean hospital stay of 24.5 days, minimum 3 days and maximum 143 days). From the total of 18 hospitalizations, catheter-related blood stream infections (CRBSI) accounted for the majority of hospital admissions (66.7%, $n = 12$). Other catheter-related complications included catheter exteriorization/dysfunction (22.2%, $n = 4$) and venous thrombosis (11.1%, $n = 2$). Regarding the causes of death for the deceased patients: 3 patients died with acute infection (other than CRBSI), and 2 patients died from comorbidities. There were no deaths related to HPN/HPH.

Discussion

The present study included adult patients with IF from multiple etiologies, referred to a single center with a multidisciplinary NST, dedicated to IF patients and capable of providing specialized care to this complex condition. IF may occur due to acquired or congenital, gastrointestinal or systemic, benign or malignant diseases [7]. It may be a self-limiting short-term disorder (type I IF), or may become a long-lasting, chronic condition (type II or type III IF). According to a previous European cross-sectional study, SBS was the main cause of long-term IF, accounting for 74.7% of HPN indication in adults [8]. SBS is a rare disease that results from extensive intestinal resection, leading to a residual small bowel length of less than 200 cm, which translates into loss of absorptive intestinal surface. HPN/HPH represents the standard-of-care and life-sustaining therapy in long-term IF patients [4]. Although IF may be reversible in SBS patients through intestinal adaptation and rehabilitation programs, HPN weaning off is more likely to occur in patients with partial or total colon in continuity, and less likely in patients with less than 100 cm of small bowel length [9].

Table 3. Home IVS characteristics and duration for each patient

Gender	Age, years	HPN/ HPH	Kcal/bag in HPN	Volume in HPH, mL	Days per week of IVS	Duration of IVS, months
Male	71	HPN	1,600	–	7	7
Female	84	HPN	1,400	–	7	17
Male	65	HPN	2,200	–	7	8
Male	68	HPH	–	1,500	3	12
Male	69	HPH	–	1,500	3	6
Female	58	HPN	1,600	–	5	31
Female	63	HPH	–	2,000	7	38
Female	92	HPN	1,600	–	5	19
Female	83	HPN	2,200	–	7	8
Female	62	HPN	2,200	–	7	15
Male	28	HPN	2,200	–	7	6
Female	46	HPN	2,200	–	4	18
Male	36	HPH	–	2,000	7	114

HPN, home parenteral nutrition; HPH, home parenteral hydration; IVS, intravenous supplementation.

Our study population presented a heterogeneity of underlying diseases motivating IF, with SBS being the major cause. However, even patients within the same pathophysiological IF class suffered from several underlying disorders and formed a very heterogeneous group. In the present study, we did not include any patient with type I IF, which is the classic situation occurring after abdominal surgery, with IVS usually being required over a period of days to a few weeks and normally administrated during a hospital stay. Most patients in our study presented type III IF, a chronic condition in which patients are metabolically stable, and usually require long-term IVS over years. In the study population, all non-deceased patients who maintained home parenteral support at the end of follow-up presented type III IF. Of the 4 patients who were able to discontinue home parenteral support, two presented type II IF and two type III IF. Type II IF is a long-term subacute condition where IVS is maintained for weeks/months. Typically, these are metabolically unstable patients, frequently with multiple digestive fistula, needing an interdisciplinary intervention. They may need hospital care for several weeks but may also be home treated for several months with HPN, in order to become fit enough for reconstructive surgery. The 2 patients with type II IF who resumed oral feeding presented a clinical condition that could be surgically reverted after a few months of home parenteral support, reinforcing the role of reconstructive surgery in weaning off parenteral support. Regarding the two type III IF patients alive without home parenteral support, one required months of HPH after terminal ileostomy, until fistula output was stabilized, and the other required over a year of HPN due to intestinal dysmotility, but was finally able to maintain an adequate nutritional status with oral intake plus enteral supplementation. Besides reconstructive surgery, intestinal adaptation plays an important part in weaning off parenteral support. Intestinal adaptation is the natural compensatory process that occurs after massive intestinal resection and sometimes nutritional autonomy may be achieved. Adaptation is a complex process that responds to nutrient and non-nutrient stimuli [10, 11]. Stimulating the remaining bowel with enteral nutrition enhances this process. GLP-2 is an enteroendocrine peptide, released in response to luminal nutrients, responsible for initiating and maintaining small bowel adaptive responses after resection, thus improving nutrient absorption [12–14]. Teduglutide is a long-acting GLP-2 analogue, and has been approved for SBS patients as a long-term aid to parenteral nutrition weaning [15, 16]. Teduglutide's use is usually reserved for SBS patients who are unable to be weaned from parenteral nutrition despite aggressive use of the more conventional measures, particularly in those SBS patients who have developed significant complications or describe severe impairment in quality of life related to parenteral nutrition use. Gastrointestinal neoplasia constitutes a contraindication for Teduglutide's use, which some of our patients present. Also, the cost for this medication is significantly high and its accessibility is limited. In our center, no patient has yet received treatment with any GLP-2 analogue.

To the best of our knowledge, there are limited data on the effect of HPN on long-term IF patients' nutritional

status. In a small retrospective study of 12 patients with systemic sclerosis, HPN significantly improved nutrition status [17]. In our study, home parenteral support was associated with a significant increase in BMI in all patients with IF.

For long-term IF patients with benign disease, long-term survival under HPN/HPH can reach 80% at 5 years [9]. However, treatment-related morbidity and mortality are dependent on adequate patient management and follow-up by a multidisciplinary NST [2, 9]. A systematic review that aimed to assess the role of NSTs in the oversight of parenteral nutrition administration in hospitalized patients demonstrated a decreased incidence of inappropriate parenteral nutrition use in centers with NST compared to centers with no such multidisciplinary team [18], thus suggesting the benefit of an NST in managing patients under parenteral nutrition. The main long-term HPN complications are catheter related, in particular CRBSI, which can be responsible for up to 70% of hospitalizations [4]. Treatment-related complications are reported to account for around 14% of deaths in patients with long-term IF [19]. Preventing CRBSI relies on patient/caregiver education on adequate hand washing and disinfection policy, correct catheter manipulation, and regular change of intravenous administration sets [2, 4]. As for catheter-related venous thrombosis, we do not routinely use pharmacologic thromboprophylaxis for primary prevention, in accordance with the guidelines [2]. Despite optimal conditions of catheter placement, and extensive education of caregivers on catheter handling, we observed that infections and mechanical complications are still common in IF patients under HPN/HPH. Catheter-related complications, mainly CRBSI, were responsible for two thirds of hospitalization episodes, which is in accordance with the available literature [2, 4, 20]. In a large study of patients under HPN, 15% of reported deaths were due to HPN-related complications, namely central line infections and associated liver disease [21]. In the present study there were no deaths directly related with HPN/HPH, which may result from the existence of an experienced multidisciplinary NST responsible for managing these patients.

This study presented some limitations. It was carried out in a single hospital, data collection was dependent on each patient's clinical files, and the study population was small, in relation to the rarity of this clinical entity. Also, long-term complications from HPN such as cholestasis, liver disease, and osteoporosis were not accessed. Nevertheless, the present study suggests that, even in a health system where there is no tradition of long-term management of IF patients and with only a few teams with some experience, home parenteral support can be a safe and effective therapy.

In conclusion, home parenteral support remains the gold-standard and life-sustaining therapy of long-term IF due to any underlying condition. In this study, HPN significantly improved IF patients' BMI. Although HPN/HPH-related hospitalizations were common due to CRBSI, no deaths were attributed to the parenteral support, thus suggesting that HPN/HPH is an adequate and safe therapy for IF patients, especially if patients benefit from an experienced nutrition team.

Statement of Ethics

All subjects and/or their legal caregivers gave their informed consent to participate in this study. The present study was approved by the Ethics Committee of our institution.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

M.B. performed the data curation, statistical analysis, and wrote the manuscript. M.P. and C.O. were enrolled in data curation. S.C., C.O., A.P.S., G.N., C.A.S., and J.F. were enrolled in patient management. J.F. supervised the study and reviewed the manuscript.

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Validation and Application of Predictive Models for Inadequate Bowel Preparation in Colonoscopies in a Tertiary Hospital Population

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Keywords
Colonoscopy · Bowel preparation · Colonoscopy quality criteria

Abstract

Background: Bowel preparation is a major quality criterion for colonoscopies. Models developed to identify patients with inadequate preparation have not been validated in external cohorts. We aim to validate these models and determine their applicability. ***Methods:*** Colonoscopies between April and November 2019 were retrospectively included. Boston Bowel Preparation Scale ≥2 per segment was considered adequate. Insufficient data, incomplete colonoscopies, and total colectomies were excluded. Two models were tested: model 1 (tricyclic antidepressants, opioids, diabetes, constipation, abdominal surgery, previous inadequate preparation, inpatient status, and American Society of Anesthesiology [ASA] score ≥3); model 2 (co-morbidities, tricyclic antidepressants, constipation, and abdominal surgery). ***Results:*** We included 514 patients (63% males; age 61.7 ± 15.6 years), 441 with adequate preparation. The main indications were inflammatory bowel disease (26.1%) and endoscopic treatment (24.9%). Previous surgery (36.2%) and ASA score ≥3 (23.7%) were the most common comorbidities. An ASA score ≥3 was the only identified predictor for inadequate preparation in this study ($p < 0.001$, OR 3.28). The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of model 1 were 60.3, 64.2, 21.8, and 90.7%, respectively. Model 2 had a sensitivity, specificity, PPV, and NPV of 57.5, 67.4, 22.6, and 90.5%, respectively. The AUC for the ROC curves was 0.62 for model 1, 0.62 for model 2, and 0.65 for the ASA score. ***Conclusions:*** Although both models accurately predict adequate bowel preparation, they are still unreliable in predicting inadequate preparation and, as such, new models, or further optimization of current ones, are needed. Utilizing the ASA score might be an appropriate approximation of the risk for inadequate bowel preparation in tertiary hospital populations.

Validação e aplicação de modelos preditivos para preparação intestinal inadequada numa população de um hospital terciário

Palavras Chave
Colonoscopia · Preparação intestinal · Critérios de qualidade na colonoscopia

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Resumo

Introdução: A preparação intestinal é um dos principais critérios de qualidade na colonoscopia. Modelos desenvolvidos para identificar doentes com preparação inadequada nunca foram validados em coortes externas. Pretendemos validar esses modelos e determinar sua aplicabilidade clínica. ***Métodos:*** Colonoscopias entre abril-novembro/2019 foram incluídas retrospectivamente. A Escala de Preparação Intestinal de Boston ≥2 por segmento foi considerada adequada. Dados insuficientes, colonoscopias incompletas e colectomias totais foram excluídos. Dois modelos foram testados: modelo 1 (antidepressivos tricíclicos, opióides, diabetes, obstipação, cirurgia abdominal, preparação prévia inadequada, internamento e American Society of Anesthesiology [ASA] ≥3); modelo 2 (comorbilidades, antidepressivos tricíclicos, obstipação e cirurgia abdominal). ***Resultados:*** Foram incluídos 514 doentes (63% homens; idade 61.7 ± 15.6), 441 com preparação adequada. As principais indicações foram doença inflamatória intestinal (26.1%) e tratamento endoscópico (24.9%). Cirurgias anteriores (36.2%) e ASA ≥3 (23.7%) foram as comorbilidades mais comuns. Um score ASA ≥3 foi o único fator de risco identificado para preparação inadequada ($p < 0.001$, OR 3.28). A sensibilidade, especificidade, valor preditivo positivo (VPP) e valor preditivo negativo (VPN) do modelo 1 foi de 60.3, 64.2, 21.8 e 90.7%. O modelo 2 apresentou sensibilidade, especificidade, VPP e VPN de 57.5, 67.4, 22.6 e 90.55%. A AUC para a curva ROC foi de 0.62 para o modelo 1, 0.62 para o modelo 2 e 0.65 para o score ASA. ***Conclusões:*** Embora ambos os modelos sejam eficazes a prever preparação intestinal adequada, não se verifica o mesmo para a preparação inadequada e como tal, novos modelos ou otimização dos atuais são ainda necessários. Utilizar o score ASA pode ser uma aproximação adequada do risco de preparação intestinal inadequada em populações de hospitais terciários.

Introduction

According to the most recent guidelines on bowel preparation of the European Society of Gastrointestinal Endoscopy (ESGE), the adequacy of bowel preparation is a major quality criterion in colonoscopy [1]. Nevertheless, inadequate bowel preparation is still reported in up to 35% of patients [2, 3].

Two recent systematic reviews and meta-analyses [2, 3] attempted to identify predictive factors for inadequate bowel preparation. Patient age, male gender, medical history (chronic constipation, hypertension, diabetes, cirrhosis, stroke, and dementia), and current medication (opiates and tricyclic antidepressants) were identified as risk factors, while previous abdominal surgery, previous inadequate bowel preparation, and body mass index were not consistent predictors.

Based on these findings, three predictive models [4–6] were developed with the aim of identifying patients at risk for inadequate bowel preparation. To the best of our knowledge, none of these models have yet been applied outside of their development/validation cohorts and in clinical practice.

Therefore, this study aims to validate these inadequate bowel preparation predictive models in our population and to determine their applicability in clinical practice.

Materials and Methods

Study Population and Data Collection

This study was conducted in a tertiary hospital in northern Portugal. For the purpose of this retrospective cohort study, the authors considered all patients who underwent an elective colonoscopy between April and November 2019. Patient data was collected through database search and clinical records, concerning sex, age, indication for colonoscopy, type of preparation used, American Society of Anesthesiology (ASA) score, simple medical history (diabetes, cirrhosis, neurological disorders, abdominal or pelvic surgery), medication history (opioids, tricyclic antidepressants), previous inadequate bowel preparation, chronic constipation history (defined as fewer than three bowel movements per week), and current hospitalization at the time of colonoscopy.

Bowel preparation was considered adequate if every colon segment scored at least 2 points in the Boston Bowel Preparation Scale (BBPS). The exclusion criteria were absence of BBPS in the exam report, incomplete colonoscopy (for a reason other than inadequate bowel preparation), total colectomy, and incomplete patient data.

Bowel Preparation and Other Interventions

According to the implemented protocol in our hospital, all patients were provided with written and oral instructions regarding bowel preparation. A low-fiber diet was started in the 2 days prior to the procedure. Per protocol, patients are allowed to choose between low-volume polyethylene glycol (PEG) + ascorbic acid, high-volume PEG or sodium picosulfate (healthy patients, without comorbidities). A split-dose bowel preparation regimen was used for colonoscopies scheduled for the morning period, while a same-day regimen was used for afternoon colonoscopies. Additionally, a nurse was available for a face-to-face consultation with every patient that had doubts or required further instructions regarding bowel preparation regimens.

Table 1. Patient characteristics and clinical data

		Univariate, OR (95% CI)	Multivariate, OR (95% CI)
Sex, *n* (%)			
Male	324 (63.0)		
Female	190 (37.0)		
Age, mean ± SD, years	61.7±15.62		
Indications for colonoscopy, *n* (%)			
IBD	134 (26.1)		
Endoscopic treatment	128 (24.9)		
Post-polypectomy/cancer follow-up	125 (24.4)		
Screening	41 (8)		
Iron deficiency anemia	34 (6.6)		
Chronic diarrhea	15 (2.9)		
Other	37 (7.2)		
Bowel cleanser, *n* (%)			
PEG 2L + ascorbic acid	170 (33.1)		
PEG 3L	59 (11.5)		
PEG 4L	142 (27.6)		
Sodium picosulfate	19 (3.7)		
Unknown	124 (24.1)		
Previous abdominal/pelvic surgery, *n* (%)	186 (36.2)		
Partial colectomy/rectal resection	77 (15)		
Urogenital surgery	60 (11.7)		
Hepatobiliopancreatic surgery	15 (2.9)		
Other	34 (6.6)		
ASA score, *n* (%)		3.50 (2.09–5.85)	3.28 (2.04–5.28)
1	32 (6.2)		
2	358 (69.6)		
3	123 (23.9)		
4	1 (0.2)		
Co-morbidities, *n* (%)			
Diabetes	110 (21.4)	2.35 (1.38–4.02)	
Cirrhosis	6 (1.2)		
Chronic constipation	71 (13.8)	2.17(1.18–4.02)	
Stroke and/or dementia	24 (4.7)		
Chronic medication used, *n* (%)			
Opioids	9 (1.8)	5.05 (1.32–19.23)	
Tricyclic antidepressants	7 (1.4)		
Inpatient colonoscopy, *n* (%)	22 (4.3)		
Previous inadequate preparation, *n* (%)	55 (10.7)	2.06 (1.04–4.07)	

Only significant values are presented. OR, odds ratio; CI, confidence interval; SD, standard deviation; IBD, inflammatory bowel disease; PEG, polyethylene glycol; ASA, American Society of Anesthesiology.

Bowel Preparation Predictor Models

Two predictive models, previously published, were tested in our population. Model 1 by Dik et al. [5] considers tricyclic antidepressants or opioids use, diabetes, constipation, previous abdominal surgery, previous inadequate preparation, inpatient status, and ASA score ≥3. Model 2 by Gimeno-García et al. [6] considers comorbidities (diabetes, cirrhosis, and stroke history), tricyclic antidepressants use, constipation, and previous abdominal surgery. A third model, developed by Hassan et al. [4], was not tested as it did not use a validated bowel preparation scale.

Statistical Analysis

Continuous variables are expressed as medians and interquartile ranges (IQR), while categorical variables are expressed as frequencies and percentages. All potentially inadequate bowel preparation factors were subjected to univariate (χ^2 for categorical and *t* test for continuous variables) and multivariate analysis (logistic regression). Two-tailed *p* values were considered statistically significant if <0.05. A subset analysis comparing high- and low-volume PEG was performed regarding ASA score, age, comorbidities, constipation, previous surgery, current inpatient status, and previous colonoscopy with inadequate preparation as we postulated

Table 2. Bowel preparation

Bowel preparation, *n* (%)	
Adequate	441 (85.8)
Inadequate	73 (14.2)
Total BBPS, mean ± SD	7.04±1.85
0–2, *n* (%)	10 (1.9)
3–5 and 6 (at least 1 segment <2), *n* (%)	63 (12.3)
6–9, *n* (%)	441 (85.8)
BBPS per segment, mean ± SD	
Right colon	2.28±0.72
Transverse colon	2.44±0.67
Left colon	2.32±0.67

that old patients with more comorbidities were probably being offered more high-volume PEG preparations due to safety concerns.

The discriminative power of both models in predicting inadequate bowel preparation was determined by calculating the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and the area under the curve (AUC) of the receiver operating characteristic (ROC) curves.

The χ^2 test of goodness-of-fit was performed to evaluate whether the sample size was adequate, using the G*Power software and data available in the literature [5, 6]. This analysis revealed that a power of 95% for model 1 would have been achieved with 169 patients, while for model 2, enrolling 423 patients would allow for a power of 90%; in the present study, 514 individuals were included, allowing adequate power to test both models.

All statistical analyses were performed in IBM SPSS Statistics v22.0 (SPSS Inc., Chicago, IL, USA) and G*power v3.1.9.7 (Heinrich-Heine-Universität Düsseldorf, Germany).

Results

We included 514 patients, 324 (63.0%) of which were males. The median age was 64 years (IQR 53–73.25). The most common indications for colonoscopy were inflammatory bowel disease (n = 134, 26.1%), endoscopic treatment (n = 128, 24.9%), and cancer/polypectomy follow-up (n = 125, 24.4%). Previous abdominal/pelvic surgery was the most common comorbidity (n = 186, 36.2%), followed by diabetes (n = 110, 21.4%). The majority (n = 371, 72.2%) of patients underwent bowel cleansing with PEG-based solution. A more extensive description of patient clinical data and baseline characteristics can be found in Table 1.

Adequate bowel preparation, as defined in the Methods section, was observed in 441 (85.8%) patients. The median total BBPS score was 7 points (IQR 6–9), and the median right colon, transverse colon, and left colon segment scores were 2, 3, and 2 points, respectively. This data is summarized in Table 2.

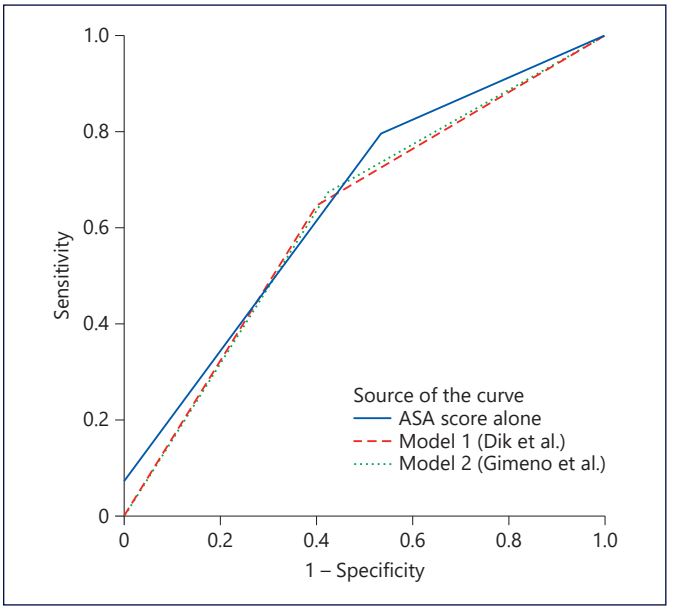

Fig. 1. ROC curves and AUC of both models and the ASA score.

On bivariate analysis, we found an association between inadequate preparation and opioid use (p = 0.027), diabetes mellitus (p = 0.001), chronic constipation (p = 0.011), previous inadequate preparation (p = 0.034), and ASA score (p < 0.001). On further multivariate analysis, the same effect was observed only for those with higher ASA scores (p < 0.001, OR 3.28, 95% CI 2.04–5.28). No association was found regarding age, sex, volume of PEG used (high versus low volume), tricyclic antidepressant use, cirrhosis, neurologic comorbidities, previous surgery (even when separated by colon resection vs. other intra-abdominal surgeries), and inadequate bowel preparation. This information is also displayed in Table 1.

Model 1 predicted a total of 202 patients as having inadequate bowel preparation, 44 of which were correctly predicted as such. On the other hand, 312 were predicted as adequate preparation, 283 of which were correctly predicted. The sensitivity, specificity, PPV, and NPV of model 1 were 60.3, 64.2, 21.8, and 90.7%, respectively. The AUC for the ROC curve of this model was 0.62 (95% CI 0.55–0.69).

Model 2 predicted 186 patients as having inadequate bowel preparation, 42 of which were correctly predicted as such. As for adequate preparation, 328 were predicted to achieve it, but only 297 did so. Model 2 had a sensitivity, specificity, PPV, and NPV of 57.5, 67.4, 22.6, and 90.6%, respectively. The AUC for the ROC curve of this

model was 0.62 (95% CI 0.55–0.70). ROC curves for both models are shown in Figure 1.

A subset analysis comparing high- and low-volume PEG regimens showed that higher ASA scores ($p = 0.001$) and inpatient status ($p = 0.008$) were significantly associated (on bivariate and multivariate analysis) with the use of higher-volume PEG regimens. Higher age was also associated with higher-volume PEG on bivariate analysis, but this was not confirmed on multivariate analysis.

Lastly, as the ASA score was the only predictive factor in our study, we tested its accuracy in predicting inadequate preparation. Utilizing an ASA score >2, 124 patients were predicted as having inadequate preparation, 34 of which were correctly predicted. On the other hand, 390 were predicted as having adequate preparation, 351 of which were correctly predicted. This translates as a sensitivity, specificity, PPV, and NPV of 46.6, 79.6, 27.4, and 90.0%, respectively. The AUC for the ASA score was 0.65 ($p < 0.001$, 95% CI 0.58–0.72). This ROC curve is also presented in Figure 1.

Discussion

In this study, we were able to replicate the data published by the authors of these scores, with similar, although slightly worse, results [5, 6].

The ongoing search for factors that can influence bowel preparation and accurately identify these patients resulted in these two previously published scores. Although the results seemed promising, some limitations are easily identified and were further confirmed in our study. More than half of the patients with inadequate preparation were identified, but there is still a significant group of patients that were not identified by either score (39.7% for model 1 and 42.5% for model 2) and in which we thus could not intervene. Although the argument can be made that all patients identified by these scores as having inadequate preparation could be offered more intensive regimens, it is also true that we would be subjecting a non-negligible number of patients to unnecessary interventions (which could further reduce compliance), as is demonstrated by the observed very low PPVs and high false positives for both scores. As such, the scores demonstrated a low value in predicting inadequate bowel preparation.

On the other hand, both scores were found to have a very high NPV, which means they could be useful in determining which patients most likely do not require additional interventions.

When comparing the original model 1 study, by Dik et al. [5], some methodological similarities and differences can be pointed out. While most of our exams were performed in an inflammatory bowel disease or endoscopic treatment setting, the original study included mostly patients undergoing screening or symptom investigation, which may induce a difference in adhesion to the bowel cleansing protocols due to different populations. Additionally, in this study, BBPS was defined as inadequate if total <6, and no reference was made to segments scoring 1 point with a total of 6, which we considered as inadequate preparation in our paper. Although the majority of patients in both our study and the original study are ASA class 1 or 2, while Dik et al. [5] only had 4.5% of patients with ASA ≥3, we had 24.1% scoring >2 points, which can be explained by an overall increased prevalence of comorbidities in our population. Overall, while there are differences in the populations being compared, model 1 performed worse in our study, with lower sensitivity (0.60 vs. 0.66), specificity (0.79 vs. 0.64), PPV (0.22 vs. 0.29), and NPV (0.91 vs. 0.95).

Regarding the original study for model 2, by Gimeno-García et al. [6], similar limitations can be described. Most examinations were also performed in a screening/symptom investigation setting, with equivalent conclusions regarding applicability. In this study, the median age of patients (60 vs. 64 in our study) was lower and comorbidities were present in a lower proportion (21.8 vs. 24.1%). Patients with dementia and previous history of inadequate bowel preparation were excluded in this study but included in our study because we believe these patients are at greater risk of inadequate bowel preparation. Additionally, the proportion of opioid (4.8 vs. 1.8%) or tricyclic antidepressant (8.2 vs. 1.4%) use was significantly higher in their population. On the other hand, as was the case with the model 1 study [5], the study by Gimeno-García et al. [6] was prospective in nature, contrasting with our retrospective study and its inherent biases. With these differences summarized, differences in model 2 accuracy were expected and were observed as a higher sensitivity (0.58 vs. 0.50) and NPV (0.91 vs. 0.88) but a lower specificity (0.67 vs. 0.80) and PPV (0.23 vs. 0.36).

Conversely, chronic constipation and abdominal surgery were not identified as predictors. This could be explained by the retrospective nature of our study, mostly in the case of chronic constipation, as we could not always use objective definitions for these categories due to incomplete data. In concordance with both studies [5, 6], we considered both partial colectomies and other intra-abdominal/pelvic surgeries the same for the purpose of

this study, and, as such, different relationships between surgeries and inadequate preparation can arise (as we do not know what surgeries the patients in the original studies had in order to make a comparison). Additionally, a sub-analysis regarding type of surgery (colon/rectum resection or urogenital surgery) found no relationship with inadequate preparation. Nevertheless, the relationship between previous surgery and inadequate preparation is controversial, as two meta-analyses with a significant number of patients failed to demonstrate any relationship [2, 3], probably due to the heterogeneity of definitions used and patients included.

The models previously described are probably more useful outside of tertiary specialized hospitals, as the population in our study (older, more comorbidities, and lower proportion of screening/symptom investigation) demonstrated substantially different results and lower AUC values than previously published.

In terms of previously identified inadequate bowel preparation predictors, we were only able to identify higher ASA scores as a predictive factor for an inadequate preparation in our population. By utilizing the ASA score alone, we demonstrated a predictive power similar but slightly better to the two models tested (AUC 0.65 vs. 0.62 on both models tested). The ASA score is widely used and easy to apply in clinical practice and categorizes patients according to their comorbidities. In populations such as ours (a tertiary hospital), utilizing the ASA score in order to triage patients who should be paid more attention regarding bowel preparation is an easier and quicker method than the two scores analyzed in this paper.

When aiming to optimize bowel preparation, several steps should be taken by all patients. Patients should adopt a clear-liquid or low-fiber diet on the previous day as both are equally effective [7, 8], although a low-fiber diet is associated with higher tolerability and willingness to repeat the exam. Bowel preparation should be undertaken as a split-dose regimen for next-day procedures or a same-day regimen for afternoon procedures [1, 9, 10]. The bowel preparation utilized (high-volume PEG, low-volume PEG, or non-PEG regimen if clinically validated) can be chosen according to patient preference, as there seems to be no difference in efficacy between regimens [11]. High-volume regimens offer better safety profiles with the trade-off of diminished tolerability (and thus more inadequate preparations), which might be more relevant in older patients with more comorbidities [12].

With all these previous measures applied, bowel preparation is more likely to be optimized, even in patients who are thought to be at risk (such as ASA >2). Nevertheless, additional measures, such as enhanced bowel preparation instructions, should be applied – such as a face-to-face or telephone nursing consultation [13, 14]. Although it may seem reasonable to prescribe additional laxatives or high-volume preparations in constipated individuals, the current available evidence shows no difference between regimens in these patients [15]. In case of a previous inadequate preparation, a modifiable reason for the failure of the chosen regimen should be sought before prescribing a different regimen or additional measures, such as nausea/vomiting or poor adherence due to patient- or preparation-related factors.

Several limitations can be readily identified, mostly due to the retrospective nature of our study and its inherent biases, such as the likelihood of suffering from missing data. Patient compliance or tolerance to bowel preparation was not registered, but nevertheless, our reported proportion of adequate bowel preparation was similar to previously published literature [5, 6] and nearly achieved the ≥90% recommended threshold [16], which probably indicates an adequate (but not perfect) compliance. Additionally, not all preparation regimens were registered, as this was not practice in out hospital at this time period, but it is reasonable to assume that most of these patients underwent a PEG solution, although the proportion of which cannot be inferred due to missing data. Regarding volume of preparation, the utilization of higher-volume PEG solutions was higher in older patients (although not significantly so), inpatients, and higher ASA scores: all inpatients are prescribed higher-volume PEG, as it is the only solution available in our hospital; as for higher ASA and age, we postulate that due to comorbidities and advanced age, these patients were probably recommended by the nursing staff or the community pharmacist to undergo higher-volume preparations for safety reasons. Although this may introduce a bias, we believe it not to be significant since the proportion of adequate preparation was the same between groups (high vs. low volume). Lastly, in our population, 26.1 and 24.9% of colonoscopies were performed in inflammatory bowel disease and endoscopic therapy settings, which limits the generalization of our data and indicates that these scores are not suitable for a tertiary hospital population such as ours.

In conclusion, although both models are capable of predicting more than half of the patients with inadequate bowel preparation, they are unable to do so in a reliable manner and, therefore, almost half of those requiring more intensive regimens are not identified when using these models. Further improvement of these models or development of new ones is necessary before they can be

applied in clinical practice. Utilizing the ASA score might be an appropriate approximation of the risk for inadequate bowel preparation in tertiary hospital populations.

Statement of Ethics

The study protocol was approved by the local ethics committee. The research was conducted ethically in accordance with the Declaration of Helsinki 2014 [9].

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Edgar Afecto: Inception, design and drafting of the article. Ana Ponte: Inception, design and critical review of the article. Sónia Fernandes: critical review of the article and final approval. Catarina Gomes: data collection and critical review of the article. João Correia: data collection and critical review of the article. João Carvalho: critical review of the article and final approval.

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Small Bowel Adenocarcinoma in a Patient with Crohn's Disease: The Role of Balloon-Assisted Enteroscopy

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Keywords
Crohn's disease · Inflammatory bowel disease · Small bowel adenocarcinoma · Enteroscopy

Abstract
Introduction: Small bowel adenocarcinoma is a rare but well-known complication of Crohn's disease. Diagnosis can be challenging, as clinical presentation may mimic an exacerbation of Crohn's disease and imaging findings may be indistinguishable from benign strictures. The result is that the majority of cases are diagnosed at the time of operation or postoperatively at an advanced stage. ***Case Presentation:*** A 48-year-old male with a previous 20-year history of ileal stenosing Crohn's disease presented with iron deficiency anemia. The patient reported melena approximately 1 month earlier but was currently asymptomatic. There were no other laboratory abnormalities. Anemia was refractory to intravenous iron replacement. The patient underwent computerized tomography enterography, which revealed multiple ileal strictures with features suggesting underlying inflammation and an area of sacculation with circumferential thickening of adjacent bowel loops. Therefore, the patient underwent retrograde balloon-assisted small bowel enteroscopy, where an area of irregular mucosa and ulceration was found at the region of ileo-ileal anastomosis. Biopsies were performed and histopathological examination revealed tubular adenocarcinoma infiltrating the muscularis mucosae. The patient underwent right hemicolectomy plus segmental enterectomy of the anastomotic region where the neoplasia was located. After 2 months, he is asymptomatic and there is no evidence of recurrence. ***Discussion:*** This case demonstrates that small bowel adenocarcinoma may have a subtle clinical presentation and that computed tomography enterography may not be accurate enough to distinguish benign from malignant strictures. Clinicians must, therefore, maintain a high index of suspicion for this complication in patients with long-standing small bowel Crohn's disease. In this setting, balloon-assisted enteroscopy may be a useful tool when there is raised concern for malignancy, and it is expected that its more widespread use could contribute to an earlier diagnosis of this severe complication.

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Adenocarcinoma do intestino delgado num doente com doença de Crohn: o papel da enteroscopia assistida por balão

Palavras Chave
Doença de Crohn · Doença inflamatória intestinal · Adenocarcinoma do intestino delgado · Enteroscopia

Resumo
Introdução: O adenocarcinoma do intestino delgado é uma complicação rara mas bem estabelecida da doença de Crohn. O seu diagnóstico pode ser desafiante, na medida em que a apresentação clínica pode mimetizar uma agudização da doença de Crohn e os achados imagiológicos podem ser indistinguíveis de estenoses benignas. Em consequência, a maioria dos casos são diagnosticados durante ou após a cirurgia em estadio avançado. ***Descrição do caso:*** Um homem de 48 anos com antecedentes de doença de Crohn ileal estenosante, com 20 anos de evolução, apresentou-se com anemia ferropénica. O doente referia melenas aproximadamente um mês antes, mas encontrava-se atualmente assintomático. Não apresentava outras alterações laboratoriais de relevo. A anemia era refratária a suplementação com ferro endovenoso. Foi submetido a enterografia por tomografia computorizada, que revelou múltiplas estenoses ileais com caraterísticas sugestivas de atividade inflamatória e uma área de saculação com espessamento circunferencial das ansas de intestino delgado adjacentes. Assim, foi submetido a enteroscopia assistida por balão, onde se identificou uma área de mucosa irregular e ulceração na região da anastomose ileo-ileal. Biópsias desta área revelaram a presença de adenocarcinoma tubular com infiltração até à *muscularis mucosae*. O doente foi submetido a hemicolectomia direita com enterectomia segmentar da região da anastomose onde a neoplasia se encontrava localizada. Ao fim de 2 meses, o doente encontra-se assintomático e sem evidência de recorrência. ***Discussão:*** Este caso demonstra que o adenocarcinoma do intestino delgado pode ter uma apresentação clínica subtil e que a enterografia por tomografia computorizada pode não ter precisão suficiente para distinguir estenoses benignas de neoplasias malignas. Os clínicos devem, portanto, manter um elevado índice de suspeição diagnóstica para esta complicação em doentes com doença de Crohn ileal de longa duração. Neste contexto, a enteroscopia assistida por balão pode ser uma ferramenta útil em casos de suspeita de neoplasia maligna, esperando-se que possa contribuir para um diagnóstico mais precoce desta complicação severa.

Introduction

Small bowel adenocarcinoma (SBA) is a rare malignancy accounting for less than 5% of gastrointestinal cancers, with an incidence rate of 0.2–0.3/100,000 person-years in the general population [1]. Although Crohn's disease (CD) is associated with a 22-fold increased risk of SBA, this is an unusual complication that develops during the course of CD in approximately 0.2% of patients [2] at an incidence rate of 0.3/1,000 person-years [3] and usually appears at a much younger age than in the general population [4].

Diagnosis of SBA associated with CD can be quite challenging. Obstruction is the most common presenting manifestation, whereas less common clinical presentations include hemorrhage, fistula, or perforation. Unfortunately, all of these symptoms are hard to distinguish from those of a CD exacerbation. Besides, these malignancies are often radiologically indistinguishable from long-standing CD and imaging techniques may miss small lesions. The result is that the majority of cases are diagnosed at the time of operation or postoperatively at an advanced stage [4]. The prognosis of SBA in CD is usually unfavorable with a 5-year survival of 20–30% [5].

We report a case that illustrates diagnostic difficulties associated with SBA in patients with CD and that aims to increase clinicians' awareness of this rare but severe complication and to demonstrate that balloon-assisted enteroscopy may play an important role in achieving an early diagnosis.

Case Presentation

A 48-year-old male with a previous medical history of CD presented with iron deficiency anemia. His hemoglobin level was 10.7 g/dL, with mild microcytosis (86.2 fL) and low levels of both serum iron (33 mg/dL) and transferrin saturation (9%). The patient reported melena approximately 1 month earlier but was currently asymptomatic. He denied abdominal pain, diarrhea, or weight loss. There were no other laboratory abnormalities associated with underlying disease activity, including leukocyte and platelet count and C-reactive protein levels, which were normal. Stool calprotectin level was also normal. His last ileocolonoscopy, performed 5 months earlier, was also normal with no signs of inflammatory

activity along colon and terminal ileum. CD had been diagnosed 20 years earlier and was characterized by ileal involvement and stenosing behavior, with associated perianal fistulizing disease (Montreal classification: A2L1B2p). There was a history of segmental enterectomy for ileal stenosis and anal fistulectomy performed 4 and 6 years after initial diagnosis, respectively. His current medications included azathioprine and infliximab (5 mg/kg every 8 weeks), which he had started 16 and 10 years earlier, respectively. The last acute exacerbation of CD requiring induction therapy with intravenous corticosteroids had occurred 8 years before and CD appeared to be in clinical and endoscopic remission since then.

Intravenous iron replacement with weekly injections of 200 mg of iron oxide was started. However, after 8 weeks, hemoglobin level had decreased to 9.2 g/dL despite correction of iron deficiency. The patient remained asymptomatic and laboratory studies once again did not reveal leukocytosis, thrombocytosis, or elevated C-reactive protein levels. Computerized tomography (CT) enterography revealed multiple ileal strictures with wall thickening, vasa recta engorgement, and prominent mesenteric lymph nodes, suggestive of inflammatory strictures. In addition, a sacculation with circumferential thickening of proximal and distal bowel loops extending for 47 and 31 mm, respectively, was found at the region of ileo-ileal anastomosis, as shown in Figure 1. Therefore, the patient underwent double balloon-assisted retrograde enteroscopy which revealed several ileal strictures, easily traversed with the enteroscope, and an area of infiltrative appearance at the region of ileo-

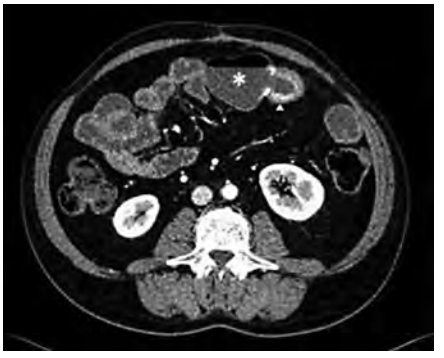

Fig. 1. Computed tomography enterography. A sacculated small bowel loop may be seen at the region of ileo-ileal anastomosis (asterisk) associated with circumferential and irregular thickening of the afferent and efferent small bowel loops (arrowhead).

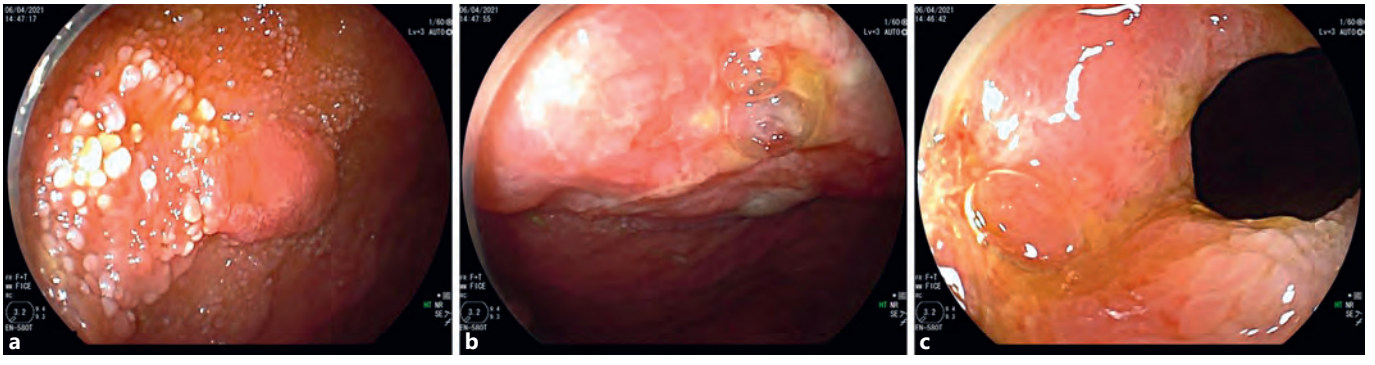

Fig. 2. Double balloon enteroscopy revealed an area of infiltrative appearance at the anastomotic region with features of polypoid component (**a**), ulceration (**b**), and stenosis (**c**) that could not be traversed with the enteroscope.

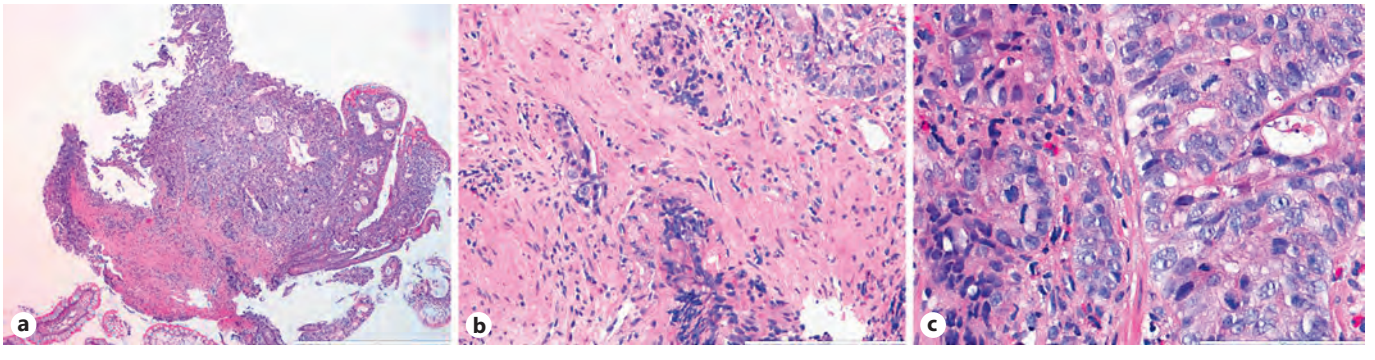

Fig. 3. Histopathological examination of biopsies performed at the region of small bowel ulceration. **a** Invasive adenocarcinoma with an enteric-type mucosa (HE, ×40). **b** An area of stromal infiltration by malignant cells is highlighted (HE, ×200). **c** The neoplasia demonstrates a high mitotic index (HE, ×400).

ileal anastomosis, with a polypoid component (as shown in Fig. 2a) and ulceration (as shown in Fig. 2b), producing a stenosis (as shown in Fig. 2c) that could not be traversed by the enteroscope. Biopsies of this area were performed. Remarkably, histopathological examination revealed tubular adenocarcinoma infiltrating the muscularis mucosae, as shown in Figure 3.

CT scan of the thorax, abdomen, and pelvis did not reveal secondary involvement of lymph nodes, lungs, liver, or other organs. The patient underwent right hemicolectomy plus segmental enterectomy of the anastomotic region where the neoplasia was located. Histopathological examination of the surgical specimen confirmed a diagnosis of mucinous SBA with infiltration of muscularis propria and lymphatic and vascular invasion (postresection stage: pT3NxM0). Immunohistochemical analysis revealed expression of MLH1, MSH2, MSH6, and PMS2. After surgery, the patient started adjuvant chemotherapy with oxaliplatin, leucovorin, and fluorouracil. After 2 months, he is asymptomatic and follow-up CT reveals no evidence of recurrence.

Discussion

Over the past several decades, it has become increasingly recognized that SBA is a rare but well-known complication of CD. A recent meta-analysis that included 7,344 patients reported that, although the relative risk of SBA in patients with CD was increased 22-fold compared to the general population, the absolute cumulative risk was only 0.23% during a median follow-up of 12.55 years [2]. However, this cumulative risk is directly proportional to the disease duration, and other studies suggest that it increases to approximately 2.2% after 25 years of ileal CD and that SBA accounts for 25% and 45% of the risk of gastrointestinal carcinoma after 10 and 25 years of CD, respectively [6]. Similarly, a prospective observational study demonstrated that the incidence rate of SBA in patients with CD increases from 0.235/1,000 patient-years to 0.464/1,000 patient-years when only patients with >8 years of disease are considered [7].

Risk factors for SBA in patients with CD include extended duration of disease, distal jejunal and ileal location, stenosing or chronic fistulizing behavior, male gender, young age at diagnosis, and the presence of a bypassed small bowel segment [5, 8, 9]. In contrast, a case-control study suggests that small bowel resection and prolonged salicylate use may be protective against development of SBA in patients with CD [10]. Interestingly, the risk of SBA appears to be much higher in patients with isolated ileal involvement than in ileocolonic CD [11]. The risk also appears to be influenced by geographical factors, with a higher relative risk of developing SBA compared to the general population in North America, the United Kingdom, and Scandinavia [11].

Unfortunately, diagnosis of SBA in patients with CD can be quite challenging as clinical symptoms may mimic an acute exacerbation of the disease and imaging findings can be indistinguishable from benign strictures. As a result, most cases are found incidentally after surgical resection for benign indications, and it is diagnosed preoperatively in only 5% of patients [6]. In a recent retrospective study involving 22 patients with SBA associated with CD, only 2 had a preoperative diagnosis; even for the remaining, where cancer was unsuspected on preoperative assessment, only 25% were diagnosed intraoperatively, whereas 75% were unexpectedly diagnosed postoperatively on final pathology [12].

The most common clinical presentation is with obstructive symptoms, including nausea, vomiting, and abdominal pain. Less common clinical presentations include hemorrhage, fistula, or perforation [4]. Two important clinical indicators of malignancy include recrudescent symptoms after long periods of relative quiescence and small bowel obstruction that is refractory to medical therapy [13]. SBA associated with CD usually occurs after a median time of 15 years of CD and is usually diagnosed at a younger age than de novo SBA (median age 47 vs. 68 years, respectively). It is typically found within areas of inflammation of the ileum and jejunum, whereas de novo SBA is distributed all along the small intestine [6].

In general, imaging techniques may miss small lesions and may not be able to differentiate areas of SBA from those of severe CD [4]. Four imaging patterns in CT enterography were distinguished, including small bowel mass, long stenosis with heterogeneous submucosal layer, short and severe stenosis with proximal small bowel dilation or sacculated small bowel loop with irregular and asymmetric circumferential thickening. These findings are nonspecific and may be completely indistinguishable from a benign fibrotic or an acute inflammatory stricture [14]. Magnetic resonance enterography has the advantage of not exposing patients to ionizing radiation and appears to be a useful imaging test for the detection of SBA in patients with CD [15] and a cost-effective approach in patients younger than 50 years old [16].

Nevertheless, cross-sectional imaging does not allow direct visualization or tissue sampling. The small bowel has always been an organ difficult to access by endoscopic procedures. However, in recent years, there has been much development in endoscopic techniques like video capsule endoscopy or balloon/spiral-assisted enteroscopy, which has allowed significant improvement in both the detection and treatment of small bowel lesions [17].

The usefulness of video capsule endoscopy in this setting may be challenged by the stenosing nature of CD (both malignant and nonmalignant strictures) that may result in capsule retention and the inability to obtain tissue samples [18].

Therefore, balloon-assisted enteroscopy appears to be of great value in the evaluation of imaging abnormalities that raise concern for malignancy in small bowel CD. Although balloon-assisted enteroscopy may be limited by invasiveness and incomplete visualization of the small bowel, it presents the advantages of allowing direct visualization and tissue sampling at a low rate of adverse events [19]. In our case, refractory iron deficiency anemia and abnormal imaging findings on CT enterography prompted balloon-assisted enteroscopy, where SBA was discovered. There is another similar previously published case where a 48-year-old man with a 21-year history of CD had SBA diagnosed by PET/CT and double-balloon enteroscopy performed during diagnostic workup for liver metastasis [20], which suggests that more widespread use of balloon-assisted enteroscopy could lead to a more frequent diagnosis of SBA in earlier stages among patients with CD.

There are no formal recommendations on endoscopic screening for SBA in CD patients. In this regard, an exploratory multi-center prospective study involving a cohort of high-risk CD patients defined as long-term small bowel disease without bowel resection was performed and the prevalence of dysplasia and SBA was 4% [21]. Because of its low sensitivity, endoscopic screening cannot be currently recommended. Further studies defining subsets of CD patients at higher risk of SBA that could benefit from screening strategies are needed.

Although previous studies suggested that SBA associated with CD was associated with worse survival than de novo SBA [4], this is controversial. A recent retrospective study involving 2,668 patients with SBA did not find significant differences in overall survival between patients with and without CD [22]. These results are supported by another study involving 2,123 patients with SBA, where those associated with CD actually presented at an earlier stage and were more likely to undergo surgery than those with de novo SBA, although no significant differences in overall or cancer-specific survival were found [23]. In contrast, a study that compared SBA associated with celiac disease to SBA associated with CD found a significantly better overall survival in the former group [24]. Prognosis is closely related to disease stage as demonstrated in a retrospective study involving 29 patients with SBA associated with CD, where significant differences in the 2-year survival for node-negative versus node-positive carcinomas (79.3% vs. 49%) and for localized versus metastatic disease (92.3% vs. 33.3%) were reported, as expected [13].

The first-line treatment is wide resection of the small bowel segment harboring the cancer as well as resection of the corresponding mesentery and lymph nodes with right colectomy for lesions of the distal ileum [5]. When surgery is not feasible because of metastatic disease, combination chemotherapy consisting of 5-fluorouracil, leucovorin, and irinotecan with or without gemcitabine may result in prolonged survival, downstaging, and successful secondary complete resection with durable remission [25].

Conclusion

SBA is a rare complication of CD that poses diagnostic challenges. This case demonstrates that clinical presentation may be nonspecific and CT enterography may not be accurate enough to distinguish benign from malignant strictures. Clinicians must, therefore, maintain a high index of suspicion for this complication in patients with long-standing CD with ileal involvement. It is also important to emphasize the role of balloon-assisted enteroscopy, which allowed an early diagnosis. Since early diagnosis has been difficult, a low threshold to perform enteroscopy in high-risk patients, especially those with long-standing ileal CD with refractory or unexplained strictures, may be expected to result in improved diagnostic accuracy, increased detection rates at an earlier stage, and better overall survival.

Statement of Ethics

Written informed consent was obtained from the patient for publication of the case and related iconography.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

E.D., M.M.-S., H.C., and F.M. were involved in the diagnostic workup and conception and design of the work; E.D. and M.M.-S. wrote the manuscript; H.C., F.M., and G.M. performed a critical revision of the manuscript; F.M. followed the patient in gastroenterology consultation; H.C. performed double balloon enteroscopy; all authors read and approved the final version of the manuscript.

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Transvenous Obliteration Procedure in the Management of Parastomal Variceal Bleeding: A Case Report

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Keywords

Parastomal varices · Balloon-occluded retrograde transvenous obliteration · Transjugular intrahepatic portosystemic shunt

Abstract

Introduction: Parastomal variceal bleeding (PVB) is a recognized complication of ostomized patients in the presence of portal hypertension. However, since there are few reported cases, a therapeutic algorithm has not yet been established. ***Case Presentation:*** A 63-year-old man, who had undergone a definitive colostomy, recurrently presented to the emergency department hemorrhage of bright red blood from his colostomy bag, initially assumed to be caused by stoma trauma. Accordingly, temporary success on local approaches such as direct compression, silver nitrate application and suture ligation was achieved. However, bleeding recurred, requiring transfusion of red blood cell concentrate and hospitalization. The patient's evaluation showed chronic liver disease with massive collateral circulation, particularly at the colostomy site. After a PVB with associated hypovolemic shock, the patient was submitted to a balloon-occluded retrograde transvenous obliteration (BRTO) procedure which stopped the bleeding successfully. The patient was subsequently proposed for a transjugular intrahepatic portosystemic shunt (TIPS) conjugated with percutaneous transhepatic obliteration (PTO). After an initial refusal by the patient, a new episode of self-limited PVB resulted in execution of the procedure. Four months later, in a routine consultation, the patient presented with grade II hepatic encephalopathy, successfully treated with medical therapy. After a 9-month follow-up, he remained clinically well and without further episodes of PVB or other adverse effects. ***Discussion:*** This report highlights the importance of a high index of suspicion when dealing with significant stomal hemorrhage. Portal hypertension as an etiology of this entity may compel to a specific approach to prevent recurrence of bleeding, including conjugation of endovascular procedures. The authors present a case of PVB, initially submitted to a variety of treatment options including BRTO, which was successfully addressed with conjugated treatment of TIPS and PTO.

Obliteração transvenosa na abordagem da hemorragia de varizes periestoma: relato de caso

Palavras chave

Varizes peristomais · Obliteração transvenosa retrógrada ocluída por balão · Shunt portossistémico transjugular intra-hepático

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Resumo

Introdução: A hemorragia de varizes periestomais é uma complicação conhecida de doentes ostomizados com hipertensão portal. Contudo, devido ao pequeno número de casos descritos, ainda não foi estabelecido um algoritmo terapêutico. ***Apresentação do caso:*** Homem, 63 anos, com antecedentes de colostomia definitiva, recorre ao Serviço de Urgência recorrentemente por sangue vivo no saco de colostomia. Inicialmente, presumindo-se trauma do estoma, foi submetido a tratamentos locais, como compressão, aplicação de nitrato de prata e sutura, com sucesso temporário. Contudo, houve recorrência da hemorragia, com necessidade de suporte transfusional e hospitalização. A avaliação do doente evidenciou doença hepática crónica com circulação colateral exuberante, predominantemente junto da colostomia. Devido a hemorragia com choque hipovolémico, foi submetido a obliteração transvenosa retrógrada ocluída por balão (BRTO). Posteriormente, foi proposto para shunt portossistémico transjugular intra-hepático (TIPS) conjugado com obliteração transhepática percutânea (PTO). Após recusa inicial do doente, ocorreu novo episódio de hemorragia autolimitado, tendo o doente concordado em realizar o procedimento. Quatro meses depois, em consulta, apresentava sinais de encefalopatia hepática grau II, tendo sido controlada eficazmente com tratamento médico. Após nove meses de seguimento, mantém-se sem novos episódios de hemorragia ou efeitos adversos dos procedimentos. ***Discussão:*** É necessário um alto índice de suspeição clínica ao abordar a hemorragia significativa do estoma. A hipertensão portal como etiologia exige uma abordagem específica para prevenir a recorrência da hemorragia, incluindo a conjugação de procedimentos endovasculares. Os autores apresentam o caso de um doente com hemorragia de varizes periestomais submetido inicialmente a vários tratamentos, incluindo BRTO e que foi tratado com sucesso com TIPS e PTO.

Introduction

Varices are abnormally large portosystemic venous collaterals most commonly recognized near the gastroesophageal junction. Varices that appear in other gastrointestinal locations are called ectopic. Although unusual, they can account for up to 5% of all variceal hemorrhages [1].

Parastomal varices (PV) usually occur in ostomized patients with chronic liver disease (CLD) and emerge at the mucocutaneous junction of the stoma. PV develop due to a portosystemic shunt between the portal circulation of the bowel and systemic circulation of the abdominal wall. There are no pathognomonic physical symptoms or signs of PV. A raspberry appearance of the stoma with visibly dilated submucosal veins and bluish discoloration and hyperkeratosis of the surrounding skin have been used to describe PV [2].

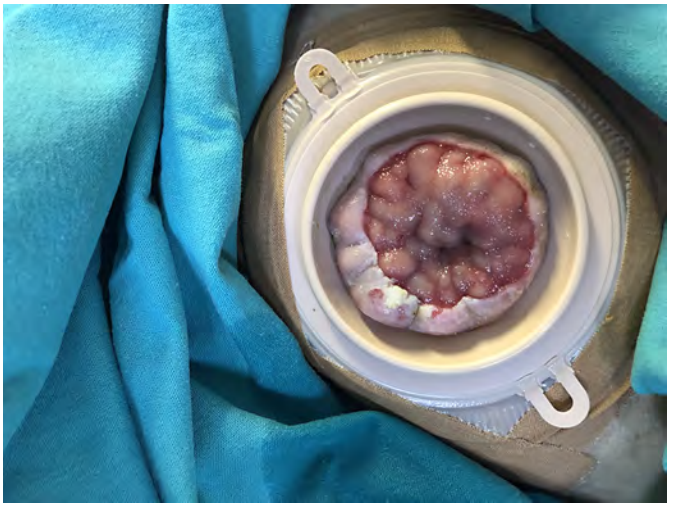

Fig. 1. Colostomy stoma, with visibly dilated submucosal veins and keratosis of the colon mucosa around it.

Doppler ultrasound, computed tomography (CT) and magnetic resonance angiography may identify varices in the region of the stoma and facilitate the diagnosis of CLD, portal hypertension and the assessment of portal patency [3].

Parastomal variceal bleeding (PVB) tends to present as chronic and recurrent rather than massive bleeding, although the need for a blood transfusion is expected in 42.9% [4]. The mortality rate of PVB is estimated at around 3–4% [2, 3]. Despite the low mortality rate, given its insidious but recurring nature, greater awareness and an established therapeutic strategy will certainly be useful.

Case Presentation

A 63-year-old man presented to the emergency department several times throughout 1 year with self-limited bright red blood in his colostomy bag. The patient had undergone abdominoperineal resection (with permanent colostomy) due to rectal carcinoma 4 years earlier. Initially, stoma bleeding due to local trauma was presumed. In the majority of those episodes, no bleeding source

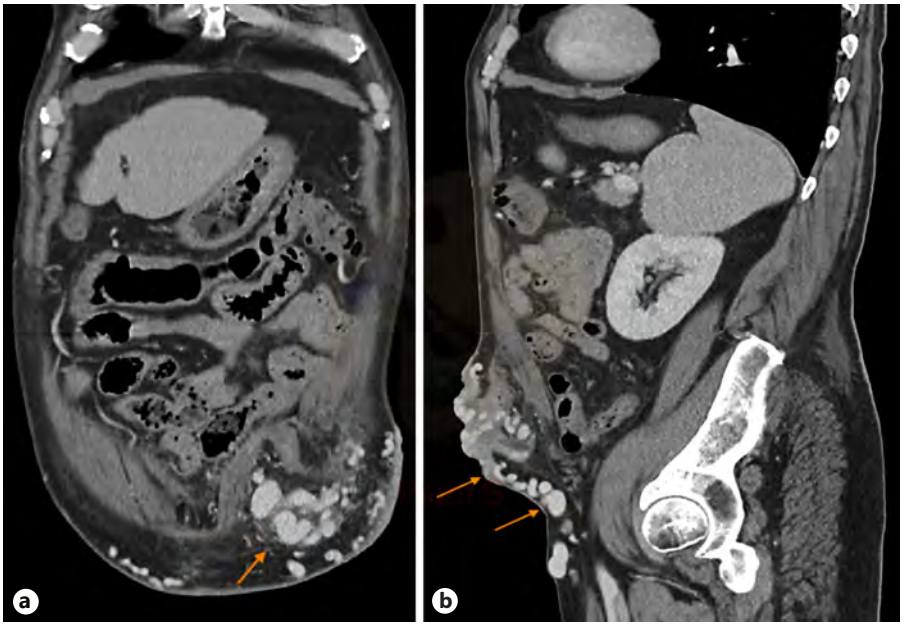

Fig. 2. Intravenous contrast-enhanced CT coronal (**a**) and sagittal (**b**) images of the abdomen with multiple varices (arrows) within the left lower quadrant stoma.

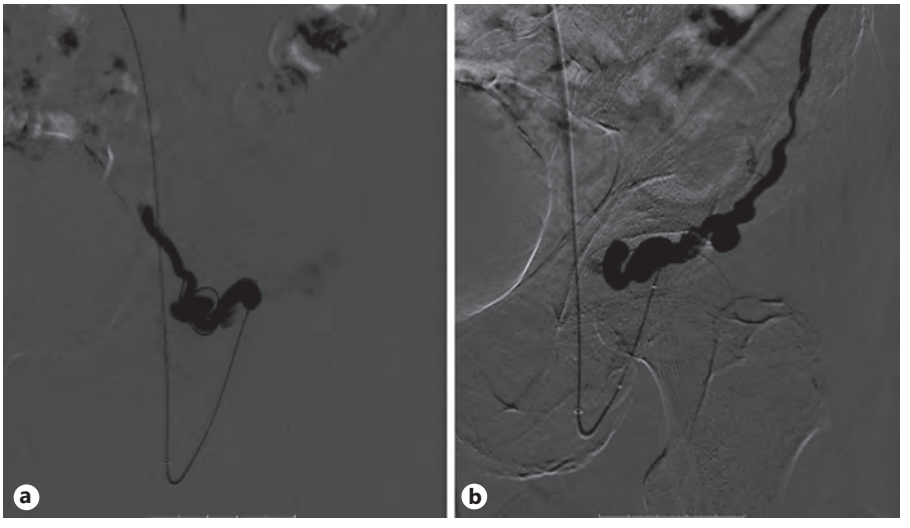

Fig. 3. Retrograde transvenous venogram from the systemic venous side of the system showing multiple parastomal systemic draining veins coursing along the medial (**a**) and lateral (**b**) aspect of the stoma.

was identified and the patient was discharged with the indication to perform a colonoscopy in an outpatient setting. On 2 occasions, a stoma bleeding site was identified and local approaches including direct compression, silver nitrate application and suture ligation were applied with transient success. However, recurrence of hemorrhage ensued, requiring inpatient admission for transfusion and additional evaluation. Physical examination evidenced stigmata of CLD and alcoholism, pallor and a raspberry appearance of the stoma with dilated submucosal veins (Fig. 1). Initial laboratory analysis revealed hemoglobin of 6.8 g/dL, platelets 53,000/mm^3 and liver function tests compatible with CLD (Child-Pugh B, MELD-Na 16). Upper endoscopy and colonoscopy were normal.

An abdominal CT showed features suggestive of cirrhosis and collateral venous circulation originating from the inferior mesenteric vein, insinuating itself in the neck of the stoma. A peristomal varicose conglomerate was observed in the thickness of the abdominal wall, giving rise to multiple varicose veins. Many of the varices were converging in the stoma, and others were running through the thickness of the lower abdominal wall, draining distally into the left common femoral vein (LCFV) (Fig. 2). The portal vein was patent.

Due to an episode of acute spurting bleeding with hypovolemic shock during hospital admission, the patient was initiated on terlipressin and agreed to be submitted to a balloon-occluded retrograde transvenous obliteration (BRTO) procedure. Through the right femoral approach, a balloon catheter was placed at the portosystemic shunt drainage site in the LCFV. A 6-F guiding sheath at the left external iliac vein was used for extra catheter support. After balloon inflation, a retrograde transvenous venogram from the systemic venous side of the system was performed, demonstrating multiple parastomal systemic draining veins (Fig. 3). A 2.7 F × 130 cm Progreat microcatheter (Terumo, Tokyo, Japan) was

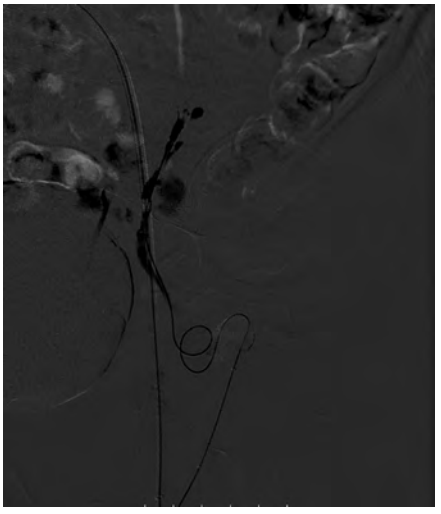

Fig. 4. Phlebography after distal catheterization of the varicose plexus using a microcatheter.

used for distal (rather proximal from a blood flow standpoint) selective catheterization of these efferent systemic draining veins (Fig. 4). N-butyl-2-cyanoacrylate embolization of PV was performed (Fig. 5). Postembolization control evaluation revealed exclusion of varicose drainage in the LCFV. The procedure proceeded uneventfully, with bleeding resolution.

The case was subsequently discussed in a multidisciplinary team meeting. Considering the preeminence of PV, with multiple portosystemic shunts, it was concluded that local obliteration of the remaining collaterals assisted by endoscopic ultrasound alone was not feasible. The patient was then proposed for a transjugular intrahepatic portosystemic shunt (TIPS) conjugated with percutaneous transhepatic obliteration (PTO).

Fearing possible complications, such as the development of hepatic encephalopathy (HE), the patient refused the procedure at first. Nevertheless, 7 days after BRTO, following terlipressin suspension and initiation of propranolol, the patient experienced a new episode of self-limited PVB and agreed to undergo the proposed treatment. Through the right internal jugular vein access, the right suprahepatic vein was selected and shunted with the right

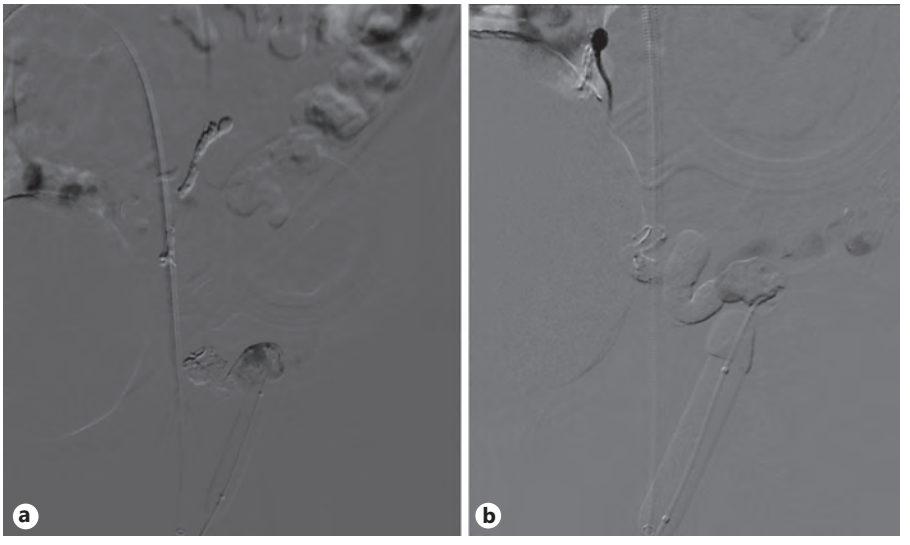

Fig. 5. a Venogram taken near the end of the "BRTO approach", after glue embolization. **b** Final venogram showing exclusion of varicose drainage into the left femoral vein.

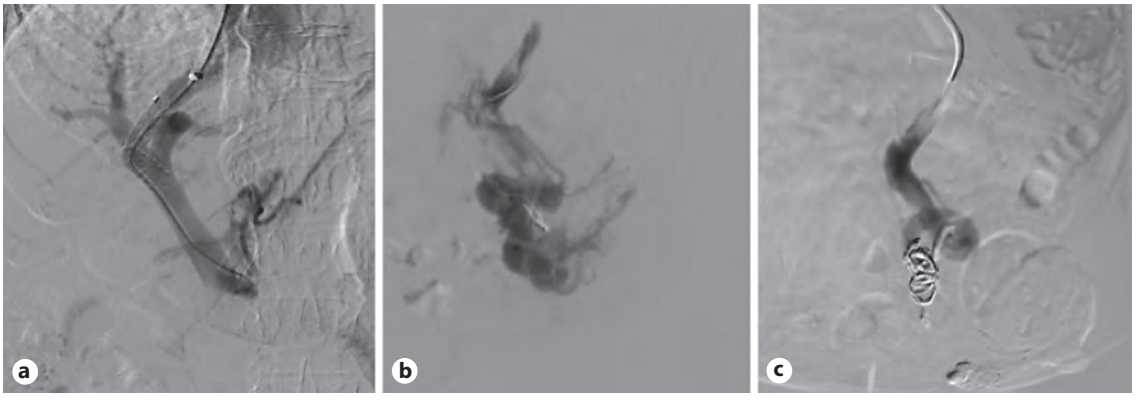

Fig. 6. a Transhepatic approach after TIPS prosthesis has been placed. **b** Stoma varicose plexus being selected. **c** Embolization of the main varix with coils.

branch of the portal vein. Upon tract balloon dilation, an 8–10 mm × 5 cm Viatorr TIPS prosthesis (W.L. Gore, Flagstaff, AZ, USA) was placed, resulting in a hepatic-venous pressure gradient (HVPG) reduction from 20 to 14 mm Hg. After selective catheterization of the inferior mesenteric vein, an anterograde transvenous venogram was performed, demonstrating multiple pericolostomy varicose veins. In phlebographic control, the pericolostomy varicose plexus was selected, with embolization of the main varix with coils (Fig. 6). The procedure proceeded uneventfully.

Four months after the procedure, the patient presented with grade II HE in a routine hepatology consultation. Nevertheless, it was successfully managed with medical therapy (lactulose and rifaximin).

After a 9-month follow-up, the patient has remained well without further episodes of PVB or other adverse effects.

Discussion

Significant parastomal bleeding must raise suspicion of portal hypertension and underlying CLD, which have to be actively excluded. The management of PVB should involve a multidisciplinary approach (with hepatologists, interventional radiologists and surgeons), with a progressive escalade in more invasive methods when local procedures are not effective. Concomitant treatment of CLD should be carried out, particularly removing the etiological factor(s) causing liver injury whenever possible [3, 4].

Simple local procedures, such as pressure dressings, epinephrine-soaked gauze, gel foam, and suture ligation have been used with success on the initial bleeding episode. However, bleeding recurrence is the rule [2–4].

Some treatments have shown considerable morbidity and/or recurrence, not being valuable options in the management of this pathology. These include sclerotherapy, which resulted in stomal damage and/or recurrent bleeding in nearly all patients [5]. Mucocutaneous disconnection and surgical relocation of the stoma were also associated with recurrent bleeding and significant perioperative surgical risk [6].

From a pathophysiological point of view, pharmacotherapy used in gastroesophageal varices management may be applied in patients with PVB by reducing HVPG [7]. However, data on the role of medical therapy in PVB is scarce. β-Blockers have presented conflicting results: older studies showed that they are not effective in PVB [4], while a few recent clinical reports showed they may delay their recurrence [8]. In 2 patients with contraindications for intravascular procedures, octreotide showed to be effective as a palliative care option, without significant side effects, suggesting it can be considered for patients for whom noninterventional care is indicated [9].

Minimally invasive endovascular techniques guided by ultrasound or CT have been safely used in the management of PVB. The simplest and least invasive procedure is direct ultrasound-guided percutaneous embolization with cyanoacrylate or coils. Nevertheless, this technique showed better results when a single dominant varix is identified and has an increased risk of embolization glue migration and mucosal damage at the stomal site. A proposed way to minimize glue migration is to combine this modality with ultrasound-guided systemic venous compression [10, 11].

The BRTO approach from the systemic venous side and PTO approach from the portal venous side are other endovascular techniques angiography-guided, which have been proving to be effective and safe. The main limitation to these procedures is long-term recurrence due to failure to embolize all feeding vessels, or due to the rapid development of new vessels [11–14].

Although embolization guided by endoscopic ultrasound has been tested successfully in PVB [15], minimal length necessity of intubation (which would make maintaining the endoscope position difficult) and the easier percutaneous approach make this modality unattractive [16].

Hypothetically, surgical portosystemic shunt can be considered as a decompressive measure [4]. However, given the increased morbidity, lower efficacy and inadequacy in transplant candidates, TIPS is clearly a preferred option. TIPS is by far the best-studied modality for managing PVB, as it ultimately reduces HVPG. Some limitations of TIPS are its contraindication in liver neoplasia and the risk of developing HE in advanced CLD (although it can usually be managed with medical treatment, as occurred in our patient). Moreover, even though it appears to be the most effective treatment modality, up to 25% of patients develop rebleeding. Although the common understanding has been that varices rarely bleed at HVPG less than 12 mm Hg, there were several cases of rebleeding by PV after TIPS despite lower HVPG [17, 18]. This statement highlights the importance of other coadjuvant treatments such as BRTO or PTO, particularly in cases with higher HVPG, as was the case in our patient. These two modalities can be performed following bleeding recurrence after TIPS, when TIPS is contraindicated or, as in this case, to complement TIPS before and during this procedure.

Statement of Ethics

The project was subjected to the standards of good clinical practice and always complied with the ethical precepts of the Helsinki Declaration. Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

J. Estorninho: literature research, manuscript preparation and drafting; P. Patrão: manuscript preparation and drafting; M.J. Temido: manuscript preparation; D. Perdigoto: critical revision; P. Figueiredo and P. Donato: manuscript final approval.

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Endoscopic Snapshot

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Sodium-Polystyrene Sulfonate-Induced Colitis

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Keywords
Sodium polystyrene sulfonate · Diarrhea · Colitis

Colite secundária à poliestirenossulfonato de sódio

Palavras Chave
Poliestirenossulfonato de sódio · Diarreia · Colite

A 77-year-old woman was admitted to the hospital because of abdominal distension and vomiting. Laboratory workup showed acute kidney injury with serum creatinine of 3.5 mg/dL and potassium of 5.7 mmol/L. Intravenous hydration, antibiotics, and symptomatic medication were started. Sodium polystyrene sulfonate (SPS) 15 g twice daily was used to treat hyperkalemia. After 48 h, serum potassium decreased to 3.7 mmol/L, and creatinine to 1.8 md/dL. On day 4 of admission she developed watery diarrhea, initially managed with probiotics and dietary modification. Infectious workup was negative for *Clostridioides difficile*, parasites, and *Cytomegalovirus*. Colonoscopy revealed edema, enanthema, and erosion into the sigmoid colon (Fig. 1). Biopsy showed typical fish scale-like SPS crystals (Fig. 2). SPS administration was discontinued, and the patient's condition progressively improved until resolution.

The use of SPS (or Kayexalate) to treat hyperkalemia dates back to the 1960s. Common side effects include constipation, bloating, nausea, and vomiting. Patients with previous kidney damage account for more than 70% of those who develop side effects, which often occur after 2 days of SPS administration. SPS-induced colitis is rarely detected by colonoscopy. Biopsy shows necrosis, ulceration, and SPS crystal deposition in more than 90% of samples. These features can distinguish SPS-induced necrosis from ischemic necrosis. A definitive diagnosis requires excluding conditions that mimic SPS-induced colitis, such as neoplasms, inflammatory bowel disease, microscopic colitis, *C. difficile* infection, and infectious colitis.

The first cases of SPS-associated ulceration and colonic necrosis were reported by Lillemoe et al. [1] in 1987. In 2013, a systematic review identified 58 cases of serious adverse reactions to SPS use. Colonic necrosis

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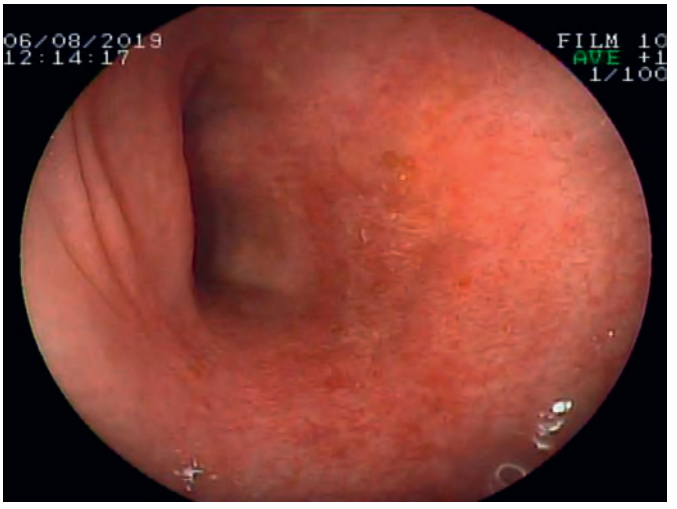

Fig. 1. Sigmoid colon, colonoscopy. Colitis: edema, enanthema, and mucosal erosion.

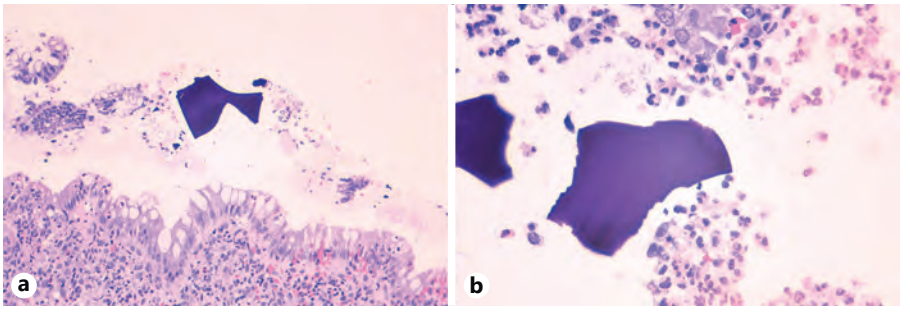

Fig. 2. Sigmoid colon, biopsy. **a** Mucosal injury with intraepithelial neutrophils (HE ×200). **b** Polystyrene crystals displaying a fish-scale appearance (HE ×600).

was the most severe complication, resulting in a mortality rate of 33% [2]. Nevertheless, a recent systematic review and meta-analysis showed that, although there was a statistically significantly increased risk for the composite outcome of severe gastrointestinal side effects based on 2 studies, there was no definite association of SPS use with intestinal necrosis [3]. In rats, SPS enema was associated with colonic necrosis and a high mortality rate [4]. Because intestinal necrosis is a life-threatening condition, caution should be exercised before prescribing SPS in patients at risk for complications [5]. Currently, there is no specific treatment for SPS-induced colitis, and medication withdrawal often results in symptom improvement.

In conclusion, SPS-induced colitis is a rare cause of diarrhea in the hospital setting. It should be suspected especially in patients with previous kidney damage who have received treatment for hyperkalemia.

Statement of Ethics

The family of the deceased patient verbally agreed to the reporting of the case.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

None.

Author Contributions

All authors equally contributed to writing and reviewing the paper.

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Solitary Peutz-Jeghers Type Hamartomatous Polyp Arising from the Appendix

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Keywords
Appendix · Hamartoma · Endoscopy

Pólipo hamartomatoso solitário do tipo Peutz-Jeghers com crescimento intra-apendiceal

Palavras Chrave
Apêndice, Pólipo Hamartomatoso, Endoscopia

Digestive hamartomatous polyps may be solitary or multiple, the latter often associated with genetic predisposition [1, 2]. Solitary Peutz-Jeghers (PJ)-type hamartomatous polyps represent a rare and distinct entity from the classic PJ syndrome, an autosomal dominant genetic disorder characterized by the development of multiple polyps in the gastrointestinal (GI) tract in association with patches of hyperpigmentation in the mouth, hands and feet [1, 3]. It is important to distinguish these two entities since the latter is associated with a lifetime cumulative risk of up to 93% for development of malignancies (such as colorectal, breast, small bowel, gastric and pancreatic cancers), but the first seems benign in its course. Solitary PJ polyps are diagnosed in patients with an isolated hamartomatous polyp of the GI tract, no familiar history of polyposis and no typical phenotype [3].

An 80-year-old man with a history of sigmoidectomy due to an obstructive T2N0M0 colorectal cancer underwent a surveillance thoracoabdominopelvic CT scan showing a voluminous endoluminal polyp at the caecum (Fig. 1). He was referred to our reference centre for colonoscopy. A 4-cm diameter pedunculated and congestive polyp was identified with a short and thick stalk arising from the appendiceal orifice. We proceeded to its en bloc resection using a 25-mm oval diathermic snare after stalk injection with diluted adrenaline 1:10,000, normal saline and methylene blue with polyp recovery for histology (Fig. 2a–c, 3a). The polyp was confirmed to be a hamartomatous polyp of the PJ type (R0 resection) with arborizing pattern of vascularized smooth-muscle tissue axes covered by elongated veliform crypts and occasional intraluminal necrosis with no dysplasia (Fig. 3b). The patient had no typical manifestations of PJ syndrome or family history. His follow-up showed no complications related to the procedure, including bleeding or acute appendicitis (prophylactic antibiotic was not used).

Solitary PJ-type hamartomatous polyps of the GI tract are rare, and appendiceal location is even rarer. Accord-

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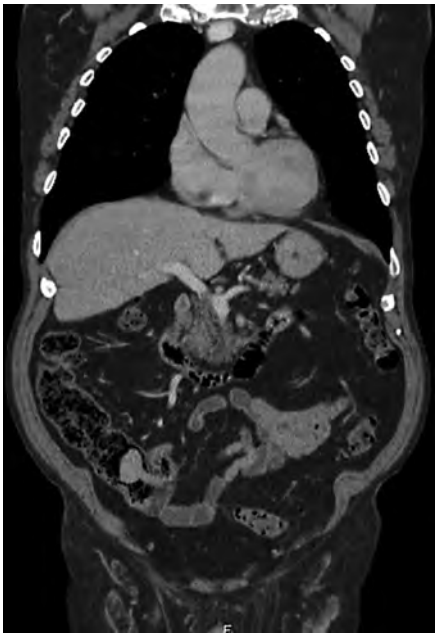

Fig. 1. Thoracoabdominopelvic CT scan (coronal section) with intravenous contrast showing a voluminous endoluminal polyp at the caecum measuring 40 × 31 mm with homogeneous enhancing. No alterations at surgical anastomosis level.

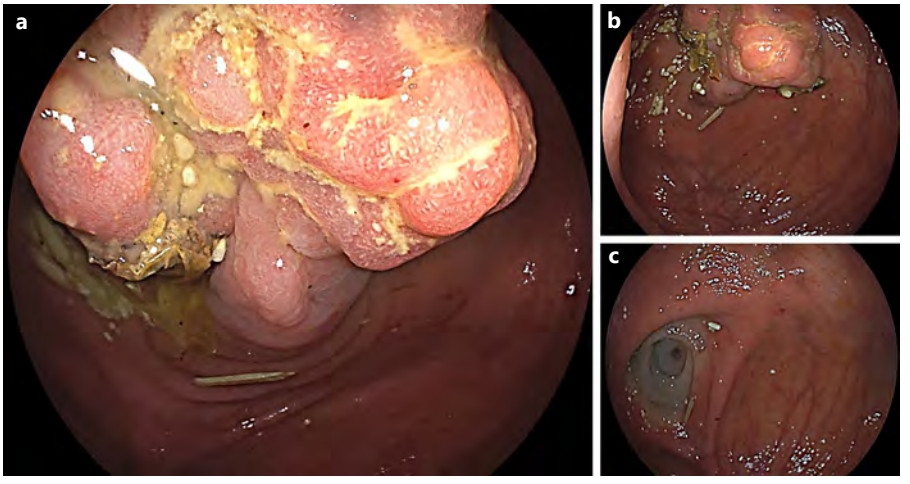

Fig. 2. a, **b** Colonoscopy performed showing a 4-cm diameter pedunculated and congestive polyp with a short and thick stalk arising from the appendiceal orifice. **c** En bloc endoscopic resection was performed using a diathermic snare after stalk injection with diluted adrenaline 1:10,000, normal saline and methylene blue with no complications.

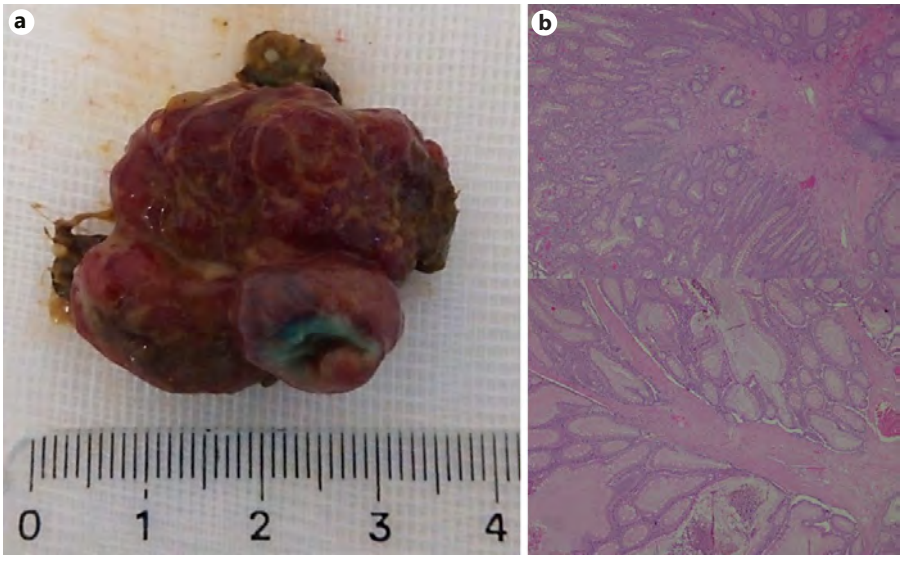

Fig. 3. a Macroscopic specimen of endoscopic resection. **b** Histopathological analysis revealed a hamartomatous polyp of Peutz-Jeghers-type with arborizing pattern of vascularized smooth-muscle tissue axes covered by elongated crypts with veliform pattern and occasional intraluminal necrosis with no dysplasia (R0 resection).

ing to the largest case study to date on the follow-up of solitary PJ polyps, they are normally large in size (>15 mm), mostly pedunculated and localized primarily in the colon (even though they have been described in all of the GI tract, except in the oesophagus) [3]. During a mean endoscopic follow-up of 4.5 years (range: 0.1–16.1 years) after excision, no recurrence was observed, making endoscopic follow-up after diagnosis of a PJ polyp unnecessary [3]. Although malignant transformation seems rare, extensive genetic and epigenetic changes have been de-

scribed in this type of polyps that may contribute to cancer risk [4]. Adding to the risk of other complications related to intraluminal polyp growth (colonic obstruction, intussusception, appendicitis or GI bleeding), and since endoscopic resection allows for a histological diagnosis, polypectomy is always advisable [2, 5]. This case highlights the importance of recognizing the existence of solitary PJ polyps as a distinct entity from PJ syndrome, with drastic consequences of misdiagnosis in terms of follow-up and prognosis. Additionally, the appendiceal location of these polyps is rare and represents a very technically challenging location for endoscopic therapy.

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Statement of Ethics

The subject of this clinical case has given us an oral consent to publish his case, including the publication of images. All information about the identity of the subject has been removed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Author Contributions

The first 4 authors participated in the endoscopic resection and have written/revised the paper. Pedro Narra Figueiredo is the head director of the Gastrenterology Department in which this case was reported and also revised the paper.

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Anorectal Endoscopic Hybrid Resection of an Uncommon Cause of Debilitating Diarrhoea: Polypoid Supra-Anal Mucosal Prolapse Syndrome

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Keywords
Colonoscopy · Chronic diarrhoea · Mucosal prolapse syndrome · Endoscopic resection · Endoscopic submucosal dissection

Resseção endoscópica híbrida ano-rectal de uma causa rara de diarreia debilitante: síndroma de prolapso mucoso polipóide supra-anal

Palavras Chave
Colonoscopia · Diarreia crónica · Síndroma de prolapso mucoso · Resseção endoscópica · Disseção endoscópica da submucosa

Endoscopic resection of supra-anal lesions is challenging due to marked fibrosis and generous venous plexus [1]. Furthermore, abundance of sensory nerve fibres in the anal canal calls for an adequate local anaesthesia otherwise not warranted in endoscopy [2]. This is the case of a 54-year-old male patient with a 2-year history of debilitating diarrhoea including inability to work (sic!), passing up to 25 watery stools with urgency. Prior gastroenterology consultations elsewhere including previous ileocolonoscopy did not indicate the cause of diarrhoea.

Currently, the patient was scheduled for endoscopic resection of an estimated 15-mm, biopsy-confirmed mucosal prolapse polyp in the supra-anal rectum involving the dentate line. The retroflexed endoscopic visualization revealed a reddened polypoid lesion with an eroded surface, consistent with mucosal prolapse syndrome (Fig. 1a). For resection, a cap-fitted, antegrade endoscopic approach was chosen to first isolate the lesion from the squamous epithelium of the anal canal, which indeed was cut into in its proximal aspects after injection of an indigocarmine saline mixture without adrenaline and a local anaesthetic (Fig. 1b). To this end, limited endoscopic submucosal dissection using a Dual Knife J (Olympus, Hamburg, Germany) was performed under deep sedation using propofol and midazolam to ensure wide-margin resection at the anal side with diarrhoea most likely attributable to chronic sphincter irritation (Fig. 1c; note marked fibrosis and prominent vessels). Only after progression to the more oral rectum did the submucosal space begin to open up adequately (Fig. 1d). To accelerate the procedure and with a view to the benign histology, we subsequently opted for a hybrid approach ensnaring the lesion (30-mm snare; Medwork, Höchstadt, Germany) after adequate trimming of the anal parts of the lesion (Fig. 1e). The final resection bed was without bleeding;

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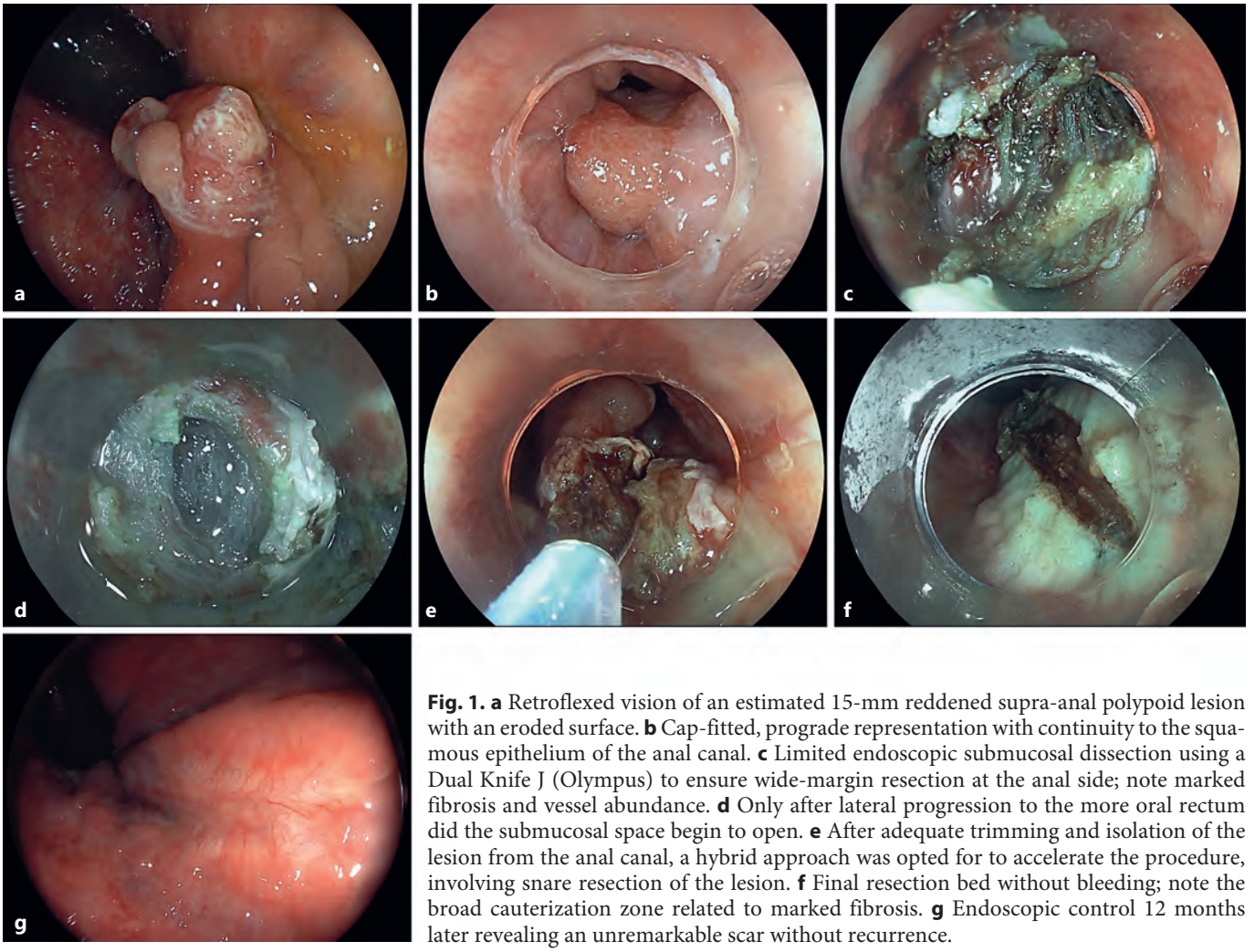

Fig. 1. a Retroflexed vision of an estimated 15-mm reddened supra-anal polypoid lesion with an eroded surface. **b** Cap-fitted, prograde representation with continuity to the squamous epithelium of the anal canal. **c** Limited endoscopic submucosal dissection using a Dual Knife J (Olympus) to ensure wide-margin resection at the anal side; note marked fibrosis and vessel abundance. **d** Only after lateral progression to the more oral rectum did the submucosal space begin to open. **e** After adequate trimming and isolation of the lesion from the anal canal, a hybrid approach was opted for to accelerate the procedure, involving snare resection of the lesion. **f** Final resection bed without bleeding; note the broad cauterization zone related to marked fibrosis. **g** Endoscopic control 12 months later revealing an unremarkable scar without recurrence.

note the broad cauterization zone related to marked fibrosis (Fig. 1f). The postinterventional course under a 3-day ibuprofen regimen was uncomplicated without pain and/or bleeding complications. The final histology of the 30 × 20 mm specimen described a mucosal prolapse polyp with formation of an inflammatory cloacogenic polyp with a serrated architecture. Dysplasia and/or (anal) intraepithelial neoplasia was excluded.

Of note, diarrhoea ceased immediately and persistently with complete normalization of stool habits, and the patient was able to resume work. An endoscopic control 12 months later revealed an unremarkable resection scar without evidence for recurrence (Fig. 1g).

Mucosal prolapse syndrome as a rare category of colorectal polyps, oftentimes presenting as polypoid supra-anal lesions, if symptomatic warranting endoscopic resection [3, 4]. Indeed, some reports have been published in which such lesions proved difficult to distinguish from malignancy [5]. Of clinical note, endoscopic resection resulted in rapid and complete normalization of stool habits in this patient with chronic debilitating diarrhoea, which has only occasionally been reported in the literature [6, 7]. Apart from endoscopic submucosal dissection in this technically demanding anatomical region, recent data suggest a similar clinical effectiveness of endoscopic mucosal resection techniques in this setting [8].

Statement of Ethics

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

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Author Contributions

V.Z.: clinical care, drafting and finalization of paper; C.H.: pathology care, critical revision and final approval.

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Images in Gastroenterology and Hepatology

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SX-ELLA Danis-Stent for Refractory Acute Esophageal Variceal Bleeding

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Keywords
Danis-stent · Upper gastrointestinal bleeding · Esophageal varices

Prótese Danis na hemorragia aguda refratária de varizes esofágicas

Palavras Chave
Prótese Danis · Hemorragia digestiva alta · Varizes esofágicas

The authors describe a 78-year-old male with alcoholic liver cirrhosis (Child-Pugh score 9 points, Meld-Na 16 points, without active drinking habits for several years). The patient had clinically significant portal hypertension manifested as refractory ascites managed with repeated large volume paracentesis and five bleeding episodes from esophageal varices. During these bleeding events the patient was treated with multiple sessions of band ligation and sclerotherapy. Two days after being discharged from the hospital due to the last bleeding episode he was readmitted due to hematemesis with hypotension and anemia. After clinical stabilization and blood transfusion to reach safe hemoglobin levels (hemoglobin at admission: Hb 6.7 g/dL), upper GI endoscopy was performed, showing in the distal third of the esophagus (37 cm from the incisors), an esophageal varix with cherry-red spots and a white nipple sign suggestive of a rupture point (Fig. 1a). Band ligation was initially tried, which was not successful due to marked fibrosis that prevented the cord to enter in the cap for banding. A massive variceal bleeding developed causing loss of endoscopic view and an SX-ELLA Danis-stent (25 × 135 mm, fully covered) was placed under guidewire with immediate technical and clinical success (Fig. 1b). The proximal limit of SX-ELLA Danis-stent was located at 29 cm of the incisors. The patient progressed favorably with no evidence of further blood loss and ICU admission was not needed. Given the several episodes of variceal bleeding despite endoscopic therapy and refractory ascites, 7 days after the index procedure a Transhepatic Portosystemic Shunt (TIPS) VIATORR® endoprosthesis with 7 mm was placed without complications reaching a

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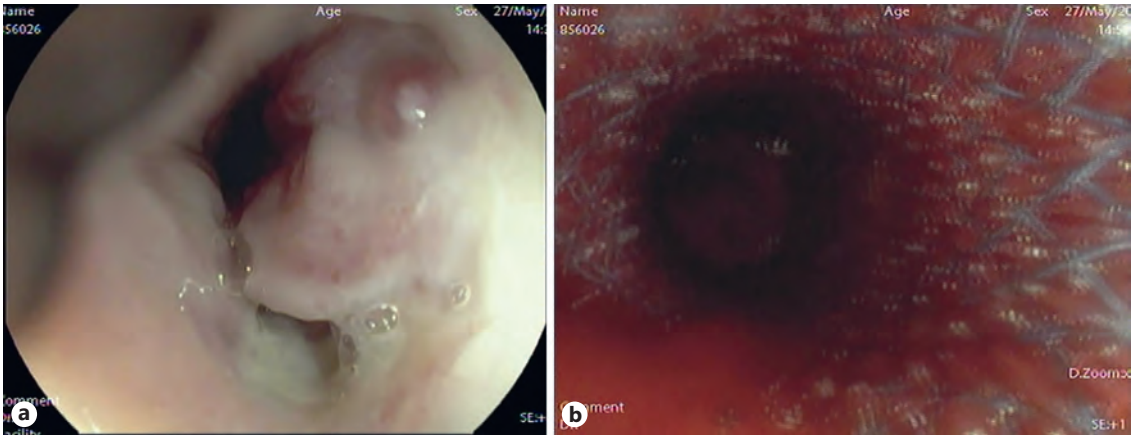

Fig. 1. EGD showing an esophageal varix cord with a nipple sign compatible with a rupture point (**a**). Massive bleeding after unsuccessful band ligation managed with the placement of an SX-ELLA Danis-stent (**b**).

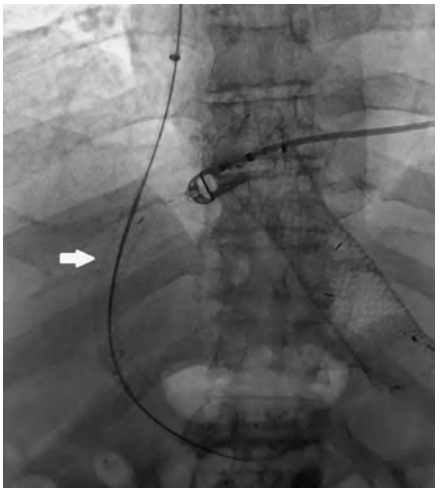

Fig. 2. TIPS was placed without immediate complications. VIATORR endoprosthesis with 8–10 mm was used. TIPS (white arrow) and SX-ELLA Danis-stent seen on X-ray.

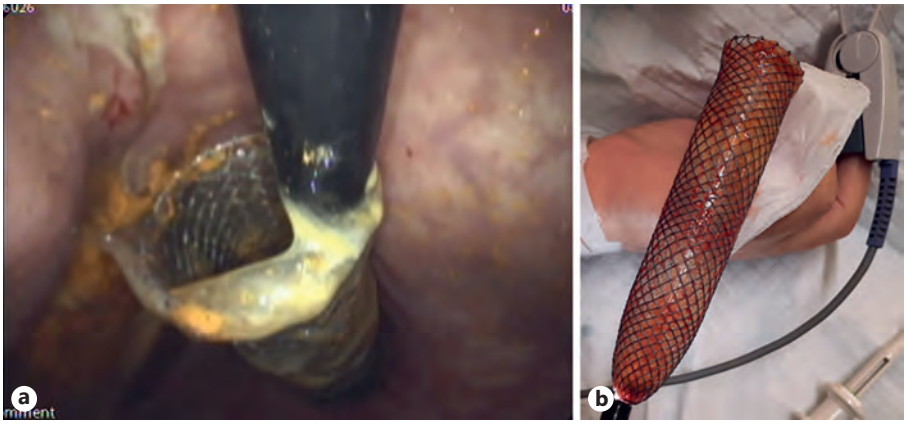

Fig. 3. SX-ELLA Danis-stent seen endoscopically in retroflexion (**a**). The stent was removed using a foreign body forceps without complications (**b**).

hepatic venous pressure gradient of 11 mm Hg (from an initial 22 mm Hg) (Fig. 2). The Danis-stent was endoscopically removed using a foreign body forceps 11 days after its placement (Fig. 3). A marked reduction in the size of the esophageal varices and a whitish scarry area in the distal esophagus coincident with the previous rupture point were observed (Fig. 4). Clinical evolution was favorable with no further bleeding recurrence or hepatic encephalopathy and partial improvement of ascites. The patient was discharged and maintained follow-up on hepatology outpatient clinic.

Discussion

Portal hypertension is the hemodynamic abnormality associated with the most severe complications of liver cirrhosis, including ascites, hepatic encephalopathy, and bleeding from gastroesophageal varices. Variceal bleeding is a medical emergency associated with a mortality of 10–20% in 6 weeks [1].

The combination of vasoactive drugs and endoscopic therapy (preferably esophageal band ligation) are recommended as the main therapeutic modality for bleeding

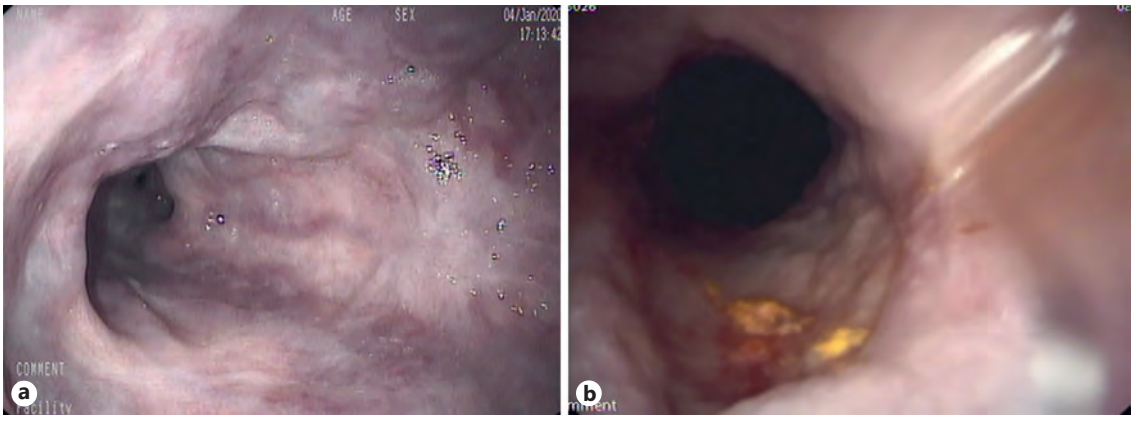

Fig. 4. EGD after stent removal showing an important reduction in esophageal varix size (**a**). On the distal esophagus a whitish scarry area, in relation with the previous rupture point, was also seen (**b**).

esophageal varices; however, it can be challenging in the presence of massive bleeding. In this scenario, as expressed in AASLD and EASL recommendations, fully covered self-expandable metallic stents and Sengstaken-Blakemore tubes (SBT) are viable options, recommended as bridge to a definitive therapy [1–3].

SBT are the most widely used, providing bleeding controls of 90%. However, it should only be used under intensive care facilities due to the high risk of severe and life-threatening complications. Dedicated fully covered self-expandable metallic stents (like SX-ELLA Danis-stent) have also been used in this setting, achieving an higher rate of bleeding control with a lower incidence of severe complications [4, 5]. In this clinical case the authors exemplify the use of an SX-ELLA Danis-stent as bridge for TIPS placement in a patient with massive variceal bleeding refractory to band ligation.

From the authors' point of view, SX-ELLA Danis-stents should generally be favored over SBT placement due to its higher efficacy, less potential complications, and the fact that it can be used by endoscopists in a urgent setting even by those without experience in fluoroscopy. Also, as Danis-stent allows an immediate control of variceal bleeding, it will reduce the time needed for airway protection and ICU admission. Nevertheless, all emergency physicians should be able do use SBT and therefore it will retain its role in a facility without gastroenterology support and in all cases of uncontrolled bleeding from gastric varices where Danis-stent placement would not be effective.

Statement of Ethics

The authors declare that all ethical procedures were followed. The patient signed written consent, allowing use and divulgation of clinical information and images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare. Moreover, they are aware that the manuscript's copyright belongs to *GE – Portuguese Journal of Gastroenterology*.

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No funding resources were used in the elaboration of the article.

Author Contributions

Gonçalo Nunes – patient evaluation, clinical data collection and performed the endoscopic procedure; Marta Patita – patient evaluation and clinical data collection; Élia Coimbra – performed the TIPS placement and gave these figures for publication; Pedro Currais – manuscript draft; Gonçalo Nunes and Jorge Fonseca – critical review of the manuscript.

Data Availability Statement

All the data and exams related to this clinical case are available on Hospital Garcia de Orta informatic system.

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An Unusual Endoscopic Finding of Gastric Crohn's Disease

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Keywords
Crohn's disease · Stomach · Bariatric surgery

Doença de Crohn gástrica – um achado endoscópico pouco comum

Palavras Chave
Doença de Crohn · Estômago · Cirurgia bariátrica

A 37-year-old woman with a past medical history of obesity (body mass index 50 kg/m^2) and Crohn's disease (Montreal classification – A2 L2+L4 B1) was referred to our institution for bariatric surgery after several unsuccessful weight loss attempts. The diagnosis of Crohn's disease was established at age 19 (Fig. 1) and at that time she started therapy with azathioprine and a prednisolone taper. Due to poor control of the disease, the patient underwent several long courses of corticosteroid therapy. At this point, she began to gradually increase her weight. Over the past 4 years, the patient has been on infliximab at 5 mg/kg every 8 weeks, with evidence of clinical and endoscopic remission.

A preoperative esophagogastroduodenoscopy was requested in order to assess the upper gastrointestinal tract for any abnormal findings as well as the presence of *Helicobacter pylori* (HP) infection. The endoscopy revealed retracted scar tissue in the gastric body (Fig. 2a) and antrum (Fig. 2b), with lesions with a bamboo-joint-like appearance and several pseudopolyps (Fig. 3). The esophagus and duodenum appeared normal. Histopathologic examination of biopsies from the stomach demonstrated mild foveolar hyperplasia and HP-negative chronic gastritis, with no signs of activity. No epithelioid granulomas, glandular atrophy, dysplasia, or signs of malignancy were identified.

The patient underwent a sleeve gastrectomy without complications. The surgical specimen did not reveal any specific sign for inactive Crohn's disease. Indeed, histopathological evaluation of the surgical specimen showed chronic gastritis and hyperplasia of the foveolar epithelium cells, without active inflammation, granulomas, dysplasia, or signs of malignancy. Five months after the surgery, she has already lost 36 kg and Crohn's disease remains in remission.

Crohn's disease is defined by chronic inflammation that may involve any site of the gastrointestinal tract.

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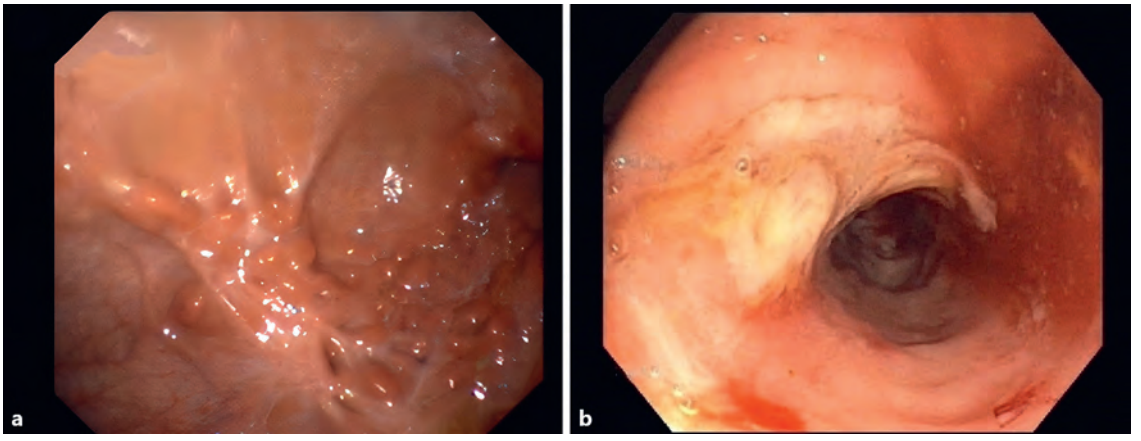

Fig. 1. Endoscopic exams at diagnosis. **a** Esophagogastroduodenoscopy – stomach with scattered scarring areas and multiple pseudopolyps. **b** Colonoscopy – congestive and friable colonic mucosa, with scattered erosions and ulcers, interspersed with normal-looking mucosa.

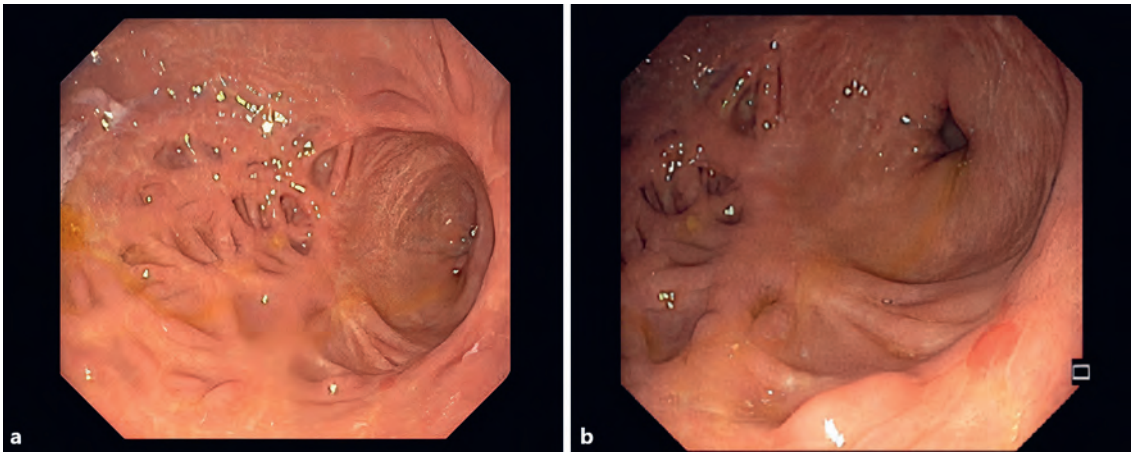

Fig. 2. Gastric body (**a**) and antrum (**b**) involvement by Crohn's disease.

Nevertheless, the stomach is rarely the sole or predominant site of Crohn's disease accounting for less than 0.07% of all cases of gastrointestinal Crohn's disease [1, 2]. We report a rare case of gastric Crohn's disease with endoscopic findings consistent with cicatricial mucosa, remarkable for its exuberance. Furthermore, it has been shown that bariatric surgery may be an effective and safe option for weight loss in carefully selected patients with inflammatory bowel disease [3].

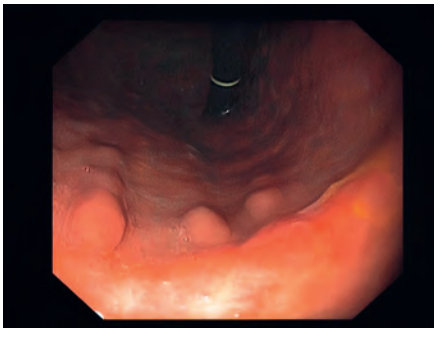

Fig. 3. Bamboo-joint-like appearance and pseudopolyps on the stomach.

Statement of Ethics

Informed consent was obtained from the patient for the publication of their information and imaging.

Conflict of Interest Statement

The authors have no disclosures to report.

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Author Contributions

Isabel Garrido drafted the manuscript. Isabel Garrido, João Santos-Antunes, and Guilherme Macedo have critically revised and finalized the manuscript. All authors have approved the final version of the manuscript.

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Errata

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In the article "Endoscopic Resection of Gastrointestinal Neuroendocrine Tumors: Long-Term Outcomes and Comparison of Endoscopic Techniques" [GE – Portuguese Journal of Gastroenterology, 2022; DOI: 10.1159/000521654] by Pimentel-Nunes et al., the original publication listed the copyright holder as Sociedade Portuguesa de Gastrenterologia due to an error by the publisher. The copyright holders for the article are the authors. The original article has been updated.

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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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