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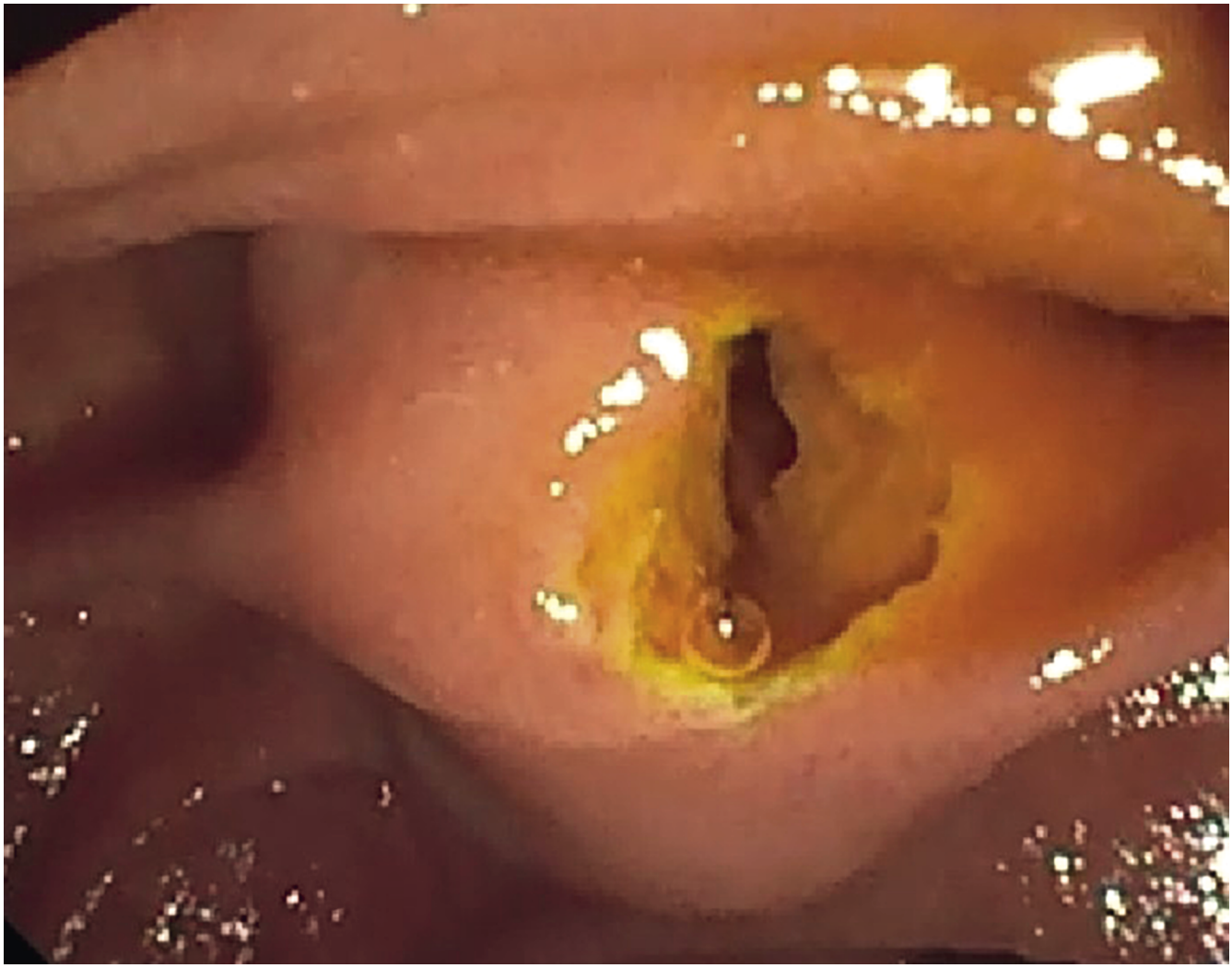

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Review article: Chronic Intestinal Failure and Short Bowel Syndrome in Adults

Research article: Standard Cannulation versus Fistulotomy for Biliary Access in ERCP: Should We Expect the Same Success when Treating Choledocholithiasis?

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Aims and Scope

The *GE Portuguese Journal of Gastroenterology* (formerly *Jornal Português de Gastrenterologia*), founded in 1994, is the official publication of Sociedade Portuguesa de Gastrenterologia (Portuguese Society of Gastroenterology), Sociedade Portuguesa de Endoscopia Digestiva (Portuguese Society of Digestive Endoscopy) and Associação Portuguesa para o Estudo do Fígado (Portuguese Association for the Study of the Liver).
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Non-Invasive versus Invasive Assessment of Portal Hypertension in Chronic Liver Disease

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Keywords
Chronic liver disease · Transjugular liver biopsy · Non-invasive assessment · Liver elastography · Spleen elastrography

Abstract
Background: Cirrhosis is one of the major causes of morbidity and mortality worldwide and the second leading cause of digestive disease mortality. Portal hypertension is the main driver of cirrhosis-related complications such as ascites and variceal bleeding. Portal hypertension is defined as a hepatic venous pressure gradient >5 mm Hg, although it is clinically significant and associated with clinical complications when >10 mm Hg. ***Summary:*** Therefore, detection of clinically significant portal hypertension (CSPH) in chronic advanced liver disease or compensated cirrhosis is of paramount importance to guide the management of these patients. ***Key Messages:*** This study aimed at revising the non-invasive and invasive tools for assessment of portal hypertension and risk stratification for CSPH in patients with chronic liver disease.

Avaliação não-invasiva versus invasiva de hipertensão portal na doença hepática crónica

Palavras Chave
Doença hepática crónica · Biópsia hepática transjugular · Avaliação não-invasiva · Elastografia hepática · Elastografia esplénica

Resumo
Contexto: A cirrose é uma das principais causas de morbimortalidade mundial e a segunda principal causa de morte nas doenças do trato gastrointestinal. O desenvolvimento de hipertensão portal é o principal gatilho para o aparecimento de complicações relacionada com a cirrose, como ascite e hemorragia varicosa. Hipertensão portal é definida quando o gradiente de pressão venosa hepática é maior que 5 mm Hg, embora seja clinicamente significativa apenas quando superior a 10 mm Hg. ***Sumário:*** Desta forma, a deteção de hipertensão portal clinicamente significativa na doença hepática crónica e cirrose compensada é fundamental na orientação e tratamento destes doentes. ***Mensagens-chave:*** O objetivo

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deste estudo é rever os métodos de avaliação não-invasiva e invasiva de hipertensão portal e estratificação de risco em doentes com doença hepática crónica.

Introduction

Liver cirrhosis is a consequence of chronic liver inflammation followed by the development of diffuse fibrosis and the growth of regenerative nodules [1]. It is one of the most common diseases worldwide and the 11th leading cause of death, ranking as the 3rd cause of death in patients aged 45–64 years [1, 2].

The main causes of liver disease are alcoholic liver disease, metabolic dysfunction-associated steatotic liver disease (MASLD) and viral hepatitis (hepatitis C [HCV] and hepatitis B). However, due to effective treatment of HCV and widespread vaccination strategies for hepatitis B, MASLD is becoming the primary cause of liver disease and is soon expected to be the leading cause of cirrhosis, hospitalization and liver transplant [3–5].

Cirrhosis is clinically classified into two prognostic stages: compensated cirrhosis (or compensated advanced chronic liver disease), when there are no episodes of decompensation, with a median survival of more than 12 years; and decompensated cirrhosis, based on the presence of complications related to portal hypertension (PH), with a contrasting median survival of 2 years [3, 6, 7]. Portal pressure results from two independent factors, as stated by Ohm's law:

$$\text{Pressure} = \text{Resistance} \times \text{Flow}$$

In the early stages, the primary factor contributing to an increase in portal pressure is resistance caused by growing fibrosis in the liver. In more advanced phases, augmented flow due to splanchnic vasodilation, angiogenesis, and the development of portosystemic collaterals become the main contributors [8].

PH is defined as an increase in the pressure between the portal vein and the hepatic veins (systemic venous pressure) above the normal level (1–5 mm Hg) [9]. Clinically significant portal hypertension (CSPH) is defined by a hepatic venous pressure gradient (HVPG) ≥10 mm Hg and is independently associated with the development of severe complications, including ascites, bleeding from gastroesophageal varices, hepatic encephalopathy, hepato-renal syndrome, and spontaneous bacterial peritonitis [3, 6, 10]. CSPH is present in all patients with decompensated cirrhosis and is associated with a 1-year mortality rate of 20% (vs. 5.4% in patients with compensated cirrhosis) [3, 6, 10]. Therefore, recent Baveno VII guidelines emphasize the importance of an early diagnosis of CSPH; the presence of CSPH will lead to the early initiation of carvedilol as it can significantly impact the prognosis, reducing the rate of cirrhosis decompensation [11, 12]. The aim of this review was to evaluate the non-invasive and invasive techniques for assessing the presence of PH (Tables 1–3).

Non-Invasive Assessment of PH

Serum Markers

Serum markers have long been tested for the detection of CSPH but have only shown moderate results. Platelet count and prothrombin levels are the most commonly studied biochemical parameters that are not sufficiently accurate to be used in clinical practice. The prothrombin index showed a good performance (AUROC of 0.89) for the diagnosis of CSPH, but it may be strongly affected by other external factors such as hematological diseases or coagulopathy [13, 14]. Thrombocytopenia is a common complication in cirrhotic patients but is a complex and multifactorial phenomenon, being not only associated with splenomegaly but also with decreased hepatic production of thrombopoietin and increased platelet destruction [15]. No specific platelet value has been found to correlate with the presence of esophageal varices or changes in portal pressure. However, in combination with spleen diameter (measured by ultrasound [US]) – the Giannini's score – a good correlation with HVPG was found, though lower than with liver elastography (AUROC 0.847 vs. AUROC 0.899) [3, 13, 16–20].

Von Willebrand factor antigen (vWF-Ag) is an indicator of endothelial activation and is frequently elevated in cirrhosis [21]. Ferlitsch et al. [21] first proposed vWF-Ag as a serum marker predictive of CSPH; using a cut-off of ≥241%, it showed an AUROC of 0.85 for predicting CSPH in compensated patients [21–23]. A systematic review and meta-analysis revealed that it was moderately correlated with HVPG measurement [24]. A more recent study, the VITRO score (vWF-Ag/thrombocyte ratio), found an AUROC of 0.86, higher than vWF-Ag alone [25].

Osteopontin is an extracellular matrix protein associated with inflammation and fibrosis and was shown to be related to the degree of fibrosis in liver disease. However, a study including 157 cirrhotic patients only showed a fair predictive capacity of osteopontin at a cut-

Table 1. Invasive and non-invasive test for PH evaluation

Invasive tests	Non-invasive test
HVPG	Serum markers • Platelet count • Prothrombin • Thrombocytopenia • vWF-Ag • Osteopontin • CD-163
EUS • Strain elastography and/or shear-wave elastography of the liver and spleen • Portal pressure gradient evaluation	Fibrosis scores • APRI • Fib-4 • Forn's index • Lok index Indocyanin green test US • Doppler US • Contrast-enhanced US CT MRI Liver elastography Spleen elastography

off of 80 ng/mL for prediction of CSPH (AUROC of 0.763) [22, 26].

CD-163 level was also shown to be predictive of the degree of HVPG. A study by Grønbæk et al. [27] found a good capacity for predicting the presence of PH (AUROC 0.8336), and, in association with enhanced liver fibrosis score (which includes hyaluronic acid, tissue inhibitor of metalloproteinase-1, and pro-collagen III), was able to identify PH with an AUROC of 0.91 [27–29].

Several fibrosis scores were also evaluated for the diagnosis of PH. The AST/platelet ratio index (APRI), fibrosis-4 (Fib-4), and Forn's index are used to grade fibrosis but showed limited accuracy for the diagnosis of CSPH [30]. Procopet et al. [31] and Lissoti et al. [32] found that the Lok index (derived from AST/ALT ratio, prothrombin index and INR, and platelet count) was predictive of CSPH and esophageal varices [3, 31, 32]. The indocyanine green retention test is used to assess liver function in patients proposed for liver surgery. A study showed that indocyanine green 15-min retention test could rule out CSPH (AUROC = 0.808) [32].

However, none of these tests, when used alone, have enough accuracy to be used in clinical practice. Therefore, the definition of algorithms and combination of tests are strongly advised [13].

Ultrasound

US is the primary non-invasive method used for diagnosing cirrhotic patients and screening for hepatocellular carcinoma (HCC). It is a cost-effective, non-invasive, and repeatable procedure. The most common US findings suggestive of liver cirrhosis are nodular surface and splenomegaly [13].

US can also be utilized for predicting the presence of CSPH. Berzigotti et al. [33] conducted a study and found that spleen diameter was the only US finding associated with CSPH (sensitivity 93% and specificity 36%), albeit only in the univariate analysis [13, 33]. However, it is not a specific indicator, as an enlarged spleen can also be observed in certain hematologic and infectious diseases.

On the other hand, the presence of portosystemic abdominal collaterals is a specific sign of PH and has been linked to a higher risk of first decompensation [34, 35]. Dilatation of the portal vein >13 mm (sensitivity <50% and specificity 90–100%), splenic vein and superior mesenteric vein (sensitivity 72% and specificity 100%), as well as reduced respiratory variation (sensitivity 79.7% and specificity 100%), are highly specific indicators but lack sensitivity for detecting PH.

Several doppler US parameters are associated with the presence of PH, including reduced portal vein velocity, reversal of portal blood flow, and increased intraparenchymal hepatic and splenic artery resistance and pulsatility index [36–38]. One study found that splenic arterial resistance index outperformed liver stiffness measurement (LSM) by shear-wave elastography in identifying PH [39]. However, doppler US has not been proven effective for the grading of PH, and variability between different diagnostic centers, as well as interobserver and interequipment variability, can limit its comparability [40–42].

Contrast-enhanced US, initially developed for evaluating the vasculature of focal lesions, has shown promising results in assessing PH. Kim et al. [43] used CEUS for measurement of hepatic vein arrival time and showed a very good correlation with the presence of CSPH. Eisenbrey et al. [44] also demonstrated a good correlation between HVPG and the use of subharmonic aided pressure estimation using perflubutane microbubbles. More recently, Berzigotti et al. [45] conducted the CLEVER study, using dynamic contrast-enhanced US with continuous infusion of SonoVue, and achieved an excellent correlation between portal pressure estimation and HVPG. Therefore, in the near future, contrast-enhanced US could potentially serve as a new tool for evaluating HVPG.

Table 2. Advantages and disadvantages of invasive and non-invasive test for PH evaluation

Methods	Advantages	Disadvantages
HVPG	• Gold-standard for portal pressure measurement and to evaluate efficacy of new therapies and non-invasive methods • Possibility of performing transjugular liver biopsy and assess other cardiac parameters (cardiac output, pulmonary artery, and capillary wedge pressure)	• Invasive • Only performed in highly specialized centers • Costly
Echoendoscopy	• Excellent correlation in all pressure measurements with HVPG • Optimized liver visualization • Potential use of elastography • Allows interventional procedures as gastric varices management with coils and/or glue or liver biopsy	• Need for sedation • Costly • Technical difficulties • Specific training with steep learning curve for echoendoscopy • Risks associated with the procedure
Serum markers	• Easy to perform and to use in clinical practice • Inexpensive (most of them)	• Lack of accuracy when used alone • Multiple potential confounding factors (ex-hepatitis, systemic inflammation, hematological disease) • Do not allow grading of portal pressure
US	• Non-invasive, cost-effective and repeatable • Doppler US parameters are associated with the presence of PH	• Interobserver and interequipment variability • Not useful for PH grading
CEUS	• Non-invasive • Recent studies achieved excellent correlation between portal pressure estimation and HVPG	• Lack of expertise • Lack of validation
CT	• Non-invasive • Operator-independent • Allows visualization of the entire liver, spleen, splanchnic vasculature, and portosystemic collaterals	• Costly • Lack of validation and expertise • Long acquisition time • Radiation • Potential allergy/nephrotoxicity to intravenous contrast
MRI	• Non-invasive • Operator-independent • Allows all liver visualization • Some studies showed good performance for PH prediction	• Costly • Limited accessibility • Lack of validation and expertise • Long acquisition time
Liver elastography	• Non-invasive and rapid • Highly reproducible e suitable for consecutive measurements • Good diagnostic accuracy • Widely validated	• Technical difficulties (obese patients, ascites) • Lack of visualization of the studied area (not a limitation with shearwave)
Spleen elastography	• Evaluation is based on the effect of PH on spleen stiffness • Non-invasive and rapid • Suitable for consecutive measurements • Advantage of predicting the first clinical decompensation and can be used to assess the response to beta-blockers	• Still awaiting validation of the optimal cut-off value for the new spleen-dedicated probe • Higher incidence of technical failures • Need of some expertise

Table 3. Performance of different methods for predicting CSPH

Methods	Best cut-off values	Sen, %	SP, %	PPV, %	NPV, %	AUROC	Authors
Prothrombin index	82.5%	87	81	83	85	0.892	Bureau et al., 2008 [14]
Gianinni's score	Rule in: ≥695	47.7	97.1	–	–	0.847	Colecchia et al., 2012 [20]
Von Willenbrand factor	• 241%	85.7	81.3				Ferlitsch et al., 2012 [21]
	• 1510,5 mU/mL	93.8	58.3				Wu et al., 2015 [23]
VITRO score	>1.58	80	70	93.2	40.1	0.86	Hametner et al., 2016 [25]
Osteopontin	80	75	63	–	–	0.763	Bruha et al., 2016 [26]
CD-163	3.95 mg/L	66	94	98	44	0.8336	Grønbæk et al., 2012 [27]
LOK index	–	–	–	–	–	0.830	Lisotti et al., 2014 [32]
ICG test	Rule out: <6.7%	95.9	27.3	66.7	81.6	0.808	Lisotti et al., 2014 [32]
CEUS	≤14 s	92.7	86.7	90.5	89.7	0.973	Kim et al., 2012 [43]
CT	Splenic clearance <125 mL/min/100 mL suggested severe PH	94	100	–	–	0.96	Talakic et al., 2017 [47]
MRI							
Spleen cT1	1,376 ms	89	100	100	91		Levick et al., 2019 [52]
Liver cT1	909 ms	88	70	73	88		
Liver elastography							
Supersonic shear-wave	13.6–34.9 kPa to rule in CSPH	79	82	–	–	0.84	Deng et al., 2017 [46]
Transient elastography		90	79	88	88		Shi et al., 2013 [57]
Spleen elastography	52.8 kPa to rule in CSPH	77	97	–	–	0.966	Colecchia et al., 2012 [20]

ICG, indocyanine green.

Computed Tomography and Magnetic Resonance Imaging

Cross-sectional imaging methods are commonly used in patients with cirrhosis, primarily for the evaluation of suspected HCC lesions detected in US. A meta-analysis reported a sensitivity of 87% and specificity of 88% for computed tomography (CT) scan to predict the presence of high-risk varices. Additionally, a small study involving 21 cirrhotic patients evaluated by CT perfusion imaging demonstrated excellent performance in detecting HVPG ≥12 mm Hg, with a sensitivity of 94% and specificity of 100% [46, 47].

Magnetic resonance imaging (MRI), due to its enhanced visualization capabilities and direct assessment of hemodynamic collateral circulation, has also been utilized to predict the presence of PH in cirrhotic patients [48]. In a retrospective study involving patients with chronic liver disease, relative liver enhancement and portal vein hyperintensity on a 20-min delayed T1-weighted gadoxetic acid-enhanced MRI were found to be predictive of HVPG ≥12 mm Hg [49]. Another study revealed a correlation between spleen volume, spleen stiffness, and liver stiffness measured by MR elastography, as well as the presence of varices [50]. Additionally, a noteworthy study demonstrated the ability to differentiate healthy individuals from patients with PH by combining hepatic architecture and splenic artery velocity obtained by MRI [51]. Levick et al. [52] also showed that cT1, a novel MRI-based quantitative metric for assessing a composite of liver inflammation and fibrosis, mainly spleen cT1, correlated well with the presence of ph.

However, high costs and limited accessibility (mainly MRI), lack of validation and expertise for both techniques,

long acquisition time, and radiation exposure (in case of the CT scans) are major drawbacks for their routine use in clinical practice.

Liver Elastography

Transient elastography is an US-based technique used to assess liver fibrosis. It measures the speed of a wave propagated by a probe, which is directly proportional to liver stiffness. This technique has been a major breakthrough in the field of hepatology in recent years and has become a routine part of hepatologists' daily practice for evaluating fibrosis and diagnosing patients with liver cirrhosis [13].

The first study to evaluate the relationship between LSM and HVPG was published in 2006. It demonstrated a direct association between LSM (a cut-off value of 8.7 kPa) and the diagnosis of PH (defined as HVPG ≥6) in patients with HCV cirrhosis after liver transplantation, with an AUROC of 0.93 [53]. Since then, several studies have been published, demonstrating the high sensitivity of transient elastography. Patients with LSM values up to 13.3 kPa have a very low risk of CSPH, while those with LSM values of at least 21.1 kPa have a very high risk of CSPH [13, 54–57]. However, LSM values in the intermediate range, referred to as the "gray zone," do not allow for an accurate diagnosis [13]. LS measurement has also been used to predict the presence of esophageal varices, which indirectly evaluate PH. A meta-analysis showed a sensitivity of 0.87 and specificity of only 0.59 for the detection of large varices when using LSM as the sole method. Moreover, when LS measurement is used alone, 30% of cases fall into the gray zone, resulting in an inaccurate diagnosis [13]. To address this limitation, several authors have suggested combining two non-invasive methods. The varices risk score, which incorporates LSM, platelet count, and spleen diameter, has shown an AUROC of 0.909, providing improved accuracy [16].

More recently, Baveno VII guidelines have placed emphasis on the use of non-invasive tests for the diagnosis of CSPH in clinical practice [11]. According to these guidelines, for patients with LSM ≤15 kPa and platelets ≥150 × 10^9/L, CSPH can be ruled out with high sensitivity and a negative predictive value (>90%) [11]. On the other hand, in patients with viral cirrhosis, alcoholic cirrhosis, or non-obese MASH cirrhosis, a LSM ≥25 kPa indicates the presence of CSPH with high specificity and a positive predictive value (>90%) [11]. For patients with MASLD cirrhosis, further validation is required to determine the appropriate cut-offs, as a high body mass index (especially if ≥ 30 km/m^2) is associated with higher LSM, regardless of the risk of CSPH [11, 58].

An interesting finding is that LSM is effective in predicting HVPG values up to 10–12 mm Hg, but its predictive accuracy decreases for higher values above. This observation can be explained by the fact that in the early phases of PH development, the main contributing factor is the accumulation of fibrillar extracellular matrix and fibrosis, which can be detected by LSM. However, in more advanced stages, the primary factors are hyperdynamic circulation and splanchnic vasodilatation, which are not effectively evaluated by LSM [13].

One of the major drawbacks of LSM using transient elastography is its limited control area of interest, as it provides a monodimensional view [59]. Shearwave elastography (two-dimensional or point shearwave), on the other hand, is a method incorporated into more advanced US devices that enables direct visualization in the region of interest and provides a quantitative measurement of liver stiffness in kPa. A meta-analysis of four studies demonstrated promising performance of shearwave elastography for diagnosing CSPH with an AUROC of 0.84, sensitivity of 79%, and specificity of 82% [60]. At the cut-off of 24.5 kPa, shearwave liver elastography showed an AUC of 0.87 for the diagnosis of CSPH [61]. Shearwave elastography has improved the accuracy of elastography in challenging patient populations (such as those with ascites or obesity), but it also faces some challenges that hinder its routine implementation. These challenges include the need for experience performing US examinations, variability in values obtained from different US devices, and variations in elastography techniques, all of which affect the definition of cut-off values and the accurate interpretation of results [8, 62, 63].

Spleen Elastography

Spleen stiffness measurement (SSM) was first described by Stefanescu et al. [64] in 2011 as a method for evaluating PH. Initially, the SSM value of 56 kPa was associated with CSPH. However, subsequent studies have shown that lower values (≤41–46 kPa) can effectively rule out the presence of CSPH and high-risk varices [20, 65, 66]. A meta-analysis of nine studies demonstrated good accuracy of SSM in detecting PH (SROC of 0.92, sensitivity of 88%, and specificity of 84%). When compared to HVPG, SSM showed a strong correlation with values >5 mm Hg and with the progression of PH from earlier to late phases [20, 66].

Theoretically, SSM is considered superior to LSM for evaluating PH because it not only reflects the increased hepatic resistance due to liver fibrosis (which LSM also

assesses) but also captures the heightened hyperdynamic circulation and splanchnic vasodilatation that occur in more advanced phases of PH [67]. Recent comparative data supports the notion that SSM may be a superior marker of PH compared to LSM, not only for viral liver disease but also for other etiologies. In a meta-analysis that included patients with chronic liver disease, SSM demonstrated superior sensitivity and specificity compared to LSM (0.88 vs. 0.83 and 0.78 vs. 0.66, respectively) for the diagnosis of esophageal varices, an indirect marker of PH [68]. SSM also offers the advantage of predicting the first clinical decompensation and can be used to assess the response to β-blockers [69–71]. However, SSM has certain limitations, including a higher incidence of technical failures compared to LSM, particularly in cases involving obesity, ascites, or invalid SSM. Additionally, previous studies utilized probes with an upper limit cut-off value of 75 kPa, which is now considered for spleen stiffness, as spleen stiffness typically exhibits higher values. The development of a novel spleen-dedicated stiffness measurement probe, capable of reaching 100 kPa, has improved the accuracy of SSM and addressed this limitation [3, 72].

SSM has gained significant importance in recent years and is now recommended in the Baveno VII guidelines. According to these guidelines, an SSM value of <21 kPa can effectively rule out CSPH, while an SSM value >50 kPa can indicate the presence of CSPH in cases of viral hepatitis [11]. However, it is worth noting that the validation of the optimal cut-off value for the new spleen-dedicated probe is still pending. Further studies and validation are needed to determine the most appropriate cut-off value for SSM using the new probe [11].

Invasive Assessment of PH

Hepatic Venous Pressure Gradient

Hepatic vein catheterization is the gold standard for measuring HVPG and determining the portal pressure. HVPG is calculated as the difference between wedge hepatic venous pressure (WHVP) and free hepatic venous pressure [6, 9].

Procedure

The procedure is performed under sedation and local anesthesia. The right jugular vein (or the femoral vein) is catheterized, usually with US guidance, and a balloon-tipped catheter is passed into the hepatic vein under fluoroscopic guidance [9, 22].

The free hepatic venous pressure is measured in the hepatic vein, 2–4 cm from its opening into the inferior vena cava, and should be similar to the value obtained in the inferior vena cava; a difference of >2 mm Hg can occur due to inadequate placement of the catheter or, less commonly, due to a hepatic vein obstruction [9, 22]. The WHVP is measured by inflating the balloon in the hepatic vein until total occlusion; adequate occlusion could be confirmed by injection of contrast dye without observing reflux.

Occluding the hepatic vein stops the blood flow, equalizing the pressure in the vascular territory, specifically in the hepatic sinusoids. Therefore, the WHVP reflects the pressure in the hepatic sinusoids, which is slightly lower than the portal pressure (~1 mm Hg) in a normal liver. Contrarily, in cirrhosis, the blood flow cannot be decompressed at the sinusoid level due to fibrosis and nodule formation, making the WHVP an accurate estimation of portal pressure [9, 73–75].

Complications

Complications during HVPG measurement are uncommon. Local injury at the puncture site, such as leakage, hematoma, or arterial-venous fistula, is one of the most frequent complications, but the risk can be reduced with ultrasonographic guidance. Self-limited arrhythmias can occur during the passage of the catheter through the right atrium; carbon dioxide can be used in patients allergic to contrast. The risk of bleeding is very low, and platelet or fresh frozen plasma transfusion before the procedure should only be considered in cases of severe thrombocytopenia (platelet level $<20 \times 10^9$/l) or low prothrombin ratio (<30%) [9, 22]. Although safe, HVPG measurement is an invasive procedure, costly, only performed in highly specialized centers, and unsuitable for consecutive measurements during the course of the disease [3].

Endoscopic Ultrasound

Endoscopic ultrasound (EUS) is an established diagnostic and interventional tool for biliary diseases. In recent years, EUS has gained importance in patients with liver disease, from assessing small liver lesions to evaluating and treating esophageal varices (EV) [76]. The concept of endohepatology has emerged recently as a field where EUS plays a key role in the diagnosis and management of liver diseases. EUS has shown promising results in the management of patients with PH as it is associated with optimized liver visualization, the potential

use of elastography, and allows interventional procedures such as gastric variceal treatment (coils and/or glue), liver biopsy, and portal pressure measurement with very good results [77].

Through the esophageal, gastric, or duodenum window, EUS has a wide visualization of the entire liver, biliary tree, and pancreas, as well as direct sonographic visualization, which increases the diagnostic success (bigger liver specimens when compared to percutaneous liver biopsies) and reduces the adverse event rates of liver biopsy (approximately 2.5%) [78, 79].

EUS can also have a predictive role in recurrent EV bleeding. A study involving 206 cirrhotic patients with previous variceal bleeding found that the presence of large peri-esophageal collateral veins and perforating veins were significant factors for recurrent EV [80, 81]. Another study also demonstrated that EUS can predict the risk of annual bleeding based on variceal cross-sectional surface area [82].

EUS-guided portal vein catheterization with portal pressure gradient measurement has also been proposed. One of the first studies was performed in three swine models, showing excellent correlation in all pressure measurements when compared with EUS measurements with HVPG without adverse events [83, 84]. Following these successful results, the same group published the first human pilot study, including 28 patients with chronic liver disease, where portal pressure gradient results were compared with clinical signs of PH. The obtained results correlated well with clinical parameters of PH (presence of varices, PH gastropathy, and thrombocytopenia), and the technical success rate was 100% [85]. The direct correlation between portal pressure measurement by EUS and HVPG in humans was studied by Zhang et al. [86], and similar results were found by both techniques without a significant difference in time needed to perform or adverse events. EUS may also have a role for non-invasive evaluation of liver fibrosis, not only in patients that failed with non-invasive techniques (due to obesity, ascites, thick subcutaneous fat, or restricted intercostal spaces) but also has the advantage of performing shear-wave elastography of both the right and left liver in the same procedure [77, 87]. A study by Robles-Medranda et al. [88] found a similar accuracy of EUS-elastography when compared to liver and spleen stiffness for the prediction of PH. In pooled analysis, EUS liver and spleen elastography parameters predicted liver cirrhosis and PH with high sensitivities and negative predictive values. However, there are limitations such as technical difficulties (lack of experienced endosonographers), high costs, need for sedation, and, although low, the expected risks associated with the procedure (mainly bleeding, perforation, and infectious complications) [81, 83].

Conclusion

The development of PH in a patient with cirrhosis is a pivotal event that profoundly impacts the prognosis and management. While HVPG measurement is considered the gold standard for evaluating PH, it is invasive and not an easily available procedure.

Serum biomarkers and scoring systems have been explored to predict the presence of PH. However, their individual performance has been suboptimal. Combining multiple markers or scores can enhance diagnostic accuracy. Echoendoscopy-guided shear-wave evaluation of the liver and spleen might be an interesting option in patients who failed transient elastography, as it also has the possibility for screening for varices, liver biopsy, or portal pressure gradient measurement.

The Baveno VII guidelines emphasize the significance of non-invasive evaluation in cirrhotic patients and recommend the use of liver and SSMs for early identification of individuals at risk of developing CSPH. This proactive approach enables the detection of patients with compensated cirrhosis/chronic advanced chronic liver disease with CSPH and the initiation of appropriate treatment to reduce the risk of decompensation of cirrhosis and improve patient outcomes.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Rui Gaspar was responsible for the acquisition and interpretation of data and the drafting of the manuscript. Guilherme Macedo was responsible for the critical revision of the manuscript.

Data Availability Statement

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

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Review Article

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Chronic Intestinal Failure and Short Bowel Syndrome in Adults: The State of the Art

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Keywords
Intestinal failure · Home parenteral nutrition · Short bowel syndrome

Abstract

Background: Short bowel syndrome (SBS) is a devastating malabsorptive condition and the most common cause of chronic intestinal failure (CIF). During the intestinal rehabilitation process, patients may need parenteral support for months or years, parenteral nutrition (PN), or hydration/electrolyte supplementation, as a bridge for the desired enteral autonomy. ***Summary:*** Several classification criteria have been highlighted to reflect different perspectives in CIF. The management of CIF-SBS in adults is a multidisciplinary process that aims to reduce gastrointestinal secretions, slow transit, correct/prevent malnutrition, dehydration, and specific nutrient deficiencies, and prevent refeeding syndrome. The nutritional support team should have the expertise to take care of these complex patients: fluid support; oral, enteral, and PN; disease/PN-related complications; pharmacologic treatment; and surgical prevention/treatment. ***Key Messages:*** CIF-SBS is a complex disease with undesired consequences, if not adequately identified and managed. A comprehensive approach performed by a multidisciplinary team is essential to reduce PN dependence, promote enteral independence, and improve quality of life.

Falência intestinal crónica e síndrome do intestino curto em adultos: o estado de arte

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

Resumo

Contexto: A síndrome do intestino curto (SIC) constitui uma condição clínica devastadora e mal-absortiva, sendo a causa mais comum de falência intestinal crónica (FIC). Durante o processo de reabilitação intestinal, estes

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doentes poderão carecer de suporte parentérico durante meses ou anos que inclui hidratação/suplementação endovenosa e/ou nutrição parentérica (NP) como ponte para a sua progressiva autonomia e adaptação intestinal. ***Sumário:*** Diferentes classificações são elencadas e que refletem diferentes perspetivas/conceitos na FIC-SIC. A abordagem destes doentes constitui um processo multidisciplinar que tem como objetivo principal a redução das secreções gastrointestinais, reduzir o trânsito intestinal, corrigir/prevenir desnutrição, desidratação e défice nutricionais, assim como prevenir a síndrome de *refeeding*. Os centros a nível nacional devem possuir competência no tratamento de doentes com FIC, nomeadamente no manejo da fluidoterapia, nutrição oral, entérica e parentérica, complicações associadas à doença e/ou à própria nutrição parentérica, tratamento farmacológico e ainda na prevenção/tratamento cirúrgico. ***Mensagens-chave:*** A FIC-SIC constitui uma entidade complexa com consequências graves SE não for corretamente identificada/abordada. Uma abordagem holística realizada por uma equipa multidisciplinar é essencial e tem como objetivo reduzir a dependência na NP, promover adaptação intestinal e melhorar a qualidade de vida dos doentes.

Introduction

Short bowel syndrome (SBS) is a malabsorptive condition that results from the loss of intestinal length due to disease or resection [1]. SBS is the most common cause of chronic intestinal failure (CIF) [2]. Due to the major loss of digestive and absorptive surface area, general consequences of CIF include diarrhea, dehydration, electrolyte abnormalities, and weight loss. Patients need parenteral support for months or years, parenteral nutrition (PN), or hydration/electrolyte supplementation. For decades, Portuguese CIF patients have been confronted with major difficulties in receiving home parenteral nutrition (HPN) [3, 4]. In 2020, a new regulation, "Norma 017/2020" [5], set the conditions for home CIF management, and more patients are being treated in an ambulatory setting. We aimed to review the general concepts, definitions, and classifications of CIF-SBS in adults, as well as to address the multimodal treatment of these patients and disease/HPN-related complications.

Concepts, Definitions, and Classification of Intestinal Failure in Adults

Intestinal failure (IF) is defined as a reduction in gut function below the minimum necessary for absorption of macronutrients and/or water and electrolytes. Intravenous supplementation is required to maintain health, growth, and body homeostasis. The reduction in absorption that does not require intravenous supplementation is called intestinal insufficiency [2]. Several classification criteria were used [2, 6–10] to reflect the different perspectives (Tables 1, 2).

From a clinical point of view, IF definition implies the necessity of intravenous support [2]. IF should be anticipated in patients with (1) a jejunostomy/ileostomy and <200 cm of proximal small bowel, (2) <100 cm of small bowel and colon in continuity, and (3) a stoma or fistula output >1.5 L/day [7]. The need for intravenous support may depend on the effectiveness of oral nutrition/hydration, quality of oral intake, and use of specific pharmacotherapy. In borderline patients, intestinal insufficiency or IF may depend on the quality of clinical management and intestinal rehabilitation.

Multimodal Treatment of CIF-SBS and Intestinal Rehabilitation

Management of CIF-SBS aims to reduce gastrointestinal secretions, slow transit, correct/prevent malnutrition, dehydration, and specific nutrient deficiencies, and to prevent refeeding syndrome [11]. Once these early targets are achieved, progression to a stable nutritional regimen is required as part of the intestinal rehabilitation process. The need for intravenous fluid/nutrition is dictated mainly by the cause of CIF, anatomy of the SBS, and pathophysiological consequences [12].

Fluid Support and Management of Dehydration in SBS

Patients with SBS are prone to dehydration [13, 14], as they are net secretors, loose fluid, and sodium from the intestine. Since the primary deficit is not chloride, which is less well cleared from the body, a balanced electrolyte solution such as Ringer's lactate is preferred instead of saline solution [13].

Gastrointestinal losses should not dictate an increase in oral liquid intake because in SBS, this leads to fluid secretion into the proximal intestine, increasing losses. Urine output is useful for monitoring dehydration in SBS, and once an acceptable volume (20 mL/kg per 24 h) has been achieved, a transition to an oral rehydration solution (ORS) may be considered, as well as a combination of

Table 1. Functional and clinical classifications for intestinal failure

Functional classification				
Type I	Acute, short-term, and often self-limiting, as for patients after abdominal surgery requiring intravenous support for a few days			
Type II	Prolonged, often in metabolically unstable patients, usually with enteric fistulas, requiring multidisciplinary care and intravenous supplementation during weeks or months			
Type III	Chronic, in metabolically stable patients, requiring intravenous supplementation over months or years (reversible or irreversible)			
Clinical classification				
	Volume of intravenous supplementation per week, mL			
	<1,000	1,001–2,000	2,001–3,000	>3,000
Intravenous energy supplementation per week, kcal/kg				
0 (A)	A1	A2	A3	A4
1–10 (B)	B1	B2	B3	B4
11–20 (C)	C1	C2	C3	C4
>20 (D)	D1	D2	D3	D4

oral/enteral and parenteral approaches [7]. The importance of restricting the intake of low-sodium fluids, such as hypotonic fluids (e.g., water, tea, alcohol, and coffee) and hypertonic fluids (e.g., regular soda and fruit juices), should be emphasized. Instead, an ORS to enhance absorption and reduce secretion is preferred in patients with an end jejunostomy [15]. ORS is rarely needed in SBS with colon in continuity because patients usually maintain adequate hydration.

Oral Nutrition

Dietary therapy should focus on the maintenance of compensatory hyperphagia. Even small amounts of luminal nutrition stimulate intestinal adaptation and protect against liver diseases and other complications [7]. Dietary counseling should be based on patient preferences to ensure high compliance. Adjustments can be made based on the tolerance, symptoms, stool output, and weight. Due to malabsorption, dietary intake must be increased by at least 50% from the estimated needs, divided into 5–6 meals throughout the day [16]. High-energy-density foods with high salt content are recommended. Patients should use salt liberally and restrict oral fluid intake during meals.

In patients with SBS and colon in continuity, a high-carbohydrate (60%), low-fat (20%) diet with oxalate restriction (e.g., peanuts and baked beans) tend to reduce fecal calorie loss, increase energy absorption, and reduce magnesium/calcium and oxalate absorption. A high content of medium-chain triglycerides should be suggested, as well as fat restriction, as it results in steatorrhea and reduces carbohydrate fermentation [13, 17]. The fat/carbohydrate ratio in patients with end jejunostomy is less important; as enteral fat is useful owing to its energy density, they do not benefit from its restriction [18, 19].

Enteral Nutrition

Enteral nutrition (EN) should be considered, especially in those with low PN dependence, who are expected to be weaned off. Even in patients with a limited potential for complete PN weaning, EN can achieve considerable benefits [6].

Considering the altered anatomy and intra-abdominal adhesions, frequent in SBS, performing a percutaneous gastrostomy can be technically challenging. The risks and benefits must always be discussed, and a trial with a nasogastric tube should be performed.

Polymeric formulas are preferred over elemental formulas because they are less costly, less hyperosmotic, and well tolerated. However, studies suggest that both formulas are similar in terms of nutrient absorption and fluid/electrolyte loss. Continuous infusion seems to enhance the benefits and tolerance of EN. Overnight feeding improves quality of life and enables normal daily activities [20].

Table 2. Pathophysiologic and morphological classifications for intestinal failure and short bowel syndrome

Pathophsiologic classification	
Condition	Most frequent underlying disorders
SBS	• Mesenteric infarction (arterial or venous thrombosis) • Crohn's disease • Radiation enteritis • Surgical complications • Intestinal volvulus • Familial polyposis • Abdominal trauma • Intestinal angiomatosis • Necrotizing enterocolitis • Complicated intussusception • Congenital malformations
Intestinal fistula	• **Inflammatory:** Crohn's disease, diverticular disease, pancreatic disease, and radiation enteritis • **Neoplastic:** colon, ovarian and small bowel malignancies • **Iatrogenic:** operation and percutaneous drainage • **Infectious disease:** tuberculosis and actinomycosis • Trauma • Foreign body
Intestinal dysmotility	• Acute: postoperative, systemic inflammatory or neurological reaction associated with critical illnesses; Ogilvie syndrome • Chronic intestinal pseudo-obstruction
Mechanical obstruction	• Obstruction (polypoid tumors, intussusception, gallstones, foreign bodies, bezoars, feces) • Intrinsic bowel lesions (stenosis or strictures: neoplastic, inflammatory bowel disease, chemical, anastomotic) • Extrinsic lesions (abdominal adhesions: previous surgery, previous peritonitis, frozen abdomen; hernias; neoplasia: desmoid tumors, peritoneal carcinomatosis; volvulus; congenital bands)
Extensive small bowel mucosa disease	• Autoimmune enteropathy • Intestinal lymphangiectasia • Protein-losing enteropathies • Common variable immunodeficiency • Crohn's disease • Celiac disease • Radiation enteritis • Chemotherapy-related enteritis
Morphologic classification (SBS)	
Group 1	End jejunostomy (the most nutritionally dependent patient)
Group 2	Jejunocolic anastomosis
Group 3	Jejuno-ileo-colic anastomosis (the most favorable phenotype)

Home Parenteral Nutrition

Indications and Aims

HPN is indicated in patients who cannot meet their nutritional requirements despite maximal medical therapy, including oral/EN and who can be safely managed outside the hospital. It aims to support nutrition, provide hydration, and avoid electrolyte disturbance. HPN also promotes autonomy and a better quality of life, as well as intestinal rehabilitation, as part of the desired weaning off process [6].

Training and Monitoring

Before starting HPN, the patient must be metabolically stable, able to cope with HPN therapy, and have adequate social support and home environment. Patients and/or

Table 3. Components and recommendations of home parenteral nutrition

Components	Recommendations
Protein	0.8–1.4 g/kg/day (0.13–0.24 g/kg/day of nitrogen)
Energy intake	20–35 kcal/kg/day
Carbohydrates	Target: glucose (fasting) <140 mg/dL; pre-infusion/meals 100–140 mg/dL; during HPN infusion 140–180 mg/dL
Lipids	1 g/kg/week containing essential fatty acids When more than 1 g/kg/day of lipid emulsion is required, alternative emulsions to reduce the risk of liver disease (olive oil, MCT, and fish oil) should be used, which tends to be high in ω-3 PUFA and α-tocopherol and low in ω-6 PUFA and phytosterol content
Vitamins	Adjustments and supplementations as needed Evaluate baseline vitamin levels and to reevaluate them once a year
Trace elements	Adjustments and supplementations as needed Evaluate baseline vitamin levels and to reevaluate them once a year
Amino acids	No evidence for routine addiction of glutamine, cysteine, taurine
Fluids	25–35 mL/kg (2–2.5 L/day)
Electrolytes	As recommended daily intake; adjustments and supplementations as needed Regular monitoring of chloride and bicarbonate is recommended to assess acid-base balance

MCT, medium-chain triglyceride; PUFA, poly-unsaturated fatty acids.

caregivers must demonstrate self-care competency before discharge [7]. Training starts during hospitalization and aims to ensure the safe practice of HPN by teaching all aspects of infusion. Catheter care and pump use should be focused on to prevent, recognize, and effectively manage possible complications. Despite its recognized importance, there are no available guidelines for training patients/caregivers [6]. The European Society for Clinical Nutrition and Metabolism (ESPEN) encourages HPN patients to join nonprofit groups that can assist in providing education, support, and networking, which are beneficial in terms of QoL, depression scores, and catheter infections [7].

Regular contact between the nutritional support team (NST) and the patient is essential, initially every few days, then weekly, and eventually monthly. Monitoring weight, urine/stoma output, and hydration status is of utmost importance. Serum electrolytes, including sodium, potassium, chloride, bicarbonate, and renal function tests, should be measured frequently until stable and then at regular intervals, monthly to every 3 to 6 months, on a case-by-case basis. Moreover, regular monitoring of chloride and acid-base status through arterial blood samples is recommended [7]. Blood counts, liver enzymes, bilirubin, and albumin levels should also be monitored to address potential complications. Vitamins and trace elements should be measured every 6–12 months. Patients starting HPN should undergo bone mineral densitometry and measurement of markers of bone turnover, such as PTH and vitamin D, at yearly intervals. Biochemistry and anthropometry must be evaluated during all visits.

Quality of care is measured by evaluating HPN-related complications, hospital readmissions, and weight change, as well as by regular audits of the patient's quality of life. The HPN-QoL is a specific questionnaire [21] that focuses on physical, emotional, and symptomatic issues, although it has not been validated in the Portuguese population.

Components of HPN

Table 3 summarizes the components of HPN [22–28]. The adequacy of HPN volume should be assessed by 24-h urine output and serial measurements of sodium, potassium, phosphate, magnesium, and calcium levels.

Venous Catheters

Patients with HPN require long-term central venous catheter (CVC). Current guidelines recommend ultrasound-guided catheter placement in a central vein (subclavian or jugular) by an experienced physician to reduce the number of immediate and late complications [7].

Essentially, 2 types of catheters are used for HPN: cuffed tunneled central catheter (*Hickman-Broviac*) and a totally implanted port catheter (Implantofix-type). The choice between them depends on the frequency of venous access required, patient compliance, and experience of the NST [6, 7, 29]. A *Hickman-Broviac* is usually preferred,

while port catheters are reserved for patients who only need parenteral hydration, who do not use the CVC daily, or who practice sports/other activities that benefit from the CVC totally implanted under the skin.

General recommendations and precautions include [7]: (1) using a single-lumen catheter; (2) choosing the maximum necessary diameter of the catheter for the type of solute to be administered; (3) using the CVC only for the administration of PN; (4) using a perfusion pump for the solute to be administered; (5) handling of the CVC by the same person and monitored by the NST; (6) performing hand hygiene and disinfection before and after handling the CVC; (7) replacing the administration system every 24 h; and (8) flushing the CVC before and after its use with saline solution.

Weaning Perspectives/Enteral Autonomy

Virtually all patients with SBS will require PN, although more than 50% will be able to be weaned completely from PN in 5 years, in parallel with progressive enteral autonomy [10]. However, rehabilitation should be initiated as soon as possible. The probability of eliminating HPN dependence is <6% if not accomplished in the first 2 years [9]. In this matter, two principles apply: avoiding exclusive or total intravenous feeding and implementing oral/EN.

Permanent IF is expected for 100 cm or less of the small intestine in patients with end jejunostomy, 65 cm of jejunum in jejunocolic anastomosis, and 35 cm of small bowel in jejunoileal anastomosis [30]. Patients with colon in continuity and initially less dependent on HPN have generally a better prognosis [31].

HPN Complications

Tables 4 and 5 summarize the disease- and catheter-related complications of HPN [32–41].

Precautions for Orally Administered Medications

Absorption of oral medication may be impaired in patients with SBS, especially in those without the proximal jejunum. Enteric-coated and delayed-release medications may not be properly absorbed and should be avoided. When feasible, alternative routes (e.g., intravenous, subcutaneous, transdermal, and rectal) may be considered.

Pharmacologic Treatment

Antisecretory Drugs

Enterectomy is associated with gastric hypersecretion and hypergastrinemia, especially within the first 6–12 months after resection, contributing to increased intestinal fluid loss and risk of peptic ulcer disease [42]. Antisecretory drugs, including proton pump inhibitors (PPI) and histamine-2 receptor antagonists, can be used to counteract these effects. However, these medications increase the risk of small-intestinal bacterial overgrowth. The beneficial effects on stool volume and dyspeptic symptoms should be weighed against this potential risk. The duration of its beneficial effects remains unclear; however, these medications should be used cautiously beyond 6–12 months. ESPEN recommends its use, especially during the first 6 months after surgery, mainly in patients with SBS with a fecal output exceeding 2 L/day, and suggests that these drugs are also effective in reducing fecal wet weight and sodium excretion in the long-term [7, 43].

Antidiarrheal Drugs

Antidiarrheal agents, such as loperamide and codeine, are used to prolong intestinal transit time, enhance absorption, and reduce fecal wet weight and sodium excretion in patients with SBS with ostomy. Since opiate drugs have central nervous system side effects, such as sedation, and may have potential for addiction, loperamide should be preferred. Nevertheless, if necessary, combining these agents can enhance their effectiveness [44]. The use of these agents should be guided by objective measurement of their effects.

High doses of loperamide are frequently needed (reaching up to 32–64 mg/day), especially in patients with SBS without ileum, as it needs to enter the enterohepatic circulation. Although higher than the recommended label dose, loperamide is well tolerated by patients with SBS [45]. Nevertheless, side effects, such as arrhythmias, should be carefully monitored when administered at such doses. Administration 30–60 min before meals and at bedtime is often suggested, although there is no robust evidence for these recommendations.

Octreotide

Octreotide should be considered for patients experiencing severe fluid loss that cannot be effectively managed using conventional treatment. Typical candidates for this therapy include patients with SBS and high output end jejunostomy [46]. Dosage is 100–300 μg subcutaneously three times per day. Careful monitoring is required because of the potential fluid retention and possible negative influence on the intestinal rehabilitation process with prolonged use.

Antibiotics

Bloating, diarrhea, abdominal discomfort, and bowel dilation should raise suspicion for small-intestinal bacterial overgrowth, and empirical antibiotic treatment should be started accordingly. Frequently used antibiotics in this context include rifaximin, metronidazole, trimethoprim-sulfamethoxazole, and amoxicillin-clavulanic acid [47, 48].

Table 4. Disease-related complications of short bowel syndrome/intestinal failure

Complication	Pathophysiology	Management	Prevention
Intestinal failure liver disease (IFALD)	• Multifactorial condition (sepsis, intestinal anatomy, oral nutrition/EN, PN infusion modality, nutrition deficiency or excess) • Soybean-lipid emulsions in excess • Steatosis (adults) • Hepatocellular injury or cholestasis (children)	• Reduce the total lipid amount and/or decrease omega-6/omega-3 PUFA ratio • Revise potential inflammatory/infectious foci • No evidence to recommend lipid-free regimens, as well as the use of ursodeoxycholic acid, choline, taurine, or carnitine	• Identify/treat sepsis • Identify/treat sepsis • Preserve small intestine length and colon in continuity • Increase oral/enteral intake • Cycled PN with soybean oil-based lipid content less than 1 g/kg/day
Gallbladder sludge and stones	• Negligible oral intake • Intestinal remnant length less than 180 cm • Crohn's disease	• Endoscopic/surgical procedures as for the general population • Increase oral/enteral intake	• Preserve small intestine length and colon in continuity • Increase oral/enteral intake
Kidney disease and stones	• Chronic dehydration (kidney disease) • Increased absorption of oxalate, hypovolemia, hypomagnesemia and metabolic acidosis (kidney stones)	• Management as for the general population	• Monitor fluid balance and renal function* • Low-fat and low-oxalate diet* • Calcium carbonate and potassium citrate supplementation*
Bone disease	• Toxicity from aluminum contamination of the nutrition formula • Increased sensitivity to vitamin D suppressing PTH secretion • Hypercalciuria • Micronutrient deficiency (vitamin C and copper) • Vitamin A toxicity	• Supplement calcium and vitamin D as needed	• Correct metabolic acidosis when present • Periodic assessment of bone mineral density, calcium, magnesium, vitamin D and supplement as needed

EN, enteral nutrition; PN, parenteral nutrition; PUFA, poly-unsaturated fatty acid. *Especially in patients with colon in continuity.

However, routine use of antibiotics in patients with colon in continuity is not recommended because it may reduce the benefit of energy salvage due to bacterial fermentation.

Glucagon-Like Peptide-2 Analogs

In recent years, there has been growing interest in the gut endocrine system [49]. In the context of SBS, there is great interest in the use of growth factors. Targeting the glucagon-like peptide-2 (GLP-2) receptor is a promising therapeutic strategy. GLP-2 is an enteroendocrine peptide that acts through a wide variety of trophic effects to enhance mucosal growth, increase mesenteric blood flow, improve gut barrier function, slow intestinal motility, decrease gastric acid secretion, and regulate inflammatory processes [50–53]. Targeting GLP-2 receptors leads to improved absorption and reduced fluid/electrolyte loss [54].

Teduglutide was the first approved GLP-2 analog for the treatment of patients with SBS. It is a recombinant analog of GLP-2 with a longer half-life than the native peptide, allowing a daily subcutaneous injection (0.05 mg/kg/day). Typically, teduglutide is used in stable patients who cannot be weaned from PN despite all other therapeutic strategies. It has been shown to reduce PN requirements and potentially lead to complete weaning off in a subset of patients [55–57]. Additional studies are needed to determine whether intestinal adaptation due to teduglutide is sustained after discontinuation.

As this drug acts as a growth factor, it is contraindicated in patients with active or recent malignancies [58]. Screening with colonoscopy before initiating and during treatment is recommended, although the optimal timing and frequency are unknown. A suggested approach involves annual colonoscopy during the first 2 years, followed by subsequent colonoscopies at a minimum interval of 5 years [59].

Clinical experience with teduglutide suggests that it is generally well tolerated, with most adverse events being

Table 5. Disease-related complications of short bowel syndrome/intestinal failure

Complication	Pathophysiology	Management	Prevention
Catheter-related infections	• Local (catheter exit site, port pocket, subcutaneous catheter tunnel), or systemic infection • Most infections are bacterial in origin, but they can also be caused by fungi	• Preserve the catheter whenever possible • Remove in case of tunnel infections, port abscesses, septic shock, complicated infections (e.g., endocarditis), and blood stream fungal or virulent bacterial infection • Reinsertion of a new device should be postponed after systemic antibiotic therapy course is completed, as well as negative blood samples	• Aseptic technique during placement and dressing changes • Tunneled single-lumen catheters are advocated if possible • Proper catheter care and monitoring for signs of infection • No evidence of using in-line filters, routine catheters' replacement, antibiotic prophylaxis, heparin or 70% ethanol lock • Catheter locking with taurolidine appears to reduce catheter-related infections
Catheter-related thrombosis	• Procoagulant conditions • Diagnosed with computed tomography with angiography or with ultrasonography	• Anticoagulation (low molecular weight heparin, followed by vitamin K antagonists for 3–6 months) • Preserve the catheter whenever possible • Remove in case of infection, occlusion, contraindication to anticoagulation or symptom persistence despite appropriate therapy	• Ultrasound-guided catheter placement • Placement of the tip at the superior cavoatrial junction • Thromboprophylaxis with heparin/ warfarin is not recommended
Catheter-related occlusion	• Usually the result of catheter thrombosis • HPN formula components (lipids and calcium-phosphate precipitates)	• Flush the catheter with saline to restore patency • Fibrinolytic agents (alteplase, urokinase) for thrombotic occlusion	• Flush the catheter with saline after PN infusion • Infusion pumps may reduce this complication

EN, enteral nutrition; PN, parenteral nutrition; PUFA, poly-unsaturated fatty acid. *Especially in patients with colon in continuity.

mild or moderate in severity. Gastrointestinal symptoms are the most reported adverse events, consistent with the underlying disease conditions and intestinal trophic actions of teduglutide [60]. Injection site reactions, stomal complications, and respiratory tract infections were also frequent.

The attractive physiological effects of GLP-2 have prompted many efforts to slow the very short half-life of the native GLP-2 peptide, enabling its use as a therapeutic agent. Longer-acting GLP-2 analogs such as glepaglutide and apraglutide are currently being studied [49]. Apraglutide is a highly selective and potent GLP-2 receptor agonist with high plasma protein binding and low systemic clearance, resulting in a longer half-life than native GLP-2 peptide and teduglutide. Glepaglutide appears to be less potent and less selective for the GLP-2 receptor than apraglutide. Some studies on apraglutide support a once-weekly subcutaneous dosing regimen, whereas studies on glepaglutide support a once- or twice-weekly subcutaneous dosing regimen, which can improve quality of life and treatment compliance [61–64].

Glucagon-Like Peptide-1 Analogs

GLP-1 analogs (e.g., exenatide, liraglutide, dulaglutide, or semaglutide) have been used for almost 2 decades in the treatment of diabetes mellitus type 2 and, recently, in obesity. Targeting the GLP-1 receptor in patients with SBS may influence proximal gut transit since GLP-1 seems to lack the intestinal trophic properties of GLP-2.

Some studies have shown a reduction in ostomy output and a reduction in PN requirements with GLP-1 analogs [65–67]. Another study evaluated the effects of continuous infusion of GLP-1, GLP-2, and a combination of both (GLP-1 and GLP-2) in adults with SBS. The authors found that all treatments significantly reduced fecal wet weight compared to the placebo. The effects of GLP-1 were less

potent than those of GLP-2, but the combination therapy was shown to have superior efficacy compared to each single agent, further supporting the rationale for a GLP-1/GLP-2 combination strategy in SBS [67].

Growth Hormone (Somatotropin)

The use of growth hormone (GH) in SBS patients showed a moderately favorable effect on intestinal wet weight loss, even though its use could be associated with significant side effects such as peripheral edema, arthralgia, and carpal tunnel syndrome. There are also concerns about the potential increased risk of diabetes mellitus and cancer [47]. The positive effects of GH have mainly been described in patients with SBS with colon in continuity. GH is approved only in the USA and its role is being replaced by GLP-2 agonists.

Clonidine

Clonidine has demonstrated some benefits in treating high output stool losses, likely due to its effects on intestinal motility and secretion [68, 69]. However, further studies are required to better understand its effectiveness.

Bile Acid Binders and Pancreatic Enzymes

Given the already diminished bile acid pool in patients with SBS, the use of bile acid sequestrants (such as cholestyramine) may exacerbate steatorrhea and fat-soluble vitamin losses and, therefore, should generally be avoided. There is still insufficient evidence supporting the efficacy of pancreatic enzyme supplementation for the treatment of SBS [7].

Surgical Prevention and Treatment of SBS

How to Avoid SBS and IF?

The role of surgery in IF often begins with prevention; therefore, early recognition of patients at a high risk for loss of critical bowel length should trigger conservative strategies [12, 70]. Operative prehabilitation of patients at risk (e.g., inflammatory bowel disease, malignancy, immunosuppression, and significant comorbidities) is indicated and aims to reduce the risk of postoperative complications. Nutritional and comorbidity optimization reduces the risk of high output stomas or the development of enterocutaneous fistulas.

In patients with Crohn's, bowel-sparing techniques (stricturoplasties) should be selected whenever possible, and wide anastomoses should be constructed to avoid stenosis recurrence. Extended bowel resection should be avoided in patients undergoing emergency surgery (ischemia or perforation). In situations of doubt regarding the viability of segments contiguous to those in the acute process, a "clip and drop" approach [11] should be chosen for damage control, laparostomy, and closure of the abdominal wall postponed until the patient is stable. This approach avoids wide resections and often recruits bowel segments with questionable vascularization in the context of shock, allowing anastomosis creation when conditions become favorable. Critically ill patients should maintain postoperative intra-abdominal pressure monitoring to prevent bowel ischemia.

When to Reoperate?

Patients with type 2 IF may be able to reestablish intestinal continuity; however, they should be assessed preoperatively, and the risks and benefits of new complications should be considered. The decision for reintervention requires knowledge of the disease origin, remanent bowel length, and other anatomic features, such as the presence of stomas, enteroatmospheric fistulas, and blind loops [71]. In this regard, Lal et al. [72] proposed a strategy that includes investigation/treatment of sepsis, assessment/optimization of nutritional status, knowledge of intestinal anatomy, and a long-term plan for each patient. This therapeutic plan was termed the "Sepsis-Nutrition-Anatomy-Plan" (SNAP), which serves as a useful guide to manage patients with type 2 IF.

The timing for reintervention should never be less than 6 months [12, 70, 71] after the last surgery. Procedure-related mortality and recurrence of intra-abdominal complications decrease when the patient is optimized and free of septic complications before the second intervention, which is often performed 9–12 months after the first [11, 73].

During this "bridge-to-surgery period," it is also important to provide psychological support. Whenever possible, it is recommended that these patients are discharged and receive ambulatory nutritional support before reintervention [11].

Preoperative evaluation requires radiological and endoscopic assessment of the entire digestive tract, including the segments distal to future anastomosis, to exclude stenosis. Abdominal/pelvic computed tomography with oral/vascular contrast is mandatory as an anatomical roadmap of segments to be anastomosed, to exclude intra-abdominal collections, and to evaluate the integrity of the abdominal wall [12]. Enterography and/or pelvic magnetic resonance imaging is indicated in patients with Crohn's disease to detect enteroenteric fistulas and perianal disease. In the presence of an ileal conduit or in patients who have undergone complex urological procedures, the urinary anatomy should be studied, as it may be beneficial to place ureteral stents preoperatively. There are indirect clinical signs that the abdomen has matured for surgery: absence of visible granulation tissue in the abdominal scars, bowel prolapse through the stoma or fistula orifice and a favorable "pinch test" (when the skin can be pinched and lifted from the underlying bowel, it means it can be easily dissected from it) [73].

Table 6. Indications for intestinal transplantation

Evidence of advanced or progressive IF-associated liver disease • Hyperbilirubinemia >4.5 mg/dL despite intravenous lipid modification strategies that persists for >2 months • Any combination of elevated serum bilirubin, reduced synthetic function (subnormal albumin or elevated international normalized ratio), and laboratory indications of portal hypertension and hypersplenism, especially low platelet count, persisting for >1 month in the absence of a confounding infectious event
Thrombosis of 3 out of 4 discrete upper body central veins (left subclavian and internal jugular, right subclavian and internal jugular) or occlusion of a brachiocephalic vein (last criterion should be evaluated in a case-by-case basis)
Life-threatening morbidity in the setting of indefinite PN dependence of either anatomical or functional cause (case-by-case basis)
Invasive intra-abdominal desmoids
Acute diffuse intestinal infarction with hepatic failure
Failure of first intestinal transplant

During the intervention, technical care should be taken to avoid postoperative complications [74]: (1) complete adhesiolysis of bowel segments; (2) repair of all desperitonization lesions; (3) avoid unnecessary additional resections; (4) prioritize meticulous and manual anastomosis; (5) avoid contact of the anastomoses with the abdominal wall; (6) remove previously placed infected/contaminated abdominal wall meshes; (7) never use a synthetic mesh for reconstruction; and (8) avoid reinterventions in suspected postoperative complications in favor of noninvasive/percutaneous procedures.

Role of Autologous Intestinal Reconstruction Surgery

In patients who reach a plateau of dependence on PN, with optimized nutritional/pharmacologic treatment and still no progression to enteral autonomy, autologous intestinal reconstruction surgery can be considered to improve intestinal absorption and facilitate the intestinal rehabilitation process [75]. Commonly performed procedures include antiperistaltic reversed segments, colonic interposition, tapering, longitudinal/spiral intestinal lengthening, serial transverse enteroplasty, and controlled tissue expansion. The main goals of autologous intestinal reconstruction surgery include [76] (1) slow intestinal transit to increase contact time between nutrients and mucosa, (2) correct short bowel stasis, (3) improve intestinal motility, and (4) increase mucosal surface area. Each procedure is designed to achieve one or several targets mentioned above and has its own indications and clinical applications, although evidence regarding which patients will benefit from these procedures and the optimal timing to perform the surgery is still scarce. The choice between the different methods should be individualized.

Indications for Intestinal Transplantation

Treatment options for irreversible CIF include lifelong HPN or intestinal transplantation (ITx) [34]. Although HPN is considered the primary treatment for CIF, early referral to intestinal rehabilitation centers with medical and surgical expertise is advised.

Four types of ITx have been described: (1) isolated bowel transplant, (2) combined liver-intestine transplant, (3) modified multivisceral transplant (stomach, jejunum, and ileum with or without the liver), and (4) multivisceral transplant (stomach, pancreas, duodenum, jejunum, and ileum with or without the liver). Classical indications that should prompt the assessment of candidacy for ITx in adults were revised in 2019 and are categorized in Table 6 [77].

Conclusion

CIF requires a comprehensive approach by a multidisciplinary team. Intestinal rehabilitation involves a multimodal treatment that includes nutritional intervention combined with medical management and, occasionally, surgical strategies that aim to reduce PN/HPN dependence, promote enteral independence, and improve quality of life.

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Statement of Ethics

Due to the nature of the article, ethical approval was not required.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Francisco Vara-Luiz, Luísa Glória, Ivo Mendes, Sandra Carlos, Paula Guerra, Gonçalo Nunes, Cátia Oliveira, Andreia Ferreira, Ana Paula Santos, and Jorge Fonseca performed literature review, selection of studies, and writing. Luísa Glória and Jorge Fonseca conceived the study design, structured the content, and critically reviewed the manuscript. All authors approved the final version of the manuscript.

Data Availability Statement

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

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Standard Cannulation versus Fistulotomy for Biliary Access in Endoscopic Retrograde Cholangiopancreatography: Should We Expect the Same Success when Treating Choledocholithiasis?

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Keywords
Choledocholithiasis · Endoscopic retrograde cholangiopancreatography · Catheterization · Needle-knife fistulotomy · Precut techniques

Abstract

Introduction: To access the common bile duct in endoscopic retrograde cholangiopancreatography (ERCP), needle-knife fistulotomy (NKF) can be associated with a shorter sphincterotomy compared to standard cannulation. We aimed to compare the success and safety of NKF versus standard cannulation in the treatment of choledocholithiasis. ***Methods:*** A cohort of 379 naïve patients with choledocholithiasis who underwent ERCP between 2005 and 2022 was retrospectively analyzed. The patients were divided into two groups: group A (179 consecutive patients) underwent NKF, while group B (180 patients) received standard biliary access and were matched for stone characteristics and ERCP year. ***Results:*** Stone removal success rate for group A was significantly lower than that for group B in the initial ERCP (82.0% vs. 92.1%, $p = 0.003$). In group A, success rates for stone removal were 90.2%, 80%, and 29.4% for stone sizes <10 mm, 10 mm–15 mm, and >15 mm, respectively ($p < 0.001$). In contrast, group B showed success rates of 99.2%, 81.5%, and 71.4% for the same stone size categories ($p < 0.001$). Pancreatitis occurred in 3.7% of group A and 5.8% of group B patients ($p = 0.340$). Regression analysis revealed that NKF cannulation, stone size (>10 mm), and having 4 or more stones were associated with lower stone removal success compared to standard cannulation in the initial ERCP (OR 0.34, $p = 0.015$; stone size 10–15 mm: OR 0.20, $p < 0.001$; stone size >15 mm: OR 0.05, $p < 0.001$; 4 or more stones: OR 0.4, $p = 0.040$). ***Conclusions:*** The removal of common bile duct stones after NKF access, although safe and effective, is less successful than after a standard cannulation, especially at the baseline ERCP.

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Canulação convencional versus fistulotomia para acesso à via biliar em CPRE: devemos esperar o mesmo sucesso no tratamento da coledocolitíase?

Palavras Chave
Coledocolitíase · Colangiopancreatografia retrógrada endoscópica · Cateterização · Fistulotomia com *needle-knife* · Técnicas de pré-corte

Resumo
Introdução: Para aceder à via biliar na CPRE, a fistulotomia com *needle-knife* (NKF) pode estar associada a uma esfincterotomia mais curta em comparação com a canulação convencional. O nosso objetivo é comparar o sucesso e a segurança da NKF versus a canulação convencional no tratamento da coledocolitíase. ***Métodos:*** Foi analisada retrospetivamente uma coorte de 379 pacientes *naïve* com coledocolitíase confirmada submetidos a CPRE entre 2005 e 2022. Os pacientes foram divididos em dois grupos: Grupo A (179 pacientes consecutivos) submetidos a NKF, enquanto no Grupo B (180 pacientes) o acesso biliar foi realizado por técnicas convencionais, sendo emparelhados quanto ao número e tamanho dos cálculos e quanto ao ano em que a CPRE foi realizada. ***Resultados:*** A taxa de sucesso na remoção de cálculos para o Grupo A foi significativamente inferior à do Grupo B na CPRE inicial (82.0% vs. 92.1%, p = 0.003). No Grupo A, as taxas de sucesso na remoção de cálculos foram de 90.2%, 80% e 29.4% para tamanhos de pedra <10 mm, 10 mm–15 mm e > 15 mm, respetivamente (p < 0.001). Por outro lado, o Grupo B apresentou taxas de sucesso de 99.2%, 81.5% e 71.4% para as mesmas categorias de tamanho dos cálculos (p < 0.001). A pancreatite ocorreu em 3.7% dos pacientes do Grupo A e 5.8% dos pacientes do Grupo B (p = 0.340). A análise de regressão revelou que no grupo A, o tamanho dos cálculos (>10 mm) e ter 4 ou mais cálculos estavam associados a uma menor taxa de sucesso em comparação com a canulação convencional na CPRE inicial (OR 0.34, p = 0.015; cálculo com 10–15 mm: OR 0.20, p < 0.001; cálculo com >15 mm: OR 0.05, p < 0.001; 4 ou mais cálculos: OR 0.4, p = 0.040). ***Conclusões:*** O tratamento da coledocolitíase por CPRE após acesso por NKF, embora segura e eficaz, é menos bem-sucedida do que após canulação convencional, especialmente na CPRE inicial.

Introduction

Choledocholithiasis accounts for 8–20% of gallstone disease, and endoscopic retrograde cholangiopancreatography (ERCP) is the gold standard for its treatment. The key step for successful therapeutic ERCP is selective deep biliary cannulation [1, 2]. However, standard techniques for biliary cannulation fail in 5–35% of cases, even with experienced endoscopists [1, 3]. Precut techniques have emerged as rescue procedures for accessing bile ducts. The European Society of Gastrointestinal Endoscopy (ESGE) recommends needle-knife fistulotomy (NKF) as the preferred technique for pre-cutting [4, 5]. Since NFK incision is made above and to the left of the papillary orifice, it avoids the contact with the pancreatic duct, being associated with a lower incidence of post-ERCP pancreatitis (PEP) [6–8].

Theoretically, NKF can be associated with a shorter sphincterotomy length, therefore creating the possibility of a lower success rate in the treatment of choledocholithiasis, when compared with larger sphincterotomies after standard cannulation. In the literature, to our knowledge, there is not a study designed to evaluate this specific topic. We aimed to compare the success and safety of NKF versus standard cannulation in the treatment of choledocholithiasis.

Materials and Methods

This was a retrospective cohort study of *naive* patients with confirmed choledocholithiasis submitted to ERCP between 2005 and 2022. Patients were selected from a prospective database maintained at our department and allocated into two groups (sample size assuming an effect size of 10%). Exclusion criteria were partial or total gastrectomy, evidence of duodenal or gastric outlet obstruction, or history of coagulopathy.

First, 179 consecutive naïve patients with confirmed choledocholithiasis submitted to NKF (as shown in Fig. 1) followed by sphincterotomy after failed standard cannulation (defined as more than 5 contacts with the papilla, more than 5 min spent while attempting to cannulate, or more than one unintended pancreatic duct cannulation or opacification) were selected (group A). The classic precut technique was not used in these patients. Subsequently, a control group (group B) with 180 naïve patients in whom standard biliary access followed by sphincterotomy was feasible was randomly selected by the investigators to match group A for stone size, number of stones, and year of the ERCP. These variables were considered important to minimize the differences in the perceived difficulty of the ERCP, potentially caused by the number or size of the stones, as well as the ability of the endoscopist.

All patients were submitted to sphincterotomy after NKF or standard cannulation. Large balloon dilatation and mechanical

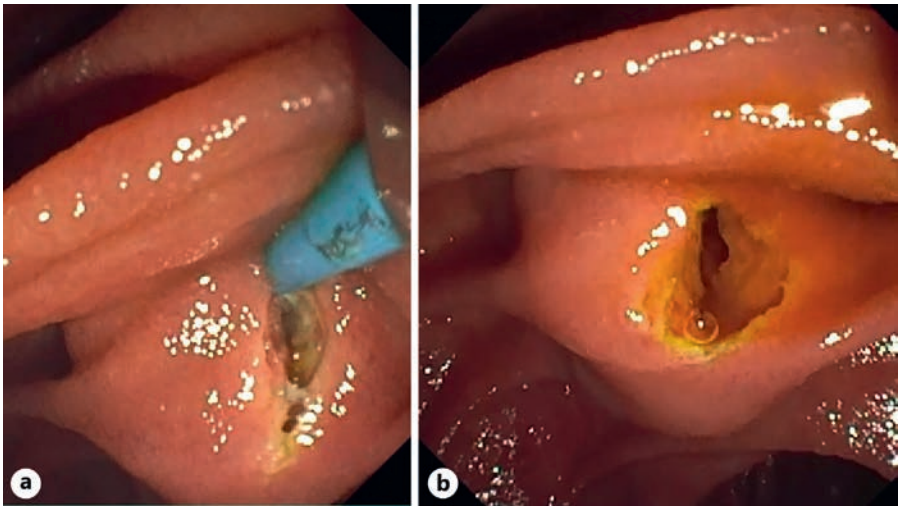

Fig. 1. a Needle-knife is used to perform an incision 3–5 mm from the papillary orifice. **b** Fistula between the duodenal and common bile duct luminae.

lithotripsy were allowed when necessary. In all patients, a stone extraction was attempted in the index ERCP in both groups. A plastic stent was placed in those patients who needed a repeat ERCP. Regarding the prophylaxis of PEP, patients received rectal indomethacin or hyperhydration with Ringer's lactate. Pancreatic stents were placed after multiple pancreatic cannulations.

The study variables included the following parameters: age (expressed in years), gender distribution, rates of pancreatic cannulation and stent placement, occurrence of adverse events (such as bleeding, pancreatitis, bowel perforation, and cholangitis), size and quantity of stones (in millimeters), initial success rate of stone removal during the first ERCP, overall success rate considering the need for additional ERCPs, techniques employed for stone extraction, and utilization of advanced ERCP techniques (if applicable), which encompassed mechanical lithotripsy, balloon dilation, and laser lithotripsy. Additionally, the rate of repeat ERCP procedures was also assessed.

The main outcomes were the rate of stone removal at baseline ERCP and adverse events. As this study was based on a prospective database, the follow-up of complications was performed in a systematic manner by the investigation team 30 days after ERCP.

Qualitative variables are summarized using absolute and relative frequencies, and quantitative variables are summarized using the mean and standard deviation or the median and range, depending on their distribution profiles. The normality of the quantitative variables was assessed using the histogram distribution and the Shapiro-Wilk test.

Differences between categorical variables were tested using a χ^2 test and Fisher´s exact test. For quantitative variables, student's *t* test and Mann-Whitney test were used for comparisons, depending on initial normality assessment.

A logistic regression was performed to evaluate predictors of success and adverse events. The model contained 5 independent variables (age, sex, number of stones, largest stone size, and cannulation type) that were selected based on the clinical probability of interfering with the success of the ERCP treatment.

The null hypothesis was rejected when the test statistics *p* values were less than <0.05. Statistical analysis and graphics were performed using Stata software (StataCorp. 2015; Stata Statistical Software: Release 14; College Station, TX, USA: StataCorp LP).

Table 1. Demographic and stone characteristics (*N* = 379)

	N (%)
Age, years	
Median, min, max	79.57 (26–97)
Sex	
Female	224 (59.10)
Male	155 (40.90)
Largest stone in *mm*	
Mean, SD	8.39, 5.28
Number of stones	
1 stone	156 (41.16)
2 stones	83 (21.90)
3 stones	45 (11.87)
≥4 stones	95 (25.07)

SD, standard deviation; IQR, interquartile range.

Results

As shown in Table 1, a total of 379 patients were included (*n* = 224, 59.1% females, mean age 75.10 years [26–97 years]). The stone removal success rate was, globally, 87.1% in the index ERCP. In 56 (14.8%) patients, a repeated ERCP was deemed necessary, and the global success rate for complete stone extraction was 97.9%. Balloon catheters (81%) and wire baskets (45.1%) were used to extract stones. There was a need for advanced stone extraction techniques in 21 patients (5.5%) in the index ERCP and 10.8% in the repeated ERCP.

Table 2. ERCP techniques, success, and adverse events

	N (%)
Stone removal success (ERCP index)	330 (87.07)
Stone removal success (global)	371 (97.89)
Stone extraction techniques	
Balloon catheters	307 (81.00)
Wire baskets	171 (45.12)
Advanced stone extraction techniques (ERCP index)	21 (5.54)
Mechanical lithotripsy	15 (3.96)
EPBD	6 (1.58)
Advanced stone extraction techniques (global)	41 (10.82)
Mechanical lithotripsy	18 (4.79)
EPBD	8 (2.11)
Laser lithotripsy	15 (3.96)
ERCP repeat	56 (14.78)
Adverse events	25 (6.60)
Pancreatitis	18 (4.75)
Bleeding	4 (1.06)
Cholangitis	3 (0.80)
Perforation	3 (0.80)
Pancreatic cannulation	60 (15.83)
Pancreatic stent placement	5 (1.32)

EPBD, endoscopic papillary balloon dilation.

Table 3. Demographic and stone characteristics per type of cannulation

	NKF, *n* (%)	Standard, *n* (%)	*p* value
Age			0.076
Median, min, max	79 (30, 97)	80 (26.96)	
Sex			0.268
Female	117 (61.91)	107 (56.36)	
Male	72 (38.13)	83 (43.74)	
Largest stone in mm (mean±SD)	8.46±6.00	8.33±4.78	0.068
<10	122 (64.55)	122 (64.21)	
≥10 or ≤15	50 (26.46)	54 (28.42)	
>15	17 (8.99)	14 (7.37)	
Number of stones (mean±SD)	2.67±1.79	2.24±1.45	0.957

EPBD, endoscopic papillary balloon dilation.

As shown in Table 2, overall, 25 procedures had complications: the rates of pancreatitis, bleeding, cholangitis, and bowel perforation were 4.8%, 1.1%, 0.8%, and 0.8%, respectively. Pancreatic cannulation was performed in 60 patients (15.8%), with 5 (1.3%) receiving a pancreatic stent.

As shown in Table 3, both groups were similar regarding age, sex, and stone characteristics. The success in the index ERCP group A was significantly lower than that of the control group (82% vs. 92.1%, $p = 0.003$), as demonstrated in Table 4.

As revealed in Table 5, the stone removal success in the NKF group at the initial ERCP, for stones <10 mm, 10 mm–15 mm, and >15 mm, was 90.2%, 80%, and 29.4%, respectively ($p < 0.001$); in group B, it was 99.2%, 81.5%, and 71.4%, respectively ($p < 0.001$). Pancreatitis occurred in 3.7% of patients in group A and in 5.8% in group B ($p = 0.340$).

In the regression analysis (Table 6), NKF cannulation was associated with a lower stone removal success rate compared with standard cannulation in the initial ERCP (odds ratio [OR] 0.34; 95% CI: 0.14–0.81; $p = 0.015$). Stone size (10–15 mm and >15 mm) and having 4 or more stones were also predictors for a lower rate of stone removal in the initial ERCP (stone size 10–15 mm: OR 0.20, $p = 0.000$; stone size >15 mm: OR 0.05, $p = 0.000$; 4 or more stones: OR 0.4, $p = 0.040$, respectively).

Table 4. ERCP techniques, success, and adverse events by type of cannulation

	NKF (n = 189), n (%)	Standard (n = 190), n (%)	p value
Stone removal success (ERCP index)	155 (82.01)	175 (92.11)	**0.003**
Stone removal success (global)	182 (96.30)	189 (99.47)	**0.031**
Stone extraction techniques			
Balloon catheters	153 (80.96)	154 (81.05)	0.980
Wire baskets	76 (40.21)	95 (50.00)	0.056
Advanced stone extraction techniques (ERCP index)	10 (5.29)	11 (5.79)	0.832
Mechanical lithotripsy	5 (2.65)	10 (5.26)	–
EPBD	5 (2.65)	1 (0.53)	–
Advanced stone extraction techniques (global)	21 (11.11)	20 (10.53)	0.217
Mechanical lithotripsy	7 (3.70)	11 (5.79)	–
EPBD	6 (3.14)	3 (1.58)	–
Laser lithotripsy	5 (2.65)	10 (5.26)	0.217
ERCP repeat	35 (18.52)	21 (11.05)	0.191
Adverse events	13 (6.88)	14 (7.37)	0.307
Pancreatitis	7 (3.70)	11 (5.80)	0.340
Bleeding	2 (1.06)	2 (1.05)	1.000
Cholangitis	3 (1.59)	0 (0.00)	–
Perforation	1 (0.53)	2 (1.05)	0.123
Pancreatic cannulation	37 (19.58)	23 (12.11)	0.461
Pancreatic stent placement	5 (2.65)	0 (0.00)	**0.024**

EPBD, endoscopic papillary balloon dilation.

Table 5. ERCP techniques, success, and adverse events by stone size (mm)

	<10 mm, n (%)	10 mm – ≤ 15 mm, n (%)	>15 mm, n (%)	p value
Cannulation technique				–
NKF	122 (50.00)	50 (48.07)	17	
Standard	122 (50.00)	54	14	
Stone removal success (ERCP index)	231 (94.67)	84 (80.77)	15 (48.39)	**0.000**
NKF	110 (90.16)	40 (80.00)	5 (29.41)	**0.000**
Standard	121 (99.18)	44 (81.48)	10 (71.43)	**0.000**
Stone removal success (global)	240 (98.36)	101 (97.12)	30 (96.77)	0.687
NKF	119 (97.54)	47 (94.00)	16 (94.12)	0.531
Standard	121 (99.18)	54 (100.00)	14 (100.00)	0.756
Advanced extraction techniques (ERCP index)	3 (1.23)	11 (10.58)	7 (22.58)	**0.000**
Mechanical lithotripsy	2 (0.08)	9 (8.65)	4 (12.90)	**0.000**
EPBD	1 (0.40)	2 (1.92)	3 (9.68)	
Laser lithotripsy	0 (0.00)	0 (0.00)	0 (0.00)	**–**
Advanced extraction techniques (global)	3 (1.23)	19 (18.27)	19 (61.30)	**0.000**
Mechanical lithotripsy	2 (0.08)	11 (10.57)	5 (16.13)	–
EPBD	1 (0.40)	4 (3.85)	4 (12.90)	–
Laser lithotripsy	0 (0.00)	5 (4.81)	10 (32.26)	**0.000**
ERCP repeat	16 (6.56)	26 (25.00)	14 (45.16)	**0.000**

EPBD, endoscopic papillary balloon dilation.

Table 6. Logistic regression model for ERCP stone extraction success

	Success ERCP index				Success ERCP global			
	OR	*p* value	95% CI		OR	*p* value	95% CI	
Age	1.01	0.597	0.98	1.03	0.97	0.419	0.90	1.04
Sex								
Female	Base case				Base case			
Male	0.57	0.123	0.28	1.17	2.20	0.387	0.37	13.09
Number of stones								
1	Base case				Base case			
2	1.06	0.909	0.40	2.77	0.58	0.614	0.71	4.78
3	0.80	0.749	0.21	3.10	0.26	0.312	0.02	3.57
≥4	0.40	**0.040**	0.35	1.65	0.84	0.869	0.10	6.91
Largest stone size, mm								
<10	Base case				Base case			
10–≤ 15	0.20	**0.000**	0.09	0.46	1.25	0.754	0.30	5.17
>15	0.05	**0.000**	0.02	0.15	1.29	0.884	0.04	41.36
Cannulation type								
NFK	Base case		1.24		Base case			
Standard	2.93	**0.015**	1.24	6.92	6.60	0.143	0.53	82.67

Discussion

In our study, the ERCP success rate for complete stone extraction was over 87% at the index procedure and nearly 98% overall. These findings are consistent with a meta-analysis evaluating ERCP quality indicators, which found that stone extraction is successful in 88% of procedures [9].

When comparing the two groups, standard cannulation proved to have a higher success rate in stone removal at the index ERCP when compared to NKF, although both techniques demonstrated a high success rate, particularly for stones under 10 mm (>90% success rate). The difference between groups was more pronounced in stones with more than 15 mm, with 29% success rate in the index NKF ERCP and 71% in the standard cannulation group. These data could support our hypothesis that the lower success rate is probably related to a smaller biliary orifice in NKF. However, when including the repeat ERCP (global ERCP success rate), the stone size did not convey a difference. This finding could be attributed to the use of plastic stents after a failed index ERCP and an increased utilization of alternative advanced stone extraction techniques in the repeat ERCP, which might have contributed to overcoming the challenges posed by larger stone sizes, such as the length of sphincterotomy. Our findings suggest that, in patients undergoing NKF, the use of large ballon dilation or a careful extension of sphincterotomy during the first ERCP could potentially enhance its therapeutic effectiveness and decrease the requirement for repeat ERCP. These observations align with Archibugi et al. [10], who reported that the reintervention rate for choledocholithiasis was significantly higher in a short term after ERCP by NKF, particularly because of incomplete common bile duct clearing.

As expected, the largest stone size and number of stones were predicting factors that influence index ERCP stone removal success, though it is important to note that the number of stones only had a significant impact on the overall success rate if there were 4 or more. Recently, there has been a growing interest in the scientific community regarding the utilization of primary NKF as a first-line approach, rather than a rescue method, for cannulating the common bile duct and gaining access to the biliary tree without any contact with the papilla orifice [11]. Canena et al.'s recent meta-analysis demonstrated that primary NKF was associated with high rates of cannulation success, low rates of complications, and shorter procedural duration [12]. However, according to our findings, NFK is not as effective as the standard cannulation when it comes to treatment of choledocholithiasis, the most common indication for ERCP.

The observed complication rate in our study was 6.6%, like those reported in the literature (5.0–15.9%) [4, 5]. Notably, the incidence of PEP was 4.8%, which was lower than the anticipated range of 5–7% [5, 13]. In our analysis, the type of cannulation did not demonstrate a statistically significant impact on the occurrence of PEP. However, there

was a notable trend toward a lower PEP rate in the NKF group (3.7%) compared to standard cannulation (5.8%).

Mavrogiannis et al. [14] published a prospective study aimed to compare the success and safeness of NKF (74 patients) with classic precuts (79 patients) that showed similar results as ours, meaning more repeat ERCP and lithotripsy are needed more often. Also, NKF proved to be safer than needle-knife precut papillotomy with respect to pancreatic complications.

As NKF is a rescue and expertise-demanding technique, it is impractical to develop randomized controlled trials comparing both techniques, so this study of 379 patients matched for demographic and stone characteristics can provide important data regarding the impact on the success rate of NKF in the treatment of choledocholithiasis. The retrospective design and 17-year timeframe are important limitations that precluded the inclusion of variables such as duration of the procedure or the morphology of the papilla. In the future, it would be interesting to study this matter in a prospective manner.

Statement of Ethics

The study was approved by the Ethical Committees from "Comissão de Ética para a Investigação em Ciências da Vida e da Saúde (CEIVCS)" – 089/2022 and "Comissão de Ética em Saúde (CES)" of Hospital de Santa Luzia – 57/2022. All the study procedures were carried out in accordance with the Declaration of Helsinki, and all patients provided written informed consent before their procedures.

Conflict of Interest Statement

The authors declare no conflicts of interest for this article.

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Author Contributions

Marta Moreira wrote the manuscript. Isabel Tarrio and Alda João Andrade helped with the data collection. Tarcísio Araújo, João Sousa Silva Fernandes, Jorge Canena, and Luís Lopes were responsible for the revision of the methodology and manuscript edition.

Data Availability Statement

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

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Deep Learning and Minimally Invasive Endoscopy: Panendoscopic Detection of Pleomorphic Lesions

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Keywords
Artificial intelligence · Capsule endoscopy · Deep learning · Panendoscopy

Abstract
Introduction: Capsule endoscopy (CE) is a minimally invasive exam suitable of panendoscopic evaluation of the gastrointestinal (GI) tract. Nevertheless, CE is time-consuming with suboptimal diagnostic yield in the upper GI tract. Convolutional neural networks (CNN) are human brain architecture-based models suitable for image analysis. However, there is no study about their role in capsule panendoscopy. ***Methods:*** Our group developed an artificial intelligence (AI) model for panendoscopic automatic detection of pleomorphic lesions (namely vascular lesions, protuberant lesions, hematic residues, ulcers, and erosions). 355,110 images (6,977 esophageal, 12,918 gastric, 258,443 small bowel, 76,772 colonic) from eight different CE and colon CE (CCE) devices were divided into a training and validation dataset in a patient split design. The model classification was compared to three CE experts' classification. The model's performance was evaluated by its sensitivity, specificity, accuracy, positive predictive value, negative predictive value, and area under the precision-recall curve. ***Results:*** The binary esophagus CNN had a diagnostic accuracy for pleomorphic lesions of 83.6%. The binary gastric CNN identified pleomorphic lesions with a 96.6% accuracy. The undenary small bowel CNN distinguished pleomorphic lesions with different hemorrhagic potentials with 97.6% accuracy. The trinary colonic CNN (detection and differentiation of normal mucosa, pleomorphic lesions, and hematic residues) had 94.9% global accuracy. ***Discussion/Conclusion:*** We developed the first AI model for panendoscopic automatic detection of pleomorphic lesions in both CE and CCE from multiple

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brands, solving a critical interoperability technological challenge. Deep learning-based tools may change the landscape of minimally invasive capsule panendoscopy.

Deep Learning e Endoscopia Minimamente Invasiva: Deteção panendoscópica de lesões pleomórficas

Palavras Chave
Deep learning · Endoscopia por cápsula · Inteligência artificial · Panendoscopia

Resumo
Introdução: A endoscopia por cápsula (EC) é um exame minimamente invasivo que avalia todo o trato gastrointestinal. Contudo, é morosa, com acuidade limitada no trato digestivo superior. As redes convolucionais neurais (RCN) são modelos baseados na arquitetura cerebral humana aperfeiçoados para análise de imagens. Contudo, o seu papel na panendoscopia por cápsula ainda não foi estudado. ***Métodos:*** Desenvolveu-se um modelo de inteligência artificial (IA) para deteção panendoscópica de lesões pleomórficas (nomeadamente lesões vasculares, protuberantes, resíduos hemáticos, úlceras e erosões). 355,110 imagens (6,977 esofágicas, 12,918 gástricas, 258,443 do intestino delgado e 76,772 colónicas) de oito dispositivos diferentes de enteroscopia e panendoscopia por cápsula foram divididas num *dataset* de treino e validação num desenho *patient split*. A classificação da RCN comparou-se com a de três especialistas em CE. O modelo foi avaliado através da sensibilidade, especificidade, valor preditivo positivo, valor preditivo negativo, acuidade e área sob curva *precision-recall*. ***Resultados:*** A RCN binária esofágica teve acuidade de 83.6% para lesões pleomórficas. A RCN binária para lesões gástricas pleomórficas teve acuidade de 96.6%. A RCN de 11 categorias de intestino delgado diferenciou lesões pleomórficas com diferente potencial hemorrágico com acuidade de 97.6%. A RCN trinaria colónica (mucosa normal, lesões pleomórficas e resíduos hemáticos) teve acuidade de 94.9%. ***Discussão/Conclusão:*** Desenvolveu-se o primeiro modelo de IA com elevada acuidade na deteção panendoscópica de lesões pleomórficas em dispositivos de enteroscopia e panendoscopia por cápsula, solucionando um desafio de interoperabilidade tecnológica. A utilização de modelos de deep learning pode alterar o panorama da panendoscopia por cápsula.

Introduction

Capsule endoscopy (CE) is a minimally invasive exam preconized in the study of the small bowel [1, 2], but capable of evaluating the entire gastrointestinal (GI) tract [3]. With the development of colon capsule endoscopy (CCE), CE-based panendoscopy is an evolving concept with the need to achieve a minimally invasive alternative for the evaluation of the entire GI tract [4, 5]. Whereas conventional esophagogastroduodenoscopy and colonoscopy are the current standards of care for evaluating the esophagic, gastric, and colonic mucosa, there is a need to consider the invasiveness of the exam, with a non-neglectable risk of complications like infection, bleeding, perforation and cardiopulmonary adverse events [6]. Moreover, the use of sedation techniques during the exam can increase costs related to the procedure and loss of working days by the patients [7], limiting the cost-effectiveness of both procedures in a screening setting.

Nevertheless, we must consider the intrinsic limitations of CE, especially in the upper GI tract. CE diagnostic performance for esophagic gastric lesions is still suboptimal. In fact, esophagus transit time is short and common pathologies are identified near the esophagogastric junction [8], with the scarcity of images affecting CE diagnostic yield. Regarding the stomach, the absence of insufflation in CE limits the observation of the complete structure, especially the more proximal region [9]. CE dependence of the peristaltic movements can also be a challenge concerning its diagnostic yield in the upper GI tract.

CE is a time-consuming exam, with reading times that can reach up to 120 min per exam [10]. The large number of frames produced by a single CE exam favors the use of artificial intelligence (AI) tools for image analysis. Convolutional neural networks (CNN) are a multi-layer architecture inspired by the human visual cortex, with high accuracy for imaging analysis, especially image pattern detection [11]. CNN models have been studied in several medical areas [12–14]. CE is the main focus of study for developing CNN-based technologies [15–17], augmenting its cost-effectiveness by increasing the diagnostic yield with a reduction in the reading time. Whereas there are several works about AI tools in CE for the evaluation of the small bowel [17, 18], colon [19], and even gastric mucosa [20], the role of this technology in the identification of esophageal lesions by CE is still to be explored. In this study, our group aimed to create the first worldwide AI-based model for panendoscopic (esophageal, gastric, enteric, and colonic) automatic detection of

pleomorphic lesions in a multi-device design, namely vascular lesions, hematic residues, protruding lesions, ulcers, and erosions.

Methods

Study Design

Our group aimed to develop an AI-based algorithm for the panendoscopic automatic detection of pleomorphic lesions including vascular lesions (red spots, angiectasia, and varices), xanthelasma, xanthomas, luminal blood, protruding lesions, ulcers, and erosions. This multicentric multi-device study was based on esophageal, gastric, small bowel, and colonic images obtained from eight different CE types (PillCam SB3™; PillCam SB1™; PillCam Crohn's™; PillCam Colon 1™, PillCam Colon 2™, MiroCam Capsule Endoscope™, Olympus Endocapsule™, OMOM HD Capsule Endoscopy System™) in two different centers (Centro Hospitalar Universitário São João and ManopH), comprising 5,846 CE exams in 4,372 patients between June of 2011 and December of 2022.

Our study was developed in a non-interventional fashion, respecting the Declaration of Helsinki, and was approved by the Ethics Committee of São João University Hospital/Faculty of Medicine of the University of Porto (No. CE 407/2020). Potentially identifying information of the subjects was omitted and each patient received a random number assignment in order to obtain effective data anonymization for researchers involved in the CNN network. The non-traceability of the data in conformity with general data protection regulation was ensured by a legal team with Data Protection Officer (DPO) certification (Maastricht University).

CE Protocol

CE procedures were conducted using eight different CE devices: the *PillCam* SB1™ system (Medtronic, Minneapolis, MN, USA), the *PillCam* SB3™ system (Medtronic, Minneapolis, MN, USA), the PillCam Colon 1™ (Medtronic, Minneapolis, MN, USA), the PillCam Colon 2™ (Medtronic, Minneapolis, MN, USA), the PillCam Crohn's™ (Medtronic, Minneapolis, MN, USA), the MiroCam Capsule Endoscope™ (IntroMedic, Seoul, Korea), the Olympus Endocapsule™ (Olympus, Tokyo, Japan), and the OMOM HD™ Capsule Endoscopy System (Jinshan Science & Technology Co., Chongqing, Yubei, China).

Images from PillCam SB3, PillCam SB1, PillCam Colon 2, and PillCam Crohn's CE were reviewed using the PillCam™ Software version 9 (Medtronic), whereas PillCam Colon 1 images were reviewed with an older version of PillCam™ software. The Olympus Endocapsule images were revised in the Endocapsule 10 System (Olympus). The MiroCam images are viewed in the MiroView Software (IntroMedic). The Vue Smart Software (Jinshan Science & Technology Co.) was used for reviewing the OMOM HD videos. After the removal of potential patient-identifying information, extracted frames were stored and labeled with a consecutive number.

Each patient underwent bowel preparation following previous recommendations by the European Society of Gastrointestinal Endoscopy [1]. Briefly, patients kept a clear liquid diet on the day before capsule ingestion, fasting the night before the exam. In the patients performing small bowel capsule endoscopy (SBCE), 2 L of polyethylene glycol solution was consumed before the exam. Simethicone was the chosen anti-foaming agent. 10 mg of domperidone was given to each patient as a prokinetic if the capsule remained in the stomach 1 h after ingestion (implying hourly image review on the data recorder worn by the patient). When performing CCE, a bowel preparation consisting of 4 L of polyethylene glycol solution was taken in split form (2 L in the evening before the exam and 2 L in the morning of the exam). Two boosters of 25 and 20 mL of a sodium phosphate solution were ingested when the capsule entered the small bowel and 3 h later.

Classification of Lesions

The different segments of each CE exam were reviewed for the identification of pleomorphic lesions. The pleomorphic lesions included vascular lesions (red spots, angiectasia, and varices), xanthomas, lymphangiectasias, protruding lesions, ulcers, and erosions. Our model was also evaluated for the detection of luminal blood. Classification scores used in SBCE were adapted for the definition of the different lesions [21]. Lymphangiectasias were considered white-colored points of the intestinal mucosa, while xanthomas were defined as yellowish plaque-like lesions.

Red spots were defined as flat punctuate lesions under 1 mm, with a bright red area, without vessel appearance [21]. Angiectasia consisted of reddish lesions of tortuous and dilated clustered capillaries. Varices were defined as raised serpiginous venous dilations. The subgroup of protruding lesions consisted of polyps, flat lesions, nodules and subepithelial lesions. Mucosal erosions were described as areas of minimal loss of epithelial layering with normal surrounding mucosa. Ulcers were defined as depressed loss of epithelial covering, with a whitish base and surrounding swollen mucosa, with an estimated diameter of >5 mm.

The lesions identified in the small bowel were classified into three levels of bleeding risk with the Saurin classification [22], with P0, P1, and P2 classification for absent, intermediate or high hemorrhagic risk, respectively. P0 lesions encompassed lymphangiectasia and xanthomas. P1 lesions comprised red spots, mucosal erosions, small ulcers and the majority of the protuberant lesions, whereas P2 classification encompassed angiectasia and varices, large ulcerations (>20 mm) and large (>10 mm) or ulcerated protuberant lesions. Three CE expert gastroenterologists, with an experience of over 1000 CE exams prior to the study, classified each of the extracted images.

CNN Development

The study design is displayed through a flowchart in Fig. 1. Table 1 displays the characteristics and methodological specificities of each CNN.

A total of 6,977 selected esophageal images were inserted in our CNN with transfer learning. The full esophageal dataset consisted of 3,920 images of normal mucosa and 3,057 images of esophageal lesions (namely vascular lesions, hematic residues, ulcers, erosions, and protuberant lesions). The images were divided into a training and validation dataset, in a patient split design (with all the images from a given patient allocated to the same dataset). The binary esophageal CNN (normal mucosa vs. pleomorphic lesions) was evaluated as the mean of the

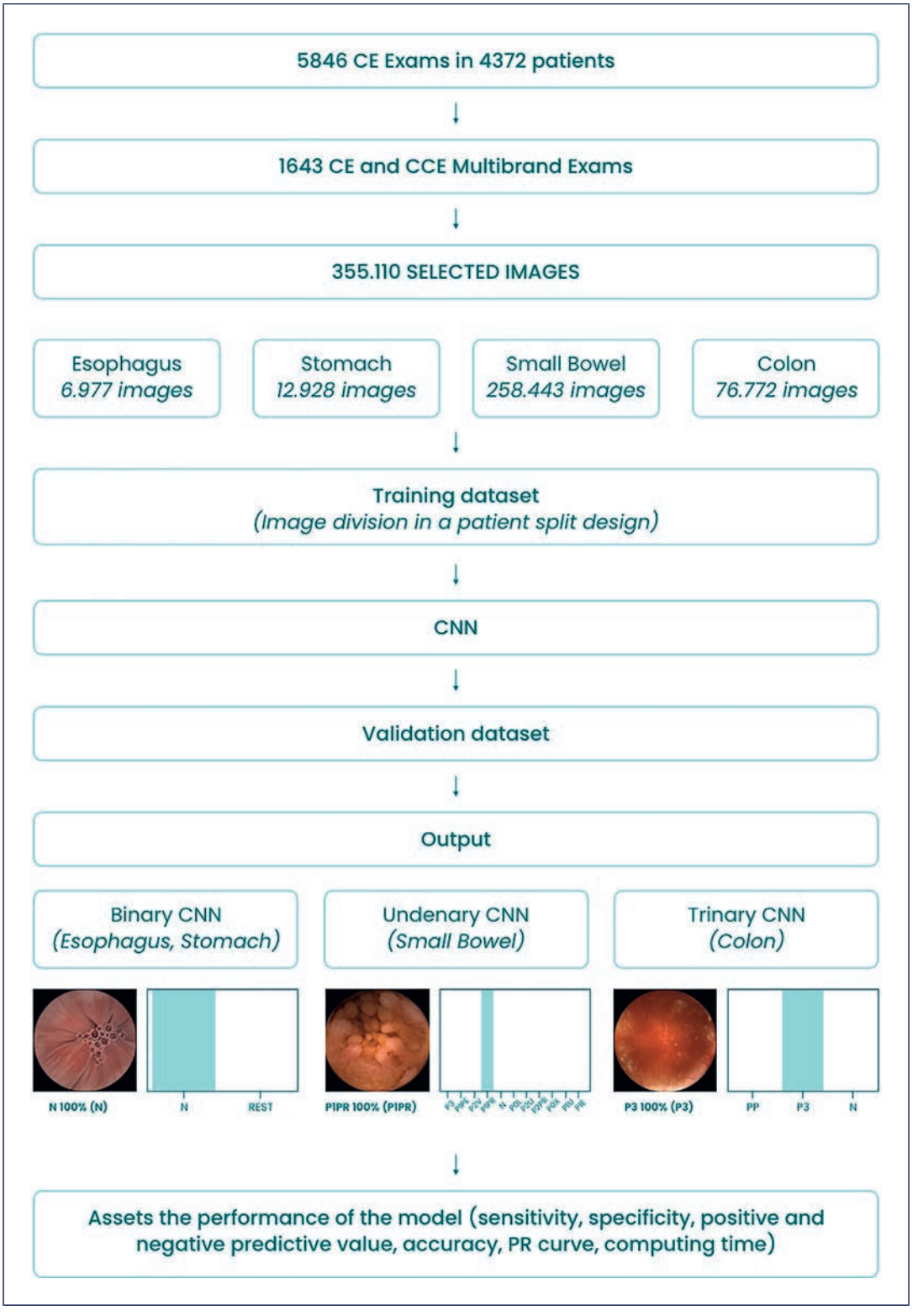

Fig. 1. Study flowchart for the training and validation phases. CE, capsule endoscopy; CCE, colon capsule endoscopy; N, normal mucosa; P3, hematic residues; P1PE, P1 red spots; P2V, P2 vascular lesions; P1PR, P1 protuberant lesions; P0L, P0 lymphangiectasia; P2U, P2 ulcers; P2PR, P2 protuberant lesions; P0X, xanthomas; P1U, P1 ulcers; P1E, P1 erosions; PP, pleomorphic lesions.

Table 1. CNN methodological characteristics in the different locations

CNN organ	No. of images	No. of exams	CE devices (No. of exams)	CNN evaluation
Esophagus	6,977	536	PillCam SB3 (270) PillCam Crohn's (207) OMOM (59)	The binary CNN (normal mucosa vs. pleomorphic lesions) was evaluated as the mean of the outcomes of three different validation dataset evaluation with different parameters
Stomach	12,918	107	PillCam SB3 (84) OMOM (14) PillCam Crohn'S (9)	The binary CNN (normal mucosa vs. pleomorphic lesions) was evaluated with the validation dataset (comprising around 10% of the total of images)
Small bowel	258,443	957	PillCam SB3 (724) OMOM (137) PillCam Crohn's (88) Colon 2 (3) MiroCam (2) PillCam SBI (2) Olympus (1)	The undenary CNN was evaluated with the validation dataset (comprising around of the total of images)
Colon	76,772	148	PillCam Crohn's (97) PillCam SB3 (25) PillCam colon 1 (17) PillCam Colon 2 (5) OMOM (4)	The trinary CNN (normal mucosa vs. pleomorphic lesions vs. hematic residues) was evaluated with the validation dataset

CNN, convolutional neural network.

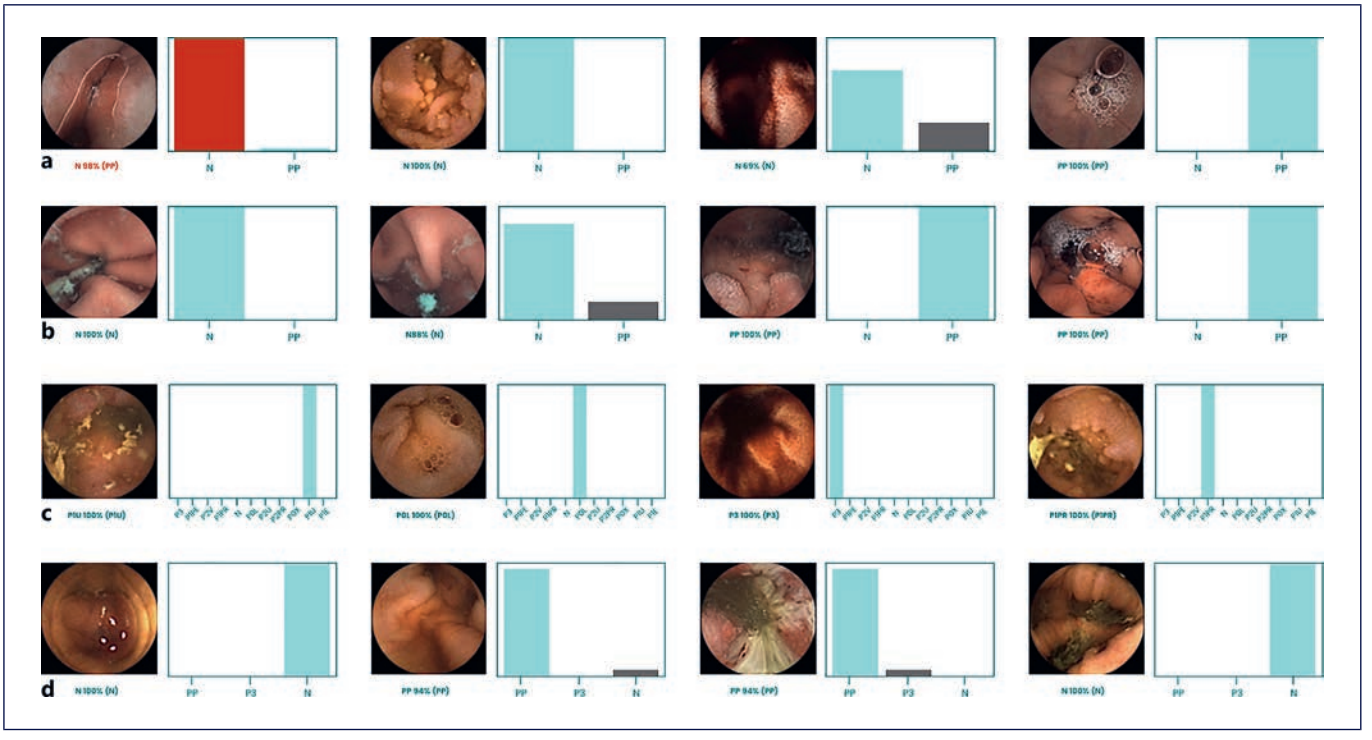

Fig. 2. Output obtained from the application of the CNN, for the pleomorphic lesions in diverse locations (esophagus [**a**]; stomach [**b**]; small bowel [**c**]; colon [**d**]). The bars represent the estimated probability by the CNN model. The finding with the highest probability was outputted as the predicted classification. The blue bars represent a correct prediction, whereas the red bars represent an incorrect prediction. N, normal mucosa; P3, hematic residues; P1PE, P1 red spots; P2V, P2 vascular lesions; P1PR, P1 protuberant lesions; P0L, P0 lymphangiectasia; P2U, P2 ulcers; P2PR, P2 protuberant lesions; P0X, xanthomas; P1U, P1 ulcers; P1E, P1 erosions; PP, pleomorphic lesions.

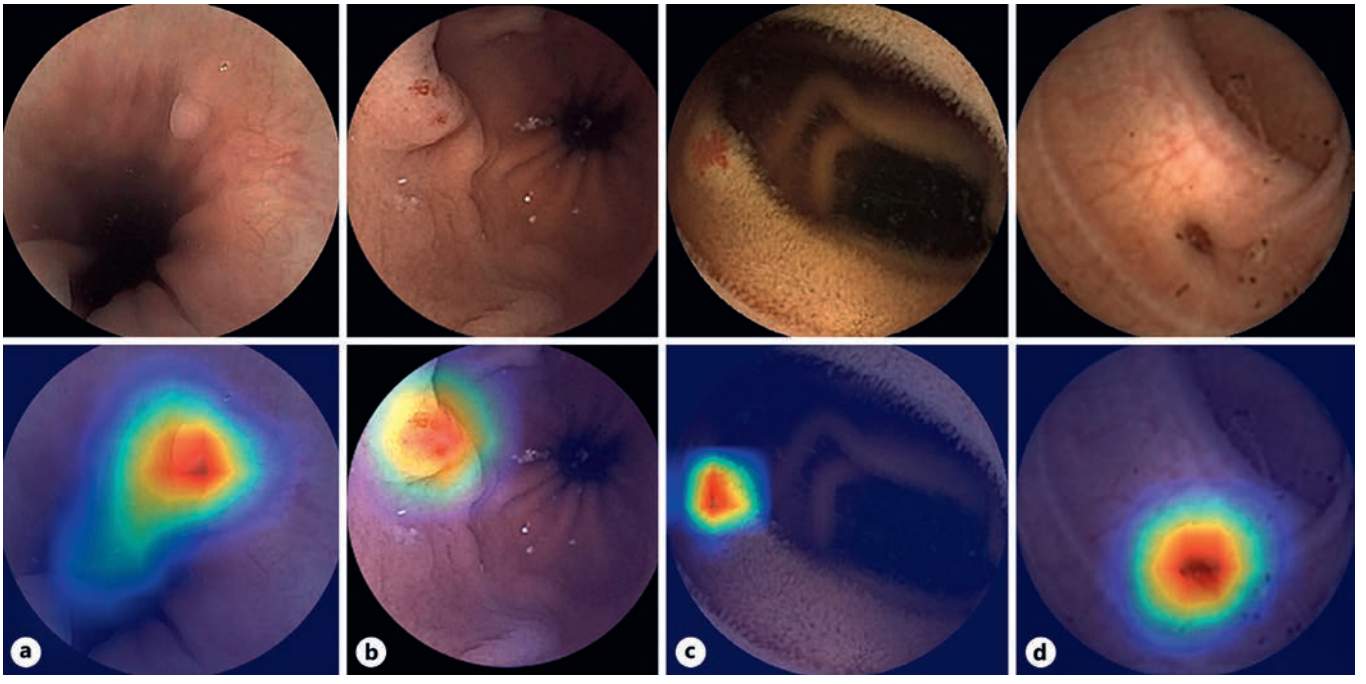

Fig. 3. Heatmaps obtained from the application of the CNN showing pleomorphic lesions in the esophagus (**a**), stomach (**b**), small bowel (**c**), and colon (**d**), as identified by the CNN.

outcomes of three different evaluations of the CNN with different model parameters.

Regarding the gastric CNN, 12,918 gastric images were used, including 6,844 normal images and 6,074 images of gastric lesions. The images were divided into a training (around 90% of the total images, n = 11,289) and validation dataset (around 10% of the total images, n = 1,629), in a patient split design. A 3-fold cross-validation was used in the development of the stomach CNN, with experimentation of different model parameters for obtaining the fittest model. The validation dataset was used to evaluate the performance of the model.

A total of 258,443 images were used for the construction of the small bowel dataset, with 62,792 normal images and 195,691 images of enteric lesions. The images were divided in a training (around 80% of the total images, n = 205,498) and validation dataset (around 20% of the total images, n = 52,945) in a patient split design. A 5-fold cross-validation was used to test the different model parameters and obtain the fittest model. The enteric CNN consisted of an undenary model, with a total of 11 categories, including normal mucosa, hematic residues and pleomorphic lesions with different hemorrhagic potential. The performance of the model was evaluated with the validation dataset.

Our colonic dataset contained 76,772 images, with 53,989 normal mucosa images, 3,918 images from hematic residues and 18,865 images from pleomorphic lesions. The images were divided into training (n = 72,438) and validation (n = 4,334) datasets, with the latter being used for the evaluation of the model. This CNN was evaluated as a trinary model, testing the CNN for distinguishing between normal mucosa, hematic residues and pleomorphic colonic lesions.

The Xception model pre-trained on ImageNet was used for the creation of the CNN. Convolutional layers of the model were kept in order to transfer this learning to our data, while the last fully connected layers were removed, and fully connected layers were attached based on the number of classes used to classify the CE images.

The model consisted of 2 blocks, comprising fully connected layers followed by a Dropout layer of 0.25 drop rate. Following these 2 blocks, a Dense layer with a size defined as the number of categories to classify was added. Our group set by trial and error a learning rate of 0.0001, batch size of 128, and the number of epochs of 20. We used Tensor-flow 2.3 and Keras libraries to prepare the data and run the model. The analyses were performed with a computer equipped with an Intel® Xeon® Gold 6130 processor (Intel, Santa Clara, CA, USA) and a NVIDIA Quadro® RTX™ 4000 graphic processing unit (NVIDIA Corporate, Santa Clara, CA, USA).

Performance Measures and Statistical Analysis

For a given image, the CNN model calculated the probability for each category (normal mucosa vs. pleomorphic lesions in the esophagus and stomach, normal mucosa vs. ten categories of lesions with different hemorrhagic potential in the small bowel, normal mucosa vs. pleomorphic lesions vs. hematic residues in the colon), with a given probability (Fig. 2), with higher probability values translating greater CNN prediction confidence. The software generated heatmaps identifying features that were the base of the prediction (Fig. 3). The CNN output was compared to the consensus classification by three CE experts', nowadays considered the gold standard for the evaluation of CE. The confusion matrix between experts and the CNN classification is presented in Table 2.

The primary performance measures included sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy (Table 3). These measures were represented with their

Table 2. Confusion matrix between experts and CNN classification

	Sn	sp	VPP	VPN	Acc	AUC-PR
Esophagus (*n* = 6,977)						
Training dataset mean	55.1 (50.4–59.4)	87.3 (85.3–89.1)	67.3 (65.0–69.5)	68.5 (67.2–69.7)	68.8 (66.7–70.8)	
Validation dataset	76.3 (71.1–80.9)	86.2 (80.5–90.9)	90.6 (86.5–93.5)	79.0 (73.7–83.2)	83.6 (79.9–86.9)	0.90
Stomach (*n* = 12,918)						
Training dataset mean	87.8 (86.9–88.7)	92.3 (91.6–93.0)	91.4 (90.6–92.0)	89.2 (88.5–89.9)	90.2 (89.6–90.7)	
Validation dataset	97.4 (96.0–98.4)	95.9 (94.4–97.1)	95.0 (93.3–96.3)	97.8 (96.7–98.6)	96.6 (95.6–97.4)	1.00
Small bowel (*n* = 258,443)						
Training dataset mean	81.5 (69.5–91.0)	98.5 (97.2–99.3)	82.6 (70.7–90.3)	98.5 (97.4–99.3)	97.5 (95.8–99.3)	
Validation dataset	78.6 (76.9–80.7)	97.6 (97.5–97.7)	72.5 (69.8–77.3)	99.2 (99.2–99.3)	97.6 (97.5–97.7)	
N versus ALL	85.2	98.4	89.9	96.6	96.5	0.95
POL versus ALL	95.2	98.0	59.5	99.8	98.0	0.91
POX versus ALL	93.1	99.8	91.6	99.9	99.7	0.97
PIPE versus ALL	87.9	99.4	82.1	99.6	99	0.93
PIPR versus ALL	96.1	99.5	99.1	97.8	98.3	1.00
PIU versus ALL	91.0	99.0	81.8	99.5	98.6	0.95
PIE versus ALL	83.1	99.5	80.0	99.6	99.1	0.91
P2V versus ALL	92.5	99.7	70.1	99.9	99.6	0.91
P2PR versus ALL	1.4	99.9	9.1	99.9	99.8	0.07
P2U versus ALL	42.3	99.8	63.0	99.6	99.5	0.55
P3 versus ALL	97.3	80.4	70.7	98.4	85.9	1.00
PO versus PI	99.1	97.5	80.6	99.9	97.6	
PO versus P2	99.9	99.5	99.9	99.7	99.8	
PO versus ALL	95.7	97.9	70.2	99.8	97.8	
PI versus P2	99.4	71.6	99.0	79.4	98.4	
PI versus ALL	95.6	96.8	96.2	96.3	96.3	
P2 versus ALL	68.0	99.5	70.9	99.5	99.0	
Colon (*n* = 76,772)						
Training dataset mean	86.5 (85.3–87.7)	93.0 (92.4–93.6)	87.6 (86.5–88.6)	94.4 (93.8–94.9)	92.5 (92.0–93.0)	
Validation dataset	85.7 (81.1–89.6)	94.0 (91.8–95.5)	87.4 (82.9–90.1)	93.5 (91.2–95.2)	94.9 (94.2–95.5)	
PP versus ALL	84.2	93.5	83.4	93.7	90.8	0.91
PP versus P3	99.4	93.6	99.6	90.7	99.1	
PP versus N	84.6	93.4	83.9	93.7	90.8	
P3 versus ALL	74.7	99.6	78.7	99.5	99.2	0.84
P3 versus N	78.7	99.6	85.5	99.4	99.1	
N versus ALL	93.1	84.4	93.2	84.1	90.4	0.98

CNN, convolutional neural network; Class, classification; N, normal mucosa; P3, hematic residues; P1PE, P1 red spots; P2V, P2 vascular lesions; P1PR, P1 protuberant lesions; P0L, P0 lymphangiectasia; P2U, P2 ulcers; P2PR, P2 protuberant lesions; P0X, xanthomas; P1U, P1 ulcers; P1E, P1 erosions; PP, pleomorphic lesions.

means and 95% confidence intervals (CI). The precision-recall (PR) curve and the area under the precision-recall curve (AUC-PR) were used to measure the performance of the model. Statistical analysis was performed using Sci-Kit learn version 0.22.2 [23].

Results

Esophagus

A total of 6,977 esophageal images from 536 CE exams in three different devices (PillCam SB3; PillCam Crohn's; OMOM HD capsule endoscopy system) were used for the development of the CNN. The esophagus CNN had a mean sensitivity of 76.3%, specificity of 86.2%, PPV of 90.6%, and NPV of 79.0%, with a mean accuracy of 83.6% and AUC-PR of 0.90. These results were achieved with an image processing time of 95 images per second.

Stomach

A total of 12,918 gastric images were obtained from a total of 107 CE exams in 3 different devices (PillCam SB3; PillCam Crohn's; OMOM HD capsule endoscopy

Table 3. CNN performance for panendoscopic automatic detection of pleomorphic lesions

	Sn	Sp	VPP	VPN	Acc	AUC-PR
Esophagus (*n* = 6,977)						
Training dataset mean	55.1 (50.4–59.4)	87.3 (85.3–89.1)	67.3 (65.0–69.5)	68.5 (67.2–69.7)	68.8 (66.7–70.8)	
Validation dataset	76.3 (71.1–80.9)	86.2 (80.5–90.9)	90.6 (86.5–93.5)	79.0 (73.7–83.2)	83.6 (79.9–86.9)	0.90
Stomach (*n* = 12,918)						
Training dataset mean	87.8 (86.9–88.7)	92.3 (91.6–93.0)	91.4 (90.6–92.0)	89.2 (88.5–89.9)	90.2 (89.6–90.7)	
Validation dataset	97.4 (96.0–98.4)	95.9 (94.4–97.1)	95.0 (93.3–96.3)	97.8 (96.7–98.6)	96.6 (95.6–97.4)	1.00
Small bowel (*n* = 258,443)						
Training dataset mean	81.5 (69.5–91.0)	98.5 (97.2–99.3)	82.6 (70.7–90.3)	98.5 (97.4–99.3)	97.5 (95.8–99.3)	
Validation dataset	78.6 (76.9–80.7)	97.6 (97.5–97.7)	72.5 (69.8–77.3)	99.2 (992–99.3)	97.6 (97.5–97.7)	
N versus ALL	85.2	98.4	89.9	96.6	96.5	0.95
POL versus ALL	952	98.0	59.5	99.8	98.0	0.91
POX versus ALL	93.1	99.8	91.6	99.9	99.7	0.97
PIPE versus ALL	87.9	99.4	82.1	99.6	99	0.93
PIPR versus ALL	9,611	99.5	99.1	97.8	98.3	1.00
PIU versus ALL	91.0	99.0	81.8	99.5	98.6	0.95
PIE versus ALL	83.1	99.5	80.0	99.6	99.1	0.91
P2V versus ALL	92.5	99.7	70.1	99.9	99.6	0.91
P2PR versus ALL	1.4	99.9	9.1	99.9	99.8	0.07
P2U versus ALL	42.3	99.8	63.0	99.6	99.5	0.55
P3 versus ALL	97.3	80.4	70.7	98.4	85.9	1.00
PO versus PI	99.1	97.5	80.6	99.9	97.6	
PO versus P2	99.9	99.5	99.9	99.7	99.8	
PO versus ALL	95.7	97.9	70.2	99.8	97.8	
PI versus P2	99.4	71.6	99.0	79.4	98.4	
PI versus ALL	95.6	96.8	96.2	96.3	96.3	
P2 versus ALL	68.0	99.5	70.9	99.5	99.0	
Colon (*n* = 76,772)						
Training dataset mean	86.5 (85.3–87.7)	93.0 (92.4–93.6)	87.6 (86.5–88.6)	94.4 (93.8–94.9)	92.5 (92.0–93.0)	
Validation dataset	85.7 (81.1–89.6)	(91.8–95.5)	87.4 (82.9–90.1)	93.5 (91.2–95.2)	94.9 (94.2–95.5)	
PP versus ALL	84.2	93.5	83.4	93.7	90.8	0.91
PP versus P3	99.4	93.6	99.6	90.7	99.1	
PP versus N	84.6	93.4	83.9	93.7	90.8	
P3 versus ALL	74.7	99.6	78.7	99.5	99.2	0.84
P3 versus N	78.7	99.6	85.5	99.4	99.1	
N versus ALL	93.1	84.4	93.2	84.1	90.4	0.98

CNN, convolutional neural network; Sn, sensitivity; Sp, specificity; PPV, positive predictive value; NPV, negative predictive value; Acc, accuracy; AUC-PR, area under precision-recall curve; N, normal mucosa; P3, hematic residues; P1PE, P1 red spots; P2V, P2 vascular lesions; P1PR, P1 protuberant lesions; P0L, P0 lymphangiectasia; P2U, P2 ulcers; P2PR, P2 protuberant lesions; P0X, xanthomas; P1U, P1 ulcers; P1E, P1 erosions; PP, pleomorphic lesions.

system). The CNN had a sensitivity of 97.4%, specificity of 95.9%, PPV of 95.0%, NPV of 97.8%, and global accuracy of 96.6%, with an AUC-PR of 1.00. The model achieved these results with an image processing time of 115 images per second.

Small Bowel

A total of 258,443 enteric images were obtained from 957 CE exams in seven different devices (PillCam SB3; PillCam SB1, PillCam Crohn's; PillCam Colon 2, OMOM HD capsule endoscopy system, MiroCam Capsule Endoscope™, Olympus Endocapsule™). The CNN revealed a global sensitivity of 78.6%, specificity of 97.6%, PPV of 72.5%, NPV of 99.2%, and accuracy of 97.6%.

When regarding the identification of specific enteric lesions, the model presented a global accuracy of 96.5% for normal mucosa, 98.0% for lymphangiectasias, and 99.7% for xanthomas. The model excelled for small protuberant lesions, ulcers, and erosions (98.3%, 98.6%, and 99.1% accuracy, respectively). The global accuracy

for vascular lesions, protuberant lesions, and ulcers with high hemorrhagic potential were 99.6%, 99.8%, and 99.5%, correspondingly. Nevertheless, the CNN presented lower sensitivities for diagnosing high-risk protuberant lesions and ulcers. These results are translated in the PR curves, with AUC-PR above 0.90 for the majority of the categories, excluding ulcers, and protuberant lesions with high hemorrhagic potential.

Finally, when considering the ability to distinguish between lesions with different hemorrhagic potentials, the CNN accurately differentiates P0 from P1 lesions (sensitivity 99.1%, specificity 97.4%, accuracy 97.6%), P0 from P2 lesions (sensitivity 99.9%, specificity 99.5%, and accuracy of 99.8%) and P1 from P2 lesions (sensitivity 99.4%, specificity 71.6%, and accuracy of 98.4%). These results were achieved with an image processing time of 282 images per second.

Colon

A total of 76,772 colonic images from 148 CE exams in five different devices (PillCam SB3; PillCam Crohn's; PillCam Colon 1, PillCam Colon 2, OMOM HD™ capsule endoscopy system) were used. The trinary CNN had a global sensitivity of 85.7%, specificity of 94.0%, PPV of 87.4%, NPV of 93.5% and global accuracy of 94.9%. The AUC-PR for normal mucosa, colonic blood and pleomorphic lesions was 0.98, 0.84, and 0.91, respectively. Furthermore, the CNN had an image processing time of 282 images per second.

Discussion

In this proof-of-concept study, our group developed the first AI model proficient in panendoscopic detection of pleomorphic lesions, in both SBCE and capsule panendoscopy devices. These results were accompanied by an image processing time that favors the clinical application of this CNN. Additionally, our group developed the first multi-device model for automatic detection of pleomorphic esophageal lesions in CE. Therefore, our group recognizes that AI-powered CE might change the landscape regarding the clinical applicability of minimally invasive capsule panendoscopy.

First, it's necessary to consider some methodologic points about the study. The division between training and validation in all the CNNs was performed in a patient split design, with all the images from a single patient included in the same dataset. This methodology significantly reduces the overfitting bias of the model (as the model would recognize similar images in the training and testing dataset). On the other side, our group preferred PR curves instead of the more common receiver operating characteristic (ROC) curves to assess the discriminating ability of the model as ROC curves reveal excessive optimism in the evaluation of model performance in cases of data imbalance [24, 25], with PR curves being less affected [26]. In our CNNs, the presence of normal mucosa images was commoner than pleomorphic lesions, thereby justifying the use of PR curves, given our objective of determining all the lesion images, instead of the commoner true negative images (implied in the ROC curve concept).

The interoperability challenge is one of the main points of interest in the discussion of the AI-based technology's role in Medicine [27, 28], with the generalization of a given technology in multiple devices as a requisite for the clinical applicability of an AI tool. Therefore, our group results in eight different CE devices, either in SBCE or capsule panendoscopy, solve the interoperability challenge with proof of diagnostic accuracy in different devices. This is, to our knowledge, not only the first panendoscopic CE CNN for detection of pleomorphic lesions but also the first capable of automatic detection in eight different CE devices, being the AI model with the largest representation of devices worldwide.

In recent years, CE-based panendoscopy has been a matter of discussion [29, 30], despite CCE is a time and resource-consuming exam, producing up to 50.000 image frames [31]. Additionally, despite numerous deep learning-based studies about small bowel and colon evaluation by CE [10, 16], there is a scarcity of studies about CNN models for esophagogastric evaluation in CE. Specific esophageal and gastric CNNs are of uttermost importance for increasing diagnostic accuracy while reducing the exam reading time and subjective bias in image evaluation by experts, which is pivotal for the implementation of minimally invasive panendoscopy.

Regardless, it is important to consider some intrinsic limitations of CE in the evaluation of the upper GI tract, which explains the different technology readiness levels (TRL) of the specific CNNs. The absence of air insufflation and dependence on abdominal peristalsis is associated with a scarcity of esophageal images and a reduction in stomach surface visualization, especially the cardia and fundus [9]. Recently, some works about CNN models for gastric evaluation have been published [32], inclusively with the use of magnetically controlled CE (MCE). However, our work is performed in much commoner CE devices (in both SBCE and CCE devices) devices and is methodologically stronger, with a patient split design that solves the overfitting problem.

On the other side, the diagnostic yield of CE in the esophagus is suboptimal, mainly because of the short transit time and scarcity of esophageal images, with a reduced number of lesion image frames [8]. The development of specific esophageal CE devices has partially overcome these limitations, without augmenting sufficiently the diagnostic yield [33]. The use of AI tools could increase the diagnostic yield of esophageal evaluation by CE. Our group developed the first multi-device CNN model for pleomorphic esophageal lesions detection, with good accuracy and image processing time.

The comprehension of the upper GI characteristics is important for the interpretation of the different CNN results. These specificities justify the lower TRLs of the esophageal and stomach CNN, with a lower number of images. However, the existence of an AI-based panendoscopy is dependent on specific gastric and esophageal models, assuring a high diagnostic yield in all GI tract locations.

This study has several limitations. First, it was performed in a retrospective manner. In the future, larger prospective multicentric studies are needed to study the clinical applicability of these technologies. Additionally, the results were based on the evaluation of still images, and studies with real-time evaluation of CE videos are needed in the future for the application of the AI model in a real-life scenario.

In conclusion, AI-based technologies might change the landscape of minimally invasive panendoscopic CE. To our knowledge, this is the first AI model capable of panendoscopic detection of pleomorphic lesions, with excellent image processing times, in both SBCE and CCE devices. This is the first study about CNN-based esophageal evaluation in CE. Additionally, this is the first study about CNN-based stomach evaluation in both SBCE and CCE devices. Furthermore, the AI model is the first to distinguish between several categories of small bowel lesions with different hemorrhagic potential in a patient split design, being also the first to excel in the diagnosis and differentiation of pleomorphic colonic lesions. The AI model was totally constructed in a patient split design, with a methodological advantage that reduces the overfitting bias of the model.

The application of these systems will improve the cost-effectiveness of a panendoscopy CE evaluation, increasing the diagnostic yield of the exam while reducing its time-consuming nature. In the future, larger real-time multicentric studies are needed for the development and application of these models.

Statement of Ethics

Our study was performed respecting the Declaration of Helsinki and was approved by the Ethics Committee of São João University Hospital/Faculty of Medicine of the University of Porto (No. CE 407/2020).

Conflict of Interest Statement

João Ferreira is a paid employee of DigestAID.

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Author Contributions

Miguel Mascarenhas and Francisco Mendes: equal contribution in study design, image extraction, drafting of the manuscript, and critical revision of the manuscript. Tiago Ribeiro and João Afonso: bibliographic review, image extraction, and critical revision of the manuscript. Pedro Marílio Cardoso and Miguel Martins: bibliographic review, image extraction, drafting of the manuscript, and critical revision of the manuscript. João Ferreira: construction and development of the CNN, statistical analysis and critical revision of the manuscript. Patrícia Andrade, Hélder Cardoso, Miguel Mascarenhas Saraiva, and Guilherme Macedo: study design and critical revision of the manuscript. All authors approved the final version of the manuscript.

Data Availability Statement

There is a limitation on data sharing due to intellectual property concerns as well as regarding non-traceability and anonymization of potentially identifying information of patients' data.

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Endoscopic Snapshot

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Tulip-Bundle Technique for Endoscopic Closure of 2 Chronic Gastrocutaneous Fistulas

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Keywords
Gastrostomy · Enteral nutrition · Gastrointestinal endoscopy · Digestive system fistula

Técnica de "Tulip-Bundle" no encerramento endoscópico de 2 fístulas gastrocutâneas crónicas

Palavras Chave
Gastrostomia · Nutrição entérica · Endoscopia gastrointestinal · Fístula do trato digestivo

Introduction

Percutaneous endoscopic gastrostomy (PEG) should be considered a first-line technique for long-term enteral feeding. This option is not definitive, and if the tube is removed the gastrocutaneous tract is expected to start healing within 24 h. Nonetheless, in some patients the tract fails to heal and the gastrocutaneous fistula persists. Endoscopic management is nowadays considered the first-line step in these cases. Through-the-scope (TTSC) or over-the-scope clips, argon plasma coagulation (APC) or even endoscopy-assisted suturing are options in avoiding surgical intervention in these fragile patients [1, 2]. The authors present 2 cases with chronic and refractory gastrocutaneous fistulas, after removal of PEG tubes, in which a different endoscopic approach was attempted.

Case 1

An 82-year-old woman, with enteral tube feeding due to amyotrophic lateral sclerosis since October 2020, was hospitalized for peristomal leakage 1 year later. Analytically, there were no relevant abnormalities. Her 24-Fr PEG tube was removed, the fistula borders were endoscopically cauterized by APC and the fistula partially closed with 3 TTSC. A 20-Fr PEG tube was placed but, 1 month later, we opted for permanent removal due to maintained peristomal drainage. Two weeks later the fistula persisted, so we proceeded with closure with an adapted tulip-bundle technique. The fistula edges were cauterized by APC, at 1.5L/min 50W, and an Endoloop® was positioned, anchored to the bordering normal mucosa, with five 11 mm TTSC, as seen in Figure 1a and b. The Endoloop® was tightened, with

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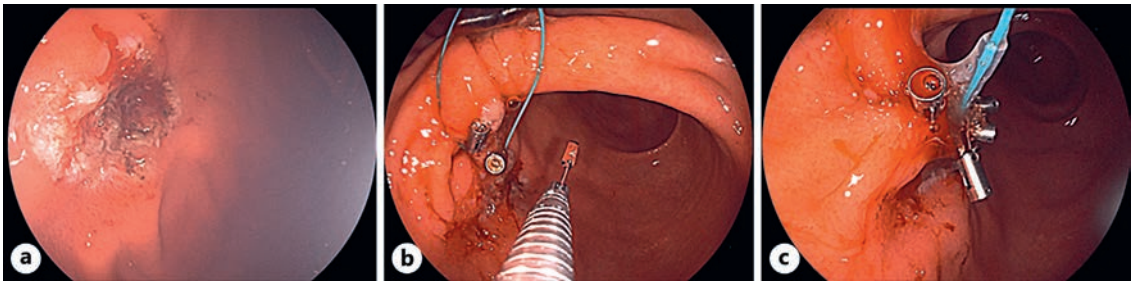

Fig. 1. Endoscopic closure of a chronic and refractory gastrocutaneous fistula in an 82-year-old woman. **a** Cauterization by APC of the defect borders. **b** After Endoloop® introduction and positioning, 5 TTSC were required and anchored in the adjacent normal mucosa. **c** Endoscopic closure of the defect after Endoloop® tightening.

adequate endoscopic closure (shown in Fig. 1c). No procedure-related complications were reported. The patient passed away in April 2022 without fistula recurrence.

Case 2

A 42-year-old quadriplegic man, under PEG tube feeding since June 2015, was first admitted for abdominal wall cellulitis in September 2021, as seen in Figure 2. At admission, hemoglobin, albumin, and natremia were low (10.3 g/dL, 2.8 g/dL, and 135 mmol/L, respectively). His 24-Fr feeding tube was removed, a guidewire was positioned in its place, and antibiotics were started. As drainage persisted, we opted for endoscopic treatment. The fistula edges were cauterized by APC, at 1.5L/min 50W, before an over-the-score clips was positioned. Although with initial success, 2 months later the fistula reoccurred and a new endoscopy attempt was performed with 8 TTSC. An unsuccessful attempt to use the tulip-bundle technique was made, with Endoloop® failure. Five months later drainage persisted, and endoscopic treatment with tulip-bundle technique was proposed. Following cauterization of the edges, an Endoloop® was anchored to the mucosa bordering the defect using six 11 mm TTSC. The Endoloop® was tightened and closed the fistula edges, as illustrated in Figure 3a–c. This procedure was uneventful, and the patient was discharged with successful fistula closure. Unfortunately, 1 year later, probably due to patient's intrinsic frailty, the fistula recurred, and surgical repair was deemed necessary.

Only a handful of cases using the endoscopic tulip-bundle technique for closure of chronic gastrocutaneous fistulas have been described so far [3, 4]. Even so, it is an efficient and safe nonsurgical option, particularly helpful in high-risk patients. One could argue its role as an early approach for gastrocutaneous fistulas in the hope of reducing recurrence.

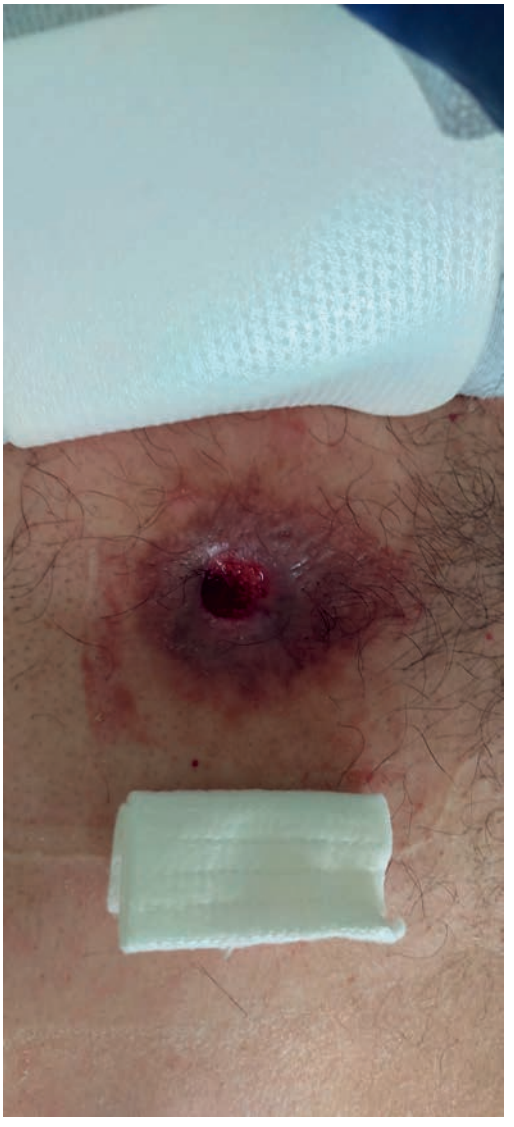

Fig. 2. Abdominal wall cellulitis in a 42-year-old quadriplegic man with enteral tube feeding.

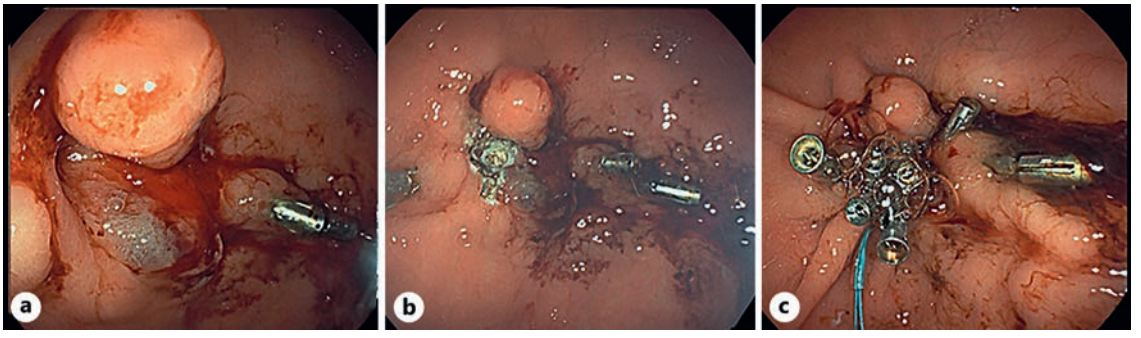

Fig. 3. Endoscopic closure of the second chronic and refractory gastrocutaneous fistula described. **a** and **b**: Cauterization by APC of the defect borders. **c** The Endoloop® was positioned using 6 TTSC and tightened, successfully closing the fistula.

Statement of Ethics

Informed consent was obtained from participants' next-of-kin for publication of the details of their medical case and accompanying images. This type of manuscript (case report) did not require ethical approval due to local laws.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Mara Sarmento Costa and Raquel Pimentel were responsible for the report's conception and design, acquisition of data, analysis and interpretation of data and drafting the manuscript and thus should be considered co-first authors. Andrea Silva, Margarida Ferreira, Nuno Almeida, and Pedro Figueiredo were responsible for critical revision of the article. All authors agreed with the final revision of the manuscript.

Data Availability Statement

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

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Images in Gastroenterology and Hepatology

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Solitary Gastric Extramedullary Plasmacytoma EUS Features: A Case Report

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Keywords
Gastric plasmacytoma · Endoscopic ultrasound features · Subepithelial lesion

Plasmocitoma gástrico – diagnóstico complementado com ecoendoscopia

Palavras Chave
Plasmocitoma gástrico · Ecoendoscopia · Lesão subepitelial

We present a 71-year-old female with no relevant past medical history. The patient was started on a proton pump inhibitor for dyspepsia, with complete symptomatic improvement. One year later, there was symptom recurrence with weight loss. Upper endoscopy revealed a 10 cm gastric subepithelial lesion, with central erosion (Fig. 1). Pathology evaluation was negative for malignancy. Computed tomography showed an extensive gastric wall lesion, with no adenopathies (Fig. 2). Endoscopic ultrasound (EUS) evaluation revealed an 8 cm subepithelial polycyclic hypoechoic lesion, with transition zone suggestive of the third/fourth layer origin (Fig. 3a). Quantitative elastography evaluation showed strain histogram 68 (Fig. 3b). The fine needle biopsy using a 22-G Franseen needle revealed clonal proliferation of plasma cells, positive for CD45/CD138 and

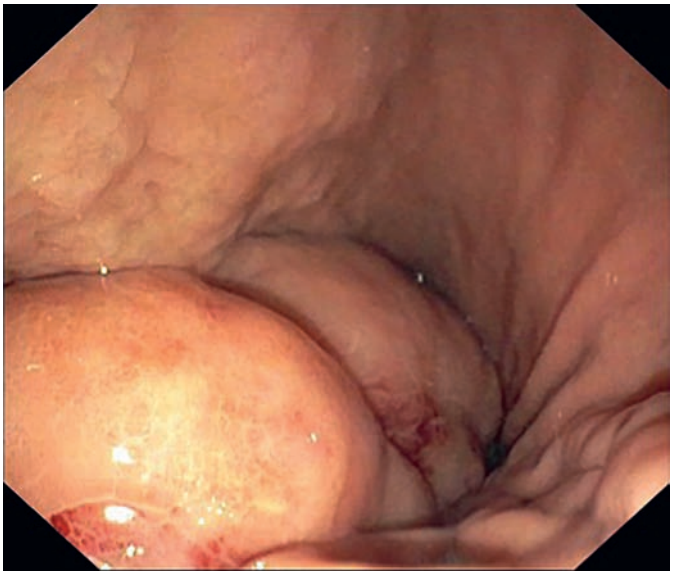

Fig. 1. Upper endoscopy revealing a 10-cm gastric subepithelial lesion, with central erosion.

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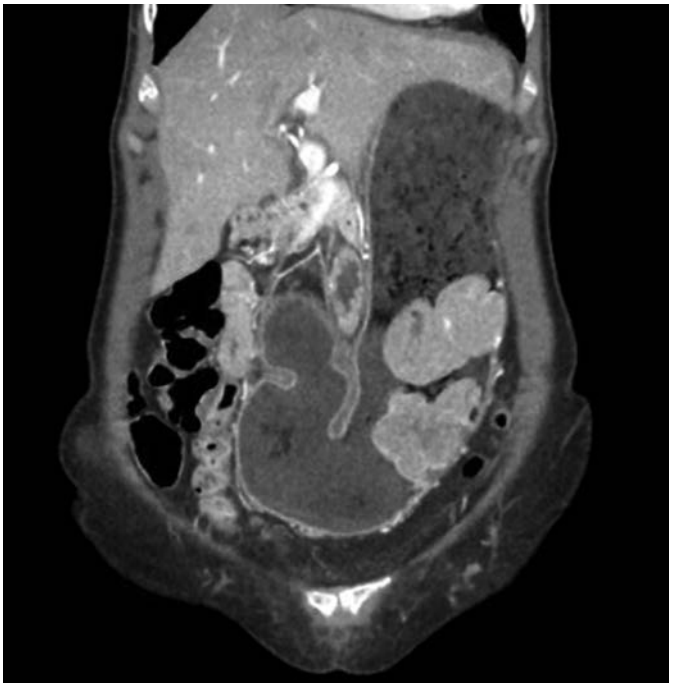

Fig. 2. Computed tomography showing an extensive proliferative gastric wall lesion.

negative for CD3/CD20/CD56 (Fig. 4). There was no anemia, hypercalcemia, or kidney impairment, and no abnormalities were found on bone marrow biopsy and myelogram apart from mildly increased plasma cell proliferation (5–10% of total cells). The positron emission tomography/computed tomography scan showed increased gastric uptake, with a maximum standardized uptake value of 3.3. Treatment consisted of surgical resection and the patient had an uneventful postoperative course. The surgical specimen confirmed the diagnosis.

Solitary extramedullary plasmacytomas are plasma cell tumors arising outside of the bone marrow, accounting for approximately 3% of plasma cell malignancies [1]. Within this category, gastric plasmacytoma accounts for less than 2% of extramedullary plasmacytomas [2]. They frequently present as solitary lesions, although sometimes the endoscopic appearance can only reveal erosion of the mucosa [3]. Symptoms are nonspecific, with epigastric discomfort, abdominal pain, nausea, and vomiting commonly reported. Diagnosis requires biopsy-proven extramedullary tumor with evidence of clonal plasma cells, with flow cytometry immunophenotyping assuming a major role in most hematologic malignancies, along

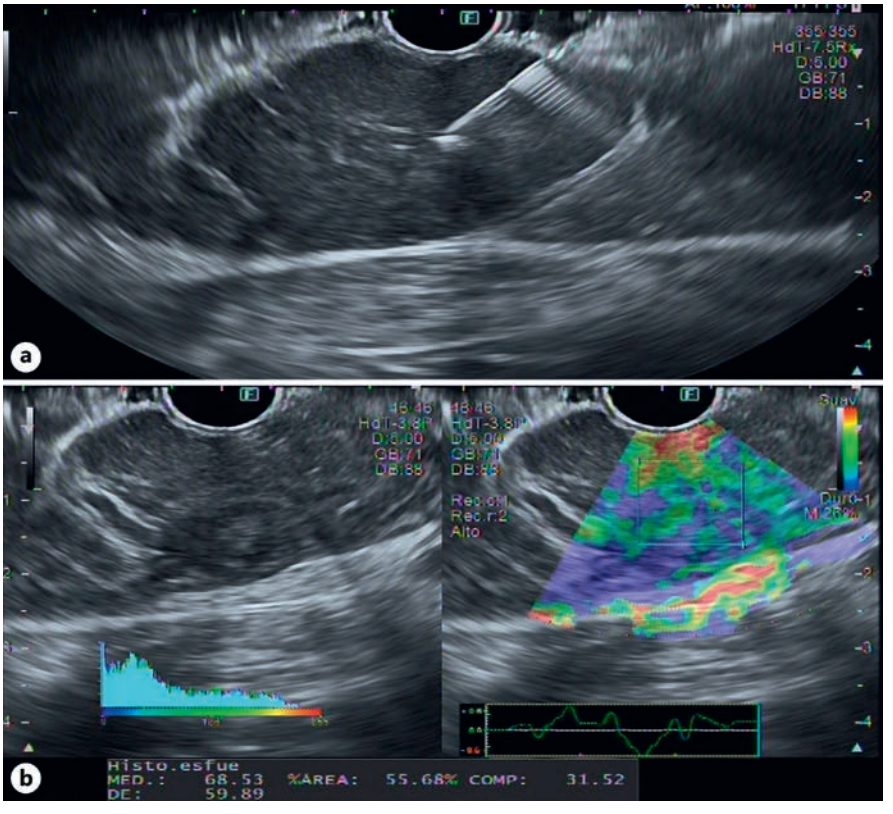

Fig. 3. EUS showing an 8-cm subepithelial polycyclic hypoecoid lesion, with transition zone suggestive of the third/fourth layer origin (**a**). Quantitative elastography evaluation showed strain histogram 68 (**b**).

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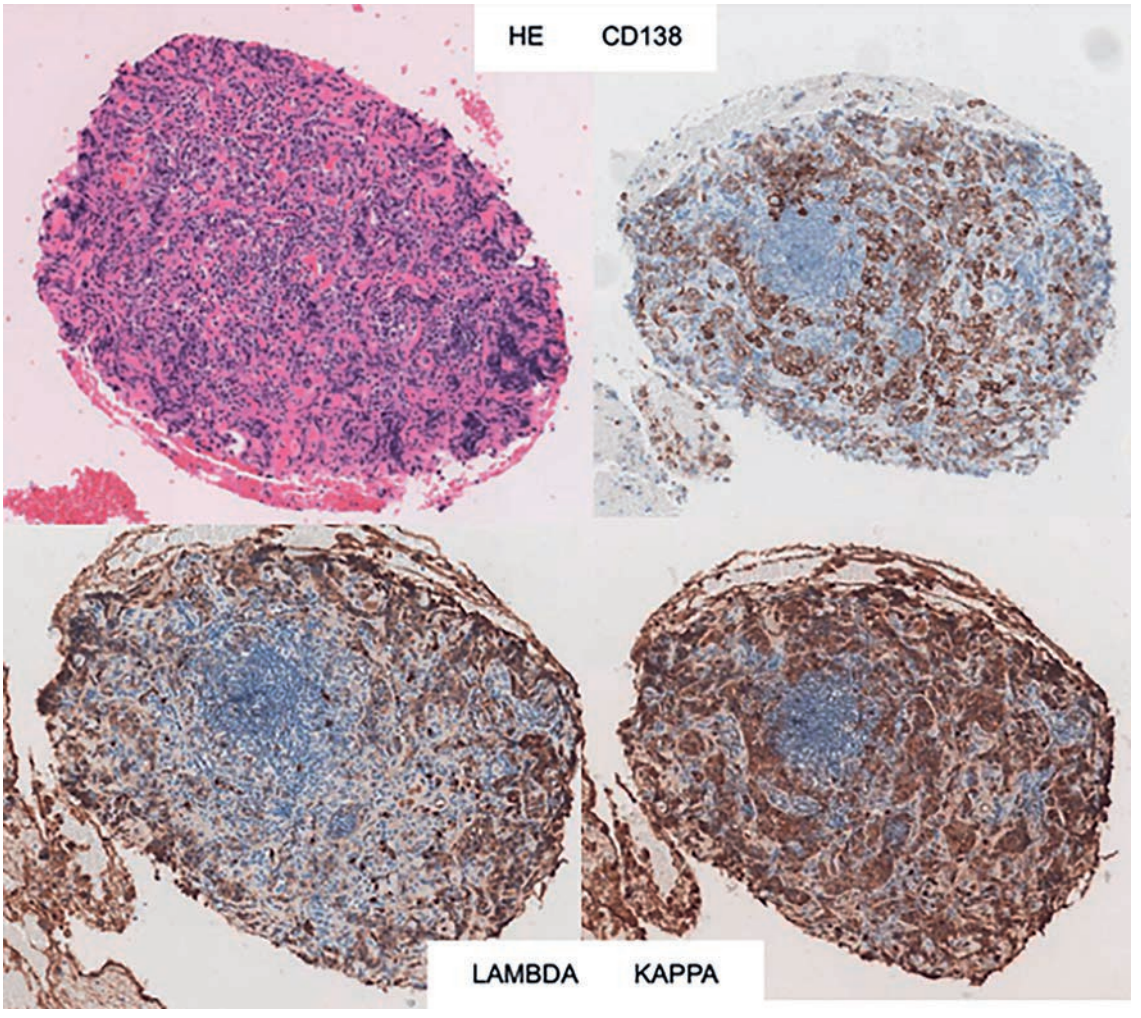

Fig. 4. Histopathology examination showing clonal proliferation of plasma cells, positive for CD45/CD138 and negative for CD3/CD20/CD56.

with normal skeletal and bone marrow survey and the absence of end-organ damage attributable to the underlying plasma cell disorder [4]. The role of EUS is not standardized, and data are scarce regarding EUS features of a gastric plasmacytoma [5]. Surgery is usually the treatment of choice, with a good prognosis [6]. The authors highlight the EUS role as part of the diagnostic workup of gastric plasmacytoma, a rare clinical entity.

Statement of Ethics

Ethical approval was not required to this type of manuscript due to local laws. The patient has given written informed consent for publication (including the publication of images).

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Francisco Vara-Luiz and Marta Patita wrote the manuscript; Susana Mão de Ferro performed upper endoscopy evaluation; Pedro Pinto-Marques performed EUS

evaluation; Raquel Ilgenfritz performed histopathology evaluation; and Pedro Pinto-Marques, Susana Mão de Ferro, Raquel Ilgenfritz, and Manuela Bernardo critically reviewed the manuscript. All authors approved the final version of this paper.

Data Availability Statement

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

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Iron Deficiency Anemia and Unexplained Recurrent Abdominal Pain: Look for the Answer through the Fossa

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Keywords
Jejunal diverticulosis · Paraduodenal hernia · Iron deficiency anemia

Anemia ferropénica e dor abdominal recorrente e inexplicada: procura a resposta através da fossa

Palavras Chave
Diverticulose jejunal · Hérnia paraduodenal · Anemia ferropénica

A 75-year-old female presented to the emergency department with fatigue. She denied overt gastrointestinal blood loss or other gastrointestinal symptoms. Laboratory work showed iron deficiency anemia (Hb 9.2 g/dL, iron 18 μg/dL, ferritin 7.6 mg/dL, and transferrin saturation 3%).

Her past medical history was notable for atrial fibrillation under apixaban and a 6-month history of intermittent upper quadrant abdominal pain and vomiting under investigation in an outpatient clinic. Recent upper and lower gastrointestinal endoscopic exams were unremarkable.

After receiving intravenous iron supplementation, she was discharged to a gastroenterology consultation, where a small bowel capsule endoscopy was requested to proceed with the iron deficiency anemia etiologic investigation. By this time, the patient denied having abdominal pain and vomiting in the previous months. This examination was incomplete due to capsule retention in a segment with multiple diverticula with friable mucosa (shown in Fig. 1a–c). Capsule expulsion was later confirmed by the patient.

Abdominal computed tomography revealed herniation of intestinal loops through the fossa of Waldeyer associated with partial mesenteric torsion without upstream dilation, compatible with a right paraduodenal internal hernia. Within these herniated jejunal loops, several small bowel diverticula were noted, the largest measuring 28 mm (shown in Fig. 2a, b).

The diagnosis of right paraduodenal hernia with acquired jejunal diverticulosis was made. Although these two particularly rare entities have been described separately, exceptionally they can be present in association, where it is hypothesized that the jejunal diverticulosis is secondary to high intraluminal pressures within the herniated segment [1, 2]. Furthermore, this case depicts the third reported case of this diagnosis in the literature,

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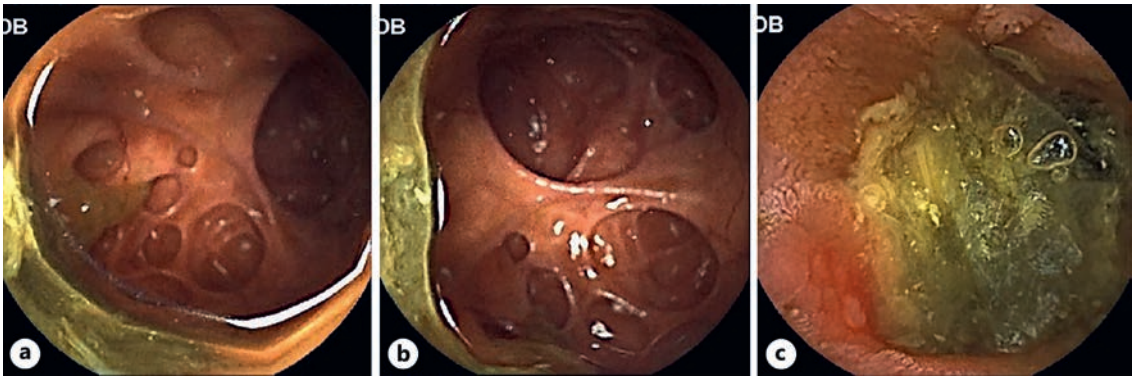

Fig. 1. a–c Jejunal diverticulosis identified in small bowel capsule endoscopy, with friable mucosa in (**c**).

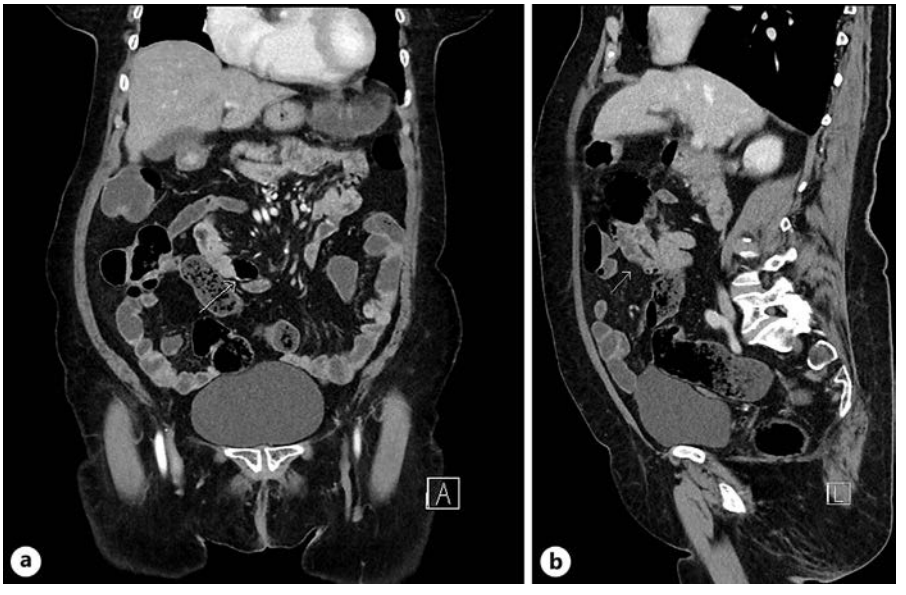

Fig. 2. a Right paraduodenal internal hernia identified in abdominal computed tomography (arrow indicates diverticulum) – coronal plane. **b** Right paraduodenal internal hernia identified in abdominal computed tomography (arrow indicates herniated intestinal loop) – sagittal plane.

as well as its first reported capsule endoscopy iconography, which triggered computed tomography investigation and made the final diagnosis possible [2, 3]. This diagnosis was considered the cause of the iron deficiency anemia since the intestinal mucosa in the diverticula area was friable, which in the context of anticoagulation could lead to chronic blood losses. No other cases of jejunal diverticulosis secondary to paraduodenal hernia manifesting as iron deficiency anemia were found in the literature.

Although extremely uncommon, it is important to be aware of this diagnosis in the presence of otherwise unexplained current or past abdominal pain, particularly when accompanied by other signs, namely vomiting and iron deficiency anemia since internal hernias may course with acute and severe complications such as perforation or bowel obstruction [4]. We also highlight the importance of considering this diagnosis even in older patients or in the absence of persistent abdominal symptoms. The case was discussed with the surgical team, however, since the patient remained asymptomatic and with good hematologic response for oral iron supplementation, surveillance was decided, with a low threshold for surgical repair of paraduodenal hernia in case of symptomatic recurrence or refractory iron deficiency anemia.

Statement of Ethics

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

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

No funding was required.

Author Contributions

Ana Rita Franco, Catarina Félix, Andreia Roque, Rita Barosa, and Cristina Chagas contributed to the manuscript concept and design. Ana Rita Franco drafted the manuscript. Rita Barosa performed a critical revision of the manuscript for important intellectual content.

Data Availability Statement

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

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Endoscopic Retrieval of Migrated Uterine Device: Case Report

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Keywords
Intrauterine device · Rectum · Endoscopy · Case report

Remoção endoscópica de um dispositivo intra-uterino migrado: relato de caso

Palavras Chave
Dispositivo intra-uterino · Recto · Endoscopia · Relato de caso

Case Report

A 58-year-old asymptomatic woman was referred to the gynaecology clinic due to an incidentally found intrauterine device (IUD) in a pelvic X-ray. The patient inserted the device 15 years ago, but it was thought to have been naturally expelled 1 year later during an unplanned pregnancy. Since it was implanted at a different institution, no information about the type of IUD was available. A subsequent pelvic and abdominal CT scan revealed the migration of the IUD to the rectum, confirmed by a sigmoidoscopy that demonstrated its transmural placement in a partially intraluminal position in the rectum, at 12 cm from the anal verge (Fig. 1, 2). After a multidisciplinary discussion with gastroenterologists, gynaecologists, and surgeons, it was decided to attempt an endoscopic removal with salvage surgical intervention if deemed necessary. The procedure was performed in the operating room under conscious sedation after bowel preparation and the device was removed in one piece using grasping forceps traction. The defect was prophylactically closed with three through-the-scope clips. The patient underwent 24-hour hospital surveillance with no immediate post-procedure complications. Prophylactic antibiotic therapy with amoxicillin-clavulanic acid was initiated and continued for 1 week. After 1 month of clinical follow-up, the patient remained asymptomatic and free of further complications.

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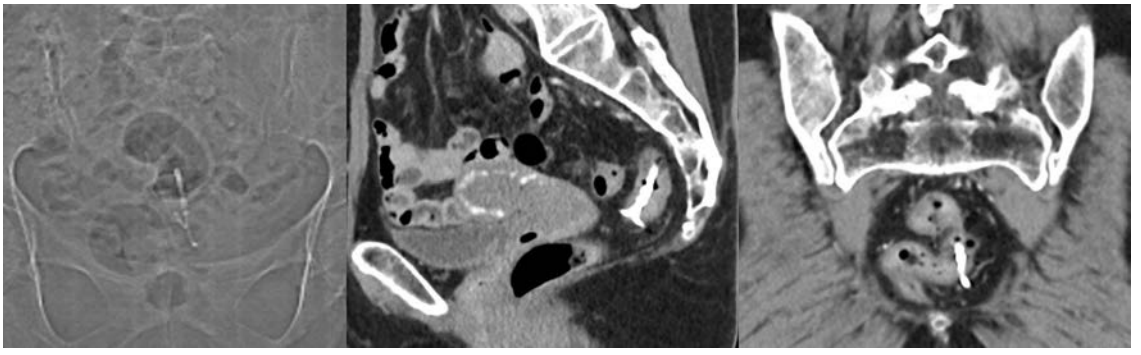

Fig. 1. CT scan revealing the location of the intrauterine device with one stalk in the lumen of the rectum and the rest of the device in the mesorectum, unrelated to the uterus, below the peritoneal reflection.

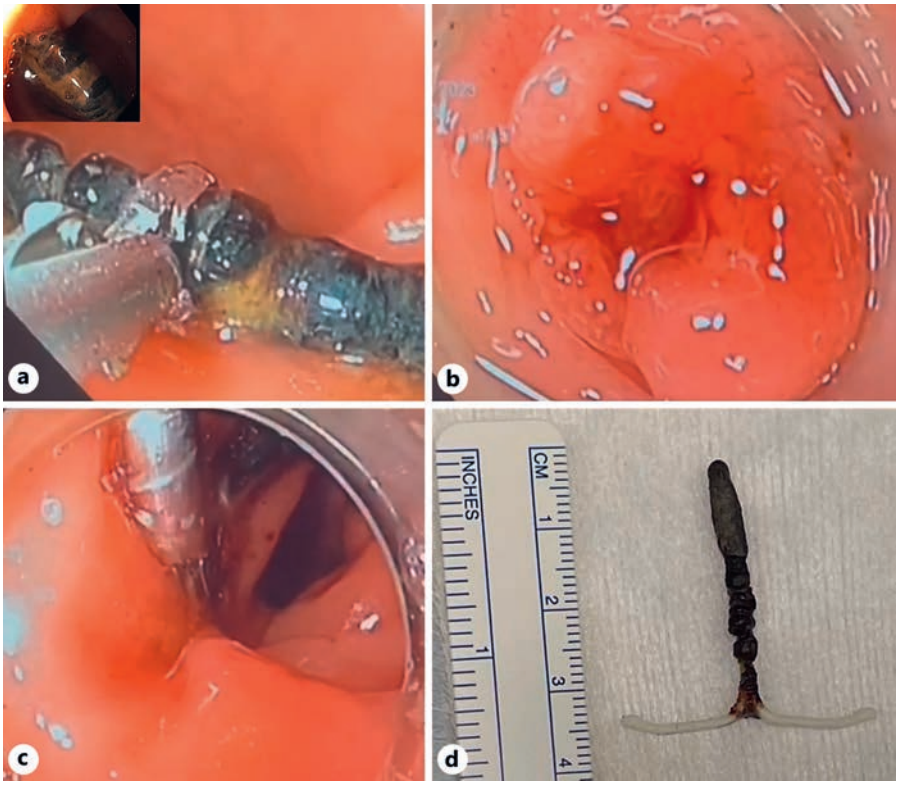

Fig. 2. Sigmoidoscopy revealing the transmural position of the intrauterine device and its removal using grasping forces (**a**), the mucosal defect after removal (**b**), defect closure using through-the-scope clips (**c**), and the intrauterine device after *en-bloc* removal (**d**).

Discussion

IUDs are commonly employed for birth control but can lead to severe complications such as uterine perforation and intra-abdominal migration (0.06–0.16%), including adjacent organ involvement, such as the digestive tract [1]. The sigmoid colon is the most common site of intestinal perforation, with the rectum affected in 1/5 of the cases [2]. Approximately 15 cases of rectal IUD migration have been reported in the literature [2]. Migration can occur during insertion or gradually over time. Risk factors for perforation include IUD type, operator skill, uterus size/position, postpartum insertion within 6 months, lactation (due to low estrogen levels leading to uterine atrophy), and unplanned pregnancy with an inserted IUD, as observed in our case [3].

Patients may experience lower abdominal pain, fever, rectal bleeding and/or diarrhoea, but many remain asymptomatic until the migrating device is incidentally detected. In some cases, IUD strings protrude from the rectum [3]. Regardless of presentation, migrated IUDs always require removal due to

potential complications, including infection, bowel perforation, obstruction, fistula formation, and abscesses [4].

Removal of migrated IUDs can be made endoscopically, surgically or using a combined approach [1, 2, 5]. The success of endoscopic removal depends on the location of the device and depth of the perforation. Endoscopic removal is effective for recto-sigmoid migration without adjacent organ involvement or complications. Following IUD extraction, closure of the defect typically involves the use of through-the-scope or over-the-scope clips [2, 5]. The selection between these devices primarily hinges on the specific location of the defect.

This report highlights the successful endoscopic removal of a rare rectally perforated IUD. It underscores the importance of tailored decision-making and vigilant monitoring for IUD migration, especially in patients who become pregnant after IUD insertion.

Statement of Ethics

Written informed consent for publication of the details of the medical case and any accompanying images was obtained from the participant. This type of manuscript, case report, does not require ethical approval according to national laws.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

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Author Contributions

Joana Revés and Ana Figueiredo contributed to the manuscript design. Joana Revés, Ana Catarina Bravo, Bárbara Abreu and Mariana Gamito wrote the manuscript. Ana Figueiredo and Rui Loureiro provided significant revisions to the manuscript. All authors critically revised the manuscript. All authors have approved the final version of the manuscript.

Data Availability Statement

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

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Clinical Case Study

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Gastric Mixed Neuroendocrine-Non-Neuroendocrine Neoplasm: An Unusual Tumor and Its Presentation in a Young Adult

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Keywords
Gastric cancer · Mixed neuroendocrine-non-neuroendocrine neoplasm · Upper gastrointestinal bleeding

Abstract
Introduction: Gastric cancer is the fourth most common cause of cancer death, with more than 90% of the cases being adenocarcinomas. Among the diverse subtypes, mixed neuroendocrine-non-neuroendocrine neoplasm (MiNEN) is one of the rarest types. Gastric cancer can manifest with significant bleeding in up to 5% of patients. ***Case Presentation:*** The authors present a case of a healthy 26-year-old male who experienced two episodes of major upper gastrointestinal bleeding that were resolved with endoscopic treatment. During the second endoscopy, a 15-mm nodular subepithelial lesion was identified at the gastroesophageal junction. Endoscopic ultrasound revealed a homogeneous and hypoechoic lesion with well-defined limits in the deep mucosa. Histological examination of the biopsies showed an adenocarcinoma. The patient later underwent a distal esophagectomy and a total gastrectomy, followed by chemotherapy. Histological examination of the surgical specimen showed a mixed adenoneuroendocrine carcinoma composed of an adenocarcinoma with tubular/glandular pattern and signet ring cells and a large cell-type neuroendocrine carcinoma. The neoplasia had infiltrated the outer muscular layers of the stomach and had disseminated to 3 regional lymph nodes, leading to its classification as stage IIb. Two years following the treatment, there is no evidence of recurrence. All genetic tests applied were negative. ***Discussion:*** A MiNEN occurs when both neuroendocrine and non-neuroendocrine components represent at least 30% of the lesion. Due to its rarity, epidemiology and standard treatment are not well established because most data published are from case reports. In this context, we present a compelling case study, highlighting the patient's young age, the rarity of this specific cancer, and its uncommon presentation.

Neoplasia gástrica mista neuroendócrina e não-neuroendócrina (MiNEN): um tumor raro e a sua apresentação clínica num doente jovem

Palavras Chave
Cancro gástrico · Neoplasia mista neuroendócrina e não-neuroendócrina · Hemorragia digestiva alta

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Resumo

Introdução: O cancro gástrico é a quarta causa mais comum de morte por cancro, sendo, em mais de 90% dos casos, adenocarcinoma. Entre os vários subtipos de tumores gástricos, a neoplasia mista neuroendócrina e não-neuroendócrina (MiNEN) é dos mais raros. O cancro gástrico pode-se manifestar como hemorragia digestiva major em até 5% dos doentes. ***Apresentação do caso:*** Os autores apresentam o caso de um jovem saudável de 26 anos que se apresentou com dois episódios de hemorragia digestiva *major* tratadas endoscopicamente. Na segunda endoscopia observou-se uma lesão subepitelial nodular com 15 mm na junção esofagogástrica que, na ecoendoscopia, apresentava-se como uma lesão homogénea e hipoecóica, com limites bem definidos, na dependência da mucosa profunda. As biópsias da lesão revelaram presença de adenocarcinoma. O doente foi submetido a uma gastrectomia total com esofagectomia distal e, posteriormente, a quimioterapia. Na peça cirúrgica foi identificado um carcinoma misto adenoneuroendócrino composto por um adenocarcinoma com padrão tubular/glandular e células em anel de sinete e um carcinoma neurodendócrino de células grandes. O tumor invadia a camada muscular externa do estômago e apresentava 3 adenopatias locais, sendo classificado como estadio IIb. Após 2 anos de seguimento, não há sinais de recidiva. Todos os testes genéticos realizados foram negativos. Um MiNEN é definido pela presença de um componente neuroendócrino e um não-neuroendócrino, sendo que cada um representa, pelo menos, 30% da lesão. A epidemiologia e o tratamento mais adequado ainda não estão bem estabelecidos, dado que é um tumor raro e a maioria da informação disponível advém de casos clínicos. Neste contexto, os autores apresentam um caso clínico em que se destaca a idade jovem do doente, a raridade do tumor e e a sua apresentação incomum.

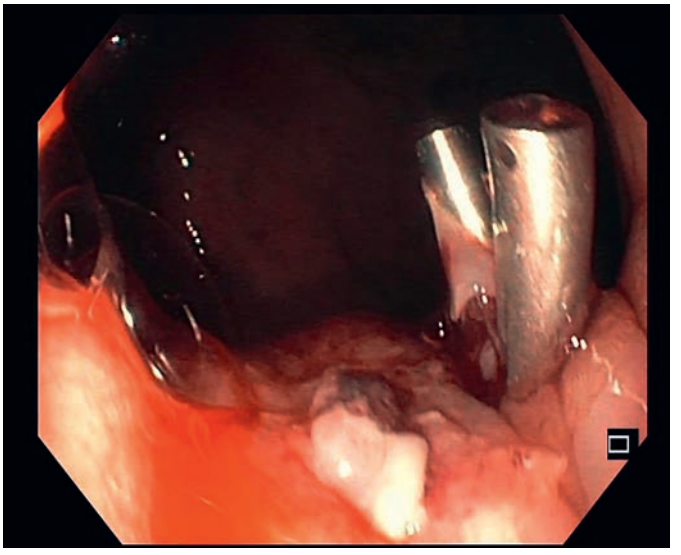

Fig. 1. Forrest Ib ulcer with active oozing at the cardia treated with diluted adrenaline and polidocanol injection since clip placement in the vessel was unsuccessful.

Introduction

Gastric cancer remains an important worldwide clinical problem. It ranks as the fourth most common cancer in males and the seventh in females [1], accounting for an estimated 1.0 million new cases in 2020 [2]. It stands as the fourth leading cause of cancer-related deaths, with an estimated annual total of 768,000 deaths [2]. Gastric cancer exhibits a higher incidence among males and older people [3]. Adenocarcinoma constitutes over 90% of gastric cancers, while lymphoma, neuroendocrine, or mesenchymal tumors are comparatively less frequent [4]. Neuroendocrine neoplasms (NENs) of the stomach are a diverse group of tumors that arise from neuroendocrine cells within the stomach, exhibiting a wide range of clinical behaviors. The classification of neuroendocrine neoplasms considers both histological features, such as differentiation and proliferation indices (mitotic account and Ki-67), to determine the grade and potential behavior of the tumor [5, 6]. The classification of these tumors has evolved to better reflect their clinical behavior and molecular characteristics. Mixed neuroendocrine-non-neuroendocrine neoplasms (MiNEN) represent a combination of both neuroendocrine and non-neuroendocrine components, each of which is morphologically and immunohistochemically recognizable and constitute ≥30% of the overall neoplasm [5, 6]. Most gastric neoplasm patients are diagnosed during advanced stages of the disease, presenting with common symptoms such as weight loss and abdominal pain [7]. Gastric cancer can cause minor bleeding, often culminating in chronic microcytic hypochromic anemia. However, it can also provoke major bleeding episodes in up to 5% of patients. Beyond this, emergency presentations of gastric cancer can encompass visceral perforation and gastric outlet obstruction, both of which are comparatively rare but are often associated with a higher stage of disease and poorer

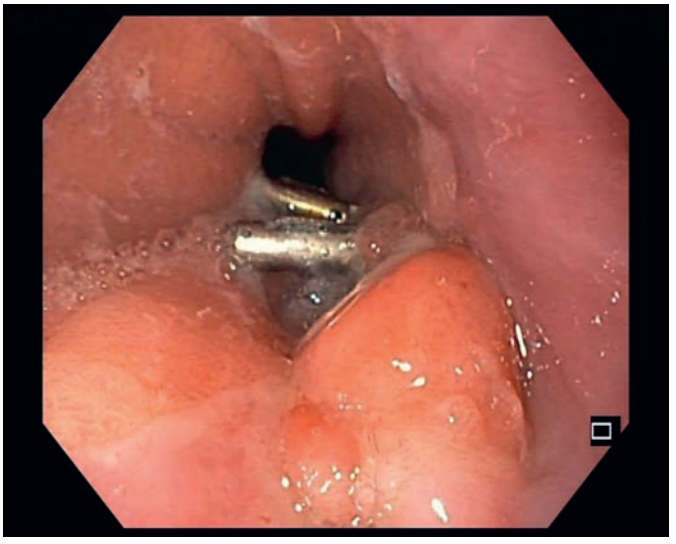

Fig. 2. 15-mm nodular subepithelial lesion at the gastroesophageal junction with ulceration in the proximal margin of the gastric mucosa.

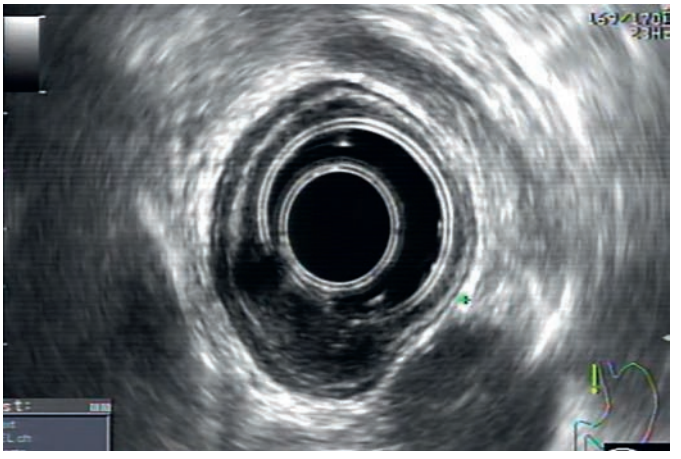

Fig. 3. Homogeneous and hypoechoic lesion of 15 × 6 mm and well-defined limits, originated at the deep mucosa without local adenopathy's.

prognosis [8]. The authors present an unusual case of an emergency presentation of gastric cancer in a 26-year-old male.

Case Report

We present the case of an asymptomatic 26-year-old male, non-smoker, overweight, with no prior family history of cancer who presented to the emergency department (ED) due to a 2-day history of melena and asthenia. Although the patient appeared pale, his hemodynamic condition was stable. Anemia was evident from his blood count, revealing a hemoglobin of 7.1 g/dL. An emergency upper endoscopy showed a Forrest Ib ulcer situated at the cardia, displaying active oozing (shown in Fig. 1). An injection of 3.5 mL of diluted adrenaline (1:10,000) and an additional 3.5 mL of polidocanol 2% effectively managed the condition. The clinical presentation was assumed to be a possible Mallory-Weiss syndrome, and the patient was discharged after a 5-day observation period. As it was an ulcer at the cardia, a follow-up endoscopy was scheduled in 12 weeks.

One week before the scheduled endoscopy, the patient once again presented at the ED, experiencing a recurrence of melena for 2 days and a blood count showing a hemoglobin of 11.6 g/dL. Subsequent endoscopy unveiled a distinctive 15 mm nodular subepithelial lesion at the gastroesophageal junction, with ulceration and a visible vessel at the proximal margin of the gastric mucosa. It was treated with 4 mL of diluted adrenaline injection and a clip placement on the vessel (shown in Fig. 2). An endoscopic ultrasound (EUS) revealed a homogeneous and hypoechoic lesion measuring 15 × 6 mm with well-defined limits at the deep mucosa (shown in Fig. 3). No local suspicious lymph nodes were observed. Histological examination of the biopsies of the lesion confirmed the presence of an adenocarcinoma. Subsequent computed tomography scans of the chest and abdomen revealed that the lesion retained clear cleavage plans with the surrounding structures, without suspicious adenopathies in its vicinity. After staging, the patient decided to change the health institution, which led to a month-long delay in treatment. Following a comprehensive multidisciplinary discussion, it was decided to proceed with a surgical approach, namely a distal esophagectomy and total gastrectomy.

Histological examination of the surgical specimen showed a mixed adenoneuroendocrine carcinoma composed of an adenocarcinoma with tubular/glandular pattern and signet ring cells and a large cell-type neuroendocrine carcinoma, where both components represented at least 30% of the lesion. The neuroendocrine component displayed positive staining for synaptophysin and chromogranin and a Ki-67 proliferation index exceeding 80% (shown in Fig. 4). The tumor had an infiltrative pattern and an extensive lymphovascular invasion. The neoplasia had infiltrated focally the outer muscular layers of the stomach wall and had disseminated to 3 regional lymph nodes (pT2 N2 M0) with negative resection margins (R0), therefore a stage IIb.

The multidisciplinary tumor board decided that the patient should undergo adjuvant treatment due to the tumor stage. Currently, there is no evidence supporting adjuvant therapy for patients with resected gastrointestinal neuroendocrine tumors. Therefore, the patient underwent chemotherapy with the FOLFOX regimen for the adenocarcinoma component. Two years after the chemotherapy regimen, there is no evidence of neoplastic disease. All the genetic tests were negative for known mutations, including the CHD1 gene.

Discussion

The classification of neuroendocrine neoplasms has been improved in the 5th edition of the World Health Organization (WHO) Classification of Digestive System

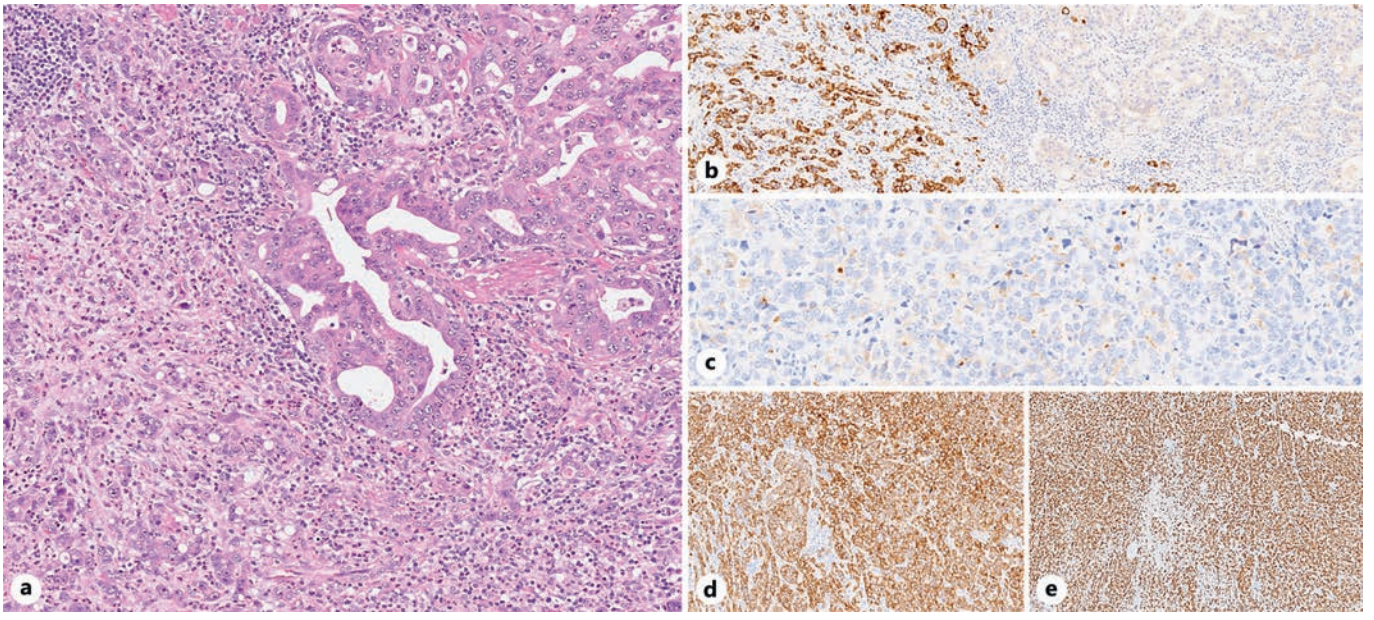

Fig. 4. Mixed neuroendocrine-non-neuroendocrine neoplasm (MiNEN), composed of an adenocarcinoma and a large cell neuroendocrine carcinoma. In mixed adenoneuroendocrine carcinoma (MANEC), each component constitutes more than 30% of the neoplasm. **a** Tubular/glandular pattern (right) and poorly cohesive cells (left). **b** Synaptophysin positive. **c** Chromogranin positive (focally). **d** Cam5.2 positive. **e** Ki-67 proliferation index more than 80%.

Tumours. The presence of focal neuroendocrine differentiation may be present in any adenocarcinoma. MiNEN classification requires both components to represent ≥30% of the overall neoplasm [5, 6]. When an adenocarcinoma is accompanied by a neuroendocrine carcinoma (NEC) component, these neoplasms are categorized under mixed adenoneuroendocrine carcinoma, as is the case herein [5, 6]. The neuroendocrine component is frequently characterized by poorly differentiated neuroendocrine carcinoma, which can be either a small or large cell type. Various types of MiNENs arise across distinct sites throughout the digestive system, and the diagnosis for each should use site-specific terminology that portrays the nature of the components. It is noteworthy that independent neuroendocrine and non-neuroendocrine neoplasms arising in the same organ should not be classified as MiNEN, even if they abut one another (referred to as true collision tumors), because the MiNEN category applies only to neoplasms in which the two components are presumed to be clonally related [5]. The epidemiology of MiNEN remains uncertain because most of the literature is based on clinical cases. However, it appears to affect more males with an average age ranging from 60 to 65 years [9, 10]. A standardized therapy protocol is yet to be established for this uncommon type of tumor. Ideally, treatment should encompass surgical resection with lymphadenectomy, followed by optional chemotherapy. Usually, the aggressiveness of the tumor is determined by the endocrine component. The most beneficial chemotherapy remains a subject of controversy; the decision should be guided by the more aggressive component [9, 11]. However, guidelines for adenocarcinoma and neuroendocrine carcinoma differ if chemotherapy is used as an adjuvant or first-line treatment. Currently, after surgery, there is no high-level evidence supporting the benefit of adjuvant therapy in resected gastrointestinal neuroendocrine tumors [12]. The prognosis of MiNENs is strongly related to stage and tumor type. Commonly, the prognosis of MiNEN is poor due to their frequent diagnosis at advanced stages. Some studies suggest that patients with gastric MiNENs have a comparatively better median overall survival than those with pure neuroendocrine carcinomas. This apparent distinction could be attributed to the latter's higher stage diagnosis [13]. Our patient's initial presentation was marked by a life-threatening gastrointestinal bleed. Gastric cancer typically presents with non-specific symptoms such as abdominal pain and weight loss. An emergency presentation is rare, and it's more associated with advanced stages of the disease. In this instance, the diagnosis

revealed a cancer stage of IIb, further highlighting its exceptional nature. This case is also particularly uncommon due to severe upper gastrointestinal bleeding (UGIB). While UGIB is frequently attributable to peptic ulcers and esophageal or gastric varices, upper gastrointestinal tract neoplasms account for approximately 3.1% of cases, with malignancy itself contributing to only 1% of severe UGIBs. When malignancies occur, they are often large and ulcerated masses [14]. The EUS has understaged the tumor, indicating a uT1 status with no nodal involvement, whereas histological examination later revealed it to be a pT2 with 3 lymph nodes involved. Studies indicate that in patients with gastroesophageal tumors, the small size of the lesion, and carcinoma with signet ring cells, there is a higher risk of lower accuracy in EUS [15, 16]. Studies are also very heterogeneous regarding accuracy of N staging. A study indicates that the diagnostic accuracy for detecting lymph node involvement has a sensitivity of 83% and a specificity of 67% and is higher for N2 than N1 [15]. Also, there is a time lapse between EUS and surgery of more than 1 month, and this is a very aggressive tumor, so tumor progression can contribute to this difference.

Throughout this case, we emphasize not only the patient's young age and rarity of the cancer type but also the exceptional presentation of gastric cancer as an emergency presentation in a non-advanced stage. To our knowledge, this case constitutes the youngest patient documented with gastric MiNEN.

Statement of Ethics

This type of manuscript (case report) does not require ethical approval due to local laws. The patient gave consent for the publication of the case and accompanying iconography. The authors declare that the procedures followed were under the World Medical Association Declaration of Helsinki.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Tânia Carvalho was responsible for the drafting of the manuscript. Dália Fernandes performed the endoscopy and EUS and was responsible for interpreting and critically revising the work for important intellectual content. Andreia Coutada and Manuel Jácome performed the histological analyses. All authors read and approved the final manuscript.

Data Availability Statement

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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Transjugular Liver Biopsy: The Key to a Rare Etiology of Cholestatic Hepatitis after Bone Marrow Transplantation

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Keywords
Transjugular liver biopsy · Liver graft-versus-host disease · Hepatic sinusoidal obstruction syndrome · Hematopoietic stem cell transplantation

Abstract
Introduction: Hematopoietic stem cell transplantation (HSCT) is associated with multiple complications, such as sinusoidal obstruction syndrome (SOS) (hepatomegaly, ascites, jaundice, and thrombocytopenia) and graft-versus-host disease (GVHD) (with the skin, gastrointestinal tract, and liver being the main targets). These entities may present overlapping clinical findings, being considered differential diagnoses, but their coexistence is rare. ***Case Presentation:*** A 29-year-old male with acute myeloid leukemia underwent HSCT. On day (D)+20, he developed hyperbilirubinemia, pleural effusion, ascites, and painful hepatomegaly. Abdominal ultrasound was suggestive of SOS, and defibrotide was initiated. On D+44, acute cutaneous, intestinal, and hepatic GVHD developed which improved after treatment with methylprednisolone. On D+132, there was worsening cholestasis and abdominal pain. MRCP revealed strictures in several segments of the intrahepatic bile ducts and irregularity of the main bile duct. Due to aggravation of liver enzyme changes and clinical worsening, he was admitted to the Intensive Care Unit. Due to persistence of severe hyperbilirubinemia (30 mg/dL) and thrombocytopenia (30,000 cell/uL), he underwent a hepatic hemodynamic study which revealed a hepatic venous pressure gradient of 10 mm Hg. The transjugular liver biopsy revealed canalicular hepatic cholestasis, bile duct injury, and focal hepatocellular necrosis suggestive of GVHD as well as injury to centrilobular veins and centrilobular necrosis compatible with possible SOS. Mycophenolate mofetil was started, but on D+195, the patient died of septic shock. ***Discussion/Conclusion:*** This case is notable for its complexity and for demonstrating the rare coexistence of histological features of SOS and GVHD. Although the clinical and laboratory findings may be sufficient for the diagnosis, it is important to highlight the importance of liver hemodynamic study and transjugular liver biopsy in these patients who often have severe thrombocytopenia, for the characterization and histological confirmation of cholestatic hepatitis, especially when the etiology may be multifactorial.

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Biópsia hepática transjugular: a chave para uma rara etiologia de hepatite colestática após transplante de progenitores hematopoiéticos

Palavras Chave
Biópsia hepática transjugular · Doença do enxerto contra hospedeiro hepática · Síndrome de obstrução sinusoidal hepática · Transplante de progenitores hematopoiéticos

Resumo
Introdução: O transplante de progenitores hematopoéticos (HSCT) está associado a múltiplas complicações, como Síndrome de Obstrução Sinusoidal hepática (SOS) (hepatomegalia, ascite, icterícia e trombocitopenia) e Doença do Enxerto contra Hospedeiro (GVHD) (pele, tracto gastrointestinal e fígado como principais alvos). Estas entidades podem apresentar quadros clínicos sobreponíveis, sendo consideradas diagnósticos diferenciais mas a coexistência é rara. ***Caso Clínico:*** Um homem de 29 anos com leucemia mieloide aguda foi submetido a HSCT. No dia (D)+20, apresentou hiperbilirrubinemia, derrame pleural, ascite e hepatomegalia dolorosa. Ecografia foi sugestiva de SOS e foi iniciado defibrotido. No D+44, desenvolveu GVHD cutânea, intestinal e hepática aguda, com melhoria após tratamento com metilprednisolona. No D+132, agravamento de colestase e dor abdominal. A CPRM revelou estenoses em vários segmentos das vias biliares intra-hepáticas e irregularidade da parede da via biliar principal. Devido ao agravamento clínico e analítico, foi internado na Unidade de Cuidados Intensivos. Por manter hiperbilirrubinemia (30 mg/dL) e trombocitopenia (30.000 células/uL), foi submetido a estudo hemodinâmico hepático que revelou gradiente de pressão venosa hepática de 10 mm Hg. A biópsia hepática transjugular revelou colestase hepática canalicular, lesão dos ductos biliares e necrose hepatocelular focal sugestivos de GVHD, assim como e lesão de veias centrolobulares e necrose centrolobular compatível com possível SOS. Iniciou micofenolato de mofetil, mas em D+195 faleceu no contexto de choque séptico. ***Discussão/Conclusão:*** Este caso destaca-se pela sua complexidade e por demonstrar a rara coexistência de aspectos histológicos de SOS e GVHD. Embora o quadro clínico e analítico possa ser suficiente para o diagnóstico, é de relevar a importância da biópsia hepática transjugular em doentes imunossuprimidos com trombocitopénia grave para caracterização e confirmação histológica de quadros de hepatite colestática, sobretudo quando a etiologia pode ser multifactorial.

Introduction

In patients undergoing hematopoietic stem cell transplantation (HSCT), adverse events may develop in up to 80% of patients, and these include Graft-versus-host disease (GVHD) and sinusoidal obstruction syndrome (SOS) which result in significant morbidity and mortality [1–3]. Early diagnosis is essential to guide treatment [1, 3]. SOS results from chemotherapy or radiation-induced destruction of hepatic microvasculature during conditioning of the bone marrow [1, 3–7], and results in reduced hepatic outflow and post-sinusoidal portal hypertension [1, 5, 7].

Clinical and laboratory features of SOS usually develop ≤3 weeks after HSCT [1, 3, 6, 7]. SOS represents the most common cause of liver disease (10–60%, depending on risk factors and conditioning regimen) during the first 20 days after HSCT, although it may also present later (15–20%) [1, 3, 6, 7]. SOS may progress to systemic vasculitis and multi-organ failure [3, 4]. Severe SOS is associated with a mortality rate of up to 85% [4, 6–8].

Acute GVHD is a frequent immune-mediated adverse event after HSCT and is associated with high morbidity and mortality [9, 10]. It develops due to destruction of the recipient tissues and organs by the donor immune effector cells [9, 10]. It usually occurs ≤3 months after HSCT but may occur later [10]. Acute GVHD most frequently affects the skin, liver, and gastrointestinal tract [2, 3, 9, 10].

Gastrointestinal involvement occurs in 30–75% of cases and its diagnosis is based on clinical features, imaging tests, and histopathology [3]. The diagnosis of liver GVHD is often challenging [6, 10]. Usually, cutaneous and gastrointestinal manifestations are present when jaundice develops, but liver involvement may be the presenting feature [6].

Chronic GVHD can affect any organ without a defined time limit and develops in 40–73% of patients [2, 3, 10]. It is characterized by progressive destruction of small intrahepatic bile ducts, leading to vanishing bile duct syndrome and end-stage liver disease [10]. Although SOS and GVHD represent different entities, clinical manifestations may overlap or resemble other adverse events, which can be an important diagnostic challenge which potentially influences their timely management [3].

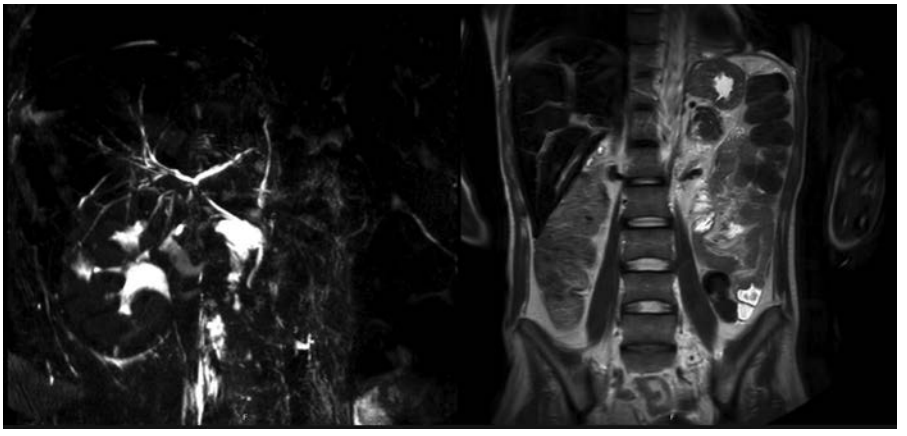

Fig. 1. MRCP-revealed segmental strictures in the intrahepatic bile ducts and irregularity of the main bile duct.

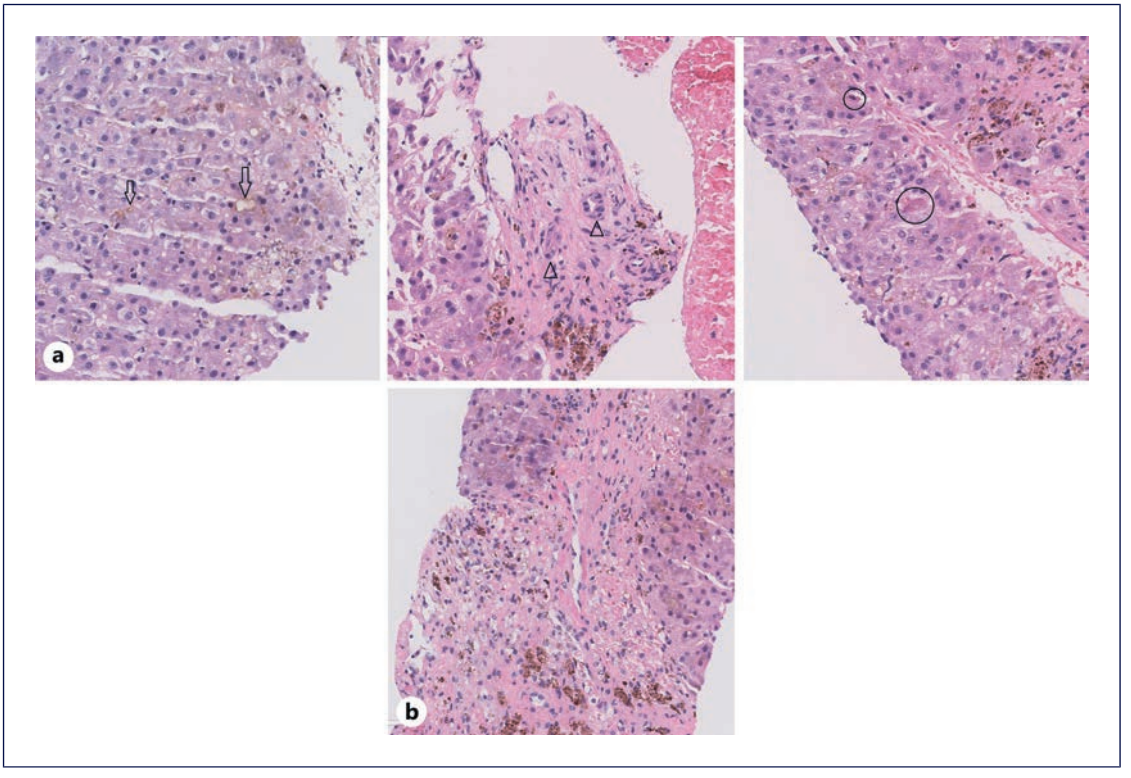

Fig. 2. Histological features of TJLB. **a** Features of GVHD: liver tissue biopsy with canalicular cholestasis (arrow), small bile duct injury (arrowhead), and focal hepatocellular necrosis (circle). **b** Features of SOS: liver tissue biopsy with central vein narrowing and extravasated erythrocytes.

Case Report

A 29-year-old male patient with bone marrow aplasia since 2014 underwent HSCT in August 2022 for acute myeloid leukemia. Prophylaxis against GVHD (anti-thymocyte globulin from day (D)-3 to D-1, total dosage 378.7 mg; tacrolimus from D-2; mycophenolate mofetil from D-0 to D+56, 1000 mg 12/12 h) and against SOS (ursodeoxycholic acid 500 mg 8/8 h; acetylcysteine 300 mg 12/12 h during the entire hospital stay) was done. The donor was unrelated, with HLA correspondence of 9/10 and major AB0 incompatibility.

On D+20 after HSCT, he developed liver enzyme changes with cytolysis, which evolved to cholestasis, as well as weight gain, pleural effusion, ascites, and painful hepatomegaly. Ultrasound (US) findings of homogeneous hepatomegaly, thickening of the gallbladder wall, ascites, and bilateral pleural effusion without vascular hemodynamic changes were suggestive of late hepatic (severe) SOS. The patient was administered defibrotide

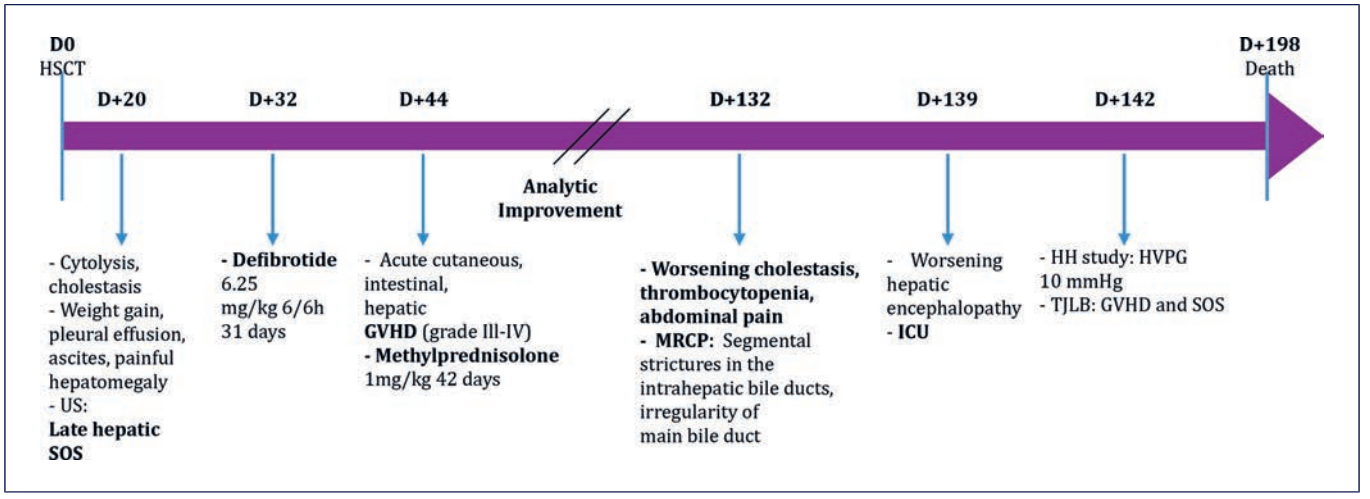

Fig. 3. Timeline of patient evolution. D, day; GVHD, graft-versus-host disease; HH, hepatic hemodynamic; HVPG, hepatic venous pressure gradient; ICU, intensive care unit; MRCP, magnetic resonance cholangiopancreatography; SOS, sinusoidal obstruction syndrome; TJLB, transjugular liver biopsy; US, ultrasonography.

Table 1. Summary of the liver enzyme changes along the clinical course of the patient

	Platelets, 10^9/L/μL	PT, s	INR	Total bilirubin, mg/dL	AST, UI/L	ALT, UI/L	ALP, UI/L
D+20	26	16.5	1.5	2.17	36	74	206
D+32	71	20	1.8	5.02	480	945	188
D+44	82	14.8	1.3	17.00	119	175	285
D+132	18	11.1	1.0	11.75	198	1,028	379
D+139	30	10.8	0.9	30.00	137	359	359
D+142	39	10.4	0.9	29.19	129	407	284

(6.25 mg/kg 6/6 h) on D+32, this was maintained for 31 days, and it resulted in clinical improvement and a significant improvement of cholestasis (total bilirubin 1.15 mg/dL, ALP 206 U/L).

On D+44, the patient developed acute cutaneous, intestinal, and hepatic GVHD [grade III-IV – total bilirubin of 17 mg/dL, AST 119 UI/L, ALT 175 UI/L, prothrombin time (PT) 14.8 s]. He was started on methylprednisolone (1 mg/kg for 42 days), and there was a progressive improvement of cholestasis. On D+132, in the context of worsening cholestasis (total bilirubin 11.75 mg/dL, AST 198 UI/L, ALT 1028 UI/L, ALP 379 U/L, PT 11.1 s), thrombocytopenia, and abdominal pain, an MRCP was performed, and it revealed segmental strictures in the intrahepatic bile ducts and irregularity of the main bile duct (shown in Fig. 1).

Due to worsening hepatic encephalopathy, he was admitted to the intensive care unit (ICU). On D+139, despite treatment with steroids, there was progressive worsening of cholestasis (total bilirubin 30 mg/dL, ALP 359 U/L, AST 137 UI/L, ALT 359 UI/L, PT 11.3 s) and persistence of severe thrombocytopenia (30×10^9/L/uL). On D+142, a hepatic hemodynamic (HH) study was performed by the bedside in the ICU, and it revealed a hepatic venous pressure gradient (HVPG) of 10 mm Hg. The transjugular liver biopsy (TJLB) revealed canalicular cholestasis, bile duct injury, and focal hepatocellular necrosis suggestive of GVHD, as well as features suggesting injury to centrilobular veins and centrilobular necrosis, which are observed in SOS (shown in Fig. 2a, b). There was extensive hemosiderosis. Mycophenolate mofetil (1,000 mg 12/12 h) was started. However, due to chronic GVHD and consequent septic shock, the patient died on D+195 (timeline and laboratory values shown in Fig. 3 and Table 1, respectively).

Discussion

This case exemplifies the crucial role of HH studies and TJLB in determining the etiology of post-HSCT cholestasis with the rare coexistence of GVHD and SOS. The patient had risk factors for SOS and GVHD which were mainly transplant related (allogenic transplant, unrelated, and HLA-mismatched donor) [3, 10].

The revised European Group for Blood and Marrow Transplantation (EBMT) criteria in adults include: classical SOS (≤21 days after HSCT with bilirubin ≥2 mg/dL and two of the following: painful hepatomegaly, weight gain, ascites); late-onset SOS (>21 days: the same features as classical, histologically proven, and two of four criteria for classical SOS plus hemodynamic/US evidence of SOS) [4, 7].

US and Doppler US can be useful in distinguishing hepatic GVHD from SOS [3, 4] and can reveal nonspecific abnormalities (hepatomegaly, splenomegaly, gallbladder wall thickening [>6 mm], ascites, periportal cuffing, signs of portal venous flow abnormalities) [3, 4, 7]. The reversal of portal venous flow is more specific but often occurs late during the course of SOS [7]. CT features suggestive of SOS include periportal edema, ascites, and a right hepatic vein diameter <0.45 cm [3].

In GVHD, radiologic imaging is important for early diagnosis and treatment [2, 3]. Imaging findings are frequently nonspecific and include enhancement of the biliary tract, gallbladder wall thickening, dilatation of the common bile duct, pericholecystic fluid, and biliary sludge [2, 3].

The histologic confirmation of SOS is limited to some centers and is rarely performed early after HSCT due to concerns regarding the potential complications of percutaneous liver biopsy [4, 10]. This limitation also explains why the diagnosis of acute GVHD of the liver is often one of exclusion [10]. Due to its sensitivity and specificity, liver stiffness measurement can be useful for a preclinical diagnosis of SOS and in monitoring response to treatment [4, 7].

However, HH study with TJLB is the gold standard and is safe even in patients with thrombocytopenia. It can be performed by the bedside in severely ill and unstable patients in the ICU, as was the case with our patient. It allows the measurement of HVPG and adequate histology for diagnosis [4, 6, 10, 11]. A HVPG ≥10 mm Hg defines clinically significant portal hypertension [3, 4, 6, 7]. The prognosis is especially poor when the HVPG is ≥ 20 mm Hg [3].

The typical histopathological features of GVHD include bile duct damage which may be severe, active hepatitis, and venulitis [2, 4, 10]. Liver histology may also be evaluated for drug toxicity, bacterial, viral, and fungal infection, and iron overload [3].

HSCT patients often have iron overload due to ineffective erythropoiesis coupled with increased intestinal absorption and multiple transfusions [2, 12]. It may mimic GVHD exacerbation, resulting in unnecessary continuation/intensification of GVHD immunosuppressive therapy [12, 13].

In conclusion, this case highlights the importance of HH study and TJLB in a patient who developed cholestatic hepatitis and severe thrombocytopenia after HSCT. The TJLB performed by the bedside in the ICU revealed the rare coexistence of SOS and GVHD as the causes of the cholestatic hepatitis after HSCT.

Statement of Ethics

The authors declare that all ethical procedures and standards were followed. The patient gave consent to the publication of the case report and accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

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Author Contributions

All authors fulfilled criteria of ICMJE for authorship: acquisition, analysis, or interpretation of data for the work; drafting the work or revising it 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 inquiries can be directed to the corresponding author.

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Hepatocellular Adenoma: A Life-Threatening Presentation of a Rare Liver Tumor – Case Report and Literature Review

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Keywords
Hepatocellular adenoma · Liver tumor · Bleeding

Abstract
Hepatocellular adenoma is a rare benign liver tumor that occurs predominantly in young women who use exogenous estrogens. We describe a case of a 40-year-old woman on birth control pill who presented with acute right hypochondrial pain and signs of hemodynamical instability triggered by a large bleeding tumor in the right liver lobe. Arterial embolization was performed with cessation of bleeding. To determine etiology, magnetic resonance imaging was conducted with findings suggestive of a hepatocellular adenoma. The tumor was surgically resected, and histologic examination made the definite diagnosis of an inflammatory hepatocellular adenoma. This is a noteworthy case of a rare but potentially fatal complication of liver tumors, whose diagnosis requires a high index of suspicion. Clinicians should consider this diagnosis in young women on oral contraceptive pills who present with severe unexplained abdominal pain and hemodynamical instability. This case aimed to raise awareness of this condition, while reviewing important aspects concerning the management of hepatocellular adenomas.

Adenoma Hepatocelular: Uma Apresentação Grave de um Tumor Hepático Raro – Caso Clínico e Revisão da Literatura

Palavras Chave
Adenoma hepatocelular · Tumor hepático · Hemorragia

Resumo
O adenoma hepatocelular é um tumor hepático benigno, raro, que ocorre predominantemente em mulheres jovens sob contraceção oral. Apresentamos o caso de uma mulher de 40 anos, medicada com contracetivo oral, que se apresentou com dor súbita no hipocôndrio direito com instabilidade hemodinâmica, com origem num volumoso tumor no lobo direito do fígado com hemorragia ativa. A doente foi submetida a embolização arterial com cessação da hemorragia. Posteriormente, realizou uma ressonância magnética nuclear com achados sugestivos de um adenoma hepatocelular. O tumor foi ressecado cirurgicamente, tendo a histologia confirmado o diagnóstico de adenoma hepatocelular de subtipo inflamatório. Este é um caso singular de uma complicação rara, mas potencialmente fatal dos tumores hepáticos

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benignos, cujo diagnóstico requer um elevado nível de suspeição. Deve ser considerado em mulheres jovens sob contracetivos orais que se apresentem com dor abdominal intensa e instabilidade hemodinâmica. O presente caso pretende alertar para esta entidade, revendo aspetos importantes na abordagem de adenomas hepatocelulares.

Introduction

Hepatocellular adenoma (HCA) is a rare benign liver tumor [1]. It occurs predominantly in young women who use exogenous estrogens [2, 3]. The clinical presentation is heterogeneous, and the diagnosis is usually done incidentally on abdominal imaging. When they are symptomatic, the most common presentation is mild and nonspecific abdominal pain. However, the pain may be severe as a result of bleeding [4]. The main risk factor associated with a higher bleeding risk is size (larger than 5 cm) [5]. HCA also carries a risk of malignant transformation which also correlates strongly with size, as well as male gender and β-catenin activation [6–8]. Magnetic resonance imaging (MRI) with hepatocyte-specific contrast agents is the best imaging modality for its diagnosis [9].

Bleeding from a liver tumor is a rare but potentially life-threatening complication, with an estimated prevalence of 1% in Western countries [10]. It is a medical emergency that requires prompt management. The patient should be hemodynamically resuscitated, and an urgent contrast-enhanced abdominopelvic computer tomography (CT) should be performed. If active bleeding is detected, arterial embolization is preferable over surgery [11]. After the bleeding is controlled, an imaging study should be repeated to determinate etiology and define further management [12].

Case Report

A 40-year-old Caucasian woman presented with right hypochondrial pain with 24 h of evolution. The patient denied fever, nausea, vomiting, jaundice, gastrointestinal or constitutional symptoms. Her past medical and family histories were irrelevant, with no history of intravenous drugs or alcohol use. She was on oral contraceptive pill for 10 years.

On physical examination, she was normotensive, tachycardic, with a painful hepatomegaly and a tender abdomen, with an otherwise unremarkable examination. Her body mass index was 27 kg/m^2.

Table 1. Initial and additional workup

Hemoglobin [13–17], g/dL	7.3
MCV [87–103], fL	89
MCH [27–33], pg	31
White blood cells [4.5–11.4], 10^3/μL	15.00
Neutrophil, 10^3/μL	8.7
Platelets [150–350], 10^3/μL	414
Coagulation tests	
INR [0.8–1.2]	1.2
aPTT [25.1–36.5], s	30.6
AST [5–34], U/L	65
ALT [<55], U/L	199
GGT [12–64], U/L	447
ALP [40–150], U/L	1,302
TBil [<1.2], mg/dL	1
Albumin [3.4–4.8], g/dL	3.6
C-reactive protein [<0.5], mg/dL	4
Procalcitonin, ng/mL	0.21
Lactate, mmol/L	2.3
AFP [<8], ng/mL	2
CEA [<5], ng/mL	2
CA 19.9 [<37], U/mL	11
B and C hepatitis virus	Negative
HIV 1 and 2	Negative

AFP, alpha-fetoprotein; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; CA 19.9, cancer antigen 19-9; CEA, carcinoembryonic antigen; GGT, gamma-glutamyltransferase; HCO3, bicarbonate; HIV, human immunodeficiency virus; MCH, mean corpuscular hemoglobin; MCV, mean corpuscular volume; TBil, total bilirubin.

Prompt resuscitation with intravenous fluids and red blood cell units was initiated. Laboratory tests revealed a normocytic normochromic anemia with platelet count and coagulation profile within normal range and a cholestatic liver injury (shown in Table 1). Urgent abdominal CT angiography revealed 10 × 21 × 20 cm tumor of uncertain etiology in the right liver lobe with intratumoral active bleeding, with no signs of chronic liver disease (shown in Fig. 1).

The case was discussed with Interventional Radiology and the Hepato-Biliary-Pancreatic Surgical team, and an urgent arterial embolization was performed, halting the bleeding (shown in Fig. 2). She was transfused with a total of 3 units of red blood cells, resulting in a final hemoglobin level of 8.3 g/dL.

Further workup revealed negative serologies for hepatitis B and C virus. Regarding tumor markers, alpha-fetoprotein, carcinoembryonic antigen, and carbohydrate antigen 19-9 were within normal range (shown in Table 1). To determine etiology, an abdominal MRI with hepatobiliary-specific contrast was performed, with findings

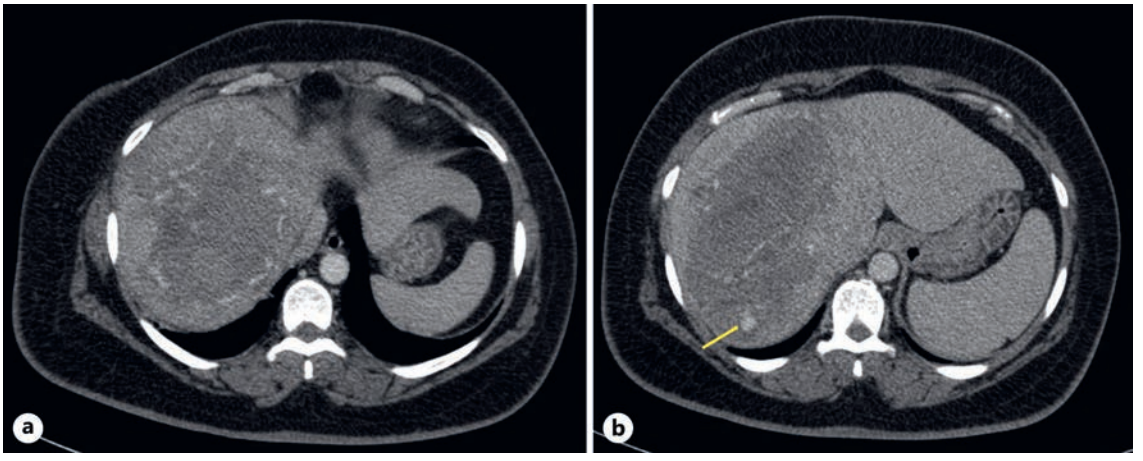

Fig. 1. Abdominal contrast-enhanced CT. **a** A 10 × 21 × 20 cm tumor of uncertain etiology in the right liver lobe with intratumoral spontaneously hyperdense foci suggestive of blood products. **b** Active bleeding (arrow) in the early arterial phase in segment VII.

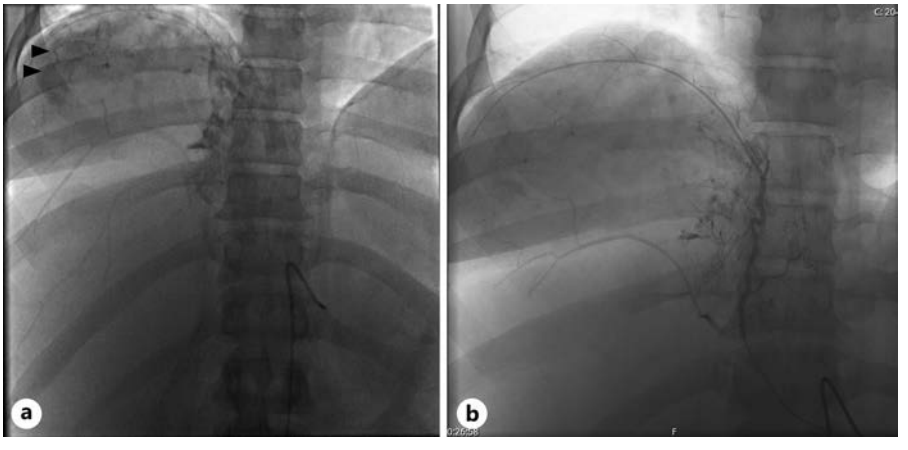

Fig. 2. Angiography images before (**a**) and after (**b**) embolization. Angiography was used to identify the vascular supply to the tumor, with the phrenic artery showing significant vascular supply (arrows). Supra-selective arterial embolization of the right and medium hepatic and phrenic arteries with polyvinyl alcohol embolic particles was performed, with cessation of bleeding.

compatible with a 7.2 × 6.1 × 4.6 cm HCA, more likely inflammatory or hedgehog subtype (shown in Fig. 3). The patient was discussed in a multidisciplinary team meeting, and surgery was proposed.

A robot-assisted laparoscopic extended right hepatectomy was performed with no complications. Histologic examination confirmed the definite diagnosis of an inflammatory HCA (shown in Fig. 4).

Follow-up was uneventful, with normalization of hepatic biochemistry and an unremarkable abdominal ultrasound performed 6 months after surgery. The patient opted for a non-hormonal intrauterine device.

Discussion

HCA is a rare benign epithelial tumor of the liver with a reported prevalence of 0.001–0.004%. It occurs predominantly in women of reproductive age, with a reported female:male ratio of 10:1 [12]. It is well established that exogenous estrogens are a risk factor for HCA, accounting for a 30–40-fold increase in the incidence of HCA, with long-term users bearing the highest risk [2, 3]. Furthermore, the incidence of HCA has increased in anabolic androgenic steroid users, noticeably in men for sport performance enhancement [2]. HCA is also associated with genetic syndromes, including glycogen storage disease type I and type III, with frequencies of 22–75% and 25%, respectively, and familial adenomatous polyposis [1, 5, 12]. Rarer associations include MODY3 diabetes and McCune-Albright syndrome [12], as well as conditions involving high levels of endogenous androgens or estrogens, like Klinefelter syndrome [13]. In recent years, metabolic syndrome and obesity are also emerging as risk factors [12].

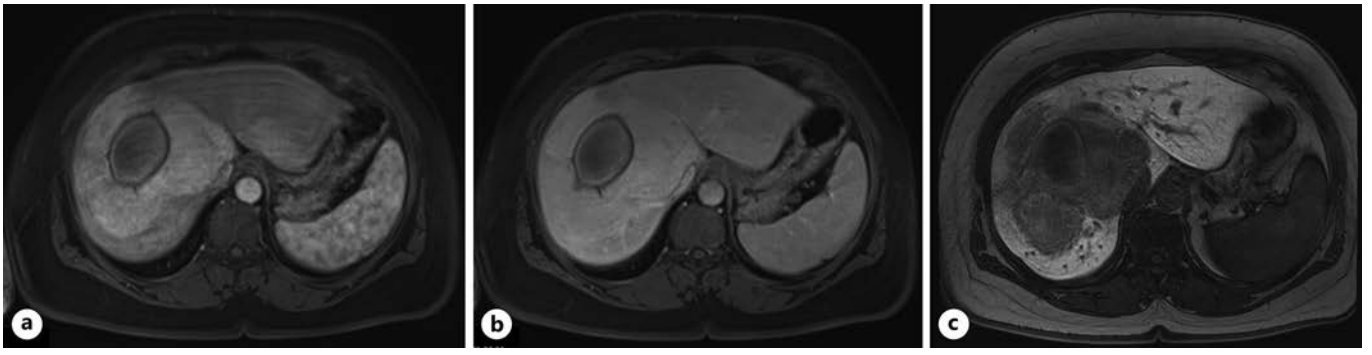

Fig. 3. Abdominal MRI with hepatobiliary-specific contrast. Peripheral solid component showing enhancement on arterial phase (**a**), isointense (no washout) on portal phase (**b**), and hypointense on hepatobiliary phase (**c**) mass with 7.2 × 6.1 × 4.6 cm in segments VII, VIII, and I with a central hematic area secondary to the previous bleeding, suggestive of an HCA, more likely inflammatory or hedgehog subtype.

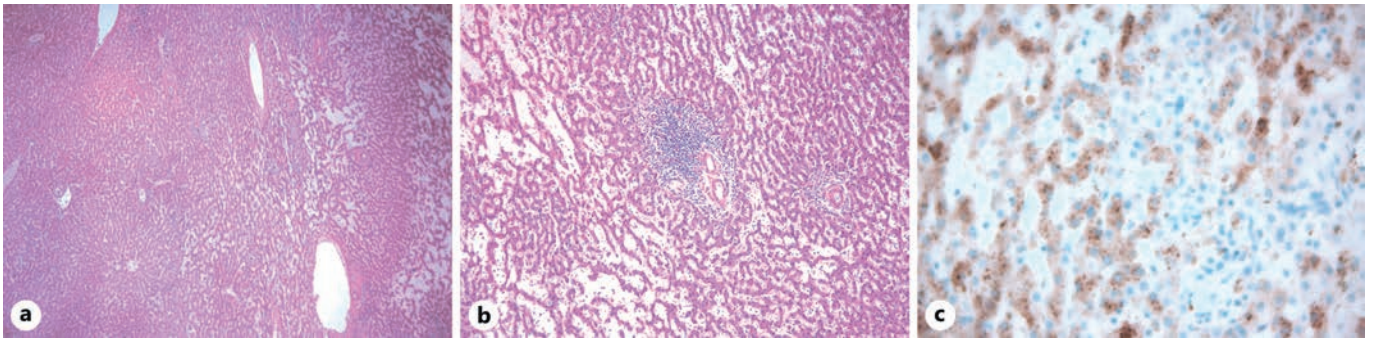

Fig. 4. Histologic examination. Low- (**a**) and high-power views (**b**) showing hepatocellular proliferation with trabecular growth pattern, sinusoidal dilatation, and inflammatory infiltrates. Immunohistochemistry staining of the tumor was liver fatty acid binding protein (LFABP) normal and heat shock protein 70 (HSP70) negative, excluding HCC. Furthermore, reticulin staining was intact, serum amyloid A (SAA) staining was positive (**c**), with normal nuclear β-catenin and glutamine synthetase staining, confirming the definite diagnosis of an HCA of inflammatory subtype.

HCA is usually solitary. However, up to half of patients may have multiple HCA, a condition termed liver adenomatosis [1, 5, 12]. This condition is associated with germline and somatic mutations in HNF-1α and MODY3 diabetes [12], although obesity, steatosis, and metabolic syndrome are also linked with hepatic adenomatosis [5, 6, 14].

Regarding genetic and pathological features, HCA is categorized into four subtypes with implications in management: HNF1-A mutations, inflammatory, β-catenin mutations, and unclassified. The clinical presentation is heterogeneous. Most HCA is found incidentally on abdominal imaging, though up to 14% of cases may exhibit abnormal serum liver tests. When they are symptomatic, the most common presentation is mild and nonspecific right hypochondrial pain, observed in 37% of patients. However, the pain may be severe as a result of bleeding [15].

While hemorrhage is an infrequent complication associated with hepatic tumors [10], HCA ranks as the second most prevalent tumor connected with bleeding, following hepatocellular carcinoma (HCC), with up to 30% of HCA patients experiencing spontaneous bleeding [5, 16]. When bleeding occurs, it may be intratumoral or the tumor may rupture, leading to subcapsular or intraperitoneal hemorrhage presenting as an acute hemoperitoneum. Hemodynamic instability occurs in fewer than 10% of cases and is more commonly observed in patients with intraperitoneal bleeding rather than intratumoral bleeding, in contrast to the presented case [17]. Rupture is more likely in patients with large (>5 cm), solitary, and superficial tumors. Additional risk factors include inflammatory subtype, hormone use, and pregnancy [5]. Our patient presented multiple risk factors associated with a higher bleeding risk, namely, the size, hormone use, and HCA subtype.

HCA also has a risk of malignant transformation. Surgical series report a 4–10% incidence of HCC within resected adenomas [16, 17]. Known risk factors include activating mutations in β-catenin, occurring in up to 5–10% of cases, male gender, and tumor diameter larger than 5 cm [6–8].

Concerning diagnosis, non-ruptured HCA is usually an incidental finding in abdominal imaging. Ultrasonography reveals variable echogenicity depending on the fat content, with a sensitivity of only 30% [18]. Contrast-enhanced ultrasound may help differentiate from other tumors [19]. Computed tomography can be diagnostic in cases of typical HCA, showing an isoattenuating or hypodense lesion with arterial phase enhancement, returning to near isodensity on portal venous and delayed phase images. However, only 75% of cases have typical features [20]. MRI with hepatocyte-specific contrast agents is the best imaging modality for its diagnosis with 80–90% specificity [21], allowing identification of the HCA subtype in up to 80% of patients and differentiation from other tumors [5, 12]. Despite the significant variation in MRI findings associated with HCA subtypes, the predominant observation is hypointensity on hepatobiliary sequences [5, 22]. However, β-catenin activated HCA and its distinction with unclassified HCA and HCC is not possible by any imaging technique. Furthermore, it also can be difficult to distinguish HCA from focal nodular hyperplasia in some cases [9]. Although imaging alone establishes a diagnosis in most cases of HCA, if it is inconclusive, referral to specialized centers with experts in this field is recommended. Performing a liver biopsy in this setting carries a low but non-negligible hemorrhagic risk given the vascular nature of HCA and other tumors which are part of the differential diagnosis. In a retrospective review involving 60 patients who underwent percutaneous biopsy, complications were documented in 12% of individuals, with a single episode of severe bleeding [23]. For these reasons, international guidelines suggest reserving liver biopsy for cases in which imaging is inconclusive and histology results will significantly impact treatment decisions [12, 24].

All patients should be advised to discontinue oral contraceptives, hormone-containing intrauterine devices, and anabolic steroids. Further management is dependent on gender, tumor size, the presence of symptoms, and whether bleeding or malignancy is suspected.

In non-ruptured HCA, the most relevant factors to consider are gender, size, and growth pattern. In asymptomatic nonpregnant women, discontinuing exogenous estrogens, control of body weight, and imaging reevaluation with contrast-enhanced MRI after 6 months are recommended. If the tumor size is or decreased to less than 5 cm, it can be managed conservatively. There is no consensus in the definition of stable disease and its follow-up. Most societies recommend interval imaging every 6 months for 12–24 months, followed by annual imaging for stable lesions [9, 12, 24]. However, if the HCA is persistently greater than 5 cm or increased in size, surgery is recommended given the risk of hemorrhage and malignancy. Furthermore, surgery is also recommended in patients who are symptomatic and male or have a proven β-catenin mutation, in cases where a biopsy was performed to establish the diagnosis. The last two are indications for surgery irrespective of tumor size given their higher risk of malignant transformation [9, 12, 24]. Surgery is the first line of therapy for curative treatment. Nonsurgical modalities are reserved for high surgical risk patients or tumors in challenging anatomical locations [9, 24].

If bleeding occurs, it is a medical emergency that requires prompt management. Intravascular volume replacement should be immediately started and an abdominopelvic CT with angiography should be performed. If active bleeding is detected, arterial embolization is preferred over surgery since it is minimally invasive and has lower morbidity. Surgery should be reserved for patients with persistent and severe hemodynamic instability or when embolization is ineffective or unavailable. When surgery is unavoidable, a damage control surgery with an abbreviated laparotomy with perihepatic packing is recommended [11]. Once the bleeding is controlled, etiology must be determined and an imaging study should be repeated since hemorrhage induces significant changes that may hinder a diagnosis in the acute setting. After establishing the diagnosis of a HCA, further management is dependent on its persistence. Surgical resection is advised if there is residual viable lesion on follow-up imaging [5, 12], as it happened in the case described. The management of HCA is determined by gender, tumor size, presentation, and progression pattern, and, importantly, requires the expertise of an experienced multidisciplinary team.

Statement of Ethics

Ethical approval was not required for this study, in accordance with local/national guidelines. Informed consent was obtained from the patient for publication of the medical case and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Author Contributions

Sara Ramos Lopes drafted the paper. All authors read and approved the final manuscript.

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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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