Portuguese Journal of Gastroenterology

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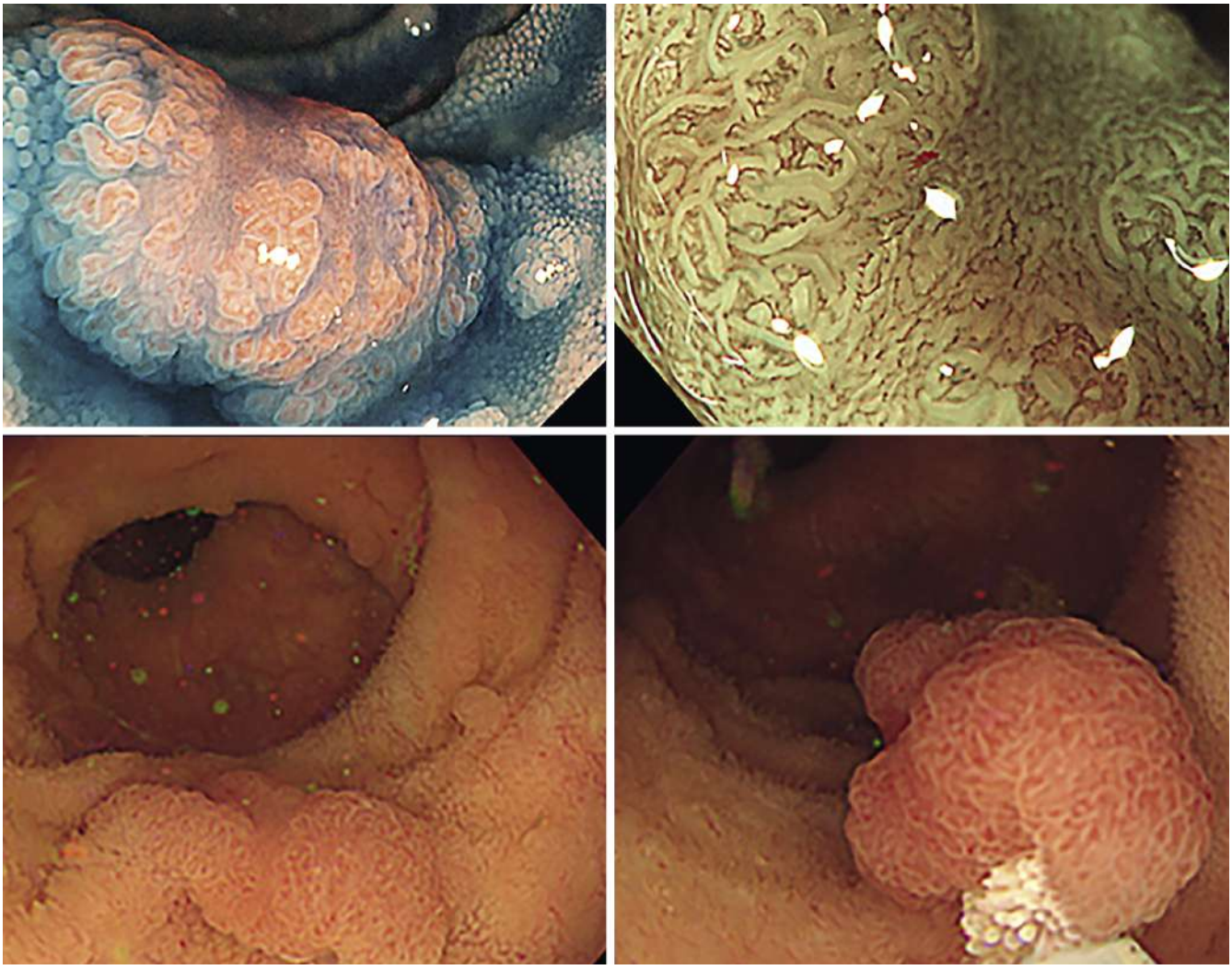

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Review Article

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Management of Nonmalignant Portal Vein Thrombosis in Cirrhosis

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Keywords
Portal vein thrombosis · Cirrhosis · Anticoagulation · Transjugular intrahepatic portosystemic shunt · Prognosis

Abstract
Nonmalignant portal vein thrombosis (PVT) is a common complication of cirrhosis especially at the stage of decompensations. The diagnosis of PVT in cirrhosis is often incidental and it may be detected during routine semestral abdominal ultrasound with Doppler during screening for hepatocellular carcinoma or during hospitalization for decompensated cirrhosis. After detection of PVT on abdominal ultrasound, it is important to evaluate patients with cross-sectional imaging to determine the age of thrombus, whether acute or chronic, the extent and degree of luminal occlusion of the portal vein, and to rule out hepatocellular carcinoma or other underlying malignancy. Factors influencing management include the degree and extent of luminal occlusion of PVT, potential listing for liver transplantation, and portal hypertension (PHT) complications such as variceal hemorrhage and refractory ascites, severity of thrombocytopenia, and other comorbidities including chronic kidney disease. Anticoagulation is the most common therapeutic option and it is specially indicated in patients who are candidates for liver transplantation. Interventional procedures including transjugular intrahepatic portosystemic shunt (TIPS) placement and mechanical thrombectomy may be used on a case-by-case basis in patients with contraindications or adverse events related to anticoagulation, who develop worsening PVT while on anticoagulant therapy, or have chronic PVT and PHT complications that are not manageable medically or endoscopically.

Abordagem à trombose não neoplásica da veia porta no doente cirrótico

Palavras Chave
Trombose da veia porta · Cirrose · Anticoagulação · TIPS · Prognóstico

Resumo
A trombose da veia porta (TVP) é uma complicação frequente na cirrose, especialmente na fase de descompensação. O diagnóstico é na maioria das vezes realizado de forma incidental. durante o rastreio semestral para o carcinoma hematocelular com ecografia abdominal com doppler ou durante o internamento por episódio de descompensação da cirrose. Após a deteção de TVP numa ecografia abdominal com doppler, é importante a realização de um método de imagem

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complementar de corte axial para avaliar a idade do trombo, se agudo ou crónico, a extensão e grau de oclusão luminal da veia porta e para excluir carcinoma hepatocelular ou outra neoplasia subjacente. A gestão do doente depende do grau de oclusão e da extensão do trombo na circulação portal, mas também da possibilidade de ser candidato para transplante hepatico, complicações da hipertensão portal, gravidade de trombocitopenia e da existência de outras comorbilidades relevantes como a doença renal crónica. A anticoagulação é a principal opção terapêutica mas outros procedimentos como a colocação de TIPS e trombectomia mecânica devem ser pensados caso a caso, quando existem contraindicações à anticoagulação, a resposta à terapêutica anticoagulante não é adequada ou existem complicações da hipertensão portal não abordáveis com terapêutica médica ou endoscópica.

Introduction

Nonmalignant portal vein thrombosis (PVT) is a common vascular disorder that develops in advanced liver disease [1]. Patients with cirrhosis have a higher risk of developing hepatocellular carcinoma (HCC), and therefore, it is very important to rule out tumoral invasion in those who develop PVT since this influences therapeutic strategy [1].

The management of PVT starts with an adequate evaluation and risk stratification of the patient at the time of diagnosis. This implies an estimate of the age of the thrombus, whether acute (<6 months) or chronic (>6 months) and the extension and degree of luminal occlusion of the portal vein (PV), splenic and superior mesenteric veins, and exclusion of HCC with cross-sectional imaging with either contrast enhanced computed tomography (CT) or magnetic resonance imaging (MRI) [2].

As the incidence of PVT increases with increasing severity of liver disease, the clinical challenge is to choose the patients who will benefit most from treatment, which in most cases relies on anticoagulation [3]. However, as these are very complex patients often with alcohol dependence, concomitant thrombocytopenia, and comorbidities including chronic kidney disease, management of PVT should be individualized [4].

Epidemiology

PVT is common in patients with cirrhosis but is relatively rare in the general population [1]. In a study involving more than 20,000 autopsied patients, the prevalence of PVT was 1%, with patients with cirrhosis being almost 8 times more prone to develop this condition [5]. The incidence of PVT increases with increasing severity of cirrhosis and is more common in patients belonging to Child-Pugh class B and C and those with high MELD score [6].

In the study by Nery et al. [7], in which 1,243 patients with cirrhosis were prospectively evaluated, the 5-year cumulative incidence of PVT was 10.7%. In a prospective study involving 241 patients, the 1- and 3-year incidence of PVT was 3.7% and 7.6%, respectively [8]. In another prospective study involving 369 patients, the incidence of nontumoral PVT was 1.6%, 6%, and 8.4% at 1, 3, and 5 years, respectively [3]. The prevalence of PVT increases with the severity of the cirrhosis, being less than 1% in patients with compensated cirrhosis and varying between 8% and 25% in those who are candidates for liver transplantation [9].

PVT is partial in 73%–86% of patients and is often asymptomatic [7]. Approximately 40% of PVT will have spontaneous resolution, typically within 3 months, although there are no clearly identified clinical predictors of recanalization [1]. Nonetheless, progression or stability is more common than regression in untreated PVT [10]. The risk of rethrombosis is also significant in these patients and may occur in a third of patients, and therefore, surveillance for de novo PVT should be continued after recanalization [11].

Risk Factors

The pathophysiology of PVT is multifactorial and, like other venous thrombosis, is believed that thrombotic risk is due to blood stasis, hypercoagulability, and endothelial injury, which are the components of Virchow's triad [1]. Nonetheless, the pathophysiology of PVT seems to be unique, and the relation of these three with it is not totally clear [12].

The splanchnic circulation has unique conditions related to its slow-flow and high-volume hemodynamics that are disturbed by cirrhosis and subsequent portal hypertension (PHT) [1]. The velocity of PV flow is an independent predictor of PVT development, especially in patients with PV blood flow velocity <15 cm/s, making these patients a high-risk subgroup, probably due to blood stasis [6, 13].

Presence of esophageal varices and prolonged prothrombin time are independent predictors of development of PVT [7]. Additionally, previous decompensation

of cirrhosis and thrombocytopenia has been found to be independent predictors of development of PVT [8].

A study conducted in virus-related cirrhosis suggested that large portosystemic collateral vessels contribute to increased risk of PVT, which could be explained by the steal effect that reduces the PV blood flow [14]. A recent meta-analysis concluded that nonselective β-blockers, used for primary and secondary prophylaxis of variceal bleeding, could increase the risk of PVT in cirrhotic patients [15]. However, some authors defend that the main driver for the higher risk of developing PVT is the severity of PHT, which often correlates with more advanced liver disease and leads to the prescription of nonselective β-blockers, and not the use of the medication itself [3].

Patients with cirrhosis have complex hemostatic alterations with a delicate balance between procoagulant or anticoagulant factors, with a tendency to tip toward thrombosis in the presence of inflammation and infection [3]. The assessment of prothrombin time and international normalized ratio does not truly represent the hemostatic balance of these patients who are not naturally anticoagulated but who actually have a tendency for thrombosis [16]. Although prothrombotic disorders, like congenital or acquired thrombophilias or myeloproliferative neoplasms, are associated with noncirrhotic PVT, the screening for thrombophilic disorders in patients with cirrhosis is currently not yet recommended [2]. A large recent prospective study could not prove a direct link between genetic and acquired prothrombotic factors and the development of PVT in cirrhotic patients [12].

It has been postulated that the direct and indirect damage to portal venous endothelium is mostly promoted by bacterial translocation, inflammation, and endotoxemia in patients with cirrhosis due to the underlying PHT [10]. The association of these conditions with development of PVT needs confirmation with robust studies, but previous decompensation of cirrhosis and thrombocytopenia appear to correlate well with its development, indirectly reflecting the pathophysiological role of the severity of PHT in the development of thrombosis in the splanchnic circulation [8]. Other independent risk factors for the development of PVT in cirrhosis that have been determined include obesity, metabolic syndrome, and nonalcoholic steatohepatitis [17, 18].

The gap between pathophysiology of systemic venous thrombosis and thrombosis in portal vascular territory has been a matter of debate [12]. A recent study in a series of 63 nonmalignant PVT in patients with cirrhosis showed that tunica intima thickening of the vessel wall prevails in a significant proportion of patients rather than fibrin-rich thrombus, which may explain the lower PVT recanalization rates with anticoagulant therapy. This could offer an explanation for the limitations of anticoagulant therapy in some patients. Nonetheless, the study has important limitations and more studies are required to validate this new paradigm in the pathophysiology of PVT [19].

Diagnosis and Classification

In patients with cirrhosis, PVT is often asymptomatic and it is diagnosed incidentally during semestral screening for HCC with abdominal ultrasound with Doppler [20]. Nonetheless, PVT should be suspected in any patient with cirrhosis who develops a clinical decompensating event or abdominal pain [1].

The current guidelines [9, 21] do not provide a formal recommendation to screen these patients for PVT, but as they already undergo abdominal ultrasound screening for HCC every 6 months, the assessment of PV could be done at the same time with abdominal ultrasound ideally with Doppler, which has a higher sensitivity to detect a thrombus in the PV without consuming additional resources and time [11].

Abdominal ultrasound with Doppler is the first-line approach to detect PVT and some imaging features may allow distinction between acute or recent (<6 months) and chronic (>6 months) thrombosis [2]. In an acute PVT, the clot is normally hypoechoic or isoechoic with a mildly dilated PV, in contrast to the hyperechoic material and the cavernous transformation with multiple small vessels in chronic PVT [2]. The performance of abdominal ultrasound with Doppler is not perfect, with a sensitivity of 90% for complete PVT and 50% for partial PVT, with the additional limitation of being operator-dependent [11]. Additionally, there may be technical difficulties in evaluating concomitant superior mesenteric vein (SMV) thrombosis in these patients [10].

The detection of PVT on abdominal ultrasound with Doppler should be followed by a cross-sectional imaging method, contrast-enhanced abdominal CT, or MRI to confirm the diagnosis, to determine the age of the thrombus and extent and degree of luminal occlusion of the splanchnic circulation by the thrombus, and to rule out HCC and other abdominal malignancies [10]. Anatomically, PVT involves mainly the PV trunk and branches and may involve the SMV and splenic vein [13] (shown in Fig. 1).

The lack of standardized nomenclature in PVT has been a problem, and in order to address this issue, the American Association for the Study of Liver Disease (AASLD) proposed a new standardized nomenclature for the description of PVT [22]. In terms of time course, PVT

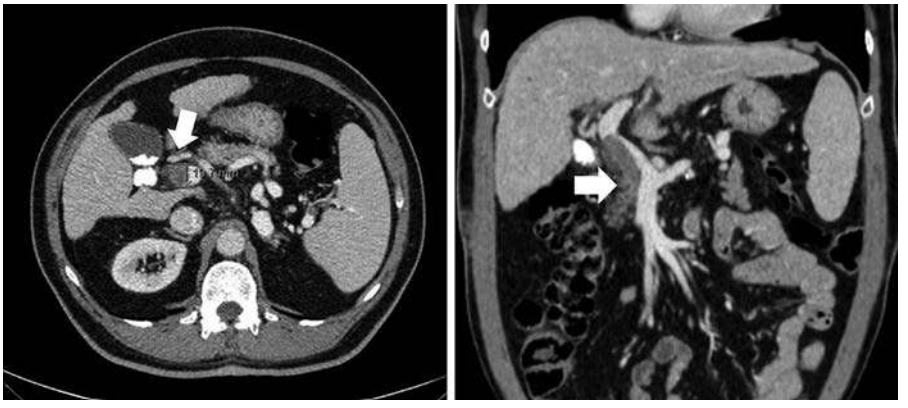

Fig. 1. Images of a thrombus occupying more than 50% of the PV trunk.

is classified as recent (<6 months) or chronic (>6 months) and a reference is made to cavernous transformation, which is associated with chronic PVT and lower probability of PVT recanalization [22]. With regard to the severity of occlusion of the main PV, degree of luminal occlusion is classified as <50% and >50%. Finally, during the follow-up, PVT should be defined as progressive, stable, or regressive [22]. All these definitions have important implications on management and outcome.

Despite several proposed classification systems, the one suggested by Yerdel et al. [23] using anatomic criteria continues to be widely used, because of its simplicity and reproducibility, which includes: site, degree of occlusion, and extension of the thrombus as shown in Figure 2 [24]. As this classification is only anatomical, although it is useful for surgical management, including liver transplantation, it lacks information for a clinical therapeutic decision [25].

Recently, Sarin et al. [25] proposed a more integrated classification taking into account also functional aspects including the occurrence of symptoms and timing of thrombosis. This classification has been developed for patients with cirrhosis, with the possibility of adding other variables like anticoagulation, type of underlying liver disease, and presence of clinical significant PHT [25].

After detection of PVT, an upper endoscopy should be performed to assess the presence and size of esophageal varices and/or gastric varices, and if required, primary or secondary prophylaxis of variceal bleeding should be initiated promptly prior to anticoagulant therapy [11].

Treatment

After confirming the diagnosis of nontumoral PVT and its extent and degree of luminal occlusion, it is important to stratify patients according to the possibility of undergoing liver transplantation, presence of concomitant PHT complications like variceal hemorrhage and refractory ascites, age, thrombocytopenia, and comorbidities including chronic kidney disease, in order to individualize clinical management decisions that primarily involve anticoagulant therapy [26]. In potential candidates to OLT, the extent and degree of luminal occlusion in PVT have implications on liver transplant surgery strategy as well as postoperative morbidity and early mortality. The outcome of grade 1 PVT patients (<50% luminal occlusion) does not differ from non-PVT patients, but grades 2–4 have poorer outcomes [23]. This highlights the importance of 50% luminal occlusion cutoff to determine which patients should be promptly treated. Fortunately, majority of patients with cirrhosis have partial thrombosis of the PVT often causing <50% luminal occlusion and were transient and completely disappeared spontaneously during the follow-up in two-third of the patients as was shown in the study by Nery et al. [7].

The therapeutic options include anticoagulation with conventional anticoagulants or direct oral anticoagulants in compensated (Child-Pugh A) cirrhosis and low molecular weight heparin (LMWH) in advanced cirrhosis (Child-Pugh B and C). In patients with contraindications, adverse events related to anticoagulation, progression of PVT on anticoagulation, or that have concomitant clinical indication for it, and interventional radiology techniques such as transjugular intrahepatic portosystemic shunt (TIPS) and mechanical thrombectomy are recommended [2]. A multidisciplinary team involving gastroenterologists, imaging specialists, interventional radiologists, and surgeons could be useful to provide the best treatment option for patients with cirrhosis and nontumoral PVT [27].

Anticoagulation

The aim of anticoagulant therapy is to recanalize the thrombosed veins and prevent further extension of the thrombus and complications such as intestinal ischemia due to extension of the PVT into the SMV [7]. An upper

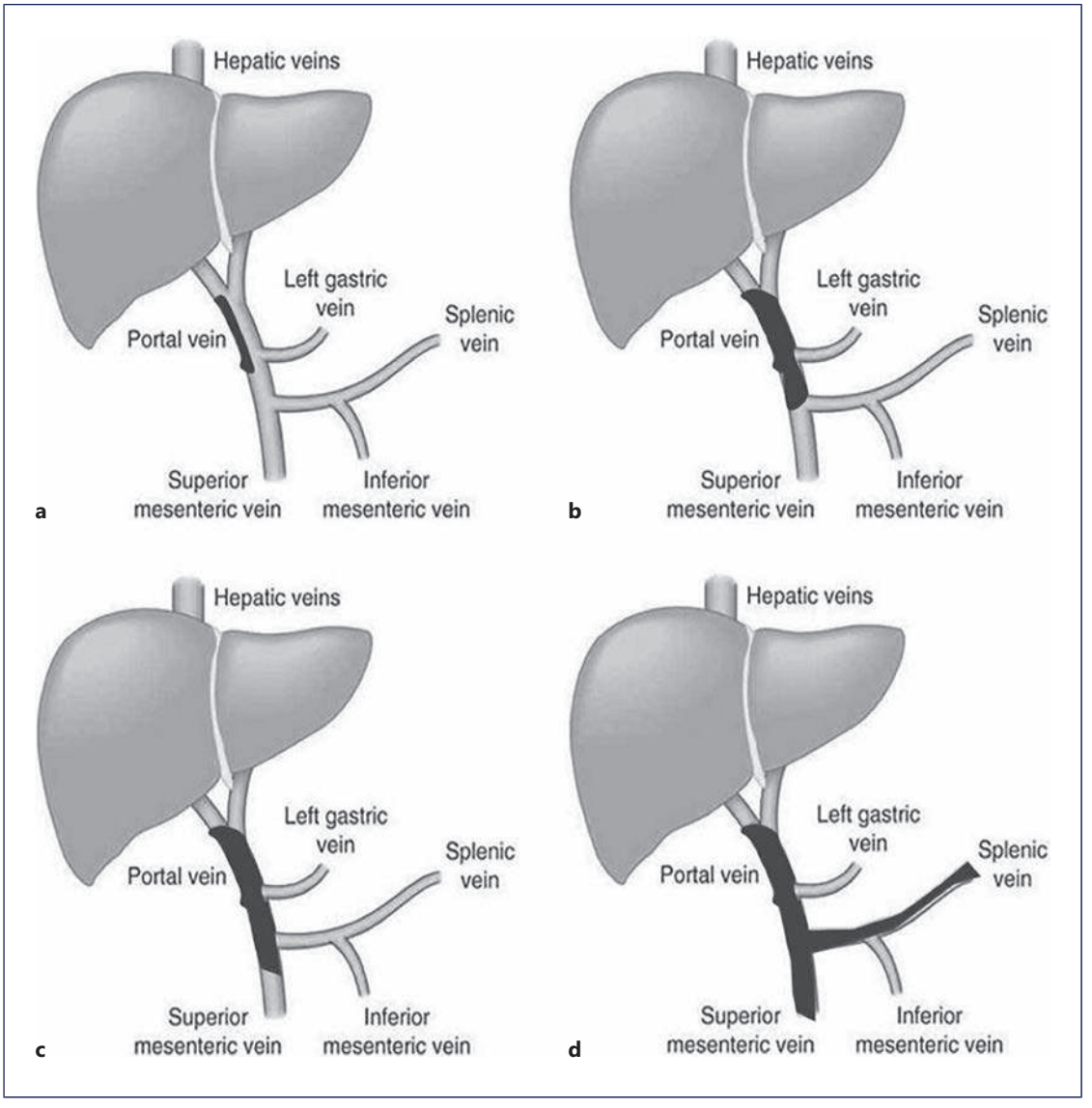

Fig. 2. a–d Yerdel classification of PVT. Adapted from Chen et al. [24].

endoscopy for screening of esophageal varices and gastric varices is recommended in all patients candidates for anticoagulant therapy, and when indicated, primary or secondary prophylaxis of variceal bleeding should be initiated prior to starting anticoagulation [4]. However, this recommendation is not consensual and recent practice guidelines from the AASLD suggest that endoscopic band ligation is safe under therapeutic anticoagulation, and therefore, anticoagulant therapy, if indicated, should not be delayed until varices are eradicated [22].

In patients with cirrhosis and PVT, especially in liver transplant candidates, anticoagulation is indicated for those who are symptomatic, have luminal occlusion of the PV trunk over 50%, have extension to the SMV, and do not meet these criteria at the time of diagnosis but show progression of PVT during the follow-up [2]. Patients with chronic occlusion of PV or cavernous transformation with collaterals may not have a clear benefit of anticoagulation in terms of recanalization of occluded segment of PV [22]. In patients with thrombosis involving <50% of the lumen of PV trunk and/or branches, follow-up abdominal ultrasound with Doppler is recommended every 3 months to detect progression or resolution of the thrombus [1].

The strategy and clinical decisions guiding management of nontumoral PVT in patients with cirrhosis are shown in Figure 3. Nonetheless, it is important to make

individualized decisions, taking into account, ongoing alcohol abuse, compliance to treatment of complications of cirrhosis, patient fragility, and comorbidities such as chronic renal failure and the risk of fall [2].

The success of anticoagulation is correlated with early diagnosis of PVT and early initiation of anticoagulant therapy with patients that start anticoagulation within 6 months of detection of PVT being more likely to successfully recanalize PVT [28]. The pooled recanalization rates of PVT with anticoagulant therapy have been shown to be around 58% in a recent meta-analysis [29]. Factors like Child-Pugh class A, less extensive PVT, and absence of prior variceal bleeding appear to predict higher recanalization rates [30]. Anticoagulation significantly reduces all-cause mortality, compared to no treatment, and this benefit appears to be independent from PVT recanalization itself [29].

Anticoagulation appears to be safe in patients with cirrhosis when correctly selected, and a large systematic review showed that PVT patients treated with LMWH or vitamin K antagonists (VKA) achieved higher recanalization rates compared to placebo (72% vs. 40%), without significant differences in bleeding complications [31]. In the meta-analysis evaluating anticoagulant therapy in nontumoral PVT in cirrhosis by Guerrero A et al. [29], the bleeding rate was similar between the groups (anticoagulation and no treatment), with no significant differences in PHT-related bleeding in the 2 groups of patients. The risk of bleeding appears to correlate with platelet counts at baseline <50,000 cells/μL, low serum albumin, and prior variceal bleeding [31].

The incidence of variceal bleeding in patients with cirrhosis and PVT was found to be significantly lower in those receiving anticoagulation compared to untreated ones (2% vs. 12%) [32], highlighting the benefit of anticoagulation in preventing future decompensations of cirrhosis. However, potential biases involving prophylaxis of variceal bleeding in patients receiving anticoagulation compared to untreated ones may have explained differences in variceal bleeding rates.

LMWH and VKA are considered as first choice in patients with cirrhosis and PVT, but the patient profile is extremely important [11]. LMWH is the initial treatment of choice at the standard dose of 1 mg/kg twice a day subcutaneously (with the necessary adjustments for kidney function). In patients with thrombocytopenia and renal failure, half the conventional dose of LMWH is often administered [4].

The main advantages of LMWH when compared to VKA are the fixed dose without the need for laboratory monitorization [33]. However, due to the need for parenteral administration and cost issues, oral options are normally preferred for long-term treatment [2]. VKA appear to be a safe option for Child-Pugh A and B (7 points). However, maintaining the international normalized ratio between 2 and 3 could be a challenge in these patients [2].

Direct oral anticoagulants (DOACs) are becoming an alternative to VKA [34]. However, despite several cohort studies confirming their efficacy and safety, there are still limited data from large studies regarding their safety in patients with cirrhosis as most of these patients were excluded from clinical trials [35]. In Child-Pugh class A patients, DOACs seem to be safe, but caution is needed in Child-Pugh class B patients and they are not indicated in Child Pugh class C [36]. Dose adjustment of DOACs is required in patients with renal impairment as shown in Table 1.

In patients with advanced cirrhosis (Child-Pugh B ≥8 points and Child-Pugh C), LMWH seems to be a safer option for long-term treatment [4]. During the course of treatment, an abdominal CT or MRI should be done after 3 months and then at 6 months to evaluate the efficacy of anticoagulation [1]. Anticoagulant treatment should be maintained for at least 6 months or indefinitely in patients on liver transplant waiting list and in those with SMV involvement [2]. The recurrence of thrombosis after stopping anticoagulant therapy in these patients is high with rates varying between 27% and 38%, and therefore, maintaining patients on anticoagulation should be considered especially in the absence of contraindications or adverse events [4, 29].

Thrombolysis

Thrombolysis, as used in other venous territories, has been reported to be effective in patients with cirrhosis who develop PVT, but significant procedure-related morbidity and mortality have been reported and there is no evidence that it is superior to anticoagulation alone in recent or acute PVT and therefore the most recent guidelines do not recommend this approach routinely [2]. In selected cases of recent PVT in whom intestinal ischemia persists despite anticoagulation, this approach could be an option [22].

Transjugular Intrahepatic Portosystemic Shunt

TIPS creates a low-pressure channel to bypass portal venous flow directly to the hepatic veins through a stent [11]. TIPS can be placed in a recanalized main PV or in a dominant collateral [37]. Often, the aim of TIPS is not to recanalize the thrombus, but to treat the PH-related complications due to it and guarantee the patency of portal tract [2].

TIPS may be useful in selected patients with PVT who have contraindications for anticoagulant therapy due to severe thrombocytopenia or in those who develop adverse events related to anticoagulant therapy, have progression of

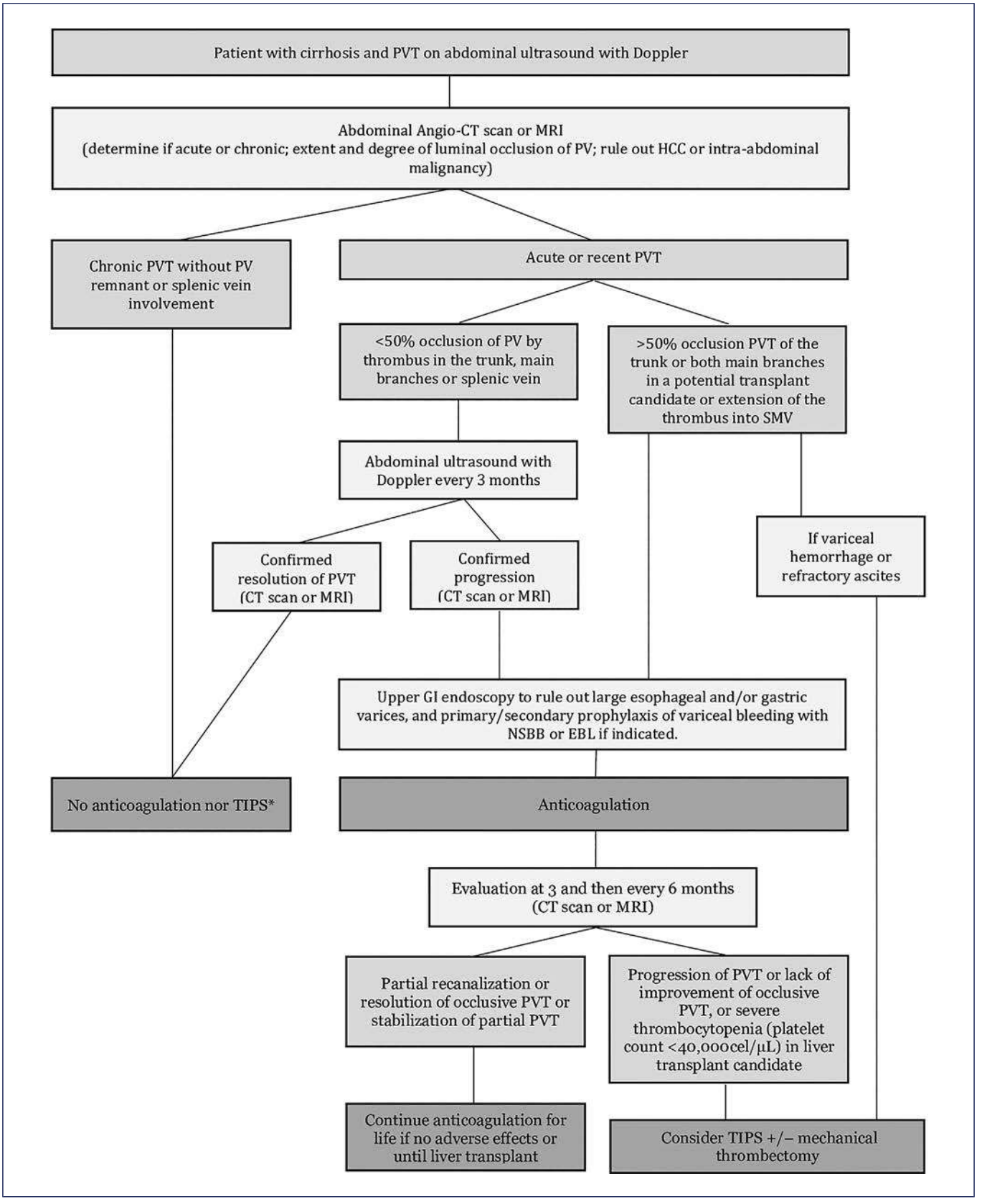

Fig. 3. Flowchart illustrating management of nontumoral PVT in cirrhosis. Adapted from Senzolo et al. [2].

Table 1. DOAC treatment doses for PVT treatment

DOAC	Hepatic metabolism	Dose adjustment for renal impairment	Standard manutention dose for PVT treatment	Child-pugh class
Rivaroxaban	Yes	Yes	20 mg once daily 15 mg once daily if creatinine clearance ≤50 mL/min	Safe in child-pugh A; use with caution in child-pugh B; contraindicated in child-pugh C
Apixaban			5 mg twice daily 2.5 mg twice daily if at least two of the following conditions: age ≥80 years old, ≤60 kg, or creatinine ≥1.5 mg/dL	
Edoxaban			60 mg once daily 30 mg once daily if at least one of the following conditions: ≤60 kg and creatinine clearance ≤50 mL/min	
Dabigatran			150 mg twice daily 110 mg twice daily if the age is ≥80 years old or increased bleeding risk Not recommended if creatinine clearance ≤30 mL/min	

PVT on anticoagulation, and have PHT complications or no response after 6 months of anticoagulation [2, 38]. In some patients with cirrhosis, PVT is detected at the time of a clinical decompensation event such as acute variceal bleeding. The indication for TIPS placement in refractory variceal bleeding or preemptive TIPS (Child-Pugh C <14 or Child-Pugh B >7 with active bleeding at index endoscopy or HVPG >20 mm Hg at the time of hemorrhage) is not affected in those patients who have concomitant PVT [39].

A recent meta-analysis demonstrated that TIPS for PVT recanalization was feasible, effective, and safe [38]. The technical success is around 95% [38], and failure to place TIPS was closely related to associated portal cavernoma and the degree of thrombosis within each venous segment of the portal venous system and extension into the SMV and splenic vein [37, 38]. In potential OLT candidates with chronic and complete PVT, PV recanalization and TIPS creation could also be considered to facilitate transplant eligibility [40]. Another key point in TIPS is the patency of the stent (around 89%), with a better performance with covered stents [38]. The use of a trans-splenic approach followed by TIPS creation in order to reestablish a patent main PV has been reported in a single-center case series [41].

There is controversy about post-TIPS anticoagulation to prevent de novo PVT as well as to prevent thrombus extension and maintain the recanalization of PV achieved [42, 43]. In the meta-analysis by Guo et al. [44], post-TIPS anticoagulation was found to be associated with a higher risk of rebleeding. A recent randomized control trial suggested that TIPS placement alone can achieve high PVT recanalization rates possibly due to an increase in blood flow velocity in the splanchnic circulation [45]. However, the study results require validation and a risk-benefit evaluation should always be considered. We continue to favor anticoagulant therapy in extensive PVT especially when the SMV is involved.

The TIPS procedure is invasive, with risks that increase when this technique is combined with mechanical thrombectomy and direct catheter thrombolysis [38]. Also, post-TIPS cardiac dysfunction and encephalopathy are important safety concerns [46]. Post-TIPS encephalopathy has been reported to occur in 17–29% of patients [38].

The TIPS studies on PVT have some limitations. First of all, in most of the studies the indication for TIPS was PHT complications such as variceal hemorrhage and refractory ascites, and not the PVT itself, and most studies excluded chronic PVT, with an unknown impact on the technical success rates and adverse events [46].

The differences in PVT recanalization rates and adverse events and limitations of anticoagulant therapy and TIPS placement for management of PVT are summarized in Table 2. After TIPS placement in patients with cirrhosis and PVT, a careful follow-up with scheduled TIPS venography in the first 2 months is crucial to access its patency and existence of residual PVT. Depending on the findings, interventions to perform additional PV recanalization or embolize spontaneous competing portosystemic shunts could be needed to maintain efficacy [40].

Table 2. Comparison of anticoagulant therapy versus TIPS in the management of nontumoral PVT in cirrhosis

	Anticoagulation	TIPS
Indications according to clinical orientations/ guidelines	Recent occlusive or partially occlusive (>50%) thrombosis of the main PV or mesenteric veins [22] In PVT, consider anticoagulation at the therapeutic dose for at least 6 months [21] In patients with SMV thrombosis, with a past history suggestive of intestinal ischemia or liver transplant candidates, consider lifelong anticoagulation [21] Once PVT has recanalized, consider prolonging anticoagulation for some months and until transplant in liver transplant candidates [21]	TIPS should be considered in liver transplantation patients with chronic PVT that hinders a physiological anastomosis between graft and recipient PV [22] TIPS should be considered in patients with chronic PVT and recurrent bleeding and/or refractory ascites not manageable medically or endoscopically [22] In liver transplant candidates, who have progressive PVT not responding to anticoagulation, consider referring the patients for TIPS [21]
Recanalization success	57.6% of patients receiving anticoagulation achieved partial or total recanalization rate [29]	The 12-month recanalization rate in cirrhotic patients was 81% [38] Recanalization rates between 57.1% and 91.7% [44]
Complications	Bleeding rate was similar between groups (anticoagulation and no treatment), with no differences between hypertension-related bleeding [29]	Encephalopathy at 12 months varying between 17% and 29%. [38] Encephalopathy after TIPS in almost one-third of the patients [44] Post-TIPS encephalopathy and cardiac dysfunction are important safety concerns [47]
Procedure technical execution		TIPS creation was feasible in 95% of patients [38]
Procedure complications		The 12-month TIPS patency was 89%, with a better performance with covered stents [38] Anticoagulation post-TIPS was associated with more risk of rebleeding [44]
Impact on survival	Anticoagulation significantly reduced all-cause mortality, compared to no treatment. The benefit is independent from recanalization itself [29]	Survival of 89% at 12 months [38] No studies comparing TIPS versus anticoagulation in the management of PVT in cirrhosis
Bias and conditionings	Patients receiving anticoagulant therapy were more likely to receive prophylaxis of variceal bleeding compared to those who did not	The TIPS procedure is combined in some cases with mechanical thrombectomy and direct catheter thrombolysis [38] Some studies combined anticoagulation after TIPS [38, 44] In most of the studies, the indication for TIPS was PH complications like variceal hemorrhage and refractory ascites, and not the PVT itself [47] Most exclude chronic PVT, with an unknown impact on the procedure technical execution success rates [47]

PVT, portal vein thrombosis; TIPS, transjugular intrahepatic portosystemic shunt scan.

Prognosis

The impact of PVT on hepatic decompensation and mortality in cirrhosis is still unclear. A large multicenter study showed that while the development of PVT correlates with the severity of liver disease at baseline, there was no association between PVT and progression of hepatic decompensation over time [7]. A small prospective randomized controlled trial comparing enoxaparin to placebo in the prevention of PVT in high-risk patients with cirrhosis without PVT at baseline showed not only efficacy in the prevention of development of PVT but also a higher survival and lower risk of decompensation in those who received enoxaparin during 1 year [48]. In this study, patients receiving anticoagulation were found to have lower rates of bacterial translocation and lower levels of inflammatory markers in the serum compared to those who did not receive anticoagulation [48].

There are no clear data about the impact of PVT on pretransplant mortality, with studies being contradictory [49, 50]. The same applies to posttransplant survival, with some studies showing no differences between patients with PVT and without and other studies showing higher morbidity and short-term mortality post liver transplant in those patients who had PVT at the time of liver transplantation [49, 51, 52]. In a recent study, comparing PVT recanalization or progression of the thrombus in cirrhosis, there were no differences observed between these patients in terms of 2-year survival, episodes of hepatic decompensation, hospital admissions, or need for liver transplantation [53].

In another study, in a subgroup analysis, any anticoagulant therapy in Child-Pugh B and C patients with PVT was associated with significant improvement in OLT-free survival [4]. In the same study, there was no overall difference in OLT-free survival in patients with any recanalization of PVT compared to no recanalization. These findings suggest that the potential benefit of anticoagulant therapy may go beyond macroscopic recanalization of PVT and may improve survival in patients with advanced cirrhosis [4]. Recently, in a meta-analysis by Guerrero et al. [29], anticoagulant therapy in nontumoral PVT in cirrhosis was found to significantly improve survival compared to no anticoagulation and this benefit was independent of the degree of PVT recanalization.

Conclusion

PVT is a common complication in patients with advanced cirrhosis. Cross-sectional imaging with CT scan or MRI is essential to correctly determine the age of thrombus whether acute or chronic and the extent and degree of luminal occlusion in PVT and to rule out malignancy.

Anticoagulation is the cornerstone of PVT treatment especially in those patients who are candidates for liver transplantation, who are symptomatic, and in those with concomitant thrombosis of the SMV. Management decisions should be individualized after carefully evaluating potential risks and benefits of anticoagulant therapy. The risk of rethrombosis is not negligible, and the anticoagulant therapy should not be stopped, especially in liver transplant candidates. TIPS should be considered in patients who have contraindications to anticoagulation, have concomitant PH complications, develop adverse events, or have progression of thrombosis on anticoagulant therapy.

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Statement of Ethics

Ethical review and approval were not required, as the study is based exclusively on the published literature.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Pan-Enteric Capsule Endoscopy: Current Applications and Future Perspectives

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Keywords

Capsule endoscopy · Pan-enteric endoscopy · Digestive bleeding · Inflammatory bowel disease · Crohn's disease

Abstract

Background: The role of capsule endoscopy in the evaluation of the small bowel is well established, and current guidelines position it as a first-line test in a variety of clinical scenarios. The advent of double-headed capsules further enabled the endoscopic assessment of colonic mucosa and the opportunity for a one-step noninvasive examination of the entire bowel (pan-enteric capsule endoscopy [PCE]). ***Summary:*** We reviewed the technical procedure and preparation of patients for PCE, as well as its current clinical applications and future perspectives. In non-stricturing and non-penetrating Crohn's disease affecting the small bowel and colon, PCE monitors disease activity by assessing mucosal healing, a major treatment outcome, with a higher diagnostic yield than cross-sectional imaging or conventional colonoscopy. Also in ulcerative colitis, double-headed capsules have been used to monitor disease activity noninvasively. Currently, validated scoring systems have been specifically devised for these double-headed capsules and permit a standardized assessment of the inflammatory burden. In suspected mid-lower digestive bleeding, some exploratory studies have demonstrated the feasibility and high diagnostic yield of PCE, which may work as a filter indicating which patients may benefit of further invasive procedures, namely, for planned hemostatic procedures. The possibility of using PCE is also discussed in the context of polyposis syndromes with simultaneous involvement of the small intestine and colon. ***Key Messages:*** PCE is a feasible, effective, and safe diagnostic procedure to evaluate the small bowel and colon. It has been increasingly explored in the setting of inflammatory bowel diseases and, more recently, in suspected mid-lower digestive bleeding. PCE is

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expected to reduce the demand for invasive procedures and expand the scope of noninvasive intestinal evaluation in the coming future.

Cápsula Endoscópica Pan-Entérica: Aplicações Atuais E Perspetivas Futuras

Palavras Chave
Cápsula endoscópica · Endoscopia pan-entérica · Hemorragia digestiva · Doença inflamatória intestinal · Doença de Crohn

Resumo
Introdução: O papel da endoscopia por cápsula na avaliação do intestino delgado encontra-se bem estabelecido, e as orientações atuais posicionam-na como um teste de primeira linha numa variedade de cenários clínicos. O advento das cápsulas de dupla câmara permitiu expandir a sua aplicação para a avaliação endoscópica da mucosa do cólon, oferecendo a oportunidade de um exame não invasivo de todo o intestino (endoscopia pan-entérica por cápsula, PCE). ***Sumário:*** Procedemos a uma revisão de vários aspectos do procedimento e preparação dos doentes para a PCE, bem como as aplicações clínicas atuais e as perspetivas futuras das cápsulas de dupla câmara. Na doença de Crohn não estenosante e não penetrante localizada ao intestino delgado e cólon, a PCE permite monitorizar a atividade da doença e avaliar a cicatrização da mucosa, um indicador importante da eficácia da terapêutica, com um rendimento de diagnóstico superior aos métodos convencionais, nomeadamente os exames imagiológicos ou a colonoscopia invasiva. Também na colite ulcerosa, as cápsulas de dupla câmara têm sido utilizadas para monitorizar a atividade da doença de forma não invasiva. Existem índices endoscópicos validados e especificamente concebidos para as cápsulas de dupla câmara, que permitem uma avaliação sistematizada e quantificação objetiva da atividade inflamatória. Na suspeita de hemorragia digestiva média ou baixa, alguns estudos exploratórios demonstraram a aplicabilidade e o elevado rendimento diagnóstico da PCE, podendo funcionar como um filtro de modo a permitir indicar quais os doentes que mais irão beneficiar de um procedimento invasivo subsequente, nomeadamente para a realização de procedimentos hemostáticos dirigidos. A possibilidade de utilização da PCE é também discutida no contexto das síndromes de polipose com envolvimento simultâneo do intestino delgado e do cólon. ***Mensagens-chave:*** A PCE é um procedimento diagnóstico eficaz e seguro para avaliar diretamente a mucosa do intestino delgado e cólon. A sua aplicação tem vindo a expandir-se no contexto das Doenças Inflamatórias Intestinais e, mais recentemente, na suspeita de hemorragia digestiva média ou baixa. Existe a expectativa de que no futuro próximo possamos assistir a uma redução substancial da demanda por procedimentos endoscópicos invasivos, face à utilização crescente da PCE enquanto método de diagnóstico pan-intestinal não invasivo.

Introduction

Capsule endoscopy, first described in 2000, was one of the most important advances in the investigation of small bowel diseases. A swallowed pill camera acquires images, subsequently converted to video format on a computer, as peristalsis propagates it through the gastrointestinal (GI) tract, allowing a noninvasive endoscopic evaluation of the GI tract [1, 2]. Since its first use 20 years ago, several models were developed, with the purpose of evaluating other GI segments, beyond the small bowel [3].

In 2006, the first double-headed capsule for colonic observation was developed – the PillCam COLON® (Given Imaging, Medtronic) which has been primarily used for colorectal cancer screening in average risk populations or when colonoscopy is contraindicated or incomplete [4, 5]. With two cameras recording simultaneously, one in each side of the capsule, the first-generation capsules had a sleep mode to save battery while traveling through the GI tract. The capsule shut down 5 min after ingestion and re-started to transmit images again 2 h after ingestion, in order to preserve the battery life during the progression of the capsule along the small bowel [3]. In 2009, a second generation of this capsule was developed (PillCam COLON2®), allowing a wider angle of vision and an enhanced adaptative frame rate – a technology that permits changing the rate of image capture from 4 to 35 frames per second, according to the velocity of progression of the capsule [3, 5]. Some recent studies have focused on the potential role of double-headed capsules in patients with ulcerative colitis (UC) and colonic Crohn's disease (CD) [6].

Table 1. Technical details of double-headed capsules currently used to perform PCE

	PillCam COLON2® (Medtronic, Given Imaging Inc.)	PillCam Crohn's® (Medtronic, Given Imaging Inc.)	OMOM CC® (Jinshan)
Dimensions, mm	11.6 mm × 31.5 mm	11.6 mm × 31.5 mm	11.6 mm × 31.5 mm
Optical domes	2	2	2
Resolution (pixels)	256 × 256	256 × 256	360 × 360
Lens angle (degrees)	172° per side	168° per side	172° per side
Frame rate (frames per second, fps)	4–35 fps	4–35 fps	4–35 fps
Sleep mode	Yes (can be deactivated)	No	No
Battery life	≥10 h	≥10 h	15 h

The idea of observing the entire small bowel and colon mucosa, in a single noninvasive procedure, was tested in several clinical scenarios, from GI hemorrhage to inflammatory bowel disease (IBD), due to the development of those double-headed capsules with long-lasting batteries [3, 7]. A few studies have reported the use of the PillCam COLON® for a complete evaluation of the GI tract by turning off the sleep mode, this marking the beginning of pan-enteric evaluation [3]. Boal Carvalho et al. [4] demonstrated that PillCam COLON2® allows for a new concept of noninvasive, safe, and well-tolerated examination of the entire GI tract.

In 2017, a new double-headed capsule named PillCam Crohn's® (Given Imaging, Medtronic) was released, combining two wide-angle cameras that permit a 344°-wide view between the two extremities of the device, with a long-lasting battery (over 12 h) [3, 6]. The pill is similar to the second generation of the PillCam COLON® in its hardware components but is designed to allow complete coverage of the gut from the mouth to the anus without any interruption in recording, allowing a panoramic vision of the GI tract in a single procedure. This new capsule comes with a dedicated software, in which the small bowel is divided into three segments according to their approximate length and the colon is divided into two parts (right and left) [8]. Not having a sleep mode avoids the need for early activation or manual turnoff, which eliminates the risk of accidental loss of small bowel frames [3]. Recently, another double-headed capsule was released for use in clinical practice (OMOM CC®, Jinshan), fulfilling the technical characteristics required to perform a pan-enteric capsule endoscopy (PCE) – Table 1.

PCE reduces the need for invasive procedures with the associated increased risk of complications and extra costs, allowing observation of all the bowel in a single procedure, in a more attractive and comfortable way for the patient [3, 7, 9]. Capsule endoscopy avoids insufflation or sedation, although it still requires bowel preparation, and the risks associated with the procedure are reduced (capsule retention and potential bowel obstruction), although still more frequent in patients with established Crohn disease [4].

Procedure

The PillCam® Crohn's system is composed of four subsystems: the PillCam® Crohn's capsule; the PillCam® recorder; the PillCam® software, and the Given® Workstation [10]. Bowel preparation includes a clear liquid diet on the day prior to capsule swallowing and administration of a polyethylene glycol electrolyte solution divided into two doses: in the evening before and in the morning of the examination day [11]. Following capsule ingestion and depending on its progression through the digestive tract, the recorder receives and interprets real-time input from the capsule and provides audiovisual guidance to patients throughout the procedure; an additional laxative boost, such as the sodium phosphate, is required in order to enhance capsule propulsion and maintain adequate cleansing of the colon [10, 11]. Table 2 summarizes the current standard bowel preparation protocol for PCE.

The PillCam® data recorder emits sequential alerts along the examination, which trigger patient procedures and assist medical decisions: alert 0 informs the patient should take a prokinetic drug, such as metoclopramide 10 mg or domperidone 10 mg tablet by mouth; alert 1 suggests the intake of a laxative boost; alert 2 suggests the intake of a second laxative boost, after 3 h; alert 3 is given when there is a need to take a 10 mg bisacodyl suppository, after 2 h; alert 4 allows to eat a standard light meal, 2 h later; alert 5 marks the ending of the procedure and can occur any time after receiving alert 1.

All laxative boosts should be followed by the intake of additional water during the following hour. Clear liquid ingestion is permitted throughout the examination and preparation [11].

Table 2. Bowel preparation protocol for PCE

D-2
Low-fiber diet
D-1
Clear liquid diet
19.00 h–21.00 h – 2 L PEG
Examination day
06.30 h–07.30 h – 1 L PEG
08.15 h – 10 mg metoclopramide/domperidone
08.30 h – addition of 100–200 mg simethicone in water for capsule ingestion
09.30 h – check real-time viewer. Additional 10 mg metoclopramide/ domperidone if capsule remains in stomach
First alert (capsule detected in SB) – sodium phosphate, 30 mL + 1 L water
Second alert (3 h after 1st booster) – sodium phosphate, 15 mL + 0.5 L water
Third alert (2 h after 2nd booster) – 10 mg bisacodyl rectal suppository
Light meal allowed

Clinical Applications

Current main indications and contraindications for PCE are summarized in Table 3.

Inflammatory Bowel Diseases

IBDs are a group of GI disorders characterized by chronic inflammation of the GI tract. The two main types of IBD are CD and UC. Colonoscopy and small bowel capsule endoscopy have a definite role in the management of patients with IBD [12]. The advent of PCE, allowing concomitant enteric and colonic evaluation, has created the expectation that this modality may allow a comfortable and accurate evaluation of the GI involvement in IBD in a single examination [3, 13]. Moreover, for IBD evaluation, patients are often submitted to separate colonic and small bowel evaluations, the latter frequently by radiologic exams. Hence, pan-enteric systems may also allow the avoidance of repeated exposure to radiation and overcome the limited sensitivity of radiology in recognizing inflammatory activity in proximal segments of the small bowel and colon segments [14]. Figures 1–3 document some examples of small bowel and/or colonic ulcerated lesions detected by PCE.

Crohn's Disease

Given CD's discontinuous nature and disease location, a pan-enteric approach is a valuable option for simultaneous evaluation of SB and colonic lesions, making PCE a convenient method to evaluate disease severity, extent, and distribution [15]. In fact, PCE can provide high diagnostic yields for lesion detection in the entire GI tract in these patients [16–18]. In a recent study by Yamada et al. [19], the diagnostic yield of PillCam COLON2® for detection of lesions in both small and large bowels was analyzed using double balloon enteroscopy as the gold standard. Overall, PCE sensitivities for ulcer scars, erosion, and ulcers were 83.3%, 93.8%, and 88.5%, respectively, and the specificities were 76.0%, 78.3%, and 81.6%, respectively. Other studies have evaluated the diagnostic performances of PCE using the PillCam COLON2® or PillCam Crohn's® capsule in patients with CD. A recent systematic review and meta-analysis by Tamilarasan et al. [2], which included seven studies evaluating the performance of PCE for the detection of CD lesions, found a comparable diagnostic yield of PCE compared to magnetic resonance enterography and colonoscopy (pooled OR of 1.25 [95% CI: 0.85–1.86%]). In fact, there was a trend to superiority of PCE over MRE and colonoscopy, with an increased diagnostic yield of 5% and 7% for PCE compared with MRE and colonoscopy, respectively.

The role of PCE in postoperative settings has also been addressed. A study by Hausmann detected 50% (6/12) of active disease 4–8 months after surgery, whereas ileocolonoscopy detected significant inflammation in 33% (5/15) [20]. Mucosal healing is increasingly recognized as an important treatment goal in patients with IBD. The concept of treat-to-target underlying IBD management frequently requires endoscopic evaluations to assess mucosal healing. For that reason, a single-time pan-enteric evaluation is appealing. In a multicentric study by Tai et al. [21] PCE was performed in 71 patients with established CD and led to a change in disease management in 33 (46.5%) of patients.

Despite the good performance of PCE in comparison with other endoscopic and imaging modalities, PCE detects only mucosal changes, so it might be insufficient to fully assess disease status (transmural and extramural involvement) [22]. Scoring systems allow for the standardization of reporting, increasing reproducibility and interobserver

Table 3. Indications and contraindications for PCE

Indications	Contraindications
CD Inflammatory-type (non-stricturing, non-penetrating), extensive (affecting the small bowel and colon) • Scheduled monitoring to evaluate mucosal healing in response to treatment (to justify and guide treatment change) • Evaluate disease distribution and severity: stratify patients to low versus high risk (prognosis); asymptomatic CD patients with abnormal analysis; exclude active CD/ investigation of symptoms unrelated to disease activity • Establish diagnosis in patients with IBD-U, suspected CD, or UC with atypical type, location, or distribution of lesions Gastrointestinal bleeding Suspected mid-lower GI bleeding (overt or occult)	1. Known or suspected intestinal strictures and/or fistulae (if patency not proven based on cross-sectional imaging and/or patency capsule assessment) 2. Magnetic resonance imaging examination scheduled for same day or following days (requires prior confirmation of capsule excretion) 3. Special conditions/relative contraindications: pregnancy, children under 8 years of age, swallowing disorders; gastric surgery; implanted cardiac electric devices: pacemakers, defibrillators, ventricular assist devices, telemetry; allergy or contraindications to any of the drugs or products used in the protocol; patients unable to walk for short periods and/or with neurological and/or psychiatric condition potentially favoring protocol deviations

IBD-U, inflammatory bowel disease-type unclassified; CD, Crohn's disease; UC, ulcerative colitis.

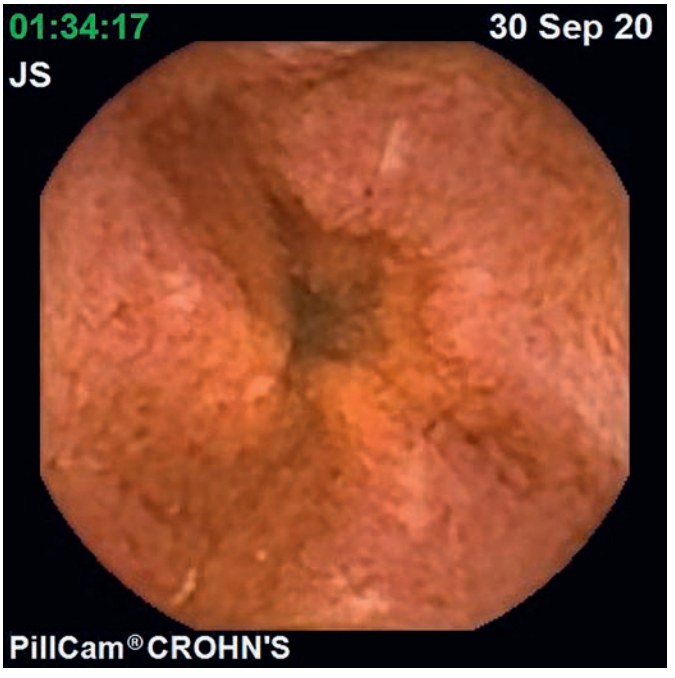

Fig. 1. Small bowel aphthous ulcers.

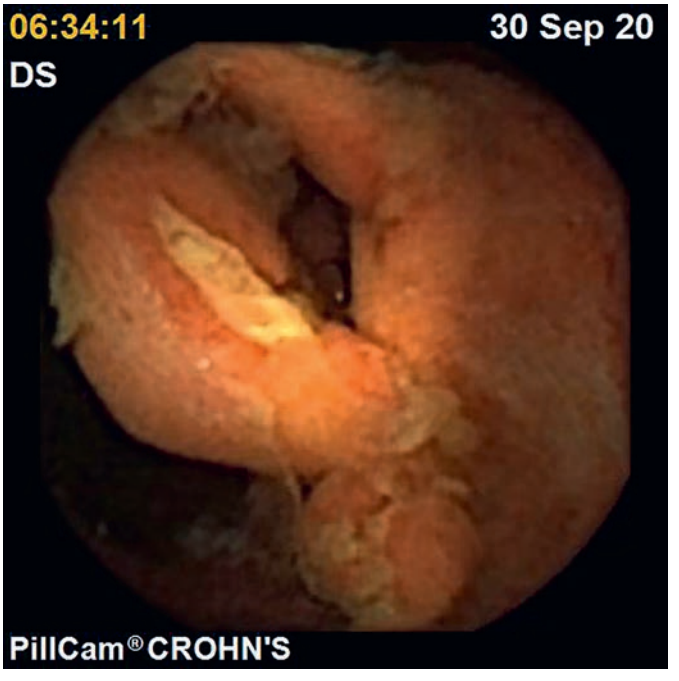

Fig. 2. Ileocecal valve ulcer.

agreement [23]. Whereas most scores have been established for colonoscopy and small bowel CE, their application in PCE to monitor IBD mucosal disease activity has also been proposed [13]. Niv et al. [24] extended the validated Capsule Endoscopy Crohn's Disease Activity Index (CECDAI) score to include the colon, introducing the novel CECDAIic score, allowing for an objective pan-enteric assessment of CD inflammatory activity [25]. In 2019, Arieira et al. [26] applied the CECDAIic score in a cohort of CD patients who underwent PCE and found an excellent interobserver agreement (Kendall's coefficient 0.94) and strong correlation with inflammatory parameters, especially calprotectin (r_s = 0.82; p = 0.012).

A novel PillCam Crohn's® capsule score (Eliakim score) for quantification of mucosal inflammation in CD was also developed. In this score, the whole bowel is

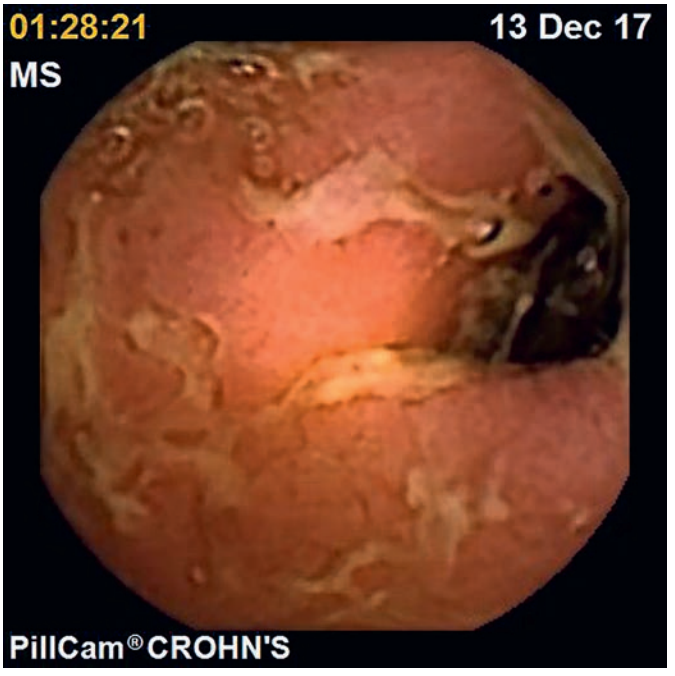

Fig. 3. Colon ulcers.

divided by length into five segments: the small intestine is divided into three tertiles, and the colon is divided into two (the right colon and the left colon). The score integrates the most common lesion, the most severe lesion, the extent of disease, and the presence of strictures [11]. In this initial study, the correlation between the two readers was excellent for Lewis score and PillCam Crohn's® capsule score (0.9, $p < 0.0001$ for both). The correlation between PillCam Crohn's® score and fecal calprotectin was stronger than for Lewis score ($r = 0.32$ and 0.54, respectively, $p = 0.001$ for both) [27].

Regarding safety, a recent systematic review and meta-analysis reported a 2% rate of capsule retention for all indications, with a twofold increase in the setting of CD (relative risk = 4%) [28], while another meta-analysis described a retention rate of 4.63% (32 studies, 95% CI: [3.42; 6.25]) in patients with established CD versus 2.35% (16 studies, 95% CI: [1.31; 4.19]) in patients with suspected CD [29]. Although the risk of capsule retention is increased overall in patients with CD [29], it may be significantly decreased with the rationale use of dedicated small bowel imaging such as CT or MR enterography and/or patency capsule, particularly in the case of obstructive symptoms, known stricture or prior SB surgical anastomosis [30–32], where a patency capsule is still required even in cases of unremarkable cross-sectional imaging [31].

PCE seems to be a safe and feasible tool to examine the whole GI tract in patients with CD with a high diagnostic yield for CD lesions detection [33]. However, despite these encouraging results, the precise role and indication for PCE in CD remain unclear due to lack of large scale and randomized controlled trials.

Ulcerative Colitis

In recent years, several studies have shown a very good overall agreement between PCE and colonoscopy for assessing disease activity [34–36]. In 2013, a study by Hosoe et al. [37] found that endoscopic scores determined by the PillCam COLON2® showed a strong correlation with scores obtained by conventional colonoscopy (average ρ = 0.797) in UC patients. In 2018, Hosoe et al. [33] developed an endoscopic severity score for the PillCam COLON2®. The final scoring system was fixed as "vascular pattern sum (proximal + distal) + bleeding sum + erosions and ulcers sum (minimum-maximum, 0–14)" and was named Capsule Scoring of Ulcerative Colitis (CSUC) [33]. Overall, the CSUC was an easy-to-use score consisting of three simple parameters (vascular pattern + bleeding + erosions). The correlation coefficient of CSUC with biomarkers and clinical score was similar to that of the Ulcerative Colitis Endoscopic Index of Severity (UCEIS) [38].

More recently, a systematic review and meta-analysis, including data from seven studies, showed that PCE had a diagnostic sensitivity of 94% and a specificity of 70% for the detection of UC [2]. Interestingly, a 2014 study using the PillCam COLON® or PillCam COLON2® in UC patients found that a small percentage of patients (7.1%) changed the diagnosis of UC to CD due to inflammation observed in the small bowel [39]. In fact, IBD remains unclassified in up to 10–15% of cases after conventional colonoscopy and histology [12], and PCE may have an important role for clarifying the diagnosis in patients with unclassified IBD. Histopathology is crucial not only for the diagnosis but also for disease monitoring. Histological remission is considered a desirable target along with symptomatic and endoscopic remission [22]. Moreover, initial diagnosis and surveillance for dysplastic changes or colitis-associated cancers are also needed [40]. The use of PCE for diagnosis and surveillance lacks the ability to provide histological information.

Cost-Effectiveness Considerations

There is already a great volume of publications on the topic of cost-effectiveness in the use of PCE for colorectal cancer screening. However, there is still little evidence of its use in IBD. A British National Health Service study

proposed to evaluate the cost impact of PCE in IBD patients (vs. colonoscopy ± MRE). The authors found that, although initial costs were higher using PCE due to the earlier initiation of biologics, in the longer term, there was a financial benefit due to reduction in surgical interventions [41]. A study from USA assessed the cost and patient impact of using PCE for scheduled monitoring of CD. The results showed that the patient groups of PCE showed increased quality of life and increased life expectancy, making it a cost-effective option [42]. There are no data available on the cost-effectiveness in patients with UC.

PCE in Gastrointestinal Bleeding

Despite being far more well established in the setting of IBD investigation, PCE is currently gaining further interest as a potentially useful procedure in many other clinical scenarios [43]. One of the most prominent and recently studied indications is GI bleeding, either overt (presenting as melena and/or hematochezia) or in the *occult* form as chronic iron deficiency anemia, due to its large prevalence in everyday clinical practice.

Esophagogastroduodenoscopy represents the first-line examination in patients presenting with melena [44]. Nevertheless, the examination can be inconclusive in up to 20–25% of the cases [45]. Therefore, colonoscopy is subsequently used to investigate patients presenting with melena after a nondiagnostic esophagogastroduodenoscopy. However, its diagnostic yield is not as high as expected, with the rate of therapeutic colonoscopies in this setting being even lower [45].

Small bowel capsule endoscopy has systematically been recommended as the first-line investigation procedure in patients with obscure GI bleeding – bleeding from the GI tract with negative findings in both esophagogastroduodenoscopy and ileocolonoscopy – which accounts for approximately 5% of all GI bleeding events [46]. Ever since, capsule endoscopy application in the event of obscure GI bleeding or iron deficiency anemia has almost exclusively been reserved to isolated small bowel examination.

However, after PCE establishment, there has been a shift in this classical scenario, due to hypothetical advantages associated with this innovative diagnostic procedure. On one hand, capsule endoscopy now allows the examination of all GI segments on a single procedure [47]. Furthermore, an adequately timed pan-enteric evaluation may eventually avoid unnecessary inconclusive examinations, with subsequent organizational and economic benefits, as described by Rondonotti et al. [48]. Finally, capsule endoscopy is a technique easily accepted by patients when compared to other conventional

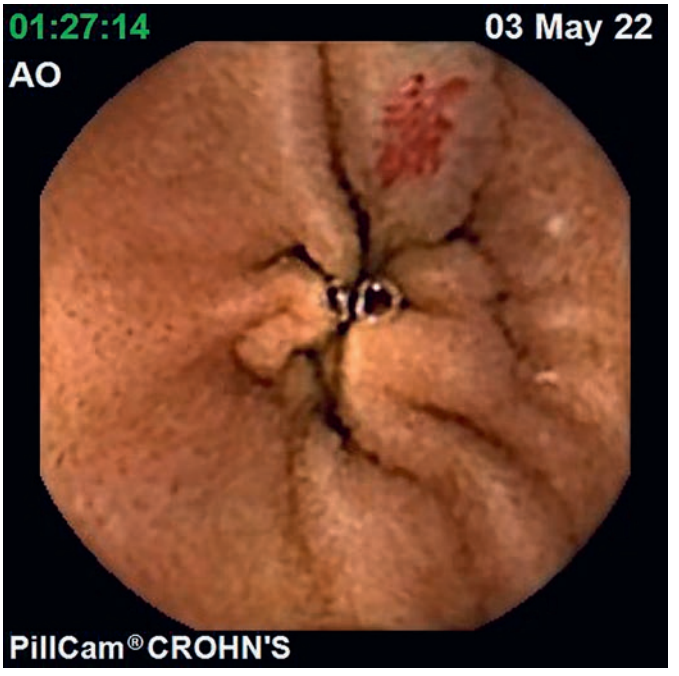

Fig. 4. Small bowel angioectasia.

endoscopy procedures, especially in terms of safety and comfort [49]. Figures 4, 5 represent cases of small bowel and colonic angioectasias, respectively, detected by PCE. For these reasons, there is now an ever-growing evidence on the use of a pan-enteric endoscopic approach in patients with GI bleeding, especially those in whom an upper digestive tract lesion has already been excluded, as this strategy could lead to a quicker identification of the bleeding site, drive further management, and potentially avoid other unnecessary examinations [50]. Moreover, it is already known that capsule endoscopy is able to detect proximal lesions missed by upper digestive endoscopy in a significant percentage of the individuals [51].

In 2018, Yung et al. [52] reported that patients with negative upper GI endoscopy and subsequent small bowel capsule endoscopy had shorter mean times from admission to capsule and hospital stays compared to those patients who underwent capsule endoscopy after negative upper and lower GI endoscopy. Therefore, the authors finally concluded that earlier access to capsule endoscopy in patients with melena or iron deficiency anemia, no signs of lower GI pathology, and negative upper GI endoscopy resulted in shortened hospital stays, good diagnostic yield from both the small bowel and upper GI tract, and two-thirds less unnecessary colon investigations.

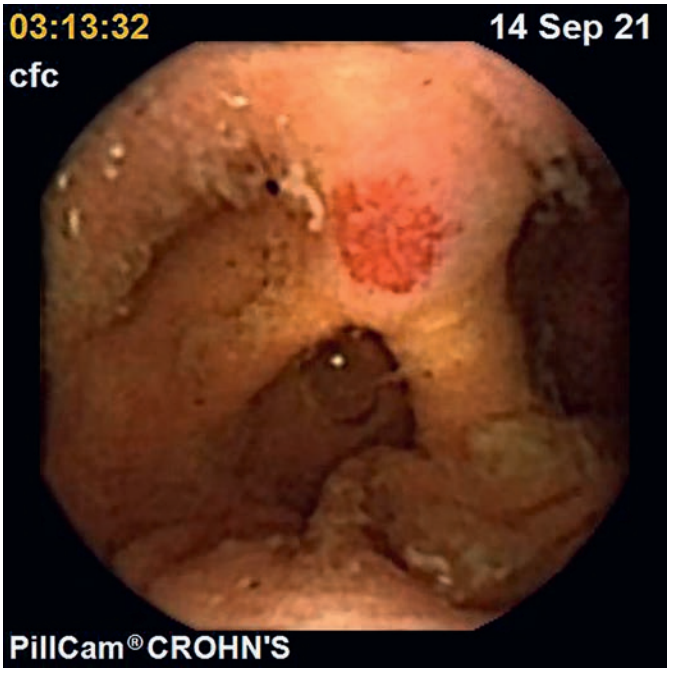

Fig. 5. Colon angioectasia.

In 2021, Mussetto et al. [50] conducted a study aiming to assess the feasibility and performance of PCE in patients presenting with melena and negative digestive upper endoscopy. This investigation included a total of 128 consecutive patients presenting with melena, clinically significant bleeding and negative esophagogastroduodenoscopy, who then underwent PCE by swallowing the PillCam COLON2® capsule. In this proof-of-concept study, PCE was feasible and safe, identifying the bleeding site in 83% of patients. This led to small bowel therapeutic interventions in 50% of patients, thus avoiding unnecessary standard colonoscopy in a significant percentage of the included individuals.

A similar retrospective investigation was made by Carretero et al. [7] by analyzing 100 consecutive PCE performed in a GI bleeding setting. Positive findings were observed in 61% of the patients, with 46% having a previous negative upper endoscopy. The capsule detected small bowel lesions in 68% and colonic findings in 81% of the individuals. According to the authors, no further endoscopic studies would be needed in nearly 65% of the patients with negative gastroscopy. Thus, PCE with a capsule device could be useful and safe in bleeding high-risk patients by selecting those who would eventually need further therapeutic endoscopy.

Due to these recent developments, there is a new and interesting window for the use of PCE in suspected GI bleeding and investigation. Further prospective and multicenter studies are needed in order to clarify the practical role of capsule endoscopy in this setting, especially in patients presenting a high risk for invasive endoscopic procedures, and the specific indications and timing to use it.

Other Clinical Applications: Limitations and Future Perspectives of PCE

Although the clinical applicability of PCE in the context of IBD, particularly CD [16, 17, 21, 53], and digestive hemorrhage [50, 52], has been demonstrated in recent studies, its window of use in other clinical scenarios remains narrow. Capsule endoscopy has previously been shown to be useful in the diagnosis of various esophageal diseases, such as varices [54] and Barrett's esophagus [55]; however, it has not been proven cost-effective when compared with traditional endoscopy. Its role in the diagnosis of gastric lesions, on the other hand, is limited by the extent of the mucosal surface and inability to control capsule movements.

The possibility of using a noninvasive pan-endoscopic method may seem appealing in the context of polyposis syndromes with simultaneous involvement of the small intestine and colon, such as familial adenomatous polyposis, Peutz-Jeghers syndrome, or juvenile polyposis syndrome. The role of conventional small bowel capsule endoscopy in the surveillance of polypoid syndromes is well established. Schulman et al. [56] prospectively evaluated 29 patients with familial adenomatous polyposis. From patients with duodenal adenomas, 24% had additional polyps in the jejunum or ileum. The authors concluded that this endoscopic capsule should be considered in the evaluation of these patients. In another study of patients with Peutz-Jeghers syndrome, Caspari et al. [57] demonstrated a superior diagnostic accuracy of CE compared to magnetic resonance imaging in detecting polyps <5 mm. Regarding colon evaluation, double-headed capsules have demonstrated validity in recent years in diagnosing polyps and screening for colon-rectal cancer – Figure 6. A prospective study of 884 asymptomatic patients evaluated initially by the PillCam COLON2® and subsequently conventional colonoscopy demonstrated a sensitivity of 81% and specificity of 93% for detection of polyps ≥ than 6 mm and a sensitivity of 80% and specificity of 97% for polyps ≥ 10 mm [58]. In 2017, the American Multi-Society Task Force positioned capsule colonoscopy as a 3rd-line test in colorectal cancer screening. ESGE also recommends its use as a screening method for colon-rectal cancer only in moderate risk groups, when conventional colonoscopy is incomplete or contraindicated [59]. The limitations of this method are mainly related to the suboptimal adequate preparation

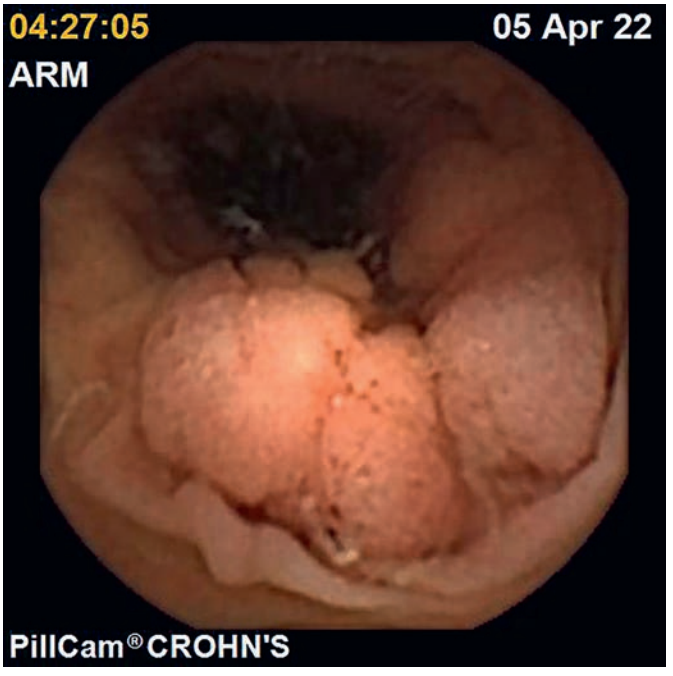

Fig. 6. Colon polyps.

rates, the rate of incomplete examinations, the complexity of bowel preparation regimens, and lack of therapeutic capabilities.

These limitations are also transposable to the limitations of PCE. The diagnostic accuracy of the capsule as a pan-endoscopy tool is highly dependent on several parameters such as preparation quality, transit time, complete exam rate. Its applicability also depends on other factors such as patient acceptance and availability of human resources for reading and interpretation [49].

In a recent paper by Vuik et al. [49] evaluating PCE, the rate of patients with adequate colonic preparation (76.6%) was clearly below the standard recommended in conventional colonoscopy (>90%) [60]. The issue of adequate preparation is furthermore corroborated by a recent systematic review [3], where only 54% of studies had >90% of exams with adequate preparation. Vuik et al. [49] also reported complete ("mouth-to-anus") examination rates of only 51%, similar to other publications [7, 11, 19] and clearly lower than recommended [60]. Another limitation relates to patients' acceptability. Although capsule endoscopy is a painless and noninvasive method compared to conventional colonoscopy, the complexities of bowel preparation regimens negatively influence its acceptability [49, 61].

In the same work by Vuik et al. [49], the limitations of gastric/esophageal evaluation became apparent. The Z-line was visualized in less than 50% of the patients, indicating an overly rapid esophageal transit; and although visualization of the gastric mucosa was considered good/excellent in most patients, capsule endoscopy does not allow for adequate observation of the gastric fundus.

The introduction of artificial intelligence systems for assisted reading of these exams is expected to address other current limitations of pan-enteric techniques, decreasing reading times and improving lesions' detection [62]. In a proof-of-concept study conducted by Ferreira et al. [63] in the setting of CD, a deep learning model for automatic detection of small bowel and colonic ulcers and erosions using PillCam Crohn's® capsule images was developed, with an overall sensitivity and specificity for lesions' detection of 90.0% and 96.0%, respectively.

Conclusion

New perspectives in the field of capsule endoscopy are being devised. PCE seems feasible, effective, and safe, and it has been increasingly explored in IBD and, more recently, GI bleeding, with promising results. Used individually, traditional endoscopic means for evaluation of the esophagus, stomach, and colon remain superior to PCE. However, PCE offers the unique opportunity to evaluate several digestive segments at the same time in a single noninvasive examination. Current well-established clinical indications include the evaluation of inflammatory-type (non-stricturing, non-penetrating) and extensive (affecting the small bowel and colon) CD, mainly for scheduled monitoring to evaluate mucosal healing in response to treatment. The use of PCE may also be useful to establish the diagnosis in atypical cases of UC, suspected CD, or inflammatory bowel disease-type unclassified. More recently, in the context of GI bleeding, PCE has been proven useful in patients with suspected overt or occult mid-lower GI bleeding.

With the introduction of further technological advances such as steerable capsules, intelligent image analysis systems [64], and refinement of protocols, PCE is expected to become an increasingly prevalent tool in future clinical practice, by allowing a noninvasive, safe, and comfortable diagnostic approach for a variety of diseases affecting the small bowel and the colon. PCE appears therefore in the verge of a new paradigm toward expanding the field for noninvasive endoscopy, enabling the direct endoscopic coverage of the entire surface of the small and large bowel in a single examination, and limiting the demand for invasive procedures such as conventional colonoscopy and/or device-assisted enteroscopy, which are expected to be tendentially reserved

only for those patients who require biopsies and/or therapeutic procedures, based on the findings first detected by PCE.

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Statement of Ethics

Due to the nature of the article (review 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

Bruno Rosa, Patrícia Andrade, Sandra Lopes, Ana Rita Gonçalves, and Cristina Chagas conceived the study design and the structured content. Andrea Silva, Sandra Lopes, Pedro Marílio Cardoso, Patrícia Andrade, Vítor Macedo Silva, Bruno Rosa, Juliana Serrazina, and Ana Rita Gonçalves performed the literature review, selection of studies, and writing. José Cotter, Guilherme Macedo, Pedro Narra Figueiredo, and Cristina Chagas critically reviewed the article. All the authors approved the final version to be published.

Data Availability Statement

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

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Quality Standards in Upper Gastrointestinal Endoscopy: Can Deep Sedation Influence It?

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Keywords
Upper gastrointestinal endoscopy · Quality standards · Sedation

Abstract

Introduction: According to the guideline published by ESGE/UEG, a high-quality esophagogastroduodenoscopy (EGD) implies the application of some criteria that enable better healthcare outcomes. Although intra-procedural performance measures are dependent on patient factors, there is no reference to sedation practices in the guideline mentioned above. ***Objective:*** This study aimed to evaluate whether deep sedation influences EGD performance measures established by ESGE/UEG. ***Methods:*** This was a cross-sectional study, with a prospective enrollment, that considered for inclusion consecutive patients referred for EGD. Two questionnaires were used to assess performance measures and patient satisfaction after EGD. ***Results:*** Sedation had a statistically significant impact on most quality indicators, including complete examination (77.2% without sedation vs. 97.8% with sedation), inspection time (6.17 ± 3.45 vs. 8.39 ± 2.67 min), photodocumentation (78% vs. 97.8%), biopsies (39.3% vs. 60.7%), and patient satisfaction (5.42 ± 2.93 vs. 9.1 ± 1.19). The main reason for an incomplete procedure was patient intolerance (82.6%). ***Discussion:*** Deep sedation of patients submitted to EGD proved to be a determinant in the applicability of the ESGE/UEG quality indicators. Patient intolerance was eliminated in the group with sedation, enhancing procedure completeness, adequate pathology identification, management, and consequently, the effectiveness of the exam. ***Conclusion:*** Sedation administration should be considered in patients undergoing EGD since it ensures a high-quality procedure.

Critérios de qualidade em endoscopia digestiva alta -poderá a sedação profunda influenciar a sua aplicação?

Palavras Chave
Endoscopia Digestiva Alta · Critérios de qualidade · Sedação

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Resumo

Introdução: Uma endoscopia digestiva alta (EDA) de qualidade proporciona melhores resultados em termos de saúde e implica a aplicação dos critérios descritos pelas recomendações da ESGE/UEG. Embora os critérios per-procedimento sejam dependentes da colaboração e tolerância do doente, não está explicito o papel da anestesia. ***Objetivos:*** Este estudo pretende avaliar se o recurso a anestesia influencia o cumprimento dos critérios de qualidade para a EDA publicados pela ESGE/UEG. ***Materiais e métodos:*** Estudo transversal, com recrutamento prospetivo, que incluiu pacientes consecutivamente encaminhados para realização de EDA. Foram utilizados 2 questionários para avaliar medidas de desempenho e satisfação dos pacientes após realização de EDA. ***Resultados:*** A anestesia teve um impacto estatisticamente significativo na maioria dos indicadores de qualidade: exame completo (77,2% sem anestesia vs. 97,8% com anestesia); tempo de inspeção (6,17 ± 3,45 vs. 8,39 ± 2,67 minutos); fotodocumentação (78% vs. 97,8%); biópsias (39,3% vs. 60,7%); satisfação do paciente (5,42 ± 2,93 vs. 9,1 ± 1,19). O principal motivo para um procedimento incompleto foi a intolerância do paciente (82,6%). ***Discussão:*** A sedação profunda dos doentes submetidos a EDA provou ser determinante na aplicabilidade dos critérios de qualidade da ESGE/UEG. Eliminando por completo a intolerância por parte do doente, proporcionou a realização de exames completos, com correta identificação e gestão de patologias, potenciando assim a efetividade do exame. ***Conclusão:*** A administração de anestesia deve ser ponderada, sempre que possível, nos doentes submetidos a EDA, visto que permite garantir a alta qualidade do procedimento.

Introduction

Esophagogastroduodenoscopy (EGD) is considered the gold standard in the investigation of gastrointestinal symptoms. A high-quality EGD is extremely important in the diagnosis and even treatment of early cancers [1].

In contrast to colonoscopy, for which there are well-defined quality benchmarks, EGD lacked criteria that would effectively standardize the quality of this exam by reducing the variability, which is still considerable, between different centers and performers. At the end of 2015, the *European Society of Gastrointestinal Endoscopy* (ESGE) and the *United European Gastroenterology* (UEG) gathered a *task force* aiming to develop standards on quality in EGD, and by the end of 2016, new guidelines for performing high-quality endoscopy were published in the journal *Endoscopy* and in the *United European Gastroenterology Journal* [2].

The new ESGE/UEG guideline does not mention patient sedation; therefore, it is assumed that this would not be essential in the achievement and compliance of all the stipulated quality parameters. In the current literature, recommendations regarding EGD sedation practices are highly variable, and there is a lack of evidence to support the potential implications with regard to safety and efficiency of the procedure [3]. The purpose of this prospective study was to determine whether the use of deep sedation, administered by an anesthesiologist, influences the fulfillment of the quality criteria proposed by ESGE/UEG for EGD.

Materials and Methods

This was a cross-sectional study, with a prospective enrollment, that considered for inclusion consecutive patients referred for diagnostic or surveillance EGD in the Gastroenterology Department of a tertiary referral hospital, Centro Hospitalar e Universitário de Coimbra, Portugal. Inclusion criteria included patients who were 18 years of age or older, had completed the required fasting time (6 h for solids and 2 h for clear liquids), and were indicated to undergo EGD only with diagnostic or surveillance objectives.

Patients non-compliant with fasting or presenting food residues in the stomach were excluded. Since this was a study that focused on the diagnostic use of EGD, all patients whose indication for the examination included the performance of endoscopic therapy or exams performed in an emergency context were excluded. The patient's refusal to participate in the study was also an immediate exclusion criterion. Another exclusion criterion was the history of previous esophageal, gastric, or duodenal surgery.

When inclusion criteria were fulfilled and there was no exclusion criterion, the patient was allocated to one of the following groups, according to the assistant physician's request that considered the patient's preferences/demands: EGD without sedation or EGD with sedation. The investigators had no interference in this decision process.

A selection bias is related to the fact that not all EGDs at the center were included. Only EGDs performed by the 3 endoscopists, who were aware of quality evaluation and were equally distributed in the sedation and non-sedation suites, were included.

Regarding sedation, its depth varies in a continuous spectrum, and it can be graduated into 4 levels: minimal, moderate, deep, and general anesthesia. To assess the true impact of sedation in EGD, deep sedation with propofol administered by an anesthesiologist was the approach used in the sedation group. All procedures were performed by three gastroenterologists with extensive experience in endoscopy, and the patients were monitored according to standard parameters (pulse oximeter, heart rate, blood pressure, capnography and electrocardiogram).

Table 1. Sample characterization

	Without sedation *n* (%)	With sedation *n* (%)	*p* value
Variables	*n* = 92	*n* = 92	
Gender			
Male	38 (41.3)	31 (33.7)	0.381
Female	54 (58.7)	61 (66.3)	
Age (mean±SD)	59.9±17.8	62.4±15.9	0.231
ASA classification			
I	NA	13 (14.1)	
II	NA	62 (67.4)	
III	NA	17 (18.5)	
Indication for EGD			
Dyspepsia	28 (30.4)	38 (41.3)	0.003
IM surveillance	10 (10.9)	8 (8.7)	
Gastric cancer screening	2 (2.2)	10 (10.9)	
Pre-bariatric surgery	13 (14.1)	1 (1.1)	
Dysphagia	6 (6.6)	5 (5.4)	
Anemia	1 (1.1)	8 (8.7)	
Post-neoplastic recession surveillance	7 (7.6)	0	
EV screening	5 (5.4)	2 (2.2)	
Gastric polyps	3 (3.3)	2 (2.2)	
GERD	8 (8.7)	8 (8.7)	
PUD	3 (3.3)	3 (3.3)	
Achalasia	2 (2.2)	0	
Vomiting	1 (1.1)	4 (4.3)	
BE surveillance	0	3 (3.2)	
Post-UGIB	1 (1.1)	0	
Weight loss	1 (1.1)	0	
Esophageal stricture	1 (1.1)	0	

SD, standard deviation; ASA, American Society of Anesthesiologists; BE, Barrett's esophagus; EGD, esophagogastroduodenoscopy; EV, esophageal varices; GERD, gastroesophageal reflux disease; IM, intestinal metaplasia; PUD, peptic ulcer disease; UGIB, upper gastrointestinal bleeding

In each case, two questionnaires were applied. One, for the researcher, focused on evaluating the compliance of the quality parameters proposed by ESGE/UEG. The other questionnaire was designed to allow the assessment of the degree of the patient's satisfaction regarding the exam, on a numerical scale of 0–10 (0 – not at all satisfied; 10 – extremely satisfied).

Sample size calculation was performed. Assuming that it will be possible to meet the quality criteria in 70% of endoscopies performed without sedation and in 90% of cases performed with sedation, the sample size, calculated for a 95% confidence interval and 10% margin of error, was 92 patients in each group. So, inclusion for each group stopped once this number was achieved.

Data was recorded between July 2019 and March 2021. All statistical analyses were performed using the Statistical Package for Social Sciences software (SPSS, Version 23.0).

This study was approved by the Ethics Committee of the Faculty of Medicine, University of Coimbra, Coimbra, Portugal, on June 24, 2019. The privacy of the research patients participating was guaranteed, and the protocols followed the tenets of the Declaration of Helsinki.

Results

A total of 184 patients were included in the study, 92 of whom underwent EGD without sedation and the remaining 92 with deep sedation. Table 1 shows the sample characterization. Females predominated (62.5%) in both groups, representing 66.3% (n = 61) and 58.7% (n = 54) of the cases with and without sedation, respectively. The mean age of the sample was 61.3 ± 16.9 years (62.7 ± 15.9 in the anesthetic group vs. 59.9 ± 17.8 in the non-sedation group; p = 0.231). The mean age of intolerant patients was lower, compared with patients who underwent complete examination, but this difference was not statistically significant (52.2 vs. 61.2 years, p = 0.089) (Table 2).

In the group of patients who underwent EGD under sedation, the majority had an ASA II classification (67.4%), followed by ASA III (18.5%) and ASA I (14.1%),

Table 2. Characterization of no sedation group

	Tolerant patients *n* (%)	Intolerant patients *n* (%)	*p* value
Variables	*n* = 71	*n* = 19	
Gender			
Male	31 (56.3)	7 (36.8)	0.509
Female	40 (43.7)	12 (63.2)	
Age (mean ± SD)	61.2±12.2	52.2±21.8	0.089
Indication for EGD			
Dyspepsia	22 (31)	6 (31.6)	0.294
IM surveillance	10 (14.1)	–	
Gastric cancer screening	2 (2.8)	–	
Pre-bariatric surgery	8 (11.3)	5 (26.3)	
Dysphagia	2 (2.8)	3 (15.8)	
Anemia	1 (1.4)	–	
Surveillance after endoscopic tumor resection	5 (7)	–	
EV screening	5 (7)	–	
Gastric polyps	3 (4.2)	–	
GERD	6 (8.5)	2 (10.5)	
PUD	3 (4.2)	–	
Achalasia	2 (2.8)	–	
Vomiting	–	2 (10.5)	
BE surveillance	–	–	
Post-UGIB	–	1 (5.2)	
Weight loss	1 (1.4)	–	
Esophageal stricture	1 (1.4)	–	

SD, standard deviation; BE, Barrett's esophagus; EGD, esophagogastroduodenoscopy; EV, esophageal varices; GERD, gastroesophageal reflux disease; IM, intestinal metaplasia; PUD, peptic ulcer disease; UGIB, upper gastrointestinal bleeding.

respectively. In this studied sample, the predominant indications for performing an EGD were dyspepsia (*n* = 66; 35.9%), intestinal metaplasia surveillance (*n* = 18; 9.8%), and gastroesophageal reflux disease (*n* = 16; 8.7%). Other relevant indications were pre-bariatric surgery study (*n* = 14; 7.6%), dysphagia (*n* = 11; 6%), anemia (*n* = 9; 4.9%), and surveillance after endoscopic resection of esophageal, gastric or duodenal lesions (*n* = 7; 3.8%). These data are shown in Table 1. According to the results obtained, the exam indication influenced the request, or not, for deep sedation ($p = 0.003$). This association is mainly due to exams whose indications were pre-bariatric surgery (13 exams without sedation and only 1 with sedation), surveillance after neoplastic resection (all procedures without sedation), anemia (only 1 exam was performed without sedation and the remaining 8 with sedation), and gastric cancer screening (only 1 was performed without sedation and the remaining 7 with sedation).

Analyzing the impact of sedation on compliance with quality criteria published in the ESGE/UEG guideline, it was found that there was a statistically significant association ($p < 0.001$) between the use of sedation and the ability to perform a complete EGD, represented by the following variables: complete examination (77.2% without sedation vs. 97.8% with sedation); photodocumentation of the main anatomical sites (78% vs. 97.8%) (Table 3). The main reason for not performing a complete exam was patient intolerance (82.6% of the non-complete exams), which occurred exclusively in non-anesthetized patients. The impact of tolerance in the no sedation group on high-quality EGD performance is shown in Table 4. In the sedation group, only 2 patients (2.2%) did not undergo a complete examination because of hemodynamic instability, which was reversed with supportive measures. Intolerance in non-sedated patients justified the short inspection time (6.17 ± 3.45 vs. 8.39 ± 2.67 min) and the low percentage of EGD lasting more than 7 min (28%), as shown in Tables 3 and 5, respectively.

Additionally, a comparison of tolerant and intolerant patients in the no sedation group was performed, and it is shown in Tables 2 and 4. Ninety was the total number of patients included in this analysis. Two patients were

Table 3. Impact of sedation on high-quality EGD performance

Variables	Without sedation	With sedation	*p* value
Exam duration in minutes (mean ± SD)	6.17±3.45	8.39±2.67	<0.001
Complete examination, %	77.2	97.8	<0.001
Photodocumentation, %	78	97.8	<0.001
Visualization of Vater's papilla, %	71.7	79.3	0.230
Complications, %			
Mild complications	2 (25)	6 (75)	0.153
Moderate to severe complications	0	0	–

SD, standard deviation.

Table 4. Impact of tolerance in no sedation group on high-quality EGD performance

Variables	Tolerant patients	Intolerant patients	*p* value
Exam duration in minutes (mean± SD)	6.59±3.50	4.08±2.05	0.006
Complete examination, %	100	0	<0.001
Photodocumentation, %	87.3	47.1	<0.001
Visualization of Vater's papilla, %	74.6	61.1	0.201

SD, standard deviation.

Table 5. Impact of sedation on the diagnosis of gastric and esophageal lesions and on surveillance of preneoplastic gastric lesions

Variables	Without sedation	With sedation	*p* value
Heterotopic gastric mucosa (*n* = 6), *n* (%)	1 (16.7)	5 (83.3)	0.111
BE surveillance (*n* = 3), *n* (%)			
1 min surveillance per cm	0	3 (100)	0.117
Seattle protocol performance	0	3 (100)	0.117
PUD diagnosis (*n* = 12), *n* (%)			
Performing ≥4 biopsies	8 (66.7)	4 (33.3)	0.225
Celiac disease diagnosis (*n* = 6), *n* (%)			
Performing ≥4 biopsies	3 (50)	3 (50)	0.989
Inspection time ≥7 min (*n* = 93), %	28	72	<0.001
Performing biopsy protocol according to MAPS guidelines (*n* = 135), %	39.3	60.7	<0.001

BE, Barrett's esophagus; PUD, peptic ulcer disease.

excluded since the reason for an incomplete examination was not related to tolerance but to the occurrence of complications. None of the demographic characteristics or indications to perform the exam influenced the tolerance in the no sedation group.

Regarding the surveillance of premalignant gastric lesions (Table 5), it was shown that the use of sedation favors a minimum inspection time of 7 min (72% vs. 28%; $p < 0.001$) and the performance of adequate biopsy protocol according to MAPS guidelines (60.7% vs. 39.3%; $p < 0.001$) [4]. Assessing the impact of sedation on performing, at least 4, biopsies, when indicated, in the context of celiac disease and/or gastric ulcer, we found that there is no statistically significant association. However, the small number of cases of gastric ulcer ($n = 12$) and celiac disease ($n = 6$) may weaken this result (Table 5).

In relation to gastric heterotopia in the proximal esophagus, it was shown that the use of sedation favors it, although without a statistically significant difference ($p = 0.111$). In the group without sedation, the diagnosis of

Table 6. Impact of sedation in patient's experience

Variables	Without sedation	With sedation	*p* value
Satisfaction level (mean ± SD)	5.42±2.93	9.10±1.19	<0.001
Correspondence with expectations (mean ± SD)	6.39±3.56	9.25±1.16	<0.001
Repeat the exam, %	89.1	97.8	0.017
Without sedation, %	48.8	1.1	<0.001
With sedation, %	51.2	98.9	<0.001

SD, standard deviation.

gastric heterotopia was made in 1.1% of the patients (n = 1), compared with 5.4% (n = 5) in the group with sedation (Table 5).

In the patient experience area, the use of sedation provided an average level of satisfaction considerably higher than in the group without sedation (9.1 ± 1.2 vs. 5.4 ± 2.9) and allowed a greater correspondence with expectations (9.3 ± 1.2 vs. 6.4 ± 3.6). The use of sedation also influenced the predisposition to repeat the exam in the future: 98.9% of the patients who underwent EGD with sedation would repeat the exam with sedation. On the other hand, less than half of patients who underwent EGD without sedation (48.8%) would accept to perform an EGD under the same conditions (Table 6).

The high satisfaction reported by patients who underwent EGD under sedation was congruent with the greater predisposition of these patients (98.9%) to repeat the exam, as shown in Table 6. Globally, reported complications were rare (n = 8; 4.4%) and classified as mild, according to the common terminology criteria for adverse events. There was no statistical association (p = 0.153) between the use of sedation and the occurrence of complications associated with EGD (Table 3).

Discussion

The quality of health service is established by its ability to provide the best clinical outcomes. Therefore, high-quality endoscopy must be able to recognize or exclude correct and relevant diagnoses [5]. In the upper gastrointestinal tract, it is acknowledged that the detection rate of premalignant lesions is often suboptimal, in most cases due to a failure in the execution of the technique [6, 7]. At the end of 2016, a new guideline for performing a high-quality endoscopy was published in ESGE/UEG journals. [2] The ESGE/UEG guideline describes major and minor quality criteria (performance measures), which are related to pre-, per-, and post-procedure aspects. The first and the last are relatively restricted and do not depend, to a great extent, on the performer or the patient, as they are standardized. On the other hand, the per-procedural criteria require not only improved care by the gastroenterologist but also a high level of patient cooperation. The prolonged time proposed for each endoscopy often generates intolerance in non-sedated patients, frequently leading to premature interruption of the exam. The tolerance level of patients varies widely, and it is recognized that some patients need to be sedated to obtain a high-quality EGD [8–10]. In current literature, recommendations regarding sedation practices in EGD are highly variable, and there is a lack of evidence supporting the potential implications for the safety and efficiency of the procedure [3]. The ASGE suggests the use of deep sedation when it is expected to favor comfort and safety for the patient, as well as the complete performance and efficiency of the procedure. However, this is a recommendation based on low-quality evidence, implying the need for additional studies [11].

In the present study, a positive link between the use of deep sedation and the applicability of per-procedural quality criteria in the domains described by the ESGE/UEG is indorsed. After a thorough analysis of the different parameters, we found that patients intolerant to EGD were younger than those that had a complete examination. Similar data were observed in a study that highlighted a greater tolerance in the older population (>75 years) to perform the exam without sedation [12]. These data could be taken into account when selecting potential candidates for EGD under sedation.

A longer inspection time reflects a more complete examination and is associated with greater diagnostic accuracy, therefore being a major criterion [2]. A high-quality EGD should last at least 7 min from intubation to extubation [2, 10, 13]. In this study, we concluded that the mean duration in the group without sedation was suboptimal

(6.17 min), mainly associated with early interruption due to patient intolerance, which was translated into a lower rate of exam completion. Less than a third of the patients undergoing EGD without sedation benefited from a minimum gastric inspection time of 7 min, which raises concern about the lower effectiveness of the examination and possible underdiagnosis of pre-neoplastic or neoplastic lesions [6, 14, 15]. This is particularly relevant since procedures lasting at least 7 min are capable of detecting three times more dysplastic lesions and gastric cancer [2].

Appropriate photographic documentation is also a major criterion in the ESGE/UEG guideline. The present study demonstrated that this key quality criterion benefits significantly from the use of sedation, which can be explained by the reduction in artifacts associated with patient movement.

Population with atrophic gastritis and intestinal metaplasia has a higher prevalence of gastric cancer [15]. These pre-neoplastic lesions are often distributed irregularly in the stomach; consequently, their correct diagnosis and staging require biopsies [16]. The EGD performed under sedation eased the performance of biopsies, promoting higher diagnostic effectiveness. Early detection of gastric cancer allows for less invasive and more effective treatment, being an important prognostic factor and reducing the economic impact associated with the treatment of more advanced stages [17].

Regarding the impact of sedation on Barrett's esophagus (BE) surveillance, there was a predominance (98.4%) of neutral responses: "NA" (not applied). Although the number of cases of BE surveillance is limited, the Seattle protocol was only applied to patients under sedation. This protocol's performance is a major quality criterion in the field of pathology management. It ensures maximum diagnostic sensitivity, making possible the early detection of dysplasia and esophageal adenocarcinoma, with a positive impact on mortality rate (the 5-year survival rate of invasive esophageal adenocarcinoma is less than 20%) [18]. Despite the proven value of the Seattle protocol, shown in the recommendations of many societies, there is still insufficient compliance to its application (up to 20% nonadherence) [19]. The present study indicates that the risks associated with the ineffectiveness of performing biopsies which allows a safe BE surveillance probably justifies the use of deep sedation in these patients. Even if the results are not statistically significant, due to the reduced number of cases, it is fair to infer that deep sedation ensures more adequate BE surveillance (Table 5).

Overall, in agreement with the literature, it was demonstrated that patients undergoing sedation had better experience in performing EGD [3, 11, 12, 20, 21]. In the domain of experience for the patient, the use of sedation provided an average level of satisfaction considerably higher than the group without sedation, allowing a greater correspondence with expectations and predisposition to repeat the exam. Thus, it is expected that in patients enrolled in a surveillance program which requires periodic EGD, the use of deep sedation can determine a higher compliance. This attitude allows for an early diagnosis of certain lesions, promoting a better outcome for patients and reducing health costs in the long term. It is described that deep sedation is more satisfactory for the patient and increases the predisposition to repeat the exam [11, 20, 21]. Given the difficulty of having an anesthesiologist present for most of the exams performed, it would be interesting to assess, in a future study, whether the fulfillment of EGD quality criteria is compromised when using minimal or moderate sedation in comparison to deep sedation.

At a financial level, performing an exam with sedation outweighs the costs associated with the same exam without sedation. The use of sedation entails costs related to human resources, hospital supplies, and drugs. Nevertheless, it is recommended that incomplete exams due to patient intolerance be repeated under sedation [10, 12]. Therefore, it can be expected that avoiding the use of sedation in EGD may imply the cumulative cost of two exams, greater inconvenience for the patient, and exposure to iatrogenic risks, consequently surpassing the initial costs associated with performing an EGD with sedation. A cost-effectiveness analysis should be performed to determine which would be the more effective approach: EGD with no sedation, gastroenterologist-administered sedation on demand and in specific groups, or deep sedation by an anesthesiologist in selected patients.

Monitoring complications is an important criterion to establish the safety of EGD [2]. In the present study, the complication rate was low (4.4%) and showed no significant relationship with the use of sedation. Multiple studies have been comparing propofol sedation to traditional sedation, and they have confirmed the safety of deep sedation, which is considered similar to light and moderate sedation [11, 20–22].

Given the difficulties of performing all EGD under sedation, it is acceptable to select patients or outline a user profile that will certainly need to benefit from sedation to perform a quality EGD. Therefore, with this study, we can conclude that the request for an examination with deep sedation, especially in young patients or in those who must be included in a screening or surveillance program, should be considered.

This study has some limitations. The first one is the lack of randomization. In fact, patients were previously allocated to sedation or no sedation, and the investigators had no interference in such process. That can be assumed as a major bias, but on the other hand, one can assume that if a patient accepts to perform EGD without sedation, he/she might be more motivated to do so. On the contrary, if a patient requests sedation, he/she is not keen to do such procedure without sedation, and if obliged, his/her compliance would probably be worse. Therefore, it is not ethical to randomize patients to sedation or no sedation if they have previously chosen the opposite with their assistant physician. The second limitation of this study, which is tightly linked to the first one, is the presence of some differences in indications. However, when we analyze what was necessary to achieve the quality objectives such as procedure time, photodocumentation, performance of biopsies, and completeness of the exam, there is a clear difference between the procedures with and without sedation, independently of indication. Also, many patients submitted to endoscopy without anesthesiologist support stated that they would repeat the procedure only if sedation was offered to them. The third limitation was the strict inclusion and exclusion criteria. This study was performed in a tertiary referral hospital with many patients being referred for EGD with therapeutic objectives. Additionally, there is limited access to anesthesiologist-administered sedation that justifies the period necessary to achieve the desired number of patients in each group. It is also important to mention that not all EGDs at the center were included and only EGDs performed by 3 endoscopists who were equally distributed in the sedation and non-sedation suites. This can be assumed as a selection bias. Finally, as we previously stated, there are different levels of sedation, and minimal or moderate sedation, administered by gastroenterologists, was not considered in this study.

Conclusion

The present study seems to demonstrate that the use of deep sedation can influence the fulfillment of a high-quality EGD, in accordance with the ESGE/UEG criteria. The use of sedation suppressed the patient's intolerance, promoting a higher quality EGD. The administration of sedation was safe and was not associated with an increase in adverse event rates. Patients' satisfaction was also considerably higher after EGD under deep sedation.

We conclude that the use of deep sedation in clinical practice should be considered in patients undergoing EGD, to ensure a high-quality examination. A comparison with minimal or moderate sedation, administered by gastroenterologists, is needed.

Statement of Ethics

All procedures performed were in accordance with the ethical standards of the institutional and/or national research committee. This study was approved by the Ethics Committee of the Faculty of Medicine, University of Coimbra, Coimbra, Portugal, on June 24, 2019 (CE-057/2019). The privacy of the research patients participating was guaranteed, and the protocols followed the tenets of the Declaration of Helsinki. Written informed consent was obtained from participants to participate in the study.

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The authors want to dedicate this work to the fond memory of the late Dr. Carlos Gregório, who taught many of us not only the principles and tricks of endoscopy but, most importantly, the relevance of kindness and empathy with our patients.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Catarina Correia, Nuno Almeida, Raquel Andrade, Mariana Sant'Anna, and Claudia Macedo contributed to the manuscript concept and design as well as data collection and compilation. Nuno Almeida, David Perdigoto, and Carlos Gregório performed the EGDs. Catarina Correia and Nuno Almeida performed the statistical analysis and wrote the manuscript. All authors critically revised the manuscript and have approved the final version of the manuscript.

Data Availability Statement

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

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Endoscopic Retrograde Cholangiopancreatography on Pediatric Patients: Experience of a Portuguese Adult Gastroenterology Department

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Keywords
Endoscopic retrograde cholangiopancreatography · Pediatric endoscopic retrograde cholangiopancreatography · Children · Cannulation success rate · Adult-trained endoscopist

Abstract
Introduction: Experience with endoscopic retrograde cholangiopancreatography (ERCP) in the pediatric population is limited. Few medical centers have experts specifically trained in pediatric therapeutic endoscopy. As a result, patients are generally referred to adult endoscopists with high experience in the procedure. The aim of this study was to characterize the experience of an adult endoscopy unit with ERCP on pediatric patients, with a special focus on very young patients. ***Methods:*** We retrospectively analyzed indications, technical success rate, final clinical diagnosis, and complications of ERCPs in children <18 years at our tertiary referral hospital center between January 1994 and June 2022. ***Results:*** Sixty-five ERCPs were performed on 57 children with a median age of 13 years (range 1–17 years). Eleven ERCPs were performed on 9 patients up to 5 years old. Indications for ERCP were as follows: biliary obstruction ($n = 40$), mainly due to choledocholithiasis, lithiasic acute pancreatitis ($n = 19$), recurrent pancreatitis ($n = 3$), stent extraction ($n = 2$), and post-operative biliary fistula ($n = 1$). The cannulation success rate was 95.1%. Therapeutic interventions were performed in 79% of ERCP. All patients were followed up as inpatients. Complications were recorded in two procedures (3.1%), and no procedure-related mortality occurred. ***Conclusion:*** In our experience, ERCP in children can be safely performed with high success rates by advanced adult-trained expert endoscopists at a high-volume center.

Colangiopancreatografia retrógrada endoscópica na população pediátrica – experiência de um serviço de Gastrenterologia português

Palavras Chave
Colangiopancreatografia retrógrada endoscópica · CPRE pediátrica · Crianças · Taxa de sucesso de canulação · Gastroenterologista de adultos

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Resumo

Introdução: Existe pouca experiência na realização de colangiopancreatografia retrógrada endoscópica (CPRE) na população pediátrica. A maioria dos centros carece de especialistas especificamente treinados em endoscopia terapêutica pediátrica, sendo os doentes geralmente referenciados para Gastroenterologistas de adultos com elevada experiência na técnica. O objectivo deste estudo foi caracterizar a experiência de um departamento de Gastrenterologia de adultos em CPRE pediátrica, com destaque particular nos doentes muito novos. ***Métodos:*** Foram analisadas retrospectivamente as indicações, sucesso técnico, diagnósticos e complicações das colangiopancreatografias retrógradas endoscópicas (CPREs) realizadas no nosso hospital terciário em crianças <18 anos, entre Janeiro de 1994 e Junho de 2022. ***Resultados:*** Foram realizadas 65 CPREs em 57 crianças com idade mediana 13 anos (1–17 anos). Doze procedimentos foram realizados em 9 crianças com idade até 5 anos. As indicações para CPRE foram: obstrução biliar (*n* = 40), sobretudo devido a coledocolitíase, pancreatite aguda litiásica (*n* = 19), pancreatite recorrente (*n* = 3), extracção de prótese (*n* = 2) e fístula biliar pós cirurgia (*n* = 1). A taxa de sucesso de canulação foi 95.4%. Foram realizados procedimentos terapêuticos em 80.0% das CPREs. Todos os doentes foram vigiados em regime de internamento, tendo-se registado complicações em dois exames (3.1%). Não existiram mortes relacionadas com a técnica. ***Discussão/Conclusão:*** A CPRE pode ser realizada na população pediátrica com segurança e elevada taxa de sucesso por Gastrenterologistas de adultos com experiência na técnica, num centro com elevado volume de exames.

Introduction and Aim

Endoscopic retrograde cholangiopancreatography (ERCP) is a minimally invasive, nowadays essentially therapeutic, advanced endoscopic procedure for biliary and pancreatic diseases. The vast majority of ERCP procedures is performed on adult patients and increasingly in the very elderly [1], as the incidence of biliary and pancreatic diseases requiring intervention is growing in this age group. In the pediatric population, ERCP has been performed for several decades, with the first pediatric biliary sphincterotomy performed in 1982, but it remains an uncommon procedure [2].

Its conservative use in children is a result of the low incidence of bilio-pancreatic diseases requiring ERCP, the perception that the procedure is technically more difficult in this age group, uncertainties about indications and safety, and ongoing debate on the examiner's qualification [3, 4]. Frequently, pediatric patients requiring ERCP are referred to high-volume, highly specialized, adult referral centers, with high technical expertise, but less familiarity with pediatric diseases [4].

Furthermore, the pediatric age group is a nonhomogeneous population, including the very young patients with particular age-related indications (e.g., biliary atresia, choledochal cysts) and anatomical conditions requiring specific pediatric endoscope; and on the other side adolescents with clinical and anatomical characteristics that resemble adult patients [5]. The aim of this retrospective observational study was to characterize the experience of an adult endoscopy unit with ERCP on pediatric patients, with a special focus on very young patients.

Population and Methods

Our center is an academic, tertiary, and referral hospital in Lisbon (Portugal), providing health services for 1.5 million inhabitants in a country with about 10 million inhabitants. It is composed of a group of hospitals in central Lisbon and has most medical and surgical specialties for both adult and pediatric population. The Bilio-Digestive Techniques Unit is part of the Gastroenterology Department for adults and was established on 1982. It is one of the first units performing ERCP in Portugal and has been accumulating expertise over the last decades, becoming nationally recognized by many colleagues and departments from other hospitals that commonly refer their patients directly to this unit when local resources or expertise is lacking.

In our center, we perform 350–400 ERCPs in adult patients every year and provide services for children of all ages suffering from gastrointestinal, liver, or pancreatic diseases. Care for these children is organized in multidisciplinary teams, with close cooperation between adult gastroenterologists, pediatricians, and pediatric surgeons.

For this study, we reviewed every ERCP performed on individuals aged 17 years or less at the Bilio-Digestive Techniques Unit between January 1, 1994, and June 31, 2022. Physical and electronic medical records were searched and assessed, both related to the endoscopic procedure and to the respective hospital admission.

Patient characteristics, endoscopic procedure details, and registered complications were analyzed. Technical success of the intervention was defined as deep cannulation allowing accurate diagnosis and/or adequate therapy as to the pre-specified indication. Due to the procedural specificities of this particular demanding technique when performed on very young patients, a subanalysis was performed on procedures performed on patients aged 5 years or less. Statistical analysis was performed with Microsoft® Office Excel.

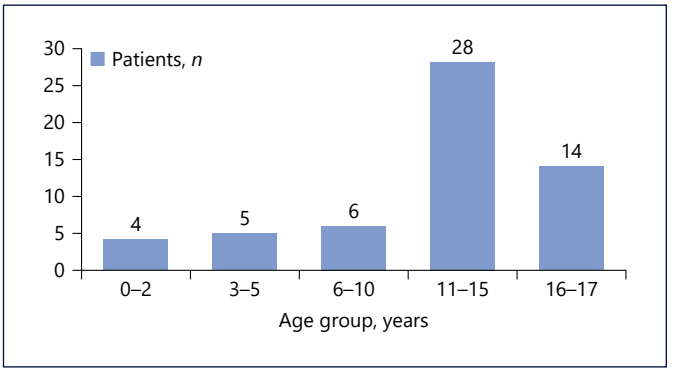

Fig. 1. Age distribution of overall population.

Results

Over the 27-year period between January 1994 and June 2022, 65 ERCPs were performed on 57 patients at the Bilio-Digestive Techniques Unit of our center.

Overall Population

Demographics

Most patients were male (n = 34; 59.6%), and the median age was 13 years (range 1–17 years). Nine patients were aged 5 years or less (corresponding to 12 ERCPs), and 4 patients were aged 2 years or less (Fig. 1). The majority of the patients (n = 51) underwent a single procedure, 5 patients underwent two procedures, and 1 patient underwent three procedures.

Indications

Indications for ERCP were biliary obstruction (n = 40; associated with cholangitis in 4 cases), mainly due to choledocholithiasis, lithiasic acute pancreatitis (n = 19), recurrent pancreatitis (n = 3), stent extraction (n = 2), and post-operative biliary fistula (n = 1).

Interventions

All procedures were performed by adult ERCP highly expert endoscopist (total of 5 endoscopists with a median of 8 procedures/endoscopist), with attending pediatricians, pediatric anesthesiologists, and therapeutic endoscopy nurses on-site, under general anesthesia, with the patient in the prone position. Adult duodenoscopes were used in all procedures. Selective biliary cannulation was performed with a catheter (5.5 Fr), and the guidewire-assisted technique has been used since 1998. Ambient air was used for insufflation until 2020 when carbon dioxide became available at our center.

Routine post-ERCP pancreatitis prophylaxis with rectal indomethacin was performed in all patients since 2010. ERCP was finished as therapeutic ERCP in 52 interventions (80%) and as diagnostic in 13 (20.0%). Successful intervention was achieved in 95.4% (62/65 ERCPs). In 3 patients with acute pancreatitis, aged 12–17 years old, cannulation of the papilla was not possible due to duodenal edema.

Diagnostic Findings

Diagnosis after ERCP was (≥1 diagnosis/patient) choledocholithiasis/cystic duct stones (n = 33; 6 patients with hemolytic anemia), primary sclerosing cholangitis (n = 3), Mirizzi syndrome (n = 3) (Fig. 2a), parasitic infestation (n = 3), choledochal cyst (n = 2), biliary rhabdomyosarcoma (n = 2) (Fig. 2b), intrahepatic lithiasis (n = 1), extraskeletal Ewing's sarcoma (n = 1), post-operative biliary stenosis (n = 1), post-operative biliary fistula (n = 1), and autoimmune pancreatitis (n = 1). The final diagnoses after the procedures are demonstrated in Figure 3. A normal cholangiography was found in 11 exams.

Autoimmune pancreatitis, an infrequently recognized disorder in this age group, was diagnosed in a 13-year-old male presenting with abdominal pain, elevated pancreatic enzymes, and cholestasis. Imaging tests showed a pancreatic head mass and dilatation of the biliary tree. Serum immunoglobulin G4 levels were elevated (280 mg/dL), and cancer antigen 19-9 was normal. He underwent endoscopic ultrasound with fine needle aspiration of the pancreatic mass, and histopathology revealed lymphoplasmacytic infiltrate with fibrosis, negative for immunoglobulin G4 staining and neoplastic cells. ERCP revealed stenosis of the intrapancreatic bile duct. Biliary drainage with stent placement and an exfoliative cytology were performed with success.

Endoscopic Therapy

Therapeutic procedures were performed in 52 ERCPs: sphincterotomy of the biliary duct (n = 42; 64.6%) with precut in two cases, common bile duct exploration with Dormia basket/Fogarty balloon (n = 41; 63.1%), extraction of biliary stones/parasites (n = 33; 50.8%), insertion of biliary plastic stents (7-10 Fr, 5–9 cm) (n = 14; 21.5%), stent extraction (n = 8; 12.3%), insertion of pancreatic stent (n = 4; 6.2%), and exfoliative cytology (n = 3; 4.6%).

Adverse Events

Clinical follow-up was done as inpatients for at least 24 h after the procedure in all patients. Complications

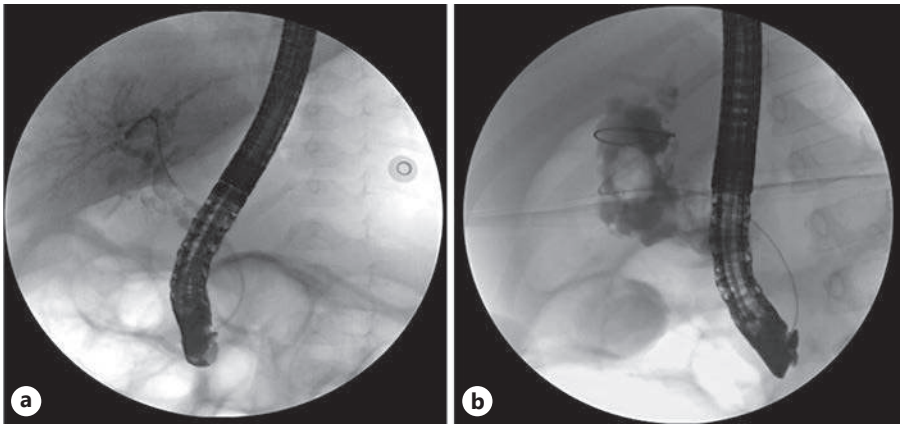

Fig. 2. Cholangiography of a 15-month-old boy with Mirizzi syndrome (**a**) and a 4-year-old boy with biliary rhabdomyosarcoma (**b**).

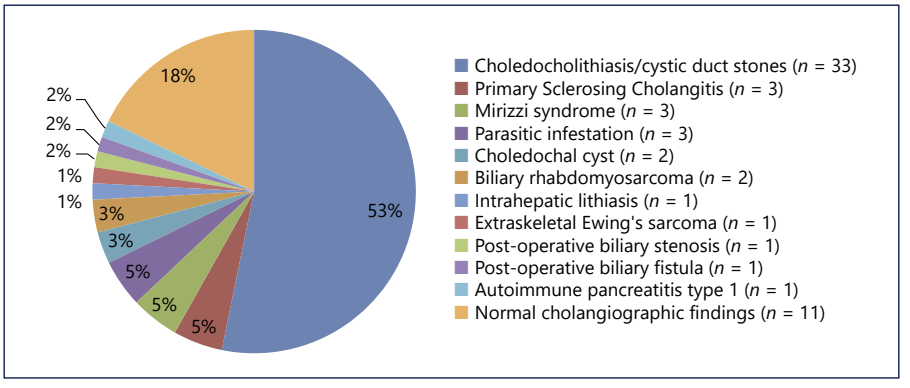

Fig. 3. Diagnoses encountered in successfully performed ERCPs ($N = 62$).

were recorded in two procedures (3.1%). There was one episode of mild pancreatitis, managed conservatively, and one case of immediate post-sphincterotomy bleeding, resolved with endoscopic therapy (adrenalin injection) during the procedure. There were no complications attributable to mechanical stress on the gastrointestinal tract, perforations, or cardiopulmonary suppression. No mortality was associated with ERCP.

Population Aged 5 Years or Less

Due to the diagnostic specificities and particular technical demands of ERCP on very young patients, we detail on this population in Table 1. In total, 12 ERCPs were performed on 9 patients aged up to 5 years.

Discussion

In our experience, ERCP in children can be safely performed with high success rates by advanced adult-trained expert endoscopists at a high-volume center. This adds to the growing evidence supporting the use of ERCP by skilled endoscopists in this age group [3]. Few pediatric gastroenterologists receive sufficient training on advanced endoscopy including procedures such as ERCP. This gap is usually filled by adult gastroenterologists. It is particularly helpful to coordinate findings and further therapeutic steps with the attending pediatrician as adult-trained endoscopists may not be familiar with specific pediatric diseases [6].

Pediatric duodenoscopes are recommended for children <10 kg or younger than 12 months of age, beyond which an adult diagnostic or therapeutic duodenoscope is acceptable [7]. A standard adult duodenoscope was used in all procedures since all the children were older than 12 months of age/weighing more than 10 kg and our endoscopy unit does not have a pediatric duodenoscope, which is in accordance with current ASGE recommendations.

In Western countries, the most common indications for adult ERCP are choledocholithiasis and acute/chronic pancreatitis, as was seen in our pediatric cohort. This is not surprising given the median age of 13 years of our population and the fact that indications in adolescents are comparable to adult ERCP.

Table 1. Diagnostic and procedure details of ERCPs performed on patients aged 5 years or less

Patient	Age	Diagnosis	Procedure details
#1	15 months	Choledocholithiasis	Biliary stenting
#2	22 months	Choledocholithiasis	Biliary sphincterotomy, stone extraction
#3	26 months	Choledocholithiasis	Biliary sphincterotomy, stone extraction, biliary stenting
#4	34 months	Parasitic infestation	Biliary sphincterotomy, parasite extraction
#5	3 years	Neoplastic biliary stenosis (biliary rhabdomyosarcoma)	Biliary sphincterotomy, biliary stenting
#6	4 years	Parasitic infestation, choledocholithiasis	Biliary sphincterotomy, stone and parasite extraction
#7	4 years	Choledocholithiasis	Biliary sphincterotomy, stone extraction
#8	4 years	Neoplastic biliary stenosis (biliary rhabdomyosarcoma)	Biliary sphincterotomy, biliary stenting
#9	5 years	Choledocholithiasis	Biliary sphincterotomy, stone extraction

Table 2. Comparison with other large single-center series of ERCP performed on patients aged up to 18 years for non-selected indications

Author	Publication date	*N* (procedures)	Technical success[a], %	Therapeutic interventions performed, %	Adverse event rate, %	Mortality, %
Keil et al. [5]	2019	856	94.6	58.8	7.2	0
Dahale et al. [9]	2019	164	90.4	86.0	4.9	0
Felux et al. [4]	2017	54	90.7	66.7	9.3	0
Yıldırım et al. [6]	2016	65	93.8	70.7	12.3	0
Kielling et al. [10]	2015	75	94.7	68.0	9.7	0
Halvorson et al. [11]	2013	70	98.6	92.9	7.1	0
Jang et al. [12]	2010	245	98.4	77.6	[b]	0
Cheng et al. [13]	2005	329	97.9	71.4	9.7	0
Coimbra et al.	2022	62	95.1	79.0	3.2	0

[a]Technical success defined as deep cannulation. [b]Reported complications were post-ERCP pancreatitis in 6.5%, ileus in 9.4%, hemorrhage in 0.8%, perforation in 0.8%, sepsis in 0.4%, and impacted basket in 0.4%.

The technical principles of selective biliary cannulation in children are similar to those used in adult patients, with the additional limitations of space within the duodenum in small patients. Despite this, the technical success rate was very high, similar to what has been reported for other pediatric (89.5–100%) (Table 2) and adult populations [6].

ERCP was performed for diagnostic intent in some procedures at the beginning of our observation period, when alternative noninvasive diagnostic methods were still unavailable. Given the development of imaging methods, especially magnetic resonance cholangiopancreatography, diagnostic indications have naturally decreased, and in the most recent years ERCP has been indicated essentially as a therapeutic procedure [5]. There was a remarkable amount of therapeutic interventions (80.0%) in this pediatric patient series. In most of the procedures, more than one intervention was performed.

The incidence of procedure-related complications in children has not been well established in prospective studies. Reports in literature suggest complication rates between 3 and 10% in children older than 1 year [2]. It is unclear whether complication rates are slightly higher in infants younger than 1 year. The overall complication rate found in the present study was lower than the rates observed in the literature in other pediatric populations, but the retrospective nature of the study may lead to its underestimation (Table 2).

There is some evidence that administration of indomethacin via rectal suppository at the time of the ERCP may help prevent post-ERCP pancreatitis, based on a preponderance of evidence in adults [8]. Children-specific recommendations on minimizing adverse events are lacking and are usually extrapolated from the adult population [3]. We routinely used indomethacin for prophylaxis since the recommendation was established for adult

patients, and as patients are monitored for at least 24 h after ERCP, post-procedure pancreatic enzyme levels are not regularly measured.

This study has several limitations that should be noted, namely, due to its retrospective nature. Complete medical reports were not available on all patients because of the use of paper charts in the 1990s and early 2000s. The best reasonable efforts were made to attain all available records, including those archived and stored at off-site facilities. Nevertheless, incomplete records may influence outcomes such as underestimating the total adverse event rate and limiting access to other important information, such as the length of stay of biliary stents and how they were removed (upper endoscopy or new ERCP). Notwithstanding these limitations, our study covers 27 years of pediatric ERCP experience from a large endoscopic referral center with an associated dedicated children's hospital.

The results emphasize the beneficial impact of ERCP in a pediatric cohort, with high success rates and a low overall rate of adverse events. The overall efficacy and safety support the performance of pediatric ERCP by experienced adult endoscopists at high-volume centers.

Pediatric patients who require ERCP should be managed in a multidisciplinary team, with close cooperation between adult and pediatric gastroenterologist. We consider this setting a prerequisite for ERCPs in this age group since adult-trained endoscopists may not be intimately familiar with specific pediatric diseases.

Statement of Ethics

This study protocol was reviewed and approved by the Ethics Committee of Centro Hospitalar Universitário Lisboa Central. Due to the characteristics of the study (approval number CES 1280/2022), informed consent was not required.

Conflict of Interest Statement

The authors have no conflicts of interest.

Funding Sources

The authors have no funding sources to declare.

Author Contributions

All authors contributed equally to the conception, analysis, and interpretation of data, as well as drafting and critical revision of the article for important intellectual content, and approved the final version of the manuscript.

Data Availability

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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The Effect of Oral Simethicone in a Bowel Preparation in a Colorectal Cancer Screening Colonoscopy Setting: A Randomized Controlled Trial

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Keywords
Colorectal cancer · Screening · Bowel preparation · Simethicone

Abstract
Introduction: Current guidelines suggest adding oral simethicone to bowel preparation for colonoscopy. However, its effect on key quality indicators for screening colonoscopy remains unclear. The primary aim was to assess the rate of adequate bowel preparation in split-dose high-volume polyethylene glycol (PEG), with or without simethicone. ***Methods:*** This is an endoscopist-blinded, randomized controlled trial, including patients scheduled for colonoscopy after a positive faecal immunochemical test. Patients were randomly assigned to 4 L of PEG split dose (PEG) or 4 L of PEG split dose plus 500 mg oral simethicone (PEG + simethicone). The Boston Bowel Preparation Scale (BBPS) score, the preparation quality regarding bubbles using the Colon Endoscopic Bubble Scale (CEBuS), ADR, CIR, and the intraprocedural use of simethicone were recorded. ***Results:*** We included 191 and 197 patients in the PEG + simethicone group and the PEG group, respectively. When comparing the PEG + simethicone group versus the PEG group, no significant differences in adequate bowel preparation rates (97% vs. 93%; $p = 0.11$) were found. However, the bubble scale score was significantly lower in the PEG + simethicone group (0 [0] versus 2 [5], $p < 0.01$), as well as intraprocedural use of simethicone (7% vs. 37%; $p < 0.01$). ADR (62% vs. 61%; $p = 0.86$) and CIR (98% vs. 96%, $p = 0.14$) did not differ between both groups. ***Conclusion:*** Adding oral simethicone to a split-bowel preparation resulted in a lower incidence of bubbles and a lower intraprocedural use of simethicone but no further improvement on the preparation quality or ADR.

O efeito adicional do simeticone oral na preparação intestinal em colonoscopia de rastreio: estudo randomizado controlado

Palavras Chave
Cancro colorretal · Rastreio · Preparação intestinal · Simeticone

Resumo
Introdução: As normas de orientação atuais sugerem a adição de simeticone oral à preparação intestinal para colonoscopia. Contudo, o seu efeito nos indicadores de

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qualidade no âmbito da colonoscopia de rastreio não está comprovado. O objetivo principal foi avaliar a taxa de preparação adequada usando polietilenoglicol (PEG) em dose dividida com e sem simeticone oral. ***Métodos:*** Estudo randomizado controlado, cego para o endoscopista, incluindo doentes admitidos para colonoscopia após teste fecal imunoquímico positivo. Os doentes foram aleatoriamente alocados para 4 litros de PEG em dose dividida (PEG) ou 4 litros de PEG em dose divida + simeticone oral (PEG + simeticone). Foram avaliados: Boston Bowel Preparation Scale (BBPS), qualidade da preparação relativa às bolhas através da Colon Endoscopic Bubble Scale (CEBuS) scale, ADR, CIR e uso de simeticone durante o procedimento. ***Resultados:*** Foram incluídos 191 e 197 doentes nos grupos PEG + simeticone e PEG, respetivamente. Comparando os grupos PEG + simeticone versus PEG, não se registaram diferenças de significado estatístico relativamente à taxa de preparação intestinal adequada (97% vs. 93%; $p = 0{,}01$) mas o *score* da escala de bolhas foi significativamente inferior no grupo PEG + simeticone [0 (0) versus 2 (5), $p < 0.01$], assim como o uso de simeticone durante o procedimento (7% *vs*. 37%; $p < 0{,}01$). A ADR (62% vs. 61%; $p = 0{,}86$) e a CIR (98% vs. 96%, $p = 0{,}14$) não diferiram significativamente entre os dois grupos, respetivamente. ***Discussão/Conclusão:*** Adicionar simeticone oral à preparação intestinal em dose dividida permitiu menor incidência de bolhas e menor utilização de simeticone durante o procedimento, mas não se associa a melhor preparação intestinal ou melhor ADR.

Introduction

Colorectal cancer (CRC) represents the second most common cause of cancer morbidity and mortality in Europe. The screening of average-risk individuals by faecal occult blood testing followed by colonoscopy for positive cases can significantly reduce CRC incidence and mortality. The long-term efficacy in preventing CRC has been associated with the quality of the screening programme, namely, with colonoscopy quality [1].

Colonoscopy quality is greatly dependent on the quality of bowel preparation, affecting all colonoscopy performance measures [2]. The standard recommendation for bowel preparation includes an oral laxative in a split regimen for morning/early afternoon exams or full-dose regimen for late afternoon exams [2].

To improve bowel cleansing, some adjunctive drugs have been tested; however, their role remains controversial. One of these drugs is simethicone, an inexpensive, safe, non-absorbable substance which reduces the surface tension of gas bubbles and thus prevents foam in the colon. Theoretically, simethicone might present several benefits, such as improving the quality of mucosal visualization, the adenoma detection rate (ADR), and the caecal intubation rate (CIR). Furthermore, it also reduces abdominal distension, increasing patient tolerance and comfort, and decreasing the time spent in bubble removal. Previous studies have evaluated the effect of adding simethicone to the bowel preparation laxative on the overall preparation [3–7].

In a meta-analysis of seven randomized controlled trials (RCTs) comparing bowel preparation with between 80 mg and 300 mg of simethicone or without simethicone, the number of bubbles was lower in patients who had taken simethicone; nonetheless, no difference in colon cleanliness was found [8]. Recently, two RCTs have reported that supplemental simethicone (1,200 mg) with 2 L of polyethylene glycol (PEG) can improve bowel preparation, bubble score, ADR, and bowel preparation tolerability [3, 6]. A subgroup analysis of a meta-analysis assessing four RCTs found that oral simethicone (400–1,200 mg) increased ADR [5]. The only study assessing the role of simethicone (480 mg) added to a split dose of 4 L of a PEG preparation found no improvement on ADR or bowel preparation. However, it resulted in lower bubble scale scores and a lower intraprocedural use of simethicone [4]. Furthermore, the optimal timing of oral simethicone addition remains undetermined [9, 10]. In summary, previous studies were mostly from Eastern countries, used low-volume PEG-based regimens or non-PEG-based agents, used simethicone in suspension, have shown conflicting results and only one study assessed colonoscopy results in a CRC screening setting.

Our primary aim was to assess the effect on the adequate bowel preparation rate of adding a higher dose of oral simethicone to a split-dose bowel cleansing regimen of 4 L of PEG, compared to a split-dose bowel cleansing regimen of 4 L of PEG without simethicone, in a pure CRC screening setting. Our secondary aims included assessing the impact on bubble rate, intraprocedural use of simethicone, ADR, CIR, and patient tolerability to the bowel preparation regimen in both regimens.

Materials and Methods

Patients

This was a single-centre, randomized, endoscopist-blinded, controlled trial conducted at the Portuguese Oncology Institute

of Coimbra, Portugal, from June 2019 to September 2022. The inclusion criterion was patients aged between 50 and 74 years, inclusive, scheduled for colonoscopy after a positive faecal immunochemical test (FIT) promoted by the regional CRC screening programme. Exclusion criteria were similar to those of the CRC screening program: (1) previous diagnosis of CRC; (2) presence of known genetic susceptibility syndromes related with CRC; (3) personal history of inflammatory bowel disease; (4) presence of gastrointestinal complaints (significant changes in gastrointestinal transit in the last 6 months or evidence of gastrointestinal bleeding); (5) a normal colonoscopy in the last 5 years; (6) known or suspected gastrointestinal obstruction or perforation; (7) toxic megacolon; (8) major colonic resection; (9) pregnant or at risk of becoming pregnant or lactating women; (10) known or suspected hypersensitivity to the ingredients of bowel preparation or to simethicone.

All procedures were conducted in accordance with the ethical principles of the Declaration of Helsinki and the study protocol was approved by the Portuguese Oncology Institute of Coimbra Ethics Committee (reference number: 06/2019). Written informed consent was obtained from all patients. This study was registered at ClinicalTrials.gov (NCT03816774).

Randomization: Sequence Generation and Allocation Concealment

Patients were randomly (1:1) divided in two groups: 500 mg of simethicone plus 4 L of split-dose PEG versus 4 L of split-dose PEG without simethicone, following a computer-generated list of random numbers, without any restriction or blocking. The computer-generated random allocation sequence was independent of patients. Enrolment was performed by a gastroenterologist not involved in the endoscopic procedure through a scheduled appointment 1-2 weeks before the colonoscopy. Patients were informed about the aims, procedures, benefits, and likely risks associated with their participation in the study and gave written informed consent prior to their enrolment. The allocation of patients was concealed using sequentially numbered, opaque, sealed envelopes.

Bowel Preparation Protocol and Colonoscopy Procedure

All patients were instructed to consume a low-fibre diet 3 days prior to the date of the procedure. On the afternoon before the examination day, patients were required to follow a clear-liquid diet only. The intervention group used a PEG split dose plus simethicone: 2 pills of 125 mg of simethicone 15 min before the PEG dose on the previous evening, plus 2 pills of 125 mg simethicone 15 min before the PEG dose ending 3 h before the colonoscopy schedule. The comparison group used the same PEG split dose without simethicone. PEG was chosen because the Portuguese-organized CRC screening offers this laxative free of charge in the primary care centre, and it is the only laxative provided by the screening programme.

Regarding the bowel preparation schedule, patients took 3 L of PEG on the previous evening (or 2 L if the procedure was scheduled after 11:00 a.m.) plus 1 L of PEG (or 2 L if the procedure was scheduled after 11:00 a.m.) in the morning of the procedure, ending 3 h before the colonoscopy. As all procedures were scheduled until 4:00 p.m., there were no evening colonoscopies requiring a same-day full bowel preparation regimen. Before the procedure, the nurses who were not blinded for group inclusion asked patients about compliance and tolerability to the prescribed cleansing regimen and simethicone prescription, if applicable.

Colonoscopies were performed under deep sedation by experienced endoscopists (>1,000 colonoscopies per year) blinded to the study groups. All colonoscopies were performed using high-definition colonoscopes with narrow band imaging (EVIS EXERA III CV185 or CV190, Olympus Inc., Tokyo, Japan). Histological analyses were performed by experienced pathologists (>1,000 gastrointestinal analyses per year) who were also blinded to the study groups.

Outcome Measurements

Patient characteristics included age, gender, occurrence of gastrointestinal symptoms during preparation, compliance to bowel preparation instructions (diet, dose, and time of PEG, dose and time of simethicone pills). Patient self-assessment of the willingness to repeat the scheme was evaluated by a visual analogue scale (1–10; 1 representing the most unfavourable outcome and 10, the most favourable). Colonoscopy data included the Boston Bowel Preparation Scale (BBPS) score, a bubble scale as reported by Lazzaroni et al. [11] (registered in the ClinicalTrials.gov site), and the Colon Endoscopic Bubble Scale (CEBuS), intraprocedural use of simethicone (recorded as a categorical variable: yes or no), CIR, withdrawal time, number, size, location, and histological type of polyps or CRC.

The BBPS score standard protocol was followed. Each individual segment score was added to calculate a total composite score. Adequate bowel preparation was defined as total BBPS ≥6 and ≥2 in each segment [12, 13].

The original bubble scale used in this study was an adaptation from the previously described scale [3, 6, 14]. The score ranged from 0 to 3 (0 [bubbles in <5% of the surface], 1 [bubbles in 5–50% of the surface], 2 [bubbles in >50% of the surface], and 3 [bubbles filling the entire lumen]), as shown in Figure 1, and were determined separately for 5 segments (caecum, ascending colon, transverse colon, descending colon, sigmoid, and rectum). After the study protocol design, our group published a two-phase evaluation study of a new bubble scale, the Colon Endoscopic Bubble Scale (CEBuS), which was also used in the results [15]. CEBuS is a three-grade scale defined as follows: 0 – no or minimal bubbles, covering <5% of the surface, not hampering mucosa visibility; 1 – moderate number of bubbles, covering between 5 and 50% of the surface, affecting mucosa visibility, and requiring additional time for removal; 2 – severe bubbling, covering >50% of the surface, obscuring mucosa visibility, and requiring additional time for removal (both grade 0 and grade 1 are similar in both scales; CEBuS grade 2 is a combination of grades 2 and 3 of the original scale). In CEBuS, the colon is divided into 3 segments: caecum/ascending colon, transverse colon, and descending/sigmoid colon.

ADR was defined as the proportion of patients undergoing colonoscopy in whom at least one histologically confirmed colorectal adenoma was detected. PDR was defined as the proportion of patients undergoing colonoscopy in whom at least one polyp was identified [16]. The withdrawal time was defined as the time spent from the caecum to the anal canal and inspection of the entire bowel mucosa at negative (no biopsy or therapy) colonoscopy and was calculated by time stamp on caecum and rectum photodocumentation [13].

Sample Size Calculation

To improve adequate bowel preparation rate (primary outcome) from 85% (value from our database) to 95% (target standard

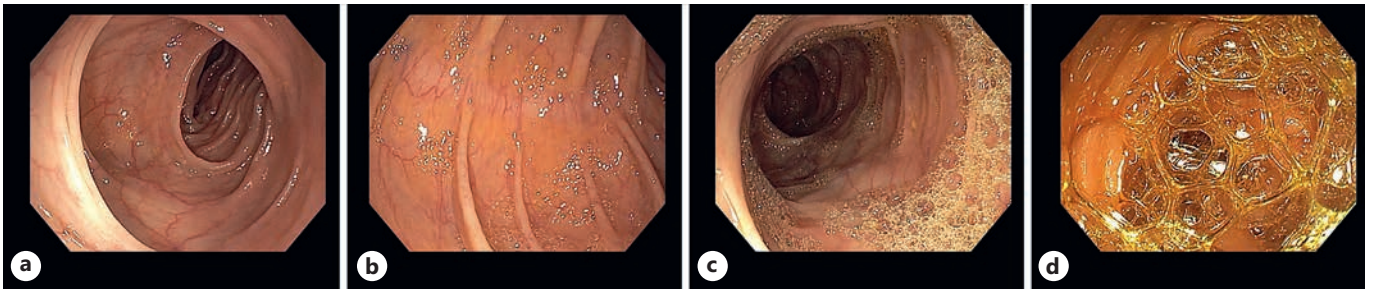

Fig. 1. Bubble scale. **a** 0: bubbles <5% of the surface. **b** 1: bubbles 5–50% of the surface. **c** 2: bubbles in >50% of the surface. **d** 3: bubbles filling the entire lumen.

suggested by ESGE [13]), assuming a normal distribution and a power of 90% ($\alpha = 0.05$), the calculated sample size of each of the 2 groups was 188. Allowing for a 10% dropout rate, the final sample size was 206 per group (412 patients overall).

Statistical Analysis

Normally distributed continuous variables were reported as mean and standard deviation, and skewed continuous variables were reported as median and interquartile range. Categorical data were expressed as absolute and relative frequency. Continuous variables with a normal distribution were compared between both groups using the Student's *T* test, whereas the homogeneity of variance or Mann-Whitney U was used otherwise. Categorical variables were compared using the Pearson's χ^2 test or the Fisher test. A two-sided *p* value of <0.05 was considered statistically significant. Statistical analyses were performed with IBM SPSS Statistics software (version 27.0, Armonk, NY: IBM Corp.).

Results

From June 2019 to September 2022, a total of 412 patients were enrolled in the study. Twenty-four patients were not included in the final analysis; therefore, 388 patients (191 PEG plus simethicone vs. 197 PEG alone) were analysed in the intention-to-treat (ITT) and 378 patients (188 PEG plus simethicone vs. 190 PEG alone) in the per-protocol (PP) analysis. The process of patient screening, inclusion, and exclusion is illustrated in Figure 2. The baseline clinical and demographic characteristics were comparable between both groups (Table 1).

As for the primary endpoint BBPS bowel preparation, the adequate bowel preparation rate was not different between the PEG plus simethicone group versus the PEG alone group, with 97% versus 93% ($p = 0.11$). The median BBPS total score did not differ between the PEG plus simethicone group versus the PEG alone group (9 [1] versus 9 [2], $p = 0.70$) for ITT and PP analysis. Also, no statistically significant differences were found between groups regarding segmental BBPS scores, both for ITT and PP analyses (Table 2; online suppl. material 1, see online suppl. material at https://doi.org/10.1159/000530866; Fig. 3).

Regarding bubble scale scores, there was a statistically significant difference between groups for the original scale of our study protocol, with patients in the PEG plus simethicone group presenting a better median total bubble scale score (0 [0] versus 2 [5] [$p < 0.01$]) under ITT and PP analysis. Segmental bubble scores were also significantly better in the PEG plus simethicone group, as shown in table 2 and online supplementary material 1. For CEBuS, patients in the PEG plus simethicone group presented a better CEBuS total score (0 [0] vs. 1 [3], $p < 0.01$) for ITT analysis and for PP analyses. These significantly better CEBuS score results for patients in the PEG plus simethicone group were also present in the right, transverse, and left colon. Regarding the intraprocedural use of simethicone, the need of simethicone was significantly lower in patients of the PEG plus simethicone group, with 7% versus 37% ($p < 0.01$) for ITT analysis and 7% versus 38% ($p < 0.01$) for PP analysis (Fig. 3).

For the ITT analysis, no significant difference was found between the PEG plus simethicone and PEG alone groups regarding PDR (68% vs. 65%, $p = 0.52$) and ADR (62% vs. 61%, $p = 0.86$). Furthermore, the ADR in the right colon (44% vs. 40%, $p = 0.47$) and the ADR for diminutive polyps (61% vs. 55%, $p = 0.28$) were similar between the PEG plus simethicone and the PEG alone groups, respectively. The results were similar for the PP analysis. The median number of detected polyps (1 [3] vs. 1 [3], $p = 0.63$) and adenomas (1 [2] vs. 1 [3], $p = 0.97$) did not differ between PEG plus simethicone and PEG alone groups, respectively (online suppl. material 2). Withdrawal time did not differ between groups: PEG plus simethicone group (7 [2] min) and PEG group (7 [2] min), $p = 0.43$. Finally, there was no significant difference in colonoscopy adverse events (2.5% vs. 1.5%, $p = 0.93$) between the groups.

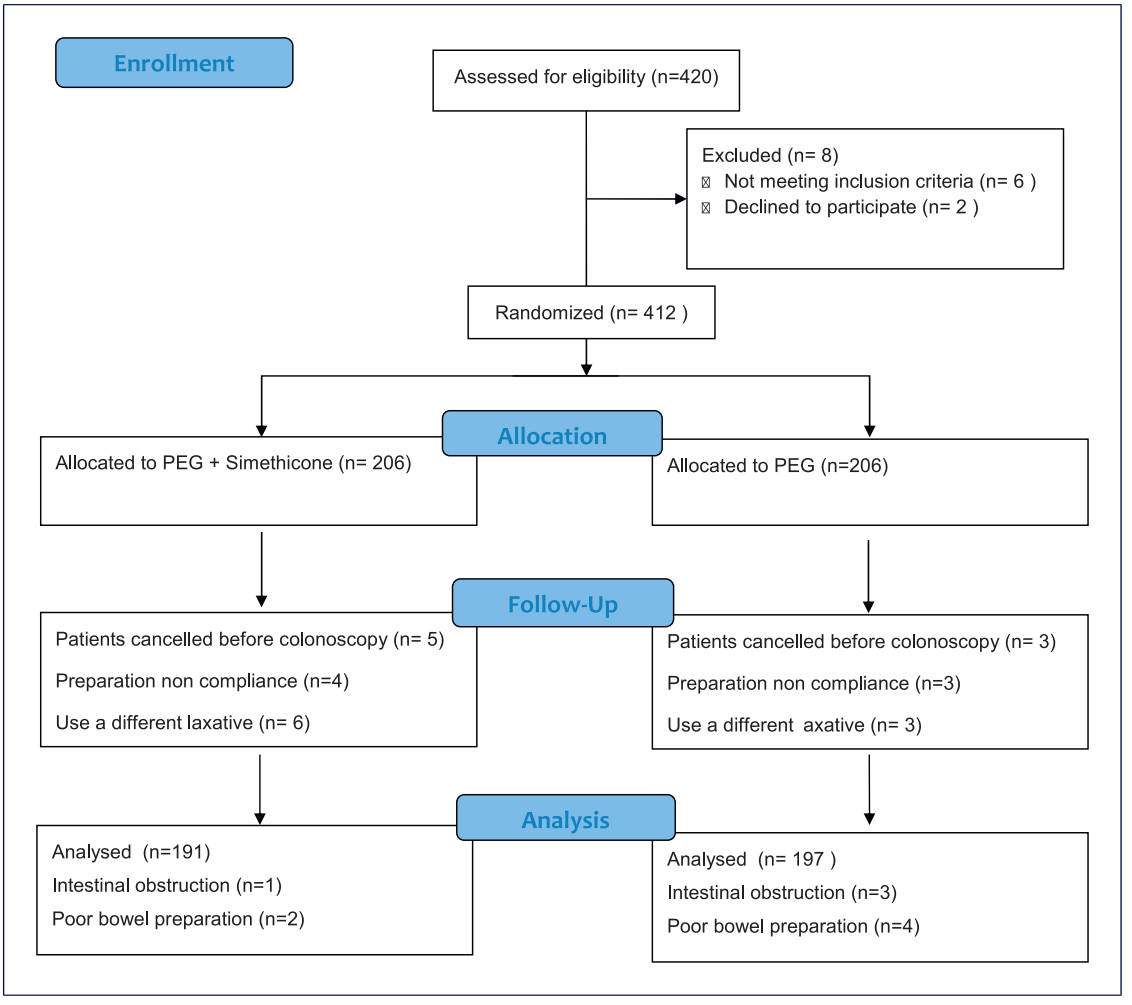

Fig. 2. Flow chart of patient recruitment and randomization. PP, per protocol; ITT, intention to treat.

Table 1. Baseline characteristics of patients included in the IIT analysis (n = 388)

	PEG + simethicone (n = 191)	PEG (n = 197)	p value
Gender, male, n (%)	100 (52)	112 (57)	0.37
Age, median (IQR), years	66 (12)	65 (13)	0.50
Diet non-adherence, n (%)	0 (0)	1 (0.5)	0.32
Reason for failed colonoscopy, n (%)			
Poor bowel preparation	1 (0.5)	4 (2.0)	0.25
Colon obstruction	2 (1.0)	4 (2.0)	

Regarding patient tolerance to the bowel cleansing regimen, no difference was found between the PEG plus simethicone group and the PEG alone group (p = 0.18). Moreover, the willingness to repeat the bowel cleansing regimen did not differ between the PEG plus simethicone group and the PEG group (8 [3] vs. 8 [3], p = 0.76), respectively.

Discussion

The main result of our study was that adding simethicone to a split-dose PEG regimen for bowel preparation significantly improved the visualization of the mucosa by presenting better bubbles scores and demanding less simethicone to flush the colon during the procedure,

Table 2. Colonoscopy indicators (ITT analysis, *n* = 388)

	PEG + simethicone (*n* = 191)	PEG (*n* = 197)	*p* value
Adequate preparation, *n* (%)	185 (97)	185 (93)	0.11
BBPS total, median (IQR)	9 (1)	9 (2)	0.70
BBPS per segment, median (IQR)			
Right colon	3 (1)	3 (1)	0.69
Transverse colon	3 (0)	3 (0)	0.38
Left colon	3 (0)	3 (0)	0.19
Bubble scale total, median (IQR)	0 (0)	2 (5)	<0.01
Bubble scale per segment, median (IQR)			
Caecum	0 (0)	0 (1)	<0.01
Ascending colon	0 (0)	0 (1)	<0.01
Transverse colon	0 (0)	0 (1)	<0.01
Descending colon	0 (0)	0 (1)	<0.01
Sigmoid colon and rectum	0 (0)	0 (1)	<0.01
CEBuS total, median (IQR)	0 (0)	1 (3)	<0.01
CEBuS, median (IQR)			
Right colon	0 (0)	0 (1)	<0.01
Transverse colon	0 (0)	0 (1)	<0.01
Left colon	0 (0)	0 (1)	<0.01
Intraprocedural use of simethicone	14 (7)	73 (37)	<0.01
ADR, *n* (%)	118 (62)	120 (61)	0.86
ADR at proximal colon, *n* (%)	83 (44)	78 (40)	0.47
ADR for diminutive lesions, *n* (%)	117 (61)	110 (55)	0.28
Polyp detection rate, *n* (%)	130 (68)	128 (65)	0.52
Adverse events			0.93
Post-polypectomy bleeding	3 (1.5)	2 (1)	
Post-polypectomy electrocoagulation syndrome	2 (1)	1 (0.5)	
Would repeat the scheme, median (IQR)	8 (3)	8 (3)	0.76
Adverse events during bowel preparation, *n* (%)			0.18
Headache	13 (6.8)	23 (11.7)	
Vomiting	5 (2.6)	11 (5.6)	
Nausea	9 (4.7)	8 (4.1)	
Bloating	10 (5.2)	4 (2.0)	
Caecal intubation rate, *n* (%)	188 (98)	190 (96)	0.14
Withdrawal time, median (IQR) in min	7 (2)	7 (2)	0.43

without compromising tolerance or side effects. However, it did not improve the quality of the bowel preparation as assessed by the BBPS, and the ADR did not differ between groups.

We found a significant difference in the mucosa visualization according to both bubble scale scores included in the study [15]. Previous studies have proven a significant reduction in bubble scale score when adding simethicone to bowel preparation, including with doses below 400 mg. However, the scales were subjective and had not been validated. This was the first study to use a validated bubble scale to prove the reduction of bubbles by adding simethicone to a PEG regimen [3, 4, 6, 17]. Another important finding of our study was the significant reduction of intraprocedural use of simethicone in the PEG plus simethicone group. This is of critical importance because recent studies have linked the intraprocedural use of simethicone to the transmission of multiple drug-resistant bacterial infections [18–20]. Although the available data have proven that there is association, although not causality, manufacturers, and the ESGE recommend that when simethicone is needed, it should be injected via the biopsy rather than the auxiliary water channel of the endoscope and at the lowest effective concentration [2, 7]. Our results showed a considerable reduction from 37% to 7% in the use of using simethicone by the channel during the colonoscopies.

Regarding the lack of improvement of the BBPS score, our result was in line with the results by Moraveji et al. [4] but differs from 3 Asian studies that found that simethicone significantly improved the BBPS [3, 6, 17]. However, some differences between our study and these

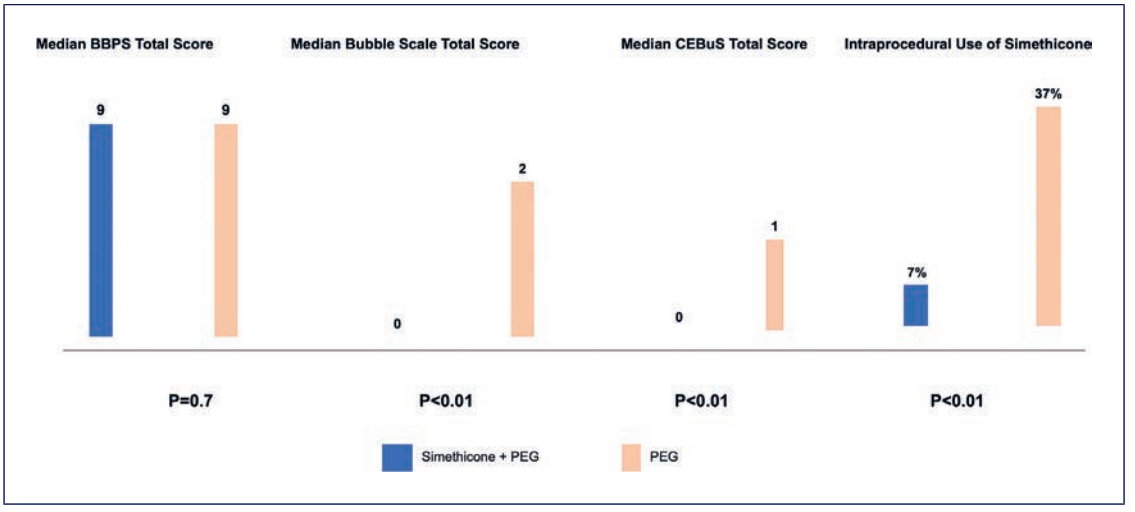

Fig. 3. Main results of the IIT analysis.

3 studies should be noted. These studies evaluated the effect of adding simethicone to low volume PEG solution without a split-dose regimen, the dose of simethicone was higher (1,200 mg), and colonoscopies were not performed in a screening setting. Moreover, the higher-than-expected proportion of adequate bowel preparation in our study should also be highlighted. The sample size was calculated for a 10% difference from 85% to 95%, whereas our control group showed 93%, hindering the study power.

Our data also show that adding simethicone to a PEG preparation did not result in an increase in ADR. Our outcome is in line with one RCT from the USA [4]. However, this result differs from another RCT from Asia specifically designed to establish a difference in the ADR. This study, which randomized patients to a 2-L PEG preparation, alone or in combination with simethicone, found a 7% increase in the ADR in the PEG plus simethicone group [3]. In another RCT from Asia, the ADR was 6% higher in the PEG plus simethicone group when a similar 2-L PEG preparation was used, although the study was not designed to establish a difference in ADR as a primary outcome [6]. The discrepancy between our results and the ones from Asia may be explained by the low-volume colon preparation agents used in those studies. Based on the available literature, it is reasonable to assume that the higher ADRs in their PEG plus simethicone groups on a 2-L PEG preparation seem to disappear once a 4-L preparation is used [4].

Regarding the tolerability and compliance, we did not find differences between groups. Our result is in line with most previous studies [4, 9].

Some limitations of our study are worth noting. Firstly, the simethicone dose (500 mg) was higher than the dose used in most studies included in the meta-analysis performed by Wu et al. [8] (<400 mg), which did not show a benefit of oral simethicone in bowel cleanliness and ADR. However, the simethicone dose is lower than two RCTs (1,200 mg) that demonstrated the effect of simethicone in bowel cleanliness and ADR [3, 6]. Secondly, the optimal timing of simethicone addition to PEG remains undetermined. In our study, simethicone pills were administered in a split-dose fashion as the laxative. Previous studies have used simethicone suspension and patients have been instructed to add it to the PEG container before drinking it [3, 4, 6]. Recently, one RCT including only morning colonoscopies demonstrated that simethicone addition to PEG in the evening of the day prior to colonoscopy can shorten caecal intubation time and improve bowel preparation and diminutive ADR in the right colon, compared with simethicone addition to PEG in bowel preparation in the morning of colonoscopy [9]. Thirdly, we reported a higher-than-expected proportion of adequate bowel preparations that could decrease the power of our study.

In summary, adding 500 mg of oral simethicone to a split-dose high volume PEG in a colonoscopy screening setting reduces the amount of bubbles in the colon, as evaluated by a validated bubble scale, and the intraprocedural use of simethicone but does not improve either the BBPS bowel preparation score or the ADR. Further studies are needed to define the effect of a higher dose of oral simethicone in a different schedule.

Statement of Ethics

All procedures were conducted in accordance with the ethical principles of the Declaration of Helsinki and the study protocol was approved by the local Ethics Committee. Written informed consent was obtained from all patients.

Conflict of Interest Statement

The authors have no conflicts of interest to declare. The authors have no disclaimers to disclose.

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Author Contributions

Mafalda João performed study conception design, data analysis and interpretation, drafting of the article, and final approval of the manuscript. Miguel Areia contributed with study conception design, data acquisition, manuscript drafting, and final approval of the intellectual content. Susana Alves, Luís Elvas, Daniel Brito, Sandra Saraiva, and Ana Teresa Cadime performed data acquisition, critical revision for intellectual content, and final approval of the manuscript. All authors agreed to be accountable for all aspects of the work ensuring questions related to the accuracy or integrity of any part of the work were appropriately investigated and resolved.

Data Availability Statement

The authors confirm that the data supporting the findings of this study are available within the article and its supplementary materials. Further enquiries can be directed to the corresponding author.

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Epithelioid Hemangioendothelioma in a Liver Transplant Recipient: A Case Report of an Extremely Rare Tumor

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Keywords
Liver transplantation · Epithelioid hemangioendothelioma · Cancer

Abstract
Epithelioid hemangioendothelioma is a very rare vascular neoplasm, which is often multifocal or metastatic at diagnosis. Most frequently arises in the liver, followed by the lung and bones. The authors present a case of a liver transplant recipient who developed a pattern of hepatic cholestasis associated with the appearance of a proliferative hepatic lesion with infiltrative growth. Histological examination and immunohistochemical study were compatible with the diagnosis of epithelioid hemangioendothelioma. Pulmonary micronodules were detected and lung metastases were hypothesized. Therefore, bronchoscopy was performed, which turned out to be normal, and cytology was negative for neoplastic cells. After a multidisciplinary discussion, liver re-transplantation was decided. After 8 years of follow-up, the patient is clinically stable, with no graft dysfunction, no neoplastic recurrence, and dimensional stability of the pulmonary micronodules.
Patients with organ transplant have higher risk of developing carcinoma compared to the general population. The development of cancer is a multifactorial process and little is known about the etiology of epithelioid hemangioendothelioma. No standard treatment strategy has been defined yet, and the natural course of the disease is heterogenous and the individual prognosis unpredictable. Complete surgical resection is offered to patients with unifocal disease, and those with unresectable disease should be evaluated for orthotopic liver transplantation.

Hemangioendotelioma epitelioide em doente com transplante hepático: um tumor extremamente raro

Palavras Chave
Transplante hepático · Hemangioendotelioma epitelioide · Tumor

Resumo
O hemangioendotelioma epitelióide é uma neoplasia vascular extremamente rara, muitas vezes multifocal ou metastática ao diagnóstico. O local mais frequente afetado é o fígado, seguido pelo pulmão e ossos. Os autores

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apresentam o caso de uma doente com antecedentes de transplante hepático que desenvolveu um padrão de colestase associado ao aparecimento de uma lesão hepática proliferativa e de crescimento infiltrativo. O exame histológico e o estudo imuno-histoquímico foram compatíveis com hemangioendotelioma epitelióide. Foram detetados micronódulos pulmonares, tendo sido colocada a hipótese de se tratarem de metástases pulmonares. Assim, foi realizada broncoscopia, que não revelou alterações, estando a citologia negativa para células neoplásicas. Após discussão multidisciplinar, foi decidido o retransplante hepático. Após 8 anos de seguimento, a doente encontra-se clinicamente estável, sem disfunção do enxerto, sem recidiva neoplásica e com estabilidade dimensional dos micronódulos pulmonares. Doentes submetidos a transplante têm maior risco de desenvolver neoplasias em comparação com a população geral. O desenvolvimento da neoplasia é um processo multifatorial, sendo a etiologia do hemangioendotelioma epitelióide ainda pouco compreendida. Não existe uma estratégia terapêutica standard, sendo o curso natural da doença heterogêneo e o prognóstico individual imprevisível. A ressecção cirúrgica é a primeira opção terapêutica nos doentes com doença unifocal, aqueles com doença irressecável devem ser avaliados para transplante hepático.

Introduction

Epithelioid hemangioendothelioma (EHE) is a very rare vascular neoplasm composed of epithelioid or histiocytoid cells with endothelial characteristics. EHE is usually diagnosed between 20 and 60 years, with a median onset of disease at the age of 36 [1, 2]. It is more common in women than in men, depending on the involved organ [3].

In the majority of these cases, EHE is multifocal or metastatic at diagnosis. EHE most frequently arises in the liver, followed by the lung and bones [4]. Presenting symptoms are often based on disease site: liver EHE may cause constitutional symptoms, nausea, abdominal pain, and jaundice. It may appear on computed tomography or magnetic resonance imaging as a solitary or multifocal mass [4].

The natural history of EHE is variable, ranging from indolent disease (similar to those with benign hemangiomas) to a more aggressive disease (similar to those with angiosarcoma). The majority of patients (50–76%) with

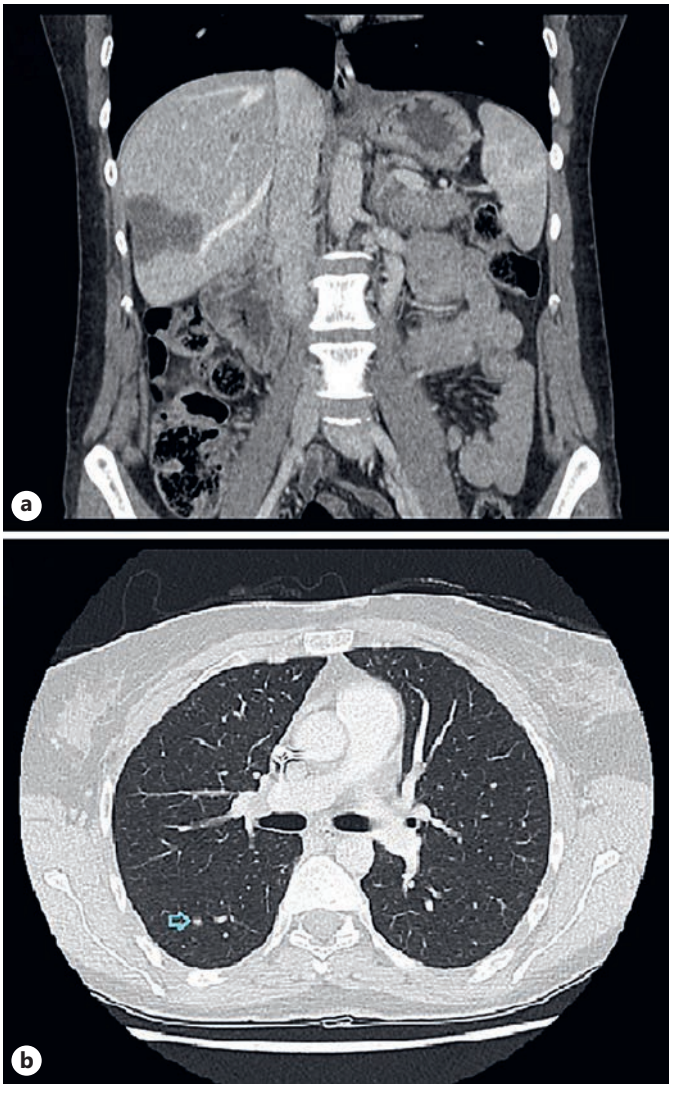

Fig. 1. a Several subcapsular hepatic lesions with hypovascular behavior, the largest with 43 mm and 23 mm. **b** Several micronodular lesions dispersed throughout both lungs' parenchyma, the largest with 3 mm.

EHE are asymptomatic at diagnosis, and the disease is incidentally detected during radiographic imaging [4]. Morphologically, EHE is characterized by epithelioid endothelial cells often organizing in strands and cords set in a collagenous stroma, and expressing endothelial differentiation markers, such as CD31, CD34, factor VIII–related antigen, ERG, and FLI-1 [5].

Case Report

The authors present the case of a 41-year-old female who underwent liver transplantation in 2003 due to symptomatic

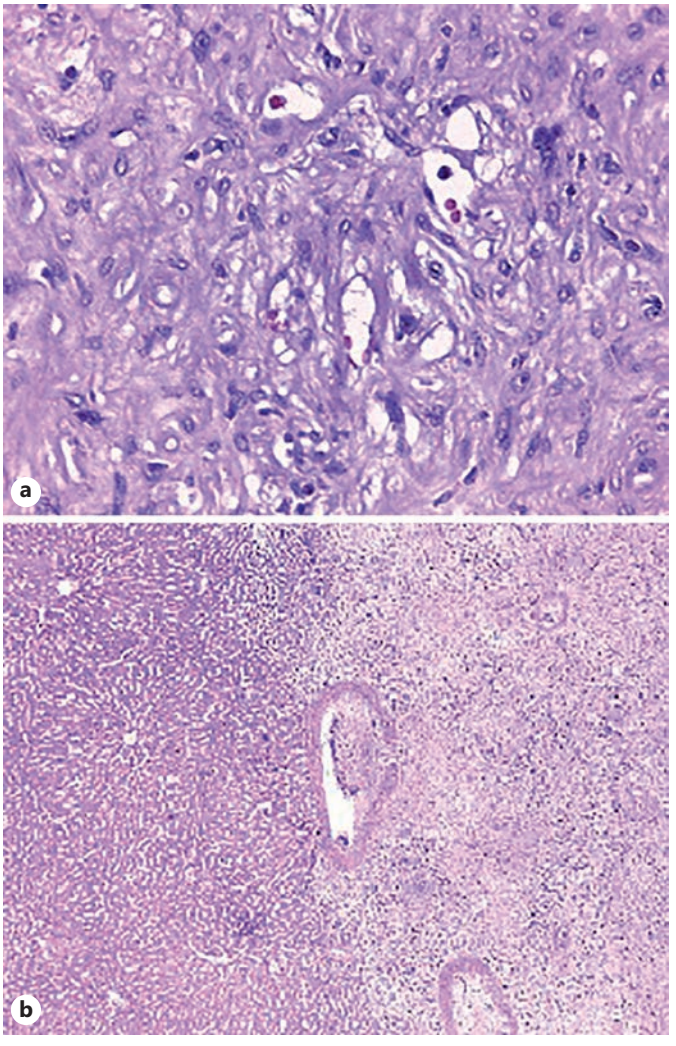

Fig. 2. a Proliferative lesion with infiltrative growth, consisting of predominantly epithelioid, monomorphic cells, with abundant cytoplasm with formation of vascular lumens. **b** Neoplasm of infiltrative borders constituted by fibromyxoid stroma whit spindle and epithelioid cells with moderate atypia.

familial amyloidotic polyneuropathy (dysautonomia and sensory polyneuropathy), immunosuppressed with cyclosporine. In March 2013, a routine analytical study revealed a discreet cholestasis pattern, with alkaline phosphatase of 151 U/L and gamma-GT of 75 U/L. The patient remained asymptomatic.

Three months later, the patient maintained a worsening pattern of cholestasis despite the increase of immunosuppression. In abdominal ultrasound, some nonspecific liver lesions were described. A thoracoabdominopelvic computed tomography was, then, performed, showing several subcapsular hepatic lesions with hypovascular behavior, the largest with 43 mm and 23 mm (shown in Fig. 1a). In the lung parenchyma, several micronodular lesions dispersed throughout both lungs were mentioned, the largest with 3 mm (shown in Fig. 1b).

An ultrasound-guided biopsy was performed and the histological examination revealed a proliferative lesion with infiltrative growth, consisting of predominantly epithelioid, monomorphic cells, with abundant cytoplasm with formation of vascular lumens (shown in Fig. 2a). The immunohistochemical study showed immunoreactivity of neoplastic cells for CD31, CD34, and factor VIII, thus favoring the diagnostic hypothesis of EHE. Bronchoscopy was normal and cytology was negative for neoplastic cells. The dose of cyclosporine was reduced and everolimus was started at a dose of 0.5 mg twice daily. The donor's medical record was reviewed: 20-year-old girl who's died of traumatic brain injury, without abdominal trauma or known medical history and with a normal abdominal ultrasound.

Throughout the 6-month follow-up, there was progression of liver lesions with dimensional stability of pulmonary micronodules, and graft function remained stable. After a multidisciplinary discussion, liver re-transplantation was decided, which was carried out in July 2014. Immunosuppression was restarted with tacrolimus, mycophenolate mofetil, and corticosteroids, and 2 months later everolimus was restarted, with progressive suspension of mycophenolate mofetil and corticosteroids.

The histological analysis of the explant showed a neoplasm of infiltrative borders constituted by fibromyxoid stroma whit spindle and epithelioid cells, moderate atypia, low mitotic index, and no necrosis, compatible with EHE (shown in Fig. 2b). Images suggestive of vascular invasion were also identified. After 8 years of follow-up, the patient is clinically stable, with no graft dysfunction, no neoplastic recurrence, and dimensional stability of the pulmonary micronodules.

Discussion

Compared with general population, patients with organ transplant have higher risk of developing carcinoma by 2.6 times [6]. The development of cancer is a multifactorial process. The effective immune system recognizes and attempts to eliminate primary tumors via cytotoxic T lymphocytes, macrophages, and natural killer cells, which can recognize tumor cells as nonself cells, delay tumor progression, and prevent angiogenesis, vascular infiltration, and metastasis [7]. The transmission of malignant tumors by donors, long-term exposure to risk factors, or potential carcinogenesis like the growth of age may be the inducing factors of tumors [8].

Therefore, the tumors of liver transplant recipients can be divided into four types: donor transmission cancer, donor-derived carcinoma, new cancer, and recurrent cancer [9]. In this particular patient, it is difficult to know if it is a donor-derived tumor or a new cancer.

In liver transplant recipients, minimization/modification of immunosuppression may be a key component of cancer prevention because the effect of immunosuppression on carcinogenesis seems to be dose-dependent [10]. However, the risk of rejection and the benefits of cancer prevention

need to be carefully weighed. Sirolimus and everolimus have potential antiproliferative properties and are considered to inhibit tumor growth, reducing the risk of death in transplant recipients with de novo malignancies by 76% [11].

Although some factors are believed to play a role in the etiology of hepatic EHE (alcohol consumption, asbestosis, oral contraceptive use), the reason for the onset of the disease is still unknown [1]. About 90% of all EHE have a t(1; 3) (p36; q25) translocation, resulting in the fusion gene WWTR1-CAMTA1 with high CAMTA1 activity [3]. The WWTR1-CAMTA1 rearrangement is a genetic hallmark of EHE and is not found in other vascular tumors [3]. In our patient, it was not possible to carry out the genetic test, so the diagnosis was made taking into account the immunohistochemical study, histological, and imaging characteristics.

No standard treatment strategy has been defined yet. Assumed the possible curative impact of local treatments and the risk of locoregional and/or systemic progression of EHE, at this state of knowledge, a prolonged watchful waiting policy for unifocal EHE is not suggested. Active surveillance should be considered only for patients who are not surgical candidates due to the presence of comorbidities or technical challenges [12].

Complete surgical resection is offered to patients with unifocal disease or disease limited to a few organs where surgery would not be overly morbid. Patients with unresectable disease that is symptomatic and/or progressive should be evaluated for orthotopic liver transplantation [13].

Unlike many other cancers, transplantation is a good option in metastatic disease. Limited and stable preexisting extrahepatic disease and lymph node invasion are not contraindications, as they do not appear to influence the prognosis nor have a negative impact on overall survival [13]. That said, despite not being 100% certain that it was a pulmonary metastatic disease, it was decided to go ahead with liver re-transplantation since the presence of pulmonary metastasis would not influence this therapeutic option. Long-term outcomes are excellent with transplant, with 10-year survival rates of approximately 74% [14].

Risk factors for EHE recurrence after transplant were pathologic evidence of macrovascular invasion, a waiting time from diagnosis to transplantation of less than 120 days, and involvement of hilar lymph nodes [14]. Longer waiting times from diagnosis to transplantation seem to be associated with a lower risk of recurrence, perhaps because of the more careful selection of patients with a better prognosis. According to Lerut et al. [15], 23.7% of patients undergoing liver transplantation (mean follow-up of 78.5 months) experienced recurrence of EHE.

Given the very limited activity of conventional chemotherapy in this disease and the absence of data suggesting a potential advantage in survival, neoadjuvant or adjuvant medical treatments are not recommended [16]. To our knowledge, this was the first case reported in the literature of an EHE of a liver transplant recipient effectively treated with liver re-transplantation.

Statement of Ethics

Ethical approval was not required for this study due to the retrospective design of the study, in accordance with local/national guidelines. Written informed consent was obtained from the patient for publication of the case and accompanying iconography. The authors declare that the procedures followed were in accordance with the World Medical Association Declaration of Helsinki.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

None.

Author Contributions

Margarida Gonçalves was responsible for drafting of the manuscript. Helena Pessegueiro, Judit Gandara, José Ramón Vizcaíno, Vitor Lopes, and Sofia Ferreira were responsible for the interpretation and critical revision of the work for important intellectual content. All authors approved the final version to be published and agreed to be accountable for all aspects of the work.

Data Availability Statement

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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Persistent Fever after COVID-19 Vaccination in a Patient with Ulcerative Colitis: A Call for Attention

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Keywords
Hemophagocytic lymphohistiocytosis · COVID-19 vaccination · Ulcerative colitis

Abstract
The development of vaccinations has been game-changing in the ongoing effort to combat the COVID-19 pandemic. Until now, adverse effects are being reported at low frequency, including thrombocytopenia and myocarditis. Careful monitoring for any suspicious symptoms and signs following vaccination is necessary. We report a case of hemophagocytic lymphohistiocytosis (HLH) after mRNA COVID-19 vaccine in a 23-year-old female with ulcerative colitis. Diagnosis was made according to HLH-2004 criteria and the patient was treated with dexamethasone with response. Our report aimed to draw attention to the potential relation between COVID-19 vaccines and HLH and the necessity of continued surveillance, especially in at-risk populations such as those with underlying immune dysregulation.

Febre persistente após vacinação contra a COVID-19 numa paciente com colite ulcerosa: uma chamada de atenção

Palavras Chave
Linfohistiocitose hemofagocítica · Vacinação COVID-19 · Colite ulcerosa

Resumo
O desenvolvimento de vacinas foi um ponto de viragem no combate contra a pandemia da COVID-19. Até ao momento, os efeitos adversos como a trombocitopenia e miocardite têm sido reportados com baixa frequência. A monitorização cuidadosa de qualquer sinal ou sintoma suspeitos é essencial. Reportamos um caso de linfohistiocitose hemofagocítica após vacinação contra a COVID-19 com uma vacina de mRNA, numa jovem de 23 anos com colite ulcerosa. O diagnóstico obedeceu os critérios HLH-2004 e a paciente foi tratada com dexametasona, com resposta. Pretendemos chamar à atenção para a potencial relação entre a vacinação

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para a COVID-19 e a HLH e a necessária contínua vigilância, especialmente em populações de maior risco, como as portadoras de doenças imuno-mediadas.

Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a highly fatal condition that is being increasingly recognized in adults. Diagnosis and management remain challenging. Fever, cytopenias, coagulopathy, and hepatosplenomegaly are hallmark findings. Identifying the trigger event is crucial but can be quite difficult due to the diverse presentations and the scarce clinical experience of most physicians with this syndrome. The primary treatment goal is to eradicate the underlying precipitating factor and suppress the massive inflammatory response with steroids, immunoglobulins, or immunomodulators.

Case Report

A 23-year-old woman with ulcerative colitis diagnosed in 2018, Montreal type E3, presented to the hospital with fever and arthralgias. She had received a first dose of the COVID-19 mRNA vaccination (BNT162b2 mRNA vaccine) 15 days previously. Management of her ulcerative colitis had been complicated in the past by the development of HLH secondary to cytomegalovirus (CMV) infection in 2019, treated with antiviral therapy (ganciclovir/valganciclovir). She had been in remission since then under vedolizumab therapy. She had no other comorbidities and medications besides vitamin D supplementation. She is a social worker and had an unremarkable travel history and unknown family history of connective tissue or autoimmune diseases. Her single brother has Crohn's disease. The patient had no risky sexual behavior or history of substance use and maintained regular contact with a domestic cat.

Her symptoms progressed despite antipyretics, and she was admitted to the hospital. She was still in good physical condition and described no gastrointestinal symptoms. The fever ranged between 39 and 40°C without any evident daily pattern. Physical examination revealed painless splenomegaly but no palpable lymphadenopathy and there was no rash, swelling of joints, or synovitis. On presentation, she had mild normocytic and normochromic anemia (Hb 11.7 g/dL), leukopenia (3.1×10^9/L), normal platelet count, C-reactive protein of 97.9 mg/L, elevated lactate dehydrogenase of 415 U/L, hyperferritinemia of 449 ng/mL, erythrocyte sedimentation rate of 31 mm/h, aspartate aminotransferase of 64 U/L, alanine aminotransferase of 31, and mild hypoalbuminemia (32.0 g/L). Other indicators of hepatic and renal function were normal. Chest X-ray was normal. Admission electrocardiography showed sinus tachycardia. A nasopharyngeal aspirate for COVID-19 (real-time polymerase chain reaction assay) and other respiratory viral infections was negative. Blood cultures (aerobes, anaerobes, fungi, mycobacteria), urinalysis, stool samples, pneumococcal, Legionella urinary antigen tests, and interferon gamma (QuantiFERON®) were negative. Epstein-Barr, varicella zoster virus, parvovirus B19, HIV, and hepatitis B and C serologies showed no evidence of active infection. Q fever and rickettsial serologies were negative. Antinuclear antibodies, anti-Sm, and anti-dsDNA were all within the reference ranges. A rectosigmoidoscopy was performed and showed no signs of endoscopic activity. Biopsies were taken and immunochemistry for herpesvirus and CMV was negative. Fecal calprotectin on day 2 was negative and stool cultures were negative too.

CMV serology detected low IgM and IgG antibody titers, and intravenous ganciclovir (5 mg/Kg twice daily) was started concerning a possible CMV reactivation. Cat scratch disease was deemed as a diagnostic possibility as the patient maintained a regular contact with a cat, so we decided to pursue a therapeutic challenge with doxycycline. However, after 10 days, there was no clear clinical or biochemical response, the quantitative PCR obtained at this time revealed no cytomegaloviremia, and the patient felt sick and feverish. A chest-abdomen-pelvis computed tomography demonstrated submental, submandibular, and bilateral axillary lymphadenopathy, hepatomegaly, and splenomegaly of 16.5 cm, without an evident focus of infection (Fig. 1). Positron emission tomography scan showed hepatosplenomegaly and heterogeneous uptake of 18-FDG diffusely involving the axial and proximal appendicular skeleton, suggesting medullary reactivity. Therefore, there were no functional changes suggestive of high-grade metabolic malignancies or active sarcoidosis. A peripheral blood smear revealed few leucocytes and platelets but no blasts. A bone marrow biopsy demonstrated occasional stromal macrophages but no evidence of hemophagocytosis. Echocardiogram showed normal biventricular systolic function without evidence of endocarditis.

Hyperferritinemia of 1,383 ng/mL, soluble CD25 elevated at 2,558 U/mL (negative control 758 U/mL), and fasting triglyceride level elevated at 415 mg/dL (4.69 mmol/L) were noted on the patient's 15th day of hospitalization. In addition, her liver test values had increased with ALT of 141 U/L, AST of 70 U/L, GGT of 244.4 U/L, and ALP of 52 U/L. A percutaneous hepatic biopsy was performed and showed liver with normal trabecular architecture with multifocal steatosis (Fig. 2).

Taking into account the whole clinical picture of high-grade fever, hepatosplenomegaly, hyperferritinemia, hypertriglyceridemia, soluble CD25 elevation, and bicytopenia in the absence of evidence for infection or malignant disease, a diagnosis of an HLH presumptively secondary to recent COVID-19 vaccination was made. Intravenous dexamethasone (10 mg/m^2 daily) was started. She became apyretic 48 h after starting steroids and concurrent symptomatic and biochemical improvements were observed. The patient was discharged home after 30 days to continue her recovery on a weaning course of oral prednisolone. Genetic testing for PRF1, STX11, STXBP2, UNC13D, DCLRE1C, RAG1, and RAG2 was requested, albeit it was not positive for any of these mutations.

Discussion

HLH is a syndrome of hyperinflammation and tissue damage due to irregular immune activation. The dysregulated immune state is thought to be caused by the lack of normal downregulation by natural killer cells and/or

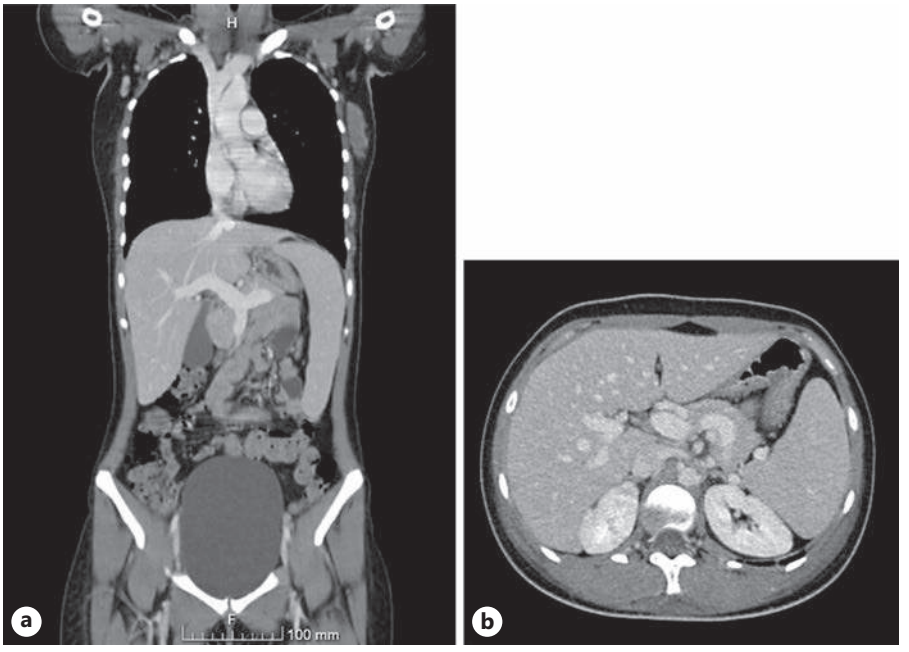

Fig. 1. Chest-abdomen-pelvis computed tomography. **a** Coronal view. **b** Axial view. Obvious hepatomegaly and splenomegaly without an evident focus of infection.

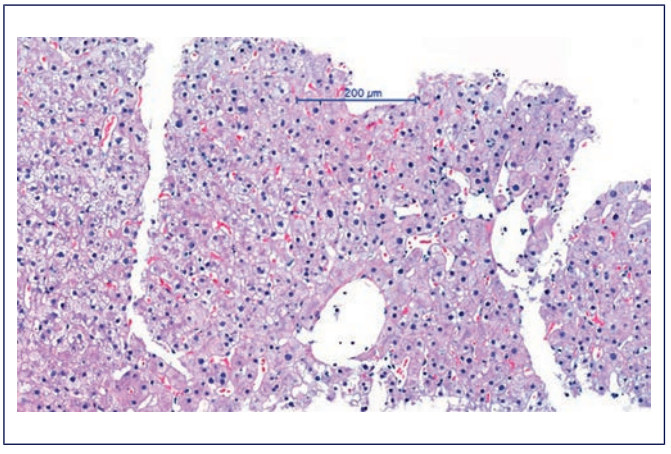

Fig. 2. Liver biopsy findings: normal trabecular architecture with multifocal steatosis but without evidence of bile duct or necro-inflammatory lesions or hemophagocytosis (HE, ×20).

cytotoxic T lymphocytes which fail to eliminate activated macrophages [1]. This absence of a normal feedback response leads to disproportionately stimulated benign macrophages in all reticuloendothelial organs such as the spleen, liver, bone marrow, and lymph nodes, with secretion of a huge amount of cytokines like tumor necrosis factor-α (TNF-α), interferon gamma (IFN-γ), interleukin-6 and -10, and macrophage colony-stimulating factor [2]. These pro-inflammatory mediators invade normal tissues, causing histiocytic hemophagocytosis, cytokine storm, and cytokine-mediated biochemical modifications, ultimately resulting in blood vessel destruction and tissue necrosis. Eventually, multiorgan dysfunction and disseminated intravascular coagulation can establish [3], and if not diagnosed and treated promptly, they may be lethal in virtually all cases [4].

Patients with HLH may have a single episode or relapsing episodes, the last ones occurring most frequently in familial HLH [5]. Up to one quarter of HLH cases are thought to be familial [5]. The genetic forms include mutations in CD8+T cells and natural killer cells that result in a loss of performance in the cytolytic pathway proteins (Table 1) and mutations associated with primary immunodeficiency syndromes (Table 2). The acquired form is associated with infections (viruses, bacteria, fungi, and parasites), hematologic and solid malignancies (such as Hodgkin and non-Hodgkin lymphomas), autoimmune diseases (such as systemic lupus erythematosus and seronegative spondyloarthropathies) [9]. Viral infection, particularly Epstein-Barr virus, is the most frequent trigger, either as a primary infection in healthy individuals or after reactivation in patients with a weakened immune system [10].

Infants are most affected with the highest incidence in those with less than 3 months. In adulthood, there may be a slight male susceptibility [10, 11], although the incidence rate in adults is not known [2].

Table 1. Gene mutations associated with familial HLH [6–8]

Disease	Genetic mutations
FHL 1	Unknown
FHL 2	PRF1/perforin
FHL 3	UNC13D/Munc13-4
FHL 4	STX11/syntaxin 11
FHL 5	STXBP2/Munc18-2

FHL, familial hemophagocytic lymphohistiocytosis.

The Histiocyte Society proposed clinical and laboratory criteria to help establish the diagnosis of HLH. The diagnosis is established if a patient has a positive genetic mutation or meets at least 5 of 8 criteria [6] (Table 3). A bone marrow biopsy may be performed for patients at high risk or with suspected malignant disease. Genetic testing is indicated in all patients who fulfill the diagnostic criteria for HLH and in those with a high probability of HLH based on the initial evaluation to rule out hereditary HLH mutations.

HLH usually presents as an acute or subacute febrile syndrome associated with hepatosplenomegaly and cytopenias, but none of these characteristics is specific [7]. Some patients may experience recurrent fever of unknown origin and manifest only a subset of the diagnostic criteria.

Typical laboratory results in HLH include high ferritin, triglycerides, transaminases, bilirubin (mostly conjugated), and sCD25 (α-chain of the soluble interleukin-2 receptor) and decreased fibrinogen [7]. A relatively normal ferritin can occasionally be seen in HLH genetic syndromes, even during a disease flare. Hemophagocytosis supports the diagnosis but is neither pathognomonic of nor required for the diagnosis of HLH and can be detected in biopsies of lymph nodes, spleen, liver, or bone marrow aspirates/biopsies. Some patients may show hemophagocytosis only later in the illness course, even if they are clinically improving [7, 8].

Most patients with HLH have hepatitis varying from mildly elevated transaminases to hepatic failure. Liver dysfunction translates into abnormal coagulation with the most frequently reported abnormality being a decrease of fibrinogen levels. Disseminated intravascular coagulopathy is also frequently observed [12]. Increased tumor necrosis factors and chronic inflammation decrease lipoprotein lipase activity, causing high triglyceride levels and cholesterol imbalance [13], but this may not be noticeable until the liver has been affected for some time [14]. Liver biopsy may show an inflammatory hepatitis-like periportal infiltrate in the liver with lymphocytes and histiocytes, explaining the possibility of obstructive jaundice [7].

One-third of patients with HLH may develop neurological alterations such as decreased consciousness, ataxia, seizures, and cranial nerve abnormalities [1, 2]. Other pathophysiological changes of hyperinflammation may be increased capillary permeability with edema and development of acute respiratory distress syndrome, severe hypotension demanding vasopressor support, and renal failure. Skin manifestations such as rashes, petechiae and purpura may also be apparent [3].

The natural history of untreated HLH syndrome is almost uniformly fatal. Prompt recognition of the HLH syndrome and diagnosis of the underlying cause of HLH disease are critical to enabling urgent and appropriate treatment. The fundamental principle of management of HLH includes a short-term strategy to control the hyperinflammatory state, using chemotherapeutic agents, immunosuppressants, and targeted biologic agents, and aims to eliminate activated T cells and macrophages and dampen the cytokine storm. Glucocorticoids are standard, and for patients where cytotoxic therapy is thought to be necessary, the etoposide-based HLH-94 and -2004 protocols and CHOP are commonly used [15]. In patients with genetic-linked HLH, the disorder can be completely eradicated only by hematopoietic stem cell transplantation [16]. Treatment for secondary HLH includes both immunosuppressive therapy and treatment of the underlying disorder, such as infection and malignancy [16]. Survival in HLH is heterogeneous and malignancy/lymphoma-associated HLH is associated with poor outcomes.

Although rare, IBD patients are theoretically at risk of developing HLH, provided the appropriate treatment makes them susceptible to opportunistic infections and malignancies [17]. In fact, opportunistic infection or malignancy was found in more than 80% of all known IBD patients with at least some biologic exposure who developed HLH in a recent systematic review [18]. Studies reporting HLH occurring in IBD show a more frequent occurrence of HLH in patients with Crohn's disease compared to UC [18, 19], yet the reason behind this susceptibility is not known. In this particular patient, in addition to biologic therapy with vedolizumab, genetic predisposition was another concern raised upon this second episode of HLH, once presentation at a late age, even in adulthood, can occur [20].

Table 2. Immunodeficiency syndromes associated with an increased incidence of HLH [6–8]

Disease	Genetic mutations
Griscelli syndrome	RAB27A
Chediak-Higashi syndrome	CHS1/LYST
X-linked lymphoproliferative disease	SH2D1A; XIAP
XMEN disease	MAGT1
Interleukin-2-inducible T-cell kinase deficiency	ITK
CD27 deficiency	TNFRSF7
Hermansky-Pudlak syndrome	HPS1, AP3B1 (HPS2), HPS3, HPS4, HPS5, HPS6, DTNBP1 (HPS7), BLOC1S3 (HPS8), BLOC1S6 (PLDN)
Lysinuric protein intolerance	SLC7A7
Chronic granulomatous disease	CYBA, NCF1, NCF2, NCF4

Table 3. Diagnostic criteria for HLH (if ≥5 criteria) [1]

1	Fever ≥38.5°C
2	Splenomegaly
3	Cytopenia with at least two of the following: (a) Hb <9 g/dL, (b) thrombocytes $<100 \times 10^9$/L, (c) absolute neutrophil count $<1.0 \times 10^9$/L
4	Hypertriglyceridemia (fasting triglycerides ≥265 mg/dL/≥3.0 mmol/L) and/or hypofibrinogenemia (fibrinogen ≤1.5 g/L)
5	Hemophagocytosis in bone marrow, spleen, liver, or lymph nodes
6	Low or absent NK cell activity
7	Ferritin >500 ng/mL
8	Soluble CD25 (IL2-receptor alpha) ≥ 2,400 U/mL

NK, natural killer.

The duration between vaccination and the onset of symptoms in this case was in accordance with other reports. The mean duration between diagnosis of underlying HLH trigger and occurrence of first symptoms is around 10 days [9] and probably correlates with the innate cytokine signature triggered within days after COVID-19 vaccination. The exact mechanisms of COVID-19 vaccination-related HLH remain unknown, but it is recognized that immune stimulation by mRNA- or DNA-based vaccines may elicit a massive cytokine storm, which may result in HLH [21]. T-cell activation through antigen stimulation plays a role in HLH pathogenesis and it is likely that T-cell expansion after vaccination could lead to increased IFN-γ production and bystander activation triggering pathologic inflammation [22]. IL1-1β is a pro-inflammatory cytokine largely involved in the hyperinflammation syndrome caused by COVID-19 [23] and its secretion can be stimulated by SARS-CoV-

2 spike protein in macrophages. Hence, a potential influence of IL1-1β hyperinflammation syndrome after mRNA SARS-CoV-2 vaccination is a likely mechanism. Molecular mimicry and a potential immune response mediated by anti-spike antibodies have also been implicated [24].

The occurrence of HLH after vaccination is a very rare condition, but it has been described for other vaccines, such as influenza [25, 26], measles [27], and BCG vaccination [28]. There are reports of HLH following other types of COVID-19 vaccines like the ChAdOx1 AstraZeneca® vaccine [29, 30] and inactive vaccine [31]. So far, up to 100 cases of HLH have been temporally associated to COVID-19 vaccination according to Vaccine Adverse Event Reporting System (VAERS) database [32], strengthening the potential relation between COVID-19 vaccination and HLH development. To the best of our knowledge, this is the first case in the literature of HLH after COVID-19 vaccination in a patient with IBD under biological therapy.

With this case, we highlight the need of awareness of the clinical syndrome of HLH to rapidly be able to instigate diagnostic evaluations and early treatment. While the benefits of vaccination are unquestionable and it should be undoubtedly encouraged, close follow-up is needed, especially in individuals with immune dysregulation, as demonstrated in this case.

Statement of Ethics

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

Conflict of Interest Statement

Paula Ministro received consulting fees and support to travel to meetings from the following companies: AbbVie, Falk Pharma, Ferring, Pfizer, Takeda, and Janssen. The remaining authors have no conflict of interests to declare.

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Author Contributions

Analysis of the case, review of the literature, and draft preparation: Cláudio Melo Rodrigues. Critical revision of the article for important intellectual content: Paula Ministro. Approval of the final version to be published: all listed authors.

Data Availability Statement

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

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Endoscopic Snapshot

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Hepaticoduodenostomy in Combined Endoscopic Ultrasound-Endoscopic Retrograde Cholangiopancreatography Biliary Drainage for Malignant Hilar Biliary Obstruction

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Keywords
Combination of endoscopic ultrasound and endoscopic retrograde cholangiopancreatography · Hepaticoduodenostomy · Malignant hilar biliary obstruction

Hepatoduodenostomia em drenagem biliar combinada por EUS-CPRE para obstrução biliar hilar maligna

Palavras Chave
Combinação de ecoendoscopia e colangiopancreatografia retrógrada endoscópica · Hepatoduodenostomia · Obstrução biliar hilar maligna

Endoscopic ultrasound biliary drainage (EUS-BD) has been increasingly used in the management of malignant biliary obstruction together with endoscopic retrograde cholangiopancreatography (ERCP). Drainage of ≥50% of hepatic volume is associated with an increase in survival and lesser risk of cholangitis, and bilateral drainage in hilar stenosis results in fewer reinterventions [1, 2]. When the left biliary system is drained through the papilla, EUS-guided hepaticoduodenostomy (EUS-HDS) is a difficult procedure that can be used to access the right system [3]. Combination of EUS-BD and ERCP (CERES) is in increasing development, particularly when the left and right biliary systems are noncommunicating [3, 4]. The authors present a case of EUS-HDS in the right hepatic duct combined with left hepatic duct stenting by ERCP in malignant hilar biliary obstruction (Fig. 1; online suppl. video; for all online suppl. material, see https://doi.org/10.1159/000530977).

A 60-year-old female patient with unresectable cholangiocarcinoma and hilar stricture (Bismuth type IV), with previous drainage of a technically difficult stricture of the left hepatic duct with a plastic stent, developed obstructive jaundice due to disease progression, incompatible with palliative chemotherapy. An ERCP was performed with plastic stent replacement in the left hepatic duct (Fig. 2a). Right hepatic duct stenting was not possible due to impossibility of passing a guidewire; cholangioscopy assistance was assumed to provide no further benefit because we were facing a very tight stricture, so EUS-BD was performed. EUS showed a dilated right hepatic duct (7.4 mm) (Fig. 2b). The right hepatic duct was punctured (Expect™ 19 G, Boston Scientific, Boston, USA), with confirmation by cholangiography (Fig. 3a). After guidewire introduction through the puncture site (Jagwire™ 0.0025″, Boston

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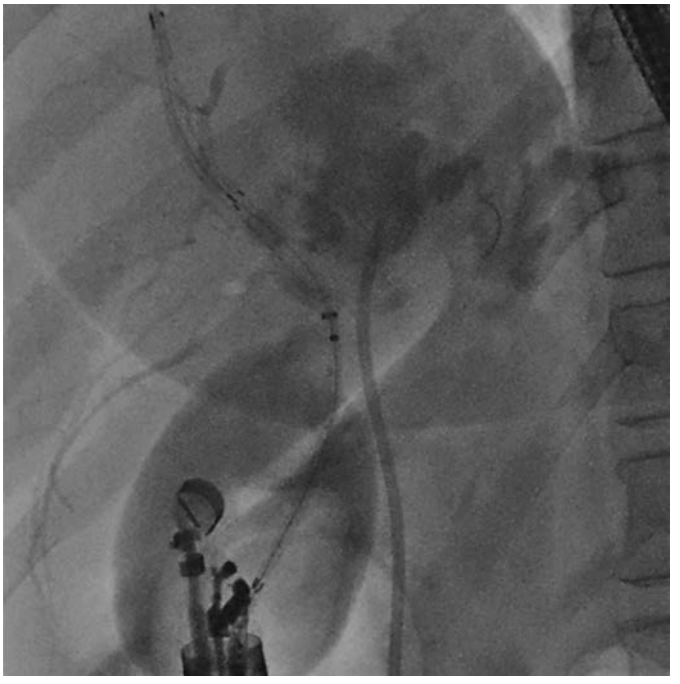

Fig. 1. Combined EUS-BD and endoscopic retrograde cholangiopancreatography in a malignant hilar biliary obstruction, restenting the left hepatic duct and hepaticoduodenostomy on the right hepatic duct, achieving bilateral drainage. EUS: after guidewire introduction, a hybrid metallic stent was placed between the right hepatic duct and the duodenal bulb.

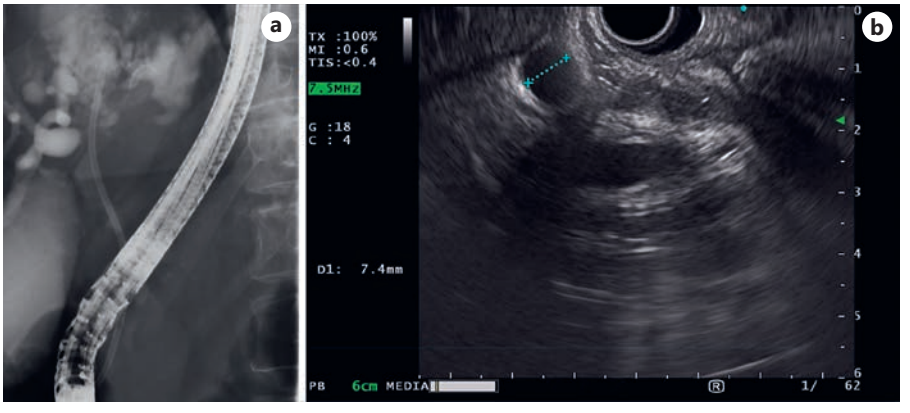

Fig. 2. a Cholangiography after plastic stent replacement in the left hepatic duct. **b** Dilated right hepatic duct.

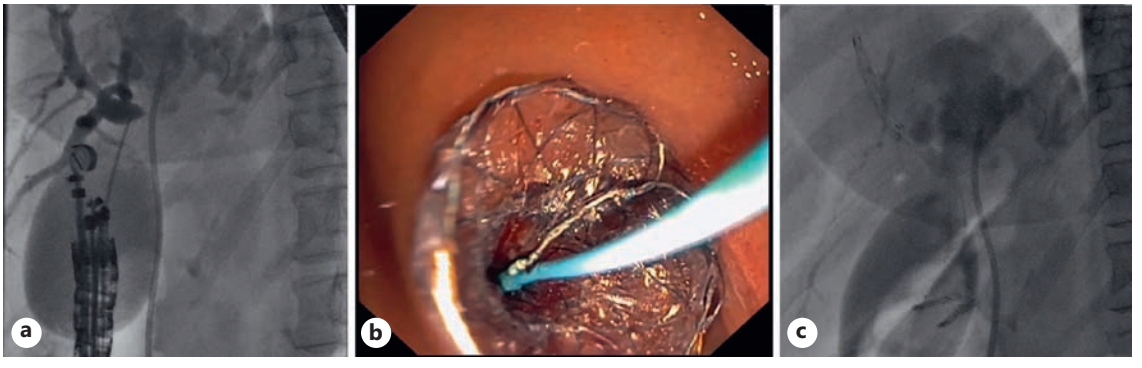

Fig. 3. a Right hepatic duct puncture confirmation by cholangiography. **b** Hybrid metallic stent placement between the right hepatic duct and the duodenal bulb. **c** Cholangiography after bilateral biliary drainage with hepaticoduodenostomy in the right hepatic duct and plastic stent on the left hepatic duct.

Scientific, Boston, USA), the needle was retrieved and a hybrid metallic stent (BPD HANAROSTENT® biliary [NC], 10*80 mm, M.I.Tech, Pyeongtaek-si, Gyeonggi-do, Republic of Korea) was placed between the right hepatic duct and the duodenal bulb (Fig. 3b, c). The stent delivery system was passed through the puncture site without the need of using a cautery or balloon dilation to create the tract. The uncovered intra-hepatic segment of the stent prevents stent migration; to further minimize the risk of migration, two through-the-scope clips (Resolution™, Boston Scientific, Boston, USA) were applied on the duodenal extremity. No adverse events were observed. Jaundice resolved, with no need for further procedures during the follow-up of 5 months.

Percutaneous transhepatic biliary drainage (PTBD) could be an alternative to EUS-HDS in the present case. PTBD requires an external drainage which disrupts the patient's quality of life, making CERES an internal and elegant solution. Preliminary data of the clinical outcomes of CERES in malignant hilar biliary obstruction have shown significantly lower recurrent biliary obstruction rates compared to PTBD, with a similar complication rate and no significant mortality difference [4, 5].

Statement of Ethics

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

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

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

Data Availability Statement

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

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A Rare Endoscopic Finding – Swiss Cheese Esophagus

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Keywords
Dysphagia · Esophageal pseudodiverticulosis · Esophageal stricture

Pseudodiverticulose esofágica – um queijo suíço

Palavras Chave
Disfagia · Pseudodiverticulose esofágica · Estenose esofágica

A 54-year-old male was referred to a gastroenterology appointment with a 15-year history of dysphagia. He had a medical history of metastatic lung adenocarcinoma and is currently under pembrolizumab treatment. He was an active smoker (63 pack-years) and drank 10 alcohol units a day. He presented with progressive dysphagia to solids and, in the last 4 years, intermittent for liquids, with progressive weight loss (10% of body weight loss in the past 6 months) with a body mass index of 16.8 kg/m^2. He was previously assessed in different hospitals and performed numerous exams, including upper endoscopy showing a sloughing esophageal mucosa with signs of candida infection and narrowing of the distal esophagus. Histopathology was compatible with esophageal candidiasis with unspecific chronic inflammation. He underwent several endoscopic dilations, the last one roughly 12 years before, with later symptom recurrence and was lost to follow-up. An upper endoscopy performed in our center displayed esophageal pseudodiverticulosis (EP) with distal strictures with underlying regular mucosa that were not transposable by the endoscope (Fig. 1). Esophageal biopsies excluded eosinophilic esophagitis. The patient was advised for lifestyle changes, including smoking cessation and alcohol abstinence. He underwent endoscopic dilation of two distal esophageal strictures using a through-the-scope balloon, with prior intralesional steroid injection (2 mg of dexamethasone into each quadrant), up to 15 mm diameter (shown in Fig. 2), with initial dysphagia improvement and weight gain. Afterward, a proton pump inhibitor was initiated in order to reduce stricture recurrence. At 3-month follow-up, the patient had symptom relapse, namely, dysphagia for solids, and was proposed to an additional endoscopic dilation.

EP is a rare condition characterized by multiple outpouching lesions of the esophageal wall, representing dilated ducts of submucosal glands [1]. Inflammation and increased intramural pressure are thought to be the main mechanisms behind these false diverticula [2]. Distribution can be segmental or diffuse [2]. Etiology is still unclear, but tobacco smoking and alcohol consumption appear to be risk factors [1, 3]. Other associations include candida infection, caustic ingestion, gastroesophageal reflux disease, or diabetes mellitus [1, 2]. The most typical

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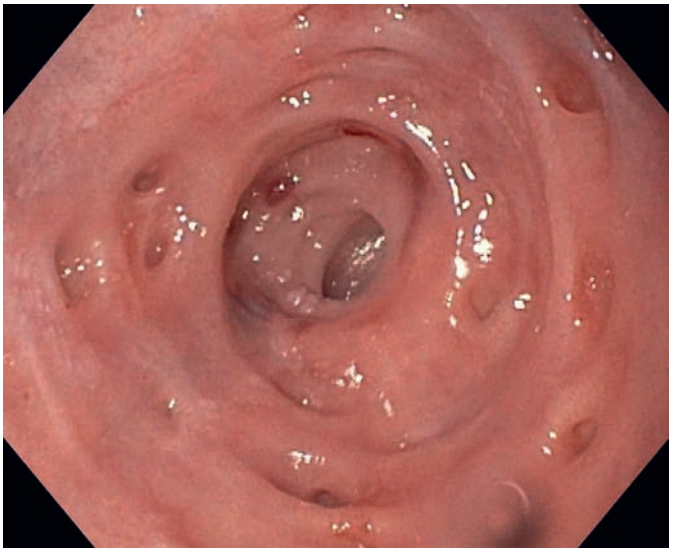

Fig. 1. Distal esophagus with pseudodiverticulosis and a regular esophageal stricture.

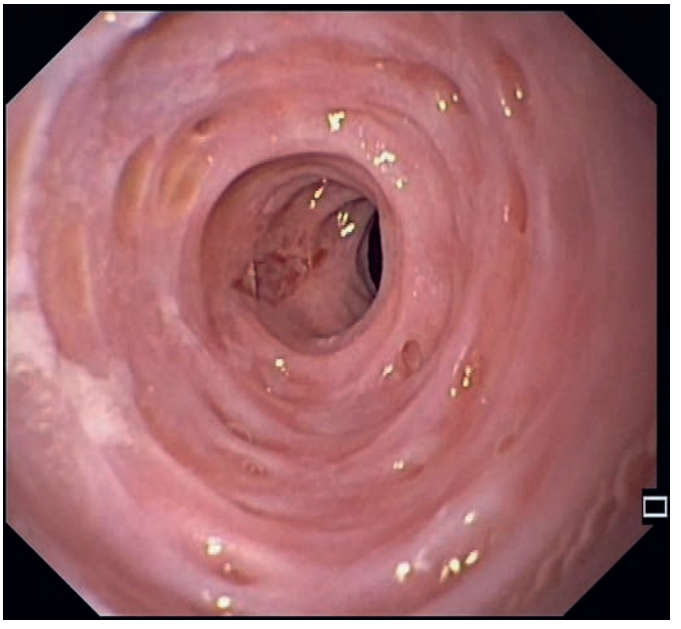

Fig. 2. Post-dilation stricture.

symptom is chronic dysphagia, which can be constant, intermittent, or progressive, classically for solids, and can persist for years [2, 3]. This symptom is usually associated with other conditions, such as esophageal stricture or candidiasis, rather than attributable to the EP [1, 2]. In the present case, a distal stenosis causing an increased intraluminal pressure is a possible mechanism for this endoscopic finding, as the outpouchings were not previously described and appeared over the course of a long-standing stricture. Endoscopy is significant for excluding coexisting disorders, especially in a patient presenting with dysphagia; however, barium studies are more sensible in diagnosing EP [2, 4]. Treatment is mainly supportive and should be directed at the underlying condition, with elimination of risk factors and control of associated comorbidities [1, 2]. In the presence of an esophageal stricture, dilation has been reported to be an effective and safe procedure, providing symptomatic improvement, with up to 57% requiring multiple procedures [2, 4].

Statement of Ethics

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

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

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Author Contributions

Inês Simão, Rui Mendo, and Pedro C. Figueiredo contributed to manuscript concept and design; Inês Simão drafted the manuscript; Rui Mendo and Pedro C. Figueiredo 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 Snapshot

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Underwater Endoscopic Mucosal Resection for a Terminal Ileum Adenoma

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Keywords
Adenoma · Crystal violet · Endoscopic mucosal resection · Ileum · Narrow band imaging

Resseção endoscópica subaquática de adenoma ileal

Palavras Chave
Adenoma · Violeta cristal · Ressecção endoscópica da mucosa · Íleo · Narrow band imaging

Tumors of the terminal ileum are rare, and their diagnosis and treatment standards have not been established. The effectiveness of underwater endoscopic mucosal resection (UEMR) in the duodenum and colon has been reported [1, 2]; however, its effectiveness in the small intestine is rarely reported [3]. We present a case of an ileum adenoma diagnosed using magnifying endoscopy and completely resected using UEMR (online supplementary video; for all online suppl. material, see https://doi.org/10.1159/000531774).

A 56-year-old woman with a lesion in the terminal ileum was referred to our hospital for treatment. Colonoscopy revealed a 10 mm slightly depressed lesion with marginal elevation in the terminal ileum (Fig. 1a, b). Magnifying narrow-band imaging showed a tubular surface pattern with regular vessels on the slightly elevated marginal area and regular brown vessels on the slightly depressed central area (Fig. 1c). Magnifying chromoendoscopy using crystal violet staining showed a branch-like or gyrus-like pattern on the marginal area and a roundish and tubular structure on the central area (Fig. 1d). The lesion was diagnosed as an adenoma in the terminal ileum, similar to a colonic adenoma; hence, we decided to perform UEMR. The lesion was completely removed using a 10 mm snare (10 mm, Captivator II; Boston Scientific, Marlborough, MA, USA) with an electric generator (Endocut Q effect 2, interval 1, duration 4; VIO 300D; ERBE, Tübingen, Germany) (Fig. 2). No intra- or post-operative complications occurred. The pathological diagnosis revealed that it was an intestinal-type low grade adenoma with negative margins. At the margins of the lesions, the tumor tended to form a villous structure, while the center appeared tubular with a relatively flat surface (Fig. 3). These histopathological findings were consistent with the magnifying endoscopic findings.

Because of the limited luminal space in the terminal ileum, it might be difficult to completely remove a lesion using conventional endoscopic mucosal resection, especially

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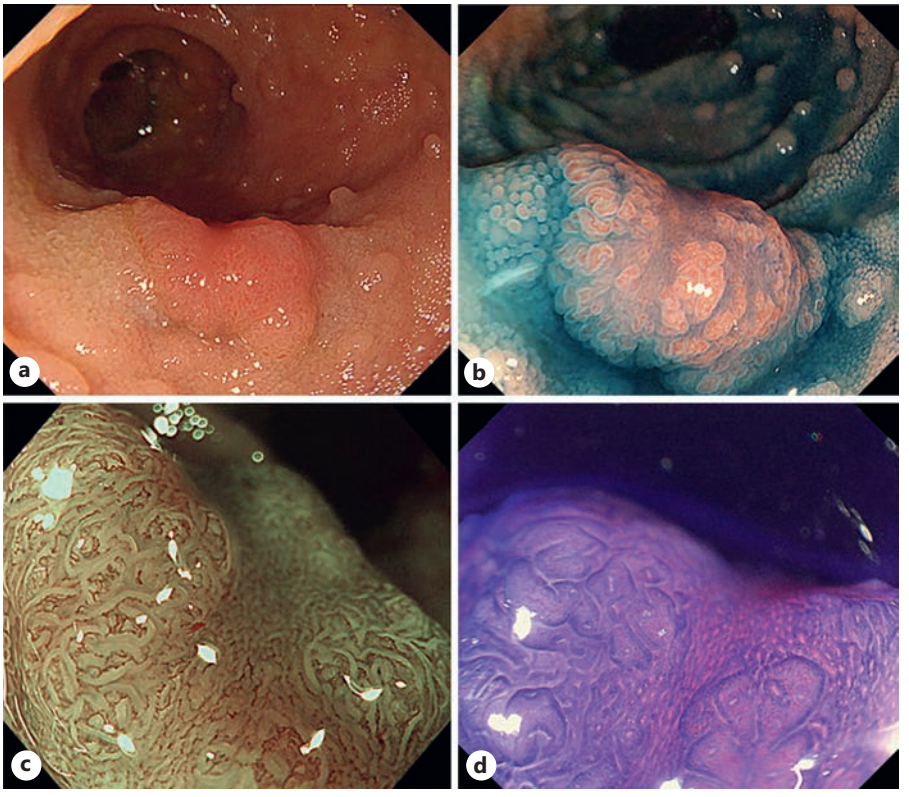

Fig. 1. Endoscopic images showing a 10 mm slightly depressed lesion with marginal elevation in the terminal ileum, suggesting type 0-IIa in the Paris classification: in white light (**a**); chromoendoscopy using indigo carmine (**b**). **c** Magnifying narrow-bind imaging: a tubular surface pattern with regular vessels on the marginal elevation area and regular brown vessels on the slightly depressed area, suggesting the Narrow-Band Imaging International Colorectal Endoscopic (NICE) classification type 2. **d** Magnifying chromoendoscopy image using crystal violet staining showing a pit pattern like type IV on the marginal area and type IIIL on the slightly depressed area.

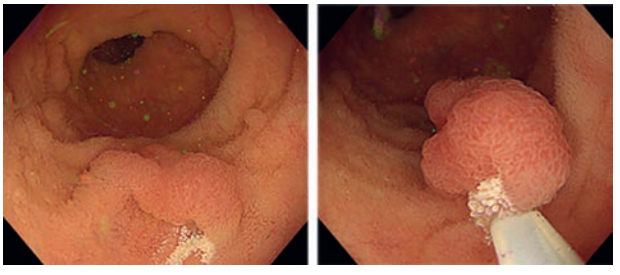

Fig. 2. After immersing the terminal ileum with normal saline and floating the lesion in it, we performed UEMR.

in cases where submucosal injection would prevent snaring. UEMR allows for easier and complete capture of the lesions by suctioning the lumen air and filling it with water, thereby making flat lesions smaller and more polypoid. Therefore, UEMR may be an effective method for terminal ileum tumor resection.

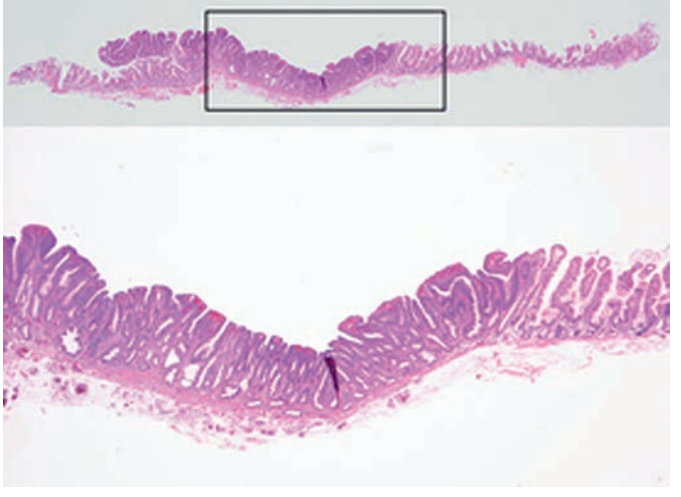

Fig. 3. Histological examination (hematoxylin and eosin stain): A villous structure at the margins of the lesions and a tubular structure with a relatively flat surface at the center. The lesion size was 13 × 9 mm.

Statement of Ethics

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

Conflict of Interest Statement

Authors declare no conflict of interests for this article.

Funding Sources

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Author Contributions

Atsushi Michigami wrote the manuscript and is the article guarantor. Satoshi Maeda performed the procedures. Shin Ichihara helped write the manuscript and developed the histological images. All authors revised this case report and approved the final version of the manuscript.

Data Availability Statement

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

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Images in Gastroenterology and Hepatology

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Bowel Obstruction after Liver Transplant: A Rare Cause

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Keywords
Liver transplantation · Cirrhosis · Bowel obstruction · Gallstone ileus · Double-balloon enteroscopy

Obstrução Intestinal Após Transplante Hepático: Uma Causa Rara

Palavras Chave
Transplante hepático · Obstrução intestinal · Íleo biliar · Enteroscopia de duplo balão

We present the case of a 67-year-old man with a medical history significant for orthotopic liver transplant 20 years earlier due to alcohol-related liver cirrhosis. The posttransplant period was complicated with posttransplant lymphoproliferative disease, treated with adjustment of immunosuppressive therapy and systemic chemotherapy, and is currently on remission. This patient developed a biliary stenosis at the level of the biliary anastomosis (choledococholedocostomy), leading to secondary graft cirrhosis. Cross-sectional magnetic resonance cholangiopancreatography demonstrated the anastomotic stricture with a concomitant dilation of the distal common bile duct (native bile duct segment), with recurrent identification of large biliary stones in this dilated section. During the posttransplant follow-up period, he had multiple hospital admissions due to acute cholangitis (last episode in 2018), requiring multiple endoscopic retrograde cholangiopancreatographies for stone extraction. The patient presented to the emergency department with right upper quadrant pain, jaundice, and fever. Laboratory workup revealed elevated total bilirubin (10 mg/dL) and C-reactive protein (77 mg/L). An abdominal ultrasound was performed and revealed a discrete dilation of intrahepatic bile ducts. The patient was hospitalized under antibiotic therapy for acute cholangitis. Given the prior episodes of acute cholangitis and lithiasis and the current clinical presentation, the patient underwent an endoscopic retrograde cholangiopancreatography which showed no evidence of dilated

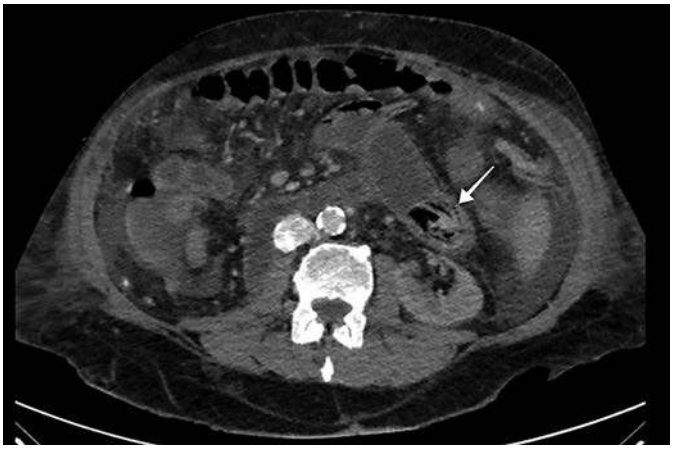

Fig. 1. Axial abdominal CT scan image showing endoluminal content within a jejunal loop (arrow) with upstream small bowel dilation. CT, computed tomography.

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intrahepatic bile ducts or biliary calculi but reported abundant gastric and duodenal stasis content. Over the following days, the patient developed recurrent biliary vomiting and abdominal distension, complicating with prerenal acute kidney injury and portosystemic hepatic encephalopathy. A contrast-enhanced abdominal computed tomography revealed dilation of the jejunal loops, with a maximum diameter of 40 mm, and the presence of obstructing endoluminal content (Fig. 1). Distal to this point, no dilation was evident. Due to his poor physical condition and underlying comorbidities, surgery was considered to carry an unacceptably high risk. A double-balloon enteroscopy (DBE) was performed revealing an impacted biliary stone with approximately 25 mm in the distal jejunum (Fig. 2). The stone was mobilized to the stomach using a polypectomy snare and ultimately removed using a retrieving basket (RothNet®, STERIS, Dublin, Ireland) (Fig. 3). The patient had resolution of obstructive symptoms and resumed oral feeding with tolerance.

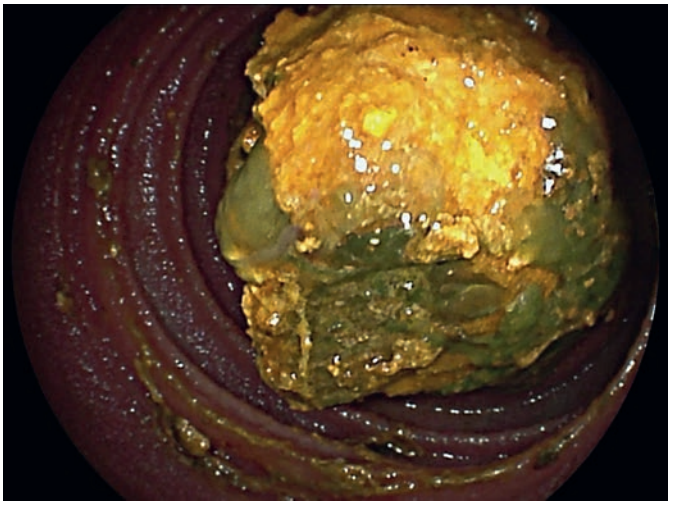

Fig. 2. Gallstone and alimentary debris impacted in the distal jejunum.

Bowel obstruction is a rare late complication after liver transplantation, occurring in approximately in 1–2% of cases [1]. The most common etiologies include intra-abdominal adhesions and internal hernias [2]. Gallstone ileus is an uncommon etiology of mechanical small bowel obstruction, accounting for up to 4% of all cases, being more frequent in women [3]. Contrast-enhanced computed tomography is the *gold standard* for the diagnosis of this entity and can be of value for decision-making regarding the therapeutic strategy. To date, cases of gallstone ileus have scarcely been described in orthotopic liver transplant patients. Recently, 2 cases of gallstone ileus have been reported after liver transplantation [4, 5]. In both cases, the patients had been submitted to liver transplantation due to biliary atresia and had a bilioenteric anastomosis, favoring stone migration, and an altered gastrointestinal anatomy (Y-en-Roux jejunojejunostomy). Both cases were managed with enterotomy for stone extraction. Opposite to these reports, in this case, the patient did not have a bilioenteric anastomosis and was managed using an endoscopic technique. Indeed, the location of stone impaction combined with the accessibility to DBE allowed a safe and efficient stone extraction in a patient with a poor surgical condition.

The resolution of gallstone ileus most often requires aggressive fluid and electrolyte followed by early intervention to relieve bowel obstruction [3]. Surgical enterotomy remains the standard of care for stone extraction and resolution of bowel obstruction. Moreover, when the presence of a bilioenteric fistula is responsible for the passage of a large stone to the small bowel, surgery allows the closure of the defect [3]. The use of DBE for resolution of bowel obstruction has scarcely been reported. Nevertheless, DBE can be a valid alternative to the standard surgical approach in patients with a poor preoperative condition. Endoscopic treatment options include electrohydraulic and mechanical lithotripsy, as well as retrieving baskets [6, 7].

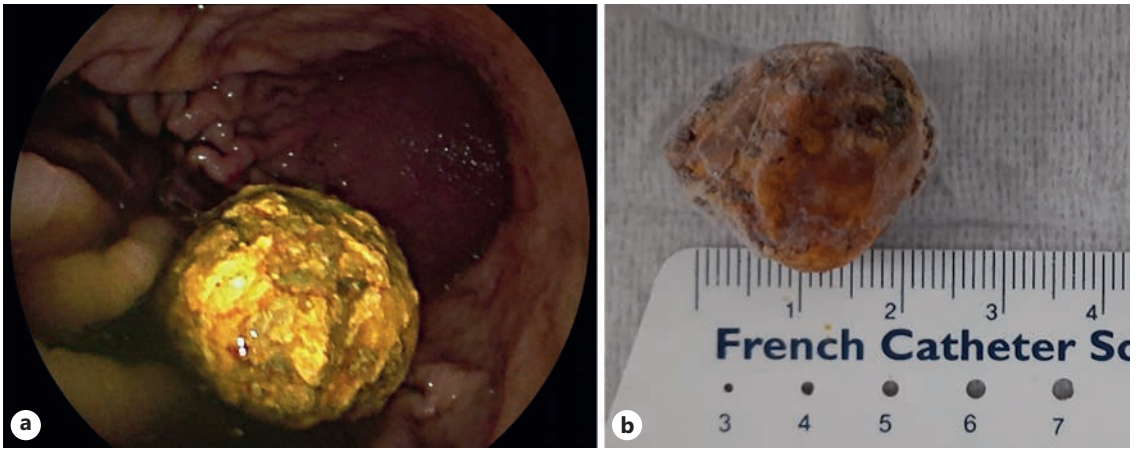

Fig. 3. a Gallstone from the stomach before being removed with a retrieving basket. **b** Subsequent measurement of the gallstone confirmed its estimated size of 25 mm (photo taken after the specimen had been several hours in a refrigerator for preservation).

Statement of Ethics

All rules of the Local Ethics Committee ("Comissão de Ética para a Saúde do Centro Hospitalar de São João/Faculdade de Medicina da Universidade do Porto, Portugal") were followed, preserving patient identity and confidentiality. Informed consent was obtained from the patient for the publication of his case. Written informed consent to share the medical case and images was obtained from the patient.

Conflict of Interest Statement

The authors declare that there was no source of funding.

Funding Sources

The authors have no funding sources to declare.

Author Contributions

Tiago Ribeiro: clinical management of the patient, collection of clinical and endoscopic data, bibliographic review, and drafting and critical revision of the manuscript. Miguel Mascarenhas: collection of clinical data, bibliographic review, drafting of the manuscript, and critical revision of the manuscript. Hélder Cardoso: performance of the endoscopic procedure and critical revision of the manuscript. Guilherme Macedo: critical revision of the manuscript and final approval of the manuscript. All authors agree to be accountable for all aspects of the manuscript.

Data Availability Statement

Data are stored in the hospital's electronic patient database and will be provided upon reasonable request.

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A Rare Cause of Dysphagia by Extrinsic Compression

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Keywords
Aberrant subclavian artery · Deglutition disorders · Manometry

Uma causa rara de disfagia por compressão extrínseca

Palavras Chave
Artéria subclávia aberrante · Distúrbios da deglutição · Manometria

A 38-year-old man presented with dysphagia for solids fluctuating in severity. This symptom had persisted for several years. He reported feeling worse in the previous month, having also lost 10% of total weight. He had no relevant past medical history and physical exam was normal.

Initial workup by upper endoscopy was normal. High-resolution esophageal manometry excluded outflow obstruction of the esophagogastric junction or peristalsis disorders but identified a horizontal and pulsatile high-pressure area below the upper esophageal sphincter (Fig. 1a, b, see arrows). The initial interpretation of the manometry, as the high-pressure area maintained itself throughout the exam, gave rise to the search for an extrinsic cause. Barium swallow was then performed, revealing an extrinsic compression at the level between the upper and middle thirds of the esophagus (Fig. 2a, b, see arrows). A thoracic computed tomography angiography identified an abnormal origin to the right subclavian artery, after the left subclavian origin (Fig. 3, see arrow).

The patient refused surgical intervention and maintains mild symptoms under general measures. The abnormal right subclavian artery, also known as the arteria lusoria, is present in 0.5–2.5% of the general population and causes symptoms in about 20% [1, 2]. Despite being congenital, it leads to dysphagia more frequently after the 5th decade of life [2]. The present case intends to raise awareness to the potential role of high-resolution manometry in the diagnosis of this rare condition.

Mara Sarmento Costa and João Oliveira Dias contributed equally as joint first authors.

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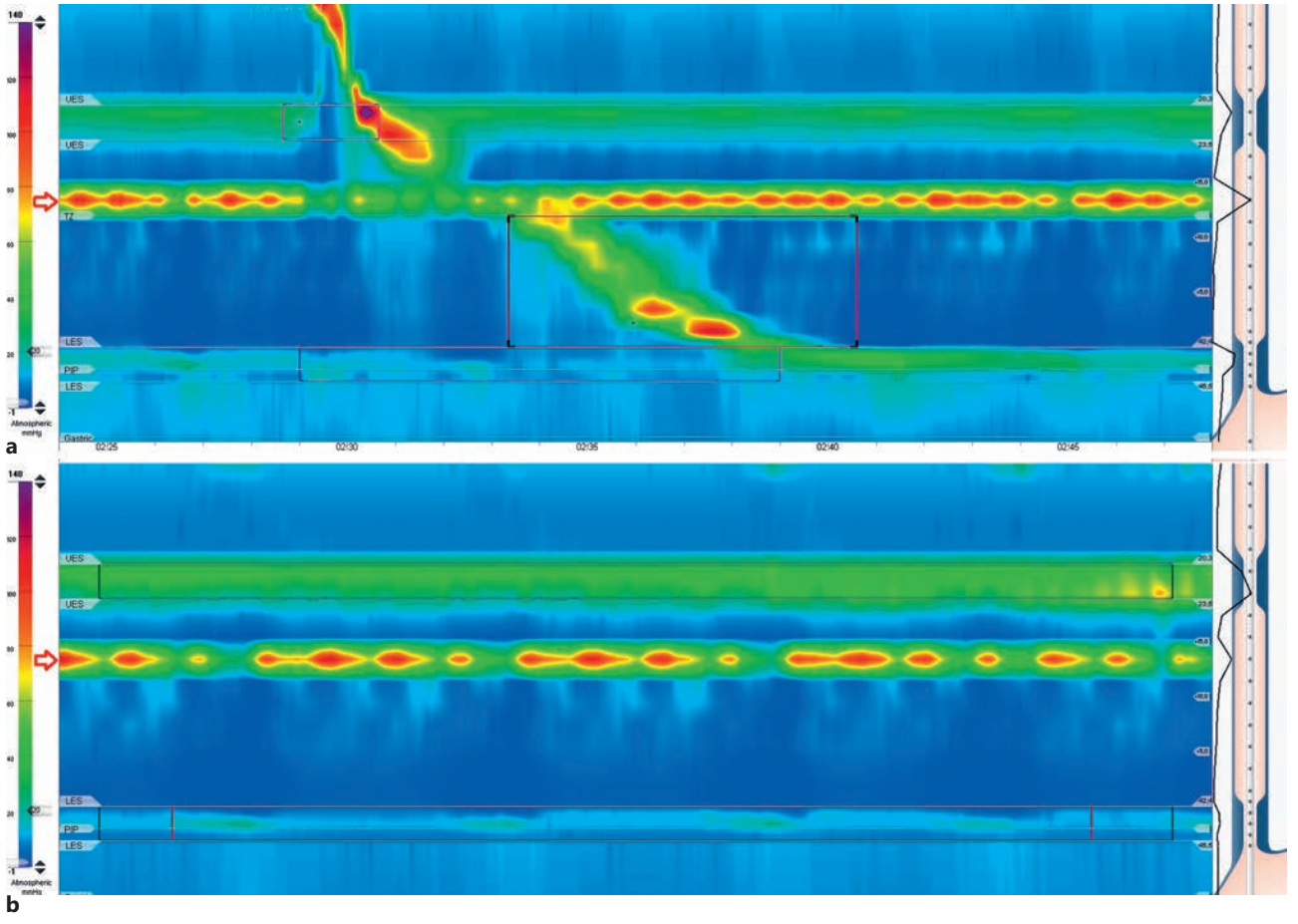

Fig. 1. a, **b** High-resolution esophageal manometry: a horizontal high-pressure area is pictured just beneath the upper esophageal sphincter.

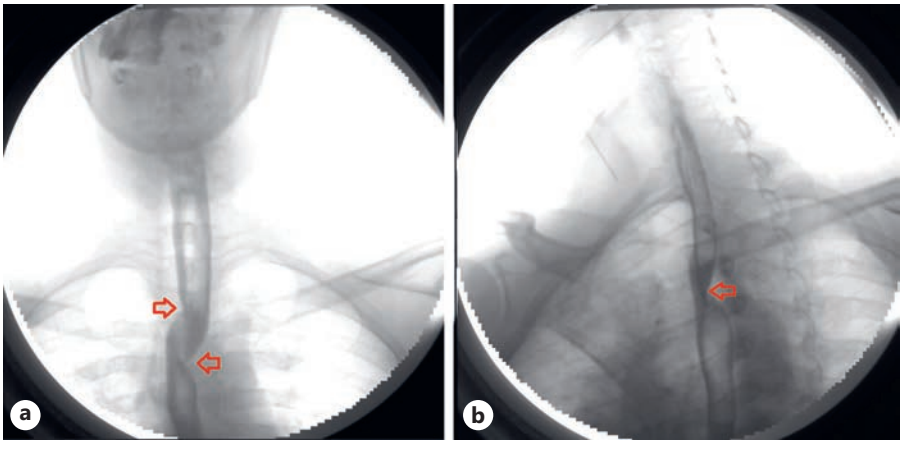

Fig. 2. a, **b** Barium swallow: an extrinsic compression can be seen, as pointed out by the red arrows, between the upper and middle thirds of the esophagus.

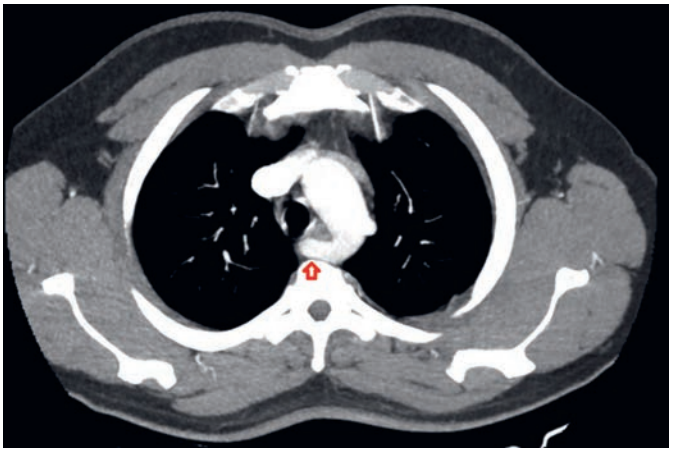

Fig. 3. Due to suspected dysphagia *lusoria*, the patient underwent thoracic computed tomography angiography confirming an abnormal origin to the right subclavian artery (see arrow).

Statement of Ethics

Written informed consent was obtained from the patient for the publication of his information, picture, and imaging.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

None.

Author Contributions

Mara Sarmento Costa, João Oliveira Dias, Patrícia Vaz Silva, Cláudia Agostinho, and Paulo Souto were responsible for the patient evaluation. Mara Sarmento Costa was responsible for data acquisition and wrote the manuscript. Mara Sarmento Costa, João Oliveira Dias, Patrícia Vaz Silva, Cláudia Agostinho, Paulo Souto, and Pedro Figueiredo reviewed and approved the manuscript.

Data Availability Statement

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

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