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Diagnostic and therapeutic features of small bowel involvement in portal hypertension

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ABSTRACT

Enteropathy is a lesser known complication of portal hypertension and consists of different changes in the mucosal layer of the small bowel which lead to the appearance of vascular and inflammatory lesions. It can be an important co-factor in the development of anemia in the cirrhotic population, and nowadays an easy and non-invasive diagnosis can be made thanks to capsule endoscopy. However, it is rarely considered in the management of patients with portal hypertension. Some aspects such as pathogenesis or incidence remain unclear and no specific recommendations are included in the guidelines regarding diagnosis or treatment.

A review of the available literature was performed with regards to the most relevant aspects of this entity.

Key words: Hypertensive enteropathy. Portal hypertension. Capsule endoscopy.

INTRODUCTION

Portal hypertension (PH) is defined as an increased gradient between the portal vein and vena cava pressure (normal values: 1-5 mmHg). PH is considered as clinically significant when this gradient is higher than 10 mmHg, as complications occur above this threshold (1,2). The development of PH is the most frequent complication of liver cirrhosis in western countries, while in other parts of the world, liver schistosomiasis and portal vein thrombosis are more common (3).

PH is caused by structural changes such as liver fibrosis, regenerative nodules, angiogenesis and vascular occlusion and dynamic changes including contraction of stellate cells and myofibroblasts around the hepatic sinusoids and of the smooth muscle inside the wall of the hepatic vessels (4). PH is asymptomatic until the occurrence of complications. Among the most relevant are ascites, varices (especially esophageal and gastric), hepatorenal and hepatopulmonary syndromes, cirrhotic cardiomyopathy and the development of changes in the microvasculature of the stomach, small bowel (SB) and colon, known as portal hypertensive gastropathy, enteropathy and colopathy (5).

Portal hypertensive gastropathy is characterized by the appearance of lesions such as erythema, red spots, mosaic pattern and diffuse hemorrhage on the gastric mucosa. This is more frequent in patients with severe PH or those with esophageal varices. It is considered a rare cause of overt bleeding but can be a relevant cause of occult bleeding and chronic anemia in cirrhotic patients, and it is usually diagnosed incidentally during routine endoscopy. The use of nonselective beta-blockers for prophylaxis has been described in the management of hypertensive gastropathy (although evidence is scarce), somatostatin and analogues in cases of active bleeding and endoscopic application of argon plasma coagulation or radioablation (5-9).

Angioectasia, inflammatory or pseudo-inflammatory changes, mucosal friability and varices along the colon and rectum of patients are found in patients with PH. It is normally asymptomatic but may manifest as chronic and occult gastrointestinal bleeding; acute or overt bleeding is exceptional. As in the case of gastropathy, this

condition is frequently diagnosed during routine endoscopic studies and can be treated with beta-blockers, although the evidence regarding the efficacy of this therapy in this setting is scarce (5,9,10).

Portal hypertensive enteropathy is the lesser known complication of PH on the wall of the gastrointestinal tract. Thanks to the expansion of endoscopic techniques for the study of the SB, especially capsule endoscopy (CE), this entity has been increasingly considered in the management of cirrhotic patients (5).

DEFINITION OF PORTAL HYPERTENSIVE ENTEROPATHY

Involvement of the SB in patients with PH has been rarely described and aspects such as pathogenesis or real incidence have not been sufficiently clarified. Hypertensive enteropathy is defined as series of alterations and pathologic changes of the mucosal layer of the SB in patients with PH (11). It has been suggested that enteropathy can be an important co-factor in cases of anemia in the cirrhotic population, but it is rarely suspected. CE has allowed the study of the typical lesions of portal hypertensive enteropathy and provides a minimally invasive diagnosis technique.

ETIOPATHOGENESIS

There is no accepted theory regarding the etiopathogenesis of the different lesions of portal hypertensive enteropathy. Three mechanisms have been proposed based on studies in laboratory animals: a) venous congestion secondary to PH could cause hypoxemia and ischemic lesions on the mucosal layer of the SB and this would lead to arteriovenous shunts and redistribution of the blood flow in the SB; b) the lesions observed in hypertensive enteropathy could be associated with an increased intestinal permeability, bacterial translocation and an excessive mast cell-mediated inflammatory response; and c) an etiopathogenic mechanism of goblet cell hyperplasia could produce anomalous remodeling of the epithelial surface, submucosal angiogenesis and the consequent appearance of the typical lesions of enteropathy in individuals with PH (12-14).

EPIDEMIOLOGY

There is a wide variability with regard to the prevalence of hypertensive enteropathy among the different series published in the literature, ranging from 15% to 96.8%. The lowest rates (up to 25%) are found in studies including conventional endoscopic procedures, mainly duodenoscopy, push enteroscopy and ileocolonoscopy (15,16). Widespread use of CE and device-assisted enteroscopy has allowed better access to the SB and more appropriate endoscopic studies in these patients. The number of individuals with enteric lesions secondary to PH is thought to be much higher than previously reported, ranging from 40% to 96.8% as shown in some series (11,17-22).

The presence of SB lesions in patients with PH is associated with Child-Pugh class B and C, as well as the concomitant presence of esophageal varices (with previous history of endoscopic treatment) and gastric or colonic lesions and low hemoglobin levels (17,19,23). It has been suggested that the presence of these conditions in a cirrhotic patient is suspicious of portal hypertensive enteropathy and should prompt the performance of endoscopic studies of the SB (24).

CLINICAL PRESENTATION

Portal hypertensive enteropathy can be silent and asymptomatic for long periods of time. The most frequent presentation is ferropenic anemia, as a chronic and occult middle gastrointestinal bleeding without external bleeding symptoms, or as an acute overt bleeding manifesting with melena, hematochezia or, less frequently, hematemesis. There are no concrete data with regard to the prevalence of anemia among patients with PH and lesions in the SB, although it is probably high, as gastrointestinal bleeding is the main indication for endoscopic studies in this population (11,18,22,25). One series showed that (11) 46.7% of patients diagnosed with PH with SB involvement had further bleeding episodes during follow-up but no associated mortality was reported. Although it is accepted that occult bleeding is probably more common than overt bleeding, there is little information in the literature regarding the real frequency of each of these forms

or presentations. Several series (18,19,25,26) have described the presence of lesions with active hemorrhage or signs of bleeding in 5.5% to 16.6% of the cases, although they do not indicate whether the patients presented with occult or overt bleeding.

The origin of anemia in the cirrhotic population is normally considered as multifactorial (causal state, hypersplenism, gastrointestinal bleeding, etc.). Although the typical lesions observed in portal hypertensive enteropathy have a bleeding risk (lesions with active bleeding have been observed in some studies) and could consequently play an important role in the development of anemia in these patients, data supporting this theory are limited in the literature. Up to 90% of the patients had lesions in the SB, and one third had intestinal varices in a study of 21 patients with PH and middle gastrointestinal bleeding who underwent CE (27). The authors concluded that the varices and angioectasias observed in the CE studies could be responsible for the anemia of the patients. Individuals with portal hypertensive enteropathy presented with significantly lower levels of hemoglobin and serum iron than those without, as shown in a more recent study of 134 patients with liver cirrhosis (28). We may assume that hypertensive enteropathy is the only cause of anemia in these patients. However, as previously mentioned, the presence of the typical lesions of portal hypertensive enteropathy is associated with more advanced stages of liver disease and the presence of lesions in other segments of the digestive tract. Thus, iron deficiency could also be associated with these additional factors.

ENDOSCOPIC FINDINGS IN PATIENTS WITH PORTAL HYPERTENSIVE ENTEROPATHY

Mucosal changes observed during the endoscopic studies (CE and device-assisted enteroscopy) suggestive of SB involvement in PH are variable and can be classified as vascular and non-vascular lesions. Angioectasia and varices are included in the first group and inflammatory lesions, red spots, villous edema, polyps, etc., in the second group. Angioectasia, red spots and varices are the lesions that more frequently cause clinically relevant bleeding (11,17,19,20,23,24). The incidence of these lesions is variable among the different published series in cirrhotic patients (11,19,21,22,29):

- The rate of cirrhotic patients presenting with any of the lesions of portal hypertensive enteropathy seen by CE or enteroscopy ranges from 40% to 96.8% in the available series. This variability could be justified by the different inclusion criteria of the series and the differences in the staging of the patients' liver disease.
- Angioectasias have been observed in 24.3% to 67% of patients with portal hypertensive enteropathy.
- Red spots have been described in 16.6% to 62.2% of the cases.
- Inflammatory lesions were present in 5.6% to 41.9% of patients included in these studies.
- Varices are the less frequently found and have been observed in 6.2% to 16.1% of the cases.

Angioectasias (Fig. 1A) are normally flat or slightly elevated lesions, like small red plaques containing arborizing vessels. Similar lesions can be found in patients with chronic renal failure, aortic stenosis or elderly individuals. However, these are smaller in number and size (11,18). Red spots (Fig. 1B) are small, symmetric (usually rounded), erythematous and flat lesions. SB varices (Fig. 2) are elevated and circular venous lesions, similar to the classic esophageal or gastric varices. They typically adopt a nodular shape with a surrounding mosaic pattern and can present with or without a bluish color (18).

Polypoid enteropathy is a rare form of presentation of portal hypertensive enteropathy. It consists of small protuberances at any point of the SB, unique or multiple, sessile or pedunculated and of different sizes that mimic polyps. Histologically, these lesions have dilated and tortuous capillaries in the lamina propria (30).

There are other more unspecific inflammatory lesions including villous edema, granularity, patchy erythema and "herring roe" pattern (Fig. 3 A and B). The clinical significance of these lesions has not been well defined but they appear to present a lower bleeding risk (11,20). In addition, these lesions are not specifically associated with portal hypertensive enteropathy and may make a differential diagnosis in patients with

unknown PH difficult (24).

When these endoscopic abnormalities are found, especially in patients with no previous diagnosis of cirrhosis or non-cirrhotic PH, a differential diagnosis must be made between hypertensive enteropathy and diseases such as inflammatory bowel disease, celiac disease, arteriovenous malformations, actinic enteritis, familial hereditary telangiectasia and familial adenomatous polyposis. Extreme caution should be exercised when taking biopsies due to the bleeding risk of the vascular lesions (12).

OTHER DIAGNOSTIC MODALITIES

Different radiologic explorations have been proposed by several investigators as predictors of portal hypertensive enteropathy. A CT-based index was designed in a multicenter Korean study. Lesions included in this scoring system are esophageal and gastric varices and the presence of other collaterals such as paraumbilical veins, signs of hypertensive gastropathy, colopathy or cholecystopathy, splenomegaly and ascites. According to this study, higher index scores (i.e., the presence of many of these lesions in CT studies) in a patient with liver cirrhosis and PH is associated with a higher prevalence of portal hypertensive enteropathy. The authors suggest that this index could be a good tool for selecting patients who would benefit from CE studies in this setting (11).

Radiologic and endoscopic abnormalities observed with CT and upper endoscopy, such as the clinical features of the patients more frequently associated with the diagnosis of hypertensive enteropathy made by CE, were analyzed in a study of 134 cirrhotic patients. Child-Pugh class B-C, the presence of portosystemic shunts, ascites, portal thrombosis, esophageal varices and hypertensive gastropathy were significantly associated with the presence of lesions of portal hypertensive enteropathy in CE studies. Shunts, especially in the splenorenal and left gastric vein, were independent predictors of enteropathy in this study (28).

Transient elastography is a non-invasive method for the assessment of hepatic fibrosis using ultrasound (31), and has been proposed as a tool for estimating the presence of PH and its complications, such as esophageal varices (1,32,33). Elastography has also been

evaluated as a predictor of hypertensive enteropathy in cirrhotic patients. The precision of an index based on endoscopic, clinical and radiological data for predicting the presence of intestinal lesions suggestive of enteropathy of PH seen in CE was tested in a prospective study of 31 cirrhotic patients. Those patients with higher scores in elastography (higher fibrosis index), Child-Pugh class B-C, esophageal varices or hypertensive gastropathy, or those with previous endoscopic therapy were significantly associated with hypertensive enteropathy lesions. The conclusion was that transient elastography can be a useful non-invasive method to predict portal hypertensive enteropathy in cirrhotic patients (29).

CT angiography and magnetic resonance imaging have been used for the diagnosis and management of collateral vascularization in the cirrhotic population, especially in patients with esophageal varices (34,35). However, there are no studies in the literature with regard to the use of these techniques for PH enteropathy. There are only some case reports describing the detection of ectopic varices by means of any of these radiologic modalities, after the diagnosis of active bleeding from the SB using CE, which were subsequently treated with interventional radiology techniques (36,37).

CLASSIFICATION OF PORTAL HYPERTENSIVE ENTEROPATHY LESIONS

Several classification strategies have been proposed for lesions observed in patients with portal hypertensive enteropathy. In a simplified version they can be divided into two groups: vascular lesions and non-vascular or inflammatory lesions.

In one of the earliest studies with regard to the diagnosis of hypertensive enteropathy using CE (19), lesions were classified in two categories: first grade lesions of inflammatory-like mucosal changes, including edema and erythema, as well as granularity, and second grade or vascular lesions, including red spots, teleangiectasias or angiodysplasia-like lesions and varices.

In a subsequent study in which portal hypertensive enteropathy lesions were evaluated using double-balloon enteroscopy (21), lesions were classified into two groups: villous abnormalities such as edema, atrophy and erythema, and vascular lesions including

angiodysplasia, dilated vessels and varices. Angiodysplasia-like lesions were also divided into the following subgroups: red spots, spider veins and lymphoid follicles with dilated vessels. Finally, dilated vessels were also subclassified as arborizing dilated vessels and coil-like fine vessels. The authors of this study stated that patients with four or more of these lesions have a higher risk of ascites, but this is not linked to a poorer evolution of laboratory parameters.

Another study regarding portal hypertensive enteropathy and CE (29) established a classification system based on four types of lesion as follows: a) type 1: red spots; b) type 2: angioectasia; c) type 3: varices; and d) type 4: inflammatory-like lesions. Types 1 to 3 are also included in a group of vascular lesions. This study also established an index and every patient was scored according to the number of lesions observed in CE. The authors concluded that individuals with higher scores in their portal hypertensive enteropathy index had a more severe liver disease and PH.

MANAGEMENT OF PORTAL HYPERTENSIVE ENTEROPATHY

With regard to diagnosis, CE should be used in cases of suspected PH as it is minimally invasive and allows the evaluation of the entire SB mucosa. Device-assisted enteroscopy can be useful in some cases as this modality allows a direct evaluation of the mucosa and enables tissue sampling for histopathologic analysis for a differential diagnosis in patients with unknown PH or unclear lesions (21,24,26).

There are no particular recommendations in clinical practice guidelines with regard to the management of bleeding or its prevention in portal hypertensive enteropathy as the available evidence is scarce.

In cases of acute bleeding, such as variceal bleeding or hypertensive gastropathy, initial management includes the stabilization of the patient and general support including intravenous fluids and a blood transfusion, etc. As with the treatment of esophageal varices, the use of vasoactive drugs such as somatostatin and its derivatives is accepted, as well as subsequent maintenance with non-selective beta-blockers. Even though their usefulness and safety in cases of portal hypertension enteropathy hemorrhage have not

been demonstrated (24). Thalidomide treatment has also been proposed due to its ability to suppress vascular endothelial growth factor. However, the experience in humans is limited to case reports (38).

Angioectasia-like lesions can be treated with argon plasma coagulation during an assisted enteroscopy. Several studies show that this technique can be safely performed in cirrhotic patients in the same way as in patients with this type of lesion in a different context (18,21). Patients with polypoid enteropathy could also be candidates for endoscopic therapy provided that the number of lesions is not excessive and they are accesible in terms of location and endoscopic polypectomy can be performed (24,30). Varices are also candidates for endoscopic therapy with band ligation, sclerotherapy or argon plasma coagulation. However, evidence is mostly limited to the duodenum and there is less evidence regarding yeyunal or ileal varices (39).

Several interventional radiology approaches are also available to treat different lesions of portal hypertensive enteropathy in particular; percutaneous embolization (used in SB varices) and transjugular intrahepatic portosystemic shunt (TIPS). Embolization consists of the use of coils to occlude the main vessel which feeds the varices. It is a relatively safe procedure and successful cases have been described (35,36). Nevertheless, high re-bleeding rates have been reported (55-67%) including early bleeding cases in the first 72 hours after the procedure (40). The use of TIPS can palliate and even reverse the changes produced by PH in the SB mucosa due to its effect in lowering portal pressure (41). Thus, it has been proposed as a treatment for different complications of portal hypertensive enteropathy, especially variceal bleeding when medical and endoscopic therapies have failed and as a prophylaxis of new bleeding events (42,43). TIPS and embolization have a risk of re-bleeding when used in variceal hemorrhage cases. Therefore, some authors suggest a combined use of both techniques in order to reduce the re-bleeding rates (40,44). Balloon-occluded obliteration is a lesser known interventional radiologic procedure than embolization and TIPS. Originally, it was described as an option for the treatment of fundic varices but it can also be used in the management of portal hypertensive enteropathy (45). With this technique, varices and afferent and efferent veins are occluded by the injection of an

endovascular sclerosant (ethanolamine) using a balloon-occlusion catheter. It can be used in patients with previous hepatic encephalopathy or when TIPS is contraindicated. Experience with this technique is limited (46,47) and patients should be carefully selected. Important changes have been described in the portal flow that can invoke a deterioration of PH and the occurrence of new varices in other areas (45,48).

Different surgical approaches can be considered, especially for emergency cases or when the procedures previously described are unavailable or have failed. Surgical ligation or intestinal resections have been described mostly in isolated cases (49). A surgical portosystemic shunt is another alternative with similar results to TIPS in some series. However, nowadays this technique is rarely performed and needs to be carried out by expert surgeons (24,50,51).

Liver transplantation is the definitive treatment for advanced cirrhosis and its associated complications. Liver transplantation has also been described as a definitive therapy in cases of PH, even in the non-cirrhotic population (52). Data in the literature regarding the evolution of esophageal varices or hypertensive gastropathy after liver transplantation are scarce (53,54), and none refer to portal hypertensive enteropathy.

In general, the management of patients will depend on their clinical situation and the manifestations of portal hypertensive enteropathy (chronic anemia or overt bleeding), the techniques available in each center, and the possibility of treating patients in a referral hospital where more complex treatments can be performed.

CONCLUSIONS

Portal hypertensive enteropathy is probably a more frequent entity than previously thought among cirrhotic patients. Vascular and inflammatory lesions observed in these patients (which are easily assessed by CE) can be an important co-factor in chronic anemia and cases of overt bleeding. In general, sclerotherapy, the use of vasoactive drugs and beta-blockers, or interventional radiology techniques are accepted techniques used in cases of portal hypertensive enteropathy as with esophageal varices bleeding or portal hypertensive gastropathy. However, studies regarding the management of the SB involvement in PH are limited to case series.

More research is needed to provide more exhaustive evidence with regard to different aspects of this entity, as well as achieving a better understanding of the physiological mechanisms in order to define the indications for diagnosis and treatment.

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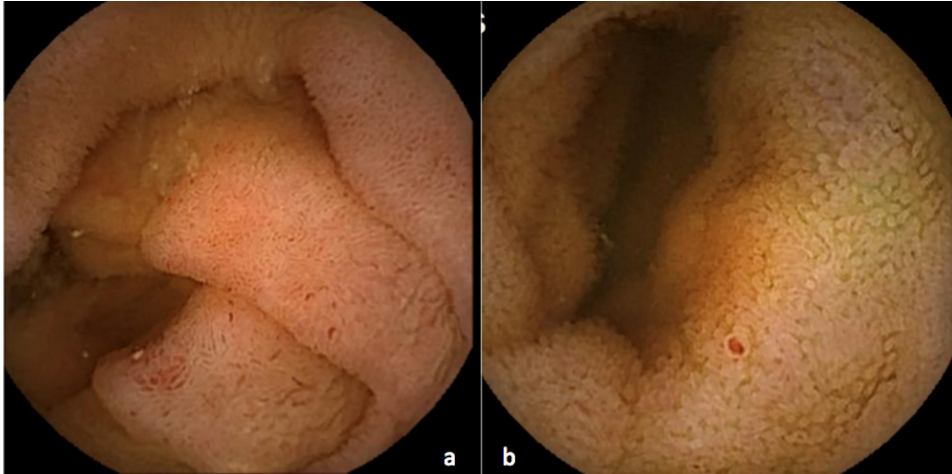


Fig. 1. A. Angioectasia. B. Red spot.



Fig. 2. Jejunal varix.

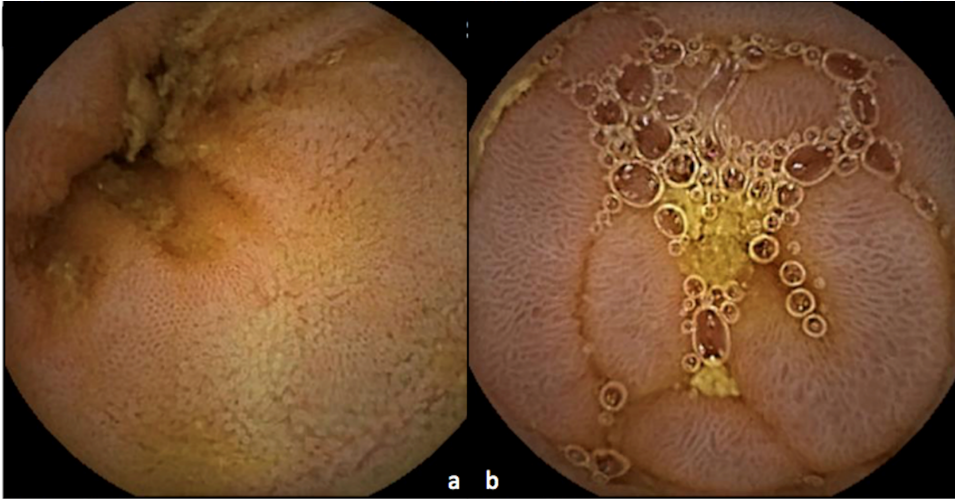


Fig. 3. A. Herring roe pattern. B. Edematous and nodular mucosa.

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