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Portal hypertensive gastropathy

a clinically significant puzzle

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SUMMARY

In this review the updated information concerning the influence of portal hypertension on gastric mucosa is presented. The term portal hypertensive gastropathy [PHG] defines a wide spectrum of endoscopic lesions that appear in the gastric mucosa of cirrhotic patients and which should be differentiated from gastric antral vascular ectasia. These endoscopic findings correspond to dilated mucosal and submucosal vessels in the absence of inflammation. There is wide variation in the prevalence of PHG, but its natural history in not clearly documented. Endoscopic variceal obliteration may contribute to the development or aggravation of these lesions. Similar influence of portal hypertension seems to be extended in the lower gastrointestinal tract. With regard to gastric mucosal hemodynamics, it is not known whether active congestion or passive congestion causes gastric mucosal hyperhemia. The pathogenesis of PHG in not well known, but both venous congestion related to raised portal pressure and increased gastric blood flow seem to be crucial factors for its development. Gastric mucosal defense mechanisms are impaired in PHG. Bleeding is its unique clinical manifestation and occurs in patients with severe lesions. Pharmacological, surgical and interventional radiological procedures are available for the treatment of bleeding PHG, but the treatment needs to be improved.

Key words: Portal hypertensive gastropathy, portal hypertensive vasculopathy, liver cirrhosis, portal hypertension

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Since the middle of 80's portal hypertensive gastropathy [PHG] has attracted the attention of endoscopists and clinical scientists involved with the physiology of portal hypertension. In recent years, although recognized as a potential source of gastrointestinal bleeding, attempts to assess the clinical importance of this as a source of bleeding, and the severity of bleeds that it may cause, have produced conflicting results.[1]

However, although the endoscopic, histological and hemodynamic features of portal hypertensive gastric mucosa have been extensively studied, the pathogenesis of PHG is still poorly understood, its natural history is not clearly documented and its treatment needs to be improved.[2]

Seven comprehensive reviews dealing with PHG were published in the years between 1988-1998;[3-9] however, there have been a considerable number of publications, containing new knowledge on this subject, since then. Thus the purpose of the present article is to review this new information regarding PHG.

ENDOSCOPIC PICTURE AND CLASSIFICATION

The endoscopic appearance of portal hypertensive gastric mucosa includes several lesions such as: fine pink speckling, scarlatina-type rash petechia, multiple bleeding spots, papules, superficial reddening, snake-skin pattern, cherry red spots and mosaic-like pattern, which are classified according to McCormack's,[10] NIEC's [New Italian Endoscopic Club for the Study and Therapy of Esophageal Varices][11] and Tanoue's[12] classifications (Table 1).

McCormack classified the mucosal changes into two main types, mild and severe, while the NIEC proposed 3

Table 1. Endoscopic findings and classification of PHG

	mild	moderate	severe
McCormack[10]	scarlatina type rash	-	red spots
	snake skin		diffuse haemorrhagic lesions
	striped appearance		
NIEC[11]	pink in center mosaic (+)	flat red spots mosaic (+)	diffusely red mosaic (+)
Tanoue[13]	mild reddening	fine red speckling	point bleeding
	mosaic (-)	mosaic (+)	mosaic (+)

types, mild, moderate and severe. This latter classification appears to be more complicated than McCormack's because it classifies the mosaic-like pattern into 3 groups without criteria for the grading or for the likelihood of bleeding.

Similarly, Tanoue's classification consists of 3 grades, mild, moderate and severe, the difference from McCormack's being that the former divides the mild stage of the latter into two grades. All three classifications, however, agree that the severe stage of PHG contains diffuse hemorrhagic spots.

The above data lead us to observe that there is an absence of a universally accepted classification system and a paucity of data regarding the application of the existing classifications. Possible sources of disagreement between the studies include differences in patient selection and lack of uniform criteria for defining the elementary endoscopic lesions of PHG.

If the two-grade scale is going to be used, Pique[8] proposes a more detailed version of McCormack's classification, including in the mild stage the mosaic pink in the center, the fine red speckling, the scarlatina type rash and the snake skin pattern and in the severe stage the red spots, the brown spots and the diffuse hemorrhagic lesions.

On the other hand, Hashizume and Sugimachi[13] consider it better to classify PHG into three stages: non-specific redness, specific mosaic pattern and red spots. However in some recently published studies there is an apparent tendency to prefer the two-grade scale.[2,14,15]

DIFFERENTIAL DIAGNOSIS

When red spots are seen in the stomach on endoscopy, it may be difficult to differentiate severe PHG from gastric vascular ectasia [GVE], the latter being a recently recognized entity, characterized by aggregates of red spots. When these aggregates are arranged in a linear pattern in the gastric antrum the term gastric antral vascular ectasia [GAVE] or "watermelon, stomach" is used, while, the ectatic red spots, which may be more diffuse and involve the proximal stomach, are termed diffuse GVE.

Since a diffuse form of red spots is the most frequent feature of GAVE in patients with cirrhosis, some investigators include this form in the severe stage of PHG.[9] However, from the practical point of view, if the background mucosa develops a mosaic appearance and red spots are present within the mosaic, the term most often used to describe the changes is severe PHG. When it is difficult, during endoscopy, to differentiate between severe PHG and GVE it might be necessary to resort to gastric mucosa biopsy.

Occult or overt bleeding occurs more frequently as a complication of GAVE than of PHG. Although the pathophysiology of these gastric vascular lesions is not fully understood yet, recent findings suggest that although GAVE is not directly related to portal hypertension, it is influenced by the presence of liver dysfunction.[16]

HISTOLOGICAL PICTURE

The unique histological feature of PHG is a marked dilatation of the capillaries and collecting venules in the gastric mucosa.[10,17] Submucosal veins appear ectatic, irregular and with areas of intimal thickening. Morphometric studies have shown that patients with PHG have a greater mean mucosal capillary cross-sectional area, compared with either patients without PHG or normal controls.[9] Misra et al[18] support the opinion that a thickened gastric mucosal capillary wall could be histological marker of PHG. These vascular alterations, present in the absence of any significant inflammatory cell infiltrate or erosion of the gastric mucosa, make incorrect the previous classification of these lesions as gastritis.[8] In addition, microvascular injection studies in both cirrhotic rabbits and humans have demonstrated large numbers

of arteriovenous shunts to have opened in the gastric submucosa.[9]

The histological features of severe PHG are different to those of diffuse GAVE. The number of mucosal vessels exhibiting fibrin thrombi and ectasia and spindle cell proliferation [smooth muscle cell and myofibroblast hyperplasia] in the superficial mucosa are greater in GAVE than in severe PHG.[19,20] Furthermore, fibrohyalinosis is more frequently observed in GAVE than in severe PHG and, if this feature is added to the GAVE score, it provides increased diagnostic accuracy in differentiating GAVE from severe PHG.[19]

PREVALENCE AND NATURAL HISTORY

Major controversies exist concerning the incidence of PHG in patients with portal hypertension due to liver cirrhosis, and the reported figures largely depend on the classification used to define mild lesions. The prevalence of PHG ranges from 4% to 98% [mean 53%]; mild PHG is the most common, occurring in 20% to 57% [mean 49%] of patients, while severe PHG is found in 7% to 41% [mean 14%] of patients.[9] An explanation for this high range could be differences within the study population and/or poor inter-observer agreement.

On the other hand, the sensitivity and specificity of PHG lesions in the diagnosis of portal hypertension have been studied by several investigators, who have consistently reported that a snake-skin pattern is of high specificity [range 93-100%]. Controversy exists as to the sensitivity of this sign.[9]

Although the natural history of PHG is not clearly documented and little is known about its evolution, it is a common observation that the endoscopic appearance of these lesions may vary over time; some workers believe that PHG is a progressive lesion, others have observed that it may regress in a fair proportion of patients.[8,9,21]

A recently published multicenter study, comprising more than 300 cases, concludes that PHG can progress from mild to severe and vice versa or even disappear completely.[1] This variation in results could be due to differences in patient population, the time when lesions appear, or the influence of endoscopic intervention for varices.

EFFECT OF VARICEAL OBLITERATION

It is not known how sclerotherapy or banding influences the natural history and the clinical course of PHG existing before endoscopic variceal eradication, from that developing during or after variceal eradication. The duration of persistence of PHG lesions, their severity, and their likelihood to bleed could possibly be different in these two clinical situations.

Several studies have shown that PHG is aggravated by the sclerotherapy and banding therapy of esophageal varices,[12,15,22-25] but long-term follow-up studies indicate that changes in the severity of PHG after variceal sclerotherapy are reversible.[25] This result was reproduced by Sarin et al,[2] who found that PHG developing after variceal eradication is often transitory and less severe, while, in the case of pre-existing PHG, endoscopic therapy for varices could worsen the PHG, with a likelihood of bleeding.

However, it should be noted that some patients exhibit less or no changes in PHG after endoscopic variceal obliteration. Recently, Iwao et al[26] demonstrated that obliteration-induced PHG develops less frequently in patients having well-developed fundal varices than in those with no or poorly developed fundal varices. Since fundal varices are usually formed by a gastrorenal shunt, this finding supports the view that the presence of a gastrorenal shunt may play a protective role in the development of PHG after variceal obliteration.

However, some discrepancies exist between clinical and hemodynamic studies on the venous consequences of endoscopic sclerotherapy, which generally appear to enhance the development of long shunts or PHG and to occlude para-esophageal varices. On the other hand, endoscopic sclerotherapy does not seem to have any significance in relation to splanchnic hemodynamics.[27,28]

EXTRAGASTRIC LOCATIONS

As increased portal venous pressure leads to hemodynamic disturbances throughout the digestive system, it would be expected that both the small and large intestinal mucosa be affected in the same manner as the gastric mucosa. Thus, the awareness of the association between portal hypertension and mucosal lesions throughout the lower digestive tract has increased over the past decade.

Two groups of investigators studying the histopathologic features of duodenal and jejunal mucosa specimens obtained from portal hypertensive patients, found an increase in the size and number of mucosal vessels, at a rate of 71% and 84%, respectively.[29,30] These findings led

them to conclude that the incidence of this condition, called portal hypertensive jejunopathy, is a part of the spectrum of portal hypertensive gastroenteropathy and occurs at least as frequently as changes in the stomach.

The colon, as the distal part of the lower gastrointestinal tract can be more easily examined by means of endoscopy than the small intestine. This fact has resulted in the accumulation of further information on the influence of portal hypertension on colonic mucosa.

Several investigators designed full-length colonoscopy studies of portal hypertensive patients in order to examine colonic mucosa for lesions similar to those of PHG. Abnormal superficial mucosal vascular patterns in the form of angiectasia-like lesions, red spots and dilated veins, as well as mucosal edema and rectosigmoid varices were prominent at a rate of 48% to 93% [mean 66%] in the patients examined.[31-35]

Scandalis et al,[37] on the contrary, reported in his series a complete absence of endoscopic and microscopic lesions related to the existence of portal hypertensive colopathy.

In one of the previous studies, morphometric analysis of the specimens obtained revealed a significantly higher mean number of capillaries and a higher mean cross-sectional vascular area per field in cirrhotic patients than in control subjects.[32] In another study, the presence of vascular ectasia was not related to the hepatic venous pressure gradient.[36] In a third study, previous sclerotherapy or the presence of gastric varices were found to have little influence on the development of these lesions.[33] Finally, in another study, portal hypertensive colopathy was not found to be associated with the severity of liver disease and the presence of PHG.[34]

It should be noted that the prevalence of portal hypertensive colopathy was found to be significantly lower in patients with anorectal varices compared to those without, and that obliteration of esophageal varices did not affect its prevalence.[37,38] It appears that anorectal varices, when present, decompress the colonic mucosa. A similar situation is seen in the stomach of patients with portal hypertension, where the presence of fundal gastric varices has been noted to be associated with a lower prevalence of PHG, whether spontaneous or associated with sclerotherapy.

PATHOGENETIC MECHANISMS

The mechanisms by which mucosal red spots and gastric vasodilatation appear in patients with portal hypertension remain unknown. Portal hypertensive gastropathy tends to develop in patients with esophageal varices rather than in those without varices. In addition, although several authors have found that the size of the esophageal varices is correlated with the severity of PHG, the latter is uncommon in patients with gastric fundal varices and splenorenal shunt.[9] A possible explanation of this is that due to angioarchitectural differences in patients with splenorenal shunts, there is a much higher collateral blood flow resulting in a substantial portal decompressive effect.[39]

As to whether portal pressure is the sole determinant of PHG, it would appear that elevated portal pressure may play an important role in the development of PHG. In support of this, it has been found that the degree of portal hypertension or intravariceal pressure relates to the severity of PHG.[9] However other evidence does not confirm this finding. According to Sarin et al[40] variceal pressure is similar in patients with or without PHG and not every portal hypertensive patient exhibits evidence of or develops PHG.

Therefore, in addition to pressure, other factors must contribute to the development of the mucosal lesions characterized as PHG. There is some evidence that this entity occurs more often in cirrhotic than in non-cirrhotic portal hypertension patients and that the degree of liver dysfunction is correlated with the severity of PHG in patients with cirrhosis.[9,41]

Some other humoral factors may also be involved in the pathogenesis of PHG. It has been proposed that increased circulating levels of vasodilators such as glucagon, or a reduced sensitivity to endogenous vasoconstrictors may play a significant role.[8] This hypothesis was supported by the fact that the levels of several vasodilators including glucagon, norepinephrine, VIP, gastrin or secretin, were found to be increased in the plasma of cirrhotic portal hypertensive patients and/or animals. However, the finding of similar plasma levels of such vasodilators in cirrhotic patients with and without PHG does not indicate a major role for these peptides in the pathophysiology of PHG.[8]

More recently, it has been suggested that several endothelial factors including prostagladins, NO and vascular endothelial growth factor may be involved.[42-44] The administration of specific inhibitors of these factors may significantly attenuate the gastric hyperemia in portal hypertensive rats. These vasoactive factors seem to interact to some extent, modulating the gastric hyperemia of portal hypertension, and are also involved in the hy-

perdynamic circulation of intra-abdominal viscera.[8] How these endothelial factors interact, modulating splanchnic vasodilatation, what stimuli are responsible for their enhanced release or increased microcirculatory sensitivity in portal hypertension, and how these factors may interact with other possible vasodilatory substances, remain to be elucidated.

MUCOSAL HEMODYNAMICS

Much effort has been devoted to the clarification of gastric mucosal hemodynamics in portal hypertensive cirrhotic patients and the pathogenesis of PHG. Several investigators using, through the endoscope, either laser-Doppler flowmetry and/or reflectance spectrophotometry found gastric mucosal perfusion to be increased in patients with PHG.[45,46] Furthermore Panes et al[47] found that the increments in laser-Doppler signal were parallel to the severity of PHG.

In contrast, other investigators using similar technology documented a reduced gastric mucosal perfusion and, furthermore, an inverse relationship between the laser-Doppler signal and the severity of PHG.[48-50] However, further investigation, using intragastric tonometry, revealed that although mucosal perfusion is reduced there is no evidence of ischemia.[51]

The reason for the discrepancy among these studies is not clear. However several technical factors may be considered. Although reflectance spectrophotometry and laser-Doppler flowmetry are endoscopic techniques that can be easily assimilated into clinical practice, they are not without pitfalls.

From the above-mentioned data it is not clear whether gastric mucosal blood flow increases or decreases in patients with cirrhosis. Second, it is also not clear how this flow is involved in the pathogenesis of PHG and whether it should by used as the most accurate index of severity. Many studies have reported values for the gastric mucosal perfusion associated with PHG, but there are few studies regarding rheologic parameters in patients with cirrhosis, such as the shear rate, which reflects endothelial-dependent microcirculatory regulation.

For that purpose Masuko et al[52] designed an elaborate study in which rheologic analysis of gastric mucosal hemodynamics in patients with cirrhosis was carried out. The investigators, using laser-Doppler flowmetry, measured volumetric flow, red blood cell volume and red blood cell velocity and, based on these results, analyzed the shear rate which reflects the status of the microcirculatory system. Additionally, to validate the technique used, they derived the relationship between red blood cell volume and cross-sectional area of submucosal collecting venules, using near-infrared endoscopy. They found that a disorder of the shear rate control mechanism in the microcirculation is associated with severe PHG.

The influence of variceal eradication by either sclerotherapy or banding on gastric mucosal perfusion seems to be related to the time lapsed from the endoscopic measurement to the last therapeutic endoscopic intervention. Although an aggravation of the mucosal blood flow is not a common finding, it seems that a redistribution of blood flow in the different gastric areas could be more prominent.[15,53-55]

GASTRIC MUCOSA DEFENSE

Previous clinical and experimental findings demonstrated that portal hypertensive gastric mucosa has an increased susceptibility to severe damage, compared with normotensive controls.[7] On the other hand, the prevalence of gastric ulcer and/or erosions in patients with liver cirrhosis is increased, compared with that in the general population.[56] Aggressive factors involved in the pathogenesis of gastric ulcer are reduced in association with portal hypertension and most of the important gastric mucosal defense mechanisms are shown to be impaired.[57,58]

It has also been found that reduced acid secretion, increased hydrogen ion back diffusion, reduced prostaglandin biosynthesis, decreased gastric mucosal blood flow, decreased bicarbonate output and a thinner gastric mucous layer occur in portal hypertensive animals.[9,58-61] Gastric permeability has also been found to be increased in both patients having PHG and in portal hypertensive animals [62-64]. The association of Helicobacter pylori with PHG seems to be weak.[58]

Little information is available with regard to the effect of PHG on the gastric mucosal repair process. Experimentally it has been found that gastric epithelial proliferation and angiogenesis are impaired in portal hypertensive rats.[57]

CLINICAL MANIFESTATIONS

The single clinical manifestation of PHG is overt or chronic upper gastrointestinal bleeding. This complication usually occurs in cirrhotics with severe PHG, whereas this is uncommon in patients with mild stage PHG. Sa-

rin et al[1] reported that acute bleeding from PHG occurred in only 2.5% of patients in his series and accounted for about 25% of all bleeds. This figure is similar to the data of McCormack et al[10] and Gostout et al,[65] but is in contrast with the data of D' Amico et al,[21] who found that PHG was the cause of about 40% of all bleeds in their series.

When the incidence and severity of bleeding from PHG is compared with that from esophageal and gastric varices, a statistically significant difference is found to exist. Thus, PHG seems to carry a lower risk of bleeding in comparison with esophagogastric varices.[1]

Chronic gastric mucosal bleeding and recurrent iron-deficiency anemia, sometimes requiring blood transfusion, are the most characteristic clinical features of patients with PHG. Chronic blood loss occurred in only about 10% of the patients in Sarin's[1] study and this figure is in sharp contrast with the 30% reported by D' Amico et al.[21]

Bleeding from PHG is an unusual direct cause of death and it is not an independent risk factor that affects survival in patients with cirrhosis. However, repeated severe bleeding episodes may contribute to the deterioration in liver function.

THERAPEUTIC ALTERNATIVES

Although the true pathogenesis of PHG is not clear, portal hypertension probably plays a major role. Thus, the reduction of portal pressure will be a rational therapeutic approach. The use of β-adrenergic blockers in this pathological condition is based on both experimental and clinical investigations demonstrating that propranolol reduces portal pressure and induces significant vasoconstriction in the overall splanchnic vascular bed.

Results from a large number of studies indicate that propranolol prevents recurrent bleeding from PHG and improves its endoscopic appearance.[66-68] However, despite the proven efficacy of this drug in preventing rebleeding from PHG, 50% of cirrhotic patients under such therapy still presented with rebleeding episodes within 2 years of follow up.[8] The reason for this may be that there are patients who do not respond or respond only poorly to propranolol administration. Some of these patients may benefit from the addition of isosorbite 5-mononitrate, as this can enhance the reduction of portal pressure.[69]

Other drugs, which acutely reduce gastric perfusion might be effective, but no clinical trials are available to assess their effectiveness in arresting bleeding from gastric mucosal lesions in cirrhotics. Preliminary studies have demonstrated that intravenous infusion of vasopressin, glypressin or somatostatin is effective in reducing gastric blood flow in cirrhotics with PHG.[8]

If the bleeding lesions are confined to a restricted area in the gastric mucosa, endoscopic photocoagulation or electrocoagulation may be effective in arresting active bleeding.[70]

Decompressive shunt surgery was found to be useful in the treatment of bleeding from PHG. Recently Orloff et al[71] have reported the results of 12 cirrhotic patients with bleeding PHG, who were subjected to portocaval shunt. In all patients definitive hemostasis was achieved, and during follow-up endoscopy, no recurrent bleeding was observed and the mucosal lesions had disappeared. Shunt surgery is not, however, considered the first treatment option for such a complication, because of the universal decline in the use of surgery to prevent rebleeding in cirrhotic patients and the introduction of effective pharmacological options for the control of upper GI bleeding in cirrhosis.

Other therapeutic alternatives to stop or prevent bleeding from PHG may be the TIPSS. Only a few reports, involving a small number of patients, have suggested that this procedure can be useful in preventing bleeding.[9,14]

The above-mentioned data has led us to conclude that, at present, although pharmacological, surgical and interventional radiological procedures are available in the treatment of bleeding PHG, neither of them could be considered as ideal. Therefore, their efficacy and safety should be examined in appropriate, controlled trials.

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