REVIEW ARTICLE

Portal hypertensive gastropathy and gastric antral vascular ectasia

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Abstract Portal hypertensive gastropathy (PHG) and gastric antral vascular ectasia (GAVE) are gastric mucosal lesions that mostly present as chronic anemia and rarely cause the acute gastrointestinal hemorrhage. Despite similar clinical manifestations, their pathophysiology and management are entirely different. PHG is seen exclusively in patients with portal hypertension, but GAVE can also be observed in patients with other conditions. Their diagnosis is endoscopic, and although generally each of them has a characteristic endoscopic appearance and distribution, there are cases in which the differential is difficult and must rely on histology. This review focuses on the management of both entities. The mainstay of management of PHG is based on portal-hypotensive pharmacological treatment while GAVE benefits from hormonal therapy, endoscopic Nd:YAG laser, and argon plasma coagulation. More invasive options should be reserved for refractory cases.

Keywords Argon plasma coagulation · Liver disease · Portal hypertension

Introduction

Portal hypertensive gastropathy (PHG) occurs as a complication of cirrhotic or noncirrhotic portal hypertension. PHG is clinically important because it may cause acute (and even) massive, or insidious, blood loss. It is characterized by an endoscopic abnormality of the gastric mucosa that is classically described as a mosaic-like pattern that resembles the skin of a snake, with or without red spots [1] (Fig. 1a, b). PHG is seen mainly in the body and the fundus of the stomach but is also seen rarely in the gastric antrum. The mechanisms involved in the pathogenesis of PHG have not been fully elucidated. However, significantly increased gastric mucosal nitric oxide synthase activity was observed in patients of PHG.

The gastric antral vascular ectasia (GAVE) is an increasingly recognized cause of persistent upper gastrointestinal (GI) bleeding. It has a unique endoscopic appearance characterized by prominent erythematous stripes radiating in a spoke-like fashion from the pylorus to the antrum (Fig. 2). The striking appearance suggestive of strips of a watermelon led Jabbari et al. to coin the term "watermelon stomach" for this condition [2]. The mechanisms involved in the development of GAVE syndrome are also unclear. More than 70 % of patients with GAVE syndrome do not have cirrhosis or portal hypertension.
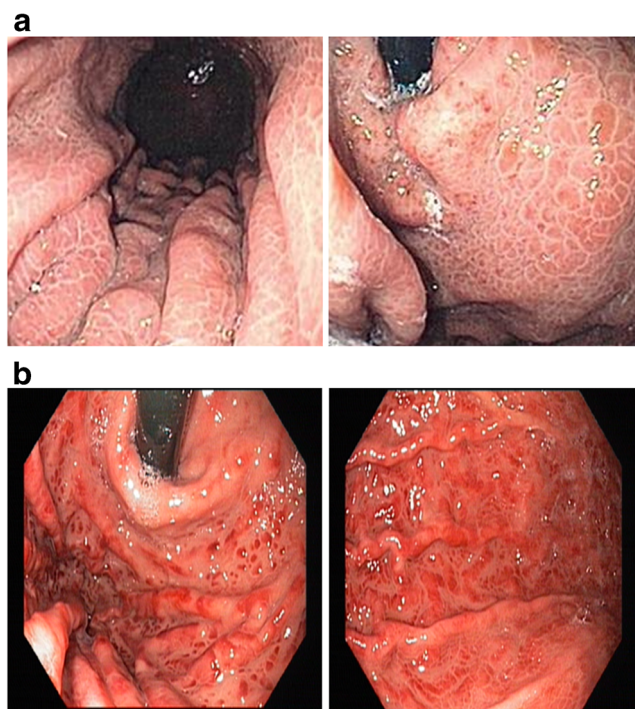
Portal hypertensive gastropathy

PHG is a distinct endoscopic gastric mucosal lesion characterized by a mosaic-like pattern and red markings [1, 3]. In PHG, changes in the gastric mucosa are typically localized to the fundus or corpus of the stomach, but PHG-like conditions have been described elsewhere in the GI tract, including the rectum, colon, and small bowel [4]. The frequency of PHG in patients with portal hypertension has been reported to vary between 10 % and 80 % [5–8]. The wide variation in the reported prevalence is most likely due to differences in the study population, specifically the proportion of patients with noncirrhotic portal hypertension, the severity of the underlying liver disease, and the proportion of patients with previous endoscopic treatment. Approximately 65 % to 90 % of those

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a

b

Fig. 1 Endoscopic appearances of portal hypertensive gastropathy. **a** Mild form is characterized by a mosaic-like pattern without red spots. **b** Severe form is characterized by numerous red spots with the background features of mild portal hypertensive gastropathy

patients have mild PHG whereas 10 % to 25 % of patients have severe PHG [9]. A higher rate of PHG is observed in patients with more severe liver disease [7, 8, 10], high hepatic venous pressure gradient [11, 12], and in patients who underwent endoscopic treatment with sclerotherapy [5, 13]. PHG is usually seen in association with either esophageal or gastric varices [10, 14].

Pathogenesis

The pathophysiology of PHG is unclear although portal hypertension plays a major role. Portal hypertension, and not liver disease, seems to be the key factor for the development of PHG because PHG is common in portal hypertensive
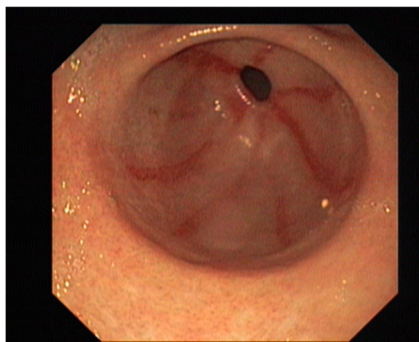
Fig. 2 Endoscopic appearance of gastric antral vascular ectasia

patients with or without liver disease [15]. And this again proved by our own study, PHG was not observed in chronic alcoholics without portal hypertension or chronic liver disease [5].

In experimental models, noxious agents such as aspirin, bile acids, or alcohol have been shown to produce gastric mucosal damage in animals with portal hypertension compared with controls [16]. Circumstantial evidence in humans has also shown similar results [17]. There is experimental evidence to suggest that gastric mucosal defense mechanisms are impaired in the presence of portal hypertension [18, 19].

Increased nitric oxide (NO) production has also been implicated in the pathogenesis of PHG [20] as it is a potent vasodilator, and increased levels have been described in cirrhosis.

Classification

PHG is generally classified as mild or severe [10, 21]. Mild lesions include snake skin or mosaic-like pattern (MLP) and severe as red markings (RM), which include the red-point lesions, cherry red spots, or black brown spots, which are typically very friable and can actively bleed during endoscopy. However, many people believe that the presence of mere mosaic pattern is not very specific for diagnosing PHG and hence grade the severity of PHG based on the extent of the RM [10].

Natural history

PHG is often a dynamic condition and could be transient, persistent, or even progressive [6, 10]. It has been reported to progress from mild to severe in up to 30 % of the cases, and it regresses or disappears in up to 20 % of cases [8, 22, 23]. EV ligation (EVL) and sclerotherapy are associated with faster progression of PHG [6, 24], but this worsening is usually transient, fewer chances of bleed, and PHG can regress in up to 44 % of patients after sclerotherapy [6].

We have also observed, patients who have PHG associated to cirrhosis-related portal hypertension have more frequently persistent and progressive PHG (which is more likely to bleed) than patients with PHG related to noncirrhotic portal hypertension [6].

Clinical presentations

PHG is mostly asymptomatic, but, when symptomatic, bleeding (mostly chronic) is the most important complication of this disease. Incidence of acute bleeding and chronic blood loss from PHG was 2.5 % and 10.8 %, respectively [23]. Acute bleeding is defined as the presence of hematemesis or melena associated with endoscopic evidence of an actively bleeding mucosal lesion, while chronic bleeding is considered to have

occurred if a decrease of 2 g/dL or more drop in hemoglobin has taken place in the past 6 months, in the absence of NSAID use [12, 25]. Patients with diffuse and severe PHG bleed much more than those with PHG in the antrum or fundus [6, 22]. In patients with chronic liver disease, PHG was associated with 4 % of all the cases of acute bleeding and 8 % of the cases of nonvariceal bleeding [26]. There is limited data on the mortality directly related to acute and active PHG bleeding. Mortality rates are lower for PHG bleed than for esophageal variceal bleed (12.5 % vs. 39.1 %, p=ns) [23].

Hemodynamics of PHG

Kumar et al. earlier studied the hemodynamics in cirrhotic patients of PHG and compared it to patients without PHG [12] and found the patients with PHG were significantly more vasodilated as indicated by significantly high mean cardiac index, mean cardiac output, low median systemic vascular resistance, and low median pulmonary vascular resistance. Thus, PHG is not merely a local phenomenon in gastric mucosa but also a severe manifestation of generalized vascular alterations of cirrhosis and portal hypertension.

Management

The most effective specific treatments in patients with PHG are those aimed at reducing portal pressure. The main pharmacological agent that has been investigated in this setting is the nonselective beta-blocker propranolol. Management of PHG depends upon the clinical presentation.

Asymptomatic PHG

The most frequent setting is finding PHG on a routine endoscopy performed to evaluate the presence of varices. In this setting, the patient may be asymptomatic with no evidence of chronic bleeding. Prophylaxis of bleeding from PHG has not been evaluated in clinical studies and is therefore not recommended. However, primary prophylaxis with propranolol for PHG bleeding should be considered in patients who have preexisting mild or severe PHG and are likely to undergo EV ligation, including the risk of progression of PHG.

Acute gastrointestinal bleeding

The treatment of acute bleeding from PHG is still unsatisfactory, partly because the pathogenesis is unclear and treatment is only directed to reduce portal pressure. Once endoscopy establishes PHG as the cause of the acute bleeding episode, specific measures to treat PHG should be undertaken. No well-designed studies have evaluated the use of endoscopic therapy of acutely bleeding PHG lesions. Besides specific local therapy, it would also appear reasonable to follow the

same recommendations that apply to variceal hemorrhage, including a cautious transfusion policy and prophylactic antibiotics. Similar to variceal bleeding, drugs to reduce portal pressure are the mainstay of the treatment. A number of pharmacologic therapies have been used in an effort to treat acute bleeding, their effects being predicated on reduction of portal pressure (Table 1). The use of propranolol was evaluated in a small open trial in acute severe bleeding from endoscopically proven PHG with early cessation of bleeding (93 %) with 3 days of drug initiation [27]. However, use of nonselective beta-blocker has some drawbacks; it requires several days before a hemodynamically effective dose is reached and the possibility of aggravating hypotension in an already vasodilated systemic circulation. Vasoactive drugs (like somatostatin and its analog, vasopressin and its analog) were also been proven effective in three different trials [28–30]. Terlipressin, a vasopressin analog, may also be effective for the treatment of acute bleeding caused by PHG and appears to have similar efficacy as octreotide [31].

Endoscopic treatment for PHG bleeding plays a small role in the treatment of PHG—because bleeding is usually diffuse. Argon plasma coagulation and possibly even coagulation therapy with the heater probe may be considered with focal bleeding—but there are no data that have addressed endoscopic treatment. In rare occasions, acute hemorrhage is not controlled with medical therapy. Nonresponse to medical treatment in the acute setting may be defined according to the standards of nonresponse to variceal bleeding [32].

Once it has been verified that refractory bleeding is associated to PHG, rescue therapies like portosystemic shunt therapies should be considered, either surgical or through the placement of a transjugular intrahepatic portosystemic shunt (TIPS). Though there is no substantial data to support this logical approach. However, TIPS and shunt surgery are both invasive and associated with substantial morbidity and mortality and should be considered only as a last resort. Orloff et al. in 1995 showed the definitive treatment of bleeding, excellent safety, and acceptable quality of life after total portacaval shunt in patients of biopsy-proven cirrhosis with active bleeding from severe portal hypertensive gastropathy [33].

Chronic gastrointestinal bleeding

In terms of management of chronic bleeding, there is limited data to make strong evidence-based recommendations. Such PHG bleed patients should be treated with iron supplementation, orally or parenterally. Taking into account the important role of portal hypertension in the development of PHG, specific treatment of PHG is mainly based on portal pressure-reducing approaches. The use of nonselective beta-blockers, particularly propranolol, has been studied in this setting. The first randomized crossover trial showed patients who received

Table 1 Treatment and prevention of portal hypertensive gastropathy

S. no.	Clinical settings	Drugs and recommendation
1	Acute bleeding	Octreotide
		Terlipresson or vasopressin
		Propanolol
		TIPS
2	Chronic bleeding	Not enough evidence for recommendations
		Propanolol or TIPS could be considered
3	Prevention of first bleeding	Not enough evidence for recommendations
		Propanolol could be considered in severe PHG
4	Prevention of recurrent bleeding	Propanolol

TIPS transjugular intrahepatic portosystemic shunt, *PHG* portal hypertensive gastropathy

propranolol had a lower rate of hemorrhage, an increase in hemoglobin level, and an improvement in the endoscopic appearance of the lesions, compared to the placebo [34]. Another randomized study [25] in a patients of recurrent bleeding (acutely or chronically) due to PHG showed the actuarial percentages of patients free of rebleeding from PHG were significantly higher in the propranolol-treated patients than in the untreated controls at 12 months (65 % vs. 38 %; p less than 0.05) and at 30 months of follow up (52 % vs. 7 %; p less than 0.05).

The results of these studies led to the consensus recommendation that nonselective beta-blockers should be used in the chronic setting once the acute episode of bleeding is controlled and the patient is stable [32].

Use of other pharmacologic agents in PHG such as losartan [35], thalidomide [36], and corticosteroids [37] has been described. However, the evidence supporting the use of these agents is weak with small open-label studies and case reports.

Patients not responding to propranolol therapy should be considered for TIPS, which has been shown to help rapid reduction in portal pressure and regression of endoscopic lesions [38].

Gastric antral vascular ectasia

Gastric antral vascular ectasia (GAVE) is characterized by the presence of red spots without a background mosaic pattern that are typically located in the gastric antrum and has a unique endoscopic and histolopathological characteristics. Besides portal hypertension, GAVE is also shown to be associated with scleroderma, diabetes, atrophic gastritis, bone marrow transplantation, and chronic renal failure [2, 17, 39–41]. It is possible that a fair number of patients with this disease may have an underlying hepatic fibrosis, especially those with diabetes and obesity.

GAVE is a less frequent condition, having been reported in only 2 % in patients of cirrhosis [42]. In contrast to PHG, GAVE is only observed in the stomach and not in other parts of the GI tract.

Pathogenesis

The exact pathogenesis of GAVE is not clear. However, it is not directly related to high portal pressure as patients do not respond to portal pressure-reducing therapies, such as TIPS or surgical shunt [43]. Some authors have proposed partial prolapse of the loosely attached gastric mucosa of the antrum induced by vigorous gastric peristalsis as the primary event [2]. This leads to intermittent obstruction of the submucosal blood vessels, resulting in vascular ectasia. This theory is strengthened by the histological features of fibromuscular hyperplasia of the lamina propria and dilatation of the mucosal capillaries. Altered antral motility [44] and role of hypergastrinemia [45] may also be responsible for the occurrence of gastric antral vascular ectasia in cirrhosis.

Clinical presentation and diagnosis

Gastric antral vascular ectasia is increasingly being recognized by endoscopists. Most of the patients diagnosed are elderly, with a preponderance of women. The majority of patients present with iron deficiency anemia secondary to occult blood loss [2, 46–48]. Indeed, 60 % to 70 % of patients are transfusion dependent due to recurrent anemia despite iron supplements [46]. In addition, some patients present with overt GI bleeding in the form of intermittent melena and, occasionally, hematemesis [40]. GAVE causes nonvariceal bleeding in about 4 % of patients with PHT [49].

The diagnosis of GAVE is established when characteristic-aggregated red spots arranged in a linear fashion in the antrum of the stomach without a background mosaic pattern (hence the name GAVE and watermelon stomach). However, the red spots could be present all over the antrum and then it is termed as diffuse GAVE. Generally, it is easy to differentiate the two lesions (Table 2), but in rare cases, the lesions of PHG and GAVE could co-exist in the antrum.

Table 2 Differentiation between portal hypertensive gastropathy and gastric antral vascular ectasia

	PHG	GAVE
Associated with portal hypertension	Always	Not always (also present in other diseases)
Distribution in stomach	Proximal	Distal
Mosaic pattern	+	−
Red spots	+, ++	+
Pathology	−	+++
Thrombi	+	++
Spindle cell proliferation	+	+++
Fibrohyalinosis		
Response to therapies directed at decreasing portal pressure	+	−
First-line treatment acute chronic salvage therapy	Octreotide/somatostatin	Endoscopic ablation
	Propranolol	Endoscopic ablation
	TIPS/shunt	Antrectomy and Billroth-1

PHG portal hypertensive gastropathy, *GAVE* gastric antral vascular ectasia

Management

Several therapeutic modalities have been used for the treatment of GAVE syndrome. Specific measures to treat patients with GAVE with acute or chronic bleeding is substantially different from those used in PHG. As different from the management of PHG, the mainstay of treatments in GAVE is the endoscopic ablation of the lesions.

Asymptomatic patients

Similar to PHG, in patients of cirrhosis, the most frequent setting is finding GAVE on a routine endoscopy performed to evaluate the presence of varices. Prophylaxis of bleeding from GAVE has not been evaluated in clinical studies and is therefore not recommended.

Acute gastrointestinal bleeding

Once endoscopy establishes GAVE as the cause of the acute bleeding episode, specific measures to treat GAVE should be undertaken. In this setting, the general therapeutic measures recommended for patients with cirrhosis and acute hemorrhage from varices will apply to patients with cirrhosis who bleed acutely from GAVE. Many different endoscopic treatment have been used for the management of GAVE-related bleed, although mostly evaluated were thermal therapy. No well-designed studies existed to suggest the endoscopic therapy of acutely bleeding GAVE lesions. The endoscopic treatment of GAVE with thermal therapies such as laser, electrocautery, and argon plasma coagulation (APC) has historically been successful and provided an alternative to surgical antrectomy. APC is a thermoablative method, which is based on producing thermal coagulation by applying high-frequency electric current that is passed through with argon gas without direct contact with the mucosa, but has significant limitations including multiple treatment sessions, persistent bleeding, and occasional complications remain [50–54]. Antrectomy is reserved for refractory cases [47].

However, a recently published controlled study showed the EBL was better than thermal therapy (APC). Patients who received banding had a significantly greater increase in hemoglobin, decrease in blood transfusion requirements, and hospital admissions [55]. The antifibrinolytic agent tranexamic acid has also been found in two separate studies to be effective in the treatment of GAVE syndrome [56, 57]. Tranexamic acid has been used previously in the treatment of upper GI bleeding and in a meta-analysis was found to cause a 20 % to 30 % reduction in bleeding, 30 % to 40 % reduction in the need for surgery, and a 40 % reduction in overall mortality in patients with a variety of causes of upper GI bleeding [58].

Chronic gastrointestinal bleeding

As already been discussed, GAVE syndrome frequently have chronic significant blood loss often resulting in transfusion dependency. Several therapeutic modalities have been used for the treatment of GAVE syndrome.

Nd:YAG laser coagulation has been found to improve lesions and decrease blood requirements but generally is not as effective in those patients with diffuse GAVE syndrome [48, 59–61]. It is the most commonly reported endoscopic modality in the treatment of watermelon stomach. The largest study so far included 45 patients with watermelon stomach, which showed after a median of one treatment session (range, 1–4); complete resolution of the disease was seen in 13 % of patients, and resolution of >90 % was seen in 80 % of patients [46].

The most number of studies evaluating the use of thermoablative methods in the treatment of GAVE are with argon plasma coagulation. Argon plasma coagulation is a no-touch electrocoagulation technique, which uses high-frequency monopolar current conducted to target tissues through ionized argon gas. The advantage of this technique is easily applied and its risk of perforation is lower than with Nd:YAG laser. Large areas of the mucosa may be treated in a single session although this is very time-consuming. Complications associated to this method are the development of hyperplasic polyps [62, 63] and gastric outlet obstruction [64]. The technique combines both focal pulse and "paint brush." The sessions should be repeated every 2–6 weeks as needed.

Wahab et al. included six patients with watermelon stomach and demonstrated the resolution of lesions in all patients with a mean of 2.8 sessions [65].

Other thermoablative techniques such as heater probe ablation [66] do not appear to have significant advantages over the previously described methods. Other endoscopic techniques with limited experience such as cryotherapy may offer some additional advantages. Cryotherapy [67] consists of rapid expansion of compressed nitrous oxide; one of the potential therapies for mucosal vascular lesions in the GI tract is the application of extremely low temperatures to achieve a controlled thermal injury with resultant tissue destruction.

Regarding the pharmacotherapy, limited experience was reported. In an open pilot study, Tran et al. demonstrated complete cessation of bleeding in four patients and reduction in transfusion requirements in all patients [68]. Despite good control of bleeding, hormonal therapy did not modify the endoscopic appearance in any of the patients. Thus, it is likely that bleeding will recur on discontinuation of therapy. Some improvement has also been described in case reports with the use of octreotide [69], corticosteroids [70, 71], thalidomide [72], serotonin antagonist [73], and calcitonin [74].

In extreme circumstances, surgical treatments including antrectomy [75] and liver transplantation [42, 76] can cure GAVE syndrome, but in the setting of portal hypertension and cirrhosis, antrectomy can be associated with a significant mortality risk [43, 77].

Conclusions

PHG and GAVE have entirely different pathophysiological mechanisms, endoscopic appearance, and management, despite their sharing similar clinical manifestations. Most cases will present as chronic bleeding, although there may be some cases of acute life-threatening bleed. PHG commonly occurs in the setting of portal hypertension, but GAVE can also be observed in patients with other conditions. The treatment of PHG is based on measures that reduce portal pressure, namely the administration of beta-blockers. On the other hand, gastric vascular ectasia responds to endoscopic treatment.

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