PORTAL HYPERTENSIVE GASTROPATHY: A COMPREHENSIVE REVIEW

Shabir Shiekh (MD, DM)¹, Showkat Kadla (MD, DM)¹, Bilal Khan (MD, DM)¹, Nisar Shah (MD, DM)²
Consultant¹, Senior Consultant³, Professor and Head²,
Department of Gastroenterology and Hepatology, Govt. Medical College, Srinagar, Kashmir, India.

Abstracts
Portal hypertensive gastropathy (PHG) encompasses the gastric mucosal changes occurring in the setting of portal hypertension, both cirrhotic and non-cirrhotic. Its significance lies in causing acute gastrointestinal bleeding and insidious chronic blood loss presenting as iron deficiency anemia. Diagnosis of PHG is straight-forward, made endoscopically often characterized by a mosaic-like pattern resembling ‘snake-skin’, with or without red spots. Treatment of acute GI bleed is hemodynamic stabilization, vasoconstrictor therapy, antibiotic prophylaxis, non-selective beta-blockers. Endoscopic treatment like APC has a small role. In severe cases, TIPS and shunt surgery can be offered. Secondary prophylaxis of PHG bleeding with non-selective b-blockers is recommended.

Keywords: Portal hypertensive gastropathy, Gastrointestinal bleeding, Cirrhosis, Beta-blockers

Introduction

Historical background
Palmer in 1957,¹ proposed that the pathogenesis of erosive gastritis in cirrhotic patients was different than that in non-cirrhotic patients and that erosive gastritis in cirrhotic patients resulted from mechanical venous back-pressure from portal hypertension, rather than acirculating, mucosal, or intraluminal toxic factor. This proposal was supported by successful reversal of erosive gastritis in cirrhotic patients with portal decompression by surgical shunts.²

In 1984, Sarfeh et al³ recognized a distinct form of gastric mucosal hemorrhage in patients who had portal hypertension, demonstrated by cirrhosis and gastroesophageal varices, which they called “portal hypertensive gastritis”. They proposed that gastric mucosa in portal hypertension reacts differently from gastric mucosa without portal hypertension and these patients with portal hypertension may benefit from portal decompressive surgery. One year later, McCormack et al⁴ reported that the gastritis in patients with portal hypertension differed from that in patients without portal hypertension in mucosal histology, non-response to standard therapy for conventional gastritis, and occasionally having very similar histological changes in other gastrointestinal (GI) organs such as the colon. They called these gastritis-like changes in patients with portal hypertension “congestive gastropathy”.⁵

Epidemiology
PHG can present at any age, including pediatric or adult patients. The reported prevalence of PHG varies greatly from 20% to 75% in patients with portal hypertension and varies greatly from about 35% to 80% in patients with cirrhosis. This wide variability likely reflects variability in classification criteria, interpretation of endoscopic lesions, study populations, and natural history of PHG. In the HALT-C trial, 374 (37%) of 1011 patients with biopsy-proven cirrhosis or bridging fibrosis from hepatitis C had PHG.⁶ The prevalence of mild PHG in patients with portal hypertension ranges from 29%-57%, and of severe PHG ranges from 9%-46%.⁷

Pathophysiology
Risk factors: Basic underlying abnormality in PHG is portal hypertension whether non-cirrhotic or cirrhotic. Other factors are the duration and severity of cirrhosis, size of esophageal varices, variceal ligation status. Sarin et al⁸ found 86 out of 967 i.e.9% patients of PHTN with prior variceal bleeding had of PHG. Wu et al⁹ and Fontana et al¹⁰ found overall rates of PHG in cirrhosis at 64% and 37%, with severe PHG rates of 11% and 3% respectively. Prevalence of PHG directly correlates with HVPG, severity of cirrhosis and grade of esophageal varices.¹⁰ PHG appears to be higher in portal hypertension with cirrhosis than in portal hypertension without cirrhosis¹¹. No definite association exists between etiology and duration of cirrhosis and PHG severity. PHG increases in frequency with CPT score as reported by Sarin et al¹² CPT class A and CPT class C had respectively 13% and 87% prevalence of PHG. Markers of severity of portal hypertension thrombocytopenia, hypoaalbuminemia and hyperbilirubinemia are independent predictors of PHG. Many studies have documented higher frequency of PHG in patients with concomitant gastric and esophageal varices.¹²,¹³
Esophageal variceal eradication:
Majority of the studies have shown that the severity of PHG increases after variceal eradication whether variceal ligation\textsuperscript{13,14} or sclerotherapy\textsuperscript{11,15} thought to be due to redistribution of residual blood flow that had passed through the previously patent varices causing increasing PHG from gastric mucosal congestion. Underlying etiology of cirrhosis/NCPH, alcoholism, use of COX-2 inhibitors/NSAID, tobacco and Helicobacter pylori infection are found not to increase the risk of PHG.

Pathogenesis
Hemodynamic changes: Fundamental predisposing factor is PHTN leading to hyperdynamic congestion. Leading to increased gastric blood flow, and most likely decreased gastric mucosal flow that leads to activation of cytokines, growth factors, and hormones that perpetuate this hyperdynamic gastric circulation. Hashizume et al\textsuperscript{16} reported that cirrhotic patients have dilated small gastric blood vessels, including arterioles, precapillaries, submucosal veins, and subserosal veins, with decreased arteriovenous resistance and straightening of arterioles. These released proinflammatory mediators inhibit growth factors which render gastric mucosa more susceptible to injury and impaired mucosal healing.

Microvascular changes:
Electron microscopy has revealed significantly larger cytoplasmic and pinocytic vesicular areas, increased capillary basement membrane thickness, arterialization of submucosal veins and thickening of arterioles in the muscularis mucosae and submucosa\textsuperscript{17}.

Molecular mechanisms:
The changes described in human and rat models in PHG occurring at molecular level can be summarized below
1. Elevation of VEGF which might accelerate mucosal angiogenesis and increase blood flow.
2. an elevated TNF-\alpha level which stimulated release of nitric oxide (NO) and prostacyclin, important mediators of a hyperdynamic circulation
3. increased serum levels of NO, a potent vasodilator released by endothelial cells particularly gastric cNOS significantly increased
4. elevated serum levels of 6-keto-PGF1\alpha, a metabolite of prostacyclin (vasodilator), in cirrhotic patients with PHG.
5. high serum level of autotoxin
6. increased gastric mucosal apoptosis and decreased mucosal proliferation
7. elevated levels of injurious free radicals and lysosomal enzymes and decreased levels of protective antioxidant enzymes in gastric mucosa

Progression/regression of portal hypertensive gastropathy:
PHG has a fluctuating course, remains stable in 30–60%, progress from mild to severe in up to 30% of the cases and it regress or disappear in up to 20% of cases\textsuperscript{18,10}. High CP scores at entry were associated with progression of PHG\textsuperscript{10}.

Table 1: Different classification systems for portal hypertensive gastropathy

<table>
<thead>
<tr>
<th></th>
<th>Mild</th>
<th>Severe</th>
<th>Moderate</th>
</tr>
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<tbody>
<tr>
<td>McCormack et al\textsuperscript{3}</td>
<td>Fine pink speckling</td>
<td>Discrete red spots</td>
<td></td>
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<td></td>
<td>Superficial reddening, especially onrugal surface (striped appearance)</td>
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<tr>
<td></td>
<td>Fine white reticular pattern separating areas of raised edematous mucosa (snakeskin)</td>
<td>Diffuse hemorrhagic gastritis</td>
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<tr>
<td>Spina et al\textsuperscript{19} (NIEC)</td>
<td>Mosaic-pattern: Presence of small, polygonal areas surrounded by whitish-yellow depressed border</td>
<td>Red point lesions (1 mm in diameter, flat)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Cherry-red spots (2 mm, slight protrusion)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Black-brown spots (irregularly shaped, persistently present after washing)</td>
<td></td>
</tr>
<tr>
<td>Sarinet al \textsuperscript{20} (Baveno-Consensus Workshop)</td>
<td>Mild ≤ 3 points\textsuperscript{3}</td>
<td>Severe ≥ 4 points\textsuperscript{3}</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gastric antralectasia</td>
<td>Gastric antralectasia</td>
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<tr>
<td></td>
<td>Absent (0)</td>
<td>Present (2)</td>
<td></td>
</tr>
<tr>
<td>Yoo et al\textsuperscript{21} 3-category classification</td>
<td>Mild reddening Congestive mucosa</td>
<td>Diffusely red areola Pinpoint bleeding Discrete or confluent red mark lesion</td>
<td>Flat red spot in center of a pink areola Severe redness and a fine reticular pattern</td>
</tr>
<tr>
<td></td>
<td>Diffuse pink areola</td>
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</table>

1 point each to mild mucosal mosaic pattern/ isolated red markings
2 points each to severe mucosal mosaic pattern / confluent red markings
Diagnosis

Endoscopy:
Endoscopy is diagnostic and the characteristic findings are mosaic-like pattern or a diffuse, erythematous and reticular cobblestone pattern of gastric mucosa ranging from pink speckled lesions within a mosaic or snakeskin pattern in mild cases, to localized small areas of intense erythema, resembling a scarlatina rash, in severe cases predominantly involving the gastric body and fundus, and rarely in the antrum. A meta-analysis concluded that the mosaic-like pattern had high specificity at 98% (range: 93%-100%), but low sensitivity at 38% (range: 7%-94%) for PHG.

Capsule endoscopy: Although limited indication, but capsule endoscopy had an accuracy of 57%, sensitivity of 96%, and specificity of 17% compared to EGD. Involving a study in cirrhosis.

Dynamic CT: The presence of transient segmental or subsegmental hypo-attenuating mucosa in the gastric fundus or body during hepatopancreatographic imaging that returns to normal attenuation on portal venous phase has per fusion defect sign has been described with a sensitivity of 75%, specificity of 88.6% for diagnosing PHG in patients with cirrhosis.

Characteristic histologic findings of PHG include capillary and venule dilatation, and markedly congested and tortuous submucosal venules. Stromal fibrosis and edema of lamina propria can occur. Inflammatory cells and fibrin thrombi are generally absent.

Clinical presentation

Acute GI bleeding: PHG is responsible for < 1% of upper GI bleeding in the general population, and for about 8% of non-variceal upper GI bleeding in patients with liver disease. Major risk factors for bleeding from PHG are increasing PHG duration, extent, and severity, advanced cirrhosis, and prior endoscopic eradication of esophageal varices.

Chronic bleeding: The frequency of chronic bleeding ranges from 3%-26% possibly due to variable definitions of chronic GI bleeding. Common definitions include: (1) > 2 g/dL decrease in hemoglobin level during > 6 mo in patients without acute GI bleeding and not receiving NSAID therapy; (2) presence of anemia in patients with cirrhosis; and (3) positive fecal occult blood (Baveno II). Blood loss from PHG is usually mild but rarely severe demanding transfusions.

Management

Pharmacotherapy for PHG

β-adrenergic receptor antagonists: They reduce portal pressure and gastric mucosal blood flow, and thereby reduce bleeding from PHG. A multi-center, randomized, controlled trial including cirrhatics with acute or chronic bleeding from severe PHG treated with propranolol rebleed significantly less frequently (P <0.05). Propranolol group also required less units of packed. Propranolol also reduced the risk of developing PHG after and the mean PHG severity score esophageal variceal eradication. Very high dose of propranolol 240-480 mg/d has been used to arrest acute bleeding from PHG.

Non-specific β-adrenergic receptor antagonists are a first line therapy for secondary prophylaxis of PHG bleeding.

Vasoconstrictor therapy: (Somatostatin, octreotide, Vasopressin and terlipressin):
These drugs cause splanchnic vasoconstriction, reduce portal pressure, reduce portal blood flow, and decrease gastric perfusion. Octreotide is a first-line treatment for acute bleeding from PHG. Octreotide at 100 mcg bolus followed by infusion of 25 mcg/min for the first 24 h and then 20 mcg/min for the second 24 h, controlled bleeding from PHG in 83% patients at 24 h and in 100% patients at 48 hand tended to be more effective than both vasopressin and omeprazole.

Somatostatin and octreotide are useful for acute bleeding but not for preventing chronic bleeding from PHG. Terlipressin is also useful in controlling acute bleeding from PHG especially when used at a dose of 1 mg IV every 4 h for 5 d.

Antioxidants: Antioxidants help in free radical scavenging and in reversing impairment of oxidative stress induced ERK2 activation. Vitamin E and Rebamipide (antiulcer drug) have been found to lead to decreased susceptibility of PHG gastric mucosa to alcoholic injury, mucosal lipid peroxidation, decreased lysosomal enzymes, and increased levels of antioxidants in some rat studies.

Estrogen and progesterone: Although not much data exists but they have been found to reduce gastric mucosal blood flow, portal pressure, and porto-collateral resistance in rats with surgically-induced portal hypertension.

Thalidomide: In one case report thalidomide (100 mg daily) was successful as a last resort. Reduction of NO leading to decrease in portal pressure is likely mechanism 34.

Corticosteroids: Prednisolone 20 mg/d was found to be effective in improving endoscopic appearance and anemia in one case report of PHG refractory to Propranolol.

Losartan: The angiotensin II receptor antagonist resulted in improvement of PHG and decreased portal pressure.

Sucralfate and acid-suppressing medications (omeprazole):
Although not very effective at reducing bleeding from PHG because most patients with PHG already have hypochlorhydria, but may indirectly stop bleeding from the stomach by raising intraluminal gastric pH and thereby stabilizing blood clots.

Endoscopic therapies: Not much data exists on efficacy of endoscopic therapy for PHG bleeding. Largely role of endotherapy is limited.
**Argon plasma coagulation (APC):** These therapies can treat a larger bleeding surface area resulting in hemostasis, rise in hematocrit and decreasing blood transfusions.  

**Hemorspray** used in few cases has led to cessation of diffuse bleeding from severe PHG after spraying hemorspray TC-325 (a nanopowder hemostatic agent).  

**Endoscopic cryotherapy** has been used as salvage cryotherapy was successful after failed TIPS and APC, with normal hemoglobin levels maintained during 4 weeks of follow-up 248.

**Chronic Bleeding**

Patients with PHG may present with chronic occult blood loss with iron deficiency anemia. They should be managed with iron-replacement. Nonselective beta-blockers have decreased rebleeding and frequency of PHG in these cases. TIPS: TIPS has been found to lower portal pressure, decreasing total gastric blood flow but increasing gastric mucosal blood. Studies have shown TIPS reduces the frequency and severity of PHG significantly. Another study has reported TIPS led to improvement or resolution of PHG findings and decreased transfusion requirements. Shunt surgery: Although rarely used now, shunt surgery decreases portal hypertension, decreases PHG severity, decreases risk of PHG bleeding, and may sometimes completely resolve the endoscopic features of PHG. Splenectomy performed for various indications in PHTN has led to decrease in PHG severity. Liver transplantation done for end stage liver disease, PHG resulted in the resolution of majority of the PHG features. Mortality: Bleeding in PHG is rarely fatal and contributes little to overall morbidity and mortality from portal hypertension. Summary of management for bleeding from portal hypertensive gastropathy (acute and chronic). Acute bleeding General measures for patient stabilization  
Blood transfusion aiming Hb > 8 gm/dl  
Consider antibiotic prophylaxis  
Vasoconstrictor therapy (Octreotide or terlipressin)  
Endo-therapy (APC)  
TIPS: Rarely required - for uncontrolled hemorrhage or for bleeding from PHG associated with variceal bleeding  
Severe coagulopathy/severe thrombocytopenia may be given FFP/Platelet transfusions  
Chronic bleeding  
Symptomatic treatment for anemia (Iron therapy/PRBCs)  
Propranolol

**Summary**

PHG can cause acute and/or chronic GI bleeding. Although pathogenesis is still not completely understood, but currently understanding relates it to portal hypertension. Diagnosis is endoscopic, rarely needs histology support. Main differential diagnosis is GAVE and in some situations needs biopsy. Management of PHG with acute bleeding, hemodynamic stabilization with IV fluids, IV antibiotics, and blood transfusion should be provided as needed. IV pharmacologic therapy to decrease portal pressure followed by nonselective b-blockers as soon as the patient is hemodynamically stable is appropriate. In patients with chronic bleeding, therapy with b-blockers and iron replacement is advised. TIPS and shunt procedures may be helpful in some situations. The most effective approach to reduction of portal pressure is liver transplantation, which should be considered in appropriate candidates.

**Disclosures**

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Shiekh Shabir is the article guarantor.  

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**Bibliography**

gastropathy in patients with liver cirrhosis: a haemodynamic study. 


