Original Article

Prevalence of Portal Hypertensive Gastropathy in Chronic Upper GI Bleeding Presenting With Iron Deficiency Anemia in Cases of Advanced Liver Cirrhosis

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Objective: To demonstrate the prevalence of portal hypertensive gastropathy in patients with advanced chronic liver disease presenting with iron deficiency anemia due to chronic upper GI bleeding.

Methods: Portal hypertensive gastropathy is a well know clinical entity that is definitely responsible for at least some cases of acute or chronic upper GI bleeding in patients with cirrhosis of liver, but the true incidence is not known. Current study was conducted to find out the incidence of PHG as a cause of chronic upper GI bleed in patients with liver cirrhosis presenting with gradual development of iron deficiency anemia and positive fecal occult blood.

Results: Of the fifty patients selected for the study 22 were males and 28 were females. Upper GI endoscopy done in these patients showed evidence of portal hypertensive gastropathy in 38 (21male; 17 female) [76 % (75%; 77% respectively)] had endoscopic evidence of PHG; while 44 (24male; 20female) [88 % (85%; 90% respectively) patients had different grades of esophageal varices and all patients with PHG also had esophageal varices.

Conclusions: PHG is a common finding among patients with chronic upper GI bleed in patients with portal hypertension due to cirrhosis of liver presenting with iron deficiency anemia.

Keywords: portal hypertensive gastropathy, cirrhosis, esophageal varices.

Introduction

Upper GI bleed, defined as bleeding above the ligament of Treitz[1] is a common cause of morbidity and mortality in patients with cirrhosis due to any cause.[2] The bleeding can be massive and exsanguinating, presenting with hematemesis and hematochezia/melena, less severe that presents with melena with rapid drop of hemoglobin, or mild and chronic presenting with gradual development of iron deficiency anemia.[3] While the leading cause of severe upper GI bleeding is bleeding esophageal or gastric fundal varices followed by peptic ulcer,[2,4,5] the cause and incidence of chronic upper GI bleed is not well understood. Gastric or duodenal erosions, gastric antral vascular ectasia (GAVE) and portal hypertensive gastropathy (PHG) are major candidates.[6] Determination of PHG as the cause of upper GI bleed may be difficult especially if no bleeding spot is visualized during endoscopy. Various studies have reported incidence of 3-60% of chronic bleeding from PHG in patients who have this lesion. The incidence of bleeding depends upon extent and severity of the lesion. Other risk factors for bleeding appear to be advanced liver disease, presence and size of esophageal varices and prior endoscopic variceal obliteration.[7] The purpose of this study was to assess the prevalence of portal hypertensive gastropathy in patients with cirrhosis of liver presenting with iron deficiency anemia due to chronic upper GI bleeding. Various criteria have been used to diagnose chronic upper GI bleeding, but the mere presence of anemia in a patient with cirrhosis may overestimate the incidence as these patients may have low hemoglobin due to other causes like hyperslenism or bone marrow suppression. Thus the criteria used in this study included a hemoglobin drop of >2 gm/dl over last six months with presence of iron deficiency anemia and a positive fecal occult blood test in patients not taking NSAIDs.[8,9]

Methods

This study was conducted in the medical department of Akhter Saeed Teaching Hospital between June 2017 and April 2018. A total of fifty patients with advanced chronic liver disease were selected for upper GI endoscopy, who presented with a gradual drop of hemoglobin of ≥2 gm/dl. over the previous six months, and a picture of iron deficiency anemia without the presence of significant leukopenia or thrombocytopenia. Stool analysis for occult blood was done to confirm chronic upper GI bleeding and patients with obvious other causes for iron deficiency anemia like those with hemorrhoids were excluded. Other exclusion criteria included use of non-steroidal

Anti-inflammatory drugs (NSAIDs), the presence of hepatic encephalopathy, bacterial peritonitis or acute upper GI bleeding, presenting with hematemesis or melena.

Results

Of the fifty patients that were included in the study 28 were females and 22 were males. Forty eight patients were positive for hepatitis C and two were having chronic active hepatitis B virus infection. Hemoglobin level ranged from 8.2 to 10.8 gm/dl (avg. 9.5±1.3) for males and 7.8 to 10.1 gm/dl (avg. 9.0±1.1) for females. Liver functions were deranged in all patients and all had positive test for fecal occult blood. During endoscopy, 38 (21male; 17 female)[76% (75%; 77% respectively)] had endoscopic evidence of PHG; while 44(24 male; 20 female) [88 % (85%; 90% respectively) patients had different grades of esophageal varices and all patients with PHG also had esophageal varices. All patients with PHG exhibited associated esophageal varices. Three patients also had small duodenal ulcers but there was no evidence of recent bleed from either of these lesions and all patients were hemodynamically stable.

Table-1: Patient characteristics.

Patients Characteristics		Findings
	Male/Female	28/22
	Age (Years)	Male: mean; 51±12
		Female: mean; 45±10
	Chronic hepatitis C	48 (96%)
	Chronic hepatitis B	02 (4%)
Hemoglobin (gm/dl):	Male	8.2 -10.8 (mean. 9.5±1.3)
	Female	7.8 - 10.1 (mean. 9.0±1.1
PGH [number (%)]:	Male	21 (75%)
	Female	17 (77%))
Varices [number (%)]:	Male	24 (85%)
	Female	20 (90%)

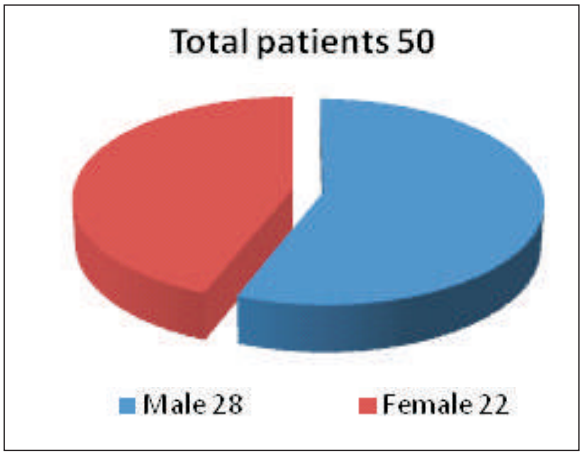

Fig-1: No. of males/females.

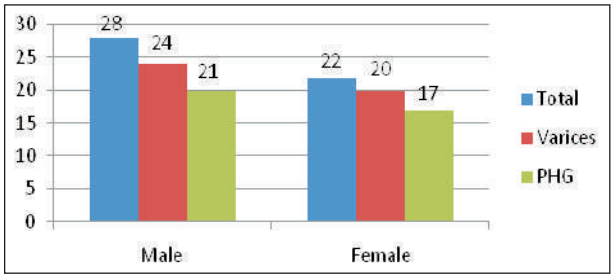

Fig-2: Number of patients with varices and PHG.

Discussion

Acute and chronic upper GI bleeding is a common life threatening condition in cases of liver cirrhosis. Most common cause of such bleeding is bleeding from esophageal or gastric antral varices.[6,10] Other possible sources of such bleeding include Gastric antral vascular ectasia (GAVE) and Portal hypertensive gastroenteropathy (PHG.[11-13] Peptic ulcers are not thought to be cirrhosis related, although 8-10% of cirrhotic patients have peptic ulcers.Gastric ulcers are known to heal more slowly and recur more frequently than in non-cirrhotic patients but majority of these ulcers are usually asymptomatic and found incidentally during upper GI endoscopy.[6,14]The true prevalence of portal hypertensive gastropathy in cirrhosis is not well known, and values ranging from 7 to 98% of patients with cirrhosis have been quoted[15]. Controversy also exists regarding incidence of acute or chronic bleeding from this lesion. Different series describe chronic bleeding from PHG as the cause of iron deficiency anemia in 3 to 60% of patients with the lesion. Acute and severe bleeding is less common (2 to 12%). This controversy is at least partly because no uniform diagnostic criteria and classification exist to diagnose and grade its severity or predict the prognosis.[16] Other causes of the controversy are different patient populations and inclusion criteria for the study. As PHG is directly related with the presence of portal hypertension, these patients also frequently have associated esophageal varices and some patients also have gastric or duodenal ulcers. In fact the presence of esophageal varices is a strong predictor for the development of PHG.[17] Obviously it is difficult to judge which lesion is responsible for the chronic bleed, unless there is clear signs of oozing from a lesion or

one type of lesion is prominently more advanced and severe. Portal hypertensive gastropathyis described as altered vascular microarchitecture with dilatation and/ or narrowing of the capillaries and veins as a result of portal hypertension. Endoscopically it is recognized as so called snakeskin like mosaic pattern of gastric mucosa, with or without red spots over it which signify more severe lesion and increased risk of bleeding.[11,12,15] Pathologically the lesion is different from that of inflammatory gastritis and the primary change is vascular ectasia. Endothelial lesions with increased capillary permeability are observed which is responsible for petechial bleeding in the gastric mucosa.[7]

The exact cause of portal hypertensive gastropathy is not well understood, but portal hypertension seems very important. There is evidence that PHG worsens after endoscopic ligation of esophageal varices[18]. While it is clear that reduction in portal pressure by shunt surgery or TIPS leads to rapid improvement in PHG, the severity of PHG has not been demonstrated to correlate with degree of portal hypertension. Definitely some other factors are also important. An apparent factor in PHG is dysregulation of gastric mucosal microcirculation leading to tissue ischemia which is responsible for bleeding and poor healing of the mucosa. Perhaps local cytokines and vascular factors also play a part.[7,19]

Portal hypertensive gastropathy can also complicate portal hypertension due to non-cirrhotic causes like extrahepatic portal venous hypertension, schistosomiasis or hepatic veno-occulsive disease, but the incidence seems to be less than in cirrhosis and is associated with less aggressive course than in cirrhosis. This is attributed to poor liver function in case of cirrhosis.[7] There is increasing evidence that portal hypertension is associated with increased incidence of gastric mucosal colonization by Helicobacter Pylori. This is especially prominent in cases with chronic liver disease or hepatocellular carcinoma due to chronic hepatitis B virus infection. But whether there is an association between this infection and development or severity of PHG is not clear.[20,21]

In our study, the vast majority of the patients had hepatitis C virus infection. All patients had altered liver function tests and all had presented with evidence of iron deficiency anemia, most likely from upper GI bleed. This was apparent from the fact that all patients included, had positive fecal occult blood test. Seventy six percent of all patients had evidence of PGH, and all of these patients had esophageal varices. This is in keeping with several observations that frequently these lesions co-exist because increased portal pressure is the most important factor for the development of both the lesions. As already mentioned, if several lesions co-exist, then there it is very difficult to judge which one of them is responsible for the bleeding, unless there is clear evidence of bleeding. This is probably the reason there is so much controversy about the incidence of bleeding from PHG.

Esophageal varices usually bleed acutely and thus PHG was the most probably the culprit lesion in this case. Other patients who didn't have PHG and they presented with gradual drop of Hb might be losing blood from other lesions like peptic ulcers (present in three of the patients). Other causes may include similar lesions in the colon and the small intestine labeled as portal hypertensive colopathy (PHC) and portal hypertensive enteropathy (PHE) respectively which are also well described lesions.[16,22] Alternatively other causes like intestinal worm infestation could have been the cause of dropping hemoglobin level in these patients.

In conclusion, portal hypertensive gastropathy is quite common finding among patients with cirrhosis especially those with evidence of chronic GI bleed and may be responsible for many of these bleeds presenting as slowly progressive iron deficiency anemia. But it is difficult to assess the exact percentage of bleeding from these lesions as other lesions which may or may not be associated with portal hypertension are also present and may be responsible. Further well planned studies are required to assess further the exact percentage of chronic bleeds from these lesions.

Conclusion

PHG is a common finding among patients with chronic upper GI bleed in patients with portal hypertension due to cirrhosis of liver presenting with iron deficiency anemia.

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References

1.Lirio RA.Management of Upper Gastrointestinal Bleeding in Children: Variceal and Nonvariceal. Gastrointest Endosc Clin N Am. 2016 Jan;26(1):63-73.

2.Hadayat R, Jehangiri AU, Gul R, Khan AN, Said K, Gandapur A. Endoscopic findings of upper gastrointestinal bleeding in patients with liver cirrhosis.J Ayub Med Coll Abbottabad. 2015 Apr-Jun; 27(2):391-4.

3.Coagulopathy and haemorrhage. In: Erwin Kuntz · Hans-Dieter Kuntz, editor. Hepatology; Principles and practice. 2nd ed. Springer MedizinVerlag Heidelberg, 2006. pp. 347-52.

4.Garcia-Tsao G., Sanyal A., Grace N., Carey W. and the Practice Guidelines Committee of the American Association for the Study of Liver Diseases, the Practice Parameters Committee of the American College of Gastroenterology (2007) Prevention and management of gastroesophageal varices and variceal haemorrhage in cirrhosis. Hepatology 46: 922938.

5.Pranav Mahajan and Vijant Singh Chandail. Etiological and Endoscopic Profile of Middle Aged and Elderly Patients with Upper Gastrointestinal Bleeding in a Tertiary Care Hospital in North India: A Retrospective Analysis. J Midlife Health. 2017 Jul-Sep; 8(3): 137141.

6.Chung WJ. Management of portal hypertensive gastropathy and other bleeding. ClinMolHepatol. 2014 Mar; 20(1):1-5.

7.Mihajlo Gjeorgjievski and Mitchell S Cappell. Portal hypertensive gastropathy: A systematic review of the pathophysiology, clinical presentation, natural history and therapy. World J Hepatol. 2016 Feb 8; 8(4): 231262.

8.Sarin,SK. Diagnostic issues: Portal hypertensive gastropathy and gastric varices. In: DeFranchis R, editor. Portal hypertension II. Proceedings of the second Baveno international consensus workshop on definitions, methodology and therapeutic strategies. Oxford: Blackwell Science; 1996. pp. 3055.

9.EleanaGkamprela, Melanie Deutsch, and Dimitrios Pectasides. Iron deficiency anemia in chronic liver disease: etiopathogenesis, diagnosis and treatment. Ann Gastroenterol. 2017; 30(4): 405413.

10.Isabelle Cremersand Suzane Ribeiro. Management of variceal and nonvariceal upper gastrointestinal bleeding in patients with cirrhosis. Therap Adv Gastroenterol. 2014 Sep; 7(5): 206216.

11.Cubillas R, Rockey DC.Portal hypertensive gastropathy: a review. Liver Int. 2010 Sep; 30(8):1094-102.

12.HitendraGargEmailauthorSubhashGuptaA C. AnandS. L. Broor. Portal hypertensive gastropathy and gastric antral vascular ectasia. Indian J Gastroenterol. 2015 Sep; 34(5):351-8.

13.K Burak, S Lee, and P Beck. Portal hypertensive gastropathy and gastric antral vascular ectasia (GAVE) syndrome. Gut. 2001 Dec; 49(6): 866872.

14.Siringo S, Burroughs AK, Bolondi L, Muia A, Di Febo G, Miglioli M, Cavalli G, Barbara L.Peptic ulcer and its course in cirrhosis: an endoscopic and clinical prospective study. J Hepatol. 1995 Jun;22(6): 633-41.

15.Massimo Primignani, Giulia Tosetti. Portal hypertensive gastropathy after variceal eradication: more bleeding risk or just more reddening? HepatolInt (2016) 10:847850.

16.Nathalie H. Urrunagaand Don C. Rockey. Portal Hypertensive Gastropathy and Colopathy. Clin Liver Dis. 2014 May; 18(2): 389406.

17Fontana R J, Sanyal A J, Ghany MG et al. Development and progression of portal hypertensive gastropathy in patients with chronic hepatitis C. Am J Gastroenterol. 2011 May; 106(5): 884893.

18.Elwakil R, Al Breedy AM, Gabal HH.Effect of endoscopic variceal obliteration by band ligation on portal hypertensive gastroduodenopathy: endoscopic and pathological study.Hepatol Int. 2016 Nov; 10(6):965-973.

19.Tan S, Chen X, Xu M, Huang X, Liu H, Jiang J, Lu Y, Peng X, Wu B.PGE2/EP4 receptor attenuated mucosal injury via β-arrestin1 /Src/EGFR-mediated proliferation in portal hypertensive gastropathy.Br J Pharmacol. 2017 May; 174(9):848-866.

20.Joanna Pogorzelska, Magda Łapińska, Alicja Kalinowska, Tadeusz W. Łapiński. Helicobacter pylori infection among patients with liver cirrhosis. Eur J Gastroenterol Hepatol. 2017 Oct; 29(10): 11611165.

21.McCormick PA, Sankey EA, Cardin F, Dhillon AP, McIntyre N, Burroughs AK. Congestive gastropathy and Helicobacter pylori: an endoscopic and morphometric study.Gut. 1991 Apr; 32(4):351-4.

22.Taiki Aoyama, Shiro Oka, corresponding author Hiroshi Aikata, Makoto Nakano, IkueWatari, Noriaki Naeshiro, Shigeto Yoshida, Shinji Tanaka, and Kazuaki Chayama. Small Bowel Abnormalities in Patients with Compensated Liver Cirrhosis. Dig Dis Sci. 2013 May; 58(5): 13901396.