Bleeding ectopic varices: clinical presentation, natural history, and outcomes

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ABSTRACT

Bleeding complications from ectopic varices are often difficult to manage. We aimed to study the natural history and outcomes of bleeding ectopic varices to better understand appropriate clinical management. This retrospective cohort study included patients admitted to the hospital with bleeding ectopic or esophageal varices from 2010 through 2019. Study subjects were identified through searching the Medical University of South Carolina's electronic medical record, and complete demographic, clinical, and procedural data were abstracted. 25 patients with gastrointestinal bleeding from ectopic varices and a matched group of 50 patients with bleeding esophageal varices were identified. Bleeding ectopic varices were identified in the following locations: duodenum (n=5), jejunum/ileum (n=5), colon (n=2), rectum (n=6), and anastomotic sites (n=7). Model for End-Stage Liver Disease scores (patients with cirrhosis), need for intensive care unit admission, and administration of octreotide and antibiotics were significantly higher in patients with esophageal variceal bleeding than those with ectopic varices. All-cause 1-year mortality of patients with ectopic varices was significantly lower than those with bleeding esophageal varices (8% vs 35%, p<0.05). Patients with ectopic varices and cirrhosis bled at lower hepatic venous pressure gradients than patients with bleeding esophageal varices (17 mm Hg vs 24 mm Hg, p<0.01). Transjugular intrahepatic portosystemic shunts (TIPS) were performed in two-thirds of patients with ectopic varices and one patient rebled due to TIPS dysfunction. The clinical features of patients with ectopic varices and those with esophageal varices were similar, but patients with ectopic varices had significantly lower 1-year mortality after bleeding events.

Significance of this study

What is already known about this subject?

⇒ The pathogenesis of ectopic varices is unclear and may or may not be closely tied to the severity of portal hypertension.
⇒ Bleeding complications from ectopic varices are often difficult to manage.

What are the new findings?

⇒ Patients with bleeding ectopic varices appear to bleed at a lower portal pressures than patients with bleeding esophageal varices.
⇒ Transjugular intrahepatic portosystemic shunt (TIPS), often with direct coil embolization, is an effective therapy for ectopic varices.
⇒ Mortality is low in patients with bleeding ectopic varices and appears to be lower than for patients with esophageal variceal hemorrhage.

How might these results change the focus of research or clinical practice?

⇒ The data presented in this study should allow clinicians to recognize ectopic varices earlier in their practice.
⇒ TIPS should be considered early in the treatment algorithm for management of ectopic varices.

INTRODUCTION

Ectopic varices are defined as non-gastroesophageal varices which develop as a result of a variety of underlying conditions that lead to the development of portosystemic shunts.[1–4] Areas in which ectopic varices may be present include but are not limited to the duodenum, jejunum, colon, rectum, gall bladder/common bile duct, retroperitoneum, and peristomal areas.[5] Ectopic variceal bleeds account for up to 5% of all variceal bleeding, and in comparison with esophageal varices, ectopic varices have been reported to have a fourfold increased risk of bleeding.[6 7]

Diagnosis and subsequent management of ectopic varices differ from that of esophageal varices due to significant variations in underlying pathologic mechanisms leading to formation of varices. A variety of treatment options have been proposed in the treatment of bleeding ectopic varices, including injection sclerotherapy, endoscopic band ligation, surgical ligation, and shunting procedures including transjugular intrahepatic portosystemic shunt (TIPS) and balloon-occluded retrograde transvenous obliteration.[5 6] Despite a multitude of treatment options, there are no controlled trials to guide treatment due to rarity of bleeding complications and variation in underlying vascular pathology.[5 6] Mortality rates for bleeding complications from ectopic varices have not been clearly defined, although multiple studies have suggested that recurrence of bleeding is common.[7 8]

In this study, we hypothesized that patients with portal hypertension have bleeding

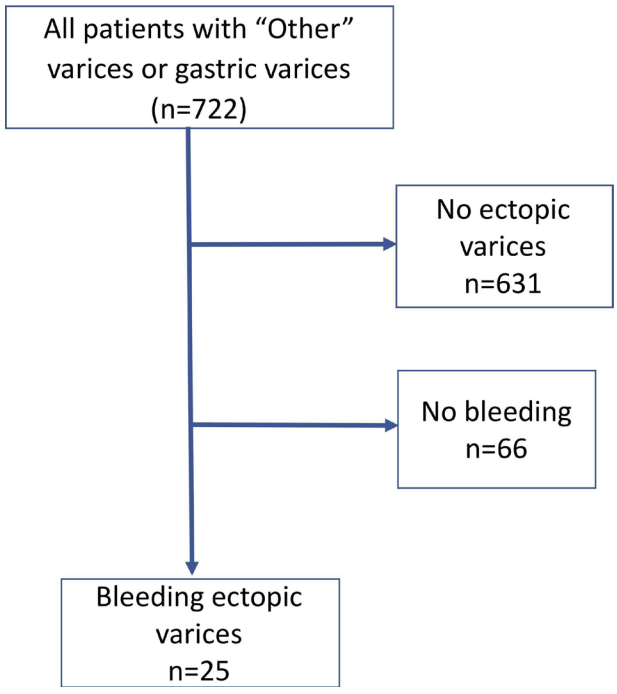

Figure 1 CONSORT diagram. Patients included in the study are shown. CONSORT, Consolidated Standards of Reporting Trials.

complications from ectopic varices at lower hepatic venous pressure gradients than patients with bleeding esophageal varices (BEV). We also believed that patients with bleeding ectopic varices had significant morbidity related to bleeding complications in addition to delays in definitive management when compared with patients with BEV. Therefore, our main objectives were as follows: (1) to determine the demographics and underlying pathology in patients with bleeding ectopic varices; and (2) to evaluate outcomes in regard to acute and definitive management of bleeding ectopic varices.

MATERIALS AND METHODS

Design and study sample

This was a retrospective cohort study of a subset of patients who were admitted to the hospital with bleeding ectopic varices and a matched group of patients with BEV at the Medical University of South Carolina (MUSC) from January 1, 2010 to December 31, 2019.

Adult patients treated at MUSC during the study period for bleeding ectopic varices were considered eligible. Study subjects were identified using internal patient registries maintained by the investigators specifically intended to track patients with cirrhosis and/or bleeding varices. To ensure complete capture of potentially eligible patients, we additionally queried MUSC's clinical data warehouse (maintained by the South Carolina Clinical and Translational Institute, supported by the institution's Clinical and Translational Science Award) using diagnosis and procedural codes for diagnosis and treatment of esophageal and extraesophageal varices. Patients with bleeding gastric varices were excluded from this study. No patients were excluded on the basis of insufficient medical records.

Data collection

Eligible patients' medical records were manually reviewed by the principal investigator (KAB). Data abstracted included the following: demographic information, etiology of portal hypertension (including cirrhotic and non-cirrhotic), etiology of cirrhosis, alcohol use, anticoagulant/antiplatelet medication use, and Model for End-Stage Liver Disease (MELD) scores for patients with cirrhosis; presence of hepatic encephalopathy, coagulopathy, ascites, concurrent esophageal and/or gastric varices; and use of beta blocker prior to initial presentation for secondary variceal prophylaxis in patients with cirrhosis. Acute interventions during admissions for bleeding complications were abstracted, including octreotide use, prophylactic antibiotics, red blood cell transfusion, and definitive interventions including injection sclerotherapy, TIPS, coil embolization of varix, and combination of TIPS and coil embolization. Outcome measures were obtained, including repeat hospitalizations for bleeding complications, 30-day rebleeding rate after definitive intervention, and 1-year mortality after initial hospitalization for bleeding.

Study outcomes

The outcomes of interest in this study pertained primarily to acute and definitive management of bleeding ectopic varices as well as mortality rates. Further rigorous analysis of outcome measures was not considered feasible due to the small sample size and retrospective nature of the study.

Statistics

Qualitative variables were described using number and per cent, and mean and SD were used to describe quantitative variables. The χ^2 test was used for qualitative variables. A Student's t-test was used to evaluate quantitative variables. A control group of patients with BEV (matched for age and gender) were included as well. Statistically significant differences were considered to be present at $p<0.05$.

RESULTS

Patient characteristics

A total of 25 patients with bleeding complications from ectopic varices and a matched (for gender and age) group of 50 patients with BEV were identified from January 2010 to October 2019 (figure 1). The mean age of patients with ectopic varices was typical of patients with cirrhosis at 54 years (table 1). The majority of patients had cirrhosis and associated portal hypertension (cirrhosis was caused most commonly by ethanol (9 of 21, 43%) or hepatitis C virus infection (5 of 21, 24%)); there were four patients with primary sclerosing cholangitis (PSC) and three patients with non-alcoholic steatohepatitis. Thrombosis in the portal venous system was the cause of portal hypertension in 4 of 25 patients (portal (n=2), splenic (n=1), or superior mesenteric vein (n=1) thrombosis).

Ectopic variceal bleeding was most commonly from the small intestine but was also present in multiple other locations. The location of bleeding ectopic varices was as follows: duodenum (n=5), jejunum (figure 2)/ileum (n=5), colon (n=2), rectum (n=6), and anastomotic sites (n=7).

Clinical presentation

Initial bleeding events in each group were similar in essentially all regards (table 2). This was true for vital signs,

Table 1 Demographic data

	Location of varices		
	Ectopic (n=25) Mean (±SD) or n (%)	Esophageal (n=50) Mean (±SD) or n (%)	P value
Age, mean, years	54 (±12)	58 (±11)	NS
Gender			
Male	15 (60)	31 (62)	NS
Female	10 (40)	19 (38)	NS
Race			
African American	6 (24)	12 (24)	NS
Caucasian	19 (76)	37 (74)	NS
Hispanic	0 (0)	1 (2)	NS

NS, not significant.

hemoglobin level, and number of units of red blood cells transfused. However, MELD scores (patients with cirrhosis only), need for intensive care unit admission, and administration of octreotide and antibiotics were greater in patients with BEV.

Clinical management

TIPS were performed in two-thirds of patients with ectopic varices (table 3). Simultaneous coil embolization of varices was also performed in three of the patients who underwent TIPS for management of jejunal, colonic, and anastomotic varices, respectively. Among the patients with bleeding ectopic varices who underwent TIPS, only one patient was readmitted for bleeding complication, which was due to TIPS dysfunction. Patients with ectopic varices and cirrhosis had lower hepatic venous pressure gradients than patients with BEV (table 3).

Outcomes

The all-cause mortality of patients with ectopic varices was 8% within the first year of presentation to the hospital (two deaths, one due to multisystem organ failure and one due to septic shock) compared with 35% in patients with BEV ($p<0.05$) (table 3).

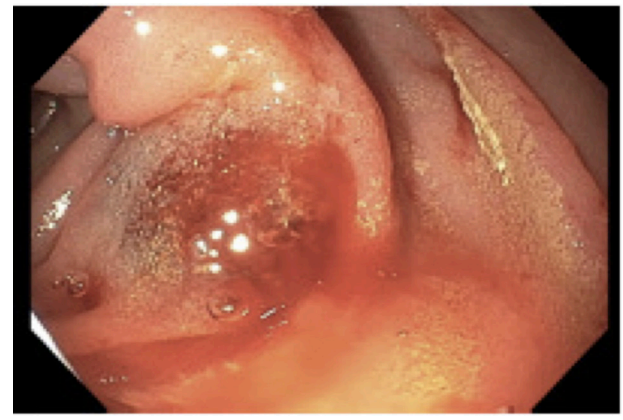

Figure 2 Actively bleeding varix in the jejunum. Shown is a pooled blood (seen in the left center portion of the image) from a bleeding varix.

DISCUSSION

In this study, we sought to investigate the clinical presentation and management of bleeding ectopic varices to provide further insight into appropriate clinical evaluation and management. We found that the clinical features of patients with cirrhosis and ectopic varices and those with esophageal varices are similar with regard to bleeding events, but patients with ectopic varices have lower MELD scores and lower mortality.

Although there are some similarities in the clinical presentations of patients with bleeding ectopic and esophageal varices, there were differences in the management and outcomes of these clinical entities. In regard to initial clinical management, patients with bleeding ectopic varices were less likely to be started on somatostatin analogs and/or antibiotic prophylaxis, which was likely due to uncertainty regarding the underlying lesion leading to clinically significant bleeding. After initial resuscitative measures are performed, patients underwent appropriate early endoscopic intervention for diagnostic evaluation and management of bleeding complications. As expected, advanced endoscopic procedures were not uncommonly performed in patients with ectopic varices. For example,

Table 2 Laboratory and clinical features

	Location of varices		
	Ectopic (n=25) Mean (±SD) or n (%)	Esophageal (n=50) Mean (±SD) or n (%)	P value
Hemoglobin level, mean, g/dL	7.4	7.2	NS
Units of red blood cells, median transfused	2.5 (1–37)	2 (0–30)	NS
MELD score (patients with cirrhosis only), mean	15 (±7)	20 (±9)	<0.042
ICU admission (initial admission)	11 (44)	48 (96)	<0.01
Octreotide administration	14 (56)	50 (100)	<0.01
Prophylactic antibiotic use	13 (52)	50 (100)	<0.01
Angiographic evaluation	18 (72)		
Evaluation with EUS	6 (24)		
Small-bowel enteroscopy	3 (12)		
Capsule endoscopy	2 (8)		

EUS, endoscopic ultrasonography; ICU, intensive care unit; MELD, Model for End-Stage Liver Disease; NS, not significant.

Table 3 Outcomes

	Location of varices		
	Ectopic (n=25) Mean (±SD) or n (%)	Esophageal (n=50) Mean (±SD) or n (%)	P value
Clinical outcome			
Readmission for bleeding	11 (44)	13 (26)	NS
TIPS (patients with cirrhosis only)	14/21 (67)	28/50 (56)	NS
Hepatic venous pressure gradient			
Pre-TIPS (mm Hg)	17 (±5)	24 (±8)	<0.01
Post-TIPS (mm Hg)	6 (±3)	8 (±4)	NS
Repeat bleeding after TIPS	1 (7)	1 (4)	NS
Time to readmission, median (range), days	87 (8–515)	90 (3–775)	NS
1-year all-cause mortality	2 (8)	17 (35)	<0.05

NS, not significant; TIPS, transjugular intrahepatic portosystemic shunt.

small-bowel enteroscopy was often performed in patients with suspected bleeding small-bowel varices, consistent with previous reports.[2 5 8], Endoscopic ultrasonography is also helpful in determining if there was a varix causing bleeding complications.[1 7] Lastly, angiographic evaluation was performed in 18 patients (72%) and was beneficial when there was complex underlying vascular anatomy, as has been previously reported.[2] There are no trials to allow for consensus recommendations on management of ectopic varices, but management algorithms have previously been proposed and are consistent with what was observed at our institution.[4–6]

The differences in management of the two groups of patients were likely due to the diagnostic challenges in assessing patients with ectopic varices, which ultimately lead to a delay in diagnosis and definitive therapy. Interestingly, bleeding from surgical anastomotic sites was commonly encountered. We suspect this was partially related to the association of PSC with inflammatory bowel disease and subsequent bowel surgery with ostomy creation, but there were also multiple patients with bleeding from anastomotic sites who had thrombosis in the portal venous system or an alternative cause of cirrhosis with portal hypertension. Despite having bleeding complications at lower portal pressures prior to TIPS, patients who underwent definitive management with TIPS or TIPS with direct coil embolization had a significant reduction in bleeding complications, consistent with previous reports.[5 9–14] With the exception of one patient who had recurrent bleeding due to TIPS dysfunction, all patients who underwent TIPS had no further admissions for bleeding complications regardless of the location of variceal bleeding. Based on these findings, we would consider TIPS in all patients with ectopic varices with bleeding complications. In patients who do not undergo targeted therapy to reduce portal pressures, there are likely further studies needed to assess the utility of secondary variceal prophylaxis with non-selective beta blockers.[2]

The findings of this study should be interpreted in the context of several limitations. First, the small sample size and retrospective nature of this study might lead to the assumption that the care of these patients can be generalized to all patients with bleeding ectopic varices. We would urge caution against this, recommending an individualized approach. Second, the capture of all admissions for bleeding complications could have been incomplete as patients may not have presented to our institution for readmission. However, it is common practice for these types of patients to be readmitted to our hospital given the complexity of their disease. Of note, patients who died (at 1 year) in the control group were not likely directly related to active bleeding; rather deaths were due to other complications of cirrhosis, especially including sepsis and multiorgan failure.

In summary, we have shown that patients with bleeding ectopic varices must undergo initial resuscitative measures followed by a thorough evaluation into the underlying pathophysiology regarding the formation of the ectopic varices. Optimal management typically requires a multidisciplinary approach to care, and angiographic interventions to reduce portal pressures often provide benefit for patients with bleeding complications.

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Competing interests DCR is an Associate Editor for the *Journal of Investigative Medicine*. No other competing interests declared.

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Data availability statement Data are available upon reasonable request. All data relevant to the study are included in the article or uploaded as supplementary information.

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REFERENCES

1 Almadi MA, Almessabi A, Wong P, *et al*. Ectopic varices. *Gastrointest Endosc* 2011;74:380–8.
2 Helmy A, Al Kahtani K, Al Fadda M. Updates in the pathogenesis, diagnosis and management of ectopic varices. *Hepatol Int* 2008;2:322–34.
3 Henry Z, Uppal D, Saad W, *et al*. Gastric and ectopic varices. *Clin Liver Dis* 2014;18:371–88.
4 Sarin SK, Kumar CKN. Ectopic varices. *Clin Liver Dis* 2012;1:168–72.
5 Norton ID, Andrews JC, Kamath PS. Management of ectopic varices. *Hepatology* 1998;28:1154–8.
6 Saad WEA, Lippert A, Saad NE, *et al*. Ectopic varices: anatomical classification, hemodynamic classification, and hemodynamic-based management. *Tech Vasc Interv Radiol* 2013;16:108–25.
7 Sato T, Akaike J, Toyota J, *et al*. Clinicopathological features and treatment of ectopic varices with portal hypertension. *Int J Hepatol* 2011;2011:1–9.
8 Kotfila R, Trudeau W. Extraesophageal varices. *Dig Dis* 1998;16:232–41.
9 Kochar N, Tripathi D, McAvoy NC, *et al*. Bleeding ectopic varices in cirrhosis: the role of transjugular intrahepatic portosystemic stent shunts. *Aliment Pharmacol Ther* 2008;28:294–303.
10 Nayar M, Saravanan R, Rowlands PC, *et al*. TIPSS in the treatment of ectopic variceal bleeding. *Hepatogastroenterology* 2006;53:584–7.
11 Oey RC, de Wit K, Moelker A, *et al*. Variable efficacy of TIPSS in the management of ectopic variceal bleeding: a multicentre retrospective study. *Aliment Pharmacol Ther* 2018;48:975–83.
12 Saad WE, Saad NE, Koizumi J. Stomal varices: management with decompression tips and transvenous obliteration or sclerosis. *Tech Vasc Interv Radiol* 2013;16:126–34.
13 Tripathi D, Jalan R. Transjugular intrahepatic portosystemic stent-shunt in the management of gastric and ectopic varices. *Eur J Gastroenterol Hepatol* 2006;18:1155–60.
14 Vangeli M, Patch D, Terreni N, *et al*. Bleeding ectopic varices--treatment with transjugular intrahepatic porto-systemic shunt (TIPS) and embolisation. *J Hepatol* 2004;41:560–6.