

Epistaxis in end stage liver disease masquerading as severe upper gastrointestinal hemorrhage

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patients with severe epistaxis thought to be severe upper gastrointestinal hemorrhage (UGIH).

METHODS: This observational single center study included all consecutive patients with ESLD and epistaxis identified from consecutive subjects hospitalized with suspected UGIH and prospectively enrolled in our databases of severe UGIH between 1998 and 2011.

RESULTS: A total of 1249 patients were registered for severe UGIH in the data basis, 461 (36.9%) were cirrhotics. Epistaxis rather than UGIH was the bleeding source in 20 patients. All patients had severe coagulopathy. Epistaxis was initially controlled in all cases. Fifteen (75%) subjects required posterior nasal packing and 2 (10%) embolization in addition to correction of coagulopathy. Five (25%) patients died in the hospital, 12 (60%) received orthotopic liver transplantation (OLT), and 3 (15%) were discharged without OLT. The mortality rate was 63% in patients without OLT.

CONCLUSION: Severe epistaxis in patients with ESLD is (1) a diagnosis of exclusion that requires upper endoscopy to exclude severe UGIH; and (2) associated with a high mortality rate in patients not receiving OLT.

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Key words: Epistaxis; Upper gastrointestinal bleeding; End stage liver disease; Cirrhosis; Nasogastric tube; Liver transplantation; Digestive bleeding; Nasal packing; Coagulopathy

Core tip: Severe posterior nasopharyngeal epistaxis in hospitalized patients with end stage liver disease (ESLD): (1) is a diagnosis of exclusion that requires upper endoscopy to rule out common causes of upper gastrointestinal hemorrhage (UGIH); (2) can usually be effectively treated with nasal packing and correction of coagulopathy; (3) was the diagnosis of the bleeding

Abstract

AIM: To describe the prevalence, diagnosis, treatment, and outcomes of end stage liver disease (ESLD)

source in 4.3 % of cirrhotic patients with a suspected UGIH; and (4) is associated with a high rate of mortality (63%) in those not receiving liver transplantation. Physicians managing patients with ESLD should be aware that epistaxis can masquerade as massive UGIH, particularly in those with severe coagulopathy.

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INTRODUCTION

Massive upper gastrointestinal hemorrhage (UGIH) in patients with end stage liver disease (ESLD) is often fatal^[1,2]. Concomitant coagulopathy is a common comorbidity in cirrhotics and it frequently worsens the outcome. Expedient diagnosis and intervention are therefore imperative when encountering such cases.

Although rare, severe epistaxis is a diagnosis that must be considered in patients presenting with signs and symptoms of severe UGIH, in order to avoid delays in the provision of potentially life-saving therapy^[3]. About 5% of epistaxis originates from a posterior nasal source^[4]. Bleeding in these cases can be especially severe. Local therapy such as nasal packing or cauterization is usually sufficient, but continued or intractable hemorrhage may require arterial ligation, embolization or more recently endoscopic ligation^[4]. Delayed treatment may lead to excessive blood loss and increased morbidity and mortality.

Literature about epistaxis and cirrhosis is limited as few case reports^[5].

Our aims were (1) to describe the diagnosis, treatment, and outcomes of ESLD patients with severe epistaxis whose initial clinical diagnosis prior to endoscopy was severe UGIH probably secondary to esophageal varices; and (2) to estimate the prevalence of epistaxis as the final diagnosis in cirrhotics who present with signs of severe UGIH.

MATERIALS AND METHODS

University of California, Los Angeles Center for Health Sciences (UCLA-CHS) is an urban, academic, tertiary care referral medical center. Nearly 30000 patients are discharged from this facility yearly. Attending gastroenterologists from the Center for Ulcer Research and Education (CURE) Hemostasis Research Group are available 24 h a day for the evaluation and treatment of patients hospitalized with severe gastrointestinal (GI) hemorrhage.

The UCLA Ronald Reagan Medical Center (RRMC) also has a liver transplant program that is one of the largest in the world by volume. As the most experienced

liver transplantation program in the western United States, UCLA serves the area from California, Oregon, Washington, and throughout the Southwest.

Cases in this report were retrospectively identified from consecutive hospitalized subjects with severe UGIH who were enrolled in our studies of severe UGIH in ESLD between September 26, 1998 and June 1, 2011. This observational study was approved by the UCLA Office for the Protection of Research Subjects. Informed consent for endoscopy was obtained before each clinically indicated procedure. ESLD disease was diagnosed based upon clinical parameters, radiologic imaging, and/or liver biopsy results. Suspected severe UGIH was defined as (1) signs or symptoms of UGI hemorrhage (hematemesis and/or melena); (2) decrease in hemoglobin from baseline of ≥ 2 g/dL; and (3) and/or transfusions of ≥ 2 units of packed red blood cell (PRBC).

All upper endoscopies were performed by experienced endoscopists using therapeutic sized video endoscopes. Patients underwent emergency endoscopy after resuscitation. Careful examination of the esophagus, stomach (including retroflex views), and duodenum was performed in each case.

Members of the CURE Hemostasis Group and a skilled research coordinator collected prospective data from the time of presentation using standardized data forms. All patients underwent clinical evaluation about bleeding symptoms: hematemesis, melena, hematochezia; bleeding severity: hypotension, shock, need for pressors; and cirrhosis data: etiology of cirrhosis, severity of cirrhosis (Child-Pugh class and Model of End Stage Liver Disease - MELD score) from the time of presentation. Laboratory data (creatinine, hematocrit, hemoglobin and coagulation tests) and endoscopic findings were also recorded from the time of presentation. The patients were prospectively followed-up from the date of diagnosis to hospital discharge, death, or liver transplantation.

Coagulopathy was defined as values of prothrombin time (PT), international normalized ratio (INR), or platelet count outside the institutional normal ranges. Child-Pugh class and MELD score were calculated according to a well-accepted classification^[6-8]. Hypotension was defined as a systolic blood pressure persistently less than 100 mmHg despite adequate volume resuscitation. Rebleeding was defined as recurrent severe epistaxis (or signs of UGI bleeding) at least 24 h after observed complete cessation of pharyngeal bleeding following appropriate treatment, with decrease in hemoglobin of ≥ 2 g/dL after resuscitation and initial diagnosis and/or ≥ 2 units of PRBC. Follow-up time was calculated from the time of presentation to the GI Hemostasis Team until death, liver transplantation, or discharge from the hospital.

Statistical analysis

All data were de-identified and entered onto data files. SAS software, version 9.1 (SAS Institute, Cary, NC) was used for data management. Missing or inconsistent data were resolved by a joint review of the medical record and discussion with program instructor (DMJ) and co-investigators

Table 1 Characteristics of patients *n* (%)

Characteristic	Data
Age (yr, mean \pm SD, range)	54.4 \pm 9.7 (40-75)
Sex (Male/Female)	12/8 (60/40)
Child Pugh class	A: 0; B: 1 (5); C: 19 (95)
MELD score, (mean \pm SD, range)	29.6 \pm 7.5
Etiology	
HCV + Alcoholic	5 (25)
Alcoholic	5 (25)
Cryptogenetic	5 (25)
HCV	4 (20)
PBC + AIH	1 (5)
Inpatient start of bleeding	18 (90)
Nasogastric tube placed prior to bleeding	16 (80)
Hematemesis	15 (75)
Melena and/or Hematochezia	9 (45)
PT (s, mean \pm SD, range)	20.7 \pm 6.8 (13.4-42.6)
INR (mean \pm SD, range)	2.3 \pm 1.4 (1.4-7.8)
Platelet count (/mm ³ , mean \pm SD, range)	51000 \pm 32082 (11000-120000)
Hematocrit (mean \pm SD, range)	23.5% \pm 2.9% (18.5%-29.9%)

AIH: Autoimmune hepatitis; HCV: Hepatitis C virus; INR: International normalized ratio; MELD: Model for end stage liver disease; PBC: Primary biliary cirrhosis; PT: Prothrombin time; SD: Standard deviation.

(JM or MC).

RESULTS

A total of 1249 patients were registered for severe UGII in the data basis, 461 (36.9%) were cirrhotic patients. Epistaxis was determined to be the source of severe hemorrhage in 20 patients with ESLD hospitalized for severe UGII. Based on the number of cirrhotic patients evaluated for severe UGIB during the same period of time, we estimated that the epistaxis diagnosis represented 4.3% (20/461) of all cirrhotic patients hospitalized for suspected severe UGII. Most patients (18/20 = 90%) developed what was clinically diagnosed as inpatient UGII after hospitalization for worsening liver disease and did not have signs of UGII on admission. In this particular subgroup of inpatients with cirrhosis and severe UGI hemorrhage, the prevalence of epistaxis was higher and was estimated to be 15.3% (18/117) (Table 1).

The age (mean \pm SD) of the subjects with epistaxis was 54.4 \pm 9.7 year with men comprising 12/20 (60%). Etiologies of ESLD were hepatitis C and alcohol in 5 (25%), cryptogenic cirrhosis in 5 (25%), alcohol alone in 5 (25%), hepatitis C alone in 4 (20%), and primary biliary cirrhosis plus autoimmune hepatitis in 1 (5%). Most patients (19/20 = 95%) were Child-Pugh class C.

The majority (16/20 = 80%) had a nasogastric (NG) tube placed prior to the onset of bleeding. The reasons of NG tube placement were intubation, decompression or suctioning the stomach, checking for bright red bleeding (BRB) in stomach to establish the acuity of bleeding, and assisting of esophagogastroduodenoscopy (EGD) by clearing of blood, clots, or gastric contents. Seventeen (85%) patients required endotracheal intubation for airway protection.

All patients had clinically severe bleeding presenting as hematemesis (15/20; 75%) or hematochezia/melena (9/20; 45%). In 9 (45%) patients, bleeding was accompanied by shock or persistent hypotension requiring administration of intravenous pressor agents.

All patients had concurrent severe coagulopathy with a mean PT \pm SD of 20.7 \pm 6.8 s (range: 13.4-42.6), INR (mean \pm SD) of 2.3 \pm 1.4 (range: 1.4-7.8), and platelet count (mean \pm SD) of 51000 \pm 32082/mm³ (range: 11000-120000). The hematocrit (mean \pm SD) before resuscitation was 23.5% \pm 2.9% (range: 18.5-29.9).

Most (14/20; 70%) patients had esophageal varices but none had active bleeding, platelet plugs, or other stigmata of recent hemorrhage^[9]. No other upper GI lesions with active bleeding, visible vessels, or adherent clots were found. Upon withdrawal of the endoscope, fresh red blood (indicating active bleeding) was found in the proximal esophagus coming down from the posterior nasopharynx in each case.

Once diagnosed by endoscopy, epistaxis was initially controlled in all cases. Fifteen (75%) patients required posterior nasal packing by an otolaryngologist in addition to correction of coagulopathy. Two (10%) patients had angiographic embolization of branches of the splenopalatine artery after failure of nasal packing.

Five (25%) patients rebled during follow-up. During follow-up, the number of RBC units transfused (mean \pm SD) was 9.8 \pm 11.7, the number of FFP units transfused (mean \pm SD) was 14.7 \pm 21.8, and the number of platelets units transfused (mean \pm SD) was 8 \pm 9.9.

Patients' outcomes were summarized in Table 2. Five (25%) patients died in the hospital, 12 (60%) received orthotopic liver transplantation (OLT) during the hospitalization, and 3 (15%) were discharged without OLT. The mortality rate was 63% (5/8) in patients who did not undergo OLT. The mean \pm SD length of time until death, liver transplantation, or discharge from the hospital was 13.6 \pm 18.3 d.

Among the 5 deaths in the hospital, one was due to uncontrolled recurrent epistaxis and very severe hemorrhage and all others were from ESLD or severe co-morbidity. The patient who died of uncontrolled epistaxis was a 75-year-old male with hepatitis C and alcoholic cirrhosis who was maintained on oral anticoagulation with warfarin for a St. Jude's mitral valve replacement. He developed epistaxis after an increase in his outpatient warfarin dose and was admitted with an INR of 7.7. The epistaxis was controlled after correction of his coagulopathy and posterior nasal packing but recurred 8 d later days after the packing was removed. At the time of the rebleed, the INR was 1.5 and platelet count was above 100000/mm. Bleeding continued despite repeat posterior nasal packing and transfusion with fresh frozen plasma and platelets, and the patient subsequently developed a myocardial infarction and cardiogenic shock. The patient's family chose to withdraw care given his very poor prognosis and he expired soon after. Among the four other deaths, one patient died during OLT pro-

Table 2 Outcomes of patients *n* (%)

	No. of patients	Age (yr)	PT (s)	INR	Platelet count (/mm ³)	MELD score	Time between diagnosis and death, OLT or discharge (d)	Rebleeding before death, OLT or discharge
OLT	12 (60)	51.5 ± 8.7	22.6 ± 7.9	2.7 ± 1.7	43333 ± 27955	31.8 ± 6.4	8.4 ± 8.2	3 (25)
Death in hospital	5 (25)	57.6 ± 10.1	17.7 ± 5.5	1.8 ± 0.5	54400 ± 41578	30.8 ± 9.5	10.8 ± 6.0	1 (20)
Discharge without OLT	3 (15)	60.3 ± 11.7	18.6 ± 0.7	1.8 ± 0.1	76000 ± 26514	20.5 ± 2.1	39.0 ± 39.9	1 (33)

MELD: Model for end stage liver disease; OLT: Orthotopic liver transplantation; PT: Prothrombin time; INR: International normalized ratio; SD: Standard deviation.

cedure and the three other patients died in intensive care unit (ICU) because of multiorgan failure due to ESLD.

DISCUSSION

Patients with ESLD presenting with massive hematemesis, hematochezia, and/or melena require rapid diagnosis and intervention to reduce the high mortality associated with cirrhosis^[2]. Many of these patients have coexisting coagulopathies that can worsen their outcomes. In patients with ESLD, epistaxis can be a cause of severe hemorrhage which may be overlooked and usually masquerades as UGIH, because of the clinical presentation^[5].

We estimated that in cirrhotic patients hospitalized for severe UGIH symptoms, epistaxis was the diagnosis in 4.3% of cases. This prevalence increased more than three times when cirrhotic patients were already hospitalized before they started bleeding (15.3%). Few data have been reported about the prevalence of epistaxis in patients presenting with signs of severe UGIH. Hutchison *et al*^[3] reported 10 cases with apparent upper gastrointestinal bleeding, comprising a 0.55% incidence of hematemesis and melena in the population studied of patients referred for UGIH without information on their liver function.

In ambulatory patients without cirrhosis, epistaxis most commonly arises from the vessels located in the anterior nasopharynx (Kiesselbach's plexus), especially in children and young adults. The source of bleeding is usually obvious, often related to local trauma, and rarely is clinically severe^[10]. In contrast, posterior nasopharyngeal epistaxis may be occult, large volume, and associated with high mortality^[11]. It is reported to be more common in older patients, less likely trauma-related given its anatomic location, and more likely the result of spontaneous bleeding from a sclerotic vessel. In contrast to published figures that only 5% of all epistaxis is from a posterior nasopharyngeal source, all of our patients with epistaxis had posterior hemorrhage and most 15 (75%) required posterior nasal packing. Although ESLD is now more often considered as a procoagulant state, in our cirrhotic patients with epistaxis, portal hypertension and coagulopathy were risk factors in all patients. These risk factors predisposed them to severe posterior nasopharyngeal hemorrhage.

One of the most common causes of epistaxis is trau-

ma. Most patients (80%) in this study had epistaxis after a recently placed nasogastric tube. Nasogastric tube placement may initiate or exacerbate pharyngeal bleeding, especially in patients with ESLD. Altered mental status from hepatic encephalopathy, shock, or mechanical ventilation related sedation might increase the risk of pharyngeal trauma during nasogastric tube placement by blunting a patient's natural response to pain or discomfort. Abnormal coagulation may also increase the risk of epistaxis arising from minimal pharyngeal trauma. Therefore, NG tube placement should be avoided as often as possible especially forceful or traumatic insertion in the patients with ESLD. However by clearing the stomach of blood, clots, or gastric contents and helping establish the acuity of bleeding, these devices may help localize a bleeding source, decrease the risk of massive aspiration, and increase the amount of gastric mucosa seen during endoscopy^[12-14]. NG or orogastric tubes are also useful for enteral delivery of medications and nutrition in ESLD patients with severe encephalopathy. If there is concern about inducing epistaxis in patients with ESLD and coagulopathy and a gastric tube is required, an orogastric tube can be considered instead of a nasogastric tube. Most patients with ESLD without epistaxis tolerate such tubes well and do not have complications in current practice. However it would be interesting to know the prevalence of epistaxis in population of patients with ESLD who underwent ng tube placement and further studies are warranted.

Mortality rates approaching 5% have been reported for all patients with posterior epistaxis^[3]. Given associated coagulopathy and other factors, it is expected that patients with ESLD who develop a severe posterior nasopharyngeal bleed would have significantly higher mortality. Our overall mortality rate of 25% (5/20) supports this idea, and the rate in those not receiving liver transplantation was even higher (5/8, 63%).

Epistaxis as a source of severe bleeding must be included in the differential diagnosis of inpatient hemorrhage for patients with ESLD and nasogastric tubes or nasotracheal intubation. However, this is still a diagnosis of exclusion. Especially in cirrhotic patients who often have variceal hemorrhage, upper endoscopy should always be performed to rule out more common causes of UGIH, and in the absence of an actively bleeding lesion on esophagogastroduodenoscopy, careful examination

of the mouth and nasopharynx should be performed. Delayed diagnosis of severe epistaxis from posterior pharyngeal sources can lead to significant blood loss and resulting hypovolemia, shock, and death^[5].

Once the diagnosis of posterior nasopharyngeal epistaxis is established, an otolaryngologist should be consulted about treatment options, which include posterior nasal packing, possible embolization of arteries supplying that region, and/or endoscopic ligation^[10,15]. Posterior nasal packing is not without potential complications, including aspiration, hypoxia, and toxic shock as the most serious. Supplemental oxygen should be provided and, whenever necessary, intubation and mechanical ventilation should be considered to help prevent aspiration and hypoxia. Nonetheless, despite rapid diagnosis and treatment, the outcome for these patients is poor, most likely influenced by their significant comorbidities, particularly ESLD and coagulopathy.

In the absence of an early otolaryngoscopic exam, turning the patient onto the side and looking for nasal blood loss may help suggest an occult posterior pharyngeal hemorrhage as well as facilitate drainage. Other measures that might influence diagnosis, treatment, and outcome include oral passage of a gastric lavage tube and early referral for liver transplantation.

In conclusion, severe posterior nasopharyngeal epistaxis in hospitalized patients with ESLD: (1) is a diagnosis of exclusion that requires upper endoscopy to rule out common causes of UGIH; (2) can usually be effectively treated with nasal packing and correction of coagulopathy; (3) was the diagnosis of the bleeding source in 4.3% of cirrhotic patients with a suspected UGIH and this prevalence increased to 15.3% in the subgroup of cirrhotic patients in whom the hemorrhage started after hospitalization for worsening liver disease and did not have signs of UGIH on admission; and (4) is associated with a high rate of mortality (63%) in those not receiving liver transplantation. Physicians managing patients with ESLD should be aware that posterior nasopharyngeal epistaxis can masquerade as massive UGIH, particularly in those with severe coagulopathy.

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COMMENTS

Background

Severe epistaxis is a rare cause of massive bleeding which can masquerade as upper gastrointestinal hemorrhage (UGIH) in patients with end stage liver disease (ESLD).

Research frontiers

Little is known about prevalence, treatment and outcomes of patients suffering from epistaxis in case of ESLD. Only few cases series are available in literature.

Innovations and breakthroughs

The authors described that epistaxis was the diagnosis of the bleeding source in 4.3% of cirrhotic patients with a suspected UGIH and this prevalence in-

creased to 15.3% in the population of cirrhotic patients in whom the hemorrhage occurred after hospitalization for worsening liver disease and did not have signs of UGIH on admission. The authors found that epistaxis in such cases could usually be effectively treated with nasal packing and correction of coagulopathy. This treatment should not be delayed. In fact, epistaxis in ESLD was associated with a high rate of mortality (63%) in those not receiving liver transplantation.

Applications

Physicians managing patients with ESLD should be aware that posterior nasopharyngeal epistaxis can masquerade as massive UGIH, particularly in those with severe coagulopathy.

Peer review

Well written and discussed study. The authors described the prevalence, diagnosis, treatment, and outcomes of ESLD patients with severe epistaxis masqueraded as upper gastrointestinal hemorrhage. We have limited knowledge in this subject and the authors made an important observation.

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