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Case Report

Tuberculous Vasculopathy of the Mesenteric Arteries: A Very Peculiar Vascular Cause of Massive Upper Gastrointestinal Bleeding

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Abstract

Background: Upper gastrointestinal bleeding (UGIB) from tuberculous vasculopathy is extremely atypical. Among reported cases, UGIB from gastrointestinal tuberculosis (GITB) was due to ulcers, aortoenteric fistulas, hemobilia, use of certain drugs and rarely, vasculopathy. Tuberculous aorto-enteric fistula accounts for < 1% of UGIB causes and tuberculous vasculopathy is thought to be rarer. We present a case of a 22 year-old Filipino male with disseminated tuberculosis and tuberculous vasculopathy presenting as massive UGIB and refractory shock.

Case Summary: A 22 year old Filipino was admitted for epigastric pain after a 3 month history of recurrent abdominal pain, intermittent melena, weight loss, prolonged cough and fever. On admission, he was normotensive, tachycardic and in respiratory distress. He was cachectic, pale, icteric, with multiple cervical lymphadenopathies. There was no abdominal bruit noted. Baseline laboratory tests revealed anemia, lymphopenia, elevated AST and ALT, elevated PT, INR and extensive pulmonary infiltrates (miliary TB pattern). The patient was initially stabilized with aggressive hydration, blood transfusion and was started on IV proton pump inhibitors. Emergency EGD revealed non-specific gastropathy. An abdominal CT scan revealed splenic abscess and multiple retroperitoneal lymphadenopathies. Empiric anti-tuberculosis medications were started. On the 5th hospital day, the patient had recurrent massive UGIB and succumbed to hemorrhagic shock. The autopsy revealed multiple creamy yellow nodules in the lungs, serosa of the stomach, small and large intestines, liver, spleen and kidneys. The intestines were adherent to the caked mesentery. The stomach showed thinning of the walls, flattening of the rugae with no ulcers, perforations or fistulas. Acid fast bacilli were demonstrated on smears taken from multiple organs. Within the intestinal walls and mesenteric vessels, granulomas adjacent to medium-sized blood vessels, perivascular inflammation with muscle wall distortion and granuloma emboli were seen indicating a vasculopathic process. The massive UGIB was most likely due to mucosal ischemia secondary to tuberculous vasculopathy.

Conclusion: This case report highlights the importance of considering tuberculous vasculopathy as a very peculiar vascular cause of UGIB. We emphasized the importance of considering TB vasculopathy in the Philippine setting as part of the long list of differential diagnosis for UGIB in patients with disseminated tuberculosis so timely and focused management can be instituted.

Keywords: *Chylolymphatic Cyst; Mesenteric Cyst; Pediatric; Infant*

Introduction

Upper gastrointestinal bleeding (UGIB) from gastrointestinal tuberculosis (GITB) is an atypical presentation of extra-pulmonary tuberculosis. Among cases reported in the literature, UGIB from GITB were attributed to mucosal ulcers, fistulas, hemobilia, drug-induced

from rifampicin intake, vasculitis or vasculopathy [1-3,7]. Tuberculosis of the stomach could present as bleeding gastric ulcers [9] The histological specimens revealed chronic granulomatous inflammation with caseating epithelioid granulomas with Langhan's type giant cells centrally. Tuberculosis of the duodenum can present as a simple bleeding ulceration, successfully treated with medications for which surgery plays a limited role. Aorto-enteric fistulas acquired vascular connections between the aorta and bowel, especially from an infectious etiology such as tuberculosis are rare causes of UGIB, accounting to less than 1%. Tuberculous vasculitis or vasculopathy are thought to be an even rarer etiology.

We present a case of tuberculous vasculopathy of the mesenteric arteries as a very peculiar vascular cause of UGIB. The objective of this case report is to emphasize the importance of considering TB vasculopathy in the local setting as part of the long list of differential diagnosis for UGIB in patients with disseminated tuberculosis so timely and focused management can be instituted.

Case Presentation

We report the case of MLR, a 22 year-old previously healthy Filipino male who consulted at the Philippine General Hospital - Emergency Room (PGH-ER) for abdominal pain. He initially presented with a 3 month history of epigastric pain, described as burning and hunger like, with a visual acuity score (VAS) of 5/10, more pronounced on an empty stomach and relieved by food intake. Intermittent melena and significant weight loss (> 20% from baseline weight) were also noted. Around 2 months prior to admission, the patient noted nightly fevers (Tmax 39°C), excessive sweating and marked anorexia. One month prior to admission, he consulted at the PGH-ER for persistent epigastric pain. He was given antacids and proton pump inhibitors with a mild relief of symptoms and was subsequently sent home. Two weeks prior to admission, he developed non-productive cough, more pronounced anorexia, profound body weakness and persistent epigastric pain, thus prompting ER consult.

He had no previous history of gastrointestinal bleeding nor any bleeding diathesis. The past medical history was unremarkable for other comorbid diseases. There was no intake of antiplatelets, anticoagulants or non-steroidal anti-inflammatory drugs. The patient's father, who lives in the same household, died from incompletely treated pulmonary tuberculosis in 2010. There was no family history of malignancy or bleeding disorder. The patient is an occasional alcoholic beverage drinker and had 2 pack-year smoking history. He denied sexual promiscuity, illicit drug use and a history of recent travel outside Metro Manila.

On admission, his blood pressure was marginal at 90/60 mmHg, tachycardic (140 beats per minute), in moderate respiratory distress (32 cycles per minute), with a nasogastric output of 350 ml coffee ground material on initial nasogastric tube insertion. Physical examination revealed a cachectic patient with temporal and peripheral muscle wasting, pale palpebral conjunctivae, icteric sclera, dry oral mucosa, multiple matted lymphadenopathies on the supraclavicular fossa and lateral neck and a left axillary lymph node. The patient had a scaphoid abdomen with direct epigastric tenderness on deep palpation. There was no rebound tenderness, signs of peritonitis, fluid wave, abdominal bruits or blood on digital rectal examination. The pulses were full and equal. The rest of the physical examination was normal.

Initial laboratory work-up revealed normocytic normochromic anemia and lymphopenia (hemoglobin 88 g/L, mean corpuscular volume 82 fL, mean corpuscular hemoglobin 27 pg, white blood cell 7.30 x 10^9/L, neutrophil 0.931, lymphocyte 0.048, platelet count 194 x 10^9/L). Blood chemistry showed an elevated aspartate aminotransferase (AST 105 IU/L), elevated alkaline phosphatase (AP 214 IU/L) and hyponatremia (Na 124 mmol/L). Random blood sugar (RBS), blood urea nitrogen (BUN), creatinine (crea), alanine aminotransferase (ALT), bilirubins (TB, DB, IB), amylase and serum potassium (K) were within normal limits.

The patient was initially managed as a case of upper gastrointestinal bleeding (UGIB) probably from a bleeding peptic ulcer or stress related mucosal injury. He was placed on nothing per orem, hydrated with 1 liter D5NR x 8 hours and was started on omeprazole drip, paracetamol and hyoscine N butylbromide. After samples for hematologic work up were collected, he was transfused with 1 unit of packed red blood cells (pRBC). He was referred immediately to the Gastroenterology Service for immediate esophagogastroduodenoscopy (EGD) after he was stabilized. The EGD revealed non-specific gastropathy and a possible duodenal bulb fistula, the latter finding pointing to-

wards possible gastrointestinal tuberculosis (GITB). Mucosal samples for AFB smears were taken. A holoabdominal CT scan with contrast was ordered.

Due to a chronic history of constitutional symptoms associated with multiple lymphadenopathies, disseminated tuberculosis (involving lymph nodes, pulmonary and gastrointestinal) versus a possible lymphoma was considered. Multiple sputum, urine and stool samples for acid-fast bacilli were ordered. Chest radiograph done showed a pattern consistent with military tuberculosis. The patient was eventually transferred to an isolation room in the Internal Medicine ward. The screening HIV test was negative for the patient.

At the Medicine Ward, he was managed as a case of UGIB and disseminated tuberculosis. Quadruple anti-Kochs therapy was started. On the morning of the 2nd ward day, he complained of hematochezia associated with tenderness on the right and left lower quadrant of the abdomen. The plan was to do an abdominal CT or an upper gastrointestinal series with small intestine and a fistulogram. The antacids, pain relievers and anti-tuberculosis medications were continued. On the night of the 2nd ward day, he had intermittent episodes of hematemesis associated with abdominal guarding and tenderness on all quadrants, associated with hypotension. Aggressive saline hydration, inotropic support and blood transfusion were given. An acute abdomen was considered, although chest and abdominal radiography did not reveal signs of pneumoperitoneum or bowel obstruction. He was immediately referred to surgery, who decided on conservative management.

On the 3rd ward day, hypotension, bleeding and abdominal pain persisted despite hydration, blood transfusion and inotropic support. Complete blood count revealed anemia (hemoglobin 77 g/L, white blood cell 9.7 x 10^9/L, platelet count 163 x 10^9/L). From a normal baseline coagulation profile, mild coagulopathy developed from continuous bleeding (prothrombin time - INR 1.52).

On the 4th ward day, the patient was still bleeding and in shock. Holoabdominal ultrasound performed showed splenic abscess and multiple retroperitoneal lymphadenopathy, probably from a tuberculous etiology. Octreotide drip was started and other supportive measures were continued. At this point, emergency exploratory laparotomy was done which showed intra-operative findings of multiple nodularities, granuloma at the jejunum, ileum, colon and matted omentum consistent with GITB. There was no note of fistula or perforated viscous. Supportive measures were continued post operatively.

On the 5th ward day, repeat surveillance EGD done showed a visible vessel at the proximal-mid gastric body, which was a possible Dieulafoy's lesion. Despite maximum medical therapy, the patient continuously bled and eventually expired from hemorrhagic shock secondary to massive upper gastrointestinal bleeding.

Full autopsy was performed 15 hours post-mortem. There was bilateral pleural effusion, with the lungs showing multiple, cream to yellow, soft, necrotic nodules on the surface and within the lung parenchyma. The same nodules were seen on the surface of the diaphragm, serosa of the stomach, small and large intestines, liver parenchyma, spleen and bilateral kidneys. The mesentery was matted and showed cream yellow, friable cut surface. The small and large intestines were adherent to the caked mesentery. There was about 300 mL and 200 mL of clotted blood seen in the stomach and jejunum, respectively. However, no ulcers or perforations were identified. The stomach also showed thinning of the walls with flattening of the rugae. Multiple enlarged lymph nodes were seen at the supracalvicular area, mesentery and paraaortic area, all showing a cream white to yellow, soft, necrotic, friable cut surfaces. Aorto-enteric fistula and hemobilia were not seen in the autopsy.

Microscopy showed chronic granulomatous inflammation with caseation necrosis and Langhans type giant cells in the lungs, liver, spleen, lymph nodes, bilateral kidneys, and within the submucosa, muscularis propria and serosa of the stomach, small intestine and large intestine. Acid-fast bacilli were demonstrated (+3) via immunofluorescence (auramine stain) on smears taken from the involved supraclavicular node. Evidence of coagulative necrosis of the gastric, jejunal, ileal and colonic mucosa were characterized by sloughing off of the mucosa, loss of nuclear basophilia, loss of architecture and acute and chronic inflammatory infiltrates.

Also seen within the walls of the involved intestines are granulomas adjacent to medium-sized blood vessels. Perivascular inflamma-

tion with beginning muscle wall distortion was seen indicating a vasculopathic process. Within the mesentery, medium- to large-caliber vessels showed the same perivascular inflammation, as well as beginning granuloma formation on the vessel wall and granuloma emboli.

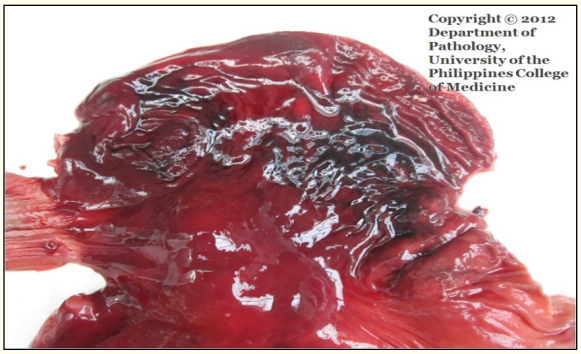

Figure 1: *Stomach. Gastric mucosa showing thinned out, hemorrhagic mucosa and flattening of ruggae in some areas. No ulcers, perforations or fistula was seen.*

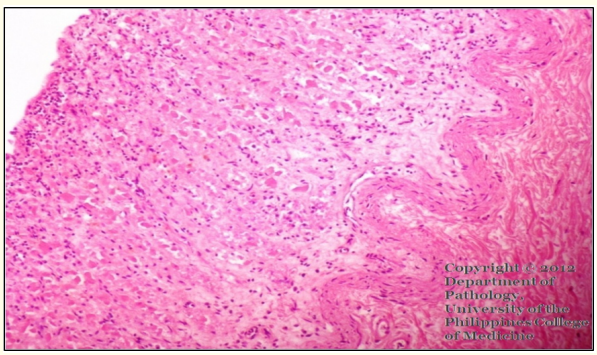

Figure 2: *Stomach. Histologic sections showing the mucosa, muscularis mucosa and the submucosa. The mucosa shows coagulative necrosis characterized by the presence of cell outlines but with loss of cellular detail. There is loss of nuclear basophilia. Scattered lymphocytes are also seen.*

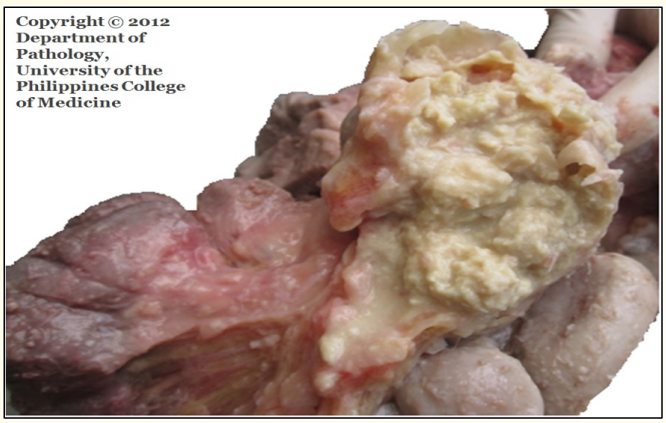

Figure 3: *Intestines and mesentery. The mesentery is converted to a yellow-white, friable material. Multiple small yellow white nodules are seen on the intestinal serosa. The intestines are adherent to the mesentery.*

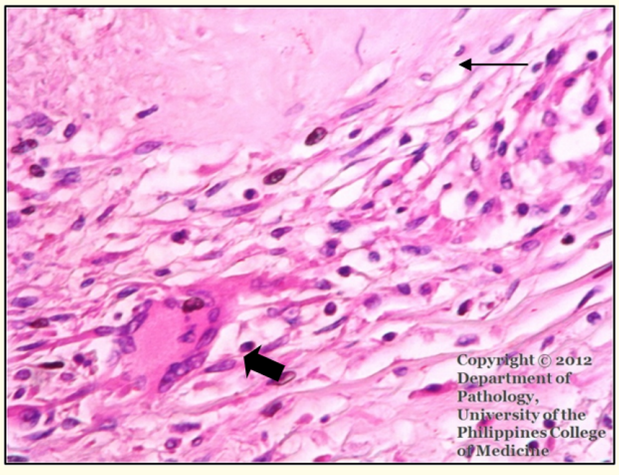

Figure 4: *Colonic wall granuloma. A portion of the central caseation necrosis is seen (thin arrow), surrounded by epithelioid histiocytes and some lymphocytes. A Langhans type giant cell is seen at the lower left (thick arrow).*

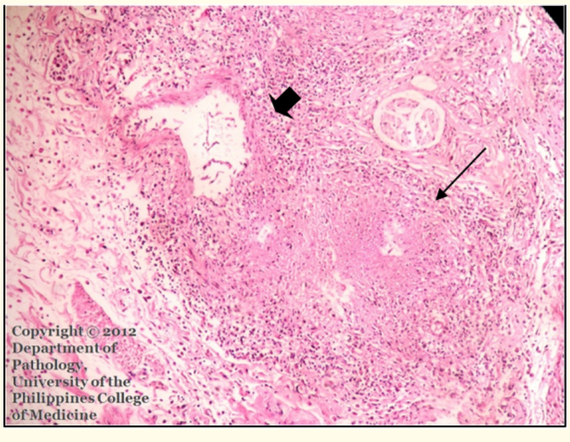

Figure 5: *Colonic wall medium-sized vessel vasculopathy. A medium-sized vessel surrounded by inflammatory infiltrates (perivascular cuffing). [Thick arrow] Adjacent to it is a granuloma. [Thin arrow].*

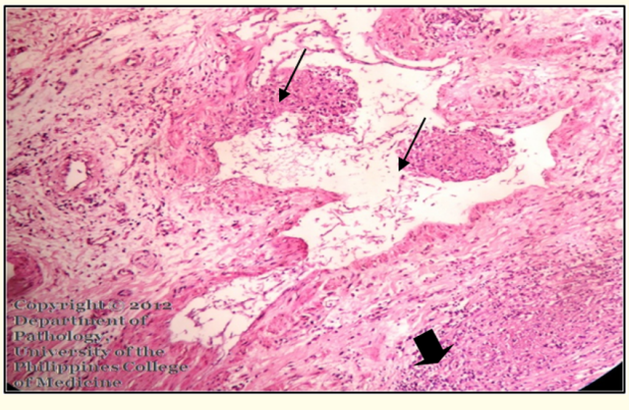

Figure 6: *Mesentery. Beginning granulomas are seen within the wall and lumen (thin arrows) of this medium-sized mesenteric vessel. A granuloma is seen beside the vessel.*

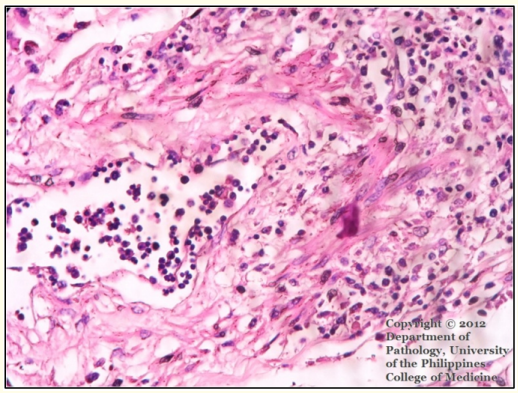

Figure 7: *Mesenteric vasculopathy. The tunica media of this medium-sized artery is infiltrated by mixed inflammatory cells.*

Discussion

The list of differential diagnosis for upper gastrointestinal bleeding in a patient with possible disseminated tuberculosis is long and extensive. The common causes of UGIB in the general population include bleeding peptic ulcer disease, stress related mucosal injury and drug induced, which should be exhausted first, however, rarer causes of UGIB should be considered in this subset of patients in the absence of the aforementioned culprits.

The patient presented with recurrent epigastric pain, constitutional symptoms, multiple lymphadenopathies, and a chest x-ray findings consistent with military tuberculosis. The initial EGD done showed a duodenal bulb fistula and this finding is suggestive of gastrointestinal tuberculosis. In a case series done by Rao et. al., the most common presentation of gastroduodenal tuberculosis were vomiting, epigastric pain, loss of appetite and weight loss, upper gastrointestinal bleeding, fever, jaundice and recurrent cholangitis, in decreasing order [4]. The Majority of these symptoms were seen in our patient.

The most common location of GI TB was the ileocecal region and rarely in the gastroduodenal region, the latter with a reported incidence of around 0.5% in international literature. In light of this observation, EGD and autopsy findings of a gastroduodenal and mesenteric vasculopathy in this patient are thus very atypical. Multiple reasons were cited in various journals elucidating the relative gastroduodenal sparing in GITB, which include high acidity of luminal contents, paucity of gastroduodenal lymphoid tissue and the rapid transit of food in the stomach [5,6] which does not favor the local growth and proliferation of TB bacilli.

Complications of gastroduodenal tuberculosis usually include obstruction of the gastric outlet, fistulous communication, perforation and UGIB, the latter of which was seen in our patient. Clinical and endoscopic findings initially suggested aorto-enteric fistula or hemobilia as possible causes of the massive bleeding. Aorto-enteric fistulas were associated with high mortality, commonly occurring in the setting of post aorto-iliac surgeries for aneurysms. The infective causes of AEF were extremely rare and usually secondary to infection of the aortic grafts. *Salmonella, Staphylococcus epidermidis* and *Streptococcus faecalis* were some of the microbes associated with this condition. Despite a high prevalence of TB infections, tuberculous AEFs were considered extremely rare. Of the documented AEF, 45% were associated with disseminated TB. It presents with a triad (seen in 6% - 27% of patients) of persistent abdominal pain, bleeding or an abdominal mass that was either palpable or radiologically detectable. Initial bleeding may be mild and obscure (herald bleed) but eventually catastrophic if not adequately diagnosed and managed [2]. Due to a very similar presentation, aorto-enteric fistula was initially considered for this patient. Hemobilia results from traumatic or operative injury to the liver or bile ducts, intra-ductal rupture of a hepatic abscess or aneurysm of the hepatic artery, biliary or hepatic tumor hemorrhage, or mechanical complications of choledocholithiasis or hepatobiliary parasitism. It presents with a triad of biliary pain, obstructive jaundice and melena. Diagnosis by means of cholangiographic evidence of blood clot in the biliary tree or selective angiographic verification may be required. Surgical ligation of the bleeding vessel has been frequently required[7]. Both hemobilia and aorto-enteric fistula were eventually ruled out because of the absence of objective findings on exploratory laparotomy and on repeat endoscopy.

On autopsy, there was a note of thinned out gastric mucosa with absent folds. Gross and histologic samples from various organs consistently showed tuberculosis confirming the diagnosis of disseminated TB. What is peculiar about this case is the demonstration of TB granulomas very adjacent to medium sized blood vessels within the walls of the involved intestines. Perivascular inflammation with beginning muscle wall distortion was seen confirming a vasculopathic process. Within the mesentery, medium- to large-caliber vessels showed the same perivascular inflammation, as well as beginning granuloma formation on the vessel wall and granuloma emboli. In literature, vasculopathy is defined as dysfunction or non-immunologic injury of small blood vessels or capillaries that led to local vascular insufficiency, thrombosis and sometimes, secondary vascular inflammation. In contrast, vasculitis, is characterized by inflammation, necrosis and hemorrhage of blood vessels, whose signs and symptoms were attributable to tissues and organs damaged by compromised vasculature [8]. Kuwajerwala., *et al.* reported mesenteric vasculopathy from tuberculosis, but the initial presentation was intestinal perforation and obstruction instead of bleeding. Histologic findings in this case included granulomas, intraluminal thrombi, subintimal fibrosis and perivascular cuffing [10]. Vasculitis is already an established pathology in tuberculosis of the central nervous system, lungs and kidneys. Vasculitis in the enteric and mesenteric vessels is beginning to be understood as an important process in the natural history of GIT tuberculosis. Tissue ischemia from the vasculitis is said to be the most common cause of intestinal perforation in gastrointestinal tuberculosis. Literature on GIT tuberculosis shows that perforation and stricture are still the most common complications. In a study by Dasgupta in 2009, small- to medium-sized vessels are more commonly involved (41.9% to 93.9%) than large-caliber vessels (6.5%). Granulomas in or adjacent to the blood vessels, subintimal fibrosis, perivascular cuffing, and intravascular organizing thrombus due to granulomatous inflammation were the reported histologic evidence of TB vasculopathy. Perivascular cuffing was seen in all cases. However, this was observed only in the small-sized vessels, mostly in the submucosa and subserosa.

Mesenteric vasculopathy was more prominent than enteric vasculopathy in this patient. Beginning granulomas were seen within medium-sized vessels in the mesentery. The smaller vessels within the intestinal walls mostly showed perivascular cuffing and adjacent granulomas. The massive UGIB this patient presented with was most likely due to mucosal ischemia secondary to tuberculous vasculopathy. Although intestinal perforation is the most common complication of tuberculous vasculopathy, this was not demonstrated on autopsy. Unfortunately, despite aggressive medical therapy, the patient expired due to continuous blood loss. An abdominal CT scan with contrast could have been useful in identifying structural causes of bleeding; however, it was not done due to financial limitations. An earlier surgical exploration with surgical resection of the diseased intestinal segment coupled with anti-TB medication for 6 months could have been performed in retrospect.

Conclusion

This case report adds to the growing literature that highlights the importance of considering atypical gastrointestinal tuberculosis presentation and its possible complications. Indeed, tuberculous vasculopathy may masquerade as one of the typical causes of UGIB, hence a high index of suspicion should be maintained and its diagnosis should be pursued after an exhaustive search of the more common causes of UGIB.

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