

March 2, 2017

Dr. Jin-Xin Kong

Editorial Office

Baishideng Publishing Group Inc.

Email: j.x.kong@wjgnet.com

RE: World Journal of Gastrointestinal Endoscopy Manuscript #: 32463

Dear Dr. Jin Xin Kong:

Thank you for your kind email letter regarding, manuscript # 32463 submitted to World Journal of Gastrointestinal Endoscopy entitled, "Two case reports of acute upper GI bleeding from duodenal ulcers after Roux-en-Y gastric bypass surgery for morbid obesity: endoscopic diagnosis and therapy by single balloon or push enteroscopy after missed diagnosis by standard EGD because of technical inability to intubate the excluded proximal duodenum". We have submitted all the required revisions as follows:

REVIEWER #03258825 CRITICISMS:

1. The prevalence of *H. pylori* infection in patients undergoing RYGB is high and there are literatures on the status of *H. pylori* and ulcer formation in RYGB patients. Please provide the status of *H. pylori* infection of these 2 cases, and comment on this in Discussion.
2. Please provide information on the status of cigarette smoking (Case 1 and 2) and NSAID-usage (Case 2).
3. Case 1 rebled after initial endoscopic treatment. Please provide the following information: the concentration and volume of epinephrine injection, the setting of heater probe, and whether the visible vessel was completely flattened after treatment.

CASE 1, CHANGE TO:

A 44-year-old woman with prior RYGB 11 years earlier for morbid obesity presented to a community hospital with recurrent melena, weakness, and orthostatic dizziness for 1 week. She had been taking non-steroidal anti-inflammatory drugs (NSAIDs) about two days per month for several months, but was not taking proton pump inhibitors (PPIs). She was a non-smoker and non-alcoholic.

FROM

A 44-year-old woman with prior RYGB 11 years earlier for morbid obesity presented to a community hospital with recurrent melena, weakness, and orthostatic dizziness for 1 week. She had been occasionally taking non-steroidal anti-inflammatory drugs (NSAIDs) for several months, but was not taking proton pump inhibitors (PPIs). On admission the hemoglobin (Hgb) was 4.1 g/dl. She was intravenously infused crystalloid solutions, transfused 4 units of packed erythrocytes, and intravenously administered PPI.

CASE 2, CHANGE TO:

A 64-year-old woman with prior RYGB for morbid obesity 10 years earlier presented acutely with melena and hematochezia, associated with dyspnea, fatigue, and syncope. She was taking ibuprofen about 800 mg/day for about 2 days per week for arthralgia, but had stopped about 3 months ago. She was not taking PPIs, did not drink alcohol, and had stopped smoking cigarettes (1 pack/day) 12 years earlier.

FROM

Case 2: A 64-year-old woman with prior RYGB for morbid obesity 10 years earlier presented acutely with melena and hematochezia, associated with dyspnea, fatigue, and syncope. Physical examination on admission revealed stable vital signs, pallor, and a normal abdominal examination. Rectal examination revealed melena and no visible hemorrhoids.

REVIEWER #02822590 CRITICISMS

1. Bariatric surgery for morbid obesity is not so popular around the world (at least in our country). If there is a difference of the reconstructive surgery for the standard surgery (e.g. for advanced gastric cancer) and the bariatric surgery, the author should describe the differences.
2. The author should describe the X-ray image with scope as each Figure for showing the locations of the ulcer.

REVIEWER #00050424 CRITICISMS

The authors report two cases with AUGIB following Roux-en-Y gastric bypass where the diagnosis and treatment were performed successfully with enteroscopy. Retrograde intubation with single or double balloon enteroscopy has been used in such cases or in small group of patients. The question remains: what is the technical and clinical success rate in a large number of patients.

REVISIONS TO CONFORM TO JOURNAL STYLE

1. Throughout the paper the references are cited in the text as numbers in superscript enclosed within brackets, rather than numbers enclosed within parenthesis: e.g. ^[1] replaces (1).

2. All references within the Reference section are cited according to journal reference style. In particular, the PMID # and the doi # are added. For example,

CHANGE TO:

1. **Ceppa FA**, GagnéDJ, Papasavas PK, Caushaj PF. Laparoscopic transgastric endoscopy after Roux-en-Y gastric bypass. *Surg Obes Relat Dis* 2007; **3**: 21-4. [PMID: 17116423 DOI: 10.1016/j.soard.2006.08.018]

FROM:

1. Ceppa FA, GagnéDJ, Papasavas PK, Caushaj PF. Laparoscopic transgastric endoscopy after Roux-en-Y gastric bypass. *Surg Obes Relat Dis*. 2007; 3(1):21-4.

In accordance with the journal's editorial style, the following sections are added under **COMMENTS**:

Case 1

Case characteristics

A 44-year-old woman with prior RYGB 11 years earlier for morbid obesity presented with melena, weakness, and orthostatic dizziness for 1 week.

Clinical diagnosis

The clinical history of melena, weakness, and orthostatic dizziness strongly suggests acute gastrointestinal bleeding. Melena strongly suggests acute upper GI bleeding, but lower GI bleeding cannot be absolutely excluded by this history. The symptoms of weakness and orthostatic dizziness suggest that the bleeding caused hypovolemia and was therefore physiologically significant and severe.

Differential diagnosis

The history of prior RYGB surgery in a patient presenting with melena suggests possible bleeding from an anastomotic (marginal) ulcer, but other common causes of upper GI bleeding are in the differential diagnosis, including ordinary peptic ulcer disease, hemorrhagic gastritis, hemorrhagic reflux gastritis, as well as relatively uncommon lesions. Bleeding from esophageal

varices is unlikely because of no history of chronic liver disease, absence of stigmata of chronic liver disease, and normal biochemical parameters of liver function. Also lower GI lesions must be considered in the differential diagnosis of patients presenting with melena when the EGD is non-diagnostic.

Laboratory diagnosis

On admission the hemoglobin level was 4.1 g/dl. This profound anemia demonstrated the importance of relatively rapidly transfusing the patient to prevent end organ injury from hypovolemia, and the patient was transfused 4 units of packed erythrocytes. A coagulopathy was not contributing to the bleeding as the coagulation profile was normal. The blood urea nitrogen: creatinine ratio was 36, consistent with upper rather lower GI bleeding. These findings are consistent with severe, upper GI bleeding.

Imaging diagnosis

EGD did not reveal any source of UGI bleeding, but the excluded proximal duodenum and stomach were not intubated and viewed. This was due to the difficulty in intubating the afferent loop status post RYGB surgery because of the long intubation needed to reach the afferent loop and acute angulation at the anastomosis to the afferent loop. Colonoscopy was performed because the EGD was non-diagnostic and did not reveal any etiology of lower GI bleeding. The patient experienced recurrent GI bleeding, with hemoglobin decline to 5.8 g/dl for which the patient was again medically stabilized. Abdominal computerized tomography with intravenous contrast was within normal limits. Single balloon enteroscopy, with intubation of the afferent loop, revealed a non-bleeding, 4-cm-wide bulbar ulcer with a non-bleeding visible vessel in the afferent limb and no other lesions. The diagnosis of a giant duodenal ulcer by single balloon enteroscopy after a non-diagnostic EGD due to failure to intubate the afferent loop at EGD is notable.

Pathological diagnosis

A giant duodenal ulcer in excluded gastroduodenal segment in afferent loop after RYGB surgery, was diagnosed by single-balloon enteroscopy and confirmed at surgery. The lesion was not resected and therefore the diagnosis was by endoscopy and surgery without a pathologic diagnosis.

Treatment

The visible vessel was ablated at single-balloon enteroscopy by injection of dilute epinephrine and by heater probe thermocoagulation. However, the patient had another episode of melena and the hemoglobin acutely declined from 9.5 g/dl to 6.5 g/dl 72 hours after therapeutic single balloon enteroscopy. Failure despite use of two methods of endoscopic hemostasis (dilute epinephrine injection and heater probe thermocoagulation) was most likely related to the exceedingly large size of the duodenal ulcer (4 cm diameter). A technetium-labeled erythrocyte (bleeding) scan and an abdominal arteriogram did not reveal an actively bleeding source. Exploratory laparotomy revealed a giant, posterior, bulbar ulcer (which had been detected at single-balloon enteroscopy), which was oversewn. The patient was discharged with no further bleeding during the hospitalization or for three months of follow-up.

Case 2

Case characteristics

A 64-year-old woman with prior RYGB for morbid obesity 10 years earlier presented acutely with melena and hematochezia, associated with dyspnea, fatigue, and syncope. Physical examination on admission revealed stable vital signs, pallor, and a normal abdominal examination. Rectal examination revealed melena and no visible hemorrhoids.

Clinical diagnosis

The clinical history of melena suggests acute upper GI bleeding, although occasionally melena may occur secondary to lower GI bleeding. The symptoms of dyspnea, fatigue, and syncope all suggest severe GI bleeding that is causing symptoms of end-organ injury or insufficiency from hypovolemia: syncope from insufficient cerebral blood perfusion; and dyspnea and fatigue from profound anemia with decreased oxygen-carrying capacity of the blood.

Differential diagnosis

The melena suggests likely upper GI bleeding. Most prominent in the differential diagnosis in a patient status post RYGB with melena is an anastomotic (marginal) ulcer. However, other common causes of upper GI bleeding are in the differential diagnosis, including ordinary peptic ulcer disease, hemorrhagic gastritis, hemorrhagic reflux gastritis, as well as relatively uncommon lesions. Bleeding from esophageal varices is unlikely because of no history of chronic liver

disease, absence of stigmata of chronic liver disease on physical examination, and normal biochemical parameters of liver function. Also lower GI lesions must be considered in the differential diagnosis of patients presenting with melena when the EGD is non-diagnostic.

Laboratory diagnosis

Laboratory analysis revealed hemoglobin=7.4 g/dl (recent baseline hemoglobin=13.3 g/dl), evident iron deficiency anemia with ferritin=25 ng/ml, platelet count=62,000/l, and serum BUN:Cr ratio=100. Liver function tests and coagulation panel were within normal limits. The current very low hemoglobin level that has recently declined from a normal hemoglobin level suggests acute, severe, GI bleeding. The iron deficiency anemia suggests the bleeding has been sufficiently long and severe to deplete iron stores. Melena usually arises from an upper GI source, but can occasionally result from a lower GI source, especially when associated with hematochezia. The highly elevated BUN:creatinine ratio strongly suggests that the melena is from upper rather than lower GI bleeding.

Imaging diagnosis

EGD did not reveal any source of UGI bleeding, including no anastomotic ulcers, but the excluded proximal duodenum and stomach (afferent loop) status post RYGB surgery was not intubated and viewed. This was due to the difficulty in intubating the afferent loop status post RYGB surgery because of the long intubation needed to reach the afferent loop and acute angulation at the afferent loop anastomosis. Colonoscopy was performed because of the history of melena and a non-diagnostic EGD, but did not reveal any etiology of lower GI bleeding. Both computed tomographic enterography and capsule endoscopy were within normal limits. Bleeding slowly resolved and she was discharged with hemoglobin of 8.0 gm/dl.

The patient was readmitted 3 days later for recurrent melena with a hemoglobin level of 5.1 g/dl. A technetium labeled erythrocyte (bleeding) scan did not reveal active GI bleeding. Push enteroscopy revealed a 5-mm-wide acute bulbar ulcer with a visible vessel that was oozing blood, and an otherwise normal examination. The visible vessel was endoscopically treated with dilute epinephrine injection, hemoclips, and argon plasma coagulation.

Pathological diagnosis

An ulcer in the duodenal bulb in the excluded gastroduodenal segment in the afferent loop after RYGB surgery, was diagnosed by enteroscopy. The bulbar ulcer was not resected and therefore the diagnosis was by endoscopy and surgery without a pathologic diagnosis.

Treatment

The patient received intravenously infused crystalloid solutions, transfused 4 units of packed erythrocytes, and intravenously administered a PPI. The duodenal ulcer lesion was endoscopically treated with dilute epinephrine injection, hemoclips, and argon plasma coagulation (APC) because it was oozing blood at the endoscopy. The patient had one further, self-limited, episode of melena, after which the bleeding resolved, and the patient was discharged. She has had no further GI bleeding during 3 months of follow-up.

Both cases

Related reports

Term explanation

RYGB is an acronym for Roux-en-Y gastric bypass surgery, a popular form of bariatric surgery, in which a large part of the stomach and the proximal duodenum is surgically excluded from the normal stream of food. This leads to decreased assimilation and absorption of food. This surgery also leads to early satiety because of the very small residual stomach pouch and decreased production of ghrelin which acts as a “hunger hormone”.

Experiences and lessons

This work reports two cases of duodenal ulcers occurring after RYGB, supplementing 22 prior case reports of peptic ulcers after RYGB. These two cases report bleeding giant or moderately-sized duodenal ulcers being missed at routine EGD performed for acute upper GI bleeding because of inability to intubate the afferent loop (excluded segment) because of acute angulation and the requirement for deep intubation. This finding has also been previously reported. This work reports that the afferent loop was successfully intubated by either a single balloon enteroscope or push enteroscope. The use of these special endoscopes permitted the diagnosis of

the cause of the acute upper GI bleeding as peptic ulcers, permitted identification of high-risk stigmata of recent hemorrhage (SRH) consisting of either a visible vessel or active bleeding, and permitted performance of therapeutic endoscopy for hemostasis. Although recurrent GI bleeding from only one of the two high risk peptic ulcers was prevented by the endoscopic therapy, these two cases illustrate the usefulness of specialized enteroscopes rather than standard esophagogastroduodenoscopes to intubate, examine, and diagnose lesions in the excluded gastroduodenal segment (afferent limb) status post RYGB surgery. This work adds to the literature by emphasizing the potential diagnostic and therapeutic benefits of push enteroscopy or single balloon enteroscopy if EGD was non-diagnostic in patients status-post RYGB surgery.

Peer-review

The authors greatly appreciate the reviewers for their insightful comments and consequent improvement of the paper.

Comments by Reviewer 02822590 led to an added figure (Figure 3) that illustrates the surgical anatomy after RYGB surgery. This figure should prove very useful to physicians who are not surgeons, but who take care of patient status-post RYGB surgery, such as internists or gastroenterologists. This added figure also clarifies why the surgical anatomy makes it difficult to intubate the excluded gastroduodenal segment after RYGB surgery by showing the extra-long path of intubation to reach this area and the potential angulation between the gastojejunal (alimentary or efferent) limb and the biliopancreatic (afferent) limb.

Comments by reviewer #03258825 led to the authors clarifying whether smoking cigarettes, NSAID usage, or H. pylori infection contributed to the formation of the peptic ulcers observed in the duodenum. In both case 1 and case 2 all these risk factors for peptic ulcer disease were not present. Comments by this reviewer also led to the reporting technical details about the endoscopic therapy performed for hemostasis. These technical details are important because the dual endoscopic therapies of dilute epinephrine injection and heater probe coaptive coagulation proved unsuccessful at preventing rebleeding and the patient had to undergo gastrointestinal surgery to stop the bleeding. The authors believe that the failure of endoscopic hemostasis is most likely attributable to the giant size (4 cm diameter) of the bulbar ulcer.

Finally, comments by reviewer #00050424 led to sharpening of the focus of the Discussion on the 2 case reports on the most important aspects of these cases.

REQUIRED REVISIONS AS PER JOURNAL STYLE

1. As requested we have added the following authors' contributions section.

Drs. S. Hakim and M. Cappell are equal primary authors.

Dr. S. Hakim helped in reviewing and editing the two case reports, and wrote a preliminary version of the Introduction, and Discussion sections.

Dr. M. Cappell was the mentor for Dr. Hakim and Dr. Reddy for this paper. As such, Dr. Cappell supervised the writing of the entire paper, including writing parts of the Introduction and Discussion sections, and thoroughly editing the entire paper.

Dr. M. Batke was the attending clinician treating patient 1, wrote up a preliminary version of this case report, and reviewed the rest of the paper.

Dr. G. G Polidori was the attending treating patient 2, wrote up a preliminary version of this case report, and reviewed the rest of the paper.

2. As requested, we have added the following Copyright Statement:

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3. As requested, we have added the following Core Tip section:

After Roux-en-Y-gastric-bypass (RYGB) surgery, the surgically excluded distal stomach/duodenum may be difficult to intubate and examine during esophagogastroduodenoscopy (EGD). Two cases are reported of acute UGI bleeding many years after RYGB surgery, in which EGD was non-diagnostic due to failure to intubate these excluded segments. However, single balloon or push enteroscopy successfully permitted this intubation, enabling endoscopic diagnosis and therapy of bulbar ulcers at high risk of rebleeding. These case reports suggest using single balloon or push enteroscopy to endoscopically evaluate acute UGI bleeding in patients status-post-RYGB-surgery when EGD was non-diagnostic because of failure to intubate the excluded gastroduodenal segments.

4. As requested, we have added an Audio Core Tip.

Thank you for your interest in this manuscript. I will gladly perform any further revisions as required for publication of this paper in this prestigious journal.

Warm regards,

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