Late-onset Life Threatening Hemorrhage of Omeprazole-Resistant Duodenal Ulcer Managed by Interventional Radiology: Report of a Case

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Abstract

A 67-year-old diabetic man was emergently hospitalized in our department because of a huge duodenal ulcer without visible vessels. Despite of intravenous administration of 40 mg omeprazole and fasting with intravenous nutritional support, endoscopically unmanageable massive bleeding occurred on the 8th hospital day. Emergent angiography showed extravasation of contrast media from a duodenal branch of the proper hepatic artery, and superselective arterial embolization was successfully achieved. The patient recovered from the hemorrhagic shock and underwent subsequent successful surgery. Analysis of CYP2C19 enzyme genotype indicated the patient was a homozygous extensive metabolizer, considered a poor responder for omeprazole treatment.

Key words: interventional radiology, omeprazole resistant peptic ulcer, extensive metabolizer of CYP2C19, hemorrhagic duodenal ulcer, endoscopic hemostasis

DOI: 10.2169/internalmedicine.45.1721

Introduction

With advancement of endoscopic hemostatic procedures and availability of proton pump inhibitors (PPI), the incidence rate of hemorrhagic peptic ulcers significantly decreased (1-9). In particular, late bleeding is considered exceptional in patients without bleeding stigmata at the initial endoscopy. We herein describe a case of duodenal ulcer presenting life threatening hemorrhage even after 7 days of hemostatic stable state under omeprazole intravenous administration and successful interventional radiology (IVR) in hemorrhagic shock state enabling subsequent successful surgery. In addition, we discuss a possible association between omeprazole-resistant peptic ulcer and genetic polymorphism of CYP2C19.

Case Report

A 67-year-old Japanese man was admitted to our hospital by ambulance in May 2004 because of epigastric pain and tarry stool. The patient had a past medical history of duodenal ulcer and diabetes mellitus with neuropathy for 15 years. Laboratory tests indicated iron deficiency anemia (hemoglobin content, 7.8 g/dL), hypoproteinemia (2.6 g/dL), and increased levels of blood urea nitrogen (42 mg/dL), plasma glucose (508 mg/dL), glycosylated hemoglobin A1c (13%), white blood cell counts (14,800 /μL) and C-reactive protein (1.6 mg/dL). Gastro-duodenoscopy performed 24 hours after admission showed a huge and deep duodenal ulcer without bleeding stigmata in the lower half circumference of the duodenal bulb (Fig. 1). Since there was a potential risk of penetrating serositis indicating inflammatory signs, we treated the patient by intravenous administration of 40 mg...
Omeprazole and fasting with intravenous nutritional support of 800 kcal daily under insulin treatment. The patient had taken no ulcerogenic agents including non-steroidal anti-inflammatory drugs. But, the patient suddenly experienced massive hematomesis and melena on the 8th hospital day and progressed to hemorrhagic shock, requiring packed cells of 12 units and fresh frozen plasma of 1,000 mL. Endoscopic hemostatic procedures failed because of poor accessibility due to the massive blood retention in the gastroduodenum. Since his circulation state was unstable to carry out an emergent operation, we attempted IVR for embolization of ruptured vessels. Emergent angiography showed extravasation of contrast material from 3 cm distal in the peripheral duodenal branch of the proper hepatic artery. Arterial coil embolization using super selective catheterization was successfully achieved in the distal and proximal parts of the ruptured vessel (Fig. 2), and the patient consequently recovered from the hemorrhagic shock. However, his hemoglobin content decreased from 10.2 to 8.1 g/dL 18 hours after the IVR. We therefore performed partial gastroduodenectomy with Billroth 1 reconstruction. The duodenal ulcer was firmly fixed and penetrated the gall bladder. Therefore, the operative time took 4.5 hours and the surgical procedure required 7 units of packed cells transfusion. Histological examination of the resected specimen showed penetrated duodenal ulcer as shown by necrotic slough and destruction of the whole muscle layer. The postoperative course was uneventful, and the patient was discharged on the 40th hospital day. On subsequent investigations, his serum gastrin level was within normal range (27 pg/mL). There was no evidence of gastric mucosal atrophy on endoscopy or *Helicobacter pylori* infection on both histology and culture. Genotype analysis with a commercially available invader assay (BML Co., Tokyo) identified the two mutated alleles of CYP2C19*2 (G681A) in exon 5 and CYP2C19*3 (G636A) in exon 4 and indicated that the patient was homozygous for the wild-type in both exon 5 and exon 4 (*1/*1).

**Discussion**

Risk assessment and prediction of re-bleeding in hemorrhagic peptic ulcers is essential in decision making of the appropriate surgical treatment. Many investigations have clarified that bleeding stigmata, shock, elderly patients over 65 years, deep penetrated ulcer, underlying serious diseases, and coagulopathy at the initial presentation are risk factors for re-bleeding (2-9). Of these, the most relevant predictor is the endoscopic findings corresponding to Forrest categories of type Ia-IIb [Ia, actively spurting bleeding; Ib, actively oozing bleeding; Iia, non-bleeding visible vessel; IIb, adherent clot (1)].

In endoscopic observations reported by Lin et al (3), about 40% of patients with hemorrhagic peptic ulcer re-bled within 72 hours after the initial presentation whereas visible vessels of potential hemorrhage spontaneously disappeared in the remaining patients. Conversely, re-bleeding after 96 hours is reported in less than 1%, even in patients with vis-
ible vessels (2-5). Accordingly, life threatening hemorrhage 7 days after stable hemostatic state in a patient with a clean based peptic ulcer as in the present case is an extremely exceptional event.

Although the reasons for massive re-bleeding in the present case remain undetermined, a homozygous extensive metabolizer (homoEM) of CYP2C19 (∗1/∗1) is considered a poor responder for omeprazole treatment. Acid suppression by the usual dosage of omeprazole in homoEM is significantly lower than in heterozygous or poor metabolizers of mutated alleles (2 and/or ’3) (10-12). In such a case, intravenous administration of histamine 2-receptor antagonist may be rather effective. In recent trials, rabeprazole (less metabolized by CYP2C19 than other PPI) or a high dose of omeprazole shows a significant increase of intragastric pH levels and reduces re-bleeding rates (6, 10).

In addition, wound healing is impaired in diabetic conditions since fibroblasts and leukocytes in the wound become dysfunctional and collagen deposition decreases (13). The healing process of the huge and deep ulcers in the elderly diabetic and mal-nutritioned patient is thought to be delayed. Ulcer healing might be more interfered by the restriction of food intake, considering a potential risk of penetration. Therefore, massive re-bleeding in the present case is associated with multifactorial problems, in addition to genetic polymorphism of CYP2C19.

Moreover, IVR could provide emergent hemostasis enabling subsequent surgery. Angiographic embolization is the best alternative option in poor surgical candidates with endoscopically unmanageable gastrointestinal bleeding (14-16). However, 10 to 20% of patients undergoing hemostatic embolization re-bleed within 72 hours, probably due to re-canalization or re-filling through the extensive collaterals (15, 16). It is critical to never be late in making the decision for surgical treatment in patients with endoscopically unmanageable late bleeding peptic ulcers, considering the possibility of omeprazole-resistant ulcers.

References