We report a case in which rabeprazole cured gastric tube ulcer after esophagectomy for esophageal squamous cell carcinoma (ESCC). A 47-year-old Japanese man was referred to our hospital with refractory ulcer of the reconstructed gastric tube one year after esophagectomy for ESCC. The ulcer proved refractory to healing by the administration of omeprazole or lansoprazole, or eradication of Helicobacter pylori after examinations concerning ischemia, acid over-secretion and H. pylori infection. Finally, metabolizer type was examined for proton pump inhibitors (PPIs), revealing the patient as a hetero-extensive metabolizer for the CYP2C19 genotype. This suggested sensitivity to rabeprazole, but resistance to omeprazole and lansoprazole. The refractory ulcer was subsequently cured after changing the PPI to rabeprazole. Examination of PPI metabolizer type might thus be important, along with an investigation of ischemia, acid secretion and H. pylori infection in the treatment of refractory gastric tube ulcer after esophagectomy.

Keywords: refractory gastric tube ulcer, esophagectomy, Helicobacter pylori, CYP2C19

Introduction

Refractory ulcer arising in the reconstructed gastric tube after esophagectomy for esophageal cancer is not uncommon. To date, ischemic condition of the lesser curvature side in the gastric tube has been considered as the major cause of gastric tube ulcer. In addition, the reconstructed gastric tube exists under post-truncal vagotomy conditions that are likely to show low acid secretion and gastric stasis, which might affect the development of peptic ulcers. The development of gastric tube ulcer thus has yet to be clarified sufficiently.

In addition, Koide recently reported Helicobacter pylori infection as an important cause of gastric tube ulcer. We report a case with refractory ulcer in the gastric tube that was successfully cured by changing the proton pump inhibitor (PPI) to rabeprazole.

Case Report

A 47-year-old Japanese man was referred to our hospital for refractory gastric tube ulcer and complaints of chest pain. He had undergone esophagectomy for esophageal cancer and reconstruction using gastric tube via a retro-sternal route one year earlier at our institute. On endoscopic examination, a bleeding ulcer was seen on the anterior wall near the lesser curvature in the middle gastric tube, 34 cm from the incisors (Fig. 1).

Intravenous omeprazole was initially administered at 20 mg twice daily, which stopped the discharge of
exudate from the ulcer. PPI administration was then switched to oral administration of omeprazole at 20 mg once daily. However, the ulcer recurred after 2 months of medication. The PPI was switched to 30 mg of oral lansoprazole, but the ulcer persisted at the former hospital. However, gastric tube ulcer was not cured. Then, the patient was referred to our hospital.

Following confirmation of *H. pylori* infection, the patient underwent successful *H. pylori* eradication therapy with lansoprazole, amoxicillin and clarithromycin. However, the gastric tube ulcer remained refractory.

In spite of the administration of lansoprazole, strong
acid secretion was detected by Congo red staining (Fig. 2a) and 24-h gastroesophageal pH monitoring revealed that the gastric pH was <2, for most of the day. The refractory ulcer was diagnosed as peptic ulcer (Fig. 2b). We, therefore, examined the genotype for cytochrome P450 (CYP)2C19, which is involved in PPI metabolism. The patient was identified as a hetero-extensive metabolizer (EM) with a mutated allele in either exon 4 or exon 5. The PPI was switched to oral rabeprazole at 20 mg/day, and the ulcer in the gastric tube completely resolved within one month (Fig. 3). No ulcer recurrence has been identified since reducing the dose of rabeprazole to 10 mg/day two months later.

Discussion

The lesser curvature of the stomach tube has been reported to show locally ischemic conditions. The blood supply by slender vessels to the lesser curvature is poorer than the supply to the rich anastomosing submucosal vascular plexus of the anterior and posterior walls of stomach tube from the right gastroepiploic artery. In addition, ischemic conditions at the lesser curvature might also be enhanced by the trunk vagotomy, which immediately reduced gastric blood flow by opening up submucosal arteriovenous shunts, seen with gastric tube reconstruction after esophagectomy. Initially, local ischemic conditions were considered as the cause of gastric tube ulcer in the present case. However, vagotomy has also been performed for the treatment of peptic ulcer, because this surgery reduces gastric acid secretion. The effects of post-vagotomy conditions on gastric tube ulcer thus remains ambiguous. In fact, ulcer formation has been reported in association with gastric stasis after vagotomy-induced gastric dysmotility and pyloric dysfunction. Delayed gastric emptying is suggested to prolong contact between mucosa and gastric contents, bile acids and pancreatic enzymes due to duodeno-gastro-esophageal reflux. This condition reportedly allows bacterial proliferation and leads to enhancement of mucosal injury.

By contrast, the present case appeared to show conditions of both ischemic ulcer and enhanced gastric acid secretion, and the gastric tube ulcer was resistant to oral administration of both omeprazole and lansoprazole. We, therefore, performed H. pylori eradication therapy, since this bacterium plays an important role in the pathogenesis of gastric ulcer. In fact, a few reports have described correlations between H. pylori infection and gastric tube ulcer after esophagectomy, and Mori suggested that H. pylori infection increases gastric acid secretion in the gastric tube after esophagectomy.

Gastric tube ulcer in the present case remained refractory despite successful eradication of H. pylori. We, therefore, examined the CYP2C19 genotype, because the acid-inhibitory effects of PPIs are significantly dependent on CYP2C19 genotype status. Based on point
mutations in exons 4 and 5 of the CYP2C19 gene, individuals can be classified as homo-EMs, hetero-EMs and poor metabolizers (PMs). In Japan, the frequency of the homo-EM phenotype is the highest (34.9%), followed by hetero-EM (46.3%), and PM phenotype (18.8%). The present patient was classified as hetero-EM, and lansoprazole has more effect for homo-EMs, but less for hetero-EMs and PMs. Therefore, the patient showed good response to rabeprazole but not omeprazole or lansoprazole because of CYP2C19 polymorphisms in the stereoselective disposition.

In conclusion, ischemic conditions, *H. pylori* infection and CYP2C19 polymorphisms should be examined in detail before treatment of gastric tube ulcer, because these ulcers are often refractory. The selection of the appropriate PPI might play an important role in the treatment of refractory gastric tube ulcer, as in the present case.

References