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【 CASE REPORT 】

Gastric Hyperplastic Polyps after Argon Plasma Coagulation for Gastric Antral Vascular Ectasia in Patients with Liver Cirrhosis: A Case Suggesting the "Gastrin Link Theory"

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Abstract:

We herein report a case of gastric hyperplastic polyps after argon plasma coagulation (APC) for gastric antral vascular ectasia (GAVE) in the antrum of a 65-year-old man with liver cirrhosis and hypergastrinemia induced by long-term proton pump inhibitor (PPI) use. Two years after APC therapy, endoscopy demonstrated multiple gastric polyps in the antrum and angle. A gastric polyp biopsy indicated foveolar epithelium hyperplasia, which was diagnosed as gastric hyperplastic polyps. One year after switching to an H2 blocker antagonist, endoscopy revealed that the polyps and GAVE had disappeared, with normal gastrin levels suggesting that PPI-induced hypergastrinemia had caused gastric hyperplastic polyps after APC therapy, and the polyps had disappeared after discontinuing PPIs.

Key words: gastric polyp, hypergastrinemia, argon plasma coagulation, proton pump inhibitor, gastric antral vascular ectasia

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Introduction

Esophageal and gastric varices, portal hypertensive gastropathy, and gastric antral vascular ectasia (GAVE) are common and characteristic findings observed by endoscopic examinations in patients with liver cirrhosis (1-6). They are the cause of anemia and acute or chronic gastrointestinal bleeding in patients with liver cirrhosis (1-6).

Although GAVE was first described in 1953 by Rider et al. as a cause of massive gastric bleeding (7), its etiology is not fully understood. Treatment includes conservative measures, such as acid suppression agents, blood transfusion, and endoscopic therapy. Endoscopic therapy, especially coagulation with argon plasma coagulation (APC), has become increasingly popular for the treatment of GAVE (8-10). In general, complications of APC for GAVE such as perforation and bleeding, are rare because of the superficial coagulation effect (11-13). However, rare cases of gastric polyps developing after APC therapy for GAVE have been reported (14-20) and termed "portal hypertension-associated polyps" or "portal hypertensive polyps" (21-24). The pathogenesis of gastric hyperplastic polyps is still unknown, but it is thought that the exaggerated repair of mucosal damage (25, 26) or hypergastrinemia may play a role in the development of the polyps (27-29).

We herein report a rare case of gastric hyperplastic polyps following APC of GAVE. In this case, hypergastrinemia was caused by the prolonged use of a proton pump inhibitor (PPI) at the time of the diagnosis of gastric hyperplastic pol-

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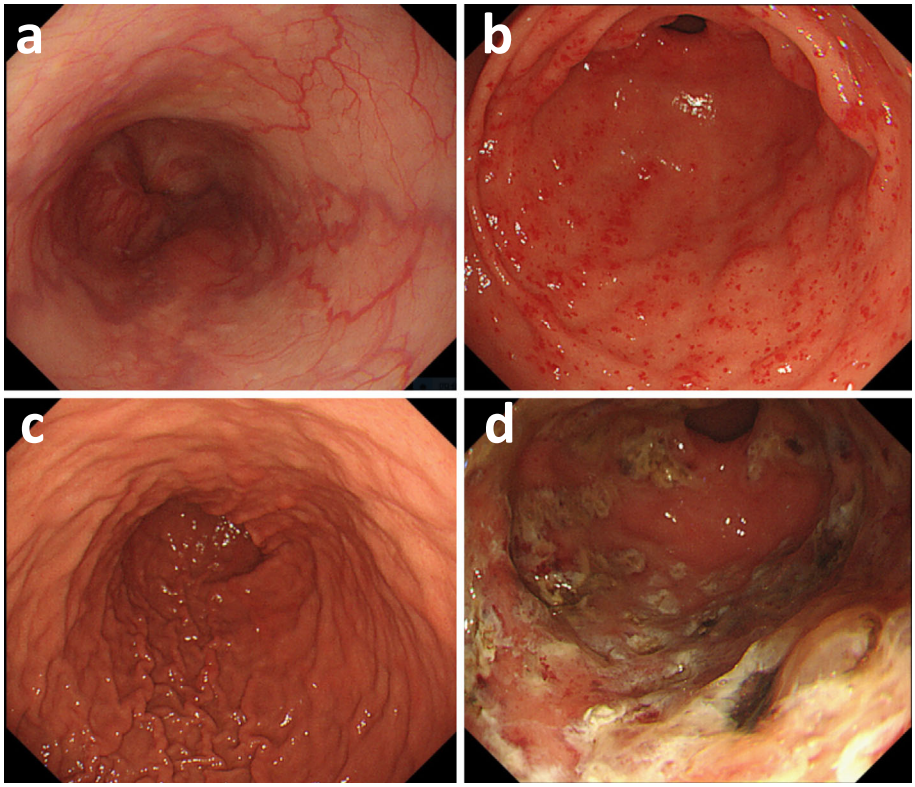

Figure 1. Initial endoscopic findings. Endoscopy revealed mild esophageal varix in the lower esophagus (a) and multiple red spots in the antrum with multiple low polyploid lesions (b). No atrophy or polyps were present (c). Multiple erosions after APC therapy (d). APC: argon plasma coagulation

yps. The discontinuance of PPIs and change to an H2-receptor antagonist with rebamipide normalized the level of serum gastrin and promoted the natural disappearance of gastric polyps with a good prognosis of GAVE.

Case Report

A 65-year-old man with liver cirrhosis and portal hypertension associated with hepatitis C virus was referred to us from an outside facility for the further evaluation of refractory iron deficiency anemia (Hb, 9.1 g/mL). He had a history of long-term use of PPIs because of suspicion of gastrointestinal bleeding.

Initial upper gastrointestinal endoscopy revealed mild esophageal varix in the lower esophagus and multiple red spots in the antrum with multiple low polyploid lesions, which were diagnosed as GAVE associated with portal hypertension and raised type-erosive gastritis. No atrophy and no polyps were found in the stomach, and APC therapy was performed for GAVE (Fig. 1). After APC therapy, a PPI (esomeprazole 20 mg/day) was subsequently readministered. Repeated endoscopies (second and third) showed multiple ulcers in the antrum at one week after APC (Fig. 2a, b), as well as multiple scars and reddish small polypoid lesions in the antrum at two months after APC (Fig. 2c, d). PPI treatment was continued for the patient, and the clinical course was good except for moderate iron deficiency anemia (Hb, 11.0 g/mL).

Five months after APC therapy, he was diagnosed with hepatocellular carcinoma (HCC) (size 1×1 cm) and treated with radiofrequency ablation without recurrence. Eight months later, he was treated for hepatitis C using direct acting antivirals and went into remission. Two years and six months after APC therapy, a fourth endoscopy demonstrated multiple reddish polypoid lesions in the anterior of the antrum and greater curvature of the stomach (Fig. 3). Biopsy specimens from gastric polyps in the antrum and angle indicated hyperplasia of the foveolar epithelium with edema and capillary dilation (Fig. 4), and the lesions were diagnosed as gastric hyperplastic polyps. The level of fasting serum gastrin was 817 pg/mL (normal range: 50-150 pg/mL), and serum *Helicobacter pylori* antibody was negative on the day of endoscopy. Therefore, we considered the cause of gastric hyperplastic polyps to be hypergastrinemia induced by PPIs and switched from a PPI to an H2 blocker antagonist (famotidine 40 mg/day) and a mucoprotective agent (rebamipide 300 mg/day).

One year later, a fifth endoscopy revealed that all polyps had completely disappeared, and GAVE was not present (Fig. 5). The fasting level of serum gastrin was in the normal range (121 pg/mL). In addition, a complete improvement in iron deficiency anemia was found (Hb, 15.4 g/mL). Four and five years after APC therapy, the sixth and seventh endoscopic examinations were performed, respectively, and no polyps or GAVE were observed. The clinical course of liver cirrhosis was stable during the follow-up period

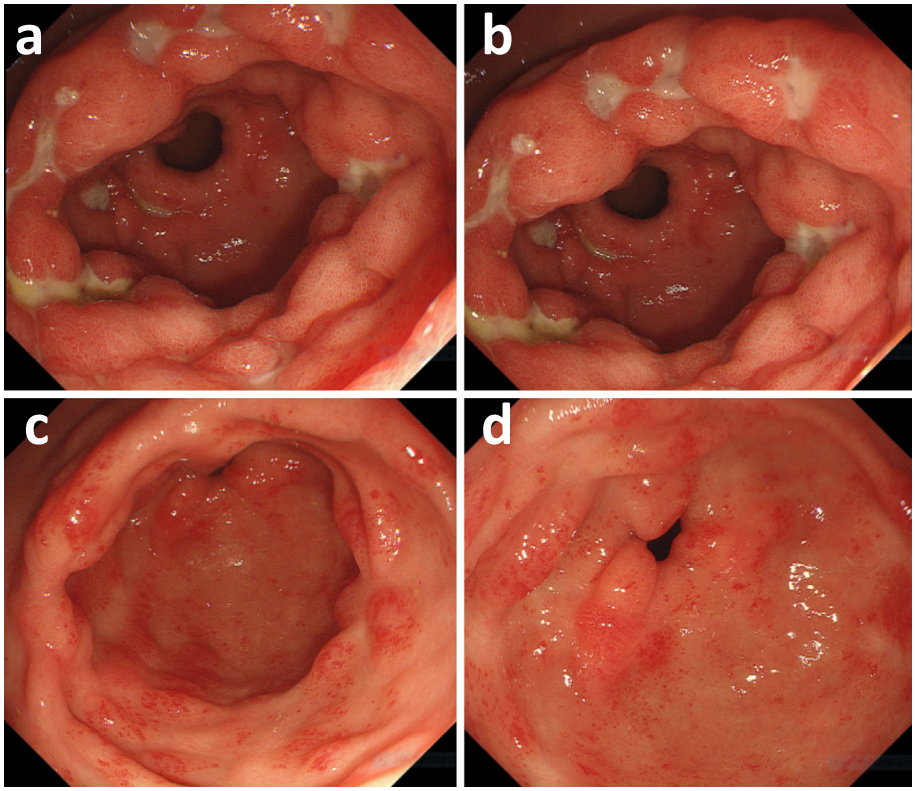

Figure 2. **Repeated endoscopies (second and third). Multiple ulcers in the antrum at one week after APC (a, b) and multiple scars and reddish small polypoid lesions in the antrum at two months after APC (c, d). APC: argon plasma coagulation**

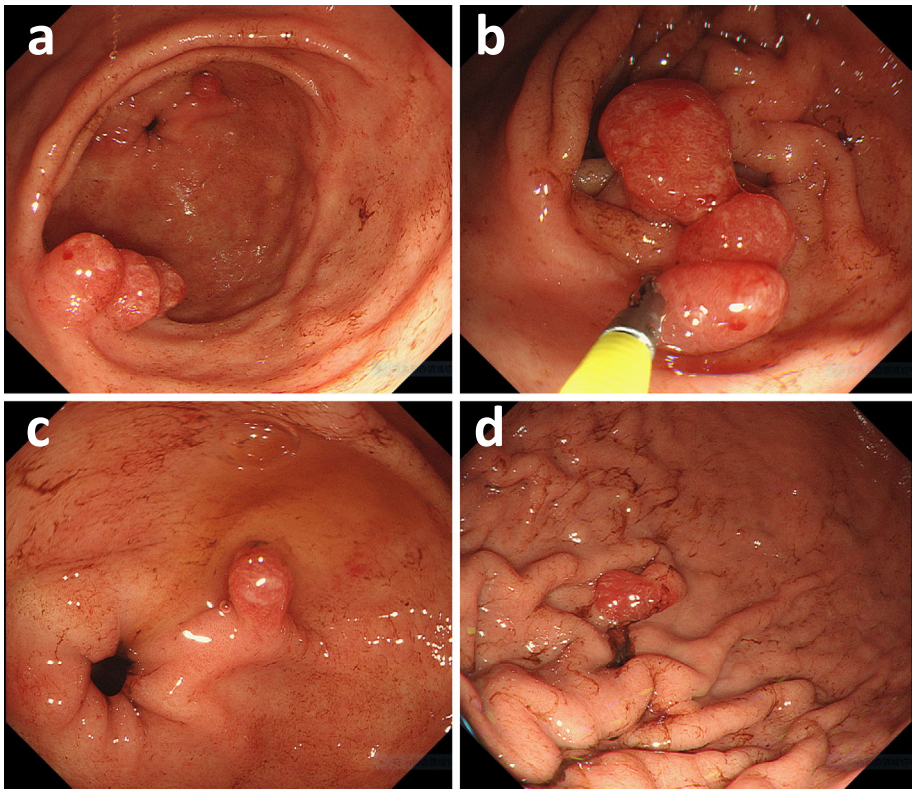

Figure 3. **Two years after APC therapy, a fourth endoscopy demonstrated multiple reddish polypoid lesions in the anterior of the antrum and greater curvature of the stomach. APC: argon plasma coagulation**

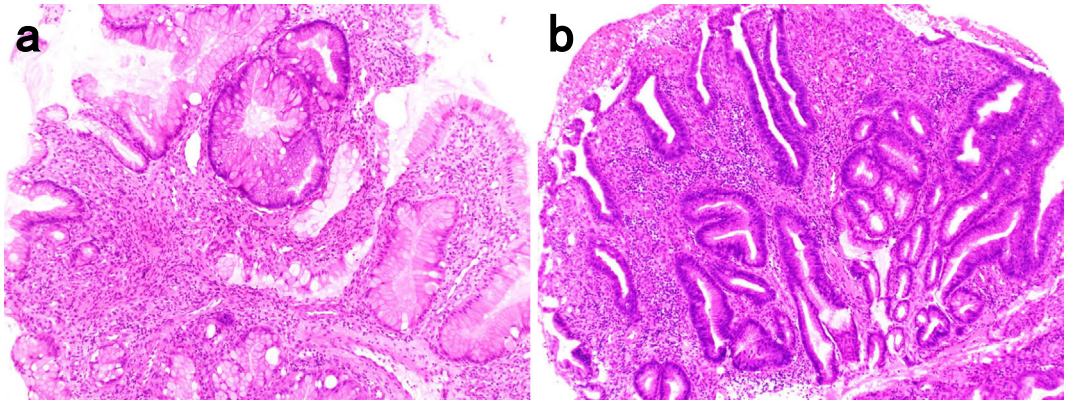

Figure 4. **Biopsy specimens from gastric polyps of the antrum (a) and angle (b) indicated hyperplasia of the foveolar epithelium with edema and capillary dilation (Hematoxylin and Eosin staining, ×100).**

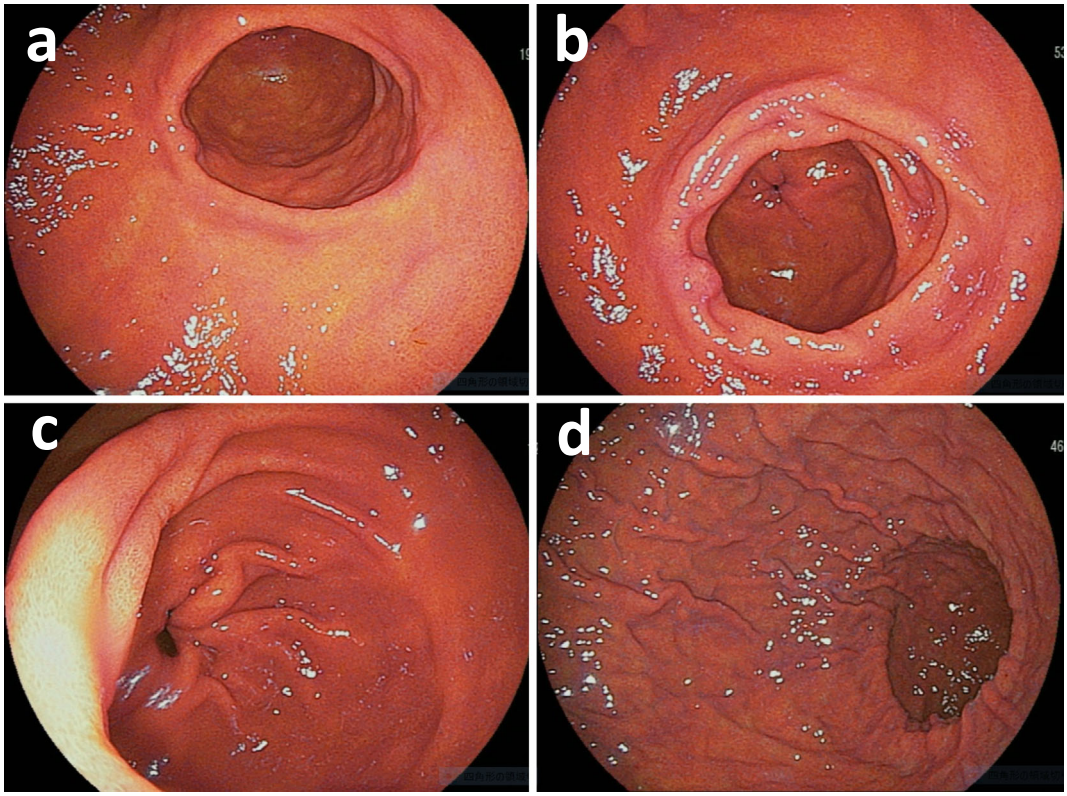

Figure 5. **One year after the fourth endoscopy, a fifth endoscopy revealed that all polyps and the remaining GAVE had completely disappeared (a-d). GAVE: gastric antral vascular ectasia**

(Fig. 6).

Discussion

Hyperplastic gastric polyps developing after electrocoagulation therapy for GAVE were first reported after endoscopic laser therapy by Geller et al. in 1996 (14). In 1998, Dohmen et al. reported the first Japanese case of gastric hyperplastic polyps at four months after heater probe therapy in a patient with liver cirrhosis (15). Subsequent reports described the development of gastric polyps as a complication of endoscopic therapy, especially APC, for the treatment of GAVE (16-20). This is the first reported case whereby switching from a PPI to an H2 blocker antagonist led to the disappearance of gastric polyps that appeared after endoscopic therapy for GAVE.

The histological findings of gastric polyps after the endoscopic treatment of GAVE indicated hyperplastic foveolar epithelium with the dilation and increase of capillaries, similar to common gastric hyperplastic polyps (14-20). The gastric polyps in our case showed a similar histology. Previous studies of gastric polyps in patients with portal hypertension used the terms “portal hypertensive polyp,” “gastric polyps in patients with portal hypertension,” or “portal

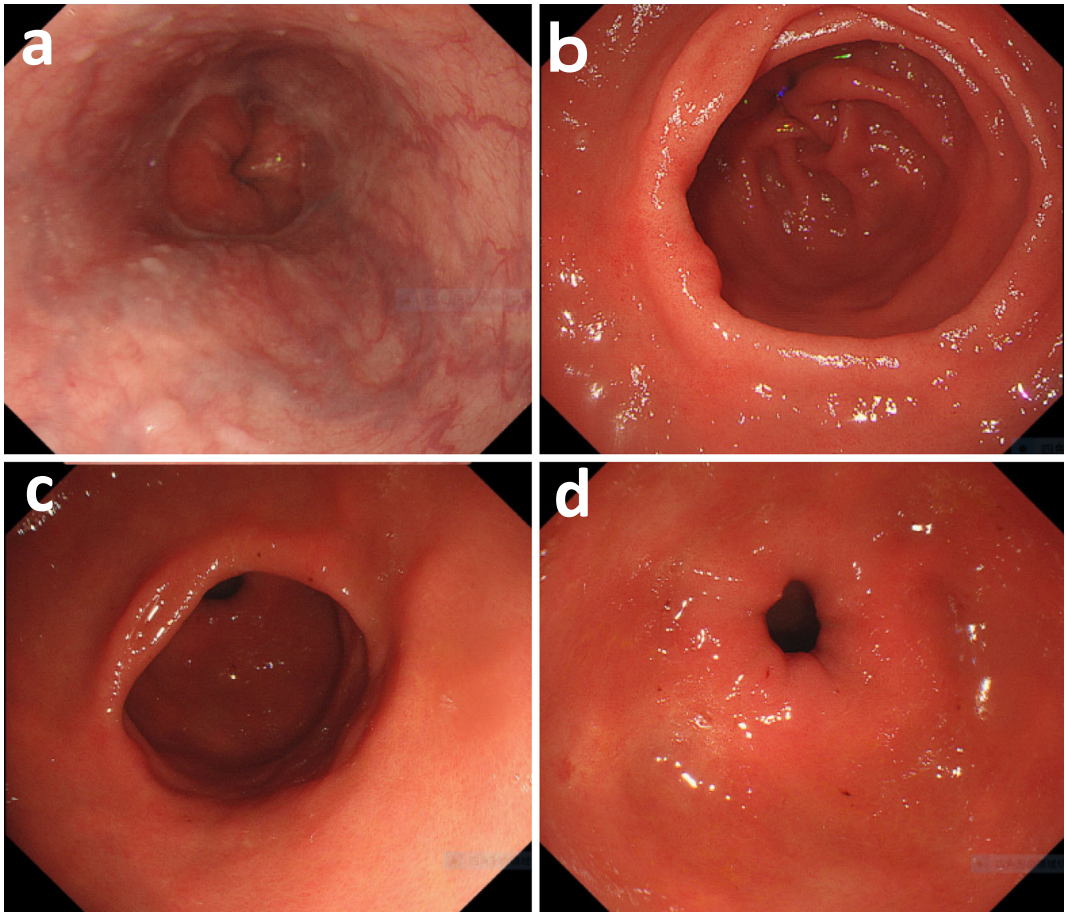

Figure 6. **Four and five years after APC therapy, the sixth (a, b) and seventh (c, d) endoscopic examinations, respectively, indicated the polyps and GAVE had not reappeared. Esophageal varix was not markedly different from that at the initial endoscopy (a). APC: argon plasma coagulation, GAVE: gastric antral vascular ectasia**

hypertension-associated gastric polyp" (21-24).

The pathogenic mechanism of gastric hyperplastic polyps in patients with liver cirrhosis or portal hypertension is currently unclear, but several previous studies have suggested that congestion caused by elevated portal pressure might have an important role in inducing mucosal proliferation and angiogenesis (14-20). Furthermore, mucosal and vascular structural damage induced by APC might be involved in the pathogenesis rather than the superficial inflammation of the mucosa. In general, common gastric hyperplastic polyps arise from atrophic gastric mucosa caused by *H. pylori* infection (25-27) or autoimmune gastritis (27, 30, 31). In our case, *H. pylori* infection was negative, and no atrophy of the gastric mucosa evaluated by endoscopy was found. Moreover, previous studies of the pathogenesis of gastric hyperplastic polyps have shown that hypergastrinemia induced by severe atrophic gastritis of the corpus (25-29) or prolonged use of PPIs might induce the development of gastric hyperplastic polys (28, 32, 33). Gastrin has trophic effects on the gastrointestinal mucosa (34) and may repair gastric mucosal damage caused by APC. When gastric hyperplastic polyps were diagnosed in the present case, hypergastrinemia (817 pg/mL) caused by PPIs was found, and the gastrin level was normalized (121 pg/mL) by changing the treatment to an H2 blocker antagonist and rebamipide, with all gastric polyps and iron deficiency anemia completely disappearing. Rebamipide was used because it decreases gastrin levels in the blood and repairs damaged gastric mucosal tissues (35-37). PPIs were reported to be related to iron deficiency anemia (38, 39); therefore, the discontinuation of PPIs might have been involved in the improvement of anemia in this case.

Recently, Okazaki et al. reported gastric hyperplastic polyps in a patient with gastroesophageal reflux disease, which might have been caused by the prolonged use of PPIs, disappeared one year after switching from a PPI to an H2 receptor antagonist (40). PPIs were suspected to have caused the development of gastric hyperplastic polyps because *H. pylori* infection was negative and atrophic gastritis was not found. In general, common gastric hyperplastic polyps develop from atrophic gastritis induced by *H. pylori* infection (25-27) or autoimmune gastritis with hypergastrinemia (30, 31). Unfortunately, the level of serum gastrin was not described in that case study. Anjiki et al. reported a case of multiple hyperplastic polyps with adenocarcinoma in which hypergastrinemia was induced by the long-term use

of PPIs; however, the gastric polyps disappeared and gastrin levels normalized after the discontinuation of PPIs (41). That case was *H. pylori*-positive, and *H. pylori* eradication therapy was performed in addition to the discontinuation of PPIs. *H. pylori* eradication therapy was reported to normalize serum gastrin levels (42, 43) and reduce gastric hyperplastic polyps (43, 44). In our case, which was negative for *H. pylori* and atrophic gastritis, the gastric hyperplastic polyps disappeared completely with the normalization of gastrin levels.

Our patient had liver cirrhosis with hepatocellular carcinoma, and various factors might have been involved in the disappearance of the polyps over a long period; however, such polyps do not disappear spontaneously. PPIs are useful for treating reflux esophagitis and peptic ulcer diseases as well as for *H. pylori* eradication therapy and the prevention of peptic ulcer diseases. Furthermore, they are often used long-term in general practice. When hyperplastic polyps are diagnosed after APC treatment of GAVE, hypergastrinemia induced by PPIs should be considered, as in the present case, and treatment by decreasing the PPI dose or switching from a PPI to an H2 receptor antagonist with rebamipide might be suitable.

Informed consent was obtained from the patient.

The authors state that they have no Conflict of Interest (COI).

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