

Gastric Hyperplastic Polyps Associated with Proton Pump Inhibitor Use in a Case without a History of *Helicobacter pylori* Infection

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Abstract

A 56-year-old man with gastroesophageal reflux disease (GERD) was referred to our hospital. Esophagogastroduodenoscopy (EGD) revealed no evidence of any polypoid lesions in the stomach, and the patient had no history of *Helicobacter pylori* infection. He received omeprazole (20 mg) once daily for the GERD. EGD was performed at 1 year after the start of omeprazole administration, and this time, gastric hyperplastic polyps (GHPs) were detected. The GHPs increased in size as the omeprazole treatment continued, but they markedly decreased in size following omeprazole discontinuation. Thus, the administration of proton pump inhibitors may be a risk factor for the development of GHP independent of *H. pylori* infection.

Key words: gastric hyperplastic polyp, *Helicobacter pylori*, proton pump inhibitor, gastrin receptor, gastrin

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Introduction

Acid-related disorders, such as gastric or duodenal ulcers and gastroesophageal reflux disease (GERD), are effectively treated by suppressing gastric acid with proton pump inhibitors (PPIs). PPIs are widely used, with an increasing number of users (1) and an increasing rate of long-term use (1, 2). Adverse effects related to long-term use of PPIs, such as fractures (3), enteric infections (4), and development of gastric polyps (5), have been reported. PPIs are also associated with pathological changes, such as parietal cell protrusions and oxyntic gland dilations (6); meanwhile, their long-term use is associated with the development of fundic gland polyps (FGPs) resulting from a trophic effect on parietal cells (5, 7, 8).

Gastric hyperplastic polyps (GHPs) are the most common type of polypoid lesions in addition to FGPs (9, 10). The

development of GHPs is strongly associated with *Helicobacter pylori* infection (11, 12), with the majority disappearing or decreasing in size after the eradication of *H. pylori* (12, 13). The development of GHPs is very rare in the normal gastric mucosa without a history of *H. pylori* infection (14, 15).

The long-term use of PPIs has also been reported to be strongly associated with the development of FGPs (8). A few cases of GHPs associated with PPI use have been reported, but the association between GHPs and PPI use remains unclear (16, 17). We herein report a patient without a history of *H. pylori* infection had GHPs associated with PPI use; in addition, we describe the pathological evaluation of the entire GHP tissue following endoscopic mucosal resection.

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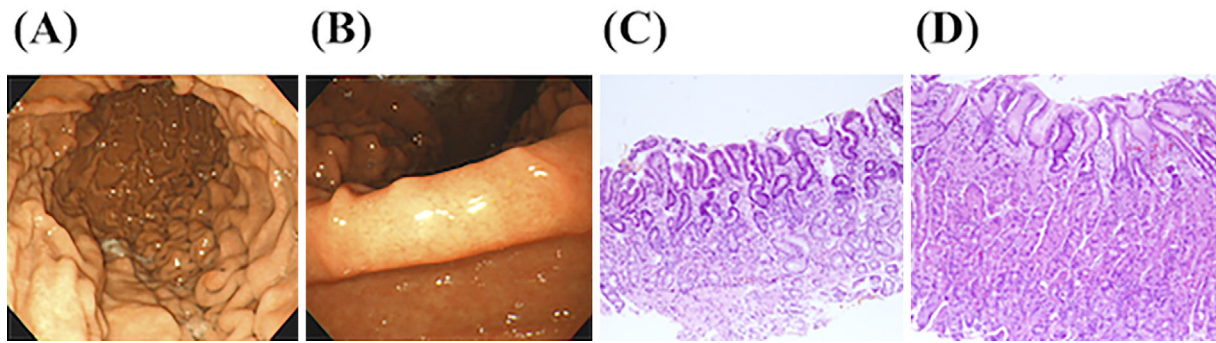


Figure 1. (A) Initial endoscopic image. Note the presence of a regular arrangement of collecting venules (RAC) and no atrophic changes in the gastric body. (B) Initial endoscopic image. Note the presence of RAC and no atrophic changes in the gastric angle. (C) Histology of a biopsy specimen from the gastric antrum showed no atrophic change, no metaplasia, and no infiltration of neutrophils. [Hematoxylin and Eosin (H&E) staining, original magnification, 100×]. (D) Histology of a biopsy specimen from the gastric body showed no atrophic change, no metaplasia, and no infiltration of neutrophils. (H&E staining, original magnification, 100×).

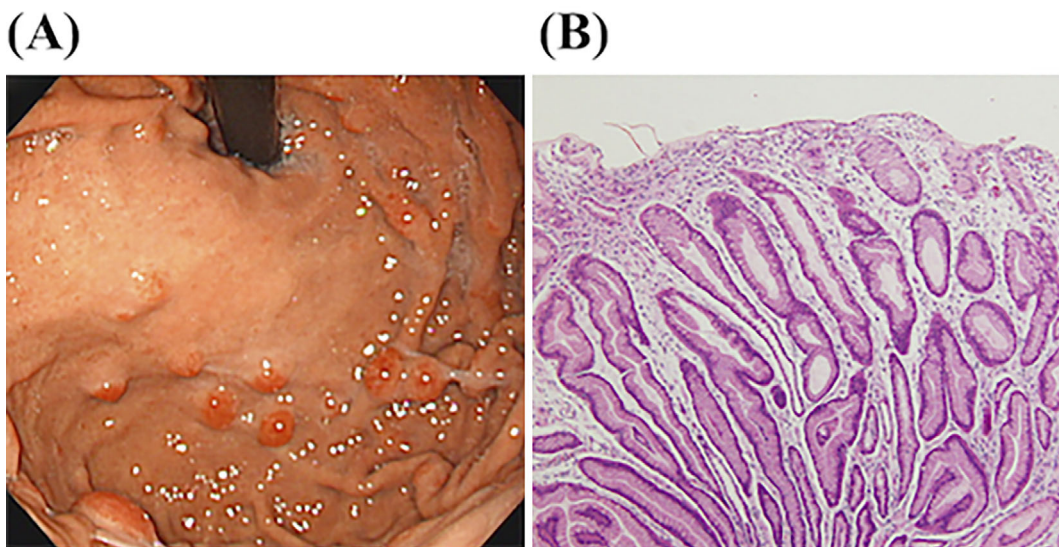


Figure 2. (A) Endoscopic image after 1 year of treatment with omeprazole, a proton pump inhibitor. Note the presence of gastric hyperplastic polyps in the gastric body. (B) Histology of a biopsy specimen from a gastric hyperplastic polyp showed elongation and the branching of foveolae. (Hematoxylin and Eosin staining, original magnification, 100×).

Case Report

A 56-year-old man with GERD was referred to Hokkaido University Hospital. Initial esophagogastroduodenoscopy (EGD) showed no evidence of any polypoid lesions. The endoscopic findings showed no infection with *H. pylori* according to the Kyoto classification (15), i.e., regular arrangement of collecting venules (RAC) in the gastric angle and no atrophic changes (Fig. 1A and B). The patient was negative for all *H. pylori* tests, including the ^{13}C -urea breath test (Otsuka Pharmaceutical, Tokyo, Japan), the rapid urease test (Otsuka Pharmaceutical), the *H. pylori* IgG E-plate (Eiken Chemical, Tokyo, Japan), culture and histological examinations of gastric biopsy tissues of the antrum and body areas.

In addition, he had no history of *H. pylori* eradication. The histological assessment of biopsy tissues showed no atrophic change, no intestinal metaplasia and no infiltration of neutrophils (Fig. 1C and D). Therefore, the patient was deemed to have no history of *H. pylori* infection. The patient received omeprazole (20 mg) once daily for GERD. Small polyps in the gastric body were endoscopically found 1 year after the initial omeprazole administration (Fig. 2A), and a biopsy led to the pathological diagnosis of GHPs (Fig. 2B). GHPs increased in size (Fig. 3) with the continual administration of omeprazole, and the serum gastrin level (SGL) after fasting increased to 529 pg/mL. At the 4-year follow-up, a large GHP was endoscopically removed. A pathological examination of the GHP tissue showed elongation, branching, twisting, and dilation of foveolae

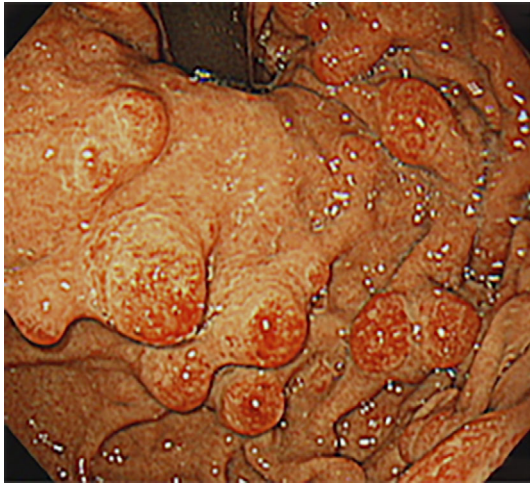


Figure 3. Endoscopic image after 4 years of treatment with a proton pump inhibitor. Note the increase in the size of the gastric hyperplastic polyps.

(Fig. 4A and B), and immunohistochemical staining revealed the expression of gastrin receptor (GR) using the polyclonal antibody OK-524 (1:100, Immuno-Biological Laboratories Corporation, Japan) (18) in the focal foveolar epithelium (Fig. 4C). Repeated EGD performed 1 year after omeprazole was discontinued showed that nearly all GHPs had markedly decreased in size (Fig. 5). SGL after fasting also returned to its normal value (165 pg/mL).

Discussion

In a patient without a history of *H. pylori* infection, GHPs occurred, and increased in size with continued PPI use, and then markedly decreased following the discontinuation of PPI administration alone. We confirmed the expression of GR in the focal foveolar epithelium of the GHP.

GHPs are the most common type of gastric polyps which are reported in 6.35% of patients undergoing EGD and comprising approximately 17% of all gastric polyps (19). *H. pylori* infection is considered to increase the risk of GHP development (20), with several reports confirming the disappearance of GHPs following *H. pylori* eradication (12, 20, 21). However, our patient had no history of *H. pylori* infection, and GHPs markedly decreased following the discontinuation of PPI administration alone.

In general, GHPs with *H. pylori* infection are histologically characterized by the dilation and elongation of the foveolar epithelium. In addition, the stroma of GHPs shows edema, myofibroblasts, and mixed inflammatory cells (22). In this case, the dilation and elongation of the foveolar epithelium and vascularity of the stroma were observed as well as GHPs with *H. pylori* infection, however, the edema and a number of inflammatory cells of stroma were fewer than the number of GHPs with *H. pylori* infection.

Ito et al. demonstrated that the polyclonal antibody OK-524 recognizes human GR and confirmed the expression of GR in parietal cells, enterochromaffin-like cells, and foveo-

lar epithelium with intestinal metaplasia (18). Takamura et al. demonstrated a significantly high expression of GR in the foveolar epithelium of the regenerating injured mucosa infected with *H. pylori* (23). Although this patient had no history of *H. pylori* infection, immunohistochemical staining of GHP using OK-524 revealed an expression of GR in the focal foveolar epithelium of GHP (Fig. 4C). We confirmed that immunohistochemical staining with OK-524 revealed no expression of GR in the foveolar epithelium of the gastric antrum mucosa as a negative control. In addition, we performed immunohistochemical staining with OK-524 of parietal cells as a positive control (Fig. 4D-2) and immunohistochemical staining with Anti-Proton Pump (H, K-ATPase α subunit) mAb (Medical & Biological Laboratories, Japan) of parietal cells (Fig. 4D-3).

Gastrin is a multifunctional polypeptide hormone that stimulates gastric acid secretion and promotes cell growth (24, 25). It stimulates the expression of regenerating islet-derived 1 α (REG1 α) protein and connective tissue growth factor (CTGF) in the gastric epithelial cells. REG1 α has a trophic effect on gastric mucosal cells and CTGF expression involved in remodeling of the gastric epithelium (26-29). SGL is usually elevated in patients taking PPIs because the feedback inhibition of gastrin release is diminished (30). Therefore, gastric foveolar epithelium expressing GR may lead to GHP development in response to gastrin stimulation.

Hongo et al. demonstrated the presence of GHPs to be related to the *H. pylori*-positive status in patients undergoing long-term PPI therapy (5). Few cases of GHPs associated with PPI use have so far been reported, but the association between GHPs and PPI use remains unclear (16, 17). These reports did not investigate whether the patient had any history of *H. pylori* infection. In this case, the patient had no history of *H. pylori* infection. Therefore, the development of GHPs was associated with PPI use and it was not affected by *H. pylori* infection. In addition, we documented not only the initial progression, but also the subsequent regression of the GHPs. In conclusion, this case suggested that PPI use may increase the risk of GHP development in patients without a history of *H. pylori* infection.

Author's disclosure of potential Conflicts of Interest (COI).

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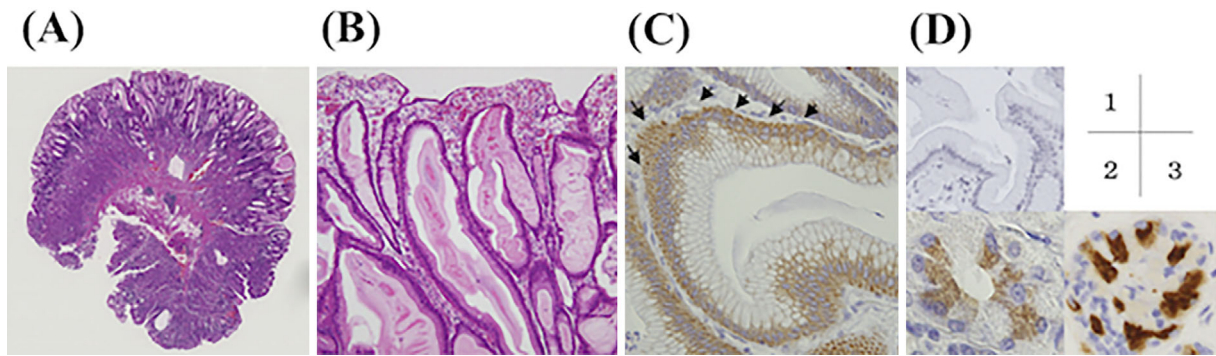


Figure 4. Pathological findings of a gastric hyperplastic polyp obtained during endoscopic mucosal resection. (A) Histology of an endoscopic mucosal resection specimen from a large gastric hyperplastic polyp. [Hematoxylin and Eosin (H&E) staining; original magnification, $\times 2$]. (B) Histology of the foveolar mucosa showing elongation and branching of the foveolae. (H&E staining; original magnification, $\times 100$). (C) Immunohistochemical staining with OK-524 revealed the focal expression of gastrin receptor (GR) in the foveolar epithelium. (Original magnification, $\times 400$). (D) 1: Immunohistochemical staining with OK-524 revealed no expression of GR in the foveolar epithelium of the gastric antrum mucosa as a negative control. 2: Immunohistochemical staining with OK-524 of parietal cells as a positive control. 3: Immunohistochemical staining with Anti-Proton Pump (H, K-ATPase α subunit) mAb of parietal cells.

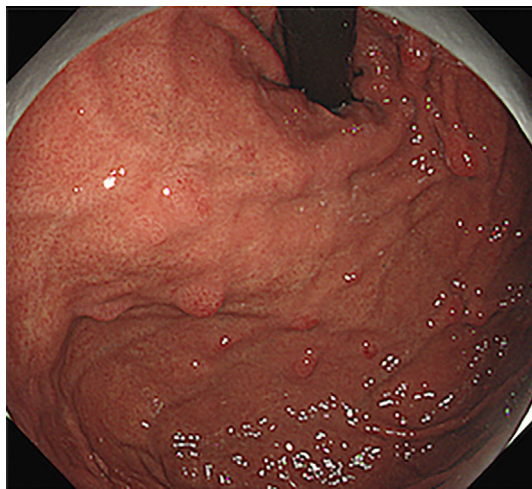


Figure 5. Endoscopic image 1 year after the cessation of proton pump inhibitor treatment. Note the near-complete disappearance of gastric hyperplastic polyps.

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