

Case Report

Gastric Inflammatory Fibroid Polyp-Like Lesion with Specific Morphology during Proton Pump Inhibitor Treatment

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1. Abstract

The patient was a 75-year-old woman who achieved *Helicobacter pylori* eradication. She started proton pump inhibitor (PPI) therapy for reflux esophagitis in 2016. Gastrointestinal endoscopy two years later (in 2018) revealed yellow sub mucosal tumor-like polypoid lesions in the greater curvature in the upper part of the gastric corpus and anterior wall. A gastric neuroendocrine tumor (carcinoid tumor) was suspected because of complication with hypergastrinemia. However, pathological findings indicated eosinophilic granuloma with neuroendocrine cell hyperplasia however, no neoplastic changes were found. An inflammatory fibroid polyp (IFP)-like gastric lesion was diagnosed. Endoscopy after PPI therapy for 2 months showed reduced and eliminated lesions, and pathological findings indicated no proliferation of endocrine. The cause of IFP remains unclear and is generally considered to be overreaction to some inflammation, however, recent studies showed gene mutation and the cause is under discussion. We propose a causal relationship between IFP-like lesions and proliferation of endocrine cells, for which a further study is required.

2. Keywords: Proton pump inhibitor; Eosinophilic granuloma; Inflammatory fibroid polyp; Neuroendocrine cell hyperplasia

3. Introduction

H2-receptor antagonists (H2RAs) and proton pump inhibitors (PPIs) inhibit gastric acid secretion and cause hypergastrinemia, resulting in hyperplasia of enterochromaffin-like (ECL) cells [1-3]. This may cause a gastric neuroendocrine (carcinoid) tumor in animals [4-6] and humans [7-13]. Gastric inflammatory fibroid polyp (IFP) is a sub mucosal tumor-like polypoid lesion and small IFPs have normal surface mucosa and a normal to slightly reddish color [14]. Most IFPs are located within the antrum [15, 16] and are accompanied by erosion and ulcer [17]. Such lesions may also involve *Helicobacter pylori* infection, and morphologic changes occur after eradication of *Helicobacter pylori* [18,19]. Cancer and adenoma may complicate the lesions [20, 21].

IFPs are benign inflammatory tumors without a definite cause. However, biopsy often gives a small specimen that prevents diagnosis of the lesion as benign or malignant. Therefore, definitive diagnosis is increasingly performed by endoscopic resection. In the case reported here, we suspected a gastric carcinoid tumor due to development of hypergastrinemia during PPI administration. However, pathological findings indicated lymphocytic and eosinophilic infiltration and proliferation of fibrous connective tissues with hyperplasia in gastric endocrine cells, and a subsequent diagnosis of IFP-like lesions was made. We report the case due to its rare course of rapid reduction and disappearance of



Figure 1. Endoscopic findings of the greater curvature in the upper part of the gastric corpus indicated a polypoid lesion with a slight recess in the center and vasodilation on the surface.

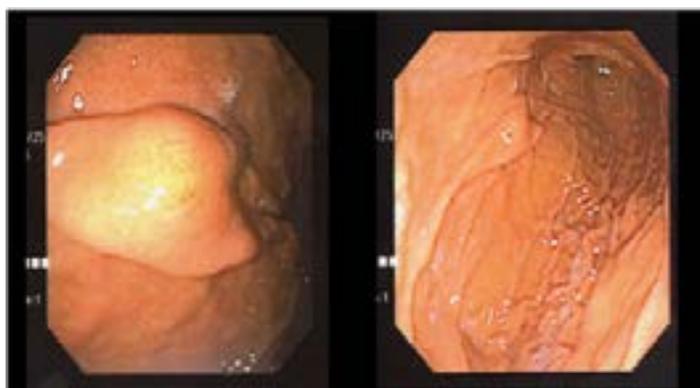


Figure 2. Endoscopic findings of the anterior wall in the lower part of the gastric corpus indicated a yellow submucosal tumor-like lesion.

these lesions as gastrin decreased.

4. Case Report

The patient was a 75-year-old woman with complete remission after eradication of *Helicobacter pylori* in 2014. Subsequently, she routinely underwent upper endoscopy. In 2016, symptoms of reflux esophagitis developed. Fasting blood gastrin was measured every 4 months after initiation of PPI administration. In endoscopy in June 2017, there were no abnormal gastric findings. Blood tests in June 2018 indicated WBC 6990 /mm³ (47.1% neutrophils, 4.9% eosinophils, 41.3% lymphocytes), hemoglobin 13.8 mg/dL, platelet count 217000 /mm³, and anti-parietal cell antibody negative (< 10). Other biochemical data were normal.

Endoscopic findings in June 2018 showed a polypoid lesion with a slight central recess and vasodilation on the surface on the greater curvature in the upper part of the gastric corpus (Figure 1). A smaller sub mucosal tumor-like lesion connecting to mucosal folds was found in the anterior wall in the lower part of the gastric corpus (Figure 2). No atrophy and no PPI-related changes were found in the gastric mucosa, including no fundic gland polyps. A neuroendocrine

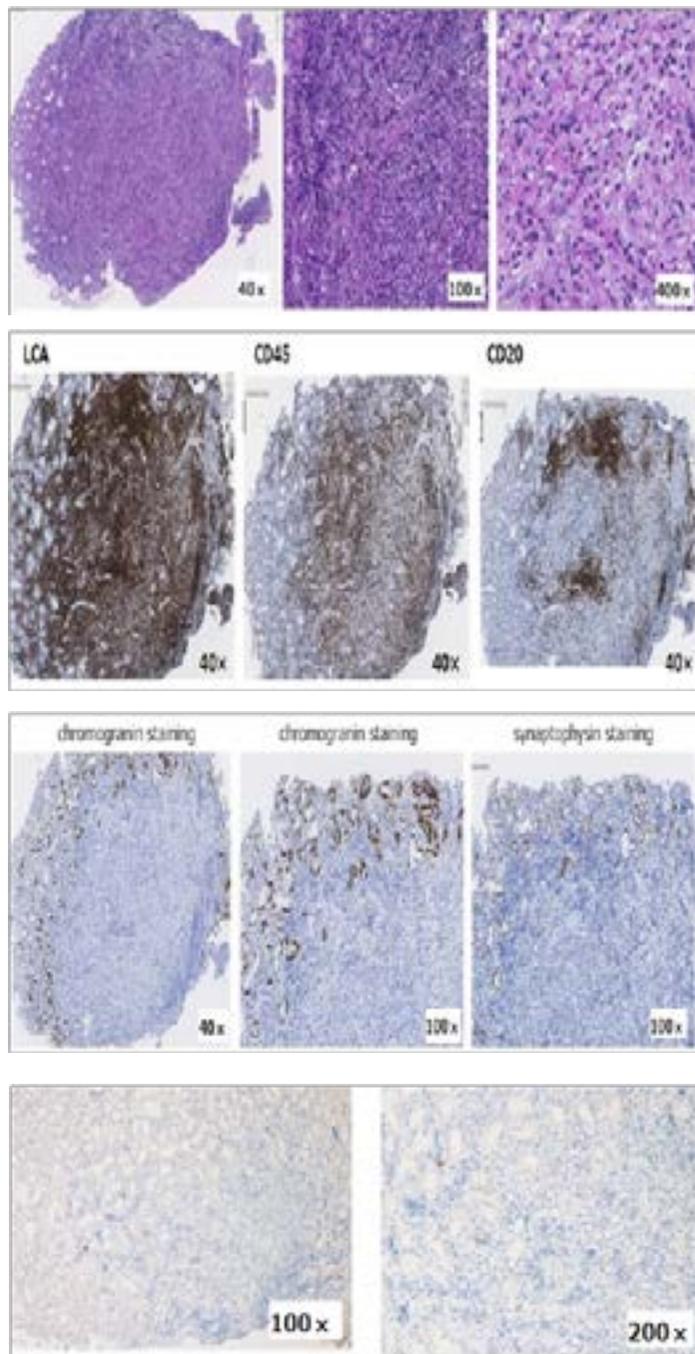


Figure 3: Pathological findings for a lesion in the greater curvature in the upper part of the gastric corpus. a. HE staining showed lymphocytic, eosinophilic and mononuclear cell infiltration with fibrous connective tissue proliferation. There was no whorl sequence in fibrous connective tissues surrounding small vessels. b. LCA immunostaining showed highly inflammatory lymphocytic infiltration without atypical lymphocytes, and infiltration of T cells (CD45) more than B cells (CD20). c. Immunostaining of endocrine cells indicated hyperplasia of chromogranin- and synaptophysin-positive endocrine cells, but no neoplastic change. d. IgG4 immunostaining showed that most infiltrated lymphocytes were IgG4-negative.

tumor was suspected based on the endoscopic findings, and biopsy was conducted.

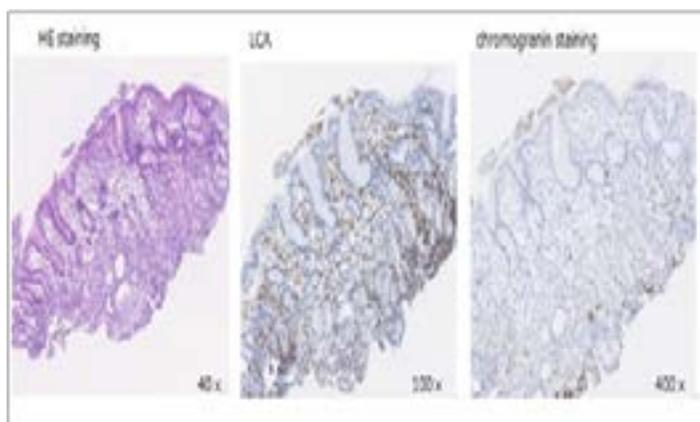


Figure 4. Pathological findings for a lesion in the anterior wall in the lower part of the gastric corpus. Fundic gland tissues had no hyperplasia and there were no atypical cells or fibrous connective tissues.



Figure 5. Upper endoscopic findings after 26 months of PPI treatment. The lesion in the upper part of the gastric corpus was reduced and the recess in the lesion center had disappeared. The lesion in the lower part of the gastric corpus had disappeared.

Hematoxylin-eosin (HE) staining showed lymphocytic, eosinophilic and mononuclear cell infiltration with fibrous connective tissue proliferation. Marked eosinophilic infiltration was detected in fibrous connective tissues, but with no whorl sequence in connective tissues surrounding small vessels (Figure 3a). Immunostaining for leukocyte common antigen (LCA) showed inflammatory lymphocytic infiltration without atypical lymphocytes, and infiltration of T cells (CD45) to a greater extent than B cells (CD20) (Figure 3b). Immunostaining in atrophic mucosae indicated diffusely or micronodularly hyperplastic proliferation of chromogranin- and synaptophysin-positive endocrine cells in ducts, but no neoplastic changes (Figure 3c). Most infiltrated lymphocytes were IgG4-negative (Figure 3d). Based on these findings, the tumefactive upper lesion in the gastric corpus was considered to be an eosinophilic granuloma with hyperplastic changes in endocrine cells, and was diagnosed as an IFP-like gastric lesion. In contrast, a biopsy specimen from the lower lesion included fundic gland tissues with no proliferation of fibrous connective tissues or hyperplasia of endocrine cells (Figure 4).

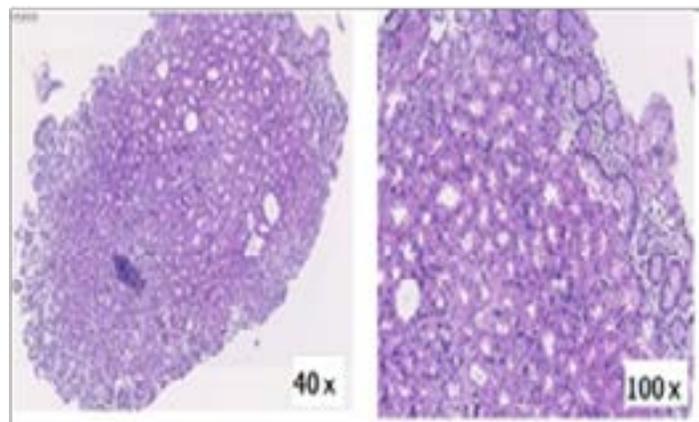


Figure 6. Pathological findings for the lesion that was reduced in the upper part of the gastric corpus. Granulation tissues detected in previous findings and hyperplasia of fundic gland tissues had both disappeared. Parietal cell hyperplasia and cystoid enlargement were present, and were considered to be caused by PPI treatment.

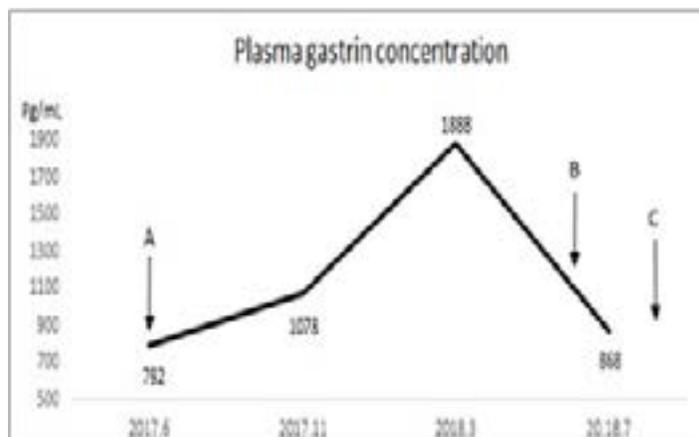


Figure 7. Changes in blood gastrin after administration of PPI A: After 12 months of PPI therapy B: After 24 months of PPI therapy (a polypoid lesion was found) C: After 26 months of PPI therapy (the polypoid lesion was reduced in size).

The patient continued PPI therapy and underwent follow-up endoscopy 2 months later. The upper lesion in the gastric corpus was reduced in size and the central recess had disappeared. The lower lesion had completely disappeared (Figure 5). A biopsy of the upper lesion showed that proliferation previously detected in granulation and endocrine cell tissues had disappeared, and fundic gland tissues had only slight inflammatory cell infiltration without atypical cells. Parietal cell hyperplasia was also found in these tissues, and cystoid enlargement was partially detected, which were thought to be changes caused by PPI treatment (Figure 6).

Fasting blood gastrin concentrations are shown in Fig.7. Gastrin at 12 months after the start of PPI therapy (arrow A, normal endoscopy findings) was high (792 pg/mL) due to PPI treatment, and further increased and reached a peak (1888 pg/mL) 3 months before endoscopy when lesions were found in the stomach (arrow

B). The level subsequently decreased to 868 pg/mL immediately before reduction or disappearance of the lesions (arrow C).

5. Discussion

PPIs inhibit gastric acid secretion and are used for long-term treatment of GERD. However, such inhibition also causes hypergastrinemia, and gastrin stimulates ECL cells and induces histamine release and ECL cell proliferation due to a trophic effect (2-4). There are some case reports of Type A gastritis causing hypergastrinemia and neuroendocrine tumor in patients with Zollinger-Ellison syndrome [22]. In animals, continuous administration of H2RAs and PPIs causes carcinoid tumor [4-6]. In humans this risk has been suggested in several studies [7-13], but without firm evidence [23].

We suspected a carcinoid tumor in the current case due to the polypoid lesion in gross pathology because hypergastrinemia occurred due to two-year PPI therapy. However, pathological findings indicated eosinophilic granuloma with marked eosinophilic and lymphocytic infiltration and proliferation of connective tissues, which suggested an IFP-like lesion, although hyperplasia in gastric endocrine cells was also found. In 1949, Vaneck described gastric eosinophilic granuloma characterized by connective tissues of fibroblasts and fibrocytes and collagen fibers with loose sequence, eosinophilic and lymphocytic infiltration, and micro vascular and lympho vascular enlargement and hyperplasia [24]. In 1953, Helwig added a fourth characteristic of a concentric sequence of fibrous connective tissues (onion skin-like lamellae) and named this condition inflammatory fibroid polyp (IFP) [25].

Gastric IFP with concentric sequences of fibrous connective tissues accounts for 54% of all cases [15]. Therefore, we diagnosed an IFP-like lesion based on pathological findings. IFPs occur in all digestive organs, but mostly in the gastric antrum. [15, 16]. Gastric IFP in the mucosa and sub mucosa appears as a sub mucosal tumor. The size is generally small (several millimeters), but large gastric IFPs can occur and are associated with erosion and ulcer, which causes anemia due to bleeding [17] and ball valve syndrome [14, 26, 27]. Differential diagnosis of malignant tumor is required, but this is difficult by biopsy, and surgical resection is often used. Many recent reports describe definitive diagnosis and treatment by endoscopic resection. Gastric IFP is benign, but sometimes occurs in combination with cancer [20, 21] and large IFPs infiltrate intrinsic muscle layers [28]; therefore, en bloc resection is preferable [28, 29].

Our case is rare in that an IFP-like lesion was diagnosed by biopsy of a polypoid lesion in the upper gastric corpus and then spontaneously

disappeared. We have not found a similar report. The origin of IFP has been proposed to be a tumor or due to allergy and inflammation, but the lesion is generally thought to develop from overreaction of hosts to a mucosal injury [30]. Involvement of blood gastrin changes and ECL hyperplasia cannot be excluded, given the changes in blood gastrin before and after appearance of the IFP-like polypoid lesion; however, no causal relationship has been found. A PDGFRA mutation (exon 12 in the small intestine, exon 18 in the stomach) has recently been found in IFP lesions, and IFP has been suggested to be a true neoplasm, rather than an inflammatory polyp [31, 32]. However, the rate of IFP with mutation varies from 21.7% to 69.6%, and the effect of the mutation is unclear [28, 31].

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