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【 CASE REPORT 】

IgG4-related Disease Manifesting as Gastroduodenal Ulcer Diagnosed by an Endoscopic Biopsy

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Abstract:
A 26-year-old man was admitted to our hospital due to upper abdominal pain. He had previously been diagnosed with gastroduodenal ulcer at 23 and 25 years old and had been treated with proton-pump inhibitors. Endoscopic hemostasis and a biopsy were performed on the hemorrhagic gastroduodenal ulcers. Laboratory and pathologic examinations demonstrated elevated serum IgG4 levels and the infiltration of IgG4-positive plasma cells into the gastroduodenal tissues. Based on the clinicopathologic findings and after excluding other causes, he was diagnosed with IgG4-related gastroduodenal ulcer. We herein report a rare case of IgG4-related disease manifesting as a gastroduodenal ulcer diagnosed by an endoscopic biopsy.

Key words: IgG4, gastric ulcer, duodenal ulcer, IgG4-related disease

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Introduction

IgG4-related diseases (IgG4-RDs) are relatively newly detected entities and are characterized by an elevated serum IgG4 level and tumefaction or tissue infiltration with IgG4-positive plasma cells (1, 2). IgG4-RDs involve one or multiple organs and have a range of clinical manifestations. In the field of gastroenterology and hepatology, the pancreas and hepatobiliary system are commonly affected; these types of diseases have been recognized as type 1 autoimmune pancreatitis (AIP), IgG4-related sclerosing cholangitis, and IgG4-related hepatopathy (3, 4).

Compared with the hepatobiliary-pancreatic involvement in IgG4-RD, IgG4-related involvement of the gastrointestinal tract is less common. However, these types of IgG4-RD are clinically important, as they often mimic malignancy and can lead to unnecessary surgical interventions. Previous reports have shown that IgG4-RD of the gastrointestinal system manifests as ulcers (5-17), polyps (18), and mass or tumor lesions, such as nodular fibrosing tumors, pseudotumors, and wall thickening (19-22). An IgG4-related gastrointestinal ulcer manifesting as a duodenal ulcer is extremely rare.

We herein report a rare case of IgG4-RD that presented as a refractory gastroduodenal ulcer and discuss the clinicopathologic findings and management of IgG4-related gastrointestinal ulcer.

Case Report

A 26-year-old man was admitted to our hospital because of persistent upper abdominal pain, nausea, and vomiting for 24 hours. He had previously been diagnosed with hemorrhagic gastroduodenal ulcer by esophagogastroduodenoscopy (EGD) and hospitalized twice at 23 and 25 years old for ulcer treatment at other hospitals. He had been taking daily lansoprazole 15 mg and sodium ferrous citrate 100 mg for gastroduodenal ulcer and iron-deficiency anemia respectively for the past 3 months. He did not have any allergies, significant family history, or history of non-steroidal anti-inflammatory drug (NSAID) use. He drank alcohol only on a social basis and had started smoking 10 cigarettes per day at 20 years old. His vital signs and general physical exami-

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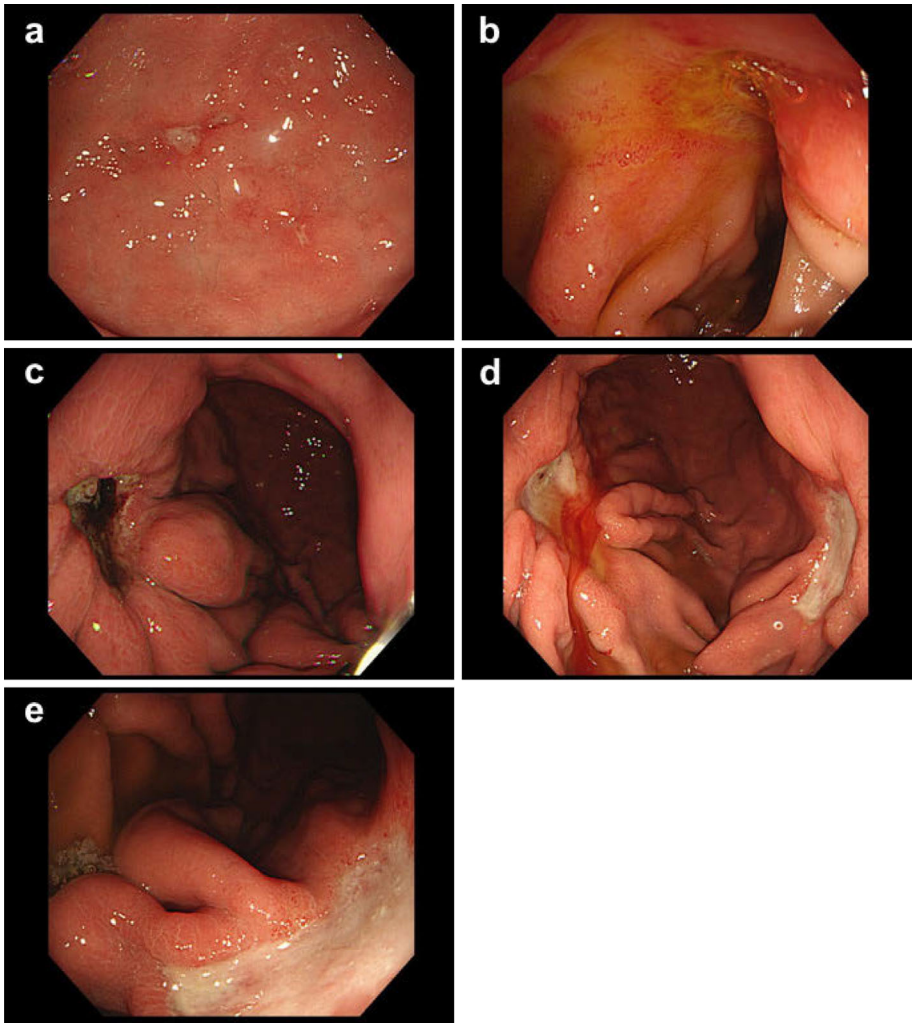

Figure 1. **Esophagogastroduodenoscopy (EGD) findings on admission. Emergency EGD showed multiple duodenal ulcers (a, b) and 2 bleeding gastric ulcers (3.5 cm in diameter) with severe edematous mucosa on the anterior wall (c) and posterior wall of the gastric body. Repeat EGD on the fourth hospital day revealed mild improvement of gastric edema (d) and regenerating epithelia with relatively few reddened lesions surrounding clean ulcer bases (e); an endoscopic biopsy was performed for the marginal zones of the two gastric ulcers and for one of the multiple ulcers on the duodenal bulb.**

nation findings were unremarkable.

Emergency EGD revealed multiple duodenal ulcers and two bleeding ulcers on the anterior and posterior walls of the middle gastric body (Fig. 1a-c). We performed endoscopic hemostasis of the protruding vessel and oozing on the gastric ulcers. After 4 days of fasting and daily treatment with lansoprazole 60 mg and sucralfate 3 g, repeat EGD revealed mild improvement of the duodenal and gastric ulcers (Fig. 1d, e). Biopsies from one of the duodenal ulcers and from the two gastric ulcers revealed mild gastritis and ectopic gastric mucosa with inflammation and fibrosis in the duodenum. The mucosal inflammation in both tissues comprised numerous lymphocytes and plasma cells (Fig. 2a, 3a). There was no evidence of malignancy or *Helicobacter pylori* infection in any of the biopsy specimens. Furthermore, both the urea breath test and serum anti-*H. pylori* IgG titers were negative.

Although the serum gastrin level and blood eosinophil count were within normal limits, the serum IgG4 was elevated at 154.0 mg/dL (normal range: 4.8-105 mg/dL). The findings from the following blood tests were either within the normal range or negative: amylase, pancreatic phospholipase A2, C-reactive protein, soluble interleukin 2 receptor, lactate dehydrogenase, carcinoembryonic antigen, carbohydrate antigen 19-9, interferon gamma release assay (QuantiFERON-TB), cytomegalovirus (CMV) antigenemia assay, *Treponema pallidum* hemagglutination test, antinuclear antibodies, rheumatoid factor, proteinase 3 antineutrophil cytoplasmic antibodies (PR3-ANCA), myeloperoxidase ANCA (MPO-ANCA), anti SS-A antibodies, and anti SS-B antibodies.

We pathologically reevaluated and stained all biopsy specimens for IgG and IgG4. Immunohistochemical staining revealed remarkable infiltration of IgG4-positive plasma

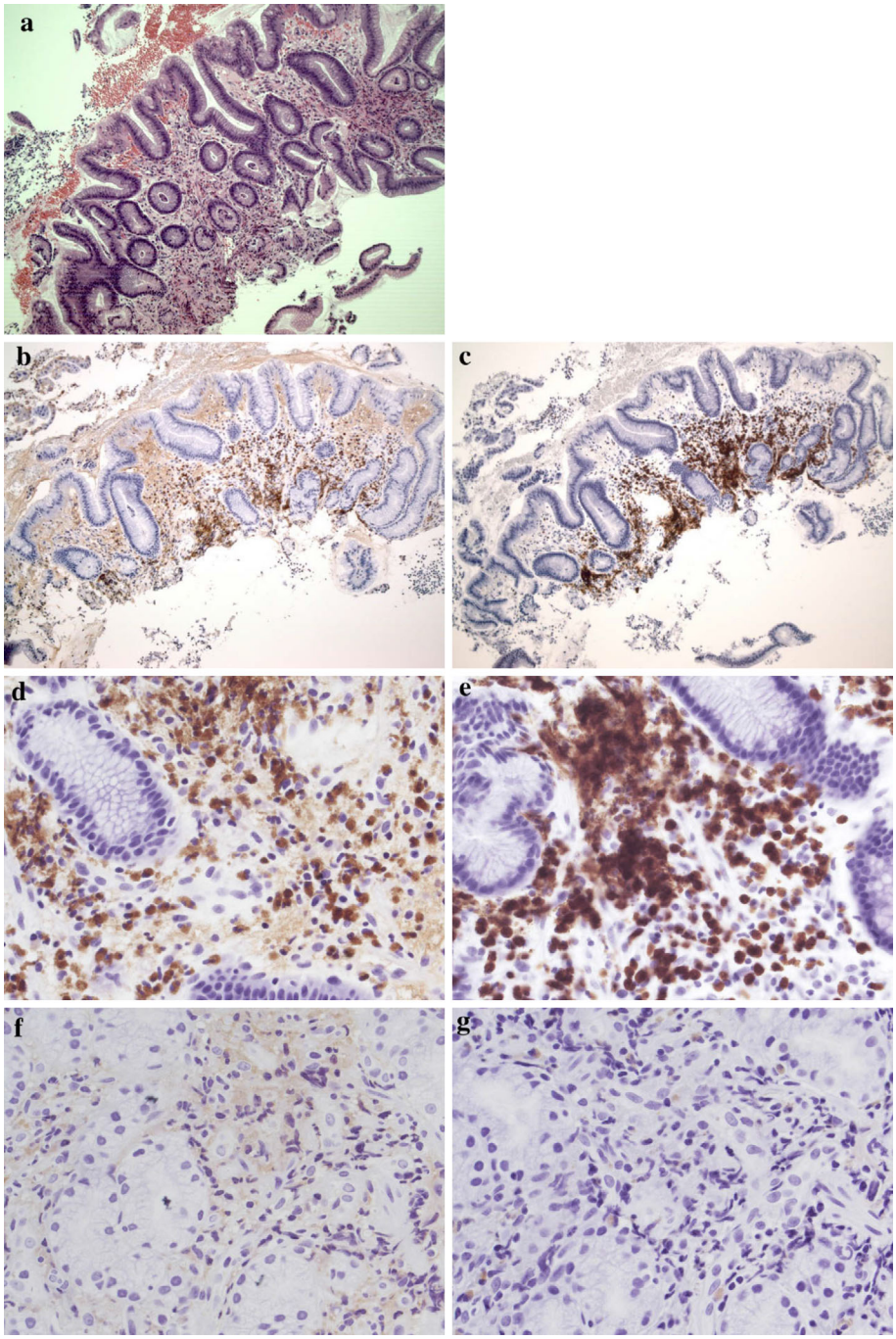

Figure 2. Histopathologic findings of the gastric lesion. (a) The gastric mucosa from the ulcer was mildly inflamed and infiltrated with lymphoplasmacytic cells (Hematoxylin and Eosin staining; ×100). There was marked infiltration of IgG-positive (b, ×100 and d, ×400) and IgG4-positive (c, ×100 and e, ×400) plasma cells in a similar distribution in the deeper portion of the mucosal lamina propria. The number of IgG4-positive cells was 104 cells/hpf, and the ratio of IgG4/IgG-positive plasma cells was >90%. After 3 months of PPI maintenance therapy, a re-biopsy from the ulcer scar showed that the infiltration and number of IgG-positive (f, ×400) and IgG4-positive (g, ×400) plasma cells had decreased to <10 cells/hpf.

cells into the gastric and duodenal tissues (Fig. 2b-e, 3b, c). In both tissues, the number of IgG4-positive cells was greater than 10 cells/hpf, and the ratio of IgG4/IgG-positive plasma cells was greater than 40%. We also found that this lymphoplasmacytic infiltration, which had abundant IgG4-positive plasma cells, tended to be observed in the deep portion of the mucosal lamina propria (Fig. 2b, c). There was no storiform fibrosis or obliterative thrombosis in any of the biopsy specimens.

Contrast-enhanced computed tomography (CT) for the evaluation of other systemic IgG4-RD did not show any significant abnormal findings, except for diffuse thickening of

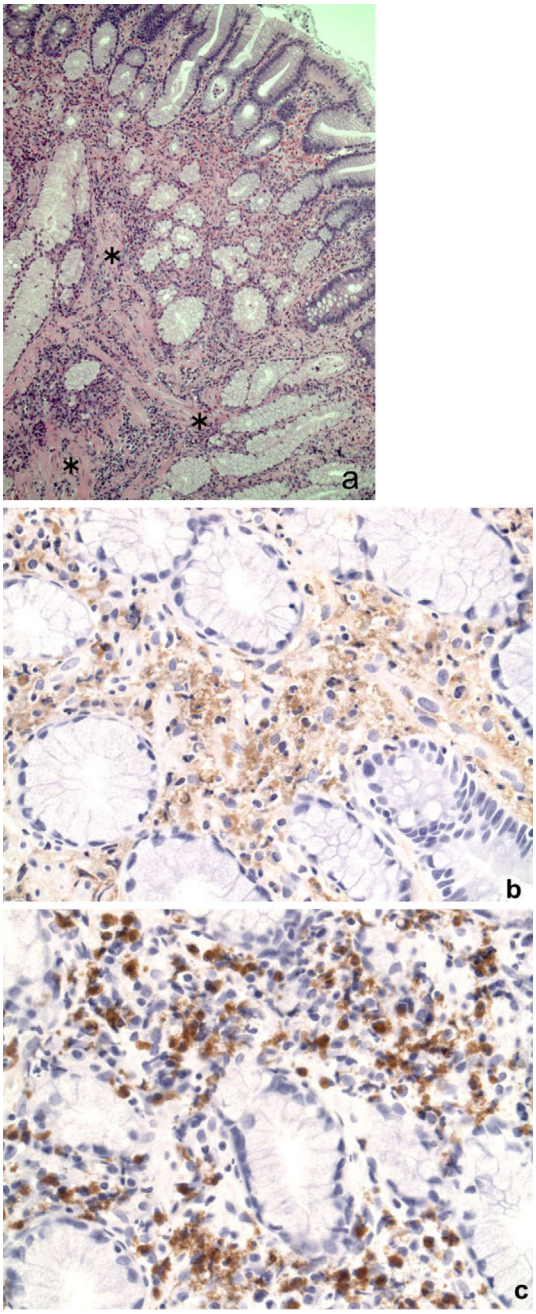

Figure 3. **Histopathologic findings of the duodenal lesion. Ectopic gastric mucosa and lymphoplasmacytic infiltration with marked fibrosis (asterisks) were observed (Hematoxylin and Eosin staining; a, ×100). A number of IgG-positive (b, ×400) and IgG4-positive (c, ×400) plasma cells were observed in the mucosal lamina propria. The number of IgG4-positive cells was 54 cells/hpf, and the ratio of IgG4/IgG-positive plasma cells was >80%.**

the gastric wall (Fig. 4a, b); the pancreas was not enlarged and had no surrounding capsule-like rim. Furthermore, colonoscopy and magnetic resonance cholangiopancreatography revealed no significant abnormal findings (data not shown), ruling out Crohn's disease and pancreatic and biliary disorders, respectively. Although sialography was not performed, he did not complain of any suggestive symptoms of dry eyes or dry mouth with salivary glands swelling.

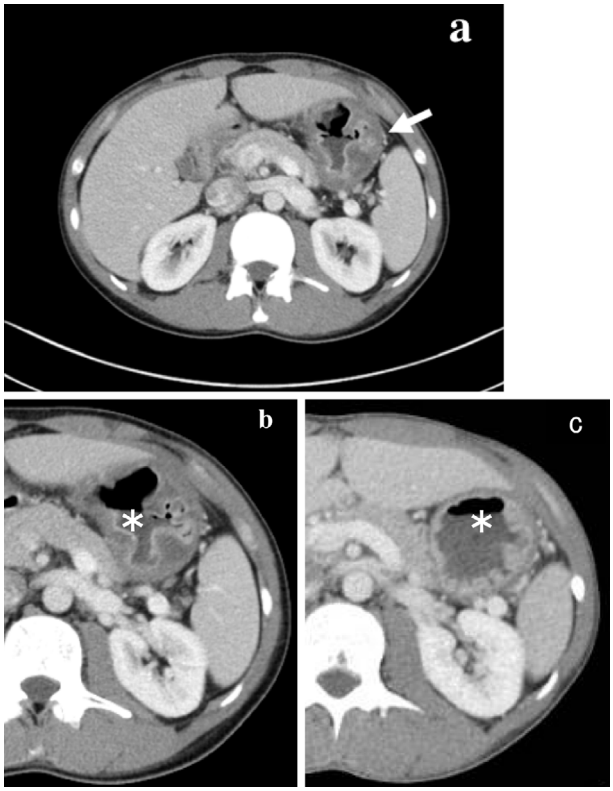

Figure 4. **Axial contrast-enhanced CT image. (a, b) The gastric wall was diffuse and thickened on admission (arrow, asterisk). (c) Follow-up CT at 13 months showed that the diffuse thickness of the gastric wall had decreased compared with the same lesion on admission (asterisks in b and c)**

Based on the clinicopathologic findings and the comprehensive diagnostic criteria for IgG4-RD, we ultimately diagnosed him with IgG4-related gastroduodenal ulcer. After presenting the treatment options and describing the risks of long-term steroid therapy to the patient, we obtained his informed consent to continue proton-pump inhibitor (PPI) maintenance alone as the primary treatment.

Three months after discharge under maintenance therapy with vonoprazan 10 mg daily, follow-up EGD indicated healing and partial scarring of the gastroduodenal ulcers (Fig. 5). We observed the convergence of large folds towards both gastric ulcer scars on the anterior and posterior walls of the middle body (Fig. 5a). A re-biopsy from the depressed lesion of the ulcer scar on the anterior wall revealed the marked improvement of the infiltration of IgG4-positive plasma cells (Fig. 2f, g). The chronological changes in the serum IgG4 levels after discharge were 235.0 mg/dL (normal range: 4.8-105 mg/dL) at 3 months, 136.0 mg/dL at 6 months, 114.0 mg/dL at 9 months, and 111.0 mg/dL at 13 months. Follow-up contrast-enhanced CT at 13 months showed that the diffuse thickness of the gastric wall had decreased compared with the same lesion at the final hospital admission (Fig. 4c). We decided to continue following him carefully with PPI therapy. He remains in remission and has been asymptomatic for more than 21 months.

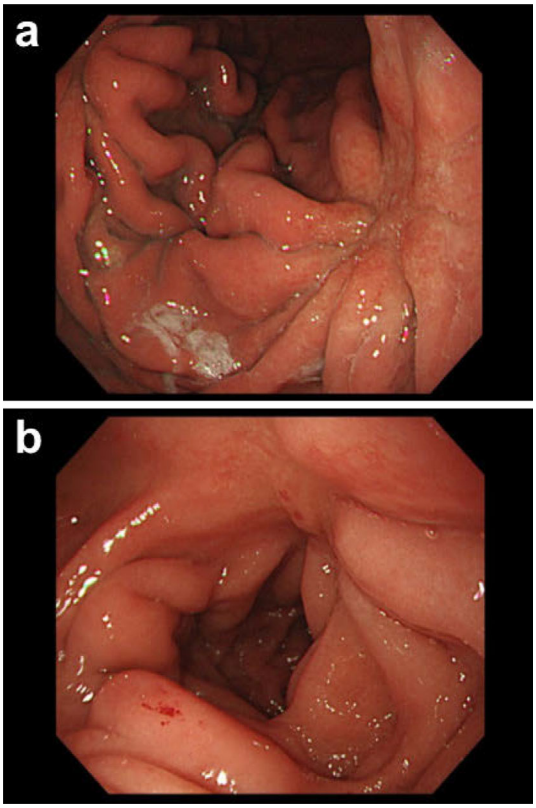

Figure 5. Follow-up EGD after maintenance therapy with PPI. After three months, ulcer scar formations were noted, with the convergence of large gastric folds on the gastric body (a) and healing of the ulcerative lesions on the duodenal bulb (b).

Discussion

In the present case in which gastroduodenal ulcer relapsed three times in three years, we had to approach the diagnosis by considering rare causes of peptic ulcers. Kim reported that, in addition to persistent *H. pylori* infection and NSAID use, the causes of refractory peptic ulcer included gastrinoma (Zollinger-Ellison syndrome); Crohn's disease; vasculitis; eosinophilic gastroenteritis; mesenteric ischemia; infectious diseases, such as CMV, tuberculosis, and syphilis; radiation; and malignant tumor (23). However, the clinicopathologic findings in the present case were not compatible with any of these diseases. Instead, we considered an IgG4-RD, based on the following comprehensive diagnostic criteria (2): 1) a clinical examination showing characteristic diffuse/localized swelling or masses in single or multiple organs; 2) a serum IgG4 concentration ≥135 mg/dL; and 3) histopathologic findings of (a) marked lymphocytic and plasma cell infiltration with fibrosis and (b) infiltration of IgG4-positive plasma cells, with a ratio of IgG4/IgG-positive cells of >40% and >10 IgG4-positive plasma cells/hpf. Therefore, a definitive diagnosis of IgG4-related gastroduodenal ulcer was made based on the above diagnostic criteria.

Interestingly, the pathologic examination in this case showed that the IgG4-positive plasma cell infiltration was in the deeper portion of the mucosal lamina propria (Fig. 2). Recently, Notohara et al. described two unique histologic findings in IgG4-related gastrointestinal disease: 1) a striated inflammatory lesion in the muscularis propria and 2) the aggregation of plasma cells in the deeper portion of the mucosa (bottom-heavy plasmacytosis) (24). Although no striated inflammatory lesion in the muscularis propria was detected in the present case, probably due to the fact that only biopsy specimens were obtained, bottom-heavy plasmacytosis was presumably identified according to the pathologic findings of this case.

Given the size and severity of gastric ulcers in this case, mild inflammation was observed in the gastric epithelium and superficial portion of gastric mucosa (Fig. 2a). A previous study reported that the activity scores of gastric ulcer lesions evaluated by the Update Sydney System were significantly lower in patients with AIP than in control patients with *H. pylori* infection (25). As there was neither evidence of AIP nor *H. pylori* infection in the present case, IgG4-related gastric ulcer may occur even with a low gastritis activity.

IgG4-related gastrointestinal diseases can present with various endoscopic findings, such as gastric ulcers (5, 8, 9), polyps (18), submucosal tumor-like mass (19), and thickened folds (26). Therefore, it should be noted that it would be difficult to differentiate from a number of diseases affecting the deep gastric mucosal layer, like gastrointestinal stromal tumor and malignant lymphomas, based on endoscopic findings alone. Only a few reports have described endoscopic findings for IgG4-related gastroduodenal ulcers, including linear ulcers, pseudo-diverticulum (5), and cratered ulcers (8, 9). In the present case, we found two giant gastric ulcer craters (>3 cm in diameter) with relatively few reddened lesions around the ulcers (Fig. 1e), and enlarged gastric folds in the scarring stage (Fig. 5a) according to the endoscopic findings. These findings might be related to the histopathological findings of relatively mild inflammation in the gastric epithelium and remarkable infiltration of IgG4-positive plasma cells in the deep portion of the mucosal lamina propria.

Although IgG4-RD manifesting as upper gastrointestinal ulcer has been rarely reported, the clinicopathologic evidence of the condition has been gradually accumulating. Two independent groups reported a high prevalence of gastric ulceration in patients with AIP, regardless of the presence of *H. pylori* infection and use of NSAIDs (25, 27). Shinji et al. were the first to report significant IgG4-positive plasma cell infiltration in biopsy specimens from gastric ulcers in patients with AIP; they found that gastric ulcerative lesions with abundant IgG4-positive plasma cell infiltration may be the extrapancreatic involvement of AIP (25). They also described an interesting case of AIP with gastric inflammation in a 66-year-old man whose multiple gastric ulcers were successfully treated with steroid therapy; therefore, IgG4-related gastric ulcer may be treatable with steroids. Subsequently, Uehara et al. suggested that AIP-

Table. Comparison of the Site and Management of IgG4-related Upper Gastrointestinal Ulcer among Reported Cases.

References	Age/ Sex	Site of ulcer	OIO	Serum IgG4 (mg/dL)	Initial treatment	Surgical intervention	Clinical course
12	23/M	Esophagus	-	NA*	-	Esophagectomy	Postoperative course was uneventful
13	63/M	Esophagus	-	138	PPI	Esophagectomy	Postoperative course was uneventful
14	63/F	Esophagus	-	NA*	PPI	Biopsy, percutaneous gastrostomy	Initially responded to steroids but relapsed under maintenance therapy with multiple immunosuppressive drugs
15	60/M	Esophagus, stomach	Liver	159	Steroids, anti-ulcer treatment	Biopsy only	Improved after 3 months of initial treatment
16	76/F	Esophagus	-	9.8	PPI	Esophagectomy	Postoperative course was uneventful
5	72/M	Stomach	-	203	PPI	Biopsy only	Relapsed but remained asymptomatic under maintenance therapy with PPI
6	73/F	Stomach	-	NA*	PPI, sucralfate	Gastrectomy	Postoperative course was uneventful
7	65/M	Stomach	-	620	-	Emergent gastrectomy	Postoperative course was complicated by respiratory failure. Subsequently, there was no relapse under steroid therapy
8	73/M	Stomach	-	53	-	Gastrectomy	Postoperative course was uneventful
9	28/F	Stomach	-	NA*	PPI, sucralfate	Gastrectomy	Lost to follow-up
17	14/M	Stomach, duodenum	-	423	PPI	Biopsy only	Relapsed with initial treatment but improved after 3 weeks of steroid therapy
Present case	26/M	Stomach, duodenum	-	154	PPI, sucralfate	Biopsy only	Remained relapse-free and asymptomatic under maintenance therapy with PPI for 21 months

F: female, M: male, NA: not available, OIO: other involved organ, PPI: proton-pump inhibitors

associated gastritis may be treated effectively with steroid therapy (28). However, consensus on the treatments of IgG4-related gastrointestinal ulcer without AIP remains elusive due to insufficient evidence based on clinical studies.

We summarized the reported cases of IgG4-related upper gastrointestinal ulcer without AIP in Table. In most cases, the ulcer was detected in the esophagus and/or stomach, and surgical resection was eventually performed for suspected malignancy, based on a partial response or refractoriness to anti-ulcer drugs; notably, in these cases, the serum IgG4 level was not measured, and IgG4 immunostaining was not performed on the biopsy specimens before operation. These clinical issues may arise due to the difficulty in considering IgG4-related gastrointestinal ulcer as a possible diagnosis of gastrointestinal ulceration in patients without AIP. Only three previous reports have described cases of IgG4-related gastric ulcer without AIP diagnosed by elevated serum IgG4 levels and an endoscopic biopsy (5, 15, 17). Two of the cases were eventually treated with steroids, and the other was managed with only PPI maintenance therapy, as in our case. Provided the patient provides their consent, PPI maintenance therapy alone may be continued as long as the disease remains in remission. However, the patient should be monitored for the possible need for steroid therapy.

To our knowledge, the present case was the second report of a patient with IgG4-related duodenal and gastric ulceration without AIP, which was diagnosed by an elevated serum IgG4 level and endoscopic biopsy. IgG4-related gastrointestinal ulcer should be considered as a differential diagnosis for relapsing and/or refractory ulcer to prevent a misdiagnosis and unnecessary surgical treatment. The present observations may provide new insight into the elucidation of the disease pathogenesis of IgG4-related gastrointestinal disease.

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

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