IgG4-related Inflammatory Pseudotumor Presenting as a Solitary Mass in the Stomach

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ABSTRACT

Immunoglobulin G4-related disease (IgG4RD) is relatively a recently recognized entity histopathologically characterized by extensive infiltration of lymphocytes and IgG4-positive plasma cells with dense fibrosis. IgG4RD is now known to affect any organ system and a few cases of gastrointestinal lesions have been also reported. However, solitary IgG4RD of the stomach is still very rare. Furthermore it can mimic malignant conditions, it is important to recognize this disease to avoid unnecessary surgery. Herein, we present a case of IgG4RD as an isolated subepithelial mass in the stomach.

Key Words: IgG4-related sclerosing disease; Pseudotumor; Stomach
INTRODUCTION

Immunoglobulin G4-related disease (IgG4RD) is relatively a recently defined condition histologically characterized by extensive infiltration of lymphocytes and IgG4-positive plasma cells with storiform fibrosis.\textsuperscript{1} At present, it is known that various organs can be affected by IgG4RD including pancreas, bile duct, gallbladder, liver, lung, salivary gland, retroperitoneum and gastrointestinal tract.\textsuperscript{2} However, isolated IgG4RD of the stomach is still very rare. Here, we report a case of IgG4RD of the stomach presenting as a subepithelial mass without any other organ involvement.
CASE REPORT

A 27-year-old woman presented for the evaluation of high blood pressure. She was diagnosed with autosomal dominant polycystic kidney disease on abdominal computed tomography (CT) and was referred to our gastroenterology clinic for further evaluation of an incidentally found an intramural enhancing mass in the gastric fundus on the CT scan (Fig. 1A, 1B). She had no gastrointestinal complaints and physical examination showed no abnormalities. The laboratory results were unremarkable except for hypocytic and hypochromic anemia (hemoglobin: 10.1 g/dL). The patient underwent an esophagastroduodenoscopy. *Helicobacter pylori* positive lymphofollicular gastritis was seen and macroscopically a 4 cm sized subepithelial mass with surface ulceration was found on fundus (Fig. 2A, 2B). Endoscopic ultrasonography (EUS) showed a 3.4 cm × 1.6 cm sized well-circumscribed homogenous hypoechoic mass located mainly in the muscularis mucosa and submucosa (Fig. 2C). Because multiple biopsy specimens only revealed chronic ulcer on microscopic examination, laparoscopic wedge resection was performed to rule out tumors with malignant potential such as a neuroendocrine tumor (NET) or gastrointestinal stromal tumor (GIST). Grossly, the resected specimen showed a well-defined whitish-gray colored solid subepithelial mass (Fig. 3A, 3B). On microscopic examination, dense fibrosis admixed with inflammatory cells was seen composing the submucosal mass that extends to subserosa (Fig. 4A). Bland-looking spindle cells were arranged in a storiform pattern in the collagenous stroma (Fig. 4B), and there was dense infiltration of polymorphous inflammatory cells composed
predominantly of plasma cells with few lymphocytes, eosinophils and neutrophils (Fig. 4C). These
spindle cells showed 1-2 mitoses per 10 high power fields (HPFs) and positive staining for smooth
muscle actin and negative staining for ALK, desmin, CD34, DOG-1, c-kit and S-100. Additional
immunohistochemical staining revealed increased IgG-positive and IgG4-positive plasma cells
(402/HPF and 102/HPF, respectively) and the ratio of IgG4+/IgG+ plasma cell was 25.3% (Fig. 4D,
4E). Because these pathological features were compatible with IgG4RD, and there was no evidence
of any other organ involvement, the patient was finally diagnosed of an isolated gastric IgG4RD.
Serum IgG and IgG4 levels were not elevated (1012 mg/dL and 295 mg/L, respectively). She was
discharged without significant postoperative complications and there has been no evidence of
disease recurrence during the 1-year follow-up period.
DISCUSSION

IgG4RD was first proposed as a new clinicopathological entity by Kamisawa et al. in 2003 as a multisystemic disease in patients with autoimmune pancreatitis.\(^3\) IgG4RD is histologically defined as intensive infiltration of IgG4-positive plasma cells and T-lymphocytes with storiform fibrosis, and clinically known to respond well to steroids.\(^1\) Multiple organs can be affected synchronously or metachronously, including pancreas, biliary tree, liver, kidneys, salivary gland, orbit, breast, pericardium, aorta, skin, lungs, prostate, meninges, retroperitoneum and gastrointestinal tract.\(^2\)

Recently, many cases of IgG4RD other than the pancreas have been reported, such as IgG4-related inflammatory pseudotumors of the liver\(^4\), lung\(^5\) and greater omentum\(^6\) with or without autoimmune pancreatitis, and isolated IgG4RD seems to have been increasing due to an increased awareness of this disease entity.

However, IgG4RD in the stomach is still rare. According to the eight cases reported so far, gastric manifestations from this disease appear to consist of two types: polypoid mass-like (six cases) or ulcerative lesions (two cases) (Table 1). Rollins et al\(^7\) first described 5~6 cm sized gastric IgG4-related pseudotumor with no evidence of any other organ involvement which was confirmed by laparoscopic resection. Chetty et al\(^8\) reported two patients with gastric sclerosing nodular IgG4RD which were diagnosed by surgical resection. Afterwards, Na KY et al\(^9\) reported a 8 mm-sized gastric nodular IgG4RD confirmed by endoscopic submucosal dissection and two cases of IgG4-
related inflammatory pseudotumors in the stomach were described by Kim do H et al\textsuperscript{10}, in which EUS showed well-defined homogenous hypoechoic mass arising from echo layer 4 (muscularis propria). On the other hand, two patients presented with chronic gastric ulcerations. Fujita et al\textsuperscript{11} reported a case with refractory gastric ulcers that worsened after standard proton pump inhibitor therapy and \textit{Helicobacter pylori} eradication, and similarly Bateman et al\textsuperscript{12} described a case of intractable gastric ulcer showing storiform fibrosis and abundant infiltration of IgG4-positive plasma cells. Of a total of eight cases reported, only one case of ulcerative type-IgG4RD was possible to confirm by conventional endoscopic biopsy with elevated serum IgG4 levels. The remaining seven cases had to undergo surgical or endoscopic resection for final diagnosis, and their serum IgG4 levels showed normal range. In this regard, Na KY et al\textsuperscript{9} suggested that predominant inflammatory infiltrate of IgG4RD in the gastric submucosa while sparing the mucosa seems a reason to make a diagnosis difficult. Furthermore, endoscopic and radiographic difficulties to distinguish IgG4RD from other malignancies or tumors with malignant potential are also the reason for troublesome diagnosis. These situations lead a higher possibility to undergo unnecessary surgery in these patients, though IgG4RD is a medically treatable condition which responds well to steroid therapy.

In our case, macroscopically a 4-cm sized subepithelial mass with surface ulceration was incidentally found on the fundus, and EUS revealed a well-circumscribed homogenous hypoechoic mass located mainly in the muscularis \textit{mucosa} and submucosa. Although the endoscopic biopsy
failed to demonstrate the disease, we considered a laparoscopic wedge resection to rule out a NET or GIST without a hesitation. After obtaining a final diagnosis and reviewing similar cases who have undergone unnecessary surgery, we learned that the most important thing to diagnose IgG4RD is clinical awareness and suspicion of this disease entity. Although *Helicobacter pylori* associated gastritis was seen in our case, there has been no evidence of a link between IgG4RD and *Helicobacter pylori* infection so far.

In conclusion, isolated gastric IgG4RD is very rare. Because it is hard to endoscopically differentiate with other potentially malignant tumors and to definitely identify by conventional endoscopic biopsy, it is most important to recognize this disease itself to avoid unnecessary surgery. Because IgG4RD is known to respond well to steroids, it is of importance to try to confirm the disease before considering invasive surgery. And we suggest to consider IgG4RD in the differential diagnosis when faced with gastric subepithelial mass which showed homogenous hypoechoic feature on EUS.
Conflicts of Interest

The authors have no financial conflicts of interest.
Acknowledgements

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REFERENCES


**Fig. 1.** Abdominal computed tomography images showing multiple cysts in both kidneys (A) and an intramural enhancing mass in the gastric fundus (B).
Fig. 2. Endoscopic findings. (A) *Helicobacter pylori* positive lymphofollicular gastritis was seen. (B) Approximately 4 cm sized hard, fixed subepithelial mass with distinct ulceration on the surface was noted in the fundus. (C) EUS showed a 3.4 x 1.6 cm sized homogenous hypoechoic mass located in the muscularis mucosa to submucosa.
Fig. 3. Gross findings after formalin fixation. (A-B) On section, a well-defined homogenous gray-white solid submucosal mass (star) is identified. The gastric mucosa (arrow) is unremarkable.
Fig. 4. Pathologic findings. (A) Dense fibrosis admixed with inflammatory cells composing the submucosal mass that extends to subserosa. (star: mucosa, triangle: submucosa, circle: muscularis propria) (H&E, x12.5). (B) Bland looking spindle cells arranged in a storiform pattern (H&E, x200). (C) Fibroblastic cells were admixed with dense lymphoplasmacytic cells (H&E, x400). (D) IgG immunohistochemical stains showed increased numbers of IgG-positive plasma cells in stroma (402/HPF, x200). (E) IgG4 immunohistochemical stains revealed increased numbers of IgG4-positive plasma cell infiltration (102/HPF, x200) and the ratio of IG4+/IgG+ plasma cell was 25.3%.
<table>
<thead>
<tr>
<th>Case No.</th>
<th>Sex/Age</th>
<th>Endoscopic Finding</th>
<th>Location</th>
<th>EUS Finding</th>
<th>Diagnostic procedure</th>
<th>Involved layer(s)</th>
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<td>Subepithelial mass with surface ulceration, 4cm</td>
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<td>Biopsy</td>
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WR, wedge resection; DG, distal gastrectomy; ESD, Endoscopic submucosal dissection; NA, not available; SM, submucosa; MP, muscularis propria; SS, subserosa.
### Table 1. Clinicopathological features of gastric IgG4RD

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<td>WR</td>
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<td>SM to SS</td>
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<td>9(^12)</td>
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Figure 1
Figure 2
Figure 3
Figure 4