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Case Report

IgG4-related disease in a non-healing gastric ulcer: case report

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Abstract: We report a 28-year-old woman with a refractory gastric ulcer in the absence of *Helicobacter pylori* infection and autoimmune pancreatitis. Histologic examination of the gastric ulcer demonstrated abundant IgG4 positive plasma cells populating a lymphoplasmacytic infiltrate with associated sclerosis. Our case suggests that treatment-refractory peptic ulcer may be related to IgG4-related inflammation. When a biopsy performed to evaluate a refractory ulcer reveals abundant plasma cells and sclerotic fibrosis, an immunohistochemical stain for IgG4 and serum IgG4 measurement might be considered.

Keywords: IgG4, gastric ulcer

Introduction

IgG4-related disease has been described as a sclerotic inflammatory condition with infiltration of numerous IgG4 positive plasma cells, affecting multiple organ systems [1-3]. Cases of IgG4-related gastric ulcer have rarely been reported. There have been a few previous case reports in the literature with IgG4-related disease in refractory gastric ulcers [5, 6] in the absence of *H. pylori* infection or autoimmune pancreatitis. To the best of our knowledge, our case is the first report of a patient presenting in this way in the United States.

Case report

A 28-year-old female with a past medical history of seizures, anxiety, and iron-deficiency anemia presented with epigastric abdominal pain, nausea and vomiting to Houston Methodist Hospital for evaluation and treatment. Initial esophagogastroduodenoscopy (EGD) in July 2015 showed a prepyloric ulcer (**Figure 1**). Antral biopsies showed chronic active gastritis with eosinophils and focal complete intestinal metaplasia, and negative for dysplasia. *Helicobacter pylori* (*H. pylori*) were not identified on routine hematoxylin and eosin (H and E) or by immunohistochemical stains. Serum amylase was 47 U/L; no clinical or radiographic evidence of pancreatitis was seen. The patient was treated with anti-ulcer drugs.

Three months later, the patient returned with gastric outlet obstruction by a non-healing peptic ulcer. The ulcer had been refractory to aggressive medical management with proton pump inhibitors (PPIs) and sucralfate (sucrose sulfate-aluminum complex). An EGD showed a prepyloric ulcer with a clean base. Biopsies of the ulcer demonstrated findings of a healing ulcer: prominent foveolar hyperplasia, expansion of the lamina propria, reactive stromal changes including reactive vascular proliferation, stromal myxoid change, and a focal mild increase in chronic inflammatory cells in the lamina propria. *H. pylori* were again not identified.

One week later, repeat EGD showed a single 1 cm non-bleeding cratered prepyloric gastric ulcer with a clean base and no stigmata of bleeding. Based on clinical indications of a refractory peptic ulcer associated with gastric outlet obstruction, a vagotomy and antrectomy with a Billroth II anastomosis was performed. The resection had an antral ulcer with sharp

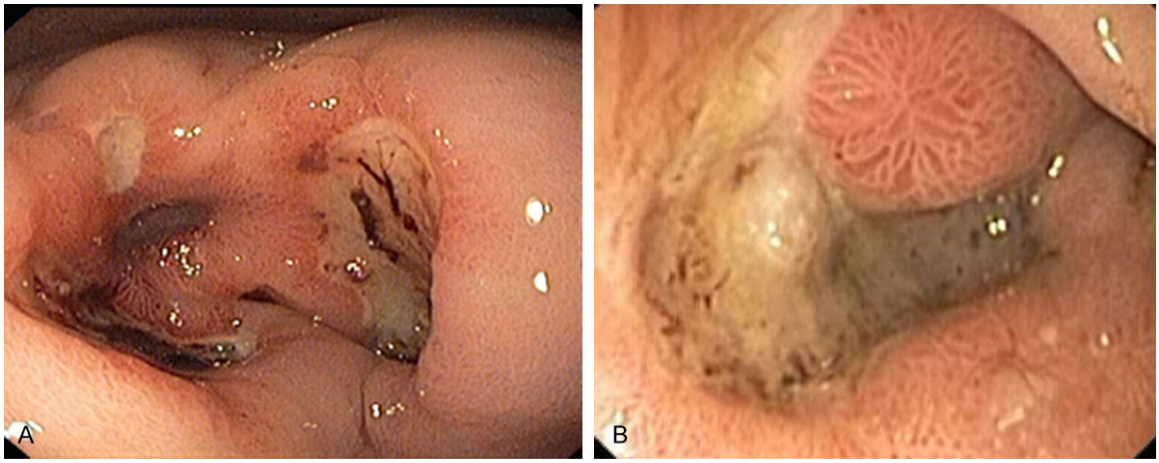

Figure 1. EGD: non-bleeding cratered prepyloric gastric ulcer with clean base, A. Initial EGD. B. EGD after four months of medical therapy.

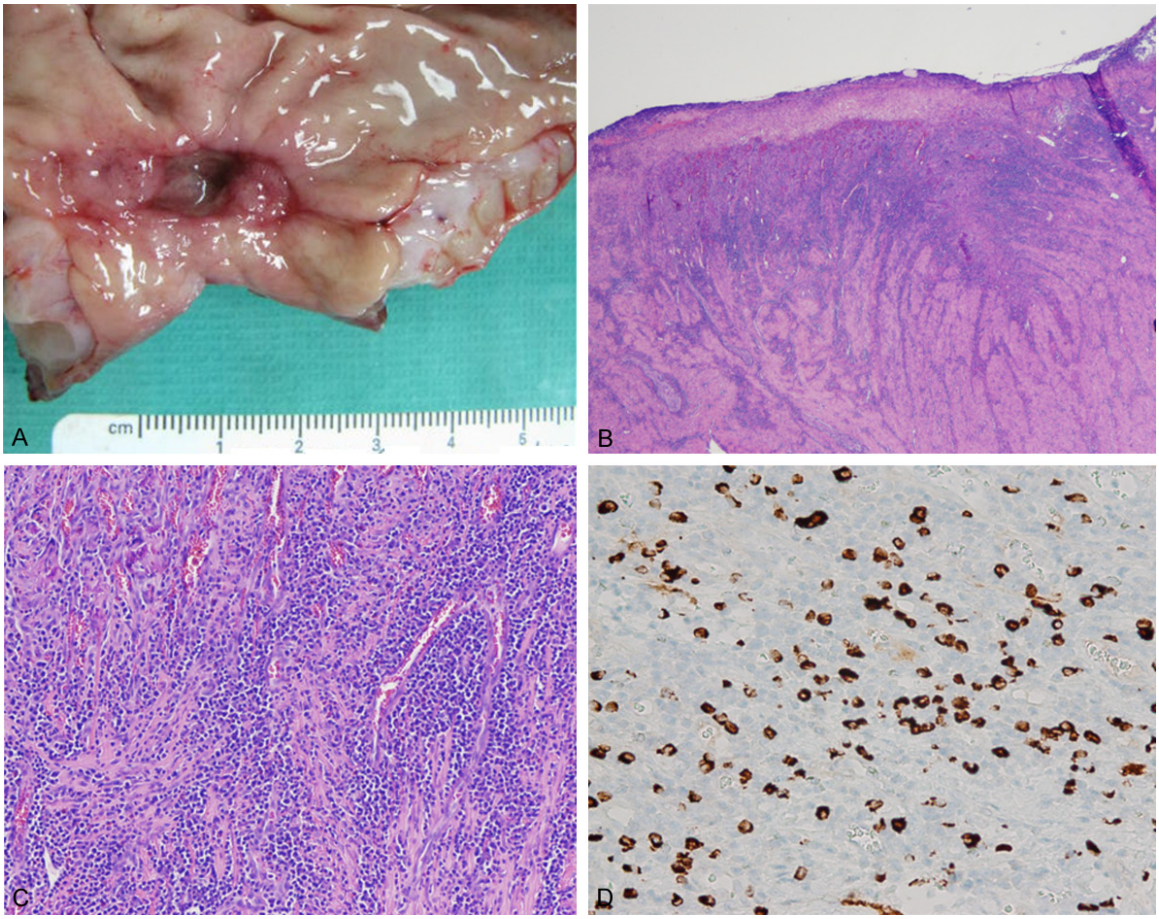

Figure 2. A. Gastric resection with ulcer surrounded by edematous mucosa. B. Ulcer with sclerosis (H&E, 2x magnification) C. Ulcer with dense lymphoplasmacytic infiltrate, storiform fibrosis, and phlebitis (H&E, 10x magnification). D. Numerous IgG4-positive plasma cells in the ulcer (>50/hpf) (20x magnification).

margins, rolled edges and surrounding tan-pink edematous mucosa (**Figure 2A**). Microscopically, there was a benign ulcer with iron pill pigment deposition. At the base of the ulcer, there was sclerosis replacing the muscularis propria, associated with heavy infiltration by lympho-

Table 1. Comparison of IgG4-related disease in refractory gastric ulcers

Reported Case	Age	Gender	Number of Lesions	Location in Stomach	Medical Treatment	Duration of Refractoriness to Medical Treatment	Surgical Intervention	*H. pylori status*	Serum IgG4 levels
Bateman AC et al.	73	F	Single	Lesser curvature	PPI and sucralfate	1 year	Partial gastrectomy	Negative	Not measured
Fujita T et al.	77	M	Multiple	Upper body and lesser curvature	Famotidine, lansoprazole, amoxicillin, rabeprazole	Stable with maintenance PPI	EGD and biopsies only	Initially negative, positive at 26 months, then treated	203 mg/dL
Moyer A et al.	28	F	Single	Prepyloric	PPI and sucralfate	4 months	Partial gastrectomy	Negative	Not measured

cytes, plasma cells and occasional eosinophils (**Figure 2B**, **2C**). No obliterative thrombophlebitis was observed. H and E, as well as immunohistochemical stains for *H. pylori* were again negative for organisms. Due to the numerous plasma cells and sclerotic inflammation, IgG4-associated sclerosing disease was considered. An immunohistochemical stain for IgG4 demonstrated numerous IgG4 positive plasma cells (greater than 50/high power field) with an IgG4:IgG ratio greater than 40% (**Figure 2D**), morphologically diagnostic for IgG4-related disease. No malignancy was found.

A retrospective review of the initial gastric biopsies showed many IgG4-positive plasma cells in the muscularis mucosa with associated active gastritis. Serum IgG4 measurement was not obtained because the patient was lost to follow up.

Discussion

IgG4-related disease is increasingly recognized as a fibro-inflammatory condition affecting multi-organ systems [1]. First described in Type I autoimmune pancreatitis [2], an increase in IgG4 serum concentration and IgG4-related disease has since been observed in nearly every organ system [3]. The relationship between abundant IgG4-plasma cells in gastric ulcers occurring in patients with autoimmune pancreatitis is independent from other known ulcer-causing agents, such as *H. pylori* infection [4]. Previous case reports from Japan [5] and the United Kingdom [6] have reported IgG4-related disease in refractory gastric ulcers in the absence of *H. pylori* infection (**Table 1**). To the best of our knowledge, our case is the first report of a patient presenting in this way in the United States.

The histologic triad for IgG4-related disease pathology is a dense lymphoplasmacytic infiltrate, obliterative phlebitis, and storiform fibrosis [1, 7]. The presence of two out of the three histologic features supports a pathologic diagnosis, as seen in our case. However, some organs lack storiform fibrosis and/or obliterative phlebitis. Thus, in the context of a strong suspicion of IgG4-related inflammation that lacks highly suggestive histologic features, immunohistochemical staining for IgG4 can provide support for the diagnosis. Furthermore, the ratio of $IgG4^+$ cells to IgG^+ plasma cells has been established as a 'more powerful tool' than IgG4 plasma cell counts alone in diagnosing IgG4-related disease [7]. Increased eosinophils and phlebitis without obliteration are additional features that can be seen in IgG4-related disease.

In our case of an IgG4-related refractory gastric ulcer, a dense infiltrate of plasma cells in association with sclerosis was observed at the base of the ulcer extending into the muscularis propria. Mucosal-only endoscopic biopsies would miss key pathologic changes and thus could be insufficient for a diagnosis of this entity.

IgG4-related disease is a rare cause of refractory gastric ulcer. As in our patient, it can present independent of both autoimmune pancreatitis and *H. pylori* infection. The histologic findings in this patient's gastric ulcer fit the criteria published in the 2012 Consensus Statement as seen in multiple other organs [7]. Although IgG4 positive plasma cells can be seen in other settings, such as reactive inflammation, the characteristic architecture coupled with establishing the presence of greater than 50 IgG4 positive plasma cells per high power field (HPF) and a ratio of $IgG4^+$ to IgG^+ plasma cells greater than 40% lends strong support to the diagnosis of IgG4-related disease. In the clinical setting of a gastric ulcer refractory to the medical treatment, an IgG4-associated gastric ulcer should be considered in the dif-

ferential. Gastric biopsies with immunohistochemical staining for IgG4 and serum IgG4 measurement are recommended for guiding clinical management. In the inflammatory phase, this condition has a good response to immunosuppressant therapy with steroids, however there is a possibility of recurrence when treatment is stopped [6]. Thus a trial with steroid therapy might be considered before surgical intervention.

In our case, preoperative serum IgG4 measurement was not performed because there was no clinical suspicion of this entity. Postoperative serum IgG4 could not be measured because the patient has been lost to follow-up. However, postoperative serum IgG4 measurement after resection may not be as informative as a high level of preoperative serum IgG4 level.

In summary, we present a refractory gastric ulcer, likely associated with IgG4-related sclerotic inflammatory disease. Based on our experience and the above discussion, we recommend awareness of this condition when diagnosing and treating patients with refractory gastric ulcers. If IgG4-related sclerotic inflammatory disease is suspected, measurement of preoperative serum IgG4 and IgG4 immunohistochemical staining of tissue sections are strongly recommended.

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References

[1] Divatia M, Kim SA, and Ro JY. IgG4-Related Sclerosing Disease, an Emerging Entity: A Review of a Multi-System Disease. Yonsei Med J 2012; 53: 15-34.

[2] Hamano H, Kawa S, Horiuchi A, Unno H, Furuya N, Akamatsu T, Fukushima M, Nikaido T, Nakayama K, Usuda N, Kiyosawa K. High serum IgG4 concentrations in patients with sclerosing pancreatitis. N Engl J Med 2001; 344: 732-8.

[3] Kamisawa T, Zen Y, Pillai S, Stone JH. IgG4-related disease. Lancet 2015; 385: 1460-71.

[4] Shinji A, Sano K, Hamano H, Unno H, Fukushima M, Nakamura N, Akamatsu T, Kawa S, Kiyosawa K. Autoimmune pancreatitis is closely associated with gastric ulcer presenting with abundant IgG4-bearing plasma cell infiltration. Gastrointest Endosc 2004; 59: 506-11.

[5] Fujita T, Ando T, Sakakibara M, Hosoda W, Goto H. Refractory gastric ulcer with abundant IgG4-positive plasma cell infiltration: A case report. World J Gastroenterol 2010; 16: 2183-2186.

[6] Bateman AC, Sommerlad M, Underwood TJ. Chronic gastric ulceration: a novel manifestation of IgG4-related disease? J Clin Pathol 2012; 65: 569-70.

[7] Deshpande V, Zen Y, Chan JK, Yi EE, Sato Y, Yoshino T, Klöppel G, Heathcote JG, Khosroshahi A, Ferry JA, Aalberse RC, Bloch DB, Brugge WR, Bateman AC, Carruthers MN, Chari ST, Cheuk W, Cornell LD, Fernandez-Del Castillo C, Forcione DG, Hamilos DL, Kamisawa T, Kasashima S, Kawa S, Kawano M, Lauwers GY, Masaki Y, Nakanuma Y, Notohara K, Okazaki K, Ryu JK, Saeki T, Sahani DV, Smyrk TC, Stone JR, Takahira M, Webster GJ, Yamamoto M, Zamboni G, Umehara H, Stone JH. Consensus statement on the pathology of IgG4-related disease. Mod Pathol 2012; 25: 1181-1192.