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
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-
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-

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

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

Differential. 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