CLINICAL VIGNETTE

IgG4-Related Esophagitis: 3 Interesting Cases

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Introduction

Immunoglobulin (Ig)G4-related disease (RD) is an immune-mediated condition characterized by dense lymphoplasmacytic inflammation, with a predominance of IgG4-positive plasma cells surrounded by storiform fibrosis and obliterative phlebitis. It can affect multiple organs and is classically implicated in autoimmune pancreatitis and cholangiopathies. IgG4-RD of the upper gastrointestinal (GI) tract is a rare entity that has not been well described. We present three patients with IgG4-related esophagitis with various presentations from esophageal stricture, through dysphagia aortica, to esophagitis dissecans superficialis with progression to invasive squamous cell carcinoma. The latter is the first known report in the literature of IgG4-related esophagitis associated with local malignancy.

Case 1

An 87-year-old female presented to our motility clinic with dysphagia to solids for one year that was refractory to sucralfate, histamine-2 (H2) blockers and proton pump inhibitors (PPI). Esophagogastroduodenoscopy (EGD) showed an esophageal stricture at 27 centimeters (cm) which was pneumatically dilated. Biopsy of the stricture showed ulcerative esophagitis with an underlying dense chronic inflammation. Immunohistochemical staining revealed a focal population of IgG4-positive plasma cells in the lamina propria, numbering up to 25/high power field (HPF). The patient was started on swallowed fluticasone inhaler treatment, which provided minimal relief, and repeat biopsy after three months showed increased inflammation with 50 IgG4-positive plasma cells/ HPF. Her refractory disease required twelve stricture dilations in a two-year period, providing only temporary relief.

Case 2

An 87-year-old female presented with a thirteen-year history of esophageal dysphagia with self-induced regurgitation. Prior endoscopies were reported to be unremarkable. She was referred for barium swallow, which showed a distal esophageal obstruction that was suggestive of achalasia. Esophageal manometry demonstrated lack of relaxation of her lower esophageal sphincter (LES) and no evidence of esophageal peristalsis. Subsequently, the diagnosis of achalasia was made. The patient underwent a Heller myotomy with laparoscopic Dor fundoplication after which her symptoms improved but did not completely resolve. Post-operative barium swallow did not differ much in radiographic appearance from her pre-operative study. In addition to a distally dilated esophagus with absent peristalsis, a long, tapered narrowing of the esophagus was seen associated with aortic compression. Subsequent EGD showed a patent gastroesophageal junction. Biopsies of the gastroesophageal junction and distal esophagus showed moderate chronic inflammation. She was started on a PPI, but after her symptoms failed to respond to medical therapy, she underwent another EGD a year later with unchanged findings. During this procedure, she had 100 milliliters Botox injected into her LES which led to moderate improvement of symptoms. The biopsy of the gastroesophageal junction was notable for erosive esophagitis with increased subepithelial IgG4-positive plasma cells, numbering up to 50/HPF, and she was diagnosed with IgG4-related esophagitis. Her esophageal manometry from three years prior was reviewed again, and it was noted to have a pulsatile character in the area of increased LES pressure, which is characteristic of a vascular disorder rather than a sphincter related one. Radiographic findings were also supportive of vascular compression as the etiology of her dysphagia. Repeat barium swallow confirmed the diagnosis of dysphagia aortica or dysphagia secondary to aortic compression of the esophagus. During the study, the patient was able to pass barium when she was in the left lateral position but not when she was in the anteroposterior position. The patient deferred surgery and was counseled on lifestyle modifications to control her positional dysphagia.

Case 3

A 65-year-old man presented with worsening dysphagia to solids and liquids and odynophagia. EGD showed diffuse narrowing of the esophagus with friable mucosa that easily peeled off with minimal contact. Biopsy showed diffuse lymphocytic esophagitis with a focal plasma cell infiltrate in the lamina propria of the proximal esophagus that correlated with esophageal wall thickening seen on endoscopic ultrasound. Staining showed polyclonal plasma cell infiltrate with mostly IgG4-positive plasma cells. The patient was started on oral

corticosteroids, but six months later returned with worsening symptoms. Repeat EGD revealed an esophageal stricture at 20cm and proximal esophagitis dissecans superficialis. Soon after, he developed white lesions on his tongue and buccal mucosa and was diagnosed with cicatricial pemphigoid. However, this diagnosis was revised after subsequent endoscopy showed invasive squamous cell carcinoma at the proximal esophagus. His tumor was moderately differentiated, invading through the muscularis propria and into the adventitia. The patient was referred to surgery and underwent an esophagogastrectomy.

Discussion

IgG4-RD is a relatively newly discovered disease, first recognized as a systemic condition in 2003 when extra-pancreatic manifestations were observed in patients with Type 1 (IgG4-related) autoimmune pancreatitis.[1] Since then, IgG4-RD has been identified in several organ systems, including the biliary tree, liver, salivary glands, kidney, lungs, and lymph nodes.[2] To date only a small number of cases have been described in the literature[3,4] including those of our group's original presentation[5] of these three additional ones. In 2017 eight additional patients were described in a case series.[6] Findings included esophageal strictures, postmyotomy treated achalasia, erosive esophagitis and esophageal nodule, in 3, 2, 1, and 1 patient/s, respectively, with one patient who had unremarkable mucosa on EGD. Patients had significantly higher numbers of IgG4-positive plasma cells and a greater IgG4 to IgG ratio, compared to controls. Stricturing disease was reported to respond to corticosteroid therapy. Another reported case involved a large 9cm IgG4 related pseudotumor associated with lung cancer that was removed by endoscopic submucosal dissection.[7] Another patient was thought to have possible recurrence of esophageal cancer, but was later diagnosed with IgG4 related esophagitis.[8]

Here we describe three patients with unique presentations, still bringing the total to fewer than twenty reported cases worldwide, with varied presentations of IgG4-RD of the esophagus. Chronic refractory dysphagia should raise suspicion for histological esophageal abnormalities, and, similarly to eosinophilic esophagitis, lead to multiple esophageal biopsies with IgG4 immunohistochemical staining. The location and extent of biopsies is to be further investigated. Interestingly, a recent study showed that patients with eosinophilic esophagitis also have a high number of esophageal IgG4-positive plasma cells which significantly decrease with budesonide therapy,[9] requiring expert pathological evaluation.

Our cases also show that IgG4-RD in the esophagus has the same unifying histopathological feature of a dense lymphoplasmacytic infiltrate arranged in a storiform pattern that is the hallmark of IgG4-related disease across all organs. This is also the first known report in the literature of IgG4-related esophagitis associated with local esophageal malignancy suggesting closer endoscopic monitoring may be a consideration for these patients.

Figures

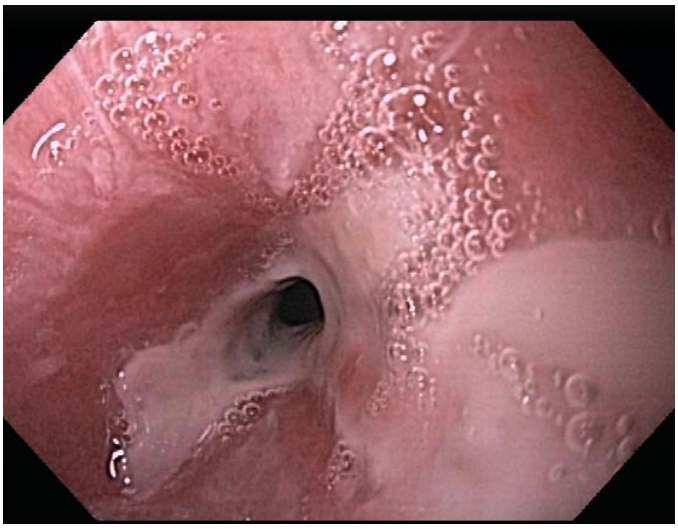

Figure 1: EGD of proximal esophageal stricture with ulcerations (Case 1)

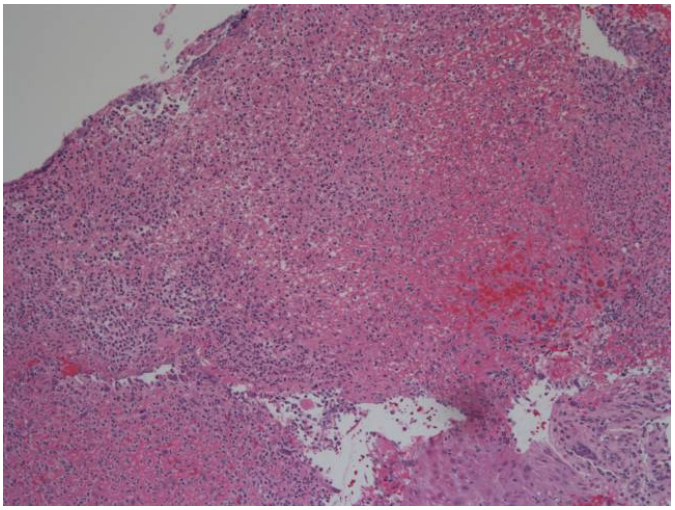

Figure 2: H&E of the esophageal stricture showing dense lymphocytic inflammation (Case 1)

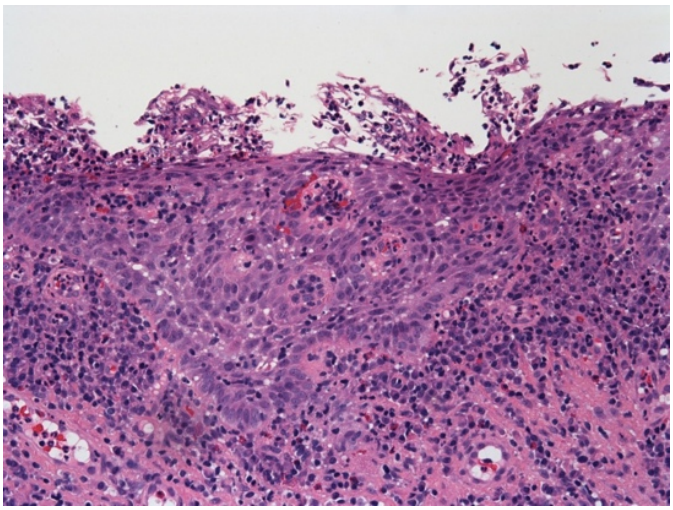

Figure 3: H&E showing dense lymphocytic inflammation (Case 3)

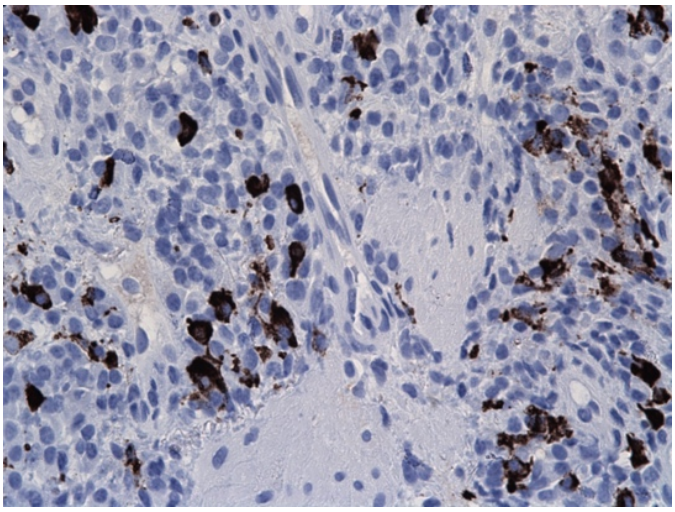

Figure 4: Staining for IgG4-positive plasma cells (Case 3)

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REFERENCES

1. **Kamisawa T, Funata N, Hayashi Y, Eishi Y, Koike M, Tsuruta K, Okamoto A, Egawa N, Nakajima H**. A new clinicopathological entity of IgG4-related autoimmune disease. *J Gastroenterol*. 2003;38(10):982-4. doi: 10.1007/s00535-003-1175-y. PMID: 14614606.
2. **Stone JH, Zen Y, Deshpande V**. IgG4-related disease. *N Engl J Med*. 2012 Feb 9;366(6):539-51. doi: 10.1056/NEJMra1104650. PMID: 22316447.
3. **Lee H, Joo M, Song TJ, Chang SH, Kim H, Kim YS, Ryoo JY**. IgG4-related sclerosing esophagitis: a case report. *Gastrointest Endosc*. 2011 Apr;73(4):834-7. doi: 10.1016/j.gie.2010.08.043. Epub 2010 Nov 9. PMID: 21067736.
4. **Dumas-Campagna M, Bouchard S, Soucy G, Bouin M**. IgG4-Related Esophageal Disease Presenting as Esophagitis Dissecans Superficialis With Chronic Strictures. *J Clin Med Res*. 2014 Aug;6(4):295-8. doi: 10.14740/jocmr1845w. Epub 2014 May 22. PMID: 24883156; PMCID: PMC4039102.
5. **Bikhchandani M, Weiss GA, Conklin J**. IgG4-Related Esophagitis. *American Journal of Gastroenterology*. 2015 Oct;110:S279. Available at: https://journals.lww.com/ajg/Fulltext/2015/10001/IgG4_Related_Esophagitis__628.628.aspx.
6. **Obiorah I, Hussain A, Palese C, Azumi N, Benjamin S, Ozdemirli M.** IgG4-related disease involving the esophagus: a clinicopathological study. *Dis Esophagus*. 2017 Dec 1;30(12):1-7. doi: 10.1093/dote/dox091. PMID: 28881885.
7. **Ekinci N, Unal Kocabey D, Gun E, Aslan F**. Giant IgG4-Related Pseudotumor of the Esophagus Resected with Endoscopic Submucosal Dissection: A Case Report and Review of the Literature. *Turk Patoloji Derg*. 2021; 37(3):258-263. English. doi: 10.5146/tjpath.2020.01515. PMID: 33432560.
8. **Enea D, Camus M, Fléjou JF**. An Unexpected Esophageal Inflammatory Lesion. *Gastroenterology*. 2021 Aug;161(2):e35-e38. doi: 10.1053/j.gastro.2020.12.020. Epub 2020 Dec 18. PMID: 33346001.
9. **Weidlich S, Nennstiel S, Jesinghaus M, Brockow K, Slotta-Huspenina J, Bajbouj M, Schmid RM, Schlag C**. IgG4 is Elevated in Eosinophilic Esophagitis but Not in Gastroesophageal Reflux Disease Patients. *J Clin Gastroenterol*. 2020 Jan;54(1):43-49. doi: 10.1097/MCG.0000000000001154. PMID: 30614939.