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CASE REPORT

# Autoimmune Esophagitis: IgG4-related Tumors of the Esophagus

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**Abstract** We present a case of a 23-year-old gentleman who presented with dysphagia, weight loss, and recurrent esophageal strictures requiring multiple dilatations. An endoscopic ultrasound with esophagogastroduodenoscopy revealed a mass present in the distal esophagus. Fine needle aspiration suggested that the mass in the lower esophagus resembled a gastrointestinal stromal tumor. After surgical resection, final pathologic analysis revealed that the tumor was comprised of benign-appearing fibroinflammatory cells with an increase and predominance of IgG4-positive plasma cells. The microscopic appearance was consistent with a benign condition as a result of an IgG4-related process. He did not, however, have any other symptoms indicative of systemic autoimmune disease or connective tissue disorders. We present the pre-operative imaging, operative management, pathologic diagnosis, and literature review of this rare condition and the first known report of autoimmune esophagitis as part of the IgG4 spectrum of diseases.

**Keywords** IgG4 · Autoimmune disorders · Esophagus · Autoimmune esophagitis

## Introduction

IgG4-related disorders represent a disease process that has in the past decade gained much attention due to the proclivity of physicians to confuse it with and treat it as a malignant tumor. This disease process is known to manifest in many organs and has been reported in the pancreas, biliary tree, salivary glands, kidneys, lungs, pituitary, and prostate, as well as the soft tissues, retroperitoneum, and lymph nodes. There is considerable clinical, laboratory, and histopathological overlap between IgG4-related diseases and known autoimmune disorders, which have likewise been shown to lead to intrinsic damage to a multitude of organ systems. On occasion, IgG4-related lesions may affect only one organ and unfortunately presents both clinically and radiologically with symptoms that mimic a malignancy. As our recognition of the potential for IgG4-related disorders to mimic malignant tumors increases and the diagnostic criteria become further elucidated, patients may be spared unnecessary surgical procedures and subsequent loss of organ function.

## Case Report

A 23-year-old Caucasian gentleman with a 6-year history of esophageal strictures, presumed to be secondary to gastro-esophageal reflux disease, presented to our clinic with debilitating dysphagia and significant weight loss over the last 12 months. His past medical history is non-contributory and there was no evidence of other autoimmune diseases or connective tissue disorders. As his symptoms progressed, he required multiple esophageal dilatations by his local gastroenterologist for symptomatic relief.

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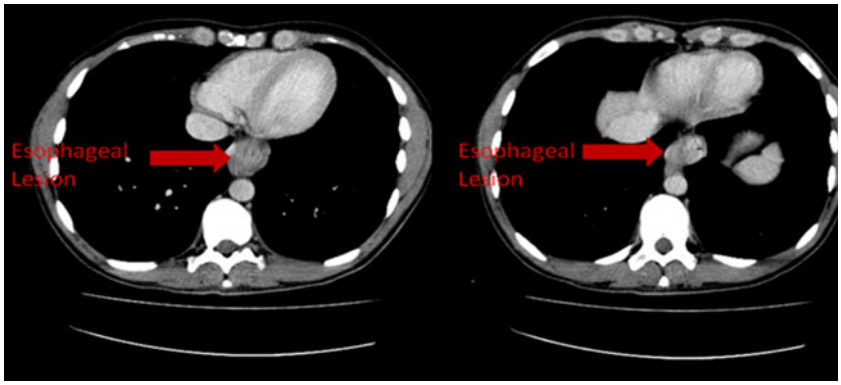


**Fig. 1** Cat scan demonstrating distal esophageal lesion.

Due to the lack of significant pathology explaining the esophageal stricture, an endoscopic ultrasound (EUS) was performed to evaluate for a mass. At EUS, a subepithelial lesion was identified that had characteristics of a mass. A fine needle aspiration of this subepithelial lesion located in the distal esophagus demonstrated a submucosal spindle cell tumor with immunostains that were positive for CD4 and CD117. This was believed to be consistent with the diagnosis of a gastrointestinal stromal tumor (GIST).

Pre-operative workup included an esophagram, computed axial tomography (cat) scan and an esophagogastroduodenoscopy (EGD). The cat scan (Fig. 1) demonstrates a large esophageal lesion in the lower third of the esophagus. Pooling of contrast in the lower third of the esophagus secondary to a presumed large, circumferential esophageal mass was seen on the esophagram. The remainder of the study showed that there was significantly delayed emptying of the esophagus with poor peristalsis. The EGD (Fig. 2) confirmed the esophagram findings, demonstrating a moderate stenosis measuring 20 (in length)×8 mm (inner diameter) at 42 cm from the incisors. An EGD performed 2 months post-dilation showed a persistent intra-luminal lesion with mass effect.

Due to his debilitating symptomatology, the multitude of dilatations, recurrent stricturing, poor peristalsis in the proximally dilated esophagus, and a distal subepithelial mass, he was counseled about a minimally invasive esophagectomy with a cervical anastomosis. Unfortunately, because preoperative immunohistochemical staining showed positivity for C-kit and the preoperative diagnosis was possible GIST, pre-operative IgG4 levels were not obtained prior to embarking on surgical therapy.

Consequently, he underwent a successful thorascopic and laparoscopic esophagectomy with a cervical anastomosis. His post-operative course was uneventful and was discharged home on post-operative day 8 tolerating a diet by mouth. He is currently 4 months post-operatively, doing well and without evidence of disease progression to other organs.

Gross examination of the surgical specimen revealed a 1.2 cm mucosal ulceration in the distal esophagus just proximal to the gastro-esophageal junction. Beneath the ulceration in the submucosa was a poorly defined, firm, white–tan mass that measured 1.5×0.8×0.4 cm. It extended deep through the muscularis, but did not involve the surgical margin. Histologic findings showed a spindle cell proliferation with prominent lymphoplasmacytic inflammation and venulitis. These features were confined to the submucosal tumor and did not extend in either direction submucosally. Additionally, there were no mucosal changes identified adjacent to the ulcer or at any distance from the ulcer, to suggest an underlying tumor of any sort.

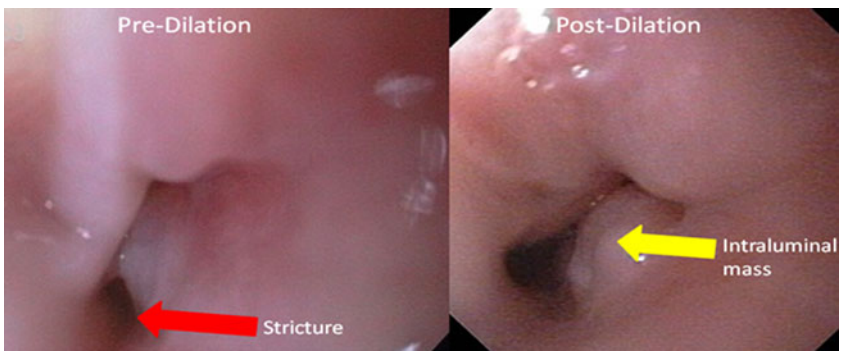


**Fig. 2** Esophagogastroduodenoscopy (EGD) demonstrating distal esophageal stricture prior to dilation. Persistent post-dilation mass is seen in follow-up EGD.

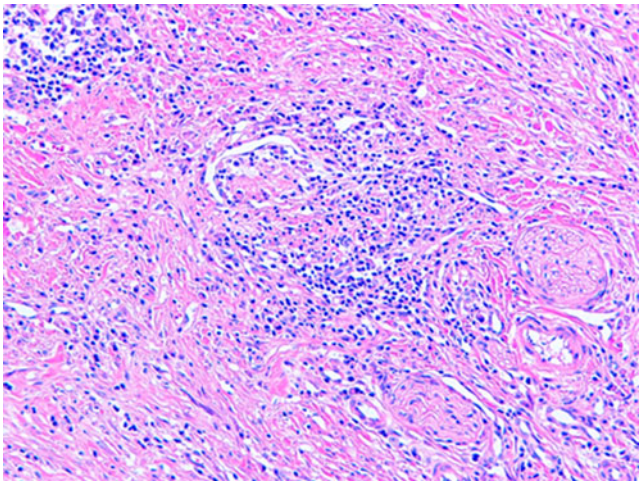

**Fig. 3** Dense chronic inflammatory infiltrate with plasma cells and a prominent myofibroblastic response. Focal venulitis was identified.

Immunohistochemistry (Fig. 2) revealed IgG4 positive plasma cells as high as 75 per high powered field and fibroblastic spindle cells staining with SMA. Stains for S-100 and ALK-1 were negative (Fig. 3). Additionally, staining for C-kit showed focal staining of interstitial cells with no evidence of GIST. Given the heightened numbers of IgG4-positive plasma cells and the lack of c-kit staining, the lesion was considered to be part of a spectrum of IgG4-related disease rather than a GIST (Fig. 4).

## Discussion

Autoimmune disorders are characterized by multisystem involvement and the ability to affect any organ[1]. Many investigators have described a wide variety of gastrointestinal manifestations with generalized autoimmune disorders. Others have shown that autoimmune disorders results in a chronic form of inflammation that can permanently damage the organ resulting in a pseudotumor effect[2–5].

Multiple reports have demonstrated that autoimmune disorders of the pancreas can present with lesions that resemble malignancy, both clinically and radiographically[2–5]. In fact, Sarles et al.[6] reported a case of pancreatic involvement associated with hypergammaglobulinemia as early as 1960. Since then, many cases have been described, with the highest volume of literature coming out of Japan, which has led to the concept of autoimmune pancreatitis[2–11].

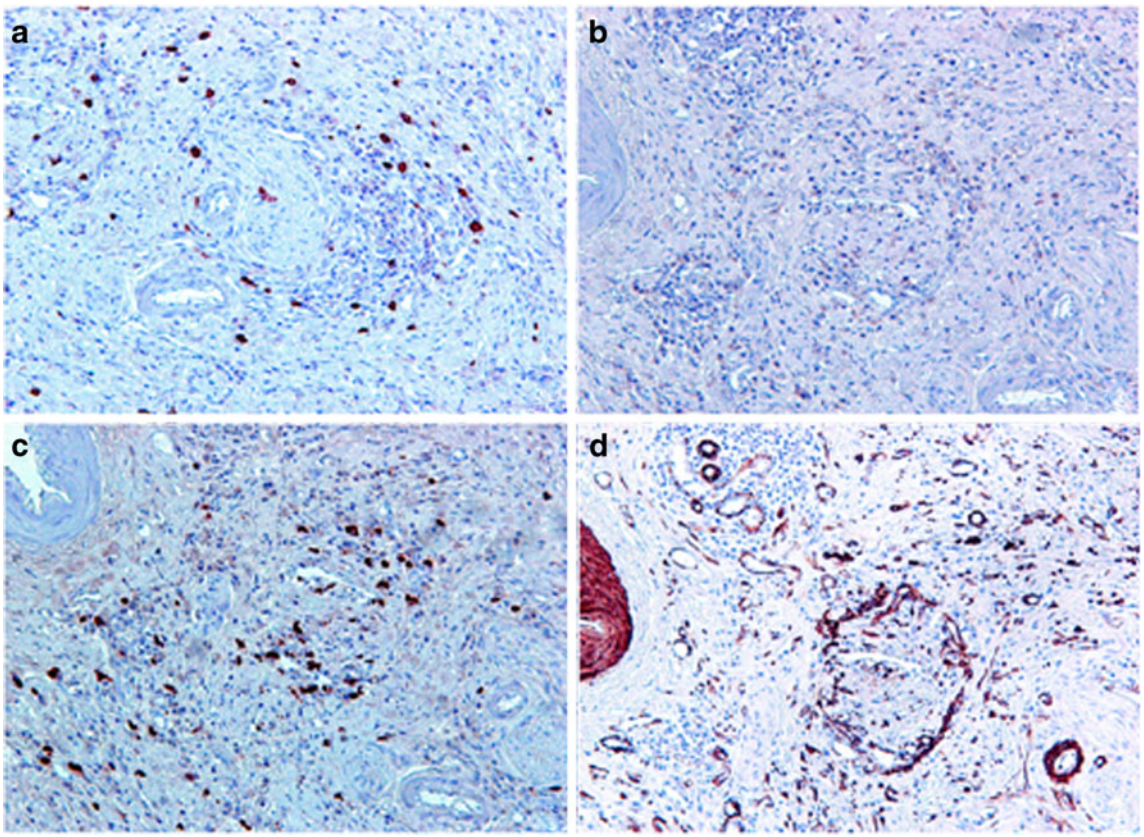


**Fig. 4** **a** c-Kit stains the interstitial cells, **b** ALK-1 is negative, **c** IgG4 stains the majority of the plasma cells in the field, **d** SMA stains the smooth muscle in the vessel walls.

Despite the first description of solid organ involvement with autoimmune disorders over 50 years ago, the precise pathogenesis and pathophysiology of autoimmune disorders-associated dysfunction remains unclear. Autoimmune disorders vary in clinical presentation based on the organ system involved and present with a wide spectrum of radiologic features with characteristic imaging seen only in a minority of cases. Hence, diagnosis is most accurately made through pathologic evaluation, with unique histologic features consistent with abundant IgG4-positive cells[7].

In the majority of patients with autoimmune disorders, there are increased serum levels of IgG4, but this is not specific to any particular organ system[5,9–11]. In fact, elevated levels of serum IgG4 have been observed in other disorders such as asthma and atopic dermatitis[8,9]. The lack of specificity of serum IgG4 only adds to the difficulty in establishing the preoperative diagnosis of autoimmune disorders. Since autoimmune disorders have been shown to mimic malignancy in organ systems both clinically and radiographically, it is not surprising that patients with autoimmune disorders are still commonly offered aggressive treatment options, including resection. It is important to try to make the diagnosis prior to attempted surgery because it has been shown that autoimmune disorders may respond to conservative management including the use of steroids, resulting in decreased inflammatory pseudotumor effect. Thus, it is imperative that there is accurate detection of the autoimmune disorders process in order to avoid surgery and spare the patient the loss of function, morbidity, and possible mortality that comes with surgical resection.

This is the first reported case of a patient with autoimmune esophagitis secondary to IgG4 that resulted in a pseudotumor causing symptomatic dysphagia and esophageal stricture. This presentation is unique, in that patients with esophageal manifestation of their autoimmune disease rarely present with an esophageal mass resulting in strictures. Furthermore, patients plagued with esophageal manifestations of their connective tissue disorder often present with a wide range of symptoms unlike those described in our case presentation[12]. Patients with systemic lupus erythematosus may present with esophageal dysmotility as seen on manometry, as well as reflux esophagitis secondary to decreased lower esophageal sphincter tone[13]. Scleroderma, on the other hand, affects the lower esophageal sphincter which will eventually lead to lower esophageal strictures but does not have any associated esophageal masses[1]. Sjogrens syndrome can lead to achalasia-like symptoms and upper esophageal webs[14]. Hence, esophageal manifestations of autoimmune disorders are most commonly ulcerations, erosions or dysmotility—not necessarily inflammatory pseudotumors[1].

## Conclusions

IgG4-related organ dysfunction is an inflammatory condition that frequently mimics malignancy. We present the first reported case of isolated esophageal involvement secondary to IgG4 plasma cell infiltration. Preoperative diagnosis remains difficult in this disease and is best done through biopsy and histologic analysis. A high index of suspicion is necessary to accurately make the diagnosis prior to resection. It is anticipated that as our experience with serum IgG4 testing and knowledge of the systemic nature of autoimmune disorders increases, patients with autoimmune disease with organ anomalies will be diagnosed promptly and be spared potentially unnecessary surgery.

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