

Immunoglobulin G4-related gastrointestinal diseases, are they immunoglobulin G4-related diseases?

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Abstract

In immunoglobulin G4 (IgG4)-related disease (RD), organ enlargement or nodular lesions consisting of abundant infiltration of lymphocytes and IgG4-positive plasma cells and fibrosis are seen in various organs. Although infiltration of many IgG4-positive plasma cells is detected in the gastric and colonic mucosa and major duodenal papilla of patients with autoimmune pancreatitis, it cannot be diagnosed as a gastrointestinal lesion involved in IgG4-RD, because none of the following is observed in these lesions: a mass-like formation; dense fibrosis; or obliterative phlebitis. Based on our review of the literature, there appear to be two types of IgG4-

related gastrointestinal disease. One is a gastrointestinal lesion showing marked thickening of the wall of the esophagus and stomach, consisting of dense fibrosis with abundant infiltration of IgG4-positive plasma cells, which usually show submucosal spreading. The other is an IgG4-related pseudotumor occurring in gastrointestinal regions such as the stomach, colon, and major duodenal papilla, showing polypoid or mass-like lesions. Most solitary IgG4-related gastrointestinal lesions that are not associated with other IgG4-RD appear to be difficult to diagnose. It is of utmost importance to rule out malignancy. However, these lesions may respond to steroid therapy. To avoid unnecessary resection, IgG4-related gastrointestinal diseases should be considered in the differential diagnosis.

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Key words: Immunoglobulin G4; Autoimmune pancreatitis; Gastritis; Colonic polyp; Ulcerative colitis

Core tip: Although the concept of immunoglobulin G4 (IgG4)-related gastrointestinal disease remains unclear, there appear to be two types of IgG4-related gastrointestinal disease. One is a gastrointestinal lesion showing marked thickening of the wall of the esophagus and stomach, consisting of dense fibrosis with abundant infiltration of IgG4-positive plasma cells, which usually show submucosal spreading. The other is an IgG4-related pseudotumor occurring in gastrointestinal regions such as the stomach, colon, and major duodenal papilla, showing polypoid or mass-like lesions. It is of utmost importance to rule out malignancy. To avoid unnecessary resection, IgG4-related gastrointestinal diseases should be considered in the differential diagnosis.

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INTRODUCTION

Immunoglobulin G4 (IgG4)-related disease (RD) is a recently recognized systemic condition characterized by elevated serum IgG4 levels and steroid responsiveness. IgG4-RD shows organ enlargement or nodular lesions consisting of abundant infiltration of lymphocytes and IgG4-positive plasma cells and fibrosis. IgG4-RD affects various organs such as the pancreas, bile duct, gallbladder, liver, salivary gland, lacrimal gland, retroperitoneum, and lymph nodes simultaneously or metachronously. IgG4-RD frequently presents both clinically and radiologically with findings that mimic a malignancy, resulting in unnecessary resection^[1-4]. According to comprehensive clinical diagnostic criteria for IgG4-RD^[4], IgG4-RD is diagnosed when there is a characteristic diffuse/localized swelling or mass in a single or multiple organs with elevated serum IgG4 levels, or there are histological findings of abundant infiltration of IgG4-positive plasma cells and lymphocytes, along with fibrosis.

Autoimmune pancreatitis (AIP) is a typical lesion of IgG4-RD, and the concept of IgG4-RD was proposed based on research on AIP^[1,2]. Although it has been reported that infiltration of many IgG4-positive plasma cells was observed in the gastric mucosa, colonic mucosa, and major duodenal papillae of some AIP patients^[5-10], it is questionable whether they are the lesions involved in IgG4-RD. To clarify IgG4-related gastrointestinal disease, this article reviews the published literature about the relationships between IgG4 and gastrointestinal diseases such as esophagitis, gastritis, colitis, and duodenal papillitis with abundant infiltration of IgG4-positive plasma cells. A PubMed database search, from 1990 to April, 2013, using the terms “autoimmune pancreatitis or IgG4-related” and “esophagus, duodenum, papilla, colon” identified 116 papers. Additional sources were identified by scanning the bibliographies of original and review articles.

IGG4-RELATED ESOPHAGEAL LESIONS

There have been two case reports of IgG4-related esophagitis^[11,12]. In both cases, esophageal stricture with thickening of the esophageal wall evoked debilitating dysphagia and weight loss. Endoscopy showed esophageal stricture without a cancerous lesion. With a diagnosis of gastrointestinal stromal tumor based on endoscopic ultrasound-guided fine needle aspiration (one case) and because of concerns regarding a hidden malignancy (one case), esophageal resection was performed in both patients. On gross examination, the resected specimens showed an esophageal submucosal stricture with mucosal

ulceration and wall thickening; histologically, they showed transmural chronic fibrotic inflammation with abundant infiltration of IgG4-positive plasma cells and lymphocytes and phlebitis. There was no evidence of other IgG4-RD. The post-operative serum IgG4 level was 138 mg/dL in one case. Both lesions are considered esophageal manifestations of IgG4-RD and should be called IgG4-related esophagitis. These lesions would probably respond to steroid therapy. Thus, IgG4-related esophagitis should be kept in mind in the differential diagnosis of unexplained esophagitis with stricture.

IGG4-RELATED GASTRIC LESIONS

It has been reported that infiltration of many IgG4-positive plasma cells was observed in the gastric mucosa in 33%-47% of AIP patients^[10,13]. Shinji *et al*^[14] and Uehara *et al*^[15] also reported that IgG4-positive plasma cells were significantly more abundant in the gastric mucosa of AIP patients. Most of the infiltrated IgG4-positive plasma cells in the gastric mucosa disappeared in the biopsy specimen from the gastric mucosa after steroid therapy^[16]. However, neither dense fibrosis nor obliterative phlebitis was observed in the gastric mucosa of AIP patients. Baez *et al*^[17] reported a patient with AIP and IgG4-related sialadenitis who showed diffusely thickened (up to 1.4 cm) and nodular gastric mucosa with abundant infiltration of IgG4-positive plasma cells. The patient's serum IgG4 level was within the normal range (58 mg/dL), but the gastric lesion improved after steroid therapy. Kaji *et al*^[18] reported an AIP patient (IgG4 level, 595 mg/dL) with multiple sporadic polyps in the gastric body with erosion and redness on the surface containing many infiltrated IgG4-positive plasma cells. On the other hand, two 3-cm-sized submucosal tumors that were laparoscopically wedge-resected showed histological findings of storiform fibrosis with abundant infiltration of lymphocytes and IgG4-positive cells (> 50/hpf), and they were reported as IgG4-related inflammatory pseudotumor of the stomach^[19]. Both cases showed normal serum IgG4 levels and no evidence of other IgG4-RD^[19]. Rollins *et al*^[20] also reported a laparoscopically resected 5.6-cm IgG4-related fibrosclerosing pseudotumor of the stomach. Three cases with well-circumscribed, sclerosing nodular lesions of the stomach composed of fibrous tissue with abundant infiltration of IgG4-positive plasma cells were reported, and they were not associated with other IgG4-RD^[21,22]. Fujita *et al*^[23] reported a case with refractory gastric ulcers that worsened after successful *Helicobacter pylori* eradication therapy. The biopsy specimens taken from the ulcers showed abundant infiltration of IgG4-positive plasma cells (50/hpf). The patient's serum IgG4 level was elevated to 203 mg/dL, but he had no other IgG4-RD.

Bateman *et al*^[24] reported a case of intractable gastric ulcer showing storiform fibrosis and abundant infiltration of IgG4-positive plasma cells (> 100/hpf). These reported lesions are considered IgG4-related gastric lesions. Anjiki *et al*^[25] reported that gastric emptying assessed by

the carbon 13 acetate breath test was impaired in AIP patients and improved to the reference range after steroid therapy, and they suggested that the stomach might be a target organ of IgG4-RD.

IGG4-RELATED MAJOR DUODENAL PAPILLARY LESIONS

It has been reported that the duodenal major papilla is swollen in 41%-65% of AIP patients^[26-28]. Abundant infiltration of IgG4-positive plasma cells is reportedly detected in 55%-80% of AIP patients^[8,10,26,27]. Both a swollen major papilla and abundant infiltration of IgG4-positive plasma cells have shown improvement after steroid therapy^[8,29]. In the resected pancreas of AIP patients, lymphoplasmacytic inflammation with many IgG4-positive plasma cells was detected in the major duodenal papilla connected to the head of the pancreas; thus, IgG4 immunostaining of biopsy specimens obtained from the major duodenal papilla might be useful to support the diagnosis of AIP^[8,26,27,30,31]. Hisa *et al.*^[32] reported a resected case of a lymphoplasmacytic granuloma with abundant IgG4-positive plasma cells localized to the major duodenal papilla. The case was not associated with other IgG4-RD. This lesion is considered to be an IgG4-related pseudotumor localized to the major duodenal papilla.

IGG4-RELATED COLONIC LESIONS

Although infiltration of many IgG4-positive plasma cells is occasionally detected in the colonic mucosa of AIP patients, dense fibrosis or obliterative phlebitis was not observed in the lesion^[1,5-7,21,33]. Although Ravi *et al.*^[34] suggested that inflammatory bowel disease might represent an extrapancreatic manifestation of AIP, in general, conventional AIP (type 1 AI) is rarely associated with ulcerative colitis (UC)^[2,35]. IgG4-positive plasma cell infiltration is sometimes detected in the colonic mucosa of UC patients^[36-40], but the mechanisms underlying IgG4-positive plasma cell infiltration in the colonic mucosa of UC patients are unknown. Matsui *et al.*^[41] reported a case of an AIP patient with a colonic polyp (ascending colon) containing many IgG4-positive plasma cells^[42] who developed colonic polyposis (descending colon) containing many IgG4-positive plasma cells 1 year after complete remission of AIP with steroid therapy. The polyposis was markedly reduced with re-administration of steroids. They suggested that enhanced T helper type 2 responses to intestinal microflora may underlie the immunopathogenesis in patients with IgG4-RD^[43]. Well-circumscribed sclerosing nodular lesions of the cecum and sigmoid colon composed of hyalinized fibrocollagenous tissue with abundant infiltration of IgG4-positive plasma cells were reported, and the two cases had no other IgG4-RD^[21]. These polypoid or nodular lesions appear to be IgG4-related colonic lesions.

IGG4-RELATED INFLAMMATORY PSEUDOTUMOR OF AN ILEAL CONDUIT

An ill-defined, fibrotic, tumor-like mass, histologically showing fibrosis with infiltration of lymphocytes and IgG4-positive plasma cells and marked obliterative phlebitis, occurred in an ileal conduit created as part of surgery for urinary bladder cancer^[44].

DISCUSSION

IgG4-RD shows organ enlargement or nodular lesions consisting of abundant infiltration of lymphocytes and IgG4-positive plasma cells and fibrosis in various organs simultaneously or metachronously^[3,4]. The first International Symposium on IgG4-RD held in 2011 suggested that the term "IgG4-related disease" aptly recognizes the ubiquity of IgG4 within involved organs, and proposes a style that employs "IgG4-related" as a prefix to the organ system affected and pathological guidelines for the diagnosis of IgG4-RD^[3,45]. The diagnosis of IgG4-RD rests on the combined presence of the characteristic histopathological appearances and increased number of IgG4-positive plasma cells. A histologically high suspicion of IgG4-RD requires the presence of at least two of three characteristic histological features including (1) dense lymphoplasmacytic infiltration; (2) fibrosis, usually storiform in character; and (3) obliterative phlebitis. The IgG4 counts required for the diagnosis differ among affected organs, ranging from 10 to 200 cells/hpf. The diagnosis of IgG4-RD requires considering both histopathological findings and clinical information such as elevated serum IgG4 levels, other organ involvement that is consistent with IgG4-RD, and effective response to steroid therapy^[45].

Comprehensive clinical diagnostic criteria for IgG4-RD^[4] were proposed in 2011. In the criteria, IgG4-RD is diagnosed when there is a characteristic diffuse/localized swelling or mass in a single or multiple organs with elevation of serum IgG4 levels or IgG4-related histological findings. However, the concept of IgG4-related gastrointestinal diseases was not included as objects of the criteria. It is unclear whether IgG4-related gastrointestinal diseases exist or what gastrointestinal lesions are regarded as IgG4-RD. To clarify these questions, this review of IgG4-related gastrointestinal diseases, the first of its kind, was conducted.

Infiltration of many IgG4-positive plasma cells is detected in the gastric and colonic mucosa and the major duodenal papillae of some AIP patients, but none of the following are observed in these lesions: a mass-like formation; dense fibrosis; or obliterative phlebitis^[5-10]. They cannot be diagnosed as gastrointestinal lesions involved in IgG4-RD, because, as in many other organ systems, increased IgG4-positive plasma cells do not mean the disease is one of the family members of IgG4-RD. At this point, both the clinical finding of mass forming and histological finding of abundant infiltration of IgG4-

positive plasma cells with fibrosis would appear to be necessary to make the diagnosis of IgG4-related gastrointestinal diseases.

IgG4-related pseudotumors have been reported in several organs, such as the liver and lung^[46-48]. On review of these papers, there appear to be two types of IgG4-related gastrointestinal disease. One is a gastrointestinal lesion showing marked thickening of the wall of the esophagus^[11,12] and stomach^[17,23,24], consisting of dense fibrosis with abundant infiltration of IgG4-positive plasma cells, which usually show submucosal spreading. The other is an IgG4-related pseudotumor occurring in gastrointestinal regions such as the stomach^[18-22], colon^[21,42], and major duodenal papilla^[52], showing polypoid or mass-like lesions. We currently consider these lesions to be IgG4-related gastrointestinal diseases. However, this is the first review of a few cases of IgG4-related gastrointestinal diseases; further studies should be conducted to confirm this concept.

Most solitary IgG4-related gastrointestinal lesions that are not associated with other IgG4-RD appear to be difficult to diagnose. It is of utmost importance to rule out malignancy. However, these lesions may respond to steroid therapy. To avoid unnecessary resection, IgG4-related gastrointestinal diseases should be considered in the differential diagnosis.

CONCLUSION

The concept of IgG4-related gastrointestinal disease remains unclear due to its rarity. There appear to be some IgG4-related gastrointestinal lesions that present with a mass-like lesion consisting of abundant infiltration of IgG4-positive plasma cells and lymphocytes and fibrosis.

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