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Gastrointestinal IgG4 Related Disease: Report of a Case and Review of Literature

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Abstract

Immunoglobulin G4-related disease is an immune mediated systemic inflammatory condition of unknown etiology. The disease was first described by Yoshida et al [1]. The disease affects skin, orbit, salivary glands, thyroid, pancreas, liver, kidney, gastrointestinal tract, retroperitoneum and lymph nodes [2]. Although IgG4 related disease affects wide range of organs and its manifestation often varies, many aspects suggest a single cohesive entity – tumefactive lesions, that mimic malignancy, synchronous or metachronous involvement of a relatively constant group of organs, elevated serum IgG4 levels, a characteristic histologic appearance, elevated number of IgG4 positive plasma cells and elevated IgG4/IgG ratio. The characteristic histologic appearance and morphology remains gold standard for the diagnosis of IgG4 related disease.

Keywords: IgG4 related disease, GastroIntestinal IgG4, Serum IgG4

Introduction

IgG4 related disease is a multisystem, mass-forming, inflammatory disorder that often mimics a neoplasm [3]. IgG4 related disease has been misclassified and is sometimes dismissed as a nonspecific inflammatory infiltrate [4]. The Disease seems diverse as autoimmune pancreatitis, sclerosing cholangitis, retroperitoneal fibrosis and inflammatory pseudotumor are now thought to belong to IgG4 related disease spectrum. The disease often affects the pancreatobiliary system, and although the involvement of tubular gut has been documented, clinically significant disease at this site is uncommon.

Here We Report A Case Of Gastrointestinal Igg4 Related Disease.

Case Report

A 63-year-old male patient presented with complaints of recurrent episodes of abdominal pain for the past 15 years. The pain was periumbilical with visible intestinal peristalsis. Along with pain he usually had multiple episodes of vomiting and constipation as well. The patient presented in early 2018 with aggravated abdominal pain associated with features of acute intestinal obstruction. CECT Abdomen done showed multiple short segments of bowel wall circumferential thickening involving distal jejunal and ileal loops with increased mesenteric vascularity and intervening normal bowel segments. Features

were suggestive of inflammatory (Crohn's Disease)/ infective etiology.

Small intestinal segmental resection was done on April 2018 with a suspected diagnosis of Crohn's disease. He underwent ileal resection and ileoileal anastomosis. Histopathology report showed no evidence of Crohn's disease. It was reported as non-specific ulcer. From 2018 to 2022 he was repeatedly admitted for similar complaints of acute abdominal pain and vomiting. He was conservatively managed. In 2022 June admission, histopathology slides of 2018 were reviewed. The diagnosis of IgG4 related disease was suspected. IgG4 IHC were done on the sections of 2018 slides and serum IgG4 was advised. The blocks and slides were reviewed at CMC Vellore by Dr Anna B Pulimood who also agreed to the diagnosis.

Resected specimen showed lymphoplasmacytic infiltrate and marked increase in IgG4 positive cells. IgG4 IHC showed 38 % in hot areas. IgG4 for five high power areas showed >38% . Serum IgG4 was not raised. It was later suspected to be IgG4 related disease. The patient was sent for further management.

He was started on prednisolone 40 mg/ day. Patient improved and there has been no acute episodes of subacute intestinal obstruction since then and is on regular follow up in our medical gastroenterology department. In November 2022 he was started on Azathioprine along with low dose steroids. Presently he is on Azathioprine 100mg with steroids 10 /5mg OD on alternate days. Currently he is symptom free. It is planned to bring down the dose of steroids to 5mg daily

Features of chronic jejunitis with lymphoplasmacytic infiltrate, fibrosis and marked increase in IgG4 positive cells were seen. The changes are those of IgG4 disease. IHC done for IgG to estimate the percentage of IgG positive cells that are also IgG4 positive to help confirm the diagnosis.

FIG.1,2 Jejunal mucosa with ulceration, broadening and blunting of villi, inflammatory granulation tissue

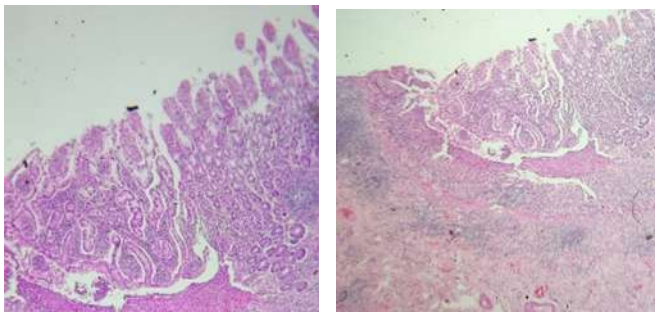

FIG.3 Lamina propria with infiltration by plasma cells, lymphocytes, neutrophils and eosinophils

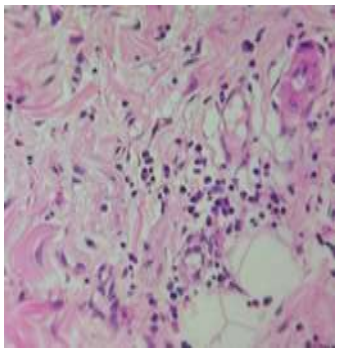

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FIG.4 Submucosa with extensive fibrosis, veins with fibrosis of walls

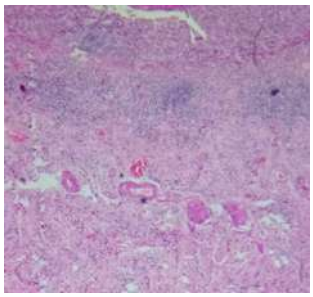
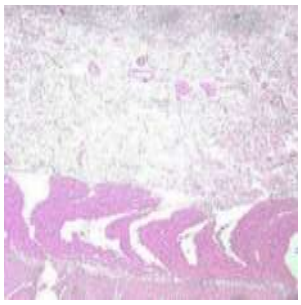


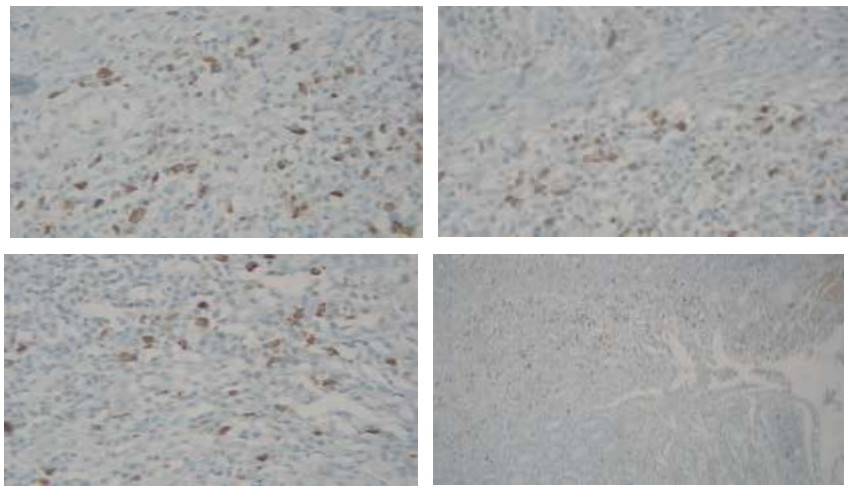
FIG.5 Muscularis propria showing focal mild lymphoplasmacytic infiltration



Other sections from the jejunal wall showed ulceration lined by inflammatory granulation tissue and acute inflammatory exudate. The adjacent mucosa showed broadening and blunting of villi with crypt hyperplasia (FIG.1,2). The inflammatory granulation tissue and lamina propria show moderate infiltrate of plasma cells, lymphocytes, neutrophils and eosinophils (FIG.3). The submucosa showed extensive fibrosis, but no definite storiform appearance. Veins in the submucosa show fibrosis of the walls (FIG.4), but definite evidence of obliterative phlebitis was not seen. The muscularis propria and submucosa showed focal mild infiltrate of plasma cells and lymphocytes (FIG.5). Immunohistochemistry showed increase in IgG4 positive cells (FIG.6).

Immunohistochemistry

FIG.6 IHC showing IgG4postive cells, 38% in hot areas



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Discussion

IgG4-related conditions affecting the digestive tract are part of a multi-organ fibro-inflammatory disorder termed IgG4-related disease (IgG4-RD), with autoimmune pancreatitis and IgG4-related cholangitis being the most prominent manifestations. Gastrointestinal symptoms include jaundice, weight loss, abdominal pain, biliary strictures, and pancreatic and hepatic masses that mimic malignant diseases. IgG4-RD manifestations occur less frequently elsewhere in the digestive tract, namely in the oesophagus, retroperitoneum or intestine. Evidence-based European guidelines frame the diagnosis and management of IgG4-related digestive tract disease. Diagnosis is based on histology (if available), imaging, serology, other organ involvement and response to therapy (HISORt criteria). Few biomarkers beyond serum IgG4 concentrations are reliable.

IgG4 –related disease of the tubular gut

Although elevated numbers of IgG4 –positive plasma cells are detected in mucosal biopsies of patients with IgG4 –related disease, involvement is not usually clinically apparent [5].

Stomach

IgG4- related gastropathy has been described only in the context of autoimmune pancreatitis [6]. The endoscopic features are non-specific. The corpus and antral mucosa have diffuse transmucosal lymphoplasmacytic infiltrate. IgG4 related gastropathy may resemble autoimmune gastritis, the antrum is usually not spared.

Ampulla

A biopsy from ampullary region may help in differentiating IgG4 related sclerosing cholangitis from primary sclerosing cholangitis [7].

Small bowel and colon

Involvement of the lower gut is extremely uncommon. The isolated finding of elevated numbers of IgG4 positive plasma cells at these locations are more likely to represent a type-2 helper T- cell dominant immunologic response than IgG4 related disease [8].

IgG4 related cholecystitis

Gallbladder involvement by IgG4-related disease is typically asymptomatic. There is transmural inflammatory infiltrate with significant involvement of subserosal tissue, which forms circumscribed inflammatory nodules [9].

Non-IgG4-related disease

Other entities associated with elevated number of IgG4 positive plasma cells include rheumatoid arthritis and Wegener granulomatosis. In the GI tract, IgG4 positive plasma cells are consistently detected in autoimmune gastritis and inflammatory bowel disease. A mere increase in IgG4 positive cells without characteristic histological features does not constitute evidence of IgG4-related disease [10].

IgG4-Related disease of Retroperitoneum and mesentery

Retroperitoneal fibrosis is the prototypic manifestations of IgG4-related disease [11].

Nodal manifestations of IgG4-related disease

Lymphadenopathy is a common occurrence in IgG4-related disease. Lymph nodes around the affected organ are often enlarged. This is characterized by an increase in IgG4-postive plasma cells (> 100/HPF) and IgG4/IgG ratio (>40%) [12].

The first-line therapy (glucocorticoids) is swiftly effective but disease flares are common at low doses or after tapering. Second-line therapy might consist of other immunosuppressive drugs such as thiopurines or rituximab. Further trials, for example, of anti-CD19 drugs, are ongoing. Although an association between IgG4-RD and the development of malignancies has been postulated, the true nature of this relationship remains uncertain at this time.

Conclusion

This case report shows Gastrointestinal IgG4-related disease often mimicking malignancy and is difficult to diagnose clinically. This entity should be included in the differential diagnosis when marked wall thickening or a lesion resembling a pseudotumor is detected in the GI Tract. Surgical resection is necessary in suspected fibrosis or GI obstruction mimicking these conditions. A multidisciplinary approach is required for diagnosis.

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