

IgG4-positive Plasma Cell Infiltration in the Setting of Ulcerative Colitis

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ABSTRACT

AIM: IgG4 has gained medical attention due to its role in IgG4-related sclerosing disease. Among these, autoimmune pancreatitis (AIP) and sclerosing cholangitis have been well documented. Several reports describe an association between IBD and chronic pancreatitis. Primary sclerosing cholangitis (PSC) also has an established association with IBD, particularly ulcerative colitis (UC). Because of the aforementioned association between UC and sclerosing diseases, further studies are in need to establish the presence and significance of IgG4 plasma cells in UC.

METHOD: Herein, we evaluate the significance of IgG4-positive plasma cells in 54 colonic biopsies of UC patients. The medical records were reviewed for demographic and clinical data including: the course of UC, the presence of any biliary symptoms or diagnosis of PSC, liver enzymes, IgG4-related disease and IgG4 serum levels. IgG4 positive plasma cells were recorded and categorized as follows: no=0, rare=1-2, few=3-9, many=10 or more.

RESULTS: Four cases had many IgG4 positive plasma cells, two

of which had refractory UC course. Seven UC patients had elevated liver enzymes. Two of the 54 patients had primary sclerosing cholangitis. These patients had IgG4 labeling of none and rare.

CONCLUSION: In colonic biopsies of UC patients, and a subset with PSC, significant IgG4 plasma cell populations were not detected by immunohistochemistry. In a subset of UC patients with many IgG4 positive plasma cells a more severe clinical course was noted. Further studies are required to explore the significance of IgG4 in UC.

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Key words: IgG4; Ulcerative colitis; Sclerosing cholangitis

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INTRODUCTION

Although normal function is not fully known, IgG4 has been shown to play a significant role in allergic reactions, such as atopic eczema, bronchial asthma, and bullous skin lesions, and has recently gained medical attention due to its role in IgG4-related sclerosing disease^[1]. Among these, autoimmune pancreatitis (AIP) has been well characterized and subclassified based on the presence of the IgG4-positive plasma cells^[2]. This unique subgroup, characterized by lymphoplasmacytic infiltrate and sclerosing process, differs clinically, pathologically, and, unlike the other form, responds to steroid therapy^[3]. Increased levels of IgG4-positive plasma cells have been identified in patients with other idiopathic-sclerosing diseases of many sites of involvement including, but not limited to, the hepatobiliary system, retroperitoneum, mesentery, mediastinum, salivary glands and lungs^[4]. Some of the studies regarding AIP have shown a significant increase in incidence of inflammatory bowel disease (IBD) in patients with AIP^[5]. Well-documented clinical case reports describe an association between IBD and chronic pancreatitis^[6-10]. Primary sclerosing cholangitis (PSC) is a chronic progressive inflammatory process with fibrosis and narrowing of the medium and large caliber hepatobiliary ducts. PSC has an

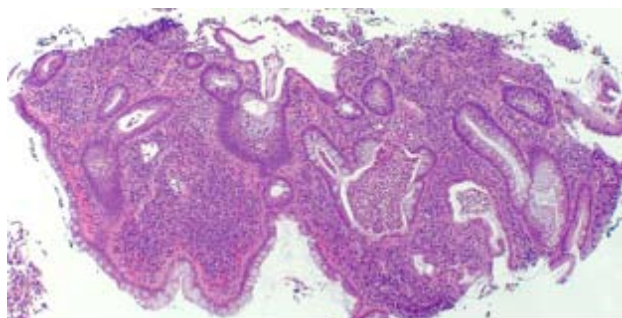


Figure 1 H&E stain at low power (40 ×) magnification showing chronic active colitis in the form of cryptitis and crypt abscesses.

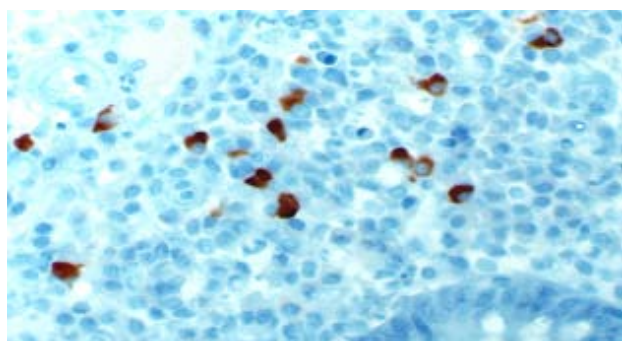


Figure 2 IgG4 immunohistochemical stain at (400 ×) magnification showing many plasma cells with cytoplasmic positivity.

established association with IBD, particularly ulcerative colitis (UC). At least 75% of PSC patients have coexisting UC, however, only 5% of UC patients develop PSC^[11]. One of the many forms of IgG4 sclerosing diseases is sclerosing cholangitis, an entity similar to PSC with few differences^[12]. Because of the aforementioned association between UC and sclerosing diseases, namely PSC and AIP, further studies are in need to establish the possible role of IgG4 plasma cells in UC.

Herein, we evaluate the presence and the significance of IgG4-positive plasma cells in 54 colonic biopsies of patients with established diagnosis of ulcerative colitis.

METHODS

The study was approved by the institutional review board at Mount Sinai Medical Center. A CPATH database was searched for colonic biopsies in patients with an established diagnosis of ulcerative colitis exhibiting chronic active colitis. Fifty-four cases were identified. Two concurring pathologists reviewed the H & E slides of the biopsies retrospectively. These cases were selected based on the presence of chronic active colitis. The criterion for activity was the presence of neutrophilic infiltration of the epithelium with cryptitis or crypt abscesses and chronicity was defined by architectural distortion and increased plasma cells in the lamina propria (Figure 1). Ten biopsy samples of normal colonic mucosa were selected for use as controls.

The medical records of the patients were reviewed for demographic and clinical data including: the onset and duration of UC, the presence of any biliary symptoms or diagnosis of PSC, abnormal liver enzymes (AST/ALT/protein/albumin/total bilirubin/direct bilirubin/alkaline phosphatase), IgG4-related disease and IgG4 serum levels.

The paraffin blocks of the 54 cases were available. Re-cut sections were immunostained utilizing monoclonal IgG4 antibody

Table 1 Demographic and clinical data.

Male	29	53.70%
Female	25	46.30%
Age (years)	22-85 (mean: 54)	
Duration of the disease (years)	1-32 (mean: 12)	
	Elevated Liver function tests	Primary Sclerosing cholangitis
YES	7 (12.96%)	2 (3.7%)
NO	47 (87.03%)	52 (96.30%)
Total	54	54
	History of IBD	Control
10 or more IgG4 positive plasma cells	4 (7.41%)	0 (0%)
Less than 10 IgG4 positive plasma cells	50 (92.59%)	10 (100%)
Total	54	10

(MRQ-44, Cell Marque, Rocke, CA) on Ventana Ultraview using standard immunohistochemical techniques. The number of immunohistochemically identified IgG4 – positive plasma cells per high power field (40× HPF) was counted in each specimen. IgG4 positive plasma cells were scored as an average number of the total count of three high power fields (40×, 20 mm field of view ocular). The average IgG4 positive cell counts were recorded and categorized as follows: no=0, rare=1-2, few=3-9, many=10 or more.

RESULTS

The mean age of our patient population was 55 years with slight male predominance (male 54%, female 46%). The mean duration of the disease was 13 years. Among the cases, thirty-four of the biopsies of UC showed no to rare IgG4 positive plasma cell labeling. Sixteen UC cases had few IgG4 positive plasma cells. Four cases had many IgG4 positive plasma cells (Figure 2). The 10 control normal colonic biopsies showed none to rare IgG4 positive plasma cells.

Seven UC patients (13%) had elevated liver enzymes. Of these, six had elevated AST, three had elevated ALT, five had elevated direct bilirubin, and three showed elevated alkaline phosphatase. One patient with elevated AST, ALT, direct bilirubin had 10 IgG4 positive plasma cells; however, this patient did not have evidence of PSC and the information about his clinical course was limited. The other patients with elevated liver enzymes had none to few IgG4 labeling. Two of the four patients with 10 or more IgG4 labeling had refractory UC course.

Two of the 54 patients (4%) had primary sclerosing cholangitis. These patients had IgG4 labeling of none and rare (2 IgG4 positive plasma cells on average), respectively. Of the remaining patients, none had biliary symptoms. No serum IgG4 levels were measured.

DISCUSSION

IgG4-related sclerosing disease is a relatively recently described clinical entity of unknown etiology with male predilection which generally responds well to steroids. While many organs can be involved, the most well characterized form of IgG4-sclerosing diseases is autoimmune pancreatitis^[4]. Another form of IgG4-sclerosing disease is IgG4-related sclerosing cholangitis, an entity that differs from PSC in that patients with IgG4-related sclerosing cholangitis are older at diagnosis and they present more abruptly with obstructive jaundice. IgG4 related sclerosing cholangitis has known association with autoimmune pancreatitis and other complex autoimmune IgG4 syndromes, but the association with IBD has not been fully explored in the literature. Histologically, IgG4 sclerosing

cholangitis has similar features to PSC but differs in that the biliary epithelium is usually intact, while PSC shows mucosal erosions. In addition, neutrophilic infiltrates of the biliary epithelium, commonly seen in PSC, are generally not a feature of IgG4 sclerosing cholangitis. Immunohistochemically, abundant IgG4-positive plasma cells are detected in the bile ducts, in contrast to PSC^[4,12]. In recent series of cases of PSC, elevated IgG4 levels were found in 9% of patients. This group also had significantly lower frequency of IBD, with only 50% of patients with elevated IgG4 showing history of IBD compared to 85% with normal IgG4 levels^[13]. In a recent study, Ravi *et al* concluded that approximately 6% of patients with proven AIP carried a diagnosis of IBD (Crohn's Disease or Ulcerative Colitis), compared to a prevalence of 0.4-0.5% in the general population. The same study showed that patients with both AIP and IBD had a more severe clinical course of IBD^[5].

In our cohort of 54 patients, four (7%) had significant IgG4 labeling of 10 or more per high power field; however, none of these had biliary disease. Of interest, half of the patients with 10 or more IgG4 labeling had a refractory UC course. The two patients with both UC and PSC in our cohort showed no significant IgG4 positive plasma cell populations (none to rare per high power field) in their colonic biopsies.

CONCLUSION

In colonic biopsies in patients with UC, and a subset with PSC, significant IgG4 plasma cell populations were not detected by immunohistochemistry. In a subset of UC patients with many IgG4 positive plasma cells a more severe clinical course was noted. Further studies are required to explore the role and possible clinical significance of IgG4 in patients with UC.

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