ORIGINAL ARTICLE

Gut and Liver, Vol. 8, No. 1, January 2014, pp. 29-34

Ulcerative Colitis and Immunoglobulin G4

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Background/Aims: Ulcerative colitis (UC) is sometimes associated with autoimmune pancreatitis (AIP). Infiltration of immunoglobulin G4 (IgG4)-positive plasma cells is sometimes detected in the colonic mucosa of AIP or UC patients. This study aimed to clarify the relation between UC and IgG4. **Methods:** Associations with UC were reviewed in 85 AIP patients. IgG4 immunostaining was performed on biopsy specimens from the colonic mucosa of 14 AIP and 32 UC patients. **Results:** UC was confirmed in two cases (type 1 AIP, n=1; suspected type 2 AIP, n=1). Abundant infiltration of IgG4-positive plasma cells in the colonic mucosa was detected in the case of suspected type 2 AIP with UC and two cases of type 1 AIP without colitis. Abundant infiltration of IgG4-positive plasma cells was detected in 10 UC cases (IgG4-present, 31%). Although 72% of IgG4-absent UC patients showed mild disease activity, 70% of IgG4-present patients showed moderate to severe disease activity (p<0.05). **Conclusions:** UC is sometimes associated with AIP, but it seems that UC is not a manifestation of IgG4-related disease. Infiltration of IgG4-positive plasma cells is sometimes detectable in the colonic mucosa of UC patients and is associated with disease activity. **(Gut Liver 2014;8:29-34)**

Key Words: Colitis, ulcerative; Immunoglobulin G; Autoimmune pancreatitis

INTRODUCTION

Autoimmune pancreatitis (AIP) is a peculiar type of pancreatitis with a presumed autoimmune etiology, and was first proposed in 1995.[1] The AIP is characterized clinically by predominantly affecting elderly individuals and men, radiologically by enlargement of the pancreas and irregular narrowing of the main pancreatic duct, and serologically by elevated serum immunoglobulin G4 (IgG4) levels.[2,3] Histology of the AIP is characterized by abundant infiltration of IgG4-positive plasma cells and lymphocytes, dense fibrosis, and obliterative phlebitis in the pancreas and is called lymphoplasmacytic sclerosing pancreatitis (LPSP).[2,3] This entity is associated with extrapancreatic lesions showing histological features quite similar to those of the pancreas, and is currently considered as a pancreatic manifestation of IgG4-related systemic disease.[3] Various organs are involved in IgG4-related disease, such as IgG4-related sialadenitis, IgG4-related dacryoadenitis, and IgG4-related retroperitoneal fibrosis.[3,4] Evidence suggests another type of AIP, which has been designed idiopathic duct-centric chronic pancreatitis (IDCP) and is histologically characterized by granulocytic epithelial lesions.[5,6] IDCP shows a different clinical profile to LPSP, with typical patients more than a decade younger and less likely to show elevated serum IgG4 levels.[5-7] Recently, LPSP has been called type 1 AIP, and IDCP has been called type 2 AIP.[8] Unlike type 1 AIP, type 2 AIP is rarely associated sclerosing diseases containing abundant IgG4-positive plasma cells, but is more likely to occur concomitant with acute pancreatitis and ulcerative colitis (UC).[5-8] Although infiltration of many IgG4-positive plasma cells is occasionally detected in the colonic mucosa of AIP patients,[9,10] whether UC may represent an extrapancreatic lesion of AIP is unknown. Although the prevalence of inflammatory bowel disease (IBD) in the general population is estimated to be 0.4% to 0.5%, Ravi *et al*.[11] reported that 5.6% of patients in a cohort of 71 patients with AIP carried a diagnosis of IBD. IgG4-positive plasma cell infiltration is also reportedly observed in the colonic mucosa of some patients with UC.[12]

To clarify the relationship between colitis and IgG4, we investigated the presence of IBD in AIP patients and examined the distribution of IgG4-positive plasma cells in the colonic mucosa of AIP patients. We also examined the infiltration of IgG4-positive plasma cells in colonic mucosa affected by UC, and investigated the clinical, endoscopic, and histological features.

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Received on January 8, 2013. Revised on February 20, 2013. Accepted on April 3, 2013. Published online on November 5, 2013.
pISSN 1976-2283 eISSN 2005-1212 http://dx.doi.org/10.5009/gnl.2014.8.1.29

MATERIALS AND METHODS

1. Study design

This study consisted of two parts. The first part examined associations with IBD in a cohort of 85 AIP patients (mean age, 65.0 years; 60 men, 25 women). AIP was diagnosed based on Asian diagnostic criteria for AIP[13] from enlargement of the pancreas (n=85), irregular narrowing of the main pancreatic duct on endoscopic retrograde pancreatography (n=85), elevation of serum IgG4 levels (n=65), histological characteristics of LPSP (n=23), and steroid responsiveness (n=63) from 1992 to 2011. According to international consensus diagnostic criteria for AIP,[14] type 1 AIP was diagnosed in 73 patients and type 2 AIP was suspected in one patient (probable type 2 AIP), but the remaining 11 patients could not be confirmed with type 1 or type 2 AIP. When UC was suspected from clinical symptoms in AIP patients, colonoscopy with biopsy and fecal culture were performed. Fourteen AIP patients (type 1 AIP [n=13] and probable type 2 AIP [n=1]) underwent colonoscopy before initiating steroid therapy, including 11 patients who prospectively underwent colonoscopy with biopsy to examine the colonic mucosa in AIP patients from 2008. IgG4-immunostaining was performed on biopsy specimens taken endoscopically from an average of 2.1 different colonic locations of the patients.

In the second part of the study, participants comprised 32 patients with UC (mean age, 46.7 years; 16 men, 16 women) in whom biopsy specimens were taken endoscopically from colonic mucosa before administration of corticosteroid or immunosuppressant. UC was medically treated using mesalazine and/or steroid, but azathioprine and total colectomy were needed in six patients and one patient, respectively. None presented with pancreatic symptoms or morphological abnormalities on computed tomography and/or ultrasonography. Serum amylase levels were elevated in only one patient. Biopsy specimens were taken from an average of 4.1 different inflammatory colonic locations in each patient. Histological severity was classified according to Matts histological classification.[15] Clinical data such as age, sex, clinical course, endoscopic severity, extent of disease, and disease activity were analyzed. The extent of disease was classified as proctitis, left-sided colitis, or total colitis on the basis of colonoscopic findings. Clinical course was classified as follows: one attack only; relapse-remitting type, in which the attack are limited and separated by varying periods of remission; chronic continuous type, in which the symptoms persist for >6 months from the onset; or acute fulminating type, in which the whole colon and rectum are affected with extensive and deep ulcerations. Endoscopic severity was classified as grade 1 or grade 2 to 3 according to Baron index.[16] Disease activity was classified as mild or moderate-severe according to the classification of Truelove & Witts.[17]

Biopsy specimens from the colonic mucosa of irritable colon syndrome (n=10) and ischemic colitis (n=10) were also immunostained for IgG4. All study protocols were approved by the Institutional Review Board. Informed consent for all invasive modalities was obtained from all patients.

2. Immunohistochemistry

Sections were prepared from formalin-fixed, paraffin-embedded specimens. These sections were stained with routine hematoxylin and eosin. Monoclonal antihuman IgG4 antibody (The Binding Site, Birmingham, UK) was applied to these sections using standard immunohistochemical techniques. Numbers of immunohistochemically identified IgG4-positive plasma cells were counted in a minimum of 5 high power fields (HPFs) in each specimen, and they were averaged. Degree of IgG4-positive plasma cell infiltration was categorized into two groups: IgG4-present, ≥average 10 IgG4-positive plasma cells/HPF; and IgG4-absent, 0 to 9 IgG4-positive plasma cells/HPF).[18]

3. Statistical analysis

Differences between IgG4-present and absent groups were analyzed using Fisher exact test or the Mann-Whitney U test with Bonferroni correction. Numbers of IgG4-positive plasma cells/HPF in specimens from UC patients were compared with those in specimens from patients with irritable colon syndrome, ischemic colitis, and AIP using the Mann-Whitney U test with Bonferroni correction. Numbers of IgG4-positive plasma cells/HPF in specimens from UC patients were compared according to Matts histological classification using the Mann-Whitney U test with Bonferroni correction. In all tests, corrected p-values of less than 0.05 were considered statistically significant.

RESULTS

1. IBDs in AIP patients

A diagnosis of UC was confirmed in two of the 85 AIP patients (2%). One was a 45-year-old man who had suffered from UC presenting as pancolitis since 14 years old and had developed type 1 AIP with diffuse enlargement of the pancreas and elevated serum IgG4 level (180 mg/dL). Both AIP and UC responded well to steroid therapy. Colonoscopy was not performed in our hospital. The other patient was a 32-year-old man who developed both segmental-type AIP of the pancreatic body and tail and UC presenting as pancolitis simultaneously. Initial symptoms were upper abdominal pain and bloody diarrhea, and AIP occurred as acute pancreatitis. Serum IgG4 level was 45 mg/dL. AIP improved after steroid therapy, but UC was progressive despite treatment with mesalazine and corticosteroid therapy. Administration of azathioprine was therefore needed. Type 2 AIP was suspected, but it could not be confirmed histologically on endoscopic ultrasonography-guided fine needle aspiration cytology. However, abundant infiltration of IgG4-positive plasma cells (20/HPF) was detected in the colonic mucosa. Drug-induced pancreatitis was ruled out in both patients.

2. Distribution of IgG4-positive cells in the colonic mucosa of AIP patients

Endoscopically, no specific findings were seen in the 14 AIP patients, with the exception of the one UC patient described above. Abundant IgG4-positive plasma cells infiltration was observed in three patients, comprising the patient with UC and two patients with type 1 AIP appearing as obstructive jaundice. Neither fibrosis nor obliterative phlebitis was observed in either of these cases.

3. Distribution of IgG4-positive cells in the colonic mucosa of UC patients

Abundant infiltration of IgG4-positive plasma cells was detected in 10 UC patients (IgG4-present patients, 31%) (Fig. 1). Number of IgG4-positive plasma cells was not significantly difference in biopsy colonic locations. Abundant infiltration of IgG4-positive plasma cells was observed in no patients with irritable colon syndrome or ischemic colitis. Numbers of IgG4-positive plasma cells/HPF in specimens of colonic mucosa from UC patients (9.3±5.7; range, 0 to 20) were greater than those from patients with irritable colon syndrome (2.3±1.8; range, 0 to 5; $p<0.01$), ischemic colitis (1.5±3.1, range, 0 to 9; $p<0.01$) and AIP (5.5±6.7, range, 0 to 20; $p<0.05$) (Fig. 2).

IgG4-present and IgG4-absent patients showed no significant differences in age, sex, extent of colitis, clinical course, or endoscopic severity. A significant difference was identified in terms of disease activity, with 72% of IgG4-absent UC patients categorized with mild disease activity, and 70% of IgG4-present patients categorized with moderate to severe disease activity ($p<0.05$) (Table 1). More severe inflammation according to histological grading was associated with greater IgG4-positive plasma cell infiltration in colonic mucosa ($p<0.01$) (Table 2). Administration of azathioprine was needed in three IgG4-present patients and three IgG4-absent patients, but one acute-onset UC patient presented with pancolitis showing abundant infiltration of IgG4-positive plasma cells (18/HPF) needing total colectomy due to refractory colitis.

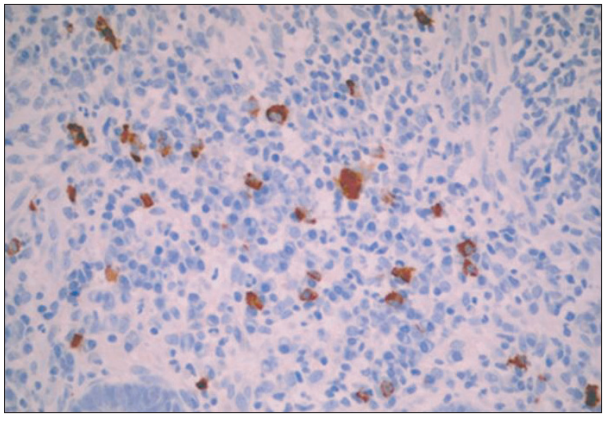

Fig. 1. Abundant infiltration of immunoglobulin G4 (IgG4)-positive plasma cells in the colonic mucosa of a patient with ulcerative colitis (IgG4 immunostaining, ×400).

DISCUSSION

An association between pancreatitis and IBD has been widely accepted in the literature. Although IBD-associated clinical pancreatitis was found in only 2% of patients, this rate might be underestimated since IBD-associated pancreatitis typically appears asymptomatic.[19,20] Autopsy studies of patients with UC have revealed the presence of macroscopic or microscopic pancreatic lesions in 14% to 53% of 86 cases.[21] Pancreatic exocrine deficiency was seen in 4% of IBD patients, while pancreatic duct abnormalities were seen in 8% of patients.[22] Recently, increasing evidence has suggested potential link between AIP and IBD. IBD is frequently associated especially with type 2 AIP.[7,8] Unlike type 1 AIP, which appears to be a pancreatic manifestation of IgG4-related systemic disease, type 2 AIP is usually devoid of IgG4-positive plasma cell and elevated serum IgG4 levels.[7,8] According to an international survey of AIP, UC was present in 10 of 64 patients (16%) with type 2 AIP, while UC was seen in only two of 153 patients (1%) with type 1 AIP.[23] In the United States, UC was associated in two of 50 patients (4%) with type 1 AIP and in three of 10 patients (16%) with type 2 AIP.[8] Type 2 AIP is sometimes detected in Western countries, but is uncommon in Japan and Korea.[23] In Italy, UC occurred in 26 of 87 AIP patients (30%).[23] In the present series of 85 AIP patients, UC was associated in 1 type 1 AIP patient, and in one patient with suspected type 2 AIP. Interestingly, abundant infiltration of IgG4-positive plasma cells was detected in the colonic mucosa of the patient with suspected type 2 AIP and UC. Although Ravi *et al*.[11] reported infiltration of IgG4-positive cells in the colonic mucosa of one patient with AIP and UC, and concluded that IBD might

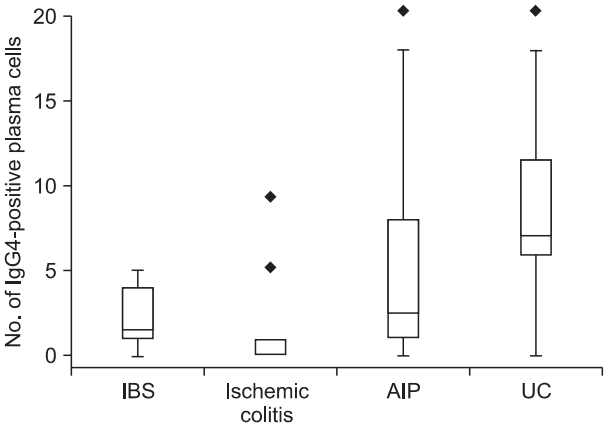

Fig. 2. Numbers of immunoglobulin G4-positive plasma cells/high power field in specimens of colonic mucosa from ulcerative colitis (UC) patients were greater than those from patients with irritable colon syndrome ($p<0.01$), ischemic colitis ($p<0.01$), or autoimmune pancreatitis (AIP) ($p<0.05$).
◆, outlier; IBS, irritable bowe syndrome.

Table 1. Clinical Differences between Ulcerative Colitis with or without Infiltration of Immunoglobulin G4-Positive Plasma Cells

	IgG4-present UC (n=10)	IgG4-absent UC (n=22)	p-value
Age, yr	43.9±14.1	48.0±15.2	NS
Male:Female	3:2	5:6	NS
Extent of colitis			NS
Proctitis	3	4	
Left-sided colitis	2	8	
Total colitis	5	10	
Clinical course			
One attack	1	4	NS
Relapsing type	2	14	
Chronic continuous type	6	3	
Acute fulminating type	1	1	
Endoscopic severity			NS
Grade 1	3	4	
Grade 2–3	7	18	
Disease activity			<0.05
Mild	3	16	
Moderate-severe	7	6	

Data are presented as mean±SD or number.
IgG4, immunoglobulin G4; UC, ulcerative colitis; NS, not significant.

Table 2. Histological Severity of Ulcerative Colitis (Matts Histological Classification) and Immunoglobulin G4-Positive Plasma Cell Count

Matts histological classification	IgG4-positive plasma cell count
Grade 1	1.8±0.5
Grade 2–3	4.3±4.6
Grade 4–5	9.3±6.4

Data are presented as mean±SD. A p<0.01 among three groups.
IgG4, immunoglobulin G4.

represent an extrapancreatic manifestation of AIP, whether this AIP was type 1 or type 2 was unclear. Park *et al*.[24] reported that six cases (5.8%) of the 104 AIP patients were diagnosed with UC, and two cases (33.3%) showed increased infiltration of IgG4-positive plasma cells into the colonic mucosa, but none with UC only. They hypothesized that UC may be an extrapancreatic manifestation of AIP. However, AIP with UC cases in this study include four cases of type 2 AIP.[24] Rebours *et al*.[12] reported that the median number of IgG4-positive plasma cells in the colonic mucosa of four patients with type 2 AIP and IBD (UC, n=3; Crohn disease, n=1) was 6.6 (range, 0 to 9).[12]

Infiltration of IgG4-positive plasma cells was detected in the colonic mucosa of two type 1 AIP patients without colonic diseases, but neither fibrosis nor obliterative phlebitis was observed in the colonic mucosa. Similar increases in IgG4-positive cell infiltration have been reported in the colonic mucosa of AIP patients with elevated serum IgG4 level.[25] As infiltration of IgG4-positive plasma cells is detected in various organs of AIP,[9,10] IgG4-positive plasma cell infiltration alone does not indicate extrapancreatic lesion of AIP. However, several cases of colonic polypoid lesions composing fibrosis and marked infiltration of IgG4-positive plasma cells have been reported.[26,27] These colonic lesions may be IgG4-related pseudotumor occurring in the colon.

In our study, positive infiltration of IgG4-positive plasma cells was detected in 10 UC patients (31%). Strehl *et al*.[28] reported that a mean number of IgG4-positive plasma cell/HPF in the colonic mucosa of nine UC cases was eight (range, 0 to 18/HPF).[28] Rebours *et al*.[12] reported that the median number of IgG4-positive plasma cell/HPF in the colonic mucosa of 20 patients with IBD (UC, n=15; Crohn disease, n=5) was 3.8 (range, 0.2 to 12.6).[12] IgG4-positive plasma cell infiltration is thus sometimes detected in the colonic mucosa of UC patients.

IgG4-positive plasma cell infiltration in the colonic mucosa of patients with UC and type 2 AIP appeared to be unrelated to type 2 AIP, but rather involved in UC itself, although whether abundant infiltration of IgG4-positive plasma cells is observed in the colonic mucosa of type 2 AIP patients without colitis is unknown. IgG4-present and -absent patients showed no significant differences in disease distribution and clinical course, although IgG4-present patients were dominant in chronic continuous UC. Disease activity was significantly more severe in patients with IgG4-present UC. The more severe is the inflammation, the greater the degree of IgG4-positive plasma cell infiltration in colonic mucosa. In addition, an interesting finding was that two IgG4-present UC patients showed blunted response to mesalazine and corticosteroid administration and needed total colectomy or azathioprine administration. IgG4-positive plasma cell infiltration may be related to disease activity and severity of UC. However, there was no relationship between IgG4-positive plasma cell infiltration and endoscopic severity. This might be attributed to the fact that 78% of the present patients were endoscopically diagnosed to be severe (≥grade 2).

The mechanisms underlying IgG4-positive plasma cell infiltration in the colonic mucosa of UC patients are unknown. However, as no abundant infiltration of IgG4-positive plasma cells was seen in the colonic mucosa of patients with irritable colon syndrome and ischemic colitis, infiltration in UC patients may be induced by dysregulation on immune response against inflammatory processes, as the dysregulation of the immune response suggested in UC appears similar to that in AIP.[29,30] Thus, the greater number of IgG4-positive plasma cell might be seen in colonic mucosa of more severe UC patients.

Key limitations of this study were retrospective nature of the study design and the relatively small number of patients. In addition, IgG4-positive plasma cell infiltration should be examined in the colonic mucosa of UC patients associated with type 1 AIP and in type 2 AIP patients without colitis. Finally, serum

IgG4 levels should be examined in UC patients with abundant infiltration of IgG4-positive plasma cells. The lack of such information limits the ability to interpret the present findings.

In conclusion, UC is rarely associated with type 1 AIP. Infiltration of IgG4-positive plasma cells was sometimes detected in the colonic mucosa of UC patients, and was related to disease activity and severity of UC. Further studies are needed to clarify the relationship between colitis and IgG4, which might involve dysregulation of the immune response.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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