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Elevated immunoglobulin G4 level is associated with reduced colectomy-free survival in patients with primary sclerosing cholangitis and ulcerative colitis

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Abstract

Background and aim: Patients with primary sclerosing cholangitis (PSC) and elevated immunoglobulin (Ig) G4 have been shown to have more severe disease with a shorter time to orthotopic liver transplantation (OLT). The aim of the study was to investigate the clinical outcomes of PSC and UC in patients with elevated serum IgG4.
Methods: We analyzed data from 50 patients with PSC and known serum levels of IgG4. They were divided into groups called high IgG4 (>112 IU/L; n=10) or normal IgG4 (n=40). We compared the requirement of OLT and colectomy between groups.
Results: High IgG4 was found in 10 PSC patients (20%). UC was associated in 9/10 patients with high IgG4 vs. 32/40 patients with normal IgG4 (p=0.67). Patients with high IgG4 were younger at PSC diagnosis (28.1±13.9 vs. 37.6±13.4 years, P=0.04), more likely to have backwash ileitis (7/9 vs. 12/32, P<0.001) and UC flares (median of 5.5 vs. 1.5, P=0.02). Kaplan–Meier curve analysis showed that patients with elevated IgG4 had reduced colectomy-free survival than patients with normal IgG4 (Log Rank p<0.001). The median time to colectomy was 5 years from UC diagnosis in high IgG4 group vs. 12 years in the normal IgG4 group (p=0.01).

Abbreviations 5-ASA, 5-aminosalicylic acid; CD, Crohn's disease; CI, confidence interval; ERCP, endoscopic retrograde pancreatocholangiography; IPAA, ileal pouch anal anastomosis; Ig, immunoglobulin; IBD, inflammatory bowel disease; MRCP, magnetic resonance pancreatocholangiography; OLT, orthotropic liver transplantation; PSC, primary sclerosing cholangitis; UC, ulcerative colitis; UDCA, ursodexoxycholic acid.

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Conclusions: Elevated IgG4 was seen in a small number of PSC patients. Most of these patients had associated UC, were younger at the time of PSC diagnosis, more likely to have backwash ileitis and had reduced colectomy-free survival than patients with normal IgG4.

1. Introduction

Primary sclerosing cholangitis (PSC) is a chronic, liver disease affecting the young and middle aged and is commonly seen in patients with underlying inflammatory bowel disease (IBD), most commonly ulcerative colitis (UC).[1,2] Approximately 70% to 80% of patients with PSC have underlying IBD and 1.4% to 7.5% of patients with IBD eventually develop PSC during their disease course.[3] UC patients who have concomitant PSC present with a unique clinical phenotype with a higher prevalence of backwash ileitis, pancolitis and colorectal neoplasia.[4–8]

In a study from the Mayo Clinic, 9% of patients with PSC had elevated serum levels of IgG4.[9] These patients also had significantly higher levels of bilirubin, and higher PSC Mayo risk scores in comparison to patients with normal IgG4.[9] Also, the time to orthotopic liver transplantation (OLT) was significantly shorter in patients with elevated IgG4, compared with patients with normal IgG4 concentration.[9] The authors suggested that PSC patients with elevated IgG4 levels could have a different, more severe disease course. In their study, IBD was less commonly seen in patients with elevated IgG4 levels.[9]

Recent studies suggest that IgG4 may play a role in the disease process of IBD in patients with or without a history of pancreatic disease.[10,11] We had shown elevated serum IgG4 in patients with chronic pouchitis following ileal pouch anal anastomosis (IPAA) surgery[10] and tissue infiltration of IgG4 positive plasma cells in the pouch and afferent limb in IPAA patients.[11] In addition, we had demonstrated IgG4-associated ampullitis and cholangiopathy in a patient with Crohn's disease (CD).[12]

Given the link between IgG4 and PSC and its role in IBD, we wanted to explore the role of IgG4 in the subset of PSC and UC patients. To our knowledge, the role of elevated serum IgG4 in patients with PSC and UC and their outcomes have not been studied.

The aims of our study were to compare the outcomes of PSC and UC in patients with and without elevated IgG4 and to study the differences in requirement for colectomy and OLT between the two groups. The secondary outcome was to study the differences in the prevalence of cholangiocarcinoma and colon carcinoma between the two groups.

2. Patients and methods

2.1. Patients

The historical cohort study was approved by the Cleveland Clinic Institutional Review Board. We identified 142 patients from a prospectively maintained EDIT (Electronic Data Interface for Transplantation) and the retrospectively collected PSC and UC database over the time period from 2001 to 2011. We identified 50 patients with serum IgG4 measured before the outcome of colectomy, colon carcinoma, cholangiocarcinoma or OLT. These 50 patients were included for analysis in the present study. Patients were divided into two groups: those with serum IgG4 greater than 112 mg/dl (high IgG4 group) and those with no elevation of serum IgG4 (Normal IgG4 group). Among the 50 patients, we identified 42 patients with associated UC and the remaining 8 patients with PSC alone. There were no patients with indeterminate colitis or CD included in the study.

2.2. Inclusion and exclusion criteria

Inclusion criteria were as follows: 1) age older than 18 years at the time of inclusion in the study and 2) presence of PSC with or without OLT. Exclusion criteria were patients with PSC who did not have follow-up at the Cleveland Clinic and patients with CD and indeterminate colitis.

2.3. Diagnostic criteria

PSC was defined as the presence of intra- and/or extrahepatic bile duct abnormalities in the form of beading, duct ectasia, and stricturing of the intra- or extrahepatic bile ducts documented in the medical record from endoscopic retrograde cholangiopancreatography, magnetic resonance cholangiopancreatography, and/or liver biopsy.[1] Small duct PSC was defined when there were histological features consistent with PSC on liver biopsy in the absence of characteristic radiological features, and clinical cholestasis with persistently elevated serum alkaline phosphatase levels for greater than 6 months.

The diagnosis of UC was confirmed with characteristic endoscopic examination of inflammation as well as from compatible histological examination described before.[13]

2.4. Demographic and clinical variables

Demographic and clinical variables were studied from patient medical records including age, gender, smoking and alcohol history, and family history of IBD, PSC, or liver/colon cancer in first degree relatives. The clinical variables were defined as follows—"duration of UC" defined as the time from the diagnosis of UC to the time of last clinical follow-up, "family history of IBD"—CD or UC in first degree relatives. "smoking"—smoking more than 7 cigarettes a week, "Alcohol use" defined as more than 2 drinks a day, extent of UC "Extensive colitis"—endoscopic, macroscopic or microscopic evidence of disease proximal to the splenic flexure.

In patients with concomitant UC, we assessed UC activity in the last 5 years of the follow-up period before the last clinic follow-up; type of UC treatment used during the whole

follow-up period (steroids, azathioprine, biologics (infliximab and adalimumab) and surgery); severity of disease at last colonoscopy (before last follow-up), assessed macroscopically; prevalence of colorectal dysplasia and/or carcinoma; PSC duration from diagnosis; severity of PSC at last follow-up or before OLT (serum albumin, bilirubin values and presence of ascites); outcome (patient alive at last follow-up, dead or had OLT). With regards to endoscopic assessment of activity, we used the definition used by Rutter et al.[14] A normal appearing mucosa or chronic changes without acute inflammation was termed as quiescent disease on endoscopy, while the rest were termed as active disease. The use of ursodeoxycholic acid (UDCA) and its dose was obtained from the database. UDCA was defined by the use of this medication for at least 50% of the follow-up period. UC flare was defined as the occurrence of clinical symptoms requiring a short course of corticosteroids with or without endoscopic confirmation of inflammation. Information pertaining to UC flares was obtained for the 5 years of follow-up. The follow-up period was calculated from the first visit to our institute to the day of OLT, death or last visit) in the two groups.

The Mayo Risk Score was calculated at entry using the revised PSC Mayo Risk Score.[15] Patients who were followed up had periodic laboratory data checked every year. For inclusion in the study, the serum IgG4 levels were to be measured before the development of end points including colectomy, OLT, colon carcinoma and cholangiocarcinoma. We obtained the earliest value available in our institution. Some patients had serum IgG4 measured several times. In those patients, the initial value was adopted. Also the IgG4 values were obtained at the time of routine follow-up and not in patients who had disease flare.

The diagnosis of cholangiocarcinoma was confirmed by histology. All patients underwent serial colonoscopic surveillance for the development of colonic neoplasia or colon cancer according to the American College of Gastroenterology guidelines.[16] Details relating to the number of surveillance colonoscopies for each patient were obtained from the electronic medical records. The stage of colon cancer was determined based on the American Joint Committee on Cancer (AJCC) system.[17] Definite dysplasia was graded as low or high grade based on criteria established by the Inflammatory Bowel Disease/Dysplasia Morphology Study Group.[18] The highest grade of dysplasia in each patient was selected for analysis.

All patients had terminal ileal intubation and thus were equally assessed for terminal ileitis. Backwash ileitis was defined as the presence of mucosal inflammation proximal to the ileocecal valve which typically is associated with pancolitis in patients with UC.[19] We classified it as endoscopic backwash ileitis in which there was contiguous endoscopic inflammation from the cecum and histologic backwash ileitis in which there were histologic signs of terminal ileal inflammation defined by cryptitis, crypt abscesses and presence of erosions/ulcer.[20] The length of involvement of backwash ileitis varied from 0.5 to 8 cm which was also recorded. The documentation of backwash ileitis was based on follow-up endoscopies done at the Cleveland Clinic. If any of the endoscopies showed backwash ileitis, we classified those patients as having backwash ileitis.

Serum IgG4 was measured by particle-enhanced immunonephelometry (Dade Behring, Inc, Newark, DE). An elevated concentration of serum IgG4 was defined by values greater than 112 mg/dl according to the reference standard used in our institution. The serum IgG4 was measured at the time of routine follow-up and not at the times of flares. All patients had serum IgG4 measured at least 8 weeks after corticosteroids were stopped for underlying UC to ameliorate the effect of corticosteroids on IgG4 levels. We compared the two groups in terms of associated diseases, laboratory data and prognosis.

2.5. Outcome measurement

The primary outcome of interest was to compare the outcomes of PSC and UC in patients with and without elevated IgG4 to study the differences in requirement for colectomy and OLT between the two groups. The secondary outcome was to study the differences in the prevalence of cholangiocarcinoma and colon carcinoma between the two groups.

2.6. Statistical analysis

Descriptive statistics were computed for all factors. These include medians, 25th and 75th percentiles, range or mean and standard deviation for continuous factors and frequencies and percentages for categorical factors. Wilcoxon's rank sum tests for continuous factors and Pearson's chi-square or Fisher's exact tests for categorical factors were used.

Survival rates were estimated using a Kaplan–Meier approach. Patients who were alive at the time of last follow-up were censored. Cumulative event occurrence rate curves were analyzed using the Kaplan–Meier technique with log-rank test. A significance level of 0.05 was used for all analyses. R 2.10.1 software (The R Foundation for Statistical Computing, Vienna, Austria) was used to perform all analyses.

3. Results

3.1. Demographic and clinical characteristics

The basic demographic and clinical information including age, sex, race, UC duration from diagnosis, PSC duration from diagnosis and colonoscopic extent of UC are summarized in Table 1. Patients with PSC were divided into two groups: 10 with elevated serum IgG4 (high IgG4 group) and 40 with normal IgG4 (normal IgG4 group). High IgG4 was found in 10 PSC patients (20%). UC was associated in 9/10 patients with high IgG4 vs. 32/40 patients with normal IgG4 ($p=0.67$) Patients with high IgG4 did not differ in the age of onset of UC compared to patients with normal IgG4. (22.0 ± 15.6 vs. 22.1 ± 15.8 years, $P=0.88$). The median time interval between UC and PSC diagnosis and serum IgG4 measurement was 8 years.

Patients with high IgG4 were younger at the time of diagnosis of PSC (28.1 ± 13.9 vs. 37.6 ± 13.4 years, $P=0.04$). The distribution of strictures in terms of location (intrahepatic, extrahepatic or both) was similar. The mean serum IgG4 in the high IgG4 group was significantly higher (695.3 ± 366.0 vs. 29.4 ± 24.5, $p<0.001$) and the mean

Table 1 Comparison of demographic and clinical variables between PSC patients with or without elevated IgG4.

Variable	PSC with normal IgG4 N=40 (80%)	PSC with elevated IgG4 N=10 (20%)	P value
Age (end of follow-up or OLT), years (mean±SD)	49.8±13.0	53.5±12.1	0.1
Male Gender	23 (57.5%)	9 (10%)	0.07
Serum IgG4 (Mean±SD)	29.4±24.5	695.3±366.0	<0.001
Serum IgG (Mean±SD)	1403.9±540.2	1933.0±975.9	0.10
Ulcerative colitis	32 (80%)	9 (90%)	0.67
Median Body mass index (g/m^2) [(median (interquartile range)]	25.9 (17.2–37)	20.9 (17.9–29.2)	0.01
Smoker			
Yes	1 (2.5%)	0 (0%)	0.99
Ex-smoker	3 (7.5%)	0 (0%)	
Alcohol			
Yes	3 (7.5%)	0 (0%)	0.67
Ex-alcohol use	2 (5%)	0 (0%)	
Age at diagnosis of PSC, years [(mean±SD)]	37.6±13.4	28.10±13.9	0.05
Age at diagnosis of UC, years [(mean±SD)]	22.1±14.8	22.0±15.6	0.88
Bile duct involvement			
Intrahepatic only	10 (25%)	4 (40%)	
Extrahepatic only	9 (22.5%)	0 (0%)	0.25
Intra- and extrahepatic	21 (52.5%)	6 (60%)	
Median initial albumin, mg/dl (range)	3.6 (1.6–4.9)	4 (2.5–4.5)	0.15
Median initial bilirubin, mg/dl (range)	1.2 (0.2–25.8)	0.5 (0.2–5.3)	0.19
Mean initial PSC Mayo risk score (SD)	0.82±1.76	−0.19±1.77	0.10
Median initial AST, IU/L (range)	58.5 (9–288)	103 (17–210)	0.71
Median final albumin, mg/dl (range)	3.2 (1.7–4.9)	3.4 (2.9–4.6)	0.53
Median final bilirubin, mg/dl (range)	8.1 (0.3–31.0)	1 (0.4–15)	0.34
Liver transplantation during follow-up	10 (25%)	2 (20%)	1
Age at orthotopic liver transplantation (Mean±SD)	42.2±14.7	49.5±12.0	0.39
Colectomy during follow-up	21 (52.5%)	9 (90%)	0.1
Age at colectomy, years median (range)	44 (11, 65)	25 (19, 61)	0.15
Azathioprine/6-mercaptopurine	4 (10%)	2 (20%)	0.59
Corticosteroid use	18 (45%)	8 (80%)	0.28
5-Aminosalicylic acid use	12 (30%)	2 (20%)	0.70
Median number of UC flares (Range)	1.5 (0–12)	5.5 (0–20)	0.02
Quiescent disease	18 (45%)	1 (10%)	0.11
Dysplasia			
Low-grade	2 (5%)	1 (10%)	0.10
High-grade	4 (10%)	3 (30%)	
Colon carcinoma	4 (10%)	1 (10%)	0.10
Dysplasia and/or colon carcinoma	10 (25%)	5 (50%)	0.14
Cholangiocarcinoma	2 (5%)	0 (0%)	1

serum IgG in the high IgG4 group was higher (1933.0±975.9 vs. 1403.9±540.2, p=0.10).

Patients in the high IgG4 group at the time of initial referral to our center had similar serum bilirubin, aspartate aminotransferase and serum albumin as compared to patients in the normal IgG4 group (Table 1). Their Mayo PSC risk score (−0.19±1.77 vs. 0.82±1.76, P=0.10) was also not significantly different from the normal IgG4 group. The median follow-up period in high IgG4 group was 12 years and 11 years in the normal IgG4 group (p=0.10).

At the end of the follow-up period, the high IgG4 group had similar serum albumin, and serum bilirubin compared with the normal IgG4 group. None of our patients had concurrent autoimmune pancreatitis and/or pancreatic carcinoma. Two patients (20%) in the high IgG4 group required OLT compared to 10 (25%) patients in the normal IgG4 group (p=1).

3.2. Clinical activity of UC

Patients with high serum IgG4 were more likely to have endoscopic and histologic backwash ileitis (7/9 vs. 12/32, P<0.001) and increased median number of UC flares during the last 5 years of follow-up (5.5 (range 0–20) vs. 1.5 (range 0–12), P=0.02). The median length of backwash ileitis was not different, 1.6 in the high IgG4 group vs. 1.8 in the normal IgG4 group (p=1). In terms of UC activity endoscopically, 2/9 (22.2%) patients with high IgG4 had quiescent disease compared to 18/32 (56.3%) patients with normal IgG4

(p=0.27). The use of azathioprine/mercaptopurine was not significantly different, 2/9 (22.2%) in the high IgG4 group vs. 4/32 (12.5%) in the normal IgG4 group (p=0.59). Corticosteroid use was also not significantly different between the high IgG4 and normal IgG4 groups (8/9 [88.9%] vs. 22 [68.8%], p=0.28). Among 10 patients with elevated IgG4, 5-aminosalicylates were used in 2 patients and corticosteroids were used in 4 patients prior to IgG4 measurement. In patients without elevated IgG4, 5-aminosalicylates were used in 12 patients and corticosteroids were used in 6 patients prior to IgG4 measurement.

3.3. Surgery for UC

The requirement for colectomy was not significantly different, 9/9 (100%) in the high IgG4 group vs. 21/32 (65.6%) in the normal IgG4 group (p=0.17). The median age at colectomy was 25 years in the high IgG4 group vs. 44 years in the normal IgG4 group (p=0.15).

3.4. Kaplan–Meier survival analysis

Fig. 1 summarizes the Kaplan–Meier curve and suggested that patients with elevated IgG4 had shorter colectomy-free survival than patients with normal IgG4 (Log Rank p=0.026). The median time to colectomy was 5 years from UC diagnosis in the elevated IgG4 group as compared to 12 years in the normal IgG4 group. (p=0.01) Figs. 2 and 3 summarize the Kaplan–Meier curve for the overall survival and OLT free survival which was no different in both groups.

3.5. Cholangiocarcinoma, dysplasia and colon cancer

Colon carcinoma and dysplasia was not significantly different between the two groups 5/10 (50%) in the high IgG4 group vs. 10/40 (25%) in the normal IgG4 group (p=0.14). Low grade dysplasia was seen in 3 (30%) vs. 2 (5%), and high grade dysplasia in 1 (10%) vs. 4 (10%), p=0.10). In the normal IgG4 group, 4 (10%) had developed colorectal cancer, while in the high IgG4 group 1 (10%) patients developed colorectal cancer; Two patients (5%) in the normal IgG4 group had cholangiocarcinoma versus 0 patient in the high IgG4 group (p=1) (Table 1).

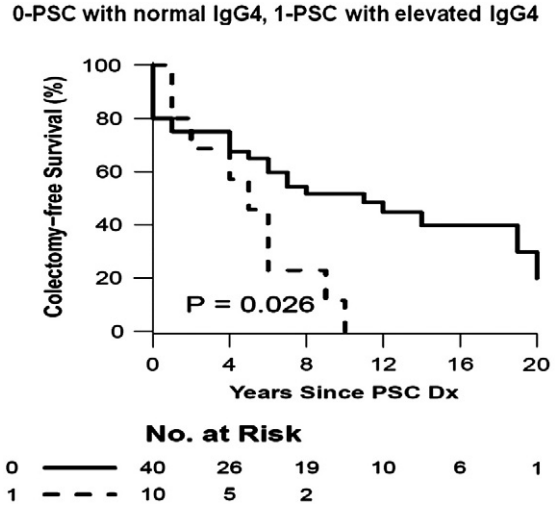

Figure 1 Comparison of Kaplan–Meier curve for colectomy-free survival in patients with and without elevated serum IgG4. Patients with elevated serum IgG4 had reduced colectomy free survival (p=0.026, Log rank test).

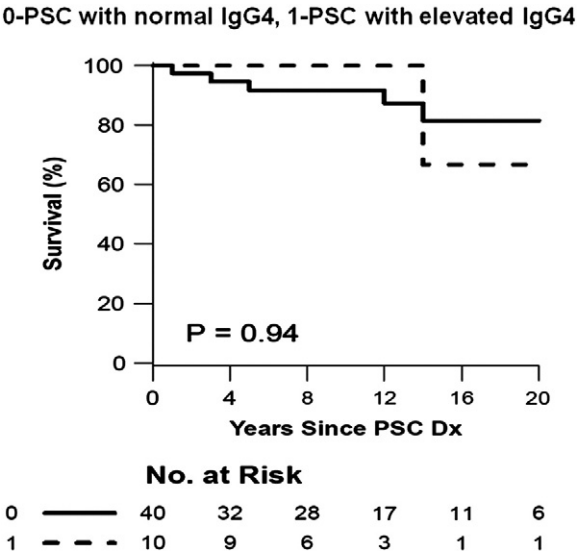

Figure 2 Comparison of Kaplan–Meier curve for overall survival in patients with and without elevated serum IgG4. We did not find any statistically significant difference between both groups (P=0.94, Log rank test).

4. Discussion

Our study showed the possible association between elevated serum IgG4 and the clinical outcome of UC associated with PSC. We also observed that elevated serum IgG4 was

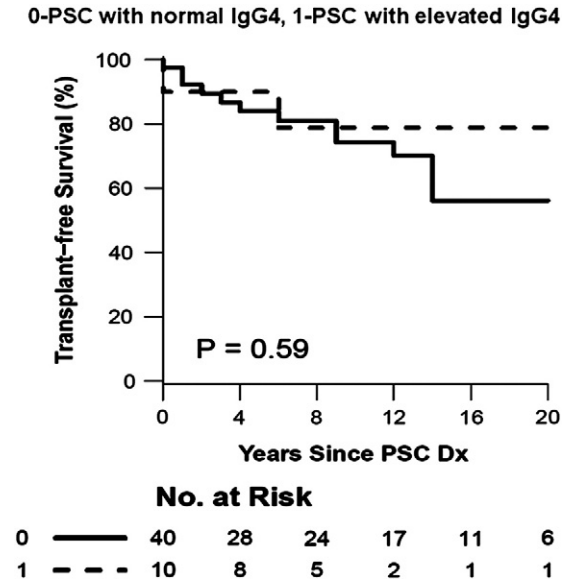

Figure 3 Comparison of Kaplan–Meier curve for OLT-free survival in patients with and without elevated serum IgG4. We did not find any statistically significant difference between both groups (P=0.59, Log rank test).

associated with backwash ileitis (both endoscopic and histologic), and reduced colectomy free survival than patients with normal IgG4. High IgG4 was seen in 20% of PSC patients. The majority of these patients had associated UC. Although these patients were younger at the time of PSC diagnosis, their time to OLT and overall survival was similar to patients with normal IgG4.

Previous studies have shown that PSC–UC is a distinct clinical phenotype with a higher prevalence of backwash ileitis, pancolitis, colorectal neoplasia, and overall a worse survival than patients without concomitant PSC.[4–8] Increased serum IgG4 level has been observed in 9% of patients with PSC and these patients had significantly higher levels of bilirubin, and higher PSC Mayo risk scores in comparison to patients with normal IgG4 with shorter time to OLT.[9] The authors suggested that PSC patients with elevated IgG4 levels could have a different, more severe disease course. Subsequently, increased numbers of IgG4+ plasma cells were found in 23% of explanted liver specimens from 99 patients who underwent OLT for PSC and these patients had a higher likelihood of recurrence of PSC than IgG4-negative PSC.[21] Thus elevated serum IgG4 or tissue IgG4 infiltration was associated with poor liver outcomes for these patients. Similarly, in a study of explanted livers of 41 PSC patients, 2 (5%) showed IgG4+ plasma cell infiltration.[22] However these patients appeared to be clinically distinct with both having associated UC and were younger. However the impact of elevated serum IgG4 on the clinical presentation, course and outcome of associated IBD has not been explored before.

IgG4 may play a role in the disease process of IBD patients with or without a history of pancreatic disease. IgG4 was even studied as a marker to differentiate UC from CD. UC patients had more IgG4-positive plasma cell infiltration (10.6 vs. 2.1/high-power field [hpf]) than that in CD and the number of IgG4+ plasma cells in UC patients correlated with more severe histologic inflammation.[23] Also in our prospective study of serum IgG4 in IPAA patients, we found that 8% of patients had elevated serum IgG4, which was associated with chronic antibiotic refractory pouchitis.[10] We also observed IgG4 plasma cell infiltration in IPAA patients and the Pouchitis Disease Activity Index (PDAI) endoscopy score in the pouch was an independent risk factors for the presence of IgG4+ plasma cell infiltration.[11] We observed that PSC was a significant risk factor for tissue IgG4+ plasma cell infiltration in univariable analysis, but not in multivariable analysis because of a small number of patients with PSC in the study.[11] Given the relationship between IgG4 and inflammation in IBD patients after surgery, we wanted to explore the relationship between serum IgG4 and outcomes of IBD before surgery.

We observed that elevated serum IgG4 was associated with endoscopic and histologic backwash ileitis in PSC–UC patients. Two previous studies have shown an increased incidence of backwash ileitis in PSC–UC patients compared with UC patients without PSC.[6,7] In contrast to the above mentioned studies, a recent study reported no difference in the presence of backwash ileitis in the PSC–UC group when compared with the UC-only group (10% vs. 7.5%).[8] The discrepant findings may be at partly explained by the varying criteria used to classify backwash ileitis and sample sizes of the studies. However we defined backwash ileitis based on both endoscopy and histology. Whether elevated serum IgG4 is a marker for the presence of backwash ileitis is unclear. However our study suggests this relationship.

We also found that elevated serum IgG4 patients had a shorter colectomy free survival than normal IgG4 group. Colectomy was also more frequent in the high serum IgG4 group. Thus the presence of elevated serum IgG4 could be a marker of more severe disease sub-type in the PSC–UC. However our results are different from the Mayo Clinic study as we did not observe worse liver-related outcomes in our patients.[9] A subsequent study from the Mayo Clinic also reported that 11.6% of patients with PSC had elevated serum IgG4 levels and also reported worse liver-related outcomes.[24] This could be explained based on variable time intervals from the measurement of serum IgG4 and also that the Mayo risk score was slightly lower in the high IgG4 group and the follow-up period was not sufficient enough to observe an adverse outcome. The other possibility is that the Mayo risk score at diagnosis in patients with elevated IgG4 was much higher in the study from Mayo Clinic than patients in our study.[9] This could have altered the time to OLT overall. It was significant that corticosteroids were used in 80% of patients with elevated serum IgG4 for their UC and this could have altered the time to OLT in our group as patients with elevated serum IgG4 and PSC may respond to corticosteroids. It is a possibility that elevated serum IgG4 may be secondary to IgG4-associated disease and these patients with PSC-like biliary lesions have the same mechanism, without the typical pancreatic findings. If patients with elevated IgG4 represented autoimmune sclerosing cholangitis and not classic PSC, one would expect them to have more prominent involvement of the lower common bile duct, rather than changes in the intra- and extrahepatic bile ducts.[25] We did not observe isolated extrahepatic bile duct involvement in any of the 10 patients with elevated serum IgG4. Also IBD was commonly associated with elevated IgG4 in our group in contrast to IgG4-associated disease in which IBD is less commonly associated.[8,25] Also none of our patients had pancreatic involvement highlighting that elevation in serum IgG4 in these patients is not a process similar to IgG4 associated disease.

The prevalence of high IgG4 was 20% in our study which was higher than 9% as reported from the Mayo Clinic. However, in a recent study from Europe, elevated IgG4 was seen in 6/23 (26.1%) of PSC patients similar to our study.[26] In our cohort of 142 patients, only 50 had serum IgG4 measured. To account for the possible bias involved in serum IgG4 measurement, we had compared disease activity in the 50 patients with serum IgG4 measurement and the remaining 92 patients who did not have IgG4 measured. There was no difference in the disease activity, requirement for colectomy and OLT between the two groups (data not shown).

Our study is clinically significant for a number of reasons. Elevated serum IgG4 is associated with backwash ileitis (both endoscopic and histologic), increased median UC flares and reduced colectomy free survival than patients with normal IgG4. Thus the presence of elevated serum IgG4 as a marker of PSC–UC patients with poor prognosis for gut related outcomes needs to be validated in a prospective cohort.

There are certain limitations of our study. The study population was recruited from a subspecialty tertiary care referral center. This contributes to a selection bias. The retrospective nature of our cohort study limited our ability

to obtain longitudinal data and its inherent study limitations. The results of our study could also be influenced by Berkson's bias as we had a selected group of patients with chronic problems which could have contributed to the high IgG4 and normal IgG4 patients to be systematically different from each other. However this bias is difficult to adjust for using statistical methods. Also because of the small sample size, it is difficult to draw conclusions about the significance in relation to other variables on multi-variable analysis. Also patients who had serum IgG4 measured had it measured at variable time periods. However we attempted to account for the bias by including patients with IgG4 measured at the time of follow-up and not at the time of disease flare. Also, we did not examine the explanted livers for IgG4 cells as the patients in our cohort had liver transplantation spanning three decades. Nevertheless, from a large cohort of PSC–UC patients, we found that elevated serum IgG4 was associated with backwash ileitis and reduced colectomy free survival.

To conclude, elevated IgG4 was seen in a small number of PSC patients. Most of these patients had associated UC, were younger at the time of PSC diagnosis, more likely to have backwash ileitis and had reduced colectomy-free survival suggesting more severe colitis than patients with normal IgG4.

Conflict of interest

The authors declared no financial conflict of interest.

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