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Inflammatory bowel disease of primary sclerosing cholangitis: A distinct entity?

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Abstract

This is a review of the characteristic findings of inflammatory bowel disease (IBD) associated with primary sclerosing cholangitis (PSC) and their usefulness in the diagnosis of sclerosing cholangitis. PSC is a chronic inflammatory disease characterized by idiopathic fibrous obstruction and is frequently associated with IBD. IBD-associated with PSC (PSC-IBD) shows an increased incidence of pancolitis, mild symptoms, and colorectal malignancy. Although an increased incidence of pancolitis is a characteristic finding, some cases are endoscopically diagnosed as right-sided ulcerative colitis. Pathological studies have revealed that inflammation occurs more frequently in the right colon than the left colon. The frequency of rectal sparing and backwash ileitis should be investigated in a future study based on the same definition. The cholangiographic findings

of immunoglobulin G4-related sclerosing cholangitis (IgG4-SC) are similar to those of PSC. The rare association between IBD and IgG4-SC and the unique characteristics of PSC-IBD are useful findings for distinguishing PSC from IgG4-SC.

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Key words: Primary sclerosing cholangitis; Primary sclerosing cholangitis; Inflammatory bowel disease; Inflammatory bowel disease-associated with primary sclerosing cholangitis; Immunoglobulin G4-related sclerosing cholangitis

Core tip: Inflammatory bowel disease (IBD)-associated with primary sclerosing cholangitis (PSC) (PSC-IBD) shows an increased incidence of pancolitis, mild symptoms, and colorectal malignancy. Although an increased incidence of pancolitis is a characteristic finding, some cases are endoscopically diagnosed as right-sided ulcerative colitis. Pathological studies have revealed that inflammation occurs more frequently in the right colon than the left colon. The cholangiographic findings of immunoglobulin G4-related sclerosing cholangitis (IgG4-SC) are similar to those of PSC. The rare association between IBD and IgG4-SC and the unique characteristics of PSC-IBD are useful findings for distinguishing PSC from IgG4-SC.

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INTRODUCTION

Primary sclerosing cholangitis (PSC) is a chronic inflammatory disease characterized by idiopathic fibrous obstruction^[1]. The fibrosis causes diffuse narrowing of the intrahepatic and extrahepatic bile ducts, and the resulting persistent biliary stasis leads to hepatic cirrhosis and a poor prognosis. Liver transplantation is indicated as a treatment for PSC. According to the diagnostic criteria for PSC proposed by the Mayo Clinic in 1999^[1] and 2003^[2], in addition to cholangiographic findings, the presence of inflammatory bowel disease (IBD) is important.

However, several related studies with contradictory results have recently been published^[3,4].

IgG4-related sclerosing cholangitis (IgG4-SC) has recently been established as a new clinical entity^[5]. The cholangiograms of IgG4-SC are occasionally similar to those of PSC^[6]. The differential diagnosis of PSC and IgG4-SC is important because IgG4-SC patients respond well to steroid therapy^[7].

In this study, we aimed to clarify the clinicopathological characteristics of PSC-IBD and the usefulness of PSC-IBD in the diagnosis of SC.

LITERATURE SEARCH

We conducted a literature search of English articles related to PSC-IBD, published between 2005 and March 2013, using the following keywords: “PSC,” “primary sclerosing cholangitis,” “PSC-IBD,” “IBD,” “immunoglobulin G4 (IgG4)-related sclerosing cholangitis (IgG4-SC),” “autoimmune pancreatitis,” and “IgG4-related disease (IgG4RD).” We connected the key words using “OR”. Pertinent articles obtained from the literature search were reviewed. All references were manually verified, and all reference lists in the retrieved articles were scrutinized to identify any additional articles that might have been missed in the PubMed search. As clinical data on PSC-IBD are limited, the authors also considered their own > 20-year clinical experience in the treatment of PSC-IBD. This study was primarily limited to adults patients, with the exception of the “frequency of PSC-IBD” section.

FREQUENCY OF PSC-IBD

PSC is strongly associated with IBD, and the prevalence of PSC-IBD is as high as 60%-80% in western countries^[8]. Approximately 80% of IBD is represented by ulcerative colitis (UC), 10% by Crohn's disease (CD), and 10% by indeterminate colitis^[9]. Conversely, only 2%-7.5% of IBD patients develop PSC^[8].

Previous reports from Europe and the United States have indicated that IBD complicates a high proportion of PSC cases. In Japan, IBD is found in only 21%-32% of PSC cases, according to surveys conducted by the

Japanese Society of Gastroenterology^[10] and the Japan Society of Hepatology^[11]. In a second nationwide analysis, only 125 of 388 patients (32%) had an established diagnosis of IBD, 79% of whom had UC, whereas only 6.4% were diagnosed with CD^[11]. Ang *et al.*^[12] also reported a low association rate of 20% (2/10) between PSC and IBD in Singapore. The association of PSC with IBD varies depending on geographical location, with higher rates in European and American populations, and a significantly lower association in Asian patients^[13]. However, the incidence of IBD in PSC patients in our series was higher (68.9%) than that already reported in Japan^[14]. We speculate that this high incidence was noted because only PSC patients who had undergone total colonoscopy at clinical onset were enrolled in our study. Yamagishi *et al.*^[15] also reported a higher incidence of IBD in PSC patients (93%) examined by colonoscopy. It is possible that we overlooked the endoscopic findings, as we did not perform a careful total colonoscopy because the symptoms of IBD are mild and the endoscopic findings of the colon show only slightly abnormal changes. The second national survey in Japan also reported that the incidence of IBD in PSC patients increased to 61% when only PSC patients examined by total colonoscopy were enrolled^[11]. Therefore, the frequency of PSC-IBD should be evaluated among patients undergoing careful total colonoscopy. This selection criterion might decrease the observed differences in frequency between eastern and western countries.

The age at clinical onset of IBD is controversial and has not been clarified. Loftus *et al.*^[9] reported that the mean age of IBD diagnosis was higher among PSC-IBD patients (32 years) compared with controls (28 years). In contrast, Brackmann *et al.*^[16] reported that IBD patients with PSC were significantly younger at the onset of IBD symptoms (PSC: 19 years *vs* no PSC: 29 years; $P = 0.04$), whereas the colitis-colorectal cancer interval was similar to that of IBD patients without PSC (17 years *vs* 20 years; $P = 0.236$). Joo *et al.*^[4] showed that PSC patients with UC presented with UC at a significantly earlier age (mean age: 24.5 years) compared with UC controls (mean age: 33.8 years).

Takikawa *et al.*^[10,11] discovered two peaks in the PSC age distribution, which has never been observed in other countries, and revealed that most Japanese PSC patients associated with IBD were adolescents or young adults. A recent study from Canada also reported two peaks in the PSC age distribution^[17]. Our previous study also showed a two-peaked age distribution, and that patients with PSC-IBD were significantly younger than PSC patients without IBD (33.6 years *vs* 58.9 years, $P < 0.001$)^[14].

Although the diagnosis of IBD precedes that of PSC in most patients, a recent study found that a shift in the timing of diagnosis of the two diseases has occurred in recent years, with PSC more often being diagnosed first. PSC was diagnosed before IBD in a recent

Table 1 character of inflammatory bowel disease-associated with primary sclerosing cholangitis

Ref./Nation	Year	Endoscopic/histological findings			Histological findings
		Extension of IBD	Backwash-ileitis	Rectal sparing	
Loftus <i>et al</i> ^[9] United States	2005	Total colitis 56/61 (92% vs CUC 54%)	19/37 (51% vs CUC 7%) by endoscopy	32/61 (52% vs CUC 6%) by endoscopy	
Joo <i>et al</i> ^[4] United States	2009	Total colitis 34/40 (85% vs CUC 45%)	10/24 (35.7% vs 26.9%) by histology	11/40 (27.5% vs 25%) by histology	
Sano <i>et al</i> ^[14] Japan	2010	Total colitis 6/20 (35% vs CUC 35%) Right-sided 11/20 (55% vs 3.3%) Left-sided 1/20 (5% vs 31.7%)	Not studied	Not studied	Significantly higher inflammation in the right colon
Jørgensen <i>et al</i> ^[24] Norway	2012	Total colitis 60/110 (55%) Right-sided 25/110 (23%) Left-sided 3/110 (3%)	11/93 (12%) by endoscopy 17/87 (20%) by histology	73/110 (66%) by endoscopy 70/107 (65%) by histology	Significantly higher inflammation in the right colon
Boonstra <i>et al</i> ^[3] The Netherlands	2012	Total colitis 207/380 (83%) Left-sided 9/380 (4%)	< 10%	< 10%	
Schaeffer <i>et al</i> ^[27] Canada	2013	Total colitis (IBD preceding PSC) Right-sided (PSC following IBD)			

CUC: Chronic ulcerative colitis; IBD: Inflammatory bowel disease; PSC: Primary sclerosing cholangitis.

cohort (2003–2007) when compared with a early cohort (1993–1997) (50% vs 35%, $P = 0.0009$)^[18].

MECHANISM OF PSC-IBD PATHOGENESIS

Several important observations, coupled with the strong association between certain human leukocyte antigen (HLA) haplotypes and the frequency of concurrent extrahepatic autoimmune disorders, support the concept that PSC is an immune-mediated phenomenon^[19,20]. Three UC susceptibility loci to be associated with PSC, harboring the putative candidate genes REL, IL2 and CARD9 were identified^[19]. A recent study reported 12 significant genome-wide associations outside the HLA region, 9 of which were new, increasing the number of known PSC risk loci to 16. Despite comorbidity with IBD in 72% of the included cases, 6 of the 12 loci showed significantly stronger associations with PSC than with IBD, suggesting overlapping yet distinct genetic mechanisms for these two diseases^[20].

The pathogenesis of PSC has been elucidated from the standpoint of PSC-IBD. Translocation of microbial flora across an inflamed, permeable gut with subsequent activation of the immune system and inflammation of the biliary tree is a hypothesized mechanism for the development of PSC. Activated intestinal lymphocytes enter the enterohepatic circulation and persist as memory cells that cause hepatic inflammation. Chemokines and adhesion molecules shared by the intestine and liver could contribute to immune cell binding at both sites^[21]. The observations that PSC can develop after colectomy^[22] and that IBD can develop after liver transplantation^[23] have led some investigators to suggest that aberrant homing of lymphocytes between the intestine and liver could be involved in the pathogenesis of PSC^[21]. Three recent studies indirectly supporting this theory have been published. Patients who received a liver trans-

plant had lower clinical and histological IBD activity than the non-transplant group^[24]. Marelli *et al*^[25] reported that progressive PSC requiring liver transplantation is associated with a milder course of UC, including reduced disease activity and less use of steroids, azathioprine, and surgery. Navaneethan *et al*^[26] reported that severe, progressive PSC requiring liver transplantation appeared to reduce the disease activity of UC and the need for colectomy.

However, these theories cannot explain why only 2%–7.5% of IBD patients develop PSC^[8], whereas PSC is strongly associated with IBD, or why CD is less associated with PSC. It is also unclear why immunosuppression does not improve PSC.

CLINICOPATHOLOGIC CHARACTERISTICS OF PSC-IBD

Previous studies have suggested that PSC-IBD differs from IBD without PSC in several aspects. Table 1 summarizes the reports concerning PSC-IBD^[3,4,9,14,24,27]. PSC-IBD has been reported to show an increased incidence of pancolitis, rectal sparing, backwash ileitis, mild symptoms, and colorectal malignancy^[8]. However, these results are controversial. All of the investigators agree that inflammation involved in PSC-IBD is milder than that in typical UC without PSC. Moreover, the majority of PSC-IBD patients show no or few IBD symptoms. Moayeri *et al*^[28] reported that the number of hospitalizations and courses of steroid therapy decreased significantly in UC-PSC patients compared with UC controls. Our study also indicated that none of the enrolled patients had a severe clinical course, and that half of them were asymptomatic^[14].

However, varied findings concerning the extent of PSC-IBD have been reported. Although some authors have reported that pancolitis is characteristic of PSC-IBD^[3,4,9], others have insisted that right-sided IBD is

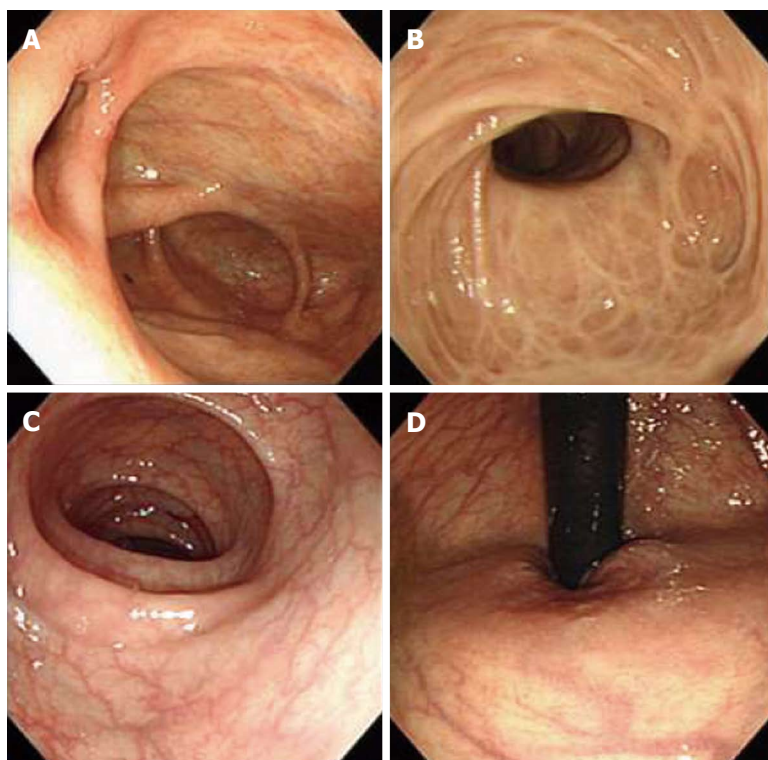


Figure 1 Colonoscopic findings at clinical onset. A: Cecum; B: Ascending colon; C: Sigmoid colon; D: Rectum. A 43-year-old female patient diagnosed with asymptomatic, concurrent primary sclerosing cholangitis-inflammatory bowel disease. The first colonoscopy showed multiple white scars in the ascending colon and right-sided transverse colon and no abnormal findings in the left-sided transverse colon, descending colon, sigmoid colon, or rectum.

characteristic^[14,24]. A recent report concluded that when IBD precedes PSC, pancolitis is common, whereas when PSC precedes IBD, right-sided IBD is common^[27].

Two reports revealed that the degree of inflammation was stronger in the right colon than the left colon using the histological studies. The first report demonstrated severe inflammatory cell infiltration in the cecum and ascending colon of PSC-IBD patients, whereas the degree was mild in the rectum/descending colon ($P = 0.0012$); goblet cell disappearance was also observed more frequently in the cecum/ascending colon than in the rectum/descending colon ($P < 0.05$)^[14]. The second report revealed that the histopathological signs of inflammation involved the right colon in 86% of patients and were purely right-sided in 23%. The frequency of inflammatory findings was higher in the right colon than the left colon ($P < 0.01$), but the general level of inflammatory activity was low^[24]. They also reported that inflammatory findings were more frequent on histology than on endoscopy.

These discrepancies may be due to differences in the geographical location between studies or the method used to assess total colitis based on the maximal extent of colitis at any time during the study period. Fluctuations in the extent of inflammation may therefore explain the high frequency of total colitis^[24,29].

The frequency of rectal sparing and backwash ileitis differs between reports, with the frequency of backwash

ileitis ranging from $< 10\%$ to 51% . Jørgensen *et al*^[24] speculated that repeated examination or different patient selection criteria account for these differing results, and also reported that the frequency of rectal sparing on histological examination (20%) was higher than that on endoscopic examination (12%). Nakazawa *et al*^[5] speculated that the different results were due to the definition and criteria of backwash ileitis.

The frequency of rectal sparing ranges from $< 10\%$ to 66% . Loftus *et al*^[9] reported that rectal sparing was observed in 52% of UC-PSC patients compared with only 6% of UC patients without PSC on endoscopy. Jørgensen *et al*^[24] reported that rectal sparing was observed in 66% of patients on endoscopy and was consistent with the results of pathological examination. In their study, the patients were considered to have rectal sparing if the inflammation involved the rectum but was less severe than that of the more proximal area of the colon. Joo *et al*^[4] reported that rectal sparing was observed in only 27.5% of patients on histologic studies. Rectal sparing was defined as predilection if all biopsies from the rectum or the entire rectal mucosa from a resection specimen showed histologically normal mucosa. Rectal sparing was considered relative if at least one biopsy from the rectum at any time period or one portion of the rectal mucosa from the colonic resection specimen showed histologic features of chronicity, but at least mild activity was present in the areas of the mucosa proximal

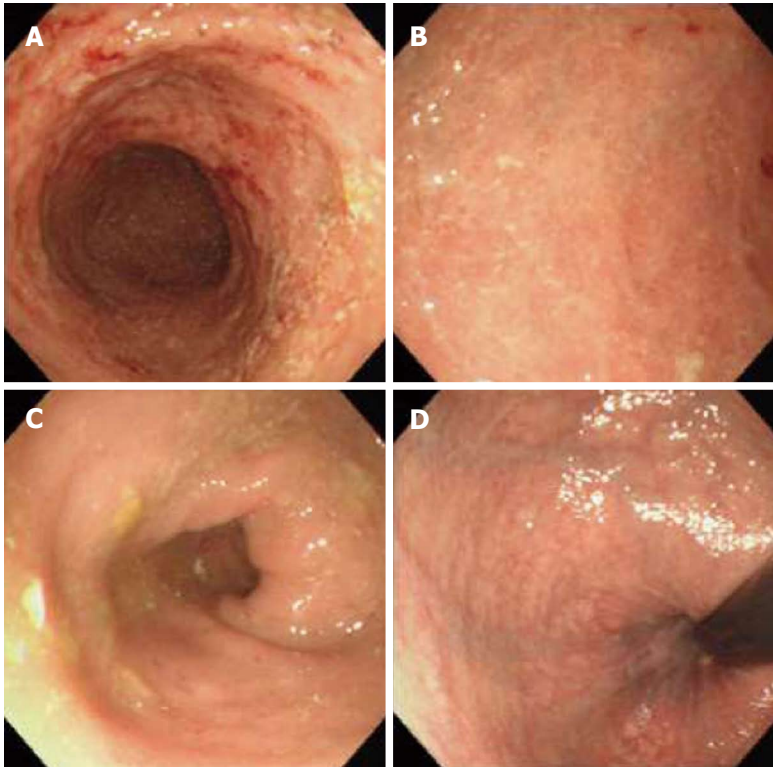


Figure 2 Colonoscopic findings seven months later. A: Cecum; B: Ascending colon; C: Sigmoid colon; D: Rectum. A repeat colonoscopy seven months later showing inflamed mucosa with multiple erosions and redness from the ascending colon to the right-sided transverse colon. Mucosal vessels are clearly visible in the descending colon, sigmoid colon, and rectum.

to the rectum.

The extent of colon involvement, rectal sparing, and backwash ileitis should be defined internationally to clarify the characteristics of PSC-IBD.

In our experiences with endoscopy, inflammation was more severe on the right, and rectal sparing appeared to be present on endoscopy (Figures 1 and 2), by contrast, less inflammatory cell infiltrations was observed in the rectum on histology. These findings are very useful in the diagnosis of PSC. In the presence of multiple biliary stenoses on magnetic resonance cholangiography, inflammatory findings dominant in the right colon and rectal sparing by total colonoscopy, invasive endoscopic retrograde cholangiography can be avoided in clinical practice.

COLORECTAL NEOPLASIA IN PSC-IBD PATIENTS

PSC-IBD patients are at particularly high risk for the development of colorectal cancer. Boonstra *et al*^[3] estimated that the colorectal cancer risk was increased 10-fold in PSC-IBD patients compared with UC controls. Claessen *et al*^[29] have reported that patients with PSC-IBD have a high long-term risk of developing colorectal cancer, and that this risk is approximately three-fold higher than that of cholangiocarcinoma. In patients with PSC-IBD, the 10-year and 20-year risks of colorectal cancer have

been reported to be 14% and 31%, respectively. Among 75 PSC-IBD patients, PSC was the only independent risk factor for the development of colorectal cancer, and the overall survival rate without liver transplantation was also reduced^[30].

PSC-IBD patients tend to be younger at colorectal cancer diagnosis^[31]. Colorectal cancer develops at a much younger age in these patients (39 years, range: 26-64 years) compared with IBD controls (59 years, range: 34-73) ($P = 0.019$)^[3].

Colorectal cancer in PSC-IBD patients predominantly develops in the right colon. The tumors were located proximally to the splenic flexure in 18 (67%) patients with PSC and in 52 (36%) patients without PSC ($P = 0.006$)^[29]. Thackeray *et al*^[32] also reported that colorectal cancer is most prevalent in the proximal colon (65%). When such patients are diagnosed with cancer, they tend to have more advanced tumors than IBD patients without concurrent PSC. In their study, patients with PSC had significantly more tumors with an American Joint Committee on Cancer tumor stage of 3A or higher when compared with patients with IBD alone (61.5% and 38.5%, $P = 0.003$). The reason for the preferential right-sided location of colorectal cancer in PSC patients remains unknown, although it has been speculated that the overall increased frequency of colorectal cancer in these patients could be due to a cytotoxic effect on the colonic mucosa caused by an altered bile acid composi-

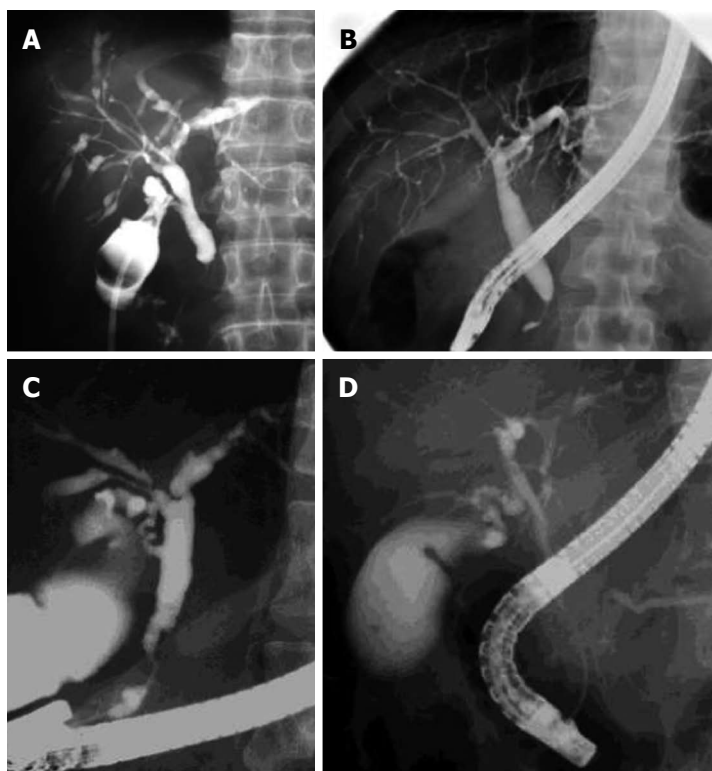


Figure 3 Cholangiographic examples of immunoglobulin G4-related sclerosing cholangitis and primary sclerosing cholangitis. Cholangiograms of immunoglobulin G4-related sclerosing cholangitis showing multiple stenoses in the intrahepatic ducts and stenosis in the intrapancreatic portion (A, B). Cholangiograms of primary sclerosing cholangitis showing a beaded appearance (C) and pruning of the intrahepatic ducts (C, D).

Table 2 Inflammatory bowel disease association in sclerosing cholangitis n (%)

Ref.	IgG4-SC	PSC	
Nishino <i>et al</i> ^[44]	0/24 (0)	15/24 (62.5)	$P < 0.0001$
Zen <i>et al</i> ^[45]	0/17 (0)	5/5 (100)	$P < 0.0001$
Ghazale <i>et al</i> ^[46]	3/53 (6)	70%	
Mendes <i>et al</i> ^[41]	NA	Elevated group (n = 12) 6/12 (50) Normal group (n = 115) 97/115 (90)	
Nakazawa <i>et al</i> ^[25]	0/62 (0)	21/31 (68)	$P < 0.0001$

IgG4-SC: Immunoglobulin G4-related sclerosing cholangitis; PSC: Primary sclerosing cholangitis.

tion. The predominance of right-sided inflammation is also a predisposing factor^[24]. The two reports showing that the histologic findings of inflammation were higher in the right compared to the left colon in PSC-IBD patients are consistent with the preferential right-sided location of colorectal cancer^[14,24].

Previous studies have shown conflicting results regarding the course of IBD after liver transplantation in patients with PSC. Recent studies have shown that the increased risk of neoplasia is maintained after liver transplant and proctocolectomy. Hanounch *et al*^[33] reported that patients with PSC-IBD after liver transplantation had a similar rate of colon neoplasia compared to those without liver transplantation (34% vs 30%, $P = 0.24$) during a mean follow-up period of 54.7 ± 47.7 mo. Jørgensen *et al*^[24] showed that macroscopic colonic

inflammation was more frequent after liver transplantation than before transplantation. The rate of relapse after transplantation was higher than that before transplantation, and the overall clinical IBD activity was also increased. Immunosuppression affects IBD activity after liver transplantation in patients with PSC.

Early cancer detection through enrollment in surveillance programs is the only strategy available to decrease cancer risk^[31]. More extensive colitis with a concurrent mild or even asymptomatic course, resulting in diagnostic delay and a lower colectomy rate, may contribute to an increased risk of colorectal cancer development^[9]. With the initial diagnosis of PSC in subjects with IBD, immediate and annual surveillance colonoscopy and biopsy analysis, of the entire colon, are recommended^[32,34].

The role of ursodeoxycholic acid (UDCA) as a chemopreventive agent is controversial. A meta-analysis showed no significant protective association between UDCA use and colorectal neoplasia. However, there was a significant chemopreventive effect on the risk of advanced colorectal neoplasia (OR = 0.35, 95%CI: 0.17-0.73), and low-dose UDCA use (8-15 mg/kg per day) was associated with a significantly reduced risk of colorectal neoplasia^[35]. There were no significant differences in cholangiocarcinoma incidence between the high-dose UDCA (17-23 mg/kg per day) and placebo groups^[36]. A recent study showed that patients treated with high-dose UDCA had a significantly higher risk of developing colorectal neoplasia during the study compared with those who received placebo (HR = 4.4, $P = 0.02$)^[37].

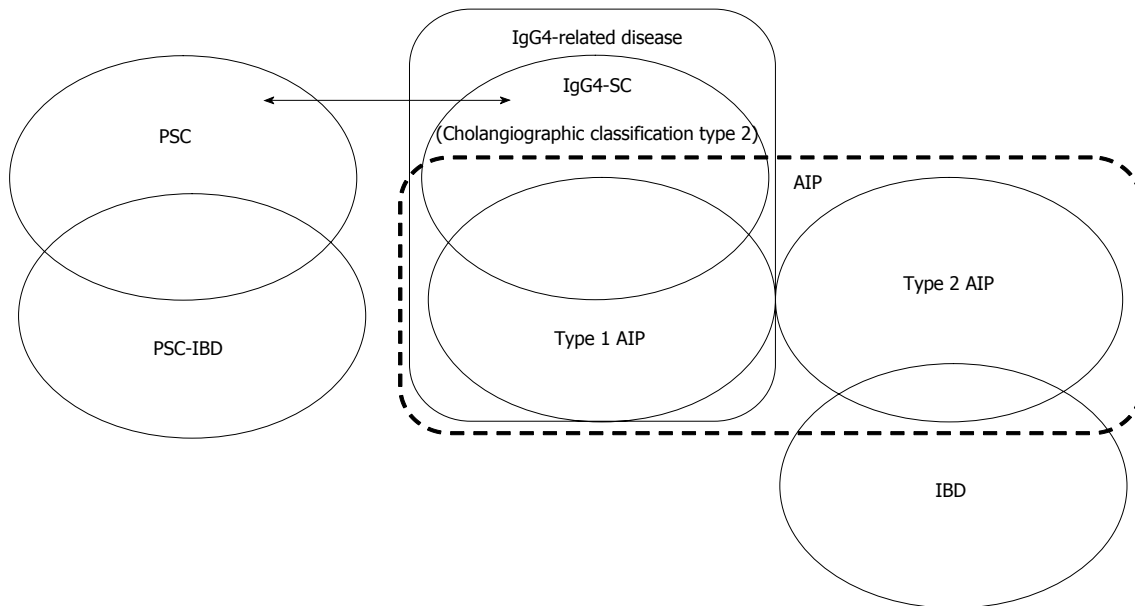


Figure 4 Correlation between inflammatory bowel disease and sclerosing cholangitis. PSC is frequently associated with characteristic PSC-IBD, whereas IgG4-SC is not associated with IBD. IgG4-SC is frequently associated with type 1 AIP, whereas type 2 AIP is frequently associated with IBD. PSC: Primary sclerosing cholangitis; PSC-IBD: IBD-associated with PSC; IBD: Inflammatory bowel disease; IgG4-SC: Immunoglobulin G4-related sclerosing cholangitis; AIP: Autoimmune pancreatitis.

THE USEFULNESS OF PSC-IBD CHARACTERISTICS IN THE DIAGNOSIS OF SCLEROSING CHOLANGITIS

Recently, IgG4-SC has attracted much attention following the emergence of clinical characteristics that distinguish it as a new clinical entity^[5]. IgG4-SC shows various cholangiographic features similar to those of pancreatic cancer, PSC, and cholangiocarcinoma^[7]. The characteristic cholangiographic features of IgG4-SC can be classified into four types based on the stricture location revealed by cholangiography and differential diagnosis^[6]. Type 2 IgG4-SC, in which stenosis is diffusely distributed throughout the intrahepatic and extrahepatic bile ducts, should be differentiated from PSC^[38] (Figure 3).

The differential diagnosis of PSC and IgG4-SC is important because patients with IgG4-SC show a good response to steroid therapy. We previously reported the differences between IgG4-SC and PSC^[7]. The age at clinical onset was significantly higher for IgG4-SC patients. Among the chief complaints in IgG4-SC, obstructive jaundice, reflecting marked concentric stenosis of the large bile duct, was most frequently observed. An elevated serum IgG4 level is a characteristic feature of IgG4-SC^[39]. An elevated serum IgG4 level and the association with type 1 autoimmune pancreatitis (AIP) are the most useful findings for discriminating between IgG4-SC and PSC^[6]. However, elevation of the serum IgG4 level alone is not useful because some PSC cases also show increased IgG4 levels. In addition, some IgG4-SC cases are not associated with AIP^[40]. Mendes *et al*^[41] measured the serum IgG4 levels in 127 patients with PSC and

found that it was elevated in 12 patients (9%). Björns-son *et al*^[42] reported elevated serum IgG4 levels in 12% of 285 patients with classic PSC. We performed a multicenter study in Japan to establish a cutoff value to differentiate IgG4-SC from controls^[43]. Serum IgG4 levels were compared between 56 patients with type 2 IgG4-SC and 110 patients with PSC. The serum IgG4 levels of the IgG4-SC patients were significantly higher than those of the PSC patients (799 ± 800 mg/dL *vs* 68.7 ± 86.0 mg/dL, respectively, $P < 0.001$). When we set the IgG4 cutoff value at 135 mg/dL, the sensitivity, specificity, and accuracy were 94.5%, 85.0%, and 90.5%, respectively. We also identified 13 of the 110 PSC patients (11.8%) with IgG4 values higher than the cutoff value of 135 mg/dL^[43]. Further studies are expected to clarify the differences between IgG4-SC and PSC patients with high serum IgG4 levels.

In contrast, the diagnosis of PSC is difficult because there are no useful markers of PSC. As such, an association with IBD is a very useful finding in the diagnosis of PSC. The frequencies of IBD associated with IgG4-SC are summarized in Table 2^[5,44,46]. No association between IBD and IgG4-SC has been reported, which is in contrast to the strong association between IBD and PSC (60%-80%)^[5,44,46]. One study reported that 6% of IgG4-SC cases were associated with IBD^[46], as IBD is common in western countries. We are unable to describe the details of IBD-associated IgG4-SC, although we speculate that the unique characteristics of PSC-IBD can be used to distinguish PSC from IgG4-SC.

IgG4-SC is frequently associated with type 1 AIP^[5]. Type 1 AIP is a different clinical entity from type 2 AIP, which is closely associated with IBD. Type 2 AIP is not

associated with IgG4-related diseases, including IgG4-SC, and elevated serum IgG4 levels are not observed^[47]. Clinically diagnosed IBD is incorporated in the diagnostic criteria for type 2 AIP in international consensus diagnostic criteria for autoimmune pancreatitis^[47]. These complicated associations are illustrated in Figure 4. There are no reports concerning the characteristics of IBD associated with type 2 AIP. If IBD associated with type 2 AIP shows characteristic findings, they might be useful not only in discriminating type 2 AIP from type 1 AIP, but also in elucidating the mechanism of sclerosing cholangitis.

In summary, PSC-IBD is associated with an increased incidence of pancolitis, mild symptoms and colorectal malignancy. Although an increased incidence of pancolitis is also a characteristic finding, some cases are endoscopically diagnosed as right-sided UC. Pathological studies have revealed that the findings of inflammation were more prevalent in the right colon than the left colon. The frequency of rectal sparing and backwash ileitis should be investigated in a future study based on the same definition. The rare association between IBD and IgG4-SC and the unique characteristics of PSC-IBD are useful for discriminating between PSC and IgG4-SC. In particular, when IBD is characterized by right-sided UC, rectal sparing, and backwash ileitis, the possible diagnosis of PSC-IBD should be considered. In the presence of multiple biliary stenoses on magnetic resonance cholangiography, inflammatory findings dominant in the right colon and rectal sparing by total colonoscopy, invasive endoscopic retrograde cholangiography can be avoided in clinical practice.

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