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Clinicopathological differentiation between sclerosing cholangitis with autoimmune pancreatitis and primary sclerosing cholangitis

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Background. The present study was undertaken to identify the clinicopathological differences between sclerosing cholangitis with autoimmune pancreatitis (SC-AIP) and primary sclerosing cholangitis (PSC). ***Methods.*** We retrospectively compared the clinical, cholangiographic, and liver biopsy findings between 24 cases of PSC and 24 cases of SC-AIP. ***Results.*** Patient age at the time of diagnosis was significantly lower in the PSC group than in the SC-AIP group. The peripheral blood eosinophil count was significantly higher in the PSC group than in the SC-AIP group, but the serum IgG4 level was significantly higher in the SC-AIP group. Cholangiography revealed band-like strictures, beaded appearance, and pruned-tree appearance significantly more frequently in PSC, whereas segmental strictures and strictures of the distal third of the common bile duct were significantly more common in SC-AIP. Liver biopsy revealed fibrous obliterative cholangitis only in the PSC specimens. No advanced fibrous change corresponding to Ludwig's stages 3 and 4 was observed in any of the SC-AIP specimens. IgG4-positive plasma cell infiltration of the liver was significantly more severe in SC-AIP than in PSC. Subsequent cholangiography showed no improvement in any of the PSC cases, but all SC-AIP patients responded to steroid therapy, and improvement in the strictures was observed cholangiographically. ***Conclusions.*** Based on the differences between the patients' ages and blood chemistry, cholangiographic, and liver biopsy findings, SC-AIP should be differentiated from PSC.

Key words: autoimmune pancreatitis, sclerosing cholangitis, primary sclerosing cholangitis, IgG4

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Introduction

Autoimmune pancreatitis (AIP) has recently been proposed to be a disease entity characterized by the following unique clinical, diagnostic imaging, and pathological features: highest incidence in elderly men, pancreatic enlargement, irregularly narrowed pancreatic duct on endoscopic retrograde cholangiopancreatography (ERCP), increased serum IgG and IgG4 levels, presence of serum autoantibodies, and lymphoplasmacytic infiltration and fibrosis of the pancreas.[1–5] AIP is often associated with sclerosing cholangitis (SC).[6–13]

The cholangiographic findings in SC with AIP (SC-AIP) and primary sclerosing cholangitis (PSC) are similar.[10,11] Both SC and the pancreatic lesions in AIP respond well to steroid therapy or biliary drainage,[9,14] whereas even when PSC is treated it remains a progressive disease that involves the intra- and extrahepatic bile ducts and leads to biliary cirrhosis. Since corticosteroid therapy is not effective against PSC, and liver transplantation is the only effective treatment for end-stage disease,[15,16] the differential diagnosis between SC-AIP and PSC must be made before deciding on treatment. In this study, we retrospectively evaluated the clinicopathological similarities and differences between SC-AIP and PSC to facilitate making the differential diagnosis.

Patients and methods

Between January 1982 and March 2005, 24 SC patients met the criteria for PSC published in 2003.[17] In brief, cholangiography had revealed typical findings throughout the biliary tree, and other causes of secondary sclerosing cholangitis had been excluded. The other 24 patients met the revised proposal criteria for AIP established by the Research Committee of Intractable Diseases of the Pancreas[18] and had biliary involvement

(SC-AIP) that mimicked PSC. The criteria for AIP were (1) diffuse or segmental narrowing of the main pancreatic duct with irregular wall on ERCP images and diffuse or localized enlargement of the pancreas according to imaging studies such as abdominal ultrasonography (US), computed tomography (CT), and magnetic resonance imaging; (2) an elevated serum γ-globulin level, IgG level, and/or IgG4 level, or the presence of serum autoantibodies such as antinuclear antibodies and rheumatoid factor; and (3) marked interlobular fibrosis and prominent infiltration by lymphocytes and plasma cells in the periductal area, occasionally with lymphoid follicles in the pancreas. Fulfillment of criterion 1 plus criterion 2 and/or 3 was required to make the diagnosis of AIP. More than one-third of the entire length of the pancreas was involved in all 24 SC-AIP patients in the present study.

Liver biopsy was performed in all 24 PSC patients and in eight SC-AIP patients. Nine of the 24 SC-AIP patients underwent surgical treatment, and 15 SC-AIP patients could be followed up. The follow-up period was measured as the interval between the time of diagnosis and the most recent follow-up examination.

Diagnostic imaging

Imaging studies, including US, CT, and ERCP, were performed. Images of the pancreatic duct and biliary tract were obtained by ERCP. The pancreas was evaluated for swelling, and the bile duct wall and gallbladder wall for thickening by US or CT, as described previously.[9]

Cholangiogram scoring

Cholangiopancreatograms were obtained by the routine procedure during ERCP in all 48 cases. The cholangiograms were reviewed retrospectively by two gastroenterologists without knowledge of the clinical findings or outcomes. Diagnoses were made by consensus.

Each cholangiogram was scored for specifically defined characteristics, including stricture length, characteristic findings, and site of the strictures, according to Craig et al.[19] and Nakazawa et al.[10]

In brief, strictures were classified and scored as follows: band-like stricture (1–2 mm) (0 = absent, 1 = one region, 2 = two or more regions); segmental stricture (>3 mm) (0 = absent, 1 = one site, 2 = two or more sites) (Figs. 1 and 2); and long stricture with prestenotic dilatation (>10 mm) (0 = absent, 1 = one site, 2 = two or more sites). Band-like strictures and segmental strictures were found in both the intrahepatic and extrahepatic ducts. Long strictures with prestenotic dilatation were found only in the intrahepatic ducts. The characteristic findings of PSC were defined as the beaded appearance of the bile ducts (short, annular strictures alternating with normal or minimally dilated segments; 0 = absent, 1 = one site, 2 = two or more sites); pruned-tree appearance (diminished arborization of intrahepatic ducts and pruning; 0 = absent, 1 = one site, 2 = two or more sites); diverticulum-like formation (outpouching resembling diverticula, often protruding between adjacent strictures; 0 = absent, 1 = one site, 2 = two or more sites); shaggy appearance (mural irregularities, producing a characteristic shaggy appearance without stenosis; 0 = absent, 1 = <3 cm in length, 2 = 3 cm or longer). Other stricture sites were scored as follows: stricture in the hepatic hilar region (0 = absent, 1 = >25% narrowing of the duct, 2 = 0%–25% narrowing of the duct) and stricture in the distal third of common bile duct (0 = absent, 1 = >25% narrowing of the duct, 2 = 0%–25% narrowing of the duct).

Histopathology and immunohistochemistry

The liver biopsy specimens from the eight SC-AIP patients and all 24 PSC patients were fixed in 20% formalin and embedded in paraffin. The blocks were cut into sections 3 μm thick, and the sections were examined after staining with hematoxylin and eosin, Mallory stain, silver reticulin stain, Victoria blue stain for copper-binding protein, and Perls' iron stain. The histologic findings in the liver biopsy specimens were evaluated according to the Ludwig criteria.[20] The histopathology was assessed by T.N. and E.H. without knowledge of the clinical or biochemical data of the patients. The immunohistochemical study was performed by the avidin–biotin complex (ABC) method with reagents provided by Vector Laboratories (Burlingame, CA, USA). The antibodies used to identify the inflammatory cells in the liver were CD4 antibody (1:100, Novocastra, Newcastle upon Tyne, UK), CD8 antibody (1:100, Novocastra), IgG1 antibody (1:500, Binding Site, San Diego, CA, USA), IgG2 antibody (1:500, Binding Site), IgG3 antibody (1:500, Binding Site), and IgG4 antibody (1:500, Binding Site). After incubation with antibody at 4°C overnight, biotinylated goat anti-rabbit serum IgG (Vector) was used as the secondary antibody, and immunoreactive deposits were visualized with 3,3′-diaminobenzidine.

The numbers of immunohistochemically identified CD4- and CD8-positive T cells and of IgG1-, IgG2-, IgG3-, and IgG4-positive plasma cells per high power field (hpf) of the liver were counted. Five fields of each specimen were analyzed per case, and the degree of infiltration was graded as: 4 (severe, ≥100/hpf), 3 (moderate, ≥30 to <100/hpf), 2 (mild, ≥10 to <30/hpf), 1 (slight, ≥5 to <10/hpf), or 0 (negative, <5/hpf).

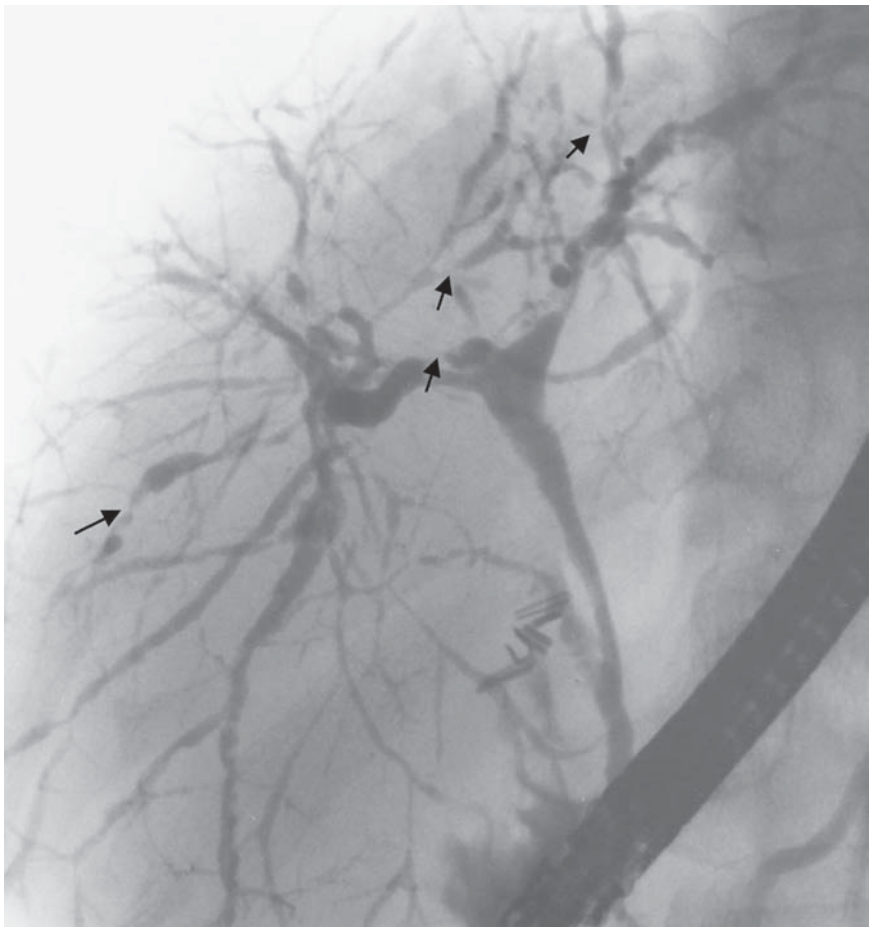

Fig. 1. Endoscopic retrograde cholangiography of a case of primary sclerosing cholangitis. Multiple band-like strictures (*arrows*) were observed

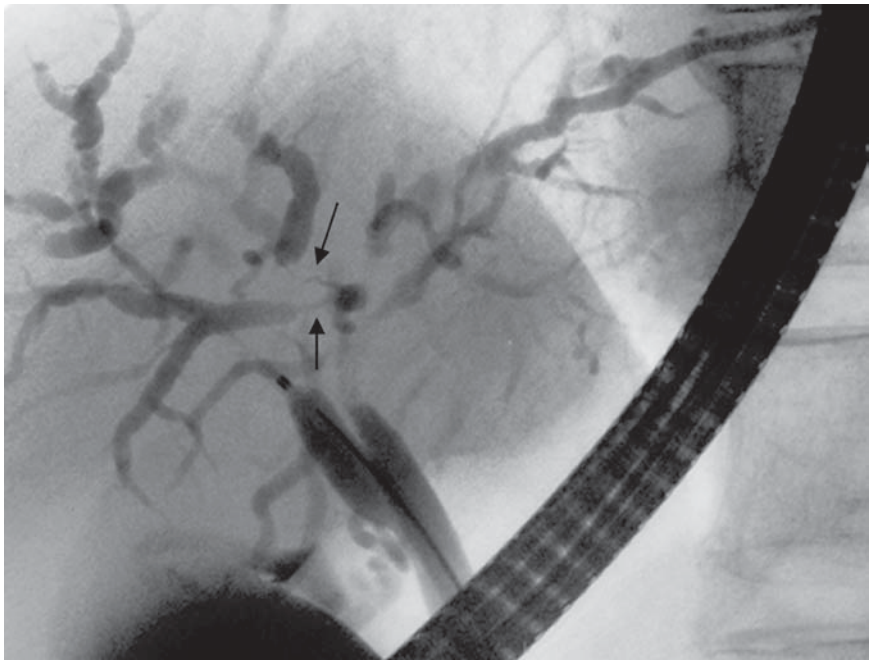

Fig. 2. Endoscopic retrograde cholangiography in a case of sclerosing cholangitis with autoimmune pancreatitis. Multiple segmental strictures (*arrows*) in the intrahepatic bile ducts were observed

Statistical analysis

The data were statistically analyzed by Student's *t* test, the χ-squared test, and the Mann-Whitney *U* test to compare parameters. A *P* value of <0.05 was considered statistically significant.

Results

Clinical features

Age, sex, initial symptoms, and associated diseases are shown in Table 1. Patient age at the time of diagnosis was significantly higher in the SC-AIP group than in the PSC group (65.3 ± 8.0 years vs. 41.0 ± 18.8 years, $P < 0.0001$). There was one peak in the age distribution of the SC-AIP patients between 60 and 70 years of age, but two peaks in the age distribution of the PSC patients, one in the second to third decade, and the other between 50 and 60 years of age. Inflammatory bowel disease was associated with PSC only and observed in 15 of the patients. Total colon-type ulcerative colitis was diagnosed in 60% (9/15), and colitis with aphthae, erosions, or erythema predominantly involving the right side of the colon that could not be definitely diagnosed as ulcerative colitis was observed in the other 40% (6/15). None of the patients in this study had Crohn's disease. There was no evidence of chronic pancreatitis with diffuse or segmental irregular narrowing of the main pancreatic duct in any of the PSC patients. Type 2 diabetes mellitus was significantly more common in the SC-AIP group [58.3% (14/24) vs. 8.3% (2/24), $P = 0.0008$]. Salivary gland swelling was detected only in the SC-AIP group (Table 1). Biliary carcinoma was associated with PSC in three cases, and the diagnosis of both was made simultaneously in all three cases (Table 1).

Laboratory findings

The laboratory findings are shown in Table 2. The serum bilirubin, transaminase, alkaline phosphatase (ALP), and γ-glutamyl transpeptidase (γ-GTP) values were elevated in both the SC-AIP group and the PSC group, and none of the differences in these laboratory values between the groups were significant. The peripheral eosinophil count was significantly higher in the PSC group, and the serum IgG4 values were significantly higher in the SC-AIP group (463 ± 355 mg/dl vs. 32 ± 10 mg/dl, $P = 0.003$). Antinuclear antibodies were positive in 80% of the SC-AIP patients and in 56% of the PSC patients (Table 2).

Cholangiographic findings

The cholangiographic findings in the SC-AIP group and PSC group are compared in Table 3. Band-like strictures (Fig. 1), beaded appearance, pruned-tree appearance, and diverticulum-like formations were found in the PSC group alone. Shaggy appearance of the bile ducts was significantly more common in PSC. Both segmental stricture (Fig. 2) and stricture of the distal third of the common bile duct were significantly more common in the SC-AIP group. Discriminant analysis did not identify any significant factors.

The time course of the cholangiographic findings in the SC-AIP group and PSC group is compared in Table 4. The cholangiographic changes in the PSC cases progressed during long-term follow up, but in the short term in several cases, they either did not progress or improved to some degree. The clinical course of the one PSC patient whose cholangiogram showed improvement was as follows. The patient was a 24-year-old man whose cholangiogram showed multiple band-like strictures in the intrahepatic bile duct and shaggy appear-

Table 1. Clinical features of SC-AIP patients and PSC patients

	SC-AIP ($n = 24$)	PSC ($n = 24$)	Statistical significance
Sex (male/female)	16/8	13/1	NS
Ages (years, mean ± SD) (median)	65.3 ± 8.0 (65)	41.0 ± 18.8 (34)	$P < 0.0001$
Duration of follow-up (months)	56 ± 53	90 ± 72	NS
Initial symptoms (yes/no)			
Obstructive jaundice	16/8	6/18	$P = 0.004$
Abdominal pain	6/18	8/16	NS
Associated diseases or symptoms (yes/no)			
Chronic pancreatitis with diffuse irregular narrowing of the main pancreatic duct	24/0	0/24	$P < 0.0001$
Diabetes mellitus	14/10	2/22	$P < 0.0008$
Salivary gland swelling	8/16	0/24	$P < 0.007$
Inflammatory bowel disease	0/24	15/9	$P < 0.0001$
Biliary carcinoma	0/24	3/21	NS

SC-AIP, sclerosing cholangitis with autoimmune pancreatitis; PSC, primary sclerosing cholangitis; NS, not significant

Table 2. Laboratory findings of SC-AIP patients and PSC patients

Parameter[a]	SC-AIP ($n = 24$)	PSC ($n = 24$)	Statistical significance
Total bilirubin (0.1–0.4 mg/dl)	4.8 ± 5.2	2.8 ± 7.4	NS
AST (13–33 U/l)	97 ± 130	84 ± 49	NS
ALT (6–30 U/l)	120 ± 136	93 ± 62	NS
ALP (115–359 U/l)	839 ± 854	1450 ± 1140	NS
γ-GTP (11–58 U/l)	453 ± 548	500 ± 520	NS
Amylase (40–125 U/l)	78 ± 58	64 ± 58	NS
WBC (/mm^3)	5850 ± 1170	7260 ± 2740	NS
Eosinophils (/mm^3)	284 ± 219	880 ± 1040	$P = 0.013$
γ-globulin (g/dl)	1.6 ± 1.0	1.3 ± 0.9	NS
IgG (870–1700 mg/dl)	2270 ± 1008	1876 ± 712	NS
IgA (110–410 mg/dl)	251 ± 83	314 ± 165	NS
IgM (33–190 mg/dl)	126 ± 81	199 ± 130	NS
IgG4 (<135 mg/dl)	463 ± 355	32 ± 10	$P = 0.003$
Antinuclear antibody-positive	80% (12/15)	56% (10/18)	NS

AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; γ-GTP, γ-glutamyl transpeptidase; WBC, white blood cell count
[a] Normal ranges are shown in parentheses

Table 3. Comparison between the cholangiograms of SC-AIP patients and PSC patients

Cholangiographic findings (scores)	SC-AIP ($n = 24$) no. of patients	PSC ($n = 24$) no. of patients	Statistical significance
Band-like stricture (2/1/0)	0/0/24	8/8/8	$P < 0.0001$
Segmental stricture (2/1/0)	4/20/0	3/7/14	$P = 0.0009$
Long stricture with prestenotic dilatation (2/1/0)	0/3/21	0/2/22	NS
Beaded appearance (2/1/0)	0/0/24	6/6/12	$P < 0.0001$
Pruned-tree appearance (2/1/0)	0/0/24	9/4/11	$P < 0.0001$
Diverticulum-like outpouching (2/1/0)	0/0/24	1/2/21	NS
Shaggy appearance (2/1/0)	0/1/23	4/7/13	$P = 0.0009$
Stricture of the bile duct in the hepatic hilar resion (2/1/0)	1/0/23	2/2/20	NS
Strictures of distal third of common bile duct (2/1/0)	9/14/1	1/2/21	$P < 0.0001$

Table 4. Comparison between the time course of cholangiographic changes and clinical course of SC-AIP patients and PSC patients

	SC-AIP	PSC
Cholangiographic changes	$n = 15$	$n = 19$
Progressive	1	15
No change	0	3
Improvement/remission	14	1
Clinical course	$n = 15$	$n = 24$
No recurrence	14	1
Recurrence/progression	1	12
Liver failure	0	8
Death from biliary Ca	0	3

ance of the extrahepatic bile duct. He also had colitis with aphthae, erosions, and erythema predominantly involving the right side of the colon. The liver biopsy specimen showed Ludwig's stage 1 fibrosis. After four and a half years of treatment with sulfadimethoxine, a second cholangiogram showed slight improvement of the band-like strictures, and the shaggy appearance in the extrahepatic bile duct had completely resolved. The serum IgG4 level was 32 mg/dl. By contrast, all SC-AIP patients responded to steroid therapy, and their cholangiograms improved in every case but one. The exception was a case in which a cholangiogram showed recurrence of the stricture, and a temporary increase in the dose of oral prednisolone was required.

Thickening of the bile duct wall and gallbladder wall

Thickening of the bile duct wall was detected in all 24 SC-AIP cases (extrahepatic bile duct alone in 21 cases, both the intra- and extrahepatic bile ducts in the other three cases). Thickening of the bile duct wall was often detected in segments with no abnormal findings on cholangiography as well as in the stenotic portion. Thicken-

ing of the bile duct wall was also detected in all 24 PSC cases (extrahepatic bile duct alone in 15 cases, intra- and extrahepatic bile ducts in five cases, and intrahepatic bile duct alone in three cases). The part of the bile duct wall that was thickened usually corresponded to the stenotic portion on cholangiography, but it was slightly more difficult to detect thickening of the intrahepatic bile duct wall than of the extrahepatic bile duct wall. The echogenic pattern of thickening of the bile duct wall was similar in both the SC-AIP and PSC patients.

Thickening of the gallbladder wall was observed in 15 of the SC-AIP patients (15/24, 63%), as opposed to in only four of the PSC patients (4/24, 17%). The difference in prevalence was statistically significant (P = 0.0011).

Pancreatic changes

Diffuse or segmental enlargement of the pancreas was detected in all SC-AIP patients with a narrowed main pancreatic duct, but no abnormal findings were detected by US, abdominal CT, or pancreatography in any of the 24 PSC cases.

Liver biopsy findings and immunohistochemical findings

None of the liver biopsy specimens from the SC-AIP patients showed advanced portal or periportal fibrosis, corresponding to Ludwig's stage 3 and stage 4, respectively. Portal or periportal hepatitis consisting of plasma cell and lymphocyte infiltration (8/8) was mild to moderate and associated or not associated with lobular hepatitis. Mild to moderate eosinophilic infiltration was also observed. Duct and ductular proliferation (8/8) with or without zone 3 cholestasis was also seen, but fibrous cholangitis (onionskin appearance) was detected in only one of the liver biopsy specimens (Table 5).

The liver biopsy specimens from the PSC patients showed stage 1 to 4 fibrosis (stage 1, two cases; stage 2, ten cases; stage 3, eight cases; and stage 4, five cases) (Table 5). Inflammatory infiltrates consisting of lymphocytes and plasma cells were mild to severe. Mild to moderate eosinophil infiltration was also observed. Duct and ductular proliferation was conspicuous. Fibrous cholangitis was observed in 38% (9/24) of the PSC patients, and fibrous obliterative cholangitis in 21% (5/24). Piecemeal necrosis was observed in 25% (6/24).

Immunohistochemically, there were no differences between the SC-AIP group and the PSC group in the numbers of CD4-positive and CD8-positive lymphocyte infiltrates. IgG4-positive and IgG1-positive plasma cell infiltration was significantly more severe in the SC-AIP group than in the PSC group (Table 6; Figs. 3 and 4).

Table 5. Liver biopsy findings in SC-AIP patients and PSC patients

	SC-AIP (n = 8)	PSC (n = 24)
Ludwig's stage		
1	1	2
2	7	10
3	0	8
4	0	5
Fibrous cholangitis (onionskin appearance) (yes/no)	1/7	9/15
Fibrous obliterative cholangitis (yes/no)	0/8	5/19
Piecemeal necrosis (yes/no)	0/8	6/18

Clinical course

Fourteen SC-AIP patients received steroid therapy, and the other SC-AIP patient was followed up without steroid therapy. All SC-AIP patients had a favorable outcome without liver failure. The PSC patients, on the other hand, had a progressive clinical course based on the cholangiographic findings and/or histological findings (Table 4). Eight of the 24 PSC the patients developed liver failure, and three other PSC patients died of biliary cancer.

Discussion

The median age at the time of diagnosis of PSC in Western countries has been reported to be in the fourth decade.[15] The average age of the PSC patients at the time of diagnosis in this study was 41 years, almost the same as in Western countries. The average age of the SC-AIP patients, however, was 65 years, significantly higher than that of the PSC patients, and comparable to that of AIP patients.[5,6,9] Takikawa et al.[21] recently reported two peaks in the age distribution of PSC patients in Japan: the first at the time of diagnosis in the second to third decade, and the second between

Table 6. Immunohistochemical findings in the liver in SC-AIP and PSC

Type of infiltrating cell	SC-AIP (n = 8)	PSC (n = 11)	Statistical significance
CD4	3.0 ± 0.9	3.4 ± 0.9	NS
CD8	3.3 ± 0.8	3.5 ± 0.5	NS
IgG1	2.0 ± 0.6	1.2 ± 0.9	P = 0.048
IgG2	1.2 ± 0.8	1.0 ± 0.9	NS
IgG3	0.5 ± 0.5	0.2 ± 0.4	NS
IgG4	2.2 ± 0.8	0.1 ± 0.3	P = 0.002

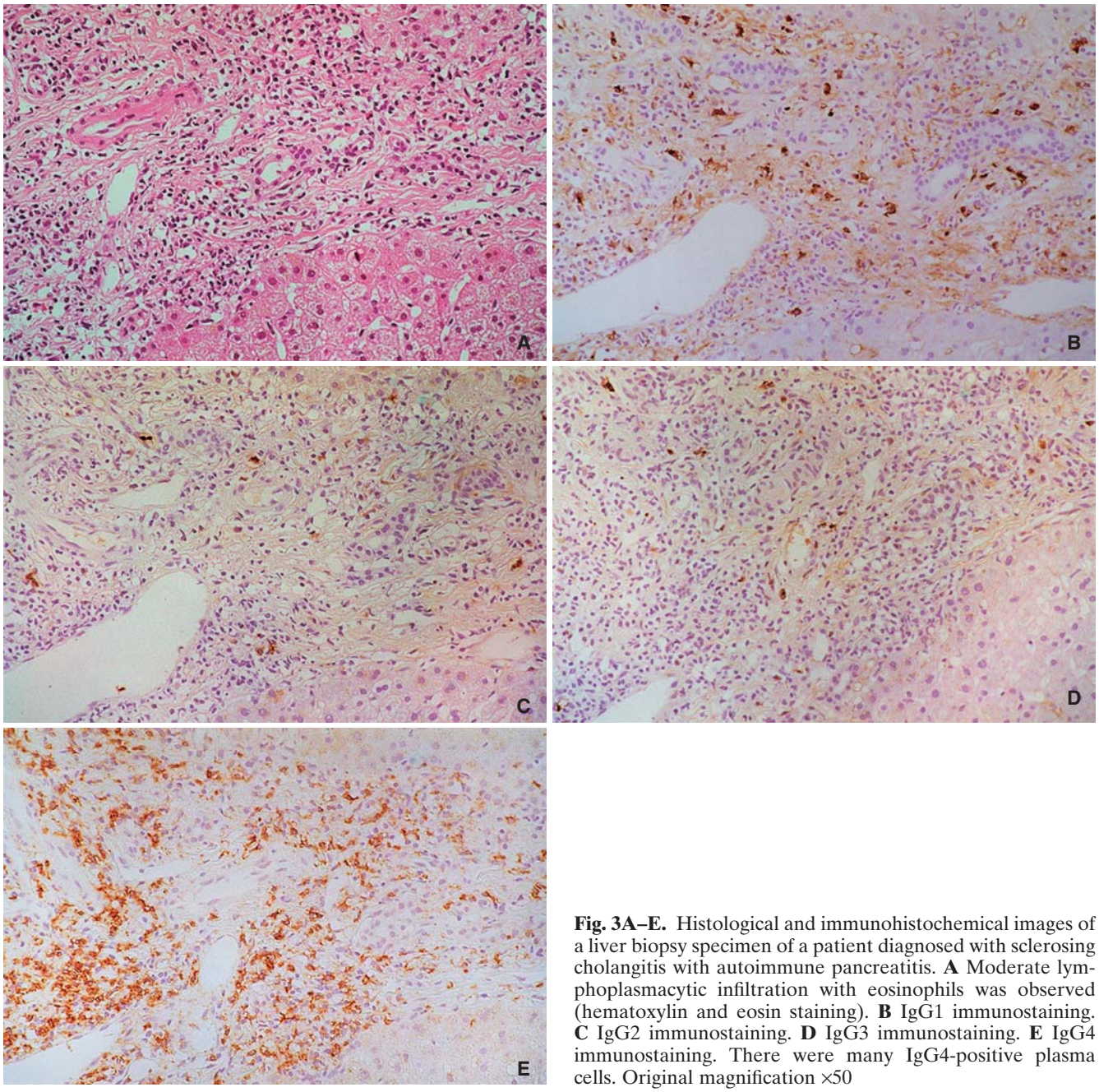

Fig. 3A–E. Histological and immunohistochemical images of a liver biopsy specimen of a patient diagnosed with sclerosing cholangitis with autoimmune pancreatitis. **A** Moderate lymphoplasmacytic infiltration with eosinophils was observed (hematoxylin and eosin staining). **B** IgG1 immunostaining. **C** IgG2 immunostaining. **D** IgG3 immunostaining. **E** IgG4 immunostaining. There were many IgG4-positive plasma cells. Original magnification ×50

50 and 60 years of age, and the same two peaks in the age distribution of PSC patients were observed in the present study.

Inflammatory bowel disease was associated with PSC alone in this study, and its frequency was 63% (15/24), about the same as in Western countries.[22,23] Total colon-type ulcerative colitis was observed in 60% (9/15) of the 15 PSC patients with inflammatory bowel disease, and colitis with aphthae, erosion, or erythema predominantly involving the right side of the colon that could not be definitely diagnosed as ulcerative colitis was observed in the other 40% (6/15). The latter type of colitis was considered consistent with the so-called colitis associated with PSC that has been proposed by several other authors.[24,25] The SC-AIP in our study, however, was never complicated by inflammatory bowel disease.

Hamano et al.[3] reported finding a significant and specific elevation of the serum IgG4 level in AIP patients. The serum IgG4 values in our study were significantly higher in the SC-AIP patients than in the PSC patients, and none of the PSC patients had an elevated IgG4 level. Nakazawa et al.[10,11] reported that an elevated serum IgG4 level is a clinically significant means of differentiating SC-AIP from PSC, and we agreed with

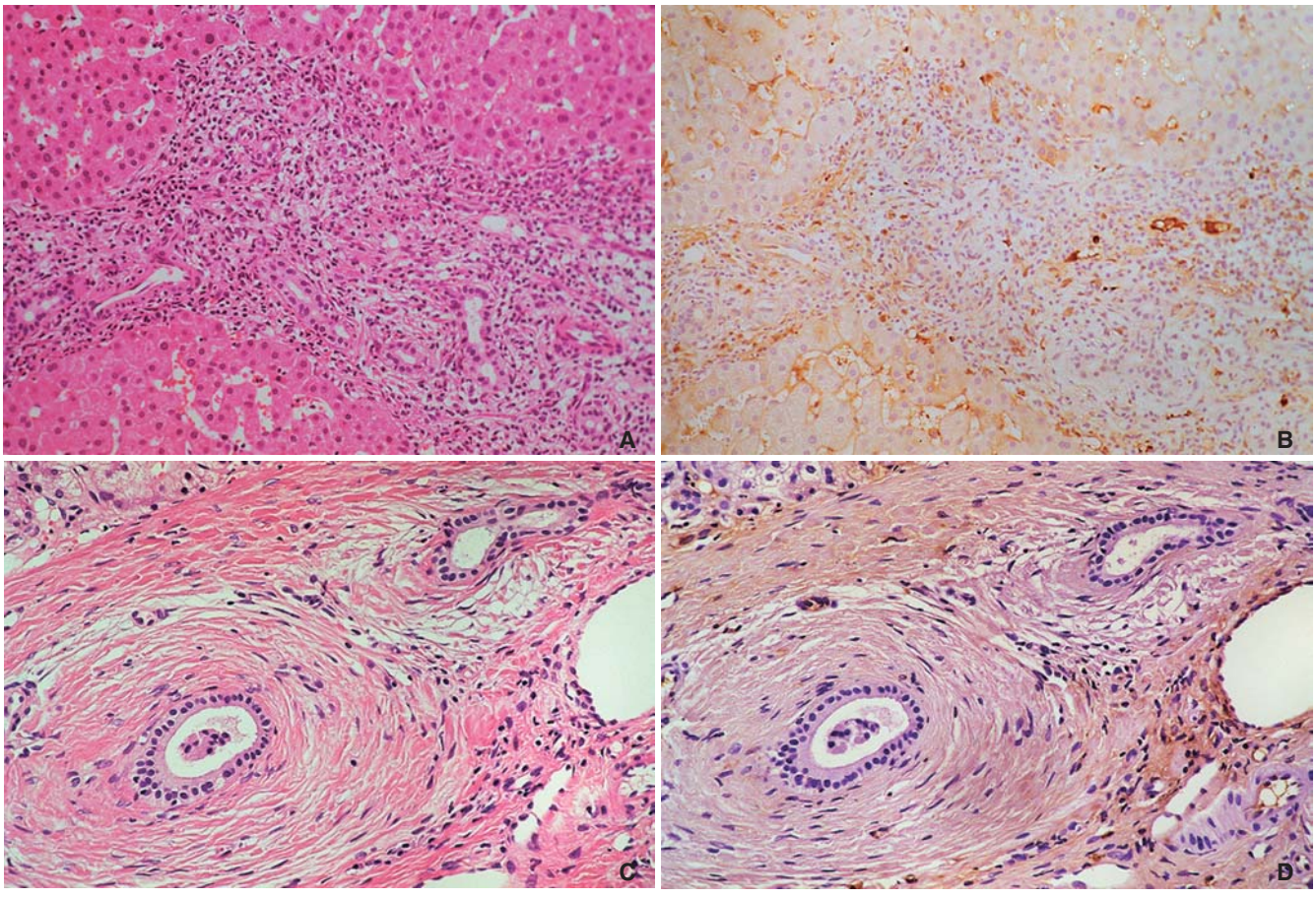

Fig. 4A–D. Histological and immunohistochemical images of a liver biopsy specimen of a patient with primary sclerosing cholangitis. **A** Various degrees of lymphocytic infiltration with a moderate degree of eosinophils were observed (hematoxylin and eosin staining). **B** IgG4 immunostaining. There were a few IgG4-positive plasma cells. **C** Fibrous cholangitis was observed. **D** IgG4 immunostaining. Hardly any IgG4-positive plasma cells were observed. Original magnification ×50

their proposal that the serum IgG4 level is a useful marker for differentiating between SC-AIP and PSC.

The cholangiographic findings in the present study can be summarized as follows. Band-like strictures, beaded appearance, and pruned-tree appearance of the bile duct were observed significantly more frequently in PSC, whereas segmental strictures and stricture of the distal third of the common bile duct were significantly more common in SC-AIP. Nakazawa et al.[10] reported that band-like strictures, beaded or pruned tree appearance, and diverticulum-like formations were significantly more frequent in PSC, whereas segmental stricture, long stricture with prestenotic dilatation, and stricture of the distal common bile duct were significantly more common in SC-AIP. The cholangiographic findings in our study were consistent with those of Nakazawa et al.[10] We concluded that the characteristic cholangiographic features allow differentiation of PSC from SC-AIP.

Subsequent cholangiography showed no improvement in any of the PSC cases, whereas most of the SC-AIP patients responded to steroid therapy, and improvement in the strictures was observed. Moreover, the clinical course of most PSC patients was progressive, and some PSC patients developed liver failure. By contrast, all of the SC-AIP patients had a favorable outcome, as previously reported.[26]

Abdominal US or endoscopic US studies have demonstrated bile duct wall thickening in segments with no abnormal findings on cholangiography, as well as in the stenotic portion in AIP patients.[8] We confirmed that bile duct wall thickening was also present in segments with no abnormal findings by cholangiography in SC-AIP patients. We also confirmed detection of bile duct wall thickening in all PSC patients, but because the echogenic pattern of the bile duct wall thickening in the SC-AIP patients and PSC patients was similar, we could not differentiate SC-AIP from PSC based on the evidence of bile duct wall thickening. In the present study, we also demonstrated a high prevalence of gallbladder wall thickening in SC-AIP patients, as previously reported,[9] and the prevalence of gallbladder wall thicken-

ing was significantly higher in the SC-AIP patients than in the PSC patients. We concluded that the gallbladder wall should be carefully examined to determine whether it is thickened.

Zen et al.[13] reported observing extensive and dense fibrosis with marked lymphoplasmic infiltration, especially by IgG4-positive plasma cells, in affected bile ducts in the liver of sclerosing pancreatitis-associated sclerosing cholangitis, which corresponds to SC-AIP, but they detected few or hardly any IgG4-positive plasma cells in the affected bile ducts in the liver in PSC. We also observed that the extrahepatic bile ducts of the AIP patients were characterized by diffuse lymphoplasmacytic infiltration and marked interstitial fibrosis, and immunohistochemistry revealed that the diffusely infiltrating cells predominantly consisted of CD8- or CD4-positive T lymphocytes and IgG4-positive plasma cells.[9] The results of the histological examination of the liver biopsy specimens in the present study can be summarized thus: (1) fibrous tissue around the bile duct was observed in SC-AIP as well as in PSC, but was less severe in SC-AIP; (2) fibrous obliterative cholangitis was observed in PSC alone; and (3) IgG4-positive plasma cell infiltration was significantly more severe in SC-AIP than in PSC. We consider the difference between fibrous cholangitis and fibrous obliterative cholangitis and its clinical significance to be that fibrous obliterative cholangitis is a feature of advanced destructive cholangitis and a pathological clue for PSC, whereas fibrous cholangitis represents a healing stage of any type of cholangitis.[27] We concluded that the abundant IgG4-positive plasma cell infiltration in the liver is another useful marker for differentiating between SC-AIP and PSC.

Based on the patients' ages, blood chemistry findings, associated diseases, cholangiographic findings, liver biopsy findings, and clinical course, SC-AIP and PSC are different clinicopathological entities, and in this study we identified clinicopathological differences that facilitate making the differential diagnosis between them.

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