

IgG4-related Sclerosing Cholangitis With and Without Hepatic Inflammatory Pseudotumor, and Sclerosing Pancreatitis-associated Sclerosing Cholangitis

Do They Belong to a Spectrum of Sclerosing Pancreatitis?

Yoh Zen, MD, PhD,*† Kenichi Harada, MD, PhD,* Motoko Sasaki, MD, PhD,*
Yasunori Sato, MD, PhD,* Koichi Tsuneyama, MD, PhD,‡ Joji Haratake, MD, PhD,§
Hiroshi Kurumaya, MD, PhD,¶ Kazuyoshi Katayanagi, MD, PhD,¶ Shinji Masuda, MD, PhD,||
Hideki Niwa, MD,|| Hideo Morimoto, MD, PhD,** Atsuo Miwa, MD, PhD,†† Akio Uchiyama, MD,††
Bernard C. Portmann, MD, FRCPath,‡‡ and Yasuni Nakanuma, MD, PhD*

Abstract: Sclerosing cholangitis (SC) is a heterogeneous disease entity. Different etiologies such as choledocholithiasis, biliary tumor, or pericholangitis can manifest as SC. Hepatic inflammatory pseudotumor (IP) is rarely associated with SC (sclerosing cholangitis associated with hepatic inflammatory pseudotumor; SC-hepatic IP), but sclerosing pancreatitis (SP) is not infrequently associated with bile duct lesions (sclerosing pancreatitis-associated sclerosing cholangitis; SP-SC). In this study, we compared the histologic changes of hepatic hilar and extrahepatic bile duct lesions of SC (7 cases), SC-hepatic IP (5 cases), SP-SC (5 cases), and typical primary sclerosing cholangitis (PSC) (5 cases). Histologically, all SP-SC cases showed extensive and dense fibrosis with marked lymphoplasmacytic infiltration, many eosinophils, and obliterative phlebitis. Four cases of SC showed bile duct lesions similar to those of SP-SC, whereas other three cases of SC showed milder lymphoplasmacytic infiltration, scant eosinophilic cell infiltration, and no obliterative phlebitis. All SC-hepatic IP cases showed bile duct lesions identical to those of SP-SC. Immunohistochemically, many IgG4-positive plasma cells were found in the bile duct lesions of all SP-SC cases, 4 SC cases with marked lymphoplasmacytic infiltration, and all SC-hepatic IP cases.

By contrast, IgG4-positive plasma cells were scarce or hardly found in the remaining 3 SC cases and all PSC cases. In conclusion, 4 SC cases and all SC-hepatic IP cases showed bile duct lesions identical to those of SP-SC, suggesting that these three conditions may be a single disease entity. Their pathogenesis may be similar or closely related to that of SP, and in that respect they may represent an IgG4-related biliary disease. They may respond to steroid therapy as SP does.

Key Words: primary sclerosing cholangitis, sclerosing pancreatitis, IgG4, inflammatory pseudotumor, steroid therapy

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Sclerosing cholangitis (SC) is a heterogeneous disease, which may be associated with choledocholithiasis, biliary tumor, obstruction of bile ducts, infection, or pericholangitis. SC of unknown etiology is called primary sclerosing cholangitis (PSC), which is a chronic cholestatic syndrome characterized by chronic fibrosing inflammation of the intrahepatic and extrahepatic biliary tree.^{18,19} PSC is not a uniform disease clinically; for example, some PSC cases are associated with ulcerative colitis or Crohn's disease, and some cases have antineutrophil cytoplasmic autoantibody (ANCA) in serum.¹⁹ In addition, several clinicolaboratory characteristics are reportedly different between western countries and Japan: PSC patients in Japan have higher incidence of eosinophilia, less high frequent association with inflammatory bowel disease, and relatively frequent association with chronic pancreatitis compared with those in western countries.^{19,34} As will be discussed later, one of the reasons for such geographic differences may be dependent on whether SC associated with sclerosing pancreatitis (SP) or autoimmune pancreatitis¹¹ is included in PSC or not.

From the *Department of Human Pathology, Kanazawa University Graduate School of Medicine, Kanazawa, Japan; †Department of Pathology, Fukui Saiseikai Hospital, Fukui, Japan; ‡First Department of Pathology, Toyama Medical and Pharmaceutical University School of Medicine, Toyama, Japan; §Department of Pathology, Kurobe City Hospital, Kurobe, Japan; ¶Department of Pathology, Ishikawa Prefectural Central Hospital, Kanazawa, Japan; ||Department of Pathology, Kouseiren Takaoka Hospital, Takaoka, Japan; **Department of Gastroenterology, Kanazawa National Hospital, Kanazawa, Japan; ††Department of Pathology, Toyama Prefectural Central Hospital, Toyama, Japan; and ‡‡Institute of Liver Studies, King's College Hospital, London, UK.

Reprints: Yasuni Nakanuma, MD, Department of Human Pathology, Kanazawa University Graduate School of Medicine, 13-1 Takaramachi, Kanazawa 920-8640, Japan (e-mail: pbcp@kenroku.kanazawa-u.ac.jp).

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There are several case reports of hepatic inflammatory pseudotumor (IP) associated with sclerosing cholangitis (SC-hepatic IP),^{14,23} in which SC is considered either as the condition preceding or associated with hepatic IP.³⁶ Hepatic IP is a rare benign lesion often mistaken for primary malignant neoplasm of the liver.^{3,39} It is histologically characterized by polyclonal lymphoplasmacytic infiltration with various degrees of dense fibrosis.^{4,31}

SC sometimes occurs associated with SP (sclerosing pancreatitis-associated sclerosing cholangitis, SP-SC).^{8,12} SP, also called autoimmune pancreatitis or lymphoplasmacytic SP,^{15,40} is a unique form of chronic pancreatitis characterized by irregular narrowing of the pancreatic duct (duct-stenotic type) and/or prominent swelling of the pancreatic parenchyma occasionally presenting as a mass lesion (mass-forming type). Clinically, it may be mistaken for pancreatic cancer on endoscopic retrograde cholangiopancreatography (ERCP).^{15,40} At present, SP is regarded as an autoimmune disease and is effectively treatable by steroid therapy.^{8,12,15,17} A high serum level of IgG4 was recently found to be a very specific and sensitive marker for SP.⁹ This finding makes an operation unnecessary in SP by distinguishing it from pancreatic malignancy.⁹ SP is histologically characterized by diffuse lymphoplasmacytic infiltration with marked interstitial fibrosis, acinar atrophy, and obliterative phlebitis of vein branches of the pancreas.¹⁵

In this study, we retrospectively analyze histopathologic similarities and differences between SC, SC-hepatic IP, SP-SC, and typical PSC. The participation of IgG4-positive plasma cells in each of these lesions is also evaluated immunohistochemically.

MATERIALS AND METHODS

Anatomy of the Biliary Tree

For the purpose of this study, the biliary tree is classified into the extrahepatic bile ducts (common hepatic duct and common bile duct), the gallbladder, the right and left hepatic ducts, and their branches. Intrahepatic large bile ducts correspond to the first to third branches of the right and left hepatic ducts, and the intrahepatic small bile ducts are composed of septal and interlobular bile ducts.²⁴ Hepatic hilar ducts in pathologic conditions include the hepatic portion of the common hepatic duct, the right and left hepatic ducts, and the intrahepatic large bile ducts. Peribiliary glands are present around the intrahepatic large bile ducts³⁵ and also scattered glandular elements surround the extrahepatic bile ducts and the cystic duct of the gallbladder.

Patients and Preparation of Tissue Specimens

This study consists of 7 cases of SC, 5 cases of SC-hepatic IP, 5 cases of SP-SC, 5 cases of typical PSC, and 7 cases of hepatolithiasis (HL), which were collected from hepa-

tobiliary file of Department of Human Pathology, Kanazawa University Graduate School of Medicine and affiliated hospitals in Japan in between 1980 and 2001, and from Institute of Liver Studies, King's College Hospital in London between 2001 and 2003. HL cases are used as disease controls.

Ages, gender, clinical diagnosis, and associated non-hepatobiliary diseases are shown in Table 1. All cases of SC, SC-hepatic IP, and SP-SC underwent operation, and both hepatobiliary and pancreatic surgical specimens were obtained during the operation (Table 1). All cases of typical PSC underwent liver transplantation, and specimens from the explanted livers were used in this study. Those cases were estimated as "typical" PSC based on the radiologic findings of diffuse and irregular narrowing (beaded appearance) of the intrahepatic and extrahepatic bile ducts on ERCP, a complication of ulcerative colitis, and histologic examination of the explanted livers.

The diagnosis of SC was made by radiologic and pathologic examinations in all cases.²⁰ ERCP revealed irregular strictures of the intrahepatic, hepatic hilar, or extrahepatic bile ducts. Radiologically, a biliary tumor was suspected and constituted the indication for surgery. Histologically, the diagnosis of SC was made on the basis of diffuse inflammation and fibrosis without tumor cells. All SC-hepatic IP cases were radiologically suspected as intrahepatic or hepatic hilar malignancy, and intrahepatic tumorous lesions were resected. Tumorous parts were compatible with a diagnosis of IP in all cases. All SP-SC cases except one (case no. 17) were diagnosed by pathologic examination of surgically resected specimens. Although the pancreatic lesion of case no. 17 was not evaluated histopathologically, the diagnosis of SP-SC was made based on a history of swelling of the pancreatic head which was relieved by steroid therapy 15 months prior to cholecystectomy and lobectomy of the liver.

All HL cases used in this study were of a primary one without any preceding biliary lesions. We thought HL as a good disease control because it is a rather homogeneous disease and is causally related to bacterial infection and bile stasis, and the affected hilar and/or intrahepatic bile ducts show constantly ductal fibrosis with chronic inflammatory cell infiltration and proliferation of peribiliary glands.^{22,29} While the bile duct lesions of HL apparently resemble SC or PSC, the etiology and pathogenesis of primary HL seem to be different from SC or PSC.

Histologic Evaluation

More than three tissue samples from each surgically resected specimen were fixed in neutral formalin and embedded in paraffin. Surgically resected specimens from submandibular glands (case nos. 4 and 15) and transurethral electron-resection specimens of prostate (case no. 15) (Table 1) were similarly processed. More than 20, 4- μ m-thick, sections were cut from each paraffin block, stained with hematoxylin and

TABLE 1. Clinical Data of the Cases Used in This Study

	Case No.	Age (yr)	Sex	Clinical Diagnosis	Treatment	Other Manifestations
SC	1	55	M	CBD cancer	Choledochectomy, cholecystectomy	Diabetes, LN swelling
	2	76	M	CBD cancer	Choledochectomy, cholecystectomy	Diabetes
	3	62	F	Hepatic hilar cholangiocarcinoma	Choledochectomy, cholecystectomy	LN swelling
	4	75	M	Stenosis of common bile duct	Choledochectomy, cholecystectomy	Sialoadenitis
	5	69	F	CBD tumor	Pancreatoduodenectomy	Diabetes, LN swelling
	6	65	M	CBD cancer	Choledochectomy, lobectomy of the liver	
	7	67	F	Hepatic hilar cholangiocarcinoma	Choledochectomy, segmentectomy of the liver	
SC-hepatic IP	8	59	M	Liver cancer	Segmentectomy of the liver	Diabetes
	9	79	M	ICC	Segmentectomy of the liver	Chronic pancreatitis
	10	56	M	ICC	Lobectomy of the liver	LN swelling
	11	64	M	ICC	Lobectomy of the liver	LN swelling
SP-SC	12	67	M	Hepatic hilar cholangiocarcinoma	Lobectomy of the liver	
	13	68	F	Pancreatic head cancer	Pancreatoduodenectomy	LN swelling
	14	68	M	Pancreatic head cancer	Pancreatoduodenectomy	
	15	65	M	Pancreatitis, mass-forming type	Pancreatoduodenectomy	Sialoadenitis, prostatitis, LN swelling
	16	71	M	Pancreatic cancer	Pancreatectomy, choledochectomy	Diabetes, LN swelling
	17*	74	F	Hepatic hilar cholangiocarcinoma	Choledochectomy, lobectomy of the liver	
PSC	18	41	F	PSC	Hepatectomy for liver transplantation	Ulcerative colitis
	19	49	M	PSC	Hepatectomy for liver transplantation	Ulcerative colitis
	20	55	F	PSC	Hepatectomy for liver transplantation	Ulcerative colitis
	21	53	M	PSC	Hepatectomy for liver transplantation	Ulcerative colitis
	22	30	M	PSC	Hepatectomy for liver transplantation	Ulcerative colitis
HL	23	70	F	HL	Segmentectomy of the liver	
	24	66	F	HL	Segmentectomy of the liver	
	25	45	F	HL	Segmentectomy of the liver	
	26	68	F	HL	Segmentectomy of the liver	
	27	55	M	HL	Segmentectomy of the liver	
	28	76	M	HL	Segmentectomy of the liver	
	29	71	F	HL	Segmentectomy of the liver	

SC, sclerosing cholangitis; SC-hepatic IP, sclerosing cholangitis with hepatic inflammatory pseudotumor; SP-SC, sclerosing pancreatitis-associated sclerosing cholangitis; PSC, primary sclerosing cholangitis; HL, hepatolithiasis; CBD, common bile duct; ICC, intrahepatic cholangiocarcinoma; LN, lymphnode.

*Case no. 17 was diagnosed as SP-SC based on a history of the swelling of the pancreatic head, which was relieved by steroid therapy.

eosin, Azan-Mallory, and elastica van Gieson (EVG), the remaining being used for immunohistochemistry. In SC and SP-SC cases, the thickness of the affected hepatic hilar and extrahepatic bile ducts with the most prominent inflammation was estimated using a microscopic measure. The following histologic features were assessed by two pathologists (Y.Z. and Y.N.): inflammatory cell infiltration (–, absent or minimal; +, mild; ++, moderate; +++, severe), plasma cell infiltration (–, absent or minimal; +, mild; ++, moderate; +++, severe), lymph follicle with germinal center (–, absent; +, present), and obliterative phlebitis (–, absent; +, present). The degree of eosinophil infiltration was defined as mild (+), 0 to 1 cell / HPF (high power field); moderate (++), 1 to 5 cells / HPF; and severe (+++), >5 cells / HPF. Obliterative phlebitis was assessed on EVG stained sections.

Immunohistochemistry for IgG and IgG4, and In Situ Hybridization for EBV

Representative blocks of extrahepatic or hepatic hilar duct lesions of SC, SC-hepatic IP and SP-SC, of intrahepatic tumor of SC-hepatic IP, of hepatic duct lesions of typical PSC, and of intrahepatic large bile duct containing calculi of hepatolithiasis were chosen for immunohistochemistry and in situ hybridization as appropriate in each case. Immunostaining of IgG and IgG4 were performed using a mouse monoclonal antibody against human IgG (Dako, Glostrup, Denmark), and a mouse monoclonal antibody against human IgG4 (ZYMED Laboratory Inc., San Francisco, CA), respectively. Deparaffinized sections were microwaved in ethylenediaminetetraacetic acid buffer (pH 8.0) for 20 minutes. After blocking the endogenous peroxidase, the sections were incubated in normal

goat serum for 20 minutes and then incubated overnight at 4°C with the primary antibody. These sections were incubated for 1 hour at room temperature with goat anti-mouse immunoglobulins, which were conjugated to peroxidase labeled polymer (Envision+, Dako). 3,3'-Diaminobenzidine tetrahydrochloride was used as the chromogen, followed by light counterstaining with hematoxylin. Negative controls were evaluated by substituting the primary antibody with similarly diluted nonimmunized mouse serum. The degree of IgG- or IgG4-positive plasma cells was estimated as absent (-), mild (+), moderate (++), and severe (+++).

In situ hybridization for EBER [Epstein-Barr virus (EBV)-encoded RNA] was automatically performed by HX System Benchmark (Ventana Medical System, Tuscon, AZ) as per the manufacturer's instructions, using a probe for EBER (INFORM EBER probe, Ventana Medical Systems). Signal detection was made by Alkaline Phosphatase Enhanced Detection Kit (Ventana Medical Systems). Specimens from Hodgkin lymphoma and lymph nodes showing reactive follicular hyperplasia resected during the operation for gastric cancer were used as positive and negative controls, respectively.

Statistics

Values are given as the mean $\pm$ standard error of the mean. Means of two groups were compared with the Mann-Whitney *U* test. Values of $P < 0.05$ were regarded as statistically significant.

RESULTS

Clinical History

Clinical histories of the cases examined are shown in Table 1. SC and SP-SC predominantly affected males, and all cases of SC-hepatic IP were male. Clinical diagnoses of SC, SC-hepatic IP, and SP-SC, except case nos. 4 and 15, were neoplastic diseases, in most instances malignant tumors. Although SP was radiologically suspected in case no. 15, operation was performed because pancreatic cancer could not be ruled out. No radiologic changes suspicious of SP such as diffuse narrowing of the main pancreatic duct or swelling of the pancreas were detected in any cases of SC or SC-hepatic IP. Of the 7 SC patients, choledochectomy was performed in 6 cases, and hepatic lobectomy and segmentectomy were simultaneously done in case nos. 6 and 7, respectively. Case no. 5 had a pancreatoduodenectomy. In SC-hepatic IP cases, intrahepatic tumors were resected by hepatic segmentectomy or lobectomy. Surgical treatments, not stenting of the bile duct, were chosen for the primary therapy for all cases of SC and SC-hepatic IP based on the clinical diagnosis of early curable stages of hepatobiliary malignancy. In SP-SC cases, pancreatic lesions were predominant over biliary lesions. Pancreatoduodenectomy was performed in case nos. 13, 14, and 15 for an-

ticipated "tumor" of pancreatic head, and in case no. 16 for diffuse swelling of the pancreas. Case no. 17 had a history of swelling of the pancreatic head, which was first relieved by corticosteroid therapy, but during the medical follow-up (15 months later), stenosis of upper common bile duct and hepatic ducts were demonstrated by ERCP, and choledochectomy and hepatic lobectomy were performed based on the clinical diagnosis of hilar cholangiocarcinoma. All choledochectomies were followed by enteric anastomosis, not reanastomosis, of the bile ducts. Hepatic segmentectomy for calculi-containing bile ducts was performed in all cases of HL.

All typical PSC cases had ulcerative colitis, which was diagnosed by endoscopic and histologic examination. ANCA with a perinuclear pattern (p-ANCA) was detected in case no. 21. Anti-Saccharomyces cerevisiae antibodies (ASCA) were not examined. By contrast, ulcerative colitis was not found in any SC, SC-hepatic IP, and SP-SC cases examined. Colonoscopy, which was performed in all of those cases before surgical therapies, did not reveal any mucosal changes suggestive of inflammatory bowel diseases, although histologic examination of multiple biopsies and serological test for ANCA and ASCA were not performed in those cases.

Case nos. 1, 2, 5, 8, and 16 had a history of diabetes mellitus. Case no. 9 was diagnosed as "ordinary" chronic pancreatitis, not SP, based on ERCP findings. This patient had neither history of deteriorating pancreatitis nor "tumor" formation of the pancreas during the medical follow-up. Interestingly, case nos. 4 and 15 had a history of submandibular gland swelling, and the lesions were resected because of a clinical diagnosis of salivary gland tumor. Chronic sialoadenitis-associated tumor (Kuttner's tumor) was diagnosed based on the histologic findings of diffuse lymphoplasmacytic infiltration and acinar destruction of the salivary gland. In addition, case no. 15 had a history of swelling of the prostate and transurethral electroresection for suspicion of prostate cancer. Histologically, diffuse lymphoplasmacytic infiltration with glandular destruction was observed, without evidence of malignancy. Preoperative radiography revealed lymph node swelling around the common bile duct and pancreatic head in case nos. 1, 3, 5, 10, 11, 13, 15, and 16, and metastases were suspected, but histology of the resected lymph nodes revealed reactive follicular hyperplasia only.

Laboratory Data

Laboratory data at initial presentation of all of the cases examined except for case no. 17, which was a consultation case, were available. Almost all cases irrespective of groups showed marked elevation of alkaline phosphatase (ALP) and γ -glutamyltranspeptidase (γ -GTP). Hyperbilirubinemia was seen in 6 of 7 cases (86%) of SC (range, 2.3–12.4 mg/dL), 4 of 5 cases (80%) of SC-hepatic IP (range, 1.2–7.0 mg/dL), 1 of 4 cases (25%) of SP-SC (3.3 mg/dL), 5 of 5 cases (100%) of typical PSC (range, 2.4–6.8 mg/dL), and 6 of 7 cases (86%) of

hepatolithiasis (range, 1.7–4.5 mg/dL). In SC, SC-hepatic IP, SP-SC, and typical PSC cases, all cases except for case nos. 6, 8, 12, 18, 20, and 22 showed elevation of serum γ -globulin. Furthermore, serum IgG, which was examined in 5 cases, was elevated in case nos. 4 (4,270 mg/dL), 15 (2,940 mg/dL), 16 (1,880 mg/dL), and 21 (2,360 mg/dL). No HL cases examined showed hypergammaglobulinemia. ANA was detected in case nos. 2 ($\times 80$), 3 ($\times 160$), 4 ($\times 320$), 15 ($\times 20$), and 22 ($\times 80$). Aspartate and alanine aminotransferase, which were mildly to moderately elevated in almost all cases examined (79.6 ± 42.2 IU/L and 104.0 ± 79.3 IU/L, respectively), became within the normal range after surgery, and those cases did not show any laboratory abnormalities suggestive of autoimmune hepatitis during a medical follow-up until now. Tumor markers such as carbohydrate antigen (CA) 19-9, CA 125, carcinoembryonic antigen, alpha-fetoprotein, and DUPAN-2 were measured in all cases, and CA19-9 was elevated in case nos. 2, 3, 13, 14, and 15 (range, 68.0–135.6 U/mL), with elevated carcinoembryonic antigen (12.2 ng/mL) in case no. 2. HCV antibody was detected in case no. 8. Anti-mitochondrial antibodies were not measured in any cases of SC, SC-hepatic IP, and SP-SC.

Histologic Examination

Pancreatic lesions of SP-SC cases consisted of poorly circumscribed fibrosing lesion with severe lymphoplasmacytic infiltration and eosinophils. Lymphoid follicles were also observed in case nos. 13, 14, and 15. This sclerosing inflammatory process destroyed and replaced the exocrine pancreas

and also extended to the peripancreatic adipose tissue (Fig. 1). Obliterative phlebitis was conspicuous in all cases of SP-SC.

The results of histologic examination of the bile ducts are shown in Table 2. The affected bile ducts of all cases of SP-SC showed unevenly distributed and dense fibrosis, moderate to severe degree of lymphoplasmacytic infiltration, moderate to severe degree of eosinophil infiltration, and obliterative phlebitis. Lymph follicles with germinal centers were observed in case nos. 13 and 15. These bile duct lesions were continuous with the pancreatic lesions in case nos. 13, 14, 15, and 16. In addition, a few small-sized epithelioid granulomas without necrosis were admixed with the bile duct lesions of case nos. 13 and 15 within the wall of the common bile ducts. Affected bile ducts in SC cases showed identical histologic changes as those seen in SP-SC in case nos. 1, 2, 4, and 6 (Fig. 2), while the affected bile ducts of SC case nos. 3, 5, and 7 showed only a mild degree of inflammatory cell infiltration with scant eosinophils and absent phlebitis. The former was designated as group A SC and the latter as group B SC in this study. Tumorous parts of all cases of SC-hepatic IP showed diffuse fascicular proliferation of spindle shaped fibroblasts, moderate to severe lymphoplasmacytic infiltration with many eosinophils, and also obliterative phlebitis. The adjacent bile ducts showed histologic changes identical to those of SP-SC, and these lesions merged with those of IP.

In all SP-SC, group A SC, and SC-hepatic IP cases, the fibrosing inflammatory lesions of bile ducts extended into the intrahepatic peribiliary glands and the connective tissue in-

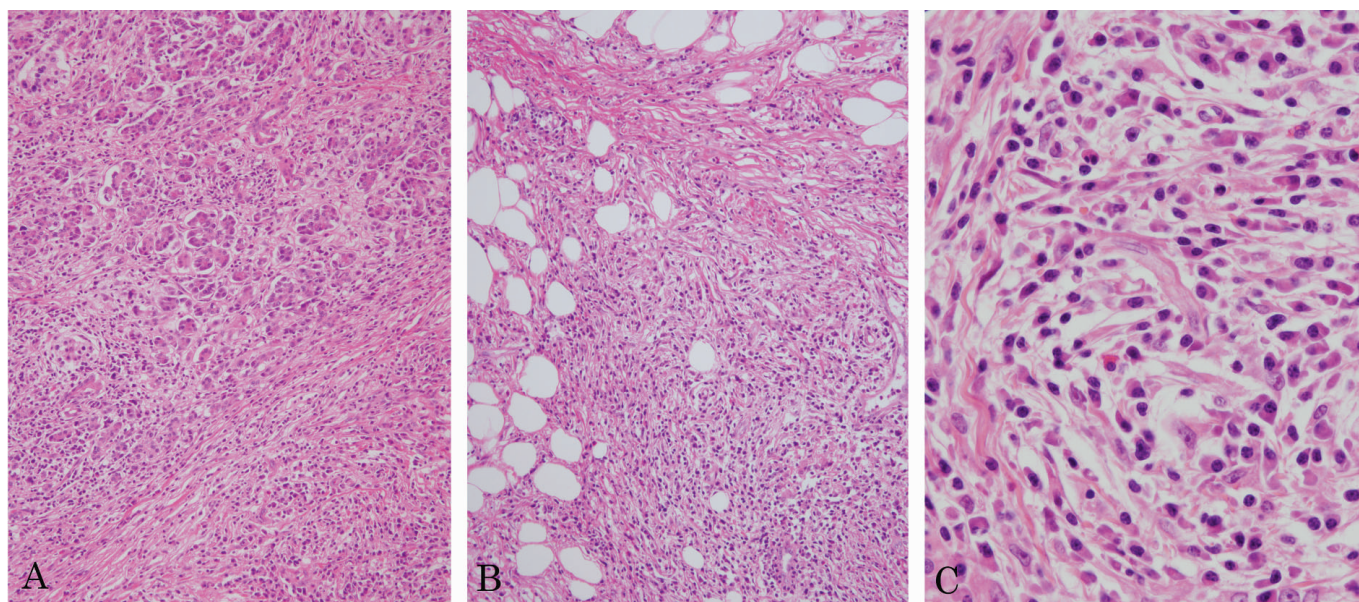


FIGURE 1. Histopathology of sclerosing pancreatitis. A, Sclerosing lesion with severe inflammatory cell infiltration irregularly involves pancreatic parenchyma (hematoxylin and eosin, original magnification $\times 100$). B, Inflammatory process extends to the peripancreatic adipose tissue (hematoxylin and eosin, original magnification $\times 100$). C, Severe lymphoplasmacytic infiltration with several eosinophils are observed (hematoxylin and eosin, original magnification $\times 400$).

TABLE 2. The Histologic Examination of Intrahepatic Large Bile Ducts and Hepatic Hilar and/or Extrahepatic Bile Ducts

	Case No.	Lesional Distribution	Thickness of CBD (mm)	Inflammatory Cell Infiltration	Plasma Cell	Lymph Follicle	Eosinophil	Obliterative Phlebitis	IgG-positive Plasma Cell	IgG4-positive Plasma Cell
SC	1	CBD, IBD	4.2	++	+++	—	++	+	+++	+++
	2	CBD (upper, middle)	2.7	+++	+++	—	++	+	+++	+++
	3	CBD (upper), HD (left, right)	2.2	+	+	—	—	—	++	—
	4	CBD (upper), HD (left, right)	4.1	+++	+++	—	+	+	+++	+++
	5	CBD (upper, middle)	2.2	+	+	—	—	—	++	—
	6	CBD (upper, middle), HD (right)	6.8	+++	+++	+	+++	+	+++	+++
SC-hepatic IP	7	CBD, HD (left), IBD	3.1	+	+	—	—	—	++	—
	8	IBD	NE	++	+++	+	+	+	+++	+++
	9	Panc (head), IBD	NE	+++	+++	+	—	+	+++	+++
	10	IBD	NE	++	+++	—	+++	+	+++	+++
	11	IBD	NE	+++	+++	+	+	+	+++	+++
	12	HD (left)	NE	+++	+++	—	++	+	+++	+++
SP-SC	13	Pan (head), CBD (total), HD, CD	6.1	+++	+++	+	+++	+	+++	+++
	14	Panc (total), CBD (middle, lower)	4.9	+++	+++	—	+++	+	+++	+++
	15	Panc (head), CBD (total), HD, CD	3.2	+++	+++	+	+++	+	+++	+++
	16	Panc (total), CBD (middle, lower)	3.1	++	+++	—	++	+	+++	+++
PSC	17	CBD (upper), HD	6.8	+++	+++	—	++	+	+++	+++
	18	IBD, HD, CBD	NE	+++	+++	+	+	—	++	+(3/10HPF)
	19	IBD, HD, CBD	NE	+++	+++	—	++	—	+++	+(5/10HPF)
	20	IBD, HD, CBD	NE	+++	++	—	—	—	++	—
	21	IBD, HD, CBD	NE	++	++	—	++	—	++	—
	22	IBD, HD, CBD	NE	+++	+++	+	++	—	+++	+(2/10HPF)
HL	23	IBD	NE	+	+	—	—	—	+	+(2/10HPF)
	24	IBD	NE	+	+	—	+	—	++	+(3/10HPF)
	25	IBD	NE	++	+	+	+	—	+	—
	26	IBD	NE	++	++	+	—	—	+	+(3/10HPF)
	27	IBD	NE	++	++	+	+	—	+	—
	28	IBD	NE	++	+	+	—	—	++	+(1/10HPF)
	29	IBD	NE	+	+	—	+	—	++	+(7/10HPF)

SC, sclerosing cholangitis; SC-hepatic, IP, sclerosing cholangitis with hepatic inflammatory pseudotumor; SP-SC, sclerosing pancreatitis-associated sclerosing cholangitis; PSC, primary sclerosing cholangitis; HL, hepatolithiasis; CBD, common bile duct; HD, hepatic duct; Panc, pancreas; NE, not examined; IBD, intrahepatic bile duct; CD, cystic duct; —, absent or minimal degree; +, present or mild degree; ++, moderate degree; +++, severe degree.

cluding nerve fibers and fatty tissue around the affected bile ducts (Fig. 2A, B), and both extent and degree of activity of the periductal lesions parallel those of bile duct lesion. The peribiliary glands showed glandular epithelial damage, too.

None of the cases who underwent lobectomy or segmentectomy of the liver showed morphologic changes suggestive of autoimmune hepatitis (chronic active hepatitis with evident interface necrosis and many plasma cells) or primary biliary cirrhosis (chronic nonsuppurative destructive cholangitis or epithelioid granulomas in the portal tract). Epithelioid granulomas in case nos. 13 and 15 were located in the wall of the

extrahepatic bile ducts. That feature was different from that of primary biliary cirrhosis, although anti-mitochondrial antibodies were not tested in case nos. 13 and 15.

In all cases of typical PSC, intrahepatic large bile ducts were fibrously thickened with moderate to severe lymphoplasmacytic infiltration intermixed with neutrophils and eosinophils. The bile duct wall near the lumen showed relatively intense inflammatory cell infiltration with epithelial erosion, neutrophilic infiltration, and edema, while such inflammatory changes of the outer side of the bile duct wall was rather mild with occasional lymphoid aggregates (Fig. 3). Obliterative

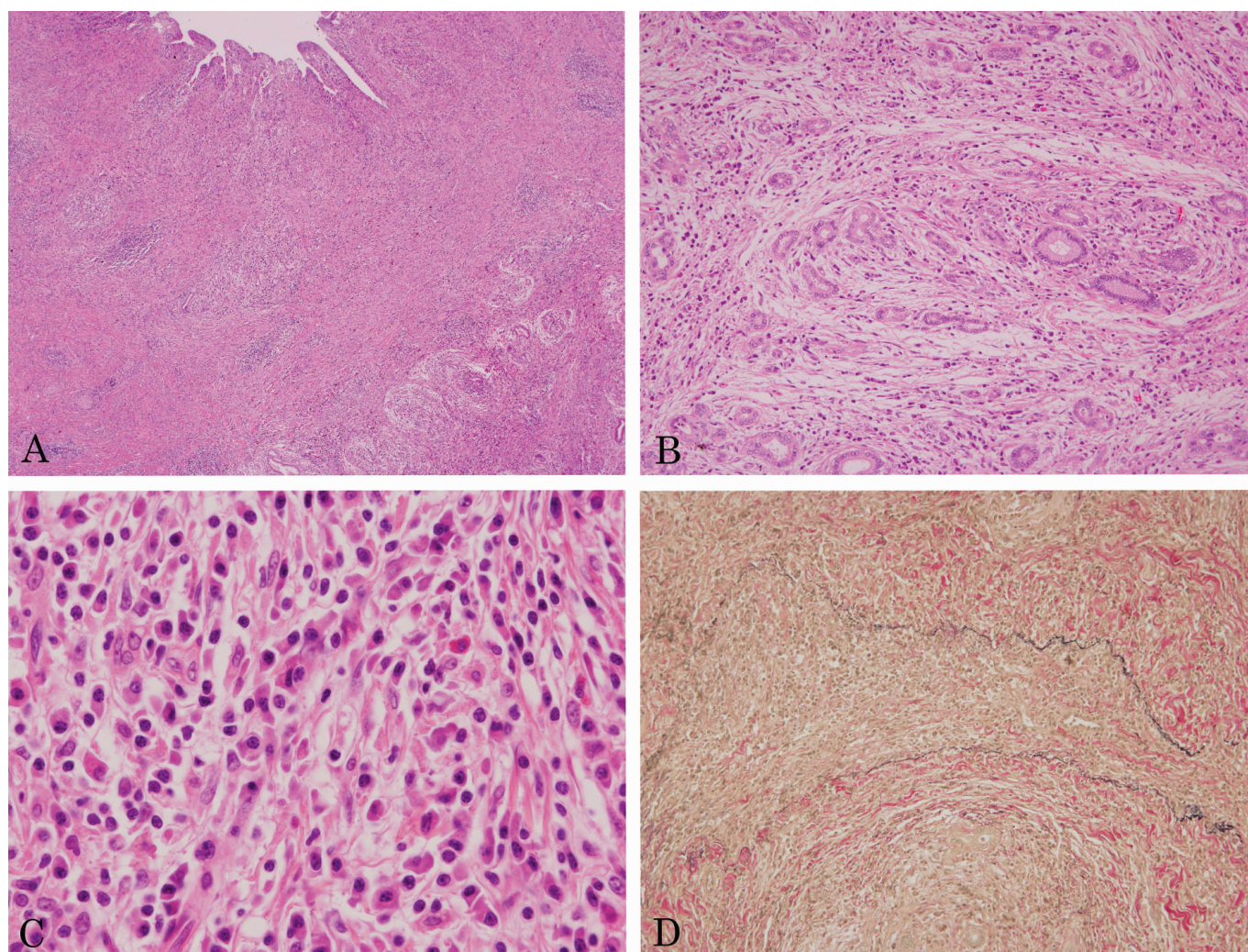


FIGURE 2. Histopathology of common bile duct in case 4 (group A sclerosing cholangitis). A, Common bile duct is markedly thickened by diffuse fibrosis and marked inflammatory cell infiltration (hematoxylin and eosin, original magnification $\times 20$). B, Chronic fibrosing inflammation extends to peribiliary glands (hematoxylin and eosin, original magnification $\times 100$). C, Inflammatory cells are mainly composed of lymphocytes and plasma cells. Several eosinophils were observed in this field (hematoxylin and eosin, original magnification $\times 400$). D, Obliterative phlebitis is seen (Elastica-van Gieson stain, original magnification $\times 100$).

phlebitis was not observed in any case of these typical PSC. Background liver of all of these PSC cases showed the features of biliary cirrhosis with marked intrahepatic cholestasis. Intrahepatic small bile ducts showed fibrous obliteration or periductal concentric fibrosis.

In all cases of HL, mild to moderate lymphoplasmacytic infiltration with variable neutrophils, a few eosinophils and dense fibrosis were observed in the large, stone-containing, intrahepatic bile ducts. Variable proliferation of peribiliary glands was constantly found in the affected bile ducts, but obliterative phlebitis was not a feature.

Comparative estimation of the thickness of hepatic hilar or extrahepatic bile ducts was performed in all SC and SP-SC cases; the common bile ducts were thicker in SP-SC (5 cases)

and group A SC cases (4 cases) than in group B SC cases (3 cases) (4.66 ± 0.52 mm in the former two vs. 2.50 ± 0.30 mm in the latter, $P = 0.026$). The thickness of the common bile ducts was not measured in typical PSC cases because hepatectomy specimens did not include the identifiable common bile ducts.

Immunohistochemistry for IgG and IgG4

The results of immunostaining of IgG and IgG4 are shown in Table 2. Moderate to severe and diffuse infiltration of IgG-positive plasma cells was seen within the affected lesions (bile duct walls, pancreas, and hepatic IP) of all cases of SC, SC-hepatic IP, SP-SC, and typical PSC. Infiltration of IgG-

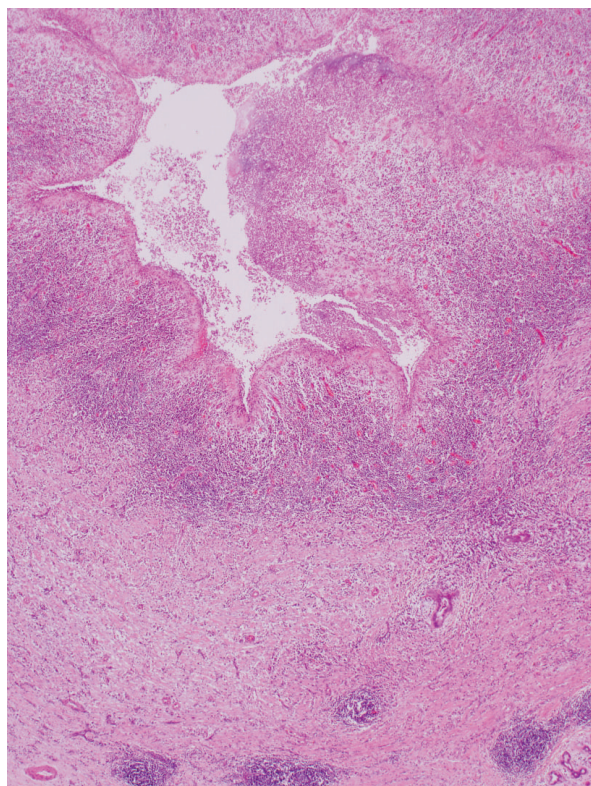


FIGURE 3. Histopathology of hepatic duct in typical primary sclerosing cholangitis. Hepatic duct is fibrously thickened by inflammatory cell infiltration and fibrosis. Inflammatory cell infiltration is more intense on luminal side, while only mild infiltration with several lymphoid aggregates is seen on serosal side of the bile duct (hematoxylin and eosin, original magnification $\times 20$).

positive plasma cell was, however, mild to moderate degree in the affected bile ducts of HL cases.

Infiltration of IgG4-positive plasma cells was severe within the affected bile ducts and pancreatic lesions of all cases of SP-SC, within the bile duct lesions and hepatic IP of all cases of SC-hepatic IP, and within the bile duct lesions of 4 cases of SC (case nos. 1, 2, 4, and 6; all group A). By contrast, IgG4-positive plasma cells were scarce or hardly found in the remaining cases of SC (case nos. 3, 5, and 6; all group B), in all cases of typical PSC, and HL (Fig. 4). Interestingly, many IgG4-positive plasma cells were also observed in the submandibular lesions of case nos. 4 and 15, and in the pancreatic lesion of case no. 15.

In Situ Hybridization for EBV

No EBER-positive cell was detected in all the cases in this study.

DISCUSSION

This study revealed that group A of SC (4 cases) and all cases of SC-hepatic IP showed extensive and dense fibrosis of

the hepatic hilar and extrahepatic bile ducts with a marked lymphoplasmacytic infiltration, many eosinophils, and also obliterative phlebitis. In addition, the infiltrates included numerous IgG4-positive plasma cells. These histologic findings themselves are quite similar to those described in SP,¹⁵ suggesting that a sclerosing lesion identical to SP may occur in the hepatobiliary system. In this context, our data support the currently proposed disease entity named “sclerosing pancreato-cholangitis” for such pathologic conditions.^{8,12,37} Recently, Toosi and Heathcote³⁷ reported that pancreatic pseudotumor occurs in association with sclerosing pancreato-cholangitis. In addition, there have also been several reports describing SC with hepatic IP or SC with local exaggerating inflammatory lesion.^{14,23,25} The present study disclosed that the bile duct lesions of group A SC, SC-hepatic IP, and SP-SC were histologically identical to the pancreatic lesions of SP. Furthermore, hepatic IP itself also showed similar histologic changes. In this context, we would like to propose that IgG4-related SC with (SC-hepatic IP) and without hepatic IP (group A of SC), and may belong to a spectrum of SP. Conventional SP without SC, which usually present with a mass formation of the pancreatic parenchyma (mass-forming type) or diffuse narrowing of the pancreatic ducts (duct-stenotic type)^{16,27,28} could be included in this spectrum of SP, although such cases (SP without SC) were not presented in this study. Their topological distribution along the hepatobiliary and pancreatic axis is shown schematically in Figure 5.

These diseases show a similar histology with many IgG4-positive plasma cells, suggesting that they could share similar pathogenetic mechanisms. Based on this assumption, one can speculate that some cases of SC, particularly group A, and SC-hepatic IP could benefit from steroid therapy similar to SP. Actually, there have been a few reports of SC, in which clinical and histologic findings were improved after corticosteroid treatment,^{5,7,21} and these cases may correspond to group A SC in this study.

Whether group A SC cases represent PSC or a variant of it is still questionable. No cases of group A SC have ulcerative colitis. In addition, ERCP suggested biliary tumor in all group A SC cases. Given these clinical data, group A SC may appear different from “typical” PSC. However, if cholestasis persists in group A SC, it is reasonable to expect progressive fibrosis and eventually a biliary cirrhosis to occur similar to the natural history of “typical” PSC. That is, advanced cases of group A SC might be clinically diagnosed as liver cirrhosis due to “typical” PSC, but that is only speculation at this point. In addition, it is also possible to think that the difference of histopathology and IgG4 profile of group A and B of SC, SC-hepatic IP, SP-SC, and typical PSC may reflect different pathologic stages of the same disease. Follow-up studies of these cases are mandatory to solve this issue.

IgG4 is the rarest among the IgG subclasses and in the normal subject accounts for less than 6% of the total IgG frac-

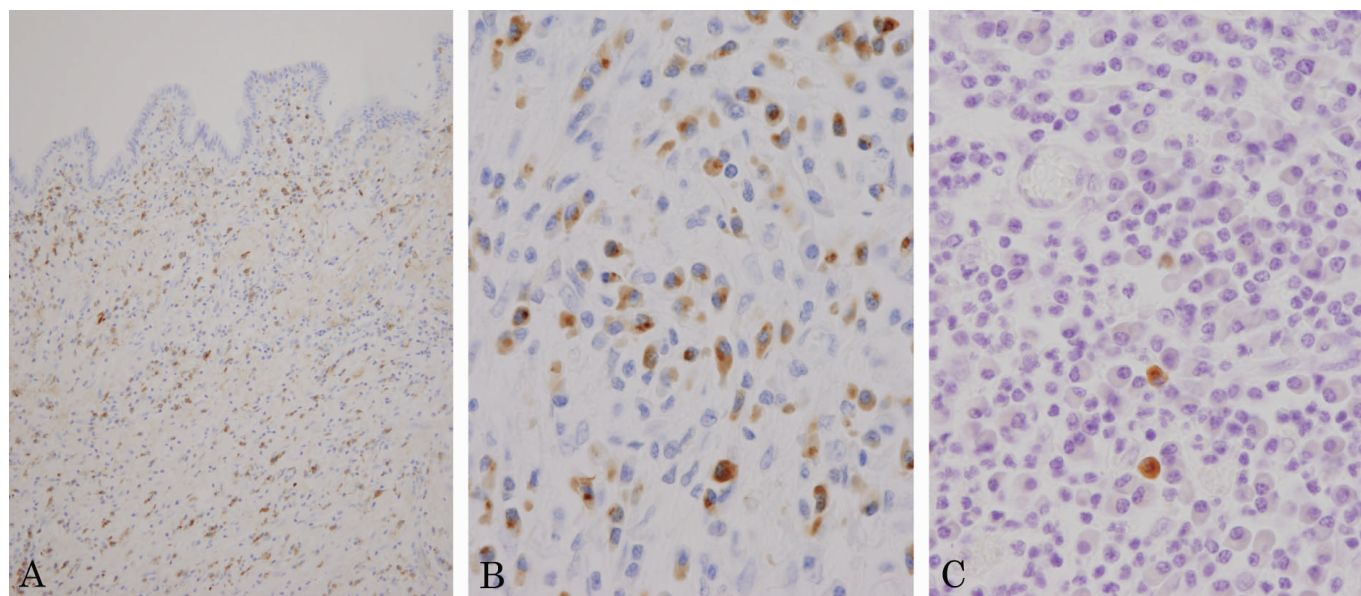


FIGURE 4. Immunostaining of IgG4 in group A sclerosing cholangitis (A, B) and typical primary sclerosing cholangitis (C). A, Many IgG4-positive plasma cells are infiltrating diffusely in the fibrously thickened common bile duct wall (original magnification $\times 100$). B, A lot of plasma cells are positive for IgG4 (original magnification $\times 400$). C, Most of plasma cells are negative for IgG4. Only three IgG4-positive plasma cells are observed in this field (original magnification $\times 400$).

tion in the serum.^{1,38} High serum IgG4 is only found in a limited number of conditions, such as atopic dermatitis and pemphigus vulgaris.^{13,33} Among the hepatobiliary and pancreatic diseases, high serum IgG4 is thought to be specific to SP.⁹ Serum IgG4 was not measured in all the cases considered in this study because the majority of our cases were investigated prior to the report describing IgG4 in SP.⁹ However, it is likely that group A SC and SC-hepatic IP would have an elevated IgG4 in serum based on histopathologic similarity to SP and the high content of IgG4 containing plasma cells in the inflammatory infiltrate. IgG4 might be a good marker to differentiate group A SC from “typical” PSC and possibly delineate a subgroup of PSC, which could respond to steroid therapy similar to SP. In addition to serum IgG4 level, this study revealed that immunostaining of IgG4 might be a useful tool to differentiate IgG4-related diseases from typical PSC and group B SC. Histologic findings on hematoxylin and eosin staining could also give a clue for such differentiation. In group A SC, intense and diffuse lymphoplasmacytic infiltration with sclerosis was seen in the fibrously thickened bile duct walls, while in typical PSC, lymphoplasmacytic infiltration was rather intense near the lumen of the affected bile ducts. Obliterative phlebitis was frequently observed in group A SC, not in typical PSC or group B SC. The present study also showed that immunostaining of IgG was not enough to determine IgG4-related diseases or not, because both group B SC and typical PSC showed many IgG-positive plasma cells within their lesions in the absence of dense infiltration of IgG4-positive plasma cells.

Stenosis of the common bile duct was not infrequently detected in the cases of SP, and most of them were localized at

the lower part of the common bile duct. It has been controversial so far whether the extrapancreatic bile duct lesions are a continuous extension of the pancreatic lesion to the biliary tree or a nonspecific change secondary to stenosis of the intrapan-

A spectrum of sclerosing pancreatitis

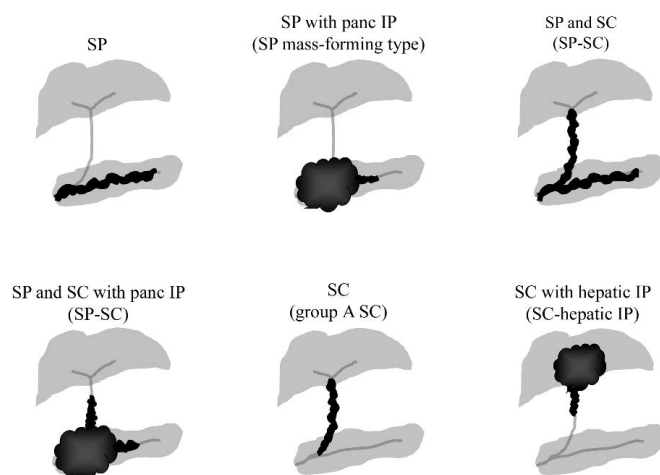


FIGURE 5. Scheme of sclerosing pancreatitis. IgG4-related sclerosing lesions occur along the biliary tract and pancreatic duct, presenting with mass-forming or duct-stenosis. Conventional SP without SC, which present with mass-formation or diffuse narrowing of the main pancreatic duct, could be also included in this disease entity, in addition to group A SC, SC-hepatic IP, and SP-SC. Black nodules and thick black wiggly lines are the site of the IgG4-related lesions.

creatic portion of the biliary tree due to SP. The histologic similarity between bile duct of SP-SC cases and pancreatic lesions of SP may suggest a direct extension of the pancreatic process. Furthermore, case no. 17 with a history of pancreatic head swelling cured by steroid treatment, found during medical follow-up to have a “tumor” (SC-hepatic IP) in the hepatic hilum detected radiologically, suggests that SC and SP could occur asynchronously at multiple points of the pancreato-hepato-biliary system.

Interestingly, case no. 4 (group A) and case no. 15 (SP-SC) had extrahepatic and extrapancreatic complications, such as sialoadenitis and prostatitis. Those lesions histologically showed diffuse lymphoplasmacytic infiltration with fibrosis and many IgG4-positive plasma cells, which is very similar to those of SP. These 2 cases suggest that sclerosing pancreato-cholangitis could occur as one manifestation of a multifocal fibrosclerosis. Similar cases of SC or SP associated with multifocal fibrosclerosis have been occasionally reported.^{2,10,26} Thus, IgG4 could be involved in the pathogenesis of some cases of multiple fibrosclerosis.

Hepatic IP exhibits a broad spectrum of histologic appearances and is subcategorized as plasma cell granuloma, pseudolymphoma, or inflammatory myofibroblastic tumor.^{4,30} Recently, it was proved that follicular dendritic cell tumor associated with EBV infection could morphologically mimic IP in the liver.^{6,32} Inflammatory pseudotumor in this study (SC-hepatic IP) and the similar cases in literature could be histologically identified as plasma cell granuloma, not follicular dendritic cell tumor.^{23,36} Moreover, in situ hybridization for EBV did not reveal the association with EBV in IPs (SC-hepatic IP) in this study.

In summary, this study suggests that sclerosing lesions identical to those of SP can affect various levels of the biliary tree. Some of those cases present as SC, some as hepatic IP. These cases could benefit from steroid therapy similar to SP.

REFERENCES

1. Aalberse RC, Van Milligen F, Tan KY, et al. Allergen-specific IgG4 in atopic disease. *Allergy*. 1993;48:559–569.
2. Akahane C, Takei Y, Horiuchi A, et al. A primary Sjogren's syndrome patient with marked swelling of multiple exocrine glands and sclerosing pancreatitis. *Intern Med*. 2002;41:749–753.
3. Anthony PP, Telesinghe PU. Inflammatory pseudotumour of the liver. *J Clin Pathol*. 1986;39:761–768.
4. Anthony PP. Inflammatory pseudotumour (plasma cell granuloma) of lung, liver and other organs. *Histopathology*. 1993;23:501–503.
5. Burgert SL, Brown BP, Kirkpatrick RB, et al. Positive corticosteroid response in early primary sclerosing cholangitis. *Gastroenterology*. 1984;86:1037.
6. Cheuk W, Chan JK, Shek TW, et al. Inflammatory pseudotumor-like follicular dendritic cell tumor: a distinctive low-grade malignant intra-abdominal neoplasm with consistent Epstein-Barr virus association. *Am J Surg Pathol*. 2001;25:721–731.
7. Chutaputti A, Burrell MI, Boyer JL. Pseudotumor of the pancreas associated with retroperitoneal fibrosis: a dramatic response to corticosteroid therapy. *Am J Gastroenterol*. 1995;90:1155–1158.
8. Erkelens GW, Vleggaar FP, Lesterhuis W, et al. Sclerosing pancreato-cholangitis responsive to steroid therapy. *Lancet*. 1999;354:43–44.
9. Hamano H, Kawa S, Horiuchi A, et al. High serum IgG4 concentrations in patients with sclerosing pancreatitis. *N Engl J Med*. 2001;344:732–738.
10. Hamano H, Kawa S, Ochi Y, et al. Hydronephrosis associated with retroperitoneal fibrosis and sclerosing pancreatitis. *Lancet*. 2002;359:1403–1404.
11. Hirano K, Shiratori Y, Komatsu Y, et al. Involvement of the biliary system in autoimmune pancreatitis: a follow-up study. *Clin Gastroenterol Hepatol*. 2003;1:453–464.
12. Horiuchi A, Kawa S, Hamano H, et al. Sclerosing pancreato-cholangitis responsive to corticosteroid therapy: report of 2 case reports and review. *Gastrointest Endosc*. 2001;53:518–522.
13. Hussain R, Poindexter RW, Ottesen EA. Control of allergic reactivity in human filariasis: predominant localization of blocking antibody to the IgG4 subclass. *J Immunol*. 1992;148:2731–2737.
14. Jafri SZ, Bree RL, Agha FP, et al. Inflammatory pseudotumor from sclerosing cholangitis. *J Comput Assist Tomogr*. 1983;7:902–904.
15. Kawaguchi K, Koike M, Tsuruta K, et al. Lymphoplasmacytic sclerosing pancreatitis with cholangitis: a variant of primary sclerosing cholangitis extensively involving pancreas. *Hum Pathol*. 1991;22:387–395.
16. Kim KP, Kim MH, Lee SS, et al. Autoimmune pancreatitis: it may be a worldwide entity. *Gastroenterology*. 2004;126:1214.
17. Kram MT, May LD, Cooperman A, et al. Lymphoplasmacytic sclerosing pancreatitis and cholangitis. *Gastrointest Endosc*. 2002;55:588–590.
18. LaRusso NF, Wiesner RH, Ludwig J, et al. Current concepts: primary sclerosing cholangitis. *N Engl J Med*. 1984;310:899–903.
19. Lee YM, Kaplan MM. Primary sclerosing cholangitis. *N Engl J Med*. 1995;332:924–933.
20. Ludwig J. Surgical pathology of the syndrome of primary sclerosing cholangitis. *Am J Surg Pathol*. 1989;13:43–49.
21. Myers RN, Cooper JH, Padis N. Primary sclerosing cholangitis: complete gross and histologic reversal after long-term steroid therapy. *Am J Gastroenterol*. 1970;53:527–538.
22. Nakanuma Y, Yamaguchi K, Ohta G, et al. Pathologic features of hepatolithiasis in Japan. *Hum Pathol*. 1988;19:1181–1186.
23. Nakanuma Y, Tsuneyama K, Masuda S, et al. Hepatic inflammatory pseudotumor associated with chronic cholangitis: report of three cases. *Hum Pathol*. 1994;25:86–91.
24. Nakanuma Y, Hosoi M, Sanzen T, et al. Microstructure and development of the normal and pathologic biliary tract in humans, including blood supply. *Microsc Res Tech*. 1997;38:552–570.
25. Nonomura A, Minato H, Shimizu K, et al. Hepatic hilar inflammatory pseudotumor mimicking cholangiocarcinoma with cholangitis and phlebitis: a variant of primary sclerosing cholangitis? *Pathol Res Pract*. 1997;193:519–525.
26. Oguz KK, Kiratli H, Oguz O, et al. Multifocal fibrosclerosis: a new case report and review of the literature. *Eur Radiol*. 2002;12:1134–1138.
27. Okazaki K. Clinical relevance of autoimmune-related pancreatitis. *Best Pract Res Clin Gastroenterol*. 2002;16:365–378.
28. Okazaki K. Autoimmune-related pancreatitis. *Curr Treat Options Gastroenterol*. 2001;4:369–375.
29. Portman BC, Nakanuma Y. Diseases of bile ducts. In: MacSween RNM, Burt AD, Portman BC, et al, eds. *Pathology of the Liver*, 4th ed. London: Churchill Livingstone; 2001:435–506.
30. Sharifi S, Murphy M, Loda M, et al. Nodular lymphoid lesion of the liver: an immune-mediated disorder mimicking low-grade malignant lymphoma. *Am J Surg Pathol*. 1999;23:302–308.
31. Shek TW, Ng IO, Chan KW. Inflammatory pseudotumor of the liver: report of four cases and review of the literature. *Am J Surg Pathol*. 1993;17:231–238.
32. Shek TW, Ho FC, Ng IO, et al. Follicular dendritic cell tumor of the liver: evidence for an Epstein-Barr virus-related clonal proliferation of follicular dendritic cells. *Am J Surg Pathol*. 1996;20:313–324.
33. Shirakata Y, Shiraishi S, Sayama K, et al. Subclass characteristics of IgG autoantibodies in bullous pemphigoid and pemphigus. *J Dermatol*. 1990;17:661–666.

34. Takikawa H, Manabe T. Primary sclerosing cholangitis in Japan: analysis of 192 cases. *J Gastroenterol*. 1997;32:134–137.
35. Terada T, Nakanuma Y, Ohta G. Glandular elements around the intrahepatic bile ducts in man: their morphology and distribution in normal livers. *Liver*. 1987;7:1–8.
36. Toda K, Yasuda I, Nishigaki Y, et al. Inflammatory pseudotumor of the liver with primary sclerosing cholangitis. *J Gastroenterol*. 2000;35:304–309.
37. Toosi MN, Heathcote J. Pancreatic pseudotumor with sclerosing pancreato-cholangitis: is this a systemic disease? *Am J Gastroenterol*. 2004;99:377–382.
38. Van der Zee JS, Aalberse RC. Immunochemical characteristics of IgG4 antibodies. *N Engl J Allergy Proc*. 1988;9:31–33.
39. Wiernik PH, Rader M, Becker NH, et al. Inflammatory pseudotumor of spleen. *Cancer*. 1990;66:597–600.
40. Yoshida K, Toki F, Takeuchi T, et al. Chronic pancreatitis caused by an autoimmune abnormality: proposal of the concept of autoimmune pancreatitis. *Dig Dis Sci*. 1995;40:1561–1568.