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Primary Sclerosing Cholangitis in Japanese Patients: Association with Inflammatory Bowel Disease

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Abstract

To characterize primary sclerosing cholangitis (PSC) in Japanese patients and its association with inflammatory bowel disease (IBD), 155 reported cases of PSC, including 6 cases of our own, were reviewed. The prevalence of IBD was less in Japanese PSC patients than in Western patients (23% versus 62-100%). Japanese PSC patients with IBD were younger (mean age, 33.1 versus 51.8 years) and were more often women (51% versus 36%) than those without IBD. Seventy-four percent of PSC patients with IBD had extensive colonic lesions, and 89% of those developed IBD simultaneously, with or prior to PSC. There were 3 cases of neutrophilic cholangitis among the PSC patients with IBD but none in those without IBD. Based on these observations, we speculate that there may be subtypes of PSC which differ pathophysiologically.

KEYWORDS: primary sclerosing cholangitis, inflammatory bowel disease

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Review

Primary Sclerosing Cholangitis in Japanese Patients: Association with Inflammatory Bowel Disease

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To characterize primary sclerosing cholangitis (PSC) in Japanese patients and its association with inflammatory bowel disease (IBD), 155 reported cases of PSC, including 6 cases of our own, were reviewed. The prevalence of IBD was less in Japanese PSC patients than in Western patients (23% *versus* 62-100%). Japanese PSC patients with IBD were younger (mean age, 33.1 *versus* 51.8 years) and were more often women (51% *versus* 36%) than those without IBD. Seventy-four percent of PSC patients with IBD had extensive colonic lesions, and 89% of those developed IBD simultaneously with or prior to PSC. There were 3 cases of neutrophilic cholangitis among the PSC patients with IBD but none in those without IBD. Based on these observations, we speculate that there may be subtypes of PSC which differ pathophysiologically.

Key words: primary sclerosing cholangitis, inflammatory bowel disease

Primary sclerosing cholangitis (PSC) causes fibrous stenosis of the bile duct. The etiology of PSC is unknown. The most frequently used diagnostic criteria are LaRusso's (1) which include: a) more than twice the normal level of serum alkaline phosphatase, b) sphenoid changes detected on cholangiography, c) histologically proven fibrous obliterative cholangitis, and d) absence of biliary stone or prior surgery on the bile duct.

Ulcerative colitis (UC) and Crohn's disease (CD) are inflammatory bowel diseases (IBD) of unknown etiology which initially affect, respectively, the mucosal and submucosal layers of the bowel wall. PSC and IBD have been reported to co-occur, and we recently treated 2 patients with PSC and IBD (2); one of which has not yet been reported. PSC with IBD is rarely seen in Japan, and there are no comparative studies on PSC patients with and without IBD in Japan. We have reviewed 6 patients with PSC in our institution (2 cases were published) (2, 3) and 149 cases in the Japanese literature from 1967 to 1995 (4-126). The epidemiology and clinical features are summarized, and the association with IBD is compared with that in Western countries.

PSC in Japan. PSC cases in Japan are listed in Table 1: 94 men and 61 women. The male to female ratio was 1.5, similar to that in Western countries (127-129). The mean age at diagnosis in Japan was 47.6 years, slightly higher than the ages, 32.9-46 years, observed in Western countries (127-130).

One hundred and twenty-one cases (78%) had the following symptoms: jaundice in 73, abdominal pain in 40, general fatigue in 22, and fever in 19. The other 34 cases (22%) were asymptomatic. Extrahepatic lesions alone were found in 60 cases (39%), intrahepatic lesions in 17 (11%), intrahepatic and extrahepatic lesions in 76 (49%), and unknown in 2 (1%). In Western countries, symptoms were reported in 64-75% of patients with PSC (128, 129, 131), and intrahepatic and extrahepatic lesions were found in 70-78% (128, 129).

Serum total bilirubin was abnormal in 96 cases (66%) and was more than 10 mg/dl in 24 cases (16%). Alkaline phosphatase levels were elevated in 135 cases (92%). For autoantibody production in 101 cases, 41 (40%) were positive; anti-nuclear antibody was observed in 24 (24%), and anti-smooth muscle antibody was detected in

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Table 1 Summary of 155 patients with primary sclerosing cholangitis (PSC) in Japan

Sex Male/Female	94/61	Total bilirubin (mg/dl)	
(Male/Female ratio 1.5)		< 1.2	50
		1.3 4.9	48
Age range	8-84 years	5.0 9.9	24
(Mean age 47.6 years)		10 <	24
Symptomatic type	121(78%)	Alkaline phosphatase	
Jaundice	73	Normal	12
Abdominal pain	40	< 2 fold	35
General fatigue	22	2 fold <	100
Fever	19		
Asymptomatic type	34(22%)	HLA	
		DR2	14/33(42%)
Location		DR4	5/33(15%)
Extrahepatic lesions	60(39%)	B8	1/33(3%)
Intrahepatic lesions	17(11%)	DR3	0
Intrahepatic and extrahepatic lesions	76(49%)	Treatment	
Unknown	2(1%)	Predonisolone	41
		Ursodeoxylic acids	20
Associations		Cholestilamine	2
Inflammatory bowel disease	35(23%)	D-penicillamine	1
Chronic pancreatitis	18	Cyclophosphamide	1
Eosinophilia	11	Azatioprine	1
Sjögren syndrome	3	Cyclosporine	1
Esophageal varices	3	Laparotomy	70
Chronic thyroiditis	2	Liver transplantation	1
Polyarthritis	1		
Uveitis	1	Cause of death	
		Liver failure	11
Malignant tumors		Severe cholangitis	3
Cholangiocarcinoma	4	Sepsis	2
Colon cancer	1	Pneumonia	1
		Renal failure	1
Autoantibodies		Esophageal varices	1
Negative	60(60%)	Peritoneal carcinomatosa	1
Positive	41(40%)		
Anti-nuclear antibody	24		
Anti-smooth muscle antibody	20		
Anti-microsomal antibody	5		
Anti-DNA antibody	3		
Anti-mitochondrial antibody	2		

20 (20%). In addition, anti-mitochondrial antibody was found in 2 cases (2%) though transiently. Regarding HLA, a high prevalence of B8 and DR3 was observed in Western countries (132, 133). HLA-B8 and HLA-DR3 are related to such autoimmune diseases as lupoid hepatitis, type 1 diabetes mellitus, myasthenia gravis, and thyrotoxicosis (134). Therefore, autoimmune phenomena may play some role in the pathogenesis of PSC in patients with HLA-B8 or HLA-DR3. In Japan, 33 patients were examined, and B8 was detected in only 1 case, DR3 was not found, and DR2 was found in 14 patients (42%). There was a report in the Western literature that PSC patients who did not possess HLA-B8 or HLA-DR3 had an association with HLA-DR2; HLA-DR2 was found in 69% of HLA-DR3-negative PSC patients compared with 34% of control subjects (134).

IBD was observed in 35 PSC patients (23%) in Japan; this rate was lower than the 62-100% values reported in Western countries (Table 2) (127-131). Other complications observed in the present Japanese population were chronic pancreatitis in 18, eosinophilia in 11, and Sjögren's syndrome in 3. Cholangiocarcinoma was found in 4 cases and colon cancer in 1 case.

For medical treatment, prednisolone (41 patients) and ursodeoxycholic acid (20 patients) were most frequently used. Seventy patients had laparotomy, including 39 patients who were suspected of having cholangiocarcinoma or pancreatic cancer. One case of liver transplantation was reported (110).

Nineteen deaths were reported in the literature. The cause was liver failure in 11 cases; infections such as severe cholangitis, sepsis, or pneumonia in 6 cases; renal failure in 1 case; bleeding from esophageal varices in 1 case; and peritoneal carcinomatosa due to cholangiocarcinoma in 1 case.

PSC associated with IBD. Of the 35 Japanese patients with PSC and IBD (2, 18, 21, 22, 30, 34, 36, 44, 46, 49, 52, 55, 60, 61, 64, 65, 70, 71, 74, 77, 78, 80, 84, 86, 90, 94, 99, 110, 114, 118, 122), 29 patients had ulcerative colitis (UC). Only 2 patients (2, 90), including 1 reported by us (2), had Crohn's disease (CD)

Table 2 Frequency of IBD in patients with PSC

Reference	PSC No.	IBD No. (%)	UC No. (%)	CD No. (%)	Other No. (%)
Chapman (127)	29	21 (72)	21 (72)		
Herzberg (128)	53	33 (62)	31 (58)	2 (4)	
Stockbrügger (129)	46	43 (93)	36 (78)	2 (4)	5 (11)
Aadland (130)	45	45 (100)	37 (82)	6 (13)	2 (5)
Rabinovitz (131)	66	47 (71)	39 (59)	8 (12)	
Present study	155	35 (23)	29 (19)	2 (1)	4 (3)

PSC: Primary sclerosing cholangitis; IBD: inflammatory bowel diseases; UC: ulcerative colitis; CD: Crohn's disease.

Table 3 Extent of colitis in 35 patients with PSC and IBD

Type of colitis	Number of patients	Extent of colitis		
		Total	Left-sided	Unknown
UC	29	23	3	3
CD	2	2		
Other	4	1[a]	1[b]	2
Total	35	26(74%)	4(12%)	5(14%)

a : Eosinophilic colitis; *b* : Aphthoid colitis
Abbreviations: See the footnote to Table 2.

Table 4 Characteristic of PSC patients with and without IBD

		PSC with IBD (n = 35)	PSC without IBD (n = 120)
Sex	Male/Female	17:18	77:43
	Male/Female ratio	0.95	1.8
Age	Range	11-64 years	8-84 years
	Mean	33.1 years	51.8 years
Symptomatic type		16 (46%)	105 (88%)
Location			
Extrahepatic		5 (15%)	55 (46%)
Intrahepatic		7 (21%)	10 (8%)
Intrahepatic and extrahepatic		21 (64%)	55 (46%)
Autoantibody (positive)		11/28 (39%)	30/74 (41%)
HLA			
DR2		6/15 (40%)	8/18 (44%)
DR4		3/15 (20%)	2/18 (11%)
B8		0/15	1/18 (6%)
Liver histology			
Periductal fibrosis		24/33 (73%)	43/91 (47%)
Cell infiltration		18/33 (55%)	67/91 (74%)
Lymphocyte predominant		6	47
Neutrophil predominant		3	0
Cell type not described		9	20

Abbreviations: See Table 2.

(Table 2). In Western countries, 58-82 % of PSC patients had UC and 4-13 % had CD (Table 2). In our review, total colitis was detected in most of the IBD patients with PSC (74 %), particularly all of the 2 cases with CD (Table 3). Stockbrüger *et al.* (129) reported that 84 % of patients with IBD and PSC had total colitis. There have been few studies on PSC associated with CD, and there have been no small intestinal-type CD cases reported to be associated with PSC. Aadland (130) and Rabinovitz (131) reported 6 and 8 cases of CD with PSC, respectively, and all their patients had extensive colonic lesions. Regarding the chronology of onset of PSC and IBD, simultaneous development was observed in 21 cases. IBD developed prior to PSC in 10 cases, and PSC occurred earlier in 4 cases. According to Stockbrügger *et al.* (129), IBD developed earlier than PSC in 32 of 43 PSC patients. Simultaneous development was observed in 7 cases, and PSC occurred earlier than IBD in 2 cases. Chapman *et al.* (127) also reported that IBD developed earlier than PSC in 17 of 21 PSC patients with IBD. In those cases where IBD develops prior to PSC and is associated with extensive colonic lesions, IBD may play a role in the development of PSC.

Comparison between PSC with and without IBD. PSC patients with IBD were compared to those without IBD (Table 4). Analysis of variance and the chi-square test were used for statistical analysis.

The percentage of women was higher in PSC patients with IBD than in those without IBD (51 % *versus* 36 %; $P < 0.05$). Additionally, patients with IBD were markedly younger than those without IBD (33.1 *versus* 51.8 years; $P < 0.05$). Because autoimmune diseases are often observed in young women, the association of IBD in young female patients with PSC implies that an autoimmune condition is involved in the pathophysiology in this group of patients.

The prevalence of symptomatic PSC was lower in patients with IBD than in those without IBD (46 % *versus* 88 %; $P < 0.05$). The prevalence of both intrahepatic and extrahepatic lesions was high in patients with IBD (64 %), whereas patients without IBD had extrahepatic lesions in 46 % and both intrahepatic and extrahepatic lesions in 46 %.

In Western countries, Rabinovitz *et al.* (131) reported on 47 patients with IBD and 16 without IBD; men were more likely to have IBD, and no difference was found regarding the mean age. Thus, PSC with IBD in Western countries differs from those in Japan. However, the incidence of symptomatic type and the location of lesions were similar between Western countries (131) and Japan.

No difference was observed between patients with or without IBD in the rate of HLA-DR2-positive cases (40 % *vs* 44 %). In Western countries, the incidence of HLA-B8 or HLA-DR3 was higher in cases of UC associated with PSC than in UC without PSC (135).

There was essentially no difference in the rate of autoantibody-positive cases (39 % *versus* 41 %). There

have been some reports from Europe and the United States on autoantibodies associated with PSC and IBD. It has been reported that, as compared to IBD patients without PSC, those with PSC are more likely to produce autoantibodies (136). Anti-colonic antibodies have been detected in 67.5 % of UC patients with PSC and in 17 % of those without PSC (137). A 40-KDa protein was extracted recently from human colonic mucosa, and antibodies to this protein were detected in colonic specimens of patients with UC (138). Furthermore, a monoclonal antibody to this 40-KDa protein reacted with epithelium of the colon and bile duct (139), suggesting a shared epitope between the two tissues. An autoantibody that reacted with this epitope has been detected in the serum of PSC patients (140). Perinuclear anti-neutrophil cytoplasmic antibody (pANCA), which reacts specifically with the perinuclear region of neutrophils (141), was measured in the sera of patients with PSC and IBD (142). pANCA was observed in 83 % of UC patients. Low titers of pANCA were detected in 25 % of CD patients, and high titers in 77 % of PSC patients. In cases of UC, high titers of pANCA were found mainly in those with active disease, while the titers of pANCA did not correlate with the severity of CD or PSC. Furthermore, elevated levels of pANCA can persist for 2–3 years after liver transplantation or proctocolectomy (143). It has been speculated that the appearance of pANCA may not be a secondary reaction (*e.g.* inflammation) but may be related to shared pathogenic mechanisms between these diseases.

In histologic examination of liver tissue, PSC-specific periductal fibrosis was found in 73 % of patients with IBD and in 47 % of those without IBD. Cell infiltration of the periductal region was observed in 55 % of patients with IBD and in 74 % of those without IBD. Generally, infiltrating cells of liver tissue in PSC consist mainly of lymphocytes, together with plasmacytes, histiocytes, and occasional polymorphonuclear leukocytes (127). In our review, the type of major infiltrating cells was described in 56 cases: 9 cases of PSC with IBD and 47 cases without IBD. Infiltration mainly by neutrophils was observed in only 3 cases with IBD (36, 65); lymphocytes predominated in all 47 cases without IBD. Also in Western countries, neutrophil-predominant infiltration of liver tissue has been reported in PSC patients with IBD (144). Recent studies have reported that a proinflammatory bacterial peptide synthesized by colonic bacteria in the rat may cause portal inflammation and neutrophilic cholangitis similar to the histopathologic lesions noted during the early stages of PSC (145). Another study showed that intestinal bacterial overgrowth in rats was associated with hepatic inflammation similar to that observed in PSC (146). Whether neutrophilic cholangitis is due to bacterial infection through injured colonic mucosa as a result of IBD, leading to the development of PSC, remains to be elucidated. In addition, because PSC may develop through the foregoing pathway, intrahepatic lesions alone or both intrahepatic and extrahepatic ducts involvement may occur more often in patients with IBD than in those without IBD (85 % *vs* 54 %).

Summary

In comparison between PSC in Japan and in Western countries, the association with IBD was much weaker in Japanese. The difference in the correlation with HLA typing may be responsible for the weaker association with IBD. In PSC cases associated with IBD in both Japan and in Western countries, there were often extensive colonic lesions. There were some cases of neutrophilic cholangitis in PSC patients with IBD, and this may be explained by bacterial infection through extensive colonic lesions of IBD. PSC with IBD was more frequent in female and younger patients, as is the case with autoimmune diseases. Based on these observations, subtypes of PSC may differ in various terms of genetics, infection, and autoimmunity, but further investigation is needed before we can conclude whether these differences explain the association with IBD.

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