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Rapid communication

Clinical features of primary sclerosing cholangitis with onset age above 50 years

Kenji Hirano, Minoru Tada, Hiroyuki Isayama, Yoko Yashima, Hiroshi Yagioka, Takashi Sasaki, Hirofumi Kogure, Osamu Togawa, Toshihiko Arizumi, Saburo Matsubara, Yousuke Nakai, Naoki Sasahira, Takeshi Tsujino, Takao Kawabe, and Masao Omata

Department of Gastroenterology, Faculty of Medicine, University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan

Background. Although there are two peaks in the age distribution of primary sclerosing cholangitis (PSC) in Japan, the clinical differences between the patients with an older or younger onset age have not been reported. ***Methods.*** We compared clinical features of 18 patients with onset age less than 50 years (younger group) and ten PSC patients with onset age above 50 years (older group). ***Results.*** An association with ulcerative colitis (UC) was recognized in six patients in the younger group and in one in the older group. High serum IgE (>170 IU/ml) was observed more frequently in the older than in the younger group (1/10 vs. 7/8, $P = 0.0029$). Mean serum IgM tended to be higher in the younger group (198 vs. 119 mg/dl, $P = 0.083$). More patients received liver transplantation or continuous bile drainage, or developed liver failure or cholangiocellular carcinoma in the younger than in the older group (11/18 vs. 1/10, $P = 0.016$). ***Conclusions.*** Older PSC patients have higher IgE, possibly less association with UC, lower IgM, and a better prognosis. The pathogenesis of PSC may be different between older and younger patients.

Key words: primary sclerosing cholangitis, ulcerative colitis, onset age, IgE, IgM

Introduction

Primary sclerosing cholangitis (PSC) is a chronic cholestatic liver disease characterized by diffuse inflammation and fibrosis of both intra- and extrahepatic bile ducts. About 75% of PSC patients have inflammatory bowel disease (IBD), especially ulcerative colitis (UC), among European and North American populations.[1] The underlying pathophysiology is still unclear, and its prognosis is poor without liver transplantation. The mean age at diagnosis is about 40 years, and about twice as many men as women are affected.[2] In Japan, there are two peaks in the age distribution of PSC, which has never been reported in other countries.[3] Interestingly, most PSC patients with IBD are in their teens or twenties. Patients 50–60 years old, in the range of the second peak in the PSC age distribution, rarely have IBD. Some older patients with PSC may have sclerosing cholangitis (SC) associated with autoimmune pancreatitis (AIP), but the second peak in the age distribution is still clearly present even after elimination of probable SC associated with AIP.[3–5] Thus, we examined the clinical differences between younger- and older-onset PSC patients.

Patients and methods

Twenty-eight patients diagnosed with PSC at our department by the end of 2006 were enrolled in the present study. We used diagnostic criteria published by the Mayo Clinic in 2003,[6] but excluded patients with SC with AIP who fulfilled the diagnostic criteria of AIP proposed by the Mayo Clinic[7] or the revised Japan Pancreas Society criteria.[8] We also excluded two patients with seemingly IgG4-related SC, who were diagnosed on the basis of their extremely high IgG4 levels (828 and 1260 mg/dl), an association with retroperitoneal fibrosis, often observed in AIP, their good clinical course (good response to steroid treatment in one, and spontaneous remission in one), and their lack of pancreatic lesions.[9,10] Patients in whom SC and biliary stones were found at the same time were diagnosed as having PSC if they had no past history of symptoms related to repeated biliary infection. We divided the 28 patients into two groups according to their age at

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Reprint requests to: K. Hirano

disease onset: >50 years (older group, $n = 10$) and <50 years (younger group, $n = 18$). We compared the two groups in terms of associated disease, affected portions of the bile duct, laboratory data (mainly immunological parameters), and liver function prognosis. Patients with uncontrollable jaundice or needing liver transplantation or palliative biliary drainage (percutaneous or endoscopic), or those who developed cholangiocellular carcinoma (CCC), were regarded as having a poor prognosis. We examined the proportions of patients in each group with a poor prognosis. We defined onset as when the abnormalities in biliary enzymes or biliary imaging findings (sclerogenic change of the biliary tract) were first found. Possible *Helicobacter pylori* infection was examined in 14 patients by measuring serum IgG antibodies to *H. pylori*. The histological stage of PSC was confirmed by needle biopsy in 12 and by surgery in five patients.

Results

The clinical features of the PSC patients are summarized in Table 1. The mean age at onset in the younger group, 11 men and seven women, was 30 years (range, 12–48 years). The mean age at onset in the older group was 66 years (range, 52–79 years), and this group consisted of three men and seven women. The mean observation period without liver transplantation was 110 (28–222) months for the younger group and 49 (8–94)

Table 1. Clinical features of PSC patients

			Affected portion of the biliary tract							
Patient	Onset age/sex	Ulcerative colitis	lower CBD	Middle to upper CBD	Hilus	IHBD	ANA (≧80)	IgA (110–410 mg/dl)	IgG (870–1700 mg/dl)	IgM (35–220 mg/dl)
Age of onset <50 years										
1	12/F	+	−	+	−	+	−	943	1947	155
2	12/M	+	+	+	+	+		365	2636	460
3	15/M	+	+	+	+	+	−	369	2884	400
4	18/M	−	+	+	+	+	+	298	2480	175
5	22/M	+	+	+	+	+	−	841	1930	114
6	23/F	−	−	−	+	+	−	280	1425	275
7	20/M	−	−	−	+	+	−			
8	25/F	−	+	+	+	+	−	415	1693	419
9	28/F	−	+	+	+	+	−	351	1015	203
10	33/F	+	−	+	+	+	−	388	1121	236
11	35/M	−	+	+	+	+	−	240	1429	59
12	42/F	−	+	+	+	+	−	195	1282	190
13	42/M	−	−	+	+	+	−	290	1771	101
14	42/M	−	−	−	+	+	−	126	749	43
15	42/F	−	−	−	+	+		536	2607	174
16	43/M	−	−	−	−	+	−	432	1298	103
17	44/M	+	−	+	+	+	−	390	1505	134
18	48/M	−	−	−	+	+	−	222	1534	125
Age of onset >50 years										
19	52/F	−	−	−	+	+	−	181	2712	101
20	56/F	−	+	+	−	+	−	682	1957	137
21	58/M	−	+	−	+	+	−	323	2111	60
22	60/F	−	−	−	−	+	−	212	3229	249
23	62/M	+	−	−	+	+	−	374	3760	256
24	69/F	−	−	+	+	+	−	159	1640	119
25	71/M	−	−	+	+	+	−	485	1509	103
26	73/F	−	+	+	+	+	−	234	1884	88
27	75/F	−	+	+	+	+	−	235	1381	24
28	79/F	−	−	+	+	+	−	224	1707	52

PSC, primary sclerosing cholangitis; CBD, common bile duct; IHBD, intrahepatic bile duct; ANA, antinuclear antibody; LLT, living liver transplantation; OLT, orthotopic liver transplantation; CCC, cholangiocellular carcinoma; EBD, endoscopic biliary drainage; PTBD, percutaneous transhepatic biliary drainage

months for the older group ($P = 0.0007$). An association with UC was recognized in 6/18 patients in the older group and in 1/10 in the younger group ($P = 0.364$). No association with Crohn's disease was found in either group. Gallbladder stones in the younger and older groups were recognized in five and three patients, respectively. Five patients in the younger group and three in the older group had intrahepatic or common bile duct stones. *Helicobacter pylori* infection was recognized in 0/7 and 2/7 patients in the younger and older groups, respectively. Two patients (patients 15 and 28, Table 1) had bronchial asthma, and one (patient 23) had chronic eczema.

Histological stages (I/II/III/IV) were 1/2/1/5 in the younger group and 1/3/4/0 in the older group. In 11 patients (nine in the younger group and two in the older group), no liver tissue was examined. Affected portions of the bile duct (lower/middle to upper/hilus/intrahepatic) in the younger and older groups were 8/12/16/18 and 4/6/8/10, respectively. There was no remarkable difference between the two groups.

Laboratory data for the two groups are summarized in Table 2. IgG4 was not measured in four patients, and IgE was not measured in ten. High IgA (>410 mg/dl), IgG (>1700 mg/dl), IgM (>220 mg/dl), and IgG4 (>135 mg/dl) and positive antinuclear antibody did not differ in frequency between the two groups. High IgE (>173 IU/ml), however, was significantly more frequent in the older group (1/10 vs. 7/8, $P = 0.0029$). Although average IgA, IgG, IgM, and IgG4 levels were not sta-

IgG4 (<135 mg/dl)	IgE (<170 IU/ml)	Eosinophilia (>500/μl)	Histological stage (Ludwig)	Latest status	Poor Prognosis	Follow-up period without liver transplantation (months)
52.2		–	IV	Death from recurrence after LLT	+	139
105	290	–		Uncontrollable jaundice (wait for OLT)	+	222
317		–	IV	OLT	+	63
	167	–	IV	OLT	+	15
18	9	–	II	CCC (chemotherapy), EBD	+	211
9.6	141	–		Stable	–	86
		–		Stable	–	108
		–	IV	OLT	+	101
		–		Death from CCC	+	102
26	17	+	I	Stable	–	30
27.4	120	–		Stable	–	109
35	39	+	III	PTBD	+	91
157		+		Stable	+	124
10.1	2	–		Stable	–	128
99		–	IV	OLT	–	78
73.2		–		Death from liver failure	+	152
82.8	37	–		EBD	+	190
16.2	39	–	II	Stable	–	28
67.8	681	+	II	Stable	–	36
18.5		–	I	Stable	–	72
213	1202	–	III	Stable	–	31
78	320	+	III	Stable	–	94
439	1900	+	II	Stable	–	45
12	401	–		PTBD	+	91
67.3		–	II	Stable	–	42
99	584	–	III	Stable	–	62
27	167	+		Stable	–	12
64	1457	–	III	Stable	–	8

Table 2. Comparison of laboratory data between the younger and older groups

	Frequency of abnormally high values			Average (range)		
	Younger group	Older group	*P*	Younger group	Older group	*P*
IgA	5/17	2/10	0.678	393 (126–943)	311 (169–682)	0.152
IgG	7/17	7/10	0.237	1724 (749–2884)	2189 (1381–3760)	0.100
IgM	5/17	2/10	0.678	198 (43–460)	119 (24–256)	0.083
IgG4	2/14	2/10	0.999	73 (9.6–317)	109 (12–439)	0.425
IgE	1/10	7/8	0.0029	86 (2–290)	839 (167–1900)	0.010

tistically different, IgG tended to be higher in the older group (1724 vs. 2189 mg/dl, $P = 0.100$), and IgM tended to be higher in the younger group (198 vs. 119 mg/dl, $P = 0.083$). Three patients in the younger group and four in the older group had eosinophilia (>500 μl). The eosinophilia was severe (>3000 μl) in two patients in the older group (patients 19 and 22), and they were diagnosed as having hypereosinophilic syndrome (HES).

More patients in the younger group than in the older group had a poor prognosis (11/18 vs. 1/10, $P = 0.016$). CCC was recognized in two patients in the younger group. Three patients died in the younger group, whereas there was no death in the older group.

Discussion

Despite the apparent importance of age of onset of PSC, to our knowledge, no study has analyzed differences in patients with PSC in relation to age of onset, except one that examined the frequency of associated IBD.[3] In the present study, the most impressive difference between the two patient groups was observed in IgE. High IgE levels in PSC associated with HES have been reported previously.[11] In this study, two patients in the older group had HES, but high serum IgE was also observed in other older group patients without HES (5/6). On the other hand, high IgE was observed in only one patient in the younger group. This finding suggests that the pathogenesis of PSC differed between the older and younger groups. It is possible that a type I allergic reaction induced by unidentified agents may be related to the pathogenesis of PSC in older patients. Terasaki et al.,[12] who reported on three patients with primary biliary cirrhosis (PBC) and bronchial asthma, suggest that such an association might occur in PBC. IgM, whose elevation was previously reported to be characteristic of PSC,[13] tended to be higher in the younger group (especially those under 30 years) than in the older group. This may also suggest a different pathogenesis between groups. We speculate that the difference in the frequency of associated IBD derives from the presumed difference in pathogenesis.

Bile duct imaging findings did not differ between the two groups. Initially, we suspected that affected portions were less diffuse in the older group, leading to the better prognosis, but we could not confirm this finding.

Because in the older group there was only one patient with liver failure and none with CCC, and because the histological stage indicated less progression, the prognosis has apparently better in the older group. It is difficult, however, to compare the two groups because of a difference in the observation period and because the histological stage was not confirmed in all patients. Serum IgE is often elevated in SC with AIP (85%, 11/13, in our institute), which shows good response to steroid treatment,[5] and some may therefore suggest that by analogy steroids should be more effective in older PSC patients. Three patients in the older group (patients 19, 22, and 24) received steroid treatment (initial dose, 30–40 mg/day). In the two patients with HES (patients 19 and 22), their eosinophilia normalized and liver function became stable (normal in one) after steroid treatment, but no dramatic improvement in the bile duct imaging findings, seen in SC associated with AIP, was observed.[4,5,10] Patient 24 showed no improvement. Thus, we are wary of using steroids at present in other older PSC patients without marked eosinophilia.

Four case reports document cases of younger patients (15–28 years) with sclerosing cholangitis with marked eosinophilia.[11,14–16] Among them, one patient showed high IgE.[11] However, because such cases are rare, it is difficult to decide whether high IgE is characteristic of PSC with marked eosinophilia.

The term "eosinophilic cholangitis" is sometimes used for cholangitis with eosinophilia and eosinophilic infiltration in the bile duct. Our two PSC patients with HES might fit this category. Such assertion, however, is difficult because the concept of eosinophilic cholangitis is still confused, and some papers seem to report IgG4-related SC with eosinophilia as eosinophilic cholangitis.[17,18]

We also examined *H. pylori* infection, which is a possible pathogenesis of PSC,[19] We are skeptical of the pathogenicity of *H. pylori*, however, because infection was recognized in only two patients in the older group.

Because of its retrospective nature, this study includes many problems. We were unable to obtain many data because of insufficient follow-up. It may be undesirable to compare two groups with different follow-up period. In addition, it was difficult to determine the exact onset time, especially in older patients who had not had regular physical check-ups. It is likely that the period during which the older patients suffered from PSC is probably longer than our observation period.

In summary, older PSC patients showed a less frequent association with IBD, lower IgM, higher IgE, and a better prognosis. As the size of our study was small, our results should be confirmed by a larger scale study. If our findings are reasonable, a new grouping of PSC in terms of age at onset or IgE levels should be considered.

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