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Case report

Concomitant colitis associated with primary sclerosing cholangitis

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Between 1985 and 2001, seven Japanese patients (four males and three females) were diagnosed as having primary sclerosing cholangitis (PSC) in our hospital. All seven patients received total colonoscopy with distal ileoscopy. All four male patients were diagnosed as having colitis by colonoscopy, while none of the three female patients had colitis. The four patients with colitis did not have any symptoms attributable to colitis, such as diarrhea or hematochezia. In three of the four patients, unclassified colitis was the most suitable diagnosis, because there were no typical findings of ulcerative colitis or Crohn's disease. The remaining patient was diagnosed as having eosinophilic colitis. By colonoscopic visualization, the right-sided colon, including the terminal ileum, was mainly involved, but the lesions were not severe. The main findings were redness, erosion, stenosis, and insufficiency of haustral formation. Histologically, these lesions were nonspecific inflammatory changes in the three patients with unclassified colitis. In the patient with eosinophilic colitis, remarkable infiltration of eosinophils was observed. Thus, unclassified colitis appeared to be the main complication in these patients with PSC. Males predominated in regard to concomitant colitis, and they had no symptoms of the colitis. Colonoscopic examination revealed that the lesions were not severe. The main lesions were found in the right-sided colon, with nonspecific inflammatory changes. These results suggest that colonoscopic surveillance of patients with PSC should be performed even if they do not have any colitis symptoms.

Key words: primary sclerosing cholangitis, unclassified colitis, ulcerative colitis, eosinophilic colitis, Crohn's disease

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Introduction

Primary sclerosing cholangitis (PSC) is a chronic, cholestatic liver disease of unknown etiology, and is characterized pathologically by concentric periductal fibrosis of the intra- and extrahepatic biliary ducts. It has been shown that there are some differences in the characteristics of PSC between Japan and Western countries. In Japan, two peaks in the age distribution at diagnosis are observed, and the mean age at diagnosis is higher than that in Western countries.[1] Perinuclear antineutrophil cytoplastic antibodies (pANCA) are observed in about 80% of patients with PSC,[2] and HLA-B8 and HLA-DR3 are strongly related to PSC in Western countries.[3,4] In contrast, the pANCA positivity rate is low, and no association with HLA-B8 or HLA-DR3 is found in Japan.[1] Inflammatory bowel disease (IBD) is the most common disease associated with PSC in Western countries, whereas IBD is found in only 21% of Japanese PSC patients, according to a report of the Japanese Society of Gastroenterology.[1] Thus, PSC patients in Japan appear to have different clinical characteristics compared with those in Western countries.

With regard to concomitant bowel disease with PSC, other than IBD, previous reports have described unclassified colitis as a complication of PSC, but the clinical details of the colitis were not described in these reports.[5,6] We found that the frequency of concomitant colitis in Japanese patients with PSC was higher than expected. Here, we describe the clinical features of concomitant colitis associated with PSC in Japan.

Case report

From 1985 to 2001, seven patients were diagnosed as having PSC in our hospital. Four of the seven patients were male and three were female. The mean age at diagnosis was 48.6 years (Table 1). The patients were

Table 1. Characteristics of patients with PSC

Patients	Sex	Age (years)	ALP	Ludwig's stage	Bile duct damage	Complications	Treatment	Follow-up period
1	M	21	768	II	Intra + extrahepatic	Colitis	UDCA, PSL, MTX	10 Years
2	M	37	1257	II	Intrahepatic	Colitis	UDCA	5 Years, 5 months
3	M	48	270	I	Intra + extrahepatic	Colitis	UDCA	3 Years, 4 months
4	M	51	486	ND	Intrahepatic	Colitis, ITP	UDCA	3 Years, 9 monhts
5	F	83	488	I	Intra + extrahepatic	Bronchial asthma	UDCA	9 Months
6	F	64	1320	II	Intrahepatic	Chronic hepatitis C, renal failure	UDCA	4 Years, 5 months
7	F	36	311	I	Small-duct PSC	Chronic thyroiditis	(−)	3 Years, 11 months

PSC, Primary sclerosing cholangitis; ALP, alkaline phosphatase (normal value, 100–280 U/l); ND, not done; ITP, idiopathic thrombocytopenic purpura; UDCA, ursodeoxycholic acid; PSL, prednisolone; MTX, methotrexate

followed-up for 9–120 months, with the mean follow-up duration being 54.1 months. During the observation period, two patients (patients 2 and 4) died due to hepatic failure, and 1 patient (patient 1) underwent living-related partial liver transplantation in 2001.

Six of the seven patients had characteristic findings of PSC on cholangiography. A beaded appearance of the bile ducts was seen in five patients and a "shaggy" sign was seen in one patient. Three patients had intrahepatic bile duct involvement and three had both intra- and extrahepatic bile duct involvement. In one patient (patient 7), the cholangiography findings were normal, but histological examination revealed concentric periductal fibrosis. This patient was diagnosed as having small-duct PSC (Table 1). Fibrous obliterative cholangitis was confirmed in five of six patients in whom a liver biopsy was performed. The staging system proposed by Ludwig et al.[7] was used. The stage in each patient was based on the results of the first liver biopsy (Table 1). Although serum levels of alkaline phosphatase (ALP) were markedly high in three patients, the levels were within double the normal upper limit in three patients and at the normal upper limit in one patient. With regard to complications, idiopathic thrombocytopenic purpura was found in one patient (patient 4), bronchial asthma was present in one patient (patient 5), chronic renal failure and chronic hepatitis were seen in one patient (patient 6), and chronic thyroiditis was found in one patient (patient 7).

All seven patients received total colonoscopy with distal ileoscopy, and four were diagnosed as having colitis. None of these four patients had symptoms of colitis, such as diarrhea or hematochezia, during the observation period. However, one patient (patient 1) had complained of diarrhea in his childhood. There was no past history concerning colitis in the other three patients. Colitis was diagnosed only by colonoscopy in two patients and by colonoscopy and double-contrast barium enema in two patients. Interestingly, all four patients with colitis were male, and colitis was not associated with PSC in the three female patients. Colonoscopic surveillance was carried out in three of the four patients with concomitant colitis at the time of diagnosis of PSC. The remaining patient (patient 4) had the colonoscopy 4 years after diagnosis. Follow-up colonoscopy was performed in two patients (patients 1 and 3). One (patients 1) received three colonoscopies during a follow-up of 10 years, and the other (patients 3) had two colonoscopies during a follow-up of 3 years and 4 months. A diagnosis of unclassified colitis was made if colitis could not be classified as ulcerative colitis (UC), Crohn's disease (CD), or as other bowel diseases, such as infectious colitis, ischemic colitis, or eosinophilic colitis. Three of the four patients were diagnosed as having unclassified colitis because there were no typical or significant findings suggestive of UC, CD, or other bowel diseases. One patient (case 3) was diagnosed as having eosinophilic colitis, because remarkable infiltration of eosinophils was found in the mucosa of the ileocecal valve. Eosinophilia was transiently found throughout the observation period in this patient. The characteristics of these patients with unclassified colitis and eosinophilic colitis are presented in Table 2. In cases 1 and 4, colitis was found in the terminal ileum and ascending colon. Case 2 had colitis in the ascending colon and case 3 in the ileocecal valve. Thus, the right-sided colon and the terminal ileum were generally involved, although these lesions were not severe. The predominant findings were redness, erosion, stenosis, and insufficiency of haustral formation. Histologically, these lesions showed nonspecific inflammatory changes, and they showed no histological changes suggestive of UC. In case 1, we could not completely rule out CD because the biopsy specimen of the ascending colon revealed minute granuloma-like changes. This patient may develop CD in the future. However, the patient received three colonoscopies during a follow-up of 10 years and endoscopic findings showed no change. In two patients, including this

Table 2. Colonoscopic findings of PSC patients with concomitant colitis

	Location of colitis	Findings
Case 1	Terminal ileum	Erosion
	Ascending colon	Erosion, redness, insufficiency of haustral formation
Case 2	Ascending colon	Stenosis, insufficiency of haustral formation
Case 3	Ileocecal valve	Erosion
Case 4	Terminal ileum	Erosion
	Ascending colon	Redness, insufficiency of haustral formation, disappearance of vascular network pattern

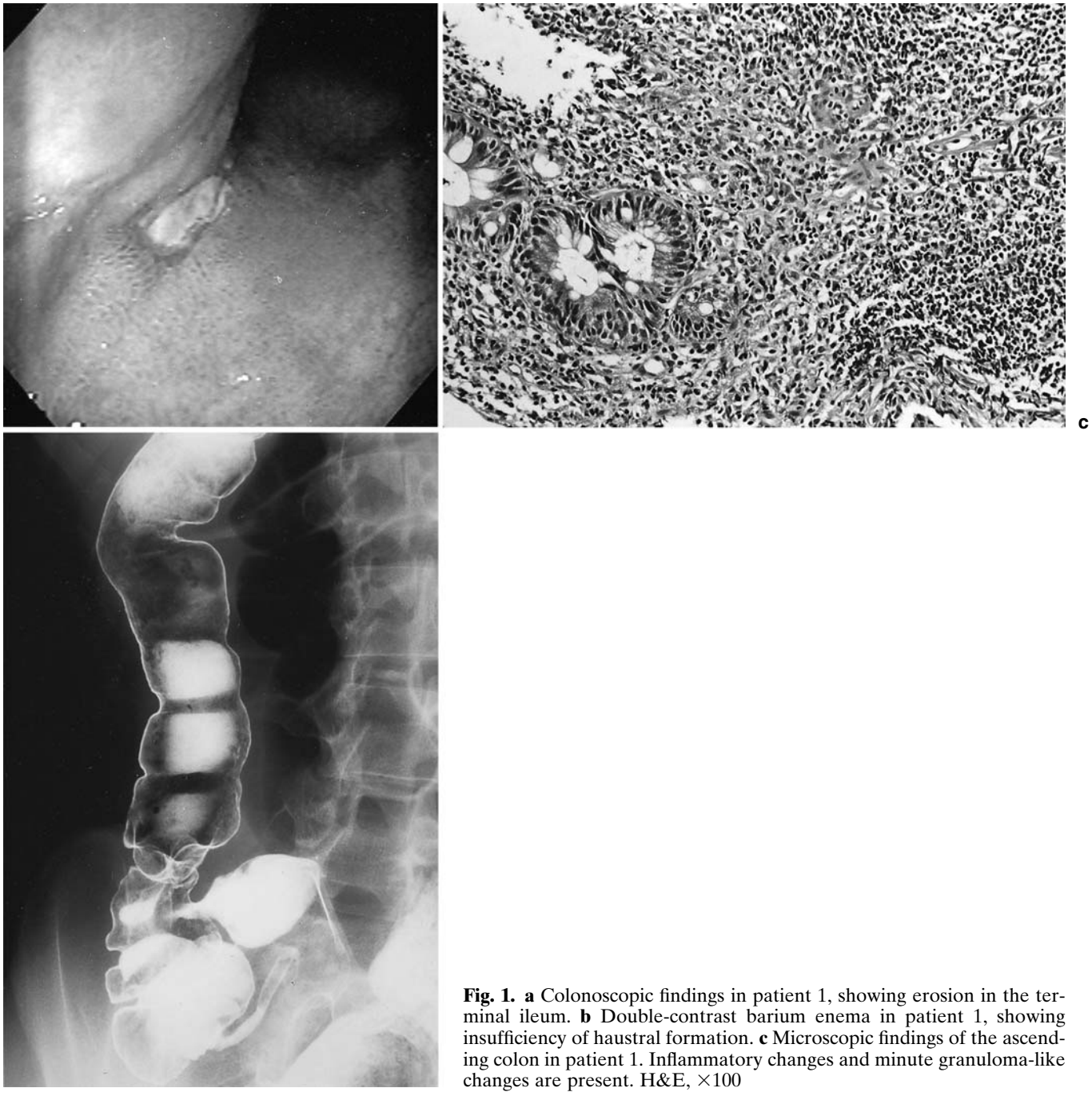
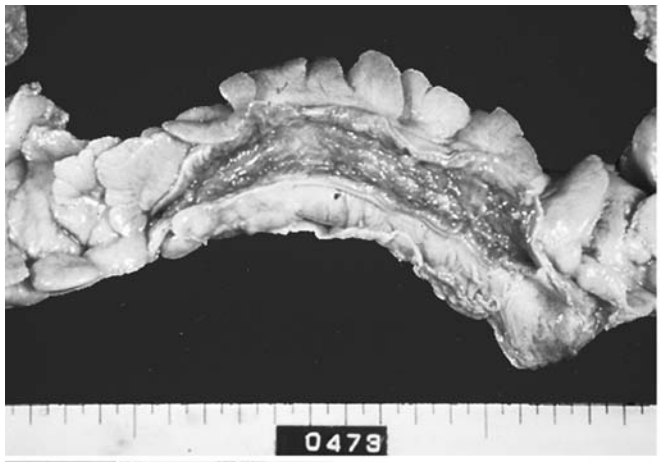
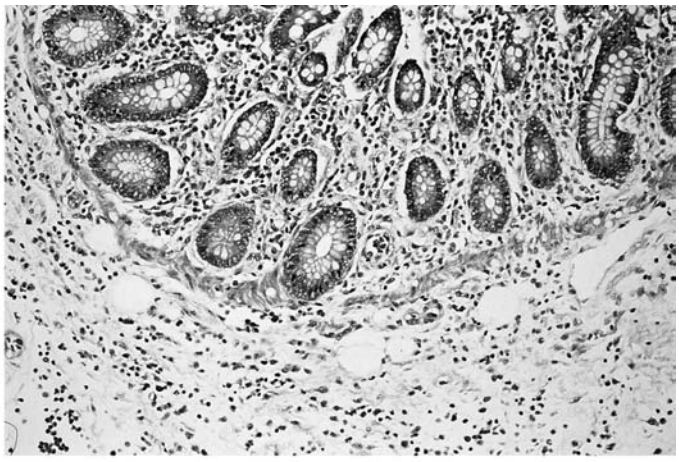


Fig. 1. **a** Colonoscopic findings in patient 1, showing erosion in the terminal ileum. **b** Double-contrast barium enema in patient 1, showing insufficiency of haustral formation. **c** Microscopic findings of the ascending colon in patient 1. Inflammatory changes and minute granuloma-like changes are present. H&E, ×100



a



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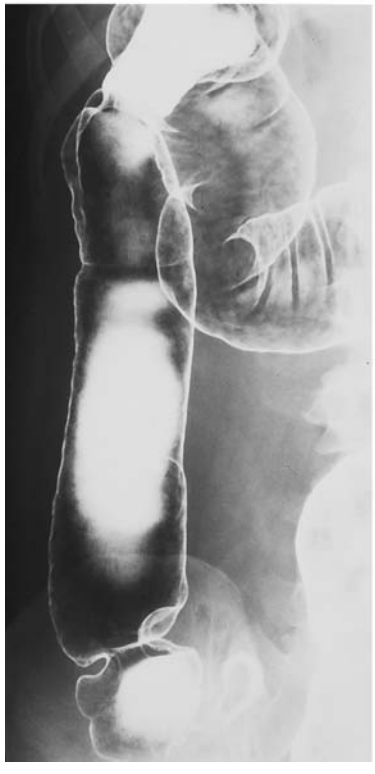

b

Fig. 2. **a** Macroscopic findings in patient 2, showing stenosis and thickening of the ascending colon. **b** Double-contrast barium enema in patient 2, showing insufficiency of haustral formation. **c** Microscopic findings in patient 2. Prominent lymphocytic infiltration was seen in the lamina propria of the bowel wall, and the submucosa was markedly edematous. H&E, ×40

patient (patients 1 and 3), who had follow-up colonoscopy, the findings of the follow-up colonoscopy were similar to the first ones. Because none of these four patients had symptoms of colitis, none of them received treatment for colitis. The colonoscopic findings, results of double-contrast barium enema, and pathological findings in three of these patients (patients 1, 2, and 3) are shown in Figs. 1–3.

Discussion

UC is a chronic inflammatory bowel disease of unknown etiology. Interestingly, approximately 80% of patients with PSC have UC in Western countries,[8–10] while only 2% to 5% of patients with UC have PSC.[8,11–13] There is a very close relationship of etiology between PSC and UC. Serum anti-colon antibodies which cross-react with proliferating bile ductules were found in approximately 60% of PSC patients with UC.[14] With regard to concomitant bowel diseases other than UC, some investigators have reported that unclassified colitis and eosinophilic colitis were associated with PSC. Monache et al.[6] reported that IBD was present in 91% of PSC patients, and 23% of these patients were diagnosed as having unclassified colitis. Aadland et al.[5] found that, of 27 patients with PSC, all had bowel disease and 2 (7.4%) had unclassified colitis. Hirano et al.[15]

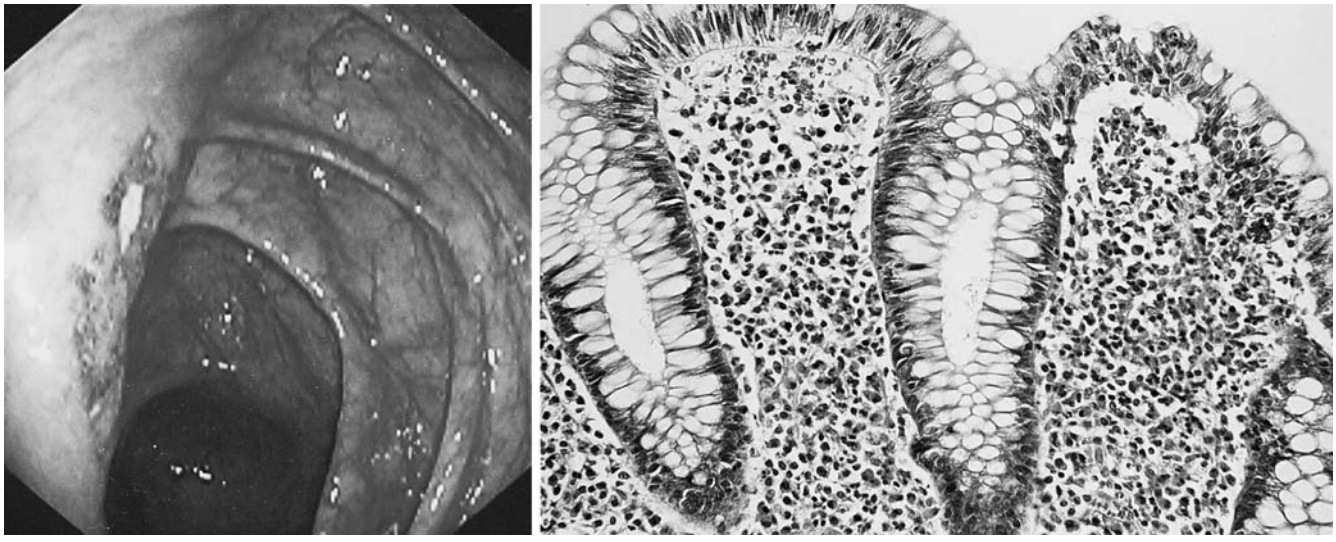

Fig. 3. **a** Colonoscopic findings in patient 3, showing erosion on the ileocecal valve. **b** Microscopic findings of the ileocecal valve in patient 3, showing remarkable infiltration of eosinophils. H&E, ×200

reported a patient with PSC and eosinophilic colitis involving the right-sided colon.

It has been reported that most PSC patients with IBD had no, or at most, mild colonic symptoms.[8,16] Furthermore, most of them had total colitis.[5,17] In contrast, our four patients with unclassified colitis or eosinophilic colitis had the colonic lesions in the right-sided colon and the terminal ileum. None of our four patients had colitis involving the entire colon. With regard to symptoms, our four patients did not have any symptoms. Indeterminate colitis is recognized as idiopathic colitis which cannot be classified as either UC or CD. Indeterminate colitis is more common among women and generally has an acute onset with abdominal pain, diarrhea, and rectal bleeding.[18] All patients with unclassified colitis in our experience were male. Moreover, the mucosal changes in the colitis of our patients were not severe, and none of them had colonic symptoms, such as diarrhea and hematochezia, during the observation period. Therefore, we did not diagnose our patients as having indeterminate colitis. Histological examination of the biopsy specimens in the patients with unclassified colitis revealed nonspecific inflammatory changes with infiltrating cells mainly consisting of lymphocytes. In the patient (case 3) who was diagnosed as having eosinophilic colitis, remarkable infiltration of eosinophils was observed.

In six of our seven patients with PSC, ursodeoxycholic acid was administered, and one of them (patient 1) transiently received prednisolone and methotrexate. In two patients (patients 1 and 3) who had follow-up colonoscopies, the findings of the follow-up colonoscopy were similar to the first ones. In these two patients, the treatment for PSC did not affect the colitis.

In general, concomitant UC in PSC patients is quiescent; indeed, 80% of patients were either asymptomatic or mildly symptomatic at the time PSC was diagnosed.[8,16] In our experience, none of the patients with unclassified colitis or eosinophilic colitis had any symptoms, and we therefore suggest that colonoscopic surveillance of patients with PSC should be performed even if they do not have any colitis symptoms. This may lead to a better understanding of the pathogenesis of PSC and its interrelationship with concomitant colitis. Further studies with a larger number of patients are necessary to clarify the characteristics of unclassified colitis associated with PSC. In addition, a multicenter study is needed, because the number of patients with PSC is especially small in Japan. It is considered that the recorded prevalence of concomitant bowel diseases in Japanese patients with PSC may increase if colonoscopy is performed in all patients.

In summary, unclassified colitis and eosinophilic colitis associated with PSC is predominantly seen in the right-sided colon. The colonoscopic findings of the lesions are not severe, and a male predominance, with no symptoms due to the colitis, is observed in Japanese PSC patients.

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