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Case report

Primary sclerosing cholangitis with marked eosinophilic infiltration in the liver

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Abstract: A 16-year-old boy was diagnosed as having primary sclerosing cholangitis (PSC), based on retrograde cholangiography showing mixed features of narrowing and dilatation of the common hepatic and intrahepatic bile ducts. However, periductal fibrosis was not observed in the needle biopsy liver specimen. The liver biopsy specimen obtained 11 years previously, at the onset of the disease had disclosed a marked infiltration of eosinophils in the portal tract with eosinophilic catinonic protein immunostaining, with marked eosinophilia (54%) being noted. In Japanese reports, eosinophilia of more than 7% was reported in 13 of 32 (40.6%) PSC patients. However, the early stage of PSC, with marked eosinophilia and eosinophilic infiltration in the liver, such as in the present case, has rarely been reported. The findings in this case suggest that eosinocytes are related to the pathogenesis of PSC.

Key words: primary sclerosing cholangitis, eosinophilia

Introduction

Primary sclerosing cholangitis (PSC) is a rare idiopathic disease characterized by fibrosis and inflammation of the bile ducts, leading to stenosis.[1,2] Recently, there have been more reports of this disease, probably due to increased use of the endoscopic retrograde cholangiography technique.

Eosinophilia and eosinophilic infiltration in the liver have been found in drug-induced hepatitis, primary biliary cirrhosis, and hepatic allograft rejection.[3,4] Secretory proteins such as eosinophil cationic protein (ECP) are known to play important roles in inflammatory processes.[5,6] We describe here a 16-year-old boy with PSC and eosinophilia. Histological examination of a liver biopsy taken at the age of 5 years, at the onset of the disease, revealed a marked infiltration of eosinophils in the portal area with ECP immunostaining. However, this feature was not observed in a biopsy taken at age 16.

Case report

A 16-year-old boy was admitted on August 30, 1993 because of liver dysfunction. Eleven years previously, in 1982, when he was 5 years of age, he had been admitted to the Department of Pediatrics at our hospital because of atopic dermatitis, and liver dysfunction was found for the first time. Some of the laboratory data obtained in 1982 are shown in Table 1.

Table 1. Laboratory findings at onset (August 28, 1982)

CRP	1+
ESR	37/72 mm
WBC	12900/mm^3
Eo.	54%
AST	77 KU
ALT	72 KU
LDH	345 WrU
ALP	40 KAU
LAP	821 GRU
γ-GTP	257 mU/ml
T. Bil	0.3 mg/ml
TTT	10.6 KU
ZTT	17.6 KU
TP	7.8 g/dl
γ-gl	1.77 g/dl

CRP, C-reactive protein; *ESR*, erythrocyte sedimentation rate; *Eo*, eosinophils; *γ-gl*, γ-globulin

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Leukocytosis (12900/mm^3) and marked eosinophilia (54%) were noted. A slight increase in transaminase levels and a moderate increase in the levels of alkaline phosphatase (ALP), leucine aminopeptidase (LAP), and γ-glutamyltranspeptidase (γ-GTP) were noted. Needle biopsy of the liver was done on December 23, 1982, and histological examination revealed a marked infiltration of eosinophils and bileductular proliferation in the portal tract area, without periductal fibrosis, as seen in Fig. 1a. Immunohistochemical examination, carried out by an indirect immunoperoxidase method with EG2, an agent that binds to eosinophil cationic protein (ECP), revealed EG2-positivity in the infiltrating eosinophils (Fig. 1b). Since 1983, the patient has suffered no serious symptoms. On admission his height was 170 cm, body weight 70 kg, blood pressure 120/70 mmHg, and pulse 68/min, regular. Atopic dermatitis with a crust was observed on his palms and both feet. No remarkable change was noted in the condition of his heart, lungs, and abdomen.

Laboratory data on admission are shown in Table 2. The white blood cell count was 6400, with slight eosinophilia (9%). A slight increase in transaminase levels and a marked increase in levels of ALP, γ-GTP, and LAP were noted. The results for HBs-antigen and anti-HCV-antibody were negative. Autoantibodies to nuclei, mitochondria, and smooth muscle were not detected. The serum level of IgE was normal. No

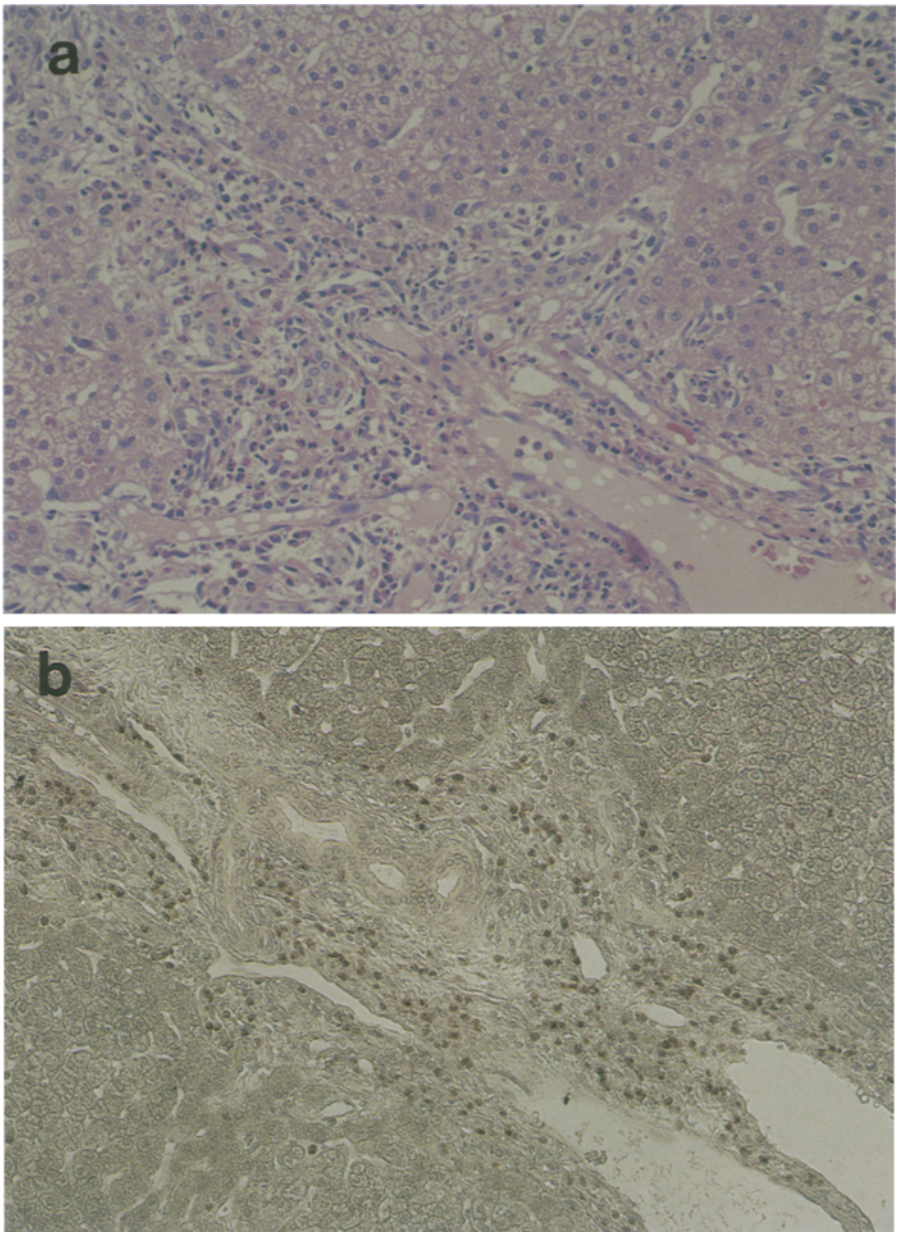

Fig. 1. a Histological findings of the liver biopsy taken on December 23, 1982. A widened portal area with an increased number of eosinophils and bile ductular proliferation are noted. However, no prominent change, such as fibrosis in the interlobular bile duct and periductal region, is found. **b** Immunohistochemical EG2 staining in the liver. Numerous infiltrated eosinophils in the portal tract are positive for EG2

Table 2. Laboratory data on admission (August 30, 1993)

ESR	1/8 mm	HBsAg	(−)
CRP	0.6 mg/dl	HCVAb	(−)
WBC	6400/mm^3	ANA	(−)
St.	7%	AMA	(−)
Se.	44%	ASMA	(−)
Eo.	9%	LE-T	(−)
Ba.	1%		
Mo.	32%		
Ly.	7%	IgG	1972 mg/dl
RBC	514 × 10^4/mm^3	IgA	269 mg/dl
Hb	14.5 g/dl	IgM	182 mg/dl
Plt	23.2 E 10^4/mm^3	IgE	158 mg/dl
PT	70.3%		
HPT	70%	ALP isozyme	
AST	51 IU/L	ALP1	8.24%
ALT	126 IU/L	ALP2	63.14%
LDH	441 IU/L	ALP3	28.62%
ALP	834 IU/L		
LAP	299 IU/L	HLA typing	A2, A31(19)
γ-GTP	535 IU/L		B54(22), B61(40)
CHE	248 IU/L		Cw1, Cw3
TB	0.6 mg/dl		DR1, DR6
DB	0.2 mg/dl		
TTT	5 KU		
ZTT	11.8 KU		
		ICG(15)	2%
AFP	3.7 ng/ml	Allergic test	House dust 5+
CEA	3.7 ng/ml	Urine	Normal
CA19-9	32.8 U/ml	Faces	Occult(−)
			Parasites(−)

parasite ova were found in the stool. HLA typing showed A2, A31(19), B54(22), B61(40), Cw1, Cw3, DR1, and DR6.

Abdominal computed tomography (CT) scan (Fig. 2a) and echography (Fig. 2b) revealed wall thickening and dilatation of intrahepatic bile ducts, especially in the left hepatic lobe.

Endoscopic retrograde cholangiography revealed mixed features of narrowing and dilatation (maximum diameter, 10 mm) of the common hepatic duct and intrahepatic bile ducts, characteristic features of PSC, as shown in Fig. 3.

Histological examination of the liver specimens obtained by needle biopsy on August 13, 1993 showed a slightly enlarged portal tract area with lymphoid infiltration and fibrosis. No findings of eosinophil

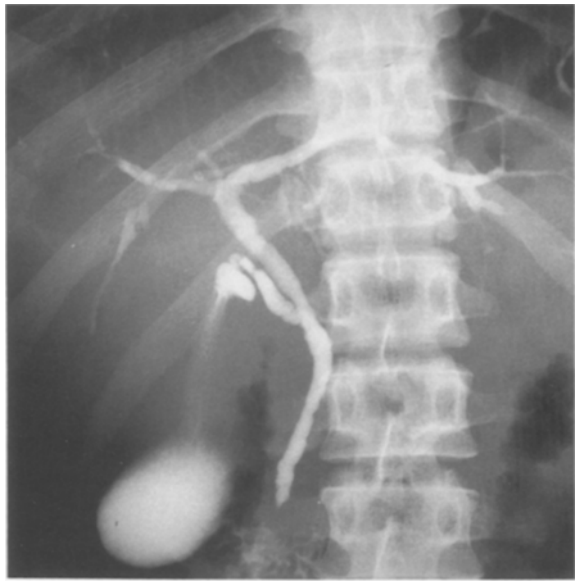

Fig. 3. Endoscopic retrograde cholangiography reveals a mixture of narrowing and dilatation (maximum diameter, 10 mm) of both the common hepatic duct and intrahepatic bile ducts throughout all lobes

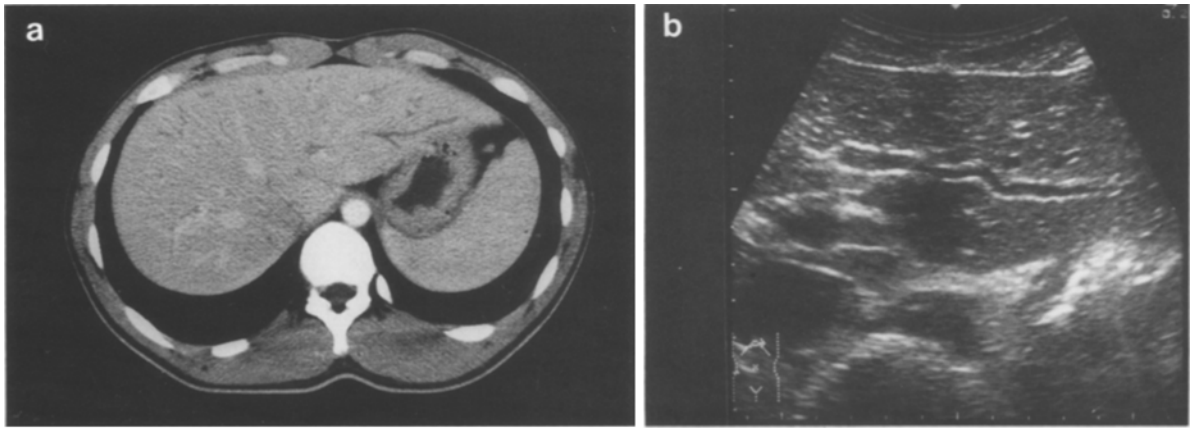

Fig. 2. a Abdominal computed tomography scan reveals dilatation of intrahepatic bile ducts, especially in the periphery. **b** Ultrasonography reveals wall thickening and dilatation of intrahepatic bile ducts in the left hepatic lobe

infiltration, periductal fibrosis, or destruction of interlobular bile ducts were noted in these specimens, although there was a decrease in the number of bile ducts as shown in Fig. 4.

The clinical course of this patient from 1982 to 1994 is shown in Fig. 5. The marked eosinophilia continued for 6 months early in the course and decreased gradually along with the improvement of atopic dermatitis. The serum AST level has remained at a low level since September, 1983. However, serum levels of ALP and γ-GTP have remained high after the improvement of atopic dermatitis, even though the patient has been treated with ursodeoxycholic acid, at a dose of 600 mg/day, since August 1993.

Discussion

Primary sclerosing cholangitis (PSC) is a chronic cholestatic hepatobiliary disease of unknown cause, first reported by Delbet[7] in 1924. The diagnostic criteria of PSC were established by Schwartz and Dale[8] in 1958, as follows: (1) diffuse generalized involvement of the intrahepatic and extrahepatic biliary tracts; (2) absence of previous biliary surgery; (3) absence of gallstones; (4) exclusion of cholangiocarcinoma by a reasonably long-term follow-up study. Based on these criteria, the patient presented here was diagnosed as having PSC with typical features on endoscopic retrograde cholangiography. However, the histological findings of the liver biopsy did not reveal the characteristic features of periductal fibrosis.

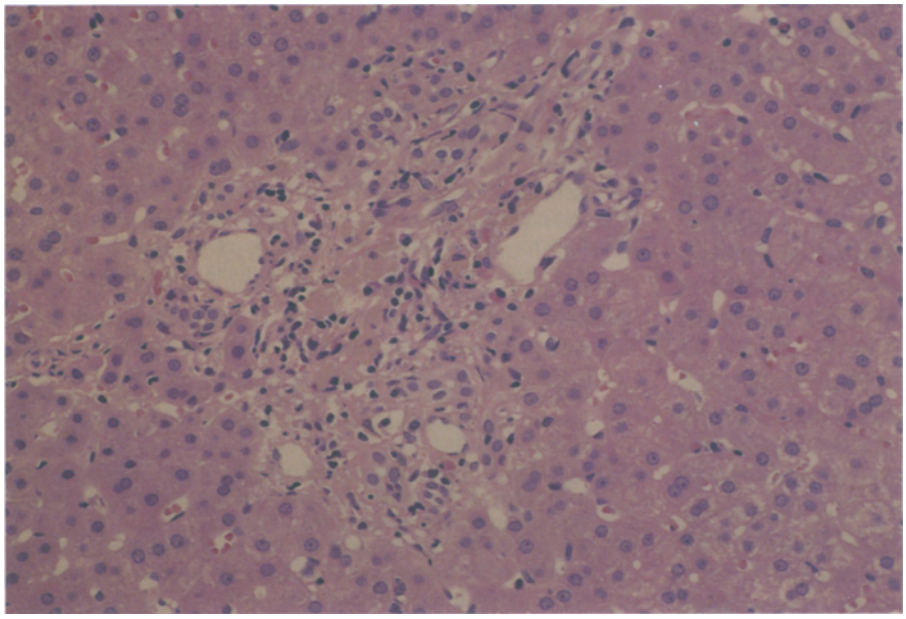

Fig. 4. Histological findings of the liver biopsy taken on August 13, 1993. Slightly enlarged portal tracts with lymphocyte infiltration, decrease in the number of bile ducts, and fibrosis are noted. However, no remarkable changes, such as destruction or fibrosis in the interlobular bile ducts or periductal region, or eosinophilia, can be recognized

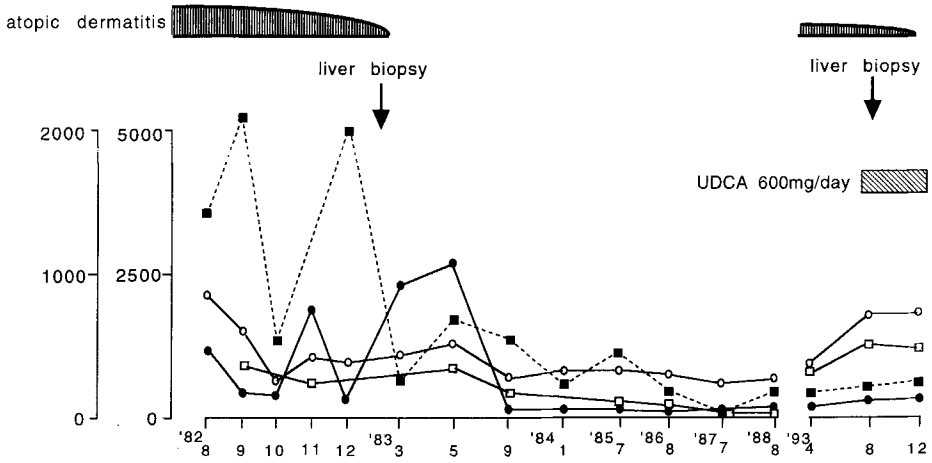

Fig. 5. Clinical course from 1982 to 1994. *Dots* indicate aspartate aminotransferase (*AST*; IU/l); *circles*, alkaline phosphatase (*ALP*; IU/l); *open squares*, gamma glutmyl transpeptidase (*γ-GTP*; IU/l); *closed squares*, eosinophils (/mm^3); *UDCA*, ursodeoxychotic acid

Marked eosinophilia is rarely recognized in PSC.[9] However, in the literature in Japan, eosinophilia of more than 7% was reported in 13 of 32 PSC patients (40.6%), similar to the rate of occurrence in primary biliary cirrhosis (PBC).[10] Eosinophilic infiltration in the liver was reported by Kakimoto et al.[11] in a pediatric patient with PSC showing portal tract infiltration by eosinophils without periductal fibrosis, as was observed in our patient. Similarly, eosinophilic infiltration in the liver was observed in a patient with primary biliary cirrhosis.[12] Therefore, it would appear that the eosinophilia and the eosinophilic infiltration in the liver observed at the onset of the disease in our patient can plausibly be explained in terms of a relationship to the pathology of PSC. The atopic dermatitis observed in this patient may have caused the eosinophilia, but would not have produced the eosinophilic infiltration in the liver. The patient's atopic dermatitis has improved since August, 1983, with a decrease in the eosinophilia; however moderate increases in the levels of ALP and γ-GTP and in the level of eosinophilia were sustained after the improvement of atopic dermatitis. Thus, it is possible that moderate increases in the level of eosinophilia may reflect liver dysfunction.

Foong et al.[13] reported a patient with eosinophil-induced chronic active hepatitis in the idiopathic hypereosinophilic syndrome, suggesting that hepatocytes are the target of damage caused by the release of cationic eosinophil granule protein such as major basic protein (MBP). In our patient, a high level of AST was noted on first admission and infiltrating eosinophils in the liver were stained with EG2, indicating the secreted form of ECP, supporting, the idea that activated eosinophils cause hepatocyte damage. Since destruction of interlobular bile ducts was not recognized, although reduction in bile duct diameter was observed in the liver biopsy specimen taken 11 years after the first admission, it would seem that the relation between the progression of PSC and eosinophil infiltration may not be direct.

A significant increase in the frequency of HLA-B8 (60%) and a decrease in the frequency of HLA-B12 (8%) were previously reported by Chapman et al.[14]; these HLA antigens were not recognized in our patient. The frequency of A2, A31(19), B54(22), and B61(40) in our patient was not significantly different from that in a control group.[14]

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