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Case report

Three cases of primary biliary cirrhosis associated with bronchial asthma

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Abstract: The association of primary biliary cirrhosis (PBC) and bronchial asthma was observed in three patients. All of these patients were female (53, 54, and 41 years old, respectively), and were positive for antimitochondrial antibodies. The patients fulfilled the diagnostic criteria of both PBC and bronchial asthma. Bronchial asthma preceded PBC in two patients, and the reverse order was seen in the other. Patient the clinical symptoms were mainly due to the bronchial asthma. Two patients had asymptomatic PBC and the third patient complained of pruritus. The liver histology showed mild to moderate eosinophilic infiltration in addition to the ductal and hepatic parenchymal changes characteristic of PBC. A survey of 266 cases of PBC referred to us disclosed that, in 6 of these, the PBC was associated with bronchial asthma, while no association with bronchial asthma was the material of found in 166 patients with viral hepatitis in our liver biopsy files. The 3 present cases we experienced suggest that bronchial asthma may be included in the list of extrahepatic diseases associated with PBC. The significance of this association is unclear and may merit further study. Steroid therapy, which is known to cause adverse effects in PBC, was employed for bronchial asthma in these 3 patients. Another therapeutic approach will have to be considered in patients with bronchial asthma associated with PBC.

Key words: primary biliary cirrhosis, bronchial asthma, eosinophils

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Introduction

In recent years, peripheral blood and/or liver tissue eosinophilia have been reported in primary biliary cirrhosis (PBC),[1–3] this phenomenon being usually seen in about one-third of PBC cases.[1–3] Histologically, the infiltrated eosinophils on occasion showed periductal accumulation, and it was suggested that the eosinophils may participate in the pathogenesis of PBC.[1] Peripheral and pulmonary tissue eosinophilia are also found in bronchial asthma, the pathogenesis of which shows the deep involvement of the type I hypersensitivity reaction and eosinophils.

We recently encountered three cases of PBC associated with bronchial asthma. To the best of our knowledge, the association of PBC and bronchial asthma has not been reported in the international and Japanese literature. This study reports these three cases with emphasis on their clinicopathologic findings and also surveys this association in PBC cases referred our laboratory.

Materials and methods

Patients

A total of 266 cases of PBC (33 male and 233 female patients; mean age, 54.9 years), were referred by many institutions in Japan, including our University Hospital, during the period September, 1977 to January, 1991. These patients were over the age of 25 years, showed elevated serum alkaline phosphatase and/or γ-glutamyl transpeptidase, and their livers showed florid duct lesions and/or considerable loss of small bile ducts.[4–6] Two hundred and ten patients were positive for antimitochondrial antibodies (AMA), this finding being diagnostic of PBC. The remaining AMA-negative patients showed both florid duct lesions and bile duct loss histologically and were finally diag-

nosed with PBC. Other clinical and laboratory findings reported were consistent with a diagnosis of PBC.

PBC was histologically classified into four stages according to a classification combining the staging systems of Scheuer[7] and Ludwig et al.[5] As a control, we surveyed the association of on-going bronchial asthma in 166 viral hepatitis patients whose specimens were collected in our liver biopsy files, the etiology being hepatitis A viral infection in 3, hepatatis B viral infection in 23, and cryptogenic in 140. The patients were all adults, of whom 25 had acute viral hepatitis (AVH), 13 had chronic persistent hepatitis (CPH), 121 had chronic active hepatitis (CAH), and 7 had liver cirrhosis with CAH. Clinical information was available from the clinical protocols sent with the liver biopsy specimens. Early history of bronchial asthma during childhood was not examined in these viral hepatitis patients on the PBC patients.

Liver biopsy specimens from patients with PBC and viral hepatitis who had received specific therapy with such agents as ursodeoxycholic acid, colchicine, D-penicillamine, prednisolone, or azathiopurine, and specimens from patients with parasitic diseases showing eosinophilia[6] were not included in this study.

The association with bronchial asthma was surveyed in the PBC and viral hepatitis cases.

Results

Report of 3 cases of PBC associated with bronchial asthma

The main clinicopathological features of these three patients are summarized in Table 1.

Case 1. The patient was a 53-year-old woman. Liver function abnormalities were noted at regular health checks. Alkaline phosphatase and γ-glutamyl transpeptidase were elevated and AMA were negative at this time. Peripheral blood disclosed eosinophilia (30% of total white blood cells). Liver biopsy disclosed chronic nonsuppurative destructive cholangitis (Fig. 1), and a diagnosis of PBC (stage 1) was made. In the liver tissue, eosinophils were clustered here and there in the enlarged portal tracts (Fig. 2). During the follow up, typical attacks of bronchial asthma developed, and steroid therapy was begun. Four years later, a diagnosis of hepatolithiasis of the left hepatic lobe was made, and left segmentectomy was done. At this time, AMA were positive (×40). Wedge liver biopsy from the right hepatic lobe was done during the operation. Liver histology showed typical florid duct lesions, non-

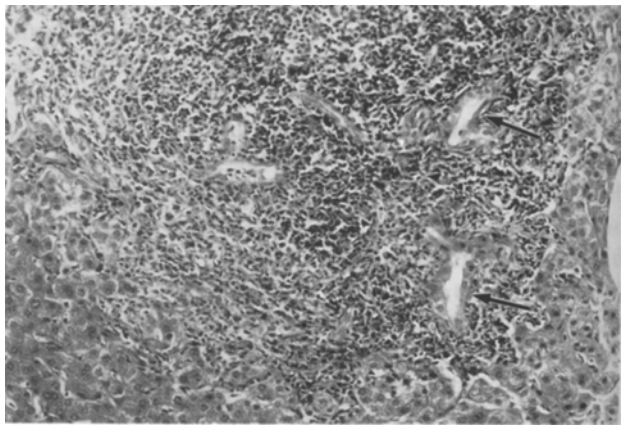

Fig. 1. Liver histology in case 1 shows chronic nonsuppurative destructive cholangitis (*arrows*). H&E, ×350

Table 1. Main clinicopathologic features in three patients with primary biliary cirrhosis associated with bronchial asthma

	Case 1		Case 2	Case 3
	First	Second		
Age in years at the time of liver biopsy	45	53	54	41
Sex	Female		Female	Female
Age at onset of bronchial asthma (years)	51		52	38
AMA (titer)	Negative	×40	×40	×80
IgG (mg/dl)	5800	NA	1442	1422
IgA (mg/dl)	285	NA	274	313
IgM (mg/dl)	358	NA	555	464
Peripheral blood eosinophils (%)	30	23	13	19
Histologic stage of PBC	I	III	III	I
Glutamic oxaloacetic transaminase (IU/l)	127	154	88	33
Glutamic pyruvic transaminase (IU/l)	121	120	108	60
Alkaline phosphatase	32.3 KA (2.2–10.0)	57.6 KA (2.2–10.0)	1425 IU/l (<115)	20.7 KA (2.2–10.0)
Total bilirubin (mg/dl)	0.7	1.3	0.7	0.4

AMA, antimitochondrial antibodies; ( ), normal value; *NA*, not available

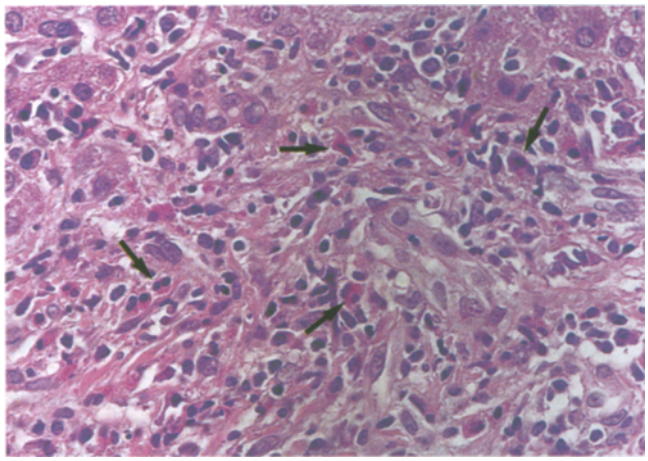

Fig. 2. Case 1. Enlarged portal tract shows eosinophil infiltration (*arrows*). H&E, × 584

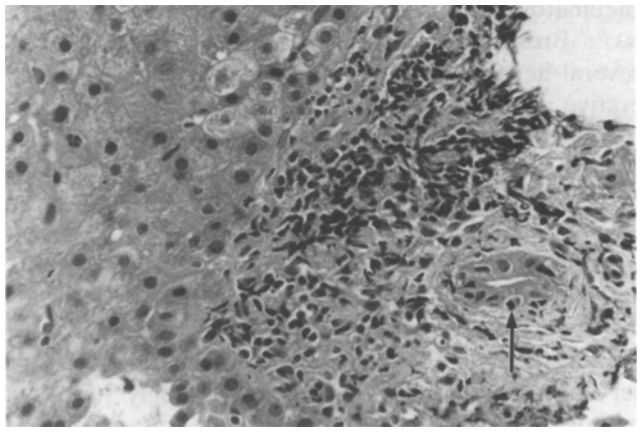

Fig. 4. Liver histology in case 3 shows chronic nonsuppurative destructive cholangitis (*arrow*). H&E, × 560

caseating epithelioid granulomas, and a number of eosinophils in enlarged portal tracts with moderate to marked lymphoplasmacytic infiltration. A diagnosis of PBC (stage 3) was made.

Case 2. The patient complained of wheezing and dyspnea at the age of 52, and had been treated with steroids under the diagnosis of bronchial asthma. She complained of asthma attacks and was admitted to our hospital. At this time, peripheral blood eosinophilia (13%) was detected, and she also complained of skin itching. Liver dysfunction (elevated alkaline phosphatase and γ-glutamyl transpeptidase) and elevation of serum IgM were detected, and AMA were found to be positive. Liver biopsy was done 3 months later, and disclosed portal widening and bridging fibrosis connecting adjoining portal tracts. A majority of interlobular bile ducts were lost, and there was mild to moderate lymphoplasmacytic infiltration with a few eosinophils (Fig. 3). One epithelioid granuloma was found in one portal tract. These histologic findings were compatible with PBC (stage 3). A diagnosis of PBC was finally made. This patient also had a long history of rheumatoid arthritis.

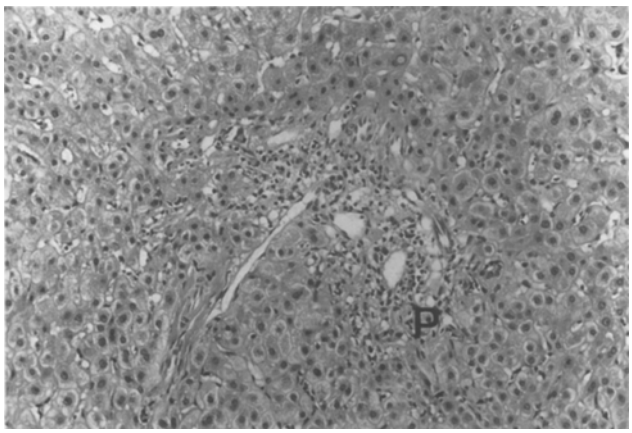

Fig. 3. Liver histology in case 2 shows bile duct loss in a portal tract (*P*). H&E, × 350

Case 3. The patient had a history of bronchial asthma from age 38. She had been treated with steroids. During the treatment for the bronchial asthma, liver dysfunction was defected and this had persisted until the present admission. She was admitted to our hospital for examination of the liver at age 41. Alkaline phosphatase and γ-glutamyl transpeptidase were elevated and AMA were positive (× 80). Peripheral blood showed 19% of eosinophils. Liver histology showed portal inflammation with moderate lymphoplasmacytic infiltration and nonsuppurative destructive cholangitis (Fig. 4). There was mild eosinophilic infiltration in the portal tracts.

Survey of bronchial asthma in PBC and viral hepatitis

The survey study disclosed an association with typical bronchial astham attacks in 6 of the 266 collected PBC patients and in the 3 of 6 patients reported here. This association was not seen in any of the 166 viral hepatitis patients. Clinicopathologically, the 3 patients with PBC associated with bronchial asthma collected from the survey had typical PBC. All of these 6 patients with PBC and bronchial asthma were clinically negative for hepatitis viral infection and the condition was not thought to be associated with drug-induced liver injury.

Discussion

It is well known that, in about one-third of PBC patients, there is an association with extrahepatic immune-mediated diseases such as Sjögren's syndrome,

rheumatoid arthritis, or progressive systemic sclerosis.[8,9] Bronchial asthma is occasionally associated with several hepatobiliary diseases, such as nodular regenerative hyperplasia.[10] As to the association of pulmonary disease in PBC patients, there have been a few case reports of interstitial alveolitis.[11–13] However, to the best of our knowledge, there have been no reports of an association of PBC and bronchial asthma. Though bronchial asthma is known to occur in about 2% of the general population, the present survey study disclosed that this association of bronchial asthma was significant in PBC when patients with viral hepatitis served as controls. These findings strongly suggest a pathogenetic significance, rather than a chance occurrence, of PBC and bronchial asthma. However, the precise frequency of bronchial asthma in patients with PBC has not been epidemiologically surveyed nationwide in Japan or in other countries.

The pathogenetic correlation between PBC and bronchial asthma is only speculative, although these two diseases may share a common mechanism. Bronchial asthma, which is associated with peripheral blood and lung tissue eosinophilia, particularly peribronchiolar eosinophilia, is pathogenetically caused by tissue injuries due to released eosinophilic granular proteins, and type I hypersensitivity is speculated to be deeply involved. In PBC, peripheral blood eosinophilia has been noted, on occasion, particularly during the early histologic stages and/or asymptomatic phases.[2,3] We have recently reported occasional eosinophilic infiltration and deposition of eosinophilic granular proteins around the damaged bile ducts in PBC.[1] Eosinophils are regarded as important for the induction of various liver injuries.[14–18] Thus, eosinophils and their secretory products[14,19,20] may be, at least in part, responsible for both the bile duct damage and the bronchial damage followed by bronchial asthma in our three patients. It is thought that cytokine(s) may be responsible for the proliferation of eosinophils in the liver and lung and for the release of their secretory products.[21–24]

Cytotoxic and helper T cells are now thought to be important in the pathogenesis of PBC.[25] It remains unclear why only one-third of PBC patients showed eosinophilia in the liver and about 2% of PBC patients were affected with bronchial asthma. Morever, the relation of type I hypersensitivity and cytotoxic and helper T cells in PBC patients is speculative at this stage.

Finally, this report raises the problem of how to treat PBC patients with associated bronchial asthma from the clinical standpoint. Bronchial asthma is usually treated with steroids.[26] However, these drugs are contraindicated in PBC. All of our patients were asymptomatic or oligosyndromatic, and were subsequently treated with steroids. However, in future, another therapy should be substituted for steroid therapy of although in PBC patients.

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