Two cases of systemic sclerosis with hepatocellular failure due to primary biliary cirrhosis

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Abstract: Primary biliary cirrhosis (PBC) and nodular regenerative hyperplasia (NRH) were reported to be associated with some patients with systemic sclerosis (SSc). However, the prognostic importance of hepatic involvement in patients with SSc has not been well studied. In this report, clinical courses and characteristics of two SSc patients who died of hepatocellular failure due to PBC were discussed. Limited scleroderma associated with PBC was diagnosed in the first case, a forty-seven-year-old woman. Diffuse scleroderma associated with PBC was diagnosed in the second case, a fifty-five-year-old woman. Both anti-centromere antibody and anti-mitochondrial antibody were detected in these patients. PBC may be one of the important complications in patients with SSc from the viewpoint of the prognosis even when diffuse scleroderma is diagnosed. Therefore, it is necessary to investigate anti-centromere antibody and anti-mitochondrial antibody and to examine the clinical symptoms of portal hypertension when hepatic involvement is suspected in patients with SSc.

Key words: Systemic sclerosis, Scleroderma, Primary biliary cirrhosis, Hepatocellular failure.

Hepatic involvements such as primary biliary cirrhosis (PBC) and nodular regenerative hyperplasia (NRH) are infrequent in patients with...

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systemic sclerosis (SSc)\textsuperscript{1, 2)}, and renal, cardiac and pulmonary involvements are emphasized as predictors for survival in such patients\textsuperscript{3). However, we have experienced two cases of SSc, who died of hepatocellular failure due to PBC. In this report, we studied the clinical courses and characteristics of these two cases.

CASE REPORTS

Case 1: A forty-two-year-old Japanese woman first visited Keio University Hospital in July, 1971 because of recent development of jaundice with mild pruritus. In 1966, she noticed Raynaud's phenomenon and polyarthralgia, but she had not had any treatments. Sclerodactyly, mild jaundice, hepatomegaly and increased alkaline phosphatase (Al-p) were found at her first visit to the hospital. Serum anti-mitochondrial antibody and anti-smooth muscle antibody tests were positive, and a liver needle biopsy specimen showed dense mononuclear cell infiltration into the portal tracts and destruction of bile ducts during her first hospitalization in 1974 (Fig. 1). Epithelioid granulomas were noted. The pruritus and jaundice were temporarily relieved with azathioprine (AZP), but she was hospitalized again in 1976 because of the recurrence of generalized pruritus and jaundice. Physical examination showed sclerodactyly, diffuse pigmentation, Velcro rales in the auscultation for lung, scleral icterus, superficial venous dilatation and hepatomegaly. Digital pitting scar, calcinosis and telangiectasia were not found. Laboratory abnormalities included increased bilirubin (total bilirubin 8.6 mg/dl, direct bilirubin 7.4 mg/dl), serum enzymes (AST 115 K.U., ALT 40 K.U., Al-p 33.1 K.A.U., \textgamma GTP 261 IU/l) and immunoglobulins (IgG 1680 mg/dl, IgM 255 mg/dl). Serum hepatitis B surface antigen test was negative, and the preserved serum showed a positive reaction for anti-centromere antibody test. Ascites was of a transudative nature. Mild pulmonary fibrosis, and esophageal dysfunction and varices were found by chest x-ray and esophagography, respectively. Although she was treated with high dosage of AZP in combination with prednisolone (PSL) and diuretics, she died of hepatic encephalopathy in October, 1976 (Fig. 2).

Case 2: A forty-eight-year-old Japanese woman was first seen at Tokyo Metropolitan Okubo Hospital for evaluations of liver disease in 1982. Because she had Raynaud's phenomenon for about one year before her visit to the hospital, and her family physician found her to have liver dysfunction and a positive ANA test. Anti-
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centromere antibody positive SSc associated with Sjögren's syndrome and Hashimoto's thyroiditis as well as chronic active hepatitis associated with esophageal varices were diagnosed at this hospital. When she had episodes of hematemesis and melena in 1984, 1986 and 1987, endoscopic sclerotherapy was performed on her bleeding esophageal varices. She was admitted to Keio University Hospital in May, 1987 for further evaluations. She was once admitted to Tokyo Metropolitan Ohtsuka Hospital for treatment of esophageal varices in 1988, but she returned to Keio University Hospital because of hematemesis in October, 1989. Physical findings included diffuse scleroderma with digital pitting scars, shortening of tongue musculature, joint contractures, diffuse pigmentation, subcutaneous calcinosis and telangiectasias, as skin sclerosis was found on her upper and lower extremities, face, anterior chest wall and back. Anemia, pulmonary fibrosis and hepatosplenomegaly were also found. Laboratory examination showed anemia (RBC 184x10^4/mm^3, Hb 5.2 g/dl), abnormal coagulation test (prothrombin time 53%), an increase in serum enzymes (AST 41 IU/1, ALT 27 IU/1, Al-p 392 IU/1), reduced levels of branched-chain amino acids such as valine, leucine and isoleucine, and increased immunoglobulins (IgG 3612 mg/dl, IgA 488 mg/dl). Serum anti-centromere antibody and anti-mitochondrial antibody tests were positive, but hepatitis B surface antigen and anti-smooth muscle antibody were not detected. Ascites was of a transudative nature. After receiving intensive care such as hyperalimentation, blood transfusion, branched-chain amino acids, H-2-receptor antagonist and endoscopic sclerotherapy, she was discharged in March, 1990. However, she was admitted to Tokyo Metropolitan Ohtsuka Hospital because of increased ascites, and died of hepatocellular failure with hepatorenal syndrome in August, 1990 (Fig. 3). Histopathologic examination of the liver at autopsy showed extensive fibrosis and mononuclear cell infiltration into the portal area, which was compatible with the scarring stage of PBC (Fig. 4). Pruritus and jaundice were not found during her clinical course.

DISCUSSION

Two patients with SSc who died of hepatocellular failure were reported. Case 1 could be regarded as limited scleroderma or incomplete CREST syndrome associated with PBC. Case 2 could be regarded as typical diffuse scleroderma associated with asymptomatic PBC. Although the pathogenesis of neither SSc nor PBC has been fully
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clarified, the autoimmune mechanism and the genetic predisposition have been considered to be possible etiologic factors in these disorders. These may be the reasons why the relatively high frequency of the association between SSc and PBC is found. It was reported that PBC tended to be associated with CREST syndrome rather than diffuse scleroderma. Only two reports could be found about diffuse scleroderma associated with PBC like our case. It was reported that PBC tended to be associated with CREST syndrome rather than diffuse scleroderma. Only two reports could be found about diffuse scleroderma associated with PBC like our case. The common clinical characteristics in our case and O'Brien's case were diffuse pigmentation and telangiectasias.

Hepatic involvement in patients with SSc have not been stressed compared to the cardiopulmonary involvement from the viewpoint of the prognosis. This might be due to relatively low frequency of hepatic complication. However, we have shown that PBC is one of the most important complications in the course of SSc. Because they had hepatic failure and recurrent hemorrhages from esophageal varices due to portal hypertension. Thus, it is important to find hepatic complications in SSc patients as early as possible.

Sera of our two SSc patients associated with PBC contained anti-centromere antibody and anti-mitochondrial antibody from the early stage of the disease. This was compatible with the serological characteristics in SSc patients associated with PBC.

Therefore, it is necessary to investigate anti-centromere antibody and anti-mitochondrial antibody when hepatic involvement is suspected in patients with SSc even if patients had diffuse scleroderma. Further studies are necessary to determine the pathogenesis of these antibodies in the development of SSc associated with PBC.

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Fig. 1. Histologic feature of the liver biopsy in case 1. (Hematoxylin and eosin stain, X100).

Fig. 2. Clinical course in case 1.
Fig. 3. Clinical course in case 2.

Fig. 4. Histologic feature of the liver at autopsy in case 2. (Hematoxylin and eosin stain, X100).