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Case Report

Nodular Regenerative Hyperplasia of the Liver in a Patient with Systemic Sclerosis

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Summary **We report on a 33-year-old female patient with systemic sclerosis and nodular regenerative hyperplasia of the liver (NRHL). A needle biopsy of the patient's liver did not reveal the histology of NRHL or liver cirrhosis at her first visit to our hospital, when portal hypertension was demonstrated by percutaneous transhepatic portography. After 11 years, the patient died of hepatic and renal failure. At the time of autopsy, multiple nodules were found in the liver, and a microscopic examination showed a histology compatible with NRHL. It is suggested that the immunological disturbance was related to the patient's portal hypertension and NRHL.**

Key words **Systemic Sclerosis, Scleroderma, Nodular Regenerative Hyperplasia, Portal Hypertension.**

INTRODUCTION

Cardiac, pulmonary and renal involvements are important prognostic clinical features in patients with systemic sclerosis (SSc) (1,2). Hepatocellular failure, which leads to poor prognosis, is, however, found in some patients with SSc (3). Primary biliary cirrhosis (PBC) as well as congestive liver and drug-induced hepatitis are found in patients with SSc (4). On the contrary, nodular regenerative hyperplasia of the liver (NRHL) is a rare complication in patients with SSc (5-8). NRHL is characterized by diffuse nodularity of the liver with little or no fibrosis, and has been found in patients with rheumatoid arthritis, Felty's syndrome, systemic lupus erythematosus, haematological disorders and renal transplantation (8-12). Patients with NRHL present clinical manifestations of portal hypertension (13). However, the aetiologies of NRHL and portal hypertension are still unknown.

We report on a patient with SSc who had portal hypertension and NRHL. Portal hypertension was demonstrated by the percutaneous transhepatic portography, when a needle biopsy of the liver failed to reveal a histology of NRHL or liver cirrhosis. NRHL was confirmed at the time of autopsy. Furthermore, the patient was not diagnosed as having PBC. The immunological mechanisms are suggested as the aetiology of NRHL in this patient.

CASE REPORT

A 33-year-old female patient visited Keio University Hospital in March 1979, for further evaluation. She had experienced severe degrees of sustained Raynaud's phenomenon over the last 10 years, and was diagnosed as having Sjögren's syndrome confirmed by sicca symptoms, positive results from rose-bengal dye staining, Schirmer's test and sialography, as well as histological abnormalities in a salivary gland biopsy conducted by her family physician in 1978.

Sclerodactyly and hepatosplenomegaly were found at her first visit. Laboratory examinations showed normal values for AST (25 IU/l) and ALT (15IU/l), and positive serological reactions of anti-U1-RNP antibodies, anti-SS.B (La) antibodies and anti-SS.A (Ro) antibodies by the double immunodiffusion method. Anti-Sm antibodies and anti-DNA topoisomerase I antibodies were negative by the double immunodiffusion method. Anti-centromere antibodies were not detected by the indirect im-

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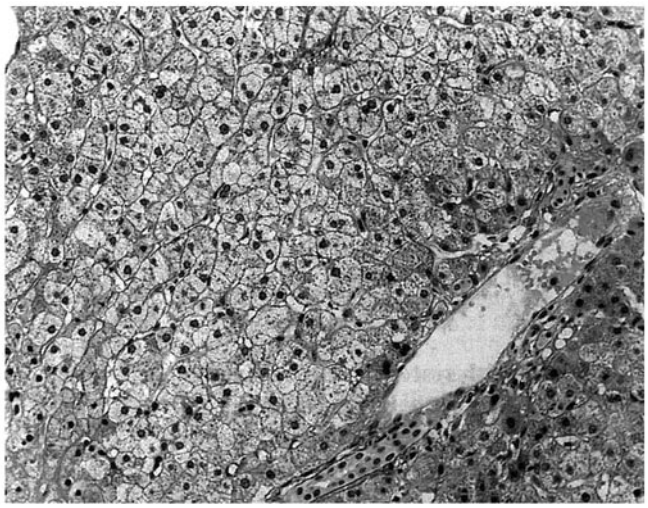

Fig. 1: Histology of the liver by percutaneous needle biopsy of the liver in 1979. (X200, Hematoxylin eosin staining.) The histology shows normal liver structure without any evidence of nodular regenerative hyperplasia or cirrhosis.

munofluorescence using HEp-2 cells as substrate and by the immunoblots using mitotic chromosomes from colcemide arrested HeLa cells as antigen. Her preserved serum did not contain IgG anticardiolipin antibodies and IgG phospholipid-dependent anti-β_2-glycoprotein I (β_2-GPI) antibodies examined by the enzyme-linked immunosorbent assay. Percutaneous transhepatic portography revealed portal hypertension with wedged hepatic vein pressure 270mmHg and narrowing branches in the portal vein. A needle biopsy of her liver showed a preserved architecture (Fig. 1). She was treated with prednisolone, 30mg/day.

Digital pitting scars, shortening of tongue musculature and superficial venous dilatations on the abdominal wall were observed in 1983. Thrombocytopenia (8000/μl) with positive reactions of platelet-associated IgG was found in 1987. Thrombocytopenia was relieved by treatment with prednisolone 60mg/day and intravenous gammaglobulin therapy; however, she developed ascites. Laboratory examinations showed liver dysfunction, such as AST 46IU/l (normal; 8-32IU/l), ALT 82IU/l (normal; 3-34IU/l), alkaline-phosphatase 652IU/l (normal; 80-290IU/l), choline esterase 740IU/l (normal; 1500-3500IU/l), and renal dysfunction, such as serum creatinine 1.7mg/dl (normal; 0.4-0.7mg/dl) and BUN 45.7mg/dl (normal; 10-20mg/dl). Other laboratory data included prothrombin time 71% (normal; 80-110%), total bilirubin 0.6mg/dl (normal; 0.4-1.5mg/dl) and albumin 3.5g/dl (normal; 3.5-4.4g/dl). Serological tests for anti-mitochondrial antibodies and anti-smooth muscle antibodies were negative. Ascites was relieved by treatment with diuretics.

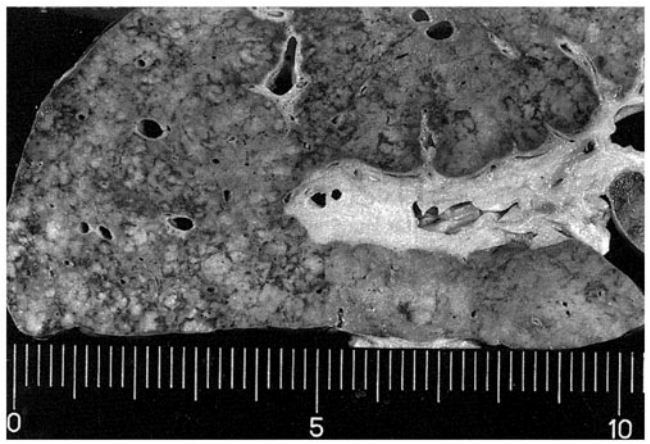

Fig. 2: Cut surface of the liver at the time of autopsy in 1990. Numerous nodules are scattered throughout the liver parenchyma.

In February 1990, she developed ascites again, and was hospitalized. Physical examinations showed sclerodactyly, digital pitting scars, microstomia, superficial venous dilatations on the abdominal wall, Velcro rales on ausculation of the lung, massive ascites and pretibial oedema. Laboratory examinations showed liver dysfunction (prothrombin time 61%, albumin 2.6g/dl, total bilirubin 0.6mg/dl, LDH 660IU/l, AST 22IU/l, ALT 21IU/l, alkaline-phosphatase 1084IU/l, γ-GTP 409IU/l, choline esterase 890IU/l, ammonia 60umol/l) and renal dysfunction (serum creatinine 2.6 mg/dl, BUN 46.5mg/dl). Hepatitis B surface antigen was negative, and hepatitis C antibodies in her preserved serum were not detected. The ascites was of transudate nature, with gross straw-coloured appearance and laboratory examinations disclosed a specific gravity 1.007 and protein 0.9g/dl. Pulmonary fibrosis was found in chest X-ray films. Although she was treated with prednisolone, diuretics and peritoneal dialysis, refractory ascites might have disturbed systemic haemodynamics and renal perfusion. The level of serum creatinine and BUN gradually increased, and she finally died of hepatic and renal dysfunction in April 1990. At the time of autopsy, multiple nodules were found in her liver (Fig. 2). Histological examination showed findings compatible with NRHL, such as various nodules of hyperplastic hepatocytes without fibrous capsules compressing adjacent liver tissue (Fig. 3). Each nodular lesion was formed by hepatocytes without cell atypia. Thrombotic obstructions were not found in portal vein and radicles.

DISCUSSION

The patient presented here was diagnosed as having SSc according to the preliminary criteria for the classification of SSc by the American Rheumatism Associa-

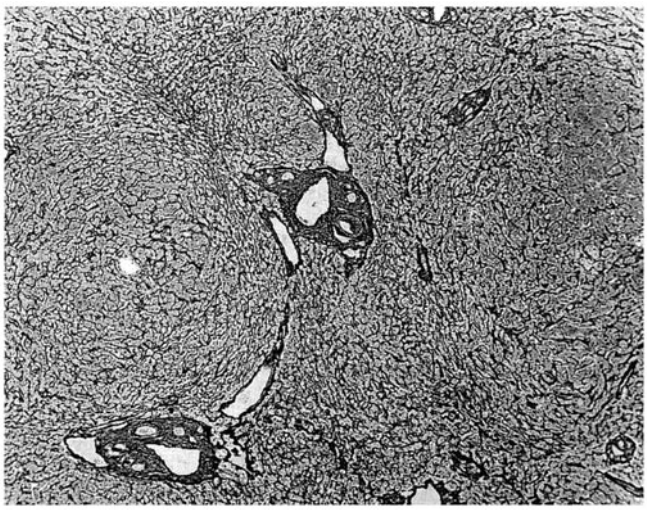

Fig. 3: Histology of the liver at the time of autopsy in 1990. (X40, silver staining.) The histology shows findings compatible with nodular regenerative hyperplasia of the liver. Several nodules made up of hepatocytes are formed, applying pressure to the surrounding tissue. Intervening liver parenchyma is somewhat atrophic, and there is no fibrous tissue proliferation.

tion (American College of Rheumatology) (14). Although Sjögren's syndrome, antinuclear antibodies and autoimmune-mediated thrombocytopenia were found, other clinical features of systemic lupus erythematosus as well as polymyositis or dermatomyositis were not evident.

It has been reported that in liver involvement is not frequent patients with SSc (15). In patients with SSc, PBC is a popular liver involvement as congestive liver and drug-induced hepatitis in patients with SSc (4). NRHL is characterized by histologic evaluation as the nodular transformation of the hepatocytes without distinct fibrous capsules, and is a rare complication in patients with SSc. Since Lurie et al. reported the first case of limited scleroderma with NRHL (5), similar cases have been found by other investigators (6-8). Furthermore, a new clinical entity of limited scleroderma with NRHL and PBC has been proposed (7). It was also reported that NRHL represents the early histological stage in PBC (16); however, serological tests and histological examinations did not indicate that our patient had PBC. Portal hypertension was found in the early period of our patient's clinical course. Although the precise aetiologies of NRHL and portal hypertension are not clear, it has been reported that immunological and vascular factors play important roles in NRHL (8, 17). Furthermore, it has been reported that portal hypertension in NRHL is caused by the compression of portal veins near the hilum by the expanding nodules (8). The association between serum anticardiolipin antibodies and recurrent hepatic infarction, and the subsequent development of NRHL was also reported (18). Although the histology was examined only by a needle biopsy of the liver, NRHL could not be found in the early stage of our patient. At that time, however, portal hypertension was confirmed. Tests for serum anticardiolipin antibodies and phospholipid-dependent anti-β_2-GPI antibodies were negative in our patient.

The clinical course of our patient indicates that the perfusion defects might be related to the pathogenesis of NRHL. The ischaemia was not sufficient to produce massive necrosis of hepatic cells, but to result in NRHL, as suggested by other investigators (6,9). Patients with SSc and idiopathic portal hypertension have been reported (19-21). The aetiology of idiopathic portal hypertension has not been fully understood, but some immunological mechanisms and vasospastic visceral Raynaud's phenomenon were suggested (21). Our patient had various immunological abnormalities such as Sjögren's syndrome and autoimmune-mediated thrombocytopenia, and severe degrees of Raynaud's phenomenon. These manifestations were similar to those reported by Wanless et al. (17). Therefore, it is also suggested that the immunological disturbance caused NRHL through portal hypertension.

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