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CASE REPORT

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A case of systemic sclerosis complicated by idiopathic portal hypertension: case report and literature review

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Abstract We encountered a 62-year-old woman who had systemic sclerosis (SSc) complicated by idiopathic portal hypertension (IPH). She had a 10-year history of scleroderma and Raynaud's phenomenon. She also had pancytopenia, splenomegaly, and esophageal varices. Treatment with prednisolone and endoscopic variceal ligation resulted in improvement of her symptoms. According to our literature review, the prognosis of patients with SSc complicated by IPH is relatively poor. However, the factors that predict outcome of these patients have not been elucidated.

Key words Esophageal varices · Idiopathic portal hypertension (IPH) · Pulmonary hypertension · Raynaud's phenomenon · Systemic sclerosis (SSc)

Introduction

The etiology of idiopathic portal hypertension (IPH) is unknown. It is characterized by the occurrence of portal hypertension and a marked increase of blood flow in the splenic circulation without evidence of cirrhosis, obliteration of the extrahepatic portal veins and hepatic veins, or any of the other changes that are known to cause portal hypertension.[1] The common initial symptoms of IPH include hematemesis, melena, and anemia due to ruptured varices, although asymptomatic IPH is sometimes identified based on peripheral blood changes, such as pancytopenia. In some patients IPH is complicated by autoimmune diseases, such as chronic thyroiditis, systemic lupus erythematosus (SLE), Sjögren's syndrome, or autoimmune hemolytic anemia. Here we report a case of systemic sclerosis (SSc) complicated by IPH and discuss the etiology based on a review of the relevant literature.

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Case report

A 62-year-old woman became aware of Raynaud's phenomenon around 1993. She visited our clinic in July 2003 because of persistent arthralgia of the fingers of both hands. Laboratory tests revealed pancytopenia as well as increased levels of antinuclear antibodies (ANA) and anti-U1-RNP antibodies. The patient was hospitalized for further investigation. On physical examination, scleroderma and pigmentation of the distal portion of her both hands were observed. Pitting scars affected the fingers of both hands. The shortness of frenulum linguae was seen. The liver was enlarged (one finger breadth). Weakness of the muscle was not observed.

Laboratory tests revealed hypoproteinemia, with a total protein (TP) of 6.4 g/dl and an albumin (Alb) of 2.9 g/dl, but there were no abnormalities of hepatic and renal function or electrolytes. There were no abnormalities revealed by urinalysis and examination of the urinary sediment. The white blood cell, red blood cell, and platelet count was 1700/μl, 3 200 000/μl, and 116 000/μl, respectively. The erythrocyte sedimentation rate (ESR) was slightly increased (28 mm/h), and C-reactive protein was weakly positive (0.9 mg/d). There were no abnormalities of coagulation parameters, including the prothrombin time (99%), activated partial thromboplastin time (27.4 s), and fibrinogen level (337 mg/dl). The level of IgG was 2021 mg/dl, but those of IgA, IgM, C3, and C4 were within the normal range. The titer of antinuclear antibodies (ANA) was 2560× positive and the immunofluorescence pattern was speckled. In addition, anti-U1-RNP antibody was positive (186.2 U/ml), but IgM- and IgG-rheumatoid factors, anti-DNA, anti-Sm, anti-Scl-70, anti-centromere, anti-mitochondria M_2, and anti-smooth muscle antibodies, and PR-3- and MPO-antineutrophil cytoplasmic antibodies were all negative. Immune complex (C1q) and cryoglobulins were not detectable.

The levels of anti-cardiolipin β_2-glycoprotein I complex antibodies, Lupus anticoagulant (measured by the diluted Russell's viper venom time method), and Krebs von den

Table 1. Reports on the association between IPH and SSc

Case no.	First author (year)[Ref.]	Age (years)	Sex	Type of SSc	Interval from Raynaud to IPH (year)	Esophageal varices	PH	Serositis
1	Morris (1972)[6]	53	F	Limited	5	+	–	–
2	Morris (1972)[6]	49	F	ND	20	+	–	+
3	Morris (1972)[6]	63	F	Limited	11	+	–	–
4	Morris (1972)[6]	65	F	ND	19	+	–	–
5	Yui (1982)[7]	41	F	Diffuse	3	+	–	–
6	Umeyama (1982)[8]	41	F	Diffuse	3	+	–	–
7	Tajima (1985)[9]	45	F	Diffuse	9	+	–	–
8	Nakanuma (1995)[10]	61	F	Diffuse	4	+	–	+
9	Kaburaki (1996)[11]	33	F	Limited	10	ND	–	+
10	Sanchez (1997)[12]	54	F	Limited	6	+	–	–
11	Asai (1998)[13]	58	F	Limited	14	+	–	–
12	Querfeld (1999)[14]	53	F	ND	5	+	ND	ND
13	Querfeld (1999)[14]	49	F	ND	0	+	ND	ND
14	Querfeld (1999)[14]	63	F	ND	1	+	ND	ND
15	Querfeld (1999)[14]	65	F	ND	0	+	ND	ND
16	Watanabe (1999)[15]	44	F	Diffuse	5	+	–	–
17	Tsuneyama (2000)[16]	60	F	Diffuse	4	+	–	–
18	Tsuneyama (2000)[16]	57	F	Diffuse	13	+	–	–
19	Ishii (2003)[17]	53	F	Diffuse	8	+	–	–
20	Our case (2006)	62	F	Limited	10	+	–	+

IPH, idiopathic portal hypertension; SSc, systemic sclerosis; Raynaud, Raynaud's phenomenon; PH, pulmonary hypertension; ANA, antinuclear antibody; ND, not described; Sp, speckled type; ACE, anticentromere type; ER, esophageal resection; SX, splenectomy; GC, glucocorticoid; EVL, endoscopic variceal ligation; Ds, discrete speckled type

Langen-6 were all within the normal range. The serum levels of histamine, angiotensin II, and endothelin-1 were all normal (0.7 nmol/l, 13 pg/ml, and 2.05 pg/ml, respectively), and there were no abnormalities of type IV collagen or other markers of hepatic fibrosis. Bone marrow examination revealed normocellular and normoplastic marrow.

Although echocardiography showed a small pericardial effusion, wall motion was good and there was no evidence of an increase in right atrial pressure or right ventricular pressure. In addition, electrocardiogram was within normal limit, and cardiothoracic ratio of chest X-ray was 43%. According to these investigations, we confirmed that this case did not have pulmonary hypertension. With respect to respiratory function parameters, the percent diffusion capacity for carbon monoxide was reduced to 45.4%, while the percent vital capacity and the forced expiratory volume in 1.0 s were both normal. Chest computed tomography (CT) (Fig. 1a) revealed fibrosis in the lower lobes of both lungs and pleural effusion. On abdominal CT (Fig. 1b), the liver was irregular and distorted, while splenomegaly and ascites were also observed. On abdominal magnetic resonance imaging (MRI), the portal vein appeared to be normal and no shunts were seen (data not shown). Hypoperistalsis was not seen by esophagogram. Liver biopsy revealed round areas of fibrosis and narrowing of portal vein branches, although Glisson's capsule was still intact, as shown in Fig. 2.

Based on the above findings, the patient was diagnosed as having IPH and treatment was started with diuretics. At first, however, pleural and abdominal effusions did not improve. We then evaluated that these effusions resulted from

Pattern and titers of ANA	Anti-Scl70 Ab/Anticentromere Ab	Anti-U1-RNPAb	Sjögren's syndrome	Hyper-γ-globulinemia	Treatment	Outcome
×20	ND	ND	–	ND	Shunt	Alive
×12	ND	ND	–	ND	Shunt	Alive
ND	ND	ND	–	ND	Shunt	Dead
×80	ND	ND	–	+	ER	Alive
Sp × 400	ND	ND	–	+	SX + ER	Alive
Sp	ND	ND	–	+	SX + ER	Alive
Sp × 2560	ND	ND	–	+	ND	Alive
ND	–/+	ND	–	ND	ND	Dead
ND	–/–	+	+	ND	GC	Dead
Ds × 2560	–/+	ND	–	ND	Shunt	Alive
Ds × 2560	–/–	ND	–	–	EVL	Alive
×20	ND	ND	–	ND	ND	ND
×12	ND	ND	–	ND	ND	ND
ND	ND	ND	–	ND	ND	ND
×80	ND	ND	–	ND	ND	ND
Sp × 1280	–/–	+	+	+	SX + EVL	Alive
Ds × 20480	–/+	–	–	ND	ND	Dead
Sp × 320	+/–	–	–	ND	GC	Dead
ND	+/–	–	–	ND	ND	Dead
Sp × 2560	–/–	+	–	+	GC + EVL	Alive

serositis. After 10 days, we started prednisolone at a dose of 30 mg/day. As a result, her pleural effusion and ascites improved. She underwent endoscopic variceal ligation (EVL) because esophageal varices were detected by upper gastrointestinal endoscopy. Her symptoms remained stable postoperatively and she was discharged from the clinic in September 2003. She remained stable in general condition at least until January 2006.

Discussion

The present patient was diagnosed as having SSc based on the scleroderma of the fingers and the dorsum of her hands.[2] She had also suffered from pulmonary fibrosis and Raynaud's phenomenon for 10 years. Based on the detection of splenomegaly and esophageal varices, the presence of portal hypertension was obvious.

It has been reported that thrombosis due to the antiphospholipid antibody syndrome is associated with the development of portal hypertension complicating various types of systemic rheumatic disease, including SSc.[3–5] However, antiphospholipid antibody was negative in the present case and no evidence of thrombosis was seen on liver biopsy or abdominal MRI. The presence of cirrhosis was also excluded by the liver biopsy findings and other data. Thus, this patient was diagnosed as having IPH.

Table 1[6–17] summarizes the previously reported cases of SSc complicated by IPH. There have been 6 deaths among

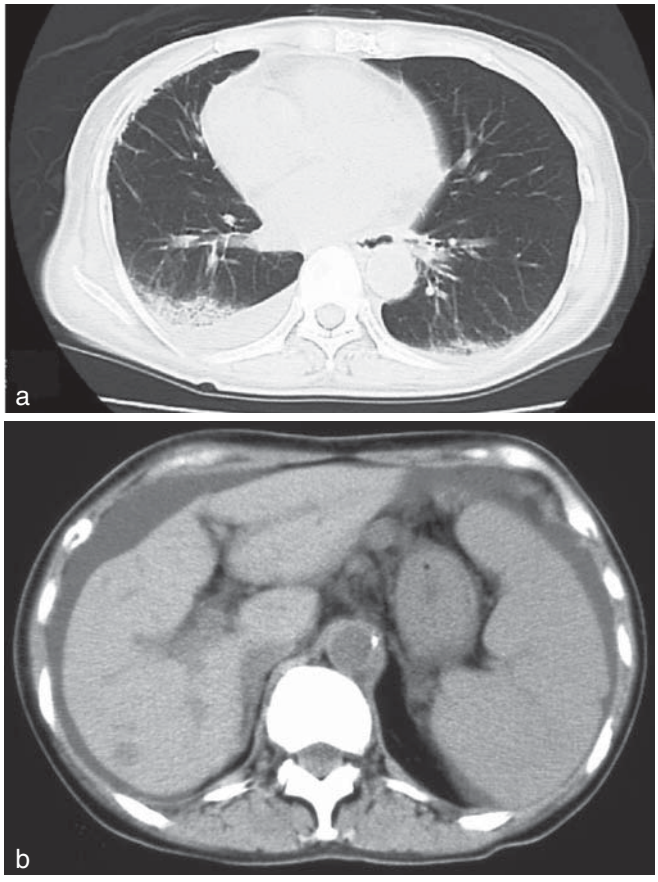

Fig. 1. **a** Computed tomography of the chsest. Fibrosis can be observed in the lower lobes of both lungs as well as bilateral pleural effusion. **b** Abdominal computed tomography findings. The liver is irregular and distorted, the spleen is enlarged, and ascites can be seen

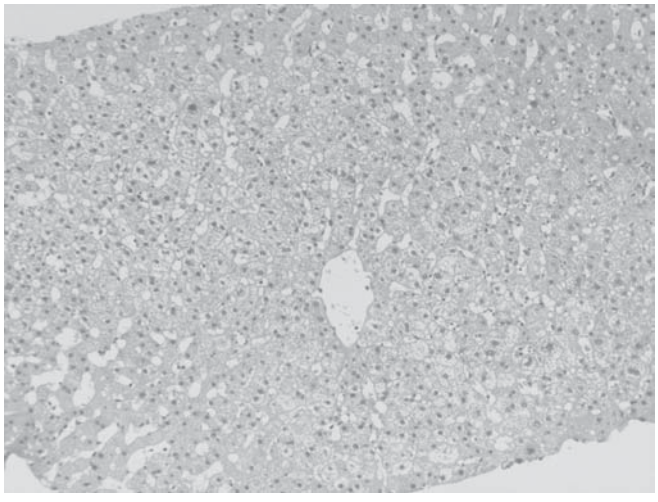

Fig. 2. Photomicrograph of the liver biopsy specimen (×200) Round areas of fibrosis and narrowing of portal vein branches can be seen, but Glisson's capsule remains intact

the 16 patients identified, with the causes of death including hepatic encephalopathy ($n = 3$), pneumonia ($n = 1$), septic shock ($n = 1$), and ruptured esophageal varices ($n = 1$). All of the patients were women aged between 33 and 65 years, and none of them had pulmonary hypertension in 16 patients identified. The time from the appearance of Raynaud's phenomenon to the onset of IPH ranged from 3 to 20 years and all except one patient had esophageal varices. Some patients underwent endoscopic treatment of their varices, such as EVL, while surgical treatment (such as esophagectomy) was performed in others. According to these reports, the prognosis of SSc complicated by IPH is relatively poor. However, the factors that predict the outcome of these patients have not been elucidated.

Because portal hypertension is sometimes associated with primary pulmonary hypertension, Robalino and Moodie[18] suggested that the same vasoactive agents such as angiotensin II and endothelin-1 might be involved in the development of both diseases. However, the serum concentrations of these agents were normal in our patient. Among the six cases available in Table 1, only three of these patients were positive for anti-U1-RNP antibodies. Rai et al.[19] reported on six cases of mixed connective tissue disease (MCTD), 100% positive with anti-U1-RNP antibodies, complicated by IPH, and stated that pulmonary hypertension was frequent in such patients. In contrast, among the cases of SSc complicated by IPH that we reviewed, none of the patients had pulmonary hypertension. Therefore, it might be possible that the etiology of IPH in patients with MCTD and that in patients with SSc were different.

Tsuneyama et al.[16] reported histopathological findings revealing the dense fibrosis and vascular damage in patients with SSc complicated by IPH. They suggested that common fibrogenetic processes and vascular damage were operating in both organs in these patients. They hypothesized that transforming growth factor-β and connective tissue growth factor might be associated with common immunopathological factors in these patients. However, we did not measure these factors in this case. Further studies are required.

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