—Report on Experiments and Clinical Cases—

Association of Limited Scleroderma and Pulmonary Hypertension in a Patient with Primary Biliary Cirrhosis

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Abstract

We report a male patient with primary biliary cirrhosis (PBC) who developed limited scleroderma (l-SSc) and pulmonary hypertension (PHT). He had noticed shortness of breath seven months earlier, which slowly progressed before admission. Sclerodactyly and telagiectasia of the fingers and chest wall were found. Chest X-ray and Doppler echocardiography suggested the presence of PHT. Histologic examination of the liver (needle biopsy) revealed stage two PBC, and histologic findings of the skin (obtained from the dorsum of right finger IV) were compatible with l-SSc. Direct measurement of pulmonary arterial pressure revealed PHT with normal capillary wedge pressure during right heart catheterization. A striking increment of plasma thromboxane B_2 across the lungs was found, which suggested that thromboxane A_2 (precursor of thromboxane B_2) contributed considerably to a rise in pulmonary vascular resistance leading to PHT.
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Key words: hepatopulmonary syndrome, intrapulmonary vasodilatation, thromboxane B_2, endothelin-1, nitric oxide

Introduction

Pulmonary hypertension (PHT) leading to hypoxemia is one of the important complications of scleroderma, and its prevalence reaches about 50% in these patients[1–8]. Both scleroderma and primary biliary cirrhosis (PBC) have the common feature of immune abnormalities being related to the onset, and the frequency of concurrence is quite high[9–16]. PBC is a disorder in which progressive destruction of interlobular bile ducts leads to cirrhosis and portal hypertension. Patients with advanced cirrhosis (including end stage PBC) also have hypoxemia, mainly due to hepatopulmonary syndrome (HPS) caused by intrapulmonary vasodilatation, or rarely due to portopulmonary hypertension (P-PHT) caused by pulmonary vascular constriction[17–19]. We report a hypoxemic patient who had PBC associated with limited scleroderma (l-SSc) and PHT.

Case Report

In January 2003, a 70 year-old man who had a history of PBC for twenty years and hypothyroidism presented to the outpatient clinic with the chief complaints of shortness of breath on exertion and easy fatigability. He initially noticed shortness of

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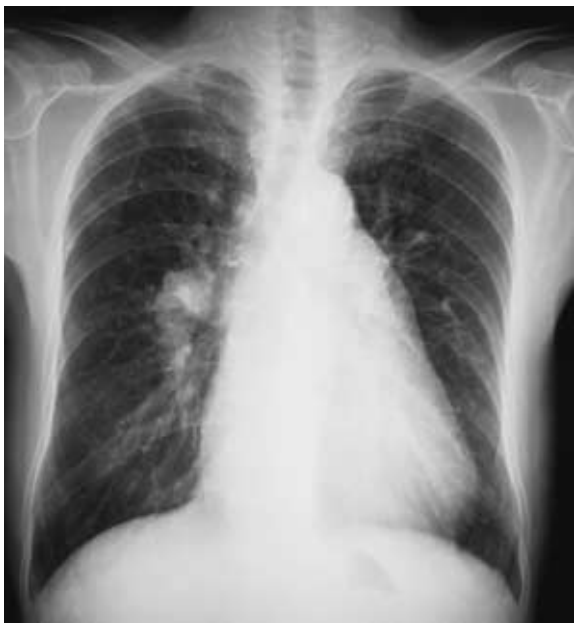

Fig. 1 Chest X-ray disclosed prominent pulmonary arteries and expansion of the left second arch without abnormalities in the lung fields.

breath and fatigability 7 months earlier and it slowly progressed before admission. On examination at admission, the patient showed sclerodactyly and telangiectasia of the fingers and chest wall, and generalized pigmentation of the skin. The heart rate was 70/min and was irregular with no pulse deficit. Blood pressure was 124/88 mmHg. The second heart sound was accentuated with a pulmonary ejection murmur (Levein II/VI). Breath sounds were normal. Ascites, organomegaly, and abdominal tenderness were not recognized.

Chest X-ray revealed prominent pulmonary arteries and expansion of the left second arch without abnormalities of the lung fields (**Fig. 1**). Transthoracic echocardiography demonstrated a dilated right atrium and right ventricle with mild mitral prolapse, and Doppler echocardiography revealed a pulmonary arterial systolic pressure of 98 to 108 mmHg. ECG revealed atrial fibrillation, and also suggested left ventricular hypertrophy.

Table 1 Laboratory data on admission

Peripheral blood		Virological tests	
WBC	6,500 / μl	HBsAg	(−)
RBC	563 × 10^4 / μl	HbsAb	(−)
Hb	15.5 g/dl	HCV-Ab	(−)
Platelets	13.8 × 10^4 / μl	HCV-RNA	(−)
Urinalysis		Immunoglobulin	
Protein	(−)	IgG	1,996 mg/dl
Glucose	(−)	IgA	402 mg/dl
Sediment		IgM	250 mg/dl
RBC	1 ～ 4 /HPF	Autoantibodies	
WBC	1 ～ 4 /HPF	Anti-centromere Ab	(+), (C.O.I; 190.6).
Casts	(−)	MPO-ANCA	< 10 EU
Biochemistry		PR3-ANCA	< 10 EU
AST	37 IU/L	Anti-scl-70 Ab	< 7.0 U/ml
ALT	24 IU/L	Anti-cardiolipin Ab (IgG)	< 8.0 U/ml
LDH	511 IU/L	Anti-RNP Ab	< 7.0 U/ml
ALP	142 IU/L	Anti-nuclear Ab	> 1 : 640
Total bile acids	80.7 μmol/l	Anti-ds-DNA-IgG Ab	< 5 IU/ml
γ-GTP	116 IU/L	Anti-mitochondrial Ab	1 : 20
CPK	84 IU/L	Anti-mitochondrial M2 Ab	55.0
Blood urea nitrogen	28.2 mg/dl	Anti-smooth muscle Ab	(−)
Creatinine	1.35 mg/dl	Anti-LKM1 Ab	(−)
Total protein	8.4 g/dl	Anti-thyroglobulin Ab	(−)
Albumin	4.8 g/dl	Anti-microsome Ab	(−)
Sodium	140 mEq/L	Anti-Sm Ab	< 7.0 U/ml
Potassium	4.4 mEq/L	Anti-Jo-1Ab	(−)
Chloride	101 mEq/L	Anti-SS-A Ab	< 7.0 U/ml
Prothrombin time	72.4 %	Anti-SS-B Ab	< 7.0 U/ml

Abdominal CT demonstrated that the liver was moderately enlarged (particularly the left lobe) but that its surface was smooth. There was also moderate splenomegaly. No significant porto-systemic collateral channels were found by contrast enhanced abdominal CT scanning. Esophago-gastroscopy did not reveal any esophago-gastric varices or portal hypertensive gastropathy. Contrast echocardiography using manually agitated saline revealed intrapulmonary vasodilatation, but its magnitude was slight. Lung perfusion scintigraphy with ^{99m}Tc-macroaggregated albumin (^{99m}Tc-MAA) showed no segmental perfusion defects in the lungs, and there was no extra-pulmonary uptake of radioactivity. Both the immunological findings (**Table 1**) and histologic examination of a biopsy from the skin on the dorsum of right finger IV (revealing a thin epidermis and flatted rete ridges) were compatible with l-SSc. Liver function tests indicated inactive disease, but immunological findings were compatible with PBC, and histologic examination of the liver (needle biopsy) revealed damage or loss of interlobular bile ducts as well as ductular proliferation and mild fibrosis (compatible with stage two of PBC) (**Fig. 2**).

Direct measurement of the pulmonary arterial pressure revealed PHT with elevated pulmonary vascular resistance during right heart catheterization (**Table 2**). Although the patient had atrial fibrillation and left ventricular hypertrophy with moderate mitral prolapse, the pulmonary capillary wedge pressure was 9 mmHg, indicating that PHT was mainly of pre-capillary origin. The hepatic venous pressure gradient, which is an indicator of the intra-sinusoidal pressure, was within the normal range. Arterial blood gas analysis disclosed respiratory alkalosis with hypoxemia and an increased alveolar-arterial oxygen difference. Esophagraphy and a lower esophageal sphincter pressure tracing did not show dilatation of the esophagus or abnormal peristalsis, respectively. There was slight restrictive impairment of the lung function, and carbon monoxide diffusing capacity (DLco) was decreased. Intrapulmonary shunting was estimated after placing the patient on 100% O_2 for 15 min, and was found to be increased. The plasma

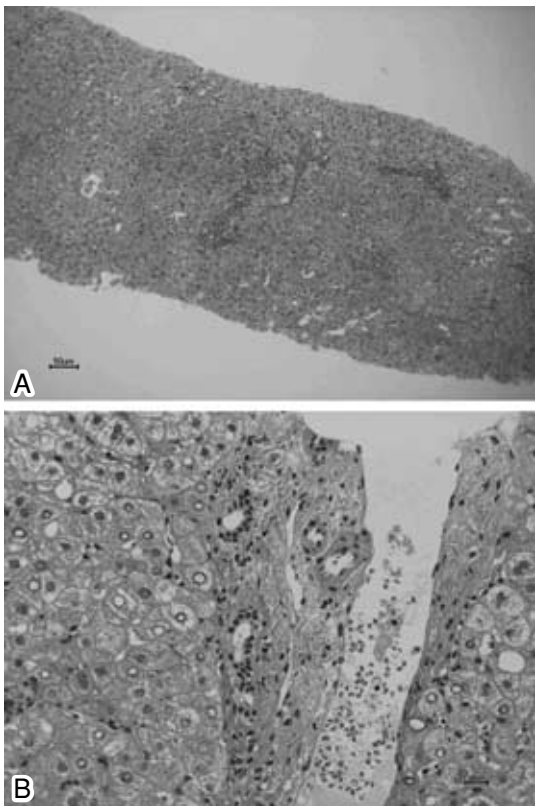

Fig. 2 Histologic examination of the liver tissue obtained by needle biopsy revealed damage or loss of interlobular bile ducts as well as ductural proliferation and mild fibrosis, being compatible with stage two of primary biliary cirrhosis. Hematoxylin-Eosin stain, Original magnification **A** × 100, **B** × 400.

thromboxane (Tx) B_2, plasma prostaglandin (PG)-E_2, and serum nitrate/nitrite levels increased across the lungs (from the main pulmonary artery to the femoral artery), while endotelhin-1 (ET-1) showed a decrease (**Table 3**). Human atrial natriuretic peptide and brain natriuretic peptide levels showed an increase across the right heart (from the inferior vena cava to the main pulmonary artery).

Discussion

The present patient with l-SSc and PBC had pre-capillary PHT associated with arterial hypoxemia, and showed intrapulmonary vasodilatation. Spirometery revealed almost normal lung function, but DLco was significantly reduced and intrapulmonary shunting (determined during inhalation of pure oxygen) was considerably

Table 2 Hemodyamics, respiratory function, and arterial blood gases

Pulmonary and systemic hemodynamics		Lung function tests	
Pulmonary arterial pressure (mean)	56/26 (37) mmHg	%VC	77.9%
Pulmonary capillary wedge pressure	9mmHg	$\%FEV_1$	107.9%
Pulmonary vascular resistance index	1,167★	$\%DL_{CO}$	29.0%
Heart rate	61/min	%Estimated residual volume	39.2%
Blood pressure (mean)	134/66 (100) mmHg	Arterial blood gases	
Cardiac index	1.92L/min/m^2	pH	7.481
Systemic vascular resistance index	3,875★	PaO_2	75.6mmHg
Central venous pressure	7mmHg	$PaCO_2$	29.0mmHg
Circulating plasma volume index	1,139ml/m^2	HCO_3^-	21.4mEq/L
Hepatic venous catheterization		SaO_2	95.0%
Wedged hepatic venous pressure	12mmHg	Alveolar-arterial oxygen difference	37.2mmHg
Free hepatic venous pressure	7mmHg	Intrapulmonary shunt (100% O_2 inhalation)	21.9%
Hepatic venous pressure gradient	5mmHg	Intrapulmonary vasodilatation	(+)☆

★; dynes・sec・cm^{-5}・m^{-2}, ☆; detected by contrast enhanced echocardiography using agitated saline.

Table 3 Partitioned plasma levels of vasoactive agents in patients with limited scleroderma

	Normal range★	Femoral vein	Main pulmonary artery	Femoral artery
Nitrate/nitrite	10～77μmol/l*	44	49	50
Endothelin-1	< 2.30pg/ml	3.54	3.55	3.02
Thromboxane B_2	< 35pg/ml	330	35	290
Prostaglandin E_2	< 8.4pg/ml	11.0	6.9	8.9
Human atrial natriuretic peptide	< 40pg/ml	100☆	160	NT
B-type natriuretic peptide	< 20pg/ml	201☆	247	NT

NT; not tested, ★; normal range in peripheral venous blood, *; serum level, ☆; blood obtained from the inferior vena cava, The nitrate/nitrite level in azygos vein blood was 47μmol/l.

increased. PBC had been present for twenty years, but the histological changes of the liver had remained at stage two, and there were no definite signs of portal hypertension (such as esophageal varices or portal-systemic collaterals on contrast CT of the abdomen) apart from moderate splenomegaly. It was considered that l-SSc had arisen simultaneously or shortly before the onset of PHT. There was a striking increase in the plasma level of TxB_2 across the lungs.

The prevalence of l-SSc ranges from 3 to 18% among PBC patients[11–14]. On the other hand, PBC is encountered most frequently in l-SSc patients, and its prevalence is as high as 51.2% among l-SSc patients with liver dysfunction[11,15,16]. It has been reported that approximately 70% of patients with l-SSc show pulmonary involvement at autopsy[6,20]. Changes in the lungs not only cause impairment of respiratory function (reduced diffusing capacity, restrictive abnormalities, or airway obstruction), but also lead to abnormalities in the pulmonary circulation (mainly PHT)[21,22]. Since our patient showed hypocapnea, airway obstruction (indicated by impairment of FEV_1 or an increased residual lung capacity) seemed unlikely to contribute much to the impairment of arterial oxygenation. Thus, it was considered that his arterial hypoxemia originated from abnormalities in the pulmonary circulation or impairment of diffusion, rather than alveolar hypoventilation.

Patients with l-SSc often show impaired diffusion due to interstitial pneumonia[6–8,22], but chest CT did not demonstrate any interstitial changes in the lungs of this patient. Minimal intrapulmonary vasodilatation was detected by contrast echocardiography, and there was almost no extrapulmonary uptake of ^{99m}Tc-MAA on lung perfusion scintigraphy. Accordingly, it was

considered that the contribution of intrapulmonary vasodilatation to hypoxemia was small. However, the shunt detected with pure oxygen inhalation (the standard technique for measurement of shunting) was moderately large, contradicting the results of contrast echocardiography and the radioisotope study. An increase in venous admixture via bronchial arteries and/or venous admixture via the Thebesian vessels may be a possible explanation for this discrepancy, but it is difficult to resolve from our data[23].

It is well known that arterial hypoxemia, intrapulmonary vasodilatation, and chronic liver disease with portal hypertension constitute the triad of features in HPS[18,24]. It has recently been proposed that pre-capillary PHT in patients with cirrhosis and portal hypertension should be recognized as P-PHT[24,25]. Both HPS and P-PHT manifest similarly with arterial hypoxemia. Since PBC existed in the present patient as the underlying liver disease, the possibility of HPS or P-PHT is also raised. However, his PBC had not developed to the cirrhotic stage and no definite porto-systemic collaterals were found. Although the mechanism is unknown, it has been reported that approximately one-third of patients with collagen diseases show intrapulmonary vasodilatation on lung perfusion scintigraphy using ^{99m}Tc-MAA, so the present patient may also belong to this category[26].

The mechanism of PHT in l-SSc is not fully understood, but it has been speculated that an imbalance between vasoconstrictor and vasodilator factors (such as nitric oxide, PGs, TxA_2, and ET-1) contributes to pulmonary circulatory abnormalities[18,19,27–31]. Since the biggest vascular bed that exists between the main pulmonary artery and fermoral artery is the lungs, it can be considered that an increment of vasoactive factors across the lungs indicates production or release of such factors in the lung tissue[32]. If the increment of vasoactive factors across the lungs in this patient is assumed to indicate release or production in the lungs, the vasoconstrictor TxA_2 (precursor of TxB_2) probably has a major influence on the pulmonary vascular bed.

In conclusion, this patient had l-SSc and PHT associated with PBC. Since the l-SSc had arisen simultaneously with the onset of PHT, it was considered that the development of PHT was closely related to the onset of l-SSc rather than PBC. A striking increment of TxB_2 across the lungs suggested the production or release of intrinsic vasoconstrictors such as TxA_2 in the lung tissue, which probably contributed to an increase in pulmonary vascular resistance that led to pre-capillary PHT.

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