Pulmonary Hypertension and Antiphospholipid Antibody in a Patient with Sjögren's Syndrome

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A 57-year-old female patient with Sjögren's syndrome was complicated with pulmonary hypertension (PH) and antiphospholipid antibody (aPL). She had a history of fetal losses, deep vein thrombosis and chronic thyroiditis. On admission, severe pulmonary hypertension, thrombocytopenia, lupus anticoagulant and a decreased level of protein C were found. Pulmonary artery perfusion scintigram revealed multiple defects. She died suddenly despite an intensive therapy. Intimal proliferation with angiomatoid lesions in small pulmonary arteries was observed by autopsy. Since a close relationship between PH and aPL in connective tissue disease is found, it is important to carefully analyze the antiphospholipid antibodies in patients with PH. (Internal Medicine 33: 768-772, 1994)

Key words: pulmonary thromboembolism, lupus anticoagulant

Introduction

Pulmonary hypertension (PH) which originates in the pulmonary vasculature itself has been denoted as "primary PH". However, the same clinical and pathological features of primary PH often occur in association with connective tissue diseases, such as systemic lupus erythematosus (SLE) (1), mixed connective tissue disease (MCTD) (2), scleroderma (3), and particularly in the CREST syndrome (4).

Recently, antiphospholipid antibodies (aPL) have been reported to be related to PH with pulmonary thromboembolism and even in cases with no clinical evidence of pulmonary thromboembolism (5, 6). PH has hitherto been rarely reported in Sjögren's syndrome (7). We report PH and aPL in a patient with Sjögren's syndrome.

Case Report

A 57-year-old female was admitted to our hospital because of severe dyspnea and leg edema in early January 1992. She had a history of two fetal losses. In 1981, she had deep vein thrombosis in her left leg and underwent treatment in a local hospital. She suffered from keratoconjunctivitis sicca and xerostomia, and was diagnosed as Sjögren's syndrome and chronic thyroiditis at that hospital. She had a slight dyspnea from 1989, and PH was suspected due to the finding of enlarge-

ment of pulmonary arteries on chest X-ray, but she received no specific treatment for PH. On admission (Jan. 1992), she was 152 cm tall and weighed 38 kg. Her body temperature was 35.1°C. Blood pressure was 142/80 mmHg and heart rate was 84/min, regular. Both lobes of the thyroid gland were swollen. Systolic murmur of Levine II/VI at 4th intercostal space was audible and coarse crackle sound was audible at both lower lung fields. Raynaud's phenomenon, xerostomia and livedo reticularis were recognized.

On laboratory examination, White blood cell count (WBC) and platelets were decreased to 2,450/ μ l and 9.5×10^4 / μ l respectively. aPTT was markedly prolonged at 40.2 sec (control: 29.4 sec). An elevated level of LDH was noted (479 IU/l). Antinuclear antibody (ANA) was 1:1,280 (speckled). Anti-dsDNA antibody was negative. Anti-SS-A and SS-B antibodies were positive. Anti-Sm, RNP, Scl-70, centromere and Jo-I antibodies were negative. Lupus anticoagulant (LA) was positive (diluted prothrombin time method) but anticardiolipin antibody (aCL) was negative. On February 14, 1992, antigen titers of protein C were decreased to 51% (normal range: 70-150) and protein C activity was likewise decreased to 27% (normal range: 55-140). An increased level of platelet-associated IgG (PAIgG) was found (Table 1).

Chest X-ray revealed enlargement of the right ventricle and pulmonary artery and right pleural effusion (Fig. 1). Chest CT examination demonstrated enlargement of the pulmonary arter-

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Received for publication January 27, 1994; Accepted for publication August 3, 1994

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PH and aPL in a Sjögren's Syndrome Patient

Table 1. Laboratory Data on Admission

White blood cell count	2,450/ μ l	C-reactive protein	4.8 mg/dl
Red blood cell count	433×10^4 / μ l	Erythrocyte sedimentation rate	20 mm/hr
Hemoglobin	13.1 g/dl	Antinuclear antibody	$\times 1,280$ (speckled)
Hematocrit	43.5%	Anti-DNA Ab	6.1 IU/ml (<7)
Platelet	9.5×10^4 / μ l	LA	(+)
Activated partial thromboplastin time	40.2 sec (29.4)	aCL IgG	<0.5 (<1.0)
Prothrombin time	15.5 sec (12.6)	IgM	<0.5 (<1.0)
Thrombin time	37% (90)	Serological test for syphilis	(-)
Platelet associated IgG	$114.5 \text{ ng}/10^7$ cells	Anti-Sjögren's syndrome-A antibody	$\times 16$
		Anti-Sjögren's syndrome-B antibody	$\times 8$
Coombs direct	(-)	Anti-Smith antibody	(-)
indirect	(-)	Anti-n-ribonucleo protein antibody	(-)
		Anti-scleroderma 70 antibody	(-)
Na	136 mEq/l	Rheumatoid arthritis particle agglutination	$\times 40$
K	4.2 mEq/l		
Cl	107 mEq/l	Thyroid stimulating hormone	6.1 μ U/ml
Fasting blood sugar	93 mg/dl	Free triiodo thyronine	2.9 pg/ml
		Free thyroxine	0.98 ng/ml
Alkaline phosphatase	3.0 B-LU	Anti-microsome antibody	$\times 1,600$
Aspartate aminotransferase	45 U		
Alanine aminotransferase	8 U	Protein C activity	27% (55-140)
Lactate dehydrogenase	479 IU/l	Protein C antigen	51% (70-150)
Leucine aminopeptidase	48 IU/l		
Gamma-glutamyl transpeptidase	31 IU/l	Pulmonary function test	
Cholinesterase	0.55 Δ PH	% vital capacity	60.2%
Total-bilirubin	1.1 mg/dl	Forced expiratory volume 1.0%	85.7%
Direct-bilirubin	0.5 mg/dl	% diffusion capacity co	33.8%
Creatine phosphokinase	67 IU/l		
Blood urea nitrogen	20.8 mg/dl	Blood gas analysis (room air)	
Creatinine	0.9 mg/dl	PH	7.49
Total cholesterol	133 mg/dl	PaCO ₂	23.1 Torr
Triglyceride	78 mg/dl	PaO ₂	50.3 Torr
Total protein	8.8 g/dl	HCO ₃	17.8 mEq/l
Albumin	3.9 g/dl

Fig. 1. Chest radiographs on January 8, 1992. Cardiomegaly, enlargement of pulmonary arteries and right pleural effusion are demonstrated.

ies and an increase in vascular shadows at the peripheral lung area (Fig. 2). Electrocardiogram showed right ventricle hypertrophy. Severe tricuspid regurgitation and enlargement of the right atrium-ventricle were demonstrated on echocardiogram. The estimated pressure of the right ventricle was 40 to 60 mmHg. Pulmonary artery perfusion scintigram revealed multiple defects in both lung fields (Fig. 3). Ascites, thickening of the gall bladder wall and enlargement of the inferior vena cava were demonstrated on abdominal echogram.

Systemic lupus erythematosus (SLE) was suspected from the anti-nuclear antibody level and leucopenia, but pleural effusion was derived from heart failure. This case was not suitable for diagnostic criteria of SLE. She was diagnosed as pulmonary hypertension by pulmonary thromboembolism and was treated with 40 mg/day furosemide, 80 mg/day aspirin, 3–6 mg/day warfarin potassium, 0.25 mg/day digoxin, 200 mg/day of ticlopidine and inhalation of O₂ 2 l/min. Her symptoms were relieved with this therapy, thus she was discharged on February 15, 1992. After discharge she was treated with home

oxygen therapy for 4 months. However, she suffered from dyspnea again in early June. Severe hypoxia and marked pulmonary dilatation on chest X-ray was revealed. She was admitted on June 20, she was unresponsive to any therapy, and died suddenly on 11th hospital day. The cause of death was diagnosed to be pulmonary hypertension and chronic respiratory failure due to pulmonary thromboembolism. Autopsy revealed occlusion of recanalization of pulmonary small arteries, medial hypertrophy with elastofibrosis and intimal proliferation with angiomatoid lesions (Fig. 4). The pathological classification of the grade of PH was Heath-Edwards III to IV. No apparent pulmonary thrombosis and little interstitial pneumonitis was demonstrated. The right ventricle showed marked dilatation and hypertrophy. Chronic epicarditis, marked pleural fibrous adhesions and effusion were demonstrated in both pleura. The salivary gland was markedly atrophic with lymphocyte infiltration. The thyroid was diffusely hypertrophic. No apparent thromboembolisms were found in other organs.

Discussion

Pulmonary hypertension (PH) has been reported to be associated with 5–15% of various connective tissue diseases (CTDs). Positive anti-nRNP antibody and thrombocytopenia have been reported more frequently in patients with CTDs associated with PH than in patients with CTDs without PH (8). Multiple factors have been implicated in its pathogenesis, such as vasculitis, extensive immune complex deposition or thromboembolism, but the underlying cause still remains unknown (9). Recently, it is postulated that aPL is closely related to the occurrence of the thromboembolic type of PH, as aPL (LA and aCL) has come to be associated with a variety of venous and arterial occlusions (5, 6). Asherson et al (5) reported 24 SLE patients with PH, in whom aCL and LA were 63% and 54% respectively, whereas 29% showed anti-nRNP antibody in their sera. The background frequency of aCL in SLE without PH was about 30–40%.

We speculate that the present case of PH was the thromboembolic type due to the detection of pulmonary artery perfusion scintigram and the pathology of recanalization of the pulmonary small artery. A few cases of PH associated with primary Sjögren's syndrome have been reported (7). It appears that in the present case, the association with aPL is more important in the development of PH. A decreased amount and decreased activity of protein C were found in the present case. It is reported that a decreased activity of protein C may be induced by ACA and/or LA (10). Since protein C is one of the factors which is thought to prevent intravascular endothelial coagulation (thrombomodulin-protein C-protein S), the multiple pulmonary thromboembolism in the present case may be explained by the decreased amount and/or activity of protein C.

Plexiform or angiomatoid lesions occur in pulmonary arterioles. Over-proliferation of endothelial cells in the lesion causes septum formation, and they appear as an assembly of capillaries. Originally, these lesions have been assumed to be a congenital vascular anomaly and it has been postulated that plexiform or angiomatoid lesions cause primary PH due to

Fig. 2. Chest CT scan on January 20, 1992 reveal marked dilatation of pulmonary arteries (a) and increased vascular shadows in the peripheral lung area (b).

Fig. 3. Pulmonary artery perfusion scintigrams reveal multiple defects in both lung fields.

obstruction of the vessels (11). Now, these lesions are commonly seen in very advanced PH, and even in CTDs. It is reported that these lesions are found in 8 out of 12 (67%) patients with MCTD and in 6 out of 6 SLE associated with PH (8). These lesions were seen in the present case, therefore, it was demonstrated not only clinically but also pathologically that the present case had advanced PH. Since the etiopathology of PH has not been fully elucidated, the treatment of PH remains undetermined and it usually has a poor prognosis. In PH associated with aPL, corticosteroids, immunosuppressives and antiplatelet drugs theoretically may be a useful treatment (12). However, it has been reported that in spite of this combination therapy, death frequently occurs within 5 years, and often in one year after the diagnosis of PH in the majority of the patients. This probably is the reason why PH has been reported as an end stage lung disease (5). This is one of the reasons why we did not use steroids or immunosuppressants.

Recently, Hughes et al proposed the concept of anti-phospholipid syndrome (APS) as a combination of venous or arterial thrombosis, thrombocytopenia and antibodies against phospholipids. Since the present case had livedo reticularis, PH, recurrent spontaneous abortion and thrombocytopenia, this case was considered as a case of APS (12). It was considered

that the catastrophic APS could be ruled out due to the presence of localized thromboembolic lesions and its slowly progressive course (13).

In conclusion, PH and aPL show a close relationship, suggesting that aPL should be determined in patients with PH, and vice versa.

Acknowledgments: The authors would like to express their deep gratitude to Dr. S. Saiki (Pathology of St. Luke's Hospital) for valuable suggestions, and also to Dr. H. Kaneko, T. Takahashi and Y. Moriya (Department of Rheumatology, Juntendo University School of Medicine) for their intensive and careful treatment of the patient.

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Fig. 4. Histologic features of the lung at postmortem examination. Left: Occlusion and recanalization of small artery with angiomatoid lesion (HE stain, $\times 140$). Right: Intimal proliferation and medial hypertrophy with elastofibrosis (HE stain, $\times 70$).

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