Systemic Lupus Erythematosus with Pulmonary Hypertension

Shigeru KOYAMA, Takeo ICHIYOSHI, Masaaki CHINO and Takayuki KANBAYASHI

A 50-year-old Japanese female with a long history of Raynaud's phenomenon presented with progressive dyspnea due to pulmonary hypertension. The diagnosis of systemic lupus erythematosus was confirmed by proteinuria, lymphocytopenia, bilateral pleurisy, and a seizure of convulsion which was consistent with neurological manifestations of systemic lupus erythematosus, whereas the antinuclear antibody showed a low titer. Despite improvement in the activity of systemic lupus erythematosus, steroid treatment did not alter the progression of pulmonary hypertension, which increased in severity, eventually resulting in her death. We believe pulmonary hypertension to be an unusual but critical complication of systemic lupus erythematosus. (Internal Medicine 35: 39–42, 1996)

Key words: Raynaud's phenomenon, antiphospholipid antibody, lupus anticoagulant, collagen vascular disease

Introduction

Pulmonary hypertension (PH) is one of the more rare complications in patients with systemic lupus erythematosus (SLE) (1). The pathophysiology of PH is unknown, and in many patients the condition generally carries a poor prognosis despite treatment, sometimes following a rapidly progressive course leading to right-sided heart failure and death (2). We describe a case of SLE with supervening PH, who developed right-sided heart failure and respiratory failure with poor response to treatment.

Case Report

A 50-year-old Japanese female was admitted to our hospital on October 30, 1993 because of progressive dyspnea on exertion and worsening fatigue. She had a long history of Raynaud's phenomenon for 32 years, and recurrent digital gangrene of both hands had supervened from 1981, which had been treated in the department of dermatology of our hospital. In 1988 and 1993 routine chest X-ray films showed increasingly accentuated central pulmonary vasculature with peripheral pruning, with some prominence of the right ventricle and clear lungs. Consecutive electrocardiograms (Fig. 1) disclosed increased anterior R-wave voltage with right bundle branch block, consistent with right ventricular enlargement. These findings suggested progressing pulmonary hypertension, but no further

investigations were performed. She also had a self-limiting illness with edema, occasional proteinuria, and episodic dyspnea on exertion from 1992, which became worse gradually. She had not been suffering from photosensitivity, alopecia, oral ulcers, or rashes. She was a nonsmoker and had no history of taking oral contraceptive drugs and had no history of deep vein thrombosis; she had never been pregnant. She did not have preceding fever, arthralgia, and pleural chest pain.

For editorial comment, see p1

Physical examination on admission disclosed a cooperative, thin female with a normal temperature and a pulse rate of 84 beats/min. Her blood pressure was 138/80 mmHg. She was noted to have peripheral cyanosis, a loud pulmonary component of the second heart sound, a palpable liver descending 9 cm below the right costal arch, and peripheral edema. There were no rales over the lung fields and no findings of lymphadenopathy, arthritis, swollen hands, swollen fingers, sclerodactyly, and cutaneous telangiectasia. Admission laboratory data included the following values: hemoglobin, 16.8 g/dl; hematocrit, 49.5%; white blood cell (WBC) count, 3,900/mm³ (lymphocyte, 2%); platelet count, 36.8×10⁴/mm³; prothrombin time (PT), 17.7 seconds (45%); activated partial thromboplastin time (APTT), 42.7 seconds; fibrinogen, 235 mg/dl; fibrinogen and fibrin degradation product (FDP), 17 µg/ml; FDP-D dimer, 9.2 µg/ml. A urinalysis showed 3+ protein (1.3 g/day)

From the Department of Internal Medicine, Nagano Red Cross Hospital, Nagano

Received for publication July 10, 1995; Accepted for publication October 17, 1995

Reprint requests should be addressed to Dr. Shigeru Koyama, the Department of Internal Medicine, Nagano Red Cross Hospital, 1512-1 Wakasato, Nagano 380

Figure 1. Consecutive electrocardiograms showed increased anterior R-wave voltage with right bundle branch block and marked T-wave abnormalities, consistent with progressive right ventricular enlargement.

and 3+ occult blood without any cellular casts. The sedimentation rate was 21 mm/h. The sGOT, sGPT, LDH, and creatinine levels were normal. The albumin and gamma globulin concentrations were 2.4 g/dl and 1.6 g/dl, respectively, with a total protein of 6.0 g/dl. Serological tests showed marked elevation of CRP of 18.1 mg/dl. Complement studies revealed a normal CH_{50} level of 40.6 U/ml. The antinuclear antibody (ANA) titer was 1:40 (undetermined pattern), and the other autoantibodies, such as anti-U1 sn ribonucleoprotein (RNP) antibody, anti-double strand deoxyribonucleic acid (DNA) antibody, anti-Sm antibody, and rheumatoid factor, were not detected. Lupus anticoagulant (LAC) and anti-cardiolipin antibody were also negative. Arterial blood gas analysis revealed PaO_2 50.0 Torr, $PaCO_2$ 26.7 Torr, and pH 7.50 on room air. Chest radiography (Fig. 2) demonstrated bilateral pleural effusion without significant parenchymal disease in the lungs. Echocardiography (Fig. 3) showed enlargement of right ventricle and right atrium, and pulmonary artery systolic pressure was estimated to be about 87 mmHg which was calculated from the sum of the peak tricuspid insufficiency – Doppler

Figure 2. Chest radiography on the admission (October 30, 1993) demonstrated bilateral pleural effusion, accentuated main pulmonary arteries with some prominence of the right ventricle, and no significant parenchymal disease in the lungs.

pressure gradient. There was no left to right shunt. Perfusion lung scan was normal. She did not undergo cardiac catheterization. SLE was suspected on the basis of proteinuria, lymphocytopenia, bilateral pleurisy, and vasculitic skin lesions. As her condition was thought to reflect active lupus, therapy with prednisolone at 60 mg/day was begun. On November 12, she had a seizure of convulsion with loss of consciousness and urinary incontinence. Magnetic resonance imaging of the head (Fig. 4) showed small punctuate areas of hyperintensity in the pons and the bilateral thalami to the midbrain. These findings were thought to be compatible with vasculitic changes in SLE. Therefore, the diagnosis of SLE was confirmed by the manifestations of proteinuria, lymphocytopenia, pleurisy, and a seizure in the diagnostic criteria of the American Rheumatism Association. After pulse therapy with methylprednisolone at 1 g/day for three days, she was administered prednisolone at 100 mg/day. While her clinical condition was thought to be improving regarding SLE, such as pleurisy and the level of consciousness, the electrocardiogram failed to demonstrate any effect on the increasing right ventricle overload consistent with progressive PH (Fig. 1). On March 5, 1994 her cardiac state deteriorated rapidly, and she developed severe respiratory failure owing to PH. Despite aggressive therapeutic measures including steroid pulse therapy, the patient died on March 6. A postmortem examination was not obtained.

Figure 3. Echocardiographic images. Top, Apical four-chamber view showed enlargement of right ventricle and right atrium. Center, Continuous-wave Doppler study and two-dimensional echocardiogram showed tricuspid insufficiency of the third to fourth degree, which was estimated to be a peak pressure gradient of 77 mmHg with a mean gradient of 40 mmHg. Bottom, Parasternal short axis view showed fair contraction of the left ventricle with its ejection fraction of 0.89. There was no left to right shunt.

Discussion

PH is considered a rare pulmonary complication of SLE although a prevalence of 0.5% to 9% has been reported (3). PH may occur as a result of significant parenchymatous disease in the lungs or secondary to a cardiac disorder such as a left to right shunt, however such a condition of lungs and heart was not found in the present patient. The most common association of

Figure 4. Serial T2-weighted magnetic resonance imaging of the brain revealed small punctuated areas of hyperintensity in the pons (Top) and the bilateral thalami to the midbrain (Bottom).

PH in collagen vascular disease has been with mixed connective tissue disease and scleroderma, particularly in the CREST variety, but it has been increasingly reported in SLE (4). PH association with SLE may have a relentlessly progressive course with a variable response to treatment and a generally poor prognosis (5); death within two years is the rule (1).

Asherson and coworkers (2) report that symptoms of PH occur within three months to 11 years after the diagnosis of SLE has been made. The average time for the development of PH is between two and five years in most of the patients, and the cause of death is sudden, usually from end-stage circulatory collapse (2), which also developed in our patient. The incidence of hypertensive pulmonary vascular disease is not reflected to the severity or activity of SLE itself such as high anti-DNA binding values and/or grossly elevated erythrocyte sedimentation rates (1), but is often associated with the presence of anti-U1 sn RNP antibody, rheumatoid factor and LAC (6). Various theories as

to the pathogenesis of PH in SLE have been proposed, such as thrombo-embolic disease, vasoconstriction of the pulmonary arteries, immune complex vasculitis, and interstitial pneumonia (5). It has been also noted that LAC as well as anti-cardiolipin antibodies are found in SLE associated with PH, although these were absent in our patient. An increased frequency of Raynaud's phenomenon in the condition suggests that a vasospastic factor plays an important role in the etiopathogenesis (2); the frequency of Raynaud's phenomenon in SLE is about 25%, while it is present in 75–80% of the patients with PH-associated SLE (7, 8). In our patient, Raynaud's phenomenon antedated the onset of PH by a number of years, leading to gangrene of the fingers. An autopsied case of SLE with PH shows hypertrophy of the smaller muscular pulmonary arteries, marked thickening of the intima by cellular fibromuscular tissue and plexiform lesions (9). It is possible that chronic "pulmonary Raynaud's phenomenon" can lead to chronic PH in some patients with SLE (10).

The prognosis of PH is poor and once established, heart/lung transplantation may be the only effective therapy (9). Irreversible changes in the resistance vessels are no longer capable of dilatation even with vasodilator agents (1). At an early stage in the course of PH, increased pulmonary vasomotor tone and reactivity may permit a beneficial pulmonary vasodilator response to these agents (1). As supervening PH should always be considered in patients with SLE, serial Doppler echocardiography is necessary for routine screening in order to

detect these early preclinical stages and the development of PH (7).

References

- 1) Asherson RA, Oakley CM. Pulmonary hypertension and systemic lupus erythematosus. *J Rheumatol* **13**: 1, 1986.
- 2) Asherson RA, Higenbottam TW, Dinh Xan AT, Khamashta MA, Hughes GRV. Pulmonary hypertension in a lupus clinic: experience with twenty-four patients. *J Rheumatol* **17**: 10, 1990.
- 3) Groen H, Bootsma H, Postma DS, Kallenberg CGM. Primary pulmonary hypertension in a patient with systemic lupus erythematosus: partial improvement with cyclophosphamide. *J Rheumatol* **20**: 1055, 1993.
- 4) Asherson RA, Hackett D, Gharavi AE, Harris EN, Kennedy HG, Hughes GRV. Pulmonary hypertension in systemic lupus erythematosus: a report of three cases. *J Rheumatol* **13**: 416, 1986.
- 5) Turner A, Samanta A, Nichol FE. Primary pulmonary hypertension associated with systemic lupus erythematosus. *Clin Rheumatol* **10**: 320, 1991.
- 6) Roncoroni A, Alvarez C, Molinas F. Plexogenic arteriopathy associated with pulmonary vasculitis in systemic lupus erythematosus. *Respiration* **59**: 52, 1992.
- 7) Simonson JS, Schiller NB, Petri M, Hellmann DB. Pulmonary hypertension in systemic lupus erythematosus. *J Rheumatol* **16**: 918, 1989.
- 8) Quismorio FP Jr, Sharma O, Koss M, et al. Immunopathologic and clinical studies in pulmonary hypertension associated with systemic lupus erythematosus. *Semin Arthritis Rheum* **13**: 349, 1984.
- 9) Greenstone MA. Delayed diagnosis of systemic lupus erythematosus associated pulmonary hypertension. *Br J Rheumatol* **30**: 391, 1991.
- 10) Kanemoto N, Sato M, Moriuchi J, Ichikawa Y, Goto Y, Sasadaira H. An autopsied case of systemic lupus erythematosus with pulmonary hypertension – a case report. *Angiology* **39**: 187, 1988.