Pulmonary Hypertension in Systemic Lupus Erythematosus: A Report of an Autopsied Case

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An autopsied case of systemic lupus erythematosus with pulmonary hypertension is reported. A 29-year-old woman with a seven-year history of polyarthralgia, butterfly rash, nephrotic syndrome and Raynaud's phenomenon was admitted because of progressive dyspnea on exertion. Tests for antinuclear antibody, anti-cardiolipin antibody and lupus anticoagulant were positive. Echocardiographic examination revealed right ventricular hypertrophy and a moderate pericardial effusion. Estimated systolic pulmonary arterial pressure was 53 mmHg. Despite treatment with corticosteroids including pulse methylprednisolone therapy, lipo-PGE1 and warfarin, she died of progressive congestive heart failure. Postmortem examination of the pulmonary vasculature revealed findings consistent with plexogenic pulmonary arteriopathy, without evidence of vasculitis, fibrinoid necrosis, or thromboemboli.

Key words: anti-cardiolipin antibody, Raynaud's phenomenon, plexiform lesion, lupus anticoagulant, Sjogren's syndrome

Introduction

Systemic lupus erythematosus (SLE) is a chronic inflammatory disease of unknown etiology which may affect various organs. Pulmonary hypertension (PH) is a rare complication in SLE; only a few reports of such a complication have been published until recently (1-9). We present here an autopsied case of SLE associated with PH, Raynaud's phenomenon and a lupus anticoagulant.

Case Report

A 29-year-old woman was admitted in February 1989 because of progressive dyspnea on exertion and bilateral finger ulcers. In 1982, polyarthralgia and butterfly rash had developed. She had visited another hospital in November 1984 because of fever, polyarthralgia and butterfly rash. Antinuclear factor and anti-DNA antibody were positive, and she was diagnosed as having systemic lupus erythematosus (SLE). Prednisolone at 30 mg daily was started, and she responded promptly. In March 1986, nephrotic syndrome developed and she was treated with prednisolone 60 mg daily. In December 1987, Raynaud's phenomenon and bilateral parotid swelling developed. She gradually experienced dyspnea on exertion from September 1988. In February 1989 she had ulcersations of the finger tips of both hands and dyspnea on exertion, and the Raynaud's phenomenon became exacerbated, and was admitted to our hospital. There was no history of thrombophlebitis or embolic episodes.

On physical examination at admission, she had hair loss, butterfly rash and ulcerations of finger tips on both hands. Blood pressure was 126/86 mmHg and pulse rate was 90 per minute. The pulmonic sounds were accentuated, and a grade 2 pulmonic ejection murmur and a right ventricular summation gallop were audible. Breath sounds were normal. Abdominal examination was negative.

A urine test was positive for protein (0.48 g/day); urinary sediment was normal. A test for lupus erythematosus (LE) cell preparation was positive. A test for antinuclear antibodies was positive at a titer of 1:320, with a speckled pattern. Tests for anti-DNA antibody (426 U/ml), anti-RNP antibody (1:16), anti-Sm antibody (1:8), anti-SS-A antibody (1:256), were positive. Anti-SS-B antibodies was negative. A lupus anticoagulant was positive, and both IgG (16.0 U/ml) and IgM (5.5 U/ml) anti-

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cardiolipin antibodies were positive. The serum complement levels were decreased (CH50 12.1 U/ml, C3 32 mg/dl, C4 16 mg/dl). A serologic test for syphilis was negative. The serum IgG was 5,320 mg/dl, IgA 328 mg/dl and IgM 621 mg/dl. Arterial blood gas analysis on room air showed the following: oxygen tension (PO2) 86.1 mmHg, carbon dioxide tension (PCO2) 34.8 mmHg, HCO3⁻ 23.4 mEq/l, pH 7.437, base excess 0.4 mEq/l.

A chest X-ray showed mild cardiomegaly with the dilatation of main pulmonary arteries and clear lung fields. The ultrasonographic examination of the heart showed right ventricular hypertrophy and presence of a moderate pericardial effusion. The systolic pulmonary arterial pressure was estimated as 53 mmHg by Doppler echocardiography. Pulmonary function studies showed VC of 89.6% and FEV1 1.0% of 93.5%. The diagnosis of pulmonary hypertension associated with SLE was made. The results of Schirmer’s tear test, sialography and lip biopsy were compatible with Sjögren’s syndrome. Prednisolone (30 mg daily) and lipo PGE₁ (10 μg daily) was started, and the patient was discharged in April 1989. She was readmitted two months later because of progressive dyspnea on exertion. Arterial blood gas studies on room air showed: PO2 55.1 mmHg, PCO₂ 24.0 mmHg, HCO₃⁻ 19.1 mEq/l, pH 7.511, and base excess −1.4 mEq/l. Oxygen therapy was started against progressive hypoxemia. Pulse methylprednisolone 1,000 mg daily for three days was administered, followed by 60 mg prednisolone daily. The prednisolone treatment was gradually tapered over the following month and warfarin was added. Progressive congestive heart failure developed despite this therapy. She also developed congestive liver dysfunction in February 1990. Arterial blood gas studies on 50% oxygen mask showed: PO2 66.0 mmHg, PCO₂ 19.8 mmHg, HCO₃⁻ 17.8 mEq/l, pH 7.562, and base excess −1.8 mEq/l. The patient died suddenly on March 15, 1990. The direct cause of death was respiratory and right cardiac failure.

Autopsy findings

The right lung weighed 235 g and the left lung 350 g. Neither pleural thickening nor fibrosis of the lungs were present. Histologically, numerous plexiform lesions of the peripheral pulmonary arterial branches were present around the respiratory bronchi. Many angiomatoid lesions were found adjacent to the plexiform lesions. Edema of the media, particularly, of the peripheral pulmonary arteries were present. Fibroelastic intimal thickening and medial thickening of the larger pulmonary arterial branches were found. Dilatation and scattered atheroma of the major pulmonary arterial branches were found near the pulmonary hilus. No fibrinoid necrosis of the pulmonary arterial wall was present. The heart weighed 410 g, the right ventricular wall was 5 mm in thickness. Both right atrium and ventricle were markedly enlarged. Scattered small foci of myolysis in the bilateral ventricular myocardium were found. Translucent pericardial fluid (110 ml), was found. The right kidney weighed 225 g and the left 215 g. Both kidneys showed mild edematous swelling with congestion of the medullae. Histologically, diffuse thickening of the glomerular basement membranes with spike formation and subepithelial deposits were found. Mild mesangioliparlification and a few mesangial deposits were present. Neither hematoxylin body nor wire loop lesion was demonstrated. Lupus nephritis was classified as WHO Class V. Marked congestion of the liver (nutmeg liver, 1,300 g) and the spleen (200 g) were found.

Discussion

Pulmonary hypertension (PH) is a serious complication in SLE. Its association was recognized relatively recently, al-

![Fig. 1. Chest roentgenogram showing the dilatation of main pulmonary arteries and cardiac silhouette suggestive of right ventricular hypertrophy.](image)

![Fig. 2. Plexiform lesion of the peripheral pulmonary arterial branch was present adjacent to the respiratory bronchi. No evidence of venous thrombus or pulmonary emboli were found (EVG staining, ×100).](image)
though pulmonary vascular disease has often been described in this condition. In fact, in several reviews written between 1962 and 1981 (10–12) hypertensive pulmonary vascular disease was not mentioned. In other connective tissue diseases, such as progressive systemic sclerosis and mixed connective tissue disease, PH is relatively common. PH is also found in rare occasions in rheumatoid arthritis, dermatomyositis or primary Sjögren’s syndrome. The first report of isolated PH cases with demonstrable PH appeared in 1962 (13), and only recently several articles have been published (1–9).

Recent studies using Doppler echocardiography and right heart catheterization indicate that the incidence of PH is 14% in SLE (14). PH was diagnosed in the present patient when she was alive, based on clinical, radiological and hemodynamic evidence, and it is clear that this case fell into the group of "primary" PH as defined by the World Health Organization in 1975 (15).

As to the pathogenesis, vasoconstriction and vasculitis are proposed as the pathogenetic mechanisms of the primary PH. Factors implicated in the pathogenesis of plexogenic arteriopathy in SLE include: [1] frequent or permanent vasoconstriction, [2] vasculitis, and [3] in situ arteriolar thrombus and/or thromboembolism associated with abnormal coagulation. Arterial and venous thrombosis have been observed in 17 of 180 patients with SLE reviewed by Gladman and Stenberg (6). The lupus anticoagulant (LAC) was detected in 5 of 6 SLE patients with PH (4), 2 of whom presented with venous thrombosis. The LAC may cause hypercoagulable state and thrombotic disorder (16). The present patient had evidence of LAC and anti-cardiolipin antibodies. On autopsy, many plexiform lesions of the peripheral pulmonary arterial branches were demonstrated, but no venous thrombosis or pulmonary embolism was found.

Fibroid necrosis and vasculitis, associated with plexiform lesions, have been found in primary PH, congenital heart disease and hepatic cirrhosis. The vasculitic changes may be caused by sustained vasoconstriction including muscle necrosis and secondary inflammatory reaction (17, 18).

The cases reported by Quismorio et al (5), were of particular interest since extensive immune complex deposits were detected in the pulmonary arteries as well as in the alveolar septa. Similar deposits have been described by other authors in the lungs of patients with SLE (19) without PH and therefore, they may not be involved in the pathogenesis of PH, but merely represent the generalized immune complex deposition.

Since Raynaud’s phenomenon was present in 5 of 6 cases of PH reviewed by Nair et al (1), the sustained vasoconstriction was implicated as the pathogenic mechanism of PH. Walcott and colleagues (20), also suggested a link between Raynaud’s phenomenon and PH in connective tissue diseases after finding this association in 7 of 23 cases. The present case showed both Raynaud’s phenomenon and positive anti-cardiolipin antibody, so both factors may have contributed to the development of PH. Vasoconstriction of muscular pulmonary arteries, so-called “pulmonary Raynaud’s phenomenon” is implicated in the pathogenesis of plexiform lesions. We consider that obstinate Raynaud’s phenomenon, hyper-viscosity due to hyper-gammaglobulinemia and anti-cardiolipin antibody might have played a role in the development of PH in the present case.

References