

Li-Ju Chen¹
Hung-Chou Chang²
Ling-Ying Lu¹
Jui-Cheng Tseng¹
Jui-Chieh Hu¹
Chien-Kai Kau¹
He-Hsiung Cheng¹

¹ Allergy, Immunology and Rheumatology
Section;

² Chest Surgery Section, Kaohsiung
Veterans General Hospital, Kaohsiung,
Taiwan, R.O.C.

Case Report

Prolonged Survival After Single Lung Transplantation for Pulmonary Hypertension Secondary to Systemic Lupus Erythematosus

Pulmonary hypertension is one of the life-threatening complications of systemic lupus erythematosus, but these patients are often excluded from lung transplantation candidacy due to the nature of underlying multiple system involvement. We report a long-term survival after single lung transplantation in a case of systemic lupus erythematosus with severe pulmonary hypertension. It suggests that single lung transplantation may be considered in such patients, especially in condition of limited donor organ supply.

Key Words

pulmonary hypertension;
single lung transplantation;
systemic lupus erythematosus

Systemic lupus erythematosus is an autoimmune disease with multiple organ involvement. Part of these patients represent variable degrees of pulmonary hypertension. There are no consensus guidelines for the treatment of pulmonary hypertension secondary to connective tissue disorder, such as systemic lupus erythematosus (SLE). Lung transplantation had been reported for severe pulmonary hypertension with increasing frequency, but limited data about the long-term survival after lung transplantation for pulmonary hypertension secondary to SLE were available. Here we describe a case of SLE with long-term survival after single lung transplantation for severe pulmonary hypertension.

CASE REPORT

A 50-year-old woman with SLE was referred to our hospital in December 1996 for evaluation of pulmonary

hypertension. She was diagnosed as SLE in August 1993 on the basis of arthritis, serositis (pericardial effusion), thrombocytopenia, positive antinuclear antibody (ANA), elevated anti-double-stranded DNA, and reduced complement level. She also had symptom of Raynaud's phenomenon. Her disease activity was controlled well by prednisolone 10 mg daily and hydroxychloroquine 100 mg twice a day in the initial 3 years. But she experienced progressively worsening dyspnea for 3 months in December 1996. Transesophageal echocardiogram was done and showed pulmonary hypertension. Then she was admitted to our hospital for further evaluation.

According to the patient's report, she had an operation for ovarian tumor in 1986. She didn't drink alcohol and was a nonsmoker. There was a family history of SLE.

Physical examination disclosed mild cardiopulmonary embarrassment at rest (blood pressure: 120/88 mmHg, pulse rate: 98/min, respiratory rate: 28/min, body tem-

Received: June 11, 2003.
Accepted: October 3, 2003.

Correspondence to: Li-Ju Chen, MD, No.8-3, Alley 9, Lane 546, Houchang Road, Nantz, Kaohsiung 811, Taiwan.
Tel: +886-0937-565-585; Fax: +886-7-361-6319; E-mail: airlijuchen@yahoo.com.tw

perature: 36.2 °C), and cyanosis of peripheral limbs. She was in New York Heart Association (NYHA) class III-IV after evaluation. The cardiac examination showed fixed splitting second heart sound, and no murmur was heard. Examination of other systems showed no significant findings.

Admission laboratory data included the following values: ANA titer: 1:640 homogenous type and 1:320 speckle type; anti-dsDNA: 57 IU/mL; C3:53.9 mg/dL (reference range: 72-142 mg/dL), C4:9.53 mg/dL (12-43 mg/dL); IgG: 2800 mg/dL (135-1770 mg/dL), IgA: 522 mg/dL (61-476 mg/dL), IgM: 85.3 mg/dL (47.5-226 mg/dL); negative rheumatoid factor (< 20 IU/mL); ENA (extractable nuclear antigen) panel: positive anti-RNP (ribonucleoprotein) and anti-SSB (Sjögren's syndrome-B) antibody; positive anticardiolipin antibody: 22 GPL (G = IgG; PL = phospholipid) units/mL (> 13 positive); negative HBs Ag and anti-HCV Ab; negative Coombs test; WBC count:4090/cumm, hemoglobin: 15.5 g/dL, platelet count: 86,000/cumm; urinalysis, liver and renal function were normal; negative VDRL and HIV test; arterial blood gas analysis at room air: PH: 7.485, PO₂: 40 mmHg, PCO₂: 24.8 mmHg, serum bicarbonate: 18.5 mmol/L, saturation: 74.8%.

A chest X-ray film showed enlarged heart shadow with mild pulmonary congestion, suggesting pericardial effusion. An ECG disclosed normal sinus rhythm, right atrium enlargement and right ventricle hypertrophy. A pulmonary function test showed normal ventilatory function and mild reduction of gas exchange. A sonogram examination of abdomen showed borderline splenomegaly and normal kidney size. She received transesophageal echocardiogram examination which showed right ventricle global hypokinesis with right ventricle failure but preserved left ventricle systolic function and present patent foramen ovale with right-to-left shunt. A ventilation-perfusion scan was done which disclosed small nonsegmental perfusion defect in the lingual portion of the left upper lobe, maybe due to fissure sign, and moderate ventilation defect in the left apex, compatible with right-to-left shunt.

We consulted the chest surgery section and lung transplantation was planned. So she also underwent cardiac catheterization with the following findings. The pulmonary artery pressure was 106/37 mmHg, with a mean pressure of 59 mmHg. Cardiac output was 1.8

L/min, with an index of 1.1 L/min/m². The CAG (coronary arteriogram) was normal. The results were concluded as severe pulmonary hypertension with opening of patent foramen ovale and right- to-left shunt.

The patient underwent left lung transplantation in January 1997 with smooth operative course. She received immunosuppressive agents including methylprednisolone, azathioprine, cyclosporine, antithymocyte globulin and intravenous PGE1 during immediately postoperative days. Routine prophylactic antibiotics including ceftazidime, clindamycin were given for 1 week. Gancyclovir and Baktar[®] were also given to prevent cytomegalovirus (CMV) and *pneumocystis carinii*, respectively. Low grade fever was noted in the initial 3 days, but was thought to be due to surgical intervention for negative bacteriologic studies from the recipient. Her pulmonary artery pressure reduced to 48/20 mmHg in 1 week after lung transplantation. The lung perfusion scan showed 14% over the right lung and 86% over the left lung at the 2 weeks after operation. She was treated with prednisolone 20 mg daily, Baktar[®] 2 tablets every 6 hours, azathioprine 50 mg daily, and cyclosporine 275 mg every 12 hours after discharge.

The patient was admitted in June 1997 due to an upper respiratory tract infection event. Then she had another admission in August 1998 because of poorly controlled hypertension related to cyclosporine, and her trough cyclosporine level was 260 ng/mL under the dose of cyclosporine 125 mg bid. The patient had lupus activity flare with malar rash and leukopenia in October 1998, and recovered after intravenous G-CSF and methylprednisolone treatment.

She suffered from progressive effort dyspnea in October 2001. The chest X-ray film showed no remarkable change. A ventilation perfusion scan showed diffusely decreased perfusion of right lung, favoring pulmonary hypertension-related. The perfusion ratio was 18.9% over the right lung and 81.1% over left lung. The pulmonary function test disclosed normal ventilatory function and severe reduction of gas exchange. The cardiac echo showed preserved left ventricular systolic function, and peak systolic pressure gradient across the tricuspid valve was around 47 mmHg. A gallium inflammation scan of the lung showed negative finding. HRCT of the chest revealed progressive air trapping in the left lung, which might be an indirect sign of chronic rejection, and

bronchiolitis obliterans of the left lower lobe was suspected. Then bronchoscopic biopsy was done and disclosed mild airway inflammation (grade B2) with negative CMV immunostain. No evident pathogen was found from biopsy tissue. Supportive care was performed, and the patient's symptoms gradually resolved later. The patient has just passed the 6-year point since her transplantation. She is in NYHA class I now. Pulmonary function tests have shown stable mild airflow obstruction, with FEV1 of 1.87 L (85% of predicted), and FVC of 2.74 L (103% of predicted). An echocardiogram revealed preserved left ventricular systolic function, mild right ventricular (RV) hypertrophy with mild RV systolic dysfunction, and peak systolic pressure gradient across the tricuspid valve: 63 mmHg. She has stable immunoserologic status now. The current medications included prednisolone 10 mg daily, ciclosporine 100 mg daily, Baktar[®] 2 tablets daily, labetalol 200 mg twice daily, amlodipine 5 mg daily. Her trough ciclosporine level was kept around 150-200 ng/mL.

DISCUSSION

Pulmonary hypertension is one of the serious and life-threatening complications associated with connective tissue disease. It happens with variable prevalence in different connective tissue diseases. In SLE patients, the prevalence rate ranges from 0.5% to 14%.¹ The underlying mechanisms causing pulmonary hypertension are still not elucidated, but vasculitis, antiphospholipid antibody syndrome, severe interstitial lung disease and pulmonary vasoconstriction are generally thought to be the possible pathophysiology.² There is strong association between Raynaud's phenomenon and pulmonary hypertension secondary to connective tissue disease, as was seen in our patient.

There are no consensus guidelines about the treatment of pulmonary hypertension secondary to connective tissue disease now. The major therapeutic strategies include anticoagulant therapy, immunosuppressive therapy, and oral or intravenous vasodilator therapy. The minor measures include oxygen therapy, diuretics and digoxin. Anticoagulant therapy is used for patients with antiphospholipid antibody syndrome and high risk for

thromboembolic event. Some publications report that immunosuppressive therapy is quite helpful for pulmonary hypertension secondary to connective tissue disease, and the most efficient treatment seems to be corticosteroid with bolus cyclophosphamide infusion. The intravenous vasodilator therapies such as epoprostenol (PGI₂) or iloprost (PGI₂ analogue) are used for patients with poor response to oral vasodilator therapies including calcium channel blocker or ACE inhibitor.¹ Surgical interventions should be considered in end-stage right heart failure refractory to medical treatment. Lung or heart-lung transplantation for pulmonary hypertension provide significant improvement in both quality of life and physiologic aspects.³

Lung transplantation for severe pulmonary hypertension secondary to connective tissue disease is controversial due to the nature of underlying multiple system involvement. Prolonged survival after heart-lung transplantation in SLE with pulmonary hypertension was reported by Levy *et al.*⁴ Now single lung transplantation is performed for pulmonary hypertension with increasing frequency and success. Single lung transplantation has the advantages of more recipient per donor, shorter waiting period, simple surgical procedure, early normalization of hemodynamics, less graft-related coronary artery disease and less bronchiolitis obliterans.^{5,6} But disadvantages of single lung transplantation for pulmonary hypertension were also suggested, such as no significant improvement in cardiac index, more frequent post-transplantation pulmonary edema, more severe hemodynamic instability, significant ventilation/perfusion mismatch, higher graft-related mortality, and significantly poorer graft survival.⁷

Long-term survival after single lung transplantation for pulmonary hypertension has been reported.⁸ Short-term survival after lung transplantation depends on complications of surgical procedure. Long-term survival is associated with complications specific to lung transplantation and immunosuppression, such as infection, rejection and bronchiolitis obliterans.

Patients with pulmonary hypertension who do not undergo lung transplantation eventually die of cardiovascular events such as sudden death, heart failure, and arrhythmia. The long-term survival of our patient suggests that pulmonary hypertension secondary to connective

tive tissue disease is not necessarily absolute contraindication for lung transplantation. Lung transplantation including single lung transplantation still can be considered if the patient has relatively quiescent disease status and no involvement of other major organs, such as kidney or liver.

Long-term survival depends on an integral transplant program including appropriate patient selection, close post-operative monitoring, and regular clinic follow-up. The practical roles of single lung transplantation for pulmonary hypertension secondary to connective tissue disorder need more investigation in the future.

REFERENCES

1. Sanchez O, Humbert M, Sitbon O, Simonneau G. Treatment of pulmonary hypertension secondary to connective tissue disease. *Thorax* 1999;54:237-7.
2. Horn CA. Pulmonary hypertension and autoimmune disease. *Chest* 1993;104:279-80.
3. Mendeloff EN, Meyers BF, Sundt TM, Guthrie TJ, Sweet SC, de L, *et al.* Lung transplantation for pulmonary vascular disease. *Ann Thorac Surg* 2002;73:209-19.
4. Levy RD, Guerraty AJ, Yacoub MH, Loertscher R. Prolonged survival after heart-lung transplantation in systemic lupus erythematosus. *Chest* 1993;104:1903-5.
5. Frist WH, Carmichael LC, Loyd JE, Merrill WH, Stewart JR, Biggs VJ, *et al.* Transplantation for pulmonary hypertension. *Transplant Proc* 1993;25:1159-61.
6. Pasque MK, Trulock EP, Cooper JD, Triantafillou AN, Huddleston CB, Rosenbloom M, *et al.* Single lung transplantation for pulmonary hypertension: Single institution experience in 34 patients. *Circulation* 1995;92:2252-8.
7. Bando K, Armitage JM, Paradis IL, Keenan RJ, Hardesty RL, Konishi H, *et al.* Indications for and results of single, bilateral, and heart-lung transplantation for pulmonary hypertension. *J Thorac Cardiovasc Surg* 1994;108:1056-65.
8. Frist WH, Loyd JE, Merrill WH, Stewart JR, Dummer JS, Hoff SJ, *et al.* Single lung transplantation: a temporal look at rejection, infection, and survival. *Am Surg* 1994;60:94-102.