Prolonged Survival After Heart-Lung Transplantation in Systemic Lupus Erythematosus*

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Patients with multisystem involvement of connective tissue disorders are generally excluded from consideration for heart-lung and lung transplantation because of profound donor organ shortages. A 23-year-old woman with systemic lupus erythematosus (SLE) was referred for evaluation of severe, progressive pulmonary hypertension. She underwent an uneventful heart-lung transplant and received cyclosporine A, azathioprine, and prednisone on a long-term basis. Bronchiolitis obliterans resulted in the development of moderate airflow obstruction 18 months after transplantation, but the process was stabilized with augmented immunosuppression consisting of high-dose parenterally administered corticosteroids, and subsequently a course of antithymocyte globulin. Four years after transplantation, despite the persistence of reduced complement levels, the patient remains functionally well without clinical manifestations of SLE. This patient’s long-term successful outcome indicates that connective tissue disorders such as SLE do not necessarily represent absolute contraindications to heart-lung and lung transplantation.

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SLE = systemic lupus erythematosus

Patients with multisystem diseases generally have been excluded from consideration for heart-lung and lung transplantation. The major reason cited for this policy is to allocate a limited number of donor organs to those recipients with the best anticipated chances for long-term survival. It would be desirable to be able to offer these treatment options to patients suffering from advanced complications of connective tissue diseases such as systemic lupus erythematosus (SLE), especially since those afflicted are often young. In this report, we describe the long-term survival of a young woman with SLE who underwent combined heart-lung transplantation for severe pulmonary hypertension.

CASE REPORT

A 23-year-old woman was referred to the McGill University Heart-Lung Transplant Program in 1987 with severe pulmonary hypertension. In 1974, at age 10 years, she had presented with fever, alopecia, buccal ulcerations, and a malar skin rash. There was no history of Raynaud’s phenomenon, drug use, or family history of cardiovascular or connective tissue disease. Laboratory investigations showed a weakly positive antinuclear antibody (homogeneous pattern), positive anti-DNA and anti-ribonuclear protein antibodies, and a reduced serum C3 level of 0.52 g/L (normal, 0.55 to 1.20 g/L). Biopsy of the rash was consistent with a diagnosis of SLE. The patient had a good response to prednisone, the dosage of which was then tapered off after 2 years.

The patient was rehospitalized in 1981 with fever, arthralgia, headache, a confusional state, and lymphopenia. An EEG showed focal abnormalities consistent with encephalitis. The manifestations responded to a further course of prednisone.

The patient remained well on a dose of 5 to 10 mg of prednisone daily until 1985, when she noted progressive exertional dyspnea. She was found to have an accentuated second heart sound and mild peripheral edema. At right heart catheterization, wedge pressure was 12 mm Hg; right atrial pressure, 5 mm Hg; pulmonary artery pressure, 80/48 mm Hg; cardiac index, 1.04 L/min/m²; and pulmonary vascular resistance, 1,829 dynes/sec/cm⁵. Systemic blood pressure fell in response to administration of sublingual nifedipine.

At the time of referral to the transplant program in 1987, the patient was experiencing dyspnea while walking up six stairs. Blood pressure was 90/65 mm Hg and heart rate 100 beats per minute. Jugular venous pressure was normal. Cardiac examination showed a right ventricular heave, a loud P₂, and a right-sided S₃. Complete blood cell count, platelet count, prothrombin time, partial thromboplatin time, blood chemistry studies, and serum protein electrophoresis were normal. The serum C3 value was low at 0.53 g/L (normal, 0.55 to 1.20 g/L) and C4 level was 0.7 g/L (normal, 0.20 to 0.59 g/L). Urinalysis was normal, 24-h urinary protein excretion was 0.11 g, and the creatinine clearance was 52 mL/min. An echocardiogram demonstrated severe pulmonary hypertension, right ventricular hypertrophy without tricuspid regurgitation, and a small pericardial effusion. Nuclear ventilation and perfusion scans disclosed low probability for thromboembolic disease. Radionuclide angiography estimated right ventricular ejection fraction at 60 percent. Arterial blood gas analysis (with the patient breathing room air) showed pH 7.49, Pco₂ 69 mm Hg, HCO₃⁻ 24 mm Hg, and serum bicarbonate 19 mmol/L. Pulmonary function tests were normal except for single-breath carbon monoxide diffusing capacity of 68 percent predicted. The patient was unable to perform an exercise test due to severe breathlessness.

In view of a long waiting list and concerns regarding the multisystem nature of the disease, the patient was turned down for transplantation by the McGill University Heart-Lung Transplant Committee. She was referred to the transplant program at the Harefield Hospital in the United Kingdom, where she was accepted as a recipient.

The patient underwent heart-lung transplantation in March 1988. Pathologic examination of the explanted lungs revealed a pleurogenic pulmonary arteriopathy without evidence of thromboembolism or pulmonary fibrosis. The postoperative course was complicated in the month after surgery by two episodes of acute rejection which were treated with high doses of corticosteroids. The patient returned to Canada 2 months after transplantation while she was receiving therapy with cyclosporine A, azathioprine, and prednisone. Persistent neutropenia resulted in azathioprine being discontinued for 6 months; however, it was then gradually reintroduced without problems. One year after transplantation, immunosuppression therapy consisted of cyclosporine A, 4 mg/kg/d; azathioprine, 1 mg/kg/d; and prednisone, 0.25 mg/kg on alternate days. Eighteen months after transplantation, the patient noted new onset of dyspnea and airflow obstruction became evident on pulmonary function tests (Fig 1). Bronchiolitis obliterans was documented by transbronchial biopsies. Lung function stabilized after treatment with high doses of corticosteroids, and subsequently, with a course of antithymocyte globulin.

For the past 2 years, the patient’s course has remained unremarkable without clinical manifestations of SLE. She has recently passed the 4-year point since her transplantation. Physical examination is normal except for mild systemic hypertension which is controlled with nifedipine. A chest radiograph, ECG, echocardiogram, and coronary arteriogram are normal, and the pulmonary artery pres-
sures are 24/12 mm Hg. Complete blood cell count, lipids, profile, liver function tests, and serum biochemistry studies are normal, with the exception of a serum creatinine level of 133 µmol/L (normal, 55 to 110 µmol/L). Creatinine clearance level is 84 ml/min. Complement levels remain below normal with a serum C3 value of 0.50 g/L (normal, 0.55 to 1.20 g/L) and a serum C4 level of 0.13 g/L (normal, 0.20 to 0.59 g/L). Pulmonary function tests have shown moderate airflow obstruction (Fig 1), with FEV₁ of 1.98 L (62 percent predicted) and forced vital capacity of 3.07 L (81 percent predicted). Maximum oxygen uptake on incremental bicycle exercise testing was 21 ml/kg/min (65 percent of predicted), which is in the range generally seen after heart-lung and lung transplantation. She is currently completing a university degree in pharmacy, has no functional restrictions, and travels frequently.

**DISCUSSION**

Plexogenic pulmonary hypertension is an uncommon complication of SLE which is of uncertain etiology.² It often is associated with a devastating course, both in the "primary" variety,¹ as well as when seen in association with SLE.³ Although the natural history may be modified in some patients with the use of vasodilators,⁴ their overall impact on long-term survival probably is limited in most cases.³

Despite heart-lung and lung transplantation being associated with substantial morbidity and mortality,⁵ these interventions can offer a chance for long-term survival with a reasonable quality of life to selected patients with advanced cardiopulmonary disorders. Because of the small number of donor organs available, transplantation centers must apply strict criteria to recipient selection. Patients with connective tissue diseases, by virtue of their multisystem involvement, generally have been excluded from consideration as suitable candidates.¹ This is in part by virtue of the nephrotoxic and hepatotoxic side effects of cyclosporine A in patients with concurrent involvement from the underlying disease. Furthermore, many transplant groups consider that the natural history of connective tissue diseases such as SLE render the patients unacceptable candidates.⁷ In fact, a review of the existing literature reveals only one other patient with SLE who underwent heart-lung or lung transplantation;⁸ however, details with respect to this latter patient’s course were not provided.

A general policy of careful screening of potential recipients seems judicious in view of the relatively small size of the donor pool. However, transplantation may be a reasonable consideration in certain patients with multisystem disorders who have relative quiescence of the disease process in organs other than that to be transplanted. In fact, experience with renal transplantation in patients with lupus nephritis indicates that a good outcome (ie, absence of recurrence) can be anticipated, especially in those patients without antinuclear and anti-DNA antibodies prior to transplantation.⁹ A further consideration is the potential therapeutic activity of the routine posttransplantation immunosuppressive regimen in connective tissue diseases. The value of prednisone and cytotoxic drugs, such as azathioprine, is well established in the treatment of SLE.¹⁰ In contrast, however, the effectiveness of cyclosporine A in SLE is uncertain.¹¹

In conclusion, the long-term survival of our patient suggests that multisystem involvement with a connective tissue disease is not necessarily an absolute contraindication to heart-lung or lung transplantation. It is hoped that our findings will stimulate further studies to clarify the precise role of transplantation in connective tissue disorders as well as the therapeutic effects of immnosuppression in these patients.

**REFERENCES**

Severe Respiratory Failure Caused by Recurrent Pulmonary Hemorrhage in Takayasu’s Arteritis*

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We encountered a 52-year-old man with Takayasu’s disease (pulueseless disease) and severe respiratory failure due to recurrent pulmonary hemorrhage. Angiography revealed occlusion of multiple branches of the pulmonary artery, which were filled via collateral circulation from the coronary, intercostal, and intermammary arteries. This is a rare case that causes massive pulmonary bleeding and respiratory failure in Takayasu’s arteritis. 

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Pulueseless disease (Takayasu’s arteritis) occurs worldwide, although the majority of cases have been reported from Asia and Africa and most large series consist of Asians, with a heavy predilection for women. This is a systemic disease with generalized as well as local symptoms. More than half the patients with this disease have pulmonary artery involvement. Local symptoms in pulmonary artery involvement are subtle such as a hemoptysis. We report a case of severe respiratory failure caused by recurrent pulmonary hemorrhage in Takayasu’s arteritis.

CASE REPORT

A 52-year-old man was admitted to the hospital with acute respiratory distress. He had received the diagnosis of pulseless disease 4 years prior to this, due to the absence of the right radial artery pulsation and bruits of bilateral carotid arteries. His condition was stable until severe and progressive dyspnea awoke him from his sleep.

On physical examination, he appeared to be in respiratory distress. The blood pressure was 209/90 mm Hg as measured by arterial transducer applied to the right femoral artery. The pulse rate was 140 beats per minute, and the respiratory rate was 40 breaths per minute. His body temperature was 37.1°C. Bruits were audible at both carotid arteries and the mid-abdomen. Harsh systolic heart murmur was audible in the third left sternal border. His breath sounds were slightly wheezy and crackled in both lungs.

The hemoglobin value was 9.8 g/dl; the WBC count was 22,500/mm³, with 70 percent neutrophils, and the platelet count was 43.5 × 10⁹/mm³. Arterial blood gas analysis disclosed that partial pressure of oxygen was 31.0 mm Hg; partial pressure of carbon dioxide, 43.5 mm Hg; and pH, 7.43. A chest x-ray film showed bilateral consolidation, especially at the right upper middle lobe.

He was intubated and ventilated by a respirator under positive end-expiratory pressure. The pulmonary arterial pressure was 10 to 43 mm Hg. Massive blood was aspirated from the endotracheal tube and recurrent bleeding was observed during hospitalization.

Selective angiography showed obstruction of the left common carotid artery, the right subclavian artery, and the bilateral bronchial arteries, and a marked stenosis of the left subclavian artery. The celiac artery and the superior mesenteric artery also were occluded, and both were filled by the meandering artery from the inferior mesenteric artery. Pulmonary arteriography showed complete occlusion of vessels to the right middle and lower lobes and the left lingual lobe, without signs of either cutting off or thrombus (Fig 1).

Bronchial arteries were communicated with bilateral coronary arteries and filled the right middle lung. Aortography showed an enlarged intercostal artery and an intermammary artery supplying both lungs (Fig 2). His bleeding gradually improved with antihypertensive drug treatment and supportive therapy.

DISCUSSION

Clinical signs and symptoms of pulmonary artery involvement in Takayasu’s arteritis are usually subtle and rarely appreciated in conditions such as minor little hemoptysis or dyspnea. The incidence of pulmonary artery involvement has been reported in 118 out of 210 patients. However, there has been no reported case that has been asymptomatic, presenting with an abrupt onset of respiratory failure. In our patient, acute respiratory distress was caused by massive recurrent pulmonary hemorrhage. It is considered that the abnormality of the pulmonary arteries is chronic, because rich collateral circulation and mild elevation of the pulmonary arterial pressure were present. Pulmonary arteries were obstructed in many vessels, and the bronchial artery also was obstructed at the ostium. Lung perfusion may have been filled by an enlarged intercostal artery, intermammary artery, and both coronary arteries with connection to bronchial arteries. So it is less likely that pulmonary hemorrhage was due to occlusion of pulmonary arteries. There are three suspected causes for his bleeding: rupture of collateral vessels, rupture of microaneurysm due to

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