

LUNG TRANSPLANTATION FOR LYMPHANGIOLEIOMYOMATOSIS

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ABSTRACT

Background Lymphangioleiomyomatosis is a rare disease of unknown origin that usually leads to progressive deterioration of lung function and eventual death from respiratory failure. It occurs in women of reproductive age and people with tuberous sclerosis. Lung transplantation is a recent therapeutic approach.

Methods We conducted a retrospective study by questionnaire of 34 patients, treated at 16 transplantation centers, who underwent lung transplantation for end-stage lymphangioleiomyomatosis between 1983 and 1995.

Results Of the 34 patients, 27 received single-lung transplants; 6, bilateral transplants; and 1, a heart-lung transplant. As of August 31, 1995, the actuarial survival calculated by the Kaplan-Meier method was 69 percent after one year and 58 percent after two years. Eighteen patients were alive a mean (\pm SD) of 33 ± 20 months (range, 3 to 74) after transplantation. Forced expiratory volume in one second increased from 24 ± 12 percent of the predicted value before transplantation to 48 ± 16 percent six months after transplantation. Five early deaths (within one month) were due to hemorrhage (in one patient), acute lung injury (in three), and dehiscence of the bronchial anastomosis (in one). Eleven late deaths (after one month) were due to infections (in eight patients), bronchiolitis obliterans (in two), and metastatic nephroblastoma (in one). Disease-associated problems were extensive pleural adhesions in 18 patients, leading to moderate-to-severe intraoperative hemorrhage in 4; pneumothorax in the native lung after single-lung transplantation in 6 patients; postoperative chylothorax in 3; and recurrent lymphangioleiomyomatosis in the allograft in 1 patient, who died of disseminated aspergillosis.

Conclusions Although disease-related complications are frequent, lung transplantation can be a valuable therapy for patients with end-stage lymphangioleiomyomatosis. (N Engl J Med 1996;335:1275-80.)

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LYMPHANGIOLEIOMYOMATOSIS is a rare disease of unknown origin, first described in 1937.¹ It occurs in women of reproductive age and in patients of both sexes affected by tuberous sclerosis. The pulmonary complications are due to a hamartomatous proliferation of smooth-muscle cells preferentially along the bronchovascular structures, resulting in obliteration of the airways and the consecutive development of

cysts in the lungs.^{2,3} The disease is usually progressive, and patients die of respiratory failure.^{4,5}

The predominant occurrence of lymphangioleiomyomatosis in women during their reproductive years suggests hormonal involvement. Treatment is therefore targeted against the production and effects of estrogens⁶⁻¹¹ but remains largely ineffective. In recent years, lung transplantation has become a therapeutic approach.¹²⁻¹⁸ However, most lung-transplantation centers have had experience with only one or a few patients each. We therefore conducted an international survey to obtain information on transplantation for lymphangioleiomyomatosis.

METHODS

From November 1992 to August 1995, we performed 30 lung transplantations at the University Hospital of Zurich, Switzerland,¹⁹ 4 of them (13 percent) for lymphangioleiomyomatosis. In August 1994, questionnaires were sent to 18 other lung-transplantation centers identified through the International Lung Transplant Registry, in St. Louis, or by personal communication. By August 1995, 15 centers had responded. The three centers that did not respond had performed transplantations in five patients. Five of the patients described here have been included in previous reports.^{12,13,15,17,18,20,21} Data on two patients were incomplete and were excluded from some calculations. Data are expressed as means \pm SD. Survival was calculated with the use of Kaplan-Meier statistics.²²

RESULTS

Sixteen transplantation centers, including ours (see the Appendix), reported on 34 patients who received transplants for end-stage pulmonary lymphangioleiomyomatosis. All were women. The mean age at the onset of symptoms was 29 ± 8 years (range, 5 to 44). The age at the diagnosis of lymphangioleiomyomatosis was 34 ± 10 years (range, 8 to 55). The interval between the first symptoms and diagnosis was 5 ± 5 years (range, 0 to 20). The age at transplantation was 40 ± 9 years (range, 24 to 55). The interval between the onset of symptoms and transplantation was 11 ± 6 years (range, 3 to 24).

The clinical and radiologic characteristics of the patients at the time of diagnosis are summarized in Table 1. Almost all the patients had shortness of breath. Typical features were a history of pneumothorax (25 patients), chylothorax (7), and chylous ascites (1). All available chest radiographs demonstrated pathologic

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TABLE 1. CHARACTERISTICS OF THE PATIENTS WITH LYMPHANGIOLEIOMYOMATOSIS AT THE TIME OF DIAGNOSIS.

CHARACTERISTIC	VALUE*	PER-CENT
Clinical		
Shortness of breath	30/32	93
History of pneumothorax	25/32	78
Cough	13/32	41
Chest pain	8/32	25
History of chylothorax	7/32	22
Hemoptysis	7/32	22
Clubbing	4/32	13
History of chylous ascites	1/32	3
On chest radiography		
Hyperinflation	14/32	44
Cysts and bullae	13/32	41
Reticulonodular shadows	9/32	28
Pleural effusion	5/32	16
Pneumothorax	2/32	6
On CT of the thorax		
Bilateral lung cysts	24/24	100
Hyperinflation	12/24	50
Pleural effusion	4/24	16
Hilar or mediastinal lymphadenopathy	3/24	13
Pneumothorax	2/24	8
Extrapulmonary lymphangioleiomyomatosis†		
Lymph-node involvement (5 retro-peritoneal, 3 mediastinal)	8/30	27
Renal angiomyolipoma (3 unilateral, 2 bilateral)	5/30	17
Para-aortic abdominal angiomyolipoma	1/30	3
Thoracic angiomyolipoma	1/30	3
Pelvic myoma	1/30	3
Ocular involvement	1/30	3

*Values are ratios of the number of patients with positive findings to the total number of patients for whom data were available. Some patients had multiple findings.

†Three patients with tuberous sclerosis were excluded.

findings such as hyperinflation (14 patients), cysts and bullae (13), and reticulonodular shadows (9).

Before lung transplantation, 26 patients had severe obstructive ventilatory defects (Table 2). Three patients had restrictive patterns, and an additional three had combined obstructive and restrictive patterns. Carbon monoxide diffusing capacity was severely reduced in all the patients for whom data were available. The diagnosis of lymphangioleiomyomatosis was made in 23 patients by surgical lung biopsy, in 9 by high-resolution computed tomography (CT), and in 1 as an incidental finding (in the explanted lung of a patient with end-stage pulmonary disease of unknown origin). Data were lacking for one patient. The presence (+) or absence (−) of hormone receptors was reported in seven patients, as follows (given as progesterone/estrogen): +/+ (1 patient), +/- (2 patients), -/+ (2 patients), and -/- (2 patients).

In three patients, pulmonary lymphangioleiomyomatosis coincided with tuberous sclerosis. All three

TABLE 2. PULMONARY FUNCTION AT THE TIME OF EVALUATION FOR LUNG TRANSPLANTATION.*

VARIABLE	VALUE
Obstructive pattern†	
No. of patients (%)	26/32 (81.2)
FEV ₁ — % of predicted (range)	24±12 (13–66)
FEV ₁ /FVC — % (range)	38±12 (20–61)
Restrictive pattern — no. of patients (%)‡	3/32 (9.4)
Combined obstructive and restrictive pattern — no. of patients (%)	3/32 (9.4)
Decreased carbon monoxide diffusing capacity§	
No. of patients (%)	25/25 (100)
% of predicted value (range)	26±13 (10–59)
Hypoxemia¶	
No. of patients (%)	24/25 (96)
Arterial PO ₂ — mm Hg (range)	56±11 (41–79)
Hypercapnia — no. of patients (%)	3/25 (12)

*Fractional values are ratios of the numbers of patients with positive findings to the total numbers of patients for whom data were available. Plus-minus values are means ±SD. The total number of patients does not equal 34 because data were missing for some subjects (see the Methods section). FEV₁ denotes forced expiratory volume in one second, FVC forced vital capacity, TLC total lung capacity, and PO₂ partial pressure of oxygen.

†An obstructive pattern is defined as a total lung capacity ≥80 percent of the predicted value, and an FEV₁/FVC ratio <75 percent.

‡A restrictive pattern is defined as a total lung capacity <80 percent of the predicted value, and an FEV₁/FVC ratio ≥75 percent.

§A normal carbon monoxide diffusing capacity is ≥80 percent of the predicted value.

¶Hypoxemia is defined as a partial pressure of arterial oxygen <80 mm Hg. To convert values for partial pressure of oxygen to kilopascals, multiply by 0.133.

||Hypercapnia is defined as a partial pressure of arterial carbon dioxide >45 mm Hg.

had kidney, skin, and cerebral involvement. In addition, one of them had cardiac, bone, and liver hamartomas. The age at the onset of pulmonary symptoms in these three patients was between 21 and 27 years, and the age at transplantation was between 23 and 38 years.

Extrapulmonary manifestations of lymphangioleiomyomatosis (Table 1) were lymph-node involvement in eight patients, renal angiomyolipomas in five, para-aortic abdominal angiomyolipoma in one, and thoracic angiomyolipoma in one. As of August 1995, these extrapulmonary manifestations had caused no complications, either during surgery or later.

Before lung transplantation, all the patients had undergone at least one trial of medical treatment. Sixteen had been treated with steroids, 23 with progesterone, and 9 with antiestrogens. Five had undergone ovariectomy, and one had received a synthetic analogue of luteinizing hormone-releasing hormone. Seventeen patients had received more than one treatment.

The lung transplantations were performed between 1983 and 1995. Twenty-seven patients received single-lung transplants (13 right lungs and 14 left lungs). Bilateral lung transplantation was per-

formed in six, and one received a heart–lung transplant. In four single and five bilateral transplantation procedures, cardiopulmonary bypass was necessary.

Extensive pleural adhesions caused the main intraoperative problems (Table 3). About half the patients had substantial adhesions, which were judged on clinical grounds to be moderate in 8 cases and severe in 10 cases. The adhesions were reported to be due to the lymphangioleiomyomatosis itself in 13 patients and to lymphangioleiomyomatosis as well as prior pleurectomy after spontaneous pneumothorax in 5. Moderate-to-severe hemorrhage occurred in four patients, leading to intraoperative death in one patient and requiring repeat thoracotomy in two. Involvement of the mediastinal lymph nodes was not reported to have caused surgical problems.

The actuarial one-year and two-year survival after lung transplantation (Fig. 1) was 69 percent and 58 percent, respectively. Eighteen patients (53 percent) were alive as of August 31, 1995, which was 33 ± 20 months (range, 3 to 74) after transplantation. The five early deaths (within one month) were due to acute lung injury (three patients), hemorrhage (one patient), and dehiscence of the bronchial anastomosis with sepsis (one patient). Eleven patients died 2 to 43 months after transplantation because of infections (eight patients), bronchiolitis obliterans (two patients), and metastatic nephroblastoma transferred by the lung allograft²⁰ (one patient). Four of the eight patients who died of infection had previously received augmented immunosuppression for bronchiolitis obliterans (this therapy consisted of repeated steroid pulses, antithymocyte globulins or anti-CD3 monoclonal antibodies, and augmentation of the maintenance regimen for immunosuppression, which was a combination of prednisone, azathioprine, and cyclosporine).

The forced expiratory volume in one second (FEV₁) was 48 ± 16 percent of the predicted value 6 months after surgery (range, 24 percent to 105 percent; reported in 23 of 25 survivors) and 49 ± 19 percent of the predicted value 12 months after transplantation (range, 25 percent to 115 percent; reported in 20 of 21 survivors). The FEV₁ was 46 ± 16 percent of the predicted value after six months (range, 24 percent to 105 percent) in 20 of the 22 surviving single-lung–transplant recipients, and 55, 61, and 89 percent of the predicted value in the 3 surviving patients with bilateral transplants.

Postoperative complications (Table 4) consisted of 35 episodes of pneumonia and 37 episodes of acute rejection in the 29 patients surviving more than one month (1.3 episodes per patient). Two patients had invasive aspergillosis of the native lung. One of them died, and another underwent pneumonectomy, which was successful. Bronchiolitis obliterans was found in 6 of the 18 surviving patients; in 1 patient, it was severe.

TABLE 3. PREVIOUS SURGERY AND TRANSPLANTATION-SPECIFIC SURGICAL PROBLEMS.

VARIABLE	VALUE*	PERCENT
Previous surgery		
Pleurectomy (6 unilateral, 1 bilateral)	7/33	21
Pleurodesis (3 unilateral, 3 bilateral)	6/33	18
Surgical lung biopsy	23/33	69
Intraoperative problems		
Moderate or severe adhesions	18/33	54
Due to lymphangioleiomyomatosis	13/18	
Due to previous pleurectomy and lymphangioleiomyomatosis	5/18	
Moderate-to-severe hemorrhage	4/33†	12
Postoperative problems		
Reperfusion injury	2/33	6
Bronchial stenosis or dehiscence	6/33	18
Hemothorax	2/33	6
Hemorrhage due to omentopexy	1/33	3
Left phrenic-nerve paralysis	2/33	6
Cerebral embolism	1/33	3

*Values are ratios of the numbers of patients with positive findings or complications to the total numbers of patients for whom data were available. The total number of patients does not equal 34, since data were missing for 1 patient. Some patients had multiple findings.

†One patient died during surgery, and two required a second thoracotomy.

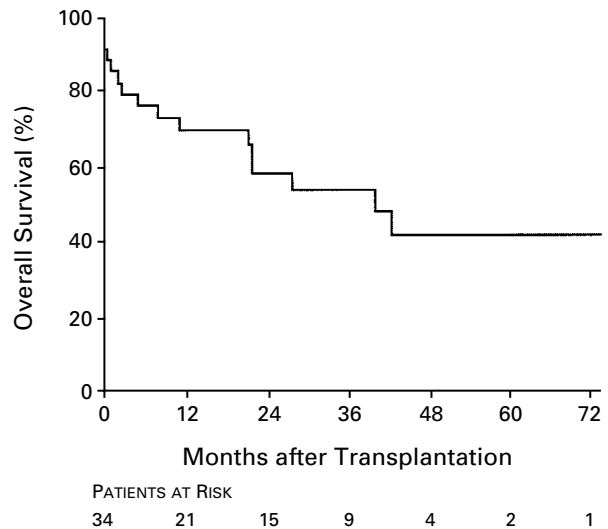


Figure 1. Overall Survival (Kaplan–Meier Curve) after Lung Transplantation in 34 Patients with Lymphangioleiomyomatosis.

The most important post-transplantation complications of lymphangioleiomyomatosis were six episodes of pneumothorax in the native lung after single-lung transplantation in five patients, and chylothorax in three patients. In one patient, a right-sided chylothorax occurred eight weeks after bilateral lung transplantation and resolved after thoracic-duct ligation. Another patient had undergone thoracic-duct ligation for chylothorax before transplantation.

TABLE 4. COMPLICATIONS AFTER LUNG TRANSPLANTATION.

EVENT	NO. OF EPISODES	NO. OF PATIENTS
Pneumonia*	35	18
Bacterial	12	9
Cytomegalovirus	10	7
Other viruses	4	4
Aspergillus†	5	5
<i>Pneumocystis carinii</i>	2	2
Nocardia	1	1
<i>Mycobacterium avium</i> complex	1	1
Acute rejection episodes (in patients surviving >1 month)	37	28
Mean number of acute rejection episodes per patient	1.3	
Bronchiolitis obliterans (in 18 surviving patients)	6	6
Complications specific to lymphangioleiomyomatosis	10	9
Pneumothorax after single-lung transplantation (native lung)	6	5
Need for chest-tube drainage	5	4
Chylothorax	3	3
Recurrence of lymphangioleiomyomatosis in allograft	1	1
Other complications‡	8	8

*Numbers for patients with pneumonia do not add up to the totals shown because some patients had multiple complications.

†Invasive aspergillosis occurred in the transplanted lung in three patients and in the native lung in two patients.

‡The following complications occurred in one patient each: bilateral cerebral cortical ischemia, colitis due to *Clostridium difficile*, encephalitis of unknown origin, urosepsis, recurrent pneumatoxis coli, metastatic nephroblastoma, allograft lymphoma, and pulmonary embolism.

Nevertheless, a right-sided chylothorax developed in this patient after right single-lung transplantation and was successfully treated with thoracostomy and a diet containing medium-chain triglycerides. The third patient had a large right-sided chylothorax before receiving a heart–lung transplant; the chylothorax was evacuated intraoperatively. A left-sided chylothorax developed postoperatively in this patient and was managed successfully by needle aspiration. Recurrent lymphangioleiomyomatosis in the lung allograft was found at autopsy in one patient, who died of disseminated aspergillus infection.¹⁵

With the exclusion of the 5 patients who died early after transplantation and the 3 with tuberous sclerosis, hormonal treatment was continued after transplantation in 8 patients at four centers and was discontinued in 18 patients at nine centers.

DISCUSSION

Our survey demonstrates the value of lung transplantation in patients with end-stage lymphangioleiomyomatosis, taking into account the various problems associated with this disease. The first successful transplantation for lymphangioleiomyomatosis — a combined heart–lung transplantation — was performed in 1983.^{12,17} A single-lung transplantation

was performed in 1988, in one of the patients included in our survey.^{13,14} Our aim was to use pooled data from different centers to identify aspects of the disease that could potentially affect the outcome of lung transplantation. Therefore, the limitations of a retrospective, multicenter study have to be considered. Data sets may be incomplete, and the reliability of the information obtained depends on the accuracy of the participants' recollections.

The mean interval of 11 years between the onset of symptoms and the time of lung transplantation is in accordance with the natural history of lymphangioleiomyomatosis, with reported 10-year survival rates of 23,⁶ 40,⁴ and 78 percent.⁵ Kitaichi et al.⁴ discussed whether the hormonal therapy they used was responsible for the better survival among their patients than in an earlier series of untreated patients.⁶ Although all the patients we studied had received some kind of hormonal treatment, however, end-stage disease developed in all of them.

Before transplantation, 81 percent of the patients had severe obstructive ventilatory defects. The FEV₁ was 13 to 33 percent of the predicted value, except in one patient with an FEV₁ 66 percent of the predicted value, who had to undergo transplantation because of refractory bilateral pneumothorax. These values are lower than have been reported in other series^{2,23,24} and represent a selection of patients with end-stage pulmonary disease. In many cases, an FEV₁ below 25 to 30 percent of the predicted value might be used as a referral guideline for lung transplantation.

Surgical lung biopsy was performed in the majority of patients to establish the diagnosis of lymphangioleiomyomatosis. In about a quarter, however, the diagnosis was based on high-resolution CT alone and was confirmed histologically in the explanted lung. High-resolution CT is considered a reliable, noninvasive diagnostic method.²⁵ Patients with a history of smoking must be evaluated most carefully, however, since emphysema may mimic the radiologic pattern of lymphangioleiomyomatosis.

When CT is used in the diagnostic workup, the enlargement of hilar or mediastinal lymph nodes may be detected more frequently. These may be a feature of lymphangioleiomyomatosis itself,²⁶ although other diagnoses such as tuberculosis and sarcoidosis should be considered.²⁷

Extrapulmonary manifestations of lymphangioleiomyomatosis occur in some patients.^{26,28} Seventeen percent of the patients we studied, excluding those with tuberous sclerosis, had kidney involvement with unilateral or bilateral angiomyolipomas. This tumor is well known in patients with tuberous sclerosis and is less often reported in those with lymphangioleiomyomatosis.²⁹ So far, experience with the course of angiomyolipoma in patients who have received transplants is limited. In our series, no complications have been observed, but the follow-up time after lung

transplantation is still short. Excessive retroperitoneal bleeding and an increased incidence of renal-cell carcinoma have been reported.³⁰ In our view, lymphadenopathy due to lymphangioleiomyomatosis should not be considered a contraindication to lung transplantation. However, lymphadenopathy may lead to diagnostic confusion in the post-transplantation period if this condition is not recognized beforehand.

In three study patients, pulmonary lymphangioleiomyomatosis coincided with tuberous sclerosis. Tuberous sclerosis presenting with end-stage pulmonary disease is not a contraindication to lung transplantation. Since patients with this condition often need antiepileptic therapy, however, the interaction of antiepileptic drugs with immunosuppressive drugs is of great concern. Also, some patients with tuberous sclerosis are mentally retarded, a fact that might lead to problems in compliance with treatment after transplantation.

Multiple pleural adhesions were the most important problems complicating lung-transplantation surgery. The majority of pleural adhesions were present in patients who had not previously undergone chest operations and therefore have to be attributed to the disease itself.

The overall actuarial one-year and two-year survival rates after lung transplantation, reported in the St. Louis International Lung Transplant Registry (in April 1996), were 71 and 63 percent, respectively. The rates were 64 and 55 percent for patients with pulmonary fibrosis, and 77 and 69 percent for those with emphysema, respectively. The survival rates in our survey (69 and 58 percent, respectively) are similar.

Infections after single-lung transplantation, particularly in the remaining native lung, which may contain many large cysts, have been considered a major post-transplantation problem associated with lymphangioleiomyomatosis. Surprisingly, infections in the native lung were reported in only two patients; both were due to invasive aspergillosis. In the other 33 cases, pulmonary infection occurred in the lung allograft and only occasionally spread to the native lung.

Recurrent chylothorax, another complication associated with lymphangioleiomyomatosis, occurred in three patients after transplantation. It could be explained by a leakage of chylous fluid from dilated and torn lymphatic vessels in the mediastinum after single-lung procedures as well as after bilateral and heart-lung transplantations.

Six episodes of spontaneous pneumothorax of the remaining native lung after single-lung transplantation occurred in five patients and caused mild-to-moderate chest pain. No severe functional impairment was reported since the transplanted lung was predominant and sufficient for ventilation and perfusion.

Recently, two patients with recurrent lymphangioleiomyomatosis in the lung allograft after single-

lung transplantation were described.^{15,16} Each received a transplant from a male donor. One is included in this series.¹⁵ Both patients had progressive airway obstruction, suggesting obliterative bronchiolitis, but postmortem examinations revealed characteristic findings of lymphangioleiomyomatosis in the transplanted lungs. In contrast to the other patient described,¹⁶ the patient included in our study¹⁵ had no evidence of obliterative bronchiolitis, suggesting that the obstructive ventilatory defect was due to the recurrence of lymphangioleiomyomatosis.

Disease recurrence should be included in the differential diagnosis when pulmonary function deteriorates after lung transplantation for lymphangioleiomyomatosis. Recurrence of underlying disease in the lung allograft has been described in patients with sarcoidosis,^{31,32} and in a single case each of giant-cell pneumonia³³ and diffuse panbronchiolitis.³⁴ Sarcoid granuloma recurs in lung allografts within months after transplantation in 18 to 80 percent of patients^{31,32} but is probably not of clinical concern. In contrast, recurrent lymphangioleiomyomatosis is rare (occurring in 1 of 29 patients who survived for more than one month in our series). It is not known whether hormonal therapy after transplantation can delay or prevent recurrence in the allograft. In the majority of the patients in this survey, including the patient with recurrent disease, hormonal therapy was discontinued after transplantation.

We found that lung transplantation can be a valuable therapy for patients with end-stage lymphangioleiomyomatosis and that the outcome after several years is similar to that in patients who receive lung transplants for other diseases. Nonetheless, a wide range of problems associated with lymphangioleiomyomatosis can complicate the transplantation procedure and the post-transplantation course.

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APPENDIX

The following institutions participated in the survey and contributed data on their patients: *North America*: Washington University, St. Louis (five patients); Stanford University, Stanford, Calif. (four); Toronto Hospital, Toronto (three); Cedars-Sinai Medical Center, Los Angeles (two; one of them underwent transplantation at Stanford University and is now being followed at Cedars-Sinai Medical Center); University of Minnesota, Minneapolis (two); University of Alabama, Birmingham (one); University Hospital, London, Ont. (one); McGill University, Montreal (one); Virginia Commonwealth University, Richmond (one); *Europe*: Hôpital Universitaire Erasme, Brussels, Belgium (four); Universitätsspital, Zurich, Switzerland (four); Hospital Universitari Vall d'Hebron, Barcelona, Spain (three); Hôpital Beaujon, Clichy, France (one); Medizinische Hochschule Hannover, Hannover, Germany (one); Hôpital Louis Pradel, Lyon, France (one); and Universitätsklinik Vienna, Austria (one).

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