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Mayo clinic experience of lung transplantation in pulmonary lymphangioleiomyomatosis

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ABSTRACT

Objectives: Lymphangioleiomyomatosis (LAM) is a rare, cystic lung disease that generally results in progressive decline in lung function. Despite advancement of pharmacological therapy for LAM, lung transplantation remains an important option for women with end-stage LAM.
Methods: Patients with LAM undergoing lung transplantation at the Mayo Clinic campuses in Rochester, Minnesota and Jacksonville, Florida since 1995 were retrospectively reviewed.
Results: Overall, 12 women underwent lung transplantation. Nine of 12 (75%) underwent double lung transplant. The mean age was 42 ± 8 years at the time of transplant. One patient (8%) had a chylothorax and 7 (58%) had recurrent pneumothoraces, 4 (33%) of which required pleurodesis. All had diffuse, cystic lung disease on chest CT consistent with LAM which was confirmed in the explant of all patients. The average length of ICU and hospital stays were 5 ± 4 and 19 ± 19 days, respectively.
Mild to moderate anastomotic ischemia was evident in all patients but resolved with time. No patient was treated with sirolimus pre-transplant. Seven patients received sirolimus post-transplant; however, clinical benefit was documented in only 2 patients, 1 of which was treated for large retroperitoneal cysts with ureteral obstruction and another with persistent chylothorax and retroperitoneal lymphangioleiomyomas. Five patients are deceased. The median survival by Kaplan–Meier analysis was 119 months with a median follow-up of 68 months (range 2–225 months).
Conclusions: Lung transplant remains a viable treatment for patients with end-stage LAM. The role of sirolimus peri-transplantation remains ill-defined.

1. Introduction

Lymphangioleiomyomatosis (LAM) is a rare, cystic lung disease that generally results in progressive decline of lung function and almost exclusively affects women. In addition, 30–40% of women with tuberous sclerosis complex (TSC) develop pulmonary LAM [1–3]. The pathobiology largely involves the growth and migration of LAM cells identified by a pathological staining for receptors such as HMB-45. Despite a histologically benign appearance, LAM cells can be isolated from peripheral blood; therefore, capable of hematogenous spread to the lung [4]. Furthermore, LAM has recently been characterized as a low-grade, destructive, metastasizing disease [1,5]. Sirolimus has demonstrated treatment benefit in LAM; however, patients with advanced disease may require lung transplantation (LT) [1,6].

Abbreviations: 6MWT, 6-min walking test; DLT, double lung transplant; ECHO, echocardiogram; FEV1, forced expiratory volume in one second; LAM, lymphangioleiomyomatosis; LT, lung transplantation; MILES, Multicenter International LAM Efficacy of Sirolimus; mTOR, mammalian target of rapamycin; PFT, pulmonary function testing; RHC, right heart catheterization; SLT, single lung transplant; SRTR, Scientific Registry of Transplant Recipients; UNOS, United Network for Organ Sharing.

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LT was first performed for LAM approximately 3 decades ago [7,8]. Between October 1987 and December 2002, the United Network for Organ Sharing (UNOS), lists less than 1% (79 of 10,026) of all LT as performed for LAM [9]. Despite the limited numbers, the LT survival rate for LAM was comparable to that of LT for other end-stage lung diseases [9]. Importantly, it appears that LT is also associated with significantly improved quality of life in patients with advanced disease [10]. Nonetheless, outcomes of LT in the modern era may be influenced by the peri-transplant utilization of sirolimus. Sirolimus reduces the rate of pulmonary function deterioration in LAM, but is also associated with impaired bronchial anastomotic integrity post-transplant; therefore, the risk-benefit ratio in the immediate peri-transplant period is unknown [1,11]. The primary aim of our study was to describe the outcomes of patients with LAM who received LT at Mayo Clinic. By clinical protocol, sirolimus was not used pre-transplant or in the first 30 days after LT. Nonetheless, the limited postoperative experience beyond 1 month was reviewed.

2. Materials and methods

The study was approved by the Mayo Clinic Institutional Review Board. Patients with LAM undergoing LT at the Mayo Clinic campuses in Rochester, Minnesota and Jacksonville, Florida since 1995 were identified and reviewed. Demographics, clinical history, medical treatments, such as hormonal therapy and the use of sirolimus after transplantation, were reviewed in all patients. The results of pre-transplant testing were collated including: chest CT scan, pulmonary function testing (PFT), 6-min walking test (6 MWT), echocardiogram (ECHO), and right heart catheterization (RHC). Outcomes post-transplant, including bronchial anastomosis integrity and survival data, were collected. All pre-transplant diagnoses of pulmonary LAM were confirmed in the explant.

A MEDLINE search of the English literature between 1970 and 2014 was performed using the keywords “pulmonary lymphangioleiomyomatosis”, “lymphangioleiomyomatosis”, and “lung transplantation” in combination. The results were reviewed and summarized.

Descriptive statistics were used to analyze the patient characteristics. Normally distributed continuous data were described as means and standard deviations. The categorical variables are reported in percentages of total subjects. Kaplan–Meier estimates were used to depict survival. The data were analyzed using SPSS version 16, Inc., Chicago, IL.

3. Results

Twelve patients with LAM underwent LT at the two sites, seven at the Florida campus between 1999 and 2008 and five at the Minnesota campus between 1992 and 2010. Demographics and pre-transplant characteristics are presented in Tables 1 and 2. Almost all patients had sporadic LAM. All were women, with an average age 6 years older at the time of medical record review than at the time of transplantation. All patients presented with dyspnea, most with World Health Organization functional class 3. Mean body mass index was in the normal range at 21.9 ± 3.1 kg/m^2. Two patients were in pre-transplant respiratory failure and required mechanical ventilation.

All had diffuse, cystic lung disease consistent with LAM on chest CT. The diagnosis was confirmed either by pre-transplant surgical lung biopsy (7 patients, 58%) or examination of the explanted lung (all patients). Two patients had multiple large cystic retroperitoneal masses compatible with lymphangioma. Patient 1 had several masses were filled with chylous fluid and required extensive retroperitoneal resection later because of interval progression and significant intra-abdominal mass-effect. One patient had small complex retroperitoneal fluid collections (Patient 12). Two patients (Patient 7 and 8) with sporadic LAM had unilateral renal angiomyolipoma.

As displayed in Table 2, the pre-transplant PFT demonstrated severe obstruction (post-bronchodilator forced expiratory volume in 1 s [FEV1] 0.7 ± 0.3 L) with hyperinflation (total lung capacity >120%), air trapping (residual volume >120% predicted) and exertional hypoxemia (SpO2 <88%). The average 6 MW distance was severely reduced at 273 ± 117 m. Eight of 12 (67%) had objective evidence of pulmonary hypertension either by ECHO (3) or RHC (5) [12].

The average donor age was 28 ± 18 years. The average lung allocation score was 45 ± 17 (32–83). Most patients had double lung transplantation (Table 1). The average lengths of ICU and hospital stays were less than 1 week and 3 weeks, respectively. The average ischemic time was 288 ± 112 min and utilization of cardiopulmonary bypass was required in 3 patients (25%).

Nine patients underwent LT without intra-operative complications. Patient 2 had an accidental tear of the carina that healed without major consequence. Patient 9 developed an asystolic cardiac arrest in the operating room and required internal cardiac massage for 4 min before recovery without long-term sequelae. Patient 12 experienced significant intraoperative blood loss due to a retained hemothorax on the side of prior pleurodesis. Her hospitalization was complicated by coagulopathy that resulted in intracranial hemorrhage and death on the 56th postoperative day.

Postoperatively, patient 3 experienced severe dynamic hyperinflation, auto-positive end expiratory pressure, and hypotension shortly after double lung transplantation. After optimization of sedation and pain control, the patient improved and was extubated the same day. Patient 7 had a history of bilateral pleurodesis pre-LT and severe, persistent diaphragmatic paresis/paralysis afterwards with persistent hypercapnic respiratory failure requiring tracheostomy for prolonged ventilatory support. She was ultimately decannulated, but has continued using nocturnal non-invasive positive pressure ventilation. She achieved nearly full recovery and is a long-term survivor (9 years).

Mild to moderate anastomotic ischemia was evident by bronchoscopy in all patients, but complete mucosal healing was seen in 100% of the anastomoses by 3-month post-transplant. Patient 6 initially appeared to have complete bilateral anastomotic healing within 1 week, but evidence of distal airway necrosis by endoscopic inspection. Ultimately, she developed necrotic debris at both anastomotic sites at 1 month post-transplant leading to left bronchial stenosis that required bronchial dilatation and coagulation with argon plasma. As no patient received sirolimus pre-transplant, there was no data to review for any potential impact of sirolimus on the integrity of the anastomosis.

All patients received combination triple-drug immunosuppressive therapy after transplantation. Four patients received combination cyclosporin, azathioprine, and prednisone (patients 1, 8, 9 and 10). Patient 2 was switched from cyclosporine to tacrolimus because of nausea and vomiting. Five patients received tacrolimus, azathioprine, and prednisone (patients 2, 7, 11 and 12). Three patients received tacrolimus, mycophenolate, and prednisone (patients 3, 4, 5 and 6).

Five (42%) patients received hormonal therapy pre-transplant, 2 with intramuscular medroxyprogesterone (patients 7 and 8) and 3 with oral formulation (patients 1, 9 and 11).

No patient was retransplanted. No evidence of diffuse allograft recurrence of LAM was encountered in our cohort. Patient 10 developed renal failure due to cyclosporine nephrotoxicity that required kidney transplantation 10 years after LT.

Seven patients received sirolimus post-transplant but only