Lung Transplantation in Sarcoidosis

Lori Shah, M.D.[1]

ABSTRACT

Lung transplantation (LT) is an appropriate therapeutic option for patients with severe, fibrocystic pulmonary sarcoidosis refractory to medical therapy. Survival rates following LT for sarcoidosis are generally comparable to other indications. Timing of transplantation for patients with sarcoidosis is challenging because mortality rates are high (27 to 53%) among sarcoid patients awaiting LT. Deciding when to refer patients for LT is difficult because models predicting mortality have not been validated. Importantly, algorithms or parameters predicting mortality in idiopathic pulmonary fibrosis and other interstitial pneumonias may not apply to sarcoidosis. Pulmonary function tests do not correlate well with mortality risk in patients with sarcoidosis. However, retrospective studies have shown that the presence of pulmonary arterial hypertension in sarcoidosis is an ominous sign and warrants referral for LT. This article reviews indications and contraindications to LT among patients with sarcoidosis, examines risk factors for mortality, and discusses optimal timing of referral for LT. Early referral of patients allows for timely evaluation of patients for possible listing. If the risks specific to transplantation in sarcoidosis are considered and carefully evaluated, outcomes are reasonable and match those of other diagnoses. Recurrent sarcoidosis in the lung allografts can occur but does not affect survival or risk for complications.

KEYWORDS: Sarcoidosis, lung transplant, allograft, pulmonary arterial hypertension

Sarcoidosis is a multisystemic disease characterized by frequent remissions and exacerbations, with multiple pulmonary and extrapulmonary symptoms that may be difficult to assess and manage and with a limited treatment armamentarium.

Sarcoidosis commonly presents as a mild, self-limited disease that frequently does not require treatment. When treatment is required, corticosteroids are the first line of therapy. Although corticosteroids have been shown to improve symptoms and may correct laboratory, radiographic, or pulmonary function abnormalities, no current evidence demonstrates that corticosteroids significantly alter the natural history of the disease.

Throughout their clinical course, almost all cases of sarcoidosis are marked by pulmonary involvement. The prognosis of patients with isolated pulmonary sarcoidosis is generally good. A majority of these patients undergo spontaneous remission or stabilization of disease within 2 to 5 years of diagnosis. Patients with stage 1 chest radiographs have a $>80\%$ rate of radiographic resolution compared with patients with stage 2 (60%) or stage 3 (30%). A small number of patients may progress to end-stage lung disease. Mortality rates range from 1 to 6%, with the majority of deaths resulting from respiratory failure.[1]

Lung transplantation (LT) has evolved into an important therapeutic option for patients with sarcoidosis unresponsive to conventional medical therapy. LT for sarcoidosis represents 2.5% of all transplants performed internationally and is the sixth most common indication for LT.[2] Due to its protean manifestations and variable

[1]Division of Pulmonary, Critical Care, and Sleep Medicine, The Mount Sinai Medical Center, New York, New York.

Address for correspondence and reprint requests: Lori Shah, M.D., Division of Pulmonary, Critical Care, and Sleep Medicine, The Mount Sinai Medical Center, One Gustave L. Levy Place, Box 1232, New York, NY 10029. E-mail: Lori.Shah@mountsinai.org.

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Table 1 General Guidelines for the Selection of Lung Transplant Candidates[a]

Indications:

End-stage lung or pulmonary vascular disease demonstrating functional decline despite optimal therapy, in which survival is limited
Severe functional limitations/significant diminution in quality of life
Age $\leq$ 55 for heart–lung; age $\leq$ 60 for double-lung; age $\leq$ 65 for single lung

Absolute Contraindications:[b]

- Significant renal (CrCl $<$ 50 mg/mL/min) or hepatic dysfunction[c]
- Presence of extensive coronary disease or left ventricular dysfunction[c]
- Significant end-organ disease secondary to hypertension, diabetes mellitus, or other systemic diseases
- Malignancy within the past 2–5 years depending on type
- Acute and/or critical illness
- Significant and active psychiatric problems
- Cigarette smoking or other substance addiction within the past 6 months
- Poor functional status with inability to perform pulmonary rehabilitation
- Current body weight less than 70% or more than 150% of ideal body weight
- Progressive neuromuscular disease
- HIV or HbsAg positivity or hepatitis C infection with biopsy proven evidence of significant liver disease

Relative Contraindications:[b]

- Poorly controlled hypertension, diabetes mellitus, seizures, peptic ulcer disease, or other medical disorders
- Requirement for invasive mechanical ventilatory support
- Presence of a peripheral or large aspergilloma with significant pleural reaction[c]
- Prior lobectomy, other extensive thoracic procedure, or pleurodesis
- Underlying and active collagen vascular disease with evidence of extrapulmonary end organ damage
- Symptomatic osteoporosis with prior fractures
- Documented history of noncompliance with follow-up visits and medications

[a]Adapted from Reference 3.
[b]These contraindications should be considered individually in the context of the underlying pulmonary disease and the patient.
[c]Specific sarcoidosis related issues that should be considered.
CrCl, creatinine clearance; HbsAg, hepatitis B surface antigen; HIV, human immunodeficiency virus.

clinical course, the transplant community has found it challenging to outline clear, evidence-based recommendations regarding appropriate timing of referral and listing for LT in sarcoidosis. The most recently published guidelines for the selection of LT candidates outline general indications, and relative and absolute contraindications for LT (Table 1), but do not delineate well-defined, disease-specific guidelines for referral of sarcoidosis patients.[3] Until recently, extrapolation from pulmonary fibrosis recommendations have suggested the following are reasonable referral guidelines: (1) a forced vital capacity (FVC) less than 60% predicted, (2) diffusing capacity less than 50% of predicted, (3) rest- or exercise-induced hypoxemia, or (4) failure to maintain lung function despite treatment with steroids or other immunosuppressive agents. These recommendations may seem reasonable given that the mortality rate for patients with sarcoidosis on the LT waiting list was 28% in one study, similar to patients with pulmonary fibrosis.[4] Baughman and colleagues followed the clinical course of 479 sarcoidosis patients over 7 years and found that an FVC of less than 1.5L was present in the majority of patients who died from respiratory failure.[5] However, multiple other studies failed to show a correlation between pulmonary function and mortality in sarcoidosis patients.[6,7]

Earlier studies have outlined multiple risk factors associated with worsened prognosis in sarcoidosis (Table 2).[1,8,9] However, these variables were identified in a more heterogeneous population of sarcoidosis patients, not specifically in sarcoidosis patients awaiting LT. When this particular subgroup of patients was analyzed, additional risk factors for mortality were elucidated.

Arcasoy and colleagues analyzed the characteristics of 43 patients with sarcoidosis on their LT waiting list and identified an elevated right atrial pressure as the only variable independently associated with mortality in multivariate analysis. The authors noted that a right atrial pressure of $>$15 mg Hg resulted in a 5.2-fold increase in risk of death. Interestingly, the mean pulmonary artery pressure (mPAP) at the time of LT was significantly higher than at the time of listing. Almost all the patients studied had marked progression of pulmonary arterial hypertension (PAH) while awaiting transplantation, suggesting that more careful monitoring of

Table 2 Risk Factors Associated with Worsened Outcomes in Sarcoidosis

African American race
Lupus pernio
Chronic uveitis
Age of onset after 40
Chronic hypercalcemia
Nephrocalcinosis
Progressive or prolonged symptoms > 6 months
Absence of erythema nodosum
Splenomegaly
Nasal mucosal involvement
Cystic bone lesions
Neurosarcoidosis
Myocardial involvement
Involvement of > 3 organ systems
Stage III/IV pulmonary disease
Risk Factors Associated with Mortality on Lung Transplant Waiting List
Elevated right atrial pressure
Underlying pulmonary hypertension
Amount of supplemental oxygen required
African American race

From Hunninghake et al,[1] Shorr et al,[6] Arcasoy et al,[7] Newman et al,[8] Judson et al.[9]

right ventricular hemodynamics can predict who is at increased risk for death.[7] Although repeated right heart catheterizations may not be feasible, either or both repeat echocardiograms and monitoring B-type natriuretic peptide (BNP) levels may be helpful to identify worsening PAH.[10,11]

A more recent review of 405 sarcoidosis patients listed for LT in the United Network for Organ Sharing (UNOS) database[6] indicated that there was no significant difference between pulmonary function testing parameters in survivors and nonsurvivors; however, the presence of underlying PAH, the amount of supplemental oxygen required, and African American race were significant predictors of mortality. Shorr and colleagues observed that African American race conferred a more than twofold increased risk of mortality. Although mPAP was elevated in both survivors and nonsurvivors, mPAP of patients who died on the waiting list was 33% higher. The marked PAH noted in nonsurvivors was not thought to be reflective of either cardiac sarcoidosis or chronic left ventricular dysfunction, due to the nearly normal cardiac indexes and pulmonary capillary wedge pressures.[6] These data suggest that referral guidelines should be modified to include these particular risk factors, at least until further prospective studies are performed.

The high mortality of sarcoidosis patients awaiting LT is multifactorial; including late referral practices, patient reluctance to be evaluated for LT, and in some cases, prolonged pretransplant evaluation in which numerous tests are performed to properly risk stratify patients. Unfortunately, these issues may lead to a protracted course of events resulting in a patient missing the "transplant window of opportunity," in which a transplant team feels that the transplant may be performed with the utmost safety and best possible outcome. The new allocation system for LT that has been enacted by UNOS/ OPTN (Organ Procurement and Transplantation Network) allows for a lung allocation score to be assigned to each patient, based on variables including pulmonary function testing, pulmonary hemodynamics, functional status, and oxygen requirements. This score attempts to estimate the patient's urgency for transplantation and balance it with a patient's benefit from LT. This new system, which came into effect in May 2005, may mislead referring physicians into believing that delaying referral for LT has no adverse risk because patients who are more ill will simply rate higher lung allocation scores. However, it is important to understand that the score calculation not only factors a patient's need for transplantation based on severity of illness but also takes into account risk factors for poorer outcome, which may lead to a diminution of calculated score. Thus physicians may do a disservice to their patients by delaying referral. When unsure, erring on the side of early referral is likely the best practice.

Once a patient is referred for LT and is being considered for potential listing, specific sarcoid-related issues need to be considered. Both pulmonary and extrapulmonary manifestations of sarcoidosis need to be carefully evaluated to best assess whether single, double, or heart–lung transplant is indicated, and to best minimize both peri- and postoperative risks.

Computed tomography (CT) of the chest should be performed as part of the sarcoid patient's pretransplant evaluation. Evidence of bronchiectasis is commonly seen in pulmonary sarcoidosis (Fig. 1). Bronchiectasis with resultant colonization of the airways is considered a suppurative or septic lung disease and is an indication for double LT because the allograft would be subject to contamination from the native lung. Another concern

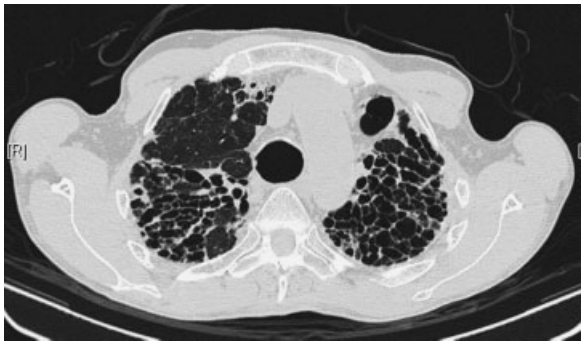

Figure 1 Bronchiectasis in sarcoidosis.

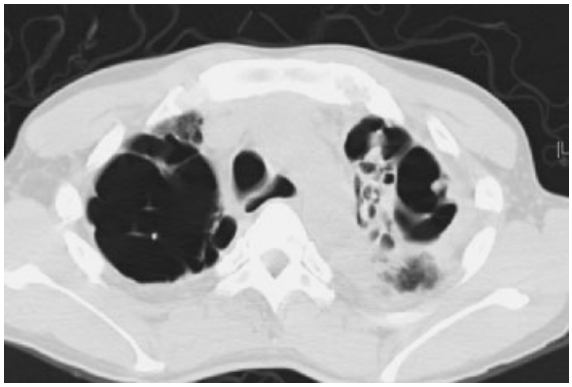

Figure 2 Aspergilloma in sarcoidosis.

includes the presence of a mycetoma, which may occur in patients with fibrocystic lung disease (Fig. 2). Currently, the presence of a mycetoma is considered a relative contraindication to LT. The presence of an aspergilloma may increase risk for seeding of the thoracic cavity during explantation resulting in disseminated *Aspergillus* infection, prolonged cold ischemic times if adjacent pleural thickening results in prolonged time for surgical resection of the native lung or difficulty achieving hemostasis, or increased risk for *Aspergillus*-related death in the setting of postoperative immunosuppression.[12,13] Worsened posttransplant outcome in sarcoidosis patients with mycetomas was suggested by Hadjiliadis and colleagues who retrospectively reviewed 13 patients transplanted for sarcoidosis[14]; nine patients had evidence of mycetoma. The median survival of the mycetoma group after transplantation was 16 months, compared with 56.7 months for all other pretransplant diagnoses without mycetomas. The survival of sarcoidosis patients with and without mycetomas were not significantly different (median survival 16 months vs 18 months, respectively), but the authors cautioned against making definitive conclusions without additional studies with greater numbers.[14] Preoperative treatment with antifungal therapies, including inhaled amphotericin or oral itraconazole, has not been shown to effectively eliminate mycetomas[15] but may decrease the burden of fungal organisms and therefore minimize the likelihood of infection post-LT. In addition, due to the risk of radiographically unidentifiable mycetomas in either lung and increased risk of developing mycetomas in the native lung, there should be a case-by-case consideration for double LT in any patient with evidence of mycetoma. Posttransplantation prophylaxis in patients with known or suspected mycetomas may include inhaled amphotericin, oral itraconazole or voriconazole, or intravenous amphotericin.

Clinically apparent cardiac involvement occurs in ~5% of patients with sarcoidosis, although myocardial granulomas were noted in up to 30% of cases during postmortem examination.[16] Conduction abnormalities ranging from first-degree atrioventricular (AV) block to complete heart block are some of the most common cardiac abnormalities. Complete heart block occurs in ~30% of patients, of which a vast majority had episodes of syncope. Cardiac manifestations may also include pulmonary hypertension with resultant right ventricular dysfunction, mitral regurgitation, congestive heart failure related to left ventricular dysfunction, ventricular aneurysms, pericardial effusions and tamponade, pericarditis, ventricular arrhythmias, and sudden death.[17] Oral corticosteroid therapy should strongly be considered in patients with evidence of active cardiac involvement. Pre-LT cardiac assessment may include an electrocardiogram, echocardiogram, right or left cardiac catheterization or both, and possible cardiac magnetic resonance imaging (MRI) or PET scan to identify left ventricular dysfunction or PAH related to sarcoidosis. Patients with significant left ventricular dysfunction may be more appropriate candidates for heart–lung transplantation.

In patients with sarcoidosis, the prevalence of pulmonary hypertension and right ventricular dysfunction has been reported to range from 4 to 28%.[18] In most cases, sarcoidosis-related PAH is mild to moderate or is manifest only with exercise. Severe PAH and right heart failure have been described in sarcoidosis, usually in association with severe fibrotic parenchymal disease. Right ventricular failure has been reported in up to 30% of sarcoidosis-related deaths and has been shown to be an important predictor of mortality in patients with sarcoidosis awaiting LT.[6,7,19] Interestingly, Sulica and colleagues[19] reported that only 21% of sarcoidosis patients had signs and symptoms of PAH including elevated jugular venous pressure, S3 or S4 right heart sound, hepatojugular reflex, lower extremity edema, or right ventricular heave. Only 60% of patients with PAH demonstrated stage IV sarcoidosis by chest radiographs, characterized by honeycombing, hilar retraction, bullae, cysts, or emphysema. These findings highlight the need for a high index of suspicion for PAH in sarcoidosis patients with suggestive clinical, radiographic, and pulmonary function testing abnormalities.

The identification and estimation of PAH is an important part of a patient's preoperative assessment and risk stratification and may play a role in the decision for single versus bilateral LT. The notion that patients with moderate to severe PAH who undergo single LT may expose the allograft to nearly the entire cardiac output secondary to high vascular resistance in the native lung, potentially leading to increased incidence of primary graft failure and possible worsened posttransplant outcomes, has been contested in multiple studies with varying results.[20–25] A recently published review of the impact of secondary PAH on LT outcomes[26] specifically analyzed outcomes for patients with elevated pulmonary artery pressures (mPAP $>$ 40 mm Hg), and found that acute lung injury indices including PaO_2:FiO_2 ratio and

PAO_2–PaO_2 gradients were significantly worse in the high pulmonary artery pressure group, and these patients required more frequent use of cardiopulmonary bypass during LT and increased use of inhaled nitric oxide and supplemental oxygen in the early postoperative period. However, this increased incidence of early lung injury did not result in prolonged ventilator dependence or intensive care unit (ICU) stay, increased incidence of early acute rejection, or bronchiolitis obliterans syndrome (BOS).

However, mortality data from patients with secondary PAH due to idiopathic pulmonary fibrosis indicates that increased pulmonary artery pressure is associated with increased mortality.[20] The decision of whether to perform single or double LTs in these patients should be handled on an individual basis, with specific considerations given to the degree of right ventricular impairment, underlying diagnosis, and center experience.

Sarcoidosis may affect any organ system, but one of the most common organs involved is the liver (20%). Liver function testing should be obtained to assess hepatic involvement. The spectrum of disease in liver is also wide and ranges from asymptomatic liver dysfunction, chronic cholestasis, portal hypertension, cirrhosis, and nodular regenerative hyperplasia.[27] Patients with evidence of significant liver dysfunction are considered poor candidates for LT because of high morbidity and mortality resulting from hepatic insufficiency both peri- and postoperatively. A total bilirubin level of more than 2.0 mg/dL has been associated with worsened 1 and 5 year survival post-LT.[2]

If these particular risk factors are taken into account, outcomes post-LT are acceptable for sarcoidosis and match those of nonsystemic diseases. Survival rates for all LT recipients from January 1994 through June 2004 were 78% at 1 year, 61% at 3 years, 49% at 5 years, and 25% at 10 years.[2] Multiple studies have suggested that outcomes for sarcoidosis patients roughly match those of overall transplant patients with 1 year survival ranging from 62 to 75%, 3 year survival ranging from 50 to 70%, and 5 year survival at ~55%[7,28–30] (Table 3).

Overall, mortality rate is highest in the first year. A diagnosis of sarcoidosis has the fourth highest relative risk for 1 year mortality among adult LT recipients, preceded only by primary pulmonary hypertension, pulmonary fibrosis (not idiopathic pulmonary fibrosis), and α-1-antitrypsin deficiency emphysema.[2] Disease-specific risk factors for sarcoid-related deaths were analyzed by Shorr and colleagues.[29] Thirty day mortality rates for sarcoid patients versus nonsarcoid patients were 83% versus 91%, respectively, suggesting a nearly double unadjusted risk for mortality in the sarcoid cohort. Patients were ~50% more likely to die at 30 days after LT if they were African American, required heart–lung transplantation, were in an ICU at the time of transplantation, or had received organs from African Americans. The most common cause of death was graft failure, which was true for nonsarcoid patients as well, but sarcoid patients were 2.7 times more likely to succumb to this complication. Thus, although perioperative mortality may be higher, sarcoidosis patients seem to recover to an average survival rate at 5 and 10 years.

Several studies have also shown that there is no significant difference in the incidence of acute or chronic rejection among patients with sarcoid versus nonsarcoid LT recipients.[30,31]

There are multiple reports in the literature of sarcoidosis recurrence posttransplantation, including recipients of lung, heart, and kidney transplants. Several of these reports identified cases of recurrent sarcoidosis associated with clinical deterioration and several that did not correlate recurrence of granulomas with worsened outcomes.[32–35] Overall, accepted practice is that LT should not be withheld despite evidence of recurrence, which does not seem to contribute to increased morbidity or mortality.

Due to the multisystemic nature of the disease, sarcoidosis may considerably and adversely affect the quality of life of patients afflicted. LT is an appropriate option for patients with pulmonary sarcoidosis. Only patients with severe physiological impairment refractory to medical therapy should be considered for LT. Early referral of patients allows for timely evaluation of patients for possible listing. Early educational efforts should be undertaken by the transplant team to further inform patients regarding their disease process and LT. If the risks specific to LT in sarcoidosis are considered and carefully evaluated, outcomes are reasonable and

Table 3 Lung Transplant Survival

Time	Overall Survival ISHLT '94–'04	Overall Survival UNOS (US only) '00–'04	Sarcoid Patients: UNOS	Walker et al	Arcasoy et al	Shorr et al	Nunley et al
30 day	91%			75%		83%	
1 year	78%	81%	72%	75%	62%		67%
2 year		72%	67%		62%		
3 year	61%	65%	58%	70%	50%		
5 year	49%	50%	54%	56%			

From Trulock et al,[2] Arcasoy et al,[7] Nunley et al,[30] Walker et al,[28] Shorr et al[29]; personal communication; UNOS.
ISHLT, International Society for Heart and Lung Transplantation; UNOS, United Network for Organ Sharing.

match those of other diagnoses. Although recurrence is possible, it does not seem to limit survival or increase risk for complications.

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