REVIEW

Lung transplantation for pulmonary sarcoidosis

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Lung transplantation for pulmonary sarcoidosis. M.A. Judson. ©ERS Journals Ltd 1998.
ABSTRACT: Patients with end-stage sarcoidosis have now undergone lung transplantation sucessfully with good short-term and intermediate-term results. Lung transplantation for sarcoidosis requires several considerations unique to this disease.

Selection of pulmonary sarcoidosis patients for transplantation requires that medical therapy has been exhausted. This may involve the use of corticosteriods and alternative medications. Causes of pulmonary dysfunction other than pulmonary sarcoidosis, such as bronchiectasis and myocardial sarcoidosis, must be excluded before candidates are considered for transplantation. The extent and severity of extrapulmonary disease must also be assessed and may preclude lung transplantation. The presence of mycetomas is considered a relative contra-indication by some transplant centres and an absolute contra-indication by others.

Relatively few patients with pulmonary sarcoidosis have undergone transplantation and, therefore, there are few data on outcome. Sarcoidosis frequently recurs in the allograft, but rarely causes symptoms or pulmonary dysfunction. More severe acute rejection episodes may occur in sarcoidosis transplant recipients, although at present there is no evidence of an increased risk of obliterative bronchiolitis or increased mortality.
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Sarcoidosis is a multisystem noncaseatous granulomatous disease of unknown cause. Although essentially all organs of the body may be affected by sarcoidosis, the lung is the most commonly involved. In most cases pulmonary involvement stabilizes or clears in over 80% of affected patients [1]. However, permanent severe pulmonary dysfunction may occur and accounts for most morbidity and mortality [2]. Seventy five per cent of all deaths related to sarcoidosis are from advanced pulmonary involvement [3].

Long-term success of lung transplantation for selected patients with irreversible respiratory failure has only been achievable since 1983 [4]. Although patients with systemic diseases including sarcoidosis were initially excluded from consideration of lung transplantation [5], such patients have now been successfully transplanted with good short and intermediate-term results [6]. This review will examine the clinical aspects of lung transplantation for sarcoidosis, which involves several considerations unique to this disease.

Who and when to transplant

Ensure medical therapy has been exhausted

Lung transplantation should be considered a procedure "of last resort" that should only be entertained when all medical options have been exhausted. Therefore, sarcoidosis patients should only be considered for transplantation when they have failed an adequate trial of pharmacotherapy. Corticosteroids are the mainstay of therapy for sar-

coidosis [7]. Although there is a paucity of controlled data, there have been anecdotal reports of other medications that have been successful for patients who could not tolerate corticosteroids or were therapeutic failures. Of these alternative agents, methotrexate has been studied in most detail. Sarcoidosis patients given methotrexate (10 mg·week^{-1}) were shown to have a similar improvement in spirometry as patients given corticosteroids (40 mg·day^{-1} for 2 months, then 20 mg·day^{-1}) [8]. In addition, there was a similar decrease in bronchoalveolar lavage (BAL) lymphocyte percentage and BAL macrophage activity in the two groups. Although methotrexate is probably as effective as corticosteroids in the short-term, the long-term outcome with this drug is hampered by the cumulative risk of side effects. In a study of 50 chronic sarcoidosis patients given methotrexate for at least 2 yrs [9], 33 had an improvement in vital capacity or improvement in one organ system and 13 were able to totally discontinue corticosteroids. However, six had to discontinue methotrexate because of hepatotoxicity confirmed by liver biopsy and an additional 31 patients discontinued the drug because of the wish to avoid liver biopsy. Eighty eight per cent of the patients who discontinued methotrexate had a relapse of their sarcoidosis. Of the 27 patients rechallenged with methotrexate, 26 noted improvement in symptoms. These data suggest that methotrexate is an effective drug for sarcoidosis, but its chronic use is associated with severe side effects in a significant number of patients and discontinuation of the drug commonly leads to relapse.

Other medications have been studied for sarcoidosis patients who have either been unable to tolerate or failed corticosteroid therapy. However, most of these reports

have been uncontrolled trials or case reports, and none of them have involved chronic therapy. Azathioprine, which was found to be of benefit in two small, uncontrolled short-term studies [10, 11], may be the most promising agent in that it has little cumulative toxicity. However, the long-term benefit with this agent is unknown. Chlorambucil is also effective for acute exacerbations of sarcoidosis [12, 13], but cumulative toxicity including the risk of malignancy prevents its chronic use. Hydroxychloroquine has been found useful for cutaneous sarcoidosis [14], but its efficacy for severe pulmonary sarcoidosis is limited [7]. It may be useful as a corticosteroid sparing agent. Several studies [15–19] have suggested that inhaled corticosteroids are beneficial in pulmonary sarcoidosis, including a double-blind controlled study [20], which showed no difference in symptoms or spirometry in stage II or III sarcoidosis patients maintained on 10 mg·day^{-1} of prednisone *versus* 1,600 µg·day^{-1} of inhaled budesonide daily after both groups had received 6 weeks of corticosteroids. However, the efficacy of inhaled corticosteroids for sarcoidosis must still be questioned because of two negative studies [21, 22], including a recent well designed double-blind placebo-controlled trial [22].

The clinician needs to be cognizant of certain points when determining if corticosteroids or alternate therapy has failed in the treatment of sarcoidosis:

1) The presence of pulmonary dysfunction does not imply that the disease is active. Pulmonary fibrosis may occur in sarcoidosis and results in permanent pulmonary dysfunction. Therefore, the presence of pulmonary symptoms, pulmonary function test abnormalities and/or abnormalities on chest radiograph may be the result of fibrosis and does not imply that sarcoidosis is active and requires pharmacotherapy. A recent study of acute sarcoidosis [23] demonstrated that almost all patients can be successfully tapered off corticosteroids if objective criteria are used and if stability, rather than return to normal pulmonary function, is used as a criterion for tapering of corticosteroids.

2) Active disease does not mandate treatment. Active sarcoidosis suggests that the inflammatory process is occurring, resulting in the formation of "fresh granulomas." Active granulomatous inflammation mandates treatment in the case of tuberculosis. However, it is not clear that "active" disease carries the same mandate for sarcoidosis.

During the immunological cascade of sarcoidosis, a huge number of measurable substances are elaborated including CD4 lymphocytes, activated macrophages, receptors and cytokines [2]. Studies have indicated that three clinical tests may reflect "active disease" by the elaboration of these substances: 1) serum angiotensin converting enzyme (SACE) [24, 25]; 2) BAL cell count differentials [26]; and 3) gallium radionuclide scans (^{67}Ga) [27]. However, conflicting data from other studies indicate that these tests do not accurately predict prognosis [28], the response to treatment [29–31] or the presence or intensity of inflammation in sarcoidosis [32–35].

Recently, high resolution computed tomography (HRCT) scan of the chest has been proposed as a test to measure disease activity of pulmonary sarcoidosis [36]. Ground glass areas of airspace infiltration have been thought to represent areas of active alveolitis [37]. However, correlation between HRCT scans and lung histology revealed that ground glass attenuation did not correlate with alveolitis, but represented

the accumulation of many granulomatous lesions [35]. HRCT findings of lung distortion and nonseptal lines correlate with pulmonary dysfunction and do not resolve [38, 39]. Nodules and airspace consolidation do resolve [38, 39], but there is no evidence that these findings are useful in determining when treatment should be used.

Even if the above tests did accurately reflect active inflammation in sarcoidosis, it is still questionable whether such activity mandates treatment. Granulomatous inflammation often resolves spontaneously in sarcoidosis, although it may resolve faster with therapy [40–42]. Most permanent organ dysfunction in sarcoidosis relates to the development of fibrosis, and it is unclear if this is dependent solely on the presence or degree of the granulomatous inflammation or if other additional factors are required [2, 43]. To date, no data exist to support the contention that therapy based solely on the results of any of the indices of activity will alter the eventual outcome of a patient with sarcoidosis. Therefore, sarcoidosis patients with stable pulmonary function should not be considered to have failed medical failure therapy solely on the basis of laboratory evidence of "active disease."

3) Pulmonary dysfunction should not be assumed to be the result of sarcoidosis. Although sarcoidosis can cause end stage pulmonary fibrosis and respiratory failure, the latter can occur by other mechanisms. Patients with pulmonary sarcoidosis "refractory" to corticosteroids have been found to have bronchiectasis, which is common in stage IV sarcoidosis [23], and may improve with antibiotics. Congestive heart failure has also been found in sarcoidosis patients who failed to respond to corticosteroids [23] and such patients have responded to diuretics. Therefore, alternative causes of respiratory dysfunction should be investigated prior to assuming that they have failed medical therapy and require lung transplantation.

4) Corticosteroid dependence does not imply failure of medical therapy. Although chronic corticosteroid therapy is associated with several complications, it may be superior to alternate therapy, withdrawal of therapy or lung transplantation. Long-term treatment for 2–20 yrs, or longer, is required for a subgroup of patients with pulmonary sarcoidosis [44]. Most of these patients require 5–15 mg of prednisone daily or on alternate days to control their disease, as most will relapse when corticosteroid therapy is withdrawn. Such therapy is generally well tolerated for many years, and the relatively infrequent problems related to it are greatly exceeded by the clinical benefits [44]. Therefore, risks and relatively short life expectancy (*vide infra*) with lung transplantation may make it an inferior choice to chronic corticosteroids in sarcoidosis patients with severe but stable disease. Alternate-day corticosteroid regimens may also help reduce the risk of complications [40].

Consideration of extrapulmonary disease

The decision to perform lung transplantion in patients with extrapulmonary sarcoidosis must be individualized and based on the clinical course of their disease. Patients should be excluded from consideration of transplantation if they have severe or progressive extrapulmonary disease.

Extrapulmonary disease of the nervous system and heart are of most concern, since most deaths from ex-

tra-pulmonary sarcoidosis are from involvement of these organs [3]. Information concerning the functional prognosis of neurosarcoidosis is scanty [45]. A retrospective study of 50 consecutive patients with neurosarcoidosis found that patients with cranial nerve involvement had a good prognosis with a low likelihood of progressive disease, while approximately 40% of patients with cen-tral nervous system lesions (12 out of 30) or peripheral nerve involvement (four out of nine) had progressive disease [46]. Patients with seizures also had a relatively poor prognosis, with five out of nine having progressive disease. On the basis of these data, sarcoidosis patients with central nervous system lesions, seizures and debilitating peripheral nerve lesions are poor candidates for lung transplantation.

Clinical evidence of myocardial involvement is present in 5% of sarcoidosis patients [47], although up to 30% have myocardial granulomas at autopsy [48]. Manifestations of myocardial involvement include conduction disturbances, every form of arrhythmia, cardiomyopathy and sudden death [47]. Although the decision to perform lung transplantation must be individualized, patients with left ventricular dysfunction from sarcoidosis should generally be excluded from lung transplantation, and heart-lung transplantation could be considered. In fact, patients with any heart symptoms are at high risk of a poor outcome, since these patients have a high frequency of sudden unexpected deaths [45, 49].

Although transplant recipients usually receive potentially hepatoxic immunosuppressive medication, elevation of alkaline phosphatase and other liver enzymes from hepatic sarcoidosis is not a contra-indication to lung transplantation, as this form of hepatic involvement is rarely progressive [50]. Patients with poor protein synthetic function, portal hypertension and cirrhosis should be excluded from consideration of lung transplantation, although liver-lung transplantation could be considered. Rarely, involvement with other organs will preclude transplantation, such as severe skin involvement that would predispose the patient to sepsis after transplantation when immunosuppressive therapy is required.

The timing of transplantation

Identification of the most appropriate time for transplantation is one of the most difficult aspects of patient selection. The 1 yr actuarial survival after lung transplantation is 70%, and the 5 yr survival is less than 50% [51, 52]. Although quality of life issues play an important role in the decision to perform transplantation, it is hard to justify lung transplantation in a patient with a relatively long life expectancy who is statistically likely to "lose" years of life from the procedure. An attempt is made to perform transplantation within the "transplant window," during which time the patient's life expectancy is likely to be improved by transplantation, but the patient is not so sick that the risks of transplantation are prohibitive [53]. For this reason patients are generally considered for lung transplantation if they have irreversible and progressive pulmonary disease and life expectancy is less than 3 yrs [54, 55]. Although formulae have been developed to predict the life expectancy of patients with progressive pulmonary disorders such as cystic fibrosis [56], primary pulmonary hypertension [57], silicosis [58] and chronic obstructive pulmonary disease [59], no such formula has been developed for pulmonary sarcoidosis.

Mycetoma

Mycetomas are often present in end-stage sarcoidosis patients with fibrocystic disease [60]. Therefore, many sarcoidosis patients referred for consideration of lung transplantation have mycetomas. It is unclear whether the presence of a mycetoma is a relative or absolute contra-indication to lung transplantation. Clearly, the lung(s) with the mycetomas need to be removed, as there is a great chance that the mycetomas may become invasive with immunosuppression. Even a percentage of immuno-competent hosts with mycetomas develop invasive fungal disease [61].

Even if all mycetomas are resected during lung transplantation, there are two additional concerns. First, surgical resection of mycetomas is difficult and associated with a mortality rate of 5–13% and a high incidence of major postoperative complications [62–65]. Second, there is a concern that although the lung with a mycetoma is removed, there may be radiographically undetectable mycetomas in the contralateral lung. Even if all mycetomas are removed by performing a double lung transplant, the trachea and main bronchi proximal to the anastomoses may be colonized with Aspergillus which may result in the development of a postoperative infection of the airway or invasive pulmonary Aspergillus. Despite this theoretical concern, FLUME et al. [66] reported that of 17 cystic fibrosis patients who underwent double lung transplantation with preoperative sputum cultures positive for Aspergil-lus species, nine were colonized with Aspergillus after transplantation, and none required treatment for Aspergillus post-transplant.

Nonetheless, a case has been reported [67] of a double lung transplant recipient with end-stage sarcoidosis with mycetomas who underwent heart-lung transplantation and eventually died of invasive Aspergillus. The authors recommended that strategies should be used to reduce the fungal burden prior transplantation such as inhaled amphotericin B, itraconazole or low dose liposomal amphotericin B. In our lung transplant programme, the presence of an aspergilloma in a potential candidate does not prohibit transplantation, but is considered a major relative contra-indication.

Characteristics of sarcoidosis patients considered for lung transplantation

The pulmonary function data of sarcoidosis patients listed for lung transplantation at the Medical University of South Carolina are shown in table 1. Most candidates had a severe restrictive ventilatory defect. The transfer factor of the lung was discordantly low when compared to the vital capacity of these patients. Most had a history of long-standing sarcoidosis, although several did not have significant dyspnoea or any other pulmonary symptom until years after the diagnosis. This is in contrast to the study of VESTBO and VISKUM [68] in which all sarcoidosis patients who died from respiratory failure had pulmonary symptoms at their initial presentation. These conflicting results may be explained by the fact that all the lung transplant candidates at the Medical University of South

Table 1. – Pulmonary function data of sarcoidosis patients listed at the Medical University of South Carolina

Parameter	Mean±SEM	Range	n
Age yrs	40±7	26–52	10
Time after diagnosis yrs	12.6±6.5	0–22	9
Duration of dyspnoea yrs	7.9±3.5	2–13	9
FVC % pred	42±16	20–70	9
FEV1 % pred	42±15	20–70	9
TLC % pred	55±15	27–75	9
FRC % pred	63±26	26–101	9
RV % pred	75±56	28–201	9
TL,CO % pred	21±11	9–39	5
TL/VA % pred	48±21	27–76	4
6MWD m	305±119	48–421	7
Exertion on 6MWD*	7.6±2.7	3–10	6

FVC: forced vital capacity; % pred: percentage predicted value; FEV1: forced expiratory volume in one second; TLC: total lung capacity; FRC: functional residual capacity; RV: residual volume; TL,CO: transfer factor of the lung for carbon monoxide; TL/VA: transfer coefficient; 6MWD: 6 min walking distance. *: perceived rating on a scale of 0–10.

Carolina were black, whereas all the patients in the previous study were white, and the clinical course of sarcoidosis may be more severe in black patients [13, 69]. In any event, our results suggest that patients with sarcoidosis should be monitored for the development or progression of pulmonary symptoms, even if they are absent at initial presentation. Although the number of transplant candidates was too small to make meaningful statistical conclusions, patients who died on the waiting list could not be distinguished from those who survived on the basis of any physiological parameter.

Four of the five candidates who have died on our lung transplant waiting list had sarcoidosis, while one had pulmonary fibrosis. Although the small number of patients precludes a meaningful statistical analysis, these data suggest that mortality of sarcoidosis patients awaiting lung transplantation is at least as high as with pulmonary fibrosis, which has been reported to have the highest mortality rates among emphysema, Eisenmenger's Syndrome, cystic fibrosis and primary pulmonary hypertension [70]. A review of data on our sarcoidosis patients (not shown) suggested that patients who died had poorer gas exchange and more severe pulmonary hypertension than those who survived. It is also interesting that three of the 44 patients listed at our centre were withdrawn from the list because of significant improvement of their lung disease, and two of these three patients had sarcoidosis. This suggests that even when pulmonary sarcoidosis reaches "end-stage," there is still a chance for improvement.

It should also be noted that one of the patients who died on our waiting list was listed for heart-lung transplantation because significant cardiac involvement was detected during the lung transplant evaluation. This reinforces the point that significant occult cardiac disease may complicate cases of end-stage pulmonary sarcoidosis.

Procedure of choice: single *versus* double lung transplantation

Although double lung transplant recipients have superior pulmonary function compared to single lung transplant recipients [71], exercise performance in both groups is similar [71, 72]. This equivalence in exercise perform-

ance has caused single lung transplantation to become the procedure of choice for most patients, because the dearth of donor lungs limits the number of patients who may receive a lung transplant. This scarcity, coupled with the increased number of patients waiting for a lung transplant [73] has resulted in an increase in the death rate of lung transplant candidates on waiting lists to over 30% [70].

However, the transplantation procedure of choice for pulmonary sarcoidosis has not been determined because of potential problems associated with single lung transplantation that are unique to this disease. First, patients with fibrocystic (Stage IV) sarcoidosis have a high incidence of bronchiectasis [23]. These patients often have recurrent infections that respond to antibiotics [23]. Single lung transplantation is not adequate for diffuse suppurative pulmonary diseases in which the transplanted lung would be endangered by spillage from the native lung [55, 74].

Another concern are mycetomas which, as previously mentioned, are often present in end-stage sarcoidosis patients with fibrocystic disease [60]. Clearly, a lung harbouring a mycetoma must be removed, as there is an increased chance that the mycetoma may become invasive. However, even if there is no radiographical or serological evidence of a mycetoma at the time of transplantation, a mycetoma may develop in the native lung if single lung transplantation is performed (fig. 1).

A pneumothorax may occur in patients with end-stage fibrocystic sarcoidosis, and this complication may develop in the native lung after single lung transplantation [74]. These secondary spontaneous pneumothoraces are rarely permanently treated with tube thoracostomy [74, 76]. Thoracoscopic talc poudrage [74, 77] and thoracoscopic parietal pleurectomy [78] have both been successful forms of treatment.

Finally, sarcoidosis may recur in the allograft (*vide infra*). Therefore, there may be a theoretical benefit of supplying the recipient with the greatest amount of healthy lung tissue by performing a double lung transplant, so that if recurrent sarcoidosis occurs, there will be increased pulmonary reserve. Nonetheless, we are currently following a single lung transplant recipient without evidence of recurrence more than 5 yrs after transplantation.

In summary, it is not presently clear whether single or double lung transplantation is the procedure of choice for sarcoidosis. Such a decision should be made on an indi-
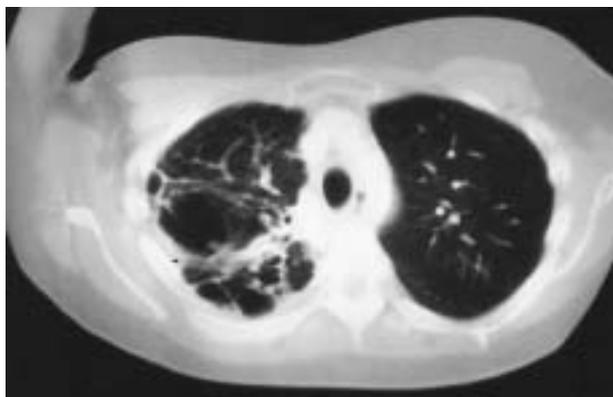

Fig. 1. – Asymptomatic patient who received a left single transplant 5 yrs earlier. Computed tomography scan reveals fibrocystic sarcoidosis in the right (native) lung with a small aspergilloma.

Table 2. – Recurrence of sarcoidosis in the allograft

First author [Reference]	Transplants n	Time of post-transplant recurrence	Other pulm. diagnosis	Pulmonary symptoms
BJORTUFT et al. [78]	2*	6 months	OB	Yes
JOHNSON et al. [79]		9 months	OB	Yes
MULLER et al. [80]	4	2 weeks†		No
MARTEL et al. [82]				
MARTINEZ et al. [83]	1	6 months		No
	1	24 months		No
	2	3 months+		No
		13 months		Yes

*: one patient, two separate lung transplants; †: resolved at 4 weeks; +: heart-lung transplant. pulm.: pulmonary; OB: obliterative bronchitis.

vidual basis. Patients with bilateral bronchiectasis should undergo double lung transplantation. Patients with bilateral mycetomas, if they should be transplanted at all, should receive double lung transplants. In most cases, we believe single lung transplantation is adequate for these patients. Native lung pneumothoraces can be managed after transplantation, and the concern about providing more healthy lung tissue to offset recurrence of sarcoidosis in the allograft remains conjectural at present.

Recurrence in the allograft

Ten cases of recurrence of sarcoidosis in the allograft after lung transplantation are reported in table 2 [79–83]. Because relatively few lung transplants have been performed for sarcoidosis, the frequency of recurrent sarcoidosis after transplantation is not known. However, two lung transplant groups have reported recurrence in one of three [79], and four of five [80] sarcoidosis transplant recipients. Sarcoidosis is usually asymptomatic in these patients, appearing as noncaseating granulomas on surveillance transbronchial biopsies in patients without pulmonary symptoms or dysfunction related to sarcoidosis [80, 81]. However, rarely recipients may develop pulmonary symptoms or dysfunction from recurrent sarcoidosis [80, 83, 84]. Recurrent sarcoidosis may occur early after transplantation and then resolve [80] or may develop more than 1 yr after transplantation [84].

Outcomes

There are few data in the medical literature directly addressing the outcome of lung transplantation for sarcoidosis. Although sarcoidosis often recurs in the allograft, it has rarely caused pulmonary symptoms or dysfunction [79, 84] and in these instances the effects have not been permanent. A series of five sarcoidosis lung transplant recipients, showed that these patients have more severe, acute rejection episodes (grade 2.1±0.3 versus 1.6±0.1, p< 0.042) than other lung transplant recipients [80]. Although acute rejection is a major risk factor for the eventual deve-lopment of obliterative bronchiolitis after lung transplantation [82], presently there is no evidence

that obliterative bronchiolitis is more common in sarcoidosis lung transplant recipients. Recently, the outcome of lung transplantation for sarcoidosis has been reviewed [85]. Although the small number of patients does not allow for statistical analysis, it appears that the survival rates and incidence of obliterative bronchiolitis are comparable with lung transplantation for other pulmonary diseases.

Summary

Transplantation is an option for pulmonary sarcoidosis patients. Patients should be considered if they have end-stage pulmonary dysfunction that is progressive and unresponsive to medical therapy. Single lung transplantation is acceptable for many sarcoidosis patients. Double lung transplantation should be performed in patients with bilateral bronchiectasis and bilateral mycetomas. Sarcoidosis often recurs in the pulmonary allograft, but it is often transient and rarely causes significant pulmonary dysfunction.

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