CHAPTER 22

Transplantation for sarcoidosis

I. Saleem, S.O. Beirne¶, J.J. Egan*,#*

**Advanced Lung Disease and Irish National Lung Transplant Program, The Mater Misericordiae Hospital, #Saint Vincent's University Hospital and Our Lady Hospital for Sick Children, and ¶The Conway Institute, Dublin Molecular Medicine Centre. University College Dublin, Dublin, Ireland.*

Correspondence: J.J. Egan, The Mater Misericordiae Hospital, University College Dublin, Eccles Street, Dublin 7, Ireland. Fax: 35 316605451; E-mail: jegan@mater.ie

The course and prognosis of sarcoidosis varies greatly. A characteristic feature is the high rate of spontaneous remission, however, chronic disease may occur in 10–30% of patients. Chronic sarcoidosis is defined as disease which persists for >2 yrs. Mortality from sarcoidosis is only 1–5%, but 75% of all deaths are due to advanced pulmonary sarcoidosis. To date, it remains difficult to predict which patients may develop chronic progressive severe disease.

Regrettably, the treatment options for chronic stage IV sarcoidosis are limited. Generally, lung transplant is reserved for those who have failed to respond to maximal medical therapy. Due to the variability of the clinical course of sarcoidosis, timing of transplant can be difficult. Accurate, disease-specific predictors of mortality in sarcoidosis patients with chronic pulmonary disease have not been well defined. Furthermore, the relative rarity of end-stage sarcoidosis makes the creation of mortality prediction models difficult. This chapter will review both the current understanding of the optimal criteria applied for estimating the need for transplantation and the outcome of sarcoidosis patients who undergo transplantation.

Pulmonary function testing

The most common pulmonary function abnormalities seen in sarcoidosis are a reduction in the carbon monoxide diffusing capacity of the lung ($D_{L,CO}$) and a reduction in lung volumes and vital capacity (VC). Obstructive defects may occur (~30% of cases) and are generally unresponsive to bronchodilator therapy. Most sarcoidosis patients considered for lung transplantation have a severe restrictive ventilatory defect. Patients with a forced vital capacity (FVC) of <1.5 L are at the greatest risk of mortality [1]. Often the transfer factor is discordantly low compared with the VC. However, a lack of consistency in the ability of lung function testing to reliably predict mortality may reflect the heterogeneous patterns of disease which occur in stage IV disease.

Radiological evaluation

High-resolution computed tomography (HRCT) patterns and their relationship to pulmonary function testing may clarify why lung function tests may be of limited value in predicting disease severity. In a study of 80 patients, sarcoidosis-related fibrosis was divided into three categories based on the dominant HRCT findings [2]. These patterns

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included central bronchial distortion, honeycomb pattern and a linear pattern, which occurred in 47%, 29% and 24% of patients, respectively. The fibrotic changes, particularly bronchial distortion and honeycombing, are predominantly in the upper and/or middle lobes in most patients, whereas linear opacities are often diffuse.

These radiological patterns are associated with different clinical and lung function characteristics. The mean duration of disease was longest in patients with bronchial distortion, a mean of 13 yrs, compared with 9.6 yrs in patients with honeycombing and 8.7 yrs in patients with linear opacities. The patients who demonstrated honeycombing had a greater degree of lung function impairment compared with those with linear and bronchial changes. Patients with HRCT honeycombing had a mean total lung capacity of 62% of predicted (% pred), the FVC was 58 % pred and $D_{L,CO}$ was 44 % pred (fig. 1) Patients with dominant bronchial distortion had a FVC of 93 % pred, a forced expiratory volume in one second (FEV_1) of 64 % pred and a $D_{L,CO}$ of 58 % pred. Linear opacities on HRCT were generally found to cause less functional impairment, the FVC was 84 % pred, FEV_1 77 % pred and $D_{L,CO}$ was 65 % pred. A minority of patients with linear opacities had a pattern of diffuse septal reticulation which was associated with pulmonary hypertension. This subgroup had severe functional impairment. Nodularity, suggestive of reversible disease, occurred most commonly in association with linear opacities and only rarely with honeycombing.

Criteria for referral for transplant

In order to define clinical parameters which may illustrate factors determining survival, a single centre retrospective analysis has characterised sarcoidosis patients who were referred and underwent lung transplantation [3]. Between 1991 and 2000, 56 patients were evaluated for lung transplantation, and 43 out of this group were listed. The mean age of patients was 45 yrs and the diagnosis was made 13 yrs prior to listing. A

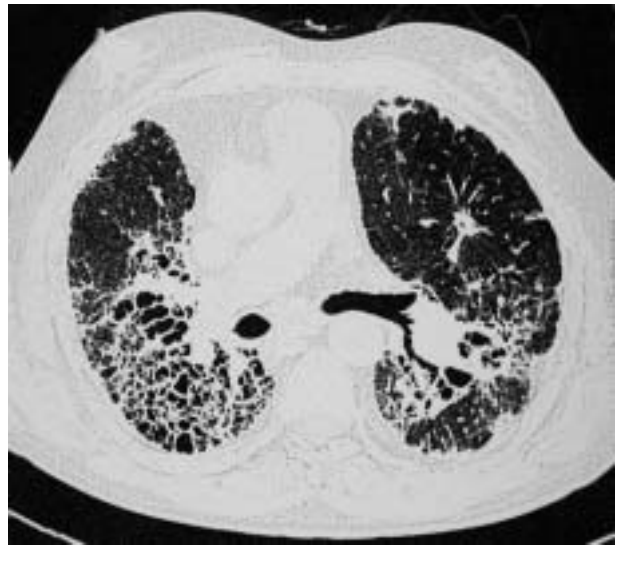

Fig. 1. – A 62-yr-old male with Sarcoidosis. High-resolution computed tomography scan showing upper lobe end-stage fibrosis with honey combing and traction bronchiectasis. The patient's pulmonary artery is dilated consistent with pulmonary hypertension.

total of 23 (55% of patients) died awaiting transplantation. The mean pulmonary artery pressure (P_{pa}) and right atrial pressure (RAP) were significantly higher in the group of patients who died. Of the patients who died, 80% had a mean P_{pa} of 35 mmHg compared with 40% of living patients (unadjusted relative risk (RR) of mortality=3.2; p=0.02). Significant elevation of RAP (*i.e.*, $\geq$15 mmHg) was present in 45% of deceased patients (unadjusted RR of mortality=7.6; p<0.0001). When these were adjusted for confounding variables, a RAP >15 mmHg was the only variable independently associated with death on the waiting list.

In an effort to further characterise the features of sarcoidosis patients requiring lung transplantation, SHORR *et al.* [4] retrospectively examined the outcome of sarcoidosis patients (n=427) listed for lung transplantation in the USA and compared them with the 2,115 idiopathic pulmonary fibrosis (IPF) patients [4]. Sarcoidosis patients made up only 3.5% of the total number registered for transplantation, whilst 17.3% had IPF. Compared with IPF patients (mean age=51.4 yrs), sarcoidosis patients were significantly younger (mean age=45.4 yrs; p<0.0001). Sarcoidosis patients were also predominantly female (66%) and African American (70%), while IPF patients were predominantly White (79.5%) and male (60.7%). Lung function was lower in sarcoidosis patients, with a FVC of 42.6 % pred and an FEV_1 of 36 % pred, compared with IPF patients whose FVC was 45 % pred and FEV_1 was 46 % pred. Notably, sarcoidosis patients were more likely to have pulmonary hypertension, mean P_{pa} of 34.4 mmHg compared with 25.6 mmHg in IPF patients. Mortality after listing was high in both groups; 28% of sarcoidosis patients and 31% of IPF died on the waiting list.

Consequently the United Network of Organ Sharing (UNOS) registry was reviewed and data pertaining to sarcoidosis patients was collected in an effort to derive a model of variables capable of providing an ability to predict survival [5]. A total of 405 patients were identified of whom 27% died on the waiting list. Lung function studies did not discriminate between those who died and those who continued to survive. African Americans had significantly greater risk of dying with an odds ratio of 2.5. Elevated P_{pa} was again observed as being associated with limited survival. Survivors had a mean P_{pa} of 31 mmHg compared with 41 mmHg in nonsurvivors. The use of supplemental oxygen was greater in the nonsurvivors (mean=2.9 $L \cdot min^{-1}$) compared with survivors (mean=2.1 $L \cdot min^{-1}$). Combining these three variables allowed a predictive mathematical model of moderate ability to be derived discriminating between survivors and nonsurvivors in 65% of cases. Therefore, patients, especially African Americans, requiring oxygen with elevated P_{pa} are at greatest risk of death. Generally, a greater understanding and knowledge of the clinical variables influencing survival is required.

Outcome following lung transplantation

Limited data exists on the outcomes of sarcoidosis patients undergoing lung transplantation. A single centre study has described the outcome of sarcoidosis patients who have undergone lung transplantation [3]. A total of 12 patients underwent lung transplantation, four single lung and eight double sequential lung transplants. This occurred, on average, 494 days following listing for transplantation. Of the 12 patients, five died following transplantation. Aspergillus infection was the cause of death in three of the patients, one death due to intraoperative haemorrhage and one due to aspiration pneumonia and haemolytic uraemic syndrome. Two of the 12 lung transplant recipients developed evidence of recurrent sarcoidosis on biopsy, but this was considered to be of little clinical significance.

A larger study was performed by SHORR *et al.* [6], evaluating the short-term outcome of

UNOS-registered sarcoidosis patients who underwent lung transplantation between 1995 and 2000. In total, 4,721 lung transplants were carried out, of which 133 (2.8%) were for sarcoidosis. Unadjusted 30-day survival for sarcoidosis was 83% compared with 91% for other diagnoses. This indicated a near double unadjusted risk of mortality for the sarcoidosis cohort compared with others. Sarcoidosis patients were more likely to be African American and female. Medicaid (USA) was the most frequent insurer in sarcoidosis patients (13.5% *versus* 7.5%). Sarcoidosis patients were also younger than patients undergoing lung transplantation for other indications. There was a trend towards sarcoidosis patients being more likely to require mechanical ventilation (4.5%) at the time of transplantation than other groups (2.2%). Furthermore, sarcoidosis patients were more likely to undergo heart-lung transplant and double lung transplantation.

The strongest predictor of short-term mortality was heart-lung transplantation. Being present in the intensive care unit at the time of transplantation also increased the risk of mortality. Graft failure was the most common cause of death at 30 days, accounting for two of every five deaths. It was 2.7 times more likely to be the cause of death in sarcoidosis patients. Infection was the cause of death in only 8.7% of sarcoidosis patients compared with 22.1% in other groups of patients.

Overall, sarcoidosis confers an increased risk of mortality at 30 days compared with transplantation for other conditions, but this increased risk can be explained by factors other than the underlying diagnosis. Sarcoidosis patients are more likely to require heart-lung transplantation and to be female and African American. Race influenced mortality, with African-American recipients and those receiving organs from African American donors being 50% more likely to die at 30 days. This impact was independent of insurance status.

The distribution of donor races was similar for all diagnosis. Thus, as most Sarcoidosis patients in the USA were African American, they were more likely to have donor-recipient racial mismatching. This racial mismatching may be a factor in predisposing patients to subclinical rejection. Immunosuppressive therapies to date have been studied predominantly in White populations and their pharmacokinetics and pharmacodynamics may not be the same in the predominantly African-American population undergoing lung transplantation for sarcoidosis.

Disease recurrence

A retrospective analysis of 1,394 lung transplant recipients has been undertaken in an effort to define the impact and characteristics of recurring primary pulmonary diseases, including sarcoidosis [7]. Computed tomography (CT) scans and pathologic specimens of patients were reviewed. Of 26 patients who underwent transplantation for sarcoidosis (three single, five double and one heart-lung), sarcoidosis recurred in nine cases (35%) and, overall, was the commonest disease to recur. The CT findings of sarcoidosis disease recurrence following lung transplantation were variable. Radiological manifestations included either a solitary pulmonary nodule or numerous miliary nodules.

In another study, the natural history of sarcoidosis following lung transplantation has been reported in nine single lung transplant recipients [8]. In this study, two contemporaneous recipients receiving transplants for chronic obstructive pulmonary disease (n=30) and inflammatory lung disease (n=13) served as control groups. All recipients survived beyond 30 days and 1-yr survival was 67%. Sequential lung biopsies were performed in eight of the nine sarcoidosis recipients. Recurrence of granulomas was identified in five of these eight recipients (62.5%). The mean time to diagnosis of recurrent

sarcoidosis was 224 days. There was no radiological evidence or symptoms relating to disease recurrence in any of these five patients.

All recipients showed significant improvement in FVC from 1.54 L to 2.55 L. Sarcoidosis patients with recurrent disease also showed improvement in VC from 1.53 L to 2.71 L. There was no difference in the prevalence of acute cellular rejection between the groups. Chronic rejection (obliterative bronchiolitis) occurred in 50% the sarcoidosis recipients.

In another series, lung transplantation was performed on 12 sarcoidosis patients [9]. Ten underwent single lung transplantation and two underwent double lung transplantation. Survival was 70% at 3 yrs and 56% at 5 yrs. Three patients developed obliterative bronchiolitis at 6, 18, and 45 months. Three patients had histological evidence of sarcoidosis recurrence. The transbronchial biopsies had been undertaken for other reasons and incidentally identified noncaseating granulomas. A diagnosis of recurrent sarcoidosis was made after exclusion of mycobacteria, fungi, and *Pneumocystis carinii* infection. The granulomas were identified at 5, 6, and 56 months after transplantation. In one patient, the appearance of granulomas was associated with an irreversible decline in lung function despite aggressive medical therapy, including increasing immunosuppression. This deterioration necessitated re-transplantation. In the other two patients the appearance of granulomas was transitory and without any serious clinical problems. Whilst histological recurrence is common after lung transplantation for sarcoidosis, this is usually not of clinical significance.

Disease-specific characteristics and lung transplantation

There are several unique, disease-specific characteristics which need to be considered in sarcoidosis patients in the context of selection for transplantation and post-operative management. These include the presence of mycetomas, pulmonary hypertension and bronchiectasis.

Mycetoma

A particular complication of stage IV sarcoidosis in patients with fibrocystic disease is the development of mycetomas. These are saprophytic fungal infections usually caused by members of the Aspergillus family developing within cavities in the lungs of patients with advanced sarcoidosis. They may give rise to life-threatening haemoptysis. Surgical resection is often difficult and carries significant mortality and morbidity rates. Embolisation of bronchial arteries has been utilised to treat this problem. Generally, a mycetoma is considered to be a relative contraindication to lung transplantation.

The presence of mycetomas in the lungs of patients undergoing lung transplantation is predictive of poor post-transplant outcome. Careful screening for mycetoma by chest radiograph and computed tomography (CT) is essential prior to transplant to identify these patients at higher risk. Antifungal therapy prior to transplant will not usually eradicate the mycetoma and, generally, patients are often to unwell to undergo resection. The removal of diseased lung during the transplant removes most of the fungal organisms, but enough may remain in the trachea and proximal bronchi potentially resulting in post-transplant fungal infection.

Pulmonary hypertension

The presence of pulmonary hypertension in sarcoidosis patients is a consistent feature of patients with limited survival (fig. 2). Some studies report an incidence of 50% in

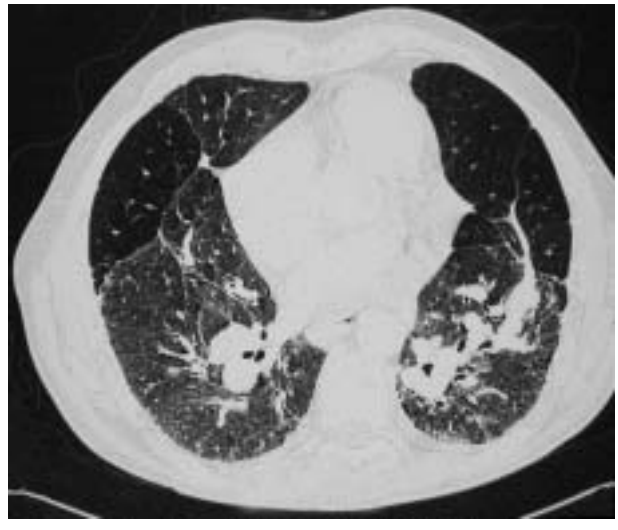

Fig. 2. – A 60-yr-old man with sarcoidosis. High-resolution computed tomography scan showing extensive confluent areas of linear fibrosis and dilated pulmonary arteries consistent with pulmonary hypertension.

patients with stage III disease. The mechanism(s) of pulmonary hypertension in sarcoidosis has not been defined with great clarity. It may be due to fibrosis of the lung parenchyma and destruction of pulmonary vessels resulting in an obliterated pulmonary vascular bed. Extrinsic compression of pulmonary vessels by sarcoidosis lymphadenopathy may also contribute. An open study of 14 patients receiving vasodilator therapy suggests that vasoconstrictive mediators may also play a role in sarcoidosis-associated pulmonary hypertension [10]. In this study, eight patients received an acute challenge with inhaled nitric oxide (iNO), six patients received *i.v.* epoprostenol and five patients received calcium channel blockers. A favourable short-term response was defined as a >20% decrease in pulmonary vascular resistance (PVR). This was observed in seven out of the eight in response to the iNO, four of the six who received *i.v.* epoprostenol and two out of five in response to oral calcium channel blockers. Both iNO and epoprosentol significantly reduced the PVR and increased cardiac output, but iNO was the only vasodilator to significantly reduce the P_{pa}. The only significant response to calcium channel blockers was to reduce systemic vascular resistance.

Long-term vasodilator therapy was then commenced in the patients who had a response to the vasodilator challenge. Five patients received long-term iNO and one received *i.v.* epoprostenol. Follow-up 6-minute walk test improved in all five of the patients on long-term iNO. Follow-up haemodynamic data collected in three patients showed a sustained effect. These three patients subsequently died (although only one had progressive right heart failure). The two remaining patients continued on iNO. These data suggest that patients with sarcoidosis-related pulmonary hypertension often have clinically relevant pulmonary vascular reversibility, despite severe parenchymal lung disease.

Bronchiectasis and type of transplant

The transplant procedure of choice for sarcoidosis has not been specified. Generally, the decision is made on an individual patient basis. Patients with fibrocystic pulmonary disease have a high incidence of bronchiectasis. Recurrent infections are common in this

group of patients; therefore, double sequential lung transplant is indicated. Double lung transplant recipients have superior pulmonary function compared with single lung recipients, but exercise tolerance in both groups is similar. Therefore, because of the great shortage of organs, single lung transplant is an acceptable alternative for patients with honeycomb-pattern fibrosis. Heart-lung transplantation may be offered to patients with associated pulmonary hypertension. However, the presence of associated pleural disease in some sarcoidosis patients may result in significant problems following heart-lung transplantation, as the need for bypass may augment bleeding from the pleural surfaces.

Cardiac, renal and liver transplantation for sarcoidosis

Rarely, patients may be considered for solid organ transplantation for sarcoidosis-related heart, liver or kidney disease. Generally, if required, isolated heart or liver or kidney transplantation is appropriate in patients with end-stage extrapulmonary disease. The limited data available indicates that outcome following transplantation is acceptable in these other forms of organ transplantation. However, such patients remain at risk of disease recurrence as is observed following lung transplantation. A key consideration in such patients is that the advanced disease is isolated to one organ.

Up to 16 heart transplant recipients with a diagnosis of sarcoidosis have been described in the literature [11, 12]. A total of 15 liver and 51 kidney transplants have also been identified. Isolated cases of histological disease recurrence have been described following heart, liver and kidney transplantation, but the clinical course of these cases have been favourable.

Summary

Organ transplantation is an accepted method of treatment for sarcoidosis patients with advanced organ failure, including lung, liver or heart disease. Transplantation can be performed successfully in sarcoidosis patients. However, predicting the precise time for referral can be difficult and, therefore, early referral is advised. The management of sarcoidosis-associated pulmonary hypertension is important in this circumstance.

Survival statistics vary but a primary diagnosis of sarcoidosis, carries an increased risk of mortality following transplantation. Recurrence is frequent (estimated to be ~50% following lung transplantation), but is most often asymptomatic, and tends not to compromise graft function or patient survival. Regrettably, transplantation is limited by the availability of donated organs.

Keywords: End-stage, recurrence, sarcoidosis, transplantation.

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