

**Management of End-Stage Sarcoidosis: Pulmonary Hypertension and Lung Transplantation**

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## 1) Introduction

Sarcoidosis is not only a multisystem, but also a multinational disease that is prevalent throughout the world including in Europe, the United States and Japan (1, 2). In Europe, especially in the Scandinavian countries and Ireland, it affects the Caucasian population, while in the United States it tends to occur in African-Americans more commonly. It has a reported incidence in females of 21.6 and in males 15.3 cases per 100,000 population per year (2).

Lung involvement in sarcoidosis is seemingly invariable with up to 95% of patients manifesting some form of pulmonary disease during the course of their lifetime (1). On the other hand, the natural history of sarcoidosis in the lung is quite variable and spans the spectrum from spontaneous resolution to advanced fibrocystic disease. Fortunately, in most cases, there is more of a propensity for the former and more benign clinical course. However, in about 5% of cases permanent severe pulmonary dysfunction occurs which accounts for most the morbidity and mortality seen with the disease (Figure 1) (1). Indeed, respiratory failure is the most common cause of death from sarcoidosis in the United States and Europe as opposed to Japan where cardiac sarcoidosis is the major cause of mortality (3). Advanced sarcoidosis will be the subject of this review with a special focus on pulmonary hypertension and lung transplantation as a last resort treatment option for select patients with end-stage disease.

## 2) **Pulmonary Hypertension**

### **a. Overview**

Sarcoidosis is characterized pathologically by non-caseating granulomas and it is the sequela of these that determine the clinical manifestations of the disease. Patients who progress to develop stage IV fibrocystic disease commonly manifest physiologically with varying degrees of restrictive and obstructive disease and a decreased diffusion capacity (1). Pulmonary hypertension (PH) is an increasingly recognized complication of sarcoidosis with a reported prevalence between 1 and 28% of all patients at rest and up to 43% with exercise (4, 5, 6). PH most commonly occurs in association with advanced stage IV disease, but can also occur in the context of relatively normal lung function and preserved parenchymal architecture. Patients with recalcitrant dyspnea and normal left ventricular function have a higher reported PH prevalence of approximately 53% (7). Sarcoidosis patients who are listed for lung transplantation have an even higher rate of ~74% (8). In our own clinic, we have found a similar prevalence of PH (~75%) based on right heart catheterization of 104 transplant and non-transplant candidates with advanced sarcoidosis evaluated over a 14 year period (Figure 2).

### **b. Pathophysiology of PH in Sarcoidosis**

The most recent World Health Organization (WHO) conference (Dana Point, California 2008), categorized PH into five groups. Group I or Pulmonary Arterial Hypertension (PAH) includes the prototypical disease of idiopathic pulmonary arterial hypertension and other forms of associated PAH, while group II is PH related to left sided heart disease, group III is seen in association with lung disease, group IV is due to chronic thromboembolic disease and group V is comprised of miscellaneous conditions. Sarcoidosis is categorized within the last group since the pathogenesis of associated PH is complex and multifactorial with characteristics and similarities to all four former groups (Figure 3) (9, 10).

The majority of sarcoidosis patients with PH has stage IV disease and associated impaired pulmonary function tests (PFTs) (Figure 2) (11). PH is therefore usually attributed to the destruction of the capillary bed by the fibrotic process and/or regional hypoxemic vasoconstriction. However, the severity of PH does not always correlate with

the degree of parenchymal lung disease and blood gas abnormalities, suggesting that other mechanisms may be playing a role (Figure 3) (4, 8, 11). These other contributors may be directly related to the pulmonary vasculature or extrapulmonary, either within the mediastinum or in the form of an associated co-morbidity.

Granulomatous involvement of the pulmonary vessels is common in sarcoidosis-associated PH, and has been described in 69-100% of patients with PH (12). The granulomatous inflammation tends to involve the lung in a lymphatic distribution, thus neighboring the granulomas adjacent to the pulmonary arteries and veins in the bronchovascular bundles and interlobular septae. The granulomas may be found in all layers of the vessel wall, but other pathologic findings are commonly seen, including inflammation, necrosis, destruction of the musculoelastic media of the small and medium-sized vessels, endothelial proliferation and disruption of the basal lamina. As a result, an occlusive vasculopathy may develop, especially in the small arterioles and venules (12, 13). When the granulomatous infiltration involves the pulmonary veins preferentially, this may result in a clinical picture that mimics pulmonary veno-occlusive disease (PVOD) (14, 15, 16). In addition, an intrinsic venopathy may result in a PVOD-like picture (11). In-situ thrombosis (thrombotic angiopathy) is another intravascular mechanism which has been described (13). More proximally, mediastinal or hilar adenopathy and any accompanying fibrosis can result in mechanical extrinsic compression of the large pulmonary arteries and an increased pulmonary vascular resistance (Figures 1, 4) (11, 17, 18, 19).

The geographical distribution of the non-caseating granulomas and fibrosis differentiates the PH related to sarcoidosis from WHO group I PAH, which tends to involve the pulmonary vasculature in a more homogenous fashion. Typically the architectural distortion that results from fibrocavitary disease favors a more central and upper lobe distribution. Parenchymal remodeling may also result in vessel tortuosity, turbulent flow and shear stresses which may perpetuate the development and progression of PH (20). The heterogenous distribution of disease might contribute to the apparent dissociation between the degree of restrictive physiology, a surrogate for the parenchymal disease burden, and the prevalence and severity of PH. The central predilection specifically may involve the proximal lobar vessels with a greater propensity for the

subsequent development of PH. Fibrosis in proximity to the pulmonary arterial circulation may also adversely affect the vascular capacitance, a surrogate of vessel stiffness. A low vascular capacitance has been demonstrated to portend a worse prognosis in patients with PAH (21). If the same holds true for the PH of sarcoidosis, this might help explain the significant mortality implications of even mild elevations in PA pressures.

There are a number of cytokines that have been found to be up-regulated in sarcoidosis that could perpetuate the development of PH. One such example is endothelin-1 (ET-1), which has been implicated in the pathogenesis of both idiopathic PAH and various interstitial lung diseases (22, 23, 24). ET-1 is produced primarily by endothelial cells, smooth muscle and airway epithelial cells, with production induced by hypoxia, shear stress and various growth factors and cytokines (24). It is a potent vasoconstrictor which is also thought to have long term vascular remodeling properties (24). Tumor necrosis factor (TNF) alpha, which is thought to play a central role in the pathogenesis of sarcoidosis, has also recently been implicated in the inflammatory pathway of PAH (25, 26). Conceptually therefore, the up regulation of these, and perhaps other cytokines, may contribute to the development of PH. The prospect of cytokine “cross-talk” may therefore provide an additional explanation for the disproportionate PH that is seen in the context of well-preserved lung volumes.

There also may be increased pulmonary vasoreactivity in sarcoidosis, as suggested by the favorable acute response to vasodilators, including nitric oxide (NO) and prostacyclin. The mechanism for this is not clear, but may be partially explained by endothelial damage from sarcoidosis granulomas, with a subsequent decrease in synthesis and release of NO and prostaglandins. This may have long-term sequela with chronic, pulmonary vasoconstriction and associated remodeling (27, 28).

In some cases, extra-pulmonary manifestations of sarcoidosis may also contribute to the development of PH. Not infrequently, direct myocardial involvement by granulomas and myocardial fibrosis may lead to left ventricular systolic and diastolic dysfunction (29). In one study, 30% of sarcoidosis patients with evidence of PH demonstrated elevated pulmonary capillary wedge pressures (PCWP). This underscores the need to rule out left-sided heart disease in the comprehensive evaluation of PH related

to sarcoidosis (30). As with all forms of PH, right heart catheterization is therefore mandatory in establishing the diagnosis.

Hepatic granulomatous infiltration and subsequent cirrhosis may be seen as a complication of the disease, and therefore porto-pulmonary hypertension should be considered in patients with stigmata of liver dysfunction (31). Other common comorbidities, which are not necessarily sarcoidosis-specific, including obstructive sleep apnea (OSA), should not be overlooked if patients are thus predisposed. Indeed, the prevalence of OSA in sarcoidosis has been reported to be 17%, which is much higher than what might be expected in a healthy patient population (32). Finally, while chronic thromboembolic disease should be considered as a potential cause of or contributor to PH, acute pulmonary embolism might also warrant exclusion in the context of new acute or subacute shortness of breaths and/or signs of increasing right-sided heart failure (33, 34).

### **c. Impact and Outcomes of PH in Sarcoidosis**

The presence of PH has been shown to be associated with greater supplemental oxygen requirements, reduced functional capacity and greater caregiver dependency (35). The mortality implications of any PH, both precapillary and venous, in the context of sarcoidosis are also profound with a >10-fold increase in mortality and an estimated 5 year survival of only 59% (11, 30). Sarcoidosis PH patients are more likely to be listed for lung transplantation and not surprisingly, also have a greater likelihood of succumbing while on the wait list (8, 36). One of the issues in sarcoidosis, as with all forms of parenchymal lung disease associated PH, is whether patients are succumbing because of PH or in the presence of PH. With regards to the latter scenario, it might be that PH is a surrogate for another disease-related process that is driving mortality. In one study which demonstrated that PH was associated with sarcoidosis mortality, the only hemodynamic factor that remained predictive of mortality after multivariable analysis was the right atrial pressure (RAP) (36). Moreover, this study also demonstrated hemodynamic progression of PH in the patient cohort. This evidence of right-sided heart

failure infers that patients with sarcoidosis-related PH are indeed dying from their PH, rather than the PH being an epiphenomenon.

#### **d. Clinical Presentation and Diagnostic Testing**

The diagnosis of PH in sarcoidosis can be difficult as the most common symptom is dyspnea on exertion which is frequently attributed to the underlying parenchymal lung disease (37). One study reported no difference in the presenting symptoms of sarcoidosis patients with and without concomitant PH (4). PH should be suspected in any patient with signs and symptoms of right-sided congestive heart failure, especially lower extremity edema. However, the clinical signs of right-sided heart failure have a low sensitivity, manifesting in as few as 21% of patients with PH (4). Therefore a high index of suspicion needs to be maintained, especially in patients with symptoms that appear to be out of proportion to the degree of parenchymal lung disease, or who have more subtle signs of PH including a loud or palpable P<sub>2</sub> heart sound.

Although PH is more common in patients with advanced fibrosis, there are no specific radiographic findings that predict the presence or absence of PH (5, 11). Chest roentonography frequently shows evidence of hilar adenopathy, however hilar fullness may also be due to pulmonary artery enlargement. In this regard, computed tomography (CT) chest scans can be very helpful in providing the structural detail necessary to discern these. The presence of large PA segments on CT scanning should raise the suspicion for underlying PH, although the predictive accuracy of this finding does require further study. There are additional CT findings that should raise the suspicion for PH including evidence of extrinsic compression of large pulmonary arteries by lymphadenopathy or fibrosis (Figure 4).

Blood tests that have been shown to correlate with the presence or severity of PAH include brain natriuretic peptide (BNP) and N-terminal fragment–proBNP (NT-proBNP) levels. There is data to suggest that an elevated BNP is a marker of a poor prognosis in patients with chronic lung diseases (38). In one study of patients with interstitial lung disease, an elevated BNP was the strongest predictor of overall mortality, independent of the severity of the underlying fibrosis (39). However, the BNP might be a global biomarker of cardiac dysfunction, rather than being specific for PH. Indeed, in a



recently published echocardiography-based prospective study of 150 Japanese patients with sarcoidosis, NT-proBNP was found to be a useful biomarker in identifying cardiac sarcoidosis, but not PH (40).

Pulmonary function data may provide helpful information. Specifically, there is some indication that the lower the diffusion capacity ( $DL_{CO}$ ), the greater the likelihood of underlying PH. A diffusion capacity below 60% of predicted has been reported to be associated with a seven fold increase in underlying PH (41). Although sarcoidosis-PH patients tend to have more restrictive disease, the correlation between PH and measures of lung volumes is poor, since PH can develop at any stage of the underlying disease (Figure 2).

Sarcoidosis-PH patients have greater supplemental oxygen needs, shorter 6 minute walk test distances (6MWT) and lower oxygen saturations ( $SpO_2$ ) with exercise (4, 8). Patients who desaturate below 90% are 12-fold more likely to have associated PH (41, 42). Conversely, the absence of desaturation below 90% with exercise implies a low likelihood of significant PH (41, 42). The association of PH with a lower  $SpO_2$  raises the pathophysiologic conundrum of whether the PH is causing the desaturation, or if hypoxemia is perpetuating the PH. It is likely that both scenarios are true with each pathologic element perpetuating the other. Indeed, the temporal nature of the pathophysiologic sequence is semantic since neither scenario diminishes the utility of the 6MWT as a screening tool for PH. Also, any hypoxemia should warrant the institution of supplemental oxygen, especially in the presence of documented PH (42). The multisystem nature of sarcoidosis invokes other possible reasons for a lower distance. It is possible therefore that the distance component is more useful to evaluate response to therapy, rather than as a screening tool for PH (41, 42, 43). In an attempt to account for both the distance and  $SpO_2$  components of the 6MWT, the composite distance saturation product (DSP) has been examined in sarcoidosis and indeed, a lower DSP has been demonstrated to be associated with echocardiography-diagnosed PH (44).

Continuous Doppler flow transthoracic echocardiogram (TTE) is the most reliable non-invasive test to screen for the presence of PH. TTE allows calculation of the right ventricular systolic pressures (RVSP) from the maximal velocity of the tricuspid regurgitation jet and an estimation of the right atrial pressure. However, there are

inherent variables which can affect the accuracy of this calculation, which may be further compromised in the presence of chronic lung diseases (45). Specifically, in a study of 374 subjects with various forms of advanced lung disease including sarcoidosis, the RVSP could only be estimated in 44% of the patients. Additionally, in approximately one half of these cases, pressure estimations were inaccurate when compared to right heart catheterization-derived numbers. TTE tends to overestimate, but can also underestimate the true RVSP, and therefore does not have sufficient predictive properties to be solely relied on to diagnose or rule out PH (45). However, TTE is very useful in assessing for other cardiac abnormalities, such as left ventricular systolic or diastolic dysfunction, valvular abnormalities, the presence of shunts and pericardial effusions (43). In the absence of tricuspid regurgitation, the diagnosis of PH should still be suspected when there are signs of right ventricular (RV) dysfunction, including dilatation, hypertrophy, systolic dysfunction and flattening or bowing of the interventricular septum (43). The presence of any of these or other clinical features suspicious for the presence of PH should prompt right heart catheterization to further characterize the pulmonary hemodynamics (37).

As with all forms of PH, right heart catheterization remains the gold standard for the diagnosis of PH in sarcoidosis. In addition to allowing the direct measurement of the pulmonary artery pressures (PAPs), the right atrial pressure and cardiac output are also obtained, all of which impart additional important prognostic information (35, 36). Measurement of the pulmonary capillary wedge pressure (PCWP) is also essential in differentiating between arterial and venous pulmonary hypertension. There are no guidelines as to when a RHC should be obtained in patients with sarcoidosis. This should be evaluated on a case by case basis taking into account the patients' clinical presentation which might include their symptoms, clinical signs, ECHO findings, 6MWT distance, PFT data or BNP. The decision to proceed with RHC should also be predicated on whether this will impact the patients' management. For example, the hemodynamic variables might provide important prognostic data including informing the decision about the timing of lung transplantation. Also, if there is a strong likelihood that the PH will be deemed sufficiently severe to warrant therapy, then this might provide reason to proceed with RHC.

#### **e. Management of PH in Sarcoidosis**

The optimal management approach to PH associated with sarcoidosis is unknown, and is based on limited evidence. Modifiable risk factors and co-morbidities should be sought and treated where indicated. Hypoxemia correlates to some extent with the severity of PH, and supplemental oxygen is thus recommended to reverse resting hypoxemia. The presence of any contributory co-morbidities, including OSA, cardiac dysfunction or thromboembolic disease, warrants standard therapeutic interventions (13). The treatment of sarcoidosis with anti-inflammatory and other immunomodulating therapies has a theoretic role if the predominant pathologic potentiator of the PH is active sarcoidosis. However, such an approach has not demonstrated consistent benefits with response rates of only 20-30% reported in small series (11, 46, 47, 48). However, in no studies have patients with Stage IV disease, the most common stage associated with PH, showed a significant hemodynamic response to corticosteroids. Thus, steroids should be avoided in patients with evidence of advanced fibrocystic disease and ought to be considered only for patients with evidence of active disease and/or compression of central vascular structures by bulky lymphadenopathy (47, 48).

The use of currently available pulmonary vasoactive agents is controversial since there have been no randomized, placebo-controlled studies to demonstrate their efficacy in sarcoidosis patients. When therapy is being considered, the term “disproportionate PH” is frequently referred to with the inference being that there is a component of the pressure increase that is not explained by or directly due to the extent of the parenchymal lung disease. This is a concept that is frequently spoken of in the context of not only sarcoidosis, but many other forms of diffuse parenchymal lung diseases. However, there are no studies attempting to address what constitutes “disproportionate PH”, but it is likely that it cannot be defined by a single pressure cut-point. An alternative concept or methodology to address this is to regard PH as “disproportionate” if when treated, it results in a measurable clinical improvement.

When therapy is being considered, it is important to bear in mind the potential to do more harm than good in patients with significant parenchymal lung disease.

Specifically, any pulmonary vasodilatation may potentiate ventilation/perfusion mismatching with worsening hypoxemia, while it is also possible that a pulmonary edema pattern might be precipitated in those patients with pre-existing PVOD-like lesions (19, 49, 50). Despite these cautionary caveats, there are a number of small case series attesting to the potential utility of PAH-specific therapies in patients with sarcoidosis (Table1). The current available approved therapies for PAH target one of three pathways, which include the endothelin, nitric oxide and prostacyclin pathways.

#### **i. The Endothelin Pathway**

The finding of increased endothelin-1 levels in patients with sarcoidosis and in subjects with idiopathic pulmonary arterial hypertension provides a theoretical rationale for the use of endothelin receptor antagonists (ERAs). However, experience in sarcoidosis is mostly limited to a few retrospective case series, where ERAs have been used alone or in combination with other medications. Baughman and colleagues reported 5 patients in whom there was a decrease in the mean pulmonary artery pressure (mPAP) from an average of 50mmHg to 35mmHg after at least 4 months of treatment (7). Another study described 7 patients treated either with bosentan alone (n=3) or in combination with prostanoids (n=4), in whom ~50% responded to therapy after 6-18 months of follow-up (51). A two-center retrospective study by Barnett and associates, reported outcomes in 22 sarcoidosis patients with PH who received a variety of vasoactive therapies, including bosentan (n=12 ) and also sildenafil (n=9) (52). An overall improvement in the mPAP, pulmonary vascular resistance (PVR) and 6MWT distance was demonstrated, especially in those patients with limited fibrosis. Despite this apparent salutary response, the overall prognosis remained quite poor, with a 3 year survival of only 74%. There has been one randomized, placebo-controlled study of ambrisentan, a selective endothelin receptor A blocker, in 17 patients with sarcoidosis-related PH. Unfortunately this was a negative study that has only been reported in abstract form thus far (53). A large prospective randomized 16 week study of bosentan in this patient population is currently underway, with an anticipated completion date of December 2012 (54).

## **ii. Nitric Oxide and Phosphodiesterase Inhibitors**

Nitric oxide (NO) is a potent vasodilator with a very short half-life, that may be delivered via the inhaled route. There has been one report describing the use of ambulatory inhaled NO in 8 patients with sarcoidosis, of whom 5 had improvements in their 6MWT distance (27). This is not as yet a feasible therapeutic option due to the lack of approved and available ambulatory delivery systems. The NO pathway may be targeted by selective phosphodiesterase type 5 inhibitors (PDE-5). This blockade increases local NO levels in the arterial smooth muscle cells, thereby promoting short and long-term vasodilation and possibly long-term anti-proliferation of vascular smooth muscle cells (19, 50). Aside from the 9 patients reported in the Barnett paper, there has been one additional retrospective study of 12 patients who were treated with sildenafil for a range of 1-12 months (52, 55). Although there was no significant change in the 6MWT distance, the study did demonstrate an improvement in the pulmonary hemodynamic profile with a reduction in the mPAP and PVR accompanied by an increase in the cardiac index. Although these findings are encouraging, the ultimate role of PDE-5 inhibitors in sarcoidosis-related PH remains to be determined by further prospective studies.

## **iii. The Prostacyclin Pathway**

This pathway is targeted by prostanoid analogues that may be administered intravenously, subcutaneously or via the inhaled route. These agents are potent vasodilators which may also inhibit platelet aggregation (19, 26, 50). There is very limited data on the use of IV epoprostenol in sarcoidosis, but in one study of 6 patients with advanced fibrotic disease, there was an improvement in functional class in all but one of the patients (56). Improvements in functional class and pulmonary hemodynamics have also been demonstrated in another study that included the use of either inhaled nitric oxide (NO) or both inhaled nitric oxide and epoprostenol in combination (27). An open-label study of inhaled iloprost in 22 cases of sarcoidosis-related PH, demonstrated hemodynamic improvement in six patients, with a more than 20% decrease in the PVR (57). Additionally, there were downstream clinical correlates noted with an overall increase in the 6MWT distance (~30 meters) and improvements in patients' quality of life.

## **f. Conclusion**

The cumulative evidence from the growing body of literature suggests a potential benefit of PAH-specific agents in select patients with sarcoidosis-associated PH. However, before these therapies can be universally endorsed and adopted, it is necessary for the appropriate prospective, randomized, double-blind clinical trials to be undertaken and completed. Such studies are mandatory to validate that this therapeutic approach is of benefit and to best define the patient phenotypes most likely to respond and least likely to deteriorate. In the absence of such trials, if any such therapy is contemplated, it should be implemented with caution and with the full knowledge and “buy in” of the patient. Each case should be treated as an “N of one” study with close serial follow-up. Monitoring of patients should include an assessment of their symptoms, the impact on their quality of life and an objective functional study, such as the 6MWT. Consideration should be given to discontinuing the medication in the absence of any improvement or in the presence of any untoward side-effects.

### **3) The Role of Lung Transplantation**

#### **a. Overview**

Lung Transplantation (LTx) has evolved into an important therapeutic option for many patients with various forms of advanced lung disease, including sarcoidosis. Based on data from the International Society of Heart and Lung Transplant (ISHLT), sarcoidosis represents 2.6% of all conditions for which transplants have been performed, compared to 31% for IPF, the most commonly transplanted fibrotic disorder (58). Although sarcoidosis is a more common condition, fewer patients will advance to stage IV disease and therefore require transplant consideration. On the other hand, IPF is a disease of the elderly with more patients being disqualified by virtue of their age. National statistics from the USA of admissions and deaths based on ICD-9 codes from 2009 provide a “snapshot” view of patients with either “IPF” or “sarcoidosis” of sufficient severity to warrant hospital admission. There were 3,289 IPF admissions (~one third <64 years of age), whereas, there were 7,034 hospital admissions for sarcoidosis (~85% <64 years). As a surrogate of disease severity there were 478 IPF deaths versus 83 sarcoidosis related deaths from amongst these patients. Thus for every 5.75 IPF in-hospital deaths, there was 1 sarcoidosis mortality event. However, the IPF to sarcoidosis transplant ratio is double that at ~12:1. Comparison of these ratios, albeit accompanied by many caveats, does provide a foundation whereupon one might speculate about a relative under-representation of patients with sarcoidosis receiving lung transplants.

Lung transplantation carries with it significant risk of both morbidity and mortality and therefore, as for all diseases, should only be considered for patients who have failed all other therapeutic modalities. In the context of sarcoidosis, transplantation is reserved for those patients with advanced fibrocystic disease in whom there is no possibility of spontaneous resolution and who have invariably previously failed medical therapy. While it is hoped that transplantation will result in an improved quality of life, conceptually the timing of the procedure is mostly determined by when it is deemed to confer a survival advantage.

There are very few studies which have examined the factors that predict the development of end stage pulmonary disease in sarcoidosis. In the largest non-transplant

cohort of 479 sarcoidosis patients followed for up to 7 years, the factors influencing the development of respiratory failure included both radiographic findings of fibrosis and a vital capacity below 2.5 liters. A vital capacity of less than 1.5L was present in all patients who subsequently developed end stage disease (59). The ISHLT listing guidelines are primarily based on studies examining the United Network of Organ Sharing (UNOS) database as well as a much smaller study of 43 patients from a single transplant center (33, 60, 61). Univariate analysis from this latter study demonstrated that resting hypoxemia, pulmonary hypertension ( $mPAP \geq 35 \text{ mmHg}$ ), cardiac index  $\leq 2 \text{ L/min/m}^2$ , and  $RAP \geq 15 \text{ mmHg}$  were all significantly associated with increased mortality on the waiting list. However, multivariate analysis identified only the  $RAP \geq 15 \text{ mmHg}$  as an independent prognostic variable with a 5.2 fold increased risk of death (61).

The study that examined the UNOS database compared 427 sarcoidosis to 2,115 IPF patients, and found that the  $mPAP$  was significantly higher in the sarcoidosis group (60). The authors went on to develop a mortality prediction model which confirmed that PH played a prominent role in determining outcomes. Specifically, transplant list survivors had a mean  $mPAP$  of  $31.7 \pm 11.5$  compared to  $41.1 \pm 14.4 \text{ mmHg}$  for those who succumbed on the list (35). Differences in PH were not attributable to primary cardiac dysfunction as the PCWP was similar in the two groups. Other prognostic factors that were determined from this study included African American race (odds ratio 2.5) and the amount of supplemental oxygen used at rest ( $2.2 \pm 2.0$  versus  $2.9 \pm 1.7 \text{ L/min}$ ).

The ISHLT consensus guidelines for the referral and selection of lung transplant recipients, acknowledges the paucity of data and the difficulty in predicting outcomes for sarcoidosis (62). Therefore due to the unpredictable, variable and chronic nature of the disease, the optimal timing of listing and transplantation is difficult to discern. Nonetheless, when patients develop New York Heart Association (NYHA) class 3 and 4 symptoms, referral for transplant evaluation is recommended. Furthermore, the guidelines recommend that in concert with these symptoms, the presence of either hypoxemia at rest, PH or a  $RAP$  above  $15 \text{ mmHg}$  should prompt listing for transplantation.

Although these recommendations appear reasonable, they remain quite broad and often do not offer guidance to practitioners dealing with individual patients. This lack of



clarity might be responsible for the poor outcomes previously noted for listed sarcoidosis patients. In this regard, a single center USA-based study in 2001 reported outcomes of listed sarcoidosis patients and demonstrated an astonishingly high mortality rate of 53% (61). A larger and broader-based cohort of patients drawn from the UNOS database was shown to have a wait list mortality of 28%, which is still unacceptably high (35). This attrition was equivalent to that of IPF patients who were listed for lung transplantation. The diagnosis of sarcoidosis is generally attained many years prior to patients' progression to advanced stage IV fibrocystic disease, as opposed to IPF patients who are frequently diagnosed closer to the window of opportunity for transplantation. Therefore, this does raise the concern of whether the referral of sarcoidosis patients for transplant consideration might be unduly delayed.

These latter studies represent outcomes prior to the institution of the current USA lung allocation score (LAS) which was implemented in April 2005. Instead of the time-on-the list candidate ranking model, the LAS system utilizes an organ allocation approach where lungs are distributed on the basis of both medical urgency (i.e. risk of death without a transplant) and "net transplant benefit" (i.e. the anticipated survival prolongation enabled by transplantation). Scores are calculated from survival models which capture projected one year survivals with and without transplantation. The higher the score, the greater the likelihood patients will succumb to their disease without transplant and the greater the likelihood they will do well post-transplant (63).

The implementation of the LAS system has significantly shifted the landscape of patients who receive transplants (64). This has been closely evaluated in the more commonly transplanted conditions such as COPD, IPF, cystic fibrosis and pulmonary hypertension. The influence of this change has not been systematically examined in sarcoidosis. Nonetheless, a UNOS data query for the two and a half year period after the implementation of the LAS system (May 2005-December 2007), suggests that there has been a change in the severity of illness and outcomes on the list of sarcoidosis patients since the implementation of the LAS (Nathan SD, personal communication). Although prior data would suggest that sarcoidosis patients are generally "sicker" at the time of listing for transplantation, the distribution of LAS scores compared to those of IPF patients suggests that the opposite is true (Figure 5). For example, 42% of the sarcoidosis

patients listed for bilateral lung transplantation had relatively low scores of between 30 and 35, as opposed to only 13.4% of IPF patients. The 6 and 12 month mortality rate of these two cohorts in the absence of transplantation was 1.75% versus 5.26% and 3.51% versus 10.7%, for sarcoidosis and IPF respectively. These outcomes are noteworthy, especially in lieu of the longer median wait time for sarcoidosis (390 days) compared to IPF patients (196 days). This difference in outcomes also underscores the imprecise nature of survival prediction models for both sarcoidosis and IPF. This era-dependent prognostic switch could reflect that milder patients with IPF and possibly sicker patients with sarcoidosis are less likely to be referred or listed for lung transplantation.

## **b. Sarcoidosis Specific Issues: Implications for Transplantation**

### **i. Sarcoidosis as a Multi-system Disease**

Sarcoidosis is a multisystem disease, and therefore, extra-pulmonary manifestations need to be taken into considerations during the work up for transplantation. While the thorax is the most common site of disease, cutaneous, ocular, neurological and cardiac sarcoidosis occur in 25-30% of patients (65). Indeed, although the characteristic non-caseating granulomas have been reported in virtually every organ system, their presence does not necessarily imply current or future organ dysfunction and in many cases is an incidental finding. Therefore, the decision to perform lung transplantation must be individualized based on the severity of the lung disease and the pathophysiologic consequences of any extra-pulmonary manifestations.

Cardiac sarcoidosis may potentially have the greatest implications on lung transplantation candidacy since it may portend a poor prognosis (29). Evidence of cardiac granulomas has been reported in up to 25% of autopsy specimens in the US and in 50% of patients in Japan (65, 66). Clinically apparent disease occurs in only ~5% of patients in the US and up to 20% of patients in Japan (67).

There is no consensus approach to screen for cardiac sarcoidosis. However, there are a number of studies which have examined various modalities such as positron emission tomographic scanning, gallium scintigraphy and cardiac magnetic resonance imaging (68). Although there is utility to these modalities in the detection of occult sarcoidosis, the ultimate decision with regards to whether this impacts their lung

transplant candidacy, depends on the cardiac pathophysiologic manifestations of the disease process. For the same reason, documentation of the presence or absence of granulomas is immaterial. Indeed, it is also possible that those patients with cardiac manifestations, especially diastolic dysfunction, are thus predisposed by other comorbidities, rather than the sarcoidosis itself (30). Cardiac sarcoidosis can affect any part of the heart and conduction system. Granulomas and subsequent fibrosis may induce conduction abnormalities including heart block and ventricular arrhythmias. Other manifestations may also include mitral regurgitation, left ventricular dysfunction, congestive heart failure, ventricular aneurysms, pericarditis, pericardial effusion and cardiac tamponade (29). Patients may present with syncope, heart failure, and sudden death. Therefore, studies that should be obtained as part of a lung transplant evaluation include an ECG, echocardiogram and left and right heart catheterizations. An MRI might also provide useful information in select cases in which the cardiac status warrants additional investigation. For patients who have symptoms of dizziness or syncope, an event monitor might be helpful to discriminate between arrhythmias and pulmonary hypertension.

The most important predictor of survival in cardiac sarcoidosis appears to be left ventricular function with an ejection fraction (EF) <50% associated with an increased mortality risk (69). Patients with significant left ventricular dysfunction may be considered for heart-lung transplantation. However, the presence of compromised left ventricular function can represent a transplant conundrum in that the ejection fraction might not be low enough to warrant heart transplantation, but could be sufficiently reduced to represent a contraindication to lung transplantation alone.

## **ii. Parenchymal Complications**

### **1. Cavities and Mycetomas**

Cavitary lesions can be seen in all the stages of sarcoidosis, but are most common in Stage III and IV disease, with a reported prevalence on CXR of 0.6-1.3% and on CT scan of 2.2% (70, 71, 72). Most cavitary lesions do not resolve, but spontaneous resolution has been reported in about 10-25% of patients (72). They tend to be multiple in most cases and either unilateral or bilateral with an upper and mid-lung zone

predilection (Figures 1, 6). The cavities may vary in diameter from 10-100 millimeters and can be both thin and thick-walled in nature. Thin-walled cavities are more common in the absence of complicating aspergillomas while, in the presence of aspergillomas, thick-walled cavities predominate.

Mycetomas are masses of fungal mycelia that grow in preexisting lung cavities and are therefore most commonly seen in Stage III and IV sarcoidosis (73) (Figure 7). Although fungus balls can be caused by many fungi, most are caused by members of the *Aspergillus* genus (72, 74). The exact incidence of aspergillomas in sarcoidosis is uncertain, although studies report an incidence of ~2% (72, 75).

The natural history of aspergillomas is variable. Most are stable and do not progress under observation. Some increase in size, and approximately 10% resolve spontaneously (76). Data from our Center suggests that the presence of aspergillomas does appear to be associated with worse outcomes (Figure 8) (77). Whether this is a direct result of the aspergilloma or if its presence is a surrogate for disease severity remains uncertain.

Many fungus balls are asymptomatic and are only discovered during routine roentgenographic surveillance. Some patients present with hemoptysis, which is the most important clinical feature of this complication. It is estimated that 90% of the patients experience at least one episode of hemoptysis. The magnitude of the hemoptysis ranges from trivial to massive. Hemoptysis has been ascribed to local vascular invasion of the cavity wall by *Aspergillus* organisms. Collateral vessels from the bronchial arteries and from systemic arteries of the chest wall may augment the blood supply to inflammatory tissue around the cavity, predisposing to serious bleeding (72-75, 78). Other potential pathogenic mechanisms have been proposed including friction of the mobile fungus ball against a hypervascular wall, toxins or enzymes released by the fungus, a type III antibody-antigen reaction and conversion to chronic necrotizing aspergillosis. The source of the bleeding is not always evident, especially in the context of multiple aspergillomas, and the possibility of any hemoptysis being due to other causes such as tracheobronchitis is always worth considering. There are a few reports of dissemination to invasive pulmonary aspergillosis, but the risk is generally considered negligible (79). Indeed, it is likely that it only those patients who receive immunosuppressive and

cytotoxic drugs who are at risk of developing invasive disease (74).

The diagnosis is usually established by the presence of a seemingly mobile mass within a cavity seen on chest X-ray or CT scan. Characteristically, the lung cavities containing the aspergilloma have thickened walls (72). Cultures and serologic evaluation may also be helpful, but are not necessary to establish the diagnosis (71, 78). The organism can usually be cultured from expectorated sputum, while 100% of patients with an established aspergilloma have serum precipitins against *Aspergillus*, usually with multiple bands. The occasional negative precipitin test ordinarily occurs in the context of a non-fumigatus *Aspergillus* species.

There is no consensus or guidelines for the treatment of sarcoidosis-associated aspergillomas. There are some early reports proposing observation while more recent studies advocate the implementation of therapy (80-82). Drug therapy of aspergillomas has not been examined in a systematic manner, although the use of itraconazole and more recently voriconazole has been reported (81, 83). These may result in symptomatic improvement and even complete resolution of the radiographic findings (84). The use of intracavitary amphotericin B and voriconazole are also purported treatment approaches (85, 86).

Although resection of the abnormal lung has the potential to be curative, most patients have underlying lung disease that is too advanced to withstand a surgical resection (75, 78, 87, 88). Additionally, there is the risk of other serious surgical complications, including postoperative infection, bleeding, and the development of bronchopleural fistula (75).

Life-threatening hemoptysis may require emergency surgery, which until recently was the only viable treatment option. In medical centers where the technology is available, bronchial artery embolization under radiographic guidance can be attempted to control the bleeding. Direct instillation of amphotericin B or saturated solution of potassium iodide into the cavity may also be associated with decreased bleeding and is an alternative option for patients who are poor surgical candidates (89, 90).

Currently, the presence of a mycetoma is considered a relative contraindication for transplantation. Theoretically, there may be an increased risk for seeding the thoracic cavity during explantation, especially if there are cavities that abut the pleura.

Additionally, a peripherally located aspergilloma and the associated pericavitary inflammatory response can promote pleural thickening which may complicate the explant part of the procedure. A tedious resection may be associated with a greater propensity for pleural bleeding, especially in those patients who require cardiopulmonary bypass. A complicated surgery may also result in an unduly prolonged cold ischemic time and increase the risk for primary graft dysfunction (PGD) (91).

The impact of pre-transplant aspergillomas on post-transplant outcomes has not been systematically studied. One small study reported results of 9 patients with mycetomas with various underlying diseases, six of whom had sarcoidosis (92). All six received bilateral lung transplant, and 5 survived the transplant. Outcomes of the group were significantly worse, with a median survival of only 16 months compared to 56.7 months for other transplant recipients. Although the number of sarcoidosis patients was too small for any meaningful comparison, the authors suggested that aggressive pre-transplant antifungal prophylaxis may impact survival favorably by decreasing the burden of fungal organisms. It is also recommended that the presence of mycetomas be considered as a form of suppurative disease that mandates a bilateral procedure.

## **2. Bronchiectasis**

Bronchiectasis is commonly seen in conjunction with radiographic stage IV disease. It is felt to result from mechanical stretch of the airways due to parenchymal fibrosis (93). Traction bronchiectasis becomes evident as parenchymal disease progresses and has been reported in up to 40% of patients with the fibrotic stages of sarcoidosis (94, 95). Localized bronchiectasis of the right middle lobe caused by obstructing sarcoidosis granuloma has also been described (96).

Traction bronchiectasis and bronchial distortion seldom cause bronchiectatic symptoms (93). Nonetheless, those patients who do manifest with a chronic productive cough should be considered to have suppurative lung disease. It seems reasonable to extrapolate management strategies from the cystic fibrosis literature, since there are no studies in sarcoidosis-related bronchiectasis, and it is unlikely that such studies will ever be performed. Sputum culture to determine the nature and sensitivity of colonizing organisms with consideration of therapy based on these is therefore prudent. Sarcoidosis

with clinical bronchiectasis is an indication for double lung transplantation, since a single lung will place the allograft at risk of infection from the residual native side (97). Indeed, a higher proportion of bilateral versus single transplants have been performed for sarcoidosis (2.9% versus 2.1%) (58). This bias towards the bilateral procedure is likely predicated by additional factors, including patient age and the presence of underlying PH.

### **c. Transplant Operative Considerations**

Sarcoidosis represents one of the more challenging disease processes for transplant surgeons. Not only is there a heightened propensity for pleural thickening and adhesions, but bulky hilar adenopathy and perihilar fibrosis may also result in a difficult surgery. Further, many of these patients have complicating PH and refractory hypoxemia that renders the surgery difficult to complete off cardiopulmonary bypass. This heightens any bleeding predisposition that may result from an extensive native lung resection. The presence of cavities with aspergillomas in the proximity of the resection always carries the added risk of contamination of the pleural space. In such situations, it is the policy at our Institution to irrigate the pleural space with amphotericin B enriched solution after implantation. If there is documented contamination during the surgery, then this irrigation is continued for the first 24 hours post-operatively.

### **d. Post Transplant Outcomes**

Post-transplant survival in sarcoidosis is equivalent to that of other lung diseases. Specifically, the most recent ISHLT report attests to a 1, 3, 5 and 10 year survival of 72.2%, 56.8%, 50.6% and 31.1%, respectively (58). However, during the first year, sarcoidosis patients have a high mortality, which is second only to those patients with idiopathic pulmonary arterial hypertension.

Short term outcomes were examined in a retrospective UNOS analysis of all sarcoidosis patients who received lung transplants between 1995 and 2000 (98). The study confirmed that only a minority of transplants were performed for this indication (2.8%) and that such recipients in the USA were more likely to be African American, female and younger. They were also more likely to receive double and heart-lung transplant. Thirty day survival rates for the sarcoidosis versus non-sarcoidosis patients

were 83% and 91%, suggesting an almost two-fold unadjusted mortality risk in the sarcoidosis cohort. Multivariate analysis determined that the strongest risk factors for increased short term mortality included the need for combined heart-lung transplant as well as donor and recipient race. Specifically, African-American patients were nearly 50% more likely to die during the initial post-operative period. This difference persisted after excluding heart-lung recipients and controlling for recipient-donor racial mismatch. Finally, the most common cause of death at 30 days after transplant was primary graft dysfunction, whereas infection was the most common culprit among other lung transplant recipients (98). One might speculate that the greater early mortality due to primary graft dysfunction could be related to a more complicated surgical procedure in many of these cases. Despite a greater risk of death during the first year, sarcoidosis patients seem to achieve long term survival rates equivalent to other disease types.

Most theories of the etiology of sarcoidosis invoke either an infectious or immunologic source, either of which could impact the post-transplantation course. With regards to these patients immunologic profile, several studies have examined the incidence of acute and chronic rejection in this population and found no difference (99, 100). There have however been many reports of sarcoidosis recurrence in the allograft with an estimated incidence as high as 66% (101-103). The noncaseating granulomas evident on transbronchial lung biopsy specimens usually represent a histopathologic curiosity, occasionally accompanied by radiographic abnormalities, but rarely resulting in physiologic impairment or symptoms (Figure 9). Nonetheless, there have been isolated case reports of clinically significant recurrence post-transplantation, that usually respond favorably to increased steroid therapy (101-103).

#### **e. Conclusion**

Although a minority of sarcoidosis patients progress to advanced stages of their disease, respiratory failure does remain a major cause of morbidity and mortality. A high index of suspicion should be held for underlying PH in all sarcoidosis patients with advanced disease or symptoms that appear disproportionate to the extent of the underlying parenchymal lung disease. A comprehensive work-up of PH should always



be considered, as there might be other treatable contributory co morbidities.

Management of PH and other sequelae of advanced disease including bronchiectasis and aspergillomas may improve patients' quality of life, possibly improve survival and hopefully forestall the need for transplantation. Lung transplantation is a viable potentially life-saving therapeutic option for select patients with advanced sarcoidosis and may be an underutilized resource for this population. As with all forms of advanced lung disease, early referral for transplant consideration should always be encouraged.

## **References**

- 1) Baughman RP, Teirstein AS, Judson MA, et al. Clinical Characteristics of Patients in a Case Control Study of Sarcoidosis. *Am J Respir Crit Care Med* 2001;164:1885-1889
- 2) Rybicki BA, Major M, Popovich J Jr, Maliarik MJ, Iannuzzi MC. Racial Differences in Sarcoidosis Incidence: A Five Year Study in a Health Maintenance Organization. *Am J Epidemiol* 1997; 145:234-241
- 3) Iwai K, Sekiguti M, Hosoda Y, et al. Racial Differences in Cardiac Sarcoidosis Incidence Observed at Autopsy. *Sarcoidosis* 1994;11:248-251
- 4) Sulica R, Teirstein AS, Kakarla S, NEmani N, Behnegar A, Padilla ML. Distinctive Clinical, Radiographic and Functional Characteristics of Patients with Sarcoidosis-Related Pulmonary Hypertension. *Chest* 2005;128:1483-1489
- 5) Handa T, Nagai S, Miki S, et al. Incidence of Pulmonary Hypertension and its Clinical Relevance in Patients with Sarcoidosis. *Chest* 2006;129:1246-1252
- 6) Gluskowski J, Hawrylkiewicz I, Zych D, Wojtczak A, Zielinski J. Pulmonary Haemodynamics at Rest and During Exercise in Patients with Sarcoidosis. *Respiration*. 1984; 46(1):26-32.
- 7) Baughman RP, Engel PJ, Meyer CA, Barrett AB, Lower EE. Pulmonary Hypertension in Sarcoidosis. *Sarcoidosis Vasc Diffuse Lung Dis*. 2006; 23:108-16.
- 8) Shorr AF, Helman DL, Davies DB, Nathan SD. Pulmonary Hypertension in Advanced Sarcoidosis: Epidemiology and Clinical Characteristics. *Eur Respir J*. 2005; 25(5):783-788.

- 9) Simmoneau G, Robbins I, Beghetti M, et al. Updated Clinical Classification of Pulmonary Hypertension. *JACC* 2009; 54(1), S43-54.
- 10) Baughman RP. Pulmonary Hypertension Associated with Sarcoidosis. *Arthritis Res Ther* 2007; 9 (Suppl 2):S8.
- 11) Nunes H, Humbert M, Capron F, et al. Pulmonary Hypertension Associated with Sarcoidosis: Mechanisms, Haemodynamics and Prognosis. *Thorax* 2006; 61:68-74.
- 12) Takemura T, Matsui Y, Saiki S, et al. Pulmonary Vascular Involvement in Sarcoidosis: A Report of 40 Autopsy Cases. *Hum Pathol* 1992; 23:1216-1223.
- 13) Corte T, Wells AU, Nicholson AG, et al. Pulmonary Hypertension in Sarcoidosis: A Review. *Respirology* 2011; 16:69-77.
- 14) Damuth TE, Biwer JS, Cho K, et al. Major Pulmonary Artery Stenosis Causing Pulmonary Hypertension in Sarcoidosis. *Chest* 1980; 78:888-891.
- 15) Hiffstein V, Ranganathan N, Mullen JBM. Sarcoidosis Stimulating Pulmonary Veno-Occlusive Disease. *Am Rev Respir Dis* 1986; 134:809-811,
- 16) Portier F, Lerebourg-Pigeonnaiere G, Thiberville L, et al. Sarcoidosis Simulating Pulmonary Veno-Occlusive Disease. *Rev Mal Respir* 1991; 8:101-102.
- 17) Toonkel RL, Borczuk AC, Pearson GD, et al. Sarcoidosis-Associated Fibrosing Mediastinitis with Resultant Pulmonary Hypertension: A Case Report and Review of Literature. *Respiration* 2009; 79:341-345.
- 18) Smith LJ, Lawrence JB, Katzenstein AL. Vascular Sarcoidosis: A Rare Case Report of Pulmonary Hypertension. *Am J Med Sci* 1983; 285:38-44.
- 19) Rosen Y, Moon S, Huang CT, et al. Granulomatous Pulmonary Angiitis in Sarcoidosis. *Arch Pathol Lab Med* 1977; 101: 170-174.

- 20) Thannickal VJ, Toews GB, White ES, Lynch III JP, Martinez FJ. Mechanisms of Pulmonary Fibrosis. *Annu Rev Med*. 2004; 55:395–417.
- 21) Mahapatra S, Nishimura RA, Sorajja P, Cha S, McGoon MD. Relationship of Pulmonary Arterial Capacitance and Mortality in Idiopathic Pulmonary Arterial Hypertension. *J Am Coll Cardiol*. 2006; 47(4):799–803.
- 22) Galie N, Manes A, Branzi A. The Endothelin System in Pulmonary Arterial Hypertension. *Cardiovasc Res* 2004; 61:227-237.
- 23) Terashita K, Kato S, Sata M, et al. Increased Endothelin-1 Levels of BAL Fluid in Patients with Pulmonary Sarcoidosis. *Respirology* 2006; 11:145-151.
- 24) Letizia C, Danese A, Reale MG, et al. Plasma Levels of Endothelin-1 Increase in Patients with Sarcoidosis and Fall after Disease Remission. *Panminerva Med* 2001; 43:257-261.
- 25) Sutendra G, Dromparis P, Bonnet S, et al. Pyruvate Dehydrogenase Inhibition by the Inflammatory Cytokine TNF alpha Contributes to the Pathogenesis of Pulmonary Arterial Hypertension. *J Mol Med* 2011; 89:771-783.
- 26) Chen ES, Moller DR. Sarcoidosis – Scientific Progress and Clinical Challenges. *Nature Rev Rheumatol* 2011; 7:457-467.
- 27) Preston IR, Klinger JR, Landzberg MJ, et al. Vasoresponsiveness of Sarcoid-Associated Pulmonary Hypertension. *Chest* 2001; 120:866-872.
- 28) Barst RJ, Ratner SJ. Sarcoidosis and Reactive Pulmonary Hypertension. *Arch Intern Med*. 1985; 145(11):2112-2114.
- 29) Barghout R, Kelly RF. Sarcoid Heart Disease: Clinical Course and Treatment. *Int J Cardiology* 2004; 97:173-182.

- 30) Baughman RP, Engel PJ, Taylor L, et al. Survival in Sarcoidosis Associated Pulmonary Hypertension: The Importance of Hemodynamic Evaluation. *Chest* 2010; 138(5):1078-1085.
- 31) Salazaar A, Mana J, Sala J, et al. Combined Portal and Pulmonary Hypertension in Sarcoidosis: *Respiration* 1994; 61:517-520.
- 32) Turner GA, Lower EE, Corser BC, et al. Sleep Apnea in Sarcoidosis. *Sarcoidosis Vasc Diffuse Lung Dis* 1997; 14:61-64.
- 33) Swigris JJ, Olson AL, Huie TJ, et al. Increased Risk of Pulmonary Embolism Among US Decedents With Sarcoidosis From 1988 to 2007. *Chest* 2011; 140(5):1261-12666.
- 34) 1Crawshaw AP, Wotton CJ, Yeates DG, Goldacre MJ, Ho LP. Evidence for Association between Sarcoidosis and Pulmonary Embolism from 35-year Record Linkage Study. *Thorax* 2011; 66(5):447-448.
- 35) Shorr AF, Davies DB, Nathan SD. Predicting Mortality in Patients with Sarcoidosis Awaiting Lung Transplantation. *Chest* 2003; 124:922-928.
- 36) Arcasoy SM, Christie JD, Pochettino A, et al. Characteristics and Outcomes of Patients with Sarcoidosis Listed for Lung Transplantation. *Chest* 2001; 120:873-880.
- 37) Diaz-Guzman E, Farver C, Parambil J and Culver D. Pulmonary Hypertension Caused by Sarcoidosis. *Clin Chest Med* 2008; 29(3): 549-566.
- 38) Leuchte HH, Baumgartner RA, Nounou ME, et al. Brain Natriuretic Peptide is a Prognostic Parameter in Chronic Lung Diseases. *Am J Respir Crit Care Med* 2006; 173:744-750.

- 39) Corte TJ, Wort SJ, Gatzoulis MA, et al. Elevated Brain Natriuretic Peptide Predicts Mortality in Interstitial Lung Disease. *Eur Respir J* 2010; 36:819-825.
- 40) Handa T, Nagai S, Ueda S, et al. Significance of Plasma NT-preBNP Levels as a Biomarker in the Assessment of Cardiac Involvement and Pulmonary Hypertension in Patients with Sarcoidosis. *Sarcoidosis Vasc Diffuse Lung Dis* 2010; 27(1):27-35.
- 41) Bourbonnais JM, Samavati L. Clinical Predictors of Pulmonary Hypertension in Sarcoidosis. *Eur Respr J* 2008; 32:296-302.
- 42) Baughman RP, Sparkman BK, Lower EE. Six Minute Walk Test and Health Status Assessment in Sarcoidosis. *Chest* 2007; 132:207-213.
- 43) Palmero V, Sulica R. Sarcoidosis-Associated Pulmonary Hypertension: Assessment and Management. *Semin Respir Crit Care Med* 2010; 31(4):494-500.
- 44) Alhamad EH, Ahmad Shaik S, Idrees MM, Alanezi MO, Isnani AC. Outcome Measures of the 6 Minute Walk Test: Relationships with Physiologic and Computed Tomography Findings in Patients with Sarcoidosis. *BMC Pulm Med* 2010; 10:42-49.
- 45) Arcasoy SM, Christie JD, Ferrari VA, et al. Echocardiographic Assessment of Pulmonary Hypertension in Patients with Advanced Lung Disease. *Am J Respir Crit Care Med* 2003; 167:735-740.
- 46) Rodman Dm, Lindenfeld J. Successful Treatment of Sarcoidosis-Associated Pulmonary Hypertension with Corticosteroids. *Chest* 1990; 97:500-502.
- 47) Davies J, Nellen M, Goodwin JF. Reversible pulmonary hypertension in sarcoidosis. *Postgrad Med J* 1982; 58(679):282-285.

- 48) Gluskowski J, Hawrylkiewicz I, Zych D, Zielinski J. Effects of Corticosteroid Treatment on Pulmonary Hemodynamics in Patients with Sarcoidosis. *Eur Respir J* 1990; 3:403-407.
- 49) Palmero V, Sulica R. Sarcoidosis-Associated Pulmonary Hypertension: Assessment and Management. *Semin Respir Crit Care Med* 2010; 31:494-500.
- 50) Diaz-Guzman E, Farver C, Parambil J, Culver DA. Pulmonary Hypertension Caused by Sarcoidosis. *Clin Chest Med* 2008; 29(3):549-571.
- 51) Culver DA, Minai OA, Chapman JT, et al. Treatment of Pulmonary Hypertension in Sarcoidosis. *Proc Am Thoracic Soc* 2005; 2:A862.
- 52) Barnett CF, Bonura EJ, Nathan SD, et al. Treatment of Sarcoidosis-Associated Pulmonary Hypertension. A Two-Center Experience. *Chest* 2009; 135:1455-1461.
- 53) <http://clinicaltrials.gov/ct2/show/NCT00581607> (last accessed on 10/05/2011).
- 54) Judson MA, Ford HJ, Donohue JF, et al. Ambrisentan for Sarcoidosis Associated Pulmonary Hypertension. *Am J Respir Crit Care* 2010; 181:A2368.
- 55) Milman N, Burton CM, Iversen M, Videbaek R, Jensen CV, Carlsen J. Pulmonary Hypertension in End-Stage Pulmonary Sarcoidosis: Therapeutic Effect of Sildenafil? *J Heart Lung Transplant* 2008; 27:329-334.
- 56) Fisher KA, Serlin DM, Wilson KC, Walter RE, Berman JS, Farber HW. Sarcoidosis-Associated Pulmonary Hypertension: Outcome with Long-Term Epoprostenol Treatment. *Chest* 2006; 130(5):1481-1488.
- 57) Baughman RP, Judson MA, Lower EE, et al. Inhaled Iloprost for Sarcoidosis Associated Pulmonary Hypertension. *Sarcoidosis Vasc Diffuse Lung Dis* 2009; 26:110-120.

- 58) Hertz MI, Aurora P, Christie JD, et al. Scientific Registry of the International Society for Heart and Lung Transplantation: Introduction to the 2010 Annual Reports. *J Heart Lung Transplant* 2010; 29(10):1083-1141.
- 59) Baughman RP, Winger DB, Bowen EH, Lower EE. Predicting Respiratory Failure in Sarcoidosis Patients. *Sarcoidosis Vasc Diffuse Lung Dis* 1997; 14(2):154-158.
- 60) Shorr AF, Davies DD, Nathan SD. Outcomes for Patients with Sarcoidosis Awaiting Lung Transplantation. *Chest* 2002; 122:233-238.
- 61) Arcasoy SM, Christie JD, Pochettino A, et. al. Characteristics and Outcomes of Patient with Sarcoidosis Listed for Lung Transplantation. *Chest* 2001; 120:873-880.
- 62) Orens JB, Estenne M, Arcasoy S, Conte JV, Corris P, Egan JJ, Egan T, Keshavjee S, Knoop C, Kotloff R, Martinez FJ, Nathan S, Palmer S, Patterson A, Singer L, Snell G, Studer S, Vachiery JL, Glanville AR. International Guidelines for the Selection of Lung Transplant Candidates: 2006 Update-A Consensus Report From the Pulmonary Scientific Council of the International Society for Heart and Lung Transplantation. *J Heart Lung Transplant* 2006; 25:745-755.
- 63) Egan TM, Murray S, Bustami RT, et al. Development of the New Allocation System in the United States. *Am J Transplant* 2006; 6:1212-1227.
- 64) Chen H, Shiboski SC, Golden JA, et al. Impact of the Lung Allocation Score on Lung Transplantation for Pulmonary Arterial Hypertension. *Am J Respir Crit Care Med* 2009; 180:468-474.
- 65) Iannuzzi MC, Fontana JR. Sarcoidosis: Clinical Presentation, Immunopathogenesis and Therapeutics. *JAMA* 2011; 305(4):391-399.



- 66) Silverman KJ, Hutchins GM, Bulkley BH. Cardiac Sarcoid: A Clinicopathologic Study of 84 Unselected Patients with Systemic Sarcoidosis. *Circulation* 1978; 58:1204-1211.
- 67) Mehta D, Lubitz SA, Frankel Z et al. Cardiac Involvement in Patients with Sarcoidosis: Diagnostic and Prognostic Value of Outpatient Testing. *Chest* 2008; 35(5):933-941.
- 68) Patel MR, Cawley PJ, Heitner JF, et al. Detection of Myocardial Damage in Patients with Sarcoidosis. *Circulation* 2009; 120(20):1969-1977.
- 69) Yazake Y, Isobe M, Hiroe M, et al. Central Japan Heart Study Group. Prognostic Determinants of Long-Term Survival in Japanese Patients with Cardiac Sarcoidosis Treated with Prednisone. *Am J Cardiol* 2001; 88:1006-1010.
- 70) Freundlich IM, Libshitz HI, Glassman LM, Israel HL. Sarcoidosis. Typical and Atypical Thoracic Manifestations. *Clin Radiol* 1970; 21:376-383.
- 71) Wollschlager C, Khan F. Aspergillomas Complicating Sarcoidosis: A Prospective Study in 100 Patients. *Chest* 1984; 86(4):585-588.
- 72) Hours S, Nunes H, Kambouchner M, et al. Pulmonary Cavitory Sarcoidosis, *Medicine* 2008; 87(3):142-151.
- 73) Gorske K, Fleming RJ. Mycetoma Formation in Cavitory Sarcoidosis. *Radiology* 1970; 95:279-285.
- 74) Dar MA, Ahmad M, Weinstein AJ, Mehta AC, Golish JA. Thoracic Aspergillosis (Part I): Overview and Aspergilloma. *Cleve Clin Q* 1984; 51:615-630.
- 75) Pena T, Soubani AO, Samavati L. *Aspergillus* Lung Disease in Patients with Sarcoidosis: A Case Series and Review of the Literature. *Lung* 2011; 189:167-172.

- 76) Hammerman KJ, Christianson CS, Huntington I. Spontaneous Lysis of Aspergilloma. *Chest* 1973; 64:697-699.
- 77) Nathan SD, Saleeb PG, Saft H, Shlobin OA, Ahmad S, Barnett SD. Prevalence and Impact of Aspergillomas in Patients with Advanced Sarcoidosis. *Am J Respir Crit Care Med* 2007; 175:A361.
- 78) Israel HL, Ostrow A. Sarcoidosis and Aspergilloma. *Jour of Med* 1969; 47: 243-250.
- 79) Waldhorn RE, Tsou E, Kerwin DM. Invasive Pulmonary Aspergillosis Associated with Aspergilloma in Sarcoidosis. *Southern Medical Journal* 1983; 76(2):251-253.
- 80) Kaplan J, Johnson Johns C. Mycetomas in Pulmonary Sarcoidosis: Non-Surgical Management. *The Johns Hopkins Med Jour* 1979; 145:157-161.
- 81) Stevens DA, Kan VL, Judson MA, et al. Practice Guidelines for Disease Caused by *Aspergillus*. *Infectious Dis Soc of Amer* 2000; 30:696-709.
- 82) Sharma OP, Chwogule R. Many Faces of Pulmonary Aspergillosis. *Eur Respir J* 1998; 12:705-715.
- 83) Dannaouli E, Garcia-Hermoso D, Naccache JM, et al. Use of Voriconazole in a Patient with Aspergilloma Caused by an Itraconazole-Resistance Strain of *Aspergillus fumigatus*. *Journal of Medical Microbiology* 2006; 55:1457-1459.
- 84) De Beule K, De Doncker P, Cauwenbergh G, et al. The Treatment of Aspergillosis and Aspergilloma with Itraconazole, Clinical Results of an Open International Study (1982-1987). *Mycoses* 1988; 31(9):476-485.

- 85) Kravitz JN, Bullington WM, Schabel S, Judson MA. Intracavitary Amphotericin B for Pulmonary Aspergilloma Complicated by Serious Hemoptysis in Fibrocystic Sarcoidosis. *Am J Respir Crit Care* 2010; 181:A2951.
- 86) Kravitz JN, Steed LL, Judson MA. Intracavitary Voriconazole for the Treatment of Hemoptysis Complicating *Pseudallescheria Angusta* Pulmonary Mycetomas in Fibrocystic Sarcoidosis. *Medical Mycology* 2011; 49:198-201.
- 87) Lencher GS, Atkinson GW. Sarcoidosis and Aspergilloma. The Role of Surgery. *Chest* 1982; 82:430-432.
- 88) Gueraa M, Santos N, Miranda J, et al. Surgical Management of Pulmonary Aspergilloma. *Rev Port Cir Cardiothorac Vasc* 2008; 15(3):135-138.
- 89) Jackson M, Flower CDR, Shneerson JM. Treatment of Symptomatic Pulmonary Aspergillomas with Intracavitary Instillation of Amphotericin B through an Indwelling Catheter. *Thorax* 1993; 48:928-930.
- 90) Rumbak M, Kohler G, Eastridge Cm Winter-Muram H, Gravant M. Topical Treatment of Life Threatening Haemoptysis from Aspergillomas. *Thorax* 1996; 51:253-255.
- 91) Judson MA. Lung Transplantation for Pulmonary Sarcoidosis. *Eur Respir J* 1998; 11:738-744.
- 92) Hadjiliadis D, Sporn TA, Perfect JR, et al. Outcome of Lung Transplantation in Patients with Mycetomas. *Chest* 2002; 121:128-134.
- 93) Polychronopoulos VS, Prakash UB. Airway Involvement in Sarcoidosis. *Chest* 2009; 136(5):1371-1380.

- 94) Akira M, Kozuka T, Inoue Y, et al. Long-Term Follow-up CT Scan Evaluation in Patients with Pulmonary Sarcoidosis. *Chest* 2005; 127:185–191.
- 95) Abehsera M, Valeyre D, Grenier P, et al. Sarcoidosis with Pulmonary Fibrosis: CT Patterns and Correlation with Pulmonary Function. *Am J Roentgenol* 2000; 174:1751-1757.
- 96) Rockoff SD, Rohatgi PK. Unusual Manifestations of Thoracic Sarcoidosis. *Am J Roentgenol* 1985; 144:513-528.
- 97) Shah L. Lung Transplantation in Sarcoidosis. *Semin Respir Critic Care Med* 2007; 28:134-140.
- 98) Shorr AF, Helman DL, Davies DB, et al. Sarcoidosis, Race and Short-term Outcomes Following Lung Transplantation. *Chest* 2004; 125:990-996.
- 99) Nunley DR, Hattler B, Keenan RJ, et al. Lung Transplantation for End-Stage Pulmonary Sarcoidosis. *Sarcoidosis Vasc Diffuse Lung Dis* 1999; 16(1):93-100.
- 100) Wille KM, Gaggar A, Hajari AS, et al. Bronchiolitis Obliterans Syndrome and Survival Following Lung Transplantation for Patients with Sarcoidosis. *Sarcoidosis Vasc Diffuse Lung Dis* 2008; 25:117-124.
- 101) Milman N, Andersen CD, Burton CM, Iversen M. Recurrent Sarcoid Granulomas in a Transplanted Lung Derive from Recipient Immune Cells. *Eur Respir J* 2005; 26:549-552.
- 102) Johnson BA, Duncan SR, Ohori NP, et al. Recurrence of Sarcoidosis in Pulmonary Allograft Recipients. *Am Rev Respir Dis* 1993; 148(5):1373-1377.
- 103) Martinez FJ, Orens JB, Deeb M, et al. Recurrence of Sarcoidosis Following Bilateral Allogeneic Lung Transplantation. *Chest* 1994; 106:1597-1599.

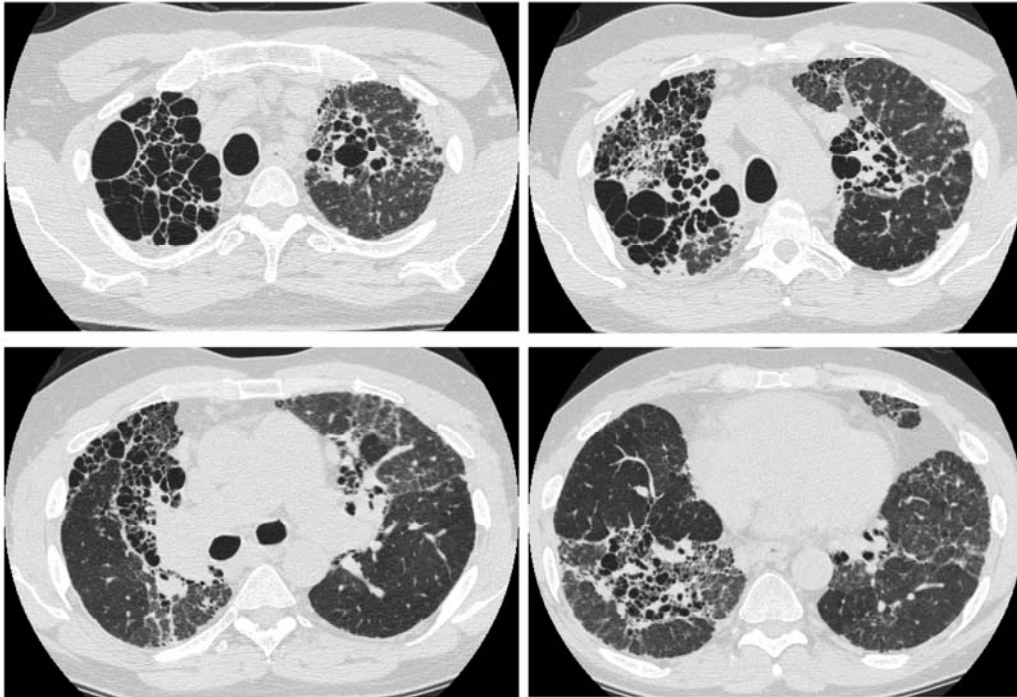
**Table 1.** Summary of currently available studies on treatment of sarcoidosis associated PH.

	<b>Study Type (number treated)</b>	<b>Therapy (number treated)</b>	<b>Outcomes</b>
Preston et al. <sup>27</sup>	Prospective observational (8)	Inhaled NO (5), inhaled NO with IV EPO (1), CCBs (2)	Short term 20% decrease in PVR and mPAP; Long term ↑ in 6MWT
Baughman et al. <sup>57</sup>	Prospective open label 16 weeks (22)	Inhaled iloprost (15)	6/15 patients showed ↓mPAP/PVR, 3/15 improvement in 6MWT
Fisher et al. <sup>56</sup>	Retrospective case series (7)	IV EPO (6), SQ treprostinil (1)	Improved NYHA Class
Barnett et al. <sup>52</sup>	Retrospective case series (22)	IV EPO (1), bosentan (12), sildenafil (9)	Improved 6MWT, NYHA Class Reduction in mPAP and PVR
Milman et al. <sup>55</sup>	Retrospective chart review (12)	Sildenafil (12)	↓mPAP/PVR, ↑cardiac output, no change in 6MWT
Culver et al. <sup>51</sup>	Retrospective chart review (7)	Bosentan (3), bosentan and IV EPO (4)	Reduction in mPAP at 6-18 months in half of the patients
Baughman et al. <sup>30</sup>	Retrospective chart review (5)	Bosentan (5)	Reduction in mPAP from 50mmHg to 35mmHg in 3/5 patients at 4 months
Judson et al. <sup>54</sup>	Prospective placebo-controlled 12 weeks (20)	Ambrisentan (17 patients at 4 weeks, 12 patients at 8 weeks and 7 patients at 12 weeks)	No change in 6MWT 9 patients discontinued drug

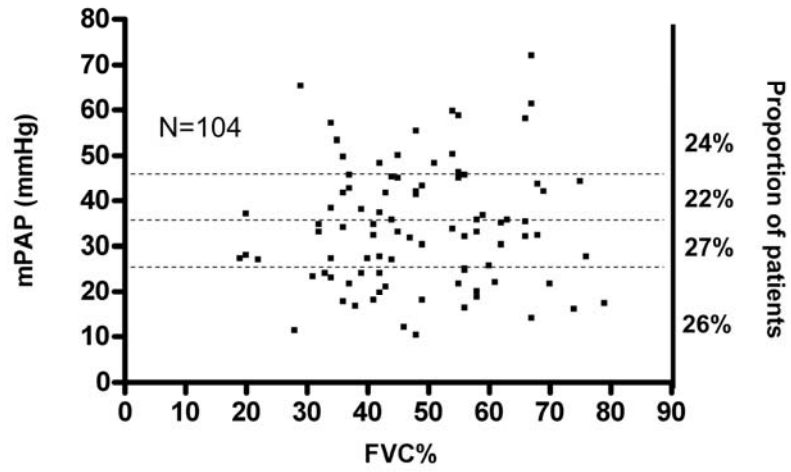
Abbreviations: 6MWT – six minute walk test; CCB—calcium channel blocker; EPO – epoprostenol; IV – intravenous; NO – nitric oxide; NYHA – New York Heart Association; mPAP – mean pulmonary artery pressure; PVR – pulmonary vascular resistance; RHC – right heart catheterization; SQ – subcutaneous.

**Figure Legends**

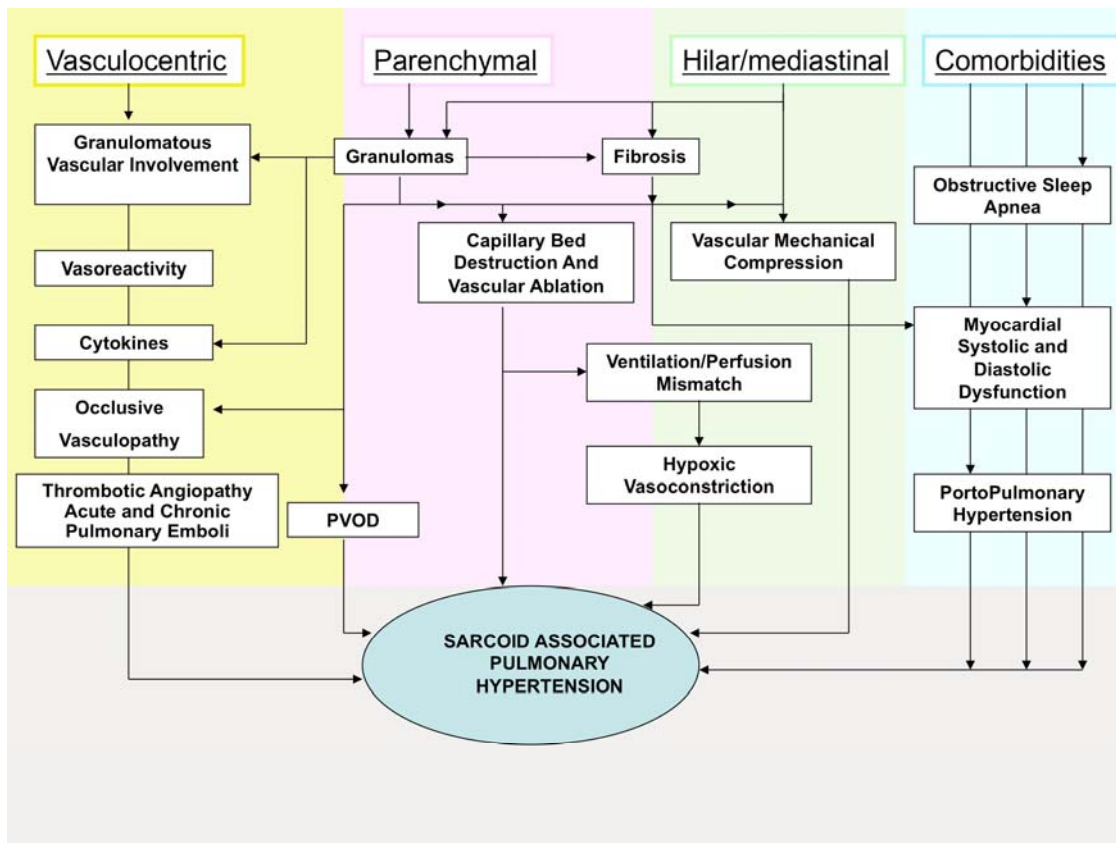
**Figure 1.** CT scan of chest of stage IV sarcoidosis with associated PH (mPAP 49 mmHg).



**Figure 2.** Distribution of mean pulmonary artery pressures in relation to the FVC% predicted in a cohort of 104 patients with sarcoidosis. The horizontal dashed lines and right y axis stratify the patients by severity of PH (Inova Fairfax Hospital data).  
Abbreviations: FVC – forced vital capacity; mPAP – mean pulmonary artery pressure.

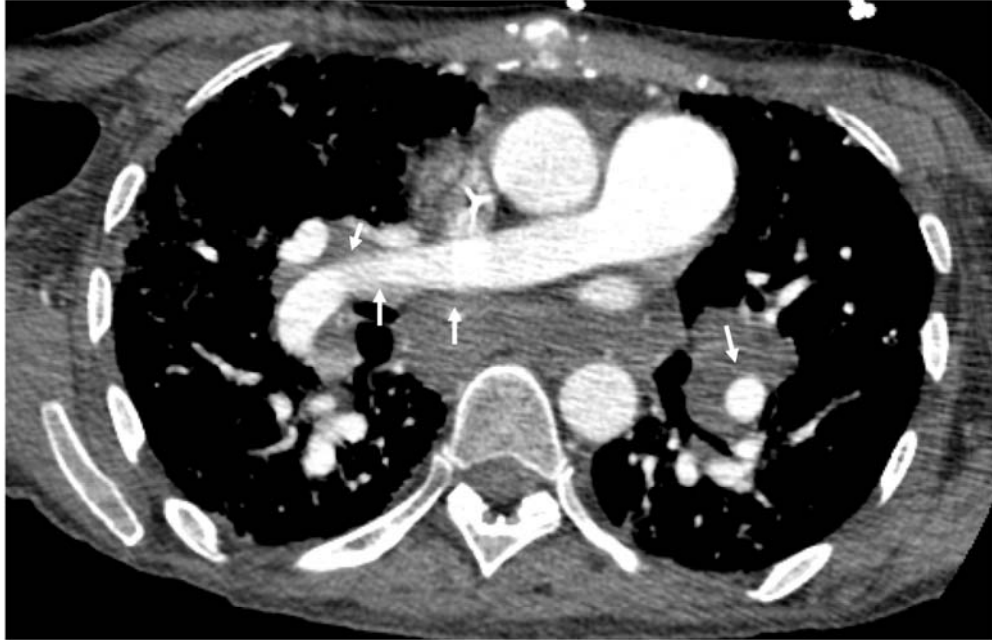


**Figure 3.** Schematic representation of the interplaying factors contributing to the pathogenesis of PH in sarcoidosis.  
 Abbreviations: PVOD – pulmonary veno-occlusive disease.

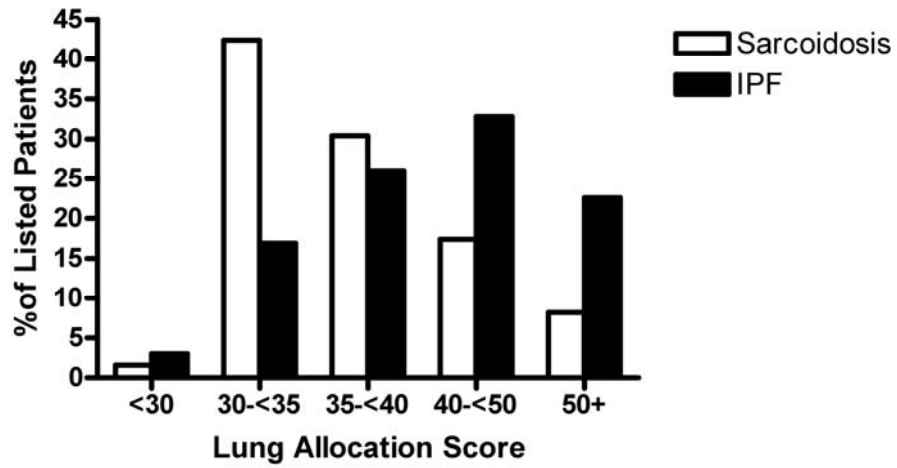


**Figure 4.** CT scan of the chest of a sarcoidosis-PH patient with lymphadenopathy (white arrows) surrounding the right pulmonary artery.



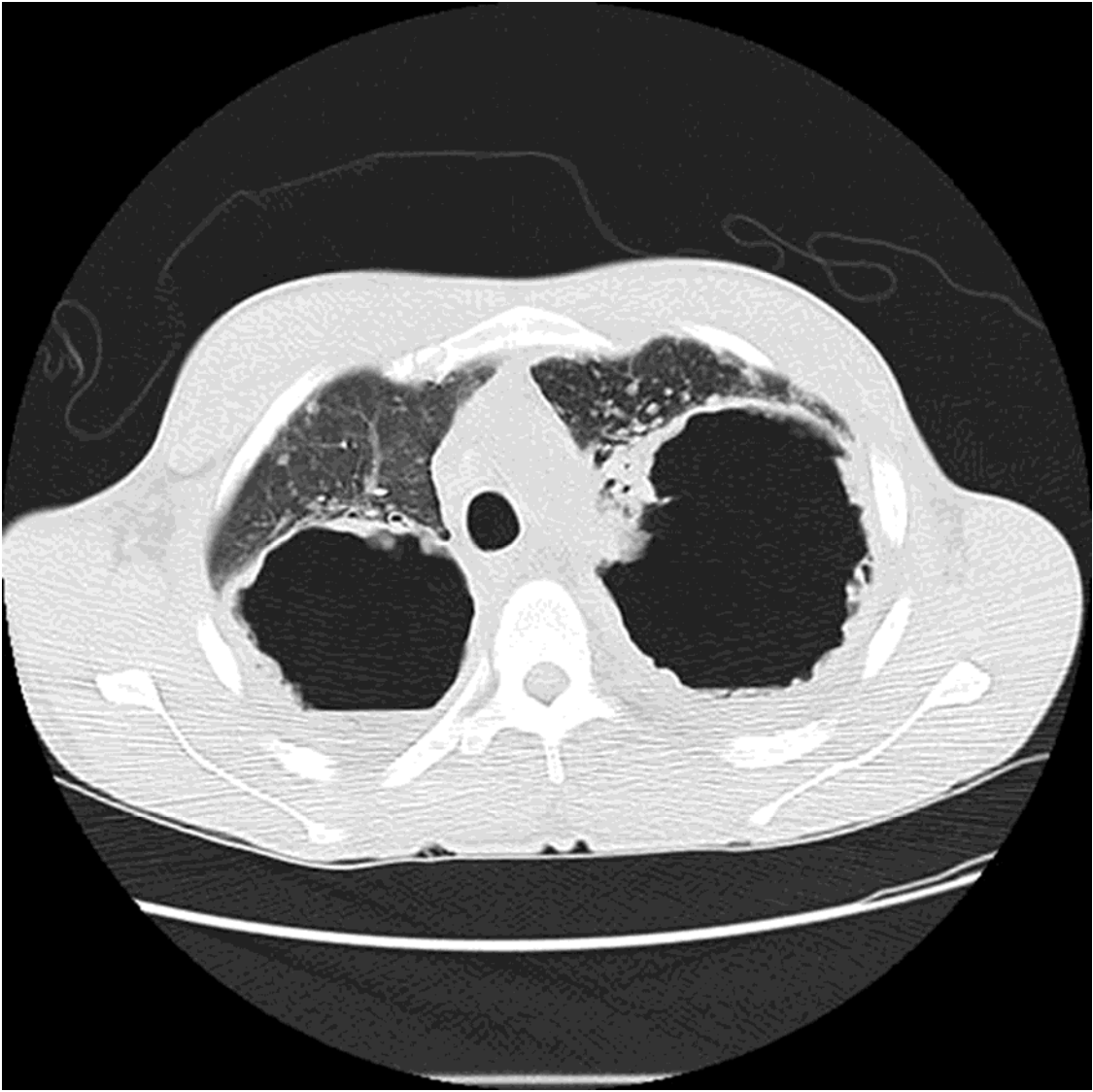


**Figure 5.** Distribution of LAS Score of patients with sarcoidosis and idiopathic pulmonary fibrosis (UNOS Query, 2008).  
Abbreviations: IPF – Idiopathic Pulmonary Fibrosis; LAS – Lung Allocation Score.  
UNOS – United Network for Organ Sharing

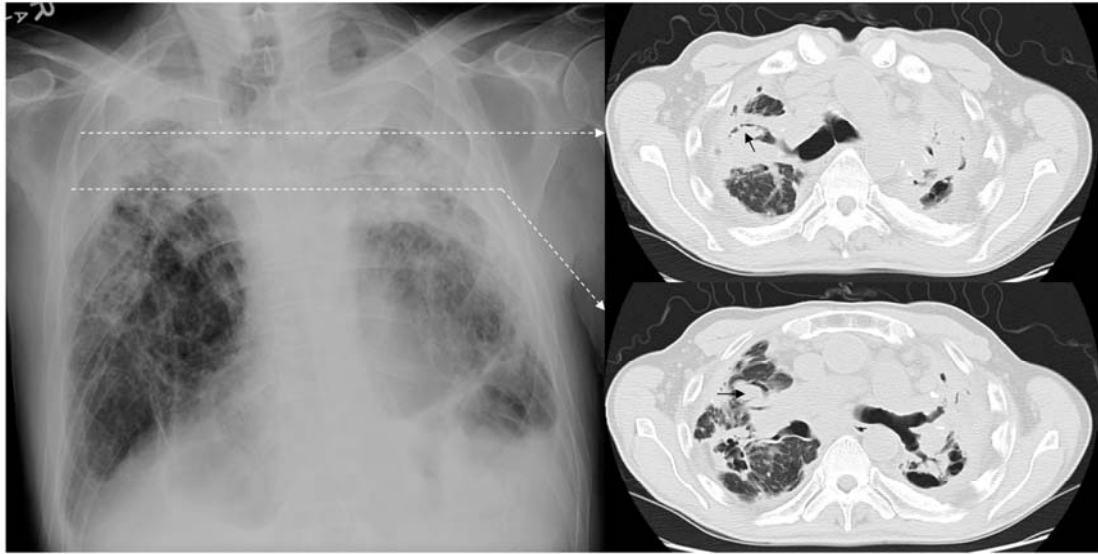


UNOS data from May 4<sup>th</sup> 2005-December 31<sup>st</sup> 2007  
N=1339 IPF and N=184 sarcoidosis registrants

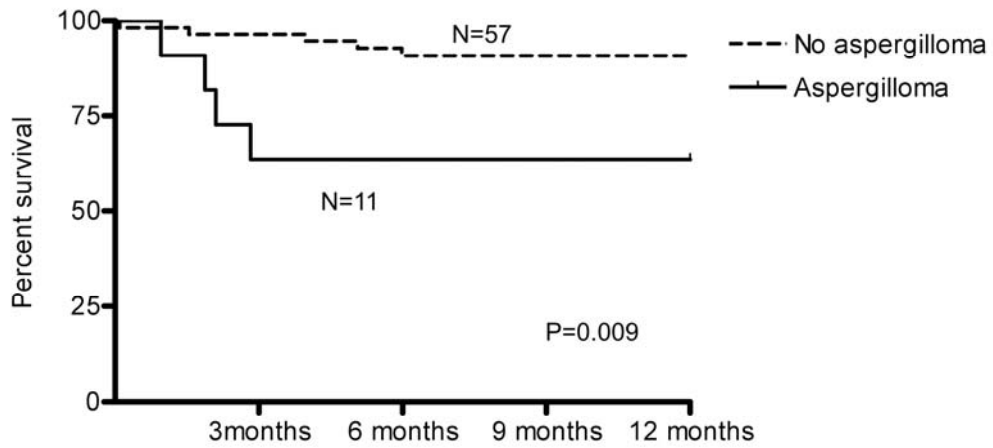
**Figure 6.** Cavities in stage IV sarcoidosis.



**Figure 7.** Multiple bilateral mycetomas in stage IV sarcoidosis (black arrows on CT scan images).



**Figure 8.** Kaplan-Meier survival curves of patients with advanced sarcoidosis stratified by the presence or absence of aspergillomas.



Inova Fairfax data Sep 2006

**Figure 9.** Sarcoidosis recurrence post-bilateral lung transplantation in two patients demonstrating diffuse reticular nodular infiltrates (panel A) and scattered nodules (white arrows, panel B). In both cases the patients were asymptomatic and transbronchial biopsies demonstrated non-caseating granulomas.

