Pulmonary Hypertension Associated With Sarcoidosis

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Case Vignette

A 62-year-old African American female with a history of cutaneous sarcoidosis was hospitalized with progressive dyspnea and signs of right heart failure. Computed tomography of the chest demonstrated patchy ground-glass densities without fibrosis (Figure 1). Pulmonary function was with mild restriction and diffusing capacity for carbon monoxide (DLCO) of 50% predicted. Doppler echocardiogram (DE) showed severe right heart enlargement and an estimated right ventricular systolic pressure (RVSP) of 105 mm Hg. Right heart catheterization (RHC) confirmed severe pulmonary hypertension (PH) with mean pulmonary artery pressure (mPAP) of 54 mm Hg, pulmonary artery wedge pressure (PAWP) of 10 mm Hg, right atrial pressure (RAP) of 12 mm Hg, and cardiac index of 1.11 L/min/m^2. An arterial blood gas while receiving supplemental oxygen through a non-rebreathing mask revealed a PaO_2 of 51 Torr, $PaCO_2$ of 33 Torr, and pH of 7.46. Computed tomography angiography and perfusion lung scanning were not suggestive of pulmonary embolism. Intravenous epoprostenol was initiated. The patient became acutely hypotensive and more hypoxemic, requiring discontinuation within hours. Chest radiograph was unchanged. Subsequently, sildenafil was started. This was well tolerated and within a few days, her oxygen requirements had fallen to 2 L by nasal cannula and she was discharged. At follow-up, she had NYHA class III symptoms and 6-minute walk distance (6MWD) was 321 m. Because of worsening symptoms despite 50 mg TID of sildenafil, an open lung biopsy was requested by her rheumatologist. This demonstrated intimal proliferation and hyalinized vascular lesions suggesting healed granulomas (Figure 2). No clear pulmonary venous pathology was found. A trial of prednisone was commenced, without benefit. Inhaled iloprost was ineffective. Her 6MWD fell to 191 m; bosentan was subsequently added. Her condition gradually improved to NYHA class II and 6MWD increased to 347 m. Doppler echocardiogram showed reduced RV size and RVSP of 50 mm Hg. PaO_2 on room air was 62 mm Hg. She remains well 4 years after initial presentation with no clinical signs of right heart failure.

Key Words—sarcoidosis, hypoxia, granulomas, pulmonary hypertension, bosentan

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Pulmonary vascular disease with cor pulmonale has long been recognized as an infrequent, yet serious complication of chronic pulmonary sarcoidosis.[1,2] The rapid expansion of therapies available for pulmonary arterial hypertension (PAH) have generated considerable interest in sarcoidosis-associated PH (SAPH) in recent years.[3] Sarcoidosis as a cause of PH is categorized as "PH with unclear multifactorial mechanisms," or Group 5, within the subgroup systemic diseases (Group 5.2) in the most recent World Symposium on PH.[4] Considering sarcoidosis in a separate category from lung disease–related PH (Group 3) recognizes the relatively frequent occurrence of severe PH and the multiple possible mechanisms, including direct pulmonary vascular involvement by the pathognomonic granulomatous inflammation characteristic of this disorder.

It is clear that therapy directed toward the granulomatous inflammation (eg, steroids) does not favorably impact the pulmonary vascular process in many patients with SAPH.[5] The potential for pulmonary vasoactive therapy in this condition was first reported by Dr Barst nearly 25 years ago.[6] Unfortunately, no controlled clinical trial data are available and none of the agents currently approved for PAH are labeled for use in sarcoidosis. Nevertheless, most PH practitioners have observed beneficial clinical effects in selected patients and several recent case series support the potential efficacy of PH targeted therapy.[7-10] This article will provide an overview of PH in sarcoidosis and summarize these reports.

Prevalence and Clinical Characteristics of Pulmonary Hypertension in Sarcoidosis

There are limited data regarding the true prevalence of PH in sarcoidosis. In the largest study to address this, Handa et al performed DE on 246 consecutive Japanese patients.[11] The mean duration of sarcoidosis was 8.75 years. An RVSP, obtainable in 86% of the cohort, ≥40 mm Hg was observed in 12 or 5.7%. The degree of RVSP elevation in the PH group was mild with an average value of 45 ± 5 (SD) mm Hg. Patients with PH had lower lung volumes, more advanced radiographic stage, were more likely to be male, and had a slightly reduced transcutaneous oxygen saturation compared with the no PH group. Most subjects in this series had minimal lung involvement. Five of the 12 PH cases had no parenchymal lung disease on plain chest radiograph. In an Italian cohort of 50 patients who underwent RHC, 3 or 6% had a

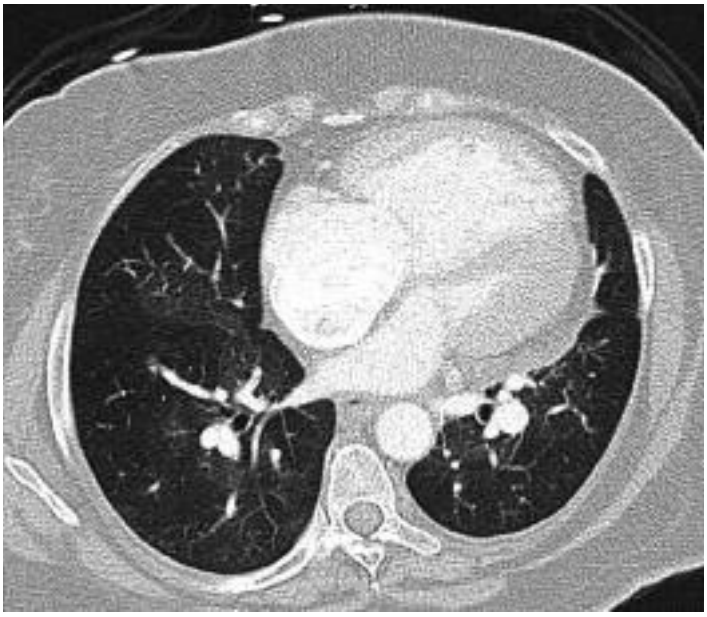

Figure 1. Computed tomographic image of lungs showing patchy ground glass densities in a patient with severe PH and sarcoidosis with stage 0 chest radiograph.

resting mPAP ≥25 mm Hg.[12] An additional 10 subjects had an abnormal rise in mPAP with exercise. A high frequency of exercise-induced PH has been noted by others.[13]

Data from urban US sarcoid programs provide useful information regarding the prevalence of PH in a population with predominantly chronic pulmonary disease. Among 354 patients in New York City, 106 had DE over a 5-year time period for various clinical indications.[14] Pulmonary hypertension was detected in 54, yielding an overall prevalence of 15%. The degree of PH was considerable with an average RVSP of 59 mm Hg. Compared with the 52 patients who underwent DE and had no evidence of PH, the elevated RVSP group had a higher proportion of stage 4 (fibrotic) disease (60% vs 23%). Vital capacity was also lower (54% vs 64% of predicted), but not after controlling for chest x-ray stage. Within the same radiographic stage, DLCO was significantly reduced in the PH group (33% vs 43% predicted for stage 4 and 42% vs 55% for stages 1-3 combined). There was also a trend for lower maximal mid-expiratory flow rates in stage 4 patients with PH, suggesting a relationship between pulmonary vascular and small airways disease. More patients in the PH group required supplemental oxygen (35% vs 15%). There was no difference in demographics with a mean age of 50 and African American females comprising roughly two-thirds in both groups, a typical profile of chronic pulmonary sarcoidosis in the US.[15,16]

In a cohort of 162 cases, largely African American (88%) and female (77%), in Detroit, 35 patients underwent RHC for suspicious echocardiographic findings or persistent functional limitation despite negative DE. Twenty-two or 14% had PH documented by RHC.[17] Similar to the findings of Sulica et al,[14] lung volumes and DLCO were markedly reduced in the PH group and chest x-ray stage was more advanced. In addition, exercise capacity as measured by the 6MWD was significantly lower (343 ± 116 [SD] vs 426 ± 105). Whereas resting oxygen saturation was similar, the PH group demonstrated more desaturation at the end of the walk test. In a multivariate analysis, oxygen saturation <90% at the end of a 6MWD and DLCO <60% were significantly associated with PH.

Baughman and coworkers in Cincinnati retrospectively identified 53 patients, out of a total clinic population of 1223, who underwent RHC to evaluate persistent dyspnea despite medical management of sarcoidosis.[8] Mean PAP was >25 mm Hg in 30, 5 of whom also had PAWP >15 mm Hg. The demographics of the PH group were similar to the entire RHC cohort, with a mean age of 52 years, an even distribution of Caucasian vs African American race, and a female-to-male ratio of 1.6. After excluding those with left ventricular (LV) dysfunction, there was a strong inverse correlation between mPAP and DLCO percentage predicted.

The prevalence of PH in sarcoidosis patients listed for lung transplantation in the US is exceptionally high. Among 363 candidates with RHC data in the United Network for Organ Sharing (UNOS) database, Schorr et al found mPAP >25 mm Hg in 74% and ≥40 mm Hg in 36%.[18] This proportion is considerably greater than in lung transplant candidates with idiopathic pulmonary fibrosis (IPF), where 46% had PH, and only 9% had mPAP ≥40.[19] While the majority of PH patients were African American (74%) with a slight female predominance (64%), there was no difference in the frequency of PH based on race or gender. As has been observed with IPF[19] and COPD,[20] PH in advanced sarcoid is occasionally associated with mild to moderate elevations in PAWP.[18] In this study, PAWP averaged 14 ± 9 (SD) mm Hg in severe PH compared with 8 ± 1 mm Hg in the no PH group and 13 ± 8 mm Hg in the entire PH group. Both PAWP and oxygen requirement were independently associated with PH. The proportion of subjects with PAWP >15 was not specified.

The French group identified 22 subjects, 15 with radiographic evidence of fibrosis (stage 4) and 7 with stages 0-3.[21] In contrast to the US experience, the majority were Caucasian males with mean age of 46 years. Pulmonary hypertension was severe with mPAP >35 mm Hg in 14. Interestingly the average mPAP and pulmonary vascular resistance (PVR) tended to be higher in the non-fibrotic group compared with stage 4 (52 vs 40 mm Hg and 23 vs 15 IU/m^2, respectively). Pulmonary artery wedge pressure was ≤12 mm Hg in all patients by study inclusion criteria. When compared with sarcoid control patients without PH matched for age, sex, and chest x-ray stage, the PH cases had lower forced vital capacity (FVC), DLCO, and PaO_2. We recently reviewed our experience in collaboration with the group in Fairfax, VA.[7] The clinical features of 27 patients are summarized in the table. Five subjects in this cohort had an elevated PAWP of >15 mm Hg (range: 17-25), none of whom had reduced LV systolic function, left sided valvular heart disease, or known cardiac sarcoid involvement.

Pathology and Pathophysiology: Mechanisms of Pulmonary Hypertension in Sarcoidosis

Several potential mechanisms have been invoked to account for PH in sarcoidosis. Given the strong association with stage 4 disease and restrictive lung function, fibrotic destruction of the pulmonary vasculature is likely a contributing factor. However, this is an inadequate explanation for the sizeable proportion of cases without advanced radiographic disease. Moreover, compared with IPF subjects with comparable reductions in lung volumes, PH in sarcoid is more frequent and more severe. In an analysis of sarcoid and IPF patients awaiting lung transplantation in the UNOS database, the average mPAP was 34 ± 13 mm Hg in the sarcoid group vs 26 ± 10 in IPF (P<0.0001), whereas FVC and FEV_1 were significantly lower in the former.[22] Compression and distortion of the large pulmonary arteries in the hilar regions by enlarged lymph nodes and/or fibrous retraction can be present in a minority of cases.[3]

As mentioned previously, elevated left heart filling pressures

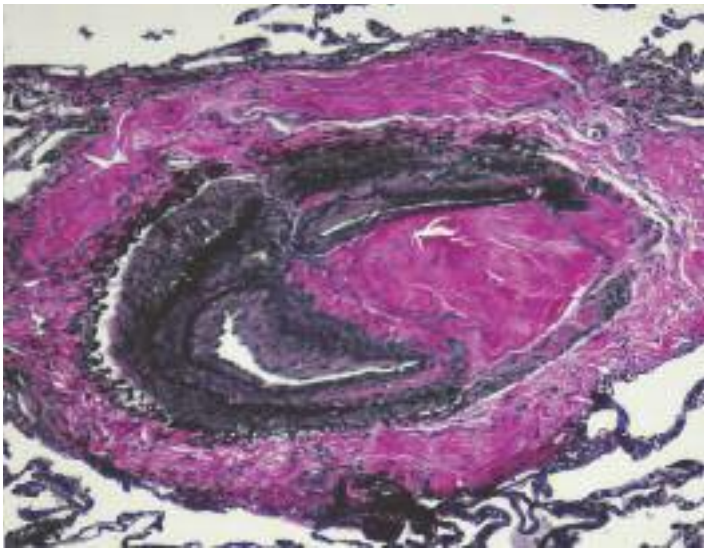

Figure 2. Surgical lung biopsy specimen showing hyalinized lesion with disruption of elastic lamina consistent with healed granuloma in medium sized pulmonary artery (Movat's pentachrome stain).

are present in roughly 20% of SAPH, similar to the 18% found in IPF patients with PH listed for lung transplantation.[19] The basis for this is not clear and is likely multifactorial. Clinically apparent myocardial sarcoid involvement is rare in the US, but subclinical evidence of diastolic LV dysfunction may be more frequent.[23] This population has a high prevalence of systemic hypertension and diabetes, which may also contribute to left heart disease. Repetitive hypoxemia with activity or nocturnally, perhaps associated with obstructive sleep apnea may impair LV function.[24] Alternatively, the altered thoracic mechanics associated with pulmonary fibrosis may interfere with LV filling and in cases with massive right heart distention, the LV cavity may be compromised as a consequence of interventricular dependence.

The most important mechanism of PH in sarcoidosis is likely direct pulmonary vascular involvement by granulomatous inflammation. Pathologic surveys have documented that specific vascular lesions are extremely common in sarcoidosis, irrespective of the presence of PH. In an analysis of 128 open lung biopsy samples, Rosen and coworkers found active granulomatous angiitis in 69%.[25] The extent of vascular lesions correlated weakly with the extent of parenchymal granulomas, but not with chest radiographic stage. Clinical information regarding PH was not available. The size of vessels involved ranged from larger interlobular to small intraparenchymal, frequently associated with severe narrowing and occlusion. Venous involvement, observed in 92% of the cases with granulomatous angiitis, was more frequent than arterial (39%).

In a Japanese autopsy series of 40 cases, Takemura and colleagues described granulomatous vascular involvement and/or evidence of healed vascular lesions, defined as disruption of elastic fibers with fibrous thickening of vascular walls, in all the specimens.[26] The ubiquitous nature of the vasculopathy was despite the fact that only 17 patients had pulmonary disease as their main clinical feature, which is typical in Japan where cardiac involvement predominates. All cases also had either active or healed parenchymal granulomas, which correlated with the extent of vascular lesions. Lesions were observed throughout the vascular tree, from the large elastic pulmonary arteries to the interlobular veins with occasional luminal obliteration. Similar to the findings of Rosen's study,[25] the number of venous lesions exceeded those seen in arteries.[26] Because the anatomic distribution of sarcoid granulomas corresponds to lymphatic networks, these structures were carefully examined. Prominent involvement of the lymphatic capillaries and collecting channels that surround arteries and veins in the bronchovascular bundle and interlobular septa, respectively, was observed. The authors hypothesized that blood vessel wall granulomas originate in the surrounding lymphatics.[26] Four cases in this series had anatomic cor pulmonale.

The proclivity for pulmonary venous pathology in sarcoidosis is well documented. Several cases of PH with clinical features of pulmonary veno-occlusive disease (PVOD), a prominent venopathy, and relatively little arterial remodeling have been reported.[21,27,28] Some authors suggest avoiding the term PVOD in sarcoid, considering it a typical component of the disease process.[3] In some cases with severe PH, direct vascular involvement by granulomas has been absent, but rather vascular remodeling reminiscent of PAH with fibromuscular intimal proliferation, medial hypertrophy,[6] and in one case, plexiform lesions[29] have been observed. This raises the possibility that vasoactive mediators and/or growth factors elaborated from nearby parenchymal granulomas could lead to vascular remodeling.

Finally, as in other chronic lung diseases, alveolar hypoxia has been implicated in the pathogenesis of SAPH.[30] While oxygen requirements are clearly greater among patients with PH compared to those without,[18] severe hypoxemia is by no means universal in sarcoid PH. In the Nunes series, only 2 of 7 nonfibrotic and 6 of 15 stage 4 patients had a PaO_2 <55 mm Hg despite the presence of severe PH.[21] Thus, hypoxic vasoconstriction is unlikely to be the predominant mechanism. On the other hand, pulmonary vascular remodeling in the setting of parenchymal lung disease can have a dramatic impact on gas exchange, particularly with exercise. In an elegant physiologic study, Agusti and colleagues showed that IPF patients with more structural vascular disease, identified as impaired release of hypoxic pulmonary vasoconstriction, had more PH, ventilation/perfusion (V/Q) inequality, and hypoxemia with exercise.[31] In addition, reduced mixed venous oxygen saturation (as a consequence of low cardiac output) can have a considerable impact on arterial PaO_2 in the setting of venous admixture (low V/Q units), shunt, and/or diffusion limitation.

Clinical Impact and Prognosis

In addition to greater supplemental oxygen use, PH complicating sarcoidosis is associated with reduced exercise capacity. As mentioned above, the Bourbonnais series demonstrated a reduced 6MWD.[17] A report from the Cincinnati group[32] also found that 6MWD was significantly lower in 14 patients with known PH (median: 280 m) compared with the remaining 128 (median: 411 m, P<0.0001). Among lung transplant candidates, those with PH were more likely to report needing assistance with activities of daily living and to be unemployed due to illness.[18]

Data from patients awaiting lung transplantation indicate a strong impact of PH on mortality. Shorr et al reviewed the outcomes of 405 sarcoid patients in the UNOS database.[33] Twenty-seven percent died while on the waitlist. African American race, oxygen requirement, and mPAP were found to be independent predictors of mortality. Mean PAP was 41 mm Hg in nonsurvivors vs 32 among survivors (P<0.01). Cardiac index (CI) and PAWP did not differ between the 2 groups. In a single center study of 43 lung transplant candidates with a 53% waitlist mortality, hypoxemia, PH, reduced CI, and elevated RAP were significantly asso-

Table. Clinical Features of 27 Cases of SAPH

Characteristic	Mean ± SEM
Age at PH Diagnosis – years	46.4 ± 1.2
Female – no. (%)	21 (78)
African American Race	27 (100%)
Sarcoidosis Radiographic Stage – no. (%)	
0	4 (15)
I	0 (0)
II	4 (15)
III	3 (11)
IV	16 (59)
New York Heart Association Class – no. (%)	
1	0 (0)
2	2 (7)
3	20 (74)
4	5 (19)
Hemodynamics	
Right Atrial Pressure, mm Hg	11.6 ± 2
Mean Pulmonary Artery Pressure, mm Hg	47.1 ± 2
Cardiac Output, L/min	4.2 ± 0.4
Pulmonary Vascular Resistance, dynes sec cm-5	818 ± 83
Pulmonary Artery Wedge Pressure, mm Hg	11.9 ± 1
Pulmonary Function Tests	
FVC, % predicted	55 ± 3
FEV_1, % predicted	53 ± 3
TLC, % predicted	61 ± 2
DLCO, % predicted	38 ± 4
Supplemental Oxygen Use (%)	19 (70)
6-Minute Walk, meters	201 ± 27

ciated with death.[34] On multivariate analysis, only RAP was an independent predictor.

Clinical right heart failure is not uncommon, noted in one-fifth of sarcoid PH patients reported by Sulica et al[14] and in 5 of 22 patients in the Nunes series.[21] This is an important clinical observation in that it supports a causal relationship between PH and increased mortality rather than simply a marker of advanced lung disease. The development of RV decompensation is a sentinel development in the clinical course of pulmonary hypertensive states that is strongly associated with increased mortality.[35] There are scant data regarding right heart structure and function in sarcoidosis, in contrast to several systematic surveys for left heart abnormalities in the detection of cardiac involvement.[23,36-38] The Mount Sinai series described right heart abnormalities by echocardiography in 65% of the subjects with RVSP >40 mm Hg, compared with only 5% where RVSP was normal.[14] The relative contribution of right heart vs respiratory failure to the higher death rate in sarcoid PH has not been systematically investigated and would undoubtedly be difficult to separate since each process can exacerbate the other.

Diagnosis

Given the prevalence and clinical impact of PH in chronic sarcoidosis, a high index of suspicion is warranted. Persistent exertional dyspnea and reduced exercise capacity despite conventional therapy for pulmonary sarcoidosis signal a high risk for the presence of PH, with a prevalence of over half in one series.[8] Physical signs of PH may be difficult to appreciate in the setting of pulmonary fibrosis. Evidence of right heart failure may be present.[14] As discussed previously, PH is more often associated with advanced radiographic changes and reduced lung volumes, but severe PH in the absence of significant parenchymal abnormalities is not uncommon. As with other lung diseases,[30] reduced DLCO and either resting hypoxemia or exercise desaturation correlate with the presence of PH in sarcoidosis.[8,11,14,17,18] The EKG may show signs of right heart enlargement, but has low sensitivity. Radiographic evidence of pulmonary artery dilatation also has a poor sensitivity.[8]

The limitations of DE in the detection of PH in advanced lung disease has been well documented.[39-41] Diseased lungs overlying the heart interfere with the obtainment of satisfactory acoustic windows. Estimated RVSP is unobtainable in a high proportion of cases and when measured, is often inaccurate. Interestingly, overestimation of RVSP is more common than underestimation, yielding a low positive predictive value. Incorporating right heart abnormalities does not substantially improve the diagnostic accuracy.[39] Similar studies comparing DE with invasive hemodynamics in unselected patients are lacking in sarcoidosis, but several examples of false-negative results make it clear that echocardiography cannot be relied upon to exclude PH.[8,17] The utility of MRI to identify right heart abnormalities in the diagnosis of PH in sarcoidosis has not been studied, but may overcome some of the limitations of DE.[42] Brain natriuretic peptide (BNP) levels appear to have diagnostic utility for PH in lung disease, but require further validation.[43]

A potentially important confounder with both cardiac imaging studies and BNP in the assessment of SAPH is cardiac involvement. Myocardial granulomas are detected at autopsy in 25% of cases in the US, but clinically apparent cardiac sarcoid is relatively rare at less than 5%.[23] However, a systematic clinical evaluation incorporating cardiac MRI and PET reportedly yields a much higher prevalence.[37] While LV abnormalities (both systolic and diastolic dysfunction) predominate in cardiac sarcoid, isolated or predominant RV changes have been described.[44] BNP levels are elevated in cardiac sarcoidosis,[45,46] thus, potentially reducing the specificity of this test for PH.

As with any type of PH, RHC is required to reliably diagnose PH, exclude left heart disease as a contributing factor, and assess right heart function. Invasive hemodynamic assessment should be strongly considered if screening DE is suggestive of PH and when DE is negative, but clinical findings, such as persistent dyspnea, reduced DLCO, or hypoxemia raise the suspicion of PH, and is mandatory prior to initiating any PH targeted therapy.

Treatment

Immunosuppression

The cornerstone of therapy for chronic pulmonary sarcoidosis is immunosuppression, primary corticosteroids.[47] There are limited data regarding the effects of steroid treatment on PH. Gluskowski et al performed RHC before and after 12 months of prednisolone in 24 patients, only 3 of whom had resting PH.[5] An additional 18 had an abnormal rise in mPAP, defined as an increase of 10 mm Hg. Steroid treatment induced significant improvement in lung function, oxygenation, and chest radiographs in all but 2 subjects. However, hemodynamic improvement was only observed in half,

suggesting that the pulmonary vasculopathy is independent of the parenchymal process. Of the 3 patients with resting PH, 2 experienced a dramatic fall in mPAP. In the Nunes series, 3 of 5 patients without fibrosis improved with immunosuppressive therapy, whereas none of 5 stage 4 subjects had a response, suggesting that those with less advanced pulmonary disease may be more likely to derive benefit.[21] Thus, the precise role of immunomodulating drugs in sarcoid PH is poorly defined, and most sarcoid experts recommend use of these agents to control active parenchymal disease based on pulmonary function and chest radiographic findings rather than pulmonary vascular disease.[3;8]

Vasoactive Therapy

Three potential concerns need to be considered with the use of pulmonary vasoactive therapy in PH associated with sarcoidosis. As with any lung disease with ventilation-perfusion mismatching, pulmonary vasodilatation can increase perfusion to poorly ventilated units and worsen hypoxemia.[48] Second, in the setting of fixed PVR, nonselective vasodilators can induce a fall in systemic blood pressure, resulting in RV ischemia and worsening RV function. Finally, in the presence of veno-occlusive disease or impaired left heart function associated with sarcoidosis, pulmonary arterial vasodilatation may precipitate or exacerbate pulmonary edema. Several uncontrolled, small, open-labeled reports provide some information regarding the safety and efficacy of PH targeted therapy.

Clinically significant acute vaso-responsiveness appears to be rare in SAPH. None of the 22 patients in the Nunes series demonstrated an acute vasodilator response, defined as a fall in mPAP and PVR of >20%,[21] but Baughman reported one patient with a hemodynamic response after 4 months of calcium channel blocker (CCB) therapy.[8] Preston and coworkers performed acute vasodilator challenge with inhaled nitric oxide (iNO) in 8 patients.[49] Seven demonstrated a 20% reduction in PVR, but only one met revised criteria predictive of long-term response to CCB.[50] Three of 5 patients treated with continuous iNO had sustained symptomatic improvement after 1 year, but remained with NYHA class III. The remaining 5 patients, including 2 treated with CCB, died by 1 year of follow-up.[49]

Fisher et al reported their experience with IV epoprostenol.[9] All 7 patients studied had at least a 20% reduction in PVR during acute challenge (mean 45% reduction), but none met revised criteria. Six were treated with continuous infusion. One patient died suddenly after initiating therapy. Two others developed transient pulmonary edema and worsening oxygenation, respectively, but continued treatment and along with the other 3, all had symptomatic benefit with long-term therapy ranging from 15-49 months. Milman and coworkers treated 12 patients being evaluated for lung transplant with sildenafil.[10] Follow-up RHC was performed in 9 after 4-6 months. A significant reduction in mPAP (48 to 39 mm Hg) and PVR (10.7 to 5.6 WU) was observed without an improvement in 6MWD. There were no apparent deleterious effects and resting pulse oximetry was slightly improved. Several reports have described clinical benefit,[8,51] some quite dramatic,[52] with bosentan therapy. A small trial of inhaled iloprost has been completed, but appears to have been ineffective and poorly tolerated (personal communication: R. Baughman).

We recently reported our experience treating PH in sarcoidosis in collaboration with Barnett and colleagues at Inova Fairfax.[7] Twenty-two consecutive patients with RHC confirmed PH with PAWP ≤15 mm Hg who received PH targeted therapy were included. Initial treatment was bosentan in 12, sildenafil in 9, and epoprostenol in 1. Eight subjects were eventually treated with a combination regimen. After a median follow-up of 11 months (range: 5-47 m), NYHA class improved in 9, deteriorated in 2, and was unchanged in the remaining 11. Paired 6MWD (available in 18) increased by 59 m (P=0.03). Patients with a vital capacity above the median of 51% of predicted had a greater improvement in 6MWD (+119 m) compared to no change (+4 m) in those with lower FVC. Other authors have also noted a better response in those with preserved lung volumes.[3] Among patients with follow-up hemodynamic assessment (N=10), PVR was significantly reduced (11.1 to 6.8 WU). No consistent changes in oxygenation were observed and therapy was generally well tolerated. Four deaths occurred during the observation period and 6 underwent transplant, yielding a 2-year transplant-free survival rate of 74%.

Lung Transplantation

Despite the apparent short- to medium-term improvements with PAH therapies observed in the above reports, clinical responses appear to be variable, of limited benefit, and often nonsustained. Thus, the need for lung transplantation remains common.[3] Under the current lung allocation system in the US, the presence of PH dramatically increases the priority score in sarcoidosis[53] and appropriate candidates should be referred early. Survival following transplantation (70 and 57% at 1 and 3 years, respectively) for sarcoidosis is comparable to that observed for IPF, but lower than for COPD and cystic fibrosis.[54] Recipients with sarcoidosis have an increased risk of primary graft dysfunction following lung transplantation, which is the leading cause of perioperative deaths.[55] In an analysis of the UNOS database, Shorr et al reported a reduced 30-day survival of 83% in sarcoid recipients compared with 91% for all other diagnoses.[56] However, after adjusting for other variables, a diagnosis of sarcoidosis was not associated with an increased risk. Independent variables included African American race (both recipient and donor), mechanical ventilation or ICU care at time of transplant, and need for supplemental oxygen.

Summary and Outlook

Pulmonary hypertension is a relatively common and serious complication of sarcoidosis. The availability of effective therapy for PAH has generated renewed interest in this condition. Compared to other types of lung disease, SAPH appears to be more responsive to therapy, but mortality and the need for lung transplantation remain high. A randomized controlled trial is currently underway with bosentan, as well as an open-label trial of ambrisentan (clinicaltrials.gov). Both are relatively small and unlikely to provide definitive data. Larger trials will be required to demonstrate a clear benefit of PH targeted therapies and, ideally, identify which patients are most likely to respond (eg, less advanced parenchymal disease) and whether certain classes of drugs are more effective than others.

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