CHEST

Original Research

PULMONARY HYPERTENSION

Treatment of Sarcoidosis-Associated Pulmonary Hypertension*

A Two-Center Experience

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Background: **Pulmonary hypertension (PH) is a common complication of sarcoidosis that is associated with increased mortality. The pathogenesis of PH in sarcoidosis is uncertain, and the role of pulmonary arterial hypertension (PAH)-specific therapies remains to be determined.**
Methods: **We conducted a retrospective study of patients with sarcoidosis and PH at two referral centers. New York Heart Association (NYHA) functional class, exercise capacity, hemodynamic data, pulmonary function tests, and survival were collected and analyzed.**
Results: **Twenty-two sarcoidosis patients treated with PAH-specific therapies were identified. After a median of 11 months of follow-up, NYHA class was improved in nine subjects. Mean 6-min walk distance (n = 18) increased by 59 m (p = 0.032). Patients with a higher FVC experienced a greater increment in exercise capacity. Among 12 patients with follow-up hemodynamic data, mean pulmonary artery pressure was reduced from 48.5 ± 4.3 to 39.4 ± 2.8 mm Hg (p = 0.008). The 1- and 3-year transplant-free survival rates were 90% and 74%, respectively.**
Conclusions: **PAH-specific therapy may improve functional class, exercise capacity, and hemodynamics in PH associated with sarcoidosis. Prospective, controlled trials of PAH therapies for sarcoidosis are warranted to verify this apparent benefit. Mortality among the study population was high, highlighting the need for urgent evaluation at a lung transplant center.**
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Key words: bosentan; prostacyclin; pulmonary hypertension; sarcoidosis; sildenafil

Abbreviations: DLCO = diffusing capacity of the lung for carbon monoxide; MPAP = mean pulmonary artery pressure; NYHA = New York Heart Association; PAH = pulmonary arterial hypertension; PAWP = pulmonary artery wedge pressure; PH = pulmonary hypertension; PVR = pulmonary vascular resistance; 6MWD = 6-min walk distance

Pulmonary hypertension (PH) is a serious complication of sarcoidosis. The exact prevalence is not clear with a reported range of 1 to 28%.[1] Among patients listed for lung transplantation in the United States, 74% had PH documented by right heart catheterization.[2] Sarcoidosis is classified under the miscellaneous category (group 5) and considered separately from other respiratory disorders, such as interstitial and obstructive lung diseases (group 3), in the Venice 2003 clinical classification of PH.[3] The basis for this is the relatively frequent occurrence of severe PH in sarcoidosis patients, even in the absence of overt parenchymal lung disease[4,5] and the potential for direct pulmonary vascular involvement by the inflammatory process. Indeed, granulomatous vascular lesions are extremely common.[6,7]

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The presence of PH in sarcoidosis patients is associated with persistent dyspnea,[8] reduced exercise capacity,[9] and increased oxygen requirements.[2] Moreover, it appears to be an independent predictor of mortality.[10,11] There are sparse data regarding the treatment of PH associated with sarcoidosis. Reports[12–17] of therapeutic responses to corticosteroids and other immunosuppressants are limited and have yielded variable results. Several efficacious pharmacologic agents are now available for the treatment of

pulmonary arterial hypertension (PAH).[18] Whether these drugs are useful in PH that is associated with sarcoidosis or other lung diseases remains to be determined.[19] Small case series have described favorable outcomes with epoprostenol,[20] bosentan,[8] and sildenafil[21] therapy. We performed a retrospective analysis to describe our experience with PAH-specific therapies in patients with sarcoidosis-associated PH.

Materials and Methods

Patients from two regional referral centers (Johns Hopkins University; Baltimore, MD; and Inova Fairfax Hospital; Falls Church, VA) were studied. The study was approved by the respective institutional review boards of the two institutions. Records were reviewed to identify patients with sarcoid-associated PH who had been treated with PAH-specific therapy. All patients with sarcoidosis and PH confirmed by right-heart catheterization who had received PAH-specific therapy, including sildenafil, bosentan, or any prostanoid analog, were included in the study.

PH was defined as a mean pulmonary artery pressure (MPAP) $\geq$ 25 mm Hg with normal left ventricular systolic function by echocardiography and a pulmonary artery wedge pressure (PAWP) $\leq$ 15 mm Hg. Patients were excluded if they had evidence of another cause for PH such as HIV infection, connective tissue disease, portal hypertension, congenital or valvular heart disease, obstructive sleep apnea, thromboembolic disease, or a history of anorexigen use. All decisions regarding the diagnostic evaluation and treatment of patients found to have sarcoidosis-associated PH were made by expert clinicians on an individual patient basis independently at both institutions.

Patient demographics, sarcoidosis radiographic stage, and pulmonary function test results obtained closest to the date of the initial right heart catheterization were recorded. Pulmonary hemodynamics, 6-min walk distance (6MWD) and New York Heart Association (NYHA) functional class were collected at baseline and at the most recent follow-up assessment after the initiation of PAH-specific therapy. The 6-min walk test was performed at both institutions according to standard American Thoracic Society criteria[22] by trained, dedicated staff. Survival was ascertained by chart review, telephone contact, and the Social Security Death Index.

Statistical Analysis

Data are expressed as the mean $\pm$ SEM. The paired Student *t* test was used to compare mean values for initial and posttreatment hemodynamics and 6MWD. The analyses were performed using patients with baseline and at least one follow-up data point for the variable being analyzed. After the data were collected, an exploratory statistical analysis was performed to look for relationships between baseline variables and outcome after therapy. The unpaired Student *t* test was used to assess changes in 6MWD and hemodynamics with treatment between patients grouped according to baseline lung function test results and radiographic stage. Correlation coefficients were determined and linear regression was performed to look for relationships among changes in 6MWD, hemodynamics, and pulmonary function test results. The Mann-Whitney test and Spearman correlations were used to examine the relationship between nominal and continuous variables and ordinal and continuous variables, respectively. Time to death or lung transplantation was characterized with the Kaplan-Meier method. Overall survival was determined by censoring transplanted subjects at the time of transplant.

Results

Patient Characteristics

Twenty-seven patients were identified, 5 of whom had a PAWP > 15. These latter patients were excluded, and therefore 22 patients were included in the analysis. The demographic and clinical features of the group are shown in Table 1. Sarcoidosis was confirmed by biopsy in 21 patients. In one case, the diagnosis was made based on typical clinical findings. The majority of patients (68%) had advanced pulmonary fibrosis (radiographic stage IV disease). Pulmonary function testing revealed moderate restriction and a profoundly reduced diffusing capacity of the lung for carbon monoxide (DLCO). Two subjects had a combined obstructive/restrictive ventilatory defect as indicated by an FEV_1/FVC ratio < 0.7 and a decreased total lung capacity. Twenty subjects had moderate-to-marked functional limitations (NYHA class III-IV). The degree of PH was severe with an average MPAP of 46 mm Hg. Fifteen patients required supplemental oxygen at an average flow rate of 2.3 L/min. All but one patient had been treated with corticosteroids but had been judged by the treating physician to have clinically significant PH despite receiving adequate immunosuppressive therapy. Six patients were also treated with methotrexate, two with plaquenil, and one with azathioprine.

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