Confronting the Challenge of Sarcoidosis-Associated Pulmonary Hypertension

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Pulmonary hypertension (PH) associated with sarcoidosis (World Health Organization Group 5) carries a poor prognosis and likely occurs through multiple mechanisms. Routine monitoring and a high clinical suspicion must be maintained to establish early diagnosis. Imaging and other ancillary tests may suggest PH in these patients, but as with all PH groups, right heart catheterization is needed for confirmation and for differentiating contributors to PH. Although there appears to be a role for treatment in select patients with significant concomitant pulmonary arterial hypertension (PAH), pulmonary vasodilator therapy can also risk worsening hypoxia secondary to ventilation/perfusion mismatch. The medical management of patients with sarcoidosis-associated pulmonary hypertension (SAPH) will be better informed with further study in large, randomized trials. At this time, there are no US Food and Drug Administration-approved therapies, including PAH medications, for patients with SAPH.

Presentation: Our patient is a 57-year-old African-American woman who was diagnosed with pulmonary sarcoidosis with lung biopsy 34 years prior to presentation. Over this period, she had relatively mild disease: 2 episodes of hemoptysis successfully treated with prednisone, and proteinuria secondary to renal involvement that also resolved. She had no other known comorbidities and was leading a fairly active life, working as a medical receptionist until the past year. Her medications consisted of a low-dose diuretic and albuterol inhaler as needed. Over the year preceding her presentation, our patient developed functional class III symptoms, with new, progressive dyspnea and difficulty performing her activities of daily living. She also reported several occurrences of atypical chest pain. She endorsed significant daily fatigue and a weight gain over the past year despite decreased appetite. Continuous oxygen was also prescribed recently for hypoxemia.

Assessment: Physical examination revealed an African-American woman in no respiratory distress. Her vital signs were notable for requiring 4 liters per minute of oxygen to maintain saturation above 90%. Pertinent findings on physical examination included jugular venous distension, right ventricular (RV) lift, 2+ edema to her knees, and distal extremities that were cool to touch. Her 6-minute walk distance at baseline was 207 meters, with oxygen saturation nadir of 81%. Laboratory values showed elevated N-terminal pro-brain natriuretic peptide (NT-proBNP). Pulmonary function tests were consistent with obstructive lung disease (FEV1=0.9 L, FEV1/FVC ratio=65%) and diffusing capacity for carbon monoxide (DLCO) was 22% predicted. Imaging of her lungs with computed tomography scan demonstrated apical bullae and lower lobe fibrosis (Figure 1). Echocardiography (Figure 2) revealed severe RV enlargement and dysfunction with estimated right ventricular systolic pressure (RVSP) of 70 mm Hg, consistent with a presentation of advanced pulmonary hypertension (PH). Diagnostic laboratory tests including antinuclear antibody, human immunodeficiency virus, and ventilation/perfusion (V/Q) scan were performed as part of our routine initial PH evaluation and were negative for autoimmune, infectious, and thromboembolic etiologies of pulmonary arterial hypertension (PAH).

Diagnosis: With the echocardiogram that demonstrated an elevated RVSP with severe RV enlargement and dysfunction, we then performed right heart catheterization, which revealed right atrial pressure (RAP) of 24 mm Hg, pulmonary artery pressure 78/40 (54) mm Hg, and pulmonary capillary wedge pressure 17 mm Hg, calculated Fick cardiac index of 1.39 L/min/m² and pulmonary vascular resistance of 15.4 Wood units. Nitric oxide trial was not performed at this time due to its unknown predictive value in this population and the potential risk of harm in the patient’s decompensated state. As her hemody-
namics demonstrated decompensated right heart failure (markedly elevated RAP) with cardiogenic shock (markedly depressed cardiac index), we admitted our patient to the hospital after the cardiac catheterization results. She was treated with diuretics to unload the RV-pulmonary circuit, but her dyspnea remained.

After consideration of the patient’s hypoxemia, low DLCO, and poor functional capacity, we decided to try off-label PAH therapy after discussion with the patient of the potential risks of worsening clinical condition (through potential V/Q mismatch with her significant lung disease). Given her cardiogenic shock and risk for decompensation with treatment, we elected to treat with intravenous (IV) epoprostenol. Although using inhaled therapy may potentially decrease the risk of V/Q mismatch, we felt that continuous, titratable IV epoprostenol would be most effective for our patient with cardiogenic shock, and could be stopped quickly with its short half-life if she had any worsening hypoxia. She did not experience worsening hypoxia as the treatment was slowly titrated up to 25 ng/kg/min with careful monitoring as an inpatient, with the plan for further titration as an outpatient. She was maintained on epoprostenol and IV diuretics during her hospitalization, and a long-term central catheter was placed for continued therapy with the epoprostenol at the time of discharge. Over the next several days, she noticed a small improvement in her breathing and edema. Because of a lack of evidence in this population, we did not start anticoagulation.

Outcomes: As an outpatient, her epoprostenol was successfully titrated up to 75 ng/kg/min with tolerable side effects of headache and flushing. Her clinical RV failure resolved, and her weight decreased from 160 to 115 pounds (close to her dry weight) over the next 6 months. Her follow-up 6-minute walk distance at 6 months was 373 meters, and the NT-proBNP had normalized to 70. Her repeat echocardiogram confirmed improved RV size and function (Figure 3). However, her baseline oxygen requirement remained at 5 liters per minute. Our patient has resumed her daily activities.
with New York Heart Association functional class II symptoms and follows up in the PH clinic for serial monitoring of functional capacity, RV function, and lung disease in conjunction with her sarcoidosis specialists. Lung transplantation remains an option for her should she further decompensate.

**Discussion:** Pulmonary sarcoidosis typically presents in patients between 20 and 60 years of age and more commonly in African Americans in the United States (lifetime risk of 2.4% vs 0.8% in whites). PH has an overall prevalence of approximately 5% to 30% among all sarcoidosis patients based on available data, but is found in 50% or more of sarcoidosis patients worked up for significant exertional dyspnea. The delineation between sarcoidosis-associated pulmonary hypertension (SAPH) and PH associated with lung disease is not always clear, as some patients with SAPH can present with fibrotic lung changes. However, SAPH is classified separately as part of World Health Organization Group 5 because it can also occur despite relatively normal pulmonary function. Several possible mechanisms to explain SAPH have been proposed, including extrinsic compression secondary to hilar lymphadenopathy, inflammatory and fibrotic changes of lung parenchyma, and direct granulomatous invasion of pulmonary vasculature. It is unknown how many patients with SAPH have fixed obstruction of the pulmonary vasculature (ie, PAH component). In this report, we discuss a patient with long-standing history of pulmonary sarcoidosis who presented to us for initial evaluation of PH. The presence of PH significantly worsens prognosis in sarcoidosis, with a 5-year survival of approximately 60%. Additionally, management can be extremely challenging compared to patients with PH secondary to lung diseases. Even if significant PH is diagnosed with right heart catheterization, the disease is dynamic and may be difficult to fully characterize even with integration of available tools (ie, imaging, functional capacity, and hemodynamics). Finally, once the decision to treat is made, the insurance approval process for drugs is often prolonged and may delay treatment initiation.

Our patient with long-standing pulmonary sarcoidosis presented with signs and symptoms of advanced PH. Although the course of her pulmonary sarcoidosis was considered benign, she was likely developing worsening pulmonary vascular disease insidiously over a longer period. Dyspnea with exertion is the most common symptom of both pulmonary sarcoidosis and PH, and differentiation of the 2 etiologies can be challenging. Lower DLCO, lower nadir of oxygen saturation on 6-minute walk test, and echocardiography can be useful screening tests. Patients should be worked up for other causes of PH as well at this time to evaluate for other treatable causes. Once identified as SAPH, the decision to use a pulmonary vasoactive agent can be challenging given a paucity of data, but may be beneficial in some patients. Careful consideration of potential harm with treatment must be considered, including worsening V/Q mismatch and unmasking pulmonary veno-occlusive disease (PVOD). While an uncommon clinical condition of postcapillary PH, PVOD is especially relevant in this situation given the risks of lymphadenopathy or distorted architecture compressing pulmonary veins, and direct granulomatous infiltration of the veins. This case illustrates the importance of monitoring patients with pulmonary sarcoidosis for PH development and challenges in their management, and highlights the need to include SAPH patients in future studies.

**Teaching Points**

1. Dyspnea with exertion is the most common symptom of both pulmonary sarcoidosis and PH, and differentiation of the 2 etiologies can be challenging.
2. Characterization of pulmonary vascular disease in SAPH patients should be attempted with a combination of multiple modalities, including imaging and right heart catheterization.
3. Recent expert recommendations and guidelines acknowledge the lack of available evidence and advise referral of SAPH patients to expert PH centers for consideration of whether to treat on an individualized basis.
4. Large-scale trials of PAH-specific medications in patients with SAPH are needed, but at this time none have been conducted.
5. Although further study is needed, carefully selected SAPH patients may benefit from treatment with PAH medications when SAPH is thought to have a significant component of PAH.

**References**

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