Pulmonary Hypertension in Sarcoidosis

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KEYWORDS

• Bosentan • Sarcoidosis • Pulmonary hypertension • Dyspnea

KEY POINTS

- Pulmonary hypertension is recognized as a complication of advanced pulmonary sarcoidosis and is associated with increasing morbidity and mortality.
- Pulmonary hypertension should be suspected in patients with persistent dyspnea, reduced 6-minute walk (6MW), or desaturation with exercise. Echocardiography and pulmonary artery (PA) size as assessed by computed tomographic (CT) scan may suggest pulmonary hypertension. However, right heart catheterization remains the definitive test for confirming pulmonary hypertension.
- There is increasing evidence that sarcoidosis-associated pulmonary hypertension (SAPH) may respond to treatment, including agents that lead to PA vasodilation.

INTRODUCTION

Sarcoidosis is a worldwide disease. Although the prognosis of sarcoidosis is usually quite good,[1] some patients will still succumb to the disease. In referral sarcoidosis clinics, the mortality is around 5%, with most patients dying of respiratory failure.[2] Despite the introduction of newer antiinflammatory treatments for sarcoidosis, the mortality from sarcoidosis appears to be rising over the past 20 years.[3,4] Patients with advanced, chronic sarcoidosis have an increased risk for death.[5] SAPH is a major cause of death in patients with advanced pulmonary disease.

Sarcoidosis leading to pulmonary hypertension has been recognized as a complication of advanced disease for many years.[6,7] Over the past 10 years, the condition has been more widely studied, which is partly because of the recognition that it has a major impact on the outcome of disease.[8] Also, as treatments for pulmonary arterial hypertension became available, these have been used to treat SAPH. In this review, the authors discuss the cause, risk factors, diagnosis, and treatment of SAPH.

CAUSE OF SARCOIDOSIS-ASSOCIATED PULMONARY HYPERTENSION

Sarcoidosis is an interstitial lung disease that can lead to pulmonary fibrosis. Other interstitial lung diseases such as idiopathic pulmonary fibrosis and hypersensitivity pneumonitis can lead to pulmonary hypertension.[9–11] In studies of SAPH, patients often have fibrosis on chest roentgenogram and low forced vital capacity (FVC).[6,12] In some cases, not only fibrosis but also emphysematous type changes are present (**Fig. 1**).[7] This combination of fibrosis and emphysema is similar to what has been observed in combined

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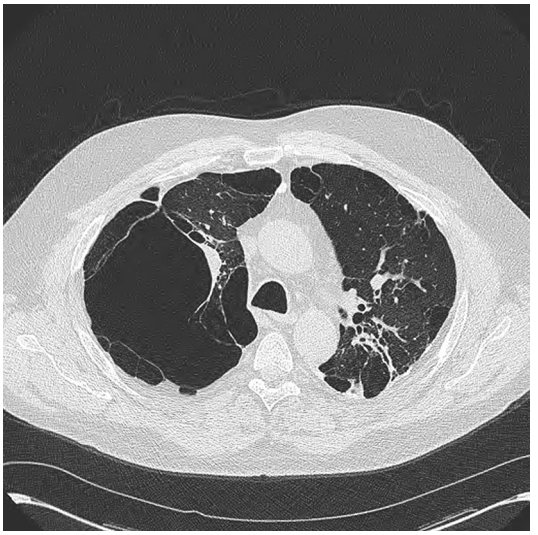

Fig. 1. High-resolution CT scan demonstrating emphysematous as well as fibrotic changes in a patient with chronic sarcoidosis and pulmonary hypertension.

pulmonary fibrosis and emphysema syndrome.[13] This combination may lead to quite severe pulmonary hypertension as a result of the 2 pathologic processes causing severe destruction of lung vasculature.

As opposed to most interstitial lung disease, sarcoidosis can lead to pulmonary hypertension by several other mechanisms beyond just fibrotic lung disease (**Box 1**).[14,15] One mechanism is compression of pulmonary vasculature by enlarged lymph nodes and associated mediastinal fibrosis.[16,17] **Fig. 2** shows the example of a patient with cutaneous and pulmonary sarcoidosis who was found to have severe pulmonary hypertension. Her chest radiograph and CT scan demonstrated adenopathy and fibrosis in the hilum and mediastinum, especially in the area of the right upper lobe. On pulmonary angiogram, there was reduced flow to the right upper lobe as a result of extrinsic compression of the PA.

Box 1
Causes of pulmonary hypertension in sarcoidosis

- Fibrotic: obliteration of the pulmonary vascular bed
- Pulmonary vascular compression due to adenopathy
- Granulomatous arteritis
- Pulmonary venoocclusive disease
- Sarcoidosis-associated cirrhosis and portopulmonary hypertension
- Left ventricular systolic and/or diastolic dysfunction
- Hypoxia/pulmonary vasoconstriction

In some cases such as this, PA stenting can be used to improve pulmonary blood flow,[17] However, this could not be performed in this case because of technical reasons.

Pulmonary arteritis can occur as a result of sarcoidosis[14,18]; this may be responsive to corticosteroids or other antiinflammatory drugs.[14,19,20] The incidence of pulmonary hypertension responding to antiinflammatory drugs alone is unknown, but it seems to be fairly rare. However, it may be underrecognized because most patients with chronic pulmonary sarcoidosis will have received corticosteroids for treatment of their pulmonary disease. Workup for pulmonary hypertension is usually reserved for when a patient has failed antiinflammatory therapy and has ongoing symptoms. In studying pulmonary sarcoidosis with early disease using exercise testing, evidence for mild pulmonary hypertension may be seen in patients with no clinical evidence for pulmonary hypertension.[21,22] Pulmonary arterial hypertension due to portopulmonary hypertension has also been reported,[23] but it seems to be rare.

Pulmonary venoocclusive disease has also been reported in SAPH and may be more common than appreciated clinically.[14,18,24] This condition does not seem to respond to antiinflammatory drugs. In general, patients with pulmonary venoocclusive disease may develop pulmonary edema when treated with pulmonary vasodilators such as epoprostenol and bosentan.[25] However, some patients with pulmonary venoocclusive disease have been treated successfully with PA vasodilators.[26] One should consider clinically significant pulmonary venoocclusive disease in a patient with SAPH who is failing to respond or who develops worsening oxygenation of new infiltrates during treatment of their pulmonary hypertension.

Left ventricular (LV) dysfunction can lead to pulmonary hypertension[27]; this can be due to LV dysfunction from myocardial sarcoidosis, resulting in heart failure with reduced ejection fraction. Notably, heart failure with preserved ejection fraction can also occur in patients with sarcoidosis. In both of these cases, the cause may well be LV infiltration from sarcoidosis itself.[15,28] In some cases, MRI scanning of heart may be useful in predicting who has LV dysfunction related to sarcoidosis.[29]

In summary, pulmonary hypertension in sarcoidosis can be caused by pathologic changes similar to those that cause pulmonary arterial hypertension alone (World Health Organization [WHO]