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Review Article

Pathogenesis, Clinical Manifestations and Treatment of Sarcoidosis Associated Pulmonary Hypertension

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Abstract

Pulmonary hypertension is a well-recognized and a serious complication of sarcoidosis. The exact prevalance is unknown due to the different measurement techniques and diagnostic modalities used with distinct criteria for patient selection but may occur in up to 74% of the sarcoidosis patients. The frequency usually depends on the severity of parenchymal involvement while pulmonary hypertension may also occur in the early stages of the disease. Pulmonary hypertension causes a substantial morbidity and adversely affects the survival causing a major impact on the sarcoidosis patients leading to major functional and prognostic consequences. In advanced disease it appears to be a crucial and a major factor for patient death causing up to ten fold increase in mortality. Therefore, screening, diagnosis and treatment of pulmonary hypertension in sarcoidosis carries the upmost importance. Lack of current treatment guidelines for sarcoidosis associated pulmonary hypertension leaves the clinician to design an individual treatment protocole for each patient consistng of imunosuppressive and pulmonary hypertension targeted agents. Pulmonary hypertension targeted therapy may improve short-term pulmonary hemodynamics without enhancing exercise capacity while steroids or immunosuppressive therapy may improve hemodynamics in selected patients. This review incorporates the risk factors, pathogenesis, clinical manifestations, diagnosis,

treatment and prognostic sequela of sarcoidosis associated pulmonary hypertension in regard to current literature. We have also analyzed the clinical charactersitics of the patients, pitfalls in diagnosis and the potential treatment options. Although the prognosis is dreadful, treatment may alleviate patient symptoms, improve quality of life and prolong life expectancy in these patients.

Introduction

The natural history of sarcoidosis is extremely variable from spontaneous remission to pulmonary fibrosis with ongoing remissions and exacerbations. In approximately 5% of the patients, perpetual pulmonary fibrosis occurs. As in all forms of advanced parenchymal lung disease, the prevalence and impact of pulmonary hypertension tend to be greater in the later stages of sarcoidosis. However, sarcoidosis associated pulmonary hypertension (SPH) may arise in the early stages of disease. Patients with chronic fibrotic pulmonary sarcoidosis have an increased mortality risk while pulmonary hypertension may arise as a major cause of death in patients with advanced disease [1,2]. SPH is known as a complication of advanced disease for years and has been widely investigated in the past ten years due to its major impact on the prognostic outcome of sarcoidosis patients [3,4]. Pathogenesis of SPH is complex and associated with multiple factors. Pulmonary hypertension associated with other fibrotic lung diseases may be mild as opposed to many cases of SPH. The exact incidence of SPH is unknown. The wide availability and common use of echocardiography has led to an increased diagnostic yield of this complication. In this review, pathogenesis, risk factors, clinical findings and diagnosis of SPH are discussed with the current treatment options.

Patophysiology and Epidemiology of SPH

Pulmonary hypertension is a well-known sequela of sarcoidosis that may occur in up to 74% of the patients [5,6]. The exact incidence of SPH is unknown due to the different measurement techniques and the patient selection criteria. The incidence varies between centers. Approximately 5-6% of sarcoidosis patients have pulmonary hypertension identified by echocardiography or right heart catheterization [7]. SPH is identified in nearly half of the patients with dyspnea out of proportion to their pulmonary function abnormalities [8]. The prevalence of SPH is between 1% and 28% at rest while rises up to 43% with exercise [7,9,10]. Althoug SPH is more common in patients advanced pulmonary sarcoidosis in 40 to 60% there is no radiologic evidence of advanced lung disease or pulmonary fibrosis while SPH may be more astringent when it develops without pulmonary fibrosis [9,11]. This finding suggests that there are other mechanisms other than advanced pulmonary parenchymal disease accomodating with the development of pulmonary hypertension. Clinicians should note that pulmonary fibrosis is one the of most crucial factors leading to pulmonary hypertension in sarcoidosis patients by causing fibrotic obliteration of the pulmonary vascular bed.

Extrinsic mechanical compression of pulmonary arteries due to enlarged lymph nodes may lead to pulmonary hypertension which is the pathologic mechanism in approximately one fifth of the patients with stage IV disease [2,12]. Pulmonary arteritis that may be responsive to antiinflammatory treatment is another responsible factor pulmonary hypertension of sarcoidosis. Venoocclusive disease may also lead to pulmonary hypertension in sarcoidosis which may be more common than clinically detected [11,12]. Hypoxia associated pulmonary vasoconstriction, left ventricular systolic or diastolic failure and cytokine derangement may

play a role in SPH [13,14]. Endothelin-1 produced mainly by endothelial cells and induced by hypoxia, shear stress and various growth factors acts directly on smooth muscle cells leading to vasoconstriction. This mediator may also play a role for vascular remodelling in sarcoidosis [15]. The above mentioned mechanisms lead to hypertension alone or in combination. Causes of pulmonay hypertension in sarcoidosis are depicted in Table 1 [2,5,6]. Identification of the liable mechanism may culminate in better treatment results.

Table 1: *Causes of sarcoidosis associated pulmonary hypertension (2,5,6)*

Fibrosis of the vascular bed
Granulomatous inflammation of the arteries
Vascular compression due to adenopathy
Hypoxic pulmonary vazoconstriction
Pulmonary venoocclusive disease
Sarcoidosis associated cirrhosis and portopulmonary hypertension

Clinical Findings and Diagnosis of SPH

Diagnosis of pulmonary hypertension in sarcoidosis patients is often late in the course of the disease because it is perplexed by the symptoms of underlying sarcoidosis [15]. Dyspnea, cough, decreased exercise tolerance and fatigue are frequently encountered in both situations. The most common symptom is worsening of dyspnea on exertion which is usually attributed to underlying sarcoidosis associated parenchymal disease. There may be other symptoms such as extremity edema, dizziness, syncope, palpitations and chest pain that are assigned to other common diseases. The clinical signs of right heart failure are not reliable as they have a low sensitivity and are present in only 21% of the patients [9]. A high index of suspicion is required for the identification of SPH. BNP and NT-proBNP levels are elevated in pulmonary hypertension. They may be useful for diagnosis and predicting the prognostic outcome. Fibrin, D-dimer, Troponin-T, uric acid and exhaled NO levels may be other crucial diagnostic markers.

The first clue to diagnosis is the unexplained dyspnea. Clinicians should also bear in mind that dyspnea of SPH may not correlate with pulmonary function tests or the radiologic stage of sarcoidosis [16]. The 6MW test is a useful screening test for pulmonary hypertension and the 6MW distance is less than 450 meters in most of the SPH patients [17-20]. However, it should be noted that there are other factors associated with sarcoidosis such as fatigue, airway disease and muscle involvement leading to decreased 6MW distance. Factors associated with pulmonary hypertension in sarcoidosis is shown in Table 2 [2,6,9]. The next test for for pulmonary hypertension is echocardiography. It is a non-invasive method and the measured pulmonary artery systolic pressure shows a good correlation with that of estimated by right heart catheterization [2,8]. Computed tomography demonstrates the size of the pulmonary artery and may be useful for diagnosis by revealing enlargement of the artery. Pulmonary angiography is the most accurate and definitive method for the diagnosis of pulmonary hypertension. Pulmonary angiography also differentiates between arterial and venous pulmonary hypertension. In the absence of lung disease, transthoracic echocardiogram appears to be the most reliable non-invasive screening test for pulmonary hypertension. On the other hand, low FVC,

TLC and DLCO may be useful to support the diagnosis of SPH while the correlation between pulmonary hypertention and lung function tests is poor.

Table 2: *Factors associated with pulmonary hypertension in sarcoidosis (2,6,9)*

Dyspnea
Fatigue
Advanced parenchymal disease
Reduced TLC and DLCO
Hypoxemia
Desaturation with 6MW
Less than normal 6MW distance

Treatment and Prognosis

The ideal treatment for SPH is still controversial due to the limited data in different patient profiles. Current data available on the long term influence and benefit of pulmonary hypertension targeted medications in SPH is scarce. Most of the studies consist of retrospective case series with only three prospective studies [21-23]. The first step in treatment is the search for risk factors and comorbid diseases. Heart failure, thromboembolic disease, muscle involvement of sarcoidosis, obstructive sleep apnea, resting, exertional and nocturnal hypoxemia requires conventional treatment. On the other hand, the use of currently available pulmonary vasodilators is debatable due to the lack of studies that indicate their effect in SPH patients. There are no prospective therapeutic trials in patients with SPH. Indeed, these patients have specifically been excluded from trials in patients with pulmonary arterial hypertension (PAH, WHO group 1) while there have been a number of case series attesting to the potential utility of medications for SPH patients. In patients with significant parenchymal lung disease, there is the theoretical possibility of worsening of hypoxemia due to the ventilation perfusion mismatch that necessitates meticulous use of pulmonary vasodilator agents. The currently available treatment protocole includes the endothelin, nitric oxide and the prostacyclin pathways while which of these mechanisms play a more dominant role in SPH is unknown [24]. Steroids should be considered in patients with active disease and in cases with bulky lymphadenopathy where compression of the central vessels is a feature since none of the studies with stage IV patients revealed a significant hemodynamic response to corticosteroids [10,24].

High levels of endothelin-1 in SPH is the fundamental indication for the use of endothelin receptor antagonists in these cases. Experience with these agents is limited to a few case series. Baughman has revealed a decrease of 15mm Hg in the mPAP after 4 months of treatment [8,24]. Barnett has shown improvement in the mPAP, pulmonary vascular resistance and 6MWT in patients with limited fibrosis but the 3 year survival prognosis was poor [25]. Bosentan has been proved to be useful in this patient population [19,26]. Nitric oxide is a potent vasodilator with a short half-life that is delivered by inhalation. Although nitric oxide produces reduction in mPAP and RVR with an increase in cardiax index there is no significant change in the 6MMW distance. The role of phosphodiesterase inhibitors should be determined by further studies [21,24,25]. The prostanoid analogues are potent vasodilators that also inhibit platelet agregation. They are

administered intravenously, subcutaneously or via the inhaled route [25]. Data about epoprostenol use in SPH is very limited but the agent may cause more than 20% decrease in the PVR (21). Treatment options for sarcoidosis associated pulmonary hypertension are depicted in Table 3 [26-29].

Table 3: *Treatment of sarcoidosis associated pulmonary hypertension (26-29)*

Class/Agent	Result
Prostacyclin	
Epoprostenol	Clinical improvement
Inhaled iloprost	Improved hemodynamics
Endothelin receptor antagonist	
Bosentan	Improved hemodynamics
Ambrisentan	Improvement in HRQoL
Phosphodiesterase inhibitor	
Sildenafil	Improvement in hemodynamics but not 6MW distance

Endovascular procedures with angioplasty and stent placement may be other treatment options in patients with extrinsic compression of the pulmonary arteries. These treatment methods carry a high mortality and should be used only in selected patients. Lung transplantation may be considered in patients unresponsive to conventional treatment strategies. Several factors are to be noted for reduced survival in SPH patients (Table 4). Patients with a high PVR, a PA systolic pressure higher than 50mm Hg, a low FVC and a low DLCO are associated with high mortality and a worse prognosis [30].

Table 4: *Factors associated with reduced survival in sarocidosis associated pulmonary hypertension (2,13,17)*

Low FVC
Reduced DLCO
Highr PVR
Low ejection fraction
Higher than 50 mm Hg PA systolic pressure
Advanced fibrosis
Low PAPSE score

Conclusions

SPH is a significant diagnostic and a therapeutic challenge for the pulmonary clinician. The pathogenesis is complex involving mechanisms other than parenchymal fibrosis and hypoxemia. SPH leads to a decreased survival which is the primary target of treatment. Patients also present with life disturbing symptoms like dyspnea that interferes with the quality of life. It is mandatory to define a therapeutic approach for the individual patient phenotype who will respond and least likely detoriate from treatment. Each patient should

be closely monitored and followed objectively preforming 6 MWT and echocardiogram at three months apart on outpatient basis. The treatment should be discontinued in the absence of improvement or in the presence of significant drug side effects. Pulmonary vasodilators may increase quality of life, decrease symptoms and improve exercise tolerance in some patients. Further studies with larger populations are required to determine whether the vasodilator treatment will change the prognostic outcome and the natural disease course in the SPH patients.

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