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Review article

Pulmonary arterial hypertension in the setting of scleroderma is different than in the setting of lupus: A review

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ABSTRACT

Pulmonary hypertension (PH) is a clinical syndrome that is subdivided into five groups per the World Health Organization (WHO) classification, based largely on hemodynamic and pathophysiologic criteria. WHO Group 1 PH, termed pulmonary arterial hypertension (PAH), is a clinically progressive disease that can eventually lead to right heart failure and death, and it is hemodynamically characterized by pre-capillary PH and increased pulmonary vascular resistance in the absence of elevated left ventricular filling pressures. PAH can be idiopathic, heritable, or associated with a variety of conditions. Connective tissue diseases make up the largest portion of these associated conditions, most commonly systemic sclerosis (SSc), followed by mixed connective tissue disease and systemic lupus erythematous. These etiologies (namely SSc and Lupus) have been grouped together as connective tissue disease-associated PAH, however emerging evidence suggests they differ in pathogenesis, clinical course, prognosis, and treatment response. This review highlights the differences between SSc-PAH and Lupus-PAH. After introducing the diagnosis, screening, and pathobiology of PAH, we discuss connective tissue disease-associated PAH as a group, and then explore SSc-PAH and SLE-PAH separately, comparing these 2 PAH etiologies.

1. Introduction

Pulmonary hypertension (PH) is a clinical syndrome defined by physiologic/hemodynamic criteria that results from several etiologies [1]. It can eventually lead to right heart failure and death. PH is defined as a mean pulmonary artery pressure (mPAP) of ≥25 mmHg at rest [2]. Per the World Health Organization (WHO) classification, PH is divided into five categories largely based on etiology and pathophysiology [1]. Importantly, these groupings have paved the way for categorizing patients to be enrolled into clinical trials that in turn led to identification of effective therapies [3,4]. WHO group 1 is a specific subtype of PH that is commonly termed pulmonary arterial hypertension (PAH), which includes multiple subgroups including connective tissue disease (CTD) – associated PAH.

There is an autoimmune element to PAH pathophysiology even in the non-CTD-PAH [5]. This review will summarize the pathobiology and clinical characteristics of PAH, focusing on CTD-PAH associated with systemic sclerosis (SSc) and systemic lupus erythematosus (SLE) given the relatively high prevalence of PAH associated with these two diseases compared with other CTD. This review is not meant to be exhaustive of the similarities and differences between SSc-PAH and SLE-PAH. What is clear from evaluating and summarizing the areas of focus in this review, is that CTD-PAH should not be thought of or studied as a uniform subset of PAH; rather, the parsing out of the differences can serve as the springboard for further research that may define better classification systems, diagnostic tools, and treatment modalities for what should be appreciated as two distinct categories of PAH.

Specifically, this review will focus on the similarities and differences in etiologies for PH in both SSc and SLE, the relationship (or lack thereof) to severity or flares of the underlying CTD, the differences in response to immunomodulatory treatment, and the difference in survival.

2. Pulmonary arterial hypertension

In addition to having a mPAP ≥25 mmHg, the other diagnostic

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Table 1
Summary table of differences between SSc-PAH and SLE-PAH (with respect to the areas considered in this review).

	Systemic Sclerosis	Systemic Lupus Erythematosus
Estimated Prevalence in the United States (per 100,000)	20–30	20–200
Prevalence of PAH	7%–12% of SSc patients	1%–5% of SLE patients
% of CTD-PAH	60%–80%	15%–20%
Age of onset of CTD-PAH	60 - 65 years	40 - 45 years
% of CTD with positive anti-U1 RNP[b]	2%–14%	20%–40%
Association with CTD disease activity	No	Yes
Clinical course of CTD-PAH	Progressive	Variable and unpredictable
Response to immunosuppressants	No	Potentially Yes[a]
Prognosis, 3-year survival on PAH therapy	50%–60%	75%–85%
Clinical pulmonary & cardiovascular manifestations	• Pulmonary Arterial Hypertension • Interstitial Lung Disease • Recurrent aspiration • Pulmonary venoocclusive disease • Pulmonary capillary hemangiomatosis • Pulmonary Emboli • Diastolic LV dysfunction • Myocardial fibrosis • Increased lung cancer risk • Rarely LV systolic dysfunction • Pleural effusions are uncommon	• Pulmonary Arterial Hypertension • Interstitial Lung disease • Lupus Pneumonitis • Pulmonary Emboli • Alveolar Hemorrhage • Organizing Pneumonia • Pleuritis • Pleural effusion • Diastolic dysfunction • Valvular pathology • Shrinking Lung Syndrome

PAH: pulmonary arterial hypertension. SSc: Systemic Sclerosis (scleroderma). SLE: Systemic Lupus Erythematosus. CTD: Connective tissue disease.
[a] When/if responds to immunosuppressants, long-term response is not known, and likely only transient.
[b] anti-U1 RNP antibody is associated with PAH incidence, and with better survival in PAH.

criteria for PAH include pulmonary artery wedge pressure of ≤15 mmHg and a pulmonary vascular resistance (PVR) of > 3 Wood units (all measured at rest) [2]. The gold-standard for making these measurements is right heart catheterization (RHC), and RHC is considered mandatory before the initiation of any PAH-specific therapy.

The pathobiology of PAH is complex, with multiple cell types, molecules, and pathways being implicated to varying levels [6]. Pulmonary artery endothelial cell dysfunction is thought to underlie many of these pathogenic processes. On the molecular level, diseased endothelium in PAH has impaired ability to produce nitric oxide (NO) and prostacyclin. It also overexpresses vasoconstrictors such as endothelin-1, leading to increased vascular tone [7].

At the tissue level, endothelial cell dysfunction plays a role in the development of plexiform lesions occasionally seen in PAH. Plexiform lesions are made up of tufts of capillaries that form a network of vascular channels with a core of myofibroblasts and lined with endothelial cells that have undergone enhanced proliferation [8]. Such proliferation is thought to either be the result of loss of factors that lead to apoptosis of endothelial cells or activation of factors that promote unchecked endothelial cell proliferation. Evidence of monoclonal expansion of endothelial cells in histopathological specimens from plexiform lesions in idiopathic PAH supports this later concept [2,9,10], though this work needs to be independently validated.

There is evidence that changes in cell signaling via the transforming growth factor-beta (TGF-β) family of proteins are important drivers of endothelial and vascular smooth muscle cell proliferation [10]. In particular, the bone morphogenetic protein receptor 2 (BMPR2) which is a member of the TGF- β signaling family of proteins is expressed in both pulmonary artery endothelial cells and pulmonary vascular smooth muscle cells [11]. The gene encoding this protein is mutated in as many as 60–70% of patients with heritable PAH, and about 25% of sporadic cases [12–14]. The presence of a mutation in *BMPR2* is not sufficient for the development of PAH, as only the minority of patients (~20%) with this mutation develop the clinical syndrome of PAH [13]. This suggests that there is susceptibility conferred by *BMPR2* mutations, but a "second hit" is necessary. BMP has been shown to modulate endothelial cell production of NO and endothelin and to regulate endothelial cell migration, survival, and proliferation [11,15–17]. Such changes in the dysfunctional endothelial cells and concomitant changes in vascular smooth muscle cell number and size lead to medial hypertrophy and intimal thickening of pulmonary arteries and pre-capillary vessels that over time may lead to right heart failure [18,19].

In patients with CTD, the immune dysregulation underlying those conditions may play a role in the pathophysiology of PAH [20]. Macrophages, lymphocytes, antinuclear antibodies, immunoglobulin G, and complements have been identified histologically in the pulmonary vasculature of patients with CTD-associated PAH [20–22].

Upregulation of chemotactic cytokines has been noted in patients with PAH, and these chemotactic cytokines help recruit inflammatory cells to the pulmonary vasculature [20]. For example, CX3CL1 levels are elevated in T lymphocytes of PAH patients, and this chemotactic cytokine has been shown to induce proliferation of pulmonary artery smooth muscle cells in animal models [23]. RANTES, another chemotactic cytokine which recruits monocytes and T lymphocytes, has been found to be expressed in higher amounts in lung tissue from PAH patients. Further, RANTES has been demonstrated to induce endothelin expression [24]. The antibody profile of CTD patients may be helpful in predicting PAH development. Whether these antibodies are in the pathogenesis pathway or 'innocent bystanders' is controversial.

3. CTD-PAH

PAH can complicate CTD, and the two most common CTD's associated with PAH are SSc and SLE [1,25]. Typically, these two etiologies are grouped together in studies of PAH-specific therapies under the general category of CTD-PAH. However, recent evidence regarding the progressive evolution and pathogenesis of these diseases, suggests that vascular changes in SSc-PAH and SLE-PAH are different (Table 1) with distinct responses to therapy and vastly different overall prognosis [26]. Grouping these patients together may be affecting the outcomes of these studies [26,27].

There are geographic differences in the prevalence of SSc and SLE. SLE is much more prevalent for example in China than in Western countries, while SSc is less prevalent in East Asia than in Europe, Australia, or North America.

The prevalence of SSc in the United States is ~24 per 100,000 adults [28]. SSc is a disease that is characterized by progressive fibrosis of the skin, muscle (both skeletal and cardiac), lung, and by a diffuse multi organ vasculopathy which is not typically inflammatory and show a nonuniform and limited response to treatment with traditional