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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

immunosuppressant agents. There are distinct subtypes including limited cutaneous SSc, diffuse cutaneous SSc, and SSc without skin involvement. Its pathophysiology is notable for the production of autoantibodies (e.g., anti-centromere, anti-SCL-70, anti-RNA pol III), and increased deposition of extracellular matrix. The ACR/EULAR classification criteria for SSc include a weighted scoring system for clinical findings such as skin thickening of the fingers of both hands (with different weights to the score depending on if the thickening is proximal to the metacarpophalangeal joints), fingertip lesions, telangiectasias, abnormal nailfold capillaries, PAH or interstitial lung disease (ILD), Raynaud's phenomenon, or SSc-related antibodies (anti-centromere, anti-SCL-70, anti-RNA pol III) [29].

These criteria do not extend to patients without skin thickening or those with scleroderma-like disorders, such as eosinophilic fasciitis, nephrogenic sclerosing fibrosis, or scleromyxedema. The classification criteria are meant to help determine which patients may be included in SSc trials rather than to be diagnostic criteria. As such, a patient with a strong clinical suspicion for SSc should be worked up for such even if not scoring enough points on the classification criteria scale at the time of presentation.

SLE is also a multi organ inflammatory condition with a prevalence range estimated at 20 to 240 per 100,000 people in the United States. Classification of a person as having SLE can be done per the Systemic Lupus International Collaborating Clinics (SLICC) criteria [30]. These include eleven clinical criteria and six immunologic laboratory criteria. The criteria do not have to be present concurrently, but can be present cumulatively. A patient may be classified as having SLE if she/he satisfies four of the SLICC criteria including at least one clinical criterion and one immunologic criterion. A person may also be classified as having SLE if the patient has biopsy-proven nephritis compatible with SLE and with ANA or anti-dsDNA antibodies. Like the SSc criteria, the SLICC criteria are meant for classification usually for clinical studies, and a patient whose clinical picture strongly suggests SLE, should be investigated for the presence of such even if not fulfilling all aspects of the classification criteria.

4. Systemic sclerosis-associated PAH

SSc accounts for up to 60%–80% of all CTD-PAH [31–34] in the United States and Europe. On the other hand, the prevalence of PAH in SSc is ~7–12% [35–37]. There is a wide range of reported SSc-PAH prevalence (between 5% and 35%) because of different screening methods and diagnostic criteria used in each study [38]. There seems to be an increased risk of developing PAH in those with the limited form of SSc as opposed to those with diffuse skin disease; however, all subsets can be affected. Older age of disease onset also confers an increased risk for PAH [35]. Given that there is a higher prevalence of PAH in SSc as compared to any other CTD, there is more literature available.

The diagnosis of SSc-PAH can often be difficult, particularly given the comorbidities that are common with SSc and the non-specificity of PAH symptoms. For example, coexisting ILD [38], left heart disease with preserved ejection fraction (diastolic dysfunction), and pulmonary veno-occlusive disease (PVOD) can all cause PH that falls into a different WHO group [39]. There is also primary cardiac involvement in the disease process [40]. The distinction between these types can be challenging to make, but it is important since the treatment approach is quite different [41].

Theoretically, the clinical presentation of SSc-PAH is the same as other types of PAH. In practice, however, the classic history is difficult to obtain for several reasons. Patients with SSc often suffer from musculoskeletal abnormalities; in our experience, they may not consciously recognize shortness of breath with exertion until later stages, or after treatment has improved their symptoms that they would realize that they had dyspnea or fatigue with exertion previously. Additionally, symptoms of ILD may overlap with those of PAH thereby making the initial diagnosis more elusive [35]. Patients with SSc may also have debility and fatigue due directly to SSc and independent of PAH. Some patients with SSc also have renal disease and lower extremity swelling may be attributed to renal failure rather than right heart failure, delaying identification of right heart failure.

The antibody profile of SSc patients may be helpful in predicting PAH development. In SSc, the presence of anti-U3RNP/fibrillarin antibodies or anticentromere antibodies is associated with an increased risk of developing PAH, whereas anti-topoisomerase (Scl-70) antibodies seem to be 'protective' [42]. However, Scl-70 positivity is associated with an increased risk of developing ILD. Whether any of these antibodies has a direct etiological correlation to PAH development is unclear [22]. Although anti-U1 RNP positivity is associated with the development of PAH, anti-U1 RNP positivity seems protective and is associated with improved survival [26]. In other words, although the presence of anti-U1 RNP antibody increases the likelihood of developing PAH, the PAH patients with anti-U1 RNP antibody do better than the PAH patients who do not have a positive anti-U1 RNP antibody.

Because patients with SSc-PAH have relatively poor outcomes, repeated at least yearly noninvasive screening testing is recommended [43–46]. Moderate to severe PH can develop rapidly between 2 screening evaluations. DLCO is theorized to be a predictor of PAH in SSc patients, however the little data supporting this is not consistent [47].

Like other forms of PAH, SSc-PAH may be rapidly progressive [48,49]. PAH is a leading cause of death in SSc patients [42], but potent vasodilators (and occasionally lung transplantations) have changed its natural course [49]. Treatment options for SSc-PAH are the same as those for the other types of PAH [50] [including endothelin receptor antagonists, phosphodiesterase inhibitors, guanylate-cyclase stimulators (GCs), selective prostacyclin receptor agonists, and/or prostacyclin agonists], but patients with SSc-PAH have a more blunted response to treatment [35]. SSc-PAH is rarely vasoreactive and typically does not respond to calcium channel blockers.

Several long-term studies suggest that the outcome of patients with PAH associated with SSc is markedly worse than that of patients of IPAH, despite the use of modern therapies. The Registry to Evaluate Early and Long-term PAH disease management (REVEAL) is a multicenter, observational, United States-based registry of PAH that was designed to characterize the PAH population. It found that the one-year survival rate of patients with CTD-PAH compared with IPAH was worse (86% vs. 93%), with SSc-PAH faring worse at 82% [51]. The three year-survival of SSc-PAH patients in this cohort was 51% compared to those with non-SSc CTD [52]. Another study showed that despite similar baseline hemodynamics, patients with SSc-PAH have the poorest survival rates when compared with other CTD-PAH subgroups, including patients with systemic lupus erythematosus [51–53].

5. Lupus – associated PAH

Lung involvement in SLE often involves the pulmonary vasculature. As in SSc, PH in SLE can arise from both arterial and non-arterial etiologies. Non-arterial forms of PH in SLE can arise from pneumonitis, alveolar hemorrhage, chronic interstitial lung disease, vasculitis/capillaritis, and cryptogenic organizing pneumonia. These conditions may contribute to vascular remodeling and damage [54]. Furthermore, pulmonary venous hypertension from left ventricular dysfunction, hypoxic vasoconstriction from chronic hypoxemic lung disease, thrombosis related to antiphospholipid antibody syndrome and veno-occlusive processes related to the hypercoagulable state associated with SLE, may contribute to the development of PH[22]. These Lupus-associated processes listed here lead to WHO groups 2, 3, or 4 PH and thus will not be discussed further in this review.

The prevalence of PAH in patients with SLE has been estimated to range between 0.5 and 17.5% (though up to 43% prevalence has been previously reported) [22,55,56]. The variation in reported prevalence may be related to rarity of the disease and different diagnostic criteria

used (e.g., echocardiography versus RHC) [22], however, it is likely that the true prevalence of clinically relevant PAH in SLE is in the single digits (likely 1–5%).

The annual incidence of SLE averages 5 cases per 100,000 population with a range between 1.5 and 10.6 per 100,000 persons/year in the United States [57]. Furthermore, a high percentage of SLE-PAH patients may be asymptomatic for a long period [56]. This, combined with the epidemiological data, makes it difficult to develop consensus recommendations on PAH screening for high-risk SLE patients. Such high-risk patients include pregnant SLE patients or those with antiphospholipid antibody syndrome [56].

Severe PAH exacerbations may be brought on by flares in SLE disease activity [58] suggesting an immune/inflammatory component to the pathophysiology of SLE-associated PAH. In support of such an immune system component, there are increased levels of anti-endothelial cell antibodies in these patients, which leads to increased release of endothelin [2,22,59]. Other autoantibodies found in SLE that are thought to likely be relevant are anti-cardiolipin and anti-RNP antibodies, which are correlated with the diagnosis of PH[59]. As is the case in SSc-PAH, it is unclear whether the presence of these autoantibodies in serum is simply an association or suggestive of a direct mechanistic influence.

Unlike the case in the more prevalent SSc-associated PAH, where the 3-year survival for patients is ~50%, it is significantly better at 74% in SLE-PAH patients [60]. Since PAH in SLE may be associated with inflammatory disease activity, endothelial damage, and thrombosis, it is difficult to determine which aspect of the autoimmune disease leads to increase in mPAP in any particular patient. In these patients, treatment strategies employing both immune-modulators and pulmonary vasodilators to target multiple convergent pathophysiologic pathways are likely more beneficial than therapy with a single therapeutic modality. In patients presenting with active SLE and evidence of right ventricular failure, a strategy utilizing a combination of PAH-specific therapy and immunosuppression led to a significant reduction in hemodynamic parameters of mPAP, cardiac index, and PVR compared to immunosuppressive therapy alone [61]. In subgroup analyses, responders to this immunosuppressive approach were more likely to be anti-dsDNA and anti-Smith antibody positive and had a worse functional classification.

While both SLE and SSc are autoimmune diseases, an intriguing contrast between SLE-associated PAH and SSc-associated PAH is that immunosuppression and control of active inflammation may be beneficial in SLE-associated PAH, but this has not been found to be the case in SSc-associated PAH [35,62]. In a study using the combination cyclophosphamide plus glucocorticoid strategy of immunosuppression in patients with CTD-associated PAH, none of the patients with SSc-associated PAH showed a response with sustained improvement in hemodynamic parameters and WHO functional class after one year compared with patients with SLE-associated PAH [58]. SLE-associated PAH patients represented 62% of the responders in that study (MCTD patients represented the other 38%) [63]. One theory, for the apparent lack of benefit of immunosuppressive therapy in SSc-associated PAH is the presence of a more fibrotic component to the vascular disease process in SSc [62].

6. Conclusion

PAH is a serious complication of both SSc and SLE. The etiology of PAH involves in part endothelial cell and vascular smooth muscle cell dysfunction. The dysregulated immune mechanisms underlying the disease pathogenesis of SSc and SLE may contribute to the known immunologic and inflammatory factors at play in the development of PAH. The difference in survival rates and the fact that clinical studies suggest more benefit of immunomodulatory therapies in SLE-PAH compared to SSc-PAH suggest that there may be differences in the etiology and course of the immunologic component of PAH in these two conditions. SLE- and SSc-associated PAH behave differently and it is best if they are studied separately as their prognosis and response to therapies including the risk/benefit ratios of such therapies may be different.

Based on the above review, we hereby propose separating the WHO subgroup classification of CTD-PAH into at least 3 separate subgroupings within the associated-PAH (APAH): 1.4.1.1 being systemic sclerosis-associated PAH, 1.4.1.2 Lupus-associated PAH, and 1.4.1.3 Other CTD-PAH. More research is needed into the mechanisms underlying the development of the different CTD-associated PAH, accurate screening methods, targeted therapies, and prospective validation of the above proposed sub-classification of CTD-APAH.

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Summary of take home message

SSc-PAH & Lupus-PAH behave differently & have different clinical courses & outcomes & should be studied differently.

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