Pulmonary Hypertension and the Antiphospholipid Syndrome


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Antiphospholipid antibodies (aPL) have been implicated in the development of both idiopathic pulmonary arterial hypertension (PAH) and PAH associated with connective tissue disease (CTD) and chronic thromboembolic pulmonary hypertension (CTEPH). Pulmonary venous hypertension (PVH) can also develop as a sequela of aPL-associated valvular heart disease (Libman-Sacks endocarditis).

Antiphospholipid antibodies are a group of autoantibodies with an apparent specificity for anionic phospholipids. In the clinical laboratory, aPL are typically detected in anticardiolipin assays and by their ability to prolong coagulation tests in lupus anticoagulant assays. Most aPL are directed against certain phospholipid-binding plasma proteins rather than phospholipids. The best characterized antigenic targets are b_2-glycoprotein I (b2GPI) and prothrombin. Anti-b2GPI antibodies are detected in anticardiolipin assays. Lupus anticoagulant assays detect certain anti-b2GPI antibodies as well as antiprothrombin antibodies. Immunoassays using purified b2GPI as the antigen are also available, and antiprothrombin immunoassays have recently been developed.

The Antiphospholipid Syndrome

The antiphospholipid syndrome (APS) is the association of persistent aPL with arterial or venous thrombosis and/or recurrent pregnancy losses. Other clinical features associated, or possibly associated with aPL, include a form of valvular heart disease (Libman-Sacks endocarditis), livedo reticularis, and certain nonstroke neurological problems. International consensus criteria for the classification of definite APS were proposed in 1999 and updated in 2005.[1,2] Antiphospholipid syndrome can occur in association with systemic lupus erythematosus (SLE), or related conditions (secondary APS), or in the absence of other autoimmune disease (primary APS).

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Antiphospholipid Antibodies and Pulmonary Hypertension

Antiphospholipid antibodies have been detected in the plasma of patients with PH in 4 general settings (**Figure**): (1) patients with APS may have one or more pulmonary emboli leading to CTEPH; (2) aPL have been detected in patients with PAH associated with SLE, scleroderma, and other CTDs, in the absence of a history of venous thromboembolism; (3) aPL have been detected in some patients with idiopathic PAH (IPAH); and (4) aPL are associated with Libman-Sacks endocarditis and left-sided valvular disease can lead to pulmonary venous hypertension.

Chronic Thromboembolic Pulmonary Arterial Hypertension

Pulmonary hypertension is an infrequent albeit feared complication of pulmonary embolism (PE). Pulmonary hypertension associated with thrombosis of the pulmonary vasculature, referred to as CTEPH, is classified as a unique entity in the Venice classification of PH (class IV).[3] Until recently, this was believed to be a rare complication that occurred in less than 1% of patients with PE.[4,5] Newer data suggest that CTEPH may be present in up to 4% to 5% of patients following PE.[6,7] Given the number of patients with undiagnosed and/or asymptomatic PE, the true incidence of CTEPH may be higher than these estimates. CTEPH can occur from months to many years following the initial thromboembolic event, and the natural history of the disease is poorly understood until the time the patient develops symptoms. Similar to PAH, untreated CTEPH has a uniformly poor prognosis that correlates with the extent of PH.

Antiphospholipid syndrome. Antiphospholipid syndrome is the most common acquired cause of venous thromboembolism (VTE) and accounts for 15% to 20% of VTE in the United States. While there are case reports on the development of CTEPH in patients with APS, good systematic studies with significant numbers of patients are lacking. The lack of data is probably due to the low incidence of CTEPH in patients with PE, as discussed above, and the long lag period between occurrence of PE and the subsequent development of CTEPH.

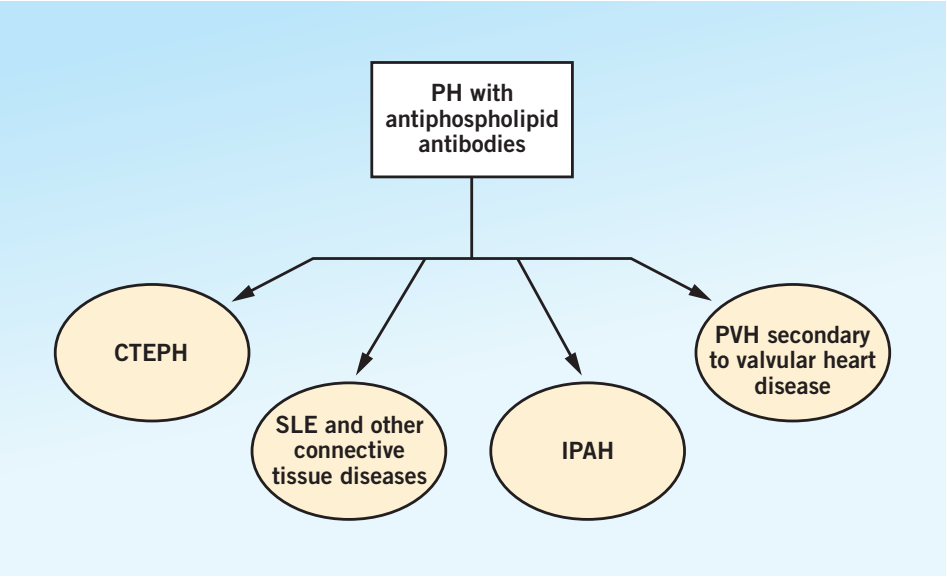

Figure. Antiphospholipid antibody associated PH. The different scenarios in which aPL have been reported in PH.

A European study of 114 patients with APS found the prevalence of PH to be 3.5% in primary APS and 1.8% in secondary APS.[8] Interestingly, Wolf and colleagues[9] observed aPL in 20% of patients with CTEPH. These data are consistent with the estimated frequency of APS as a common acquired cause of VTE and do not necessarily suggest that patients with PE due to APS are more likely to develop CTEPH than patients with PE related to other hypercoagulable conditions.

Pathophysiology. The pathophysiology of CTEPH is unlikely to be related solely to pulmonary artery occlusion from VTE, as the vast majority of the thrombi resolve within a few weeks of the acute event.[10] It has been postulated that VTE is the inciting event following which pulmonary vascular remodeling occurs over time, which results in the development of PH.[11] In addition, in situ thrombosis in the pulmonary vasculature is also well described. These thrombi are histologically indistinguishable from thromboemboli. Whether genetic and environmental factors influence the development of in situ pulmonary arterial thrombi or affect the resolution of emboli and thereby confer a susceptibility to development of CTEPH is not known. A causative role for aPL in the development of CTEPH has not be established, although a number of other risk factors for CTEPH have been identified, such as splenectomy and chronic inflammatory/infectious conditions.[12]

Clinical manifestations. The clinical manifestations of CTEPH are similar to those of PH of any etiology and include progressive dyspnea with exertion, decreased exercise tolerance, and fatigue. As the disease progresses, patients eventually develop evidence of right heart failure such as edema and ascites. A unique but rare finding in patients with CTEPH is the presence of bruits over the peripheral lung fields in the lower lobes.[13] These have been reported in up to 10% of patients with CTEPH.[11] It is important to realize that a history of VTE is a poor screening tool for CTEPH because the majority of patients with CTEPH do not report a history of symptomatic VTE.[10] Therefore, CTEPH should be considered in the evaluation of all patients in whom PH is suspected.

Diagnostic imaging. Diagnostic imaging for these patients includes echocardiography, ventilation and perfusion scans (V/Q scan) or computed tomography angiogram, and pulmonary angiography, which remains the gold standard for the diagnosis of CTEPH. The observed relatively high prevalence of aPL in CTEPH, as discussed above, supports testing for these antibodies as part of the evaluation. However, it is unclear whether the diagnosis of APS would significantly alter management of CTEPH per se (as discussed below). The presence of aPL may be helpful in calling the physician's attention to other manifestations of APS and in the evaluation of comorbid conditions, overall risk assessment, and patient education. There is no evidence for an increased prevalence of inherited thrombophilias in patients with CTEPH.[9,14]

Treatment. Treatment of CTEPH differs significantly from that of other forms of PH in that there is a well-defined role for anticoagulation and pulmonary endarterectomy (PEA), which is the treatment of choice. Lifelong anticoagulation is recommended for all patients with CTEPH in order to prevent recurrent VTE and progressive PH. Vitamin K antagonists (eg, warfarin) are used for anticoagulation with the goal of maintaining a therapeutic International Normalized Ratio (INR) between 2 and 3. While baseline prolongation of the INR has been reported in patients with aPL, this is rare. When there is concern over the reliability of INR for monitoring anticoagulation, alternative approaches such as measuring factor II activity or chromogenic factor X activity may be used concurrently to assess the accuracy of INR measurements.[15]

The use of unfractionated or low molecular weight heparins for long-term anticoagulation is not routinely recommended except in patients with recurrent thromboembolism while taking therapeutic warfarin. Pulmonary endarterectomy significantly improves symptoms and cardiopulmonary hemodynamics in these patients.[16,17] The exact stage of the disease at which PEA should be performed is unclear.

Surgery early in the course of the disease is recommended as there appears to be a correlation between preoperative pulmonary vascular resistance and perioperative mortality.[18] In addition, the degree of residual PH after surgery is a strong predictor of mortality and it has been proposed that PEA should be considered only if a significant improvement in pulmonary vascular resistance (> 50%) is expected following surgery.[16]

The benefit of placing inferior vena cava filters prior to PEA has not been established. While this is routinely performed at certain centers, this practice has not been univer-

sally adopted. Patients that are ineligible for surgery have been treated with prostanoids, phosphodiesterase 5 inhibitors, and endothelin receptor antagonists with variable success. Finally, there are case reports of significant benefit with use of prednisone in patients with APS and CTEPH, which may reflect an immune component of the pathophysiology in at least the subset of patients with CTEPH and aPL or APS.[19,20]

Pulmonary Hypertension Associated With Connective Tissue Disease

Antiphospholipid antibodies are commonly present in patients with SLE and other CTDs. Development of PAH has been reported in these patients.[21-24] The prevalence of aPL in patients with SLE and scleroderma is 30% to 50% and about 7%, respectively.[25] In the majority of cases these patients do not have APS based on current criteria. Pulmonary arterial hypertension is part of the spectrum of these diseases, and a role for aPL in the pathogenesis of PAH in these conditions has not been established.

The clinical manifestations of PAH in these patients are similar to and indistinguishable from those seen with IPAH and PAH secondary to other causes. In general, the diagnostic evaluation and management of PAH in these patients is also similar to other forms of PAH. Because the primary disorders in this subgroup are immunological, the addition of immunosuppressive agents to the therapeutic regimen may be of benefit. It is important to consider CTEPH in all patients with CTDs and PH as the management of CTEPH is significantly different from other forms of PH, as discussed above.

Idiopathic Pulmonary Arterial Hypertension

IPAH (previously termed primary pulmonary hypertension) is defined as the development of PAH in the absence of any other associated disease or cause. Antiphospholipid antibodies have been reported in these patients as well.[26] Once again, no data are available to demonstrate a causative role for these antibodies, although such a role has been speculated. Proposed mechanisms by which aPL lead to the development of IPAH include platelet and endothelial activation, which leads to pulmonary vascular remodeling and PAH. Increased levels of endothelin-1, a potent vasoconstrictor, have been demonstrated in patients with PAH and it is widely believed that endothelin-1 plays a role in the pathogenesis of PAH.[27] Increased levels of circulating endothelin-1 have been reported in patients with aPL and this has been proposed as a mechanism for the development of PAH in patients with aPL with or without thrombosis.[28]

Pulmonary Venous Hypertension Associated With Valvular Heart Disease

Valvular heart disease is a well-recognized cardiac manifestation in APS and SLE. The classic abnormality is the presence of verrucous vegetations on the valve leaflets first described by Libman and Sacks.[29] This is variably referred to as Libman-Sacks endocarditis, verrucous endocarditis, or nonbacterial endocarditis. While reports on the incidence of Libman-Sacks endocarditis vary widely, it is conservatively estimated to be present in about 20% to 30% of patients with SLE and about a third of patients with primary APS.[30-33] There are reports of an increased incidence of valvular heart disease in patients with aCL, with or without coexisting CTD.[32,34] Libman-Sacks endocarditis commonly involves the mitral and aortic valves and can result in significant regurgitation and eventually result in PVH. The exact incidence of PVH in patients with Libman-Sacks endocarditis is not known. Treatment with anticoagulation or antiplatelet agents does not improve the valvular disease in these patients.[35-37] Whether there is a role for immunosuppression in these patients is unclear as there are conflicting reports in the literature.[38,39]

Key Points

- There is significant overlap between the different subsets of PH. Indeed, patients with IPAH or PAH in the setting of SLE can subsequently develop in situ pulmonary arterial thrombosis, which further complicates this issue.
- Although aPL are associated with venous thromboembolism, it is not clear that they play any role in the pathogenesis of PH per se.
- It is essential to identify patients with CTEPH as the therapeutic approach includes pulmonary endarterectomy, which significantly improves the prognosis and quality of life in these patients.
- The presence of aPL in patients with PAH secondary to CTD or apparent IPAH should prompt evaluation for CTEPH.
- The role of immune suppression in patients with aPL-associated PH should be evaluated prospectively. ■

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