Autoimmune Aspects of Pulmonary Hypertension in Collagen Vascular Diseases

Key words: primary pulmonary hypertension, antinuclear antibodies, mixed connective tissue disease, immunosuppressive agents, Sjögren syndrome

Pulmonary hypertension (PH) in collagen vascular diseases (CVD) is relatively rare in occurrence, but relentless in its course (1). That remains one of the most challenging entities for diagnosis and treatment today. In 1998 the World Symposium on Primary Pulmonary Hypertension (PPH) cosponsored by the World Health Organization (2) proposed the use of pulmonary arterial hypertension (PAH) which includes PH related to CVD according to a new diagnostic classification, representing precapillary PH of unknown origin, because the clinical and pathological features of most PH related to CVD are quite similar to PPH and are ultimately accompanied by vascular proliferative involvement.

A small muscular pulmonary artery with a plexiform lesion is demonstrated in some cases of CVD. Eccentric medial hypertrophy and concentric intimal fibrosis are usually shown in PH with CVD (1). The histologic features of pulmonary vessels similar to those of PPH have led to two speculations (1). The first is that PPH may, in fact, represent a lesion preceding some autoimmune disease such as systemic sclerosis (SSc) that has been confined to the pulmonary vasculature. An alternative hypothesis purports that a generalized vasculopathy that afflicts systemic as well as pulmonary vessels produces PH as well as Raynaud’s phenomenon. In fact, the coexistence of PH and Raynaud’s phenomenon among certain patients has been reported.

The pathogenetic factors of PH related to CVD are multiple, complicated and for the most part unknown. In some selected cases, PH develops concomitant with interstitial lung fibrosis, pulmonary vasculitis, or antiphospholipid syndrome. The prevalence of anti-phospholipid antibodies is higher in patients with chronic thromboembolic PH. The presence of lupus anticoagulant, high levels of anticardiolipin or anti-beta2-glycoprotein I antibodies is strongly associated with that of chronic thromboembolic PH (3). Furthermore, the coexistence of thromboembolic PH related to antiphospholipid syndrome and a small muscular pulmonary artery demonstrating eccentric intimal hyperplasia has also been reported.

Major pathogenetic factors of PH related to CVD may be similar to PPH, because the clinical and pathological features are similar to PPH. Most Japanese patients with CVD and PH have autoantibodies to U1RNP, Ro (SSA) or centromere antigens. Although approximately 30 to 40% of patients with PH have antinuclear antibodies (ANA), specific auto-antibodies are not common, except for anti-Ku antibody, as reported by Isern et al (4) and anti-fibrillin-1 autoantibodies, as reported by Morse et al (5) in PPH.

The nationwide frequencies of PH in Japanese CVD have been reported by the collaboration of 2 Research Committees of the Ministry of Health, Labor and Welfare for Mixed Connective Tissue Disease (MCTD) and for Epidemiology of Intractable Diseases in 1999 (6). The frequencies of PH were 5.02% in MCTD, 2.64% in SSc, 0.90% in systemic lupus erythematosus (SLE) and 0.56% in polymyositis/dermatomyositis. MCTD showed the highest frequency of PH in Japanese CVD.

There are several reports of Sjögren syndrome (SS) with PH, but most cases are secondary SS associated with other autoimmune diseases including Hashimoto thyroiditis or SLE. For example, in 24 cases with PH from a lupus clinic, 3 SLE patients also had SS (7). However, the development of PH during the course of primary SS is very rare (8). In this issue of the Journal (9), Nakagawa et al reported an interesting case of primary SS with PH.

See also p 1248.

An interesting point of this case was the very good response of PH to high dose prednisolone therapy. This may suggest that immune-mediated pathogenesis plays an important role in this PH. Upon microscopic examinations of this lung biopsy there was no features of vasculitis, but deposits of complement protein and immunoglobulins were demonstrated in the pulmonary arteriolar walls upon immunofluorescent examinations. These findings support that the autoimmune mechanism is an important pathogenetic factor for PH.

In selected cases of PH related to SLE or MCTD, several reports stated that immunosuppressive agents including high-dose corticosteroid were effective for PH as in the present primary SS patient (10). These may suggest that immunotherapy should be tried for some selected patients with CVD and PH.
Hirobumi Kondo, MD
The Department of Internal Medicine,
Kitasato University School of Medicine,
1-15-1 Kitasato, Sagamihara, Kanagawa 228-8555

References


