Primary Pulmonary Arterial Hypertension and the Systemic Autoimmune Diseases

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Pulmonary arterial hypertension is defined as sustained pulmonary arterial pressure of more than 25 mmHg at rest, with an increase to more than 30 mmHg on exercise, and with a mean pulmonary-capillary wedge pressure and left ventricular end-diastolic pressure of less than 15 mmHg. It was reclassified in Venice in 2003 [1] into five different categories. Several systemic autoimmune diseases can present with PAH [Table 1] and they are listed in category 1 according to this classification. Category 1 also comprises patients with the so-called idiopathic primary PAH.

Most patients in this group seem to develop a progressive increase in pulmonary vascular resistance leading to right heart failure and early death, usually within less than 3 years from diagnosis, prior to the institution of newer therapies. The PAH seen in this group of patients may be due to proliferative vascular involvement in the absence of any significant parenchymal disease, or it may be associated with interstitial fibrosis, chronic hypoxia, and thromboembolism or, rarely, with pulmonary vasculitis.

The vascular form is seen most commonly in patients with systemic lupus erythematosus, rheumatoid arthritis, Sjögren's syndrome, antiphospholipid syndrome, and the CREST syndrome (Calcinosis, Raynaud's phenomenon, Esophageal dysmotility, Sclerodactyly, Telangiectasia) with far fewer patients suffering from parenchymal lung disease, which progresses to fibrosis leading to PAH. Conversely, patients with systemic sclerosis have a higher frequency of interstitial lung disease. Patients with vascular involvement may in fact demonstrate identical features to those described in patients with the "idiopathic" primary form. In the current issue of IMAJ, Bendayan et al. [2] describe their experience with 24 patients suffering from PAH associated with systemic autoimmune diseases, and compare these patients with 42 patients suffering from PAH due to other causes. Interestingly, patients with PAH associated with systemic autoimmune diseases have a slightly increased early mortality rate and the prognostic factor was a shorter distance on the 6 minutes walking distance test.

Table 1. Autoimmune diseases associated with pulmonary arterial hypertension

- Systemic lupus erythematosus
- Discoid lupus erythematosus
- Mixed connective tissue disease
- Systemic sclerosis (CREST variant)
- Primary Sjogren's syndrome
- Rheumatoid arthritis
- Antiphospholipid syndrome
- Hypothyroidism
- Polymyositis
- Whipple's disease

That an immunologic basis may exist in patients with the idiopathic "primary" form was postulated many years ago. Holt and colleagues [3] questioned its pathogenesis as early as 1983, and Rich and team [4] found a high prevalence of antinuclear antibodies in this group of patients. A few years later, in 1992, Isern et al. [5] reported the demonstration of anti-Ku autoantibodies in 23% of patients with primary PAH and, in 1995, Yanai-Landau and collaborators [6] found antinuclear antibodies in 42.5% of patients with primary PAH, antithyroglobulin antibodies in 30% as well as antibodies to ssDNA in 25%. Karmochkine et al. [7] subsequently also found a high prevalence of antiphospholipid antibodies in their patients with precapillary primary PAH.

Recently, Nicholls and associates [8] speculated on the relationship between autoimmunity and PAH and suggested a new term – "severe angioproliferative pulmonary hypertension" – to denote those patients in whom PAH developed because of endothelial cell proliferation and pulmonary vascular disease resulting from increased muscularization of vessel walls. This group included patients with idiopathic PAH as well as patients with CREST syndrome. Plexogenic lesions are common and this group is characterized by the appearance of inflammatory cells in and around pulmonary vessels (lymphocytic and mast cell infiltration may be seen), as well as the deposit of immunoglobulin G in around the narrowed or occluded vessels.

Significant clues pointed to an association of SAPPH with

CREST = calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, telangiectasia
SAPPH = severe angioproliferative pulmonary hypertension

a defect in CD4 T cells and diminished CD4+CD25 cells. The putative regulatory T cell subset (Treg) comes from the association of PAH with certain viral infections, particularly human immunodeficiency virus, human herpes virus-8 and hepatitis C virus infections, in all of which SAPPH may develop, leading to the manufacture of autoantibodies and the occurrence of autoimmune phenomena [9]. Certain autoimmune diseases, e.g., systemic sclerosis, SLE, polymyositis, Hashimoto's thyroiditis and Sjögren's syndrome, may show selective CD4 cell defects affecting particularly the Treg populations. Recent case reports of patients who developed PAH following splenectomy [10] and a patient with autoimmune polyendrocrinopathy-candidiasis ectodermal dystrophy, where there is a functional loss of the *AIRE* gene (a major autoimmune regulator), lend credence to the hypothesis that Treg cells are intimately involved in the pathogenesis of PAH [11].

Further confirmatory evidence is provided by the study of familial PAH. This familial form of PAH with linkage to chromosome 2q31-q32 (designated as PPH1) has now been well described [12-14] and it has been postulated that there is involvement of germ line mutations of bone morphogenetic protein receptor 11 (BMPR11), which is essential for thymocyte differentiation and proper Treg development in the thymus and is critical for the avoidance of autoimmune diseases [15,16]. Treg cells "regulate" (hence the name) antibody responses against self as well as against non-self-antigens and may directly inhibit B cells. Without appropriate T cell regulation, therefore, the production of autoantibodies and the development of autoimmune disease are possible. Other cells may then provide the stimulatory signals to B cells, and provide the stimulatory signals for them to produce pathogenic antibodies. Antibodies directed against vascular endothelium might result in apoptosis. Dysfunctional endothelial cell proliferation might then ensue. The generation of apoptosis-resistant endothelial cells, which share features with malignant cells, results in their proliferation, "heaping up" and narrowing of the vascular lumen. This hypothesis, presented by Nicolls et al. [8], is certainly plausible. Anti-endothelial cell autoantibodies are well described in all the autoimmune diseases associated with PAH [17-19].

The unanswered question, of course, is why PAH is in fact not more prevalent in such diseases as SLE and Sjögren's syndrome, but more prevalent in, for example, the CREST variant of systemic sclerosis? It is also relatively common in mixed connective tissue disease, which represents an "overlap" situation. One possible answer to this question might lie in the study of different genotypes in these patients in addition to another "hit" common to many situations in the development of autoimmune disease. Here again we must look at environmental "triggers," and the one that immediately springs to mind is the question of viral infection and their effect on the CD4-CD25 population of lymphocytes. Evidence of Epstein-Barr virus, parvovirus B19, and hepatitis C, E and G, as well as cytomegalovirus infection has indeed been found in patients with systemic sclerosis [20-26]. The surprisingly high frequency of PAH in patients with HIV infection enhances our understanding of the intimate role played by CD4-CD25+ cells, because it is in this condition *par excellence* that this lineage of Treg cells is severely depleted [27-30].

The high frequency of aPL noted not only in HIV patients with PAH but also in several other subsets of PAH patients – e.g., primary idiopathic PAH [7], SLE, mixed connective tissue disease [27] and the primary APS – is well established. The first papers documenting the association of PAH with SLE and aPL were published by Asherson [28,29], while Alarcón-Segovia et al. [30] included 5 patients with PAH and aPL in their first series of 500 patients with APS. In a series of 24 patients with PAH reported from the Lupus Clinic at St Thomas' Hospital [31], 16 were positive for aPL and the levels were extremely high in 3. Three of 30 patients with primary PAH in the control group were positive for anticardiolipin antibodies and one was positive for lupus anticoagulant (13%). Of these four, three were of the primary non-thromboembolic type. There have also been other single case reports of patients with primary APS and the "primary" non-thromboembolic type of PAH [32,33].

What is the cause of aPL elevations in patients with PAH? It is known that reduced levels of CD4-CD25+ cells have been detected in patients with the APS and that the APS may be associated with many differing infections. Alterations of the Treg/Bcell system may, as described above, result in the manufacture of antibodies directed mainly towards phospholipids in genetically predisposed individuals. They in themselves may activate and cause endothelial cell damage, causing the formation, again, of anti-endothelial cell autoantibodies leading to the vascular changes seen in patients with PAH.

The high frequency of Raynaud's phenomenon encountered in this group of patients also points to an endothelial disturbance simultaneously occurring in digital vessels. However, this association seems only to be present in the group of patients with PAH association to systemic autoimmune diseases and not in patients with primary "idiopathic" PAH, which is enigmatic.

An imbalance in vascular effectors may occur as a direct result of this endothelial dysfunction and affects particularly prostacycline and thromboxane, endothelin-1, nitric oxide, serotonin, adrenomedullin, vasoactive intestinal peptide, and vascular endothelial growth factors. Dysfunction of all of these have been reported in patients with PAH resulting in the stimulation and proliferation of pulmonary artery smooth muscle cells as well as promoting endothelial cell proliferation (e.g., nitric oxide synthetase present in plexiform lesions). Certain platelet defects that result for example from reduced uptake of serotonin have also been associated with PAH (storage pool disease).

In conclusion, the study of PAH in the systemic autoimmune diseases and its relation to basic immunologic disturbances may yet bring effective therapies in the future [34]. Early diagnosis and regular screening of individuals is therefore strongly advised

SLE = systemic lupus erythematosus

HIV = human immunodeficiency virus
aPL = antiphospholipid antibodies
APS = antiphospholipid syndrome

if the prognosis is to be improved. Idiopathic "primary" PHT should certainly be grouped together with the systemic autoimmune disease regarding possible pathogenesis, clinical course and therapy.

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Fine minds are seldom fine souls

Jean Paul Richter (1763-1825), German writer