Editorial Comment

Autoimmune Disease and Unexplained Pulmonary Hypertension

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The article by Barst et al. provides new and important information related to the association of unexplained pulmonary hypertension in children with the major histocompatibility complex (MHC) and has opened up a new dimension of investigation. There is good rationale for immune mediation of pulmonary hypertension as detailed in the article, given the presence of this condition in patients with autoimmune disorders such as systemic lupus erythematosi s, scleroderma, rheumatoid arthritis, polydermatomyositis, or mixed connective tissue disease. There is also a high incidence of Raynaud’s phenomenon in patients with unexplained pulmonary hypertension. It was of interest that although there was an association between unexplained pulmonary hypertension and increased frequencies of HLA-DR-3, DRw-52, Qw-2, and decreased DR-5, similar findings could not be confirmed in children with severe pulmonary hypertension secondary to congenital heart disease. Attention should, however, be drawn to a recent study by Saenz et al.2 reporting that smooth muscle proliferation associated with high pressure and flow induced in vein grafts interposed in arteries (which may have a similar pathophysiology to smooth muscle proliferation in pulmonary arteries subjected to high flow and pressure in patients with congenital heart defects) is not seen in athymic mice or in those treated with cyclosporine. This suggests that there may be an immune component of mediation even in secondary pulmonary hypertension.

Perhaps important clues related to immune mediation of vascular disease can also be obtained from ongoing studies related to the post-cardiac transplant coronary arteriopathy. In the latter situation, the endothelium of the coronary arteries is activated as judged by increased expression of MHC class II antigens3-7 and there is increased adhesion and transendothelial migration of activated lymphocytes, particularly of the CD4+ and CD8+ subtypes.7 It has also been suggested that release of cytokines from infiltrating mononuclear cells may stimulate changes in smooth muscle cell phenotype associated with increased proliferation, migration into the subendothelium, and production of extracellular matrix components, specifically fibronectin.8 In our studies of intimal proliferation in the fetal lamb ductus arteriosus, we have shown increased fibronectin synthesis and have related this to the increased migratory ability of fetal lamb ductus compared with aortic smooth muscle cells.9 More recently, in a piglet heterotopic cardiac transplant model, we have also established that there is increased production of fibronectin in donor coronary artery smooth muscle cells compared with those of the host, and the mechanism appears to be associated with expression of MHC on endothelial cells and induction of specific cytokines.10 A similar pathophysiology may prevail in unexplained pulmonary hypertension if endothelial cells show similar patterns of activation. Inflammatory cells have not, however, been identified in the walls of arteries of unexplained pulmonary hypertension, but the process may be advanced at the time of tissue diagnosis. On the other hand, inflammatory cells in pulmonary arteries (i.e., vasculitis) has been described in autoimmune disorders.

Because unexplained pulmonary hypertension likely reflects a variety of conditions for which an etiology has not been established, auto-immune phenomena may reflect a subset rather than the whole group, as is evident by the findings in this study. Conversely, there are patients with MHC who do not develop vascular changes. Thus, MHC may identify a group of patients particularly susceptible to this pathophysiology in response to minor toxic environmental influences that are as yet undetermined.

Our group has shown abnormalities in endothelial cells in patients with pulmonary hypertension and congenital heart defects,11,12 but vascular changes of medial hypertrophy in all patients and of intimal proliferation in the younger age group quickly resolve following correction of these lesions.13 That there was not an increase in MHC in the group with pulmonary hypertension secondary to congenital heart defects, even among those with changes that appeared advanced for the lesion described and for the duration of hemodynamic abnormalities, suggests that this may be a marker of a malignant form of pulmonary hypertension. The patient who develops progressive pulmonary

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vascular disease after a timely surgical intervention and correction of a congenital heart defect is certainly a rarity. It is possible that this very select subgroup does, indeed, have MHC and that the endothelial changes, once induced, perpetuate the disease.

We have suggested in an experimental model of congenital heart disease in which progressive pulmonary vascular changes are induced by the toxin monocrotaline that perturbation of the endothelium and ultrastructural evidence of endothelial abnormalities precede alterations in smooth muscle cells that include abnormal differentiation of small arteries, hypertrophy and hyperplasia in large arteries, loss of the number of small peripheral arteries, and migration of smooth muscle cells into the subendothelium. In the adult animal, injection of this toxin produces a disease that is progressive, whereas in the infant rat, it has the potential for regression. It would be interesting, therefore, to identify whether the progressive changes in endothelial injury in the older animal are reflected by unmasking of MHC. We have also shown in this model that there is an increase in elastolytic activity before the development of ultrastructural changes and that increased elastolytic activity is again observed when the disease is severe but not when it has potential for regression, either in the infant rats injected with monocrotaline or in rats in which pulmonary hypertension is induced by chronic hypoxia. Further studies showed that elastase inhibitors, when administered to the animals before injection of the toxin or 1 week after, will prevent the development of the disease or retard its progression. It is entirely possible that the initial release of elastase is related to an injured endothelium but that the subsequent increase in elastolytic activity with severe and progressive disease is associated with MHC expression in endothelial cells.

Whether the pathophysiology of unexplained pulmonary hypertension is related to expression of MHC and whether this is manifest by specific alterations in endothelial cells or blood cells, one might wonder why there is little evidence of disease in systemic arteries. On the other hand, patients with autoimmune disease, although they do develop pulmonary hypertension with increased frequency, also may have widespread evidence of vasculitis in small systemic arteries. It will be interesting to look at families with a high incidence of unexplained pulmonary hypertension and study the pedigrees for consistencies in the abnormal expression of specific histocompatibility loci.

The association between autoimmune disease and unexplained pulmonary hypertension is well known. The work of Barst et al1 represents the first documentation of a specific association related to immune mediation and represents a launching point for a new avenue of investigation that will be relevant in uncovering the mechanism of progressive pulmonary hypertension in the pediatric and adult populations. Findings from these studies will also have implications in the direction of research related to the pathophysiology of atherogenesis without overt risk factors and the pathophysiology of obstructive arteriopathies while under immune suppression (e.g., post–cardiac transplant coronary arteriopathy) and perhaps may even hold a clue to the pathophysiology of coronary aneurysms in Kawasaki disease.

References


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