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Pathology of Pulmonary Hypertension

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Focus on the pathologic changes underlying pulmonary hypertension (PH) dominated the early investigations of this disease, which was first described late in the nineteenth century. Pulmonary vascular pathology continues to play an important role in the present age of cell and molecular investigation of the pathogenesis of PH. This importance stems from the permanent quest to correlate pulmonary vascular remodeling with the altered pulmonary vascular hemodynamics, a critical advancement in the late 1940s and early 1950s with a wide impact on the present understanding of the disease. However, as occurs with most descriptive tools applied to medical sciences, the pathologic insight into the extent and type of a particular form of pulmonary vascular remodeling has failed to establish cause-and-effect relationships in the natural history of PH, and has had a limited impact on diagnosis and therapy. These limitations derive largely from the reliance of current knowledge on studies of autopsies, because lung tissue is rarely available for histopathology during the course of the disease.

The pathologic diagnosis of pulmonary vascular remodeling depends on the histologic assessment of the cellular composition of pulmonary vascular walls, which, if abnormal, is described as pulmonary vascular *lesions*. Although it most relies on examination of histologic slides stained with hematoxylin and eosin stains, the pathologic interpretation of PH has benefited from the progressive use of cell-specific immunohistochemical markers to better define the structure and cellular composition of the pulmonary vascular lesions. Despite the advances in the understanding and treatments targeting the disease, the pathology of PH clearly lags behind the comprehensive approach used by pathologists in their assessment of other diseases, such as cancer. This approach presently includes the screening for abnormal expression of the p53 tumor suppressor or adenomatous polyposis coli (APC) genes, abnormal expression of cytokeratins in breast adenocarcinomas, and markers of cell proliferation in sarcomas, among several tissue markers that help in the final diagnosis, staging prognosis, and treatment. By comparison, the histopathologic diagnosis of PH infrequently fulfills some or all of these important tasks of the pathologic workup aimed at clinical management.

The functional status of the pulmonary circulation and the levels of pulmonary vascular resistance and pulmonary artery pressures ultimately determine the outcome and treatment of patients who have PH. The authors have proposed that the functional status of the hypertensive pulmonary circulation could be broadly correlated with a specific type of pulmonary vascular remodeling present at pathologic evaluation of the pulmonary arteries [1]. This article on the pathology of PH is framed within these

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Table 1
Intima remodeling

Cell	Smooth muscle cells		Extracellular matrix	Endothelial cells		
Lesion	Eccentric	Concentric	Fibrotic	Plexiform	Concentric	Dilation/Angiomatoid
Normal pulmonary artery pressure	Yes	No	No	No	No	No
Mild/moderate pulmonary hypertension	Yes	No	Yes	No	No	No
Severe pulmonary hypertension	Yes	Yes	Yes	Yes	Yes	Yes

functional categories, which are that PH can be broadly divided into mild-to-moderate versus severe based on pulmonary artery pressures, their impact on right ventricular performance, and overall mortality (Tables 1 and 2) [1]. Many non–neoplastic lung diseases with intima thickening or medial hypertrophy, such as idiopathic interstitial pneumonias (IPF) [2] and chronic obstructive pulmonary diseases (COPD) [3], present with mild-to-moderate PH. However, conditions associated with endothelial cell proliferative lesions (including plexiform lesions), marked intima fibrosis (eg, idiopathic pulmonary arterial hypertension [IPAH], and scleroderma), or medial and intimal smooth muscle cell growth (as observed in a fraction of IPF or COPD lungs) cause severe PH. As this article shows, the ability to relate the mode of pulmonary vascular remodeling to the severity of disease is rather limited. This article highlights the changes associated with IPAH as those that are paradigmatic of the pathology of severe PH.

To highlight the pathology of PH, this article follows the recommendations of the Evian meeting on pulmonary hypertension in 1998, which supported a more descriptive approach to the pulmonary vascular changes in PH [4]. Recent findings related to the pathogenesis of human PH are also reviewed (Table 3). Their translation into the pathologic diagnosis of PH may eventually lead to a more refined and clinically useful approach toward diagnosis and staging. The latest reorganization of the pathologic nomenclature of PH by the international meeting in Venice in 2004 provides a useful framework of reference to the diagnosis of pulmonary vascular lesions in PH [5]. Reviews on normal histology of pulmonary arteries [6,7] and a historical perspective of the research accomplishments in the past 100 years of studies of the pulmonary circulation [8] provide a valuable background to this article.

Table 2
Medial remodeling

Cell	Smooth muscle cells	Extracellular matrix
Normal pulmonary artery pressure	Yes[a]	No
Mild/moderate pulmonary hypertension	Yes	Yes
Severe pulmonary hypertension	Yes	Yes

[a] Medial hypertrophy is localized and restricted to some pulmonary arteries.

Intima lesions

Pathology

Intimal lesions account for most of the reduction of luminal area of small pulmonary arteries and potentially largely influence the overall pulmonary vascular resistance. Intimal lesions consist of eccentric intima thickening, and fibrotic, plexiform, concentric, and dilation or angiomatoid lesions (Figs. 1–4; see Table 1). Focal eccentric lesions can be detected in normal lungs, but these lesions are more widespread and, to a larger extent, impinge on the vascular lumen in PH. Some of these lesions may result from the organization (ie, lysis of fibrin, recanalization by newly formed blood vessels, or ingrowth of myofibroblasts) of localized thrombi, which form the nidus for a localized growth of smooth muscle cells. More advanced lesions acquire a fibrotic pattern, with interspersed myofibroblasts and marked accumulation of mucopolysaccharides