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Pathologic Assessment of Vasculopathies in Pulmonary Hypertension

Giuseppe G. Pietra, MD,* Frederique Capron, MD,† Susan Stewart, MD,‡ Ornella Leone, MD,§ Marc Humbert, MD,¶ Ivan M. Robbins, MD,# Lynne M. Reid, MD,‖ R. M. Tuder, MD**

Philadelphia, Pennsylvania; Paris and Clamart, France; Bologna, Italy; Nashville, Tennessee; Boston, Massachusetts; and Baltimore, Maryland

Pulmonary arterial hypertension (PAH) includes various forms of pulmonary hypertension of different etiology but similar clinical presentation and functional derangement. Histopathological vascular changes in all forms of PAH are qualitatively similar but with quantitative differences in the distribution and prevalence of pathological changes in various portions of the pulmonary vascular bed. The documentation of these topographic variations in the response of the pulmonary vasculature to injury may be important to understand the pathogenesis of the various subsets of PAH. To standardize the precise histopathological documentation of the pulmonary vasculopathy in PAH we propose a histopathological classification that includes both the predominant segment of the pulmonary vasculature affected and the possible coexistence of pathological changes in other vascular segments. (J Am Coll Cardiol 2004;43:25S–32S) © 2004 by the American College of Cardiology Foundation

The term pulmonary arterial hypertension (PAH) includes a variety of pulmonary hypertensive diseases with different etiologies but similar clinical presentation and, in many cases, similar response to medical treatment (1). Initially, PAH comprised primary pulmonary hypertension (PPH) and pulmonary hypertension related to left-to-right shunts, collagen-vascular diseases, portal hypertension, human immunodeficiency virus (HIV) infection, ingestion of drugs or dietary products, and persistent fetal circulation (1). At the recent Third World Symposium on Pulmonary Artery Hypertension, pulmonary veno-occlusive disease (PVOD) and pulmonary capillary hemangiomatosis (PCH) have been incorporated into PAH because of the high incidence of arteriopathy in these conditions (2,3), the similarity of risk factors with PAH (HIV, drug ingestion), the familial occurrence (4,5), and the recently discovered mutation of bone morphometric protein receptor-2 (BMPR2) in a case of PVOD (6). It has been hypothesized that PAH, PVOD, and PCH may represent part of the spectrum of the same disease, or differing reactions to similar insults.

The Evian classification (1) is based on etiology, clinical presentation, and functional data, and it assumes that all subsets of PAH have a similar spectrum of pathological lesions. This may not always be the case because morphometric studies have shown differences in the distribution and prevalence of arterial changes among PAH of different etiology (7,8). Also, in certain cases of PAH venous changes coexist with arterial lesions; that is, the pulmonary veins and venules can show intimal and adventitial thickening and even arterialization (9–12). In the proximity of organized pulmonary infarcts, veno-occlusive changes can also be present, possibly due to scarring or other disruptions of vascular relationships.

Thus, documentation of the extent of different types of vascular changes among the various subsets of PAH is essential in understanding how various segments of the pulmonary vascular tree react to injury. To standardize pathological reporting and provide clinicians with a precise description of the nature and extent of vascular lesions present in a single case, we have adopted a descriptive histopathologic system of classification (Table 1) in which both the predominant changes and the coexisting pathologic changes are recorded.

HANDLING OF LUNG TISSUE

Fixation of the lung samples in a state of distension avoids crenation of elastic laminae of muscular pulmonary arteries that may induce a state of spurious medial hypertrophy. Adequate sampling of the lungs (at least five blocks from each lobe) is essential. The histological examination should indicate whether adequate samples of blood vessels are present, the nature and number of diseased blood vessels, the presence, location, and nature of inflammatory cells, as well as any evidence of associated pathology in the airways or lung parenchyma. In addition to hematoxylin-eosin (HE), special histological stains (Movat, Masson, Verhoeff-van Gieson, Perls' iron) are essential to assess vascular pathology. Also useful are immunohistochemical markers for smooth muscle and endothelium (Factor VIII, CD31, CD 34).

From the *Department of Pathology, University of Pennsylvania, School of Medicine, Philadelphia, Pennsylvania; †Service d'Anatomie Pathologique 1, Hôpital de la Pitié, 83, bd de l'Hôpital 75651 Paris Cedex, 13, France; ‡Papworth Hospital, Papworth Everard, Cambridge, United Kingdom; §Department of Pathology, Azienda Ospedaliera S. Orsola-Malpighi of Bologna, Bologna, Italy; ¶Service de Pneumologie et Réanimation Respiratoire, Hôpital Antoine Béclère, Assistance Publique, Hôpitaux de Paris, Université Paris-Sud, Clamart, France; #Vanderbilt University Medical Center, Adult Pulmonary Hypertension Center, Vanderbilt University, Nashville, Tennessee; ‖Department of Pathology, Harvard Medical School, Boston, Massachusetts; **Division of Cardiopulmonary Pathology, The Johns Hopkins University, School of Medicine, Baltimore, Maryland.

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Abbreviations and Acronyms

BMPR2 = Bone morphometric protein receptor-2
HIV = human immunodeficiency virus
PAH = pulmonary arterial hypertension
PCH = pulmonary capillary hemangiomatosis
PM = pulmonary microvasculopathy
POV = pulmonary occlusive venopathy
PPH = primary pulmonary hypertension
PVOD = pulmonary veno-occlusive disease

PULMONARY ARTERIOPATHY

All forms of pulmonary hypertension have some common pathologic features regardless of their etiology, that is, medial hypertrophy of muscular and elastic arteries, dilation and intimal atheromas of elastic pulmonary arteries and right ventricular hypertrophy. These forms of pulmonary vascular remodeling have limited diagnostic value because they are present in all forms of severity of pulmonary hypertension. Also, pulmonary artery medial and intimal thickening can occur as an isolated nonspecific finding in localized areas of the lung or secondary to airway or interstitial diseases and tumors, with no direct relationship to the presence or not of pulmonary hypertension.

In addition to the aforementioned pathologic changes common to all forms of pulmonary hypertension, PAH is characterized by constrictive and complex arterial lesions involving to varying degrees the pre- and intra-acinar pulmonary arteries (3,12). The main histopathological features of this pulmonary arteriopathy are illustrated in Figure 1 and are briefly defined below.

Constrictive lesions. These lesions include medial hypertrophy, and intimal and adventitial thickening. These changes are believed to result from an imbalance between proliferation and apoptosis of the various cell types forming the vascular walls. Because they are diffuse lesions, they may be hemodynamically important if vasorelaxant properties are lost (i.e., prostacyclin or nitric oxide) or there is excessive

Table 1. Pathological Classification of Vasculopathies of Pulmonary Hypertension*

1. Pulmonary arteriopathy (pre- and intra-acinar arteries)	Previous WHO terminology†
Subsets	
Pulmonary arteriopathy with isolated medial hypertrophy	Pulmonary plexogenic arteriopathy Gr. 1
Pulmonary arteriopathy with medial hypertrophy and intimal thickening (cellular, fibrotic)	
Concentric laminar	Pulmonary plexogenic arteriopathy Gr. 2, 3
Eccentric, concentric nonlaminar	Pulmonary embolic arteriopathy
Pulmonary arteriopathy with plexiform and/or dilation lesions or arteritis	Pulmonary plexogenic arteriopathy Gr. 4–6
Pulmonary arteriopathy with isolated arteritis	n.a.
1a. As above but with coexisting venous-venular changes (cellular and/or fibrotic intimal thickening, muscularization)	n.a.
The presence of the following changes should be noted:	
Adventitial thickening; thrombotic lesions (fresh, organized, recanalized, colander lesion); necrotizing or lympho-monocytic arteritis; elastic artery changes (fibrotic or atheromatous intimal plaques, elastic laminae degeneration); bronchial vessel changes, ferruginous incrustation, calcifications, foreign body emboli, organized infarct perivascular lymphocytic infiltrates.	
2. Pulmonary occlusive venopathy (veins of various size and venules) with or without coexisting arteriopathy	PVOD
Histopathologic features:	
Venous changes: intimal thickening/obstruction (cellular, fibrotic); obstructive fibrous luminal septa (recanalization).	
Adventitial thickening (fibrotic); muscularization; iron and calcium incrustation with foreign body reaction:	
Capillary changes: dilated, congested capillaries; angioma-like lesions.	
Interstitial changes: edema; fibrosis; hemosiderosis; lymphocytic infiltrates.	
Others: dilated lymphatics; alveoli with hemosiderin-laden macrophages; type II cell hyperplasia.	
3. Pulmonary microvasculopathy with or without coexisting arteriopathy and/or venopathy	PCH
Histopathologic features:	
Microvessel changes: localized capillary proliferations within pulmonary interstitium; obstructive capillary proliferation in veins and venular walls.	
Venous-venular intimal fibrosis.	
Interstitial changes: edema, fibrosis, hemosiderosis.	
Others: dilated lymphatics; alveoli with hemosiderin-laden macrophages; type II cell hyperplasia.	
4. Unclassifiable‡	n.a.

*Nonvascular lung pathology needs to be listed as separate diagnosis. †Primary pulmonary hypertension. Report on a WHO meeting. Geneva, October 15–17, 1975. S. Hatano and T. Strasser, eds. ‡Atypical histopathological features or inadequate sampling of blood vessels.
Gr. = grade; n.a. = not applicable.

production of vasoconstrictors (i.e., endothelin). *Medial hypertrophy* is an increase in the cross-sectional area of the media of pre- and intra-acinar pulmonary arteries (Figs. 1A and 1B). It is due to both hypertrophy and hyperplasia of smooth muscle fibers and to an increase in connective tissue matrix and elastic fibers in the media of muscular arteries and extension of smooth muscle into nonmuscularized intra-acinar arteries. Medial hypertrophy entails both numerical and phenotypical changes of muscle fibers. *Atrophy* of the media occurs in arteries with marked intimal thickening and in developing dilation lesions.

Intimal thickening can be of three types: concentric laminar, eccentric, or concentric nonlaminar (Figs. 1C to 1F). Concentric laminar intimal thickening can be to varying degrees either cellular or fibrous (Figs. 1C and 1D). Both ultrastructurally and immunohistochemically, the intimal cells show features of fibroblasts, myofibroblasts, and smooth muscle cells (Fig. 1D). However, these morphologic features do not allow conclusions on their derivation because recent experimental work has shown the potential of endothelial cells and fibroblasts to acquire smooth muscle phenotype (13). Concentric laminar intimal thickening is a characteristic feature of the so-called pulmonary plexogenic arteriopathy and/or of scleroderma arteriopathy. Eccentric and concentric nonlaminar intimal thickenings are predominantly composed of fibroblasts and connective tissue matrix (Figs. 1E and 1F). The notion that these changes are diagnostic of thromboembolic arteriopathy needs revision because intimal thickening may result from localized proliferation of intimal fibroblasts caused by growth factors released by hemodynamic stresses.

Adventitial thickening is difficult to evaluate because of its ill-defined boundaries in conventional histological sections. In most cases of PAH, the adventitia appears uninvolved, but it is expanded in pulmonary hypertension owing to persistent fetal circulation of the newborn.

COMPLEX LESIONS

Plexiform lesions, dilation lesions, and arteritis are classified as complex lesions. They are focal changes important as markers of either the severity or rapid progression of pulmonary hypertension. It has also been suggested that endothelial proliferation in plexiform lesions of PPH may be a marker of a fundamental cellular abnormality, possibly of neoplastic nature (14,15).

The *plexiform lesion* is a focal proliferation of endothelial channels lined by myofibroblasts, smooth muscle cells, and connective tissue matrix. The lesion is located within pre- and intra-acinar pulmonary arteries and is associated with expansion and partial destruction of the arterial wall with extension of the plexiform lesion into the perivascular connective tissue (Figs. 1G and 1H). Within the plexiform lesion, fibrin thrombi and platelets are frequently present. The plexiform lesion is often located at an arterial branching point, or at the origin of a supernumerary artery, distally to marked obliterative intimal thickening of the parent artery. The frequency of the plexiform lesion in PAH remains undetermined and probably varies to a great extent. Based on studies with limited sampling, it is estimated that the plexiform lesion involves from 20% to 60% of the pulmonary arteries. It is extremely rare in PAH related to connective tissue diseases and it does not occur in PAH of persistent fetal circulation.

The localization of plexiform lesions along the arterial tree also varies; that is, in congenital left-to-right shunts they tend to occur in arteries 100 to 200 μm in external diameter, whereas in PPH they tend to occur in arteries $<$100 μm (3,12). Plexiform lesions may be difficult to distinguish from the colander-like lesion of recanalized thromboemboli (Fig. 1J). They are no longer considered pathognomonic for PPH as they have been found in PAH associated with other diseases and even in chronic thromboembolic pulmonary hypertension (16). Endothelial cells within plexiform lesions express vascular endothelium growth factor (VEGF) and its receptors (17), and the lesions are believed to result from disordered angiogenesis attributable to autonomous monoclonal endothelial proliferation in the case of PPH (14,15). Recently, the association of the vasculotropic human herpesvirus-8 with plexiform lesions of PPH has been demonstrated (18).

The *dilation lesion* is a thin-walled vein-like vessel (Figs. 1H and 1I) usually located distally to a plexiform lesion. This lesion may be the source of pulmonary hemorrhages and subsequent organization and fibrosis.

Arteritis is rarely primary in PAH; most often it is associated with other complex lesions. The arterial wall may be necrotic with fibrinoid insudation and/or be infiltrated with chronic and acute inflammatory cells (Fig. 1K).

In our histopathological classification, the terms "pulmonary occlusive venopathy" (POV) and "pulmonary microvasculopathy" (PM) replace the old terms of PVOD and PCH, respectively (Table 1).

Pulmonary occlusive venopathy (POV) (formerly PVOD) accounts for a relatively small proportion of cases of pulmonary hypertension. The diagnosis of POV and PM (described below) in vivo is difficult and is not considered in most patients until signs of marked pulmonary hypertension have developed. Although, by high resolution computed tomography, patchy centrilobular ground-glass opacities, thickened septal lines, pleural effusion, and mediastinal adenopathy are characteristic for POV and PM (19), the cornerstone of the diagnosis of POV/PM is histopathology. The main pathology of POV consists of extensive and diffuse occlusion of pulmonary venules and veins of various sizes (2,5). The occluding fibrous tissue may be loose and edematous with variable cellularity, or dense, sclerotic, and acellular (Fig. 2A). The intimal thickening of POV involves venules and small veins and rarely extends to the larger veins. The luminal occlusion can be either solid or eccentric with multiple lumina (Fig. 2B), suggestive of recanalization of occlusive thrombi. The media of the venules and veins

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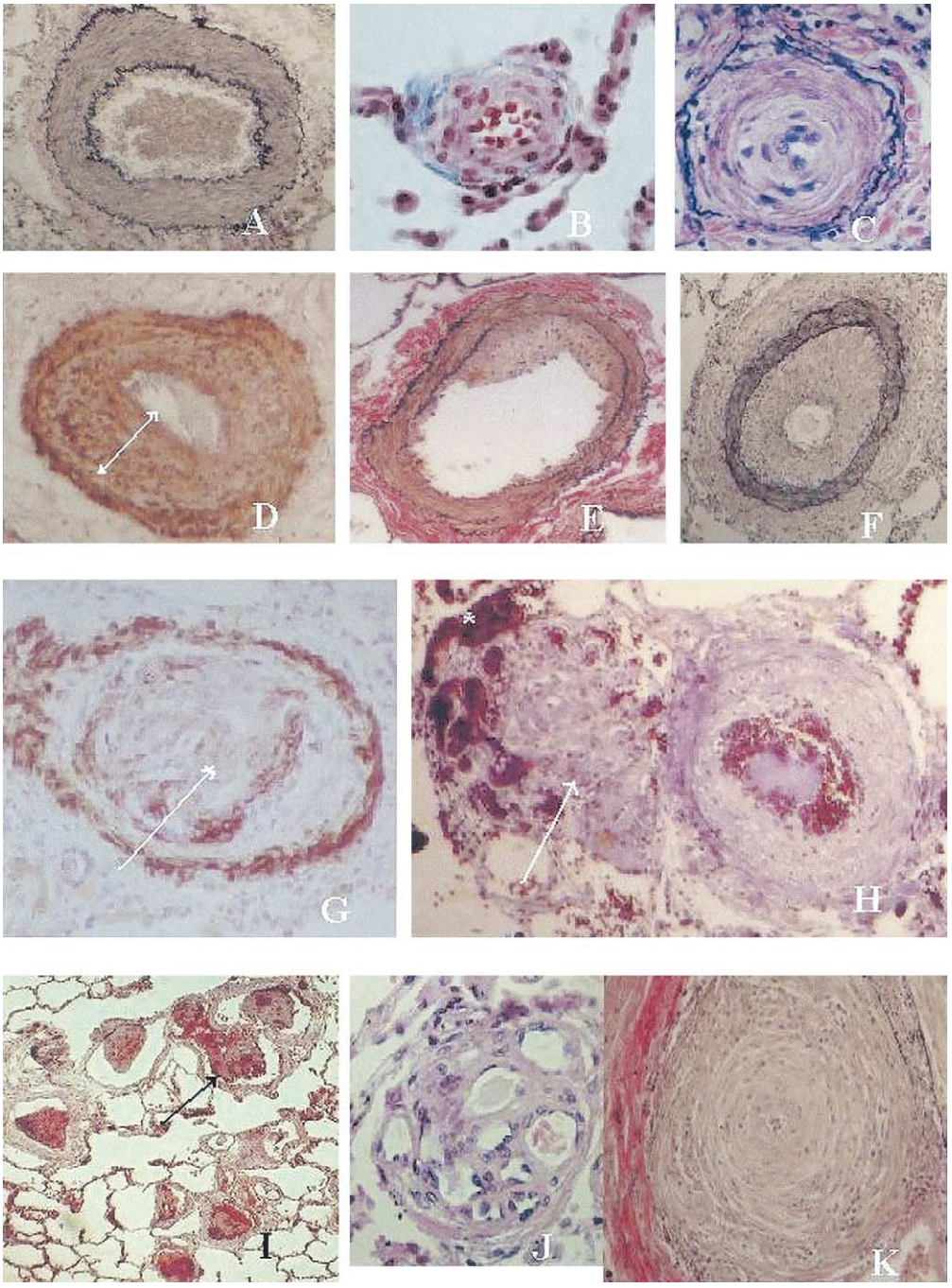

Figure 1. Main histopathological features of pulmonary arteriopathy (see text for details). (All histological sections were stained with Verhoeff-van Gieson unless specified.) Medial hypertrophy: **(A)** preacinar pulmonary artery, ×80; **(B)** intra-acinar artery, ×600. Concentric laminar intimal thickening: **(C)** intra-acinar artery, ×500; **(D)** pre-acinar artery. The vessel was decorated with anti-smooth muscle actin antibodies (SMA), revealing the intimal thickening **(white arrow)** to be composed of SMA-positive cells, ×150. Eccentric **(E)** ×100 and concentric nonlaminar **(F)** ×100 intimal thickening of pre-acinar arteries. Plexiform lesions: **(G)** intra-acinar artery decorated with SMA showing SMA-negative endothelial cells **(arrow)** surrounded by a rim of SMA-positive cells **(rusty color)**, ×380; **(H)** pre-acinar artery adjacent to a plexiform lesion **(arrow)** and dilation lesions (shown by **asterisk**) ×60. **(I)** Dilation lesions **(arrows)**, ×40; **(J)** colander-like lesion, HE ×400; **(K)** lymphomonocytic arteritis, HE, ×300.

may become thickened with an increase in elastic fibers and smooth muscle (i.e., so-called arterialization). All these morphological features are helpful in distinguishing POV from chronic venous hypertension.

A nonspecific but useful histological feature is the presence of calcium-encrusting elastic fibers in the walls of veins or adjacent alveoli. This feature, when present, renders the veins easily identifiable and is therefore a pertinent histological finding when the diagnosis of PVOD (or, indeed, pulmonary hypertension) has not been raised by the referring clinician. Another feature that is useful in distinguishing between POV and chronic passive venous hypertension is the foreign body giant-cell response to the calcium-encrusted elastic fibers. This feature is also helpful when

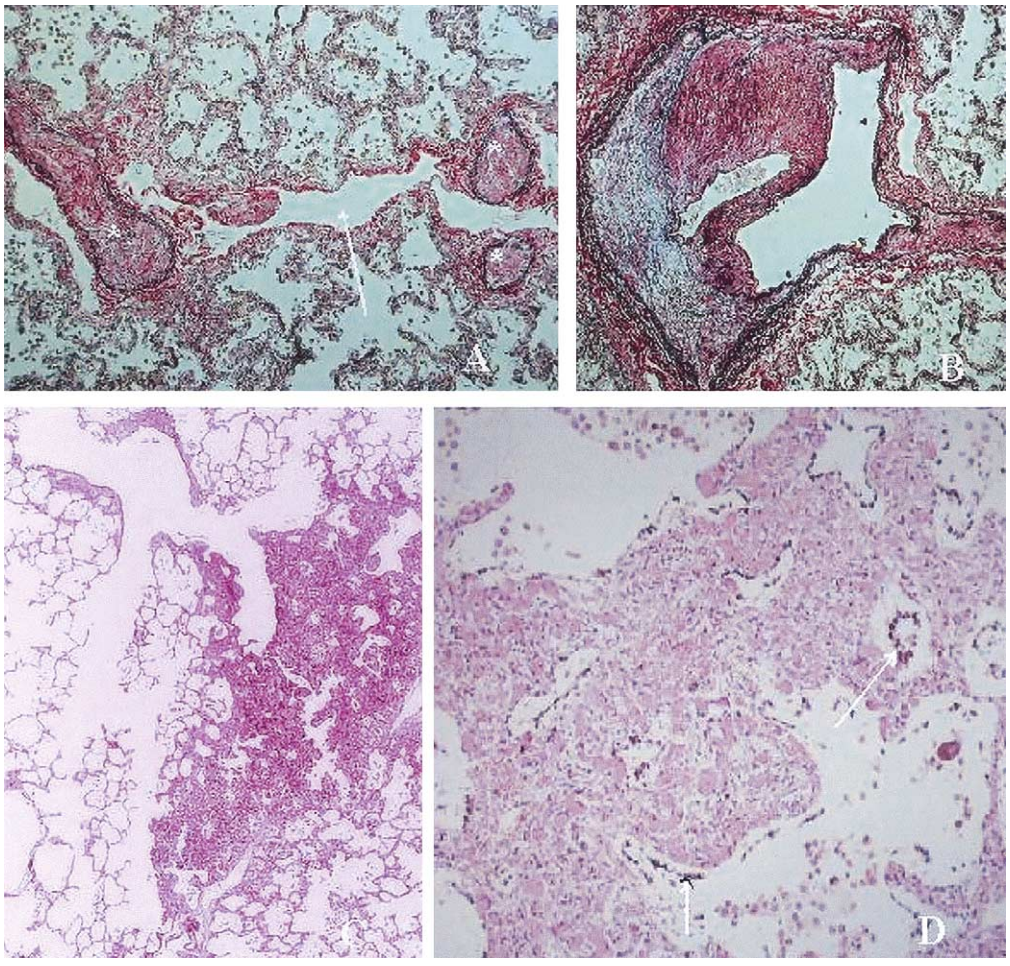

Figure 2. *Pulmonary occlusive venopathy.* **(A)** Septal veins with nearly occluded lumens by fibrous intimal thickening **(asterisk)**, marked lymphatic dilation **(arrow)**, and congested alveolar capillaries. Verhoeff-van Gieson staining, ×50. **(B)** Obstructive fibrous intimal thickening and recanalization channels in a septal vein, ×200. *Pulmonary microvasculopathy.* **(C)** Focal thickening of alveolar septa by proliferated capillaries, HE,×20. **(D)** Nodular capillary proliferation, hemosiderin-laden alveolar macrophages and type II pneumocytes **(arrows)**, HE, ×300.

POV is being considered as a supplementary diagnosis to another pulmonary pathology (i.e., interstitial lung disease or emphysema), a circumstance not uncommon in lung explant pathology.

In POV, large amounts of hemosiderin are found both within the cytoplasm of alveolar macrophages and type II pneumocytes as well as deposits in the interstitium. The presence of fresh blood and/or hemosiderin may be so prominent that idiopathic hemosiderosis or healed Wegener's granulomatosis or other vasculitis is suggested. Hemosiderosis can be quite striking, and quantification of occult alveolar hemorrhage in bronchoalveolar lavage (BAL) (19,20) has been successfully used to confirm the clinical diagnosis of POV/PM because BAL hemorrhage is not a usual feature of the other forms of PAH. The capillary vessels are engorged and prominent; they may become so tortuous as to resemble pulmonary capillary hemangiomatosis (21,22). The capillaries are generally easily identifiable within the alveolar septa and do not line both sides of the alveolar walls as seen in PM (PCH).

Pulmonary arteries and arterioles can show remodeling in approximately 50% of POV cases with moderate to severe medial hypertrophy and arterialization. Plexiform lesions and fibrinoid arteritis are not described in POV (2). The pulmonary interstitium shows edema particularly located in the lobular septa, which may progress to interstitial fibrosis. This can be sufficiently extensive to raise the possibility of interstitial lung disease such as usual interstitial pneumonitis. Inflammatory lung disease is further mimicked by the marked lymphocytic interstitial infiltrate that is seen in some cases of POV. Lymphatics within the lung and pleura are dilated in POV (Fig. 2A).

Pulmonary microvasculopathy (formerly PCH) is another rare condition characterized by localized capillary proliferation within the lung in which capillaries invade pulmonary interstitium, vessels, and, less commonly, airways (23). The distribution of PM in the lungs is usually panlobar and patchy, resembling an interstitial process at low magnification and mimicking pulmonary congestion (24). However, closer inspection shows diffuse proliferation of microvessels containing large numbers of erythrocytes (Figs. 2C and 2D). These microvessels can form glomeroloid tufts or nodules

that may project into the lumen of veins and lymphatics and within air spaces. A distinguishing feature, which is best appreciated on reticulin staining, is the presence of microvessels on both sides of the alveolar walls. Havlik et al. (25) require the microvessels to form at least two cell layers within the proliferating lesion for diagnosis. The endothelial cells of the abnormal capillaries are cytologically bland with elongated oval nuclei, diffuse chromatin, and indistinct cytoplasm. Mitoses are not frequently seen despite the apparent proliferative nature of the condition. The abnormal proliferating capillaries extend into bronchovascular bundles; they infiltrate the walls of arterioles, arteries, venules, and veins, invading muscular walls and occluding the lumens. Also, microvascular proliferation has been seen in perineural and intraneural positions, in the pleura, and in lymph nodes. Venous occlusion by proliferating capillaries and related intimal fibrosis is distinct from the nonangiogenic occlusion of veins in POV.

In the areas of capillary proliferation, a striking feature is pulmonary hemosiderosis represented by both fresh hemorrhage and abundant hemosiderin-laden macrophages and type II pneumocytes (Fig. 2D). However, cases without striking hemosiderosis are observed. The infiltrating capillaries can mimic plexiform lesions, but neither these nor dilation lesions have been described in PM. Similar to POV, the pulmonary arteries in PM show marked muscular hypertrophy and intimal thickening, but, unlike POV, lesions resembling thrombosis are not a feature.

The pathogenesis of PM (PCH) is controversial. Some investigators consider PM to be neoplastic (26), and it is interesting that some patients with PM have responded to treatment with interferon-α, which presumably acts by depressing endothelial proliferation (27,28). Conversely, PM may be due to unknown angiogenic stimuli, and the infiltrative aspect of the disease may merely be related to the extension of vascular lesions within a preexisting vascular distribution.

The PCH/PM-like lesions, as described by Havlik et al. (25), are not associated with clinical pulmonary hypertension and do not generally show invasion of small vessels with occlusion. Pulmonary microvasculopathy and PCH/PM-like lesions must be carefully distinguished from severe pulmonary congestion and atelectasis (29).

Previously PM was described as a possible hypertensive vasculopathy, such lesions had been described as prominent, hyperplastic capillaries with pseudoangiomatous features. Increasing familiarity with the entity of PM has drawn attention to overlaps and similarities between this and POV, particularly in relation to the parenchymal changes of hemosiderosis, fibrosis, lymphatic dilation and edema, and the similar arterial modifications of intimal fibrosis and medial hypertrophy. The distinction between the two entities is clear in those cases where the venous obliteration in PM is due to proliferating capillaries and in POV due to intimal fibrosis with or without recanalization.

Some cases are, however, less clear-cut, and the issue is further confounded by the description of PCH/PM-like lesions that can occur in several clinicopathological settings and that have even been described at autopsy in the absence of evidence of pulmonary hypertension. Clearly, use of the term "PCH/PM-like lesions" must be strict and contextual if confusion is to be avoided. This is an area where there is a likely future role for molecular pathology in distinguishing dilation and tortuosity of existing capillaries from capillary angiogenesis and in elucidating the relationship to vascular remodeling and growth factors. It is important to note that similar microvasculopathy is usual in severe mitral valve disease, and interpretation of venous and capillary congestion with or without proliferation should be made in the knowledge of any valvular disease.

As with many pathological conditions that are poorly understood, it is tempting to consider lesions as part of a continual spectrum, and this view has been justified in relation to POV, POV with PM-like lesions, and true PM, according to whether the venous or capillary lesions are believed to predominate. This can be a hazardous approach if the nature of the sample is not specified. It is likely that explant or autopsy examination of an entire lung will produce a different emphasis on a putative spectrum than will analysis of biopsy material. One point that is abundantly clear, however, is the critical importance of recognizing both POV and PM as rare causes of unexplained pulmonary hypertension because the treatment with vasoactive agents is contraindicated and may even be life-threatening (30,31). Presently, the final distinction between POV and PM requires tissue diagnosis, which is not always feasible. Both the role and the need for lung biopsy in the diagnosis and management of pulmonary hypertension are still under debate.

Pulmonary occlusive venopathy and PM are rather uncommon (fewer than 200 cases have been reported in the published data) but increasingly recognized causes of pulmonary hypertension. They could represent part of the spectrum of vasculopathies of PPH, but they are distinct from the precapillary causes of PAH. The hypertensive angiopathies with exclusive involvement of the precapillary bed share similar morphological lesions of intimal fibrosis, medial hypertrophy, and plexiform lesions, and they generally have a favorable response to drugs such as epoprostenol. Patients with POV and PM may respond to vasodilators with life-threatening edema, and it is therefore of great clinical importance that they be distinguished from precapillary PAH (30,31). It is well recognized that POV in some cases shows extensive abnormality of the pulmonary arterial vascular bed with apparently equal involvement of the venous and arterial components of the circulation. For this situation, the term "pulmonary vascular occlusive disease" has been adopted, but in the current state of pathogenetic knowledge it may itself be confusing (32).

In relation to the second issue, the term *pulmonary vascular occlusive disease* (or vaso-occlusive) generally denotes *extensive* involvement of large and small pulmonary arteries

by narrowing or occlusion of the *same* type of intimal fibrosis as seen in the pulmonary veins, indicating that the tendency to thrombosis was not limited to the veins but also affected the arteries. The availability of explant or autopsy tissue may define the main focus of the vascular pathology on either the venous or arterial aspects of the pulmonary circulation (as compared to biopsy material), but there is no doubt that, even with whole lungs to examine, some cases are difficult to classify. Significant advances in the genetics and pathogenesis of pulmonary hypertension may help to resolve these issues.

Additionally, it is now well described that abnormalities in bone morphometric protein receptor-2 (BMPR2) signaling plays a significant role in the majority of familial and in some sporadic cases of pulmonary hypertension. It is therefore fascinating to note a case (6) of POV (PVOD) apparently caused by an inherited mutation in BMPR2. There was no histopathological assessment of the proband mother's pulmonary hypertension, but features characteristic of POV were found in the proband herself (6) upon review of the open-lung biopsy. Interestingly, the patient improved clinically with epoprostenol and has remained stable for many years, which is quite uncommon in POV. It is likely that the systematic and uniform description of the nature and extent of widespread arterial lesions in PVO/PM and the coexistence of venous lesions in PAH, as recommended in the new pathological classification, together with studies of BMPR2, BMPR1a, TIE-2, and angiopoietin expression in the various forms of pulmonary vasculopathy, will provide information about the position of predominantly arterial, venous, capillary, or mixed forms on a clinical and histological spectrum (33). These exciting developments will surely enable a better informed analysis of the links between POV and PCH/PM with precapillary pulmonary hypertension. This may also allow further refinement of PCH-like lesions in these settings and also in chronic pulmonary venous hypertension. Similar studies may shed light on capillary angiogenesis versus congestion and dilation. Primary pulmonary hypertension appears now to be an angioproliferative disease, and PCH/PM may represent uncontrolled angiogenesis, either de novo or arising from a reactive/hyperplastic process.

Reprint requests and correspondence: Dr. Giuseppe G. Pietra, Via San Giorgio 23, CH 6976 Castagnola, Switzerland. E-mail: gkpietra@freesurf.ch.

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