Clinical Primary Pulmonary Hypertension

Three Pathologic Types

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SUMMARY  Clinically, there is a group of patients with elevated pulmonary arterial pressure in whom the underlying cause is not apparent. The pulmonary arterial wedge pressure is not elevated. For such cases, the designation of primary pulmonary hypertension may be made clinically. From the clinical categorization of primary pulmonary hypertension, three distinct pathologic entities emerge, namely 1) plexogenic pulmonary arteriopathy, 2) recurrent pulmonary thromboembolism, and 3) pulmonary veno-occlusive disease.

The plexogenic type is characterized initially by pulmonary arterial vasoconstriction with medial hypertrophy. Secondary proliferative intimal lesions, including the plexiform lesion, develop. Recurrent pulmonary thromboembolism is characterized by the presence of arterial thrombi of varying ages involving the microscopic-sized pulmonary arteries. Thrombi may be embolic in nature or may develop in situ.

Pulmonary veno-occlusive disease is characterized by obstructive lesions of pulmonary veins and venules.

The clinical presentation of the three pathologic types may be so similar that definitive diagnosis depends upon histologic examination of the lung from tissue obtained either by biopsy or at necropsy.

THE EXISTENCE OF PULMONARY HYPERTENSION is readily established by both clinical and invasive studies. In most instances, the underlying cause is apparent, the pulmonary hypertension being recognized as a feature of the underlying condition. There is a residuum of cases with pulmonary hypertension for which no cause is evident. Such cases are usually listed as primary pulmonary hypertension.

In 1973, the World Health Organization (WHO) held a conference to deal with primary pulmonary hypertension. This conference subdivided into three pathologic categories that form of pulmonary hypertension which, from a clinical aspect, appeared to have no known cause and which, clinically, therefore, would be termed primary pulmonary hypertension.

The three pathologic entities include 1) plexogenic pulmonary arteriopathy, 2) recurrent pulmonary thromboembolism, and 3) pulmonary veno-occlusive disease. Clinically, these may be so similar that definitive diagnosis may be established only by histologic examination of pulmonary tissue obtained either by biopsy or at necropsy.

The usual presenting symptoms of clinical primary pulmonary hypertension are fatigue and dyspnea on exertion.5, 3 The clinical course is characterized by progressive dyspnea and ultimately right-sided cardiac failure. Sudden death occurs relatively frequently.3, 8 Other symptoms which are common to the three morphologic forms of clinical primary pulmonary hypertension include chest pain, syncope, hemoptysis and occasionally cyanosis.5, 3

As in any instance in which the pulmonary arterial pressure is chronically elevated, patients with clinical primary pulmonary hypertension exhibit right ventricular hypertrophy and right ventricular and pulmonary arterial hypertension. The pulmonary arterial wedge and the left atrial pressures are characteristically normal.5

Although the clinical presentations of these three disease groups are often quite similar, the histologic presentations are usually very distinct.3 This report is primarily concerned with the histologic findings characteristic of each disorder and the etiologic factors which are thought to be responsible. One should be aware that the pulmonary vascular lesions to be described are focal and that large segments of most pulmonary vessels are therefore normal. As a result of this, the extent of involvement of the pulmonary vasculature in any one tissue section may appear deceptively scant.2, 3

Plexogenic Pulmonary Arteriopathy

Plexogenic pulmonary arteriopathy is a disease of the muscular pulmonary arteries and arterioles.4 The primary defect is probably prolonged vasoconstriction of unknown cause, and the initial structural manifestation of this is medial hypertrophy of muscular pulmonary arteries and muscularization of the arterioles.5, 6 At this stage, the pulmonary vascular bed is responsive to agents causing pulmonary vasodilatation. In children with plexogenic arteriopathy, the clinical course is often rapid,2 and marked medial hypertrophy may be the only change identified in the pulmonary vasculature.4, 6 (fig. 1).

However, in some children and in almost all adults, other pulmonary arterial changes characteristically develop with time. These lesions, in contrast to medial hypertrophy (fig. 2a), are located in the arterial intima. Intimal cellular proliferation may be seen early in the course of the disease (fig. 2b), but concentric laminar intimal fibrosis (or fibroelastosis) soon becomes the more common lesion (fig. 2c).3 Such fibrotic intimal lesions usually involve the large muscular pulmonary arteries and are associated with secondary medial dilatation and/or atrophy.2 These lesions are obstructive and are often associated with high levels of fixed pulmonary vascular resistance.

The intimal plexiform lesions, from which the designation

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plexogenic pulmonary arteriopathy is derived, character-
istically involve the small muscular pulmonary arteries.1,2 These lesions are most commonly present at branching sites or origins of small muscular pulmonary arteries from large muscular parent arteries (fig. 2d). The plexiform lesion is considered to be the morphologic manifestation of irreversible pulmonary hypertension. The highly cellular, intraluminal, plexiform tuft is usually associated with distal dilatation of the involved artery. Occasionally, fresh thrombosis occurs over the plexiform lesion itself or as in situ thrombosis distal to the obstructive plexiform lesion. Other pulmonary arterial lesions include “dilatation lesions” and pulmonary arteritis.

The alveolar capillaries and the pulmonary venules and veins are normal.2 Pulmonary hemosiderosis may be present but is usually mild.4 The elastic pulmonary arteries are commonly dilated and involved by medial hypertrophy as well as by focal intimal atheromas.5

Recurrent Pulmonary Thromboembolism

Thromboembolic pulmonary hypertension is characterized by organic, obstructive lesions involving the muscular pulmonary arteries and arterioles. These lesions are comprised of thromboemboli in various stages of organization, indicating the recurrent nature of this disease.2,4,5

We would exclude from the category of recurrent pulmonary thromboembolism those cases in which gross pulmonary embolism was part of the picture. We would also exclude those cases in which an underlying disease was a likely cause of thrombosis, such as polycythemia or malignant tumors that yielded emboli of particles of tumor. This would leave for consideration cases that clinically resemble the plexogenic type of pulmonary hypertension.

Obstruction of the muscular pulmonary arteries and arterioles rather than the larger elastic ones is the process in recurrent thromboembolism that clinically appears as primary pulmonary hypertension. Thromboemboli may be recent and undergoing organization (fig. 3a and b) or may be old and organized. The older organized thromboemboli may present as recanalized thrombi, fibrous luminal septa, eccentric nonlaminar intimal fibrosis, or fibroelastic intimal pads (fig. 3c and d).2,5 Plexiform lesions are absent, although some organizing thrombi may be difficult to distinguish from plexiform lesions.

In recurrent thromboembolism, the secondary changes in the pulmonary vasculature occur at the precapillary level. Medial hypertrophy of the muscular pulmonary arteries is the most prominent secondary change, although the severity is usually less than that seen in plexogenic pulmonary arteriopathy.2 Alveolar capillaries and pulmonary venules and veins are normal.2

In patients with recurrent embolism to large pulmonary arteries, there is a tendency for a step-like clinical course with acute exacerbations of dyspnea and chest pain and with intervening periods which are relatively symptom-free.2 In contrast, that type of thromboembolism which is likely to lead to a clinical diagnosis of primary pulmonary hypertension is characterized by an insidious onset and an unrelenting course of progressive dyspnea.2

Pulmonary Veno-Occlusive Disease

Pulmonary veno-occlusive disease involves the pulmonary venules and small veins and is most likely of thrombotic origin.2,4,6,7 Organized thrombi may yield large recanalized channels, partially obstructive intimal pads, or luminal fibrous plugs (fig. 4a–c). The latter may be loose and edematous or densely fibrotic.4 Proximal to a focus of venous obstruction, the pulmonary vein or venule may respond to increased luminal pressure with medial hypertrophy and “arterialization.”2,5

Secondary changes may involve any portion of the pulmonary vasculature proximal to the level of the pulmonary veins. These changes resemble those characteristic of mitral stenosis. Since the pulmonary capillaries and lymphatics are involved, the histologic picture in pulmonary veno-occlusive disease is very much different from that of either plexogenic or thromboembolic pulmonary hypertension.

Pulmonary capillaries are engorged, and their course is often dilated and tortuous.2 Alveolar hemorrhages are occasionally seen, and pulmonary hemosiderosis is often extensive (fig. 4d).2 Pulmonary and pleural lymphatics are dilated, and interlobular septa are edematous.5 Fibrovascular pleural adhesions are common and may afford a col-
lateral route for egress of venous blood from the lungs. In response to elevated pressure, the muscular pulmonary arteries develop medial hypertrophy. Thrombi, either recent or organized, may occasionally be seen in small pulmonary arteries, but plexiform lesions are absent. Focal patchy areas of interstitial fibrosis and interstitial pneumonia are often also present.

**Comment**

The three pathologic patterns presented may each yield a clinical picture of pulmonary hypertension of unknown cause. There is more similarity than difference among each of the three. Among the differences is the tendency for age distribution, although overlap is common. Pulmonary veno-occlusive disease tends to occur in infants and children and uncommonly in young adults. The plexogenic type tends to involve children and young adults, while the thromboembolic type is usually seen in young adults.

Sex distribution is about equal in pulmonary veno-occlusive disease. The thromboembolic type strongly favors the female. In children, the plexogenic type affects males and females about equally, while in affected adults the female dominates.

Each of the three pathologic types is associated with progressive severity of the disease. In pulmonary veno-occlusive disease, survival has usually been only one to two years after the onset of symptoms, with a tendency for somewhat longer survival (up to three years) in the plexogenic type. The thromboembolic type tends to be the most protracted with generally longer survival.

The thoracic roentgenogram may be helpful to some extent in distinguishing the veno-occlusive form from the other two types. Diminished peripheral pulmonary vascular markings are usually present in the plexogenic and thromboembolic forms of pulmonary hypertension. However, in pulmonary veno-occlusive disease the peripheral pulmonary venous markings are often increased, and Kerley B lines are commonly present.

While specific histologic changes occur for each pathologic type of primary pulmonary hypertension, the exact basis for the stimulus of the initial lesion is not known. In pulmonary veno-occlusive disease, there is lack of unanimity as to the underlying basis for the occlusive lesion; many accept these as thrombi. Even if one accepts this view, there is no ready explanation for the occurrence of thrombosis in the pulmonary veins and venules. The theory that a
viral pneumonia is the underlying basis for the venous thrombosis awaits proof.2, 4, 7

The condition called thromboembolism is, by its very name, an admission of ignorance as to whether the thrombotic material which is the basis for vascular obstruction had arisen by thrombosis in situ or had been derived through embolism.

Studies of a large volume of material by the Wagenvoorts2, 4, 8 lends strong support to the view that the primary process in the plexogenic type is pulmonary arterial vasoconstriction and that the plexiform and other associated intimal lesions are secondary to the pulmonary hypertension resulting from the initial process of vasoconstriction. The basis for the vasoconstriction is, as yet, unknown.

It is known that chronic alveolar hypoxia, as occurs in residence at high altitudes, and in such conditions as obesity, musculoskeletal disorders and chronic airway obstruction, may lead to pulmonary vasoconstriction and pulmonary hypertension.2, 9, 10 If there is a recognized hypoxic cause of pulmonary hypertension, this would be a basis for exclusion from the category of primary pulmonary hypertension. It is of additional interest that pulmonary hypertension resulting from chronic pulmonary alveolar hypoxia is not associated with the severity of pulmonary arterial structural changes seen in plexogenic pulmonary arteriopathy, including absence of the plexiform lesion.

All of the pulmonary vascular lesions of plexogenic pulmonary arteriopathy herein described may also characteristically be seen in congenital cardiac shunts with pulmonary hypertension.2, 9, 11, 12 Identical pulmonary vascular changes may also occasionally develop in cases of hepatic cirrhosis,13 in patients ingesting various anorexogenic drugs,14 and in schistosomiasis.15 Such conditions or states must be ruled out before the diagnosis of idiopathic plexogenic pulmonary arteriopathy is acceptable.

The plexogenic type of pulmonary hypertension is now thought to result from prolonged pulmonary arterial vasoconstriction in individuals with hyperreactive pulmonary vessels. In experimental animals, intense pulmonary arterial vasospasm may result in medial hyper-
trophy, fibrinoid necrosis, pulmonary arteritis, and occasional plexiform lesions. It is of interest that some patients with digital vasospasm (Raynaud phenomenon) may exhibit pulmonary hypertension in which the changes are like those of primary plexogenic pulmonary arteriopathy.

A very interesting phenomenon of pulmonary veno-occlusive disease is lack of elevation of the pulmonary arterial wedge pressure. This serves both to separate pulmonary veno-occlusive disease from other forms of pulmonary venous obstruction and, at the same time, to place it in the overall problem of primary pulmonary hypertension, clinically.

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