CRITICAL REVIEW

Pulmonary Veno-occlusive Disease*

Entity or Syndrome?

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Pulmonary veno-occlusive disease is a rare and usually fatal condition in which there is gradual obliteration of the pulmonary veins and venules. Without a lung biopsy the clinical diagnosis of this disease is difficult. If there is pulmonary hypertension with roentgenographic signs of pulmonary edema and of congestion in the absence of signs of increased left atrial pressure, the diagnosis must be considered. The morphologic picture of the lungs is characteristic. The small veins, and sometimes also the major veins, are narrowed or occluded by fibrous tissue, almost certainly on the basis of organized thrombi. Nodular areas of congestion, interstitial fibrosis, and pneumonitis are regularly present. A viral etiology has been suggested in a number of cases. If we may assume, however, that thrombosis of pulmonary veins is the initial event, the possibility has to be considered that this may be elicited by a virus in some patients and by toxic factors or by clotting disorders in others. Pulmonary veno-occlusive disease might then well be a syndrome rather than an etiologic entity.

In most patients with pulmonary hypertension, the clinician will be able to identify the cause for the elevation of pressure in the pulmonary circulation. There are, however, cases in which he is unable to do so. A World Health Organization committee has recently proposed the use of the term, "primary pulmonary hypertension," for all cases of pulmonary hypertension in which the cause is clinically unknown.

Sometimes the pathologist may recognize a cause which remained clinically undetected but which explains the increased pulmonary arterial pressure. Chronic silent pulmonary thromboembolism is an example. In these instances the term, primary pulmonary hypertension, is no longer applicable, and the case may be properly classified. However, there are cases, generally with marked alterations in the pulmonary vasculature, in which even extensive pathologic examination fails to find a cause for these vascular lesions and for the associated pulmonary hypertension.

Usually we are then dealing with one of two different patterns of pulmonary vascular alterations. One of these is characterized by changes in the muscular pulmonary arteries, including medial hypertrophy, concentric-laminar intimal fibrosis, fibrinoid necrosis and arteritis, and the so-called plexiform lesions. This pattern, for which the term, "plexogenic pulmonary arteriopathy," has been proposed, occurs commonly, either in its complete form or incomplete, in patients with congenital cardiac malformations with a shunt, such as a ventricular septal defect. Sometimes it is observed in the absence of heart disease. Up to now, these fairly uncommon cases of unexplained plexogenic pulmonary arteriopathy have usually been described as primary or idiopathic pulmonary hypertension.

An entirely different form of pulmonary vascular pathology, which is even rarer, is seen in patients with pulmonary veno-occlusive disease, which, as the name implies, is characterized by progressive fibrotic obstruction of the veins and particularly of the venules of the lung.

INCIDENCE

Although pulmonary veno-occlusive disease is a rare condition, its incidence is apparently on the increase. Before 1960, pulmonary veno-occlusive disease was virtually unknown, though two cases from that period are now generally accepted as such. Up to 1970 a total of ten cases had been reported in detail. Now this number has risen to over 30. Is this increase genuine, or is the condition only recognized more often than before? There can be little doubt that clinicians and pathologists are becoming gradually more and more aware of this disease. Even so, the possibility of an increased incidence cannot easily be dismissed.

Generally, pulmonary veno-occlusive disease af-
ffects children and young adults. The average age of the 31 patients who, to our knowledge, have been reported up to this moment or whose material was submitted to us was 19 years. The youngest patient was an infant eight weeks of age, and the oldest was a woman aged 48 years.

Unlike primary pulmonary hypertension, (the incidence of which in women after sexual maturity is approximately four times higher than in men), there is no sex preference in pulmonary veno-occlusive disease. Of the 31 patients, 17 were male, and 14 were female.

CLINICAL PICTURE

The clinical diagnosis of this condition presents great difficulties and is not often made without a lung biopsy. Shortness of breath, particularly on exertion, is universally present and almost always the first symptom. It is gradually progressive. Apart from symptoms of pulmonary hypertension, there are few clinical signs so consistent that they can be used for arriving at a firm diagnosis. Cyanosis and clubbing, syncope, dizziness, and hemoptysis have been described in some instances. The patients are usually afebrile, and laboratory data are of little help in the diagnosis. Cardiac catheterization will establish the marked rise in pulmonary arterial pressure, while the wedge pressure is often normal, though sometimes mildly elevated.

The chest roentgenogram in many instances may give an important clue. Signs of pulmonary edema with bilateral increased interstitial markings and Kerley B lines are regularly present. The vague patchy or reticulate pattern of the lungs may be misinterpreted as pneumonia. There is increased vascular prominence, but—and this may be of help in differentiating this condition from chronic congestive pulmonary hypertension due to valvular heart disease—the pulmonary veins are not visible on routine roentgenograms, while the vascular markings are no more prominent in the upper lobes than in the lower lobes. If the chest roentgenogram suggests a postcapillary origin of the pulmonary hypertension and if, on the other hand, there are no signs of elevated left atrial pressure, it should be possible to arrive at a correct diagnosis.

No adequate therapy is as yet available. The administration of anticoagulant drugs has had a temporary effect in some patients but did not generally prevent a fatal outcome. The duration of the disease varies considerably. In some infants and children, this has been in the range of one to two months; in other patients the disease took a protracted course over several years.

MORPHOLOGY

The essential gross pathologic features in patients with pulmonary veno-occlusive disease are limited to the thoracic organs. The lungs are usually large, heavy, and congested. Pleural effusions are commonly observed. There is always right ventricular hypertrophy, but cardiac anomalies are absent. In one infant, subacute myocarditis was noted.

The most striking microscopic finding is occlusion or narrowing of pulmonary veins and venules by sometimes loose (Fig 1), sometimes more dense and collagen-rich (Fig 2), fibrous tissue. If not occlusive or secondarily recanalized, these lesions are often eccentric and suggestive of organized thrombi. Intravascular fibrous septa, known to be due to excessive recanalization of thrombi, are also often found. Recognizable thrombi, recent or in the process of organization, have been found in some cases. The obliterative changes may extend over venous anastomoses into the bronchial veins. Pulmonary phlebitis is not a regular feature, but is sometimes a striking one.

There are several patients on record in whom major pulmonary veins were equally affected. This may explain why some of the smaller veins show distinct medial hypertrophy and arterialization as a result of an obstructed outflow. Occasionally the

Figure 1. Pulmonary vein subtotally occluded by loose connective tissue in pulmonary veno-occlusive disease (elastic van Gieson, original magnification X 350).
involvement of major veins is limited to one lung, producing unilateral absence of perfusion.18

The pulmonary arteries are rarely normal. In the presence of pronounced pulmonary hypertension, even of postcapillary origin, it could hardly be expected that the arterial wall would remain unaffected. Even so, there is actually a wide variation in arterial alterations in pulmonary veno-occlusive disease. Medial hypertrophy is almost always present but usually mild. In infants and children with this disease, however, it may be very severe. Eccentric, cushion-like intimal fibrosis also occurs in varying degrees in these arteries, and thrombi are fairly common and in some cases numerous. Bands and webs resulting from recanalization of thrombi are sometimes present in elastic pulmonary arteries.19

In contrast to arterial pulmonary hypertension, in pulmonary veno-occlusive disease the lung tissue exhibits distinct and often characteristic changes. These consist of nodular areas of congestion, edema, and hemorrhage (Fig 3). In these areas, there is often pronounced hemosiderosis, as well as an interstitial inflammatory reaction and interstitial fibrosis. Obstructed pulmonary venules, although not confined to these areas, are often found in or around them (Fig 4). These nodular foci, which are responsible for the patchy shadowing on the chest roentgenogram, may sometimes fuse into large areas of

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congestion and interstitial fibrosis.

Other changes in the lung tissue of patients with pulmonary veno-occlusive disease may include interstitial edema with lymphatic dilatation and hyperplasia and increased activity of bronchial mucous glands and of the goblet cells in the epithelial lining of the bronchioles.\textsuperscript{14}

**Etiology**

The etiology of pulmonary veno-occlusive disease is unknown. There is, however, no lack of hypotheses and suggestions for an explanation.

The condition is acquired and not the result of congenital malformations of the pulmonary veins.\textsuperscript{9} In the rare cases in which an intrauterine origin had to be presumed,\textsuperscript{9,20} the venous lesions were suggestive of having developed in late prenatal life. In one patient, cardiac catheterization studies showed normal pressure nine years before she developed the symptoms of pulmonary veno-occlusive disease, indicating that the condition was acquired.\textsuperscript{21}

Even so, the possibility that genetic factors are involved has to be considered, since familial occurrence has been reported in two sibling male infants,\textsuperscript{14} while in another case a brother of the patient had died previously from pulmonary hypertension of which the nature remained undisclosed.\textsuperscript{21} Also, congenital cardiac disease has been described in members of the family of these patients.\textsuperscript{22}

Any etiologic explanation must take into account the pathogenesis of the vascular and parenchymal lesions. There is a great deal of unanimity in the belief that the occlusion of the veins and venules is thrombotic in origin. This is borne out by the presence of recognizable thrombi in some, and by the nature of the fibrotic intimal cushions and septa in all patients. In this respect, it has been stressed that pulmonary venous endothelium contains less plasminogen activator than pulmonary arterial or systemic venous endothelium and that a toxic or infective agent attacking the endothelial cells of the pulmonary veins might well be responsible for inhibited lysis and, thus, for promoting thrombosis.\textsuperscript{28} It may be recalled here that some patients also show an increased tendency for pulmonary arterial thrombosis.

What then could possibly induce thrombosis in the pulmonary vasculature in patients with pulmonary veno-occlusive disease? Blood coagulation studies were done in a minority of the patients, and the results were normal except for one patient in whom increased platelet adhesiveness was demonstrated.\textsuperscript{24} Environmental factors and toxic substances could not be implicated generally, although this possibility was raised by Weisser et al.\textsuperscript{25} In the patient described by Liu and Sackler,\textsuperscript{26} a history of sniffing powdered cleanser was obtained, but in no other patient was this likely to be a causative factor.

Pyrrolizidine alkaloids from the plant genus Crotalaria, sometimes ingested as herbal medicines or as "bush tea," may produce veno-occlusive disease of the liver in man\textsuperscript{27} and also pulmonary hypertension in animals.\textsuperscript{28} There is, however, no recorded case of Crotalaria-induced pulmonary hypertension in man, nor is there any indication so far that patients with pulmonary veno-occlusive disease were in the habit of taking herbal medicines.

While on the whole there is little evidence to blame toxic substances in the etiology of pulmonary veno-occlusive disease, the possibility of an infectious origin has to be considered seriously. First of all, it has been pointed out repeatedly that the symptoms of pulmonary veno-occlusive disease are often preceded by a pyrexial respiratory illness, sometimes resembling influenza. Even though the description of such an episode is often rather vague and differs in various cases, it forms part of the case histories of many patients.\textsuperscript{8,12,14,20,26}

Toxoplasmosis has been implicated as a causative agent in one case,\textsuperscript{81} but the evidence was not convincing, and in several subsequent patients the antibody titers ruled against this possibility. There are a number of arguments for a viral etiology. It would be consistent with the regular observation of interstitial pneumonitis and of mucous gland and goblet cell hyperplasia and activity. In one infant, there was a coexistent subacute myocarditis, while in a girl aged nine years, in addition to the various histologic features of pulmonary veno-occlusive disease, the lung tissue showed hyaline membranes.\textsuperscript{82}

Corrin and co-workers\textsuperscript{83} made the interesting observation that in a lung biopsy of their patient, there were irregular deposits of immunoglobulin G and complement in the alveolar walls. These supposedly corresponded with electron-dense deposits demonstrated by electron microscopy. Corrin et al\textsuperscript{83} suggested that in this case, immune complexes might have led to thrombosis by activation of the "contact" clotting factors or platelets. They also pointed out that these immune complexes might stem from a viral infection.

So far, an infectious, presumably viral origin figures high on the list of etiologic possibilities, but the issue is far from solved. A major drawback is the inability of many workers to demonstrate the presence of a virus, for instance, by serologic methods.

But even if it would be possible to identify a virus and to prove that it is the culprit in some patients, the question may be raised whether this is the responsible agent in all cases, in other words, whether pulmonary veno-occlusive disease is a distinct entity
with a single etiologic factor.

In this respect, it is good to realize that in spite of much resemblance in clinical and morphologic features in various patients, there are also discrepancies. There are patients in whom even a careful search in their history failed to disclose any possibly relevant preceding illnesses. The course of the disease was one or two months in some, but many years in other patients.

There are cases in which the vascular obliteration is limited to the smallest venules, while in others major pulmonary veins, even in the hilar region, are affected. The degree of pulmonary arterial involvement varies widely. Interstitial pneumonitis, distinct in some, is absent in other cases. It is possible that the nodules of interstitial fibrosis, which are generally present, represent remnants of pneumonitis, but this fibrosis could also result from chronic congestion.

If we may assume that thrombosis of pulmonary venules and veins is the basis for pulmonary veno-occlusive disease, the mechanism by which this thrombosis is elicited is not necessarily the same in all cases. The possibility that environmental and toxic factors or clotting disorders may be responsible in some patients, and viral or other infectious agents in others, cannot be excluded. Pulmonary veno-occlusive disease would then be a syndrome resulting from pulmonary venous thrombosis rather than an etiologic entity.

In the face of so many uncertainties, it is urgently recommended that in any patient in whom pulmonary veno-occlusive disease is diagnosed or suspected, much attention should be paid to the case history with regard to previous illnesses and infections, environmental and occupational factors, contact with toxins, and the use of drugs. Moreover, study of the clotting mechanism and microbiologic and serologic investigations are essential.

References
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