Pulmonary Veno-Occlusive Disease

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PRIMARY pulmonary hypertension is a rare disease with a poor prognosis that occurs predominantly in women. Its cause is unknown and the term probably describes a heterogeneous group of conditions. In this disease, the pulmonary veins are usually normal, but in a minority of cases there is widespread and severe pulmonary venous occlusion. We describe such a case and suggest that the histological features in the lung are so distinctive as to constitute a distinct disease entity which should be separated from the main group of patients with classical primary pulmonary hypertension and called "pulmonary veno-occlusive disease."

Report of Case

A married woman, 37 years old, was first admitted on October 5, 1958, with a 7-month history of fainting attacks which were unrelated to exertion, excessive fatigue, and continuous dull left submammary pain. She was able to walk at a normal speed on the level, but for 1 year had been breathless on climbing hills. There was no nocturnal dyspnea, cough, or hemoptysis. She had a child 15 years old; three others had died at the age of about 10 days, allegedly from cyanotic heart disease. The patient's only past illness was pneumonia 5 years previously. She was a nervous, emotional woman. She weighed 162 pounds and her height was 63 inches. Her brachial blood pressure was 130/80 mm Hg. The heart was normal on clinical examination. The electrocardiogram was normal. A roentgenogram of the chest revealed a slight increase in the transverse diameter of the heart, but the lung fields were normal. The hemoglobin concentration was 14.0 g%, the white cell count 8,200/ mm³, and the E.S.R. 6 mm in 1 hour (Wintrobe). The results at cardiac catheterization are shown in table 1.

On her second admission on September 29, 1964, the patient reported that breathlessness with effort had increased gradually at first but more rapidly during the past 3 months. She was unable to walk more than a few yards on the level without dyspnea, complained of extreme weakness, but was still able to lie flat. Although her ankles swelled occasionally, she had lost 22 pounds since her first admission. She was breathless on the slightest exertion, but there was no cyanosis or clubbing. The heart, in sinus rhythm, was enlarged with the apex beat in the fifth left interspace 1 cm beyond the midclavicular line. There was a marked left parasternal heave and a palpable second heart sound which was very loud and narrowly split. There was no edema or elevation of jugular venous pressure. The hemoglobin concentration, white cell count, and E.S.R. were normal as were the concentrations of serum proteins, urea, and electrolytes. The Wassermann and Kahn reactions were negative. L.E. cells were not found, and serum complement was normal. The urine showed no abnormality. The electrocardiogram showed right axis deviation. A roentgenogram of the chest revealed moderate cardiac enlargement involving the right ventricle predominantly (fig. 1). The main pulmonary arteries were dilated. Cardiac catheterization was again performed and the results are shown in table 1. The results of pulmonary function tests are given in table 2.

Figure 1

Roentgenogram of the chest taken on September 29, 1964.

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A diagnosis of primary pulmonary hypertension was made, but since recurring pulmonary thromboembolism could not be excluded, she was treated with phenindione.

The patient was admitted for the third time on January 27, 1965. Breathlessness had increased and for a month she had been unable to leave her bed, nor could she now lie flat. She had developed a cough with sputum which was at first yellow and later white and frothy; there was no hemoptysis. The jugular venous pressure was moderately elevated, and there was ankle and sacral edema. The heart had enlarged further, but the signs were otherwise unchanged. There were fine crepitations at both lung bases. The hemoglobin concentration was 15.6 g%, the blood urea was 47 mg%, and the serum electrolyte concentrations were normal. The arterial

| Table 1 |
| Cardiac Output and Intravascular Pressures |
| First study | Second study |
| Oct. 16, 1958 | Sept. 25, 1964 |
| Oxygen uptake (ml/min/m²) | 187 | 141 |
| Pulmonary ventilation (L/min/m²) | 7.8 | 6.3 |
| Cardiac output (L/min/m²) | 4.1 | 2.4 |
| Arterial O₂ saturation (%) | 98.5 | 90.4 |
| Pressures (mm Hg) | | |
| Pulmonary wedge, mean | 14 | 12 |
| Pulmonary artery, s, d (m) | 42/19 (33) | 108/54 (75) |
| Right atrium, mean | 5 | 11 |
| Pulmonary vascular resistance (dynes sec cm⁻³) | 271 | 1230 |

| Table 2 |
| Results of Pulmonary Function Tests at the Time of Second Admission to Hospital |
| Patient | Predicted normal range |
| Expiratory reserve volume (L) | 0.69 | - |
| Inspiratory capacity (L) | 1.49 | - |
| Vital capacity (L) | 2.09 | 2.45 - 3.97 |
| Functional residual capacity (L) | 2.06 | 1.66 - 3.46 |
| Residual volume (L) | 1.37 | 1.13 - 2.61 |
| Total lung capacity (L) | 4.15 | 4.25 - 6.33 |
| RV/TLC (%) | 33 | 22 - 45 |
| Forced expiratory volume (1 sec) (L) | 1.94 | 1.81 - 3.41 |
| FEV/VC (%) | 93 | 70 - 91 |
| Airway resistance (cm H₂O/L/sec) | 2.16 | 0.8 - 2.1 |
| Lung compliance (ml/cm H₂O) | 124 | 80 - 180 |
| Compliance/thoracic gas volume | 60 | 38 - 70 |
| Diffusing capacity (DLCO) (ml/min/mm Hg) | 20.0 | 11.9 - 32.1 |
| Arterial O₂ tension (PaO₂) (mm Hg) | 55.4 | 83 - 102 |
| Arterial CO₂ tension (PaCO₂) (mm Hg) | 37.7 | 35 - 44 |
| Alveolar O₂ tension (PAO₂) (mm Hg) | 104.9 | - |
| PAO₂ - PaO₂ (mm Hg) | 49.5 | 4 - 22 |
| Physiological dead space (Vd) (ml) | 179 | - |
| Tidal volume (VT) (ml) | 456 | - |
| Respiratory rate (per min) | 23.7 | - |
| Vd/VT (%) | 39.3 | 12 - 34 |
| Pulmonary ventilation, rest (L/min) | 10.8 | - |
| Exercise (L/min) | 45.0 | - |
| Oxygen uptake, rest (ml/min) | 277 | - |
| Exercise (ml/min) | 709 | - |
\( P_{CO_2} \) was 28.5 mm Hg and the pH was 7.40. There was heavy proteinuria. The electrocardiogram showed signs of right ventricular preponderance with a qR pattern in the first precordial lead. The P waves were abnormally large in all the leads. Apart from further cardiac enlargement the chest radiograph was similar to the one taken 4 months previously. The patient did not respond to treatment and died suddenly a few hours after admission.

**Postmortem Report**

The heart was enlarged and weighed 420 g. This increase in weight was due to hypertrophy of the right ventricle which was 7 mm thick and 150 g in weight; its predicted normal thickness and weight (stripped of fat) was 3 mm and 65 g, respectively. In contrast the weight of the left ventricle including the interventricular septum was only 170 g; the thickness of the left ventricle was normal (15 mm). All the cardiac valves were normal in structure. The pulmonary valve was dilated, its circumference being 9 cm, but the circumferences of the other valves were normal. There were no congenital defects of the cardiac septa, and the ductus arteriosus was not patent. In particular, there was no evidence of anomalous pulmonary venous drainage or of congenital stenosis or occlusion of the major pulmonary veins. The origin, course, and distribution of the coronary arteries were normal and there was no evidence of myocardial fibrosis or disease.

The major pulmonary arteries were dilated and severely atherosclerotic, evidence of there having been considerable pulmonary arterial hypertension in this case. These large arteries contained no recent or organizing thrombi to support a diagnosis of recurrent pulmonary thromboembolism. The lungs were inflated and fixed by the Formalin stream method of Weibel and Vidone. When they were subsequently cut, they showed no evidence of emphysema. In section they appeared to be abnormally tough and fibrous, suggestive of some interstitial fibrosis. The small pulmonary arteries appeared abnormally thick-walled and stood out from the surface of the lung (fig. 2). Both lungs were congested and edematous and showed the brownish mottling characteristic of hemosiderosis; they gave a strongly positive reaction for ferric iron. There were bilateral clear pleural effusions. The organs of the abdominal cavity and the brain were congested but showed no other abnormality. The appearances at autopsy were suggestive of primary pulmonary hypertension. Frozen sections of the lung were made in the postmortem room, and these showed pronounced occlusive lesions in the pulmonary veins with only medial hypertrophy and no occlusive lesions in the pulmonary arteries. We were familiar with this combination as a similar case had previously been studied in our center by Brewer and Humphreys. Thus even at the autopsy, we were confident that this was a case of pulmonary hypertension secondary to obstruction of the intrapulmonary veins.

This impression was confirmed on histological examination of the lung. Most of the pulmonary veins and venules showed pronounced thickening of the intima by loose, edematous-looking fibrous tissues (figs. 3 to 5). A total of 307 pulmonary veins and venules from the left upper, left lower, and right lower lobes and the lingula were examined and all but 14 of them (95%) showed intimal fibrosis. In some veins, the intimal fibrosis formed eccentrically situated nodules in which elastic fibrils were also found; such appearances suggested that they had arisen as a result of organization of thrombus. This idea was supported by evidence of recanalization (figs. 4 and 5). In some veins, this presented as a central channel with a surrounding rim of condensed collagenous and muscle tissue of the type illustrated by Wagenvoort and associates. In other veins, a colander-like effect was produced, recanalization having resulted in a number of wide channels separated by fibroelastic septa (fig. 5). The intimal fibrosis affected all classes of pulmonary vein from the large lobular veins down to the smallest pulmonary venules of immediate postcapillary size. The fibrosis was exceptionally severe, especially in the venules, so that many of the affected vessels were totally occluded. In many veins, the cellular fibrous tissue reaction had extended into the adventitia and immediately adjacent lung parenchyma.

**Figure 2**

Cut surface of lung showing prominent pulmonary arteries; \( x \ 2 \).
Tranverse section of a pulmonary vein showing almost total occlusion by cellular intimal fibrous tissue. The patency of the center of the vessel suggests that recanalization of organized thrombus has taken place; $\times 135$. Elastic-van Gieson stain used for this and other photomicrograms.

The alveolar walls surrounding affected post-capillary pulmonary venules also showed gross structural changes. In many, there was striking engorgement of the capillaries with loss of erythrocytes into the alveolar spaces. Hemosiderin had been liberated in the alveoli and phagocytosed by alveolar macrophages which had grouped together to form discrete collections of siderophages to give the condition of hemosiderosis. These siderophages gave a strongly positive reaction with potassium ferrocyanide and hydrochloric acid for ferric iron. Iron salts had also been liberated and had encrusted the elastic laminae of some of the small pulmonary arteries and veins, and some of the elastic fibrils of the alveolar walls. There was no giant cell reaction to such encrusted elastic fibrils.

Many of the alveolar walls had developed a chronic fibrous reaction to the chronic congestion and edema present within them (fig. 6). Thus the typical appearances of interstitial fibrosis had developed. There was, however, no suggestion of honeycomb lung. Fibrosis had also occurred in the adventitia of the pulmonary arteries and veins and in the connective tissue septa of the lung. At these sites there was considerable dilatation of the pulmonary lymphatics and there was much edema around them (fig. 6).

There was unequivocal muscularization of the media of the small pulmonary veins. In many of them, the media was better developed and delineated than in the normal pulmonary vein, presenting as a thick distinct muscular media.
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Figure 6
Section of lung showing an edematous connective tissue septum which is thickened by cellular fibrous tissue and which includes dilated lymph channels (arrows); × 125.

sandwiched between internal and external elastic laminae. In this way, the structure of these abnormal veins had come to mimic that of a muscular pulmonary artery. The pulmonary arteries were abnormally muscular and were characterized by a thick media of circular smooth muscle, although fasciculi of longitudinally orientated muscle fibers were also situated in apposition to the media mainly within the intima. The pulmonary arteries showed little in the way of intimal proliferation (fig. 7). Neither necrotizing arteritis nor dilatation lesions, both very characteristic of primary pulmonary hypertension, were seen. The pulmonary arterioles, less than 80 μ in diameter, and characterized in the normal lung by a thin wall consisting of a single elastic lamina, were abnormal in being muscular-like systemic arterioles. They showed a distinct media of circularly oriented smooth muscle sandwiched between distinct inner and outer elastic laminae. Such muscularization affected arterioles of immediate precapillary class, as small as 15 μ in diameter. The elastic pulmonary arteries, defined as being more than 1,000 μ in external diameter, showed severe atherosclerosis, a condition clearly related to the presence of severe pulmonary hypertension in this case. Sections of the pulmonary trunk showed the typical adult pulmonary configuration of elastica consistent with the elevated pulmonary arterial pressure in this case having been acquired rather than being present from birth. Plentiful amounts of metachromatic ground substance demonstrable by toluidine blue were present in the media of the pulmonary trunk, this being another expression of the effects of chronic hypertension on this vessel. The bronchial arteries and veins were normal. No bronchopulmonary anastomoses were found. Several small spicules of bone were found in the alveolar spaces. The appearances at the autopsy were those of congestive cardiac failure brought about by pulmonary arterial hypertension secondary to obstruction of the intrapulmonary veins.

Discussion
In this patient, the clinical features and the findings at cardiac catheterization were in no way distinctive by comparison with other cases of primary pulmonary hypertension. In particular, there was nothing about the findings at cardiac catheterization which would indicate that the principal lesion lay in the pulmonary veins. The normal pulmonary wedge pressure that we found was an indirect measurement of pressure in the main pul-

Figure 7
A small muscular pulmonary artery showing slight hypertrophy of the media but no form of intimal proliferation; × 235.

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monary veins and left atrium, and did not reflect the pressure in the pulmonary venu-
ules and capillaries which was probably raised in this patient, especially during exer-
cise.

There is little published information about pulmonary function in primary pulmonary
hypertension so that it is not possible to be certain whether the present results are
distinctively abnormal. The findings are similar to those in mitral stenosis.

The brunt of the pathology fell upon the pulmonary veins rather than on the pulmonary
arteries. Intimal proliferation in the small pul-
monary veins is commonly found in association
with various forms of organic disease of the heart characterized by diminished pul-
monary flow and compensatory polycythe-
emia.5, 6 abnormally high pulmonary flow,7 or
pulmonary venous hypertension.8 However,
in the present case, the pulmonary venous
lesions were primary with no predisposing
cardiac disease and in particular no obstruc-
tion to pulmonary venous flow outside the
lung. Furthermore, they presented the unusual
combination of organizing thrombi and a
peculiarly cellular edematous intimal prolifera-
tion which extended around the veins. This
was quite unlike the changes in the pulmonary
veins found in atrial septal defect or mitral
stenosis or as a result of age.

The few published reports on patients with
idiopathic pulmonary hypertension who have shown predominant lesions in the pul-
monary veins include reference to the edema-
tous intimal fibrous tissue,3, 9-11 the organiz-
ing thrombi,12 or both.13, 14 The histological
findings are characteristic and the lesions found
in the lung in our case are identical to those
described by Stovin and Mitchinson.14 The
etiology of these venous lesions is obscure. Pre-
vious reports describe the onset of the dis-
ease with a pyrexial illness of unknown na-
ture,3, 10 suggesting that the condition may be
inflammatory. Stovin and Mitchinson14 found
high serological titers for toxoplasmosis in
their case, but they were not high enough
to be diagnostic. Since similar titers are
found in healthy subjects, their finding is of
doubtful significance. They also found un-
identified round bodies in a fibrinous exudate
from a pleural biopsy specimen. In our case,
serological tests for toxoplasmosis were not
carried out, but histological examination
of lymph nodes showed no evidence of lymph-
phistiocytic medullary reticulosis which
would be expected in toxoplasmosis.

The distinctive nature and distribution of
the vascular lesions in this disease suggest that
it should be separated from classical primary
pulmonary hypertension and recognized as a
distinct entity, pulmonary veno-occlusive
disease. An awareness of its existence as a
distinct entity and its characteristic pathol-
ogy may allow its recognition during life
by lung biopsy. Such early diagnosis coupled
with recognition of its suggested inflammatory
causation may stimulate serological in-
vestigation and other means in life to
determine its cause.

Summary

A woman, 45 years old at the time of her
death, showed the clinical features of pri-
mary pulmonary hypertension and the results
of cardiac catheterization and pulmonary func-
tion tests were consistent with this diagnosis.
Histological examination of the lung showed
that the pulmonary veins were severely in-
volved by cellular fibrous tissue. These dis-
tinctive lesions appear to constitute a sepa-
rate disease entity for which the name
"pulmonary veno-occlusive disease" is sug-

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