PULMONARY VENO-OCCLUSIVE DISEASE IN AN ELDERLY MAN: CASE REPORT AND REVIEW OF THE LITERATURE

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A 75-year-old man complaining of dyspnea and having signs of postcapillary pulmonary hypertension was diagnosed as pulmonary veno-occlusive disease and confirmed at autopsy. This is the oldest case ever reported. Almost all the small veins 2 mm or less in external diameter were partially or nearly completely occluded by intimal fibrous tissue, and the obstructive changes in the pulmonary arteries were much more limited. Pulmonary veno-occlusive disease is a rare, almost inevitably fatal disease of unknown etiology which has only recently been separated clearly from primary pulmonary hypertension as a distinct entity. Chest roentgenogram finding suggesting postcapillary pulmonary hypertension is a clue to a diagnosis and differentiates this from two other causes of clinical primary pulmonary hypertension, that is, recurrent pulmonary embolism and plexogenic pulmonary arteriopathy.

PULMONARY veno-occlusive disease is a very rare disease of unknown etiology which has only recently been separated clearly from primary pulmonary hypertension as a distinct entity. We have experienced a case of pulmonary veno-occlusive disease in which antemortem diagnosis was made and confirmed at autopsy. We report clinical and pathological findings of this case with review of the literature.

CASE REPORT

Clinical History

A 75-year-old man was admitted to our hospital on February 21, 1983 because of dyspnea.

Mild hypertension was pointed out 8 years

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before entry and he took anti-hypertensive drugs since then. He was otherwise in good health until October, 1981, when he began to experience exertional dyspnea. He visited our hospital on February, 1982 when physical examination showed that the blood pressure was 160/80 mmHg, and the pulse 76; a few crepitant rales were heard at both lung bases. An electrocardiogram (Fig. 1a) demonstrated a normal sinus rhythm at a rate of 86, a mean QRS axis of 78°, and an incomplete right bundle branch block. Chest roentgenogram revealed a slight aortic elongation, but otherwise normal. Furosemide and methyldopa were continued. On September, 1982, he suffered from acute appendicitis and was operated on. Dyspnea gradually worsened and the blood pressure fell despite cessation of methyldopa. He was admitted to our hospital.

The patient drank a little alcohol and smoked one package of cigarette for many years. There was no history of a heart murmur, orthopnea, arthritis, Raynaud's phenomenon, and inhalation

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Fig.1. Electrocardiogram on February 1982 (a) shows incomplete right bundle branch block. Progression of right axis deviation, marked R'wave in V_1 and deep S wave in $V_{4,5}$, and ST depression with negative T waves in II, III, aVF and V_{1-4} seen on February 1983 (b) are the signs of right ventricular hypertrophy and suggest the presence of marked pulmonary hypertension.

of noxious gas.

The temperature was 36.6°C , the pulse 76, the respiration 24, and the blood pressure 90/60 mmHg.

On examination the patient appeared chronically ill. The lips and nail beds were slightly cyanotic; a few vascular spiders were seen over the upper anterior chest; no lymphadenopathy or peripheral edema were noted. Neck veins were distended. Crepitant rales were heard at both lung bases. The heart was not enlarged, and the rhythm was regular. There was a wide splitting of S_2 with loud P_2 ; no S_3 , S_4 or ejection sound were heard; a Grade 3, inspiratory increasing holosystolic murmur was heard along the lower-left sternal border. The liver was palpated 3 cm below the right costal margin.

The urine gave a + test for protein. The hematocrit was 44 per cent; the white cell count 7,700, with 63 per cent neutrophils, 22 per cent lymphocytes, 8 per cent monocytes, 6 per cent eosinophils, and 1 per cent basophils. The platelet count was 151,000, and the erythrocyte sedimentation rate 16 mm per hour. The prothrombin activity was 65 per cent, the partial thromboplastin time 31 seconds, the fibrinogen

Fig.2. Chest roentgenogram on admission shows the cardiomegaly and increased vascular and interstitial marking including perivascular haze and Kerley B lines as the right lower lung field.

Fig.3. Two-dimensional echocardiogram of the left ventricular short axis view (a) and the four chamber view (b). The right atrial enlargement and the right ventricular hypertrophy and enlargement are evident. The left ventricular hypertrophy is also seen and the left atrium is small. RA = right atrium, RV = right ventricle, LA = left atrium, LV = left ventricle.

390 mg per 100 ml, and the fibrin degradation products were negative. The urea nitrogen was 40 mg per 100 ml, the creatinine 1.9 mg per 100 ml, the glucose 91 mg per 100 ml, the uric acid 5.0 mg per 100 ml, the bilirubin 0.6 mg per 100 ml. The SGOT was 72 (normal: 0–40) unit per liter, the SGPT 82 (normal: 0–35) unit per liter, the LDH 304 (normal: 100–225) unit per liter, the alkaline phosphatase 241 (normal: 25–70) unit per liter, and the creatine phosphokinase 66 (normal: 40–160) unit per liter. The serum protein was 7.7g (the albumin 3.8g and the globulin 3.8g) per 100 ml. The serum agarose-gel electrophoresis disclosed a sharp peak in the gamma globulin fraction and immunoelectrophoresis revealed a monoclonal protein of IgG- λ type. A test for a rheumatoid factor, hepatitis

Fig.4. ^{99m}Tc -MAA perfusion lung scan shows that the perfusion was diffusely decreased except in the posterior portion of the right lower lobe.

TABLE I

	Observed	Per cent Predicted
First-second vital capacity (FEV_1) (liters)	1.79	65
Vital capacity (VC) (liters)	2.63	85
Peak flow rate (liters/min)	5.76	76
Total lung capacity (TLC) (liters)	3.49	78
Single-breath carbon monoxide diffusing capacity (ml/min/mmHg)	2.2	17
Closing volume (CV)/VC	0.55	175

B surface antigen, and the antinuclear antibodies were negative.

An electrocardiogram (Fig. 1b) showed a normal sinus rhythm at a rate of 86, and a mean QRS axis of 100° ; the pattern of right bundle branch block persisted and R' wave in V_1 became more prominent, and R/S in V_5 was 1. These ECG findings suggested a right ventricular hypertrophy. A chest roentgenogram (Fig. 2) disclosed that the heart was enlarged (CTR 56%); the main-pulmonary artery segment was prominent; perivascular haze and an increased interstitial and vascular markings bilaterally, with

Fig.5. Pulmonary vein obstructed by intimal fibrous tissue. (El.v.G., $\times 200$)

Fig.6. Pulmonary vein with subtotal occlusion by paucicellular, loose and edematous tissue. (H. and E., $\times 200$)

Kerley B lines at the base of the right lung consistent with interstitial edema. A specimen of the arterial blood, drawn while the patient was breathing room air, revealed that the PaO_2 was 57 mmHg, the PaCO_2 18 mmHg, the bicarbonate 13 mEq per liter, and the pH 7.47. An echocardiogram (Fig. 3) disclosed marked enlargement of the right ventricle and right atrium, hypertrophy of the right ventricular wall, with systolic flattening of the ventricular septum; and the

hypertrophic left ventricle was displaced posteriorly. A saline contrast echo study showed no right-to-left intracardiac shunting, and contrast material refluxed into the inferior vena cava. $^{99\text{m}}\text{Tc}$ -MAA perfusion lung scan (Fig. 4) disclosed that there was no gross perfusion defect and the perfusion was diffusely decreased except for the posterior portion of the right lower lobe. The diagnostic possibility of pulmonary veno-occlusive disease was seriously considered.

Fig.7. Pulmonary vein obstructed by intimal fibrous tissue. The residual lumen is eccentric and suggestive of organized thrombus. (H. and E., $\times 200$)

Fig.8. Muscular pulmonary artery with medial hypertrophy. (H. and E., $\times 200$)

Oxygen, digoxin, furosemide, and warfarin were administered.

On the 17th hospital day the chest roentgenogram showed some resolution of the interstitial changes and the Kerley B lines. Arterial blood gas analysis (room air) showed that the PaO_2 was 39 mmHg, the PaCO_2 26 mmHg, and the pH 7.50. RI-angiography using $^{99\text{m}}\text{Tc}$ -RBC showed that the pulmonary transit time was markedly

prolonged, the right ventricle and right atrium were enlarged, and the ejection fraction of the right and left ventricle were 0.34 and 0.64 respectively. Myocardial imaging using ^{201}Tl -Cl demonstrated a dilatation of the right ventricle and a prominent uptake of the thallium into the right ventricular myocardium. A $^{99\text{m}}\text{Tc}$ -Sn-colloid liver scintigram showed diffuse uptake in the liver and there was no evidence of cirrhosis.

Fig.9. Lung tissue with thickened interstitial septa. Hemosiderin-laden macrophages are abundant in the alveolar lumen. (H. and E., $\times 200$)

Pulmonary function studies (Table I) showed moderate obstructive ventilatory impairment, markedly decreased carbon monoxide diffusing capacity, and increased closing volume.

On the 25th hospital day a right sided cardiac catheterization was performed. The pulmonary capillary wedge pressure of the right upper, right lower, left upper, and left lower lobe were 5, 5, 8, and 7 mmHg respectively; the pulmonary arterial pressure was 88/33 mmHg with a mean pressure 51 mmHg; the right ventricular pressure 87/12 mmHg; and the right atrial mean pressure 9 mmHg. The cardiac index by direct Fick method was 1.5 L/min/m², and the pulmonary arterial resistance 18.3 unit. Measurement of oxygen saturation showed no evidence of an intracardiac shunt. The administration of 100 per cent oxygen, 15 liters per minutes, by face mask failed to lower the pulmonary arterial resistance and the PaO₂ rose up from 46 to only 76 mmHg. A left pulmonary arteriogram demonstrated that the blood flow was slow, and there was no obstructive lesions not only in the pulmonary arteries but also in the visible large pulmonary veins.

The patient's condition steadily deteriorated and he became bedridden since April. The patient died suddenly on May, 1 when he was defecating. The clinical diagnosis was chronic cor pulmonale due to pulmonary veno-occlusive disease, mild azotemia, benign monoclonal

gammopathy.

Pathological Findings

The heart weighed 460g and showed features consistent with pulmonary hypertension. There was marked dilatation and hypertrophy of the right ventricle, the right ventricular wall thickness being 8 mm; the thickness of the left ventricular wall was 14 mm. The cardiac valves were grossly normal and there was no evidence of congenital heart disease. The foramen ovale was closed. The proximal pulmonary arteries were dilated and atheromatous. The pulmonary veins entered in a normal way and were patent in this area.

The most striking microscopic findings were in the pulmonary veins 2 mm or less in external diameter. Almost all the veins of this size were partially and often completely occluded by intimal fibrous tissue (Fig. 5). This is almost always paucicellular and loose and edematous with only scarce collagenous fibers (Fig. 6). The residual lumens tended to be single and central, but in some, these were eccentric and suggestive of organized thrombi (Fig. 7). The changes in the pulmonary arteries were much more limited as compared to the veins. Although some pulmonary arteries showed concentric medial hypertrophy (Fig. 8), other changes characteristic of primary pulmonary hypertension such as arteritis or plexiform lesions were absent.

In the lung tissue, pulmonary congestion was

not diffuse but limited to some areas. Interstitial septa were thickened and hemosiderin-laden macrophages were abundant in the alveolar lumen of these areas (Fig. 9).

Atherosclerosis of the aorta and its branches, arterio- and arteriolonephrosclerosis of the kidneys, and generalized arteriolosclerosis were the additional findings.

DISCUSSION

It is not common to encounter the clinical cases with pulmonary arterial hypertension of unknown etiology, and these cases are called primary pulmonary hypertension. Pulmonary veno-occlusive disease was first reported by Höra¹ in 1934, but Heath et al² were the first to recognize that the histological features in the lung were distinctive and that the condition should be separated from the main group of patients with classical primary pulmonary hypertension and be referred to as "pulmonary veno-occlusive disease". In 1973, World Health Organization (WHO)³ held a conference to deal with primary pulmonary hypertension and subdivided this into three pathologic categories, namely, 1) recurrent pulmonary embolism, 2) plexogenic pulmonary arteriopathy, and 3) pulmonary veno-occlusive disease.

Pulmonary veno-occlusive disease is a rare disease, but its reported incidence is apparently increasing. Before 1960, pulmonary veno-occlusive disease was virtually unknown. Up to 1970, a total of ten cases had been reported in detail, and now this number has risen to more than 75.⁴ There are only three reported cases of pulmonary veno-occlusive disease in Japan⁵⁻⁷ and this is a fourth one in full detail with pathological findings.

Pulmonary veno-occlusive disease was formerly believed to affect predominantly children and young adults,⁸ but the recent report⁴ showed that all age groups appear susceptible. The youngest is only 8 weeks old, and even intrauterine origin is presumed in this case.⁹ The oldest patient hitherto reported was 67-year-old woman.¹⁰ Hence, our patient, being 75 years old, is the oldest patient ever reported. There is no reported sex difference in pulmonary veno-occlusive disease.

The characteristic clinical features of pulmonary veno-occlusive disease are, as Heath et al² stated, symptoms and signs of postcapillary pulmonary hypertension, evidence of diffuse

interstitial edema on chest roentgenogram, absence of structural cardiac abnormality, arterial hypoxemia, and usually, normal pulmonary arterial wedge pressure.

The chest roentgenogram give an important clue to a diagnosis of pulmonary veno-occlusive disease in cases with pulmonary hypertension of unknown etiology.¹¹ Signs of pulmonary edema with bilateral increased interstitial markings and Kerley B lines are regularly present. There is increased vascular markings, but the large pulmonary veins are not prominent as they are in the mitral valve disease.¹²

Cardiac catheterization demonstrates severe pulmonary hypertension and, in most of the cases, a normal pulmonary arterial wedge pressure. Carrington and Liebow¹³ explained the seeming paradox of low wedge pressure and pulmonary edema in these instances as a result of the partial blockage of pulmonary and collateral bronchial venules, leading to a gradual fall of capillary pressure, after the inflow through the pulmonary artery has been interrupted by the wedged catheter. When the obstruction of the pulmonary venous outflow is located more distally, as in some cases did,^{14,15} the wedge pressure is high because the pulmonary veins will receive a flow from adjacent areas supplied by arteries not blocked by the catheter.

A few reported results of pulmonary function studies^{2,16,17} varies from case to case, but some of them showed decreased vital capacity, and this might be explained by the stiff, poorly compliant congestive lungs as can be seen in mitral stenosis.¹⁸ Severe hypoxemia is a common feature of pulmonary veno-occlusive disease, and this might be explained by the increased intrapulmonary shunt or shunt-like effect. This hypoxemia is also a clue to a diagnosis because hypoxemia is usually not so severe in classical primary pulmonary hypertension¹⁹ except for cases associated with patent foramen ovale with right-to-left shunting.

The characteristic morphologic findings in pulmonary veno-occlusive disease are, as its name implies, in the smaller pulmonary veins and venules.⁸ Many veins and venules exhibit narrowing or even complete occlusion by thrombotic, fibrous tissue. In some cases, however, the main site of obstruction were at the larger pulmonary veins.^{11,14} There may be medial hypertrophy or so-called arterialization in these veins as an adaptation to an increased pressure. Secondary changes may involve any portion of the pulmo-

nary vasculature proximal to the level of the pulmonary veins.⁸

The etiology of pulmonary veno-occlusive disease is unknown, but there is a consensus in the belief that the condition is an acquired one and that the occlusion of the veins and venules is thrombotic in origin. So far, an infections, presumably viral origin figures high on the list of etiologic possibilities, but the problem is far from solved.¹¹ Two case reports^{20,21} suggest a possible relation to connective tissue disease. It is interesting that monoclonal gammopathy was present in our case, although other immunological studies were negative.

Prognosis of pulmonary veno-occlusive disease is generally very poor, and there is no definitive therapy. In one reported case,²⁰ azathiopurine was used with steroid when pulmonary veno-occlusive disease was associated with some unidentified rheumatoid vasculitis with a good response.

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