Pulmonary veno-occlusive disease: diagnosis during life in four patients

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Abstract

Pulmonary veno-occlusive disease is a rare form of primary pulmonary hypertension of unknown aetiology. Four cases were diagnosed in young patients. The diagnosis was suspected on the basis of clinical, radiological, echocardiographic, and catheter evidence and confirmed by taking a lung biopsy sample. In all patients the histology showed obstruction of the pulmonary veins by intimal fibrosis. The clinical course of all patients has been one of progressive deterioration. Although there is no specific treatment for this disease, to establish the diagnosis during life is of great importance in overall clinical management, including counselling the patient and family.

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Pulmonary veno-occlusive disease is an uncommon disorder characterised by pulmonary hypertension secondary to progressive obstruction of the pulmonary veins and venules.¹ Approximately 100 cases have been reported in detail and the clinical diagnosis has not often been made during life.² Four patients with this disease who were managed at our hospital during the past 18 years are presented in chronological order. They were all diagnosed during life and illustrate varied presentations, use of investigative modalities, and natural history.

Case reports

CASE 1

A seven year old boy presented in 1973 with a four month history of increasingly frequent recurrent episodes of acute dyspnoea, sweating, and abdominal pain. These episodes usually lasted about one hour and settled spontaneously. He had mild asthma as an infant but was without symptoms for the previous three years.

On clinical examination he was a healthy boy without cyanosis who had neither tachycardia nor tachypnoea at rest. He was hypertensive with a blood pressure of 150/80 mm Hg. A right ventricular heave was present. Cardiac auscultation showed an accentuated pulmonary component of the second heart sound but no murmurs, and normal breath sounds were heard on auscultation of his chest. Chest radiography showed a normal cardiac outline but pulmonary changes were consistent with acute pulmonary oedema (fig 1).

The patient underwent cardiac catheterisation. These original records were not available for review, but the haemodynamic findings were interpreted as being 'consistent with a left atrial lesion', whereas angiography showed normal cardiac anatomy. As a result of these apparent inconsistencies, surgical exploration of the right and left atria was performed. This showed the presence of four normal pulmonary veins and confirmed normal cardiac anatomy. During the operation the pulmonary artery peak systolic pressure was 50 mm Hg and the mean pulmonary

Figure 1 (A) Chest radiograph of case 1 taken at the age of 8 years, showing normal cardiothoracic ratio, prominent main pulmonary artery, and pulmonary oedema. (B) Chest radiograph of the same patient taken 15 months later, showing progressive radiological changes.

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venous pressure was 4 mm Hg. In view of these findings, a lung biopsy sample was taken and the diagnosis of pulmonary veno-occlusive disease confirmed histologically.

He recovered well after the operation but the subsequent course of his illness was progressive deterioration with intermittent hospital admissions. He was treated with digoxin, frusemide, warfarin, and with oxygen at home. This regimen did not significantly alter the course of his illness, however, and he finally died 18 months after the onset of symptoms. Permission for a necropsy was refused.

CASE 2

A 17 year old presented in 1979 with an eight week history of malaise and progressive exertional dyspnoea which followed an acute febrile illness. She was referred for further investigation as she was observed to become cyanosed and dyspnoeic after minimal exertion. The only relevant past history was an episode of encephalitis following infectious mononucleosis at the age of 9 years. She had not taken any drugs.

Clinically, she was a healthy girl without resting cyanosis. On palpation there was a right ventricular heave. Cardiac auscultation showed an accentuated pulmonary second heart sound, tricuspid regurgitation, and pulmonary regurgitation. Her breath sounds were vesicular and the remainder of the physical examination was normal. The electrocardiograph showed sinus rhythm, right atrial, and right ventricular hypertrophy, and chest radiography showed prominent pulmonary arteries, increased reticular markings, and Kerly B lines, with a normal cardiac outline.

Arterial blood gas analysis confirmed the presence of hypoxaemia (oxygen partial pressure 52 mm Hg) and respiratory function testing showed the presence of a restrictive defect. Echocardiography showed right ventricular hypertrophy but no other cardiac disease. At cardiac catheterisation there was severe pulmonary hypertension (pulmonary artery phasic pressure of 65/40 mm Hg with a mean of 50 mm Hg) and the pulmonary arterial wedged pressure was 15 mm Hg. Angiography showed dilated pulmonary arteries with normal venous return to the left atrium, though blood flow in the pulmonary circulation was considered to be slow. All other investigations including viral serology, rheumatoid factor, and antinuclear factors were normal.

On the basis of this information the diagnosis of pulmonary veno-occlusive disease was suggested and an open lung biopsy sample was taken. At the operation the lung appeared macroscopically normal, but the histology of tissue from the right middle lobe confirmed the diagnosis of pulmonary veno-occlusive disease.

After the operation she was treated with oxygen, a heparin infusion, prednisone, azathioprine, digoxin, and frusemide (Lasix, Hoechst). Her respiratory function deteriorated rapidly despite this treatment and she died three months after the onset of symptoms. Permission for necropsy was refused.

CASE 3

An 11 year old girl with dysmorphic features, developmental delay, and cardiac abnormalities was admitted in early 1991 for investigation of increasing dyspnoea. She had developed asthma at the age of 5 years and, apart from intermittent exacerbations of her asthma, remained well until the age of 9 years. At this time she developed exertional dyspnoea which progressed slowly over the next two years, by which time she became dyspnoeic at rest.

She had congenital heart disease consisting of coarctation of the aorta, bicuspid aortic valve, and subaortic membrane. The coarctation was originally repaired at the age of 6 months. At the age of 5 years, the coarctation was revised and a subaortic membrane was resected. She also had some dysmorphic features including short stature, mid facial hypoplasia, prominent nasal bridge, deep set eyes, small hands, and clinodactyly of the fifth finger, which had not been classified into any syndrome. Chromosomal analysis was normal.

On examination she was not cyanosed at rest. Her respiratory rate was 50 per minute. The pulmonary component of the second heart sound was loud and there was a grade 2/6 ejection murmur in the pulmonary area. Auscultation of the chest showed fine basal inspiratory crackles. The electrocardiogram showed sinus rhythm and RSR in lead V1, whereas on chest radiography there was mild cardiomegaly, bilateral perihilar changes, and diffusely increased reticular markings.

Echocardiography excluded left sided cardiac lesions and pulmonary vein ostial stenosis as a cause for the respiratory symptoms. She had had a recent left heart catheter study, but not a right heart study because of venous access problems. As no important cardiac disease could be shown it was felt that a lung biopsy sample should be taken to exclude interstitial lung disease. At the operation the right middle and lower lobes were grossly abnormal with scarring and reddened discoloration. Pulmonary veno-occlusive disease was diagnosed histologically. The findings were typical of the disease with the small veins affected by 'fluffy' myxomatous intimal proliferation. There was no evidence of thrombosis.

On review nine months later, the child was tachypnoeic at rest and becoming increasingly tired and dyspnoeic with exertion. She required oxygen treatment and drug treatment with frusemide, nifedipine, salbutamol (Ventolin, Allen and Hanburys), and beclomethasone dipropionate (Becotide, Allen and Hanburys).

CASE 4

A 5 month old baby presented in 1991 with a two day history of irritability, poor feeding, and tachypnoea. He had been previously well with no past history of cardiac or respiratory symptoms, though there have been a history of poor weight gain.

The child was peripherally shut down on admission. He had small volume peripheral pulses and a right ventricular heave. His heart sounds were normal and a soft systolic murmur was audible at the lower right sternal edge. Fine

inspiratory crackles were heard throughout both lung fields. He had marked hepatomegaly. The electrocardiograph showed sinus rhythm, a normal axis, right atrial hypertrophy, and right ventricular hypertrophy, whereas severe pulmonary oedema with a normal sized heart was seen on chest radiography.

Echocardiography showed a grossly dilated hypertrophied right ventricle with flattening of the left ventricle. On Doppler examination there was marked tricuspid regurgitation with a calculated right ventricular systolic pressure of approximately 150 mm Hg. There was no right ventricular outflow tract or pulmonary arterial obstruction. Careful Doppler interrogation of the left atrium detected turbulent flow which could be traced into the pulmonary veins, suggesting obstruction within the pulmonary venous tree. After being ventilated he underwent cardiac catheterisation to distinguish between pulmonary vein ostial stenosis and pulmonary veno-occlusive disease. The pulmonary artery pressure was 120/70 mm Hg (mean 95 mm Hg) and the mean right and left pulmonary arterial wedged pressures were 23 and 17 mm Hg respectively. Directly measured peripheral pulmonary venous mean pressures measured in different areas of the right and left lungs ranged from 36 to 46 mm Hg. The left atrial pressure was normal. Angiography by direct injection of contrast into pulmonary veins showed multiple areas of narrowing within both lungs. The veins in their extrapulmonary course were angiographically normal. The areas of pulmonary venous obstruction so defined corresponded with the sites of marked stasis of antegrade flow.

Pulmonary veno-occlusive disease was diagnosed on the basis of these findings. After careful discussion of the prognosis of this disease with the parents, ventilatory support was withdrawn and the child died shortly afterwards. Necropsy was performed and this confirmed the diagnosis of pulmonary veno-occlusive disease with multiple acute pulmonary infarcts.

Histology

The histopathological changes common to all four patients consisted of patchy eccentric myxomatous intimal fibrosis of small pulmonary veins (fig 2). There was also dilatation of septal

Figure 2 Histology of pulmonary veno-occlusive disease in case 1. An irregular proliferation of intimal fibrous tissue (F) partially occludes the lumen of this venule (elastin Van Gieson stain $\times 300$).

Figure 3 Histology of biopsy sample from case 3. Pulmonary lobules (L) are separated by widened interlobular septa (S) producing a 'jigsaw puzzle' appearance of the lung. Septal lymphatics (arrowheads) appear dilated (haematoxylin and eosin stain $\times 70$).

lymphatics and variable haemosiderin accumulation in the alveolar septa.

The first three patients showed fibrosis of alveolar and interlobular septa giving a 'jigsaw puzzle' appearance to histological sections (fig 3).

Cases 1, 2, and 4 showed multiple lumina in small pulmonary veins, suggesting recanalisation following organisation of thrombi. Actual venous thrombus was only seen in case 4. Small veins in case 3 showed 'arterialisation' with twin elastic lamellae seen on elastin stains. Small pulmonary arteries were normal in this patient but showed grade 1 pulmonary hypertensive changes in the others.

Discussion

Pulmonary veno-occlusive disease is a rare form of primary pulmonary hypertension of unknown aetiology. Approximately 100 cases have been reported and about one third have occurred in children with an equal distribution between the sexes.³ Most patients have been diagnosed at necropsy on typical histological findings. The disease is now characterised well enough to allow an earlier diagnosis. Patients usually present with a history of progressive dyspnoea. They have signs consistent with pulmonary hypertension, including a right ventricular heave and a loud pulmonary heart sound. Inspiratory crackles which are a result of pulmonary congestion are often audible on auscultation of the chest. The chest radiographs shows a prominent right ventricle, dilated pulmonary arteries, and Kerly B lines. Electrocardiographic abnormalities include right axis deviation and right ventricular hypertrophy. Echocardiography will usually show evidence of increased right systolic heart pressure such as right ventricular hypertrophy or systolic compression of the left ventricle, and will exclude left sided obstructive lesions such as pulmonary vein stenosis, cor triatriatum and mitral stenosis. The haemodynamic findings with cardiac catheterisation are pulmonary hypertension with increased right ventricular and pulmonary artery pressures. In pulmonary veno-occlusive disease pulmonary capillary wedge pressure has been reported to be normal or increased.³ Where there is widespread disease of the pulmonary veins, however, the wedge pressure may be

considerably increased, as in case 4, and selective direct measurement of pulmonary venous pressures will show high intrapulmonary venous pressures. The left atrial pressure is normal. Although this constellation of findings is highly suggestive of pulmonary veno-occlusive disease, the definitive diagnosis can be made by taking an open lung biopsy specimen. The main diagnostic microscopic feature of pulmonary veno-occlusive disease is obstruction of the pulmonary veins and venules by intimal fibrosis consisting of loose myxoid connective tissue, often with intravascular fibrous septa thought to result from recanalisation of thrombi.²⁻⁴

Lung histology in cases of primary pulmonary hypertension has been classified into three pathological types.⁵ These are (a) plexogenic pulmonary arteriopathy, (b) recurrent pulmonary thromboemboli, and (c) pulmonary veno-occlusive disease. The histology described in our cases of pulmonary veno-occlusive disease are distinct from the other types. In plexogenic pulmonary arteriopathy the disease is in the muscular pulmonary arteries and arterioles with medial hypertrophy and intimal cellular proliferation. In thromboembolic pulmonary hypertension obstructive lesions of thrombi in various stages of organisation are present in the muscular pulmonary arteries and arterioles. These were not the changes seen in our patients.

It is thought that pulmonary veno-occlusive disease represents a syndrome rather than a single aetiological entity, though a common pathogenesis, probably thrombosis, is likely. It has been suggested that a primary disturbance of the vascular wall of pulmonary veins and arteries may result in the formation of intravascular thrombi. Various aetiological agents have been associated with this process. Respiratory infections, usually viral in nature, have been implicated⁶ and some workers have shown immune complexes resulting from such infections in the vascular tissue.⁷ This suggests the possibility of a pathological immune response to a viral infection. A genetic predisposition has been proposed because of case reports of the disease occurring in siblings.⁸⁻⁹ A toxic aetiology has been implicated with reports of veno-occlusive disease occurring following the administration of chemotherapeutic drugs¹⁰⁻¹¹ and inhalation of a toxic substance.¹²

Cases 1 and 4 had no relevant past history which would suggest an aetiology for their illness. The fact that case 4 occurred at such a young age, however, raises the question of a congenital pathological process. The onset of pulmonary veno-occlusive disease in case 2 followed an acute febrile illness and although no organism was isolated, the possibility of a viral infection remains. Case 3 developed this disease in association with a history of congenital heart disease and asthma. The latter was associated with genuine clinical bronchospasm and occurred intermittently before and after the other diagnosis was made. In this instance (and in others) it was essential to exclude obstructive lesions of the left heart.¹³ Having clearly done this, an open lung biopsy sample was taken, allowing the diagnosis of pulmonary veno-occlusive disease to be made.

Regardless of the aetiology, pulmonary veno-occlusive disease is fatal in most patients within two years of the onset of symptoms due to progressive pulmonary hypertension with right ventricular failure. Treatment with anticoagulants has not been successful¹⁴ but there have been reports of patients responding to azathioprine.¹⁵ Similarly, there have been isolated reports of prolonged survival with the use of calcium antagonist¹ and vasodilators such as prazosin.³ None of the three patients reported in this paper who received treatment appeared to respond to the treatment. In particular, case 2 followed a rapidly progressive course despite the use of intravenous heparin anticoagulation, high doses of corticosteroids, and azathioprine. Treatment with nifedipine was started in case 3 but no direct measurement of pulmonary resistance was performed to assess the effect. No drug treatment was started in case 4 because of the advanced stage of the disease process.

The four cases reported here further show the varied clinical course of this disease in children. These patients presented over a period of 18 years, and all were diagnosed while still alive. As detailed in the case discussion, diagnostic methods have evolved with progress in medical technology. When investigative information indicates obstruction within the lungs, probably at the level of the pulmonary veins, a lung biopsy sample will provide the definitive diagnosis. This applied in the first three patients, but was not felt to be necessary in case 4 where haemodynamic and angiographic data were conclusive in showing widespread intrapulmonary venous disease. Although there has been no effective treatment for pulmonary veno-occlusive disease, to establish the diagnosis during life is of great importance in overall clinical management, including counselling the patient and family. Consideration can now be given to heart-lung or lung transplantation.

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