Pulmonary veno-occlusive disease

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Two distinct pathological entities may be associated with the clinical picture of 'primary pulmonary hypertension'. In the classical form the brunt of the pathology falls upon the pulmonary arteries with the characteristic development of dilatation lesions and necrotizing arteritis. In the second rarer type the pulmonary veins appear to be primarily involved. This paper describes the clinical and pathological features of such a case of 'pulmonary veno-occlusive disease' occurring in a young girl.

Recently there has been a reawakening of interest in the pathology of 'primary pulmonary hypertension' following the epidemic of the disease in Germany, Austria, and Switzerland ascribed to the ingestion of the slimming drug Aminorex (Kay, Smith, and Heath, 1971). It has been suspected for many years that 'primary pulmonary hypertension' represents a heterogeneous group of diseases of diverse aetiology (Wade and Ball, 1957) and it has now become clear that two distinct pathological entities may be associated with the clinical picture of unexplained pulmonary hypertension. In the classical form of the disease there are dilatation lesions and necrotizing arteritis (Wagenvoort, Heath, and Edwards, 1964). In the rarer form called pulmonary veno-occlusive disease, the brunt of the disease falls initially on the pulmonary veins and venules, and leads only secondarily to effects on the pulmonary arteries and lung parenchyma. There have been few descriptions of pulmonary veno-occlusive disease and we add this further case report to describe its clinical and pathological features.

CASE REPORT

A female child was born on 22 March, 1963 following a full-term pregnancy and a normal delivery. She weighed 6 lb 12 oz (3.06 kg) at birth and was healthy during the neonatal period. At the age of 3½ years a cold and cough with pyrexia led to her admission to hospital on 6 November 1966 with a diagnosis of bronchiolitis. This was treated with tetracycline. The first chest radiograph was taken at this time (Fig. 1). Recovery was uneventful.

Her cough persisted and she did not gain weight satisfactorily. When seen on 27 April, 1968 there were rhonchi and crepitations throughout both lungs. A radiograph of the chest showed enlargement of the left atrium and a prominent pulmonary conus. There appeared to be increased vascularity of the lungs.

On 17 May 1968 she developed acute appendicitis and the appendix was removed. Her cough persisted and on 23 August 1968 she was admitted to hospital with basal bronchopneumonia.

On 18 October 1968 she was found to have enlargement of the heart and liver and was admitted to hospital once again. On examination she was found to be dyspnoeic and slightly cyanosed. There was no clubbing of the fingers. The jugular venous pressure was raised and the liver was enlarged but there was no pitting oedema of the ankles. The heart was enlarged, the apex beat being palpated one inch (25.4 mm) outside the left nipple line. A right ventricular heave was present. The second sound in the pulmonary area was loud, single, and palpable. No cardiac murmurs were heard.

The electrocardiogram showed right axis deviation and evidence of hypertrophy of both atria and of the right ventricle. As a result of this examination it was concluded that the child had congestive cardiac failure secondary to pulmonary hypertension. It was hoped that the aetiology of this would be indicated by the data obtained from cardiac catheterization.

This investigation was carried out on 15 November 1968 and the levels of percentage blood oxygen saturation and blood pressure in the right cardiac chambers and the femoral artery are shown in the Table. These studies showed that the child had moderate pulmonary hypertension, with no evidence of a left-to-right shunt, and arterial hypoxia corrected by breathing oxygen.

Angiocardiography was performed. Dye was injected into the right ventricle and showed this chamber to be hypertrophied and trabeculated with a small cavity. The pulmonary artery was enlarged. The arterial branches to the lower lobes were of small calibre. The dye returned normally to the left atrium which was enlarged. There was a hold-up of dye at the mitral valve. The left ventricle and aorta were small in size.

Following this investigation the diagnosis remained as pulmonary hypertension of unknown aetiology. The enlargement of the left atrium raised the possi-

TABLE
 DATA FROM CARDIAC CATHETERIZATION

Site	Blood O ₂ Saturation %	Pulmonary Arterial Pressure (mmHg)	
		Systolic	Diastolic
IVC	48	..	..
SVC	51	..	..
MRA	46	12	2
MRV	51	70	0
PT	51	70	35
FA	83	100	50
FA	(breathing air)	..	..
	97 (breathing O ₂)		

IVC=inferior vena cava; SVC=superior vena cava; MRA=mid right atrium; MRV=mid right ventricle; PT=pulmonary trunk; FA=femoral artery.

bility of a lesion of the mitral valve, although there was no murmur suggestive of this. The gradient across the mitral valve was measured through a bronchoscope and showed the blood pressure in the left atrium to be 20/15 mmHg and that in the left ventricle to be 90/0 mmHg. Since the left atrial pressure was raised it was decided to explore this

chamber. A chest radiograph taken before the operation is shown (Fig. 2).

Operation on cardiopulmonary bypass was performed on 4 February 1969. The left atrium was found to be dilated, hypertrophied, and tense. An increased blood pressure in this chamber was confirmed. There was no thrill over the mitral valve. On opening the left atrium no diaphragm was seen and the mitral valve was normal. There was a normal venous return. No atrial tumour was present. The patient was discharged from hospital on 31 March 1969.

The girl remained in uncontrolled congestive cardiac failure and her condition gradually deteriorated. She was admitted to hospital in extremis on 11 August 1969 and died a few hours after admission. The diagnosis at the time of death was unexplained pulmonary hypertension.

GROSS EXAMINATION OF HEART At necropsy the heart showed features consistent with pulmonary hypertension. There was dilatation and hypertrophy of the right atrium and ventricle, the right ventricular infundibular thickness being 7 mm. The main pulmonary arteries were dilated and

FIG. 1. Chest radiograph taken on 8 November 1966 shows evidence of pulmonary venous congestion and enlargement of the pulmonary artery. At that time the child had clinical evidence of bronchiolitis.

FIG. 2. Chest radiograph taken on 17 January 1969. There is cardiac enlargement with an increase in size of the right atrium and pulmonary artery.

atheromatous. The cardiac valves were normal and there was no evidence of congenital heart disease. The left atrium was dilated and hypertrophied. The left ventricular thickness was 15 mm. The heart was not weighed as it was preserved intact with attached lungs as a museum specimen. No primary disease of the lung parenchyma was found. The pulmonary arteries appeared thick-walled.

PULMONARY VASCULAR PATHOLOGY There were prominent histological changes affecting the pulmonary veins (Figs 3 to 5), the pulmonary arteries (Figs 7 to 9), and the lung parenchyma (Figs 10 to 15).

Pronounced focal intimal thickening was seen in the major pulmonary veins. The areas of thickening contained numerous wisps of elastic tissue and as a result gave a predominantly grey-staining reaction in contrast to the bright red of the collagen of the underlying venous media. The thickness of the intimal proliferation exceeded that of the media of the vein. The media was unaffected and consisted of smooth muscle, collagen, and

elastic fibrils packed together in longitudinal, circular, and oblique directions.

Many of the pulmonary veins were blocked by loose connective tissue which gave a faint staining reaction for collagen with van Gieson's stain (Figs 3 and 4). Some veins were totally occluded by this intimal proliferation but in others there were channels suggestive of recanalization of thrombi (Figs 3 and 4). All classes of pulmonary vein from large vessels down to small venules of immediate post-capillary size were involved in the occlusive process (Fig. 5).

The 'muscular pulmonary arteries' (0.1 to 1.0 mm in diameter) showed gross medial hypertrophy with crenation of elastic laminae (Fig. 6). There was slight intimal proliferation in these hypertrophied vessels, the proliferated tissue giving only a faint staining reaction for collagen. Some of the muscular pulmonary arteries showed fibrinoid necrosis of the media which was swollen (Fig. 7). The media and elastic laminae in the necrotic arteries gave poor staining reactions (Fig. 7). The media was infiltrated by cellular fibro-

FIG. 3. Longitudinal section of pulmonary vein showing blockage by loose cellular fibrous tissue. A central channel surrounded by condensed collagenous tissue runs a tortuous course through the lumen of the vein and has been sectioned in various planes (Elastic-van Gieson $\times 150$).

FIG. 4. Small pulmonary vein almost occluded by loose cellular fibrous tissue. There is a small patent central channel and this is lined by plump fusiform cells (Elastic-van Gieson $\times 345$).

FIG. 5. *Transverse section of pulmonary venule showing partial blockage of the lumen by loose cellular connective tissue not giving a positive staining reaction for collagen (Elastic-van Gieson $\times 600$).*

FIG. 6. *Transverse section of muscular pulmonary artery showing pronounced medial hypertrophy and a cellular intimal proliferation (Elastic-van Gieson $\times 375$).*

blastic tissue in places and there was thrombosis in many of the necrotic arteries. The intravascular thrombi showed early organization by cellular fibroblastic tissue not giving a positive reaction with van Gieson's stain. A few small muscular pulmonary arteries with extensive infiltration of the media by fibroblasts and occlusion of the lumen by the same tissue showed thin-walled branches filled with the same plump, pale-staining cells (Fig. 8). The appearances were reminiscent of plexiform lesions but with the associated fibroblastic infiltration of the media it is difficult to be certain of this.

The pulmonary arterioles, most less than 80 μ in external diameter, were abnormal and hypertensive in type comprising a distinct media of circularly orientated smooth muscle bounded by internal and external elastic laminae (Fig. 9). (The normal pulmonary arteriole has a wall consisting of a single elastic lamina.)

There was striking focal dilatation of pulmonary capillaries (Fig. 10) through which diapedesis of erythrocytes had occurred to give rise to pulmonary haemosiderosis, consisting of focal collections of haemosiderin-laden macrophages. There was

great fibrous thickening of the alveolar walls to give rise to the appearances of fibrosing alveolitis or interstitial pulmonary fibrosis (Fig. 11). The alveolar spaces were lined by prominent alveolar cells having the appearance of granular pneumocytes (Fig. 11). Some of the alveoli were filled with granular pneumocytes some of which contained a brown pigment not giving the staining reactions of ferric iron (Fig. 12). A few multinucleated giant cells were present (Fig. 13) these probably having been formed by fusion of granular pneumocytes.

Lymphatic vessels in the connective tissue septa were dilated (Fig. 14). In places there was early osseous metaplasia in the lung parenchyma (Fig. 15). Foci of lymphocytes were present mainly around small bronchi and bronchioles.

The pulmonary trunk was abnormally thick, the ratio of the thickness of the media of the pulmonary trunk to that of the aorta being 0.95. The elastic tissue pattern of the aorta was normal consisting of uniform, unbranched elastic fibrils. The configuration of the elastica of the pulmonary trunk was reminiscent but distinguishable from that of the aorta, consisting of uniform un-

FIG. 7. Tortuous muscular pulmonary artery cut in two planes. The vessel shows subacute necrotizing arteritis with swelling of the media which is infiltrated by fibroblastic tissue. In places the elastic laminae are thinned and there is disruption of the media. There is occlusion of the lumen by cellular fibrous tissue (Elastic-van Gieson $\times 240$).

FIG. 8. Transverse section of a muscular pulmonary artery showing medial hypertrophy and occlusion of the lumen by cellular tissue. To the right is a thin-walled branch showing pronounced proliferation of endothelial cells reminiscent of a dilatation lesion (Elastic-van Gieson $\times 360$).

FIG. 9. Transverse section of pulmonary arteriole showing the formation of a distinct media of muscle bounded by internal and external elastic laminae (Elastic-van Gieson $\times 600$).

FIG. 10. *Focal dilatation of pulmonary capillaries in the alveolar walls (Haematoxylin and eosin $\times 375$).*

FIG. 11. *Section of lung parenchyma showing interstitial pulmonary fibrosis. The alveolar walls are thickened by fibrous tissue. Granular pneumocytes are present in the alveolar spaces (H. and E. $\times 285$).*

FIG. 12. A syncytial collection of granular pneumocytes within an alveolar space (H. and E. $\times 375$).

FIG. 13. Giant cell within an alveolar space which has probably formed by fusion of granular pneumocytes (H. and E. $\times 600$).

FIG. 14. *Dilated lymphatics in fibrous septum of lung (H. and E. $\times 150$).*

FIG. 15. *Early osseous metaplasia in lung parenchyma (H. and E. $\times 300$).*

branched elastic fibrils with thinner connecting fibrils. This pattern is very similar to that described as the 'persistent configuration' by Saldaña and Arias-Stella (1963).

DISCUSSION

This child had the clinical, electrocardiographic, and radiological features of pulmonary arterial hypertension and this was confirmed at cardiac catheterization. There was no clinical evidence of any acquired or congenital abnormality of the heart to account for the raised pulmonary arterial pressure. In particular no intracardiac shunts were demonstrated by angiocardigraphy. There was no evidence of a primary lung disease likely to give rise to pulmonary hypertension apart from a history of previous chest infection. In essence the clinical picture was that of 'primary pulmonary hypertension' apart from the fact that the left atrial blood pressure was 20/15 mmHg. This finding led to the performance of a thoracotomy with surgical exploration of the mitral valve and left atrium which proved to be dilated and hypertrophied.

The finding of a raised left atrial pressure was not considered to be consistent with a diagnosis of classical primary pulmonary hypertension and this conclusion was supported by the histopathology of the lung. At necropsy there was no cardiac disease to account for the raised pulmonary arterial pressure but the histological features in the lung were characteristic of pulmonary veno-occlusive disease.

In a recent article on the subject, Brown and Harrison (1966) summarized their own case and those previously reported (Höra, 1934; Mallory, 1937; Grainger, 1958; Crane and Grimes, 1960; Brewer and Humphreys, 1960; Bürki, 1963; Stovin and Mitchinson, 1965; Heath, Segel, and Bishop, 1966). Their table shows that in all the reported cases the brunt of the pathology falls on the pulmonary veins with venous intimal fibrosis. In the majority of cases there has been thrombosis and recanalization in pulmonary veins.

We have been impressed by the similarity of the histopathological findings in the reported cases and especially in those described by Brewer and Humphreys (1960), Stovin and Mitchinson (1965), Heath *et al.* (1966), and Brown and Harrison (1966).

There are pronounced secondary changes in the pulmonary arterial tree and, as we have shown in this case, these may proceed beyond medial hypertrophy and intimal proliferation to subacute

necrotizing arteritis (Fig. 7). There is muscularization of the pulmonary arterioles.

The changes in the lung parenchyma are remarkably uniform. The central feature of the pathology is interstitial pulmonary fibrosis. It may be that such thickening of the alveolar walls is a result of repeated pulmonary infections such as occurred in this case and that this leads to fibrous occlusion of the pulmonary veins with predisposing thrombosis. An alternative view is that the venous lesions of unknown aetiology are primary and lead to chronic oedema of the alveolar walls, as in mitral stenosis, with the development of interstitial pulmonary fibrosis.

All the other histological changes noted are those known to be characteristic of chronic pulmonary venous hypertension (Wagenvoort *et al.*, 1964). These include dilatation of pulmonary lymphatics (Fig. 14), focal dilatation of pulmonary capillaries (Fig. 10), osseous metaplasia (Fig. 15), the proliferation of granular pneumocytes (Fig. 12), and hyperplasia of mast cells.

The unusual finding in the case we report here is the left atrial hypertension. In a previous case reported by one of us (Heath *et al.*, 1966), as in the patient reported by Grainger (1958), the pulmonary arterial wedge pressure was normal. In the case reported by Stovin and Mitchinson (1965) the pulmonary wedge pressure was raised, although direct measurement of the blood pressure in the left superior pulmonary vein at thoracotomy showed it to be normal. Brown and Harrison (1966) consider pulmonary veno-occlusive disease to be a syndrome of hypertension in the pulmonary arteries and capillaries but not in the pulmonary veins because the obstruction lies at the level of the pulmonary venules. This interpretation is certainly consistent with the pathological findings. We find it difficult to explain the left atrial hypertension in our present case.

The clinical features of the disease relate closely to the histopathology. The interstitial pulmonary fibrosis produces dyspnoea on exertion and some patients become cyanosed. The changes in the pulmonary arterial tree are associated with a raised pulmonary arterial pressure which gives rise to the well-known clinical signs of pulmonary hypertension and eventually to congestive cardiac failure. The electrocardiographic features of hypertrophy of the right atrium and ventricle appear. So too do the radiological features of right ventricular hypertrophy and enlargement of the pulmonary conus and main pulmonary arteries due to pulmonary hypertension.

Radiology is important in the differential diagnosis of pulmonary veno-occlusive disease from classical primary pulmonary hypertension, as pointed out by Brown and Harrison (1966). In primary pulmonary hypertension the peripheral lungfields are oligoemic but in pulmonary veno-occlusive disease there is pulmonary oedema and basal horizontal lines due to oedema of connective tissue septa.

The aetiology of the disease is unknown. In the present case there was a history of repeated attacks of bronchitis and chest infection. In the case of Brewer and Humphreys (1960) there was a history of a previous attack resembling influenza. Stovin and Mitchinson (1965) suggested that their patient had toxoplasmosis at the time of onset of the disease.

Whatever the aetiology of this condition proves to be, there is no doubt that it should be separated from cases of classical primary pulmonary hypertension on the grounds of its histopathology with pronounced involvement of the pulmonary veins and alveolar walls. Unlike classical primary pulmonary hypertension it occurs as commonly in the male as in the female. Furthermore, it may occur in childhood as in the case reported here and in the cases of Grainger (1958) and Crane and Grimes (1960) and in patients up to 48 years of age as in the case of Höra (1934).

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