NECROTIZING PULMONARY ARTERIOPATHY ASSOCIATED WITH PULMONARY HYPERTENSION*

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The occurrence of pulmonary arteriosclerosis and arteriolosclerosis has long been recognized. Such structural changes in the pulmonary vasculature have usually been considered to represent an adaptation to alterations in the haemodynamics of the lesser circulation. In particular, their presence has been related to pulmonary hypertension, and they have been compared to the changes which occur in the systemic vasculature in association with hypertension of the major circulation. It is interesting that there does not appear to be a pulmonary arteriolar counterpart of the hyaline sclerosis of the smaller systemic arterioles which is so characteristic of "essential" systemic hypertension; the explanation of the non-occurrence of this type of hypertensive arteriolar change in the pulmonary vasculature is probably to be found in the structural differences which exist between pulmonary and systemic arterioles.

There are remarkably few published observations concerning the association of pulmonary hypertension with necrotizing pulmonary arteriolar lesions which might be considered to be analogous to the necrosis of systemic arterioles seen in cases of malignant systemic hypertension. Parker and Weiss (1936) studied the lungs in a series of cases of mitral stenosis. In five of these cases in which there was clinical and morbid anatomical evidence of severe embarrassment of the pulmonary circulation they observed necrotizing pulmonary arteriolitis in addition to hyperplastic arteriolosclerosis. They stressed the similarity between these structural changes in the pulmonary arterioles and those which are found in renal arterioles in cases of malignant systemic hypertension. Desclin and Gepts described a similar case in which mitral stenosis was associated with arteriolosclerosis and arteriolitis affecting only the pulmonary vessels; they likened the arteriolitis to polyarteritis nodosa, and suggested that the various vascular changes corresponded to the conditions grouped by Rössle (1933) as the rheumatoid affections of blood vessels.

Only two cases have been reported in which a congenital cardiovascular malformation was associated with a necrotizing arteriopathy limited to the pulmonary arterial tree. In both instances the patient was a boy, aged 11 years, who had been known since birth to have a cardiac lesion which caused exertional dyspnoea and

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who died after a short, acute illness. In each case the congenital malformation was Eisenmenger's complex. The first case was reported by Old and Russell (1947, 1950); necrotizing arteriopathy, affecting predominantly the smaller muscular arteries but also arterioles, was widespread throughout the lungs and reproduced the histological appearances seen at all stages in the development and healing of the lesions of polyarteritis nodosa, except that eosinophil leucocytes were not found in the inflammatory exudate. The presence of extensive arteriolosclerosis in the lungs was interpreted as indicative of pulmonary hypertension. Old and Russell suggested that pulmonary hypertension was the factor which had determined the exclusively pulmonary distribution of the necrotizing arteriopathy; they did not commit themselves to assigning a cause to the latter. The second case of Eisenmenger's complex with pulmonary arteritis was reported by Kipkie and Johnson (1951); the pathological findings in this case were similar to those described by Old and Russell (1950), but there was in addition acute glomerulonephritis and a history suggesting that the child had been sensitive to sulphonamides, so that the authors considered that a variety of factors might have contributed to the development of the arteritis. They suggested that pulmonary hypertension and other circulatory disturbances resulting from the cardiovascular malformation could have determined the pulmonary localization of the arteritis, and that the latter might have been due either to whatever factor had caused the coexistent nephritis or to allergy to sulphonamides.

McKeown (1952), in a series of 6,770 necropsies, found only four cases in which there was an arteritis limited to the lungs. The patients had presented clinically with right-sided cardiac failure of several months' duration and of obscure origin, and in each case unexplained hypertrophy of the right ventricle was found at necropsy. The vascular lesions were histologically identical with polyarteritis nodosa. McKeown suggested that these were cases of primary arteritis involving only the pulmonary vessels, and that the pulmonary hypertension was secondary to the arteritis and not the cause of it.

From this brief résumé of the literature it can be seen that necrotizing arteriopathy, limited to the pulmonary vasculature, has been observed in cases of pulmonary hypertension secondary to congenital and acquired heart disease and also in cases of pulmonary hypertension in which no other pulmonary or cardiac lesion was demonstrable to account for the hypertension. Some of the authors considered that the necrotizing arteriopathy was partly or wholly allergic in origin, and therefore aetiologically related to polyarteritis nodosa, while others assumed that it was secondary to hypertension. Which of these interpretations was adopted by individual observers seems to have been determined mainly by the supposed morphological resemblance of the lesions in their material to polyarteritis nodosa, suggesting allergy, or to hypertensive systemic arteriolonecrosis.

In both of the following cases certain of the pulmonary vascular changes appeared morphologically to be the counterpart of hyperplastic arteriolosclerosis as seen in the systemic vasculature in essential hypertension; other pulmonary arterioles showed a lesion which appeared to correspond to the arteriolonecrosis seen in systemic arterioles in malignant hypertension, while the remainder of the arteriolar lesions exactly reproduced the picture characteristic of generalized polyarteritis nodosa.

FIG. 1

FIG. 2

FIG. 3

Report of Cases

Case 1.—A previously healthy man aged 24, developed a relentlessly progressive, right-sided heart failure of which he died within 18 months of its onset.

Necropsy revealed severe chronic systemic venous engorgement and oedema of cardiogenic distribution. The heart weighed 520 g.; the right ventricle was greatly hypertrophied, whereas the left side of the heart was normal. No valvular lesions and no congenital malformations of the heart or great vessels were found. There was slight fatty atheroma of the larger pulmonary arteries. The lungs were moderately oedematous and engorged, and the branches of the pulmonary arterial tree stood out patulous and thick-walled on the cut surfaces. There was no pulmonary emphysema, fibrosis, or inflammation.

Histological examination showed severe chronic venous congestion of the viscera, but no other vascular abnormality was found except in the lungs. The pulmonary vascular changes were practically uniformly distributed in all parts of the lungs. In the largest pulmonary arteries atheroma and slight pseudocystic mucinoid degeneration of the media were present. There was medial hyperplasia and moderate intimal fibrosis in the small muscular pulmonary arteries, and very marked hyperplastic sclerosis of the pulmonary arterioles (Fig. 1). In addition, there was an extensive necrotizing arteriopathy. Only vessels of the order of 150 μ or less in external diameter showed lesions of the latter variety, and, as far as

FIG. 1.—Case 1: pulmonary arteriolo-sclerosis. (Haematoxylin and eosin, $\times 160$.)

FIG. 2.—Case 1: pulmonary arteriolo-sclerosis with fibrinoid necrosis of the media. (Haematoxylin and eosin, $\times 140$.)

FIG. 3.—Case 1: polyarteritis-nodosa-like lesion of a pulmonary vessel, showing segmental distribution of the necrosis and cellular reaction. (Haematoxylin and eosin, $\times 200$.)

could be judged from study of serial sections, this process appeared to be limited to branches of the pulmonary tree, the bronchial vasculature being quite normal. The earliest stage of this necrotizing arteriopathy was the development of fibrinoid necrosis of the muscular coat (Fig. 2), sometimes with small haemorrhages into the fibrinoid material. In later stages, neutrophil polymorphonuclear leucocytes and a smaller proportion of large and small mononuclear inflammatory cells accumulated in all coats of the affected vessel and in the adjacent perivascular tissue; eosinophil leucocytes were very scanty. These more severe changes were often limited to only a segment of the wall of the affected vessel (Fig. 3).

Case 2.—This patient gave a history of recurrent attacks of acute rheumatic fever between the ages of 14 and 20 years, leading to mitral stenosis. His exercise tolerance remained fairly good until the age of 32, when he had an acute febrile illness, shortly after the onset of which a coagulase-positive *Staphylococcus aureus* was isolated from the blood in pure culture on two occasions. The clinical picture was that of septicaemia, but there was nothing otherwise suggestive of a bacterial endocarditis. He recovered from this illness on treatment with penicillin, but his cardiac reserve never regained its previous level. Recurrent episodes of congestive cardiac failure occurred, and during one of these, two years after the septicaemia, he died.

FIG. 4

FIG. 5

FIG. 6

FIG. 4.—Case 2: pulmonary arteriole showing fibrinoid necrosis in parts of the media and of the thickened intima, with round-cell infiltration. (Haematoxylin and eosin, $\times 180$.)

FIG. 5.—Case 2: polyarteritis-nodosa-like lesion of a pulmonary vessel, showing segmental distribution of the reaction. (Haematoxylin and eosin, $\times 140$.)

FIG. 6.—Case 2: small pulmonary arteriole with fibrinoid necrosis of the media and accumulation of fibrinoid material in the perivascular tissue. (Haematoxylin and eosin, $\times 290$.)

Necropsy showed calcification and extreme stenosis of the mitral valve, and marked hypertrophy of the right ventricle which accounted for most of the cardiac enlargement (heart weight 610 g.). The other findings were essentially the same as in Case 1.

The histological findings (Figs. 4 and 5) in the lungs were similar to those in Case 1, except that a few of the smallest calibre arterioles showed a considerable accumulation of fibrinoid material in the perivascular tissue in addition to fibrinoid necrosis of the media (Fig. 6).

Discussion

The pathological findings in Case 1 were not considered to be of such a nature as could explain the cause of the pulmonary hypertension, and the case was therefore relegated to the unsatisfactory category of essential pulmonary hypertension. In Case 2, on the other hand, it was apparent that right ventricular hypertrophy and failure had developed essentially as a consequence of mitral stenosis and the resulting impediment in the lesser circulation.

In each case the necrotizing arteriopathy was thought to be pathogenetically akin to the arteriolar necrosis of malignant systemic hypertension. Although the histological appearances in certain vessels were indistinguishable from those seen in cases of generalized polyarteritis nodosa, the lesions in the majority of the arterioles far more closely resembled the picture of hypertensive systemic arteriolonecrosis, with fibrinoid necrosis of the tunica media and very little or no cellular reaction or other evidence of inflammation. It was felt that the polyarteritis-nodosa-like lesions had developed as an inflammatory response secondary to the vasonecrosis, and there did not seem to be any grounds for suggesting that allergy was a factor in their genesis. There was no history of any allergic state in Case 1, and the only possibly allergic disease in Case 2 was the recurrent rheumatic fever during the patient's youth. No evidence of any active rheumatic condition was found at necropsy in either case, and the pulmonary vascular lesions did not closely resemble rheumatic angitis. Penicillin and sulphonamides had been used on various occasions in the treatment of each patient, but there was never any clinical evidence to suggest that either patient had developed hypersensitivity to these drugs.

It is not possible to do more than speculate about the precise mechanism by which the necrotizing and inflammatory vascular changes developed. Factors such as local oxygen deficiency and vasospasm may have interacted with hypertensive mechanical stresses to initiate the necrosis. There can be no doubt that the necrotizing arteriopathy was of considerably shorter duration than the clinical history of right-sided cardiac failure, and that it was not the cause of the latter. The absence of any unequivocal evidence of healing in the affected vessels suggested, in fact, that the necrotizing arteriopathy was of fairly recent onset, and it is noteworthy that in each case there had been a comparatively sudden and rapidly progressive increase in the severity of the cardiac failure in the period of two to three months preceding the patient's death.

It has already been mentioned that in the literature the necrotizing arteriopathy in the lungs of patients with pulmonary hypertension has been described by some authors as polyarteritis nodosa and by others as morphologically similar to hypertensive systemic arteriolonecrosis. The presence of both hypertensive arteriolonecrotic and polyarteritis-nodosa-like lesions in the two cases reported here is therefore of particular interest. As the resemblance to polyarteritis nodosa has

been considered by other authors to indicate that such vascular lesions in cases of pulmonary hypertension are allergic in nature, it is relevant in conclusion to refer to the hypertensive hypothesis of the aetiology of polyarteritis nodosa. Smith and Zeek (1947) opposed the view that polyarteritis nodosa is an allergic disease; they suggested instead that arterial hypertension plays the main role in its pathogenesis. Their evidence to support this suggestion was that lesions closely resembling if not identical with those of polyarteritis nodosa develop in a proportion of animals in which severe hypertension has been rapidly produced by any of a variety of experimental procedures. Zeek, Smith, and Weeter (1948) further claimed that polyarteritis nodosa, being of hypertensive origin, can be distinguished clinically and pathologically from another variety of necrotizing panarteritis which they believed to be genuinely of allergic origin, and which they named "hypersensitivity angiitis." This is not the place to attempt a detailed criticism of these views, but, although the findings in cases of severe pulmonary hypertension, such as the above, show that a polyarteritis-like arteriopathy can occur in vessels exposed to hypertension, there is much evidence against the general applicability of the hypertensive hypothesis of the nature of polyarteritis nodosa. The reaction of the pulmonary vasculature in some cases of pulmonary hypertension is nevertheless of interest in relation to the problem of generalized polyarteritis nodosa, and may repay further study.

Summary

Two cases are described in which there was a necrotizing arteriopathy limited to the pulmonary vasculature. Essential (primary) pulmonary hypertension was present in one case, and pulmonary hypertension secondary to mitral stenosis in the other. The lesions in the small blood vessels in each case were of three kinds: (1) arteriolosclerosis, comparable to hypertensive systemic arteriolosclerosis; (2) fibrinoid necrosis of the media of small arteries and arterioles, comparable to the arteriolonecrosis associated with malignant systemic hypertension; and (3) arteritis and arteriolitis, reproducing the histological features seen in polyarteritis nodosa.

The relevant literature is briefly reviewed, with particular reference to the various interpretations which have been suggested in explanation of these pulmonary arterial changes in cases of pulmonary hypertension.

It is suggested that necrotizing arteriopathy limited to the pulmonary vasculature and occurring in association with pulmonary hypertension is a result of the hypertension and not its cause.

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