Virchows Arch. A Path. Anat. and Histol. 372, 167–173 (1976)

Virchows Archiv A

Idiopathic Arterial Calcification of Infancy without Intimal Proliferation

A.J. Barson, R.H.A. Campbell, F.A. Langley, and R.D.G. Milner

Departments of Pathology, Child Health and Obstetrics and Gynaecology, University of Manchester, Manchester, M13 9PT, England

Summary. A case of idiopathic arterial calcification is described in a dysmature infant dying of massive pulmonary haemorrhage on the fourth day after a gestation of 36 weeks. The mother had disseminated lupus erythematosis and lupus nephritis treated with large amounts of prednisolone. Unlike most of the previously recorded cases of idiopathic arterial calcification of infancy subintimal proliferation of fibrous tissue and involvement of the coronary arteries did not occur. It is suggested that this non-occlusive form of arterial calcification may be a distinct entity.

Key words: Arterial calcification – Infant – Lupus erythematosis – Prednisolone.

Introduction

Widespread calcification of the arteries during the first year of life is a rare condition which may be attributed to advanced renal disease, hypervitaminosis or cardiac and vascular malformation, but which in the majority of cases reported in the literature has no identifiable causation (Bird, 1974). The first clear description of the disease was given by Bryant and White (1901), although Durante (1899) reported a case of "congenital atheroma" which is suggestive of the disorder. Moran and Becker (1959) gave a good review of 44 cases with two of their own and there are now in excess of 50 in the literature.

The present case is of interest because of the absence of arterial occlusion from intimal proliferation which characterises most of the previously reported cases. The infant's complex maternal history may be relevant to the aetiology of this disease.

Case Report

This was the first pregnancy of a 20 year old woman whose husband was 23. The mother had had systemic lupus erythematosis of three years duration for which she was taking chloroquine

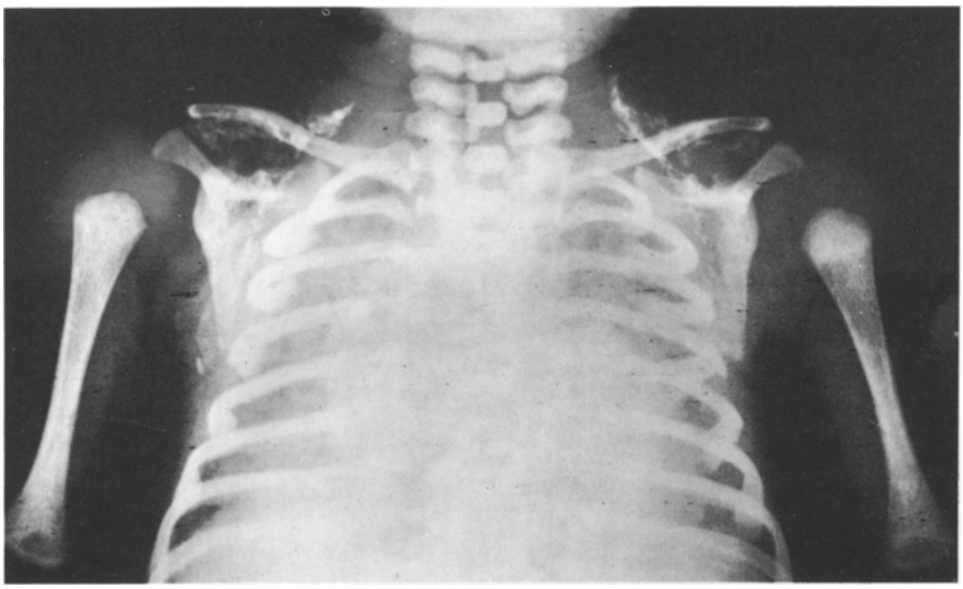

Fig. 1. Chest radiograph showing symmetrical triangular areas of calcification within the subcutaneous fat of the supraclavicular fossae. ×0.5

(250 mg daily). This drug was discontinued when she was 11 weeks pregnant by dates. At 18 weeks gestation she required hospital admission because of dyspnoea, peripheral oedema, bilateral inspiratory lower thoracic pain and moderate albuminuria. A diagnosis of lupus nephritis was made for which she was given prednisolone (100 mg daily reducing to 40 mg per day after three months). She also received frusemide and spironolactone. Spontaneous labour occurred at 36 weeks. At this time the maternal blood pressure had risen to 160/30, the blood urea to 54 mg %. There was heavy albuminuria and the serum proteins were reduced to 4.3 g %.

A male infant was born by normal vertex vaginal delivery. A hexose infusion was required from four hours of age for asymptomatic hypoglycaemia. Prednisolone (0.5 mg b.d.) was given on the second day and replaced by hydrocortisone 50 mg, 8 hourly from the third day, together with Kanamycin and penicillin. Feeds were vomited from the third day, death occurring on the fourth day after progressive abdominal distension and respiratory distress.

Necropsy Examination. The placenta weighed 210 g and measured 14 cm in diameter by 1.5 cm thick. There was a small subchorionic clot present. The body was that of a male infant weighing 1220 g with a crown-heel length of 38.4 cm and a crown-rump length of 26.5 cm. The occipito-frontal head circumference was 26.8 cm. The infant appeared poorly nourished and there was little subcutaneous fat. Fresh blood was found in the main airways and both lungs were diffusely consolidated by haemorrhage. The gross appearance of other organs was unremarkable save for the calcification which was more clearly seen radiologically.

Radiological Examination. Triangular areas of speckled calcification were seen within the subcutaneous fat positioned symetrically over the supraclavicular fossae and anterior aspects of the shoulders (Fig. 1). The lower abdominal aorta, common, internal and external iliac arteries were calcified (Fig. 2), as was the circle of Willis, the pulmonary arteries, renal arteries (Fig. 3), right axillary and left bronchial arteries. The placenta was also heavily calcified and some linear calcification was present in the umbilical arteries.

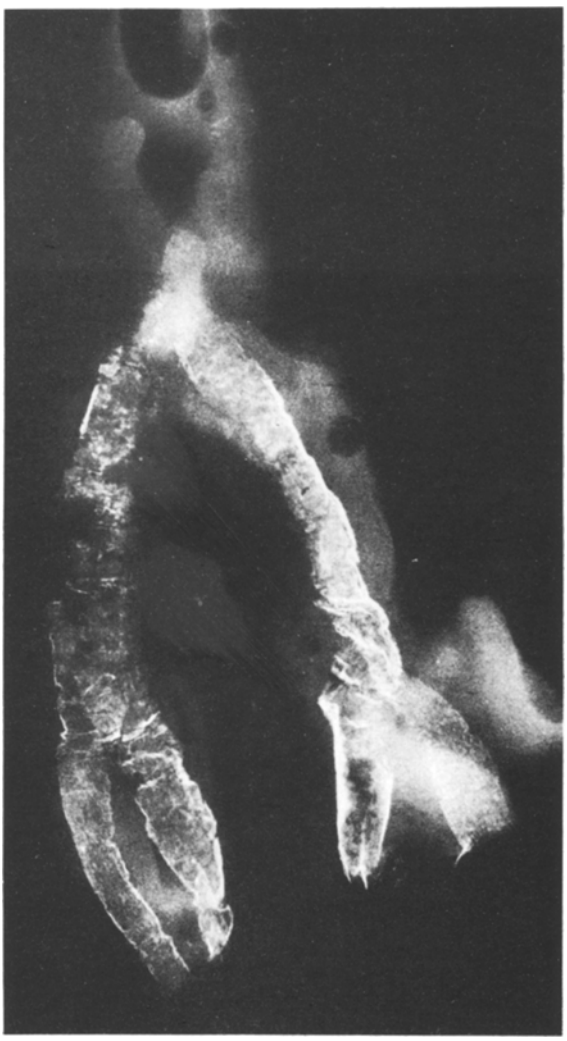

Fig. 2. Calcified abdominal aorta, common, internal and external iliac arteries. ×2.5

Microscopical Examination. The histology of the lungs confirmed the presence of a massive pulmonary haemorrhage which was probably the immediate cause of the infant's death. There was a moderate hyperplasia of the islets of Langerhans in the pancreas. The placenta showed much perivillous fibrin deposition and villous calcification. There were a number of old placental infarcts and in some areas there were foci of acute inflammation.

The calcification seen radiographically appeared on the histological sections as small saccular or finger-like deposits on both inner and outer borders of the elastic lamina (Fig. 4). Endothelial proliferation in association with this calcification was not seen and no arterial occlusion could be demonstrated with the exception of some arterioles within the renal parenchyma which were completely occluded by partially organised thrombus.

Apart from some of the small renal and pulmonary arterioles calcification was confined to large arteries, namely the abdominal aorta and iliac arteries, pulmonary, umbilical, vertebral, right

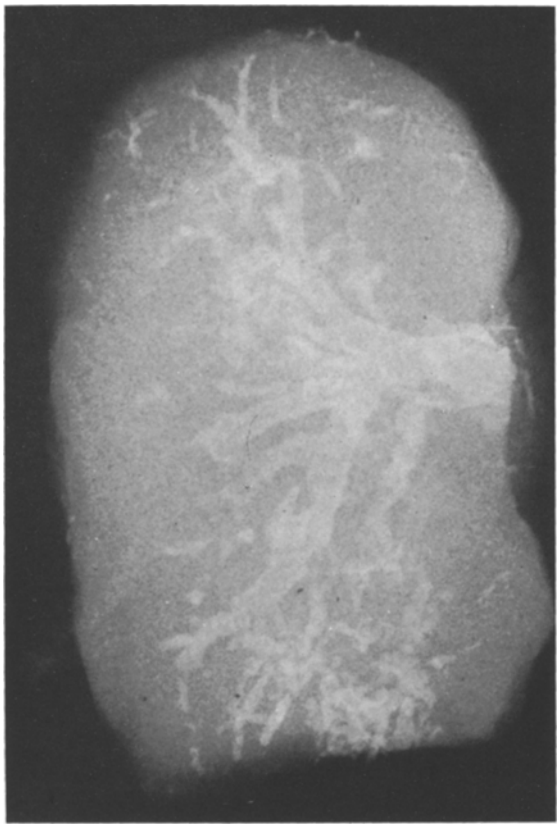

Fig. 3. Arborising calcification of the right renal artery. ×4

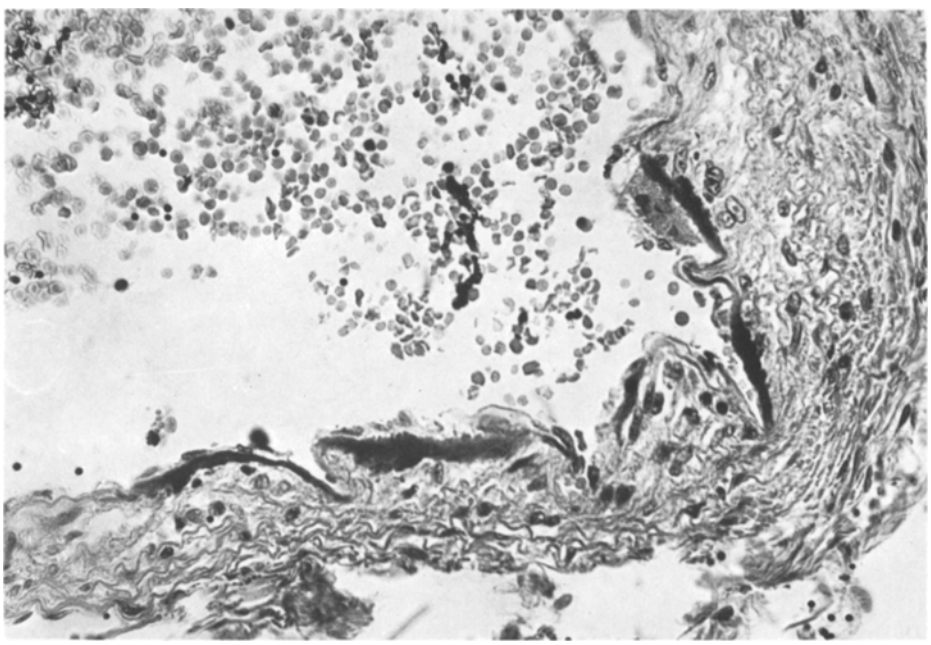

Fig. 4. Early calcification of the internal elastic lamina of a pulmonary artery. H & E ×200

axillary and left branchial arteries. No arterial calcification was observed in any of the abdominal organs apart from the kidneys, or within the coronary arteries. The arteries forming the circle of Willis at the base of the brain were calcified but the cerebral arteries within the substance of the brain were normal.

The only regions where calcification appeared unrelated to the arterial system was in the placenta where the villous calcification was identical to that commonly observed in this organ at term, and in the subcutaneous fat of the supraclavicular fossae. In this region there were numerous small calcific foci which appeared to have replaced fat cells and to have involved interstitial connective tissue. No inflammatory cell reaction was seen in the vicinity of this subcutaneous calcification or in association with the arterial lesions.

Discussion

There are enough descriptions of idiopathic arterial calcification in infancy to merit it being regarded as an entity distinct from known causes of widespread arterial calcification. The majority of cases die during the first six months of life but it has been observed in stillbirths (Ivemark, Lagergreen and Ljungquist, 1962) and up to 5 years of age (Moran and Steiner, 1962). More than a quarter of cases present with respiratory distress often associated with cyanosis of acute onset. Diagnosis is rarely made before death which usually occurs within hours or days and consequently there has been little investigation of the disease during life. When a clinical diagnosis has been made it is usually a consequence of radiological examination. Probably the most extensively investigated case was that described by Parker, Smith and Stoneman (1971). The infant was diagnosed radiologically on the fourth day of life and survived for a further twenty days. No biochemical evidence of disturbance of the calcium or phosphate metabolism was demonstrated in this or other cases in the literature.

The histological changes in the arteries closely resemble those sometimes observed complicating advanced chronic renal disease. Indeed, beyond the age of three years this is the most common explanation for widespread arterial calcification (Cochrane and Bowden, 1954). Primary hyperparathyroidism and excessive intake of vitamin D may rarely cause arterial calcification, but the idiopathic form of the disease characteristically has no morphological changes in the parathyroid glands or skeleton. Congenital heart disease and vascular malformations may predispose to arterial calcification but the association is very uncommon (Bird, 1974).

However, the association with occlusive coronary arterial disease is an important one. The great majority of cases of idiopathic arterial calcification of infancy which have been reported feature varying degrees of subintimal proliferation of fibrous tissue. Of the 44 cases reviewed by Moran and Becker (1959) all but two had demonstrable coronary arterial involvement, with myocardial infarction in 14 infants and myocardial fibrosis in 10. Subendocardial fibrosis of the cardiac ventricles has also been observed in a number of cases. The present case is of particular interest because not only was the heart morphologically normal but no subintimal proliferation of fibrous tissue was seen in any of the many calcified arteries. Only in the kidneys were arteries occluded,

but here it appeared to be due to thrombosis rather than endothelial proliferation. So commonly has arterial stenosis or occlusion been observed in cases of idiopathic arterial calcification of infancy that Witzleben (1970) suggested that the role of calcification in the pathogenesis of the disease had been overemphasised and that it would be preferable to re-name the condition "occlusive infantile arteriopathy".

That the present case is not unique and that calcification can be the prime manifestation of the disease is supported by two cases reported by Ivemark, Lagergreen and Ljungquist (1962). Both these infants were stillborn in pregnancies complicated by hydramnios. Both had widespread calcification of the arteries in relation to the internal elastic lamina, but neither displayed fibrous endothelial proliferation. One infant had a ventricular septal defect but neither had evidence of calcification or occlusion of the coronary arteries. Such cases raise the question of whether we are dealing with different stages of the same disease or whether there is a separate entity of "nonocclusive idiopathic arterial calcification of infancy" in which subintimal proliferation does not occur, although as in the present case some arteries may be secondarily thrombosed. However, most authors believed the intimal proliferation to be a secondary manifestation. The calcification may occasionally be accompanied by a giant cell granulomatous reaction with a round cell infiltration of the adventitia. The case described by Witzleben (1970) in a $7\,^1/_2$ month old infant in which there is marked intimal fibrosis with disruption of the internal elastic lamina in the absence of calcification cannot be regarded as typical of the condition.

The symmetrical triangular calcification within the subcutaneous fat of the supraclavicular fossae has not been reported before. Without a chest radiograph they are likely to be overlooked since the pathologist does not usually examine this region closely in routine necropsy. They were the only evidence in this infant of calcification unrelated to the arterial system. Calcification of the umbilical arteries has not been recorded before although it is unlikely they have been specifically examined in most patients. Placental calcification has been observed before (Ivemark et al., 1962; Jones et al., 1972) but as with the present case there were no features which distinguished it from that often seen in term placentae. Meyer and Lind (1972) described calcific deposits in the internal elastic lamina in the common and internal iliac arteries in half of a series of newborn infants, and in nearly all infants dying over one year of age. The relationship of this apparently normal phenomenon to placental calcification and pathological arterial calcification is not known.

Finally there remains the question of whether the complex maternal history in the present case was an aetiological factor for the foetal systemic arterial calcification. Patients with disseminated lupus erythematosis and receiving steroids, chloroquine and aspirin usually have small babies (Morris, 1969) and there is some evidence that steroids may reduce foetal growth more than the disease for which they are administered (Warrell and Taylor, 1968). The infant described in this paper was severely growth retarded and the association between this and fatal massive pulmonary haemorrhage from which he died is well known. However, idiopathic arterial calcification has not been linked with specific maternal disease or medication in the previous literature although calcification

of subcutaneous, muscular and periarticular tissue is known to occur in long standing cases of systemic lupus erythematosis (Quismorio, Dubois, Stebbins and Chander, 1975).

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Received August 19, 1976