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Pulmonary calcinosis

DONALD HEATH AND A. JOHN ROBERTSON

From the Department of Pathology, University of Liverpool, and The Liverpool Royal Infirmary, UK

Heath, D., and Robertson, A. J. (1977). *Thorax*, **32**, 606–611. **Pulmonary calcinosis.** The clinical and pathological features are described of a case of pulmonary calcinosis complicating cystic disease of the renal medulla. A histopathological study of the lung revealed calcification in the alveolar walls and in the blood vessels, predominantly in the pulmonary veins and venules. The calcified deposits were also studied by electron microscopy, and appearances suggestive of active growth of the deposits were recognised. Chemical analysis of the lung revealed a calcium content some 55 times greater than that of a normal lung. There was a five-fold increase in magnesium content. Reference is made to the literature demonstrating that the chemical composition of metastatic calcification differs according to whether it is visceral or non-visceral in type.

Metastatic calcification was first described by Virchow in 1854. In the following years it became clear that one of its major causes is chronic renal disease (Mulligan, 1947). With the survival of a great number of patients as a result of such advances in treatment as maintenance haemodialysis, the metastatic calcification, including pulmonary calcinosis, which may complicate uraemia or hypercalcaemia has assumed greater significance and can be expected to be seen more frequently (McLachlan *et al.*, 1968). We report here a case of pulmonary calcinosis associated with renal disease.

Clinical history

The patient, born on 9 July 1923, was well until 1944 when in south India. Over a few weeks he had nocturnal frequency of micturition and loss of appetite and became drowsy, markedly wasted, and pale. The blood urea level was 140 mg/100 ml (23·3 mmol/l) and systemic blood pressure was 100/60 mm Hg. Bone radiographs repeatedly confirmed osteoporosis. During 1945 he developed nodules in the skin flexures which were thought to be due to calcified deposits with surrounding fibrosis. The blood calcium level was 17 mg/100 ml (4·2 mmol/l) and a diagnosis was made of hyperparathyroidism, either primary or secondary to renal disease. At one time in 1945 the blood calcium level rose to 22 mg/100 ml (5·5 mmol/l) when his plasma phosphate was 3·5 mg/100 ml (1·1 mmol/l). Exploratory operation to exclude a parathyroid tumour was refused. In 1951 his blood chemistry and blood pressure were normal. He was not seen again until 1962 when his systemic blood pressure was 210/130 mm Hg. Although the calcium and phosphate were estimated frequently from 1951 for the next 22 years, they were never outside the normal range for our laboratory. In 1972 he developed an anterior myocardial infarction, and for the last eight years or so of his life the blood urea levels were between 120 and 150 mg/100 ml (20–25 mmol/l) without any steady rise. He finally died in left ventricular failure in September 1973.

At no time was there any radiological evidence of pulmonary calcinosis. Twelve chest radiographs have been re-examined, and even with hindsight no form of calcification can be detected. They showed only left ventricular failure with some changes of uraemia.

Postmortem findings

The small kidneys (right 61 g, left 74 g) showed cystic disease of the renal medulla (Strauss, 1962) with multiple cysts from 0·1 to 2·0 cm in diameter filled with gelatinous colloid material. These cysts were packed with eosinophilic granular material and were lined by flat to cuboidal epithelium. There was extensive nephrocalcinosis with medial calcification and intimal fibrosis of renal arteries.

Three parathyroids were found; all were hyperplastic with increase of the chief cells, and in one there was also a small adenoma. There was focal

calcification in the arteries to the thyroid, adrenals, pituitary, pancreas, liver, spleen, stomach, and left ventricle. There was a healed myocardial infarct of the anterior wall of the left ventricle which weighed 290 g (normal 185 g). The right ventricle was hypertrophied and weighed 125 g (normal 65 g). The lungs appeared distended and felt stiff and rubbery but no areas of calcification could be detected as either hard particles or larger nodules. The right lung weighed 855 g and the left 820 g.

HISTOPATHOLOGY

There was widespread calcification of the interstitial tissue of the alveolar walls which appeared solid and rigid (Fig. 1). The deposits ranged in size from minute particles to craggy masses which thickened and distorted the alveolar walls, displacing the pulmonary capillaries. The calcification was readily demonstrated by haematoxylin which revealed a basophilic, fibrillar change in the alveolar interstitial tissue more widespread than the calcified nodules. There was no reactive proliferation of the endothelial cells of the pulmonary capillaries or granular pneumocytes of the alveolar walls.

Calcification affected the pulmonary veins and venules and, to a much lesser extent, the pulmonary arteries and arterioles. The elastic laminae of the large pulmonary veins were incrusted by calcium salts which formed craggy masses in the media in some instances. Smaller pulmonary veins and pulmonary venules showed incrusted elastic laminae and calcified deposits at the junction of the media and adventitia (Fig. 2). Affected pulmonary veins showed severe intimal fibrosis so that frequently only a small lumen remained patent. Small granules of calcification were seen in the thick cellular fibrous layer. There was no pronounced hypertrophy of the muscular pulmonary arteries, and these vessels did not show calcification of their elastic laminae. There was no muscularisation of the pulmonary arterioles.

Ultrastructure

Electron microscopy readily demonstrated nodules of calcification in the alveolar walls as little as 0·4 μm in diameter (Fig. 3). Many had a feathery outline which was probably an expression of active deposition of calcium salts. In contrast, the outline of larger deposits tended to be smooth, suggesting that their active growth had ceased. Electron microscopy also confirmed the distortion of the alveolar capillaries and the lack of reactive pro-

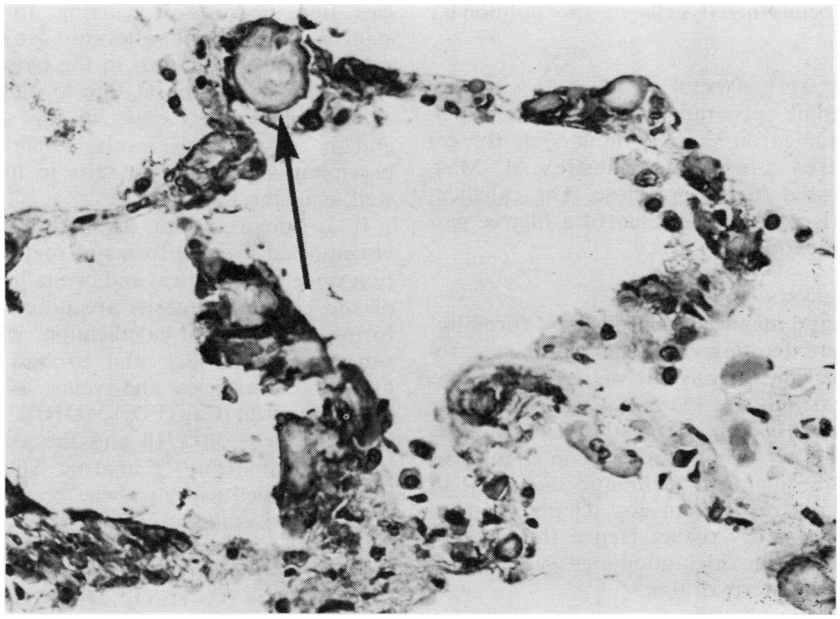

Fig. 1 *Section of lung showing extensive calcification of alveolar walls. There is intimal fibrosis in a pulmonary venule (arrow) but there is no reactive proliferation of granular pneumocytes and no desquamation of cells into the alveolar spaces (Haematoxylin and eosin ×375).*

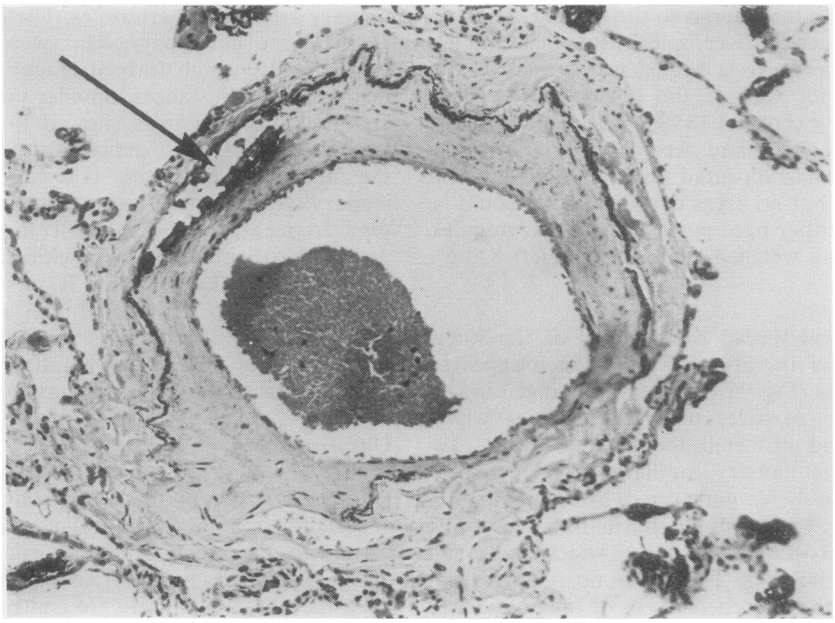

Fig. 2 *Transverse section of a pulmonary vein showing incrustation by calcium salts of elastic laminae at the junction of the media and adventitia. In one area (arrow) there is a more extensive area of calcification in the wall of the vein. There is severe reactive intimal fibrosis (Haematoxylin and eosin ×150).*

liferation of granular pneumocytes in the alveolar walls, or by endothelial cells in the pulmonary capillaries.

RADIOGRAPHIC APPEARANCES

The radiographic appearances of pulmonary calcinosis were studied on slices of lung some 0·5 cm thick. Industrial *x*-ray film (Industrex M. M54, Kodak) was used for this purpose. The calcification of the alveolar walls presented a filigree pattern of opacification (Fig. 4).

CHEMICAL ANALYSIS

The calcium and magnesium contents of formalin-fixed lung were determined by absorption spectrometry after drying to constant weight. There was 2732 mg of calcium and 153 mg of magnesium per 100 g dry weight of lung. An analysis of a disease-free lung from a second necropsy in a man of 44 years by the identical technique showed it to contain 49·4 mg of calcium and 23 mg of magnesium per 100 g dry tissue. Hence the calcium content in one of our calcinotic lungs was 55 times greater than in a normal lung.

Discussion

Calcification in the lungs is common in the dystrophic form so that calcium salts are laid down in tissues already diseased by such processes as caseation, necrosis or scarring. In these circumstances there is no alteration in the levels of calcium and phosphorus in the blood. Much rarer is pulmonary calcinosis, due to metastatic calcification following changes in the serum calcium and/or phosphorus levels which lead to the precipitation of calcium salts in many tissues as well as in the lungs.

It is important to distinguish between non-visceral and visceral forms of metastatic calcification since the chemical and crystalline composition of the calcified deposits are different in the two forms. Non-visceral calcification, which occurs in subcutaneous tissues and around tendons and joints, and arteries and veins, is composed of hydroxyapatite ($Ca_{10}(PO_4)_6.(OH)_2$). The Ca/Mg/P molar ratio is 30/1/18 and the *x*-ray diffraction pattern is by definition apatitic. Such calcification is almost identical in these respects with bone (Contiguglia *et al.*, 1973). The initial extra-osseous calcium-phosphate deposit in non-visceral calcification and in patients with hypercalcaemia appears to be brushite ($Ca\,HPO_4.\,2H_2O$). This is stable at a pH of 6·2 but is rapidly transformed to apatite (Alfrey *et al.*, 1976). Visceral calcification includes pulmonary calcinosis as well as deposits in kidney, heart, stomach, and muscle. Such deposits of

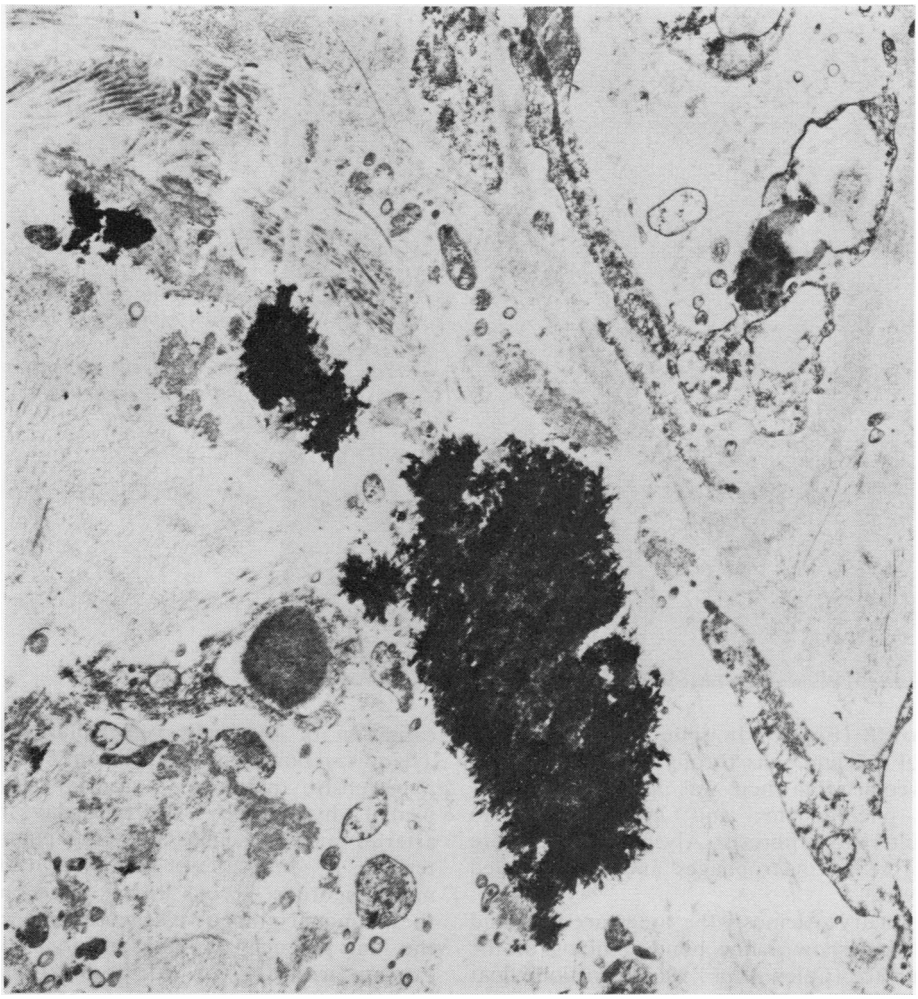

Fig. 3 *Electron micrograph of alveolar wall showing focal areas of calcification with feathery edges probably due to the mode of deposition of the calcium salts* (×*12 500*).

calification have a different Ca/Mg/P ratio of 4·9/1/4·6. The *x*-ray diffraction pattern also differs in showing the low, broad pattern of either an amorphous compound or a substance having a very small crystal size. Uraemic, visceral calcium-phosphate deposits appear to be an unique mineral high in magnesium (Alfrey *et al.*, 1976). After incineration at 500°C visceral calcification shows the diffraction pattern of magnesium whitlockite $(Ca\ Mg)_3\ (PO_4)_2$. Approximately 30% of the phosphate is present as pyrophosphate which alters the crystalline structure, preventing transformation to apatite. Deposits of visceral calcification do not contain brushite. The pyrophosphate may be deposited as the magnesium salt.

The difference in chemical composition and crystalline structure may have significance in the differing tissue reaction to the two forms. The vigorous fibrous reaction to non-visceral calcification may be related to the larger crystal size of the deposits. It contrasts with the mild fibrotic response to the amorphous and microcrystalline nature of the deposits in visceral metastatic calcification. In the present case of pulmonary calcinosis we have seen the deposits have a basophilic amorphous appearance rather than a crystalline form on histological examination, although electron microscopy shows that the edges of the small deposits have a feathery appearance, suggesting deposition of very small crystals and

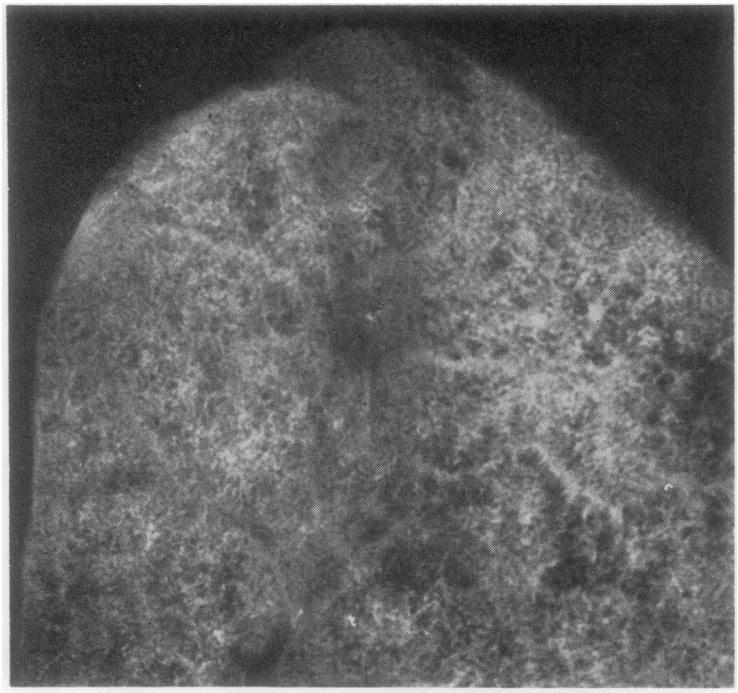

Fig. 4 *Part of a radiograph of a slice of lung, 0·5 cm in thickness, taken at necropsy with industrial x-ray film. The calcification of the alveolar walls presents a filigree pattern of opacification (×4/3 natural size).*

active growth (Fig. 3). In spite of the extensive deposits of calcium salts throughout the majority of the alveolar septa there was no proliferation of granular pneumocytes and no tendency to develop interstitial fibrosis. Alveolar spaces were virtually free of macrophages and desquamated pneumocytes.

In pulmonary calcinosis the lungs are firm and distended and show a fine honeycombing of the pleural surface (Caley *et al.*, 1962). Portions float on water. The calcified deposits appear as fine white granules or thin plates which impart to the lungs a rubbery (Caley *et al.*, 1962) or gritty (McLachlan *et al.*, 1968; Neff *et al.*, 1974) feel. Sometimes the lesions become confluent to produce calcified nodules up to 5 cm in diameter.

In contrast to the lack of diffuse fibrous reaction to the calcification in the lung parenchyma there is considerable intimal fibrosis in response to the incrustation of elastic laminae in the pulmonary blood vessels, veins being more heavily calcified than arteries (Mulligan, 1947). Possibly this is because the chemical composition and crystalline structure of the calcified deposits in the non-visceral site around arteries may be different from those in alveolar walls where the deposits may be regarded as visceral. Such occlusive changes as occurred in the pulmonary veins in the case reported here may have played some part in the causation of the right ventricular hypertrophy. There was, however, no significant development of hypertensive pulmonary vascular disease with medial hypertrophy of muscular pulmonary arteries and muscularisation of pulmonary arterioles. In some cases of pulmonary calcinosis the more vigorous fibrous reaction encountered in the pulmonary blood vessels has been seen within the lung parenchyma. Thus an organising fibrous exudate with foci of calcification has been reported in the alveolar spaces by McLachlan *et al.* (1968), and Neff *et al.* (1974) have described granular and linear deposits of calcified tissue in alveolar walls, hyalinised fibrous tissue occupying most of the alveolar spaces. In several sections metaplastic osteoid bone was seen with fatty marrow formation in several of these fields.

We were able to demonstrate a striking appearance in radiographs of lung slices at necropsy but the radiological detection of pulmonary calcinosis during life is usually difficult or impossible. Punctate shadows, 1 to 2 mm in diameter, may be detected when the surrounding lung field is clear (McLachlan *et al.*, 1968) but are easily obscured by pulmonary oedema or inflammatory changes. Even retrospective examination of chest films in patients subsequently shown at necropsy to have pulmonary calcinosis may not provide convincing confirmation of the condition.

Calcinosis of the lung has been reckoned to occur in 50% (Neff *et al.*, 1974) to 65% (Mulligan, 1947) of cases of metastatic calcification. The underlying causative diseases include primary and seondary bone disease (mostly primary and secondary neoplasms, including myeloma), chronic renal disease as in the present case, tumours or hyperplasia of the parathyroids, hypervitaminosis D, and calcium infusions for tetany.

The mechanism of production of pulmonary calcinosis is complex and depends to some extent on whether visceral or non-visceral deposition is concerned. The original concept of the transport of calcium from bones to viscera and tissues in the body was due to Virchow in 1854, and indeed it is to his original comparison of the process to spread of tumours (*Kalk-Metastasen*) that we owe our present-day terminology of 'metastatic calcification'. While there is no doubt that such calcified deposits follow supersaturation of extracellular fluid with calcium and phosphate ions, as suggested by Herbert *et al.* (1941), it has to be kept in mind that some cases of pulmonary calcinosis may occur in the absence of such biochemical disturbances (Neff *et al.*, 1974). In particular, the calcium-phosphate product appears to be less important in the pathogenesis of the visceral form of metastatic calcification (Alfrey *et al.*, 1976). Indeed, the studies of Contiguglia *et al.* (1973), by chemical and diffraction techniques, have shown that magnesium plays an important rôle in this form of mineralisation of tissues. It seems likely that the increased serum and total body concentrations of magnesium in uraemic patients may play an important rôle in the formation and retention of visceral metastatic calcification.

Local as well as general factors appear to operate in the development of metastatic calcification. For half a century it has been recognised that the sites most commonly affected are the alveolar walls of the lungs, the renal tubular epithelium, and the gastric mucosa. The usual explanation for deposits of calcium salts at these places is that excretion of free hydrogen ions at these sites renders the tissues relatively alkaline. This view, first put forward by Hueper in 1927, is still upheld in modern textbooks of pathology (Robbins, 1967). In the case of the lungs the acid product excreted is carbonic acid.

Pulmonary calcinosis has to be distinguished from dystrophic calcification of a variety of pathological lesions in the lung such as tuberculosis. It must be separated from pulmonary alveolar microlithiasis in which myriads of concretions of calcium phosphate in organic envelopes containing iron salts appear for no apparent reason in the alveolar spaces. Also to be differentiated are pulmonary osseous nodules developing in the course of chronic pulmonary venous hypertension, especially in mitral stenosis. In our patient we suspect that the calcium salts were laid down in the lung during the hypercalcaemic crisis of 1945 and that here the long-standing uraemia and nephrocalcinosis were not necessary for the production of the pulmonary calcinosis.

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Requests for reprints to: Professor D. Heath, New Medical School, Ashton Street, PO Box 147, Liverpool L69 3BX, UK.