Pulmonary metastatic calcification with respiratory insufficiency in patients on maintenance haemodialysis

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ABSTRACT A uraemic patient undergoing chronic haemodialysis developed diffuse metastatic pulmonary calcification and died from acute respiratory insufficiency after renal transplantation. Thirteen similar cases previously published are reviewed, with emphasis on the clinical and anatomical features of such calcinosis. The pathogenesis of this calcification in patients on maintenance haemodialysis and some rules for its prevention are discussed.

Metastatic calcification in chronic renal failure has been well known since Virchow's first work in 1855. Such pathological calcification is either visceral or non-visceral. The former affects the muscles, the myocardium, and the lungs, whereas the latter is arterial, subcutaneous, or par-articular.

With the advent of haemodialysis the manifestations of metastatic calcification have become prominent. Davidson and Pendas (1967), McLachlan *et al* (1968), Smith *et al* (1969), Mootz *et al* (1973), and Giacobetti *et al* (1977) have reported several cases of pulmonary metastatic calcification in patients undergoing chronic haemodialysis. We describe the case of a uraemic patient treated by chronic haemodialysis then renal transplantation who developed diffuse pulmonary micronodular calcification responsible for death from pulmonary insufficiency.

Case report

In 1955 urinalysis showed proteinuria in a 15-year-old boy. In 1969 gout occurred in the big toe, the knees and the ankles (serum urate was 112 mg/l). The blood pressure was 170/100 mmHg. Intravenous pyelography and retrograde cystography confirmed the diagnosis of advanced interstitial chronic nephritis with massive vesicorenal reflux. The blood urea was 110 mg/100 ml, creatinine clearance 12 ml/min, and proteinuria 1 g/24 hours. A low protein diet and a sodium administration did not stop his deterioration. Chronic haemodialysis was started in March 1970. Twice a week the patient underwent an eight-hour haemodialysis

period by means of a twin coil dialyser. Left nephroureterectomy was performed on 26 January 1971 with a view to transplantation later on. Microscopic examination showed advanced unclassified nephropathy and parietal calcifications of the tubules.

He continued to deteriorate, developing cardiac failure in 1972. Between then and 1975 he had a low serum calcium (mean 8.21 ± 1.11 mg/100 ml), and raised phosphate (mean 9.93 ± 2.71 mg/100 ml) and magnesium (2.73 ± 0.42 mg/100 ml). Finally, disseminated vascular calcification and demineralisation of the bones appeared in February 1975. Disseminated micronodular opacities of undetermined aetiology were progressively visible in the lungs. After five years of chronic haemodialysis, despite his poor medical condition, this patient was admitted for kidney transplantation. He could neither physically nor psychologically bear periodic haemodialysis.

A renal transplantation was performed on 7 February 1975 with a cadaver-kidney with two identities and two incompatibilities in HLA system. The cross match between the donor's lymphocytes and the recipient's serum was of course negative. After 15 hours of cold ischaemia, diuresis restarted immediately. But two hours after the operation cyanosis and collapse with respiratory distress required the assistance of a respirator. This artificial ventilation had to be continued for eight days because of severe hypoxia that was connected with left lower lobe pneumonia. The fever fell with antibiotics, but the patient remained hypoxic after extubation, Pao_2 between 55 and 66 mmHg. The $Paco_2$ remained normal, and the

Sao₂ was about 82%. At that time diuresis was more than 2.6 l/day, serum creatinine 2.6 mg/100 ml, the urea 170 mg/100 ml without evidence of rejection.

After a stormy course, during which anticoagulants were started, haemorrhage occurred into the graft, and the patient died on 23 February 1975.

Post-mortem findings

The lung lesions were the main gross findings. The right and left lungs, weighing respectively 970 g and 800 g, were diffusely solidified and rigid. On cut sections numerous irregular greyish nodules were scattered through both lungs. These lesions were raised above the lung surface and were of gritty or firm consistency. They measured up to 0.5 cm in diameter. The heart weighed 520 g with left ventricular hypertrophy. Calcific deposits infiltrated the free edge of the anteromedial cusp of the mitral valve. The right kidney weighed 40 g, and its yellowish tissue contained several simple cysts. The 220 g transplanted kidney was congested. Neither tumour nor hyperplasia of parathyroid glands were found.

Microscopic examination showed a diffuse metastatic calcification in both lungs. The septa of alveoli were thickened by fibrosis, calcification, and macrophagic giant cells (figs 1 and 2). Some alveolar spaces were filled with fibroblasts or calcific concretions. Smaller calcific granulations were also discovered in the walls of bronchi or bronchioles and in the media of arterioles or venules (figs 3 and 4). No myocardial or arterial calcification was seen after hemalum-phloxine-safranin and Von Kossa's stain. The right kidney was destroyed by advanced unclassified nephropathy, and

Fig 2 Lung showing calcified deposits surrounded by macrophagic giant cells and fibrosis (Gr $\times 220$).

Fig 3 Bronchiole showing scattered calcification through the lamina propria (Gr $\times 330$).

Fig 1 Lung, showing alveolar septa widened by fibrosis and calcification (Gr $\times 275$).

Fig 4 Wall of this arteriole or venule is destroyed by calcification (Gr $\times 137$).

calcific infiltration affected the glomeruli as well as the basal membrane of numerous tubules (fig 5). Some simple cysts were also present. The transplanted kidney showed signs of acute rejection.

Diffuse pulmonary calcinosis had induced death from acute respiratory failure after five years of chronic haemodialysis and in the days after renal transplantation.

Fig 5 Kidney, showing calcification in basal membrane of numerous tubules (Gr $\times 275$).

Discussion

Thirteen similar cases with diffuse pulmonary calcinosis have been reported in patients on maintenance haemodialysis or after renal transplantation or both. In seven of these cases death has occurred from lethal respiratory insufficiency (see table).

The visceral calcinosis is rarely present initially and is often unrecognised during life. Usually the diagnosis is made several months after the beginning of chronic haemodialysis and there is no parallel between the duration of chronic renal failure and the occurrence of calcinosis (Conger, 1975). In three cases calcific deposition has been diagnosed after renal transplantation (Kreis *et al*, 1976; Giacobetti *et al*, 1977).

Patients sometimes complain of effort dyspnoea but often there are no clinical signs. Diagnosis is usually based on pulmonary radiography. Sometimes calcinosis is predominant: calcified opacities of various size are seen in the two lung fields, occasionally associated with other visceral or non-visceral calcifications (McLachlan *et al*, 1968; Boner *et al*, 1971). Often the calcifications are less than 2 mm diameter, but occasionally they form a conglomerate and look like oedema.

Pulmonary function tests give little information, but the anatomical changes due to calcific deposits may lead to a restrictive syndrome.

The evolution varies but is lethal in most cases. Death by acute respiratory failure occurred seven times (see table). Cardiac decompensation often worsens this failure. In other cases respiratory insufficiency is an aggravating factor. Favourable evolution is rare; in one case of reversible nephrotic syndrome with acute renal failure pulmonary calcification occurred and then disappeared with haemodialysis. Yet metastatic calcification has been discovered in patients on maintenance haemodialysis or after renal transplantation or both (Mootz *et al*, 1973; Kreis *et al*, 1976; Giacobetti *et al*, 1977).

A complete pathological study performed in 11

Evolution of 13 patients with diffuse metastatic pulmonary calcifications and undergoing chronic haemodialysis

Authors	Cases	Sex and Age	Duration of haemodialysis or peritoneal dialysis	Duration of advanced uraemia	Evolution
Davidson and Pendras (1967)	1	F, 34	3 years of twice weekly haemodialysis	5 years	Death by acute cardiorespiratory failure
	2	M, 32	3 periods of haemodialysis	?	Death by acute cardiorespiratory failure
McLachlan <i>et al</i> (1968)	1	F, 34	2 periods of haemodialysis for 1 month	7 months	Death by acute pulmonary insufficiency
	2	F, 61	3 periods of haemodialysis for 2 months	2 months	Death by terminal renal failure
	3	M, 16	3 periods of peritoneal dialysis for 5 months	5 months	Survived
Smith <i>et al</i> (1969)	1	M, 43	Haemodialysis for 20 months	3 years	Death by terminal renal failure
Boner <i>et al</i> (1971)	1	F, 58	Peritoneal dialysis or haemodialysis from February to September 1970	1 year	Death by acute liver necrosis
Mootz <i>et al</i> (1973)	1	F, 24	Haemodialysis for one year. Binephrectomy. Renal transplantation	?	Death by acute pulmonary insufficiency
	2	F, 38	Four periods of peritoneal dialysis	2 years	Death by acute pulmonary insufficiency
Neef <i>et al</i> (1974)	1	M, 67	4 periods of peritoneal dialysis for two years	2 years	Death by acute pulmonary insufficiency
Kreis <i>et al</i> (1976)	1	F, 22	Haemodialysis for 3 years. Renal transplantation	3 years	Survived
	2	M, 17	Haemodialysis for 7 months	6 years	Survived
Giacobetti <i>et al</i> (1977)	1	M, 42	Haemodialysis for 2 years	?	Death by acute pulmonary insufficiency

cases showed similar lesions. The lungs are diffusely solidified. They are heavy and their weight varies from 590 g to 1800 g. On cut sections irregular or well-delineated nodules are scattered through the lung. Microscopic examination shows a fibrous widening of the alveolar septa. Multiple areas of calcification and a few lymphocytes infiltrate these walls. The alveolar lumen is often filled with exudate or calcification, sometimes surrounded by fibroblast proliferation. Calcification is also observed in the wall of bronchioles and arteries. The heart of these patients is enlarged. It may show biventricular hypertrophy and calcifications on the aortic valves or on the mitral valve. In three cases the microscopic examination showed myocardial fibrosis and metastatic calcification. In other cases calcification is seen only in the media of the coronary arteries. A slight rise in osteoclastic or osteoblastic activity was noticed in three patients. Two of them had enlarged parathyroid glands (Davidson and Pendras, 1967, cases 1 and 2). Mootz *et al* (1973) and Giacobetti *et al* (1977) reported bony changes as osteitis fibrosa cystica in patients with four grossly and microscopically hyperplastic parathyroid glands. Examination of the kidneys shows a large number of chronic renal diseases. The basal membrane of the tubules and of the glomerular capsules is often thickened by calcific deposits.

Three hypotheses of the pathogenesis are considered. Firstly, the calcification is part of the natural history of the renal insufficiency and is promoted by tissue damage, such as by the pulmonary oedema of our patient and of others (cases 1 and 2 of McLachlan). Several patients, however, have no evident antecedent pulmonary lesions. So the role of humoral disorders that are constant seems more important. In all the observations Ca X P product (mg/l) exceeds 4500. If a predominant hypercalcaemia was noticed by Davidson and Pendras (1967) serum phosphate was highly increased in all the patients reported. The serum phosphate was 100 mg/100 ml for several years.

On the other hand, the high serum magnesium of uraemic patients may explain the chemical nature of the visceral calcification. In these cases, Contiguglia *et al* (1973), using X-ray diffraction analysis of lung, heart, and muscle specimens, have shown that visceral calcification corresponds to an amorphous $(\text{Ca Mg})_3(\text{PO}_4)_2$ or whitlockite. Non-visceral and arterial calcifications are hydroxyapatite. Whitlockite is observed only in this medical condition (Gatter and McCarty, 1967). So the part played by magnesium seems to be prominent: this cation inhibits the crystalline growth

of apatite and, in contrast, stabilises whitlockite formation by decreasing its temperature of formation.

The alkaline conditions of kidney and lung favour deposition. Then at lung level the variations of blood pH from 7.35 to 7.45 decreases the phosphocalcific salt solubility by 10%. The severe changes of pH during haemodialysis may promote crystallisation.

It is difficult to specify the role of the hyperparathyroidism which is constant in uraemic patients. A parallelism between parathyroid hyperplasia and non-visceral calcification must exist, however (Contiguglia *et al*, 1973). This is not so for visceral calcifications.

Sometimes renal transplantation may increase the calcific deposition by calciphylaxis (Selye, 1962). Calciphylaxis occurs after sensitisation of the organism with direct or indirect calcifiers, such as vitamin D and parathyroid hormone (Parfitt, 1969; Rubini *et al*, 1969). The calcification appears after a critical period—exposure to a challenger or a precipitating factor such as steroids, calcium, or albumin. Giacobetti *et al* (1977) consider that the rapid development after renal graft of pulmonary calcification with documentation of normal lung by radiography six days before death supports the concept of acute deposition by calciphylaxis.

The lethal character of these calcific deposits call for careful monitoring, control of blood calcium, phosphate, and magnesium being the probable way to prevent tissue damage. Our observations and the others suggest the importance of raised magnesium and the part played by the association of pulmonary haemodynamic disorders. We propose, like Moinuddin *et al* (1976) and Schlagen and Pauwels (1976), that dialysed patients with unexplained respiratory symptoms should undergo “bone scan” with $^{99\text{m}}\text{Tc}$ pyrophosphate for pulmonary calcifications. These authors think that bone scanning “is far more sensitive than conventional radiography for demonstration of pulmonary calcification.” Finally, when visceral calcification is severe renal transplantation would seem the best solution. But we do not forget that this treatment can increase metastatic calcifications by calciphylaxis.

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