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CASE STUDY

Diffuse pulmonary calcinosis without calcium metabolism abnormalities in a renal transplant recipient

M. Romagnoli*, G. Mourad**, I. Serre+, J.P. Senac++, L. Paradis*, Ph. Godard*, P. Chanez*

Diffuse pulmonary calcinosis without calcium metabolism abnormalities in a renal transplant recipient. M. Romagnoli, G. Mourad, I. Serre, J.P. Senac, L. Paradis, Ph. Godard, P. Chanez. ©ERS Journals Ltd 1997.

ABSTRACT: Eighteen years after an uneventful renal transplantation, the chest radiograph of an asymptomatic 50 year old man showed diffuse bilateral infiltrations, predominately at the right apex.

Computed tomography (CT) scan demonstrated a diffuse alveolar pattern, the alveoli being filled with a very dense material, with some tracheal calcifications. Bronchoalveolar lavage fluid analysis was normal, but bronchial and transbronchial biopsies revealed calcium deposits in the bronchial mucosa and in the alveolar septa.

The diagnosis of diffuse pulmonary calcinosis was established, despite normal blood calcium, phosphorus and magnesium levels, based upon computed tomography scan and pathological findings at fibreoptic bronchoscopy, without the need for an open lung biopsy.

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*Clinique des Maladies Respiratoires, and ++Service d'Imagerie Médicale Thoracique, Hopital Arnaud de Villeneuve, Montpellier, France. **Service de Nephrologie and +Service d'Anatomo-pathologie, Hopital Lapeyronie, Montpellier, France.

Correspondence: P. Chanez, Clinique des Maladies Respiratoires, Hopital Arnaud de Villeneuve, 555 Route de Ganges, 34295 Montpellier Cedex 5, France

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Diffuse pulmonary calcification is a frequent complication of chronic renal failure and its treatment, such as chronic haemodialysis or peritoneal dialysis [1, 2]. It is usually a slowly progressive and asymptomatic disease. Some cases are fatal, as a result of acute respiratory failure caused by diffuse pulmonary calcinosis developing in patients on maintenance haemodialysis or after renal transplantation, or both [1, 3]. An increase in the calcium × phosphorus product is usually present. However, the condition has also been observed in patients with normal calcium and phosphate levels [4].

We describe a case of pulmonary calcinosis, occurring without any respiratory symptoms or calcium abnormalities, in a man who had been treated by chronic haemodialysis 18 yrs previously, followed by renal transplantation and subtotal parathyroidectomy. The diagnosis was made using the combination of high resolution computed tomography (HRCT) scan and transbronchial biopsies obtained at fibreoptic bronchoscopy (FOB).

Case report

A 50 year old Caucasian man was admitted to our day hospital because of the presence of bilateral pulmonary infiltrates predominately in the right apex (fig. 1). At the age of 19 yrs he had suffered from high blood pressure and proteinuria. A renal biopsy revealed a chronic glomerulonephritis of unknown origin. He received no treatment and 4 yrs later, when he was 23 yrs of age, he developed malignant hypertension with an end-stage renal insufficiency. The patient was initially treated with maintenance dialysis (haemodialysis and peritoneal dialysis) until he was 32 yrs of age, when he received a renal transplant donated by his brother. He was discharged from the hospital on immunosuppressive treatment, consisting of azathioprine (100 mg·day^{-1}) and prednisolone (5 mg·day^{-1}).

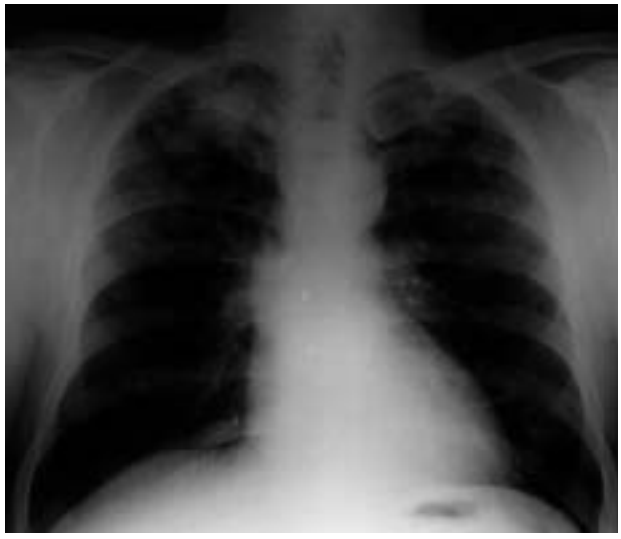

Fig. 1. – Chest radiograph at admission, showing bilateral patchy infiltrates predominantly at the right apex.

Postoperatively, the patient developed hypercalcaemia (2.50 mmol·L^{-1}) with elevated parathyroid hormone (PTH) and normal phosphate level. Two years later he underwent subtotal parathyroidectomy (adenoma), and blood

calcium (2.29 mmol·L^{-1}) and PTH levels (217 pg·mL^{-1}) normalized. The calcium × phosphate product was 2,748 mg·L^{-1} and the serum albumin level was 45 g·L^{-1}. During the course of the renal disease and after parathyroidectomy, routine chest radiographs remained normal.

The patient was recently admitted to the neurological department because of a transitory ischaemic accident, and during this hospitalization a chest radiograph was considered abnormal (fig. 1). At admission, he had no respiratory symptoms. Clinical examination was unremarkable. He was treated with azathioprine (25 mg·day^{-1}), prednisolone (5 mg on alternate days) and heparinate of calcium. His systolic arterial tension was 140 mmHg and diastolic arterial pressure 90 mmHg. Spirometric values were normal, with a vital capacity (VC) of 4.25 L (94% of predicted), forced expiratory volume in one second (FEV_1) 3.37 L (96% pred), and FEV_1/VC 101%. Transfer factor of the lungs for carbon monoxide was normal (80%). Arterial blood gas values performed with the patient breathing room air, were normal (arterial oxygen tension (P_{a,O_2}) 10.3 kPa (77 mmHg), arterial carbon dioxide tension (P_{a,CO_2}) 5.3 kPa (40 mmHg), and pH 7.44).

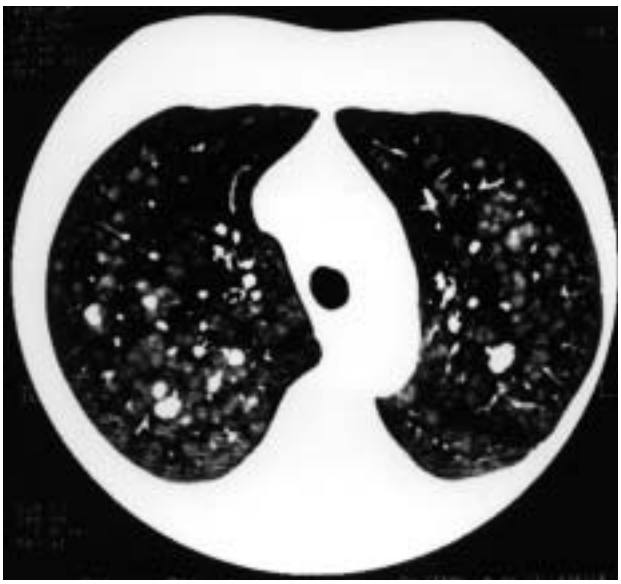

Fig. 2. – High resolution computed tomography (HRCT) scan (1.5 mm collimation, sharp-bone algorithm) of upper lobe bronchi, showing pulmonary nodules of a very dense material.

Echocardiography highlighted the presence of a mild left ventricular hypertrophy. Hypercholesterolaemia was present and the creatinine value was 150 µmol·L^{-1}. Blood calcium (2.23 mmol·L^{-1}), phosphate (0.95 mmol·L^{-1}), magnesium (0.9 mmol·L^{-1}) and PTH (203 pg·mL^{-1}) levels were normal. The calcium × phosphorus product was 1,311 mg·L^{-1}.

A HRCT scan was performed using a standard methology by a Somaton DR (Siemens, Erlangen, Germany) CT scan. The patient was investigated without infusion of intravenous contrast material. The scans were obtained at maximal inspiration using high resolution criteria: collimation of 1.5 mm, matrix of 512 × 512, and a "sharp-bone" algorithm. The window was large (1,800 Hounsfield units (HU)), with a centre at 400 HU. The scan intervals were 15 mm, with the subject in the supine position. The CT scans demonstrated a diffuse alveolar filling, especially at upper levels, with multiple nodules of a very dense material (900 HU, compatible with calcium deposition) (fig. 2), with calcifications of the wall of the main bronchi.

Fibreoptic bronchoscopy showed no macroscopic abnormalities, and bronchoalveolar lavage (BAL), bronchial and transbronchial biopsies were performed. BAL fluid analysis showed no specific pathogens, and cellularity was within the normal range with no amorphous phospholipid material or siderophages (gold score <0). Bronchial biopsy demonstrated thickening of the basal membrane by an amorphous basophilic substance, consistent with calcifications, without inflammatory cell infiltration. Transbronchial biopsies revealed extensive deposition of calcium along alveolar septae (fig. 3a and b). Neither alveolar inflammation nor ossification were seen. We suggested that the patient had bronchopulmonary calcinosis, in the absence of blood calcium and phosphorus abnormalities, based on the CT scan and the pathological findings.

Discussion

We describe the case of a renal transplant recipient who was under immunosuppressive treatment and who was admitted to our hospital with bilateral infiltrations in the two superior thirds of the lung. This radiological aspect was compatible with any infectious disease in an

a) b)

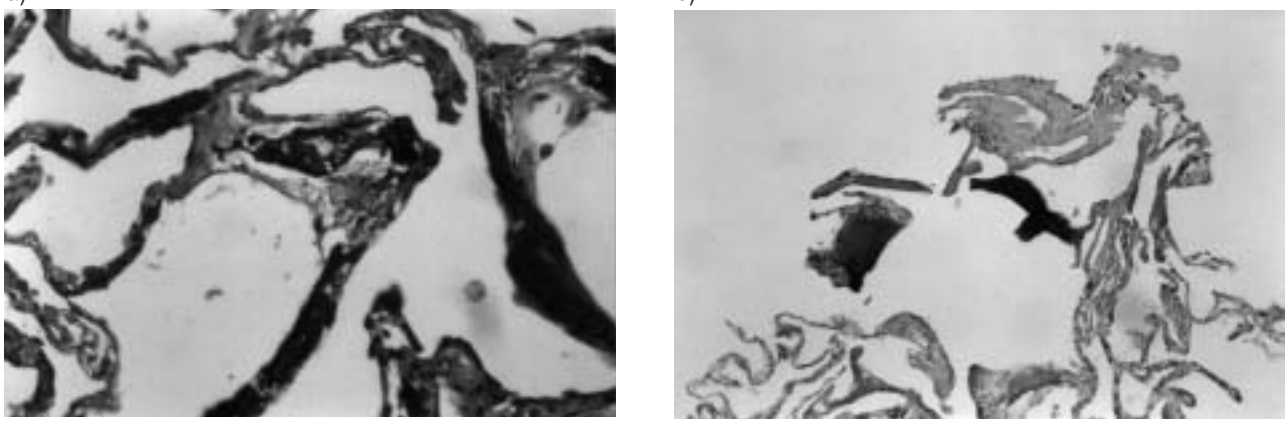

Fig. 3. – Transbronchial biopsies of the upper right lobe showing alveolar septa widened by calcification and normal alveoli. a) Haematoxylin and eosin stain; internal scale bar = 250 µm. b) Alizarine red stain; internal scale bar = 750 µM.

immunocompromised host, or with deposition of an amorphous material, *e.g.* pulmonary alveolar proteinosis, amyloidosis, alveolar microlithiasis or diffuse pulmonary calcinosis. We were able to exclude lung infection because of the clinical and functional findings. In fact, the patient was completely asymptomatic, he had no criteria of functional impairment, and his BAL fluid analysis and transbronchial biopsies showed no specific pathogens.

Pulmonary alveolar proteinosis is characterized by intra-alveolar deposition of material rich in protein, cholesterol and free fatty acids. As a predisposing factor, this patient was immunocompromised due to the maintenance immunosuppressive therapy. Chest radiography was suggestive but the clinical context and CT scan findings were not compatible with the diagnosis. Alveolar proteinosis is characterized by diffuse bilateral pulmonary shadows without calcification, but patients are more symptomatic, with dyspnoea, dry cough, weight loss and fever, and their lung function test shows a restrictive pattern. In alveolar proteinosis, CT scanning shows scattered linear densities with focal coalescences more evident at the lung bases [5]. BAL fluid analysis is the gold standard for diagnosis, showing a typical opaque milky effluent containing very few alveolar macrophages, larger acellular eosinophilic bodies in a diffuse background of eosinophilic granules, and periodic-acid-Schiff staining of the proteinaceous material, with a lack of significant Alcian blue staining [6].

Diffuse pulmonary parenchymal amyloidosis with tracheal involvement was a possible diagnosis based upon the nonspecific aspect of the chest radiograph and the CT scan. However, the findings at fibreoptic bronchoscopy and the transbronchial biopsies make this diagnosis unlikely. In this patient, there was no macroscopic evidence of amyloid deposits or endobronchial pseudotumour at fibreoptic bronchoscopy, and the transbronchial biopsies were free of amyloid deposition [7].

Idiopathic pulmonary haemosiderosis was unlikely because the patient had no anaemia of haemoptysis and this diagnosis was eliminated due to the absence of iron-laden macrophages in the BAL fluid.

Among the causes of widespread pulmonary calcification, we excluded alveolar microlithiasis, characterized by intra-alveolar calcified concretions, on the basis of radiographic appearance and CT findings. In fact, there was no radiological evidence of the pathognomonic diffuse aspect of sandstorm lung, with the "black pleural line" described by FELSON [8], and the CT scans did not reveal the high attenuation of lung parenchyma and the thin-walled subpleural cysts, as reported previously [9].

Diffuse pulmonary calcification is a disease with deposition of calcium in the walls of the alveoli and small blood vessels in an otherwise normal tissue. The disease occurs in a wide variety of clinical situations, such as primary and secondary hyperparathyroidism, chronic renal failure, chronic renal disease treated by haemodialysis or renal transplantation, vitamin D intoxication, sarcoidosis, intravenous calcium therapy, massive bone destruction caused by metastatic carcinoma, multiple myeloma, osteomyelitis, tuberculosis of the bone and milk-alkali syndrome [4]. Metastatic pulmonary calcification has been described previously in postmortem examination of a renal transplant recipient [1], and GILMAN *et al.* [4] reported the first case of the disorder occurring in a living individual. The disease was found in an asymptomatic renal transplant patient with normal serum calcium, phosphorus and magnesium, as in the present case. The diagnosis required an open lung biopsy, since at that time CT scan was not available. To diagnose the disease "antemortem" is difficult since symptoms may be absent, pulmonary function may be normal and chest radiography too insensitive [4, 10]. Calcification is rarely identified on conventional chest radiographs. When abnormalities are present, they consist mostly of nonspecific nodular infiltrates or patchy air space opacification. Technetium-99m pyrophosphate or diphosphonate bone scan could be helpful in the diagnosis of diffuse pulmonary calcinosis, revealing a diffuse lung uptake. However, its value is controversial [4] and limited when severe anaemia is present [11]. The present patient was not anaemic, but this technique was not applied, considering the pathological findings. On CT scans, multiple pulmonary nodules, which may be calcified, are the most common findings [10].

In the case reported, we based our diagnosis on the computed tomography scan and pathological findings obtained at fibreoptic bronchoscopy, avoiding open lung biopsy. The dense alveolar filling pattern, with the presence of numerous bronchial calcifications and deposits of calcium was sufficient to establish the diagnosis.

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