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CASE REPORT

Ectopic calcifications in end-stage renal failure due to different mechanisms

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Introduction

There are various mechanisms by which ectopic mineralization can take place. Metastatic calcification occurs when the calcium/phosphate solubility product in extracellular fluid is exceeded, and also when in metabolically impaired or dead tissue mineral may be deposited as dystrophic calcification despite normal serum levels of calcium and phosphate.[1,2] True bone formation or ectopic ossification may be seen in some rare disorders.[1]

There are local factors predisposing to soft-tissue calcification, i.e. local changes of pH, local changes of tissue proteins with high affinity for calcium, focal injury (infection, haematoma) and local expression of growth factors (TGF-β). Systemic factors also predispose to soft-tissue calcification, i.e. increased calcium/phosphorus product, the use of acetate instead of bicarbonate in dialysis fluid, age, and associated diseases such as secondary hyperparathyroidism, hypoparathyroidism, adynamic bone disease, aluminium overload, vitamin D intoxication and neoplasms with bone destruction.[2,3]

Soft-tissue calcifications, such as visceral, periarticular and vascular calcification, are frequently seen in persons with advanced renal failure, especially in those on long-term haemodialysis.[2–4] We report a case of two types of ectopic calcification in a man with end-stage renal failure.

Case report

A 51-year-old man with end-stage renal failure secondary to essential hypertension, and on maintenance haemodialysis for the past 7 years, was admitted for investigation of pleural effusion. He was a non-smoker with no history of tuberculosis contact. During the previous year he had presented with a cough which was initially dry but became productive with non-purulent sputum and sometimes with mild haemoptysis, associated with dyspnoea, pleuritic chest pain and an evening low-grade fever. He also had a painful mass in the left hip; the pain was exacerbated by joint use. A new mass, painless and firm, appeared 7 months later in the left shoulder. Control of serum phosphate levels had been difficult because of poor compliance with calcitriol and calcium carbonate. His respiratory symptoms persisted and he sought medical assistance in October 2002, when a chest radiograph demonstrated a large pleural effusion in the left lung (Fig. 1a). He was immediately admitted for investigation.

Clinical examination found a 10 cm mass overlying the left shoulder joint (Fig. 2a) and a 20 cm mass in the left hip joint (Fig. 3a). The masses were bulging and firm, without evidence of flocculation, necrosis or ulceration. Vesicular breath sounds were absent in the two thirds of the right hemithorax, but systemic examination was otherwise normal.

Results of laboratory assessments on admission were as follows: haemoglobin 11.5 g/dl; white blood cell count, 11.10×10^9/l, with 11% band; platelets, 218×10^3 cells/mm^3; serum creatinine, 11.1 mg/dl; serum urea, 206 mg/dl; plasma glucose, 75 mg/dl; serum calcium, 8.0 mg/dl; serum phosphate, 6.6 mg/dl; calcium/phosphate product, 52.8 mg/dl^2; and serum intact parathyroid

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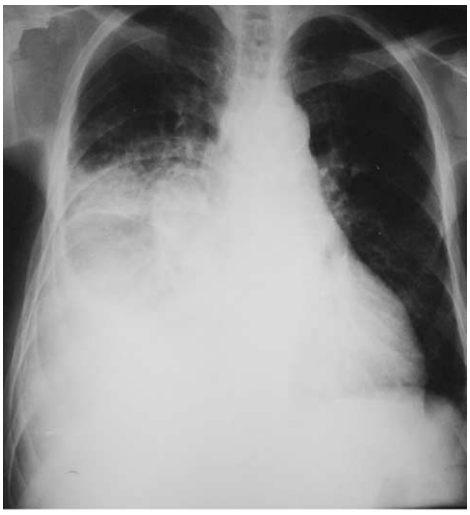

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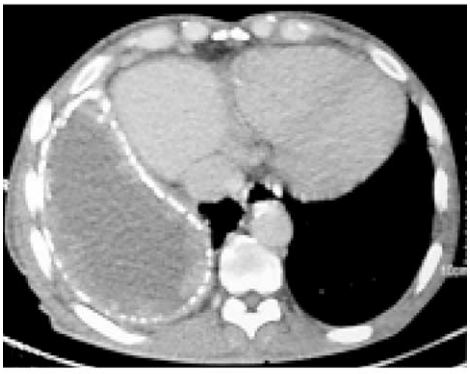


(b)

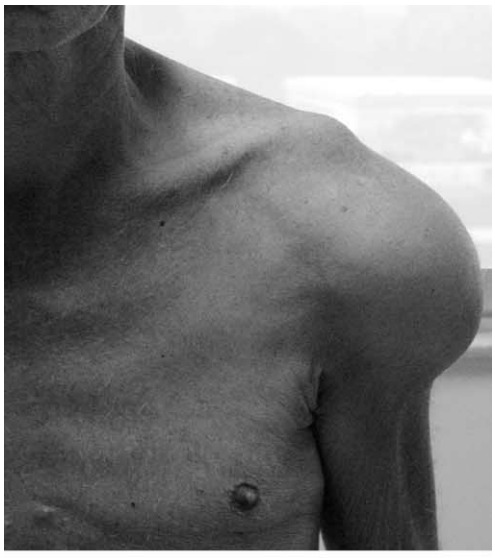
Figure 1 (a) Plain radiography and (b) computed tomography of the thorax reveal a large left pleural effusion and a calcified rim of thickened pleura.

hormone, 108 pg/ml. Radiological examination depicted extensive periarticular soft-tissue calcification, without evidence of bony involvement (Figs 2b, c and 3b, c).

At diagnostic thoracentesis the white cell count was 11.60×10^9/l, with 63% polymorphonuclear cells; pH, 6.95; lactate dehydrogenase, 11.704 U/ml; and total proteins, 3.1 g/dl. Cytological examination demonstrated haemorrhagic smears composed predominantly of lymphocytes and reactive mesothelial cells. Pleuroscopy and pleural biopsy showed a non-specific inflammatory reaction. No malignant cells or granulomas were seen and cultures, including for acid-fast bacilli, were negative.

Discussion

Two different mechanisms seem to be involved in



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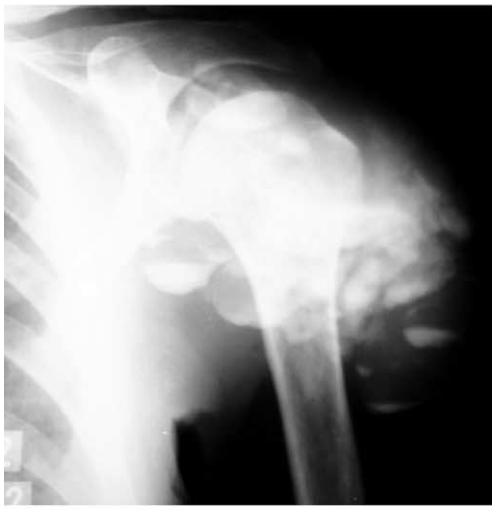

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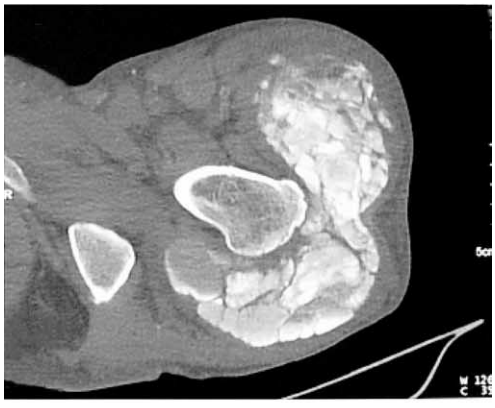
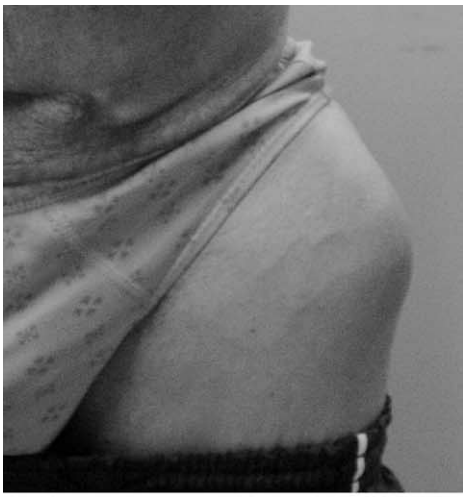
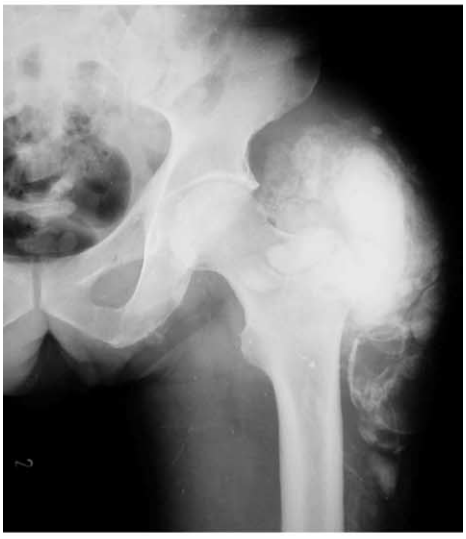


(c)

Figure 2 (a) Left shoulder mass. (b) Plain radiography and (c) computed tomography of the left shoulder reveal extensive periarticular soft-tissue calcification, without evidence of bony involvement.



(a)



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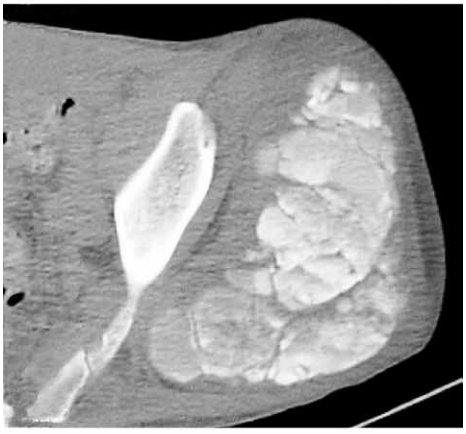

(c)

Figure 3 (a) Left hip mass. (b) Plain radiography and (c) computed tomography of the left hip demonstrate extensive periarticular soft-tissue calcification, without evidence of bony involvement.

the soft-tissue calcifications found in this man with end-stage renal failure.

Tumoral calcinosis due to long-standing hyperphosphataemia and persistently elevated calcium/-phosphate product could account for the calcification of periarticular subcutaneous tissues around the major joints.[11,12] Typically the hips and shoulders are affected, although additional joints such as elbows, feet, hands and wrists can become involved.[1,2,4,9,10] These soft-tissue masses of ectopic calcification are usually painless, with no apparent clinical symptoms.[1-3] Because the deposits are extracapsular, joint mobility is not impaired unless the tumours are particularly large.[1,4,13] In a minority of patients they can produce pain when there is compression of adjacent neural structures.[1,4]

The lesions can also ulcerate the skin[1,4,9] and this complication can lead to infection, septicaemia, anaemia, low-grade fever, regional lymphadenopathy, splenomegaly and amyloidosis.[1,2,12]. There are reports of tumoral calcinosis with signs of systemic inflammation leading to fever and other constitutional symptoms.[14] These signs may mimic infection and could therefore cause the cancellation of a renal transplantation.[10] The progression of tumoral calcinosis is usually slow but variable, and some masses can enlarge rapidly.[2]

The lesions of tumoral calcinosis are hard, lobulated and firmly attached to deep fascia.[1] They show a lobulated capsule with an internal chalky and gritty deposit that is separated by fibrous septa. Histologically the wall of the capsule contains collagenous fibrous tissues with foreign-body giant cells, and is lined with inflammatory granulomatous tissue. It differs from ossification in its lack of organization into a trabecular pattern with a cortex and medulla.[2] The fluid within the capsule may have an appearance of milky fluid,[10] and its analysis reveals high concentrations of calcium phosphate and calcium carbonate combinations.[15]

On radiographic examination, these tumours typically appear as large aggregations of irregular, densely calcified lobules confined to soft tissue. Bone erosion is rare and may be the result of repeated microtrauma to the bone which is often caused by the large size of the masses.[2] As in this case, the joints are unaffected.[1] Bone radiography is the best method to detect and localize the calcified masses[16] and also to follow the resolution of extraskeletal uptake.[17]

On the other hand, the pleural calcification is probably dystrophic. Investigation of this patient's pleural effusion demonstrated an exudate with high LDL levels and low pH, raising the suspicion of

infection or malignancy. However, a pleural biopsy and culture of the pleural effusion were negative for malignancy, tuberculosis or other infectious organisms. Chronic local inflammatory activity was thus probably responsible for the pleural calcification.

In dystrophic calcification, the levels of calcium and inorganic phosphate present in serum or extracellular fluid are too low for spontaneous precipitation but, once crystal nucleation has begun, hydroxyapatite formation can follow. Injured tissue of any kind is predisposed to dystrophic calcification because such tissue can release material that has nucleating properties. One example of this phenomenon is the caseous lesion of tuberculosis, and other diseases, such as systemic lupus erythematosus, scleroderma and dermatomyositis, can lead to this type of ectopic calcification.[1] Chronic inflammatory processes involving monocyte/macrophage infiltration further contribute directly to the calcification process by cell–cell interaction and production of soluble factors such as TNF-α.[5] Although the levels of calcium and phosphorus are characteristically normal, mineral precipitation into injured tissue is more striking and severe when the levels in extracellular fluid of these electrolytes are increased.[1]

Delay in the treatment of a parapneumonic effusion can lead to a purulent and organized stage. Intrapleural fibrinolytic therapy can facilitate thoracostomy tube drainage and prevent the appearance of thick pleural "peel"[6,7] that usually develops after treatment of complicated parapneumonic effusion.[6] This kind of calcification may resolve slowly over several months[6,8] but its presence can predict failure of non-operative treatment.[7] However, the role of intrapleural fibrinolytics and the optimal timing of surgical intervention are unknown.[7] Surgical decortication should be reserved for selected patients with established fibrothorax.[6]

Since the management of ectopic calcification is difficult, it is better to prevent its formation, and control of serum phosphate levels is crucial to prevent tumoral calcinosis. Management of tumoral calcinosis and tumour-like calcifications, particularly in patients with chronic renal failure, is often difficult and regularly unsuccessful.[2,3] Usually the treatment involves dietary phosphate restriction, phosphate binders, intensification of dialysis treatment, dialysis using a low-calcium dialysate, parathyroidectomy in those with high PTH levels[18] and surgical excision of the calcified masses.[10] Phosphorus binders constitute the mainstay of serum phosphorus level control in end-stage renal disease. Phosphorus retention is related to an imbalance between phosphorus intake and removal by dialysis, and is usually aggravated when vitamin D analogues are prescribed. The amount of phosphorus removed by standard haemodialysis is insufficient to achieve a neutral phosphorus balance when protein intake is >50 g/day, but additional protein restriction, leading to decreased phosphate absorption, may impose the risk of malnutrition. More frequent dialysis (daily) is preferable and may achieve a regression of the deposits.[19]

Good control of metabolic acidosis may also be helpful in preventing the soft-tissue calcification.[2] An alternative approach is a relatively low dialysate calcium concentration, in an attempt to decrease serum calcium and the calcium/phosphorus product.

If tumoral calcinosis is associated with high plasma PTH levels, it may reverse after surgical correction of parathyroid overfunction.[2,11,20] In patients with aluminum intoxication, pseudotumoral calcifications may regress during aluminium chelation therapy despite progression of hyperparathyroidism, because aluminium may predispose to dystrophic or metastatic calcification.[21] When calcification is associated with normal or low bone turnover, the regression is more difficult and has been obtained only after changing to more intensive haemodialysis treatment schedules with low-calcium dialysate[10,19] or after renal transplantation.[22] McGregor et al. reported a case of rapid resolution of tumoral calcinosis after successful renal transplantation.[22]

Bisphosphonates, steroidal and non-steroidal anti-inflammatory drugs have been considered for the treatment of severe soft-tissue calcifications in uraemic individuals, but no controlled studies are available.[2] These drugs may be beneficial by suppressing osteoclastic activity and releasing proinflammatory cytokines. Phanish et al. reported a case where tumoral calcinosis in the left shoulder caused an inflammatory reaction with excellent response to bisphosphonates, which enabled them to proceed with renal transplantation.[8] Others reports regarding the use of bisphosphonates in the treatment of ectopic calcification have shown either no therapeutic effect, inconsistent results[18] or complete regression of soft-tissue calcifications.[23] Radiotherapy and cortisone injections have been helpful in reducing the tumour in some studies.[15]

Surgical removal of subcutaneous calcified masses may be helpful if they are painful, interfere with function or are cosmetically unacceptable.[1] The recurrence rate has been related to the size of the lesion[2] and it is very frequent in large masses.

This case illustrates two different types of calcification: metastatic, due to hyperphosphataemia and located in the hip and shoulder periarticular joints, and dystrophic, due to a presumed chronic local inflammatory response and located within the pleura. We have not found any previous reports of both types of calcification occurring in the same person.

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