CASE REPORT

Unresolved lytic lesions following parathyroidectomy in a patient with chronic renal failure

W. M. M. Fok, H. B. Leung
From Queen Mary Hospital, Hong Kong, China

With advances in the treatment of patients with chronic renal failure, their life expectancy has increased. In turn, the prevalence of osteitis fibrosa cystica, a manifestation of secondary hyperparathyroidism, and \( \beta_2 \) microglobulin amyloidosis, a result of long-term haemodialysis, has risen. While both conditions share similar radiological features, their management is very different.

We present the case of a patient with renal failure who had been receiving haemodialysis for over 20 years. Lytic lesions had been observed in the proximal part of both femurs for ten years. A presumptive diagnosis of osteitis fibrosa cystica was made. However, no regression of the lesions occurred after parathyroidectomy. The patient subsequently developed sequential pathological fractures through the lesions, for which bilateral total hip replacements were performed. Histology of the lesions revealed that the patient was in fact suffering from amyloidosis.

In patients with chronic renal failure, osseous amyloidosis is a highly probable differential diagnosis, especially if no regression of a lytic lesion is observed after parathyroidectomy.

The use of haemodialysis extends the life expectancy of patients with chronic renal failure and produces an increase in the occurrence of osteitis fibrosa cystica and \( \beta_2 \) microglobulin amyloidosis. While both conditions share similar radiological features, their treatment requirements are different.

Osteitis fibrosa cystica, also known as a brown tumour, is an advanced skeletal abnormality in patients with hyperparathyroidism, which can be primary, secondary or tertiary.\(^1,2\) Parathyroidectomy results in a reversal of bone loss and mineralisation of these bony lesions and is therefore thought to be the most appropriate treatment for osteitis fibrosa cystica.\(^3-6\) Even though the possibility of pathological fracture can arise at the site of the bony lesion, prophylactic fixation has not been recommended as the first line of therapy.\(^4\)

\( \beta_2 \) microglobulin amyloidosis commonly occurs in patients requiring long-term haemodialysis, but may also occur in those undergoing continuous ambulatory peritoneal dialysis and even in those with early renal failure.\(^7,8\) It is believed that the increased level of \( \beta_2 \) microglobulin is a result of failure of clearance by the diseased kidney and the dialysis membranes. As a result, amyloid deposits may be found in the bone, articular cartilage and synovium, leading to a destructive arthropathy and bone cysts. Enlargement of these cysts and an increase in their number may be observed over time.\(^7\) Management includes radiological monitoring, prophylactic stabilisation, fracture fixation for pathological fractures and renal transplantation.\(^7\) We report a case of secondary hyperparathyroidism with lytic lesions located at the neck and trochanteric regions of both femurs.

Case report

A 53-year-old man suffering from end-stage renal failure due to tuberculosis of both kidneys had been receiving haemodialysis since 1980 when he was 28 years old. He subsequently developed secondary hyperparathyroidism, and a partial parathyroidectomy to remove the right inferior hyperplastic parathyroid gland was performed in 1997. He was first seen by the orthopaedic team after a hyperextension injury of his neck, resulting in tetraparesis in 1998. An MR scan showed cervical spinal stenosis resulting from the ossification of the posterior longitudinal ligament. He made a satisfactory recovery following C3-7 laminoplasty. He was able to walk with the support of a stick after rehabilitation. At that time, radiographs showed lytic lesions in the
In July 2003, he was admitted with a four-day history of pain in the left hip. There was no history of trauma. Radiographs showed an incomplete fracture at the site of a previously noted lytic defect involving the femoral neck. As the fracture was impacted in a valgus position the option of conservative management or surgery was discussed, with the patient electing to be treated non-operatively. However, one month later he returned with further pain. Repeat radiographs showed no evidence of healing and this was confirmed by CT scanning (Fig. 2). Total hip replacement (THR) was performed in September 2003 (Fig. 3). Intraoperatively, a brown soft-tissue mass was found occupying part of the femoral head, neck and trochanteric region. Histological analysis revealed a loss of bone marrow with the cavity being filled with amyloid deposits and fibrovascular tissue. No giant cells could be found, suggesting a diagnosis of amyloidosis.

His recovery was relatively slow because of the underlying end-stage renal failure and was further complicated by deep-vein thrombosis of the left subclavian vein, requiring anti-coagulation. On discharge he was only able to walk with a stick for a short distance.

He was reviewed regularly with radiological examination of both hips during the next three years. While no loosening of the left THR was detected either clinically or radiologically, the lytic lesion of the right proximal femur remained unchanged with no obvious mineralisation. In July 2006, he reported the gradual onset of pain in the right hip and difficulty in walking. Blood tests showed an increase in the level of PTH and radiographs showed a displaced fracture of the neck of the femur at the site of a previous lytic lesion (Fig. 4). A THR was performed on the right hip. As before, intra-operatively a brown soft-tissue mass was noted involving the femoral head and neck. Histological examination found amyloid tissue.

Debilitated by the long-standing end-stage renal failure, his general condition gradually deteriorated and he developed multiple pressure sores. He died of acute pulmonary oedema eight months after the second THR.

Discussion

Osteitis fibrosa cystica can occur in patients with hyperparathyroidism.\textsuperscript{4,9,10} It was first described by Von Recklinghausen in 1891\textsuperscript{11} but its association with hyperparathyroidism was only confirmed in 1925.\textsuperscript{11} An improvement in skeletal abnormalities was observed after resection of a parathyroid adenoma.\textsuperscript{11} Although a brown tumour was first considered to be characteristic of primary hyperparathyroidism, it is now increasingly seen in patients undergoing dialysis and is recognised as a characteristic of secondary\textsuperscript{4,11-14} and tertiary hyperparathyroidism.\textsuperscript{1} Radiologically, it has the appearance of a well-circumscribed expansile lytic lesion of the bone\textsuperscript{10,11,13} and may present as a single or multiple lesions. Any bone may be involved but it tends to occur preferentially in the mandible, clavicle, ribs, pelvis and femur.\textsuperscript{11,13,14} Excessive PTH produces increased bone

neck and trochanteric regions of both femurs (Fig. 1). As the radiological features were compatible with osteitis fibrosa cystica, he remained under observation, with the assumption that the bony lesions would gradually mineralise as a result of the parathyroidectomy. The parathyroid hormone (PTH) level was monitored over eight years and remained within normal limits.
breakdown by osteoclastic resorption and the resultant cavity is filled with fibrous tissue. Irregularly thickened woven trabecular bone is also present surrounded by loose fibrous tissue and increased numbers of osteoblasts and osteoclasts. The weakened bone is prone to micro-fractures from which the resulting haematoma and the growth of fibrous tissue promote an influx of macrophages and the emergence of giant cells. The brown discoloration reflects the vascular elements and haemosiderin deposition.

When osteitis fibrosa cystica is identified prior to fracture, parathyroidectomy is the most effective treatment and will encourage remineralisation and an increase in the overall bone mineral density, however, not all lesions will regress post-operatively. One report including 27 patients suffering from primary hyperparathyroidism and osteitis fibrosa cystica showed six patients had incomplete radiological regression four years after parathyroidectomy, with variable degrees of remineralisation between different patients and in lesions in the same patient. No prognostic factor was identified which would identify which tumours would regress after parathyroidectomy, but lesions located in cancellous bone seemed to have a higher chance of regression than cortical ones. This may reflect differences in the rate of bone turnover.

Curettage, bone grafting and stabilisation for pathological fractures cannot be guaranteed to produce remineralisation and even if it occurs, the rate of regression remains unpredictable. Therefore, surgical intervention may be best reserved for persistently symptomatic lesions, and asymptomatic but unregressive osteolytic lesions in sites of high stress.

β2 microglobulin amyloidosis has been documented in patients with renal failure since the mid-1980s. β2 microglobulin is an 11.8-kd glycosylated polypeptide that is an integral part of the human leukocyte antigen class I antigen complex. As the kidney is the major eliminator of β2 microglobulin its level will rise dramatically in patients with renal failure, which as it accumulates becomes deposited within the body, leading to amyloidosis. Although the plasma level of β2 microglobulin has no bearing on the clinical severity, prolonged haemodialysis of 20 years and old age at the start of therapy have been noted to correlate with an inferior outcome. β2 microglobulin amyloid may be deposited in the viscera including the heart, gastrointestinal tract and lung, leading to heart failure, and ischaemic colitis. More commonly it is deposited in the osteoarticular system, particularly in the synovial membrane, and patients may present with carpal tunnel syndrome, bony erosions and bone cysts. In severe cases, they may present with a destructive arthropathy.

Histologically, β2 microglobulin amyloid shares similar features with other amyloid deposits. On light microscopy an amorphous appearance is noted when using routine haematoxylin and eosin stains, but positive staining with Congo red producing red-green birefringence under polarised light is characteristic of amyloid. Electron microscopy shows a fibrillar appearance with the fibrils approximately 10 nm in diameter and of variable length. X-ray diffraction or infra-red techniques reveal features of proteins with a crossed β-pleated sheet.

The radiological characteristics of β2 microglobulin amyloidosis are subchondral bone cysts or lucencies, large punched-out bony erosions and peri-articular soft-tissue swelling. While the diagnosis relies on its histological findings, it is clearly suggested in patients with chronic renal failure who have the typical radiological features.
The only proven effective therapy that can halt the progression of β2 microglobulin amyloidosis is a successful renal transplant, which is likely to resolve osteoarticular symptoms and in serum levels of β2 microglobulin, but pre-existing bone lesions do not regress. Such lesions require regular radiological monitoring and prophylactic internal stabilisation if a fracture is impending. This is in contrast to the management of osteitis fibrosa cystica, for which parathyroidectomy is the treatment of choice.

In our reported patient, osteolytic lesions had been present in both femurs for more than ten years. As he had secondary hyperparathyroidism, the diagnosis of osteitis fibrosa cystica was suspected but the lytic defects remained unchanged for ten years after parathyroidectomy. The intra-operative finding was compatible with brown tumour. The diagnosis of amyloidosis became apparent histologically.

As the definite diagnosis of osteitis fibrosa cystica and amyloidosis relies on histological findings, a biopsy may be indicated for lytic lesions that do not resolve after parathyroidectomy. At the same time, the threshold for prophylactic surgical intervention may need to be lowered if the lesion shows no sign of regression.

The authors thank Dr F. O. K Po Kai for assistance in editing this manuscript. No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

References