CASE REPORT

Bilateral insufficiency fracture of the femoral head and neck in a case of oncogenic osteomalacia

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We describe a case of oncogenic osteomalacia in an adult male who presented with low back pain and bilateral hip pain. Extensive investigations had failed to find a cause. A plain pelvic radiograph showed Looser’s zones in both femoral necks. MRI confirmed the presence of insufficiency fractures bilaterally in the femoral head and neck. Biochemical investigations confirmed osteomalacia which was unresponsive to treatment with vitamin D and calcium. A persistently low serum phosphate level suggested a diagnosis of hypophosphataemic osteomalacia. The level of fibroblast growth factor-23 was highly raised, indicating the cause as oncogenic osteomalacia. This was confirmed on positron-emission tomography, MRI and excision of a benign fibrous histiocytoma following a rapid recovery.

The diagnosis of oncogenic osteomalacia may be delayed due to the non-specific presenting symptoms. Subchondral insufficiency fractures of the femoral head may be missed unless specifically looked for.

Oncogenic osteomalacia is a rare tumour-associated disorder characterised by hypophosphataemia, phosphaturia, normocalcaemia, and osteomalacia in the absence of a family history of rickets, heavy metal poisoning, or Fanconi’s syndrome. The concentration of the serum alkaline phosphatase is increased and that of the serum 1,25-dihydroxycholecalciferol is decreased. Affected patients typically present with bone pain, proximal muscle weakness and fractures. The disorder may manifest as rickets if it occurs before fusion of the growth plate. Tumours associated with this disorder are generally small, benign and of mesenchymal origin, although it has occasionally been associated with malignant tumours.

Subchondral insufficiency fractures have been reported in both osteoporotic elderly patients and recipients of renal transplants, but we are not aware of any previous report of bilateral subchondral insufficiency fractures of the femoral head in conjunction with oncogenic osteomalacia. It has been reported that at the onset of pain, unenhanced radiographs show no obvious findings, but MR imaging demonstrates insufficiency fractures as hypo-intense lines or fissures on T1- and T2-weighted and short-tau inversion recovery images. Most cases resolve with conservative treatment but collapse of the femoral head was observed in one case. We describe a case of oncogenic osteomalacia with insufficiency fractures.

Case report

A 32-year-old man, who had enjoyed good health until 18 months prior to presentation, had initially experienced pain in his right foot and gradually developed symptoms in both lower limbs, predominantly involving the hips and lower back. He had noted proximal muscle weakness for six months and had difficulty in walking for five months. Radiographs of the spine, an MRI of the lumbosacral spine and electrophysiological studies were all normal. The pain increased over a further six months and he became bedridden. Examination revealed tenderness present in the region of the right hip, with pain at the limits of movement of the right hip with a normal range of movement of the left hip. A radiograph of the pelvis revealed diffuse osteopenia of both hips with thinning of the cortex and indistinct margins. Looser’s zones were seen in the femoral necks bilaterally (Fig. 1) and a diagnosis of osteomalacia was made. The serum phosphate level was low (0.226 mmol/L) and the alkaline phosphatase level elevated (230 U/l). The serum calcium (2.2 mmol/L) and the parathyroid hormone levels (38.5 pg/mL) were normal.
The serum level of 1,25 dihydroxycalciferol was 7.9 pg ml. The renal and thyroid function tests were normal. He was treated with vitamin D and phosphate for four months without symptomatic or radiological improvement and the phosphate levels remained low.

MRI studies revealed osteoporosis. T1 and short-tau inversion recovery images showed linear hypointense signals in the subchondral region of both femoral heads and necks consistent with insufficiency fractures (Fig. 2).

These biochemical and radiological findings led to the diagnosis of hypophosphataemic osteomalacia. This was attributed to oncogenic osteomalacia due to the markedly elevated level of fibroblast growth factor-23 (FGF-23) at 673 RU/ml. Additional physical examination identified a small nodule in the right thigh which measured 2.2 cm in diameter on positron emission tomography (PET) and was seen as a hypermetabolic nodule (Fig. 3).

Further localisation (Fig. 4) suggested that the lesion was a benign mesenchymal soft-tissue neoplasm. Angiography showed a moderately hypervascular soft-tissue lesion supplied by the superficial femoral and profunda femoris arteries (Fig. 5).

The lesion was excised. He made a rapid symptomatic improvement with complete recovery after one month. The phosphate level returned to normal. Muscle recovery started after two weeks, gaining good strength by three months. The appearance of the hips on MR scans returned to normal six months later.

The histopathological diagnosis of the tumour was a benign fibrous histiocytoma.

Discussion
Oncogenic or tumour-induced osteomalacia is a rare condition in which complete remission occurs after resection of the tumour. The diagnosis of tumour-induced osteomalacia is difficult as the symptoms of osteomalacia are non-specific and may be incorrectly attributed to fibromyalgia, inflammatory arthritis or a functional disorder. Tumour-induced osteomalacia should be included in the differential diagnosis in patients with progressive weakness, bone and muscle pain and fractures. Diagnosis in our patient was delayed for about 18 months, during which time costly investigations were initiated due to lack of awareness regarding the presentation of oncogenic osteomalacia. Diagnosis can be further delayed by the small size of these tumours and their presence in multiple nonspecific locations. Routine investigations such as serum calcium, phosphate and alkaline phosphatase levels are very important in such cases, especially the fasting serum phosphate level. A persistently low fasting serum phosphate level with a raised level of alkaline phosphatase should suggest a differential
Whole-body positron emission tomographic scan showing increased metabolic activity in the lesion in the right thigh. No other area of abnormally increased tracer uptake can be seen, which would suggest active disease.

MRI of right thigh shows a lobulated mass involving the subcutaneous tissue of the anteromedial aspect of the right upper thigh. It appears isointense on a) T1-weighted axial image and hyperintense on b) Short-tau inversion recovery coronal image, measuring 2.5 cm × 1.9 cm. A transverse section c) shows near homogenous intensity post-contrast enhancement on fat suppressed T1 (arrow). These findings are suggestive of a mesenchymal benign soft-tissue tumour.

diagnosis such as autosomal-dominant hypophosphataemic rickets, X-linked hypophosphataemic rickets and tumour-induced osteomalacia.1

FGF-23 is a new marker for oncogenic osteomalacia. It is a secreted peptide hormone overproduced by the tumour in patients with this condition. It inhibits reabsorption of phosphate from the kidney resulting in hypophosphataemia. Detection of elevated FGF-23 levels in serum using enzyme-linked immuno-absorbent assays pre-operatively, and of FGF-23 expression in the causative tumour, demonstrates the value of these tests in the diagnosis of this condition. The serum levels of FGF-23 fall after surgical removal of the tumour and can be used to monitor recovery.7,8

PET scanning is an established investigation for patients with tumours. It can be used in primary imaging, following the response to treatment, for the diagnosis of recurrence and for staging. The most commonly used tracer is 2-fluoro-2-deoxy-D-glucose (FDG) labelled with fluorine 18. FDG-PET scanning is based on the principle that tumour cells have a high rate of glucose metabolism and scanning of the whole body is sensitive in detecting an occult tumour in a suspected case of oncogenic osteomalacia.9

Thorough clinical examination is essential in all cases of oncogenic osteomalacia as occasionally a small tumour can be localised through palpitation, as occurred in our patient. Subchondral insufficiency fracture is a relatively new concept and few cases have been reported.10 It can be easily
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Confused with osteonecrosis of the femoral head. This latter condition is a progressive disorder which is unlikely to resolve without intervention. As our patient improved without any medication or surgery to the femoral head it is unlikely that osteonecrosis was present. On T1-weighted images, the classic MRI appearance of osteonecrosis is that of a region of decreased marrow signal within the normally bright fat signal of the femoral head. This area is frequently surrounded by a low-signal band, representing ischaemic bone. T2-weighted images reveal a second inner band of bright signal, and the resulting appearance has been termed the ‘double line’ sign. This sign is essentially diagnostic of osteonecrosis while in insufficiency fractures low-signal intensity lines are typically seen in the femoral head in both the T1- and STIR images, representing the fracture lines. The appearance of bone marrow oedema as a low intensity signal in T1-weighted images and a high intensity signal in T2-weighted images is present in acute cases, but may be absent in chronic cases such as our patient.

Oncogenic osteomalacia is a rare acquired metabolic disorder characterised by hypophosphataemia and low serum levels of 1,25-dihydroxycholecalciferol. Diagnosis is commonly delayed due to the nonspecific nature of the symptoms, failure to determine the serum phosphate levels during the testing of blood chemistry, and difficulty in identifying the responsible tumour. Once diagnosed, an excellent outcome follows surgical treatment.

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References