Oncogenic osteomalacia caused by phosphaturic mesenchymal tumours in the proximal and shaft of the tibia: a case report

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ABSTRACT

Oncogenic osteomalacia is caused by a small mesenchymal tumour characterised by phosphaturia, hypophosphatemia, decreased serum vitamin D3 level, and osteomalacia. Phosphaturic mesenchymal tumour of the mixed connective tissue type (PMTMCT) is the commonest subtype and usually involves a single site. We report a case of PMTMCT involving the left proximal and shaft of the tibia in a 42-year-old man.

Key words: oncogenic osteomalacia; tibia

INTRODUCTION

Oncogenic osteomalacia, also known as tumour-induced osteomalacia, is a rare paraneoplastic syndrome caused by a mesenchymal tumour that produces proteins that exert a regulatory influence independently or cooperatively on phosphate homeostasis by distinct mechanisms.1–4 These proteins, also known as phosphatonins, include fibroblast growth factor 23 (FGF-23), secreted frizzled-related protein 4, matrix extracellular phosphoglycoprotein, and FGF-7.1–4 FGF-23 inhibits the sodium-phosphate renal co-transporters and suppresses 1α-hydroxylase activity, resulting in decreased renal resorption and increased urine excretion of the phosphate.2 Clinical symptoms include bone pain, muscle weakness, osteopaenia, bone fractures, and gait disturbance. Biochemical findings show hypophosphatemia, phosphaturia, low serum of 1,25-dihydroxyvitamin D, and elevated serum alkaline phosphatase.2–6

Approximately 340 cases of oncogenic osteomalacia have been reported. Most are caused by phosphaturic mesenchymal tumours of various types. The most common subtype is the phosphaturic mesenchymal tumour of the mixed connective tissue type (PMTMCT), which accounts for 70% to 80%.7 The other subtypes include osteoblastoma-like tumours, ossifying fibrous-like tumours, and non-ossifying fibrous-like tumours.8 Most of the oncogenic osteomalacia tumours are located in either
bone or soft tissue, particularly long bones of lower extremity and craniofacial region.\textsuperscript{1,2,6} The tumours are mostly benign and usually involve a single site.\textsuperscript{2,7} The male-to-female ratio is 1.2:1.\textsuperscript{2} Most cases occur in middle-aged individuals, although patients can be as young as 3 years and as old as 73 years.\textsuperscript{7}

We report a case of PMTMCT involving the proximal metaphysis and diaphysis of the tibia in a 42-year-old man.

**CASE REPORT**

In October 2010, a 42-year-old man who had undergone spinal surgery for degenerative disc disease 5 years earlier presented with a 3-year history of progressive bone pain, muscle weakness, and difficulty in ambulation. Two years after symptom onset, he required a walker for walking. Six months later, he was unable to walk and became confined to bed. Analgesic drugs were ineffective for bone pain. On examination, he was cachectic with a kyphotic back. Both sides of the ribs were tender on palpation. No palpable mass was noted over any part of his body. He had no history of trauma or familial history of metabolic bone disease.

Blood tests revealed a low serum phosphate level of 1.4 mg/dl (normal range, 2.5–4.9 mg/dl), a normal serum calcium level of 9.2 mg/dl (normal range, 8.5–10.1 mg/dl), a high serum alkaline phosphatase level of 358 UI/l (normal range, 50–136 UI/L), a normal parathyroid hormone level of 32 pg/ml (normal range, 10–65 pg/ml), and low tubular resorption of phosphorus clearance of 49% (normal range, 84%–91%). Complete blood count, erythrocyte sedimentation rate, serum protein electrophoresis, and serum thyroid-stimulating hormone were normal. Tests for plasma FGF-23 was not available in our country.

Radiography showed osteopaenia, multiple collapsed vertebral bodies, rib fractures, bilateral incomplete trochanteric fractures of both femurs, and Looser’s zone (pseudofracture) in the left ulna and right fibula (Fig. 1). There was no bony lesion in the left tibia. Bone scan showed multiple foci of abnormal uptake of the radiotracer in the ribs, both shoulders, both elbows, left radius, both wrists, both knees, both proximal femurs, right fibula, and spines (Fig. 2). Bone mineral density (BMD) of the femoral neck was 0.358 g/cm\textsuperscript{3} and the Z-score was -3.7 standard deviation (SD). Magnetic resonance imaging (MRI) showed multilevel vertebral compression fractures and incomplete fractures in the trochanter of both femurs secondary to osteomalacia. Two lesions were noted in the lateral upper and mid-shaft of the left tibia with low signal on T1-weighted images, and high signal on STIR and gadolinium-enhanced images (Fig. 3).

The patient underwent open curettage of both bony lesions, and defects were filled with bone substitutes. Histological features of the proximal tibial lesion showed clusters of spindle cells and blood vessel proliferation in bone (Fig. 4). The vessels consisted of capillaries in a hemangiopericyte blood vessel pattern. The spindle cells between bony trabeculae had oval nuclei, indistinct nucleoli, and eosinophilic cytoplasm. Numerous mature fat cells intermingled with blood vessels. Grungy or flocculent calcification

![Figure 1](image-url)  
**Figure 1**  Radiographs showing (a) collapsed lumbar vertebral bodies fixed with pedicular screws at L5 and S1 levels, (b) bilateral incomplete trochanteric fractures of both femurs (arrows), and (c) Looser’s zone (pseudofracture) at diaphyses of the left ulna and right fibula (arrows).
was noted. Mitoses were rare. Histological features of the diaphyseal tibial lesion included spindle-shaped cells in the matrix intermingling with blood vessels, which often showed thick walls with hyalinisation (Fig. 4). Spindle cells had oval nuclei, fine chromatin, and eosinophilic cytoplasm. Microcystic changes and grungy or flocculent calcification were noted. A diagnosis of PMTMT was made for both lesions, although the FGF-23 immunohistochemistry stain was not available in our facility.

One week later, serum phosphate levels returned to 2.8 mg/dl (normal range, 2.5–4.9 mg/dl). Bone pain was resolved, and the patient was able to walk with a walker one month later. The patient was treated with oral calcium, calcitriol, and phosphorous supplements. At 6 months, BMD of the femoral neck increased to 0.696 g/cm² and the Z-score was -1.1 SD, and the patient was able to walk without any walking aid. At one year, trochanteric fractures of both femurs had healed (Fig. 5).

**DISCUSSION**

The phosphaturic hormones called ‘phosphatonins’ have a critical role in oncogenic osteomalacia. FGF-23 is the main causative phosphatonin, although matrix extracellular phosphoglycoprotein, frizzled-related protein 4, and FGF-7 are also implicated.²⁰,¹⁰
FGF-23, which is produced by osteomalacia-inducing tumours,\textsuperscript{11} inhibits the sodium-phosphate renal co-transporters and causes hypophosphatemia secondary to impaired renal tubular reabsorption of phosphate. FGF-23 also suppresses 1\(\alpha\)-hydroxylase activity, which blunts the compensatory rise in serum 1,25-dihydroxyvitamin D in response to hypophosphatemia.\textsuperscript{1–4}

Oncogenic osteomalacia caused by 2 lesions in different locations is rare. In one such case, the first lesion was reported in the tibia and the second one in the maxillary sinus 2 years later, which was not metastasis because of benign-appearing tumour features on histopathology.\textsuperscript{12}

The tumour that causes oncogenic osteomalacia is usually very small, slow-growing, and difficult to locate.\textsuperscript{2,5,6} Symptoms are often non-specific and serum phosphorus levels are not routinely measured; therefore, delay in diagnosis is not uncommon. The typical time from symptom onset to a presumptive diagnosis is often longer than 2.5 years, and the average time to identify the responsible tumour is 5 years.\textsuperscript{2,4,6} Tumour-induced osteomalacia should be suspected if the patient presents with progressive, generalised bone pain and muscle weakness, and radiology reveals signs of osteopaenia such as Looser’s zone (also known as pseudofracture) or multiple fractures. Hypophosphatemia caused by impaired renal phosphate reabsorption is the biochemical indicator of the disease.\textsuperscript{2} The differential diagnosis for hypophosphatemia can be classified into genetic and acquired causes. Genetic diseases
such as X-linked hypophosphatemia, autosomal-dominant hypophosphatemic rickets, and autosomal-recessive hypophosphatemic rickets may have an onset in childhood or may be associated with a positive family history. Most of the acquired causes of hypophosphatemia are the result of direct renal tubular damage by a drug or toxin. Other disorders associated with hypophosphatemia are Fanconi-type syndrome (with more severe proximal renal tubular defects and metabolic acidosis), haematological malignancies, total parenteral nutrition, organ transplant, refeeding syndrome, correction of diabetic ketoacidosis, and dietary deficiency. The presence of renal phosphate wasting should be confirmed by percentage of tubular reabsorption of phosphate or tubular maximum for phosphate corrected for glomerular filtration rate. The 1,25-vitamin D level can be low or inappropriately normal. The serum calcium levels and parathyroid hormone levels are usually normal, although the latter can be high reflecting secondary hyperparathyroidism from low 1,25-vitamin D levels. Plasma FGF-23 levels should be high.

Investigation tools include MRI, octreotide scintigraphy, 20–25 ¹¹¹Tl scintigraphy, 99mTc-MIBI scintigraphy, 26,27 and F-18 FDG positron emission tomography (PET) 28–30 (Table). MRI is the investigation of choice owing to its high sensitivity. Indium 111 octreotide scintigraphy has been used for localisation of tumours because many of these tumours contain somatostatin receptors and analogues. Nonetheless, some tumours may be unresponsive to octreotide scintigraphy. In a study of 24 tumour-induced osteomalacia cases, 79% were positive on octreotide scintigraphy. 31 PET or computed tomography is very sensitive but also non-specific.

Octreotide therapy can improve the phosphate-wasting condition when the tumour cannot be removed due to coexisting conditions. 21 Subcutaneous administration of octreotide at a dose of 50 μg 3 times a day for 5 days and then at a dose of 100 μg 3 times a day for 8 days led to normalisation of serum phosphorus levels, phosphate clearance, and the threshold for renal tubular reabsorption of phosphate by day 10. 21 The prognosis of oncogenic osteomalacia is generally good because the responsible tumour is usually benign. Surgical removal of the tumour results in dramatic improvement. 2,5,7,32

**DISCLOSURE**

No conflicts of interest were declared by the authors.
REFERENCES