

A mysterious case of recurrent fracture: Tumour-induced osteomalacia

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ABSTRACT

We report a case of tumour-induced osteomalacia in a 59-year-old man who presented with a long-standing history of myalgia, bone pain and pathological fracture of the bilateral femur at different intervals in the past 4 years. A biochemical evaluation revealed hypophosphatemia secondary to phosphaturia. Localization study by Ga-68 DOTANOC PET-CT for adult-onset hypophosphatemic osteomalacia revealed a tumour in the right femoral head. Resection of the tumour resulted in clinical improvement as well as normalization of biochemical parameters.

Keywords: FGF-23, hypophosphatemia, tumour-induced osteomalacia

Introduction

Cases of tumour-induced osteomalacia (TIO) are often underreported due to nonspecific presentation, nonmeasurement of phosphorus, unavailability of fibroblast growth factor 23 (FGF-23), and functional imaging in many of the centres. Our report emphasizes that the measurement of serum levels of phosphorous gives important clues regarding the aetiology of osteomalacia and recurrent fractures. Adult-onset hypophosphatemia secondary to phosphaturia with elevated levels of FGF-23 should guide clinician towards making a diagnosis of TIO.

Case History

A 59-year-old man presented with bilateral lower limb pain and weakness for the last 4 years which worsened in the preceding

few months prior to presentation. Proximal muscle weakness was debilitating and affected his routine activity. He had a history of fractures of the bilateral femur following trivial trauma 4 years prior to presentation, for which he had undergone intramedullary nailing of the right femur and left dynamic hip screw fixation [Figure 1]. Even after surgery, the patient continued to have muscle aches and was unable to bear weight in bilateral lower limbs. Family history was negative for short stature, bowed legs and dental anomalies.

On clinical examination, vitals were stable with no palpable neck mass or subcutaneous swelling. Neurological examination showed grade 3 power in proximal muscles; weakness was more in lower limbs than upper limbs. Systemic examination was unremarkable. Chvostek's and Trousseau's signs were negative.

Investigations

Investigations revealed normal serum calcium of 9.2 mg/dL (8.6–10 mg/dL), alkaline phosphatase of 151 U/L (40–130 U/L), low-serum phosphorus 1.7 mg/dL (2.5–4.5 mg/dL), creatinine 0.81 mg/dL (0.7–1.2 mg/dL) and albumin 4.4 g/dL (3.5–5.5 g/dL). Renal, liver and thyroid functions were normal. Uric acid was

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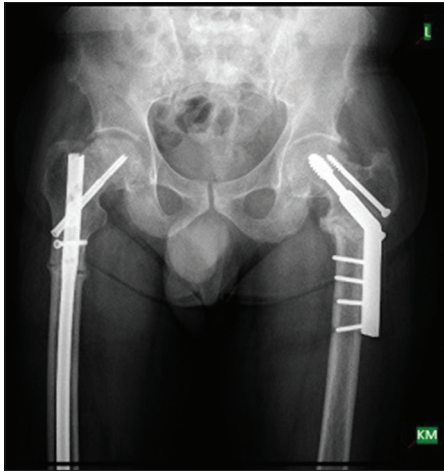


Figure 1: Transverse fracture of the right proximal femur with intramedullary nail and transfixing screws. Another proximal shaft fracture of the left femur with dynamic hip screw

normal, and there was no reversal of the albumin:globulin ratio. PTH was 60.7 pg/mL (15–65 pg/mL), 25-Hydroxy Vitamin D 21.84 ng/mL (>30 ng/mL). In view of low phosphorus, with mildly elevated PTH, Sestamibi Tc99 scintigraphy was done, which was normal.

As there was hypophosphatemia, 24-hour urinary calcium, phosphorus and creatinine were quantified. Tubular maximum reabsorption rate of phosphate to glomerular filtration rate (TmP/GFR) calculated using Bijvoet nomogram, which was 1.4, suggestive of phosphaturia. Renal tubular acidosis was ruled out, as patient had normal pH of 7.44 (7.35-7.45), bicarbonate-27 mmol/L.

Adult onset, with an absence of a family history of short stature, dental anomalies in our patient suggested acquired causes of hypophosphatemia. Our patient did not have a history of exposure to toxins, anti-retroviral therapy and chemotherapeutic agents which are the differential diagnoses for acquired hypophosphatemia. Renal parameters, urine pH and blood gas analysis ruled out acquired Fanconi syndromes.

A diagnosis of acquired adult onset hypophosphatemic osteomalacia secondary to oncogenic osteomalacia was considered. A localization study with Ga-68 DOTANOC PET-CT revealed a lesion in the right head of the femur with corresponding sclerotic lesion CT [Figure 2].

Treatment

He was started on neutral phosphate and active vitamin D supplementation, after which there was an improvement in clinical symptoms. His phosphorus levels were monitored and the dose was titrated. He was subjected to excision of the lesion. Postoperatively neutral phosphate supplementation was tapered and stopped over 1 week. He was discharged on the seventh postoperative day.

Outcome and follow-up

Postoperatively, the patient had a significant reduction in pain and weakness. Serum phosphorus was 3.9 mg/dL, being off neutral phosphate. He was gradually mobilized and was able to walk with minimal assistance by 3 weeks and without any assistance by about 10 weeks.

Discussion

TIO, also referred to as oncogenic osteomalacia, is a paraneoplastic syndrome that occurs secondary to abnormal phosphorus and vitamin D metabolism caused by small endocrine tumours that secrete the phosphaturic hormone, fibroblast growth factor 23 (FGF-23) causing impaired bone metabolism.^[1,2]

The first TIO case was reported by Robert McCance in 1947.^[3] It is often missed due to nonspecific symptoms and occult nature of the tumour. It should be suspected in a patient with recurrent fractures with low phosphorus. Rickets can also be a manifestation if this condition develops before the closure of the growth plate. TIO can be primary or secondary. Secondary TIO is associated with other diseases like prostatic cancer, oat cell carcinoma, hematologic malignancy, neurofibromatosis, epidermal nevus syndrome and polyostotic fibrous dysplasia of bone.^[4-9]

Andrea Prader was the first to introduce the idea of the 'ricketogenic' circulating factor as the cause of renal phosphate wasting.^[10] Later it was termed phosphatonin by Econs and Drezner in 1994.^[11] FGF-23 is a peptide hormone that belongs to the FGF ligand superfamily, first identified in ADHR by Econs. It plays an essential role in Vitamin-D and phosphate homeostasis. FGF-23 acts by binding to the FGF receptor, which causes reduction of NaPi-2a transcription, resulting in the decreased expression on the basal surface of renal tubular cells, causing phosphate wasting.^[12] Other phosphatonins, namely, frizzled-related protein-4, FGF-7 and matrix extracellular phosphoglycoprotein are also secreted by tumours associated with TIO.^[13-16]

Typically, these tumours are of mesenchymal origin, small, benign, slow-growing, usually situated in the head, neck and extremities and can induce hypophosphatemia.^[17-19] Common presentations are proximal muscle weakness, bone pain and recurrent fractures. In a study done by Chong *et al.*,^[20] out of the 31 patients who had TIO-like syndrome in whom genetic causes of hypophosphatemia were ruled out, tumour was localized in 19 patients (61%). Because of the occult nature of the tumour, diagnosis is usually delayed for few years. As the duration and severity of hypophosphatemia increases, the patient can have multiple fractures with poor quality of life.^[21] In this case, the patient had initially presented with fracture 4 years prior to the localization of the tumour.

Typical biochemical findings are hypophosphatemia, hyperphosphaturia, inappropriately normal serum 1,

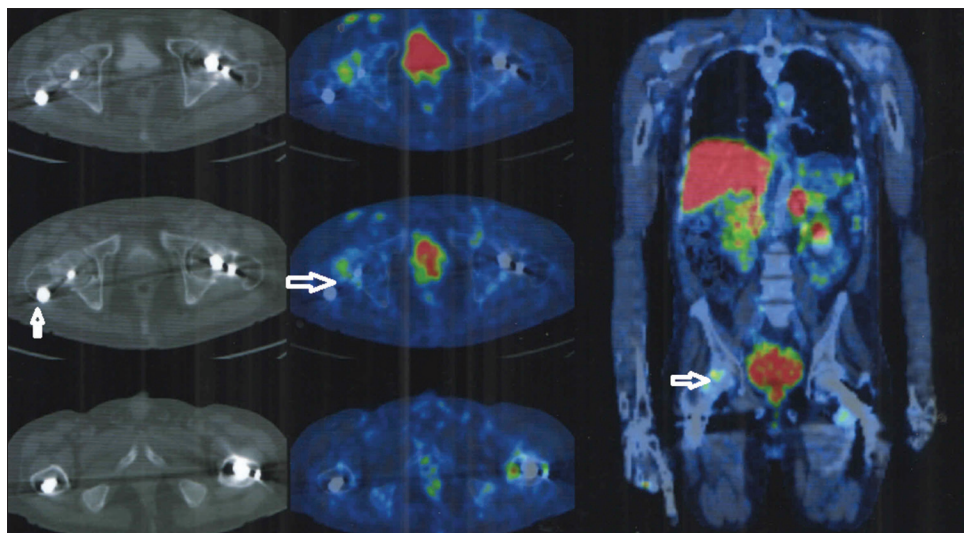


Figure 2: The 68-Ga DOTANOC PET/CT study showing a well-defined sclerotic lesion in the right femoral head with increased somatostatin receptor expression

1,25-Dihydroxy Vitamin D and elevated FGF-23,^[22] FDG-PET/CT, CT, MRI and selective venous sampling for FGF-23 can help in the localization of tumours. Selective venous sampling is useful in localizing lesions in places difficult to image or to distinguish between multiple suspected lesions. Tumour cell variably expresses somatostatin receptors (SSTR1-5), allowing SSTR-based functional imaging by octreotide scintigraphy and somatostatin analogue labelled PET-CT like DOTATATE, DOTANOC and DOTATOC.

The definitive treatment of TIO is complete wide margin excision of the offending tumour, which results in normalization of biochemical parameters and remineralization. If the lesion is not localized, use of phosphorus and calcitriol is usually advocated to achieve euhosphatemia. Recently, Burosumab, the FGF-23 antibody, has been approved for the treatment.^[23] Less commonly used treatments include radiofrequency ablation^[24] and cinacalcet.^[25] Repeat diagnostic workup is recommended in recurrent and nonremitted cases to exclude other diseases.^[26]

This case highlights the importance of detailed history taking, comprehensive investigation in a case of recurrent fracture. Work up in a case of recurrent fracture must include measurement of fasting phosphorous, which can unveil rare conditions like hyperparathyroidism, TIO and renal tubular acidosis. Early identification by clinical suspicion and appropriate evaluation can prevent morbidity in patients with TIO.

Key Messages

1. Oncogenic osteomalacia is an acquired and treatable cause of hypophosphatemic osteomalacia.
2. Serum phosphorus should be routinely measured in all patients with bone pain, nonspecific myalgia, and pathological fractures.
3. TIO must be considered in patients with adult-onset hypophosphatemic osteomalacia.

4. Early diagnosis and treatment prevent pathological fractures and chronic debility.

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Conflicts of interest

There are no conflicts of interest.

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