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Short title: Worsening of tumour-induced osteomalacia with teriparatide

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Abstract

Introduction: Tumour-induced osteomalacia (TIO) is a rare paraneoplastic syndrome characterised by refractory hypophosphataemia mediated by fibroblast growth factor 23 (FGF23) produced by small, mesenchymal tumours. Herein, we report a hitherto unrecognised case of TIO whose hypophosphataemic symptoms suddenly worsened following inadvertent use of teriparatide.

Case presentation: A 45-year-old man presented with lower limb proximal myopathy for the past 1,5 years. Six months earlier he suffered bilateral femoral neck fractures following a trivial trauma for which he underwent bilateral total hip replacement. He was started on teriparatide to promote fracture healing without prior assessment of serum phosphate levels. After one month his myopathy rapidly worsened, and within six months he became completely bedbound. Examination revealed reduced lower limb proximal muscle power with intact deep tendon reflexes. Biochemical investigations showed hypophosphataemia, normocalcaemia, elevated alkaline phosphatase, and low tubular reabsorption of phosphate corrected for

glomerular filtration rate (TmP/GFR). Serum FGF23 was elevated with inappropriately low 1, 25-dihydroxy vitamin D. ^{68}Ga-DOTATATE PET-CT showed a small tracer-avid soft tissue lesion in the left thigh. The lesion was excised, and histopathology showed phosphaturic mesenchymal tumour. Phosphate levels rose and FGF23 levels fell post-operatively. At three months' follow-up, he is able to stand and walk by himself. His serum phosphate has normalised.

Conclusion: Hypophosphataemia with teriparatide use is an oddity. Unexplained hypophosphataemia in a patient on teriparatide should make the physician think of hypophosphataemic osteomalacia. Serum phosphate levels should be estimated prior to teriparatide use and its use refrained in patients with unexplained hypophosphataemia.

Keywords: tumour-induced osteomalacia; teriparatide; hypophosphataemia; fragility fracture

Case presentation

A 45-year-old man presented with lower limb proximal muscle weakness that had begun 1.5 years back. He developed bilateral fracture neck femora following a trivial fall onto the ground one year ago (Fig. 1A). He underwent bilateral hip replacement for the same at a private healthcare facility. He was discharged on calcium and vitamin D supplements along with recombinant human parathyroid hormone (rhPTH/teriparatide) at a dose of 20 micrograms once daily to promote fracture healing. After one month of teriparatide therapy, his symptoms aggravated. His lower limb muscle power declined, soon requiring support to stand up and walk. This was associated with marked bony pain over the lower limbs. Six months later he became bedbound. The patient stopped taking teriparatide and subsequently presented to our institute. A review of previous investigations (performed at a private hospital) revealed serum calcium 9.2 mg/dL (range: 8.6–10.4), total alkaline phosphatase (ALP) 672 IU/L (range:74–138), and 25-hydroxyvitamin D 18 ng/mL. However, a serum phosphorous report was not available. Histopathology of the excised femoral heads was reported as having osteomalacia.

Physical examination revealed lower limb proximal myopathy. Distal muscle power, deep tendon reflexes and sensory system were intact. Biochemical investigations revealed hypophosphataemia (0.9–1.1 mg/dL, range: 2.8–4.5), elevated ALP (790 IU/L, range: 78–128), and vitamin D sufficiency. Urinalysis revealed renal phosphate

wasting with low tubular reabsorption of phosphate corrected for glomerular filtration rate (TmP/GFR = 0.409 mg/dL, age-specific range: 2.8–4.2). Serum FGF23 level (measured by C-terminal ELISA, Quidel, Immutopics) was elevated at 513.8 RU/mL (range: 0.0–150.0) with inappropriately low 1, 25-dihydroxyvitamin D (24.2 pg/mL, range: 19.9–79.3). Somatostatin-receptor (SSTR)-based scintigraphy with ^{68}Ga-DOTATATE PET-CT showed a 1 cm × 1 cm tracer-avid soft tissue lesion in the medial aspect of the left thigh (Fig. 1B). It was concordant on ultrasonography. The lesion was excised with a wide resection margin. Serum phosphate levels rose, reaching 2.8 mg/dL on the fourth post-operative day. Simultaneously, serum FGF23 levels fell to 103.8 RU/mL. Histopathology of the excised lesion was suggestive of phosphaturic mesenchymal tumour. At two months follow-up, there has been a marked symptomatic improvement with the patient able to stand and walk on his own. His serum phosphate has increased to 3.8 mg/dL and his ALP level has come down to 288 IU/L.

Discussion

Tumour-induced osteomalacia is a rare paraneoplastic syndrome characterised by refractory hypophosphataemia and is usually associated with benign mesenchymal soft-tissue tumours that produce FGF23 [1, 2]. FGF23, acting via FGF receptor 1 (FGFR1) and co-receptor α-klotho on renal proximal tubules promotes internalisation of sodium-phosphate co-transporters (NaPi) from the luminal membrane to the cytoplasm, thereby reducing tubular phosphate reabsorption and causing phosphaturia [3]. In addition, FGF23 also reduces renal mRNA and protein levels of NaPi-2a co-transporters [4]. Similarly, PTH, acting via G-protein-coupled PTH receptor 1 (PTHR1), increases cAMP in proximal tubular cells, reducing luminal expression of NaPi, culminating in phosphaturia. In fact, the internalisation of NaPi co-transporters seems to be faster and more effective under the effect of PTH as compared to FGF23 [4, 5]. In addition, PTH, either directly or via increase in serum 1,25-dihydroxyvitamin D, tends to increase FGF23 secretion from bone cells [5, 6]. Thus, an excess of endogenous circulating PTH is expected to increase the serum levels of FGF23 as well as potentiate its action at the renal level. The same should hold true with exogenously administered hPTH as well. Studies have shown that infusion of hPTH (1–34) in healthy human volunteers leads to a rise in circulating FGF23 levels, mostly mediated by a rise a serum 1,25-dihydroxyvitamin D levels. Thus, a milieu,

wherein PTH and FGF23 are both in excess will aggravate hypophosphataemia. This phenomenon is exemplified in our patient where the hypophosphataemic symptoms were exacerbated on inadvertently adding rhPTH in a state of underlying FGF23 excess.

Tumour-induced osteomalacia must have been the underlying cause of the fragility fractures involving the neck of the femora; however, an attempt to promote fracture healing with teriparatide acted as fuel to the fire, aggravating hypophosphataemia. Although transient hypercalcaemia is a known adverse effect of teriparatide therapy, hypophosphataemia is extremely rare [7]. Refractory hypophosphataemia in a patient on teriparatide should make the clinician think of TIO. The serum phosphate level of the index patient was not assessed before initiating teriparatide. With widespread availability of teriparatide and innumerable biosimilars on the market, there is a temptation among unwary physicians and surgeons to prescribe rhPTH for indications that are not approved by conventional guidelines. Such a practice should be condemned in routine clinical practice. In addition, physicians planning to prescribe teriparatide should beforehand order a basic biochemical panel that must include a minimum of serum calcium, phosphorous, ALP, and creatinine and refrain from its use in patients with unexplained hypophosphataemia.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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Patient consent

Informed, written consent was obtained from the patient.

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Figure 1. A. Antero-posterior radiograph of the pelvis showing bilateral fracture neck femora (marked in black arrows)**. B.** Fused ^{68}Ga-DOTATATE PET-CT image showing a 1 cm × 1 cm tracer-avid soft tissue lesion (marked in blue arrow) in the subcutaneous plane of the medial aspect of the left thigh region just anterior to the belly of the gracilis muscle [maximum standardised uptake value (SUVmax) of 12.8]