Tumour-induced osteomalacia: a curable condition

Shires R, BSc, MBBCh, PhD, FRCP(Lond)
Magan A, MBBCh, FCP(SA), Cert Endocrinology and Metabolism(SA)
Huddle KRL, MBBCh, FCP(SA), FRCP(Lond)
Division of Endocrinology, Department of Medicine, Chris Hani Baragwanath Hospital and University of the Witwatersrand, Johannesburg
Correspondence to: Prof Roy Shires, e-mail: Roy.Shires@wits.ac.za

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Introduction

Osteomalacia is a condition characterised by failure of bone mineralisation. While abnormalities of vitamin D supply, metabolism or action are the most common and well-known causes, chronic phosphate deficiency, due to either insufficient input (intake or absorption) or renal losses are also important causes of rickets or osteomalacia.[1] Hypophosphataemia also commonly co-exists with vitamin D deficiency, pursuant to secondary hyperparathyroidism. Other causes include chronic calcium deficiency, hypophosphatasia, fluoride and aluminium excess.

In respect of chronic hypophosphataemia-associated rickets/osteomalacia, the commonest aetiology is X-linked dominant hypophosphataemia, XLH, (1:20000 births).[1] Others include Fanconi syndrome, autosomal dominant hypophosphataemic rickets (ADHR) and tumour-induced osteomalacia (TIO).[2]

Case report

A 47-year-old well-nourished black female patient presented to Chris Hani Baragwanath Hospital with acute infective bronchitis and hypertension. She also complained of left hip pain, severe bilateral progressive leg weakness and was noted to have a waddling gait. Family history was non-contributory.

Investigation of the muscle weakness identified hypophosphataemia of 0.58 mmol/L (reference range [RR] 0.8–1.4 mmol/L), but normal serum calcium and renal function. PTH was 62 pmol/L (RR 12–72), and vitamin D levels were normal. Alkaline phosphatase was markedly elevated at 431IU/L (RR 40–120). Muscle enzymes were normal. Her TRP (tubular reabsorption of phosphate) was 0.58 (RR > 0.8). Glycosuria was absent.

Hip X-rays demonstrated pseudofractures (Figure 1). There was no history of malabsorption, antacid use, or family history of either osteomalacia or rickets. A diagnosis of tumour-induced osteomalacia was considered. The FGF-23 (fibroblast growth factor 23) level was less than 2RU/ml (RR 18–108).

She was treated with oral phosphate replacement and 1-α hydroxyvitamin D, 1µg daily. After three months of therapy, her phosphate level had risen to 0.97 mmol/L and muscle strength had improved somewhat. An ^{111}In-pentetreotide scan, 18 months later, demonstrated a small, abnormal area of uptake behind the right knee (Figure 2). At surgery, a benign mesenchymal tumour was excised, the histology displaying nests of mesenchymal cells with cartilaginous differentiation (Figures 3 and 4). The phosphate replacement and 1-alpha hydroxyvitamin D therapy were subsequently discontinued and she has continued to maintain normal serum phosphate levels. In addition, resolution (remineralisation) of the pseudofractures (Looser zones) has occurred.

Discussion

Our patient manifested severe hypophosphataemia and compatible clinical features. Her family history was negative for rickets and osteomalacia and her vitamin D status was normal. XLH is the commonest cause of hypophosphataemic rickets and typically has a childhood onset, although a rarer, milder form may manifest only during adulthood.[1] TIO, by contrast, is a paraneoplastic condition that usually, but not always, presents in adulthood, with the peak incidence being in the fifth decade.[2] Although initially described in 1947, the paraneoplastic nature of the condition was first recognised by Prader and colleagues in 1959.[3] The diagnosis of TIO requires a high level of awareness. The tumours are characteristically small. Over 80 percent of the tumours are of mesenchymal cell origin and usually small and difficult to detect.[1,4] This may be facilitated by imaging techniques, notably ^{111}In-pentetreotide scanning, by virtue of the fact that most express somatostatin receptors on their cellular plasma membranes.[1,5,6] Even so, many remain elusive to detection. Most (45 percent) have been located in the lower extremities, as was this patient's tumour. Other common sites are the thorax and nasopharynx.[4]

The hypophosphataemia of TIO results from impaired phosphate reabsorption by the proximal renal tubule, due to inhibition and/or down-regulation of the type 2 Na-phosphate cotransporter (NPT2a), which resides in the brush border membrane.[7,8] This inhibition is mediated by one or more phosphatonins, a group of hormones which have been identified to promote phosphaturia. The commonest and best studied of these is FGF-23 (fibroblast growth factor 23) which is over-expressed in the majority of tumours that cause TIO and identified as the causative hormone in 2001.[9] FGF-23 levels, when measured by a sensitive assay, are elevated in up to 86 percent of cases.[10] FGF-23, largely produced by bone-forming cells, osteoblasts and osteocytes, plays a physiological role in regulating phosphate reabsorption by influencing NPT2a function, as do parathyroid

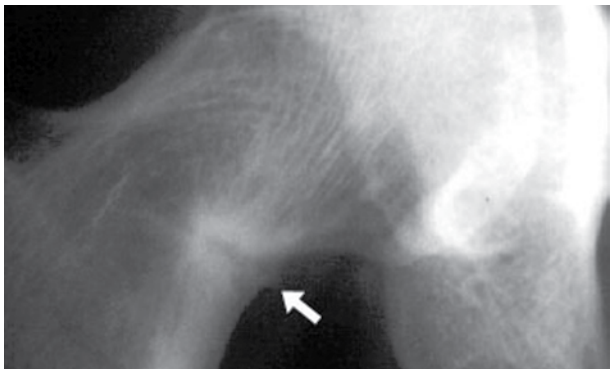

Figure 1: Hip X-ray of the patient demonstrating a pseudofracture in the metaphyses of the femur

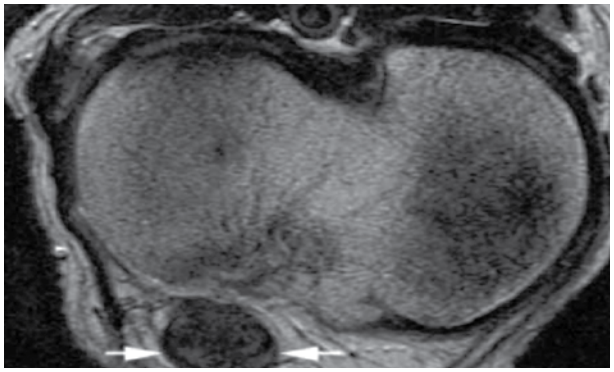

Figure 2: A negative field recovery CT image of the pentetreotide scan demonstrating a mass behind the right knee (see arrows)

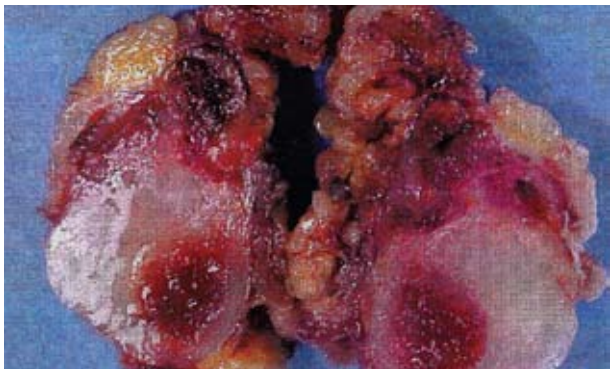

Figure 3: Macroscopic appearance of the tumour containing cartilaginous areas

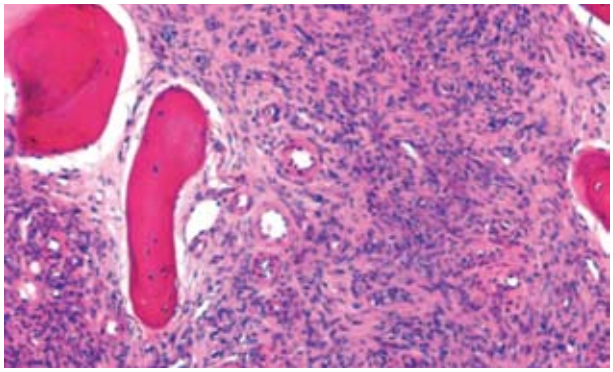

Figure 4: Histology demonstrating nests of mesenchymal cells with cartilaginous differentiation

hormone (PTH) and calcium.[8] However, unlike PTH, which increases 1-alpha hydroxylase mRNA expression and activity, FGF-23 has an inhibitory effect on the conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D.

FGF-23 excess is accountable for the phosphaturia of XLH, ADHR and most cases of TIO, but the reasons for this differ among these conditions.[11] FGF-23 is normally cleaved by an endopeptidase, encoded for by the PHEX gene (the **p**hosphate regulating gene with **h**omologies to endopeptidase on the **X**-chromosome), mapped to Xp22.1.

i In the rare condition of ADHR, the gene encoding FGF-23 has undergone a missense mutation which renders the gene product(FGF-23) refractory to proteolysis by PHEX, resulting in abnormally high FGF-23 levels.

ii In XLH, FGF-23 structure is normal. The defect resides in the PHEX gene, on the X-chromosome, which undergoes an inactivating mutation, of which approximately 140 have now been documented. Cleavage of FGF-23, by the deficient or abnormal endopeptidase, is thus impaired and accounts for the high circulating concentration of FGF-23.[11]

iii In TIO, tumour FGF-23 mRNA and the secreted FGF-23 are overexpressed in most instances.[11] However, as in the patient reported here, the FGF-23 levels may not be elevated. Indeed, in this instance they were below the normal physiological range. Detection of an elevated FGF-23 is affected by the sensitivity of the assay employed, but it is most likely that her tumour was secreting one of a number of the other phosphatonins which circulate normally and which also have been associated with TIO. These include MEPE-ASARM-protein, sFRP4, and FGF-7.[1,5,8,10]

The sentinel importance of recognising this rare condition is that, as in our patient, it is curable by resection of the tumour. The alternative, unfortunately, is lifelong therapy with oral phosphate and calcitriol replacement, for which, owing to unpleasant gastrointestinal side-effects, compliance is often sub-optimal. Since these tumours often express somatostatin receptors on their cell membranes, some success may be achieved by somatostatin analogue therapy, but this is by no means universal.[6]

Conclusion

Tumour-induced osteomalacia is a paraneoplastic condition which is rare but curable. It is usually caused by overexpression of FGF-23 by the tumour. In our patient, however, FGF-23 levels were low and the osteomalacia consequently attributable to one of the other less well studied phosphatonins.

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