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The Case | A 42-year-old male with 3-year bone pain and a soft tissue mass

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Table 1 | Laboratory results

	Unit	Reference	
Serum			
Blood urea nitrogen	mmol/l	2.0–7.2	3.7
Creatinine	μmol/l	26.5–114.9	61.9
Calcium	mmol/l	2.0–2.5	2.15
Phosphate	mmol/l	0.87–1.52	0.65
Albumin	g/l	35–50	42
Alkaline phosphatase	μkat/l	0.13–2.10	6.1
iPTH	pg/ml	12–72	216
25(OH) vitD_3	nmol/l	24.2–103.8	43.8
1.25$(OH)_2$ vitD_3	pmol/l	38.2–133.4	66.7
24-h urine			
Calcium	mmol	1.25–6.25	0.81
Phosphate	mmol	12.8–41.6	43.9
Creatinine	mmol	7.1–16.0	15.7

Abbreviations: iPTH, immunoreactive parathyroid hormone; vitD_3, vitamin D_3.

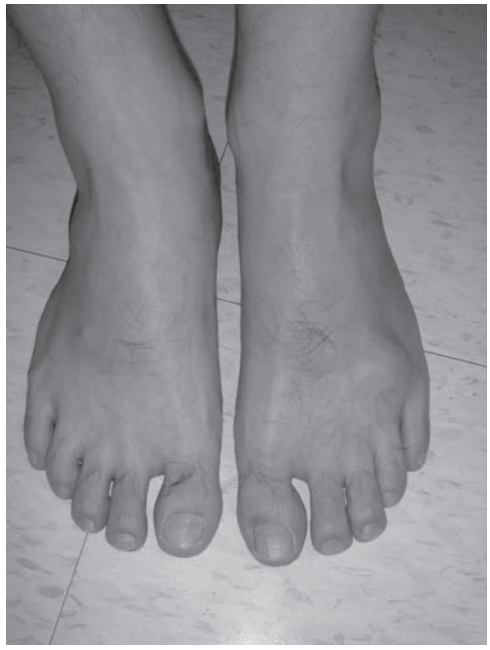

Figure 1 | Photograph of the soft tissue mass at the instep of left foot.

A 42-year-old man was referred for the evaluation of diffuse bone pain and newly found hypophosphatemia. He had progressive bone pain over the lower back, pelvis, and bilateral hips, muscle weakness and difficult ambulation since 3 years ago. Initially, he was diagnosed to have ankylosing spondylitis but failed to respond with non-steroidal anti-inflammatory drugs, etoxicomab and etanercept therapy. One month ago, he was admitted at orthopedic ward for L-spine compression fracture. Radiography revealed a Looser zone at right proximal femur. ^{99m}Tc-bone scintigraphy showed diffuse skeletal uptake including axial bone, ribs, and proximal femurs. The detailed searches including computed tomography of the chest and abdomen, immune disorders, and malignancy were unrevealing. The pertinent laboratory results are shown in Table 1. He was put on oral calcitriol 2 μg and phosphorous salt containing phosphate 2 g daily. Nevertheless, his hypophosphatemia persisted and diffuse bone pain was only partially alleviated.

On physical examination, he was a well-nourished kyphotic man with waddling gait and severe pain on any movement. Of note, a 2 × 3 cm elastic mass in the instep of left foot was identified (Figure 1).

What is the cause of his unexplained bone pain?

SEE NEXT PAGE FOR ANSWERS

The Diagnosis | Oncogenic osteomalacia

Table 2 | The common causes of severe hypophosphatemia with hyperphosphaturia

Hypercalcemia (increased serum PTH or PTHrP)	Normocalcemia (isolated renal phosphate wasting)	Hypocalcemia (tubulopathy)
Increased urine Ca^{2+} excretion	Increased serum FGF23 level	Fanconi syndrome
Primary or post-renal transplant hyperparathyroidism	XLHR (PHEX mutation)	Renal tubular acidosis
Paraneoplastic syndrome with elevated PTHrP	ADHR (FGF23 mutation), ARHR (DMP-1 mutation)	Bartter's-like syndrome
Reduced urine Ca^{2+} excretion (CaSR loss of function)	Tumor-induced osteomalacia (acquired)	
Familial hypocalciuric hypercalcemia	Decreased serum FGF23 level	
Neonatal severe hyperparathyroidism	HHRH (NaPi IIa or IIc mutation)	

Abbreviations: ADHR, autosomal dominant hypophosphatemic rickets; ARHR, autosomal recessive hypophosphatemic rickets; CaSR, calcium-sensing receptor; DMP-1, dentin matrix protein 1; FGF, fibroblast growth factor; HHRH, hereditary hypophosphatemic rickets with hypercalciuria; PHEX, phosphate regulating gene with homologies to endopeptidase on the X chromosome; PTHrP, parathyroid hormone related peptide; XLHR, X-linked hypophosphatemic rickets.

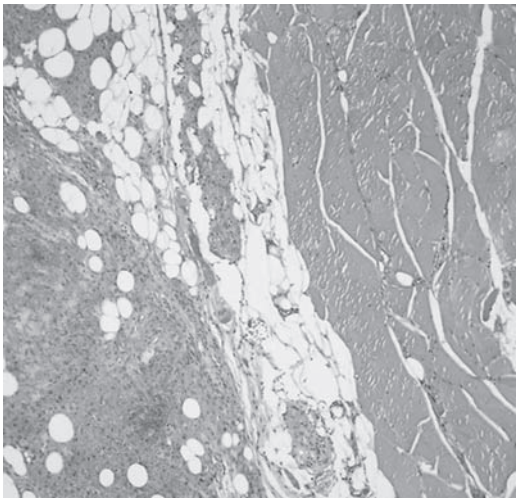

Figure 2 | Hematoxylin and Eosin staining (×100) showing phosphaturic mesenchymal tumor, mixed connective tissue type consisting of vascular, chondroid, muscular, and adipose tissue.

His bone pain, atraumatic fracture, Looser fracture at radiography and hypophosphatemia associated with elevated alkaline phosphatase were consistent with osteomalacia. His hypophosphatemia with high urinary phosphate excretion indicated renal hypophosphatemia. The causes of severe hypophosphatemia associated with hyperphosphaturia are shown in Table 2. His normocalcemia, inappropriately low serum calcitriol in response to hypophosphatemia, and high serum fibroblast growth factor-23 (FGF23, 187.5 pg/ml, reference 10–50) suggested the FGF23 associated causes. His negative family history, adult-onset, and identification of a soft tissue mass imply tumor-induced osteomalacia but not hereditary hypophosphatemic disorders. Complete tumor resection showed phosphaturic mesenchymal tumor, mixed connective tissue type (Figure 2). His serum FGF23 was 14.3 pg/ml, immunoreactive parathyroid hormone 65 pg/ml, and calcitriol 146.2 pmol/l 2 days after operation. Delayed normalization of serum phosphate level, was found because phosphate deposited into bone soon after operation, like hungry bone syndrome. Without phosphate supplement, his clinical symptoms completely resolved in 3 months.

Tumor-induced osteomalacia or oncogenic osteomalacia is a rare paraneoplastic syndrome characterized by tumor-induced renal phosphate wasting with hypophosphatemia and defective calcitriol metabolism. It is perhaps the most common cause of adult-onset hyperphosphaturic osteomalacia and usually caused by benign mesenchymal tumors that secret phosphatonins, primarily FGF23.[1] Circulating FGF23 binds with a complex of klotho and FGF23 receptor at proximal tubules to suppress both the expression of NaPi-2a/2c and 1α-hydroxylase, causing renal phosphate wasting and inappropriately low to normal serum calcitriol.[2,3] Secondary hyperparathyroidism is likely a compensatory response to maintain normocalcemia, whereas calcitriol is suppressed.[4]

Treatment of tumor-induced osteomalacia relies on early recognition, localization, and surgical removal of tumor. Tumor-induced osteomalacia is frequently misdiagnosed because clinical symptoms are often insidious and non-specific diffuse bone pain, muscle weakness, and atraumatic fracture. Without timely measurement of serum phosphate, the time from onset of symptoms to diagnosis is usually delayed, over 2–4 years. Once recognized, tumor localization is the key despite its small size and slow progression.[1] Many culprit tumors are found in soft tissues and bone in the extremities and craniofacial regions.[4,5] Special attention to these sites is important to avoid futile examinations. Selective venous sampling for FGF23, whole-body computed tomography/magnetic resonance imaging, positron-emission tomography and octreotide-labeled scintigram may aid localizing clinically occult tumor.[1,3–5] Complete cure can be achieved only by the surgical removal of offending tumor.

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