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Rare disease

Hypophosphataemia-inducing mesenchymal tumour in the foot

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Summary

Tumour-induced (or oncogenic) osteomalacia is a paraneoplastic syndrome characterised by progressive fatigue, muscle weakness, bone pain, non-healing and recurrent fractures caused by mesenchymal tumours that secrete proteins that inhibit renal phosphate transport and 1α-hydroxylation of 25-OH-vitamin D. The potentially curative treatment of choice is complete surgical excision of the tumour.

BACKGROUND

Tumour-induced (or oncogenic) osteomalacia is a paraneoplastic syndrome characterised by progressive fatigue, muscle weakness, bone pain, non-healing and recurrent fractures caused by mesenchymal tumours that secrete proteins that inhibit renal phosphate transport and 1α-hydroxylation of 25-OH-vitamin D. Rickets[1] and osteomalacia[2–4] have been linked to hypophosphataemia due to renal phosphate wasting and suppressed 1,25-$(OH)_2$ vitamin D production. Fibroblast growth factor-23 (FGF-23), a vitamin D-regulating and phosphate-regulating hormone,[2–4] may play a role.

CASE PRESENTATION

The first patient, a 71-year-old woman, had been known to have osteoarthritis of the hip, knee and shoulder as well as osteoporosis for 4 years, on the basis of fractures of vertebrae, ribs and foot, and low T-scores (–3 by dual energy x-ray absorptiometry (DXA)), unresponsive to alendronate. She was suffering from severe back pain, increasing muscle weakness and fatigue. Laboratory studies showed progressively low phosphate (as low as 0.23 mmol/litre) found to be due to renal phosphate wasting ('phosphate diabetes'). Parathyroid hormone (PTH; 117 ng/litre, normal <65) and alkaline phosphatase (286 U/litre, normal <120) were elevated but calcium, creatinine, 25-OH- and 1,25-$(OH)_2$-vitamin D were normal. Treatment with oral phosphate and calcitriol was initiated. A tumour was suspected. Skeletal scintigraphy was consistent with osteoarthritis and fractures at multiple sites and an octreoscan showed an intense uptake at the first toe of the left foot.

The second patient, a 30-year-old man, developed bone pain (right proximal femur and ribs) and progressive proximal muscle weakness. Skeletal scintigraphy showed multiple areas of increased activity (fractures) in the right proximal femur, ribs and in the thoracic spine. Laboratory studies revealed phosphate of 0.48 mmol/litre and an inappropriately low 1,25-$(OH)_2$ vitamin D (19 ng/litre, normal 20–67), despite hypophosphataemia and normal serum creatinine, calcium and 25-OH vitamin D, and high-normal serum PTH (61 ng/litre). Maximal renal tubular reabsorption of phosphate (TmPi/GFR) was low—that is, renal phosphate wasting contributed to hypophosphataemia and, thereby, to osteomalacia. Such biochemical hallmarks of an acquired disorder—that is, hypophosphataemia and low 1,25-$(OH)_2$ vitamin D, suggested tumour-induced osteomalacia. Octreotide scintigraphy revealed an increased uptake in the right foot.

OUTCOME AND FOLLOW-UP

Following surgery, FGF-23 fell quickly and serum phosphate returned towards normal and 1,25-$(OH)_2$ vitamin D increased rapidly in both patients (table 1). Histopathology of the resected tumour specimens revealed a mesenchymal tumour-mixed connective tissue variant, as described by Folpe *et al.*[5]

Table 1 FGF 23 as phosphate and 1,25 $(OH)_2$ vitamin D regulator in physiology and pathology

	FGF-23 (RU/ml)*		Phosphate (mmol/l)		1,25-$(OH)_2$ vitamin D (ng/l)	
	Case 1	Case 2	Case 1	Case 2	Case 1	Case 2
Before surgery	847	103	0.49	0.50	23	17
After 4 h		20		0.64		16
After 24 h	41	10	0.61	0.78	83	69
After 48 h	42	13	0.80	0.68	88	58
After 72 h		12		0.81		156

*By human fibroblast growth factor (FGF)-23 (C-Term) ELISA Kit, from Immutopics, San Clemente, California, USA.

Muscle weakness and pain improved over the following months in both patients. In the first patient the DXA 3 years later showed normal bone density values at the spine with an increase during this time of 43%.

DISCUSSION

We describe two similar cases illustrating the syndrome; both presenting with advanced disease and subsequently cured by surgical treatment. In a third patient (male, 50-years old) seen over the same 3-year period, the tumour was localised in the pelvic region and characterised but could not be completely removed. Serum phosphate remained low (0.45 mmol/l) and FGF-23 high (459 RU/ml). Supportive care with high dose oral phosphate and calcitriol was partially effective. This treatment seems to be also an option for cases where localisation fails due to the small size of the neoplasm.

In all three cases, FGF-23 was markedly elevated and octreotide scintigraphy localised the tumour. As opposed to neuroendocrine tumours, serum chromogranin A was not elevated and histopathology of the resected tumour specimens revealed a mesenchymal tumour-mixed connective tissue variant, as described.[5]

Clues to the diagnosis were muscle weakness, pain and a rather peculiar bone disease (which may, on isotope bone scans, occasionally mimic metastatic disease[6]); persistently low serum phosphate suggested a tumour secreting an agent causing renal phosphate loss. Whenever possible (as in the two cases we report), the tumour should be removed.

Learning points

- Progressive fatigue, muscle weakness and bone pain, or bone disease unresponsive to "standard" treatment may be clinical clues.
- Fatigue, muscle weakness and osteomalacia may result from hypophosphataemia.
- Persistent hypophosphataemia is the biochemical hallmark; when due to renal phosphate wasting and associated with an inappropriately low 1,25-$(OH)_2$ vitamin D level, it may be caused by tumour disease.
- Complete surgical removal of the causing tumour can result in cure and should be the treatment of choice, whenever feasible.

Competing interests : none.

Patient consent: Obtained.

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