CASE REPORT

Oncogenic hypophosphataemic osteomalacia: biomarker roles of fibroblast growth factor 23, 1,25-dihydroxyvitamin D₃ and lymphatic vessel endothelial hyaluronan receptor 1

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Abstract

Oncogenic osteomalacia (OOM) is characterised by tumour production of fibroblast growth factor 23 (FGF23) that results in hypophosphataemia and renal phosphate wasting, reduced 1,25-dihydroxyvitamin D₃ (1,25(OH)₂D₃) synthesis and osteomalacia. Here, we demonstrate the roles of serum FGF23 and 1,25(OH)₂D₃, together with the lymphatic vessel endothelial hyaluronan receptor 1 (LYVE-1), as biomarkers for OOM. A previously well 52-year-old man presented with a 2-year history of generalised musculoskeletal pain and proximal myopathy. He had hypophosphataemia, elevated serum alkaline phosphatase activity, low serum 1,25(OH)₂D₃ and a reduced tubular maximum of phosphate/glomerular filtration rate. These findings indicated a diagnosis of OOM, but magnetic resonance imaging (MRI) and octreotide scintigraphy did not identify any tumours. Treatment with oral phosphate and calcitriol resolved the symptoms and biochemical abnormalities within 6 months. Four years later, he relapsed whilst on treatment with oral phosphate and calcitriol. Serum FGF23 concentration was elevated and MRI identified a 2 cm tumour within Hoffa’s fat pad of the left knee. Removal of the tumour resulted in a complete resolution of symptoms and normalisation of the serum biochemical abnormalities within 6 months. Four years later, he relapsed whilst on treatment with oral phosphate and calcitriol. Serum FGF23 concentration was elevated and MRI identified a 2 cm tumour within Hoffa’s fat pad of the left knee. Removal of the tumour resulted in a complete resolution of symptoms and normalisation of the serum biochemical abnormalities including serum FGF23. Histology demonstrated a phosphaturic mesenchymal tumour, mixed connective tissue variant (PMTMCT), which revealed immunostaining with anti-LYVE-1 antibody and hence the presence of lymphatic vessels. Serum FGF23 and 1,25(OH)₂D₃ were found to be reliable biomarkers for OOM. In addition, the demonstration of lymphatics in the PMTMCT helps to distinguish this tumour from most typical benign haemangiomas.


Introduction

Oncogenic osteomalacia (OOM) is caused by small, often difficult to locate tumours, most frequently phosphaturic mesenchymal tumours, mixed connective tissue variants (PMTMCTs), which may occur anywhere in the body (1). These tumours are usually benign but over 10% of PMTMCTs may recur or produce metastases. This acquired form of osteomalacia is associated with hypophosphataemia, hyperphosphaturia, low circulating 1,25-dihydroxyvitamin D₃ (1,25(OH)₂D₃) concentrations and elevated serum fibroblast growth factor 23 (FGF23) concentrations (2). OOM tumours have been shown to contain high levels of FGF23 mRNA and protein (1), and i.v. infusions of FGF23 have been shown to inhibit renal phosphate reabsorption and 1,25(OH)₂D₃ synthesis in mice (3). In this study, we have evaluated the use of serum 1,25(OH)₂D₃, FGF23 and expression of the lymphatic vessel endothelial hyaluronan receptor 1 (LYVE-1) as biomarkers for a PMTMCT.

Case report

A previously well 52-year-old man presented with a 2-year history of progressive fatigue, generalised severe musculoskeletal pain and difficulty in walking. There was no history of weight loss, fractures, joint stiffness, alcohol excess, corticosteroid use, dietary deficiency of calcium or vitamin D, malabsorption, thyrotoxicosis, exposure to heavy metals or degraded antibiotics, or malignancy. He was a non-smoker. In addition, there was no family history of metabolic bone disease. Clinical examination revealed a proximal myopathy. He was clinically euthyroid and not Cushingoid. Bone and joint deformities or cutaneous haemangiomas were not present. His height was 1.83 m, and he had a normal body mass index of 24.5 kg/m². On investigation, he had hypophosphataemia, an elevated serum alkaline phosphatase activity, a low serum 1,25(OH)₂D₃ and a reduced tubular maximum of phosphate/glomerular filtration rate.
filtration rate (TmP/GFR) of 0.4 mmol/l (normal range: 0.8–1.35 mmol/l; Fig. 1). Serum calcium, creatinine, PTH and 25-hydroxyvitamin D₃ (25OHD₃) were normal and there was no glycosuria or aminoaciduria. These findings indicated a diagnosis of OOM (2). However, whole-body magnetic resonance imaging (MRI) and octreotide scintigraphy did not identify any tumours. Treatment with oral phosphate and calcitriol was commenced. His biochemical abnormalities and symptoms resolved within 6 months (Fig. 1). Follow up with an annual whole-body MRI did not identify the causative tumour.

Four years later, despite treatment, he relapsed. The serum FGF23 concentration (4, 5) was elevated (Fig. 1) and on this occasion MRI identified a 2 cm tumour of the left knee (Fig. 2), removal of which was associated with marked clinical improvement and normalisation of the serum biochemical abnormalities including serum FGF23 (Fig. 1). Histology revealed a haemangioma-like PMTMCT that contained lymphatic vessels; these were identified by expression of the lymphatic endothelial cell marker LYVE-1 (6) (Fig. 3). A definable geniculate artery supplying the tumour was not observed to be present. After 30 months, he remains well and asymptomatic, with no medication.

Discussion

The biochemical features of OOM include hypophosphataemia, elevated serum alkaline phosphatase activity, reduced TmP/GFR, low or inappropriately decreased circulating 1,25(OH)₂D₃ concentrations and increased serum concentrations of FGF23 (2, 4, 5). These are similar to those found in the hereditary forms of metabolic bone disease such as X-linked hypophosphataemic rickets (XLHR) and autosomal dominant hypophosphataemic rickets (ADHR) (4) (Fig. 4). While the clinical and biochemical abnormalities are lifelong in ADHR and XLHR, they resolve after removal of the PMTMCT in OOM (2, 4, 5), as illustrated by this patient. However, the similarities between OOM, ADHR and XLHR indicate that they may involve the same phosphate-regulating pathway (2). Indeed, this is the case, as OOM tumours express FGF23 and the phosphate regulating endopeptidase on the X chromosome (PHEX) (7), mutations of which cause ADHR and XLHR, respectively (4). An elevated serum FGF23 concentration and an inappropriately low circulating 1,25(OH)₂D₃ concentration in combination with hypophosphataemia are useful biomarkers for the detection of OOM (2, 4, 5). In one study, all 13 OOM patients with confirmed tumours had elevated serum FGF23 concentrations (5). Serum FGF23 is also raised in the inherited forms of hypophosphataemic rickets, XLHR and ADHR, and in renal failure (4, 5). However, in renal failure, the elevated serum FGF23 is associated with either a normal or increased serum phosphate. The measurement of serum FGF23 is also of use in monitoring the response to successful surgery, with circulating concentrations decreasing to normal values following tumour resection (Fig. 1) (4), as illustrated by this report.

FGF23, a 251 amino acid secreted peptide that is predominantly expressed in bone, is an important regulator of phosphate and vitamin D homeostasis (4) (Fig. 4). For example, mice lacking FGF23 have elevated serum phosphate concentrations and increased circulating 1,25(OH)₂D₃ concentrations as well as an abnormal bone phenotype (8). In contrast, the exogenous administration

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Figure 1 Biochemical findings over 6 years: (A) at presentation, (B) on treatment with phosphate and calcitriol, (C) relapse of symptoms, (D) pre- and (E) post-surgical excision of tumour. Reference ranges are indicated by horizontal broken lines. Fibroblast growth factor 23 (FGF23) estimations only became available during year 4.
Figure 2 MRI of the left knee. (A) Sagittal proton density fat-saturated image demonstrating a rounded lesion (arrows) of increased signal intensity in Hoffa’s fat. There are some small foci of decreased signal within the lesion corresponding to areas of calcification at histology. (B) Axial T1-weighted image demonstrating a well-defined rounded mass (arrows) in Hoffa’s fat which is of intermediate/low signal intensity.
Figure 3 Histology of the PMTMCT. (A) Haematoxylin–eosin staining showed a well-vascularised tumour containing spindle-shaped mesenchymal cells and bone trabeculae (×200 magnification). (B) Immunostaining with peroxidase and anti-LYVE-1 antibody revealed LYVE-1 expression in vessel endothelium (×400 magnification).
of FGF23 in mice leads to decreased phosphate reabsorption by the proximal renal tubule, by inhibiting the sodium–phosphate co-transporters, types IIa and IIc (NPT2a and NPT2c) (3, 9). FGF23 administration also inhibited the renal expression of 1,25(OH)2D3 by reducing the synthesis of 25-hydroxyvitamin D-1α-hydroxylase (3). This inhibition of the renal 25-hydroxyvitamin D-1α-hydroxylase by FGF23 provides an explanation for the observed low serum concentrations of 1,25(OH)2D3 in patients with hypophosphataemic OOM: hypophosphataemia would normally be expected to lead to elevated serum 1,25(OH)2D3 concentrations as this increases renal 25-hydroxyvitamin D-1α-hydroxylase activity (2). Thus, an inappropriately low serum 1,25(OH)2D3 concentration in association with hypophosphataemia is a reliable biomarker for OOM, but is not specific, as low serum 1,25(OH)2D3 concentrations are also typically found in patients with XLHR and ADHR (2).

Most tumours causing OOM are of mesenchymal origin and have been reported to be haemangiomas, haemangiopericytomas, osteo- or chondrosarcomas and giant cell tumours (1). However, more than 80% of OOM mesenchymal tumours share a distinct histological appearance, consistent with that of a PMTMCT (1). These tumours are composed of spindle-shaped neoplastic cells, prominent blood vessels, microcysts, osteoclast-like giant cells, cartilage-like matrix and bone (1). Most PMTMCTs are benign with <13% being recurrent or metastatic (1). Lymphatic vessels are present in very few vascular tumours, most notably lymphangiomas (6). Histology in this case revealed that the PMTMCT was haemangioma-like and that unlike typical benign haemangiomas it contained lymphatic vessels; these were identified by the expression of lymphatic endothelial cell marker LYVE-1 (6) (Fig. 3). LYVE-1 expression has previously been reported to occur in Kaposi’s sarcoma and angiosarcomas, but has been observed to be absent in haemangiopericytomas, and capillary, cavernous and epithelioid haemangiomas (6). Our finding of LYVE-1 expression in the tumour (Fig. 3) associating with OOM represented the first observation of lymphatic vessels in a PMTMCT, a feature which

![Figure 4](https://www.eje-online.org)

**Figure 4** Role of fibroblast growth factor 23 (FGF23) in phosphate homeostasis and oncogenic osteomalacia (OOM), X-linked hypophosphataemic rickets (XLHR) and autosomal dominant hypophosphataemic rickets (ADHR). Under physiological conditions, FGF23 is secreted predominantly by bone and undergoes degradation by the phosphate regulating endopeptidase homolog on the X chromosome (PHEX) and other proteolytic enzymes. FGF23, which mediates its actions via an FGF receptor and a likely co-receptor (Klotho), acts on renal proximal tubular (PT) cells to decrease the expression of the sodium–phosphate co-transporters NPT2a and NPT2c, and thereby reduce phosphate reabsorption. Increased amounts of FGF23 which may result from increased production or decreased degradation, will lead to urinary phosphate wasting and hypophosphataemia. Increased production of FGF23 occurs in OOM, in which PMTMCTs secrete FGF23 at levels that are several hundred fold greater than normal (thickened arrow). This overwhelms the degradation pathway and leads to inhibition of renal phosphate excretion and 1,25(OH)2D3 synthesis, with resulting phosphaturia and reduced intestinal absorption of calcium and phosphate respectively. The combined loss of phosphate and decreased concentration of 1,25(OH)2D3 lead to hypophosphataemia and osteomalacia. Decreased degradation of FGF23 occurs in XLHR and ADHR, which are due to mutations of the PHEX and FGF23 genes respectively. Thus, in XLHR, PHEX mutations lead to an inactivity of PHEX, whilst in ADHR the mutant FGF23, which is still active, is resistant to cleavage. The resulting excess FGF23 leads to phosphaturia.
clearly distinguishes this tumour from most vascular
tumours. Indeed, we have subsequently confirmed this
finding in eight other PMTMCs (10).

OOM is an acquired disorder due to usually benign
esenchymal tumours secreting humoral factors such as
FGF23, which inhibit renal tubular reabsorption
of phosphate and impair the synthesis of 1,25(OH)2D3
(2, 4, 5). Medical treatment with oral phosphate and
calcitriol is generally effective in ameliorating the
pain, myopathy, osteomalacia and fractures (2). In
some patients with OOM, oral phosphate therapy may
occasionally be insufficient, and parenteral phosphate
therapy may be required. However, some patients may
relapse despite medical therapy. Moreover, the medical
therapy may itself be associated with long-term
complications such as hypercalcaemia, hypercalciuria,
renal stones, renal failure and secondary or tertiary
hyperparathyroidism (2). Thus, the optimal treatment
for OOM is surgical removal of the tumour, which
results in a prompt improvement of the symptoms, and
resolution of the biochemical abnormalities and remi-
neralisation of the bone (2). However, these tumours are
difficult to find as they are often small and can occur
anywhere in the body (11). Hence, pre-operative
localisation is essential and a number of imaging
modalities such as computerised tomography (CT)
scans or MRI, or somatostatin receptor scintigraphy or
positron emission with CT (PET-CT) have been utilised
with varying success (11–14). CT scanning and MRI
have been widely utilised for the detection of OOM
tumours, and MRI is preferred for the detection of bone
and soft tissue lesions (12). However, these conventional
imaging methods frequently fail to identify the small
OOM tumours, and other methods have been investi-
gated to facilitate the detection of such occult tumours
(11–14). In vitro studies have revealed that many OOM
tumours express the somatostatin subtype 2 (sst2)
receptor (15) and octreotide scintigraphy has been used
to successfully detect OOM tumours in 18 cases (11,
16–18). The success rate of detecting OOM tumours by
octreotide scintigraphy in one study of seven patients
has been reported to be >70% (11). In addition, PET-CT imaging is proving to be useful in the detection
of OOM tumours (13, 14). PET most commonly employs
F-18 fluorodeoxyglucose (F-18 FDG) as its radioactive
tracer and F-18 FDG PET-CT has been used to localise
an OOM tumour (13). However, the uptake of F-18 FDG
correlates with the proliferative activity of the tumour
(19), and as OOM tumours are generally benign and
slow-growing (1), it seems unlikely that F-18 FDG
PET-CT will be of great utility for OOM tumour
detection. The use of Ga-68 DOTA-NOC, a modified
octreotide molecule with a higher affinity for sst2
receptors than existing radiolabelled somatostatin
analogue, as the PET-CT radioactive tracer, has been
highly successful in localising the tumour in one OOM
patient (14). The use of radiolabelled somatostatin
analogue appears promising but needs to be further
evaluated for the detection of OOM tumours. The
finding of sst2 receptors on OOM tumours (11, 17,
18) has not only helped in their detection but also in
treatment. Thus, the use of s.c. octreotide has been
shown to completely inhibit renal phosphate wasting in
one patient with OOM (17) and to partially improve
phosphate homeostasis in two other patients (16, 18).
In summary, surgical removal of OOM tumours remains
the treatment of choice (2), but there are challenges in
locating these small and occult tumours that require the
use of multiple imaging modalities (11–14). During the
period of these investigations, which could be several
years, medical treatment with oral phosphate and
calcitriol, will help to ameliorate the symptoms and
biochemical abnormalities (2). The use of s.c. somato-
statin analogues may also be beneficial in those patients
whose OOM tumour expresses sst2 receptors and is
detectable by octreotide scintigraphy (17).

In conclusion, low serum 1,25(OH)2D3 concentra-
tions and high serum FGF23 concentrations in
association with hypophosphataemia are reliable bio-
markers for OOM (Fig. 1), which is a paraneoplastic
disorder due to tumours that are often small and
difficult to locate, as they may occur anywhere in the
body. The majority of tumours causing OOM are
PMTMCs, and the detection by immunohistochemistry
of lymphatic endothelial cell markers such as LYVE-1
has been reported (10) to help to distinguish these
tumours from other vascular tumours, as illustrated by
our study (Fig. 3).

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