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Oncogenic osteomalacia associated with an occult phosphaturic mesenchymal tumour: clinico-radiologico-pathological correlation and ultrastructural studies

與隱性高磷酸鹽尿間葉細胞腫瘤有關聯的瘤源性軟骨病：臨床、放射和病理學的相互關聯和超微結構研究

A middle-aged man presented with bone pain at multiple sites due to tumour-induced osteomalacia. The underlying occult phosphaturic mesenchymal tumour was identified by octreotide scan 5 years after presentation and confirmed by computed tomography. Tumour resection resulted in normalisation of blood chemistry and bone densitometry. Clinico-radiologico-pathological correlation and ultrastructural studies of the tumour threw light on the pathogenesis and pathophysiology of this rare disease.

一名中年男子因腫瘤引致軟骨病，出現身體有多處地方骨痛的症狀，然而要在5年後利用奧曲肽掃描診斷，並由電腦掃描證實此診斷，才得知最終病因是患上了隱性高磷酸鹽尿間葉細胞腫瘤。當腫瘤被切除後，病人血液化學物水平和骨質密度水平已回復正常。臨床、放射和病理學的相互關聯和腫瘤的超微結構研究，能協助分辨一些罕見病症的病理機制或病理生理學情況。

Key words:

Fibroblast growth factors;
Osteomalacia;
Soft tissue neoplasms

關鍵詞：

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Introduction

Osteomalacia induced by a phosphaturic mesenchymal tumour with specific histological characteristics has been well described.¹ The term phosphaturic mesenchymal tumour, mixed connective tissue variant (PMTMCT) has long been used to describe this distinct entity, however it has not been widely accepted by histopathologists until recently.² The underlying humoral phosphaturic factor, overproduction of fibroblast growth factor 23 (FGF23), has been identified and utilised in serology and immunohistochemical tests in suspect cases.²⁻⁴ We present a classical example of PMTMCT-induced oncogenic osteomalacia (OO). Recent information combined with detailed clinico-radiologico-pathological correlation and ultrastructural studies enabled us to see the whole picture.

Case report

A 46-year-old Chinese man presented in 1997 with a 1-year history of bone pain over his ribs, both hips, and left foot. A plain X-ray revealed a stress fracture and repair over his left 4th metatarsal bone (Fig a). A skeletal survey and bone densitometry demonstrated generalised osteopenia. His lumbar spine age- and sex-matched Z score was -4.0 (Table). Bone scanning revealed hot spots over the left rib cage, left hip, and left metatarsal bone. Metabolic bone disease with multiple pathological fractures was suspected. The differential diagnoses at the time included haematolymphoid malignancy (eg multiple myeloma and lymphoma/leukaemia), Paget's disease, primary and secondary osteoporosis including uraemic osteodystrophy and hyperparathyroidism, hereditary conditions such as osteogenesis imperfecta (mild form) and osteomalacia. Detailed biochemical studies showed normocalcaemic phosphaturic hypophosphataemia, a raised serum alkaline phosphatase, and a normal parathyroid hormone level, all indicative of osteomalacia. This was confirmed by biopsies of the iliac crest and 4th metatarsal bone. Dietary and rare hereditary causes were easily excluded,

Table. Laboratory and bone densitometry findings before and after tumour resection

Variable	At presentation	On medical treatment	Postoperative day 4	Postoperative 1 year
Blood chemistry (reference range)				
Calcium (2.20-2.60 mmol/L)	2.35	2.30	2.26	2.36
Phosphate (0.87-1.45 mmol/L)	0.52	0.57	1.14	1.24
Alkaline phosphatase (42-98 IU/L)	697	127	156	116
Bone densitometry of L1-L4 spine*				
Bone mineral density (g/cm ²)	0.707	0.908	NA	0.994
Age- and sex-matched Z score	-4.0	-2.2	NA	-1.3

* NA denotes not available, and Z standard deviation from controls

thus the patient was presumed to have OO. Extensive investigations including computed tomography (CT) and magnetic resonance imaging, failed to reveal any underlying tumour, so the patient was treated conservatively with sodium phosphate supplements and 1,25-dihydroxyvitamin D3. His bone density improved to a small extent but not his blood biochemistry (Table).

Five years after presentation, with the availability of newer investigative methods,⁵ a (111)In-octreotide scan was performed. This revealed a single uptake focus between the left 7th and 8th ribs. A repeated CT scan confirmed an enhancing soft tissue mass at the corresponding site, not seen previously (Fig b). The mass was deemed the culprit and duly resected along with a segment of the 7th rib. The patient's serum phosphate level gradually returned to normal on postoperative day 4. Bone densitometry performed 1 year later also showed significant improvement (Table).

The resected dark red soft tissue mass (3 cm) was partly rimmed by intercostal muscle, situated close to the 7th rib and adherent to intercostal venous vessels. Microscopic examination showed a well-circumscribed, thinly encapsulated, vascular, spindle-celled tumour (Fig c). It consisted of mitotically inactive, round to plump-spindled cells with bland-looking nuclei and pinkish cytoplasm (Fig d). A varying amount of pale pinkish chondroid-like stroma was present in the background lacking osteoclast-like giant cell reaction or calcification. A haemangiopericytoma-like vascular pattern was prominent. Microcystic spaces containing colloid material and islands of mature fat cells were seen. The histological picture was almost identical to that described for PMTMCT.^{1,2} Immunohistochemical studies showed tumour cells negative for S100, synaptophysin, chromogranin, epithelial membrane antigen, and cytokeratin. They were only focally positive for smooth muscle actin and CD34, and in about 30% were positive of cells for FGF23. The microcystic content did not stain for FGF23 while intravascular serum served as a positive control. Ultrastructural studies on glutaraldehyde-fixed tissue showed oval to polygonal tumour cells with indented nuclei, a moderate number of cytoplasmic organelles, and interdigitating cell processes or filopodia (Figs e, f, and g). The background contained granular matrix and some collagen fibrils. Subplasmalemmal condensation of intermediate filaments, probably actin filaments, was noted. There were prominent rough endoplasmic reticula (RER),

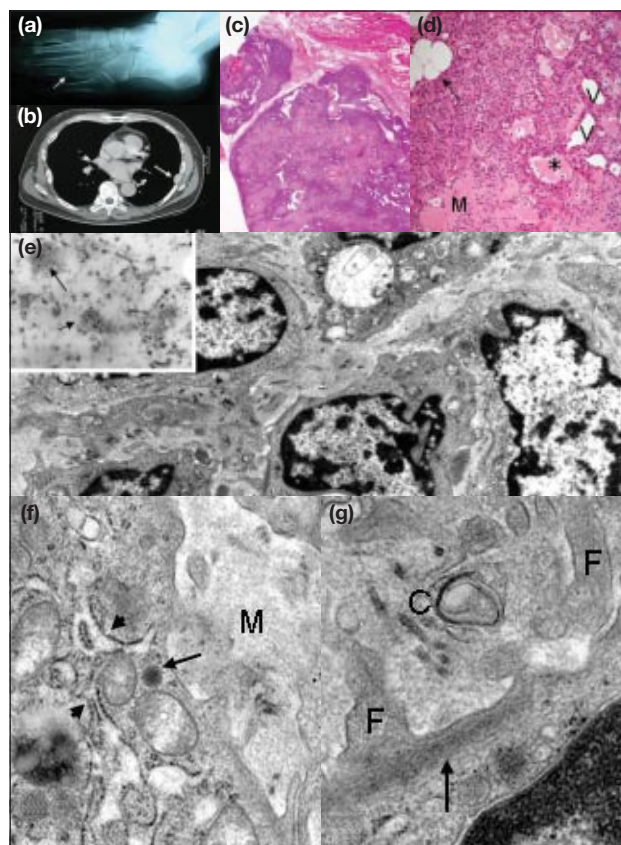


Fig. (a) X-ray of left foot with stress fracture (arrow) at 4th metatarsal bone; **(b)** computed tomographic scan with contrast-enhanced soft tissue mass (arrow) at 7th and 8th intercostal space; **(c)** circumscribed multinodular tumour; **(d)** plump-spindled cells in varying amounts of chondroid-like matrix (M) with haemangiopericytoma-like vasculature (V), mature fat cells (arrow) and microcysts (*); and **(e, f, g)** ultrastructural studies: polygonal tumour cells with interdigitating filopodia (F) surrounded by granular matrix (M) containing collagen fibrils (C), subplasmalemmal condensation of intermediate filaments (arrow in Fig g), rough endoplasmic reticula (arrow heads in Fig f) and rare electron-dense membrane-bound granules (arrows in Fig f) were noted; (Inset in Fig e) immuno-gold labelling for fibroblast growth factor 23 showed localisation of particles (arrows) within the rough endoplasmic reticulum (magnification: [e] x 4600; inset, x 28500; [f] x 25000; [g] x 34000)

mitochondria, scanty myelin bodies, and rare electron-dense membrane-bound granules. Immuno-gold labelling for FGF23 on ultrathin sections of paraffin-blocked tissue incubated with the respective antibody showed localisation

of FGF23 within the RER of the tumour cells (Fig e inset). Both immuno-histochemical and ultrastructural studies demonstrated production of FGF23 within tumour cells, thus confirming myofibroblastic or pericytic differentiation.

Discussion

Oncogenic osteomalacia is a rare paraneoplastic syndrome that is usually induced by bone or soft tissue tumours. Rarely, it is associated with prostatic cancer. Among the soft tissue tumours, phosphaturic mesenchymal tumours form the major group. Patients present with bone pain at multiple sites due to hypophosphataemic osteomalacia induced by a phosphaturic factor (phosphatonin), secreted by the tumour and acting on the kidney tubules, now known to be FGF23. Serum 1,25-dihydroxyvitamin D3 is low, while its precursor 25-hydroxyvitamin D3 is usually normal. It is interesting that the *FGF23* gene is mutated in autosomal dominant hypophosphataemic rickets, while the *PHEX* (an enzyme which normally degrades FGF23) gene is mutated in X-linked hypophosphatasia. Localisation of the culprit tumour in OO may be difficult. While (111)In-octreotide (that binds to somatostatin receptors on the tumour) scanning may help to show the rough location, high resolution CT and positron emission tomography scans are certainly more useful in defining the exact location.

The tumour demonstrated the classical histological features of PMTMCT with a chondroid-like matrix but lacking calcification and osteoclast reaction. Demonstration of a close association with intercostal veins suggests a vascular origin of the tumour. The immunophenotypic expression and ultrastructural features were similar to those previously described with the exception of the presence of rare electron dense granules.^{1,2} We were able to perform unprecedented immuno-gold labelling on ultrathin sections and localised the hormone FGF23 to the RER of tumour cells. Thus FGF23 was definitely formed by the tumour cells and precipitated the train of metabolic events that culminated in fragile bones. Resection of the tumour reversed the phosphate wasting and gradually improved bone mineralisation, proven by bone densitometry and alleviation of symptoms. Although PMTMCT is a distinct entity, there is a histological spectrum that corresponds to a parallel spectrum of abnormal gene expression and cellular synthesis.² Over-expression of *MEPE*⁶ in PMTMCT produces a high level of extracellular matrix phosphoglycoprotein that may give rise to the calcified

matrix. Over-expression of FGF23 results in renal phosphate wasting and subsequent osteomalacia. Histological PMTMCT without osteomalacia, signifying insignificant or no FGF23 over-expression, has been reported in three patients.² Guillou et al⁷ reported 13 lipomatous haemangiopericytomas morphologically, immunohistochemically, and ultrastructurally similar to PMTMCT with the inclusion of mature fat cells but lacking the chondroid-like matrix and microcystic spaces as well as the metabolic dysfunction. These may represent similar tumours that lack the over-expression of both *MEPE* and *FGF23* genes. Thus, there exists a broad group of haemangiopericytoma-like tumours and PMTMCT is a rare and distinct subset among them. Clinical awareness of OO due to PMTMCT is important. Prompt localisation of the tumour using various scanning techniques and resection can relieve agonising symptoms.

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