ONCOGENIC OSTEOMALACIA ASSOCIATED WITH PHOSPHATURIC MESENCHYMAL TUMOUR, MIXED CONNECTIVE TISSUE TYPE OF THE KNEE

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One of the most unusual and uncommon types of osteomalacia is the oncogenic osteomalacia that is predominantly caused by a soft tissue or bone tumour, mostly by a phosphaturic mesenchymal tumour, mixed connective tissue type (PMTMCT). We report a case of a 27-year-old male presented with complaints of progressive and generalized muscle weakness, bone pains and multiple fractures. Intra-articular PMTMCT of the knee was diagnosed and surgically removed. We describe histopathological features of PMTMCT and review the most recent studies concerning this diagnostic problem.

Key words: oncogenic osteomalacia, mesenchymal tumours, phosphaturia, fibroblast growth factor, FGF23.

Introduction

Oncogenic osteomalacia (OO) is a very rare paraneoplastic syndrome characterized by hypophosphatemia, hyperphosphaturia accompanied by normocalcemia and decreased 1,25-dihydroxyvitamin D3 levels as well as resistance to vitamin D supplementation [1]. It occurs in association with diverse conditions including various tumours, i.e. carcinomas, lymphomas, neurofibromatosis type 1, fibrous dysplasia and epidermal naevus syndrome, McCune-Albright syndrome; nevertheless, the majority of OO cases is related to mesenchymal tumours of soft tissue and bone [2, 3]. Since reclassification of Weidner and Santa Cruz [4] in 1987 these tumours have been reported as haemangiopericytoma, hemangioma, giant cell tumour, osteoblastoma. On the basis of common histopathological mesenchymal tumour features as well as subsequent detection of fibroblast growth factor 23 (FGF23) overexpression, a single pathological entity was suggested, designated as a phosphaturic mesenchymal tumour, mixed connective tissue type (PMTMCT) [3-5]. FGF23 is a protein that inhibits renal phosphate transport in the proximal tubules. Its high serum levels and an increased activity accompanying PMTMCT were reported [5, 6]. The other proteins participating in mineralization disturbance which seem to be overexpressed are matrix extracellular phosphoglycoprotein and dentin matrix protein 1 [7-9]. Clinically, patients with PMTMCT suffer from general fatigue, muscle and bone pain, multiple bone fractures leading to the skeleton deformation and general disability. The diagnosis is frequently delayed because of a small tumour size, its slow growth and unusual anatomical localization. Various imaging techniques are used to identify the tumour site, beginning with simple routine radiographs, ultrasonography, computed tomography, magnetic resonance of the whole body, ^{111}In-pentreptreotide or octreotide scintigraphy, ^{201}Tl scintigraphy, ^{99}mTc MIBI SPECT, positron emission tomography to the selective venous sampling for FGF23 with MR imaging [10-13]. The

only effective treatment option for a patient with PMTMCT is resection of the neoplasm.

The authors describe a case of OO associated with PMTMCT and review the most recent studies concerning this diagnostic problem.

Case description

A 27-year-old male presented with complaints of generalized, progressive muscle weakness and bone pains lasting for six years. Recently the patient has become bedridden with minimal assisted mobility. In 2003, his right arm and clavicle were fractured only with a minimal trauma. There was no significant family history of the metabolic bone disease or fracture. In addition he had functional hyperbilirubinaemia (Gilbert syndrome) and underwent tonsillectomy in 2007.

Laboratory tests

Initial laboratory tests revealed borderline hypocalcemia (2.05 mmol/l; normal range: 2.1-2.6 mmol/l), hypophosphatemia (0.27 mmol/l; normal range: 0.81-1.6 mmol/l), an elevated alkaline phosphatase level (309 U/l; normal range: 38-126 U/l) with high osseous fraction 82.9% (normal range: 40-60%), an elevated parathyroid hormone (134.7 pg/ml; normal range: 15-65 pg/ml), normal levels of vitamin 25(OH)D (12.2 ng/ml, normal range:11-54 ng/ml) and 1,25(OH)D (17.5 pg/ml, normal range: 15-70 pg/ml). In a 24-hour urine sample the phosphorus level was normal (25.7 mmol/24 h, normal range: 13.5-70.0 mmol/24 h) with considerably elevated phosphorus clearance rate (66.1 ml/min, normal range: 5.4-16.2 ml/min) and low calcium level (1.0 mmol/24 h, normal range: 2.5-6.2 mmol/24 h). There was no glycosuria or aminoaciduria. The test was performed during an oral administration of 1200 mg Ca, 600 mg PO4 and 0.25 μg 1,25(OH)D vitamin per day.

The following parameters appeared to be normal: a complete blood cell count, liver and kidney function tests, myelogram, serum protein electrophoresis; levels of antinuclear antibody, rheumatoid factor, hormones: TSH, LH, FSH, PRL, calcitonin, testosterone, IGF-1. In the differential diagnosis the malabsorption syndromes were considered. They were excluded as the anti-endomysial (EmA IgA) and anti-tissue transglutaminase (tTG IgA) antibodies were negative. Gastroscopic appearance of the oesophageal, gastric and duodenal mucosa was normal. The biopsy specimens of duodenum showed the minimal chronic inflammation.

Imaging studies

Radiographic images showed generalized osteomalacia, multiple fractures of almost all ribs, thoracic and lumbar vertebrae with severe thoracic kyphosis. Numerous pseudofractures (Looser-Milkman zones) were detected (both scapulae, left humerus, proximal methaphysis of both femurs, left inferior pubic ramus and left ischiadic bone) as well as protrusion of both femoral heads.

Scintigraphy (tectrotide, ^{99}mTc MIBI SPECT) bone scan showed an increased uptake in the lateral region of the left knee (Fig. 1.)

Sequential whole body and selective coronal, oblique and sagittal contrast enhanced magnetic resonance imaging (MRI) were done. The well-defined tumour located intra-articularly, near a lateral part of the left knee was identified. A vascular tumour was suggested since its strong, non-homogeneous solid enhancement after i.v. contrast administration (Fig. 1).

In spiral computed tomography (Angio CT) the tumour was markedly vascularized, intra-articular, 24 × 38 × 40 mm in dimension. Additionally, in the early and late arterial phase the tumour was strongly enhanced, typically of vascular neoplasm. The main arterial vasculature originated from superior lateral, middle, inferior medial knee arteries.

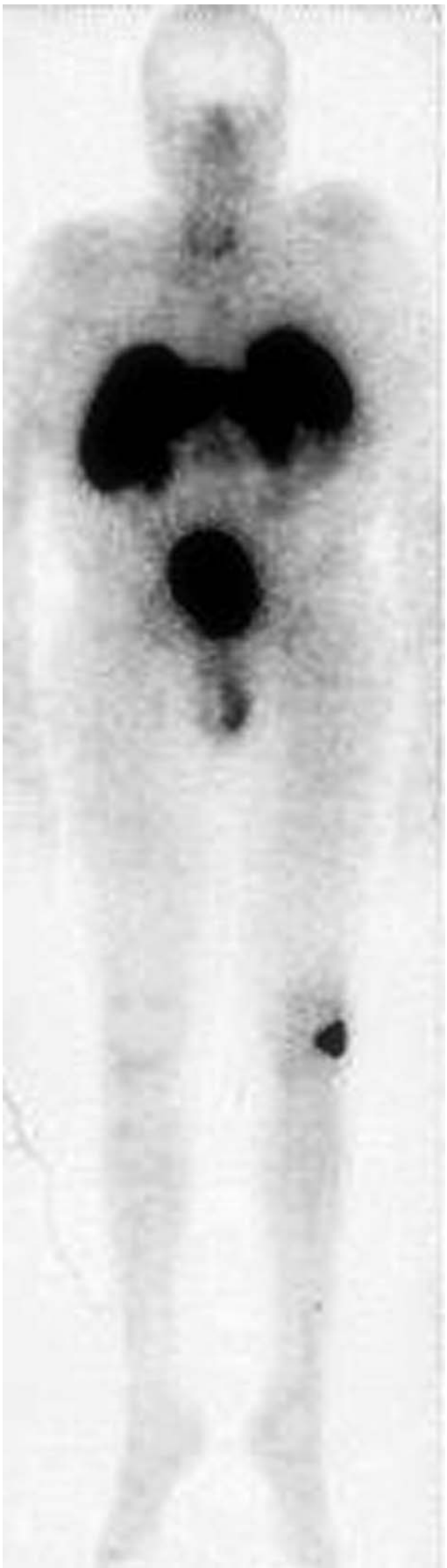
Histopathological examination

The tumour was surgically excised and a histopathological examination was performed according to routine procedures.

Macroscopically the tumour was well circumscribed, soft to dense in consistency, grey-yellow in colour with some hemorrhagic areas at the cut surface. Microscopically, the tumour had an appearance of typical PMTMCT and was composed of sheets of small, spindle to oval cells without nuclear atypia or atypical mitotic figures (Fig. 2A, 2B), aggregates of osteoclast-like giant cells (Fig. 2C), regions of woven bone (Fig. 2D), gray, flocculent and "grungy" crystals (Fig. 2E, 2F), extensive areas of haemorrhage and hemosiderin deposition (Fig. 2G), infiltration of the surrounding tissues despite circumscription on macroscopy (Fig. 2H).

Discussion

One of the most unusual and uncommon type of osteomalacia is the oncogenic osteomalacia (OO) which is predominantly caused by a soft tissue or bone tumour. The clinical and laboratory characteristics of OO include, generalised muscle weakness, bone pains and fractures, renal phosphate wasting, hypophosphatemia, normocalcemia, decreased serum concentration of vitamin 1,25(OH)D, resistance to vitamin D and phosphate/calcium oral administration. The disease may be cured by surgical removal of the neoplasm. In an up-to-date review of the literature,



approximately 150 cases of OO-associated with mesenchymal tumours have been reported. Historically, these neoplasms were classified as a histologically heterogeneous group comprising e.g. haemangiopericytoma, haemangioma, giant cell tumour, osteoblastoma [3]. The concept that mesenchymal tumours accompanied by OO may lump together into a single unique entity was proposed in the early 1970s by Evans and Azzopardi [18] and Olefski *et al.* [19]. After nearly 20 years, in 1987, Weiner and Santa Cruz [4] described morphologic features of these tumours and for the first time used the term "phosphaturic mesenchymal tumour, mixed connective tissue variant" (PMTMCT). The classic microscopic findings included low to moderate cellularity with bland spindle cells, osteoclast-like giant cells, haemangiopericytoma-like vessels, areas of haemorrhage, hemosiderin deposits, myxoid change, microcyst formation, incomplete rim of membranous ossification, distinctive "grungy" calcified matrix. The

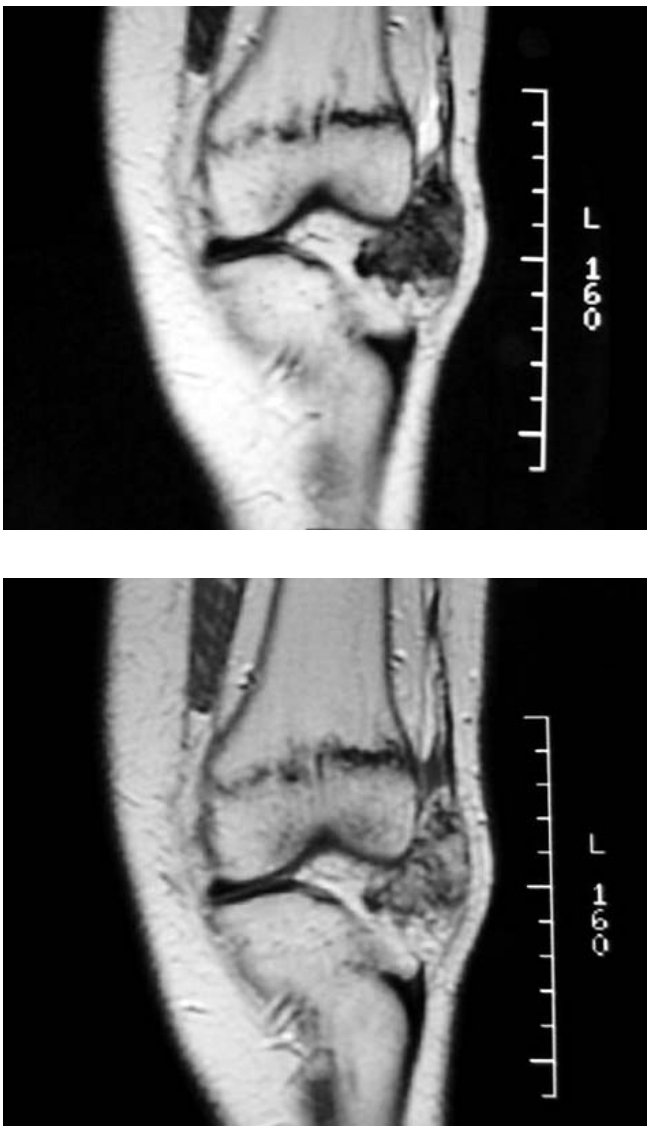


Fig. 1. The ^{99}mTc MIBI SPECT scintigraphy of the whole body and the MRI (the lower extremities scans).

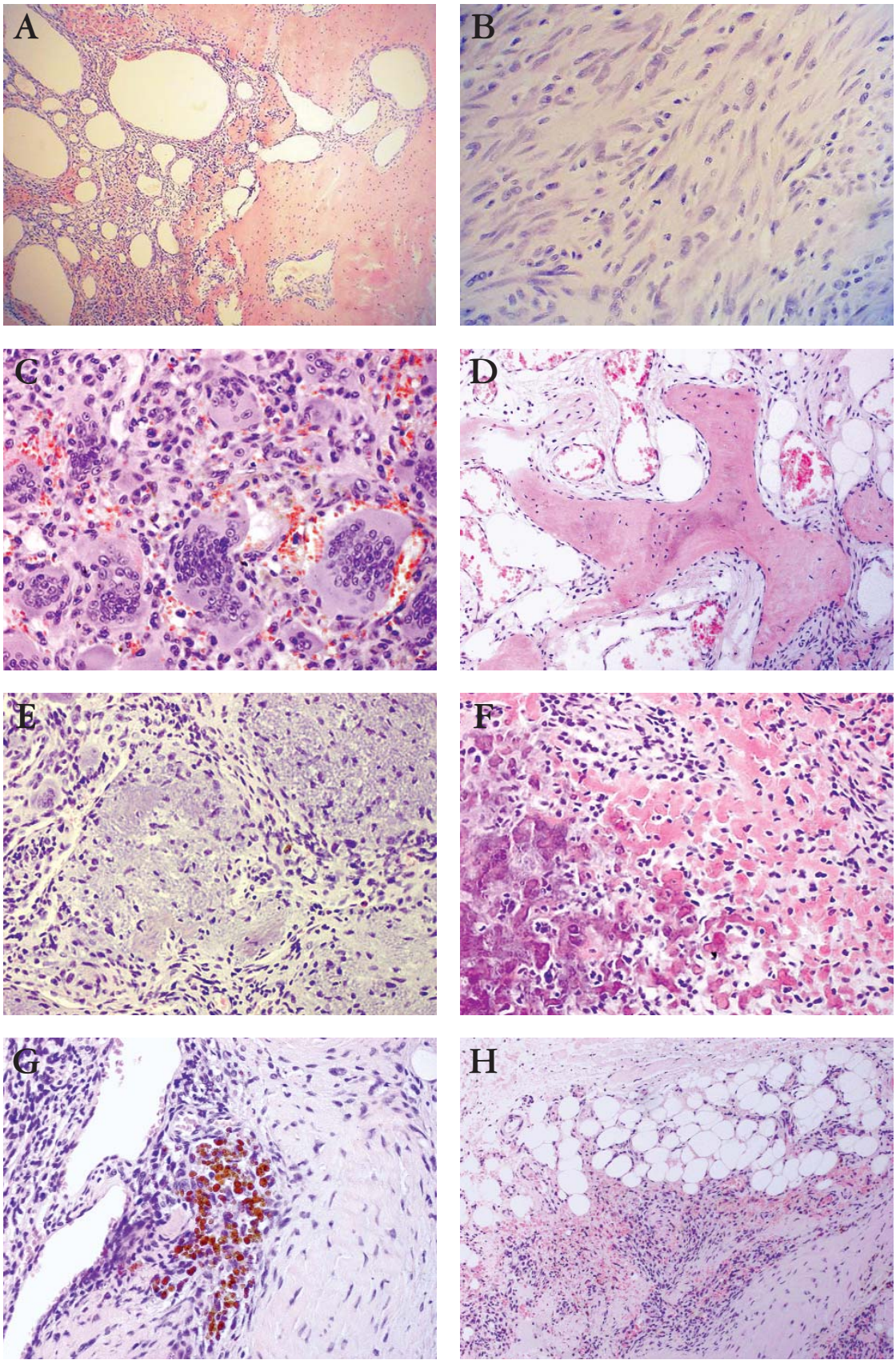


Fig. 2. Histological characteristics of PMTMCT: (A, B) sheets of small, spindle to oval cells without nuclear atypia with sparse typical mitotic figures, (C) clusters of osteoclast-like giant cells, (D) regions of woven bone, (E, F) gray, flocculent and grungy crystals, (G) extensive areas of haemorrhage and hemosiderin deposits, (H) infiltration of the surrounding tissues despite circumscription on macroscopy.

Table I. The differential diagnosis and characteristics of hypophosphaturic osteomalacia (N = normal; arrows in square brackets denote abnormality seen occasionally; alkaline phosphatase is usually increased in osteomalacia)

DISEASE	GENETICS	CA	PO_4	25(OH)D	1,25(OH)D	PTH
autosomal dominant hypophosphatemic rickets/osteomalacia (ADHR)	dysregulation of FGF23 function by mutations in *FGF23* gene*	↔[↓]	↓	↔	↓	↔[↑]
autosomal recessive hypophosphatemic rickets/osteomalacia (ARHR)	overexpression of FGF23 in bone by *DMP1*** gene mutations					
X-linked hypophosphatemic rickets/osteomalacia (XLR)	overexpression of FGF23 in bone by *PEHX*# gene mutations					
excessive Klotho+	*Klotho* gene mutations					
oncogenic osteomalacia (OO)/ tumour-induced osteomalacia (TIO)	overexpression of FGF23 by tumour cells					
McCune-Albright syndrome/ Fibrous dysplasia	overexpression of FGF23 in bone					
hereditary hypophosphatemic rickets/osteomalacia with hypercalciuria (HHRH)	mutation of *NaPi2c*++ gene	N	↓	N	↑	N
renal phosphate loss (i.e. Fanconi syndrome, intoxication with cadmium, heavy metals)		N	↓	N	N	N
excessive antacid intake		N	↓	N	↔↑	N

FGF23* *– gene encoding fibroblast growth factor 23, a 251 amino acid secreted peptide, was mapped to chromosome 12p13 {14-17}.*
DMP1* *– dentin matrix protein 1, suppress FGF23 expression in bone {8, 9}.*
***PEHX**#* *– phosphate-regulating gene with homologies to endopeptidases on the X chromosome, suppress FGF23 expression in bone {14-17}.*
***Klotho**+* *– single-pass transmembrane protein with an extracellular domain consisting of two homologous subdomains and β-glucosidase attached; expressed in kidney, parathyroid and pituitary gland, its mechanism of action in the kidney still remains unclear but α-Klotho is exclusively co-expressed with calcium permeable Transient Receptor Potential V5 channels, Na/Ca exchanger 1 and a vitamin D sensitive intracellular Ca transporting protein in a specialized region of the nephron segments where transepithelial Ca reabsorption is actively regulated. This co-localization is believed to be important for the homeostatic control of Ca reabsorption in the kidney; α-Klotho facilitates the binding of FGF23 to FGF receptors (FGFR1c, -3c and -4) and activates downstream signalling molecules by phosphorylation of FGFR {14-17}.*
***NaPi2c**++* *– sodium-phosphate cotransporter type 2c that is responsible for the vast majority of phosphate reabsorption in the renal proximal tubule; PTH is considered to be its main regulator, promoting rapid removal of NaPi2c from the membrane and its subsequent degradation {14-17}.*

latest study by Folpe *et al*. [3] concerning a large group of PMTMCT (32 cases) has confirmed that classic PMTMCT has common clinicopathological and immunohistochemical presentation. Furthermore the authors identified a small group of neoplasms with histological features of PMTMCT without known OO, the so-called "nonphosphaturic variants".

In the pathogenesis of phosphate wasting in phosphaturic osteomalacia, including OO, a key role is played by recently identified, fibroblastic growth factor 23 (FGF23) – a protein that inhibits phosphate reabsorption in the proximal renal tubules and suppresses the 1,25(OH)D vitamin synthesis. Under physiological conditions, FGF23 is produced in bones and undergoes degradation by the endopeptidase homolog (coded by *PHEX* gene on X chromosome) and other proteolytic enzymes. In renal proximal tubules FGF23 acts directly by the FGF receptor and the co-receptor α-Klotho to decrease an expression of the sodium-phosphate co-transporters NaPi2c and NaPi2a consecutively reducing phosphate reabsorption. In PMTMCT, FGF23 production is several fold greater than normal and overrides the degradation pathway. It leads to phosphaturia, inhibition of 1,25(OH)D vitamin synthesis and reduced intestinal absorption of calcium/phosphate [5, 6, 14-17]. The other rare causes of hypophosphatemic osteomalacia are summarized in Table I.

The immunohistochemical expression of FGF23 is identified in more than 80% of PMTMCT cases [3]. Nevertheless, the authors emphasize that the antibodies used against FGF23 in immunohistochemical studies are polyclonal, not entirely specific and in commercially unavailable. An expression of FGF23 was evaluated in 29 cases using RT-PCR approach [20]. It is expressed in over 90% of

PMTMCT cases with known OO and in 75% of morphologically identical neoplasms without known OO. It leads to a conclusion that some classical PMTMCTs with OO presumably produce other phosphaturic agents. The best candidates are frizzled-related protein 4 and dentin matrix protein 1 [8, 9]. It is worth to mention that the serum FGF23 concentration can be measured but only in a few laboratories.

The most recent immunohistochemical studies of PMTMCT showed that the vascular channels present in this particular neoplasm expressed markers characteristic of lymphatic vessels including LYVE1 and podoplanin [21]. These findings along with the FGF23 expression appear to be a characteristic immunohistochemical feature of PMCMCT and distinguish this neoplasm from other vascular tumours.

In conclusion, we present a case of classical PMTMCT associated with OO. The difficulties with identifying a small, radiologically indiscernible but biochemically active tumour have delayed the correct diagnosis and caused generalized osteomalacia, multiple fractures and skeletal deformation. In differential diagnosis among rare causes of hypophosphatemic osteomalacia the PMTMCT should be considered.

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Quiz
What is your diagnosis?

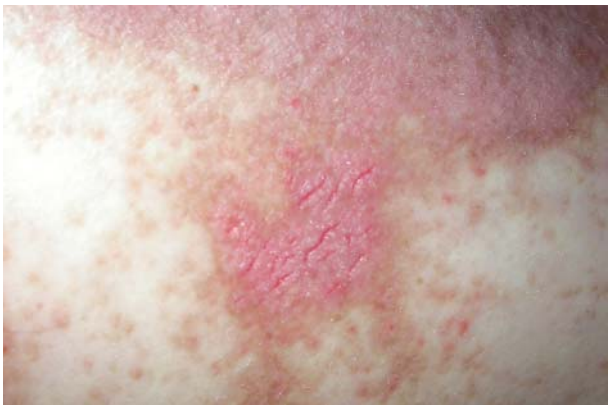

Fig. 1

Case description
60-year-old male patient was admitted to hospital because of 3 month history of skin lesions (Fig. 1) on the lumbar area, abdomen, and right groin which were accompanied by itching. Such lesions appeared first 6 years ago and were irregularly treated locally with steroids with transient effect. Tissue samples were taken for further histological (Fig. 2) and ultrastructural (Fig. 3) studies.

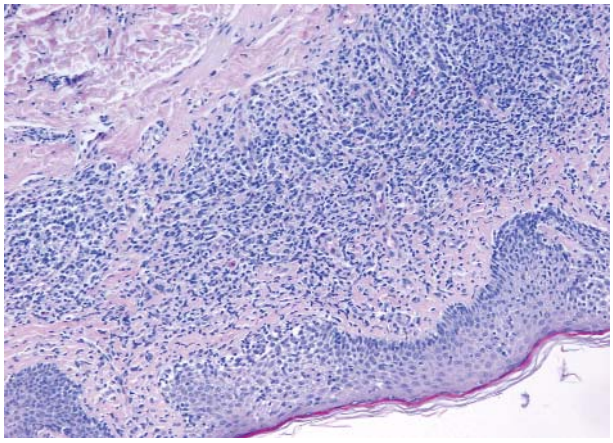

Fig. 2

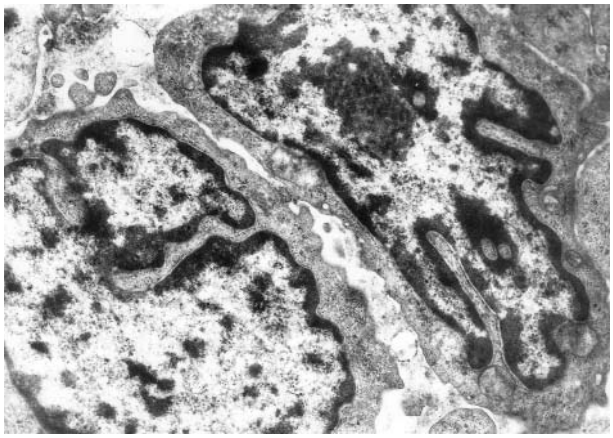

Fig. 3

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