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Case Report

Stumbling upon the unexpected: A unique presentation of phosphaturic mesenchymal tumor in the hindfoot ☆

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ABSTRACT

We describe an unexpected and unique case of phosphaturic mesenchymal tumor in a 38-year-old female presenting with a painful lump in the plantar hindfoot. Phosphaturic mesenchymal tumors are extremely rare, generally benign soft tissue or osseous tumors, which are associated with overexpression of fibroblast growth factor-23 and tumor-associated osteomalacia. Patients often present with progressive signs and symptoms including systemic bone pain, muscle weakness, and insufficiency fractures, and timely diagnosis is paramount to appropriate therapy. Tumor resection is almost always curative with normalization of laboratory markers and resolution of symptomatology.

Introduction

Phosphaturic mesenchymal tumors (PMTs) are rare, predominately benign osseous or soft tissue tumors frequently associated with tumor-induced osteomalacia (TIO). There is overexpression of fibroblast growth factor (FGF)-23 which causes hypophosphatemia. Patients typically present with nonspecific progressive signs and symptoms of systemic bone pain, muscle weakness, and insufficiency fractures. The diagnosis is not clear cut and cannot be made solely on imaging. In the absence of clinical findings, molecular analysis can be useful in further characterizing tumor biology. Once localized, tumor resection is almost always curative with normalization of serum phosphate levels as early as postoperative day 2 [1]. Herein, we describe an unexpected and unique case of a PMT in a 38-year-old female who was complaining of a painful lump in the plantar hindfoot.

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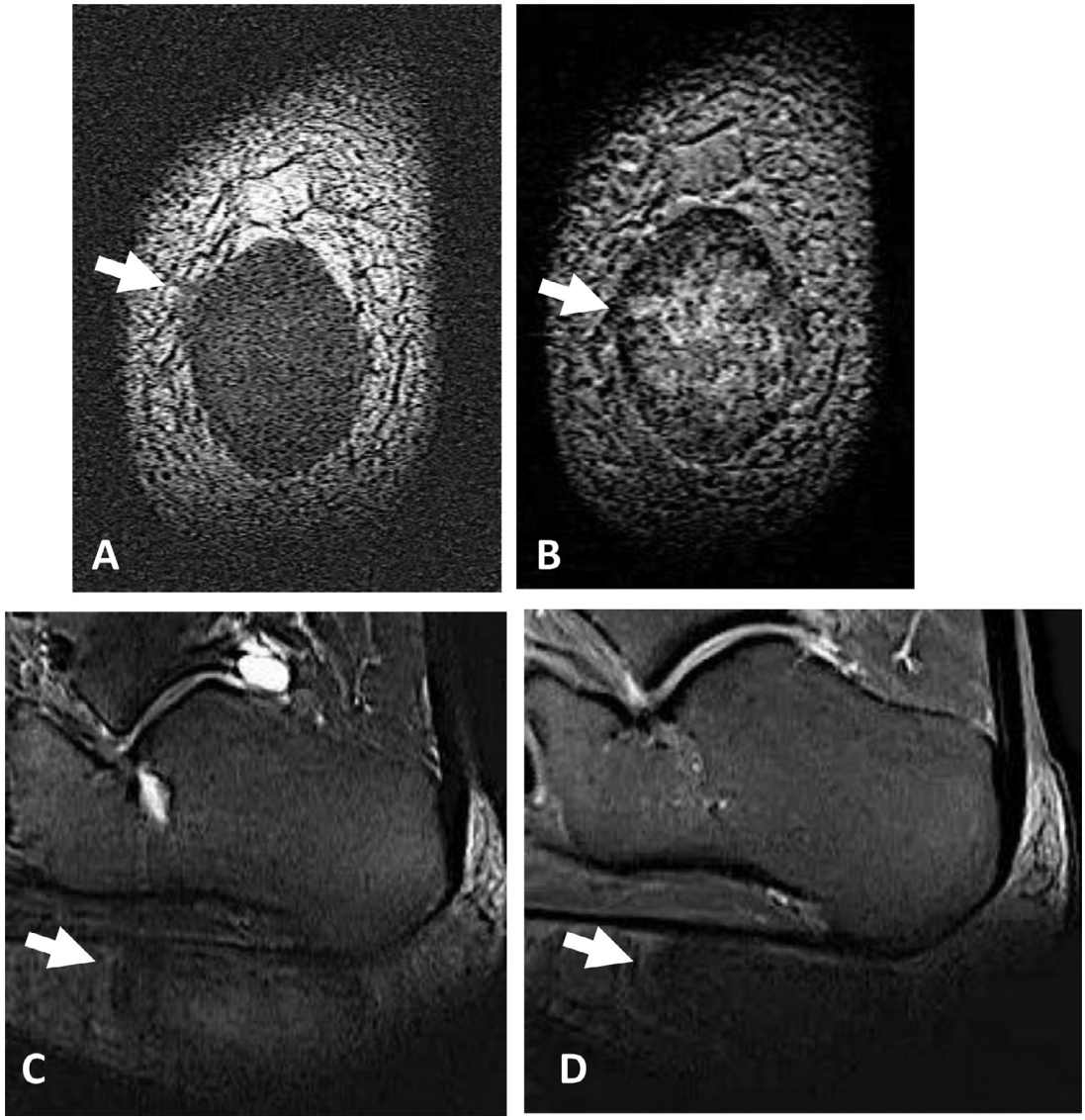

Fig. 1 – Multiplanar and multisequence MRI of the left hindfoot without and with gadolinium enhancement. (A) Axial T1 sequence demonstrates an ovoid soft tissue mass with low signal intensity, (B) Axial T2 fat sat sequence demonstrates heterogenous signal with peripheral low intensity, (C) Sagittal T2 fat sat, and (D) Sagittal T2 fat sat post gadolinium images showing no evidence of enhancement.

Case

A 38-year-old female was complaining of a painful lump in the plantar aspect of her left hindfoot, which was increasing in size over a 2-year period. The patient was seen by a number of physicians during this time and was told she had plantar fasciitis. At the time of the consultation with the orthopedic surgeon, she was unable to weight-bear because of the pain and required crutches. Physical examination demonstrated a firm mass on the plantar aspect of the hindfoot with severe pain to palpation. Passive range motion of the toes, especially in dorsiflexion resulted in increased pain. Neurovascular examination was unremarkable. Review of blood work showed that a metabolic panel was obtained 3 years prior to this presentation for work-up of low Vitamin D, 25 hydroxy level with normal phosphate, alkaline phosphatase, calcium, and PTH levels. Most recent PTH and Vitamin D, 25 hydroxy levels were within normal range.

An MRI was performed for further assessment with T1, T2, and postgadolinium sequences (Fig. 1). A 4.3 × 3.0 × 2.2 cm ovoid, subcutaneous plantar mass was identified which showed low T1 and heterogenous T2 signal with peripheral low T2 intensity. There was no definite enhancement, surrounding edema or contact with the plantar fascia. No deep invasion or abnormal marrow signal was noted. Differential considerations included a fibrous lesion and ultrasound was recommended for further characterization.

Sonographic assessment of the left plantar hindfoot showed a heterogeneous predominately hypoechoic mass

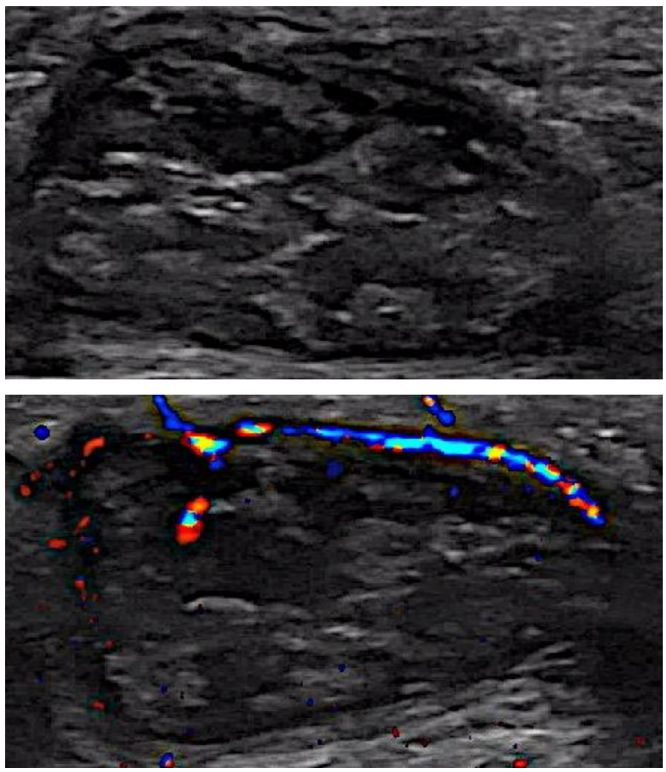

Fig. 2 – Sonographic assessment of the left plantar hindfoot without and with Doppler interrogation illustrates a heterogenous predominately hypoechoic, well-defined soft tissue mass with mild vascularity superficially.

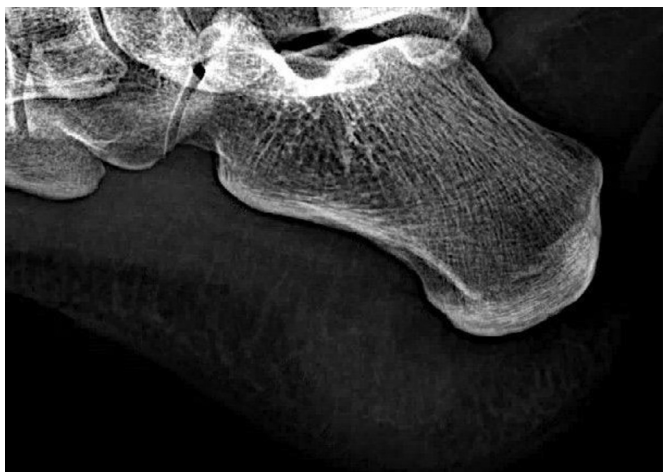

Fig. 3 – Lateral radiograph of the left hindfoot illustrates a small ovoid density within the soft tissues inferior to the calcaneus without destructive osseous changes or periostitis.

that is well-defined with some vascularity superficially (Fig. 2). Corresponding radiographs obtained on the same day showed a rounded soft tissue density inferior to the calcaneus without destructive osseous changes (Fig. 3). Following informed consent, multiple ultrasound-guided core biopsy samples were obtained and sent for histopathology assessment.

Microscopic analysis showed fibrous connective tissue composed of spindle-epithelioid cells with ovoid nuclei, minimal atypia, and low mitotic activity (1 per 10 HPFs). Areas of hyaline cartilaginous stroma, stippled calcification, and scattered multinucleated giant cells were identified as well as scattered hemosiderin deposition with siderophages.

Table 1 – Stepwise approach to the diagnosis and treatment of tumor-induced osteomalacia [1].

1. Signs and symptoms of hypophosphatemia
2. Confirmatory laboratory findings (low phosphate, low renal tubular reabsorption of phosphate, low 1,25-dihydroxyvitamin D and increased FGF23)
3. Exclude genetic causes
4. Tumor localization via functional imaging followed by targeted anatomical imaging
5. Surgical resection with wide margins for localized tumors vs. medical therapy

Immunohistochemistry analysis was positive for vimentin. Based on these findings tenosynovial giant cell tumor with chondroid metaplasia/pigmented villonodular synovitis was favored.

Surgical excision was performed by the orthopedic surgeon and molecular analysis of the surgical specimen at a tertiary care center specialized for soft tissue oncology was positive for an FN1-FGFR1 fusion gene. Based on this new information, PMT was favored as the diagnosis. Endocrinology consultation was recommended since TIO is a known paraneoplastic syndrome associated with this tumor.

Discussion

PMTs are extremely rare, generally benign osseous or soft tissue tumors associated with TIO. They can occur anywhere from head to toe with the most common location involving the extremities (95%) followed by the head and neck [2]. Both genders are affected equally and the median age is 53 years old (range 9-80) [3]. While few present with palpable lumps, most of the patients often have nonspecific and progressive symptoms including systemic bone pain, muscle weakness, and multiple insufficiency fractures in adults or rickets and growth retardation in children. Accordingly, the diagnosis is not straightforward with many patients misdiagnosed with other musculoskeletal or rheumatological diseases just as our patient was misdiagnosed with plantar fasciitis.

Table 1 summarizes the stepwise approach to the diagnosis of TIO based on comprehensive review by Chang et al. Typical laboratory findings include hypophosphatemia, hyperphosphaturia (renal phosphate wasting), elevated alkaline phosphatase, normal to low 1,25 dihydroxyvitamin D, normal serum calcium and parathyroid hormone, and elevated serum FGF-23 levels. The latter is overexpressed secondary to an FN1-FGFR1 gene fusion, which is found in nearly 50% of PMTs suggesting there are likely other tumorigenic mechanisms in these lesions [4]. By acting on renal tubules, FGF-23 impairs phosphate reabsorption and hydroxylation of 25-hydroxyvitamin D leading to hypophosphatemia and low levels of 1,25 dihydroxyvitamin D. The high serum levels of FGF-23 help to exclude acquired causes of hypophosphatemia via direct renal tubular damage secondary to medications or toxins [1].

Table 2 – Radiological and histological features of phosphaturic mesenchymal tumors.

Radiological (5)	Histological (1)
CT: 2/3 of primary bone lesions are osteolytic with a narrow zone of transition. Internal matrix is present in more than 50% of lesions, more commonly in primary bone lesions rather than soft tissue lesions **MRI:** Intermediate T1 signal and variable T2 signal (almost 90% of cases have areas of dark T2 signal). Majority of the lesions demonstrate enhancement which could be solid, heterogenous or peripheral. Few demonstrate perilesional edema (<10%) **Nuclear medicine:** Positive on 18F-FDG PET/CT, 99m Tc-sestamibi, and 68Ga-DOTATATE PET/CT (analogue of somatostatin)	Spindled to stellate in shape. Normochromatic with small nuclei and indistinct nucleoli Low nuclear grade and absent or very low mitotic activity Hemangiopericytoma-like vasculature and "grungy" calcification which can resemble chondroid or osteoid matrix with fat, microcysts, and hemorrhage Malignant cases show nuclear atypia, increased mitotic activity, and high cellularity

Once TIO is confirmed via laboratory findings, localizing the tumor can be performed in a stepwise fashion with initial functional imaging, including fluorodeoxyglucose-PET/CT or using a conjugate of Gallium-68 radiolabeled NaI3-octreotide (NOC) and 1,4,7,10-tetraazacyclododecane-N,N′,N″,N‴-tetraacetic acid (DOTA)-PET/CT). Targeted anatomical imaging using MRI and/or CT is subsequently performed of the region of abnormal uptake on the nuclear imaging. If a tumor is identified, surgical excision with wide margins is the standard of care. If a tumor cannot be identified, medical therapy with phosphate supplementation and calcitriol is recommended.

Imaging and histopathology features of PMTs are summarized in Table 2 [1,5]. Differential considerations based on those features include hemangiopericytoma, tenosynovial giant cell tumor, osteosarcoma (would have cellular atypia), neurofibroma, granulomas, and osseous fibrous dysplasia. Although the majority of PMTs are benign, there are a few cases of recurrence with local infiltration of connective soft tissues and distant metastatic disease to the lungs [2,6,7].

Our case is not the prototypical presentation of PMTs, and offers some important insights with respect to tumor biology and therefore clinical and diagnostic considerations. The diagnosis was only made after molecular analysis of the surgical specimen, indicating that this entity cannot be diagnosed solely on imaging and/or histopathological features; clinical findings of TIO if present must be made available to radiologists and pathologists to guide interpretation and appropriate management.

Patients with FN1-FGFR1 gene fusion overexpress FGF-23 and present with progressive manifestations of oncologic osteomalacia. While serum FGF-23 levels were not assessed preoperatively in our case, our patient had normal phosphate, alkaline phosphatase, calcium and PTH levels 3 years prior to her presentation. In fact, more recent PTH and Vitamin D, 25-hydroxy levels were within normal range a few months prior

to the operation. There was no evidence of osteoporosis or insufficiency fractures on other imaging studies, and the patient only presented with a painful palpable lump. To our knowledge, there is only one other case described in the literature with identical morphological features to PMT and FN1-FGFR1 gene fusion without documented osteomalacia or elevated FGF-23 [8].

Furthermore, PMTs usually have prominent vascularity and as a result the majority demonstrate gadolinium enhancement on MRI. In this case, despite some vascularity noted on ultrasound, there was no enhancement on MRI or prominent vascularity identified in the histopathological descriptions.

These findings suggest that there is likely a spectrum of PMTs with respect to tumor biology, activity, and clinical manifestations, adding to the complexity of reaching this diagnosis. Possible areas of further research could explore the association of vascularity and enhancement with tumor activity/overexpression of FGF-23.

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