A 50-Year-Old Man Presenting with Multiple Bone Lesions and a Diagnosis of Phosphaturic Mesenchymal Tumor of the Femur

Dong Ren
Katherine Wei
Ibe Ifegwu

Patient: Male, 50-year-old
Final Diagnosis: Primary phosphaturic mesenchymal tumor, mixed connective tissue subtype
Symptoms: Hip and knee pain • inability to ambulate
Clinical Procedure: Resection of the tumor
Specialty: Pathology

Objective: Rare disease
Background: Phosphaturic mesenchymal tumor (PMT) is an extremely rare mesenchymal neoplasm that is commonly seen in bone and soft tissue. It is associated with a paraneoplastic syndrome, oncogenic osteomalacia, due to tumor-induced urinary phosphate wasting. It is demonstrated to be predominantly mediated by fibroblast growth factor 23 (FGF23)/fibroblast growth factor receptor 1 (FGFR1) axis. Clinically, PMT usually presents as a solitary lesion in the bone. The diagnosis of PMT is challenging due to its non-specific clinical manifestation, radiologic findings, and morphological features.

Case Report: We report the case of a 50-year-old man presenting with multiple lytic bone lesions and associated pathologic fracture of the right femur, clinically suspicious for multiple myeloma or other metastatic malignant process. Resection from the right femur showed a hypercellular lesion composed of oval-to-spindled cells infiltrating the native trabecular bone with admixed multinucleated giant cells. Immunohistochemical (IHC) staining and in situ hybridization (ISH) demonstrated the tumor cells were positive for SATB2, ERG, FGFR1, and FGF23 ISH. DNA and RNA next-generation sequencing showed marked increases in mRNA levels of FGF23 and FGFR1. The constellation of clinicoradiologic, histomorphologic, IHC, and molecular findings supported a diagnosis of primary benign PMT.

Conclusions: This case report discusses a patient with PMT presenting with multifocal lesions due to tumor-induced osteomalacia at initial presentation. We hope that this report will increase the awareness of clinician and pathologists of PMT as a differential diagnosis in patients presenting with multifocal lytic bone lesions. In turn, this will prevent misdiagnosis and overtreatment of a typically benign process.

Keywords: Phosphaturic mesenchymal tumor, Multiple lesions, Oncogenic osteomalacia, Bone

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Background

Phosphaturic mesenchymal tumor (PMT) is a distinctive, extremely rare mesenchymal neoplasm that is frequently associated with oncogenic osteomalacia (OO) as a paraneoplastic syndrome [1,2]. The incidence of PMT is unknown, and fewer than 500 cases have been reported in the literature [3], since this entity was formally named by Weidner and Santa Cruz in 1987 [4]. In their original paper, they categorized 4 subtypes of PMT: mixed connective tissue, osteoblastoma-like, non-ossifying fibroma-like, and ossifying fibroma-like [4]. However, these subtypes are now believed to represent morphological variants rather than discrete entities [5]. PMT has an equal sex distribution and a wide age spectrum spanning from 9 to 80 years old [6]. Bone and soft tissue are the most common sites of PMT. In the bone, the most common locations are the extremities (>90%) followed by the head and neck region (<10%) [7]. PMTs are usually benign, but malignant PMTs have been reported [1].

Clinical manifestations of PMT include bone pain and fractures, osteopenia, or gait disturbance due to muscle weakness and atrophy. Biochemical abnormalities, which are typically but not always present, include hyperphosphaturia-induced hypophosphatemia, reduced levels of calcium and 1,25-dihydroxy vitamin D (1,25-[OH]2D3), and elevated alkaline phosphatase (ALP) [8].

A diagnosis of PMT is established by combining clinical presentation, laboratory assessment, imaging findings, and histopathologic and immunohistochemical evaluation. However, diagnosing PMT is challenging and often delayed. Richardson and Richardson reported a diagnostic delay of 5 years in a 37-year-old man with unresponsive hypophosphatemia [3]. Factors contributing to this delay include the rarity of this lesion and its non-specific clinical and imaging findings. In addition, due to the multifocal OO-induced sites of PMT, clinical concern for multiple myeloma, metastatic malignancies, and infectious processes take precedence. Furthermore, phosphorus, the abnormal laboratory value associated with PMT, is not included in the standard comprehensive metabolic panel [3]; therefore, hypophosphatemia may go unrecognized.

Here, we report a case of PMT in a 50-year-old man presenting with multifocal bone fractures concerning for malignancy. The addition of this case to the literature will augment our understanding and awareness of PMT as a cause of multiple lytic bone lesions.

Case Report

A 50-year-old man presented to an outside hospital for inability to ambulate. His medical history included hypertension, type II diabetes mellitus, and morbid obesity. He had no past surgical history, and he denied any smoking or alcohol use. He reported a long history of right hip and knee pain that were being managed with non-steroidal anti-inflammatory drugs (NSAIDs) but was unsure if he had ever been diagnosed with a fracture.

A contrast-enhanced computed tomography (CT) scan of the abdomen and pelvis demonstrated multiple lytic lesions throughout the pelvic bones/proximal femurs, diffusely decreased bony mineralization, and fractures of the right femoral neck, left sacral alar, left acetabular roof, and multiple sacral vertebral body (Figure 1A). Specifically, a subacute-to-chronic-appearing, displaced, angulated, pathologic fracture was identified at the right femoral neck, with associated ill-defined lytic lesions (Figure 1A). There was a lucent lesion centered at the left femoral head (Figure 1B), and 2 similar lytic lesions at the anterior right acetabulum (Figure 1C) and in the left iliac bone and the left acetabulum (Figure 1D). A subtle, subacute-to-chronic-appearing, minimally displaced left posterior acetabular fracture without well-defined associated osseous lesion was noted (Figure 1D).

He was transferred to the Orthopedic Oncology Department of our institution for management of his pathologic right femur fracture. X-rays of the pelvis and femur showed findings of numerous osteolytic foci, consistent with previous outside CT imaging. Differential considerations included multiple myeloma, metastatic carcinoma, possible lytic lesions at the early stage of Paget disease, infectious process, and autoimmune disease.

Laboratory assessment showed hypophosphatemia ranging from 1.5 to 2.0 mg/dL (normal range: 2.5-5.0 mg/dL); elevated alkaline phosphatase: 259 u/L (normal: 34-104 u/L); 1,25-[OH]2D3: 12.3 (normal value: >30.0 ng/mL); and calcium: 8.5-9.2 mg/dL (normal range: 8.6-10.3 mg/dl); and elevated potassium, albumin, BUN, and creatinine were within normal range. Urine phosphorous was not examined. His serum and urine protein electrophoresis were normal, and autoimmune and infectious workups proved negative.

The patient underwent a right hip hemiarthroplasty. Histological examination of the submitted specimen revealed a hypercellular lesion composed of small blue cells with oval-to-spindled morphology infiltrating the native trabecular bone, with admixed multinucleated giant cells (Figure 2A-2D). The tumor cells displayed mild nuclear atypia, and in some areas appeared to proliferate around blood vessels. Prominent nucleoli, mitotic figures, necrosis, or calcifications were not seen. Osteoid production was not evident.

On immunohistochemistry, the tumor cells stained strongly and diffusely for SATB2 and ERG (Figure 3A-3D). Other immunohistochemical stains were negative, including multiple...
Figure 1. Radiologic findings of multiple osteolytic lesions on CT-imaging. (A) A coronal view of a subacute-to-chronic-appearing, displaced, angulated, pathologic fracture with associated ill-defined lytic lesions (solid green arrow); (B) An axial view of a lucent lesion centered at the left femoral head (solid red arrow); (C) A coronal view of a similar lytic lesion at the anterior right acetabulum (solid blue arrow); (D) A coronal view of a similar lucent lesion in the left iliac bone (solid yellow arrow), in the left acetabulum (solid orange arrow) and left posterior acetabular bone (dotted blue arrow).
epithelial markers (CAM5.2, EMA, CK7, CK20, and AE1/AE3), lymphoplasmacytic and histiocytic markers (CD45, CD3, CD20, CD68, CD138, and MUM1), melanocytic markers (S100, SOX10, HMB45, and Melan-A), smooth and skeletal muscle markers (Desmin, Myogenin and MyoD1), and neuroendocrine markers (Synaptophysin, Chromogranin, INSM1). In addition, these cells were non-reactive for CD31, CD34, CD99, STAT6, NKX2.2, NKX3.1 TLE1, and BCOR immunostains. Ki-67 staining showed moderate proliferative index (approximately ~10%). Further work-up, including FGFR1 IHC, FGF23 ISH, and DNA and RNA next-generation sequencing (NGS) by Genomic Testing Cooperative were performed. The tumor cells showed both cytoplasmic and nuclear reactivity for these markers.

Figure 2. Histologic findings of the right femur lesion. (A-C) Representative section of the right proximal femur specimen shows a hypercellular lesion composed of small blue cells with oval-to-spindled morphology infiltrating into the native trabecular bone, 10× (A), 20× (B), and 40× (C). (D-F) Representative section of the lesion admixed with abundant multinucleated giant cells, 10× (D), 20× (E), and 40× (F).
perinuclear FGFR1 staining (Figure 3E, 3F), FGF23-ISH positivity (Figure 3G, 3H), and marked increase in mRNA level of FGF23 and FGFR1 on molecular analysis.

Based on the patient's clinicoradiographic presentation, laboratory values, and histopathologic evaluation, a final diagnosis of primary PMT, mixed connective tissue subtype, was made. No malignancy was identified.

Phosphorus levels were monitored after excision of the right femur tumor, and it showed immediate improvement after the procedure, and resolution of his hypophosphatemia (phosphorus: 2.6 mg/dL) within 2 weeks (normal range: 2.5-5.0 mg/dL). The patient's calcium level (calcium: 9.1 mg/dL) also normalized within the same time frame (normal range: 8.6-10.3 mg/dL). His 1,25-(OH)2D3 level was not examined after surgery. A 1-month follow-up, a positron emission tomography computed tomography (PET-CT) scan of the right total hip showed increased FDG (fluorodeoxyglucose 18F) radiotracer uptake at the medial aspect of the right femoral stem hardware measuring up to 5.3 SUV and less intensely in the surrounding soft tissues (Figure 4A, 4B). This was considered non-specific and
may have been related to inflammatory postsurgical changes. There was otherwise no significant FDG avidity associated with the lytic lesions in the pelvis. The patient has remained asymptomatic in the months following surgery.

While the other lytic lesions were not biopsied, based on his clinicoradiologic presentation, histopathologic examination, and outcome at follow-up (improvement of symptoms, laboratory values, and imaging findings), a diagnosis of primary PMT of the femur with tumor-induced osteomalacia was rendered.

Discussion

Imaging findings of multifocal lytic bone lesion in an adult typically elicits differential considerations of metastatic malignancy and multiple myeloma [9]. Other entities such as an infectious process, fibrous dysplasia, Brown tumor, enchondroma, and Langerhans cell histiocytosis are also well-known causes of multifocal lytic bone lesions. This case highlights a 50-year-old man presenting with multifocal lytic bone lesions with a diagnosis of benign PMT of the proximal right femur with tumor-induced osteomalacia. The addition of this case report to the literature will augment our recognition of PMT as a rare and seldomly considered cause of multifocal lytic bone lesions.
Osteogenic osteomalacia (OO), a paraneoplastic syndrome of PMT, is a metabolic bone disorder characterized by inhibition of phosphate reuptake in the renal proximal convoluted tubules, resulting in urinary phosphate wasting [16]. It is also referred to as tumor-induced osteomalacia (TIO). OO is not specific for a diagnosis of PMT and has been reported in other mesenchymal tumors such as solitary fibrous tumor [16]. It is induced by a variety of factors secreted by the tumor cells. These factors include matrix extracellular phosphoglycoprotein (MEPE) [11], secreted frizzled-related protein 4 (SFRP4) [12], and fibroblast growth factor 23 (FGF23) [13] that lead to demineralization in mature bone. Among them, the role of FGF23 and its receptor FGFR1 in maintaining phosphate balance is the best-studied axis in tumor-induced osteomalacia [14]. The binding of FGF23 to FGFR1-induced pathway activation limits the phosphate reabsorption in the kidneys by inhibiting sodium-phosphate co-transporters (SLC34A1; SLC34A3), and reduces phosphate absorption from the intestines by inhibiting 25-OH vitamin D activation and degrading 1,25 (OH)2 vitamin D [15]. In fact, the neoplastic cells from PMT produce and secrete a large amount of FGF23 and activate the FGF23/FGFR1 pathway to promote PMT-induced osteomalacia [1]. From the molecular perspective, Lee et al reported finding FN1-FGFR1 fusion in 42% (21/50) of PMTs and identified an additional molecular alteration – FN1-FGF1 fusion – in 6% (3/50) [16]. Their study highlighted the central role of the FGFs/FGFR1 pathway in the pathogenesis of PMT-induced osteomalacia.

Clinically, PMT generally presents as a solitary lesion in various areas of bone, such as femur [25,26], tibia [27,28], cervical vertebra [29,30], lumbar vertebra [31], sacrum [32], phalanx [33], metacarpal [34], maxilla [20], and mandible [35]. Notably, Nathan et al reported a patient with the first PMT in the tibia, and the second in the maxillary sinus occurring 2 years later [36]. Although the author mentioned that this was the first reported case of multiple PMTs, the lesions did present as separate, solitary lesions in different location at different points in time. Meanwhile, Ryuta et al reported a 39-year-old man with multiple fractures caused by multiple FGF23-secreting PMT, all of which were located in the halux [37]. In our case, the patient’s initial presentation included femur fracture and multifocal lytic lesions with widespread distribution, causing severe concern for multiple myeloma or other metastatic malignant processes rather than PMT. This case breaks the traditional concept of PMT typically presenting as a solitary lesion of bone.

For the vast majority of PMT patients, complete surgical resection of the lesion is the most effective treatment option, resulting in resolution of symptoms and laboratory abnormalities arising from tumor-induced osteomalacia [38-40]. Despite resection, the symptoms or lab values were reported to be not completely resolved in some PMT patients; this pattern is not specific to PMT. SATB2 positivity is thought to reflect the osteoprogenitor origin of the tumor cells, or the differentiation of the tumor cells toward an osteoblast or osteocyte lineage [5]. Meanwhile, ERG positivity has been observed in various tumors, including vascular tumors. Diffuse ERG positivity in PMT, especially when PMT morphologically presents as a lesion with prominent vasculature, may create a diagnostic pitfall. Shogo analyzed the ERG staining in PMT and found that all the cases were positive for ERG, the proportion of positive cells was more than 50%, and the staining intensity was moderate or strong in all cases [19]. Another study reported that ERG was at least weakly positive in all PMTs. In our patient, the tumor cells were negative for other common vascular markers, including CD31 and CD34; this was consistent with the findings from 2 independent studies that showed the tumor cells in PMT typically express significantly less or even negative immunoreactivity for CD31 and CD34 than observed for ERG [19,22].

FGF23-ISH and FGFR1 have emerged as more useful immunohistochemical markers for the diagnosis of PMT [23,24]. In our patient, the tumor cells showed strong and diffuse immunoreactivity for FGFR1 and patchy FGF23-ISH staining. NGS testing further revealed that the tumor cells expressed marked increase in FGF23 and FGFR1 mRNA, and did not harbor H3F3A, IDH1, or IDH2 mutations. The constellation of morphological, immunohistochemical, and molecular findings was consistent with a diagnosis of PMT.
suggested incomplete tumor resection, recurrence, or another undetected tumor contributing to the treatment failure of PMT patients [36,41]. Notably, surgical resection is not typically used for multiple lesions, and instead conservative strategies, such as dietary modification or supplementation of calcium, phosphorous and vitamin D, may be used as alternative options [42]. Translocation of FGFR1 or aberrant activation of the FGFs/FGFR1 pathway plays a pivotal role in PMT-induced osteomalacia [1,16]; therefore, the potential applicable value of FGFR1 inhibitor in PMT patients with multiple lesions warrants further investigation.

Notably, amplification or fusion aberrations of the FGFR1 gene have been well-established in a variety of malignancies such as ER+ breast cancer [43,44], head and neck squamous cell carcinoma [45], and squamous cell carcinoma of the lung [46], and strategies targeting this gene fusion has become an attractive therapeutic target in multiple cancer types [47-49].

Conclusions

This report presents a case of benign PMT in a 50-year-old man presenting with multifocal lytic bone lesions and fractures, concerning for malignancy. Combined with biochemical abnormalities, tumor histology, immunohistochemistry, and molecular analysis, a diagnosis of PMT was made. Knowledge of PMT as a differential diagnosis, albeit rare, in patients with multifocal lytic bone lesions will prevent misdiagnosis of PMT as other highly aggressive malignancies.

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Department and Institution Where Work Was Done

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Declaration of Figures’ Authenticity

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