Radiology Case Reports 14 (2019) 1518–1524

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Case Report

# Phosphaturic mesenchymal tumor: Case report

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ARTICLE INFO

*Article history:*
Received 12 August 2019
Revised 22 September 2019
Accepted 22 September 2019

*Keywords:*
Phosphaturic mesenchymal tumor

ABSTRACT

Phosphaturic mesenchymal tumors (PMT) are an extremely rare pathologic phenomenon that presents as paraneoplastic tumor-induced osteomalacia. Their diagnosis is often significantly delayed due to their rare occurrence in addition to the generalized and vague symptoms of their presentation including progressive bone pain, myopathies, arthralgias, fractures, and generalized weakness. This case report identifies a very characteristic presentation of a 37-year old African American male suffering from a PMT; with symptom onset presenting over 5-years prior to presentation with a consistent complaint of progressive and debilitating quadriparesis. The tumor was first identified by pelvic computerized tomography, although it was initially thought to be a noncontributory benign soft tissue mass. It was only after being hospitalized due to a severe and unresponsive hypophosphatemic state (less than 1 mg/dl) that the collective differential switched to one of a PMT with follow up nuclear 99mTc bone scintigraphy and magnetic resonance imaging being used to aid in the overall assessment of changes, extent, and general metabolic properties of the tumor. The confirmatory diagnosis of a PMT was later established through both serum fibroblast growth factor 23 testing and histopathologic review of the surgically removed specimen. By including this rare but curative disease into the differential of osteomalacia and thereby further examining patient serum phosphate levels, the previous 5-7 year delay in diagnosis will be dramatically reduced.



## Introduction

Phosphaturic mesenchymal tumors (PMT) are an extremely rare pathologic phenomenon that presents as paraneoplastic tumor-induced osteomalacia (TIO) caused by tumor release of phosphatonins, most notably fibroblast growth factor 23 (FGF23), which decreases proximal renal tubule reabsorption of phosphate and inhibits 1-$\alpha$-hydroxylase production of 1,25-dihydroxycholecalciferol [1,2]. On average, PMTs are not diagnosed until 5-7 years after disease presentation due to their rare occurrence, relatively small size, and slow benign growth contributing to generalized and indiscernible symptoms including progressive bone pain, myopathies, arthralgias, fractures, and generalized weakness characteristic of these paraneoplastic tumors [3]. Additionally, with serum phosphorus no longer being included in the standard comprehensive metabolic panel, PMTs naturally go undiagnosed

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https://doi.org/10.1016/j.radcr.2019.09.027

unless the given physician has the individual inclination to measure the patient's phosphorus level [2]. Since first being identified, less than 500 cases of PMTs have been reported in the literature.

This case report identifies a very characteristic presentation of a 37-year old African American male suffering from a PMT; with symptom onset presenting over 5-years prior with a consistent complaint of progressive and debilitating quadriparesis.

## Case Report

A 37-year-old African American male presented in our hospital with progressive generalized bone and muscle pain in his back and extremities, muscle spasms, and ill-defined weakness persisting chronically over the past 5 years. Recently, the patient had been diagnosed with osteomalacia and hypophosphatemia where he was subsequently placed on oral cholecalciferol and phosphorous supplementation. This intervention was, however, unsuccessful in correcting the patient's symptomatic and biochemical abnormalities, and in fact, is what led to the patient's current admission with his severely depressed and resistantly low phosphorus levels of 0.9 mg/dL.

It was during this admission that the chronicity of the patient's disease was properly identified and established, as the patient was said to have been suffering from these same debilitating symptoms for at least over 5 years now. During this time, he had been completely reliant and dependent on the use of assisted devices and help from others to ambulate and properly perform his activities of daily living. Since symptom onset, the patient was found frequenting his local emergency department and primary care office, and was even later referred out for neurology and rheumatology evaluations; all where a gamut of tests were used to rule out immune disorders, dietary deficiencies, endocrinopathies, metabolic bone disorders (Paget's disease), neuronal conduction abnormalities, and muscular dystrophies among other possible differential etiologies. However, all tests were found to be inconclusive in properly establishing a diagnosis. During this same time frame, the patient had tried but failed to find any substantial relief from his pain with the use of benzodiazepines, opioids, nonsteroidal anti-inflammatory drugs, muscle relaxers, neuroleptics, bisphosphonates, and corticosteroids. Additionally, in an earlier instance where the patient was looking to establish some semblance of pain control, he was found to have caused a self-induced and severe duodenal ulcer resulting from his chronic use of naproxen. In an unlikely set of events, it was during this earlier workup for a GI bleed that a pelvic CT scan was performed and where the patient was first found to have a subcutaneous soft tissue mass located externally adjacent to his left hip, measuring close to 6 cm in its longest diameter (Figs. 1 and 2). The mass at the time of discovery was thought to be a resultant benign process and since it was not related to his GI bleed for which he was admitted, it was not pursued for further removal or later investigation. After further review, the patient had no significant social history of smoking, alcohol abuse, diabetes, contributory medications, or use of antacids.

Since symptom onset, the patient suffered an approximated 50 kg weight loss, resulting in his current weight of 67 kg. This substantial weight loss led to the mass appearing even more pronounced on physical exam since its initial detection. The mass was grossly measured at 8 cm upon palpation confirming a firm subcutaneous mass residing just inferior and lateral to the inguinal region of the left leg. On further inspection, the mass felt slightly mobile with a firm consistency and no adenopathy was found in the surrounding areas.

The patient's family history was unremarkable for similar symptoms or for a history of short stature. Therefore, due to the patient's current height exceeding 6 ft., his presentation during adulthood, and lack of any identifiable genetic links or lower extremity deformities; it was clear that the likely and clear differential was that of a PMT, and not a resulting condition of autosomal dominant hypophosphatemic rickets or X-linked hypophosphatemic rickets.

Further biochemical examination revealed elevated alkaline phosphatase levels of 291 U/L, elevated 24-hour urine phosphorus levels of 3750 mg/24 h; and, as expected, a low maximum tubular reabsorption of phosphorus (TmP/GFR). The only unexpected lab abnormality was an elevated PTH intact value of 151 pg/mL, but this was later accounted for due to the prior advancement of supplemental phosphorus without 1,25-dihydroxycholecalciferol. Lastly, FGF23 levels were found to be elevated at 54 pg/mL.

Due to high clinical suspicion of a PMT, a whole-body nuclear 99mTc bone scintigraphy was performed showing notably increased shifts in uptake at the bony ends towards the metaphysis of the appendicular skeleton with characteristics of uniform spinal uptake shown throughout and a nonspecific pattern of heterogeneity seen in several ribs (Fig. 3). The previously identified soft tissue mass in the left hip showed a slight heterogeneous uptake as well. Additional findings included dextroscoliosis presenting throughout the cervicothoracic spine with a mild concomitant pattern of lumbosacral levoscoliosis. There additionally appeared to be artifacts of increased uptake noted near the patient's right mid-distal radius and right first metacarpal. These artifacts are consistent with extravasation from the intravenous (IV) injection sites of the right basilic vein and right cephalic vein. In a contrasting fashion, there is reduced appearance of nuclear uptake found within the tumor in the left hip, which is not representative of artifact. There was no observable pattern of metastatic disease, but the scan confirmed a pattern of uptake consistent with metabolic bone disease, correlating appropriately with the overall clinical and laboratory picture of a patient suffering from a PMT.

Follow up magnetic resonance (MR) multisequence, multiplanar images of the left thigh with and without IV contrast were performed and measured a well-circumscribed mass at $8.5 \times 7.4 \times 6.5$ cm (craniocaudal X AP X transverse) (Figs. 4–6). The mass was at a consistent level of the greater trochanter and isolated within the subcutaneous tissues with no invasion of the underlying musculature or osseous structures. Axial T1 weighted MR showed the lesion to be isointense when compared to the surrounding musculature with multiple vascular channels being noted in the periphery. Contrast T1 weighted coronal MR showed heterogeneous contrast

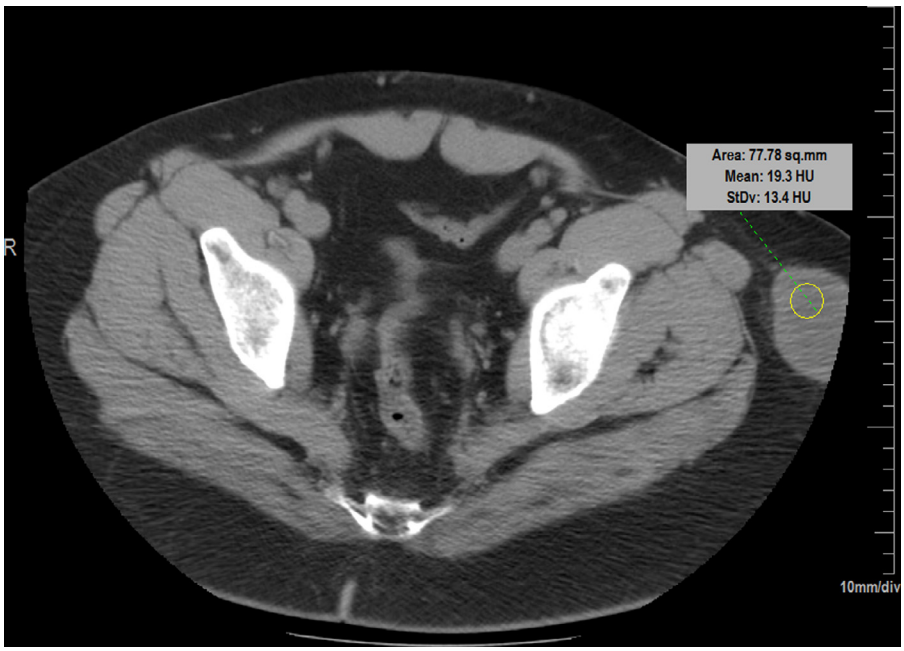


**Fig. 1 – Pelvic CT without contrast. The mass is identified just lateral to the patient's left greater trochanter with a density of 19.3 Hounsfield unit (HU), connecting the tumor to a soft tissue pathology.**

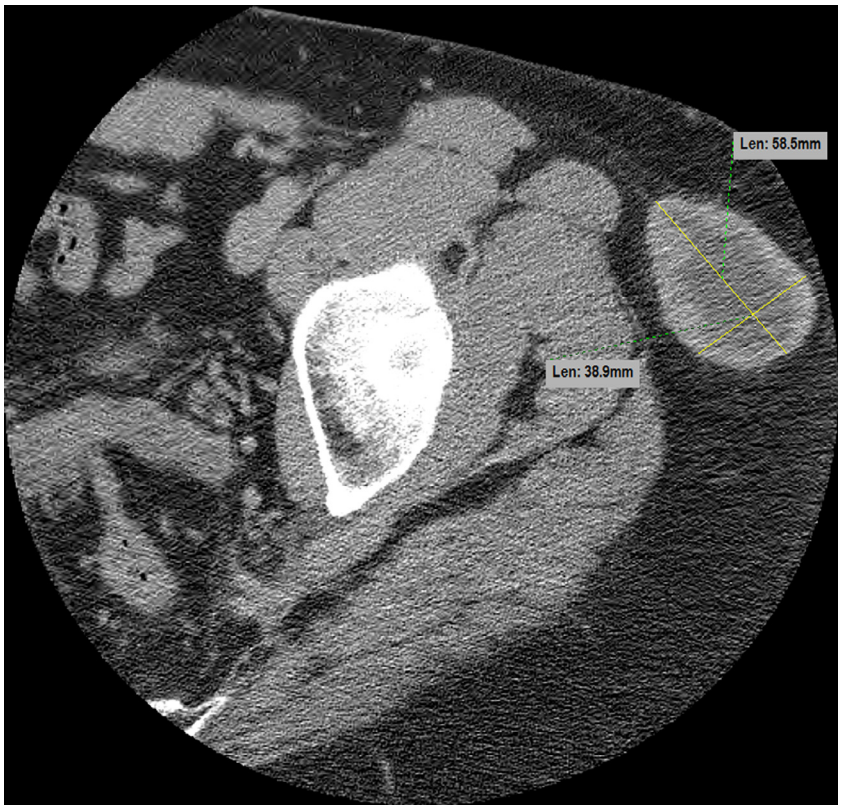


**Fig. 2 – Pelvic CT without contrast. The mass was measured at 58.5 x 38.9 mm.**

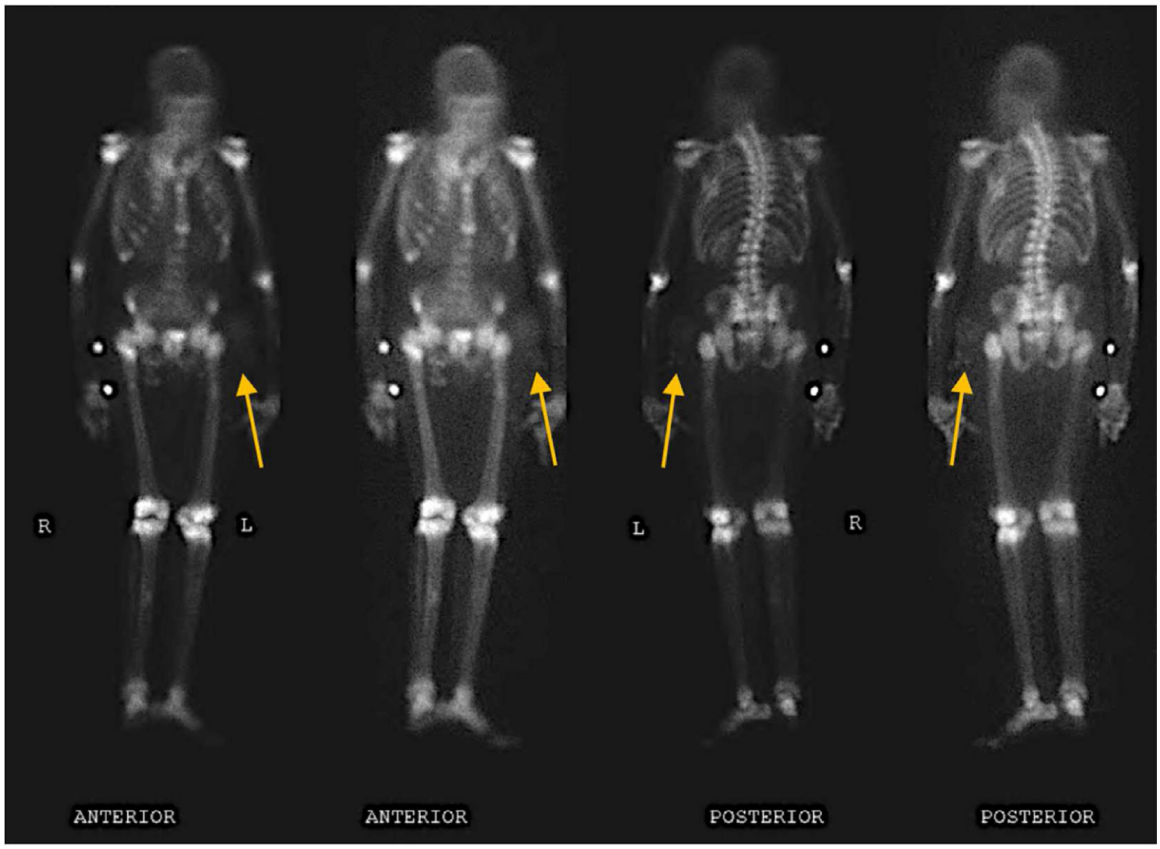


**Fig. 3 – Whole-body nuclear 99mTc bone scintigraphy. (Arrows) Demonstrates the mass with slight uptake found in the left hip. The skeletal absorption demonstrates a pattern consistent with metabolic bone disease.**

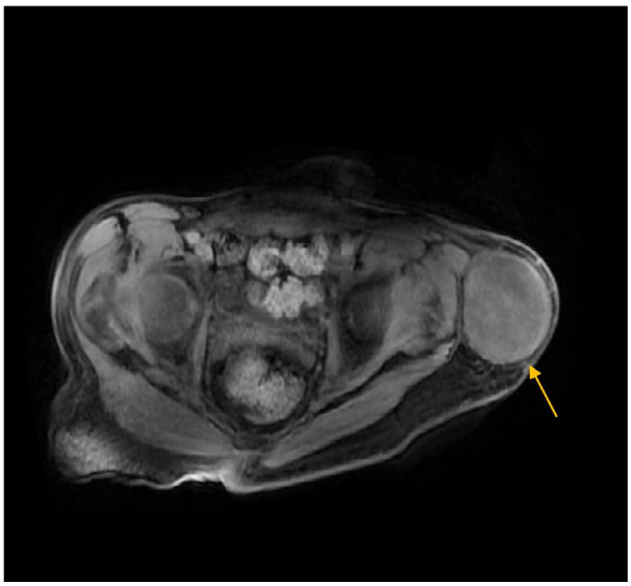

**Fig. 4 – T1 weighted MRI without contrast. (Arrow) Presenting the encapsulated mass of 8.5 x 7.4 x 6.5 cm with heterogenous isointensity in comparison to the surrounding pelvic musculature.**

enhancement throughout with avid enhancement on post-contrast imaging.

After discussing treatment options with the patient, it was determined that the best course of action would be to proceed with complete surgical resection of the mass in hopes that this would be curative. The surgical procedure involved making an 11 cm elliptical incision through the epidermal layer and extending into the subcutaneous layer. Smaller feeder vessels were then ligated, and the tumor was grossly resected with negative margins achieved on all surrounding aspects of the subcutaneous tissue. As previously seen on imaging modalities, the tumor was limited to the subcutaneous tissue without extension to the underlying muscle, bone, or fascial contents. After the operation, the patient was discharged 12 days later after showing complete resolution of his prior hypophosphatemic state.

The surgical specimen revealed dimensions of $11.3 \times 7.2 \times 6.5$ cm. After pathologic expert review from the department of pathology and laboratory medicine at Emory University Hospital, it was confirmed that the tumor was indeed a PMT of the mixed connective tissue variant, the most common variant of PMTs. Microscopic findings revealed a pathologic specimen composed of spindled, fusiform, hemangiopericytoma-like areas and osteoclastic giant cells arranged in sheets with focal microscopic cysts (Figs. 7 and 8). There were also identifiable areas of 'grungy' calcific

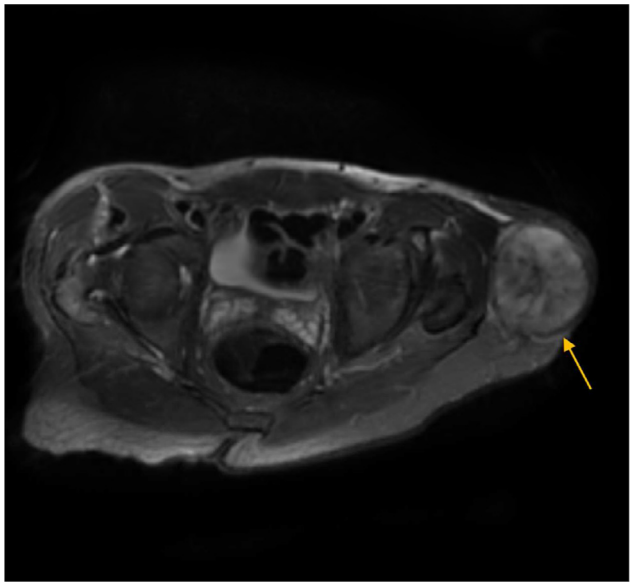

**Fig. 5 – T2 weighted MRI without contrast. (Arrow) Displaying heterogenous hyperintensity in comparison to the surrounding pelvic musculature.**

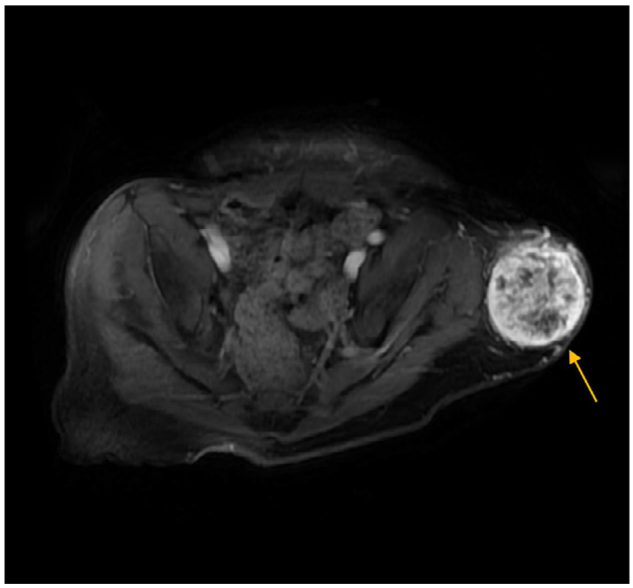

**Fig. 6 – Contrast T1 weighted MRI. (Arrow) Showing heterogeneous contrast enhancement throughout with heavy vascularity visualized on the encapsulated periphery.**

deposits representing a calcified matrix, which is a particularly distinctive feature of PMTs. Focal areas of necrosis were also seen, but no high-grade areas were discovered on review of the mass. The immunohistochemical staining for S-100, CD34, smooth muscle actin, and desmin were all negative; with the staining for FGF23 not being established. However, given that there was a complete metabolic resolution after resection, it is presumed that the tumor must have produced FGF23.

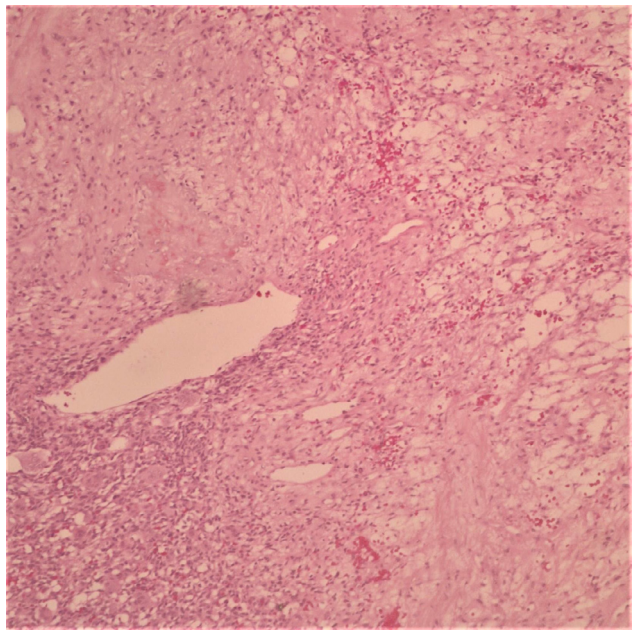

**Fig. 7 – Histologic image of phosphaturic mesenchymal tumor. Illustrating hemangiopericytoma-like areas.**

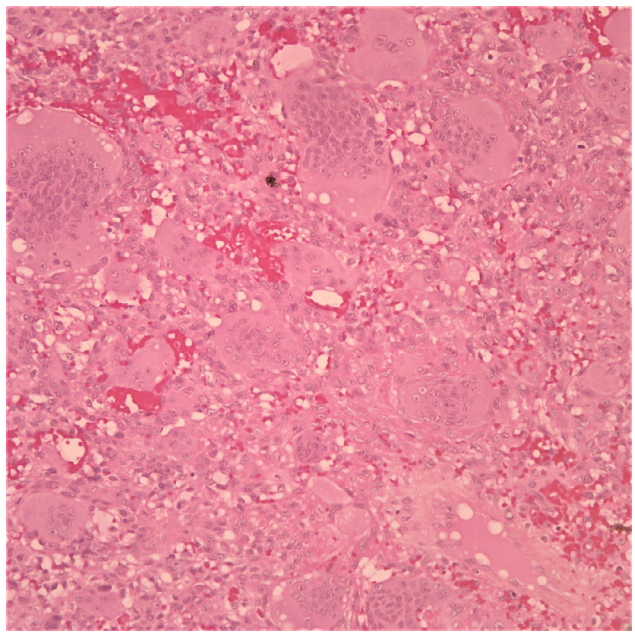

**Fig. 8 – Histologic image of phosphaturic mesenchymal tumor. Displaying osteoclastic giant cells.**

On follow up, the patient showed biochemical normalcy with no complaints or subcutaneous masses noted on physical exam or recurrence noted on repeat MR and CT imaging. Due to disease remission, additional radiographic investigations were not performed.

## Discussion

PMTs are a rare classification of soft tissue tumors that are known for their release of phosphatonins, most notably FGF23, which decreases proximal renal tubule reabsorption of phosphate and inhibits 1-$\alpha$-hydroxylase production of 1,25-dihydroxycholecalciferol [1,2]. Overexpression of FGF23 leads to increased renal excretion of phosphate, increased bone resorption of calcium and phosphate, decreased osteoblastic bone mineralization, and decreased gastrointestinal absorption of calcium and phosphate [2]. The combined effect of these pathologic mechanisms leads to an induced state of osteomalacia, with symptoms presenting in the form of gradual progressive bone pain, myopathies, arthralgias, fractures, and generalized weakness [3]. However, while these patients will have decreased serum phosphate, their calcium and PTH levels maintain homeostatic normalcy. Although 1,25-dihydroxycholecalciferol levels are actively diminished from the effects of FGF23, its effects are compensated for by the amplification of calcium and sodium reabsorption in the distal renal tubules [2,3].

Histologically, there are three known variants of PMTs which consist of the osteoblastoma-like variant, nonossifying fibroma-like variant, and mixed connective tissue variant. The mixed connective tissue variant is the most common form of a presenting PMT, but all forms are often clinically and histologically missed due to their rare occurrence, histologic heterogeneity, and morphologic qualities matching other mesenchymal neoplasms (chondromyxoid fibroma, chondroblastoma, aneurysmal bone cyst, and osteosarcoma) [5]. Additionally, with serum phosphorus no longer being included in the standard comprehensive metabolic panel, PMTs naturally go undiagnosed unless given the inclination to measure the patient's phosphorus level [2]. PMTs are not required to cause a tumor induced osteomalacic state, but they are often clinically associated with these debilitating and ill defining symptoms of osteomalacia. Some morphologic and characteristic features of PMTs include areas of low mitotic activity, grungy or wooly areas of calcification, myxoid stroma, and benign-appearing spindle cells. Additional characteristics consist of an osteoid matrix, osteoclast-like giant cells, hemangiopericytomatous blood vessels, microcystic changes, and a mature adipose-tissue component; which also may be present and support the conclusion of a PMT but individually are not pathognomonic. Immunohistochemical expression of FGF23 is highly specific at 100% for PMTs with TIO) and allows for a conclusive diagnosis of a PMT. However, this is not specific for PMTs without TIO [6].

The only definitive treatment for this medically intractable disease is complete surgical resection, resulting in approximately a 90% curative rate after surgery. Following resection, patients are expected to have a dramatic reversal of symptoms. As exemplified in this case report, the complete resection of soft tissue tumors is often a very straightforward and uncomplicated procedure due to the accompanying encapsulated contours of the mass. However, it is imperative in the prevention of recurrence that wide negative margins be achieved during the surgery; although even with recurrence, metastasis remains a reported rarity [6].

The focal problem with most PMTs is that they not only produce generalized nonspecific symptoms in characteristically middle-aged patients, but they are also usually quite small and challenging to locate [6]. These tumors have been found to originate from bone and soft tissue with 95% being identified in the extremities and appendicular skeleton [4,7]. The importance of localizing these tumors cannot be understated as the majority of these patients suffer from debilitating pain and fatigue. The previous challenge of this localization existed with the PET tracer fluoro-2-deoxy-d-glucose and its relatively low sensitivity and specificity for the overall detection of neuroendocrine tumors and PMTs. This dilemma has called for better-established methods leading to the advancement of DOTA chelators and a variety of newer-generation somatostatin analogs; all of which have shown a higher radiotracer affinity compared to conventional octreotide imaging [8–10]. The clinical choice of a particular analog is often driven by local availability, with studies directing only subtle differences in clinical utility.

Previous research has shown 68Ga-DOTA-TATE (GaTate) PET/CT to have the highest affinity for the somatostatin receptors subtype 2, which tends to be the most advantageous and overexpressed receptors found in both neuroendocrine tumors and PMTs, therefore denoting GaTate to be a well-established and reliable method for the whole-body localization of PMTs. Although PMTs manifest ultrastructural features of neuroendocrine tumors, they typically lack the immunohistochemical markers of neurosecretory tumors that typically consist of S-100, neuron-specific enolase, chromogranin, and synaptophysin markers. In a systematic process following GaTate testing for localization, systemic venous sampling should be recommended for proper confirmatory testing of serum FGF23 levels, followed by functional MR imaging for direct tumor characterization [9–11]. In contrast, the currently presented case never required these methods of localization due to previous identification and localization on prior imaging with symptom onset being coincidentally near the time of identification. Establishing this correlation raised the high probability that this was indeed a PMT, which was only confirmed after serum FGF23 testing.

The typical feature of PMTs on CT imaging shows a nonspecific pattern of a hypodense circular mass with well-formed borders. Contrasting this with MR, the manifestations are more variable and dependent on the size of the tumor, with a general isointense appearance in relation to muscle on T1-weighted imaging and markedly hyperintense on T2 weighted imaging; all of which was observed through the presented case. The previously mentioned variation occurs with the sizing of the tumor. Smaller tumors display a more homogenous intensity on both T2 and T1 weighted imaging with a uniform enhancement on post-contrast T1 weighted imaging. A larger sized tumor appears more heterogeneous on T2 and T1 weighted imaging with a similar heterogeneous pattern on post-contrast T1 weighted imaging. These heterogenous discrepancies are associated with areas of vascular flow voids within larger PMTs [4].

## Conclusion

This case report highlights the need for multidisciplinary teams with emphasis placed on the current benefits of functional imaging and the early identification of PMTs. By including this rare but curative disease into the differential of osteomalacia and thereby further examining patient serum phosphate levels, the previous 5-7 year delay in diagnosis will be dramatically reduced; thus, limiting future patient suffering and debilitation from a curative disease [5].

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