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Successful treatment of tumor-induced osteomalacia causing by phosphaturic mesenchymal tumor of the foot

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Abstract

Tumor-induced osteomalacia causing by phosphaturic mesenchymal tumor of the foot is exceedingly rare, thus may bring great challenges to the timely and proper diagnosis and treatment of clinicians. The only definitive management is removal of the phosphaturic mesenchymal tumor completely. The objective of this article is to report 2 unusual cases with tumor-induced osteomalacia causing by phosphaturic mesenchymal tumor of the foot.

We describe 2 patients with phosphaturic mesenchymal tumor involving the foot who were successfully treated with tumor resection. On presentation to our institution, the patients both had signs of severe osteomalacia, and the patients' most outstanding complaints were diffuse bone pain, general weakness, and disabled walking. A 53-year-old female underwent surgical excision of pathogenic tumor on the sole of left foot. A 62-year-old female underwent complete excision of pathogenic tumor of right plantar. The patients showed appropriate destruction of the tumor, adequate pain relief, and the elevated blood phosphorus levels compared with the previous status.

Surgical resection is the most effective treatment option for patients with tumor-induced osteomalacia who can undergo appropriate surgical treatment. This represents a safe and reasonable approach to sustainably relieve pain and other symptoms with tumor-induced osteomalacia in the foot.

Abbreviations: MRI = magnetic resonance imaging, PET/CT = positron emission tomography-computed tomography, VAS = visual analog scale.

Keywords: definite diagnosis, foot, hypophosphatemia, phosphaturic mesenchymal tumor, surgical treatment, tumor resection, tumor-induced osteomalacia

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1. Introduction

Tumor-induced osteomalacia (TIO), also known as oncogenic osteomalacia, is an exceedingly rare paraneoplastic syndrome, which is characterized by hyperphosphaturia, hypophosphatemia, and increased level of alkaline phosphatase.[1–3] Clinical manifestations commonly include bone pain, pathologic fractures, and musculoskeletal weakness, which are closely related to renal phosphate wasting and resultant reduction in bone mineralization.[2,4,5] TIO was first described in 1947 by McCance, to date, less than 500 cases have been reported in literature.[1–3] Therefore, the majority of clinicians are less aware of this rare disorder and clinical experience in diagnosis and treatment of TIO is still lacking. We present an illustrative case describing the presentation, treatment, and postoperative course of 2 patients with sacral phosphaturic mesenchymal tumor-induced osteomalacia whose symptoms resolved significantly postoperatively, followed by a review of the pertinent literature concerning diagnosis and management for such lesions.

2. Case reports

2.1. Case 1

2.1.1. Presentations and examinations. In January of 2017, a 53-year-old woman presented to our hospital, with a 5-year history of progressive pain in her back, chest, bilateral lower limbs, and feet. The patient's lower limbs were too weak to walk normally. In the medical journal of her current illness, the patient stated she had been experiencing a worsening hypophosphatemia for approximately 5 years, and she had also experienced height

loss for approximately 4 years from 166 cm to 158 cm. The pain in her chest and back can reach 8 to 9 points using visual analog scale (VAS) and cannot be alleviated with rest and hot compresses. The patient denied experiencing any other constitutional symptoms. No pertinent family history was identified, including hypertension, and cancer.

On physical exam, the patient showed pressure pain and percussion pain in her lumbar and sacral regions, chest and pelvis, and exhibited a 5-/5 strength in her bilateral lower extremities. Thoracic crush pain and pelvic crush pain were both positive. The mass sized 2.0 × 1.5 cm could be touched at the front and bottom of the third and fourth metatarsal bones of the left foot which is hard, with clear boundary, slightly poor mobility, no obvious tenderness, no pulsation, and normal skin temperature (Fig. 1A). Laboratory tests revealed hypophosphatemia (0.49 mmol/L; Normal: 0.81–1.45 mmol/L), elevated β-C-terminal telopeptide of type I collagen (β-CTX) (1.25 ng/mL; Normal: 0.21–0.44 ng/mL), elevated parathyroid hormone (PTH) (92.0 pg/mL; Normal: 12.0–68.0 pg/mL), elevated serum alkaline phosphatase (ALP) level (294 U/L; Normal: 35 to 100 U/L), and decreased level of 1,25-dihydroxy vitamin D (16.92 pg/mL; Normal: 19.6–54.3 pg/mL). The results of other laboratory studies were almost within normal range. Magnetic resonance imaging (MRI) of the left foot was ordered to visualize the lesion, assess the boundary of the mass, and to aid in the formulation of a surgical approach (Fig. 1B and C). The bone scan showed local bone metabolism was active in left foot (Fig. 1D). Somatostatin receptor imaging revealed high expression of somatostatin receptor in soft tissues at the anterior end of the left metatarsal bone, with high suspicion of pathogenic tumor (Fig. 1E). Combined with relevant examinations, it was considered as bone metabolic disease and oncogenic osteomalacia was suspected.

2.1.2. Surgical treatment. After detailed assessment, surgical excision of oncogenic tumor on the sole of left foot was performed to destroy the functional tumor under general anesthesia. The spindle incision around the soft tissue mass of the left sole was made, which was 0.5 cm away from the edge of the mass. The tumor was subcutaneous, about 2 cm in diameter, brown in color, hard, and unclear in boundary. The tumor was excised completely and sent for pathological examination. Pathological examination confirmed the diagnosis of phosphaturic mesenchymal tumor (Fig. 1F). Postoperatively, her serum phosphate level returned to normal (Fig. 2). Moreover, the patient experienced pain relief and improvement of general weakness. The patient was then discharged and monitored on an outpatient basis.

2.1.3. Follow-up. One week after the operation, the patient's muscle strength of lower extremities improved to grade V compared to the preoperative status, and the symptoms were relieved significantly. Moreover, VAS score of her back pain improved to 0 to 1 point compared to the preoperative status, 8 to

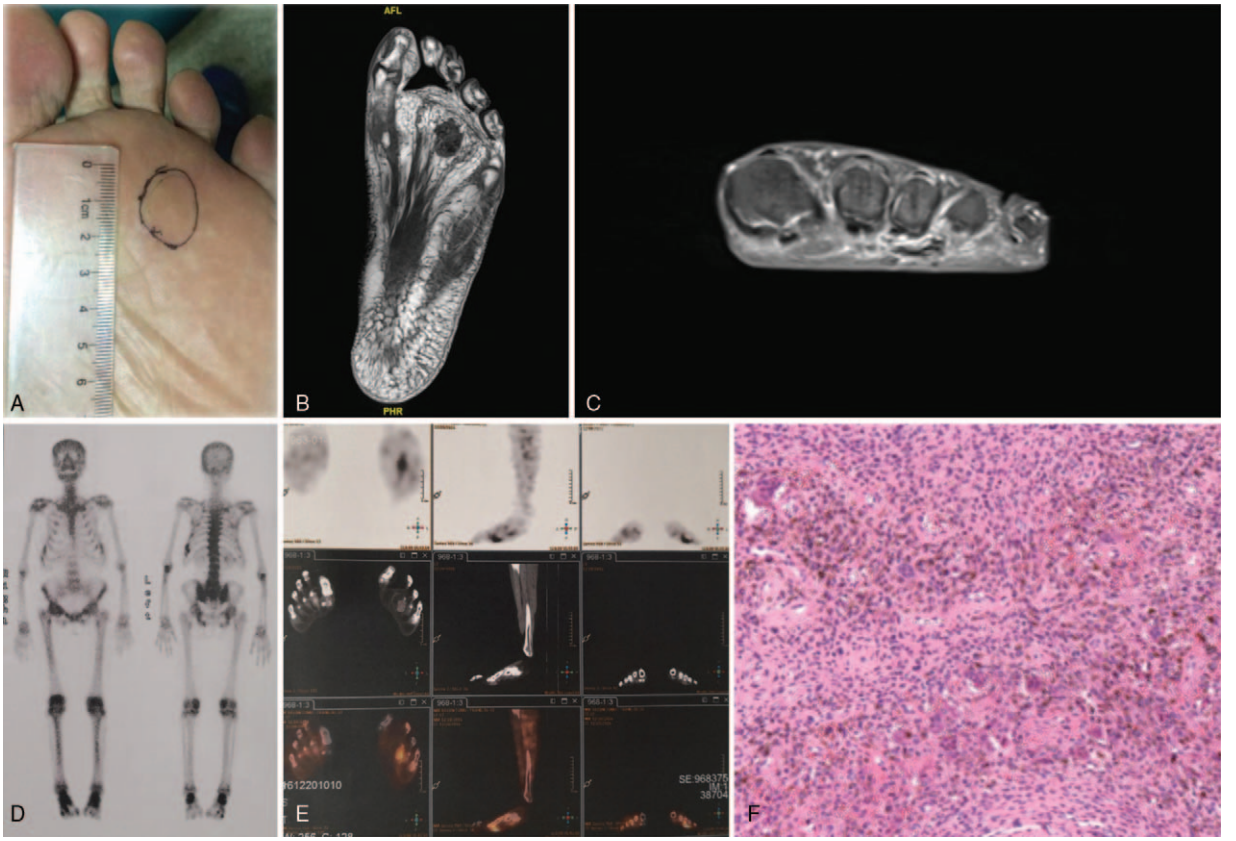

Figure 1. Case 1. (A) The mass sized 2.0 × 1.5 cm could be touched at the bottom of the third and fourth metatarsal bones of the left foot. (B,C) MRI of left foot revealing the mass, which was highly indicative of the pathogenic tumor. (D) The bone scan showing local bone metabolism was active in left foot. (E) Somatostatin receptor tomography revealed the increased expression of somatostatin in the left foot. (F) Pathologic histology of tumor specimens was consistent with the diagnosis of phosphaturic mesenchymal tumor. MRI = magnetic resonance imaging.

Figure 2. Case 1. Serum phosphorus levels significantly elevated to the normal range after the operation.

9 points. Postoperatively, the patient underwent rehabilitation therapy and was regularly monitored for blood phosphorus level. To date, the patient has no recurrent symptoms in the 2-year follow-up visit. There were no complications associated with the operation during the follow-up period.

2.2. Case 2

2.2.1. Presentations and examinations. In May of 2017, a 62-year-old otherwise healthy woman presented to our institution with increasingly serious systemic multiple bone pain. The patient suffered from right elbow pain for 4 years and the elbow pain gradually developed to systemic bone pain including shoulders, limbs, chest, and lumbosacral region. In the disease course, she gradually had difficulty in turning over, walking and lifting bilateral legs. Her height was reduced by about 2 cm compared with her younger age. Before her presentation to our institution, she had been treated in a local hospital, considering "osteoporosis", and had taken oral traditional Chinese medicine, calcium tablets, and calcitriol irregularly, to little effect. In history of present illness, the patient stated she had been experiencing a progressive systemic multiple bone pain, a gradual decrease in muscle strength in her extremities for approximately 4 years, the pain could not be alleviated with rest and hot compresses.

Physical examination revealed pressure pain and percussion pain in her back, chest and pelvis, and a 5-/5 strength in her bilateral extremities. Thoracic crush pain and pelvic crush pain were both positive, as well as "barrel chest". The tumor sized about 2.0 × 3.0 cm was on the base of right foot, without tenderness (Fig. 3A). Cranial nerves, mini-mental, and the rest of the neurological exam showed no abnormalities. Laboratory tests were ordered and revealed hypophosphatemia (0.56 mmol/L; Normal: 0.81–1.45 mmol/L), elevated β-C-terminal telopeptide of type I collagen (β-CTX) (1.21 ng/mL; Normal: 0.21–0.44 ng/mL), normal parathyroid hormone (PTH) (43.8 pg/mL; Normal: 12.0 to 68.0 pg/mL), elevated serum alkaline phosphatase (ALP) level (252 U/L; Normal: 35 to 100 U/L), and normal level of 1,25-dihydroxy vitamin D (33.65 pg/mL; Normal: 19.6 to 54.3 pg/mL). Ultrasonography demonstrated mixed subcutaneous echoes of the right plantar (Fig. 3B). Magnetic resonance imaging of the right foot showed the mixed signals in the soft tissue on the right plantar (Fig. 3C and D). Furthermore, bone scan showed suspected fractures of multiple ribs, bilateral scapula, bilateral iliac bones and bilateral pubic bones with high intake signals. Combined with the slice, the above-mentioned multiple old fractures were considered. The first-line ^{68}Ga DOTATE positron emission tomography-computed tomography (PET/CT) scan showed high intake in the right heel (Fig. 3E). Based on these findings, tumor-induced osteomalacia was considered.

2.2.2. Surgical treatment. After detailed analysis, extended excision of right plantar mass was performed according to the original surgical plan. The spindle incision around the soft tissue mass of the right plantar was taken, which was about 4 cm long and about 1 cm away from the edge of the mass. The tumor located in the deep layer of superficial fascia and was covered by deep fascia. The diameter of the tumors was about 2.5 cm × 1.5 cm, with yellow-white color and unclear boundary. Complete removal of the tumor and surrounding tissues was performed, and specimens were sent to pathological examination. Histopathologic examination including immunohistochemical staining was performed, and the diagnosis of phosphaturic mesenchymal tumor was made according to the criteria (Fig. 3F). The postoperative pathology together with symptoms and examinations was reported to be consistent with tumor-induced osteomalacia.

2.2.3. Follow-up. One week after the operation, the visual analog scale score of her systemic bone pain improved to 0 to 1 point compared to the preoperative status, 7 to 8 points. Serum phosphorus levels significantly elevated and remained within the normal range (Fig. 4). On physical exam, the patient exhibited a 5/5 strength in the lower extremities. Subsequently, we administered combination medical treatment, the symptoms were successfully relieved gradually. At the 1-year and 2-year

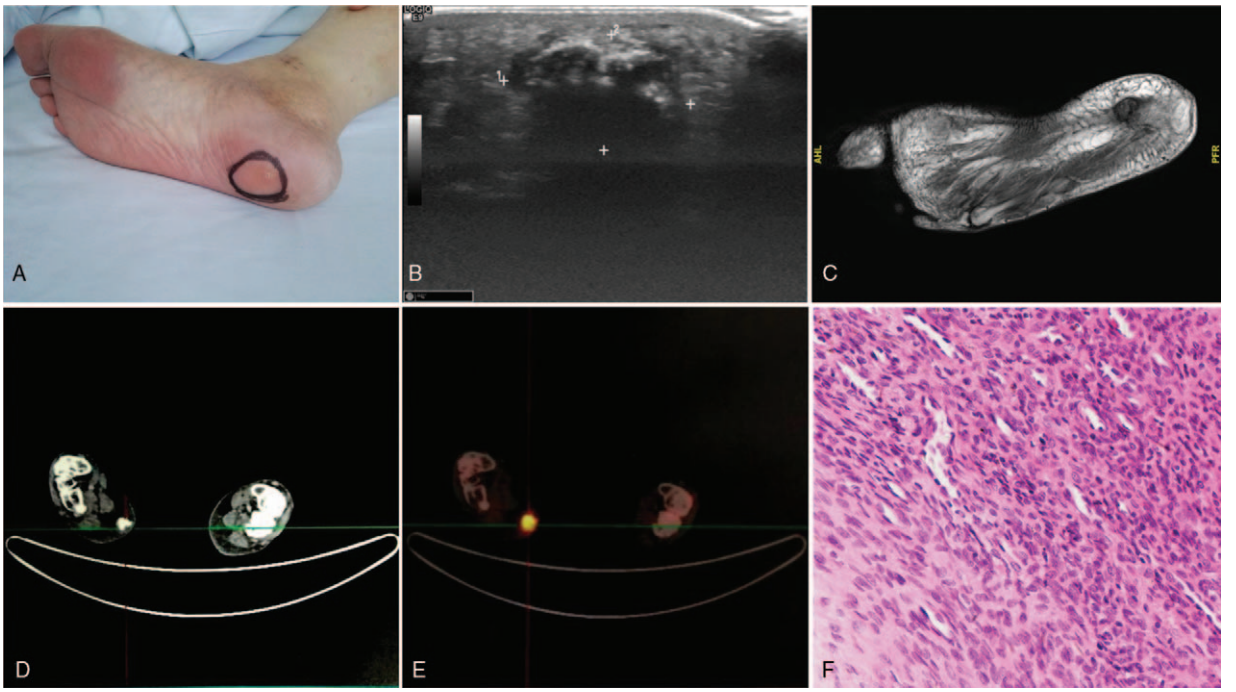

Figure 3. Case 2. (A) The tumor sized about 2.0 × 3.0 cm was on the base of right foot. (B) Ultrasonography demonstrated mixed subcutaneous echoes of the right plantar. (C,D) MRI of right foot revealing the pathogenic tumor. (E) The first-line ^{68}Ga DOTATE PET/CT scan showed high intake in the right heel. (F) Pathologic histology of tumor specimens confirmed the diagnosis of phosphaturic mesenchymal tumor. MRI = magnetic resonance imaging.

follow-up visit, she had nearly full complete remission and reported palliative bone pain. There was no complication during the postoperative period.

3. Discussion

Osteomalacia is an extremely rare metabolic bone disorder characterized by impaired mineralization process of osteoid matrix in mature bone.[1–3] Tumor-induced osteomalacia (TIO) is the most unusual type of osteomalacia clinically, which is commonly found in craniofacial locations and extremities, along with long-standing hypophosphatemia.[4,5] This article presents 2 unusual cases with phosphaturic mesenchymal tumors (PMT) in the foot which was completely excised. As is reported in literature, TIO can lead to debilitating complications and severe symptoms.[1–3,6–10] Characteristically, TIO affects adults without

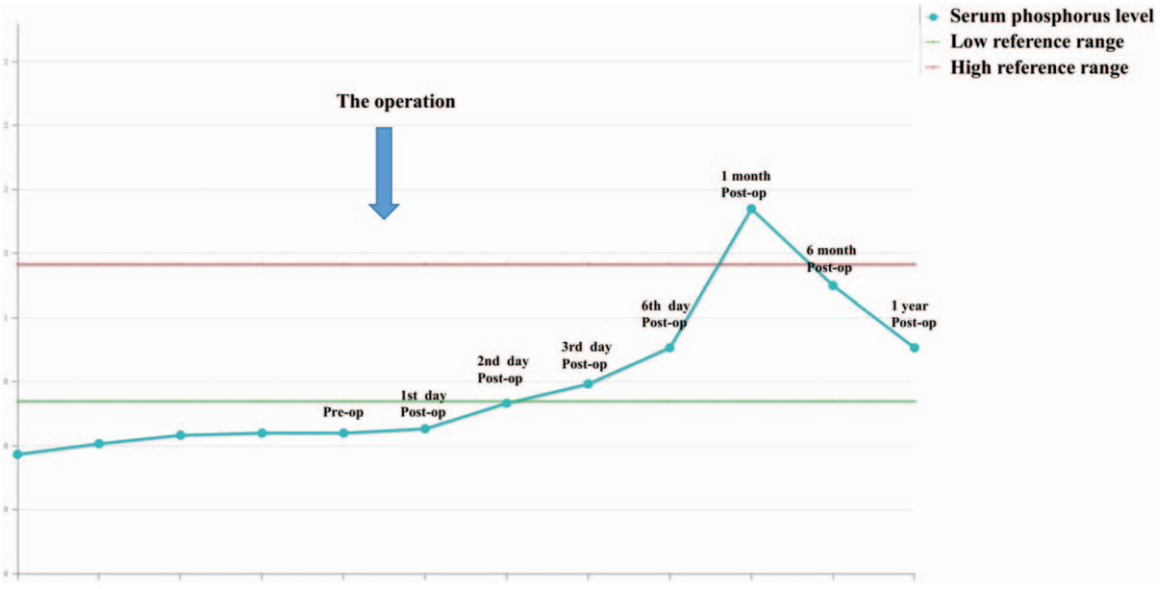

Figure 4. Case 2. Serum phosphorus levels significantly elevated to the normal range after the operation.

a predilection for gender.[1–3] Diffuse bone pain caused by poor bone mineralization is the most frequent symptom in these patients suffering from TIO.[1–3,11,12] To date, less than 500 cases have been reported in literature, thus the majority of clinicians are less aware of this disease. In addition, the clinical course of TIO is often slow, and the volume of pathogenic tumor is commonly very small. The clinical manifestations lack specificity, and the positioning diagnosis is very difficult, therefore, missed diagnosis and misdiagnosis are common to see. If treated inadequately or inappropriately, severe osteomalacia may lead to progressive and fatal consequences in some cases.[13–17]

In particular, one of the most challenging aspects of TIO is to find the pathogenic tumor. The occult nature of PMT somehow delays its recognition, diagnosis, and treatment. In our reported case, it took more than 4 years for the patient to identify the pathogenic tumor and make the final diagnosis. Based on our review of the literature on PubMed, the average time from onset of symptoms to a confirmed diagnosis of TIO often exceeds 2.5 years.[1–3,8–11,17,18] Definitive treatment is further delayed by an average of 5 years due to inability to find the underlying tumor due to the characteristics of being small and slow growing and being located in particular or atypical sites.[8–11,17,18] Typical laboratory findings include hyperphosphaturia, elevated alkaline phosphatase, and low serum 1,25-dihydroxy vitamin D in literature, respectively.[1–3,12,13] Hypophosphatemia is secondary to inhibition of renal phosphorus reabsorption, and the vitamin D synthetic defect blocks the compensatory rise of calcitriol stimulated by the hypophosphatemia.[12–14,19] Moreover, fibroblast growth factor-23 (FGF-23), associated with iron in a pathophysiological mechanism of TIO, is highly expressed in pathogenic tumors compared with normal tissues.[1–3,15–20]

On imaging examination, TIO presents with bone cortical thickness, osteoporosis, and fracture.[1–5,21,22] Unfortunately, PMTs could not be easily detected by conventional imaging techniques in most cases. The classic detecting method of TIO is ^{99}mTc-Octreotide imaging, a scanning technique that detects the expression of somatostatin receptors (SSTRs).[21–23] However, a nonspecific uptake may cause a false-positive scan due to inflammatory tissues, fractures, or other tumors, as lymphocytes can also express octreotide receptors. Similarly, a negative octreotide scan cannot absolutely exclude the diagnosis of TIO. This situation emphasizes the need to further detect and identify the tumor by PET/CT or whole body MRI (WB-MRI) examinations. However, due to the small size and occult nature of TIO, it might not be seen an increased uptake despite PET/CT utilization.[14–17,23,24] WB-MRI has been well established to have no radiological exposure and offers excellent contrast resolution of bone, soft tissues, and subcutaneous regions.[22–24]

The treatment of first choice for TIO is complete tumor resection of the pathogenic tumor, and this corrects the biochemical abnormalities and remineralizes the bone substance in most cases with TIOs.[1–3,25,26] The partial or subtotal resection might also lead to persistent serum abnormalities remained or tumor recurrence. We recommend surgical management of the spinal PMT when the tumor has caused hypophosphatemia, tumor-induced osteomalacia or destruction of spinal stability. This protocol accomplishes 2 purposes: it completely removes the pathogenic tumor as far as possible and at the same time provides histopathological specimens for making the final diagnosis, which is valuable in cases with TIO where the patient presents with atypical clinical and radiological findings.[1–3,22–26] The other notable complication is local recurrence after surgery. With regard to TIO without accurate location, the combination of vitamin D, phosphorus supplementation, and calcitriol can be used to replace progressive renal phosphorus loss, promote renal production of 1,25-dihydroxy vitamin D, and enhance renal phosphorus reabsorption [27–32]. However, medical therapy cannot maintain long-term efficacy and potential complications should also be noted, such as hyperparathyroidism, hypercalcemia, and kidney stone formation.[1–3,27,28]

In conclusion, this is a report of 2 exceedingly rare cases of phosphaturic mesenchymal tumor-induced osteomalacia which was managed by surgical excision. Although uncommon, tumor-induced osteomalacia should be part of the differential when the patient has a history of hypophosphatemia and systemic multiple bone pain and weakness. We recommend completely surgical treatment of the phosphaturic mesenchymal tumor, and it is the most effective treatment option for patients with TIO to sustainably relieve pain and destroy the tumor. If TIO is suspected, surgical management should be performed and the patient should be followed up closely.

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