The Phosphaturic Mesenchymal Tumor: Why is Definitive Diagnosis and Curative Surgery Often Delayed?

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Abstract

Background Tumor-induced osteomalacia is a paraneoplastic syndrome resulting in renal phosphate wasting and decreased bone mineralization. Phosphaturic mesenchymal tumors represent a rare etiology of tumor-induced osteomalacia. Nonspecific symptoms of fatigue, bone pain, and musculoskeletal weakness make the diagnosis elusive and lead to a delay in surgical treatment.

Questions/purposes In this case series, the following three questions were asked: (1) How do the clinical presentation and features of phosphaturic mesenchymal tumors delay the diagnosis? (2) What is the clinical course after surgical treatment of phosphaturic mesenchymal tumors? (3) How frequently do phosphaturic mesenchymal tumors recur and are there factors associated with recurrence?

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Each author certifies that his or her institution approved the human protocol for this investigation that all investigations were conducted in conformity with ethical principles of research, and that informed consent for participation in the study was obtained.

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Methods This study retrospectively reviewed the cases of five adults diagnosed and treated for phosphaturic mesenchymal tumors. Patients were identified through an internal orthopaedic oncology database with clinical, surgical, and histologic data obtained through a systematic chart review. **Results** Five patients presented with a long-standing history of osteomalacia, generalized fatigue, pain, and weakness before the diagnosis was reached at an average of 7.2 years (range, 2–12 years) after initial symptom onset. The diagnosis appeared to be delayed owing to the cryptic medical presentation, difficulty in locating tumor by imaging, and confirming histologic appearance. Two patients treated with wide surgical resection did not experience recurrence compared with three patients who did show recurrent signs and symptoms after marginal excision. A postoperative increase in fibroblast-derived growth factor-23 was associated with recurrent disease.

Conclusions Although uncommon, the diagnosis of phosphaturic mesenchymal tumor should be considered in any patient who presents with hypophosphaturic osteomalacia and no other physiologic cause. Definitive treatment is early, wide surgical resection.

Level of Evidence Level IV, therapeutic study. See the Instructions for Authors for a complete description of levels of evidence.

Introduction

Osteomalacia, a metabolic disorder of decreased mineralization of mature bone, has many causes including inborn errors of metabolism, insufficient levels of vitamin D or calcium, and even common disorders such as chronic kidney disease. Tumor-induced osteomalacia, also known as oncogenic osteomalacia, is an uncommon cause of

osteomalacia. This rare paraneoplastic syndrome, characterized by renal phosphate wasting and a resultant decrease in bone mineralization, is unique in that it can be cured by surgical resection of the tumor. Clinical characteristics often include bone pain, pathologic fractures, and musculoskeletal weakness [2]. Such vague symptoms often lead to delayed or even misdiagnosis with subsequently delayed medical and surgical treatment.

Challenges of diagnosing and treating this elusive tumor have been well documented historically. McCance [12] is credited with describing the first case of tumor-induced osteomalacia in 1947 in a 15-year-old girl who exhibited osteomalacia with vitamin D resistance; however, he did not attribute her illness to the “unusual bony defect” he resected from her femur. In 1959, Prader et al. [17] were the first to recognize a tumor, classified as a giant cell granuloma, as a possible cause of osteomalacia. The resection of the identified tumor resulted in resolution of the osteomalacia and he postulated that the granuloma was secreting a rachitogenic substance. The majority of cases of tumor-induced osteomalacia reported are benign, but malignant varieties have been described [6, 15, 22–24]. Although tumor-induced osteomalacia has been reported in association with 140 different tumors [19], most tumor-induced osteomalacia-associated tumors are of a single histopathologic entity: phosphaturic mesenchymal tumors [5, 6]. Since Prader et al. first recognized the link between neoplasia and osteomalacia, there have been approximately 250 to 300 cases of tumor-induced osteomalacia described in the literature [3, 5, 6]. These tumors are now known to cause renal phosphate wasting, hypophosphatemia, and decreased serum 1,25-dihydroxyvitamin D3 levels resistant to vitamin D supplementation.

Although there has been extensive pathologic characterization of these tumors, there is a paucity of data on the clinical and surgical history and followup of patients with

phosphaturic mesenchymal tumors. Furthermore, surgical resection of these tumors proves to be diagnostic and curative. Therefore, understanding the obstacles to diagnosis and the clinical behavior is important. Thus, we asked the following three questions: (1) How do the clinical presentation and features of phosphaturic mesenchymal tumors delay the diagnosis? (2) What is the clinical course after surgical treatment of phosphaturic mesenchymal tumors? (3) How frequently do phosphaturic mesenchymal tumors recur and are there factors associated with recurrence?

Patients and Methods

We retrospectively reviewed the cases of five adult patients diagnosed and treated for phosphaturic mesenchymal tumors at our institution. Patients were identified through an internal orthopaedic oncology database. Inclusion criteria included adult patients with final pathologic diagnosis of phosphaturic mesenchymal tumor and at least 6 months of clinical followup. All patients in our database were older than 18 years and had delay in diagnosis greater than 2 years. A total of five patients were identified, with four of the patients being diagnosed and treated within the last 10 years.

Clinical data, imaging (plain radiograph, MRI, bone scan, and octreotide scan), surgical history, laboratory data (phosphate, calcium, alkaline phosphatase, and fibroblast-derived growth factor-23), and histology findings were obtained through retrospective chart review approved by the institutional review board before investigation. Each of the patient's demographics, preoperative assessments, operative reports, histopathology, serial radiographs, and postoperative courses were systematically reviewed by the treating surgeon (BEB) and three of the independent authors (WCE, CKL, NAZ).

Table 1. Patient demographics and phosphaturic mesenchymal tumor diagnostic characteristics

Patient number	Age at time of diagnosis (years)	Sex	Tumor location	Presenting symptom	Associated symptoms	Time to diagnosis (years)	Pathologic fracture	Fracture location	Followup (months)
1	65	F	Lower leg (soft tissue)	Multiple rib fractures	F, BP, MW	12	Yes	Ribs	120
2	62	F	Foot (soft tissue)	Foot pain	F, BP, MW, SF	2	Yes	Ribs, pelvis, tibia, mandible	52
3	74	M	Calcaneus	Back pain	F, BP, MW, SF	6	Yes	Lumbar vertebrae, pubic rami	96
4	35	F	Ilium	Back pain	F, BP, MW	7	No	None	72
5	67	M	Proximal medial thigh	Generalized bone pain	F, MW	9	Yes	Pubic rami	6

F = fatigue, BP = bone pain, MW = muscle weakness, SF = stress fracture.

Results

Of the five patients found to have a final pathologic diagnosis of phosphaturic mesenchymal tumor, there were three women and two men with an average age at diagnosis of 61 years (range, 35–74 years) (Table 1). There was an average of 69.6 months (range, 8–120 months) of followup. Initially, each of the patients presented with a long-standing history of osteomalacia, generalized fatigue, pain, and weakness. Four patients eventually could localize pain to their tumor sites but this was not their primary complaint at the initial presentation. Additionally, four patients (Patients 1, 2, 3, 5) were diagnosed with pathologic fractures distant from their tumor site, most commonly in the ribs or pelvis. Every patient had been evaluated by multiple medical specialists and all but one had undergone treatment with phosphate and vitamin D supplementation for hypophosphatemia before referral and diagnosis was made by the orthopaedic oncology team. The average time to diagnosis was 7.2 years (range, 2–12 years) from first symptomatic presentation.

Multiple imaging modalities also provided variable identification of these tumors (Fig. 1). In each of the three patients with bony involvement, plain radiographs identified a lesion characterized by a mixture of sclerosis and lucency (Patients 1, 3, 4) (Fig. 1). Soft tissue masses were

seen on MR images of three patients (Patients 1, 2, 5) as heterogeneous masses with variable degrees of contrast enhancement (Fig. 1). An octreotide scan was the first diagnostic imaging modality that directly identified the tumor in one patient (Patient 5) (Fig. 1). Interestingly, the octreotide scan showed physiologic uptake in the tumor bed at the time of diagnosis in three of four patients who underwent the scan.

Four of five original tumors were available for histologic review. All four showed a heterogeneous histologic appearance with bland spindle cells intermixed with variable hyalinized, focally calcified, matrix, well-developed capillary network, and foci of osteoclast-like giant cells, consistent with phosphaturic mesenchymal tumors (Fig. 2A–B). No evidence of malignancy was seen. The remaining patient's resection (Patient 4) was done before the histologic characterization of phosphaturic mesenchymal tumors, but was described as a fibroblastic proliferation with colloid-filled cyst and multinucleated giant cells that originally was thought to be a brown cell tumor.

All but one of the patients were treated medically with phosphate and vitamin D supplementation before diagnosis and surgical resection of the tumor. Two of the three patients with soft tissue tumors (Patients 2, 5) underwent wide surgical resection as their index operation. The third patient with a soft tissue tumor (Patient 1) had intraosseous

Fig. 1A–E (A) The lateral radiograph from Patient 3 shows a phosphaturic mesenchymal tumor in the calcaneus with generalized increased sclerosis and mixed lucency. Octreotide scans from Patient 5 show (B) positive somatostatin receptor enhancement in anteromedial proximal right thigh while (C) no such enhancement is seen posterior. A heterogeneous mass is seen in the proximal anteromedial right thigh that invades the femoral vein with increased signal on (D) coronal T2-weighted and (E) intermediate signal on axial T1-weighted MR images. The findings are consistent with the diagnosis of tumor-induced osteomalacia with this patient's clinical history.

Fig. 2A–D (A) The primary tumor from Patient 1 has a smudgy matrix with bland spindle cells, occasional osteoclast-like giant cells, and prominent blood vessels (Stain, hematoxylin & eosin; original magnification, $\times 10$). (B) The tumor from Patient 3 shows more prominent osteoclast-like giant cell population, prominent vascularity, and focal matrix production with stellate cells (Stain, hematoxylin & eosin; original magnification, $\times 10$). (C) Histologic examination of the recurrent tumor in Patient 1 showed a

hypercellular spindle cell tumor with moderate atypia, increased mitotic activity (arrows), occasional multinucleated giant cells, and lack of matrix production (Stain, hematoxylin & eosin; original magnification, $\times 20$). (D) The patient had lung metastasis. Histologic examination appeared similar to that seen with the patient's primary tumor, with bland spindle cells, prominent vessels, and a calcified matrix (Stain, hematoxylin & eosin; original magnification, $\times 10$).

involvement of the cortex adjacent to the tumor observed on MR images, and the index procedure involved excision including the periosteum but with no bony resection. This patient experienced four episodes of local recurrence and ultimately had lung metastasis. The two patients for whom the tumor was located primarily in bone (Patients 3, 4) underwent curettage and bone grafting; however, both patients had local recurrence. One patient was treated further with subtotal resection of the involved bone and has experienced no subsequent disease. The other patient continued to have radiographic changes representing potential recurrence but chose to be managed expectantly. His laboratory data have remained stable, radiographs have been unchanged, and there has been no clinical pain at the tumor site.

Laboratory evaluation at the time of presentation indicated hypophosphatemia (normal range, 2.3–4.5 mg/dL) with normocalcemia (normal range, 8.7–10.2 mg/dL) in all five patients (Table 2). Phosphate levels normalized within 1 month after surgery in all but one patient. Additionally, alkaline phosphatase was elevated in three patients but this too normalized after tumor resection in all but one patient

(normal, 24–110 $\mu\text{g/L}$). Preoperative fibroblast growth factor-23 (FGF-23) levels for three of the five patients were reported to be markedly elevated (normal = $< 180 \text{ RU/mL}$). Postoperatively, FGF-23 was analyzed in three patients within 1 week of resection and in all cases had normalized (the other two patients predate the use of this measure). Followup FGF-23 levels were monitored for potential recurrence, and subsequent recurrence was detected in two patients when these levels began to elevate.

Clinical symptoms of diffuse pain, weakness, and fatigue associated with osteomalacia initially resolved in all patients after tumor removal. However, three patients with return of such symptoms had associated recurrence. These patients experiencing recurrence were also the patients who had subtotal resection of the tumor at the index procedure (one patient with stripping of the periosteum near the involved soft tissue tumor and the other two with curettage and bone grafting of a primary bone lesion). The patient with a soft tissue tumor near bone cortex (Patient 1) had multiple local recurrences and pulmonary metastasis despite gross reresections and octreotide chemotherapy (octreotide, as a somatostatin analogue, has the potential to

Table 2. Preoperative and postoperative laboratory values after surgery for phosphaturic mesenchymal tumor

Patient number	Tumor location	FGF-23		Phosphorus		Calcium		Alkaline phosphatase				
		Preoperative	Postoperative	Current	Postoperative	Preoperative	Current	Preoperative	Postoperative	Current		
1	Lower leg	4 × above normal	Normal [#]	368	1.4	2.3 [#]	2.4	9.5	8.6 [#]	56	45 [#]	69
2	Foot	NA	118 [#]	101	1.8	2.8 [#]	3.0	8.7	7.4 [#]	154	Normal	NA
3	Calcaneus	NA	NA	11,150**	1.5	2.0 [#]	2.5**	8.9	9.2 [#]	350	173	108
4	Ilium	NA	NA	MA	1.3	Normal	NA	9.3	NA	135	Normal	NA
5	Proximal medial thigh	2520	156 [#]	156 [#]	1.4	2.6 [#]	3.2	9.2	9.2	NA	186	186

NA = not available; FGF = fibroblast growth factor; reference ranges, FGF-23 = < 180 RU/mL; phosphorus = 2.3–4.5 mg/dL; calcium = 8.7–10.2 mg/dL; alkaline phosphatase = 24–110 U/L.

** during active recurrence; [#] within one week of surgery.

inhibit the activity of these tumors). The lung metastasis appeared morphologically identical to the primary tumor, while the recurrent thigh mass showed features of malignancy, including hypercellularity, moderate atypia, and increased mitotic activity (Fig. 2C–D). Phosphate levels normalized after each resection in this patient but continued to decrease during recurrence. FGF-23 remained high in this patient until amputation, after which time levels normalized. The patient's levels again increased and the most recent were above normal (Fig. 3). This patient also appeared to have the longest duration of symptoms (12 years) before definitive diagnosis. Although Patient 3 continued to have hypophosphatemia and elevated FGF-23 after initial tumor resection, he remained clinically asymptomatic and opted for serial observation of laboratory and bone mineral density as opposed to tumor bed resection. The third patient (Patient 4) with recurrence did undergo resection of the tumor bed and remained disease-free as evidenced by absences of symptoms and normal FGF-23 and phosphorus values.

Discussion

Phosphaturic mesenchymal tumors have been well described histologically and the entity of tumor-induced osteomalacia is a known, albeit uncommonly encountered, cause of osteomalacia. However, as a result of the varying clinical presentation and the typically cryptic nature of symptoms, there is often a long delay in the diagnosis and definitive treatment of patients with a phosphaturic mesenchymal tumor. Although phosphaturic mesenchymal tumors are regarded as benign, the lengthy time from onset of symptoms to diagnosis and the potential for recurrent disease may be associated with considerable morbidity. The factors leading to a delayed diagnosis include a vague and primarily medical (rather than anatomic) presentation, difficulty in tumor localization, and complicated histologic characterization. The clinical course should include medical management of hypophosphatemic symptoms until wide excision of tumor can be accomplished. Tumor recurrence appears to be associated with prolonged time to diagnosis and incomplete resection. FGF-23 and phosphate levels appear to correlate with recurrence and can be used for postoperative screening.

Our study has some limitations. First, although this review spans the entirety of our institution's surgical history and is the largest review of its kind, it is limited because of the relatively rare nature of this diagnostic entity. Additionally, the analysis is limited by the accrual of subjects over an extended period. Two of the patients predate one of the major monitoring modalities for this tumor type (quantitative serum FGF-23 levels). In addition,

Fig. 3 The laboratory values for Patient 1, who experienced multiple recurrences of her primary tumor in addition to lung metastasis, are shown. The patient's phosphorus levels remained unstable, often decreasing to below normal levels however usually normalizing after resection. The FGF-23 showed periodic decreases after complete resection but currently has increased possibly indicating recurrence.

although FGF-23 is more expensive to measure than urine phosphorus, urine phosphorus must be based on 24-hour urine collection and we have experienced difficulty with patient compliance. Normative values for 24-hour urine phosphorus levels are less well described (our laboratory declined comment on a reference range for this test). Abnormalities in serum and urine phosphorus also may be affected by numerous other physiologic changes, whereas FGF-23 is the most direct serologic marker for tumor activity. Third, the varied tumor type (soft tissue or intraosseous) make generalizations pertaining to such a small sample size difficult. Despite these shortcomings, our study provides insight into the presentation, clinical and surgical course, and factors associated with recurrence of this rare tumor.

We believe that the primary reason for the delayed diagnosis of phosphaturic mesenchymal tumors is failure to correlate the nonspecific symptoms of fatigue, bone pain, and hypophosphatemia with the presence of a tumor. Such a vague clinical presentation makes the diagnosis elusive and most patients present to their primary care physicians only to be treated for hypophosphatemia without further workup. This was the case for some of our patients in this series, leading to a delay in curative surgical treatment. Once the diagnosis of a phosphaturic mesenchymal tumor is considered, difficulty in tumor localization is the next obstacle to prompt treatment. Plain radiographs were able to localize the tumor in three patients, and MRI in the remaining two. However, the variable locations and small size renders identification challenging. Compartmental venous sampling of FGF-23 has been useful in localization of the body region in which the tumor is located after which MRI then can be performed; however, this extensive workup is not widely used in clinical practice [7]. The presence of somatostatin receptors makes indium-111 pentetreotide or octreotide scintigraphy the preferred imaging modality for localization and postoperative

tracking of these tumors [9, 14, 18]. An octreotide scan was used for diagnosis and localization of the tumor in three of four patients for whom it was performed and was the primary diagnostic imaging modality in one of these patients (Patient 5). Histologic confirmation is the last hurdle to a conclusive diagnosis, which is dependent on recognition of the entity and clinical correlation.

Several tumor types allegedly cause tumor-induced osteomalacia; however, the majority of cases are most likely caused by a single histopathologic entity—phosphaturic mesenchymal tumors [6]. Morphologically, these tumors are characterized by bland, uniform spindled to stellate cells that often are intermixed with an unusual smudgy matrix with a well-developed capillary network and variable calcification. In the majority of cases no atypia is present and mitotic activity and necrosis are absent [5, 6]. Most tumors express FGF-23 by immunohistochemistry, of which the proliferating cells in the tumor are immunoreactive [3, 6]. Multinucleated giant cells are commonly present and one of our patients previously was misdiagnosed with a giant cell tumor of bone. However, recognition of the characteristic histologic features when correlated with the clinical presentation should lead to the correct diagnosis.

Definitive treatment of tumor-induced osteomalacia from phosphaturic mesenchymal tumors remains surgical resection. As a result of the presence of somatostatin receptors on these tumors, it has been suggested that octreotide, a synthetic somatostatin analogue, would be useful in decreasing FGF-23 secretion [20]. Although there is one case report regarding use of octreotide as mitigating therapy before definitive treatment [20], few clinicians have been successful in repeating the initial success with this technique [3, 4, 13, 16]. One of our patients underwent a trial of octreotide chemotherapy, but this was unsuccessful. All five of our patients underwent subsequent surgery, which led to symptomatic resolution. A key point

is that surgery must involve total resection of the tumor. The case of Patient 1 illustrates the pitfalls of subtotal resection; the patient experienced multiple episodes of local recurrence and had histologic features develop that were concerning for malignant transformation, hypercellularity, atypia, and increased mitotic activity. This patient ultimately had pulmonary metastasis and eventually underwent an above knee amputation. Negative margins are necessary for soft tissue tumors, even if resection of bone is required. The two patients whose tumors were located primarily in bone initially had curettage and bone graft, and both experienced local recurrence. In phosphaturic mesenchymal tumors arising from bone, intralesional treatment is not sufficient for control and wide resection should be performed. This series is the first reported surgical case series for treatment of phosphaturic mesenchymal tumors and the importance of definitive surgical management cannot be overstated.

Surgical excision resulted in resolution of symptoms in all of the patients and normalization of laboratory values in all but one patient. Neither of the patients whose index procedure was wide surgical excision with clean margins has experienced recurrence. In contrast, the patients in whom the initial procedure did not completely resect the tumor have experienced recurrence of disease. The patient with the longest time to diagnosis experienced the most complicated clinical course with multiple recurrences and metastasis, suggesting that early and aggressive surgery (complete excision) may be beneficial in preventing recurrent disease. Additionally, the clinical utility of FGF-23 and diagnosis of tumor-induced osteomalacia has been well established in scientific research [1, 8, 10, 21]. FGF-23 is secreted by oncogenic cells and acts in the kidney to decrease phosphate reabsorption, leading to osteomalacia [11]. Systemic levels of FGF-23 were useful for the patients who received it preoperatively and levels were elevated in both cases. Serial values of FGF-23 also were used successfully to monitor for recurrence in three of our patients. Furthermore, the patient with several episodes of symptomatic recurrence (confirmed by MRI, octreotide scan, and biopsy of lung metastasis) repeatedly showed hypophosphatemia with elevated FGF-23 levels in each of her recurrences, with normalization of levels after each resection. Although, to our knowledge, there are no studies correlating FGF-23 directly with tumor burden, this example shows the potential for such use.

We report a series of five histologically and surgically confirmed cases of phosphaturic mesenchymal tumors, of which one was malignant with multiple recurrences. This is a rare tumor, which, as a result of the variable presentation, is generally medical in nature and continues to have a delayed diagnosis. For patients with suspected tumor-induced osteomalacia, we recommend the following

evaluations on initial presentation: serum phosphorus, 24-hour urine phosphorus, serum calcium, vitamin D (serum 1-OH and 1,25-OH cholecalciferol), FGF-23, and either an octreotide scan or a whole body positron emission tomography (PET) CT scan. Once a diagnosis is made, we use serum phosphorus and serum FGF-23 levels at least every 6 months to survey treatment response. Definitive treatment is early, wide surgical resection. The prognosis of phosphaturic mesenchymal tumor is generally good, although this series illustrates the pitfalls of delayed definitive resection. FGF-23 is useful in diagnosis and also may prove to be beneficial in long-term monitoring of patients. The diagnosis of tumor-induced osteomalacia should be considered in any patient who presents with hypophosphaturic osteomalacia with no other physiologic cause.

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