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Oncogenic Osteomalacia From a Primary Phosphaturic Mesenchymal Tumor of the Toe: A Case Report

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ABSTRACT

Oncogenic osteomalacia is an acquired, rare paraneoplastic syndrome characterized by renal phosphate wasting and subsequent hypophosphatemic osteomalacia. The condition is usually associated with a phosphaturic mesenchymal tumor, which produces fibroblast growth factor 23, the primary circulating factor responsible for reduced tubular phosphate reabsorption. Clinically, adult patients typically present with bone pain, myalgia, recurrent and/or multiple stress fractures, and fatigue, with serum levels typified by low 1,25-$(OH)_2$ vitamin D_3, increased alkaline phosphatase, and normal calcium, parathyroid hormone, calcitonin, 25-OH-vitamin D_3, and 25,25-$(OH)_2$ vitamin D_3 levels. The tumor in question is typically benign and can be of little clinical significance apart from its role in causing hypophosphatemic osteomalacia. Detection of the tumor, therefore, can often be delayed and requires an astute index of suspicion.

Oncogenic osteomalacia (OOM) is an acquired, rare paraneoplastic syndrome characterized by renal phosphate wasting and subsequent hypophosphatemic osteomalacia. It was first described in 1947 by McCance (1), although its association with a tumor was not elucidated until 1959 by Prader et al (2). In a seminal study published in 1987, Weidner and Santa Cruz (3) classified these oncogenic osteomalacia-associated tumors under a single histopathologic entity, describing them as "phosphaturic mesenchymal tumor, mixed connective tissue variant" (PMTMCT). Additional investigation revealed the overexpression of fibroblastic growth factor-23 (FGF-23) as the factor responsible for OOM, resulting in renal phosphate loss and hypophosphatemia. Although the physical locations vary, most tend to occur in the axial skeleton and soft tissues of the lower extremity. Biochemically, OOM is also typified by low serum 1,25-$(OH)_2$ vitamin D_3, increased alkaline phosphatase, and normal calcium, parathyroid hormone, calcitonin, 25-OH-vitamin D_3 and 25,25-$(OH)_2$ vitamin D_3 levels. Clinically, adult patients typically present with bone pain, myalgias, recurrent and/or multiple stress fractures and fatigue. Involvement of an orthopedic surgeon is usually in the context of a pathologic fracture requiring surgical evaluation. The tumor in question is typically benign and can be of little clinical significance apart from its role in causing hypophosphatemic osteomalacia. Detection of the tumor, therefore, can often be delayed and requires an astute index of suspicion. Although such paraneoplastic tumors are frequently encountered in the lower extremity, the incidence of such tumors involving the toes, such as was the case in our patient, appears to be rarer.

Case Report

Our patient is a 52-year-old male who presented in April 2009 to a primary care clinic with a 2-week history of intermittent left knee pain that was refractory to oral pain medication. He had no history of trauma. With the exception of a body mass index >40 kg/m^2, the patient was in good overall general health. The initial presumption was that of early osteoarthritis, and the patient was treated conservatively with nonsteroidal anti-inflammatory drugs. The radiographic findings of the left knee at that time were normal. His serum calcium level was 9.4 mg/dL. In July 2009, the patient complained of significant left knee pain, 9 of 10 in severity, and an inability to work. A magnetic resonance imaging (MRI) study of the left knee was obtained. The MRI scan showed increased T_2-weighted signal intensity within the medial and lateral femoral condyles suggestive of marrow edema and a focal 1.4-cm area of subchondral flattening along the weightbearing surface of the lateral femoral condyle that was most consistent with a stress fracture, not a contusion, and was treated conservatively. A referral was made to the orthopedics department; however, for reasons not explicit in the medical records, he did not follow-up with the orthopedics department. He presented to the emergency department in September 2011, during which he underwent a formal orthopedic evaluation. By that time, he required the assistance of a walker and had developed concomitant

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right knee and bilateral hip pain. Radiographs of the hips were obtained and showed diffuse demineralization and step off deformities of the bilateral femoral head–neck junction suggestive of minimally displaced femoral neck fractures. MRI of the pelvis revealed diffuse, mild, high T_2-weighted marrow signal intensity suggestive of osteoporosis and high T_2-weighted marrow signal intensity within the bilateral femoral necks, consistent with recurrent or impending stress fractures (Fig. 1). Subsequent bone densitometry showed osteoporosis, with left and right proximal femoral neck and total femoral T scores of −3.2 and −2.8 and −2.6 and −2.6, respectively (Fig. 2). Given the constellation of findings, the patient underwent open reduction and internal fixation of the bilateral hips with dynamic hip screws. His serum calcium at that time was 8.5 mg/dL. Owing to persistent bilateral knee pain, an MRI study was obtained, which showed severe osteoporosis and chronic insufficiency fractures involving the femoral condyles and proximal tibial metaphyses, bilaterally. The patient began bisphosphonate therapy and was referred to the endocrinology department.

A full secondary workup for osteoporosis was obtained in February 2012, and he had findings consistent with tumor-induced osteomalacia, with the following values: parathyroid hormone, 57 pg/mL; alkaline phosphatase, 289 U/L; phosphate, 1.0 mg/L; 1,25-dihydroxy vitamin D, 14 ng/mL. A 24-hour urine collection test was significant for hyperphosphaturia, with phosphate levels of 359 mg/L. An FGF-23 level was subsequently obtained and noted to be high. A closer history and physical examination revealed a mass on the left great toe. The patient stated that the mass did not cause any symptoms and that it had been present for approximately 7 years. An MRI of the left foot revealed an enhancing mass within the subcutaneous tissues of the forefoot at the level of the great toe (Fig. 3). An octreotide scan showed a focus of increased activity corresponding to the mass observed on physical examination and MRI (Fig. 4). No other focus was identified. The patient was referred to the orthopedics department for resection of the left great toe mass. Before surgery, the patient had had a moderate response to medical therapy, with his phosphate level increasing to 1.5 mmol/L with Neutra-Phos® (ALZA Corp, Mountain View, CA) and rocaltrol therapy. In March 2012, the mass was excised and sent for pathologic evaluation. The pathologic examination showed histologic findings consistent with a PMTMCT, measuring 1.4 cm in the greatest dimension (Fig. 5).

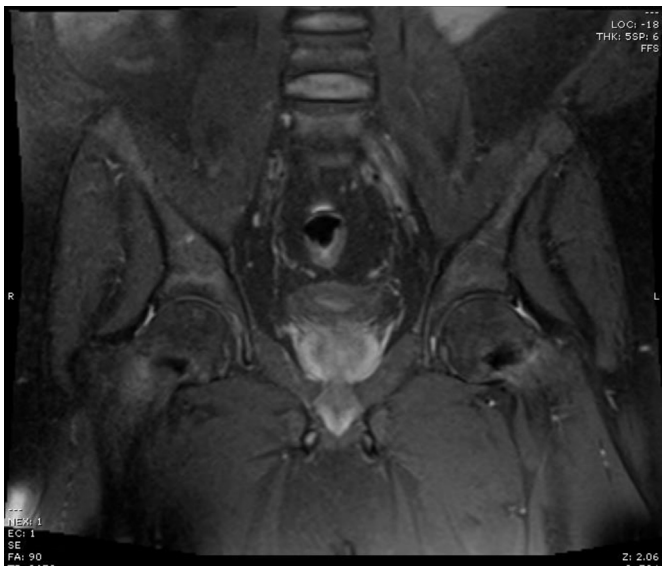

Fig. 1. Magnetic resonance imaging scan demonstrating high T_2-weighted marrow signal intensity within the bilateral femoral necks, consistent with recurrent or impending stress fractures.

Postoperatively, the patient's clinical course improved, because he had significantly decreased knee pain and was ambulating 3 weeks after resection of the tumor. By 4 months, he was ambulating with only the assistance of a cane. His clinical progress was mirrored by increasing serum phosphate levels (weekly serial measurements of 1.0, 1.5, 2.5, 3.1, 4.3, and 4.8 mmol/L, respectively). The blood work obtained in July 2012 revealed a phosphate level of 3.9 mmol/L (without medication), alkaline phosphatase of 104 U/L (bone-specific alkaline phosphatase had decreased to 31.1 from 98.2 μg/L), and vitamin D of 13 ng/mL. Despite the improved biochemical profile and clinical disposition, the patient complained of thoracolumbar back pain. MRI of the spine at 4 months postoperative revealed chronic anterior wedge deformities of T10–L2, with an approximate 40% height loss of L1 and focal thoracolumbar kyphosis, all likely secondary to osteoporotic insufficiency fractures. The patient has continued to improve with conservative management, and no surgical intervention was indicated at the last follow-up visit. Within weeks of the removal of a PMTMCT, the potential for hypocalcemia secondary to rapid remineralization and hyperparathyroidism secondary to hypocalcemia exists, but these did not occur in our patient, with calcium levels of 8.8 and 9.6 mg/dL at 3 and 5 months, respectively.

Discussion

Since its association with oncogenic osteomalacia was described in 1959 by Prader et al (2), several details have emerged related to the pathologic and histopathologic characteristics of PMTMCTs. Much has been debated, however, about their defining characteristics, given their polymorphous histologic appearance. Consequently, these tumors have often been misdiagnosed. In a comprehensive review and analysis of 32 cases, Folpe et al (4) highlighted these discrepancies and proposed an alternative method by which to fundamentally characterize PMTMCTs. Previously, hemangiopericytoma-like vasculature and numerous osteoclast-like giant cells were emphasized as critical to its diagnosis. Folpe et al (4) proposed an alternative criterion, in that PMTMCTs are characterized by a "highly vascular proliferation of bland, spindled to stellate cells," producing a matrix that appears to express FGF-23 on immunohistochemistry. FGF-23, a gene known to be mutated in autosomal dominant hypophosphatemic rickets (5), has been proposed as the primary circulating factor responsible for reduced renal tubular phosphate reabsorption and the resultant phosphaturia. This gene is overexpressed in PMTMCTs, resulting in significantly decreased bone mineralization, such as that highlighted by Shimada et al (6), in which Chinese hamster ovary cells overexpressing FGF-23 that were implanted in mice resulted in tumor-induced-osteomalacia. FGF-23, however, might not be the only phosphaturic factor contributing to PMTMCTs. De Beur et al (7) demonstrated that frizzled related protein-4, another gene overexpressed in OOM-related tumors, encodes a protein that inhibits phosphate uptake in vitro. This suggests that at least 2 proteins could perhaps work in concert or independently to induce phosphaturia. Additional studies are necessary to delineate this potential relationship. The histopathologic characteristics of the tumor specimen collected from our patient was typical of most PMTMCTs previously described, featuring round to ovoid neoplastic cells with bland cytologic features, prominent vascular stroma, and focal concentric whirling of tumor cells around vessels (Fig. 5*A* and *D*). Scattered deposits of osteoid-like to granular amphophilic matrix ("grungy" and "flocculent") were also present, assumed to express FGF-23 (Fig. 5*B*). Perivascular hyalinization with a chondromyxoid to hyaline matrix was also present in our specimen. Again, similar to that of other PMTMCTs described in previous cases, numerous osteoclast-like giant cells were present (Fig. 5*C*).