Transformation of a Long-Standing Phosphaturic Tumor Inducing Osteomalacia into Malignancy

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Abstract

Tumor-induced osteomalacia (TIO) is a rare paraneoplastic syndrome characterized by renal phosphate wasting, which leads to deranged bone turnover. TIO is usually associated with benign mesenchymal tumors, although it has also been reported in malignant tumors. We report the case of a 56-year-old individual who presented with a long clinical course of hypophosphatemia, weakness, and kyphosis, associated with a tumor in the foot. After several years, this lesion exhibited malignant behavior and was diagnosed as a high-grade sarcoma. To date, this case is among the 10 reported cases in the literature of a mesenchymal tumor associated with TIO undergoing malignant transformation. This report underscores the importance of a comprehensive evaluation of patients with unexplained hypophosphatemia, and highlights the need for diligent follow-up to detect possible malignant transformation of the underlying tumor. Clinicians should consider TIO in the differential diagnosis of hypophosphatemia, and promptly investigate for the presence of an underlying tumor, as early detection may improve the patient's prognosis.

Key words: Oncogenic osteomalacia, Case Reports, Paraneoplastic Syndromes, Rickets, Sarcoma

Introduction

Tumor-induced osteomalacia (TIO), also known as oncogenic osteomalacia, is a rare paraneoplastic syndrome that was first described by McCance in 1947 (1). This condition is characterized by renal phosphate wasting, leading to disrupted bone turnover. Clinically, TIO presents with symptoms such as muscle weakness, bone pain, and fractures. Biochemically, TIO is marked by hypophosphatemia, hyperphosphaturia, normal or low levels of 1,25-dyhydroxi-vitamin D, elevated alkaline phosphatase, normal levels of calcium and parathyroid hormone (PTH), and notably high levels of fibroblast growth factor 23 (FGF23) (2,3). The exact incidence of TIO is not precisely known, but one of the largest studies in Denmark reported it to be below 0.13 per 100,000 person-years for the total population investigated (4). Tumors responsible for TIO are highly heterogeneous, but it is typically induced by mesenchymal tumors originating from soft tissue or bone. Recently, the World Health Organization has recognized phosphaturic mesenchymal tumors (PMT) as morphologically distinctive neoplasms that cause TIO (5). The majority of tumors causing TIO are PMTs, followed by hemangiopericytoma, giant cell tumor, and hemangioma. Only 10% of the tumors in a systematic review were found to be malignant, highlighting the rare occurrence of malignancy in TIO cases (6). Due to the rarity of this condition, the limited knowledge about the disease, and the unpredictable behavior of the underlying tumor, a definitive diagnosis may take years to establish.

Case report

A 56-year-old man with hypertension presented with a six-year history of lumbar pain. Several months before his initial assessment, he developed progressive weakness in his lower extremities, leading to total disability. During the physical examination, the patient was bedridden, had a short stature, marked kyphosis, and generalized muscle weakness. His muscular reflexes were diminished, and there was no evidence of neuropathic involvement. Laboratory tests showed a normal complete blood count, preserved renal and hepatic function, negative serologic screening, and negative autoantibodies. A metabolic panel was ordered, revealing an elevation of alkaline phosphatase (543 IU/L), severe hypophosphatemia (phosphorus 1.0 mg/dL), and normal calcium levels (calcium 9.1 mg/dL). PTH levels were slightly above the normal range (57 pg/mL), and vitamin D levels were low (8 pg/mL). A 24-hour phosphorus excretion was 860 mg, and the fractional excretion of phosphorus was 51%, consistent with urinary phosphorus wasting in the context of hypophosphatemia. Urine analysis did not show any features of proximal tubule dysfunction. Hereditary rickets was unlikely given the patient's age and lack of family history; instead, FGF23-dependent hypophosphatemia as a paraneoplastic syndrome was suspected, and a tumor localization work-up was initiated. Previous chest X-ray and thoraco-abdominal CT, were normal. A whole-body bone scintigraphy with technetium-99m-hydroxymethylene-diphosphonate (TC99-HMDP) was ordered, revealing heterogeneous involvement of the maxilla, mandible, multiple ribs, right radius, sacrum, iliac, tibia, and bilateral calcaneus. Increased asymmetric uptake was observed in the right foot, so Tc99-Octreotide single photon emission computed tomography (SPECT/CT) and magnetic resonance (SPECT/MR) were performed, revealing a hypodense/hypointense localized lesion in the astragalus with lytic behavior, sclerotic border, and significantly increased metabolism, consistent with a mesenchymal tumor (Figure 1). The patient was referred for a surgical oncology consultation, but unfortunately, he was lost to follow-up.

One year later, he returned to our clinic reporting a weight loss of 23 kg over the last three months and an exophytic tumor in the same region where the previous imaging studies had revealed abnormal uptake of Tc99-Octreotide (see Figure 2). A new chest CT scan showed multiple nodular lesions in the lungs, which were compatible with metastases. Histopathological analysis with immunohistochemistry of the foot tumor confirmed a diagnosis of high-grade sarcoma with fusiform, epithelioid, and pleomorphic patterns (Figure 3). The patient began receiving oncologic treatment with a dose-adjusted AIM regimen (doxorubicin, ifosfamide, mesna). Unfortunately, he had an adverse clinical course and died within the next two months.

Discussion

TIO is a paraneoplastic syndrome characterized by the excessive expression of FGF-23. As a consequence, FGF-23 mediates the internalization of the sodium-phosphate cotransporter (NaPi) in renal tubular cells, leading to impaired reabsorption of phosphate by the kidneys. Moreover, FGF-23 inhibits the enzymatic hydroxylation of 25-hydroxyvitamin D in the kidneys, resulting in inadequate production of active 1,25-dihydroxyvitamin D, ultimately contributing to the pathogenesis of osteomalacia (7,8). Furthermore, FGF-23 in TIO can impact bone mineralization through indirect mechanisms. It has been shown to suppress the production of PTH. TThis reduction in PTH levels, mediated by FGF-23, hampers the release of calcium from bone, thereby exacerbating the mineralization abnormalities observed in TIO-induced osteomalacia (9). Furthermore, FGF-23 represses the transcription of the alkaline phosphatase gene, subsequently resulting in a diminished function of tissue-nonspecific alkaline phosphatase (TNALP) at the cell membrane. This inhibition results in a reduction in the breakdown of inorganic pyrophosphate, leading to decreased phosphate levels. In addition to this, osteopontin (OPN), a protein vital to the process of bone mineralization, has its production and release stimulated by extracellular phosphate. As such, through the suppression of TNALP gene transcription, FGF-23 indirectly attenuates the secretion of OPN, thus further modulating bone mineralization processes (10,11).

Symptoms of TIO often persist for months or even years before a diagnosis is made. The initial symptomatology predominantly comprises musculoskeletal discomfort, including diffuse muscle pain and progressive weakness, often leading to substantial impairment in the patient's mobility and quality of life. As the disease advances, it progressively impacts the skeletal system, resulting in debilitating bone pain. Furthermore, due to the decreased mineralization and consequent weakening of the bone structure, patients with TIO

frequently experience pathological fractures. These fractures occur in bones under normal physiological stresses, highlighting the profound degree of bone fragility associated with this condition (12,13).

TIO indeed represents a rare and unique disease entity. Although it predominantly manifests in middle-aged adults, it bears the potential to present across all age groups without displaying a particular gender predilection (14,15). As stated previously, it is associated with benign mesenchymal tumors in the vast majority of cases, approximately 90% (3). Yet, it is well-documented that malignant tumors, most notably sarcomas, also have the capacity to induce this condition (15–18)

In cases lacking an initial biopsy, as in the patient under discussion, it becomes challenging to conclusively determine the tumor's original nature. It remains uncertain whether the initial tumor was benign and subsequently underwent malignant transformation, or if the neoplasm was inherently sarcomatous. Given the patient's extended history of hypophosphatemic symptoms spanning six years, the radiologic findings on the 99mTc-Octreotide Scintigraphy with SPECT/CT, and the abrupt onset and rapid progression of signs indicative of malignancy, including metastatic disease and substantial weight loss over a three-month period, the likelihood of malignant transformation is substantially high.

The presentation of our patient, characterized by the manifestation of a localized mesenchymal tumor in the foot subsequently diagnosed as a high-grade sarcoma one year post TIO identification, brings to the fore the criticality of considering TIO in the differential diagnosis of unexplained hypophosphatemia. This case underscores the potential for malignant transformation within the clinical course of TIO, thereby emphasizing the imperative nature of vigilant longitudinal follow-up. Such conscientious monitoring is paramount in early detection of malignant transformation, thereby facilitating timely and appropriate therapeutic interventions, significantly impacting patient prognosis and the management of this complex disease.

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Figures:

Figure 1. SPECT/MR showing a localized lesion in the right astragalus with significantly increased metabolism.

Figure 2. Exophytic tumor in the right foot.

Figure 3. H&E. Malignant mesenchymal neoplasm with spindle cells and epithelioid patterns.