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CASE REPORT

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Transformation of a long-standing phosphaturic tumor-inducing osteomalacia into malignancy

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Key Clinical Message

Tumor-induced osteomalacia is a paraneoplastic syndrome characterized by renal phosphate wasting and deranged bone turnover. Clinicians should consider tumor-induced osteomalacia in unexplained hypophosphatemia and investigate for underlying tumors.

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 present the case of a 56-year-old individual who experienced a protracted 6-year clinical course characterized by hypophosphatemia, weakness, and kyphosis, alongside the presence of a foot tumor. Subsequently, this lesion displayed malignant behavior and was ultimately 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.

KEYWORDS

case reports, oncogenic osteomalacia, paraneoplastic syndromes, rickets, sarcoma

1 | INTRODUCTION

Tumor-induced osteomalacia (TIO), also known as oncogenic osteomalacia, is a rare paraneoplastic syndrome that was first described by McCance.[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-dyhydroxivitamin D, elevated alkaline phosphatase (ALP), 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.

2 | CASE REPORT

A 56-year-old man with hypertension presented with a 6-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 ALP (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). No fractures were found, and treatment was initiated using vitamin D and phosphate salts. A 24-h 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 workup was initiated. Previous chest x-ray and thoraco-abdominal CT were normal. A whole-body bone scintigraphy with technetium-99 m-hydroxy-methylene-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 3 months, and an exophytic tumor in the same region where the previous imaging studies had revealed abnormal uptake of Tc99-Octreotide (Figure 2). Histopathological analysis with immunohistochemistry of the foot tumor confirmed a diagnosis of high-grade sarcoma with fusiform, epithelioid, and pleomorphic patterns (Figure 3). A new chest CT scan showed multiple nodular lesions in the lungs, which were compatible with metastases. No further workup for confirmation was made due to the appropriate clinical context of a primary malignant tumor and the deteriorated state of the patient. The patient began receiving oncologic treatment with a dose-adjusted AIM (Adriamycin® + Ifosfamide + Mesna) regimen. Unfortunately, he had an adverse clinical course and died within the next 2 months.

3 | 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] FGF-23 in TIO can impact bone mineralization through indirect mechanisms. It has been shown to suppress the production of PTH. This 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 ALP 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

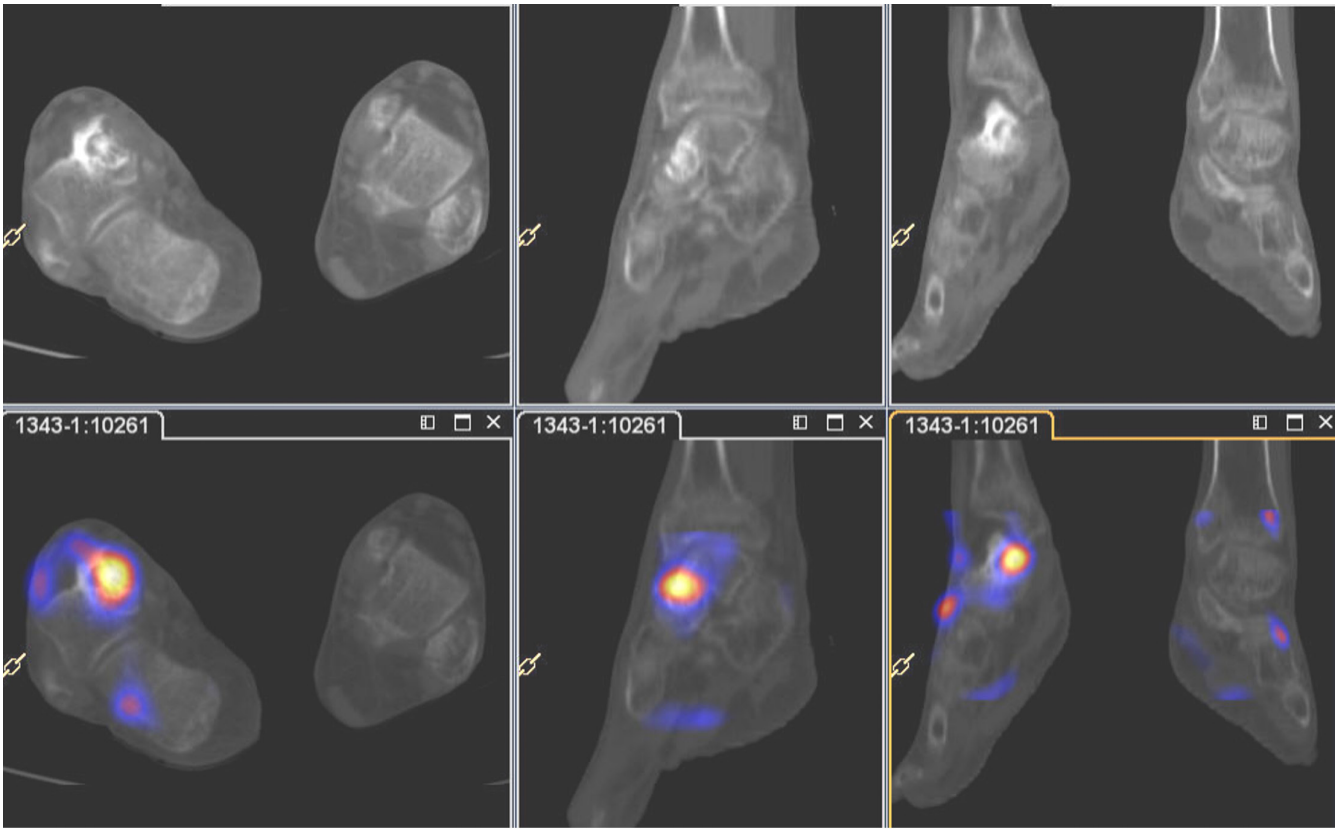

FIGURE 1 SPECT/MR showing a localized lesion in the right astragalus with significantly increased metabolism. SPECT/MR, single photon emission computed tomography/magnetic resonance.

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]

TIO indeed represents a rare and unique disease entity. The rarity of this condition, along with its nonspecific signs and symptoms, results in a diagnostic delay of several years. Systematic reviews estimate this delay to be approximately 4 years, with a wide range spanning from 0.2 to 25 years.[6,12] 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 degree of bone fragility associated with this condition.[13,14] Although it predominantly manifests in middle-aged adults, it bears the potential to present across all age groups without displaying a particular gender predilection.[15,16] 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.[16–18]

While FGF-23 measurement is commonly cited as a means to confirm the diagnosis, it was not feasible in our specific case due to resource limitations in a developing country center. Nevertheless, we established our diagnosis by considering a consistent, chronic, and debilitating clinical presentation, severe hypophosphatemia with a high phosphate excretion rate, inappropriately low levels of 1–25 vitamin D, and a comprehensive exclusion of other potential causes of hypophosphatemia. Additionally, the identification of the tumor through functional imaging with somatostatin receptors, typically in the lower extremities, and histological findings consistent with a mesenchymal tumor, collectively provided a robust basis for diagnosis.[19] Biopsy is not always needed for diagnosis, but in our case, it was performed due to suspicion of malignancy. 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 6 years, the radiologic findings on the

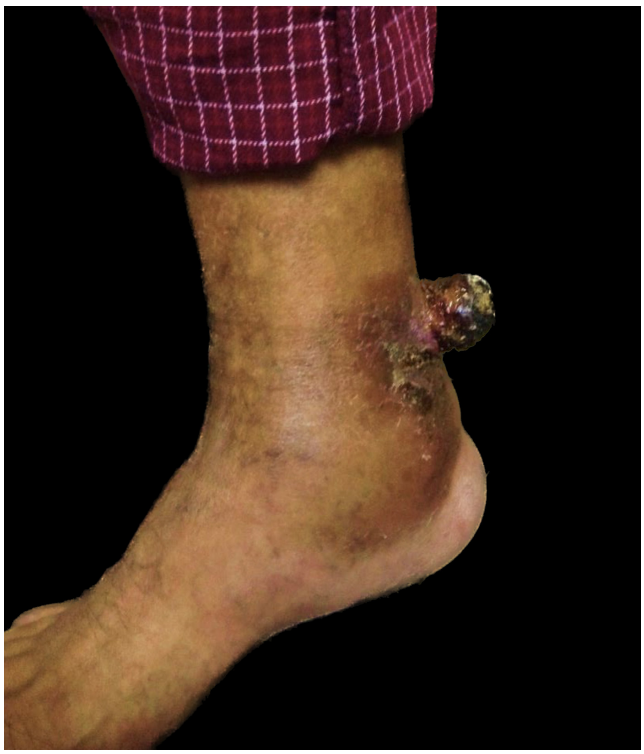

FIGURE 2 Exophytic tumor in the right foot.

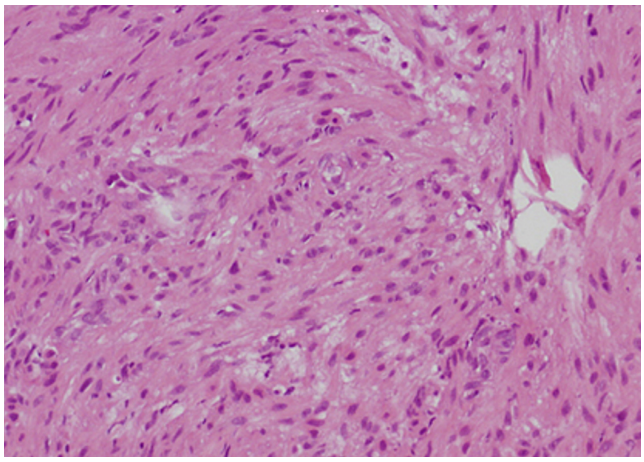

FIGURE 3 H&E. Malignant mesenchymal neoplasm with spindle cell and epithelioid patterns.

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 3-month period, the likelihood of malignant transformation is high.

The optimal treatment approach for TIO is individualized, taking into account the patient-specific circumstances. After a complete tumor resection, there is often a rapid reversal of biochemical abnormalities, with intact FGF23 levels returning to normal within 24 h and serum phosphate typically normalizing within 5 days of post-surgery. However, in cases of persistent or recurrent tumors, repeated diagnostic evaluations and imaging are essential. Medical therapy aims to alleviate symptoms, restore phosphate balance, and normalize ALP and PTH levels. Traditional therapy involving phosphate salts and active vitamin D is widely available and has been commonly used. However, newer options such as burosumab, a monoclonal antibody against FGF23, have shown promise in restoring phosphate homeostasis and improving osteomalacia. It is worth noting that the availability of these treatments may vary across different healthcare facilities and regions, particularly in developing countries such as ours.[19] For inoperable tumors due to location or morbidity risks, radiotherapy or CT-guided radiofrequency ablation are less invasive options supported by case series. Radiotherapy is used for partially resected tumors to prevent recurrence or metastasis. Although no approved alternatives exist for TIO, various approaches have been investigated, including chemotherapy, octreotide, cryoablation, and promising results with the pan-FGFR inhibitor, infigratinib, for metastatic TIO.[20] In our case report, the patient received an AIM regimen as chemotherapy for the suspected malignant neoplasm. It is important to clarify that there is no established treatment for metastatic, unresectable tumors, as was the circumstance in our case.

The presentation of our patient, characterized by the manifestation of a localized mesenchymal tumor in the foot subsequently diagnosed as a high-grade sarcoma 1 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 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.

AUTHOR CONTRIBUTIONS

Jose Malagon-Rangel: Conceptualization; supervision. **Jose Gabriel Solis:** Conceptualization; investigation; writing – original draft. **Luis Fernando Zavala-Jonguitud:** Conceptualization; investigation; writing – original draft. **Martín Roberto Basile-Alvarez:** Conceptualization; writing – review and editing. **Andrea Malagon-Liceaga:** Conceptualization; writing – review and editing.

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Health Investigation, and we hold the informed consent signed by the family of the patient for its publication.

CONFLICT OF INTEREST STATEMENT

We declare that we have no conflict of interest and did not receive funding for the elaboration of the manuscript.

DATA AVAILABILITY STATEMENT

Data sharing not applicable.

CONSENT

Written informed consent was obtained from the patient's next of kin in accordance with the journal's patient consent policy.

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