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Case report

Delayed diagnosis of occult phosphaturic mesenchymal tumor in the foot☆,☆☆,★

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ABSTRACT

Phosphaturic mesenchymal tumors are the main cause of tumor-induced osteomalacia, a distinctive paraneoplastic syndrome mediated by overproduction of fibroblast growth factor 23, that leads to renal phosphate wasting and hypophosphatemia. Diagnosis of this mesenchymal tumors is difficult and usually delayed for several years. We present the case of a 70-years-old-male with generalized bone pain, multiple pathological fractures and persistent hypophosphatemia, diagnosed with tumor-induced osteomalacia after 4 years of the onset of symptoms. The tumor was localized in the forefoot using Gallium 68-DOTANOC positron emission tomography-computed tomography and successfully surgically treated. This case report highlights the importance of recognizing these rare tumors, as early diagnosis can prevent long-term morbidity.

Introduction

Phosphaturic mesenchymal tumors (PMT) have emerged in recent decades as the main cause of the vast majority of cases of tumor-induced osteomalacia, a distinctive paraneoplastic syndrome that manifests as hypophosphatemia, renal phosphate wasting and osteomalacia. Accepted as a single entity in the World Health Organization Classification of Tumors of Soft Tissue and Bone in 2013, PMT are rare, with only about 450 reports in the literature [1]. These mesenchymal tumors are characterized by overproduction of fibroblast growth factor 23 (FGF23), recognized as the principal regulator of phosphate homeostasis and the responsible for tumor-induced osteomalacia [2].

Typically, patients present with bone pain, muscle weakness and pathological fractures. Due to its nonspecific signs and symptoms, rare occurrence and lack of clinical suspicion, PMT diagnosis is usually delayed for several years [3]. In this article, we describe the 4 year journey to diagnosis and the successful surgical treatment of a patient with a forefoot PMT.

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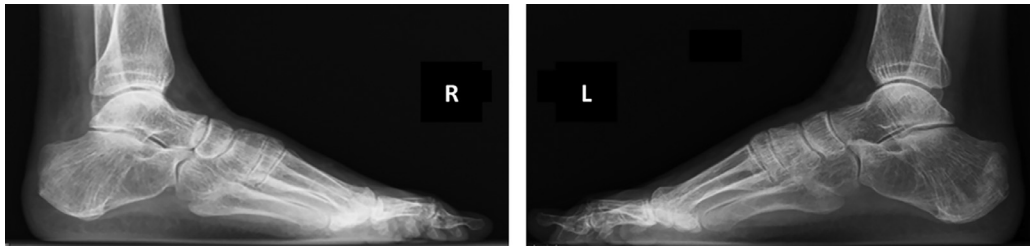

Fig. 1 – Lateral radiographs of right and left foot showing diffuse demineralization.

Case report

A 70-year-old male with a 3-year history of progressive muscle weakness and generalized bone pain was referred to rheumatology department in November 2017. Prior history included hypertension and hypercholesterolemia, but was otherwise unremarkable. The patient reported bilateral hindfoot pain for 3 year, interpreted as Achilles tendinopathy by several physicians. Through those years, the patient gradually developed generalized bone pain, particularly on shoulders, chest and knees, without receiving a definitive diagnosis.

Laboratory investigation (Table 1) documented low serum phosphate (1.2 mg/dL), normal serum calcium (9.0 mg/dL), high serum alkaline phosphatase (267 U/L), high serum parathormone (89pg/mL) and low serum 25-hydroxyvitamin D_3 (22.7 mg/mL). Radiographs of the feet were obtained and showed diffuse demineralization (Fig. 1). Technetium 99 m-hydroxyphosphonate whole-body bone scintigraphy (Fig. 2) revealed multiple areas of increased radioactive isotope uptake, including rib cage, right sacroiliac joint and both calcaneous, in a pattern suggestive of metabolic bone disease. Correlating the hindfoot pain with laboratory and imaging findings, the diagnosis of hypophosphatemic osteomalacia was proposed. The patient was prescribed with phosphate and vitamin D_3 supplementation.

A year later, the patient clinical picture was worse, with concomitant left hip pain and increased difficulty in walking. Serum phosphate level lightly increased (1.6 mg/dL), but hypophosphatemia was maintained (Table 1). Computed tomography (CT) scan of the pelvis (Fig. 3) showed signs of left hip osteoarthritis. A second technetium 99m-hydroxyphospphonate whole-body bone scintigraphy was performed (Fig. 4), revealing significant and aggravated changes, with new increased focal radioactive isotope uptake in both clavicles, rib cage, left sacroiliac joint, left acetabulum and both patellas, in keeping with pathological fractures. Decreased focal radioactive isotope uptake was noted in right sacroiliac joint and both calcaneous.

Suspecting of tumor-induced osteomalacia as the etiology of persistent hypophosphatemic osteomalacia, serum FGF23 was tested and found to be elevated (Table 1). A closer physical examination revealed a firm mass on the plantar region of the right second toe. Gallium 68-DOTANOC positron emission tomography-computed tomography (PET-CT) (Fig. 5) showed a focus of increased activity corresponding to the mass observed on physical examination. No other focus were identified. Subsequent magnetic resonance imaging of the right foot (Fig. 6) revealed an enhancing 21 × 23 × 15 mm nodular lesion in the plantar subcutaneous region of the proximal phalanx of the second toe. Based on those results, the patient was referred to the orthopedics department and submitted to a radical resection with metatarsophalangeal disarticulation of the second toe of the right foot in February 2019.

Histologic examination of the resected tissue showed a cellular area of bland spindle cells and scattered osteoclast-type multinucleated giant cells with an abrupt transition to an area of abundant basophilic matrix. (Fig. 7A). Osteoclast-like giant cells were associated with hemorrhagic foci (Fig. 7B). Nuclear pleomorphism, mitotic figures and necrosis were absent. All surgical resection margins were negative. Immunohistochemistry showed positive expression of vimentin and negative expression of AE1/AE3, S100 protein, CD31, CD34 and EMA. Those findings were consistent with the pathological diagnosis of PMT.

Following the surgical procedure, the patient reported a rapid improvement in symptoms within one month. Biochemical examination at 6 months (Table 1) confirmed the

Table 1 – Laboratory investigation.

Laboratory findings	Presentation	1 y follow up	Postoperative (6 m)	Reference range
Phosphate (mg/dL)	1.2	1.6	4.18	2.5-4.5
Calcium (mg/dL)	9.0	9.0	8.7	8.6-10
Alkaline phosphatase (U/L)	267	191	148	40-130
PTH (pg/mL)	89	64	105	15-65
25-hydroxyvitamin D_3 (ng/mL)	22.7	47.3	56	30-100
C-terminal FGF23 (UA/mL)	-	480	-	<180

PTH ; Parathormone, y; year, m; month.

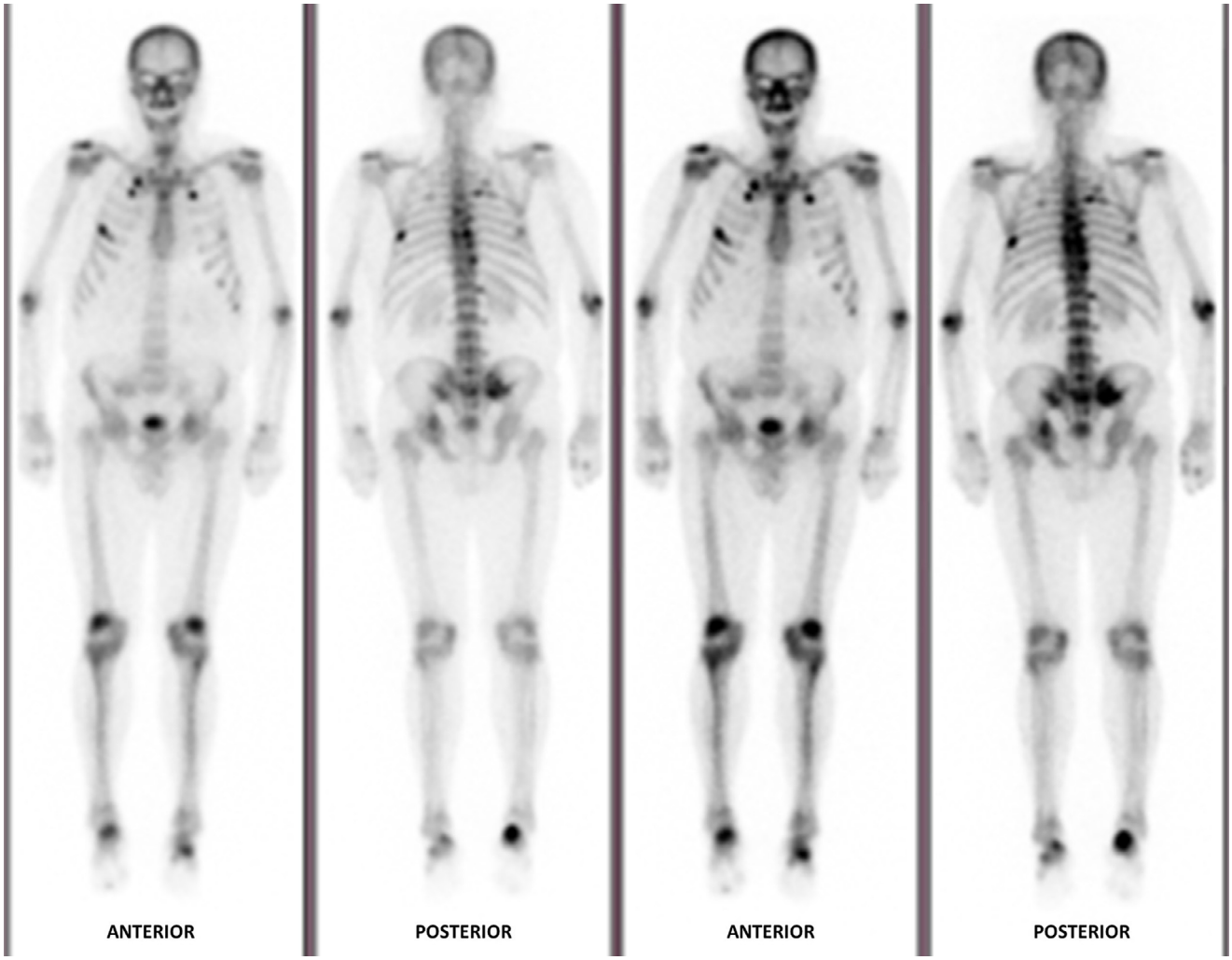

Fig. 2 – Technetium 99m-hydroxydiphosphonate whole-body bone scintigraphy revealing multiple areas of increased uptake, in a pattern suggestive of metabolic bone disease.

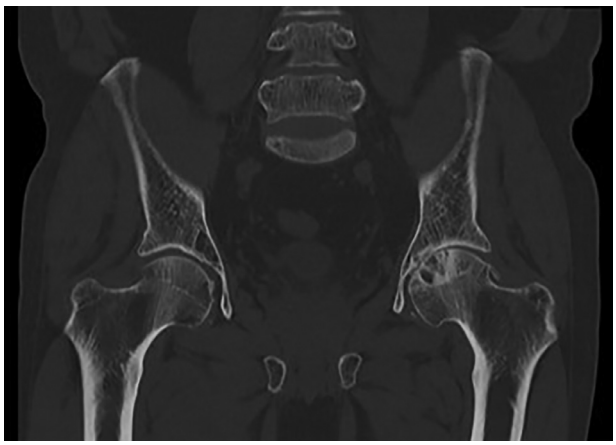

Fig. 3 – Pelvis CT showing left hip osteoarthritis.

successfull surgical treatment and a total left hip arthrosplasty was performed. At 1-year follow up, technetium 99 m-hydroxyphospphonate whole-body bone scintigraphy (Fig. 8) showed a marked improvement of previously seen bone lesions. At the time of this report, the patient remains disease-free for 22 months.

Discussion

PMT are soft tissue or bone tumors currently recognized as the main cause of tumor-induced osteomalacia, through a mechanism mediated by overproduction of FGF23. Under physiological conditions, FGF23 is secreted by osteoblasts and osteocytes and acts at the proximal renal tubule, reducing the expression of sodium phosphate cotransporters and consequently tubular reabsorption of phosphate. Additionally, FGF23 inhibits the expression of 25-hydroxyvitamin D_3 1-alpha-hydroxylase, decreasing the synthesis of 1,25-dihydroxyvitamin D_3 and consequently intestinal absorption of phosphate and calcium. In TIO, overproduction of FGF23 by tumor cells leads to a chronic

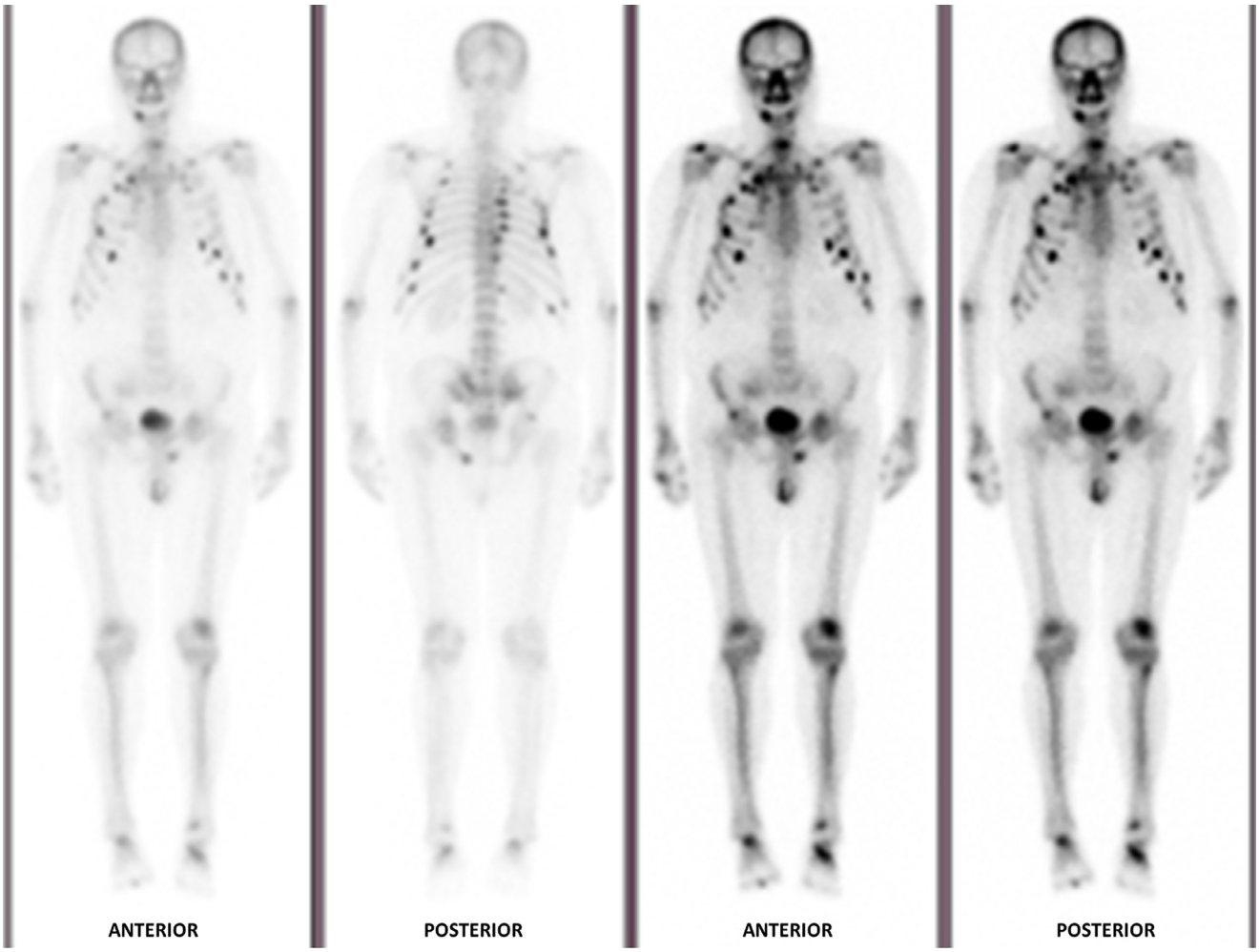

Fig. 4 – Second technetium 99m-hydroxydiphosphonate whole-body bone scintigraphy, a year later, revealing significant and aggravated changes.

hypophosphatemia, resulting in impaired mineralization of bone [4].

Typically, PMT occur in middle-aged adults with no sex preponderance. In most cases, symptoms are not related to the presence of the tumor but are the consequence of severe hypophosphatemia. Tumor-induced osteomalacia clinical manifestations include progressive bone pain, muscle weakness and pathological fractures. The lack of specificity of symptoms leads patients to years of missed diagnoses, misdiagnoses and morbidity [5,6]. Even in recently published case reports, patients still experience a diagnostic delay of 3 year [7,8,9]. Therefore, tumor-induced osteomalacia should be considered in patients with generalized bone pain and persistent hypophosphatemia. Other typical laboratory findings include low tubular phosphate reabsorption, normal serum calcium and parathormone (PTH), low or inappropriately normal serum 1,25-dihydroxyvitamin D_3 and high serum alkaline phosphatase and FGF23. Secondary hyperparathyroidism may occur in response to low serum levels of 1,25-dihydroxyvitamin D_3 [2,4]. Biochemically indistinguishable from genetic causes of FGF23-dependent hypophosphatemia, a negative family history and delayed age at onset are more characteristic of an acquired disorder such as tumor-induced osteomalacia [10].

The definitive diagnosis of tumor-induced osteomalacia is established by identification of the tumor and resolution of the clinical picture following complete resection. Tumor localization can be quite challenging as PMT are small and slow growing tumors located almost anywhere in the body, easily missed by physical examination [2]. Currently, a stepwise approach including functional imaging, followed by anatomical imaging is highly recommended to locate these tumors [11]. In the case presented, the tumor was successfully localized using Gallium 68-DOTANOC PET-CT, a somatostatin-receptor based functional imaging method. PMT express a variety of somatostatin receptors (SSTR 1-5). All the 3 Gallium 68 labeled DOTA-peptides currently available for use, DOTATATE, DOTATOC and DOTANOC, have a higher and and wider affinity for SSTR, resulting in better visualization of somatostatin avid lesions compared to Indium 111-labeled oc-

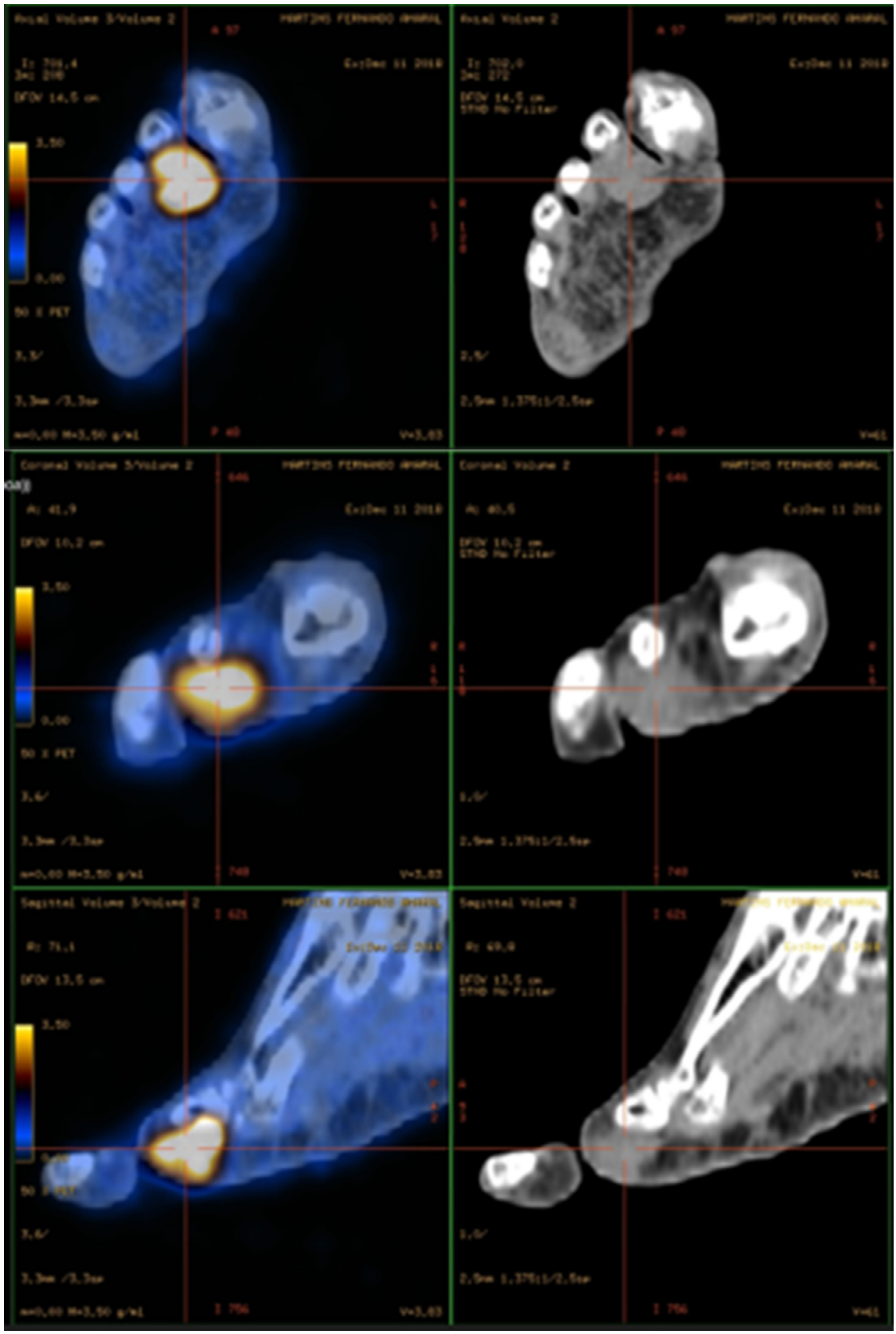

Fig. 5 – Gallium 68-DOTANOC PET-CT showing increased uptake by a soft tissue mass on the plantar region of the right foot, at the level of the second toe.

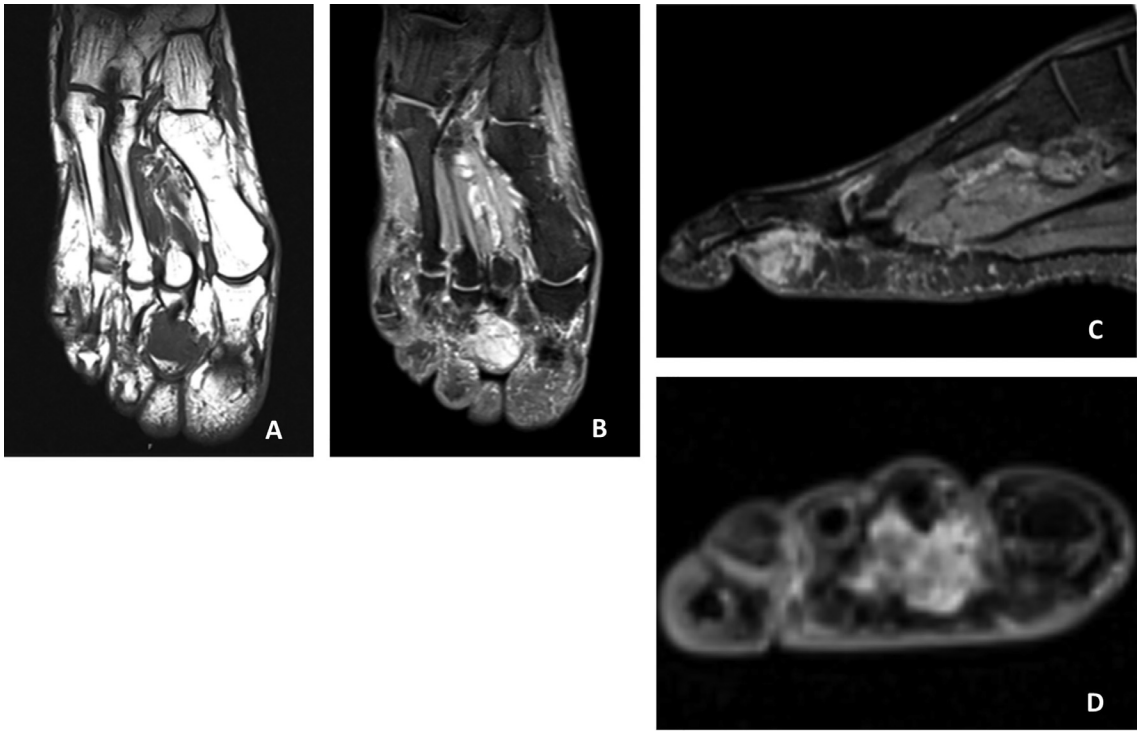

Fig. 6 – MRI of the right foot revealing a nodular lesion in the area identified on functional imaging, hypointense on T1-weighted (A) hyperintense on T2-weighted (B and C) and heterogeneous gadolinium-enhanced (D).

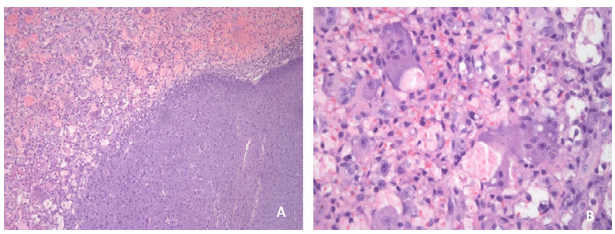

Fig. 7 – Photomicrographs of the resected tissue (hematoxylin and eosin stain). (A) Cellular proliferation of bland spindle cells with scattered osteoclast-type multinucleated giant cells and abundant basophilic matrix (40x). (B) Osteoclast-type multinucleated giant cells associated with hemorrhagic foci (400x).

treotide single-photon emission and computed tomography (SPECT) [12]. Data from a recent systematic review and meta-analysis support the use of Gallium 68 DOTA-peptides PET-CT as first-line imaging study in tumor-induced osteomalacia [13]. Lesions identified on functional imaging require a focused anatomic assessment with CT and/or MRI for preoperative planning. The majority of osseous PMT are osteolytic with a narrow zone of transition on CT. Both bone and soft tissue PMT commonly contain internal matrix and are usually T1 isointense, T2 hyperintense with areas of dark T2 signal and solidly enhancing on MRI [14]. When multiple suspicious lesions are identified by imaging studies or the suspicious lesion is located in an area associated with high surgical morbidity, selective venous sampling with measurement of FGF23 is recommended to confirm the tumor. In cases in which PMT cannot be located, imaging studies should be repeated after 1 year [4].

Complete tumor resection is the standard of care and results in correction of biochemical abnormalities and remineralization of bone. Histological features make the diagnosis of PMT. Typically, these tumors are characterized by a proliferation of bland, spindled to stellate cells, growing in a richly vascularized stroma and surrounded by a “smudgy” basophilic matrix, often with “grungy” calcification. Clusters of osteoclast-like giant cells are commonly present [1]. Although the vast majority of PMT are benign, recurrence is frequent with incomplete excision. Alternative therapies for unresectable tumors include radiotherapy, cryoablation and radiofrequency ablation. In cases where the tumor cannot be located or complete resection is not possible, medical treatment is indicated. A standard regimen includes 15-60 mg/kg/day of phosphate supplements divided into 4-6 doses in combination with 15-60 mg/kg/day of calcitriol divided into 2-3 doses to target a low-to-normal serum phosphate level. To monitor dosing and assess complications of treatment, serum levels of calcium, phosphate, PTH and urinary calcium should be checked every 3-6 months [2,4].

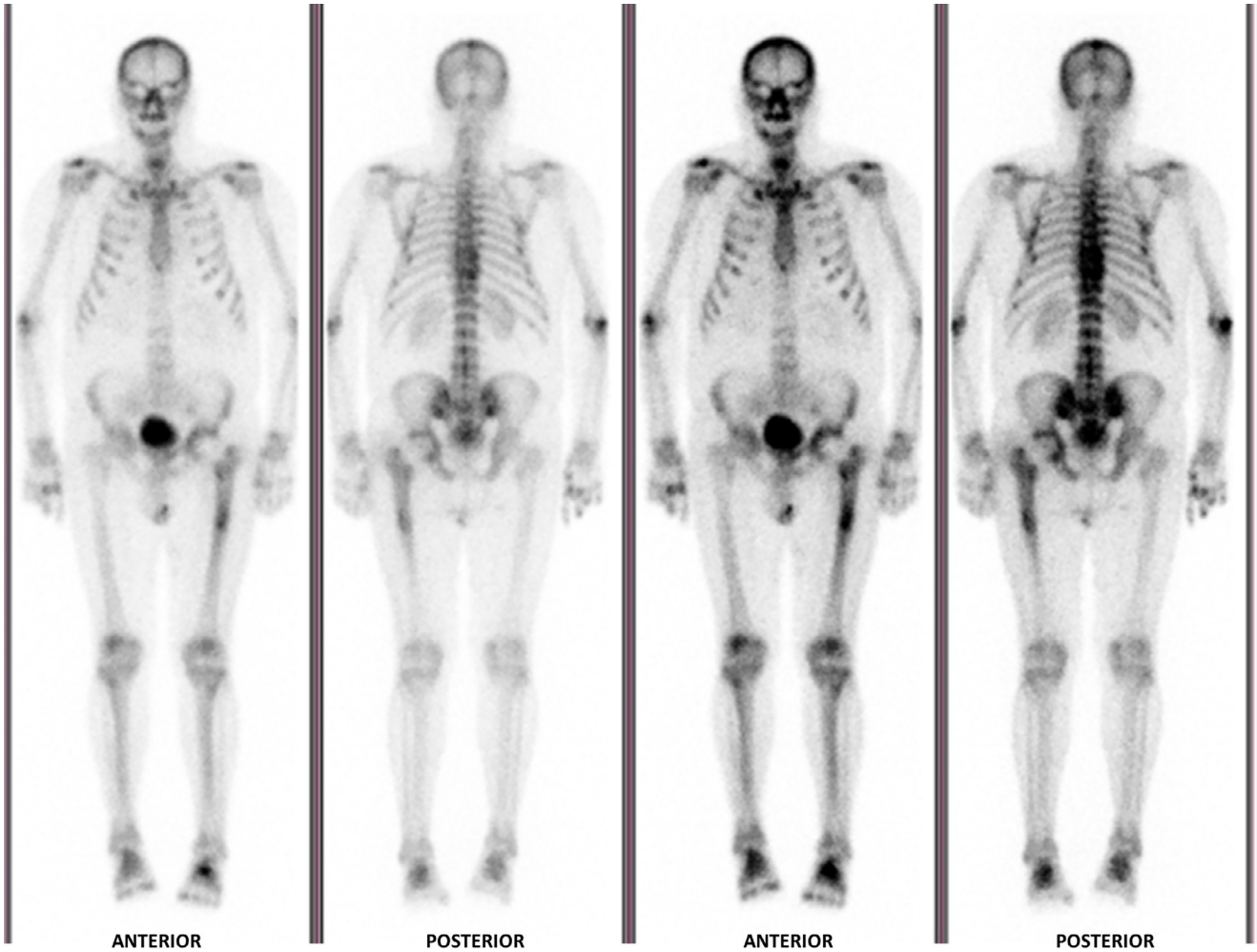

Fig. 8 – 1-year follow up technetium 99m-hydroxydiphosphonate whole-body bone scintigraphy showing a marked improvement.

Conclusion

Tumor-induced osteomalacia should be highly suspected in patients with persistent hypophosphatemic osteomalacia. Once considered, tumor localization is essential to perform a potentially curative surgery and a stepwise approach with functional and anatomical imaging is highly recommended. We believe that this case report may contributes to more awareness of this rare condition, as early diagnosis can prevent long-term morbidity.

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