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ORIGINAL ARTICLE

Tumor-induced osteomalacia: experience from a South American academic center

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Abstract
Summary The majority of tumor-induced osteomalacia cases have been reported in the Northern Hemisphere and Asia. In this first series of South American patients, we show that the clinical presentation and sensitivity of plasmatic fibroblast growth factor 23 and somatostatin analog-based imaging are similar to those described in other populations.
Introduction Describe the experience of clinical presentation, diagnostic study, and treatment of patients with tumor-induced osteomalacia (TIO) in a South American academic center in comparison to literature.
Methods Analysis of the records of patients diagnosed with TIO. The clinical presentation, diagnostic studies, and treatment were analyzed. Fibroblast growth factor 23 (FGF23) was measured by ELISA.
Results Six patients were diagnosed with TIO during the studied period. The patients' median age was 53 years (range 22–64). All patients presented with weakness and pain in the extremities. Four experienced fractures during their evolution. The median time to diagnosis was 4.5 years (1–20). Biochemical studies showed hypophosphatemia, median of 1.4 mg/dL (1.2–1.6), with low maximum rates of tubular reabsorption of phosphate adjusted for glomerular filtration rate. FGF23 was elevated in 4/6 patients and inappropriately normal in the other two. In three patients, the location of the tumor was clinically evident and confirmed with anatomical imaging. In the remaining patients, two tumors were located with ^{68}Ga DOTATATE-PET/CT and one with OctreoScan. The causal tumors were located in the lower extremities in five patients and invading the frontal sinus in one patient. In all patients, tumors were successfully removed. Within 14 days, there was normalization of phosphate and FGF23 levels and resolution of clinical symptoms in all patients. In all cases, the histopathology was compatible with a phosphaturic mesenchymal tumor.
Conclusions The clinical presentation, delay time to diagnosis, FGF23 diagnostic sensitivity and histopathology in this first series of South American patients is similar to those described in other populations. The success of localization by somatostatin analog-based imaging, suggests this may the optimal imaging modality.

Keywords ^{68}Ga PET/CT · FGF23 · Hypophosphatemia · Osteomalacia · Tumor-induced osteomalacia

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Introduction

Tumor-induced osteomalacia tumor (TIO) is a rare paraneoplastic syndrome characterized by hypophosphatemia

Table 1 Demographic data and clinical presentation of TIO patients

Patients	1	2	3	4	5	6
Gender F (female)/M (male)	F	M	M	F	M	F
Age	60	46	22	64	42	62
Clinical presentation	Bone pain/muscular weakness	Bone pain/postration	Bone pain/muscular weakness	Bone pain/extrapiramidal Syndrome	Myopathy/nasal obstruction	Bone pain/muscular weakness
Fractures	Multiple	Multiple	No	Multiple	No	Multiple
Time to diagnosis (years)	20	6	1	3	6	1
Phosphatemia (2.6–4.5 mg/dL)	1.5	1.5	1.4	1.2	1.6	1.4
Calcemia (8.5–10.5 mg/dL)	9	9.2	9.2	9.4	9.2	9.9
Alkaline phosphatase (45–115 U/L)	206	307	422	612	340	357
TmP/GFR (2.8–4.2 mg/dL)	0.75	0.35	0.7	1.14	1.25	0.9
1.25 $(OH)_2$ vitamin D (18–64 pg/mL)	12	NA	< 8	NA	NA	NA
PTH (15–65 pg/mL)	51	NA	48	42	93.3	62
FGF23	364 (<180 RU/mL)	101 (<180 RU/mL)	50 (<180 RU/mL)	114 (8–54 pg/mL)	75.9 (8–54 pg/mL)	150.3 (8–54 pg/mL)

Normal values are enclosed in parentheses

NA Not available

Table 2 Characteristics of the TIO-inducing tumors and post-resection evolution

Patient	1	2	3	4	5	6
Clinical evident tumor	No	No	Yes	Yes	Yes	NO
Imaging	OctreoScan	^{68}Ga DOTATATE-PET/CT	MR	Ultrasound	MR	^{68}Ga DOTATATE-PET/CT
Localization	Right gluteus	Right thigh	Right big toe	Right foot	Nasofrontal sinus	Right thigh
Size (cm)	4 × 2	1	3 × 2	2	8 × 4	2.7 × 1.8
Histology	Phosphaturic mesenchymal tumor	Phosphaturic mesenchymal tumor	Phosphaturic mesenchymal tumor	Phosphaturic mesenchymal tumor	Phosphaturic mesenchymal tumor	Phosphaturic mesenchymal tumor
Post-surgery phosphatemia (2.6–4.5 mg/dL)	2.8	3.3	2.9	2.5	3.3	3.3
FGF23 post-surgery	131 (<180 RU/mL)	NA	NA	6.5 (8–54 pg/mL)	8.4 (8–54 pg/mL)	8.5 (8–54 pg/mL)

Normal values are enclosed in parentheses

NA Not available

secondary to isolated renal phosphate loss and decreased or inappropriately low serum levels of $1,25(OH)_2$-vitamin D. TIO is caused by tumoral secretion of fibroblast growth factor 23 (FGF23) that can be elevated or inappropiately normal [1, 2]. FGF23 acts on proximal tubular renal cells by binding to FGF receptor subtypes, requiring the activation of its co-receptor by Klotho. Its effect is to reduce expression of the sodium-phosphate cotransporters (NaPi-2a and NaPi-2c) in the proximal renal tubule, leading to decreased renal phosphate reabsorption [1, 3–5]. In addition, FGF23 inhibits expression of 25-hydroxyvitamin D3 1-alpha-hydroxylase, resulting in inadequate production of $1,25\text{-}OH_2$-vitamin D, which is necessary for optimal enteral calcium and phosphate absorption. Enzyme-linked immunosorbent assay (ELISA) has been developed to measure FGF23 in the plasma, which recognizes intact FGF23 or its carboxy-terminal fragment [6].

Locating the causal tumor is of great importance given that complete surgical removal is curative. Most often, they are benign mesenchymal tumors located in the head or extremities and not detectable on physical examination, necessitating a search employing one or more imaging techniques [1, 2, 7]. Different modalities have been used, including computerized tomography (CT), magnetic resonance (MR), PET/CT with F18-fluorodeoxyglucose (PET-CT FDG18), and scintigraphic studies, such as with the OctreoScan, given that these tumors often express somatostatin receptors [8, 9]. In recent years, literature has shown that better diagnostic performance can be obtained with PET/CT using somatostatin analogs marked with ^{68}Ga to improve spatial resolution [2, 10–15].

Around 400 cases of TIO have been described in the literature, with the vast majority reported in the Northern Hemisphere and Asia [1, 2, 7]. Only isolated cases have been reported in South America [16–20]. To the best of our knowledge, this is the first published case series of South American TIO patients originating from a single academic center available in the literature.

In this article, we report six patients with TIO, all cured following the removal of the causal tumor. The objective is to describe the experience of clinical presentation, diagnostic study, and treatment of patients with TIO in a South American academic center in comparison to the available literature.

Patients and methods

A retrospective review was made of registered patients diagnosed with TIO between January, 1999, and May, 2016, at the Clinical Hospital of the Pontificia Universidad Católica in Santiago, Chile. All cases included demographic data, clinical presentation, biochemical analysis, including calcemia, phosphatemia, parathyroid hormone (PTH), phosphaturia and TmP/GFR (maximum tubular reabsorption of

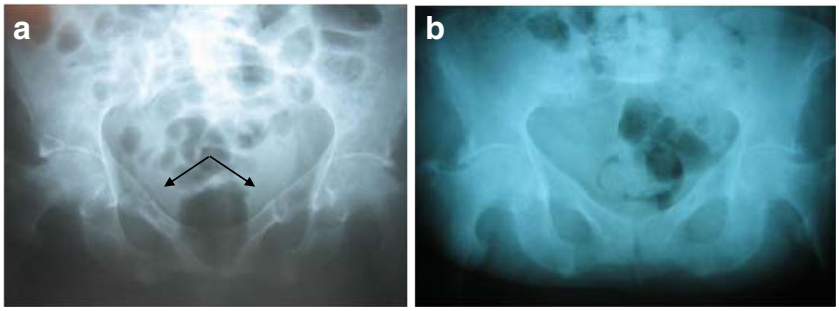

Fig. 1 **a** X-ray of the pelvis showing a bilateral iliopubic branch fracture and **b** consolidation after treatment (patient 1)

phosphorous adjusted for glomerular filtration rate), tumor-localizing studies, surgical findings, and post-operative clinical and biochemical course. All patients gave consent for their images and data to be reported.

The diagnosis of TIO was based on the presence of a compatible clinical presentation associated with acquired PTH-independent hypophosphatemia associated with a low TmP/GFR, having ruled out global renal tubular dysfunction.

Following biochemical confirmation of TIO, FGF23 plasmatic levels were measured and patients began receiving oral phosphate supplements and 0.25 to 1 mcg/day of calcitriol as necessary. A search was conducted to determine the location of the causal tumor. If the tumor was clinically evident on physical examination, directed images were obtained (CT, MR, or ultrasonography) to adequately characterize the lesion. If the tumor was not clinically evident, nuclear imaging studies with somatostatin analogues were used to locate the tumor (OctreoScan or PET/CT). After localization, the identified tumor was resected with wide margins and follow-up included clinical evaluation, biochemical analysis, and FGF23 determination.

In three cases, FGF23 was measured at Mayo Clinic in Rochester by ELISA targeting the C-terminal (normal value ≤180 RU/mL). In the remaining three cases, intact FGF23 levels were determined by ELISA using the Human Intact FGF-23 ELISA Kit (Immutopics Inc., USA) in a single research laboratory. Absorbance (450 nm) was read with a multimodal reader (GloMax®, Promega Inc., USA). All the samples were processed in duplicate (normal value 8.2–54.3 pg/ml).

Results

Six patients (three women, three men) were diagnosed with TIO during the studied period (Table 1). One patient (case 5) has been reported previously as a clinical case. [21]. The patients' median age was 53 years (range 22–64). All patients presented with weakness and diffuse pain in the extremities. Four experienced multiple fractures during the evolution of their illness (Fig. 1). The pelvis, ribs, and the vertebrae were the most common locations. The median time to diagnosis

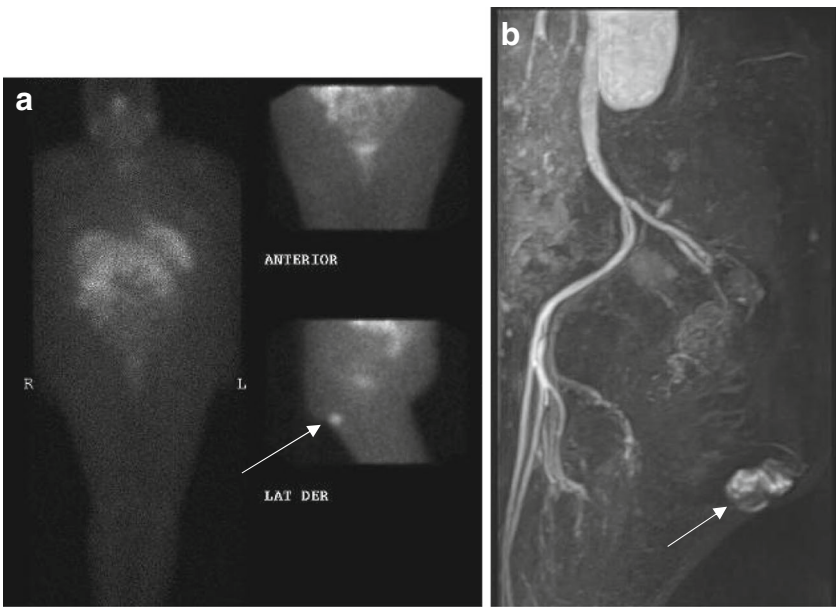

Fig. 2 **a** Octreoscan showing hyperintense lesion in right gluteus and **b** angioMR of lesion in the right gluteus (patient 1)

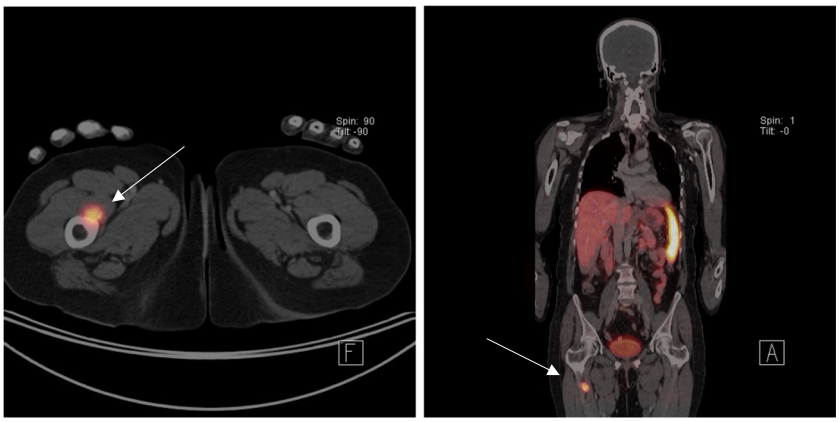

Fig. 3 ^{68}Ga DOTATATE-PET/CT lesion with overexpression of somatostatin receptors at the level of the third proximal of the right thigh (patient 6)

was 4.5 years (1–20). Biochemical studies showed hypophosphatemia, median of 1.4 mg/dl (1.2–1.6, normal 2.6–4.5 mg/dL), with low maximum rates of tubular reabsorption of phosphate adjusted for glomerular filtration rate (TmP/GFR), median of 0.82 mg/dl (0.35–1.25, normal 2.8–4.2 mg/dL). FGF23 was elevated above the reported normal range in 4/6 patients and inappropriately normal in the other two (Table 1). In three patients, the location of the tumor was clinically evident on history and physical examination and confirmed with anatomical imaging (MR, CT, or US). In the remaining patients, one tumor was located with scintigraphy with 111In-Pentetrotide (OctreoScan) (Fig. 2) and two with ^{68}Ga DOTATATE-PET/CT (Fig. 3) (Table 2). The causal tumors were located in the lower extremities in five patients and invaded the nasofrontal sinus in the sixth patient (Fig. 4). In all patients, tumors were successfully removed with wide margins. By the 14th post-operative day, phosphate levels had normalized and clinical symptoms had resolved in all patients. FGF23 levels normalized in all patients in which had been elevated at diagnosis (Table 2). Histopathology of each lesion was compatible with a phosphaturic mesenchymal tumor—mixed connective tissue type. All patients maintained normal phosphatemia and were asymptomatic on a 6-month follow-up period. Representative radiological images of the disease and of the localization studies are shown in Figs. 1–4.

Discussion

We report a series of six cases of TIO, all cured following complete removal of the causal tumor. The six cases have been diagnosed over the last 16 years at our hospital, which is a tertiary academic center, with patients that are referred to us from all over our country. This series reflects the diagnostic difficulties described for this pathology. The latency time to diagnosis, the clinical presentation, and biochemical alterations (phosphatemia and TmP/GFR) were similar to what is described in the series from the Northern Hemisphere and Asia [1, 2, 7]. For example, in three patients the tumors were discovered with very careful and comprehensive history and physical examination. This concurs with descriptions of larger TIO series in which close to half of the reported tumors are not identified on examination [1, 2, 7], necessitating the use of localizing radiologic studies. Because expression of somatostatin receptors has been found in some of these tumors [8, 9], OctreoScan has become one method of searching for tumors

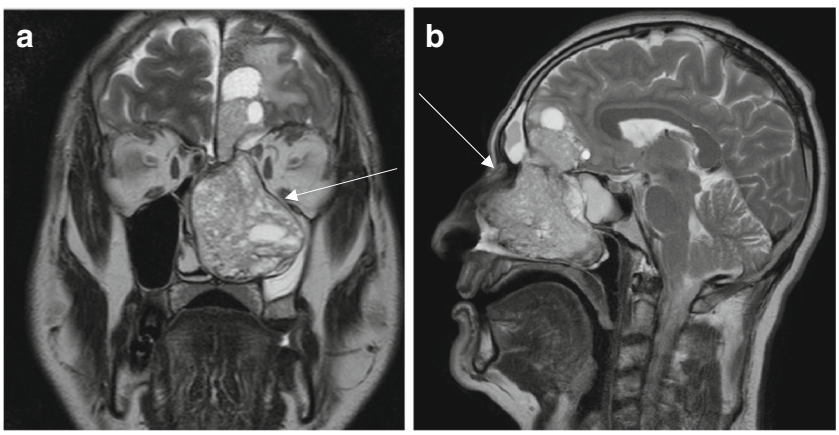

Fig. 4 **a** MR with gadolinium coronal cut and **b** sagittal cut showing a 8 × 4 cm. Mass in the left nasal fossa with extension to the frontal sinus (patient 5)

given the specificity of its results [1, 2, 7, 10]. The use of PET/CT with somatostatin analogs marked with ^{68}Ga (DOTATOC, DOTANOC, or DOTATATE) combine exploration of the complete body with better resolution and specificity with lesions detected in these cases. Literature shows the sensitivity and specificity for locating TIO tumors with these analogues has been estimated at close to 100 and 90% respectively [1, 11, 22]. There are also several reports of tumors successfully localized with PET/CT ^{18}FDG [23–26]; however, the main limitation with this method is low specificity as this modality will identify any hypermetabolic process, such as healing fractures. In a series of nine patients, Jagtap et al. [27] used PET/CT $^{18-}$FDG in eight patients, but the study identified the tumor in only four cases (50%). A recent study demonstrated a greater sensitivity and specificity of ^{68}Ga-DOTATATE-PET/CT compared to those of Octrescan and PET/CT $^{18-}$FDG, suggesting that it may be the best single study for localization of PMTs in TIO [11]. In our series, the three patients that had a clinically occult tumor were localized with somatostatin analog-based imaging, one using OctreoScan and two with ^{68}Ga DOTATATE-PET/CT.

Four of the six patients in our series (66%) had elevated plasma FGF23 levels. The sensitivity of FGF23 measurement is variable according to the ELISA assay used [28]. In a study of 13 patients confirmed with TIO, the sensitivity of intact ELISA FGF23 was 38% (Immutopics) and 100% (Kainos) and 92% for C-terminal fragment (Immutopics) [29]. More than the absolute FGF23 value, it is important to interpret the level in the context of a patient with hypophosphatemia, given that a value in the medium-to-high range of normal is inappropriate in this condition. In addition to FGF23, there are other substances potentially involved in the pathogenesis of this disease including MEPE (matrix extracellular phosphoglycoprotein), FRP4 (protein related to Frizzler), and FGF 7, with some of these possibly contributing to the hypophosphatemia even when FGF23 is in the normal range [1, 3–5].

There are limitations in the present study. It is a retrospective observational study including patients diagnosed over a long period of time, with changing and evolving diagnostic tools and treatment options. Also, with a high probability, there have been other cases evaluated in our institution that have been underdiagnosed for TIO and therefore have not been considered in the data analysis and conclusions of this study. The follow-up period was limited, so we were unable to evaluate late recurrences.

TIO should be suspected in a patient with significant acquired hypophosphatemia secondary to isolated PTH-independent renal phosphate wasting and a frankly low or inappropriately normal 1,25-OH_2-vitamin D. If prior normal phosphorus levels are not documented, a careful family history is indicated to exclude a genetic cause of hypophosphatemic rickets. Search for the causal tumor requires a thorough review of medical history and an exhaustive physical examination. FGF23 measurement, when available, should be included in the diagnostic process [1, 30–32]. If the physical examination is negative, functional testing with ^{68}Ga-DOTATATE-PET/CT is the next best step [11]. In the case that a tumor is not evident after an extensive search with specific imaging methods, whole-body venous tracking has been used to search for the FGF23 gradient. The aim of this technique is to define areas suspected as locations of tumors to proceed with exhaustive imaging studies or directly to surgical exploration. This is a complex technique, with limited accumulated experience centered in few locations globally [1]. In a percentage of cases, it is not possible to find the tumor even with the use of advanced imaging techniques [1, 11, 33]. When functional testing does identify a suspect lesion, targeted imaging (e.g., CT or MRI) along with selective venous sampling of FGF23 may be considered to confirm the pathogenicity of the lesion prior to surgery [1].

In cases where it is impossible to detect and remove the tumor, the medical treatment consists in phosphorous (1–4 g/day) and calcitriol supplements (0.25–3 μg/day) to improve the symptoms, and maintain phosphatemia in the low-normal range. The treatment should be subject to ongoing monitoring in case of complications developing such as secondary hyperparathyroidism, hypercalcemia, hypercalciuria, nephrocalcinosis, and/or nephrolithiasis [1, 33]. Medically induced hypoparathyroidism with the calcimimetic cinacalcet has been reported to decrease phosphaturia and reduce phosphate and calcitriol supplements, suggesting that FGF23 requires the presence of PTH to promote hyperphosphaturia [34]. Monoclonal antibodies against FGF23 are currently being developed. They have been shown to decrease the activity of FGF23 interfering with formation of the FGF23-Klotho-receptor complex, and in animal models have shown biochemical improvements and recovery of bone mineralization and muscular force [35]. These antibodies have been successfully tested in the treatment of X-linked hypophosphatemic rickets [36], which opens a promising line of treatment for patients with inoperable TIO [37].

In summary, the clinical presentation, delay time to diagnosis, FGF23 sensitivity, and histopathology in this first series of South American patients concurs with those of cases in other populations. The success of localization by somatostatin analog-based imaging, suggests this may the optimal imaging modality.

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Compliance of ethical standards

Conflict of interest None.

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