

Exceptional Case

Tumor-induced osteomalacia with normal systemic fibroblast growth factor-23 level

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Abstract

A 38-year-old man presenting with long bone/rib fractures was diagnosed with tumor-induced osteomalacia (TIO) caused by a giant cell tumor in the right foot with normal systemic fibroblast growth factor-23 (FGF23) levels. Multiple imaging modalities done initially and one year later were unable to localize the tumor. New-onset foot pain discovered a right foot mass with resolution of metabolic abnormalities post-surgery. Sampling from both femoral veins showed an elevated FGF23 value on the right side. This case is unique in that the patient had a normal systemic FGF23 level even with severe clinical manifestations of TIO.

Keywords: FGF23; hyperphosphaturia; hypophosphatemia; osteomalacia; TIO

Introduction

Tumor-induced osteomalacia (TIO) is a rare disease, which causes hyperphosphaturia and hypophosphatemia with inappropriately normal or low 1,25-dihydroxyvitamin D. Slow-growing benign mesenchymal or mixed connective tissue tumors are typically responsible for the syndrome, although other histologic types including carcinomas and sarcomas have been associated with it. The clinical manifestations are often profound, and most patients are debilitated by this condition.

TIO is often a diagnostic challenge due to the small size and slow growth of the tumor [1]. The time from the onset of symptoms to diagnosis is usually 2 to 4 years, which can lead to a delay in diagnosis [2]. Once diagnosed, the localization of the tumor may take an average of another additional 5 years [3]. It is important to localize the tumor as resection is curative [4].

TIO is thought to be secondary to overproduction of a phosphaturic agent, and the commonly described and characterized agent is fibroblast growth factor-23 (FGF23) [5]. Most cases of TIO are accompanied by elevated levels of FGF23. Studies have shown that selective venous sampling (SVS) of FGF23 have assisted in tumor localization [6–9]. We report a case of TIO with normal systemic levels of FGF23.

Case report

A 38-year-old man was referred to endocrinology clinic from the emergency department where he presented

with worsening bilateral shoulders, hips, knees and upper and lower back pain with general weakness, fatigue and difficulty with ambulation for past 6 months. His symptoms existed for 2.5 years prior to presentation, and he sought medical consultation as he had no relief from over the counter pain medication.

On examination, the patient had diffuse bony and muscular tenderness. X-rays of the limbs and chest showed diffuse osteopenia with partially healed fracture of the right proximal tibia, old healed fracture in the right fibula and multiple rib fractures. He denied any history of trauma.

Extensive blood work showed a serum phosphorus of 1.4 (2.5–4.5 mg/dL), alkaline phosphatase of 332 (50–120 U/L), 25OH vitamin D was 23 (32–100 mg/mL), 1,25-dihydroxyvitamin D was 29.5 (10–75 pg/mL) and PTH was 61.9 (6.5–65 pg/mL). Serum cortisol, testosterone and thyroid function tests were normal. Tissue transglutaminase and gliadin antibodies were negative. Bone densitometry showed T-scores of –3.9, –3.6 and –1.6 in the lumbar spine, left femoral neck and right femoral neck, respectively urine analysis did not reveal any evidence of Fanconi's syndrome. Urine from a 24-h collection did not show any hypercalciuria (103 mg/24 h); however, the fractional excretion of phosphorus (FeP04) was elevated at 25% (reference value 5–20%), confirming an isolated renal phosphate-wasting syndrome. FGF23 was sent to the Mayo Clinic, and the process of localization was initiated. Computed tomographs (CT) of the neck and chest and positron emission tomograph (PET) scan were unremarkable. Octreoscan revealed uptake in the left pelvic area, which on CT imaging corresponded to a left pelvic kidney. There was no visualized mass, but an inferior pubic rami fracture and

osteopenia in the visualized bones were seen. FGF-23 levels were normal: 86 RU/mL (0–180 RU/mL). A repeat FGF23 level done 3 months later was again normal: 114 RU/mL.

Eight months after presentation, he developed a right proximal ulnar and mid-shaft radial and talar fracture. His weakness was progressive, and he needed a cane for support and ambulation. The patient was started on oral phosphorus and vitamin D supplementation, but he continued to have persistent symptoms minimally ameliorated by analgesics and his phosphorus level remained low ranging from 1.4 to 2.1 mg/dL. Imaging (Octreoscan and PET scan) was repeated 1 year after presentation and again did not localize the tumor. Blood samples for FGF23 drawn from right and left arms were within the normal range: 142 and 155, respectively (0–180 RU/mL). The patient had worsening back pain ~18 months after presentation, and CT chest showed extensive compression deformities in the visualized thoracic and lumbar spine but showed no tumor. The patient was fitted with a Jewitt brace for spine support and progressed to a walker for assistance in ambulation. Bone densitometry, 20 months after the initial bone densitometry, showed worsening T-score at all sites.

On a routine clinic visit, 24 months after presentation, he was noted to be limping more than usual. He complained of increasing pain in the right leg and new onset right foot sole pain. Examination revealed a vague soft tissue prominence in the right anterior plantar area. CT scan of the right foot revealed a lobulated soft tissue density at the plantar aspect, between the right second and third proximal phalanges measuring 1.7×1.6 cm (Figure 1). Serum FGF23 levels from left and right femoral vein were drawn, and surgical excision was arranged. Final pathology showed a giant cell tumor of the tendon sheath measuring 5.0×1.5×0.8 cm (Figure 2). An FGF 23 level from the right femoral vein showed an elevated value of 202 and a normal value of 145 on the left femoral vein (0–180 RU/mL)

One week postsurgery, serum phosphorus level normalized, FePo₄ was 5% and phosphorus supplementation was reduced by 50% and discontinued 3 weeks later. His muscular and bone pains improved by week 2, and he was able to walk without support 3 months later. Repeat DEXA scan done 1 year postsurgery showed improvement in bone density at all sites.

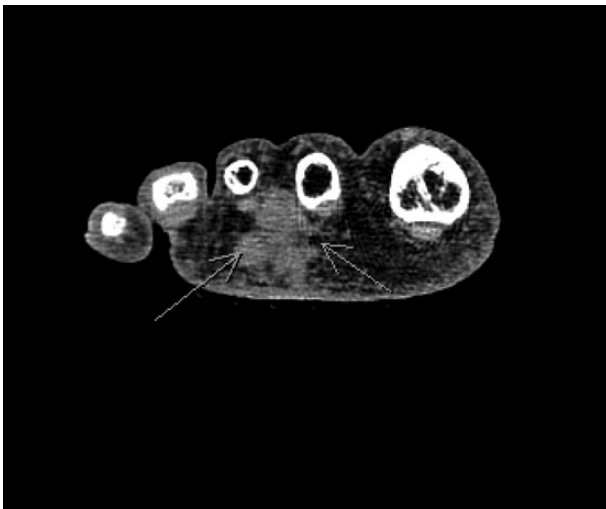


Fig. 1. CT right foot—coronal view. Lobulated soft tissue density, between the second and third proximal phalanges at the plantar aspect of the right foot.

Discussion

TIO shares the same pathophysiology as hypophosphatemic osteomalacia, X-linked hypophosphatemic rickets (XLH) and autosomal dominant hypophosphatemic rickets (ADHR) [10]. In these conditions, there is renal phosphorus loss due to increased plasma levels and activity of FGF23. In XLH, the underlying defect is a mutation in the phosphate-regulating endopeptidase homolog X-linked (PHEX) gene, which encodes an enzyme that regulates FGF23 synthesis and/or degradation. In ADHR, the underlying defect is activating missense mutations in FGF23 gene making FGF23 resistant to proteolysis with resultant increased plasma level. In TIO, there is overproduction of FGF23 by the tumor and this cannot be adequately degraded by PHEX resulting in phosphaturia [11].

FGF23 is a member of a large family of FGFs that are synthesized by osteocytes. It was cloned as a causative factor for TIO in 2001 [5]. Prior to this, it was identified as a responsible agent for ADHR [10]. FGF23 is a phosphaturic hormone that reduces renal phosphate reabsorption by suppressing the expression of type 2a and 2c sodium-phosphate co-transporter in the proximal tubules. It also reduces serum 1,25(OH)₂D by inhibiting 1- α -hydroxylase enzyme. Thus, it reduces serum phosphate by suppressing proximal tubular and intestinal phosphate absorption [12]. Most tumors that over-express FGF23 causing TIO are classified as phosphaturic mesenchymal tumor, and it is not clear why these tumors over express FGF-23 [13].

A search for an underlying tumor should be aggressively pursued in TIO as resection can be curative. Tumors reported to cause TIO are hemangiopericytoma, odontogenic fibromas and giant cell tumor of the tendon sheath. They are commonly found in the craniofacial area and extremities located in variety of soft tissues and skeletal sites. In a case series from China consisting of 39 patients, majority were phosphaturic mesenchymal tumor (27 patients) [14].

Various imaging modalities have been used to localize the responsible tumors. Routine radiographs, ultrasonography, CT, MRI, Whole body 99Tc sestamibi scanning, octreotide scan and 99Tc MIBI SPECT have been used for localization [7, 15, 16]. However, localization may be difficult as most tumors may be small, slow-growing and located in an unusual anatomical site [15]. Delay in diagnosis, with some reports of more than a decade, is not unusual. In our patient, multiple imaging modalities were negative even when repeated after 1 year of follow-up.

Even if a tumor is localized by imaging, or if there are multiple masses in different locations, one cannot be sure which tumor is responsible for increased production of FGF23. Several investigators have reported the clinical utility of selective venous sampling (SVS) for preoperative localization in such cases [6, 8, 17, 18]. This is most useful in subjects with multiple suspicious sites or an anatomically challenging resection [17]. In one study, SVS suggested the region of tumors responsible for the TIO, and a dedicated imaging of the area with the high or highest FGF23 was successful in tumor localization in 8 of 10 patients [6].

Most cases reported in the literature have an elevated level of FGF23. In our patient, FGF23 levels repeated several times were normal over a 1-year period (86, 114, 142 and 155 RU/mL, respectively). Despite this, our suspicion for TIO was high. His ‘normal’ FGF23, when interpreted in light of his serum phosphorus concentration, is

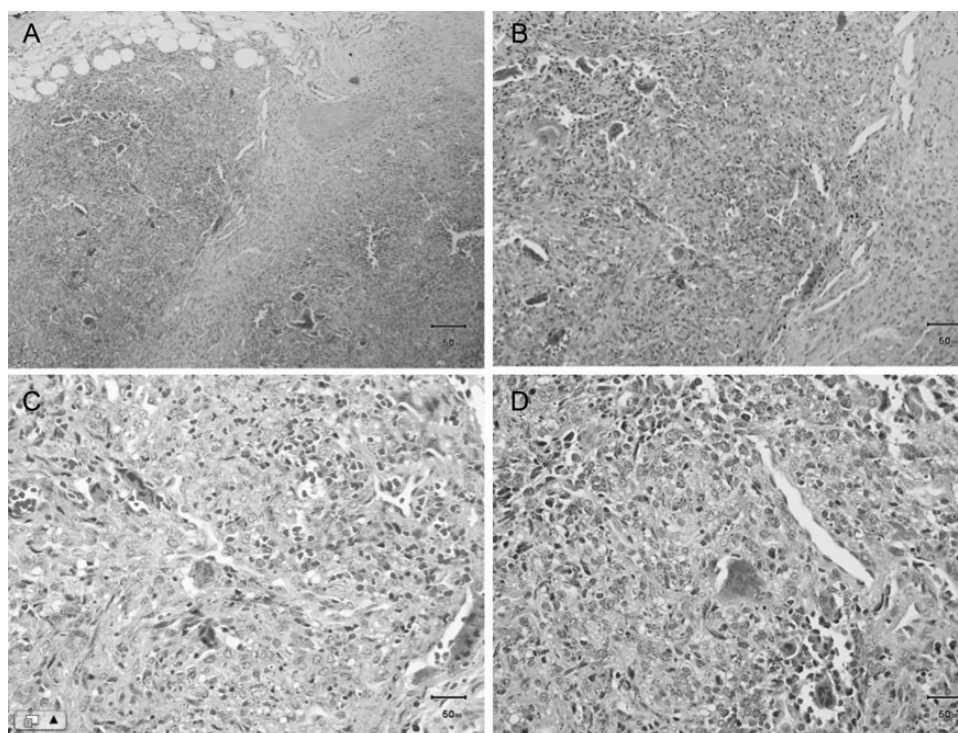


Fig. 2. Giant cell tumor of the tendon sheath (A). Lobulated pattern with fibrous septa, well-circumscribed with hyalinized stroma (B). Mononuclear cells, with small ovoid, spindly, irregular nuclei (C and D). Osteoclast-like giant cells and hemosiderin-laden histiocytes. Hematoxylin-eosin, original magnification $\times 2$ (A), $\times 10$ (B) and $\times 40$ (C and D).

inappropriately normal and should not exclude TIO as the cause of hypophosphatemia. Although we were unable to do a complete SVS for FGF23 in our patient due to technical reasons, we were able to demonstrate a gradient difference between the right and left lower extremity.

This case illustrates the discordance between clinical presentation and diagnostic testing clinicians encounter in clinical problem solving. Despite repeated normal systemic FGF23 levels, we were convinced that this presentation was consistent with TIO rather than an inherited disorder or Fanconi's syndrome. This was proven by the elevated FGF23 in the extremity where the tumor was located and resolution of his signs and symptoms after tumor resection.

Conflict of interest statement. None declared.

References

- Gore MO, Welch BJ, Geng W *et al.* Renal phosphate wasting due to tumor-induced osteomalacia: a frequently delayed diagnosis. *Kidney Int* 2008; 76: 342–347
- Jan de Beur SM, Streefen EA, Civelek AC *et al.* Localisation of mesenchymal tumours by somatostatin receptor imaging. *Lancet* 2002; 359: 761–763
- Jan de Beur SM. Tumor-induced osteomalacia. *JAMA* 2005; 294: 1260–1267
- Furco A, Roger M, Mouchet B *et al.* Osteomalacia cured by surgery. *Eur J Intern Med* 2002; 13: 67–69
- Shimada T, Mizutani S, Muto T *et al.* Cloning and characterization of FGF23 as a causative factor of tumor-induced osteomalacia. *Proc Natl Acad Sci USA* 2001; 98: 6500–6505
- Ito N, Shimizu Y, Suzuki H *et al.* Clinical utility of systemic venous sampling of FGF23 for identifying tumours responsible for tumour-induced osteomalacia. *J Intern Med* 2010; 268: 390–394
- Nasu T, Kurisu S, Matsuno S *et al.* Tumor-induced hypophosphatemic osteomalacia diagnosed by the combinatory procedures of magnetic resonance imaging and venous sampling for FGF23. *Int Med* 2008; 47: 957–961
- Takeuchi Y, Suzuki H, Ogura S *et al.* Venous sampling for fibroblast growth factor-23 confirms preoperative diagnosis of tumor-induced osteomalacia. *J Clin Endocrinol Metab* 2004; 89: 3979–3982
- van Boekel G, Ruinemans-Koerts J, Joosten F *et al.* Tumor producing fibroblast growth factor 23 localized by two-staged venous sampling. *Eur J Endocrinol* 2008; 158: 431–437
- ADHR Consortium. Autosomal dominant hypophosphataemic rickets is associated with mutations in FGF23. *Nat Genet* 2000; 26: 345–348
- de Menezes Filho H, de Castro LC, Damiani D. Hypophosphatemic rickets and osteomalacia. *Arq Bras Endocrinol Metabol* 2006; 50: 802–813
- Fukumoto S, Yamashita T. Fibroblast growth factor 23 in oncogenic osteomalacia and X-linked hypophosphatemia. *N Engl J Med* 2003; 349: 505–506
- Fukumoto S, Yamashita T. FGF23 is a hormone-regulating phosphate metabolism—unique biological characteristics of FGF23. *Bone* 2007; 40: 1190–1195
- Jiang Y, Xia WB, Xing XP *et al.* Tumor-induced osteomalacia: an important cause of adult-onset hypophosphatemic osteomalacia in china: report of 39 cases and review of the literature. *J Bone Miner Res* 2012; 27: 1967–1975
- Khadrghawar R, Singh Y, Kansara S *et al.* PET/CT localisation of a scapular haemangiopericytoma with tumour-induced osteomalacia. *Singapore Med J* 2009; 50: e55–e57

16. Kimizuka T, Ozaki Y, Sumi Y. Usefulness of ^{201}Tl and $^{99\text{m}}\text{Tc}$ MIBI scintigraphy in a case of oncogenic osteomalacia. *Ann Nucl Med* 2004; 18: 63–67
17. Andreopoulou P, Dumitrescu CE, Kelly MH et al. Selective venous catheterization for the localization of phosphaturic mesenchymal tumors. *J Bone Miner Res* 2011; 26: 1295–1302
18. Westerberg PA, Olauson H, Toss G et al. Preoperative tumor localization by means of venous sampling for fibroblast growth factor-23 in a patient with tumor-induced osteomalacia. *Endocr Pract* 2008; 14: 362–367

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