

Contents lists available at [ScienceDirect](#)

AAACE Clinical Case Reports

journal homepage: www.aaaceclinicalcasereports.com

Case Report

Tumor-Induced Osteomalacia Localized and Excised After Pregnancy

Melissa Sum, MD^{1,*}, Syed T. Hoda, MD², Timothy Rapp, MD³, Elcin Zan, MD⁴¹ Department of Medicine, NYU Langone Health, New York, New York² Department of Pathology, NYU Langone Health, New York, New York³ Department of Orthopedic Surgery, NYU Langone Health, New York, New York⁴ Department of Radiology, NYU Langone Health, New York, New York

ARTICLE INFO

Article history:

Received 3 November 2020

Received in revised form

11 June 2021

Accepted 13 June 2021

Available online 18 June 2021

Key words:

tumor-induced osteomalacia

hypophosphatemia

fibroblast growth factor 23

renal phosphate wasting

pregnancy

DOTATATE

ABSTRACT

Objective: Tumor-induced osteomalacia (TIO) is a rare osteomalacia characterized by paraneoplastic secretion of fibroblast growth factor 23. Concomitant occurrence of TIO during pregnancy is rarer still. Our objective was to report a young patient with debilitating fractures diagnosed with TIO who became pregnant and subsequently had her tumor localized by gallium-68 (Ga-68) DOTATATE positron emission tomography/magnetic resonance imaging (PET/MRI).

Case Report: A 28-year-old woman with a 2-year history of stress fractures was found to have the following: (1) alkaline phosphatase level, 220 (reference range, 30–95) U/L; (2) phosphorus level, 2.1 (2.5–5.0) mg/dL; (3) 1,25-dihydroxyvitamin D3 level, <8 (18–72) pg/mL; (4) 24-hour urine phosphorus level, 0.5 (0.3–1.3) g; and (5) fibroblast growth factor 23 levels, 1241 (reference range, <180) RU/mL. The patient became pregnant, and at term, a cesarean delivery was performed. Ga-68 DOTATATE PET/MRI showed a 9-mm intracortical mass in the right fibular head and right femoral and bilateral calcaneal stress fractures. The fibular lesion was resected; pathology showed a 1.5-cm lesion with positive fibroblast growth factor receptor 1 staining.

Discussion: This patient with TIO had an uneventful pregnancy and delivery. TIO is typically caused by benign mesenchymal tumors. Ga-68 DOTATATE PET/computed tomography has been used for localizing tumors causing TIO, yet MRI has superior contrast resolution over computed tomography. Therefore, it is not surprising that Ga-68 PET/MRI successfully localized this patient's tumor to the intracortical space of the fibular head and distinguished it from insufficiency fractures.

Conclusion: To our knowledge, this is the first report of phosphate treatment in a pregnant patient with TIO and the first report of a tumor-inducing TIO being localized by Ga-68 DOTATATE PET/MRI.

© 2021 AAACE. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Introduction

Tumor-induced osteomalacia (TIO) is a rare debilitating osteomalacia characterized by the paraneoplastic secretion of serum fibroblast growth factor 23 (FGF23) leading to renal phosphate wasting, low 1,25-dihydroxyvitamin D3 (1,25[OH]2D3) levels, and hypophosphatemia.¹ Benign mesenchymal tumors are the typical cause of TIO; the tumors can be anywhere in the body and may be

difficult to locate.² We present a case of a young woman with clinical debilitation and fractures diagnosed with TIO who became pregnant and subsequently had a mesenchymal tumor localized by gallium-68 (Ga-68) DOTATATE positron emission tomography/magnetic resonance imaging (PET/MRI) and excised.

Case Report

A 28-year-old woman with a 2-year history of hip pain presented to our endocrine clinic. The records and patient indicate that 2 years previously, she fell and developed left hip pain. Several months later, another fall led to severe hip pain and a visit to the emergency department. Imaging showed stress fractures of a left rib, left sacrum, and left femoral neck. Blood tests showed an alkaline phosphatase (ALP) level of 220 U/L (reference range, 30–95 U/L), phosphorus level of 2.1 mg/dL (2.5–5.0 mg/dL), creatinine level of 0.56 mg/dL (0.7–1.3 mg/dL), and 25-OH vitamin D level of 14.80

Abbreviations: ALP, alkaline phosphatase; FGF23, fibroblast growth factor 23; Ga-68, gallium-68; iFGF23, intact fibroblast growth factor 23; MRI, magnetic resonance imaging; PET, positron emission tomography; PTH, parathyroid hormone; SUV, standard uptake value; TIO, tumor-induced osteomalacia; TmP/GFR, tubular maximum reabsorption of phosphate per unit of glomerular filtration; 1,25[OH]2D3, 1,25-dihydroxyvitamin D3.

* Address correspondence to Dr Melissa Sum, MD, Department of Medicine, NYU Langone Health, 550 1st Avenue, New York, NY 10016.

E-mail address: melissa.sum@nyulangone.org (M. Sum).

<https://doi.org/10.1016/j.aaace.2021.06.008>

2376-0605/© 2021 AAACE. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

ng/mL (30–95 ng/mL). Outpatient endocrine workup showed the following: (1) 1,25[OH]2D3 level, <8 pg/mL (18–72 pg/mL); (2) calcium level, 9.3 mg/dL (8.2–10 mg/dL); (3) albumin level, 4.28 g/dL (3.5–5.70 g/dL); (4) parathyroid hormone (PTH) level, 37.9 pg/mL (15.0–65.0 pg/mL); (5) ferritin level, 16.9 ng/mL (5–204 ng/mL); (6) 24-hour urine phosphorus level, 0.5 g (0.3–1.3 g); (7) urine creatinine level, 0.9 g/24h (1–2g/24h); (8) thyroid-stimulating hormone level, 2.54 mIU/L (0.35–4.70 mIU/L); and (9) FGF23 level, 1241 RU/mL (<180 RU/mL). Imaging showed low bone density for age with Z-scores: (1) lumbar region, -2.5; (2) femoral neck, -1.9; and (3) a negative octreotide scan. She was treated with calcitriol and phosphate repletion and then underwent percutaneous pinning of the femoral neck. Soon after, she became pregnant. During pregnancy, her laboratory parameters were monitored on her phosphate and calcitriol regimen. Per outside clinical summaries, she underwent a genetic evaluation that did not reveal any genetic cause for hypophosphatemia including X-linked hypophosphatemia. Her family history was negative for bone disorders. At term, she underwent a scheduled cesarean delivery to avoid the trauma of pushing and delivered a healthy female infant. Meanwhile, she continued to have significant bilateral hip, knee, and ankle pain that rendered her disabled and caused her to relocate from another state into an urban housing project for familial support.

Upon presentation to our endocrine clinic, her examination was notable for slow gait, limp, and lumbar tenderness. The patient reported that her physicians were concerned about TIO but could not localize a tumor. She was on calcitriol 0.5 mcg daily and 500 mg of elemental phosphorous twice daily. Blood tests were significant for the following: (1) ALP level, 204 U/L (30–101 U/L); (2) phosphorus level, 1.6 mg/dL (2.3–4.7 mg/dL); (3) 25-OH vitamin D level, 32 ng/mL (30–80 ng/mL); (4) 1,25[OH]2D3 level, 32.4 pg/mL (19.9–79.3 pg/mL); (5) calcium level, 9 mg/dL (8.5–10.4 mg/dL); (6) albumin level, 4.2 g/dL (3.5–5.2 g/dL); and (7) PTH level, 74 pg/mL (24–86 pg/mL). Her phosphate supplement was increased to 3 times daily with improvement in the phosphorus level to 2.3 mg/dL. She was referred for Ga-68 DOTATATE PET/MRI that showed a 9 × 8-mm intracortical mass in the anterolateral right fibular head (Fig. 1 A) with a DOTATATE avidity standard uptake value (SUV) of 65 (Fig. 1 B). Additionally, a right femoral neck stress fracture with an SUV of 5.6 and bilateral calcaneal stress fractures with an SUV of 4 were noted. She underwent open reduction and internal fixation of the right femoral neck and radical resection of the right proximal fibula. Pathology showed a 1.5-cm well-circumscribed lesion (Fig. 2) comprised of a vascular-rich proliferation with spindle cell features (Fig. 3) located 1.5 cm from the uninvolved resected edge with positive FGFR1 immunohistochemistry staining consistent with a phosphaturic mesenchymal tumor (Fig. 4). Four weeks later, her laboratory results showed the following: (1) FGF23 level, 264 RU/mL (reference range, <180 RU/mL); (2) ALP level, 156 U/L; and (3) phosphorus level, 6 mg/dL. She reported feeling well and ambulating easily. Her supplements were stopped with the plan to repeat laboratory tests. Due to personal circumstances and the COVID-19 pandemic, she returned to the laboratory nearly 1 year later with a phosphorus level of 3.6 mg/dL off all supplements. Additional laboratory results showed an FGF23 level of 536 RU/mL (reference range, <180 RU/mL) and a PTH level of 62 pg/mL. Notation indicated that the Quidel Corporation C-terminal FGF23 assay being used would no longer be available with a recommendation to use the intact FGF23 (iFGF23) and that iFGF23 concentrations are not affected by iron deficiency, which can lead to false-positive results on the current assay. The patient's repeat laboratory results showed the following: (1) iFGF23 level, 18 pg/mL (<59 pg/mL); (2) phosphorus level, 3.5 mg/dL; (3) iron deficiency with a ferritin level of <2 ng/

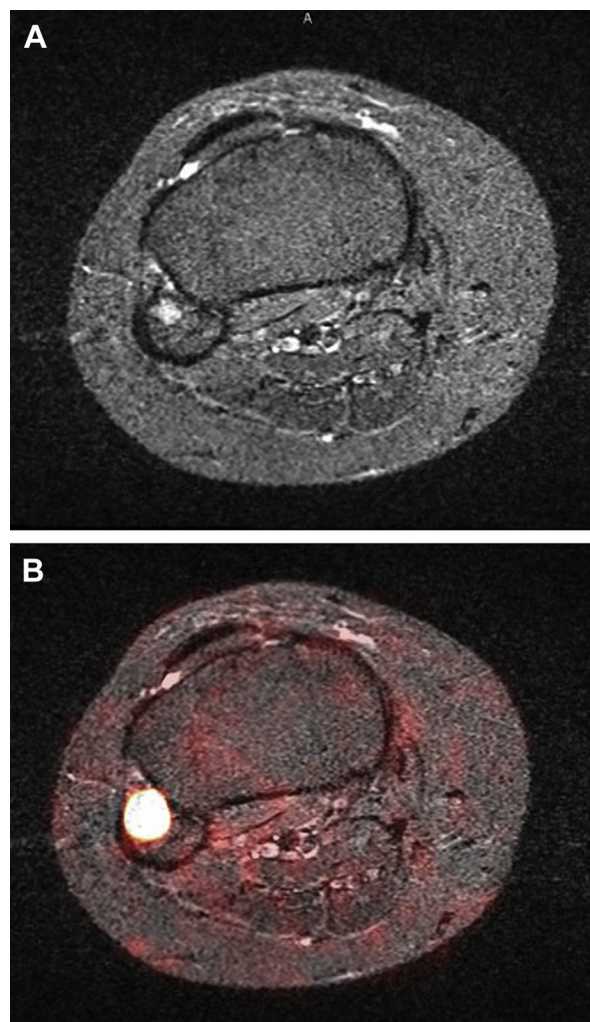


Fig. 1. A, Intracortical lesion at the right fibular head delineated with magnetic resonance imaging. B, Intracortical lesion at the right fibular head with a DOTATATE standard uptake value of 65.

mL (5–204ng/mL); (4) 25-OH vitamin D level, 25.9 ng/mL; and (5) 1,25[OH]2D3 level, 77.9 pg/mL. The patient was relieved to be feeling well with documented normal iFGF23.

Discussion

To our knowledge, this is the first report of phosphate treatment in a pregnant patient with TIO and the first report of TIO localized by Ga-68 DOTATATE PET/MRI. The patient experienced rapid clinical deterioration within a year from asymptomatic to disabled. Her laboratory results showed low phosphorus, low 1,25[OH]2D3, and elevated FGF23 levels; Ga-68 DOTATATE PET/MRI localized a 9-mm fibular lesion; and resection of the mass led to the resolution of symptoms and normalization of her laboratory results.

TIO is a rare paraneoplastic syndrome typically caused by benign mesenchymal tumors that secrete FGF23.³ FGF23 inhibits sodium-phosphate cotransporters 2a and 2c in the renal proximal tubules, resulting in urinary phosphate wasting,⁴ inhibits CYP27B1 that makes 1,25[OH]2D3 and stimulates CYP24A1 that degrades 1,25[OH]2D3, leading to the inappropriately low 1,25[OH]2D3 level in the setting of hypophosphatemia. Clinically, patients can present with multiple fractures and debilitation. TIO should be suspected in patients with consistent symptoms and hypophosphatemia, at

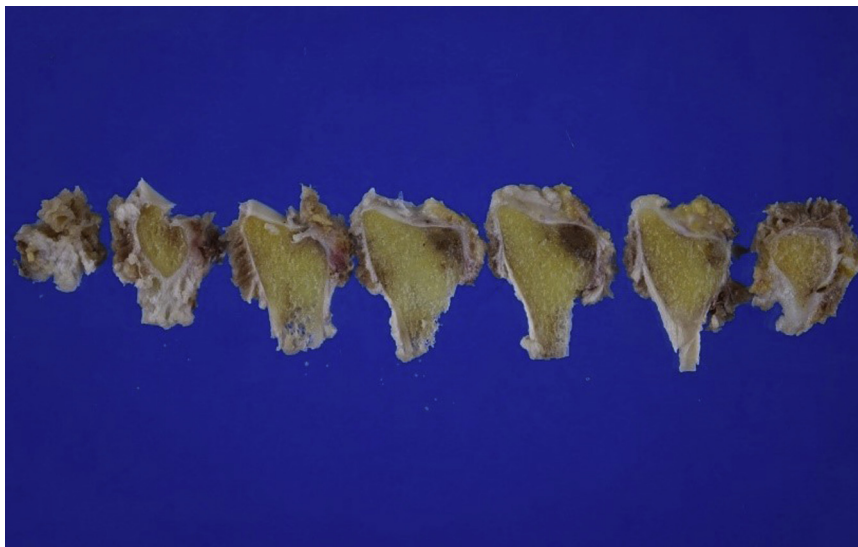


Fig. 2. Circumscribed 1.5-cm area of the fibular head involved by lesion exhibited by darkened tissue.

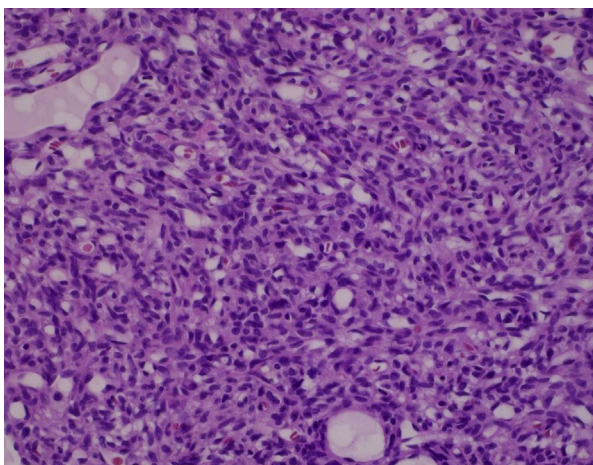


Fig. 3. Hematoxylin and eosin staining, high power (20 ×) of a vascular-rich spindle cell tumor with no significant atypia.

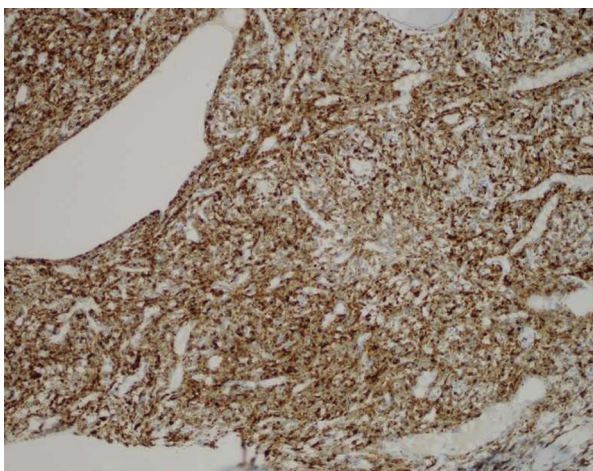


Fig. 4. Dark, diffuse positive brown immunohistochemistry staining for FGFR1.

which point the presence of renal phosphate wasting should be confirmed. Additional supportive laboratory results include normal calcium and PTH levels, low or inappropriately normal 1,25[OH] 2D3 levels, and elevated FGF23 levels. Upon diagnosing an FGF23-dependent phosphate wasting disorder, a thorough history or genetic testing can exclude genetic causes such as X-linked hypophosphatemia, and subsequently, tumor localization should occur.

Indeed, our patient exhibited clinical debilitation and hypophosphatemia. The ideal way to prove renal phosphaturia requires an assessment of the tubular maximum reabsorption of phosphate per unit of glomerular filtration (TmP/GFR) using a simultaneous collection of fasting second-morning void urine and blood.⁵ A TmP/GFR was not available in our patient, yet her fractional excretion of phosphate was 14.8%, higher than the 5% threshold and indicative of inappropriate phosphaturia. In future instances, we suggest the calculation of TmP/GFR. Our patient’s elevated FGF23 level indicated that she had an FGF23-dependent phosphate wasting disorder, and her negative family history and negative genetic evaluation heightened the suspicion for TIO.

Studies indicate that Ga-68 DOTATATE PET/computed tomography (CT) is useful for localizing TIO.⁶ In a recent review article, Rayamajhi et al⁷ note that PET/MRI would likely be superior to PET/CT because of MRI’s superior contrast resolution over CT in soft tissue and bones. Improved characterization of lesions with abnormal radiotracer uptake is of paramount importance because stress fractures, which are common in TIO, can lead to false positives during imaging. MRI was used rather than CT because it had been suggested to be of superior value to CT in the literature. MRI localized the lesion to cortical space versus bone marrow space and delineated the insufficiency fractures with related bone marrow edema. Surgical excision then resulted in rapid clinical improvement. Her elevated postsurgical FGF23 level was initially thought to be secondary to an elevated serum phosphate level. When her repeat FGF23 remained high with a normal serum phosphorus level, additional inquiry revealed iron deficiency, which can cause false-positive results on the c-terminal FGF23.⁸ Review of her prior records showed a normal ferritin level during the time of her initial FGF23 evaluation. Most recently, additional assessment showed normal iFGF23 and serum phosphorus levels along with the clinical resolution of symptoms, confirming cure.

A review of the literature shows that this may be the second case of a pregnant patient with TIO and the first in which phosphate repletion was used. In a case series of 6 patients with TIO, one was a 35-year-old woman with chronic worsening musculoskeletal symptoms with severe pelvic pain during pregnancy diagnosed as pelvic instability and sacroiliitis whose TIO was diagnosed months after delivery.⁶ In our patient, awareness of her TIO allowed for serial monitoring and medication adjustment to maintain normal phosphate levels and for a planned cesarean delivery to minimize pelvic trauma. She delivered a full-term healthy infant without complications. It would have been interesting to chart the patient's medication adjustments, but unfortunately, the records were limited. The patient denied drastic changes, and chart notes made mention of occasionally skipped phosphorus dosages due to gastrointestinal discomfort.

In conclusion, TIO must be included in the differential diagnosis of patients presenting with muscle weakness and fractures. To our knowledge, this is the first report of phosphate treatment in a pregnant patient with TIO in whom monitoring and advanced planning of delivery method resulted in an uneventful pregnancy and delivery, and this showcases the successful and precise localization of TIO using DOTATATE PET/MRI.

Disclosure

The authors have no multiplicity of interest to disclose.

References

1. Drezner MK. Tumor-induced osteomalacia. *Rev Endocr Metab Disord.* 2001;2(2):175–186.
2. Folpe AL, Fanburg-Smith JC, Billings SD, et al. Most osteomalacia-associated mesenchymal tumors are a single histopathologic entity: an analysis of 32 cases and a comprehensive review of the literature. *Am J Surg Pathol.* 2004;28(1):1–30.
3. Chong WH, Molinolo AA, Chen CC, Collins MT. Tumor-induced osteomalacia. *Endocr Relat Cancer.* 2011;18(3):R53–R77.
4. Ramon I, Kleynen P, Body JJ, Karmali R. Fibroblast growth factor 23 and its role in phosphate homeostasis. *Eur J Endocrinol.* 2010;162(1):1–10.
5. Imel EA, Econs MJ. Approach to the hypophosphatemic patient. *J Clin Endocrinol Metab.* 2012;97(3):696–706.
6. Clifton-Bligh RJ, Hofman MS, Duncan E, et al. Improving diagnosis of tumor-induced osteomalacia with gallium-68 DOTATATE PET/CT. *J Clin Endocrinol Metab.* 2013;98(2):687–694.
7. Rayamajhi SJ, Yeh R, Wong T, et al. Tumor-induced osteomalacia - current imaging modalities and a systematic approach for tumor localization. *Clin Imaging.* 2019;56:114–123.
8. Wolf M, Koch TA, Bregman DB. Effects of iron deficiency anemia and its treatment on fibroblast growth factor 23 and phosphate homeostasis in women. *J Bone Miner Res.* 2013;28(8):1793–1803.