JCEM Case Reports, 2023, **1**, 1–4
https://doi.org/10.1210/jcemcr/luad086
Advance access publication 27 July 2023
Case Report

Thermal Ablation for Treating Tumor-induced Osteomalacia in a Patient With IV Phosphate Dependency

Evert F.S. van Velsen,[1,2] Tychon E.A. Geeraedts,[3] Ariadne Bosman,[1,2] and M. Carola Zillikens[1,2]

[1]Department of Internal Medicine, Erasmus University Medical Center, 3015 CE, Rotterdam, The Netherlands
[2]Erasmus MC Bone Center, Erasmus University Medical Center, 3015 CE, Rotterdam, The Netherlands
[3]Department of Radiology and Nuclear Medicine, Erasmus University Medical Center, 3015 CE, Rotterdam, The Netherlands

Correspondence: Evert F.S. van Velsen, MD, PhD, Erasmus MC Bone Center, Department of Internal Medicine, Erasmus University Medical Center, Dr. Molewaterplein 40, 3015 CE, Rotterdam, The Netherlands. Email: e.vanvelsen@erasmusmc.nl

Abstract

Tumor-induced osteomalacia (TIO) is a rare paraneoplastic syndrome associated with tumors secreting fibroblast growth factor 23 that can be cured with complete surgical resection of the tumor. However, when these tumors are at difficult locations, less invasive modalities such as thermal ablation (TA) might be a good alternative. A 40-year-old woman was seen for a second opinion because of severe hypophosphatemia with complaints of fatigue, myalgia, and muscle weakness for which she needed IV phosphate for 15 to 18 hours per day in addition to oral alfacalcidol and phosphate. Initial laboratory results revealed hypophosphatemia (0.59 mmol/L [1.83 mg/dL]; reference range, 0.90-1.50 mmol/L [8.40-10.2 mg/dL]), increased fibroblast growth factor 23 levels (137 RU/mL; reference range, <125 RU/mL), and a reduced TmP-GFR (0.47 mmol/L; reference range, 0.8-1.4 mmol/L). Gallium-positron emission tomography/computed tomography (CT) showed moderately increased uptake at thoracic vertebra (Th) 8 and mildly increased uptake at Th7, suggestive of TIO. Complete tumor removal would have required resection of at least 1 vertebral body. Therefore, CT-guided TA was performed at Th8. No complications were observed, and in the months after, treatment with IV phosphate could be discontinued, indicating a satisfying result from the procedure. This extreme TIO case demonstrates that CT-guided TA can be an alternative to extensive or risky classical surgery.

Key Words: tumor-induced osteomalacia, thermal ablation, microwave ablation, hypophosphatemic osteomalacia

Abbreviations: ^{68}Ga, Gallium-68; CT, computed tomography; FGF23, fibroblast growth factor 23; LS, lumbar spine; MWA, microwave ablation; PET, positron emission tomography; TA, thermal ablation; TF, left femur; TIO, tumor-induced osteomalacia.

Introduction

Tumor-induced osteomalacia (TIO), also known as oncogenic or oncogenous osteomalacia, is a rare paraneoplastic syndrome of acquired hypophosphatemic osteomalacia caused by increased secretion of fibroblast growth factor 23 (FGF23) by a tumor [1]. The increased FGF23 secretion leads to the cardinal features of the disease, namely hypophosphatemia from renal phosphate wasting, a reduced 1,25-dihydroxyvitamin D serum concentration through inhibition of its synthesis, and rickets in children and osteomalacia in adults, with diffuse bone pains, fractures, and muscle weakness [1]. The tumors are of mesenchymal origin, and most of them are benign [2]. Although the majority of the tumors are located in either the lower extremities or head and neck region, localization of these tumors is often challenging because they can be small and present anywhere from head to toes [1]. Consequently, there can be a long diagnostic delay, leading sometimes to a dramatic outcome with multiple fractures and severe disability. Several techniques are being used aiming to detect the tumor of which functional imaging by Gallium-68 (^{68}Ga) positron emission tomography (PET)/computed tomography (CT), seems to be the best first step [3, 4]. Once a candidate tumor has been detected, more precise characterization can be performed using CT or magnetic resonance imaging [3, 4]. Patients with TIO can be cured completely if the tumor is properly localized and subsequently completely removed [1]. Although surgery remains the treatment of choice, these tumors are sometimes at challenging locations. Therefore, less invasive modalities such as thermal ablation (TA), which can be subdivided into radiofrequency ablation and microwave ablation (MWA), have been described in literature [5, 6]. Here, we describe a patient case with severe TIO caused by a tumor at a difficult location in the spine treated with TA.

Case Presentation

A 40-year-old woman was seen for a second opinion at the Erasmus MC Bone Center because of hypophosphatemia, which was diagnosed 5 years earlier. She had a history of uterus and double-sided adnex extirpation (8 years earlier), after which she uses ethinylestradiol/levonorgestrel, and gastrointestinal complaints because of gastroparesis (started 20 years earlier), for which she received a percutaneous endoscopic jejunostomy (5 years earlier). At presentation 5 years earlier, her main complaints were fatigue, myalgia, and muscle weakness. At initial presentation, a blood test showed hypophosphatemia (0.59 mmol/L [1.83 mg/dL]; reference range, 0.90-1.50 mmol/L [8.40–10.2 mg/dL]) with increased FGF23 levels (137 RU/mL; reference range, <125 RU/mL),

Received: 6 March 2023. **Editorial Decision:** 20 June 2023. **Corrected and Typeset:** 27 July 2023

Table 1. Laboratory values over time

	Reference range	Units	Diagnosis	Outpatient clinic	Day before MWA	Day after MWA	6 mo after MWA	1 y after WMA
Serum								
Calcium	2.10–2.55	mmol/L	2.38	2.28	2.25	2.17	2.24	2.37
	8.40–10.2	mg/dL	9.52	9.12	9.00	8.68	8.96	9.48
Phosphate	0.80–1.40	mmol/L	0.59	0.74	0.73	0.74	1.23	0.85
	2.48–4.33	mg/dL	1.83	2.29	2.26	2.29	3.81	2.63
Creatinine	50–100	µmol/L	88	98	97	90	121	104
	0.57–1.13	mg/dL	1.0	1.11	1.10	1.02	1.37	1.18
FGF23	< 125	RU/mL	137	203	331	235	736	745
Alkaline phosphatase	< 98	U/L	69		70			
PTH	1.3–6.8	pmol/L	3.3					
	12.2–64.1	ng/L	31.1					
vit D 1.25 OH	59–159	pmol/L	130					
vit D 25 OH	50–100	nmol/L	104					
Urine								
Creatinine		mmol/L	7.79					
Phosphate		mmol/L	10.5					
		mg/dL	32.51					
TmP-GFR	0.8–1.4	mmol/L	0.47					

Abbreviations: FGF23, fibroblast growth factor 23; MWA, microwave ablation; TmP-GFR, renal tubular maximum for the reabsorption of phosphate normalized to the glomerular filtration rate; PTH, parathyroid hormone.

and a reduced renal tubular maximum for the reabsorption of phosphate normalized to the glomerular filtration rate (0.47 mmol/L; reference range, 0.8-1.4 mmol/L) (Table 1).

Diagnostic Assessment

Additional genetic testing showed no abnormalities in renal phosphate handling genes (DMP1, FGF23, FGFR1, GALNT3, PHEX, SLC34A1, SLC34A3, SLC9A3R1). A dual energy X-ray absorptiometry scan, performed shortly after initial presentation in the referring hospital, showed a normal bone mineral density at the lumbar spine (LS) and the left femur (TF) (LS T −0.8 SD; TF [left] T + 0.8 SD. LS Z −0.7 SD; TF [left] Z + 0.9 SD). No follow-up dual energy X-ray absorptiometry scans was available. Because the suspicion of TIO was high, she had undergone several ^{68}Ga DOTATATE and DOTATOC PET/CTs in the past that did not show abnormalities. Because of the low phosphate levels, she was first started on oral phosphate supplementation, but because of decreasing phosphate levels and increasing complaints for which she visited the emergency department several times, alfacalcidol, and in a later stage also IV phosphate, were started. At presentation at our bone center, she used alfacalcidol (2.5 µg daily), oral phosphate supplementation (2 times 15 mmol daily), and IV phosphate using a pump (30 mmol daily for 15-18 hours). However, there were frequent problems with the IV access because of infections, causing several hospital admissions. Additionally, over time, she developed a costal fracture. Because of the lack of a diagnosis, and increasing doses of the medication needed, she underwent another ^{68}Ga PET/CT, which now showed increased uptake at lesions in the 7th and 8th thoracic vertebrae (Th7 and Th8), with the highest uptake at Th8 (9 mm) (Fig. 1). Furthermore, in retrospect, an earlier magnetic resonance imaging scan of the spine showed lesions at the site of the increased uptake, which were at that time diagnosed as hemangiomas and were not visible on CT. Biopsy of Th8 showed no abnormalities, but FGF23 staining could, unfortunately, not be performed. However, in retrospect, the biopsy was not taken from the ^{68}Ga-avid lesion, but from an intravertebral lipid lesion in Th8.

Treatment

The patient was discussed in our multidisciplinary team regarding possible treatment options. Complete tumor removal would have required resection of the 2 vertebral bodies; therefore, a less invasive procedure of CT-guided TA was proposed as a good alternative that has been described in literature [5, 6]. Another advantage of TA was the possibility to first treat the lesion at Th8 and if needed at a later stage the one at Th7. Therefore, CT-guided MWA, which is a subform of TA, was performed to treat the lesion at Th8 (Fig. 2), which did not result in any complications and was well-tolerated by the patient.

Outcome and Follow-up

In the months after CT-guided MWA, treatment with IV phosphate could be discontinued and serum phosphate levels normalized (1.23 mmol/L [3.81 mg/dL]) while using oral alfacalcidol (3.0 µg daily), and phosphate supplementation (2 times 15 mmol daily). Importantly, her complaints greatly

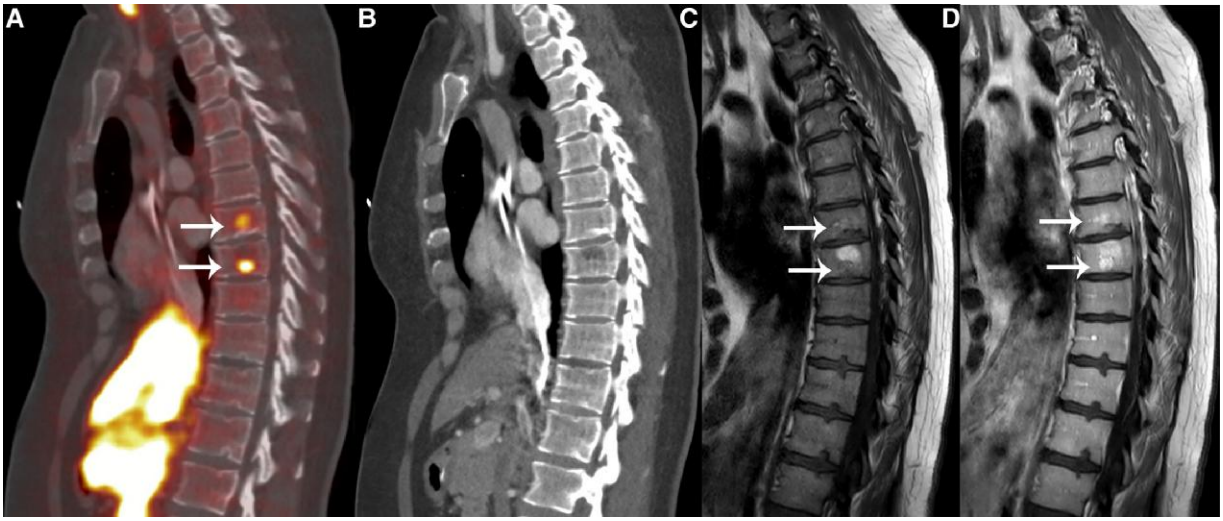

Figure 1. Sagittal images of gallium-68 PET/CT (A) with corresponding noncontrast CT (B). MRI (C, D) images of the spine showing hot spots in the 7th and 8th thoracic vertebrae (A). The lesions are marked with white arrows.

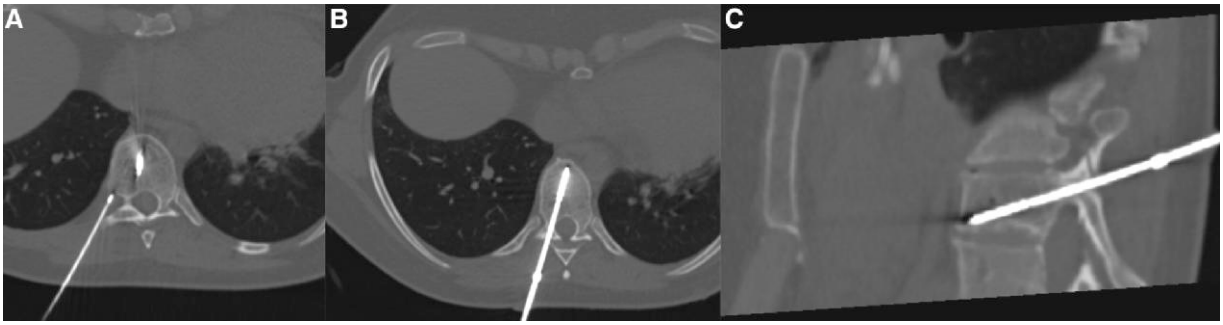

Figure 2. Axial (A, B) and sagittal (C) images of the CT scan made during MWA showing the MWA probe next to and/or inside the 8th thoracic vertebra.

improved. Especially, that continuous IVs phosphate treatment was not needed anymore gave the patient a great sense of freedom back.

Discussion

TIO is a rare phosphate-wasting disorder caused by increased secretion of FGF23 by, in most cases benign, a mesenchymal tumor. Patients with TIO can be cured if the tumor is properly localized and subsequently completely removed. Although surgery remains the treatment of choice, less invasive modalities such as TA can be a good alternative when the tumor is at a challenging location. TA is a well-established procedure for selectively removing small volumes of tissue and has several applications (eg, in localized bone or thyroid disease) [7, 8]. There have been a few earlier reports showing the ability of TA in treating and curing patients with TIO, but long-term results are relatively scarce [5, 6]. Main complications of TA include infection, hematoma, and, in case of spinal localization, possible collapse of the vertebral body because of TA-induced necrosis. The decision of TA in our patient was based on the combination of the uncertainty of which lesion was producing FGF23 and the rather difficult location, for which extensive neurosurgery was the alternative. Alternatively, the patient could have been treated with burosumab, an FGF23 monoclonal antibody [9]. However, the main drawbacks are that she would have needed this expensive treatment for the rest of her life, and long-term side effects are unknown. Therefore, burosumab treatment should be considered, in our opinion, when other therapies are unsuccessful or not possible [4]. Further, radiotherapy has been performed in the past in patients with TIO [10], but there was very little experience in our center for this indication, and we hypothesized that TA (in this patient, it was subform MWA) would have a lower risk of side effects. After MWA, the need for phosphate treatment decreased dramatically and IV phosphate could be discontinued and improved her quality of life substantially because IV medication could be stopped, which suggests MWA was effective. However, (total) FGF23 levels increased toward higher levels than before treatment despite the need of less medication. Such elevation is a known phenomenon after intervention and could indicate residual disease [4]. Alternatively, this could be related to the fact that she received her first IV iron treatment in the period after MWA. Together with the patient, we decided to wait and see while continuing treatment with oral alfacalcidol and phosphate supplementation and aim to perform MWA on the Th7 lesion, or the Th8 lesion when there are signs of recurrence.

Notably, although the suspicion of a TIO was there from initial presentation, it took almost 5 years before abnormalities became visible on the PET/CT scans. A recent review showed that the median time between initial presentation

and tumor-related treatment is 3.5 years [1]. In our case, the diagnosis was suspected, but not confirmed, because it was not visible on nuclear imaging. This was probably caused by the fact that initially the tumor was too small to be detected and grew over time until it was detected. However, it might also be caused by the availability of better resolution of the scanners over time.

In conclusion, this impressive TIO case with extreme IV need for phosphate demonstrates that CT-guided TA may be used to treat TIO, and consequently TA broadens the scope of treatment options for TIO as an effective alternative to extensive or risky classical surgery.

Learning Points

- When the diagnosis of tumor-induced osteomalacia is suspected, but imaging does not localize a tumor, it is important to repeat functional imaging every 1 to 2 years.
- In case surgical resection is not possible, thermal ablation may be a good treatment alternative for patients with tumor-induced osteomalacia.
- In case of muscle weakness, muscle and bone pain, fatigue, and/or fragility fractures, serum phosphate should be measured, and in case of suspicion, tumor-induced osteomalacia should be investigated for.

Contributors

All authors made individual contributions to authorship. E.V.V. was involved in the diagnosis and management of this patient and wrote the initial draft of the manuscript. T.G. was involved in the management of the patient and revised the manuscript. A.B. revised the manuscript. M.C.Z. was involved in the diagnosis and management of this patient and revised the manuscript. All authors reviewed and approved the final draft.

Funding

This research did not receive any specific grant from any funding agency in the public, commercial, or not-for-profit sector.

Disclosures

E.V.V. and T.G. declare no conflicts of interest and no competing financial interests exist. A.B. is supported by a grant from Health~Holland (PhosphoNorm; LSHM18029). M.C.Z. declares that her institution received a research grant form Kyowa Kirin.

Informed Patient Consent for Publication

Signed informed consent obtained directly from the patient.

Data Availability Statement

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

References

1. Bosman A, Palermo A, Vanderhulst J, *et al.* Tumor-induced osteomalacia: a systematic clinical review of 895 cases. *Calcif Tissue Int*. 2022;111(4):367-379.
2. Weidner N, Santa Cruz D. Phosphaturic mesenchymal tumors. A polymorphous group causing osteomalacia or rickets. *Cancer*. 1987;59(8):1442-1454.
3. El-Maouche D, Sadowski SM, Papadakis GZ, *et al.* (68) Ga-DOTATATE for tumor localization in tumor-induced osteomalacia. *J Clin Endocrinol Metab*. 2016;101(10):3575-3581.
4. Jan de Beur SM, Minisola S, Xia WB, *et al.* Global guidance for the recognition, diagnosis, and management of tumor-induced osteomalacia. *J Intern Med*. 2023;293(3):309-328.
5. Hesse E, Rosenthal H, Bastian L. Radiofrequency ablation of a tumor causing oncogenic osteomalacia. *N Engl J Med*. 2007;357(4):422-424.
6. Jadhav S, Kasaliwal R, Shetty NS, *et al.* Radiofrequency ablation, an effective modality of treatment in tumor-induced osteomalacia: a case series of three patients. *J Clin Endocrinol Metab*. 2014;99(9):3049-3054.
7. Rosenthal DI. Radiofrequency treatment. *Orthop Clin North Am*. 2006;37(3):475-484, viii.
8. Loncar I, van Dijk SPJ, van Velsen EFS, *et al.* Radiofrequency ablation for benign symptomatic thyroid nodules in The Netherlands: successful introduction of a minimally invasive treatment option improving quality of life. *J Vasc Interv Radiol*. 2022;33(5):530-7.e1.
9. Crotti C, Zucchi F, Alfieri C, Caporali R, Varenna M. Long-term use of burosumab for the treatment of tumor-induced osteomalacia. *Osteoporos Int*. 2022;34(1):201-206.
10. Tarasova VD, Trepp-Carrasco AG, Thompson R, *et al.* Successful treatment of tumor-induced osteomalacia due to an intracranial tumor by fractionated stereotactic radiotherapy. *J Clin Endocrinol Metab*. 2013;98(11):4267-4272.