

# Tumor-induced osteomalacia treated with T12 tumor resection

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## Summary

Tumor-induced osteomalacia (TIO) is a rare form of osteomalacia caused by fibroblast growth factor-23 (FGF23)-secreting tumors. Most of these tumors are phosphaturic mesenchymal tumors (PMTs) typically involving soft tissue in the extremities and bone of the appendicular skeleton and cranium. We report the case of a 60-year-old woman with about 3 years of persistent bone pain and multiple fractures, initially diagnosed as osteoporosis, who was found to have hypophosphatemia with low 1,25-dihydroxyvitamin D and elevated alkaline phosphatase and inappropriately normal FGF23 consistent with TIO. Her symptoms improved with phosphate supplementation, vitamin D and calcitriol. <sup>68</sup>Ga-DOTATATE imaging revealed a T12 vertebral body lesion confirmed on biopsy to be a PMT. She underwent resection of the PMT with resolution of TIO and increased bone density. This rare case of TIO secondary to a PMT of the thoracic spine highlights some of the common features of PMT-associated TIO and draws attention to PMT-associated TIO as a possible cause of unexplained persistent bone pain, a disease entity that often goes undiagnosed and untreated for years.

## Learning points

- Tumor-induced osteomalacia (TIO) is typically caused by phosphaturic mesenchymal tumors (PMTs) that are usually found in the soft tissue of the extremities and bone of the appendicular skeleton/cranium and rarely in the spine.
- TIO may be misdiagnosed as osteoporosis or spondyloarthritis, and the correct diagnosis is often delayed for years. However, osteoporosis, in the absence of fracture, is not associated with bone pain.
- The hallmark of TIO is hypophosphatemia with inappropriately normal or low 1,25-dihydroxyvitamin D and elevated or inappropriately normal fibroblast growth factor-23 (FGF23) levels.
- In patients with unexplained persistent bone pain, a serum phosphate should be measured. Consider PMT-associated TIO as a potential cause of unexplained persistent bone pain and hypophosphatemia.
- PMTs express somatostatin receptors and may be identified with <sup>68</sup>Ga-DOTATATE imaging.
- Complete surgical resection is the preferred treatment for spinal PMTs associated with TIO.

## Background

Osteomalacia is a metabolic bone disease characterized by impaired bone mineralization that results from inadequate levels of serum calcium or phosphate or inadequate alkaline phosphatase (ALP) activity. While usually attributed to prolonged vitamin D deficiency, there is a rare form known as tumor-induced osteomalacia (TIO), or oncogenic osteomalacia, first described by McCance in 1947. TIO is typically caused by tumors that secrete fibroblast growth factor-23 (FGF23), thereby reducing renal phosphate reabsorption and 1,25-dihydroxyvitamin D production in the proximal renal tubules (1). TIO is sometimes reported in association with various carcinomas; however, the majority of TIO is caused by tumors of mesenchymal origin, namely phosphaturic mesenchymal tumors (PMTs) (2).

PMTs are very rare, with only about 450 cases reported in the literature from 1947 to 2019. PMTs can occur in virtually any soft tissue or osseous location; however, they most often involve soft tissue in the extremities and acral sites and bone of the appendicular skeleton, cranium, and paranasal sinuses (1, 3, 4, 5). More common signs and symptoms of PMTs and the resultant TIO include bone pain, muscle weakness, and multiple fractures. Biochemical hallmarks are hypophosphatemia, elevated ALP, elevated or inappropriately normal plasma FGF23, and inappropriately normal or low 1,25-dihydroxyvitamin D (1, 3). Unfortunately, given the rare and insidious nature of this disease, it is often misdiagnosed, and the average time from onset of symptoms to clinical diagnosis is 3–4 years (5, 6). The majority of PMTs are benign, with complete excision resulting in resolution of osteomalacia. However, they frequently recur if not completely excised (2).

Here, we describe a case of TIO secondary to a PMT of the thoracic spine. While this case highlights some of the common signs and symptoms found with PMT-associated TIO, it is unique in that thoracic spine PMTs are rare, with only six cases previously reported in the literature. We also hope that this case helps to raise awareness of PMT-associated TIO as a potential cause of unexplained persistent severe bone pain, a nonspecific symptom often leading to a delayed diagnosis.

## Case presentation

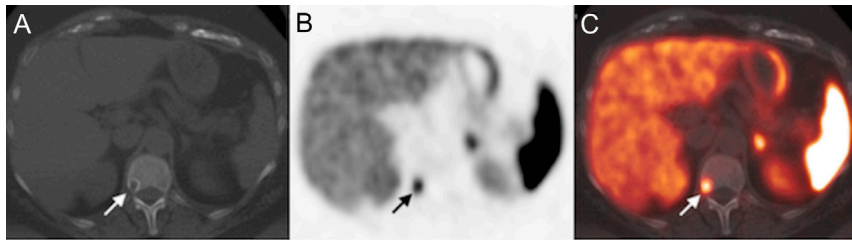
A 60-year-old woman with a past medical history notable for multiple fractures, vitamin D deficiency,

and nephrolithiasis presented to a bone health clinic for evaluation of hypophosphatemic osteomalacia. She had been in good health until about 3 years prior when she developed left hip and groin pain and was diagnosed with tendonitis. Gradually, her pain progressed to include her left buttocks, left heel, right shoulder, and right hip. She was later diagnosed with a left psoas strain, healed rib fractures, stress fractures of both heels, and an incomplete fracture of the right femoral neck and nondisplaced fracture of the right symphysis pubis for which she ultimately underwent right hip closed reduction with percutaneous pinning. She was diagnosed with osteoporosis and prescribed weekly alendronate which she did not start. In the setting of her multiple fractures, she was referred to a local endocrinologist. By that time, she was unable to ambulate due to significant pain and weakness. After an initial workup, she was referred to the bone health clinic for further management.

## Investigation

Initial laboratory workup by her local endocrinologist showed the following: calcium 9.3 mg/dL (reference: 8.3–10.1 mg/dL), phosphate 1.5–2.4 mg/dL (reference: 2.5–4.9 mg/dL), ALP 252–426 U/L (reference: 45–117 U/L), parathyroid hormone (PTH) 72.1–83.8 pg/mL (reference: 18.4–80.1 pg/mL), 25-hydroxyvitamin D 26–28 ng/mL (reference: 30–50 ng/mL), 1,25-dihydroxyvitamin D 14 pg/mL (reference: 18–72 pg/mL), normal serum protein electrophoresis, FGF23 122 RU/mL (reference: <180 RU/mL), and urinary phosphate 0.82–2.086 g/24 h (reference: 0.4–1.3 g/24 h). After being started on oral ergocalciferol 50 000 IU twice weekly, oral calcitriol 0.5 mcg twice daily, and oral sodium di-monophosphate-K phosphate four times daily, repeat laboratory studies showed calcium 8.8 mg/dL, phosphate 3.0 mg/dL, and ALP 193 U/L with improved but incompletely resolved pain.

A bone density scan nearly 2 years prior showed osteopenia with AP spine L1–L4 T-score –1.8, left femur neck T-score –2.1, and left total hip T-score –1.3. <sup>68</sup>Ga-DOTATATE imaging showed a T12 vertebral body lucent lesion (Fig. 1). MRI of the thoracic spine with and without contrast confirmed an enhancing marrow-replacing lesion within the posterior right T12 vertebral body (Fig. 2). She subsequently underwent CT-guided core biopsy of this lesion, with pathology revealing a PMT, positive for FGF23 mRNA by chromogenic *in-situ* hybridization studies and histologically benign (Fig. 3).



**Figure 1**

<sup>68</sup>Ga-DOTATATE PET/CT at the level of T12. (A) Axial CT image in bone window shows a lucent lesion (arrow) with thin sclerotic rim in the T12 vertebral body. The lesion (arrows) shows uptake on the axial (B) PET and (C) fused PET/CT images.

## Treatment

Eight months after initial presentation to the bone health clinic, and more than 4 years since her symptoms first started, she underwent thoracic hemilaminectomy with en bloc spondylectomy of the T12 tumor with T10–L2 posterior instrumented fusion, complicated by a dural tear that was repaired intraoperatively. Anatomic pathology confirmed a PMT with negative margins (<0.1 cm in some areas) (Fig. 4).

## Outcome and follow-up

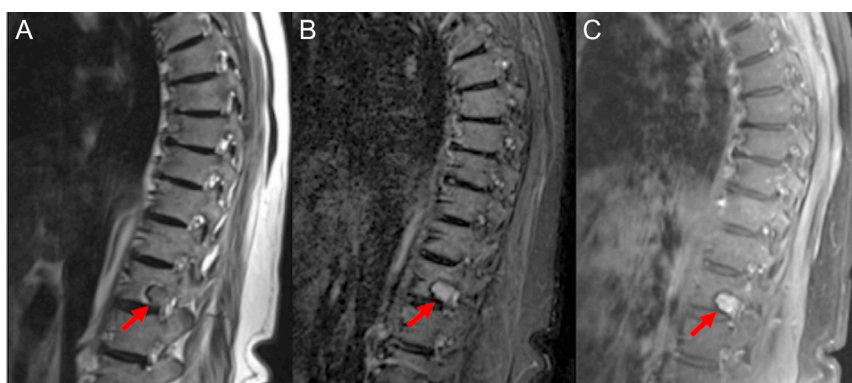
At follow up, 1-month post-op, laboratory studies revealed the following: calcium 9.5 mg/dL, phosphate 5.2 mg/dL, ALP 112 U/L, PTH 37.5 pg/mL, 25-hydroxyvitamin D 26 ng/mL, and FGF23 96 RU/mL. Her calcitriol and phosphate supplementation were discontinued, and vitamin D supplementation was changed to cholecalciferol 2000 IU daily. She was referred back to her local endocrinologist. She had a repeat bone density scan 13 months post-op showing improvement (lumbar spine T-score -0.3, left femur total T-score -1.4, and left forearm T-score -1.2). Twenty-six months post-op, her laboratory studies have remained normal with phosphate 3.5 mg/dL, 1,25-dihydroxyvitamin D 45 pg/mL, and FGF23 67 RU/mL, without recurrence of her PMT-associated TIO.

## Discussion

TIO, or oncogenic osteomalacia, is a very rare and surgically treatable osteomalacia caused by tumors that secrete FGF23, most commonly PMTs (1). In 2019, Folpe published a comprehensive review of PMTs, at which point there were only about 450 cases reported in the literature (2). Here, we present an additional case of a PMT to add to this sparse yet growing body of literature.

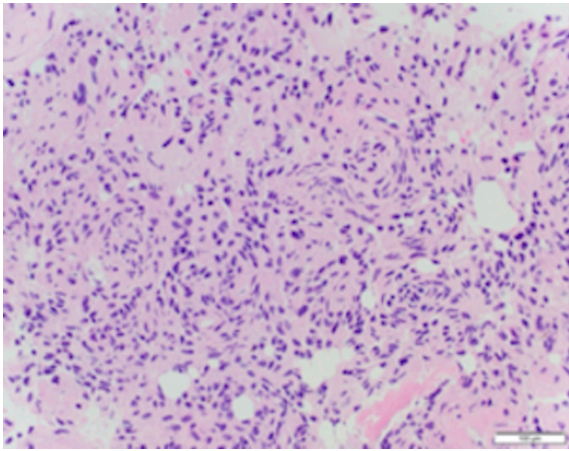
Perhaps what is most unique about this case is the location of the PMT in the thoracic spine. While PMTs can occur in virtually any soft tissue or osseous location, they most commonly involve the extremities, appendicular skeleton, and craniofacial area. Upon reviewing the literature, which includes mostly case reports and case series, only a handful of thoracic spinal PMTs have been described (1, 3, 4). Garg *et al.* in 2020 highlighted that there have been only 21 cases of TIO-associated mesenchymal tumors involving the spinal column reported in the 70 years since these tumors were first described, of which only six were PMTs involving the thoracic spine. All of these were treated surgically; four without recurrence at follow-up, one with recurrence of serum abnormalities at follow-up, and one with no follow-up documented (7).

It remains unknown why PMTs of the spine are so rare. Recent studies have shown that pathogenic fusion events involving the *FN1-FGFR1/FGF1* genes may be implicated in the tumorigenesis of PMTs, leading to abnormally

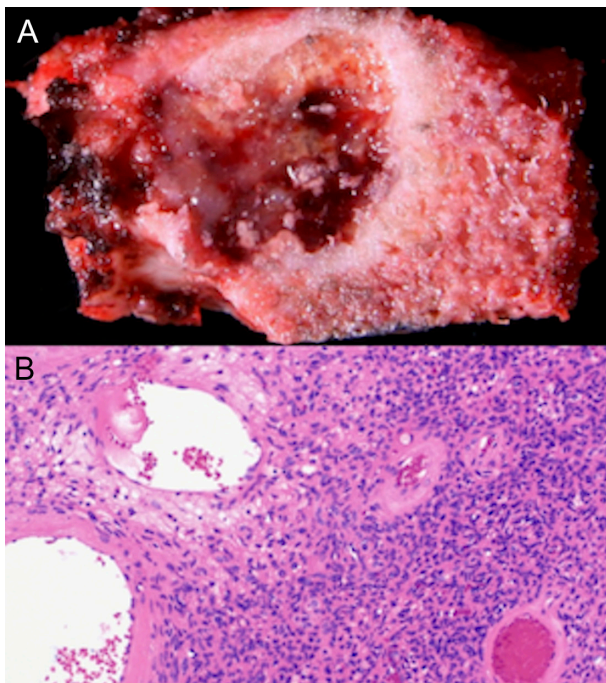


**Figure 2**

MRI thoracic spine with and without i.v. contrast. There is a 1.3 cm lesion in the inferior aspect of the T12 vertebral body (arrows) that (A) is hypointense on the sagittal T1 MR image, (B) is hyperintense on the sagittal T2 fat-suppressed MR image, and (C) has avid solid enhancement on the sagittal T1 fat-suppressed postcontrast MR image.



**Figure 3**  
Histology from CT-guided core biopsy of the T12 vertebral body lesion showing a bland spindle cell proliferation composed of a monomorphic population of cells with spindle- to ovoid-shaped nuclei with ample eosinophilic cytoplasm. There is no significant cytologic atypia or increased mitotic activity, and there are no overt features of malignancy. Scale: 100  $\mu$ m.



**Figure 4**  
Surgical pathology of the T12 vertebral body lesion. (A) Section of gross specimen revealing a 1.4  $\times$  1.1  $\times$  0.8 cm tan-yellow to red-brown, soft circumscribed mass that comes within <0.1 cm of the medial margin, <0.1 cm of the lateral margin, 0.5 cm of the superior (cephalad) margin, and 0.6 cm from the inferior margin. (B) Representative histologic section again showing bland spindle cell proliferation.

increased FGFR1 signaling and FGF23 overexpression (2). Perhaps these fusion events are only oncogenic with the support of the right microenvironment, and the spine may not possess such a microenvironment. There are known differences in immune landscape, growth rates, and physical forces in the appendicular vs axial skeleton, and it is worth noting that primary tumors of the spine are rare in general (8). Another possibility is that the spine may contain fewer of the FGF23-releasing cells which give rise to PMTs. In a mouse model of hereditary hypophosphatemia, FGF23 was expressed in the vertebrae amongst other locations (9). However, specific data regarding FGF23 expression in the human spine relative to other skeletal sites are lacking. Finally, it is possible that the apparent rarity of spinal PMTs may in part be due to previous difficulty in locating and diagnosing such tumors. Now that there have been advances in imaging modalities, spinal PMTs may be more readily identifiable.

The presented case highlights the common symptoms and findings related to PMT-associated TIO. The patient presented with years of various bone pains and multiple fractures, misdiagnosed initially as osteoporosis, which alone is not associated with bone pain. She was found to have low serum phosphate, elevated urine phosphate, elevated ALP, low 1,25-dihydroxyvitamin D, and inappropriately normal FGF23 – all of which are commonly seen with PMT-associated TIO (1, 3, 5, 6). Her tumor was localized to the T12 vertebral body through use of  $^{68}\text{Ga}$ -DOTATATE imaging, which identifies tumors rich in somatostatin receptors. She underwent CT-guided biopsy which confirmed a PMT – a diagnosis that came nearly 4 years after she started experiencing symptoms. Unfortunately, this delay in diagnosis is also very common given the nonspecific symptoms, rarity of condition, and lack of physician awareness of the disease.

Relatedly, we hope that this case will help raise awareness of PMT-associated TIO as a potential cause of unexplained persistent bone pain. As excellently outlined in a recent review by Brandi *et al.*, there are many challenges associated with the diagnosis of TIO. Almost all cases of TIO are initially misdiagnosed, with the most common misdiagnoses being intervertebral disc herniation, spondyloarthritis, and osteoporosis. In addition to the diagnostic challenges associated with delayed diagnosis as already discussed, another challenge includes the delay or failure in measuring a fasting serum phosphate in those with widespread bone pain or a suspicion of osteomalacia, particularly if ALP is elevated (10). It is unclear if a serum phosphate was measured in our patient prior to her presenting to an endocrinologist; however, if it



was measured at some point over the 3 years that she was symptomatic, it was not acted upon.

Finally, it is important to note that surgical management is the preferred treatment of spinal PMTs associated with TIO, with most authors advocating for radical or wide resection of the tumor to ensure remission and prevent recurrences (10, 11). However, disease can persist in about 11% of cases and tumors can recur in about 7% of cases with a median time to recurrence of 33 months. Risk factors for refractory outcomes include female sex, spinal tumors, bone tissue-involved tumors, malignancy, and lower preoperative serum phosphate levels (10, 12). Burosumab, a monoclonal antibody to FGF23, has also recently been approved for use in TIO. While our patient thankfully did not show signs of recurrence as of 26 months post-op, she does carry some of the aforementioned risk factors and is still relatively early in her course. As such, she will continue to be monitored closely by her multidisciplinary team.

## Conclusion

In summary, we have described a case of TIO secondary to a PMT of the thoracic spine, an entity that is very rare with only a small number of cases currently reported in the literature. We have highlighted aspects of the case that are common to others found in the literature, including the presenting signs and symptoms. We have discussed some of the challenges associated with the diagnosis of TIO, which our patient also experienced. Ultimately, we hope that this case will help raise awareness of PMT-associated TIO as a potential cause of unexplained persistent bone pain, thus leading to more efficient diagnosis and treatment.

### Patient's perspective

The most important thing I can ask as a patient is to please, please really listen to me. I saw many doctors during the course of trying to find out what was wrong, and most would focus on one symptom and ignore the rest of what I was saying. The pain I was in was hard to describe; at times it felt like a ball of crushed glass was grinding into my bones, and other times it could be dull or sharp like an ice pick. The pain was not only in my bones, it eventually felt like every muscle, tendon, and ligament in my body was in constant pain. I had so much muscle weakness I couldn't lift my foot high enough to step up onto a curb without hanging onto someone. I remember waking up in the morning thinking 'is this what the rest of my life is going to be?' and then knowing 'I can't do this much longer'. The hip and heel fractures never showed up on x-rays. It took months of misdiagnosis each time for each break before an MRI was finally ordered and the fractures were revealed. Before that I was told it was strains or pulled muscles, Achilles tendonitis, flat feet, osteoporosis...I was sometimes told the pain wasn't as bad as I seemed to think it was.

I was often prescribed high doses of ibuprofen which never touched the pain. I was sent to physical therapy four different times, to no avail. I finally found a new primary care physician who sat down and really listened to my whole story. She told me she didn't know what was causing my problem, but we were going to find out. She referred me to a local endocrinologist, who also really listened to me and ordered the tests that pointed in the direction of TIO. Once on the medication, I started getting some relief within weeks. I then went to the bone health clinic, had the PET scan to find the tumor, and, finally, had the tumor removed. That was almost 3 years ago and I've not had a recurrence of any symptoms and hopefully never will.

### Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the case reported.

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### Patient consent

Written informed consent for publication of their clinical details and/or clinical images was obtained from the patient.

### Author contribution statement

AJM did a literature search and wrote the manuscript. AOM, AS, and JHS were involved in the direct care of the patient and reviewed the manuscript. JAP and JSW provided radiological images and reviewed the manuscript. AW and GPN provided pathology slides and reviewed the manuscript. All authors read and approved the final manuscript.

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