FGF-23 transmitted tumor – induced hypophosphatemic osteomalacia: A rare case of a young woman with recurrent fractures and review of the literature

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Abstract

We present a case of tumor-induced osteomalacia (TIO) in a young woman of 22 years. The fibroblast growth factor 23 transmitting tumor in her left foot remained undetected for several years. She suffered several fractures including insufficiency fractures of both femoral necks requiring bilateral proximal femoral nailing. After phosphaturia was diagnosed any known genetic etiology was excluded. Even advanced imaging modalities were unable to detect the clinically silent tumor until an 68Ga-DOTA-TOC-PET/CT-scan revealed a mass with paraneoplastic activity in the left foot. Complete resection of the tumor proved to cure her condition after 9 years of uncertainty and suffering. Serum phosphate levels returned to normal within days.

After presentation of the case report, the current literature on published cases of TIO between 1956 and 2021 is summarized to emphasize the importance of an accurate and early diagnosis. Our case report aims to illustrate that a long latency period of diagnosis may be avoided utilizing the latest imaging techniques to spare affected patients from long treatment of symptoms instead of finding the underlying cause.

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1. Introduction

TIO is a rare paraneoplastic form of acquired hypophosphatemia, closely related to tumor-induced hypophosphatemic rickets (TIR) which was first described in 1959 [1]. In TIO a typically small tumor [2] produces fibroblast growth factor 23 (FGF 23), and causes hypophosphatemia in adults which has been reported in about 500 cases [3–5].

As the mesenchymal tumor produces phosphatonins, it leads to hypophosphatemia via reduced renal reabsorption of phosphate. Not until 2001, the disease-causing hormone was recognized as FGF 23, leading to phosphaturia [6]. Even though other proteins such as MEPE (matrix extracellular phosphoglycoprotein), FGF-7 and sFRP4 (secreted frizzled-related protein 4) are overexpressed in tumors and act as phosphatonins too, FGF 23 remains the main cause for TIR and TIO [7,8]. Algorithms for diagnosis and treatment were established [4,9], but TIO and TIR are often diagnosed with extensive delay leading to unnecessary diagnostic and intervention procedures [10]. Detecting the tumor remains a challenge due to small size and location [11]. Interpretation of results of FGF-23 levels can be challenging as a high variability of analytics, age and biology is reported [12,13]. Imaging modalities for tumor detection include MRI and FDG-PET. In case of detection failure, 68Ga-DOTA-TOC-PET/CT-scan is a more sensitive tool to find the tumor [14–16]. A genetic etiology must be excluded once TIO is suspected as X-linked hypophosphatemia, autosomal dominant hypophosphatemic rickets and autosomal recessive hypophosphatemic rickets may mimic the disease [17–20].

We present a case report of a patient who experienced a long latency period between onset of symptoms and diagnosis and
summarize the literature of published cases of TIO between 1956 and 2021 to emphasize the importance of an accurate and early diagnosis. Our case report aims to illustrate how a long latency period of diagnosis can be avoided. Affected patients suffer from long treatment of symptoms instead of finding the underlying cause.

2. Case report

A previously healthy 22-year-old female presented with lumbar back pain for 6 months in 2010. MRI and bone scintigraphy suggested a spondylarthropathy. She received treatments with steroids and various immunomodulatory drugs (Etanercept, Adalimumab) with limited success. After a pelvic fracture, osteoporosis was diagnosed in 2013 (osteodensitometry showing a best T-Score of −3.0). Despite treatment with denosumab followed by teriparatide T-scores decreased to −3.4 in 2016. She continued to have fractures (ribs, pelvis) with minimal traumas requiring crutches to walk.

Five years after the onset of symptoms, in 2015 she was found to have hypophosphatemia at 0.42 mmol/l secondary to renal phosphate wasting (fractional excretion of phosphate 16%; TmP/GFR 0.22 mmol/l). Serum calcium and PTH levels were normal, alkaline phosphatase was high. The diagnosis of osteomalacia was made. Serum FGF-23 was markedly elevated at 209 kRU/l (normal range 26–110). Her father too had a high urinary phosphate excretion with mild asymptomatic hypophosphatemia the precise cause of which was unknown, but next-generation sequencing as well as multiplex ligation-dependent probe amplification of all known causative genes were negative. Furthermore, had she had never received intravenous iron. Thus, a tumor remained the most likely cause for the osteomalacia.

An FDG-PET scan was performed in search for an underlying tumor, but results came back negative. Even though her symptoms improved significantly on oral phosphate and calcitriol and a repeat osteodensitometry showed a normalization of the T-score, she required proximal femoral nailing due to insufficiency fractures at both femoral necks (Fig. 1).

Just after the second femoral nailing in 2018 an 68Ga-DOTA-TOC-PET/CT-scan was performed, which showed a (clinically non-apparent) tumor (Fig. 2) in her left forefoot which had not been visible in the previous FDG-PET.

In January 2019 the resection was performed but the phosphate leakage remained. A second 68Ga-DOTA-TOC-PET/CT-scan and an MRI (Fig. 3) confirmed residual tumor tissue with FGF-23 activity. After complete removal during the second surgery in November 2019, FGF-23 levels normalized, and the renal phosphate leak disappeared (Fig. 4). More importantly she did not experience a single fracture related to osteomalacia thereafter. The histology showed typical findings of a phosphaturic mesenchymal tumor (PMT) (Fig. 5).

24 months after resection of the tumor her serum phosphate and FGF 23 levels remain in physiological ranges, and no further fractures are documented. An osteodensitometry performed in 2020 showed restoration of high normal density of femoral and lumbar bone. An MRI in November 2021 did not show any residual suspect lesions in her left foot.

3. Discussion and review of the literature

The case presented illustrates the rare entity of FGF-23-induced tumor-associated hypophosphatemic osteomalacia in a young patient. The first case of the closely related TIR was described by McCance in 1947 in a 15-year-old girl with rickets and vitamin D resistance, though he failed to attribute her disease to the tumor he removed from the patient’s femur [21]. The first to describe tumor-associated rickets were Prader et al in 1959 [1]. Finally in 2001, Fibroblast growth factor 23 (FGF-23) was identified as the phosphaturic hormone causing the disease [6].

We performed a systematic MEDLINE search (1959–2021) of publications in English and German. Key words were: “hypophosphatemic osteomalacia”, “FGF-23”, “phosphaturic mesenchymal tumor” and “adult”.

Possible underlying causes of hypophosphatemia are a tumor, hereditary conditions and intravenous iron administrations [22,23]. Patients with McCune-Albright syndrome and fibrous dysplasia or cases with epidermal nevus syndrome show the same mechanism of FGF-23 overproduction causing hypophosphatemic rickets. All entities except phosphaturic mesenchymal tumors as described by Weidner et Santa Cruz in 1987 were excluded in our review of the current literature [24].
A total of 502 studies were identified over the period from 1959 to 2021 using the keywords mentioned above. The vast majority (335 articles) were published in the last decade, mostly focusing on improving the diagnostic pathway. In summary approximately 500 cases of TIO have been described in literature [3,5,25,26]. While TIO is most often caused by tumors in soft tissues in adults, some cases of bony lesions are reported, some of which occurred in minors [4,27–30].

3.1. Symptoms

A sudden onset of osteomalacia and low serum phosphate levels, phosphaturia and low to normal serum calcitriol is common in patients with TIO [10]. Symptoms include bone pain, muscle weakness and multiple, inadequate fractures [11]. As phosphate is often not included in the routine serum chemistry the disorder may remain unrecognized for an extended period of time, just like in our case [31]. Latency to diagnosis is 4 years by median and can take up to 22 years [3].

3.2. Diagnostics

As illustrated above, the diagnosis can be challenging as the tumors are commonly very small in size and conventional imaging techniques fail to identify the lesion even if they cover the whole body [4,32].

111Iridium-pentetreotide scintigraphy, utilizing octreotide (a somatostatin analogon) has been successful in tumor detection in some cases [33]. FDG-PET CT scan or whole-body MRI scan succeeded in localizing some of the tumors, but may lack the specificity as they show all areas of high bone turnover [34]. Venous blood sampling for FGF-23 is a helpful tool to show the existence of the tumor rather than localizing it [35,36]. The rather new modality of 68Ga-DOTA-TOC-PET/CT-scan (using octreotide as mentioned above) is most sensitive in finding the underlying tumors [14,37,38] but fails to identify the mass in up to 30–40% [4]. As demonstrated in our case, a stepwise diagnostic approach can be effective, including 68Ga-DOTA-TOC-PET/CT-scan, venous sampling for FGF-23 levels and localized MRI of the suspected region [39].

3.3. Therapy

Complete surgical removal of the tumor cures the disease in the vast majority of cases [2,3]. Long-term follow-up is recommended as recurrence can occur. In rare cases a late metastatic relapse mostly in the lungs is described [2,4]. Normalization of serum phosphate can be expected 5 to 10 days after successful surgery. Laboratory parameters can also very well be utilized for tumor follow-up. The bony healing takes a lot longer and can be up to one year.
When surgical resection is not feasible, Burosumab, a monoclonal antibody against FGF 23, presents an alternative in treatment [40, 41]. A recent phase 2 study revealed good efficacy with 86% of patients reaching normal serum phosphate levels (0.81–1.29 mmol/L) after 22 weeks, while displaying an acceptable safety profile [42]. The FDA approved dose for adults is 0.3 mg/kg every 4 weeks, which can be titrated up to 2.0 mg/kg every 2–4 weeks [43].

4. Conclusions

TIO is a rare but increasingly recognized condition, caused by mostly benign and slow-growing PMTs secreting FGF-23 (~70–80% of cases) [2]. In 60% of cases (including this one) a FNI-FGFR1 fusion transcript is detectable. This case illustrates the common difficulties in diagnosing and treating these tumors with a delay of 9 years between the onset of symptoms and curative tumor surgery.

In a young patient with recurrent fractures and unknown cause of osteomalacia all measures should be taken to establish an early diagnosis. This will spare the patient from long suffering as symptoms are fully reversible after tumor resection. Therefore, in a young patient with hypophosphatemic osteomalacia the index of suspicion should be set rather high.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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