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Case Report

Tumor induced osteomalacia - A long way toward correct diagnosis and management

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ABSTRACT

Tumor-induced osteomalacia (TIO) is an uncommon type of osteomalacia associated with phosphaturic mesenchymal tumors (PMTs). Due to nonspecific symptoms, the diagnosis and appropriate management of the disease is often delayed for many years. Involvement of spine with TIO associated tumors is exceedingly rare. We present a 53-year-old woman with a 10-year history of bone pain, muscle weakness and multiple bone fractures that markedly impaired her quality of life. Biochemical evaluation revealed hypophosphatemia due to renal phosphate wasting and elevated plasma fibroblast growth factor 23 (FGF-23) concentration indicating PMT. It was found using ^{68}Ga DOTA TOC PET/CT scan in the vertebral body L2. The patient underwent surgical resection of the tumor. Postoperatively, there was a significant decrease in phosphaturia, normalization of serum phosphate, 1.25 dihydroxyvitamin D and plasma FGF23 concentration. Thereafter the patient's condition markedly improved concerning her motility and basic daily activities.

This case report demonstrates the first known case of TIO in the Slovakia and points to a long way from onset of symptoms toward correct diagnosis and successful surgical management.

1. Introduction

Tumor induced osteomalacia (TIO), primarily described as oncogenic osteomalacia, is uncommon syndrome caused by paraneoplastic overproduction of fibroblast growth factor-23 (FGF-23). It is clinically characterized by unspecific bone pain, multiple pathological fractures and progressive muscle weakness (Florenzano et al., 2017). Biochemically, the patients present chronic hypophosphatemia due to hyperphosphaturia, together with inappropriately normal or low serum 1.25 dihydroxycholecalciferol and elevated serum FGF-23 concentration.

FGF-23 is a phosphotropic hormone produced by osteocytes, playing a key role in mineral and bone metabolism. It reduces serum phosphate by suppressing the expression of type 2a and 2c sodium-phosphate contransporters in renal proximal tubuli. Also, the hormone decreases 1.25-dihydroxyvitamin D levels by reducing intestinal phosphate absorption. Studies in animal models demonstrated that FGF-23 itself acts as an inhibitor of bone mineralization probably due to direct effect on bone (Fukumoto, 2021). The paraneoplastic production of FGF-23 results in renal phosphate wasting with subsequent inhibition of vitamin D3 activation and disturbed bone mineralization leading to osteomalacia and bone fractures (Minisola et al., 2017; Brandi et al., 2021). Tumors causing TIO are usually small, benign, mesenchymal and localized in bone or soft tissue, anywhere in the body (Florenzano et al., 2021).

In general, TIO is a rare clinical condition and due to rarity its exact global incidence and prevalence remain unrecognized. Recently, the study from Denmark demonstrated the incidence lower than 0.13/100000 persons per year, while japanese survey revealed 0.04/100 000 per year (Abrahamsen et al., 2021; Endo et al., 2015). To date several hundreds cases were reported worldwide (Florenzano et al., 2017; Lee et al., 2021). Due to numerous nonspecific symptoms, the diagnosis of TIO is often delayed for several years and it represents the challenges for

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specialists in nephrology, endocrinology, rheumatology and orthopedics.

In this report we describe probably the first known case of TIO caused by benign PMT in the spinal region in female patient from Slovakia demonstrating a long period between onset of symptoms and final diagnosis that resulted in an appropriate management of the disease.

2. Case

A 53-year-old women was referred to the outpatient department of endocrinology in 2018 because of severe bone pain limiting her motility and daily activity as well as progressive loss of appetite. She came with crutches accompanied by her husband.

The family history and previous medical history were unremarkable until her 40-ties. In 2010 she was examined because of lower back pain with a CT finding of vertebral haemangioma of Th11. The patient underwent radiotherapy for analgesic purposes, unfortunately without the effect on the pain. Four years later she was admitted to the hospital due to left hip fracture, that was managed conservatively. At this time, the serum phosphate concentration was decreased, whereas serum calcium, calcidiol and parathyroid hormone concentrations were in normal range. Serum calcitriol levels were reduced and renal tubular reabsorption of phosphate was not measured. The patient was referred for follow up to the outpatient department of endocrinology and rheumatology. Laboratory investigations from that time are demonstrated in the Table 1.

Bone mineral density (BMD) at both lumbar and femoral sites indicated loss of bone mass in the range of osteopenia (T-score lumbar spine = −2.1, T-score at femur neck = −1.9, respectively). Due to pathologic hip fracture, and hypophosphatemia detected at biochemistry, the patient underwent ^{18}FDG-PET/CT scan that revealed multiple pathologic skeletal fractures (costae, sternum, os pubis and left hip). However pathologic tumor mass which could be responsible for these fractures, was not found by this evaluation.

Other investigations did not detect any tumor mass which could explain pathologic bone fractures and osteomalacia. Nephrologist considered the condition as a partial Fanconi syndrome and the therapy with alphacalcidol at a dose 1 μg/day plus phosphate at a dose of 1,5 g/day was prescribed. Due to adverse gastrointestinal effects of the elementary phosphate, the patient stopped to use it herself. Following years she was treated transiently with various bisphosphonates, particularly due to osteopenia and pathologic bone fractures, unfortunately her condition did not improve, and she complained to have progressive muscle weakness, loss of appetite and diffuse bone pain. Moreover, in 2017, she underwent total endoprothesis of the right hip because of pathologic fracture.

In 2018 the patient came to our department of endocrinology because of progressive worsening her condition. She presented severe lower back and leg pain and was unable to move without assistance. On physical examination, the patient was afebrile, eupnoic, and hyperstenic, able to move with crutches for a very short distance. She had normal blood pressure and heart rate.

The results of laboratory investigations at this time are shown in the Table 1. They confirmed hyposphosphatemia, increased serum bone isoenzyme of alkaline phosphatase (ALP) and lower serum 1.25-dihydroxyvitamin D concentration. Also, elevated fractional excretion of phosphate as well as decreased renal tubular reabsorption of phosphate (TmP/GFR) showed renal phosphate wasting typical for PMT.

CT scan as well as magnetic resonance imaging (MRI) of the spine (Fig. 1) visualized osteolytic tumor of the lumbar vertebral body L2, thus the ^{68}Ga DOTA TOC PET/CT was realized to better clarify the character of this pathologic lesion. This examination revealed osteolytic well vascularized tumor mass with high expression of somatostatin receptors (Fig. 2).

Based on this finding we supposed PMT and the patient was referred to the University Hospital in Prague to consider surgical removal of the tumor. The renal phosphate wasting was confirmed and together with high serum intact FGF-23, measured by chemiluminiscent immunoassay using a DiaSorin Liaison XL analyzer (DiaSorin S.p.A., Italy) indicated typical features for the presence of PMT.

Thereafter the patient underwent surgical resection of the tumor and histopathologic examination confirmed typical phosphaturic mesenchymal tumor (benign variant) (see Fig. 3). Immunohistochemical staining demonstrated positivity for FGF-23 confirming the FGF-23 secreting tumor (Fig. 3b).

Postoperatively, there was a significant decrease in phosphaturia, normalization of serum phosphate concentration and increase in serum 1.25(OH)$_2$D level. Decrease in serum FGF-23 to normal values indicated successful tumor resection (Table 1). Thereafter the patient's condition markedly improved concerning her motility and basic daily activities.

Table 1
The results of biochemical evaluation in the patient with TIO before and after treatment.

Laboratory tests	Preoperative values			Postoperative values	Reference range
	2014	2018	2020	2020	
Ca (mmol/L)	2.34	2.37	2.39	2.27	2.10–2.55
P (mmol/L)	0.59	0.51	0.46	0.82	0.74–1.52
ALP (ukat/L)	2.6	4.85	2.99	4.12	< 2.5
bALP (%)	–	76	–	–	19.1–67.7
25(OH)D (nmol/L)	75.2	38.5	58	–	>75
1.25(OH)$_2$D (ng/L)	23.1	–	12.5	149	19.9–79.3
PTH (pmol/L)	7.48	5.61	3.87	–	1.32–7.92
U-P (mmol/24 h)	15.6	23.3	–	38.63	10.0–39.90
FEPi (%)	–	23.1	26.2	1.9	7–20
TmP/GFR (mmol/L)			0.41	1.07	0.84–1.23
FGF-23 (ng/L)	–	–	1708.0	15.0	23–95.4

Abbreviations: ALP – serum total alkaline phosphatase, bALP – serum bone alkaline phosphatase, PTH –serum parathyroid hormone, FEPi – fractional excretion of phosphate, FGF-23 -– plasma fibroblast growth factor 23; U—P— urine phosphate, TmP/GFR – renal tubular reabsorption of phosphate.

3. Discussion

Herein we describe probably the first known case report of TIO caused by benign spinal PMT in the Slovak and Czech region. Moreover the present case demonstrates a typical delay between onset of symptoms and correct diagnosis due to misinterpretation of biochemical results and subsequent ineffective treatment. Commonly, patients with TIO are misdiagnosed with a variety of musculoskeletal, neurological and rheumatological diseases. The average time from onset of symptoms to correct diagnosis is referred approximately 2.9 years and to tumor resection from 5.3 to 5.7 years (Brandi et al., 2021; Feng et al., 2017) although other studies reported wider range varying from 2.5 to 28 years (González et al., 2017). For this reason the diagnosis of TIO is often challenging, as this condition may significantly impair somatic, psychological and social wellbeing of the patient (Seemann et al., 2019).

Similarly to many other cases our patient presented with nonspecific symptoms such as bone pain, progressive weakness and subsequently with multiple bone fractures. In studies on larger groups of patients bone pain together with difficulty in walking were leading symptoms of TIO (González et al., 2017; Seemann et al., 2019). As previously demonstrated, patients with TIO usually exert lower BMD which requires careful differential diagnosis with osteoporosis (Colangelo et al., 2020). In the presented case, BMD in the range of osteopenia together with multiple fractures was misinterpreted with osteoporosis, leading to inappropriate prescription of bisphosphonates.

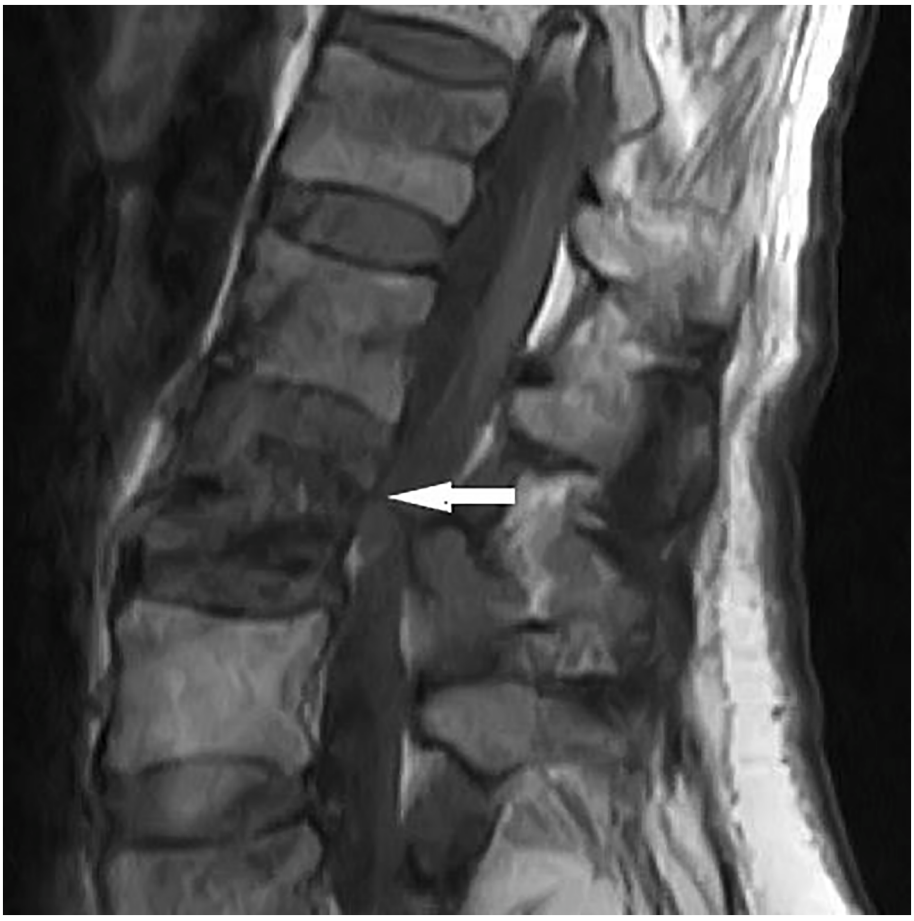

Fig. 1. Magnetic resonance imaging of the spine reveals osteolytic tumor of the L2 Vertebral body.

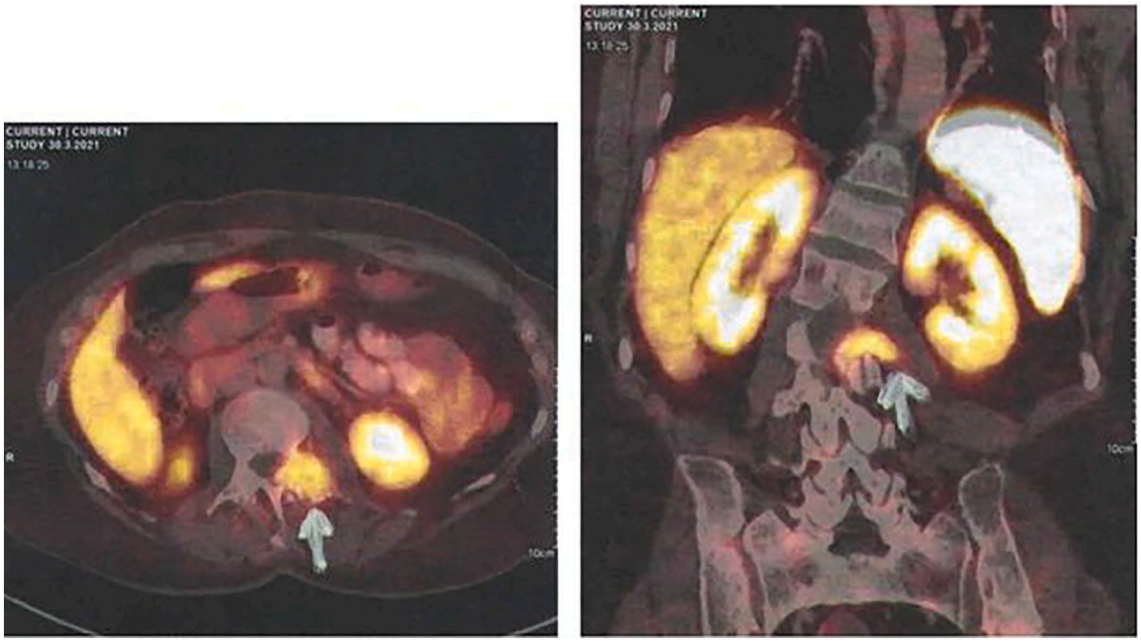

Fig. 2. ^{68}Ga DOTA TOC PET/CT demonstrates tumor mass with high expression of somatostatin receptors.

Classic laboratory findings include hypophosphatemia, renal phosphate wasting expressed by reduced TmP/GFR and elevated fractional excretion of phosphate, normal serum calcium and normal PTH concentration. There are decreased serum level of 1.25 dihydroxyvitamin D and significantly elevated serum FGF-23 concentration (Florenzano et al., 2021; Gohil and Imel, 2019). The measurement of

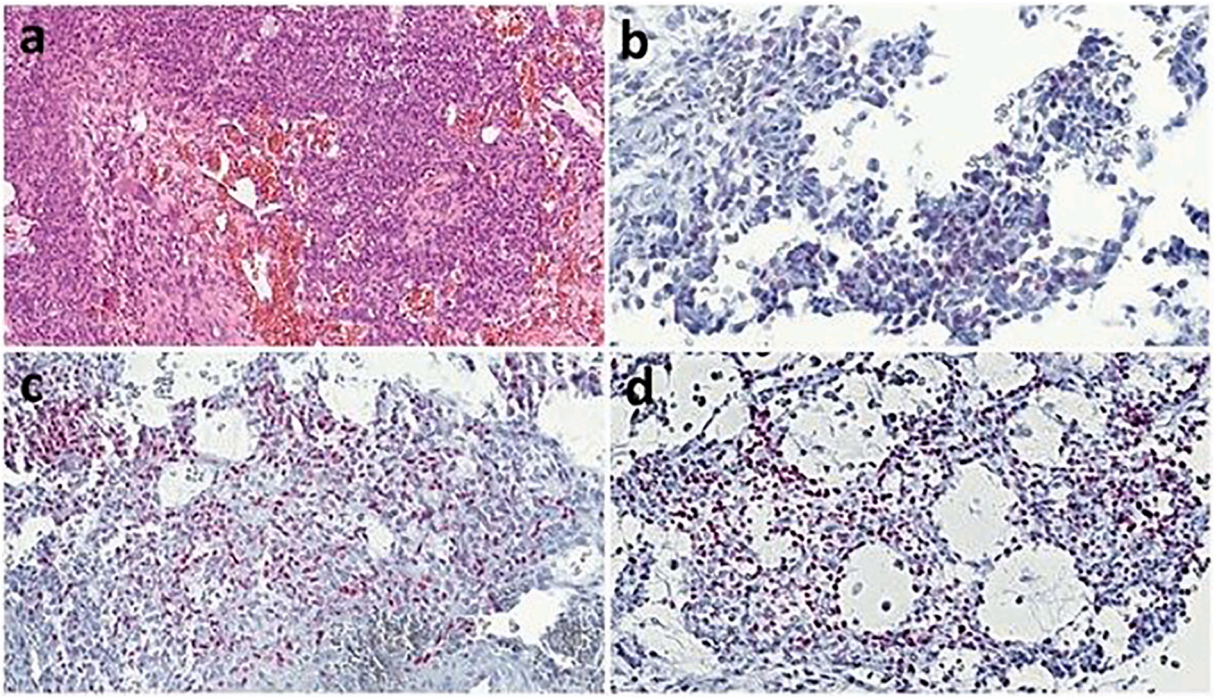

Fig. 3. Histopathological evaluation of the tumor. a) Hematoxylin&eosin staining shows relatively uniform and moderately cellular tumor composed of bland spindled to ovoid cells with minimal mitotic activity and occasional admixture of osteoclast- like giant cells. b) In some areas, FGF-23 immunohistochemistry showed a distinct dot like perinuclear expression, red staining in tumor cells, c) Diffuse strong nuclear expression was seen with ERG and d) with SATB2.
Immunohistochemical analysis was performed using a Ventana BenchMark ULTRA (Ventana Medical System, Inc., Tucson, Arizona). The following primary antibodies were used: ERG (EPR3864, prediluted, Ventana Medican Systems, Inc.), SAT-B2 (CL0276, 1:100; Atlas Antibodies, Stockholm Sweden), FGF23 (FG322-3, 1:50; Adipogen Corp., San Diego, CA, USA). The primary antibodies were visualized employing the enzymes alkaline phosphatase or peroxidase as detecting systems (both purchased from Ventana Medical System, Inc.).

TmP/GFR should be an important diagnostic component when assessing otherwise unexplained osteomalacia or multiple fractures (Minisola et al., 2017).

Once the diagnosis of TIO is established, localization of culprit tumor is crucial for further successful management of the patient (Brandi et al., 2021; Florenzano et al., 2021). Anatomical localization techniques such as CT or MRI can be helpful in the detection of the culprit tumor, which are generally osteolytic, less commonly osteosclerotic or mixed (Hussein et al., 2021). Generally CT and MRI are of advantage because of their high resolution, but there are poor data concerning the specific features of PMTs. On the other side TIO associated tumors have been demonstrated to express somatostatin receptors (SSTR), in particular type 2 (SSTR2) (Jan de Beur et al., 2002). Data indicate that ^{68}Ga DOTATOC PET/CT scan represents the most sensitive and specific functional imaging technique for detection of PMT (Zhang et al., 2015; Rayamajhi et al., 2019). In the present case the mesenchymal tumor was visualized in the lumbar vertebral body L2, also using ^{68}Ga DOTATOC PET/CT scan. After surgical removal, the benign variant of PMT was confirmed histologically and a significant drop in plasma FGF-23 level to normal values early after surgery suggested complete tumor removal.

Involvement of spine with TIO associated tumors is exceedingly rare and has been reported in a few isolated cases (Puthenveetil et al., 2013; Jiang et al., 2012). Analysis of 39 TIO cases demonstrated that most tumors originated in the lower extremities (42%) and craniofacial area (21%), but also occurred in the hip and pelvis (12%), abdomen, thorax and neck (11%) (Maehara et al., 2016). In the study of Lee et al. among 12 patients with TIO, two skeletal lesions were located in vertebral body (C2 and L3) (Lee et al., 2021). Occasionally PMTs were found in rare sites, such as glomus, scapula and various soft tissues (Florenzano et al., 2017; Puthenveetil et al., 2013; Jiang et al., 2012).

In the updated review of Wang et al. among totally 18 patients with spinal PMTs, lumbar vertebra was the most common location of the tumor. Majority of spinal PMTs were benign but two cases were malignant tumors with one invasive into the spinal canal and vertebral body (Wang et al., 2019).

Once the tumor mass is identified, its complete resection is the only definitive treatment of TIO. In most cases, the surgical treatment leads to prompt correction of all the clinical manifestations of the syndrome as well as to correction of laboratory findings (Minisola et al., 2017). For patients whose tumor cannot be detected or completely resected, management includes phosphate and calcitriol replacement (Shrivastava et al., 2021). Recently monoclonal antibody against FGF-23, *i.e.* burosumab has become preferred treatment option for these patients (Brandi et al., 2021). In the study of Jan de Beur et al., treatment with burosumab was associated with improvements in phosphate metabolism and osteomalacia (Jan de Beur et al., 2021).

Patients with TIO usually have an excellent prognosis, however some cases with recurrence of culprit tumor have been reported. In the Study of Rimesh et al. surgical resection led to cure in 72.7% of patients whereas tumor recurrence was detected in 9% of cases. Postoperative follow-up should be realized in all patients and periodic monitoring serum phosphate initially every six months is recommended (Pal et al., 2019).

In conclusion, we report a case of female patient with TIO caused by PMT located in the lumbar vertebral body L2. This paraneoplastic syndrome significantly impaired her somatic, psychological and social health as well as quality of life. Also, we point to a long way from the onset of symptoms toward correct diagnosis and successful surgical management.

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Ethics statement

Written informed consent was obtained from the patient for publications of this article.

CRediT authorship contribution statement

Lenka Filipova – substantial contribution to the acquisition of data, data analysis, drafting the article.

Vít Zikán - substantial contribution to the acquisition of data, data analysis, drafting the article.

Michal Kršek – data analysis and interpretation, revising the draft of the work.

David Netuka – acquisition of data, data analysis and interpretation.

Michael Michal - acquisition of data, drafting the article.

Ivica Lazúrová - conception and design, revising the draft of the work critically for important intellectual content and final approval of the version to be submitted.

Declaration of competing interest

The authors declare that the case report description was realized in the absence of any commercial or financial relationship that could represent a potential conflict of interest.

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