Tumor-induced osteomalacia – a mystery illness beyond aches, pains, and depression

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Objective. Tumor-induced osteomalacia (TIO) is a rare paraneoplastic syndrome characterized by chronic hypophosphatemia and osteomalacia. We present case of a patient with a protracted clinical course of TIO. TIO profoundly affected every aspect of his life with subsequent profound physical and psychosocial disabilities.

Method. The review of a complex clinical presentation, serial laboratory investigations, and imaging modalities of a patient with TIO caused by a mesenchymal tumor.

Results. The patient presented with chronic lower back pain, severe bilateral leg weakness, and multiple pathological fractures due to severe osteoporosis. His investigations revealed hypophosphatemia, low 1,25 dihydroxyvitamin D, phosphaturia and normal serum calcium, and parathyroid hormone. Elevated fibroblast growth factor 23 (FGF23) confirmed the diagnosis of TIO and ⁶⁸Ga-DOTATATE-positron emission tomography/computed tomography (PET/CT) imaging correctly identified a tumor in the left femoral head. His clinical features and biochemical abnormalities promptly recovered after successful surgical resection of the mesenchymal tumor.

Conclusion. The present case demonstrated the need to extensively investigate causes of generalized bone pain in patients with hypophosphatemia, as TIO is highly curable. Importantly, ⁶⁸Ga-DOTATATE PET/CT imaging successfully identified the FGF23 producing tumor, which was undetectable by conventional imaging, favoring its early use in suspected TIO presentation. The present report highlights the importance of timely diagnosis of this complex medical condition, aiming to improve general awareness and enable better clinical outcomes for this rare disorder.

Key words: tumor-induced osteomalacia, oncogenic osteomalacia, paraneoplastic hypophosphatemia, mesenchymal tumor, phosphatonin, fibroblast growth factor-23

Tumor-induced osteomalacia (TIO), previously known as oncogenic osteomalacia, is a rare paraneoplastic metabolic bone disorder characterized by renal phosphate wasting, hypophosphatemia and osteomalacia (Carpenter 2003; Hu et al. 2016). This complex paraneoplastic syndrome was first described in 1947 by McCance with less than 500 reported cases to date (Liu et al. 2019). Lack of awareness amongst

clinicians often leads to substantial delay in diagnosis of this rare condition with significant implications for affected individuals.

The pathogenesis of TIO is related to uncontrolled secretion of fibroblast growth factor 23 (FGF23) by mesenchymal tumor tissues. FGF23 regulates vitamin D and phosphate metabolism as it inhibits phosphate reabsorption at the proximal tubule, promoting renal

phosphate excretion and inhibiting calcitriol production (Perwad et al. 2007). Low serum phosphate is physiologically accompanied by suppressed FGF23; consequently, finding of elevated serum FGF23 in hypophosphatemia strongly suggests either TIO (Chong et al. 2011) or an hereditary syndrome such as X-linked hypophosphatemic rickets (XLH), autosomal dominant (ADHR) and autosomal recessive (ARHR) hypophosphatemic rickets (Yamazaki et al. 2002; Jonsson et al. 2003).

We present a patient with TIO in whom delayed diagnosis was accompanied by serious physical and psychosocial disabilities that have significantly improved after surgical resection of causative tumor. We highlight the importance of timely diagnosis of this rare medical condition with the aim of improving the general awareness of this rare disorder.

Subject and results

A 48-year-old man presented with an acute exacerbation of chronic lower back pain and severe bilateral leg weakness, present for at least 6 years. Pain severely restricted his mobility confining him to life in his apartment. He was of short stature with height 155 cm, weight of 80 kg and BMI of 33. Neurological examination revealed predominantly proximal muscle weakness in both upper and both lower limbs and associated muscle wasting. Whole spine magnetic resonance imaging (MRI) demonstrated mild disc disease without any obvious thoracolumbar spine fractures or enhancing lesions. Nerve conduction studies (2017) showed no evidence of generalized

large fiber neuropathy or demyelinating features, and without clear neurogenic or myopathic features in the muscles sampled. Screens for vasculitis and multiple myeloma were negative.

Biochemistry found hypophosphatemia [0.21–0.76 mmol/L, reference range (RR) 0.75–1.50 mmol/L] and despite intravenous and oral phosphate supplementations (up to 1 g/day) his phosphate values did not revert to the normal reference range. Serum calcium level remained within normal range. He had consistently raised alkaline phosphatase (ALP) between 175–347 U/L (RR 30–110 U/L), elevated intact parathyroid hormone (iPTH) up to 27.4 pmol/L (RR 1.6–6.9 pmol/L) and low 1,25-dihydroxyvitamin D [1,25(OH)₂D] of 42 nmol/L (RR 60–200 nmol/L) which improved over time with calcitriol supplementation (up to 1.25 µg per day) (Table 1). Estimated maximum tubular reabsorption of phosphorus corrected for glomerular filtration rate (TmP/GFR) revealed reduced fractional reabsorption of phosphate of 0.433 mmol/L (RR 0.9–1.35 mmol/L for male aged years 45–55), consistent with renal phosphate wasting (Jan de Beur 2005).

A whole-body bone scan revealed thoracolumbar scoliosis and lower limb arthritis. Bone mineral density (BMD) measured by Dual Energy X-ray Absorptiometry (DXA) was severely low with lumbar spine (LS) T score of –4.6, femoral neck (FN) T score of –2.9, and total hip (TH) T score of –4.1.

The patient continued to experience exacerbations of his back pain, not alleviated by CT guided steroid injections, as well pain radiating to his knees, shoulder and chest. Pelvic CT, skeletal survey and

Figure 1. 68Ga-DOTATATE ([68Ga-DOTA0-Ty3] octreotate) PET/CT scan demonstrates a single abnormal uptake in the left femoral head.

Table 1
Results of patient's laboratory tests over time

Parameters (ranges)	Preoperative values					Postoperative values	
	20/06/17	31/12/17	16/02/18	31/03/18	27/09/19	09/12/19	Reference interval
	04/07/17	16/01/18	17/02/18	31/03/18	11/11/19	14/07/20	
Na (mmol/L)	136–142	137–142	141–143	144	139–145	139–143	135–145
K (mmol/L)	3.7–4.9	5.1	4.6–4.7	4.8	4.0–5.1	4.8–5.4	3.5–5.2
Bicarbonate (mmol/L)	23–26	25–28	22–25	25	25–30	23–29	22–32
Creatinine (μmol/L)	69–86	74–76	70–77	72	60–69	56–66	60–110
eGFR (mL/min)	>90	>90	>90	>90	>90	>90	>90
Ca (mmol/L)	2.14–2.41	2.39–2.44	2.05 –2.13	2.37	2.28–2.36	2.32–2.48	2.10–2.60
Corrected Ca (mmol/L)	2.16–2.34	2.41–2.44	2.10–2.16	2.34	2.36–2.38	2.32–2.44	2.10–2.60
Mg (mmol/L)	8.82–1.06	0.80	0.77–0.79	0.78	0.77–0.83	0.73–0.89	0.7–1.1
PO4 (mmol/L)	0.34–0.68	0.49–0.60	0.24–0.69	0.21	0.49–0.76	1.32–1.66	0.75–1.50
iPTH (pmol/L)	27.4	9.9	/	/	8.1	5.5– 18.6	1.6–6.9
FGF23 (pg/ml)					205	12.7–43.1	<50
HbA1c (%)	/	5.9	/	/	/	/	4.0–6.0
25(OH)D (nmol/L)	/	58	/	/	41–53	70–77	51–250
1,25(OH) ₂ D (nmol/L)		42			62	95	60–200
Albumin (g/L)	33–41	35–38	33–34	/	31–37	34–40	33–48
Alanine aminotransferase (U/L)	31	38	/	/	5–17	/	<45
Aspartate aminotransferase (U/L)	26–28	36	/	/	11–21	/	<45
Alkaline phosphatase (U/L)	147–175	347	/	/	347	283	30–110
γ-Glutamyl transferase (U/L)	92–124	166	/	/	34–57	/	0–50
Bilirubin (μmol/L)	7–9	8	/	/	3–6	/	0–25
Creatinine Kinase (U/L)	42–63	/	/	/	/	/	<200
Free T4 (pmol/L)	/	17.6	/	/	/	/	12.0–22.0
Free T3 (pmol/L)	/	5.0	/	/	/	/	3.10–6.80
TSH (mIU/L)	/	0.6	/	/	0.7	/	0.27–4.20
ACTH (ng/mL)	17.7	3.9–6.7	/	/	12.8	7.2–14.7	7.2–63.3
Cortisol (nmol/L)	312	64–638	/	/	487	/	166–507
24 h urine free cortisol (nmol/day)		30					<166
Testosterone (nmol/L)	11.4	6.5	/	/	8.0	/	10.4–30.9
Estradiol (pmol/L)	/	71–78	/	/	/		36–155
DHEAS (μmol/L)	/	<2.1	/	/	/	/	4.5–48
LH (mIU/ml)	8.2	2.5	/	/	2.7	/	1.5–12.4
FSH (mIU/L)	2.6	3.3	/	/	2.2	/	1.7–8.6
Prolactin (mU/L)	/	477–512	/	/	391	/	86–324
IGF1 (nmol/L)	/	28	/	/	19	/	10.0–32.5
Hemoglobin (g/L)	132–153	130–147	130	146	115–127	113–121	130–180
Platelets (×10 ⁹ /L)	303–374	257–309	274	276	276–334	310–669	150–450

Abbreviations: Na – sodium; K – potassium; eGFR – estimated glomerular filtration rate; Ca – calcium, Mg – magnesium; PO4 – phosphorous; iPTH – intact parathyroid hormone; FGF23 – fibroblast growth factor 23; HbA1c – hemoglobin A1c; 25(OH)D – 25-hydroxyvitamin D; 1,25(OH)₂D – 1,25-dihydroxyvitamin D; T4 – thyroxine; T3 – triiodothyronine; TSH – thyroid stimulating hormone; ACTH – adrenocorticotrophic hormone; DHEAS – dehydroepiandrosterone sulfate; LH – luteinizing hormone; FSH – follicle-stimulating hormone; IGF1 – insulin-like growth factor 1.

repeat lumbar spine MRI showed no evidence of any lytic lesions or fractures. Over the next 18 months the patient suffered from minimal trauma fractures involving his bilateral clavicles, multiple ribs, right humeral neck and left humeral midshaft. After two years, a repeat DXA scan showed decrease in bone density with lumbar spine (LS) T score of -5.2 and total hip (TH) T score of -3.5 despite calcitriol (0.5 µg twice daily), cholecalciferol (50 µg daily) and a trial of denosumab. Review of his hormonal assays revealed hypogonadotropic hypogonadism without evidence of an additional endocrinopathy (Table 1). No pituitary pathology was found on MRI.

The patient continued to find phosphate replacement challenging, due to ongoing diarrhea, hence the persistent hypophosphatemia (Table 1). Finally, his progressive physical disability led to financial crisis when he lost ownership of his home.

⁶⁸Ga-DOTATATE ([⁶⁸Ga-DOTA0-Ty3] octreotate) positron emission tomography/computed tomography (PET/CT) scan showed a single focus of significant abnormal uptake in the left femoral head (Figure 1). At this time, serum intact FGF23 was elevated at 205 pg/mL (DiaSorin Liaison, RR <50 pg/mL). MRI revealed bilateral non-acute femoral neck fractures and left sided avascular necrosis, treated subsequently with bilateral total hip replacement. Histological analysis confirmed the presence of a phosphaturic mesenchymal tumor in the left femoral head measuring 27 mm. Post-operative FGF23 declined to 12.7 pg/mL post-operatively and remained within the normal reference at 43.1 pg/mL at 10 months after the surgery. His recovery was complicated by “Hungry Bone Syndrome” treated successfully with calcium and calcitriol replacement. He reported complete resolution of his chronic pain. He has become more independent with the activities of daily living without falls or fractures, at 10 months post-surgery. He no longer suffers from severe depression, and he has actively participated in his rehabilitation program. Mark’s progress was assessed by the 36-Item Short Form Health Survey (SF-36) with a 0–100 scale. The score of 0 in SF-36 is indicative of the maximum disability while a score of 100 is equivalent to no disability (Ware and Sherbourne 1992). Postoperative improvement in patient’s health status [quality of life (QoL) score of 80 out of 100] was reflected by his highly perceived satisfaction with change in his overall health (QoL score of 100). In particular, the patient reported a major improvement in his social functioning (QoL score of 50) with lesser change (QoL scores of 30) for both his physical functioning and emotional well-being.

Discussion

The present case illustrates the prolonged and dramatic presentation of a patient with TIO that significantly affected all aspects of patient’s life. He presented with bone pain, muscle weakness, and pathological fractures, in the context of severely low bone density, which was initially attributed to hypogonadism (Campion and Maricic 2003). Delayed diagnosis of TIO severely affected his physical health leaving him bed bound with profound depression subsequently leading to adverse financial outcomes. TIO has been previously reported to exert negative psychological impact on affected individuals due profound physical disability, severe pain, and prolonged time leading to diagnosis, in more extreme cases culminating in patient’s suicidal attempts (Seemann et al. 2019). In particular, TIO can have devastating impact on psychological wellbeing in patients, who are affected by an underlying mental illness. Nonspecific symptoms of TIO may lead to erroneous diagnoses of other rheumatological, endocrinological or neurological disorders.

Classic features of osteomalacia of any cause include bone pain, musculoskeletal weakness, and recurrent pathological fractures (Econs and Drezner 1994). Laboratory features of TIO include hypophosphatemia, phosphaturia, normal PTH and serum calcium, decreased 1,25(OH)₂D, elevated ALP and raised FGF23 (Jan de Beur 2005; Wu et al. 2017; Yu et al. 2017). Differential diagnosis includes hereditary hypophosphatemic syndromes, and clues to these include short stature, rachitic bony deformity and poor dentition; genetic testing for *PHEX* (XLH), *FGF23* (ADHR), and *DMP1* or *ENPP1* (ARHR) may be useful in excluding these disorders (The HYP Consortium 1995; ADHR Consortium 2000).

TIO tumors are divided into 4 subtypes: phosphaturic mesenchymal tumor (PMT) mixed connective tissue variant, osteoblastoma-like variant, ossified fibroid-like variant, and non-ossifying fibroma-like variant, with PMT being the most common (Econs and Drezner 1994; Wu et al. 2017). They are generally located in bone or soft tissues (Siegel et al. 2002).

Once diagnosed, TIO prognosis is generally good as most FGF23-secreting tumors are benign and rarely metastasize (Edmister and Sundaram 2002). However, diagnosis of these tumors is frequently delayed by many years due to their occult nature, small size and atypical location (Jagtap et al. 2011). Tumor resection leads to prompt correction of all the clinical and biochemical manifestations of this syndrome (Ryan and Reiss 1984; Chong et al. 2011),

and gradual re-mineralization of the osteoid matrix (Hautmann et al. 2015). Localization of FGF23 secreting tumors is often challenging as they are often small in size and slow growing, moreover, they are frequently located in atypical skeletal sites (Liu et al. 2019). Various imaging techniques are often used including functional imaging with octreotide scintigraphy, fluorodeoxyglucose (FDG) PET/CT, ^{68}Ga DOTATATE PET/CT, anatomical imaging with MRI and selective venous sampling for FGF23 levels (Colt et al. 2005; Clifton-Bligh et al. 2013; El-Maouche et al. 2016). In our case, ^{68}Ga DOTATATE PET/CT detected the tumor lesion in our patient. The high sensitivity and specificity of ^{68}Ga DOTATATE PET/CT favors its early use in suspected cases of TIO (Clifton-Bligh et al. 2013).

Medical treatment of TIO involves high doses of oral phosphate and calcitriol, as oral phosphate replacement alone is usually insufficient for correcting

hypophosphatemia. Gastrointestinal absorption phosphate remains impaired in the setting of low $1,25(\text{OH})_2\text{D}$ (Slot-Steenks et al. 2016). Oral phosphate replacement is often poorly tolerated and leads to diarrhea with subsequent noncompliance.

In summary, our case illustrates an insidious and dramatic impact of TIO on physical health, psychological and financial aspects of life in the person who is affected by this debilitating medical condition. Many factors contributed to delayed diagnosis of TIO in this case, including his physical disability with limited access to medical care, lack of awareness of this rare condition among clinicians and restricted diagnostic resources. The present case highlights the need to extensively investigate the causes of generalized bone pain in patients with hypophosphatemia, as TIO is highly curable (Siegel et al. 2002). Furthermore, prompt diagnosis and tumor excision can result in dramatic an improvement in quality of life.

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