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CASE REPORT

Tumor-induced osteomalacia originating from bones: a report of two cases and literature review

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Abstract

Tumor-induced osteomalacia (TIO) is caused by a small mesenchymal tumor and characterized by hypophosphatemia, phosphaturia, low levels of $1,25(OH)_2$ vitamin D, and elevated levels of alkaline phosphatase and fibroblast growth factor 23 (FGF-23). The typical symptoms include bone pain, pseudofracture, osteoporosis, and muscle weakness. These symptoms are due to the overproduction of FGF-23 as a phosphaturic agent. Diagnosis of this disease is challenging because of the small lesion size and chronic symptoms. The cases described in this report were two patients with bone pain, severe muscle weakness, and difficulty performing activities, who were found to have TIO. The tumors were found through various imaging modalities, including computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET). The tumors responsible for the symptoms were localized on their femurs and resection resulted in normalization of their blood chemistries and complaints.

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Key words tumor-induced osteomalacia (TIO); hypophosphatemia; fibroblast growth factor 23 (FGF-23); osteoporosis

Tumor-induced osteomalacia (TIO) was first reported by Macane in 1947 [1], and Prade later described the relationship between mesenchymal tumors and osteomalacia. Evidence suggests that tumors overexpressing fibroblast growth factor 23 (FGF-23) are responsible for the hypophosphatemia and osteomalacia [2–4]. FGF-23 is produced by osteogenic cells, osteoblasts, and osteocytes and exerts inhibitory activity on type IIa and IIc sodium-phosphate (NaPiT-IIa and IIc) co-transport systems in proximal tubules, promoting hyperphosphaturia, and inhibiting renal 1α-hydroxylation of 25-hydroxy vitamin D [2–5]. Overproduction of FGF-23 is also associated with neurofibromatosis, epidermic nevus syndrome, McCune-Albright syndrome (MAS), and fibrous dysplasia [3–5].

TIO is usually associated with benign soft tissue or bone neoplasms of mesenchymal origin. These tumors typically follow a benign clinical course and the local recurrence rate is < 5% even in the rare malignant cases [2, 6]. Successful identification and removal of the tumor leads to full recovery in the majority of cases.

We report two cases of TIO: one is a 54-year-old woman with TIO and femoral head necrosis. PET/CT and magnetic resonance images (MRI) revealed a tumor on the lateral femoral condyle; the case other is a 41-year-old man with negative PET/CT results but with a suspicious lesion on the femoral neck. Both patients were thoroughly examined and underwent tumor resection with acceptable outcomes and current prognoses.

Case reports

Case 1

A 54-year-old woman complained of pain in her left hip and lumbosacral region, as well as chronic bone pain, muscle weakness, and difficulty in ambulation since March 2012. She was admitted to a local hospital due to acute aggravation of her symptoms. She was diagnosed with femoral head necrosis and hypophosphatemic osteomalacia of unknown cause. She had undergone drilling decompression and bone grafting for the femoral head necrosis, but the surgery had no effect. Her symptoms worsened gradually; she required a walker for walking

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Table 1 Laboratory data of Case 1

Laboratory value	Serum phosphate (U/L)	Serum calcium (mmol/L)	Serum alkaline phosphatase (U/L)	Urine phosphorus (mmol/L)	Serum FGF-23 (pg/mL)
Before THA	0.47 ↓	2.16 (N)	132 ↑	/	/
After THA	0.37 ↓	2.14 ↓	140 ↑	/	/
Before resection	0.44 ↓	2.15 (N)	145 ↑	72.3 ↑	132 ↑
1 week after resection	0.86 (N)	2.25 (N)	110 (N)	68.3 (N)	40 (N)
1 month after resection	1.02 (N)	2.16 (N)	107 (N)	30.2 (N)	21 (N)
4 months after resection	1.10 (N)	2.28 (N)	102 (N)	26.3 (N)	14 (N)

The low levels of serum phosphate and high levels of serum alkaline phosphatase, urine phosphorus, and serum FGF-23 did not change until complete resection of TIO. THA: total hip arthroplasty; FGF-23: fibroblast growth factor 23; N: normal

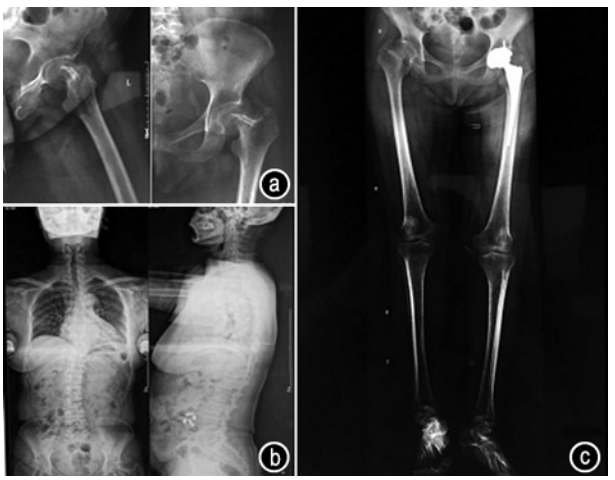

Fig. 1 X-ray of Case 1 showing femoral head necrosis (a), the change of drilling decompression bone grafting (b) and osteoporosis of the spine (c)

and often took analgesic drugs. Over the next three years, her symptoms had not improved and she ceased treatment. She was referred to our hospital (Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China) in 2015. The results of cardiovascular, pulmonary, and abdominal examinations were unremarkable. Her hip was painful during flexion, abduction, and external rotation. She denied any family history of metabolic bone disease or anything else.

Initial laboratory studies showed a low serum phosphate level (0.47 U/L), normal serum calcium level (2.16 mmol/L), and high serum alkaline phosphatase level (132 U/L; Table 1). Her parathormone level, erythrocyte sedimentation rate (ESR), and rheumatoid factor levels were also normal.

Radiography showed femoral head necrosis and osteoporosis of multiple bones (Fig. 1). Dual energy X-ray absorptiometry (DXA) scans showed a region of low mineral density (Z-score of the lumbar spine: –2.1; Z-score of the femoral neck: –2.5). Standard X-ray imaging showed no bony lesions in the femur. The patient underwent total hip arthroplasty (THA) in April 2015, and her left hip pain resolved after the operation. However, she still reported pain in the lumbosacral region and was generally weak. Laboratory testing revealed a calcium level of 2.14 mmol/L, a low serum phosphate level of 0.37 U/L, and a high serum alkaline phosphatase level of 140 U/L. Her serum FGF-23 levels were as high as 132 pg/mL (Table 1).

Unfortunately the patient did not achieve clinical remission. Her serum phosphate level remained very low. Positron emission tomography/computed tomography (PET/CT) showed foci with abnormal radiotracer uptake in her left lower limb (Fig. 2a and 2b). Additional investigations including magnetic resonance imaging (MRI) showed that the lesion was located in her left distal femur; the low-density tumor was oval in shape and 1.5 cm in diameter (Fig. 2c–2e). We suspected a close relationship between the hypophosphatemia and the lesion for a diagnosis of TIO. The high levels of FGF-23 further supported this diagnosis. The patient underwent complete resection of the lesion. The texture of tumor was soft, and rich in vessels (Fig. 3a). The tumor volume was 1.5 cm × 1.1 cm × 1.2 cm.

Histological examination of the lesion revealed spindle cells intermingling with blood vessels, and scattered deposits of calcified extracellular matrix. A few mitoses were observed in the multinucleated giant cells in the matrix with capillary proliferation in the bone (Fig. 3b–3d). Immunohistochemical analysis of the tumor was positive for CD34, but negative for CD68. There was no evidence of malignancy.

One week after surgery, her serum phosphate, calcium, serum alkaline phosphatase, and serum FGF-23 levels rapidly returned to 0.86 U/L, 2.25 mmol/L, 110 U/L, and 40, respectively (Table 1). After resection, the patient's symptoms gradually improved. She was able to walk unassisted. One month later, her serum calcium and phosphorus, and FGF-23 levels were within the normal range without medical treatment. At follow-up 4 months later, she reported to be in good rehabilitation, and her serum biochemistry results remained normal.

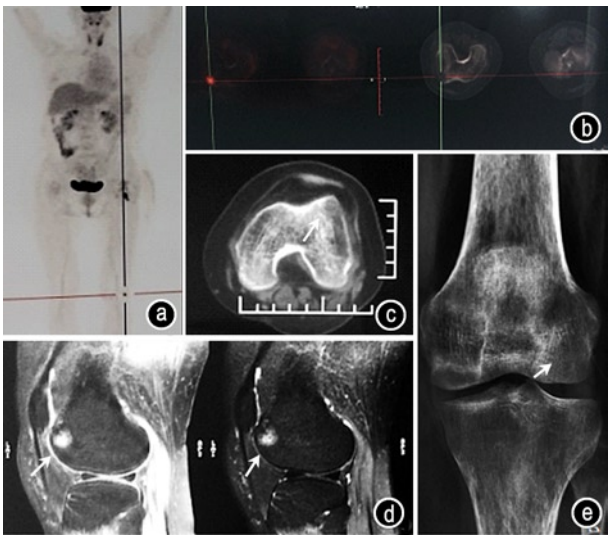

Fig. 2 (a and b) PET/CT showing foci of abnormal radiotracer uptake in the distal femur. (c–e) X-ray, CT, and MRI showing high signal intensity in the condyle of the femur and a small tumor (arrows)

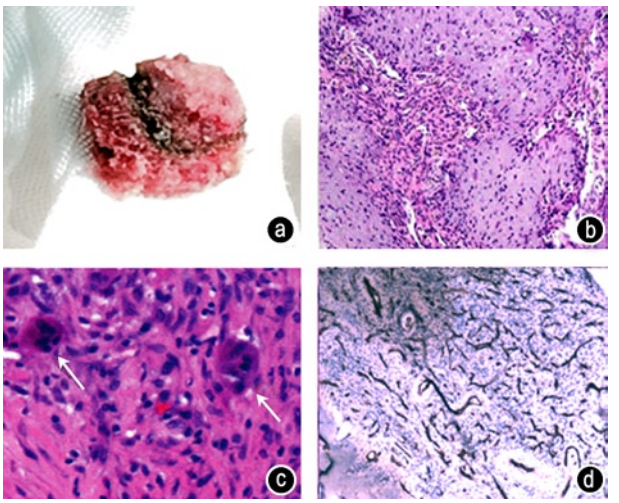

Fig. 3 (a) The tumor mainly comprised spindle cells with deeply stained nuclei and few mitoses and scattered deposits of calcified extracellular matrix; (b and c) Occasional scattered multinucleated giant cells were also visible (Hematoxylin and eosin stain); (d) Immunohistochemical examination of the neoplasm showed CD34 positivity

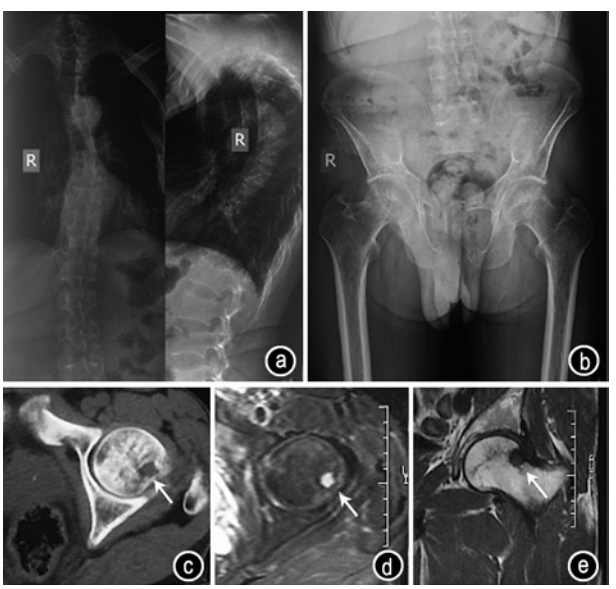

Fig. 4 (a and b) X-ray of Case 2 showing severe osteoporosis and spinal deformity; (c–e) Further CT/MRI revealed a suspicious lesion in the left collum femoris; the low-density tumor was circular, about 0.8 cm in diameter, and was not visible by PET/CT

Case 2

A 41-year-old man presented to our Endocrine Department (Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China) in November 2015 complaining of progressive multiple joint pain and muscle weakness. His initial symptoms began approximately two years earlier as bilateral pain in his hips, and he reported to the primary hospital with bilateral hip pain and muscle weakness. Initial laboratory analysis revealed a low levels of serum phosphate (0.31 U/L) and serum calcium (2.03 mmol/L); high serum alkaline phosphatase level (255 U/L); normal levels of parathormone; normal erythrocyte sedimentation rate (ESR); normal level of human leukocyte antigen B27 (HLA-B27); and reduced 1,25-dihydroxy vitamin D and 24-h urine phosphorus levels. Radiography showed osteopenia, multiple collapsed vertebral bodies, rachiterata, multiple rib fractures, and bilateral innominatum and sacrum fractures; however, no bony lesions were visible in the left collum femoris (Fig. 4a and 4b). Additional investigations including CT and MRI showed that the lesion was located in the left collum femoris and that the tumor was circular, hypodense, and 0.8 cm in diameter (Fig. 4c–4e). PET/CT imaging revealed multiple bone lesions on the ribs, vertebral body, and the body of the ilium, but no abnormal uptake in his left femur. He was diagnosed with ankylosing spondylitis and osteoporosis, but the treatment had no effect, and the patient's symptoms progressively worsened. He had no history of tumor or metabolic bone disease.

Based on these facts, we considered a diagnosis of tumor-induced osteomalacia (TIO). The patient was transferred to the Orthopedics Department for surgical treatment. In our department, the patient underwent open curettage of the collum femoris lesion and graft with bone substitutes. The texture of tumor was pliable with osteolysis around the tumor. The tumor volume was 10 mm × 8 mm × 8 mm. Histopathological examination revealed short spindle cells with deeply stained nuclei, indistinct nucleoli, and eosinophilic cytoplasm in the matrix intermingling with blood vessels. Mitoses were

Table 2 Laboratory data of Case 2

Laboratory value	Serum phosphate (U/L)	Serum calcium (mmol/L)	Serum alkaline phosphatase (U/L)	Urine phosphorus (mmol/L)	Serum FGF-23 (pg/mL)
Before resection	0.31 ↓	2.03 ↓	225 ↑	8.3 ↓	62 ↑
1 week after resection	0.76 ↓	2.29 (N)	212 ↑	12.3 ↓	52 ↑
1 month after resection	0.97 (N)	2.26 (N)	168 ↑	20.2 (N)	43 (N)
2 months after resection	1.05 (N)	2.06 ↓	108 ↑	27.2 (N)	25 (N)

This patient showed low levels of serum phosphate and urine phosphorus and high serum levels of alkaline phosphatase and FGF-23. FGF-23 gradually returned to normal levels after complete tumor resection. FGF-23: fibroblast growth factor 23; N: normal

rare. Grungy extracellular calcifications were noted. Immunohistochemical studies of the tumor were positive for CD68, CD163, SMA, S-100, and negative for CD31, CD34, β-catenin, caldesmon, desmin, and STAT6. The Ki-67 index was 3%–5%. Based on these findings, the tumor was diagnosed as a TIO.

One week after surgery, his serum phosphate level returned to 0.76 U/L and fluctuated slightly. His calcium, serum alkaline phosphatase, and serum FGF-23 levels were 2.29 mmol/L, 212 U/L, and 52, respectively (Table 2). After resection, the patient's symptoms gradually improved. He was discharged from the hospital with oral phosphate supplements, alphacalcidol, and anti-osteoporosis drugs. One month later, his levels of serum calcium, phosphorus, and FGF-23 were within normal ranges. At follow-up two months later, he had recovered well, and his serum biochemistry values remained normal. Radiography revealed no evidence of tumor recurrence.

Discussion

TIO is an uncommon disorder that typically presents with bone pain, fractures, muscle weakness, and fatigue [2]. Symptoms are often non-specific and serum phosphorus levels are not routinely measured; therefore, delay in diagnosis is not uncommon [3], as experienced in the two cases described in this report. The tumors are mostly small, benign, and develop in various sites of the body. Therefore, their identification may also be difficult [2, 7–9]. Ledford *et al* reported that the average time to correct diagnosis often exceeds 2.5 years, and an average time to identify the responsible tumor of 5 years [10]. MRI and fluorodeoxyglucose PET (FDG-PET) are two highly sensitive methods used to confirm the location of tumor, but the findings are often nonspecific [9–12]. TIO could originate from a variety of organs, including bone, soft tissue, and sinonasal locations [5, 13]. Morimoto *et al* reported two cases of malignant phosphaturic mesenchymal tumor of the pelvis, which suggests the potential for malignant TIOs [14].

While CT/MRI/PET revealed the specific tumor position in Case 1, these methods were not successful in Case 2; its identify was suspected by PET, which is considered the most sensitive examination for tumors. There are two possible reasons for this lack of findings: (1) the tumor size was at the threshold of PET scanning; and (2) regular PET/CT was unable to reveal the metabolic status of this tumor.

Most TIO tumors overexpress FGF-23, a member of the FGF family defined as humoral factors with an FGF homology region [15–16]. FGF-23 inhibits renal phosphate reabsorption in the proximal tubules. Overexpression of FGF-23 in bone suppresses osteoblast differentiation as well as matrix mineralization, which suggested that it acts directly on bone by reducing mineralization [6, 17–18]. FGF-23 is the most direct serologic marker for tumor activity. FGF-23 and phosphate levels appear to correlate with recurrence and can be used for postoperative screening. In adults, absence of family history along with elevated levels of FGF-23 should raise suspicion of TIO [4–5, 16–17]. Maria and colleagues demonstrated that overexpression of growth factor receptors were implicated in tumor angiogenesis and metastatic potential [platelet derived growth factor type A (PDGFRA), PDGFRB, and vascular endothelial growth factor (VEGF) receptor] together with increased expression of FGF-23, x-linked-phosphate-regulating endopeptidase, and KLOTHO [19]. Hautmann *et al* reported that the prognostic value of periostin expression requires more precise evaluation in a larger series of patients with TIO because periostin upregulation might be an indirect marker for a higher risk of recurrence or development of metastasis [20]. As shown by our laboratory data, FGF-23 levels are closely related to TIO and patient symptoms. Its effects on recurrence remains under follow-up.

Due to the occult nature of TIO, several radiographic imaging methods have been put into trial use. In addition to PET scanning and CT/MRI, recent studies have introduced ^{111}In-pentetreotide scintigraphy (octreotide scan), a technique that can detect the expression of somato-statin receptors (SSTRs) [21–22]. However, nonspecific uptake may cause a false-positive result due to inflammatory tissues, fractures, or other tumors that could induce lymphocytes to express octreotide receptors. Moreover, a negative octreotide scan cannot exclude a diagnosis of TIO [23]. Fukumoto demonstrated the clinical use of systemic venous sampling for identification of TIO [16]. They

collected 22 samples from the major veins of each patient and measured FGF-23 levels and performed CT/MRI on suspicious regions. While not perfect, this might be a useful supplementary method for identification of small tumors or in cases where octreotide scintigraphy is not available.

Histologically, TIO is characterized by a highly vascular proliferation of bland, spindled to stellate cells, which produce an unusual "smudgy" matrix [24]. Our pathology department could not provide a definitive diagnosis of this tumor due to its rarity and nonspecificity. However, the observations were exactly as previously reported.

The main treatment of TIO is surgical removal of the tumor, and its resection typically results in reversal of the symptoms and biochemical changes [2, 4, 25]. Kumar and colleagues from the Mayo Clinic suggested that the most appropriate treatment to be tumor resection with wide margins to ensure complete removal [24]. Most case reports indicate a rapid return of serum phosphorus concentrations, elevated renal phosphorus excretion, elevated FGF 23 concentrations, and serum 1,25-dihydroxyvitamin D concentrations to normal levels [26]. Thus, it is important to measure these variables prior to surgical resection and 24 and 48 hours following resection.

Medical treatment of TIO includes phosphate supplements, 1α,25-dihydroxyvitamin D (calcitriol), or 1α-hydroxyvitamin D (alphacalcidol). The Mayo Clinic administers 1–3 g elemental phosphorus in four to six divided doses per day. It is advised to start with 1 g elemental phosphorus per day and gradually increase the dose to 2-3 g per day because phosphorus supplements often cause gastrointestinal distress and diarrhea. Calcitriol (0.5–2 μg per day) is often required to increase the absorption of phosphorus in the intestine [24]. Seufert *et al* first reported octreotide therapy for TIO [27]. It is administered subcutaneously at 50 μg three times daily for five days, followed by 100 μg three times daily for eight days. Pithankuakul *et al* reported that this therapy leads to normalization of serum phosphorus levels, phosphate clearance, and the threshold for renal tubular reabsorption of phosphate by day 10 [9]. Both of our cases were administered alphacalcidol and anti-osteoporosis drugs; phosphate supplements were administered to one case because, while the serum phosphorus concentrations returned rapidly to normal levels in one patient, the other patient had insufficient phosphorus levels. Both patients have had good recovery progress in their follow-ups until now.

The majority of TIO tumors (70%–80%) are phosphaturic mesenchymal tumor mixed connective tissue variants [4]; however, the relationship between FGF-23 and its pathogenesis remains unknown. The primary concern is reducing the period from symptom onset to diagnosis. Specific examinations are in clinical trials; until then, clinicians should use as many methods as possible to identify suspicious lesions. Following identification of TIO, complete resection with wide margins is required. Phosphate supplements and anti-osteoporosis drugs are recommended for rapid normalization of serum phosphate and calcium levels; with proper diagnosis and treatment, good prognoses are expected.

Conflicts of interest

The authors indicated no potential conflicts of interest.

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