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Case report

# Phosphaturic Mesenchymal Tumour Arising in the Tibia with Severe Osteomalacia Treated with Extended Curettage and Calcium Phosphate Cement Filling: A Case Report

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## Abstract

**Background:** Since the identification of fibroblast growth factor-23 (FGF-23), tumor-induced osteomalacia (TIO) has become widely recognized. The mainstay of treatment is surgical removal. Reconstruction may be challenging because of bone loss after extended curettage or wide resection and possibly poor bone quality.

**Presentation of Case:** A 51-year-old woman with hypophosphatemia and significantly low bone density (T-scores; −2.1 to −3.8) was diagnosed with TIO. At the first presentation, she was wheelchair-bound and had a 5-year history of whole-body pain and generalized muscle weakness. A subarticular lytic bone lesion in the right proximal tibia was detected by fluorodeoxyglucose-positron emission tomography and FGF-23 sampling. The lesion was confirmed as benign phosphaturic mesenchymal tumor (PMT) by open biopsy. Extended curettage of the tumor, ethanolization and calcium phosphate cement (CPC) filling were performed. Post-operative course was uneventful and the patient returned to normal daily activity. At the latest follow-up 30 months post-operatively, there was no evidence of local recurrence or degenerative joint changes on X-ray. Slight absorption of CPC was observed.

**Discussion:** PMT has a high tendency to local recurrence. Adequate surgical procedure often results in large bone defects. This case report demonstrates the utility of CPC, which is safe and biocompatible with mechanical properties suitable for use in osteoporotic bone.

**Keywords:** Tumor-induced osteomalacia; phosphaturic mesenchymal tumor; extended curettage; adjuvant therapy; calcium phosphate cement.

## Introduction

Tumor-induced osteomalacia (TIO), or oncogenic osteomalacia, is an uncommon type of osteomalacia in hypophosphatemia and decreased mineralization of newly formed bone are caused by particular mesenchymal tumors. The mechanism of TIO was long unknown, but Shimada et al. identified fibroblast growth factor-23 (FGF-23) as responsible for this disease in 2001. This hormone produced by tumors causes osteomalacia by increasing renal phosphate wasting [1,2].

The majority of tumors responsible for TIO are benign phosphaturic mesenchymal tumor (PMT), which has a relatively high potential for recurrence whether the origin is soft tissue or bone [1,3,4]. Few reports on TIO have focused on surgical details, and no standard surgical strategy for TIO of benign bone origin has been established yet in terms of tumor removal and bone defect reconstruction. We hereby report a case of PMT arising in the proximal tibia with severe long-term osteomalacia treated with extended curettage, ethanol treatment, and calcium phosphate cement (CPC) filling.

## Presentation of Case

The patient was a 51-year-old woman who had a 5-year history of whole-body pain starting with bilateral knee pain, previously diagnosed with fibromyalgia. One year prior to her referral to the Department of Orthopaedic Oncology and Surgery, she was referred from a nearby clinic to the Department of Endocrinology and Diabetes due to hypophosphatemia. TIO was suspected, and fluorodeoxyglucose-positron emission tomography (FDG-PET) revealed an increased accumulation of tracer in the left proximal tibia (Fig. 1A). The result of serum FGF-23 measurement in extremities corresponded to that of FDG-PET, with the highest level of FGF-23 (253.0 pg/mL) from the left femoral vein.

On physical examination at the first presentation, the patient was wheelchair-bound and could not walk even with crutches or stand unsupported for 5 seconds. She had severe thoracic kyphosis and lost 8 cm of height, from 153 to 145 cm, in 5 years. She also

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complained of chronic back pain and generalized muscle weakness. Radiographs confirmed severe spine kyphosis and revealed thin cortices, unclear trabeculae, and an osteolytic lesion in the left proximal tibia (Fig. 1B, C). On computed tomography (CT), the lesion was partially ill defined without marginal sclerosis (Fig. 1D, E). Blood testing revealed extremely elevated levels of serum alkaline phosphatase (ALP) and FGF-23 at 1464 (normal range: 104–338) U/L and 186.6 (normal range: < 3.0) pg/mL, respectively, but serum phosphate was normal at 2.6 (normal range: 2.4–4.4) mg/dL with oral supplementation of phosphate (6 g per day) and 1,25-dihydroxyvitamin $D_3$ (1 mg per day) prescribed by the Department of Endocrinology and Diabetes. Bone mineral density (BMD) of the patient was significantly reduced, with T-scores of −2.1, −3.8, and −2.7 for the lumbar spine, right femoral neck, and left femoral neck, respectively (Table 1).

Open biopsy confirmed the pathological diagnosis of benign PMT (Fig. 2), and extended curettage together with ethanol treatment and CPC filling was performed. The surgery was conducted under general anesthesia in supine position with tourniquet on. The same anterior approach as the previous open biopsy was used. Intra-operatively, the tumor was recognized as greyish loose connective tissue, but the border of tumor and normal bone was unclear, as indicated on CT. The tumor was removed piece by piece with hernia forceps and a sharp curette through the previous biopsy tract, and then the whole operative field was dipped with dehydrated ethanol for 3 minutes twice. Between the first and second ethanol treatment, the surface of the remaining bone was extensively curetted with a sharp curette. After these procedures, 30 mL of CPC (CERAPAST®, Japan Medicalnext Co., Ltd., Japan), which is comprised of tetracalcium phosphate (TeCP) and dicalcium phosphate anhydrous (DCPA) powder mixed with liquid dextran sulphate sodium (DSS), was used to fill the bone defect.

Post-operative course was uneventful. FGF-23 dropped dramatically to normal just 24 hours after surgery. Without oral supplementation, the serum phosphate level also returned to normal 7 days post-operatively. In contrast, serum ALP, intact PTH and 1,25-dihydroxyvitamin D decreased gradually and were normalized two years after surgery (Table 2). Immediate half-weight bearing was allowed, and the patient was discharged in a wheelchair 2 weeks after the surgery, when she began to feel an improvement in proximal muscle strength. Six weeks post-operatively, full weight bearing was tolerated. Her chronic pain and whole-body muscle weakness gradually improved. Three months post-operatively, she was able to walk without a crutch. At the latest observation 30 months after the surgery, she still had moderate back pain but could walk unsupported for 30 minutes.

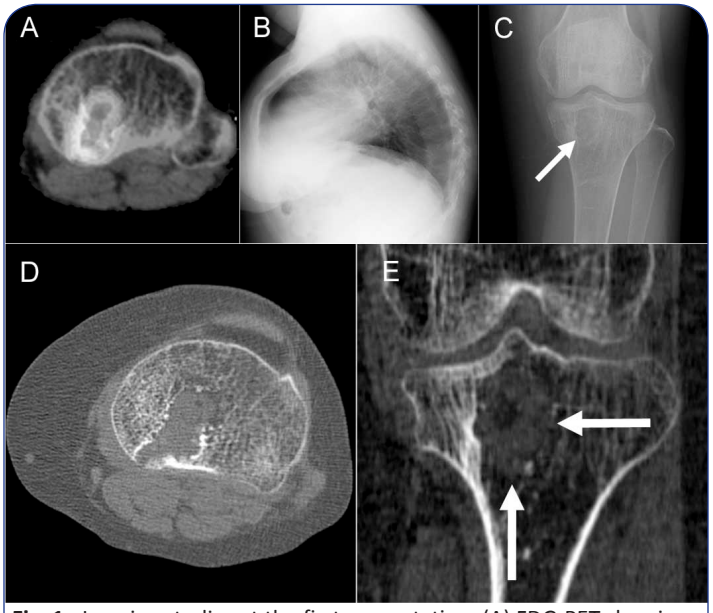


**Fig. 1.** Imaging studies at the first presentation. (A) FDG-PET showing a moderately increased accumulation of tracer (SUVmax, 3.9) in the left proximal tibia (arrows). (B, C) Radiographs of the thoracic spine and left knee before biopsy showing severe spine kyphosis, thin cortices and an osteolytic lesion in the left proximal tibia (arrow). (D, E) CT scans of the left knee showing that the lesion has no marginal sclerosis laterally and distally (arrows)

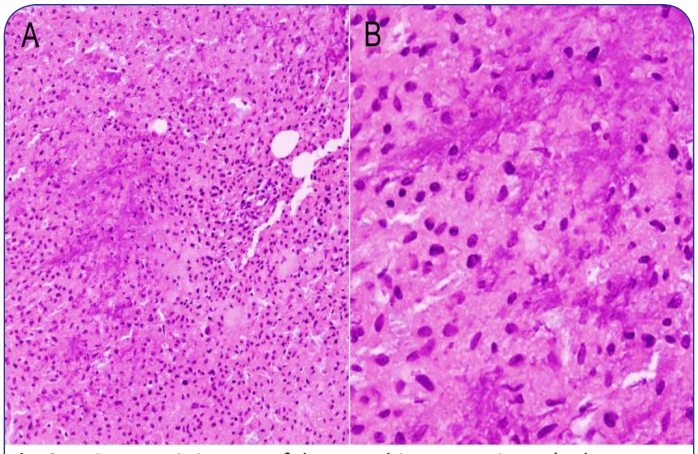


**Fig. 2.** Microscopic images of the open biopsy specimen (A. low-power view (x20), B. high-power view (x60), haematoxylin & eosin stain). The lesion was comprised of round- to spindle-shaped bland tumour cells. Note the presence of osteoid-like intercellular matrix

**Table 1.** Post-operative improvement in bone mineral density according to measurement site

| | Pre-op | 4 months | 30 months |
|---|---|---|---|
| Right femoral neck | 0.368 g/cm² (−3.8) | 0.422 g/cm² (−3.3) | 0.487 g/cm² (−2.8) |
| Left femoral neck | 0.495 g/cm² (−2.7) | 0.512 g/cm² (−2.5) | 0.555 g/cm² (−2.1) |

Figures in parentheses show T-scores

**Table 2.** Long-term changes in serum ALP, intact PTH and 1,25-dihydroxyvitamin D

| | Pre-op | 1 month | 6 months | 1 year | 2 years |
|---|---|---|---|---|---|
| ALP (U/L) [104–338] | **1464** | **1274** | **707** | **426** | 309 |
| Intact PTH (pg/mL) [10.0–65.0] | **785.7** | **298.5** | **246.8** | **105.0** | 52.4 |
| 1,25-$(OH)_2D$ (pg/mL) [20.0–60.0] | 34.7 | **151.0** | **94.5** | **65.8** | 40.5 |

Square brackets show normal ranges of each test at our institution.

Results out of normal ranges are shown in bold.

A radiograph 2 years after surgery showed a significant increase in bone density, slight absorption of CPC at medial side, and no evidence of CPC loosening, stress fracture, degenerative change in the knee joint, or tumor recurrence (Fig. 3). BMD also improved gradually, as shown in Table 1.

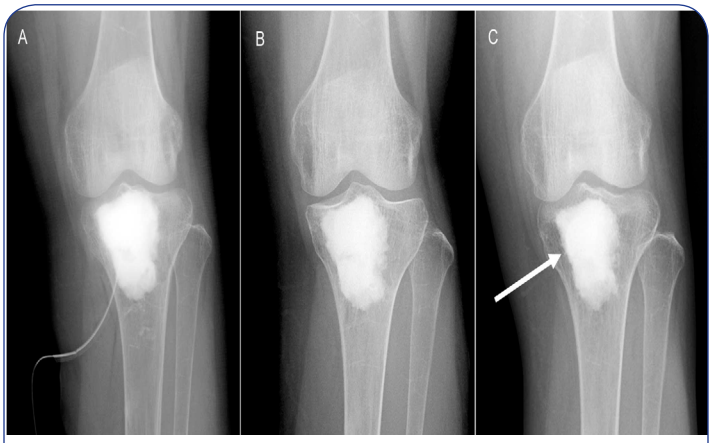


**Fig. 3.** Radiographs of the left knee immediate after surgery (A), 9 months (B) and 2 years (C) after surgery showing gradual absorption of calcium phosphate cement and bone replacement, especially at medial side (arrow)

## Discussion

TIO is a rare type of osteomalacia caused by certain mesenchymal tumors, first reported by McCance in 1947 as Milkman's syndrome [5]. The cause of this disease, FGF-23, impairs phosphate uptake and affects the parathyroid glands, leading to severe hypophosphataemia, low serum 1,25-dihydroxyvitamin $D_3$ concentrations and high serum ALP levels. Frequently, patients with TIO have a long-standing history of generalized fatigue, bone pain, fractures, height loss, and muscle weakness at the time of diagnosis [1]. This lengthy delay in diagnosing TIO has been attributed to difficulty in locating the responsible tumor, since it tends to be small, locally asymptomatic, and unrecognized [6].

In recent years, an increasing number of cases have been reported worldwide, which indicates a growing recognition of this disease and improvement of diagnostic methods including FGF-23 measurement. However, surgical treatment of patients with TIO of bone origin, which is the primary treatment for this disease, can be problematic. One surgical problem is the aggressiveness of responsible tumors. Although several successful cases treated surgically have been published so far (Table 3) [7-14], some recurrent benign PMT cases have been reported [3,15-18]. In addition, there is no consensus concerning what type of surgical procedure is appropriate for bone PMT. In a multi-institutional review of 39 TIO cases including both bone and soft tissue origins, the recurrence rate was 21% [3]. This figure implies that simple curettage of responsible bone tumors may be insufficient to cure TIO. Sciubba et al. reported micro tumor invasion into the surrounding trabecula in their en bloc specimen [19], which can explain the high potential for recurrence of PMT of bone origin.

Low bone density can be another consideration in TIO patients [20]. In our case, we chose extended curettage plus ethanolization followed by CPC filling because we believed it was the best-balanced method in terms of local control and prevention of post-operative complications. To begin with, mega-prosthetic reconstruction would be inappropriate for cases of remarkably low bone mineral density such as ours. PMMA cementing was one alternative option, but the risk of fracture as a short-term post-operative problem and secondary arthritis years after surgery could not be neglected. Stress fracture after PMMA cementation has been reported as a post-surgery complication in GCT patients with apparently normal bone density [21,22]. Di Giorgio et al. also reported 3 cases of fracture (13%) in long bones after PMMA cementation following curettage of low-grade chondrosarcoma [23]. Regarding the influence on the joint surface, Xu et al. reported that almost half of patients with 10 mm or less of residual subchondral bone thickness after PMMA filling developed degenerative joint changes within 18–113 months after surgery [24]. These complications after PMMA cementing may be more likely to occur to patients with lower BMD. By contrast, TeCP/DCPA with DSS, the CPC we chose to use for our case, was thought to be suitable because it is biocompatible and replaceable by bone after surgery. With approximately 50 MPa of compressive strength, it functions satisfactorily as bone substitute even in patients with serious osteoporosis; a clinical trial of 75 cases including 10 tumor cases demonstrated its great effectiveness as a bone defect filler without any significant adverse effects [25].

## Conclusion

We report our experience of one TIO patient with PMT in the proximal tibia treated with extended curettage plus ethanolization followed by CPC filling. As a case report, more observations would seem to be needed to confirm the long-term efficacy and wide applicability of the technique. However, given the high potential of recurrence and potentially highly decreased bone mineral density, the combination of extended curettage, ethanolization, and CPC filling should be considered a promising option for PMT of bone origin with severe osteomalacia.

## Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

**Table 3.** Summary of the past successful surgical treatments for bone PMT in the field of orthopaedics excluding spine cases

| Ref. No. | Age, Sex | Site | BMD (Z score) | Para-neoplastic symptoms | Surgery | F/U |
|---|---|---|---|---|---|---|
| [7] | 42, M | Tibia | 0.358 g/cm$^2$ (−3.7 SD) | Improved | Curettage Bone substitutes | 12 m |
| [8] | 45, F | First metacarpal | N/A | Improved | Thumb amputation | 18 m |
| [9] | 66, F | Ischium | N/A | Improved | Excision | 6 m |
| [10] | 42, F | Sacrum | N/A | No symptoms | Curettage, bone graft, and L-P stabilization | 12 m |
| [11] | 17, M | Distal fibula | N/A | Improved | Wide resection | 24 m |
| [12] | 40, M | Greater trochanter | W.N.L. | Improved | Complete removal and THR | 1 m |
| [13] | 46, M | Distal femur | N/A | Improved | Resection | 6 m |
| [14] | 38, M | Distal femur | N/A | Improved | Excision | 30 m |

*M* male, *F* female, *N/A* not applicable, *SD* standard deviation, *W.N.L.* within normal limits, *L-P* lumbar-pelvic, *THR* total hip replacement, *F/U* follow-up, *m* month(s)

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