Tumor-Induced Osteomalacia: A Case Report of Rare Disease and Literature review

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Introduction

Osteomalacia, often known as “bone softening disease,” is a generalized disorder involving softening of bones, which is generally overlooked and relatively less investigated. Pathophysiology is inadequate osteoid mineralization. It is commonly associated with nutritional deficiency. Other etiologies are malabsorptive syndromes, chronic kidney and liver diseases, and some rare causes like renal tubular acidosis, as in Fanconi syndrome, and tumor-induced osteomalacia (TIO).1,2

Robert McCance first reported TIO, also known as “oncogenic osteomalacia.” Abnormal phosphate metabolism secondary to most common endocrine tumors is characteristic of this paraneoplastic syndrome. The mean age of presentation is 40 to 45 years, with balanced distribution between sexes.3 Nonspecific presentation of symptoms often leads to
delayed diagnosis. These tumors often secrete phosphaturic hormone, fibroblast growth factor 23 (FGF23), in excess.

The clinical presentation is nonspecific, resulting in delayed diagnosis and severe morbidity to the patient. It is characterized by muscle fatigue, bony pains, and multiple pathological fractures associated with lower phosphate levels. A large number of cases are misdiagnosed as osteoporosis and treated incorrectly for years before a definite diagnosis is made. The only definitive treatment for TIO is complete tumor resection. Radiotherapy or guided ablation treatment may be used as adjuvant therapy or primary treatment in cases where it is difficult to access the tumor, or its surgical removal is deemed risky.

The diagnosis often becomes difficult due to rarity of occurrence and deficient literature. The reconstruction following resection in patients with oncogenic osteomalacia has its own technical difficulties, which are addressed in this article. We report a case of a patient with multiple impending pathological fractures in a 39-year-old female with TIO, managed successfully with excision of causative tumor and reconstruction of bone and soft tissue defect.

Case Presentation

A 39-year-old female patient presented with complaints of pain in bilateral lower limbs (Visual Analogue Scale – 8/10) with difficulty in ambulation for the past 4 years. Past history revealed a history of multiple fractures without any history of significant trauma. Further history elaboration revealed no similar complaints in the family or any significant family history. There is no history of treatment with bisphosphonates.

On general examination, moderately built, with gross wasting of bilateral thigh and calf muscles. A radiograph of the pelvis and thigh revealed a transverse fracture in both femurs with variable signs of healing (Fig. 1A). A skeletal survey revealed healed fibular fracture line on right side as well (Fig. 1B).

Hematologic Examination

Hematologic examination revealed the following:

- Red cell indices, iron profile, electrolytes, and liver function tests were within normal range.
- Serum calcium – 8.9 mg/dL (normal).
- Urine PH: 6.4.
- Serum vitamin D levels – 74 (normal).
- Serum PTH – 55 pg/mL (normal).
- Serum alkaline phosphatase (ALP) – 105 U/L (normal).
- Serum phosphorus levels were low – 1.8 mg/dL (3.5–5).
- Transport maximum of phosphorus-glomerular filtration rate – 0.61 (0.84–1.2), suggestive of tubular phosphorus wasting.
- Serum FGF23 level – 317 RU/mL (0–150 RU/mL).

The TIO is characterized by the overproduction of FGF23 which acts primarily on renal proximal tubular cells, binding to an FGF receptor in coordination with its obligate coreceptor. The effect is to reduce the expression of sodium-phosphate cotransporters (NaPi-2a and NaPi-2c) in the proximal renal tubule, leading to decreased renal phosphate reabsorption. It also inhibits the expression of 25-hydroxyvitamin D3 1-alpha hydroxylase, resulting in inadequate production of 1,25 (OH)2D required for optimal enteral calcium and phosphate absorption.

Further nuclear and radiological scans revealed:

- Bone mineral density by dual-energy x-ray absorptiometry scan showed left femur osteopenia (–1.5).
- Tc99m sestamibi scan – no uptake by parathyroid glands.
- Positron emission tomography (PET) scan (68 Ga DOTATATE scan) – A lesion over greater trochanter left side with DOTA-NOC avid (standardized uptake value max: 30.50) sclerotic lesion with diffuse osteopenia, likely represents somatostatin receptor-positive mitotic lesion (Fig. 2).
- Contrast-enhanced magnetic resonance imaging (MRI) pelvis revealed – Size of the tumor 1.40 × 1.84 cm (Fig. 3).
History, clinical, radiological, and laboratory results revealed a case of recurrent fragility fracture with chronic hypophosphatemia with elevated FGF23 levels suggestive of oncogenic osteomalacia. Therefore, she was planned for surgical excision of the tumor with reconstruction of greater trochanter with the help of an allograft and subsequent repair of the abductor mechanism.

**Surgical Technique**

With adequate preoperative planning, surgical excision of the tumor with the reconstruction of the greater trochanter with the help of an allograft and subsequent repair of the abductor mechanism was planned. With consent from the patient, the patient was taken under spinal anesthesia, and a team of consultant orthopaedic oncology surgeons performed the procedure. Through standard lateral approach to hip (∼Fig. 4), greater trochanter was identified and abductors were tagged with ethibond sutures and dissected from greater trochanter (GT). After excising GT with a 2-cm safety margin, GT was reconstructed with femoral head allograft, which was contoured similar to the shape and dimension of the excised part. It was fixed using an olecranon hook plate, and the abductors were tied to the plate's holes using ethibond. Closure was done in layer and aseptic dressing was applied.
Postoperative Period
Postoperatively, abduction was maintained using brace, and radiographs were done (Fig. 5A). On the 5th post-operative day, serum phosphorus was found to be 4.32 mg/dL. The histopathological report of the excised tumor was suggestive of phosphaturic mesenchymal tumor (PMT) with free margin. At 3 weeks' follow-up, patient had marked reduction in pain (Visual Analogue Scale score – 2/10). Radiographs of femur showed signs of healing (Fig. 5B, C). Clinically, at 3 months' follow-up, patient was walking without support, had no abductor lurch, and the fractures completely healed.

Discussion
Oncogenic osteomalacia is a rare disorder of the musculoskeletal system related to mesenchymal tumors; associated with decrease in phosphate resorption by kidney, and presenting as lower phosphate levels, generalized weakness, and osteomalacia. Literature search shows reaching a definitive and timely diagnosis of TIO is a challenge as highlighted in review by Jiang et al., which concluded that on an average there is often a lag of time exceeding 2.5 years from beginning of symptoms to a final diagnosis, and by 5 years to localize the culprit tumor and definitive treatment. Similar lag of 4 years to final diagnosis was noted in our patient, managed conservatively with calcium and vitamin supplements by multiple practitioners.

The effects of calcitriol include increased liver NPT2a expression and phosphate reabsorption, as well as increased intestinal NPT2b expression and phosphate absorption. A positive effect on intestinal and renal phosphate absorption is counterbalanced by its stimulation of FGF23. Biochemical parameters of TIO shows normal levels of calcium, serum vitamin D, and normal to mildly raised serum ALP and intact parathyroid hormone, with lower serum phosphorus. Leading to differential of osteoporosis, osteomalacia, normocalcemic hyperparathyroidism, and familial hypophosphatemic osteomalacia resulting in conservative management with calcium and vitamin supplements. Varied biochemical parameter with repeated fractures could also been seen in multiple disorders like osteoporosis and osteopetrosis and should be considered.

Following clinic-biochemical suspicion of TIO, localization of the causative tumor producing the phosphatonin is a necessity as surgical excision of tumor is associated with good functional outcomes compared to medical management alone. Varied imaging modalities are being used at present like MRI, computed tomography, and nuclear imaging modalities like bone scans, fluorodeoxyglucose-PET.
scans, and DOTANOC-PET scans. El-Maouche et al.\textsuperscript{11} in his study concluded that 68Ga-DOTATATE PET has favorable specificity and sensitivity in localizing small tumors missed on conventional imaging.

Medical management consists of high dose of oral phosphorus replacement and supportive treatment to normalize serum phosphorus levels. Poorer clinical outcomes include gastrointestinal symptoms and other side effects.\textsuperscript{6} Surgical removal of tumor is associated with return of serum phosphorus to normal range within a period of 2 to 7 days and clinical improvement in pain scores. Similar results were obtained in > 88% of cohort, in a review by Sun et al and in a report by Dutta et al.\textsuperscript{6,12}

Histopathology of our resected tumor gave the final diagnosis of PMT, which was in accordance with the study by Dutta et al and Jan de Beur, who stated that 70 to 80% showed variants of mesenchymal tumor on biopsy/histopathology.\textsuperscript{2,12}

To the best of our literature search, this is the first case to describe both resection of causative tumor around greater trochanter and further reconstruction of resected part using allograft to decrease patient morbidity.

Several important points in accordance with our successful treatment of TIO are listed as follows:

1. For clinicians, decreased serum phosphate despite adequate supplementation should raise suspicion of TIO.
2. In case of suspicion, getting early 68 Ga PET-DOTATATE scan for early diagnosis.
3. Complete surgical excision and reconstruction to prevent recurrence and decrease morbidity.

**Conclusion**

TIO is a debilitating disease with significant morbidity due to prolonged onset to diagnosis interval and difficulty in localizing the causative tumor. Thorough clinico-radiological and laboratory parameter correlation is a necessity. A rapid diagnosis followed by complete surgical excision, which remains the gold standard treatment modality that confers favorable prognosis in most patients, with strict vigilance for recurrence are necessary.

**Authors’ Contributions**

S.B. – Investigation, methodology, project administration.
V.M. – Data curation, formal analysis, manuscript writing.
B.B.N. – Data collection.
A.R. – Data collection.
K.S. – Data collection, review of literature, writing – review and editing.
M.D. – Conceptualization, planning and forming the outline of study, supervision.

**Informed Consent for Publication**

Informed consent was obtained from the patient for publication of this case report. On request, a copy of the written consent is available for review by the Editor-in-Chief of this journal.

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**Conflict of Interest**

There is no conflict of interest of any kind with the research or its outcome among the investigators.

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