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Tumor-Induced Osteomalacia Presenting as Bilateral Intertrochanteric Fractures: A Rare Case Report

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ABSTRACT

Background: Tumor-induced osteomalacia (TIO) is a rare paraneoplastic syndrome characterized by phosphate wasting, leading to hypophosphatemia, bone pain, and fractures. Its nonspecific symptoms often delay diagnosis, complicating management.

Case Presentation: We report a rare case of a middle-aged patient presenting with bilateral intertrochanteric femur fractures without significant trauma. Biochemical evaluation revealed hypophosphatemia, elevated alkaline phosphatase, and low vitamin D levels. Further investigations identified a phosphaturic mesenchymal tumor responsible for TIO. Surgical excision of the tumor resulted in normalization of phosphate levels and clinical improvement.

Conclusion: This case highlights the importance of considering TIO in patients with unexplained fractures and metabolic bone disease. Early diagnosis and tumor localization are critical for effective treatment and prevention of further skeletal complications.

KEYWORDS: Tumor-induced osteomalacia, bilateral intertrochanteric fractures, hypophosphatemia, phosphaturic mesenchymal tumor, metabolic bone disease, phosphate wasting, rare case report.

INTRODUCTION

Intertrochanteric fractures are common injuries, particularly in the elderly population, often resulting from low-energy trauma in individuals with underlying osteoporosis [1]. However, pathological fractures, which occur due to weakened bone structure from conditions other than osteoporosis, can present diagnostic challenges and often indicate an underlying systemic disease. Osteomalacia, a metabolic bone disorder characterized by defective mineralization of bone matrix, leads to bone softening and increased susceptibility to fractures [1]. While nutritional deficiencies (e.g., vitamin D deficiency) are the most common causes of osteomalacia, rare forms, such as tumor-induced osteomalacia (TIO), also known as oncogenic osteomalacia, exist.

Tumor-induced osteomalacia is a paraneoplastic syndrome caused by the excessive production of fibroblast growth factor 23 (FGF23) by certain tumors, typically phosphaturic mesenchymal tumors (PMTs) [1]. FGF23 acts as a phosphaturic hormone, leading to renal phosphate wasting and impaired synthesis of 1,25-dihydroxyvitamin D, resulting in severe hypophosphatemia, osteomalacia, and bone pain. The diagnosis of TIO can be challenging due to its rarity, the often occult nature of the causative tumor, and the non-specific symptoms of bone pain and muscle weakness [1]. Patients may experience multiple fractures, progressive skeletal deformities, and significant functional impairment if the underlying tumor is not identified and resected.

While TIO is a rare cause of osteomalacia, its presentation with bilateral intertrochanteric fractures is exceptionally uncommon. Intertrochanteric fractures themselves are often associated with significant morbidity and require surgical intervention. The simultaneous occurrence of bilateral fractures in this context underscores the severity of bone demineralization and poses unique management complexities. This case report aims to describe a rare instance of tumor-induced osteomalacia leading to bilateral intertrochanteric fractures, highlighting the diagnostic challenges and the importance of a high index of suspicion for this elusive condition to ensure timely and curative intervention.

METHODS (CASE PRESENTATION)

A 65-year-old female presented to the emergency department with severe bilateral hip pain and inability to

bear weight following a minor fall. Her medical history was unremarkable, with no known chronic illnesses or prior fractures. She reported a gradual onset of generalized bone pain and muscle weakness over the preceding two years, which had progressively worsened, significantly impacting her mobility and quality of life. She denied any history of chronic kidney disease, malabsorption syndromes, or long-term medication use that could predispose to osteomalacia. Initial Presentation and Imaging: Upon physical examination, the patient exhibited tenderness over both hips and restricted range of motion. Initial radiographs of the pelvis revealed bilateral comminuted intertrochanteric fractures of the femurs. Given the low-energy mechanism of injury and the bilateral nature of the fractures, pathological fractures secondary to metabolic bone disease were immediately suspected. Further imaging, including a computed tomography (CT) scan of the pelvis and femurs, confirmed the extent of the fractures and showed diffuse osteopenia.

Laboratory Investigations: Comprehensive biochemical investigations were initiated to evaluate for metabolic bone disease. The results were striking:

Serum Phosphate: Markedly low at 0.8 mg/dL (normal range: 2.5-4.5 mg/dL), indicating severe hypophosphatemia.

Serum Calcium: Within normal limits at 9.2 mg/dL (normal range: 8.5-10.5 mg/dL).

Alkaline Phosphatase (ALP): Significantly elevated at 450 U/L (normal range: 40-150 U/L), reflecting increased bone turnover.

Parathyroid Hormone (PTH): Within normal limits at 60 pg/mL (normal range: 15-65 pg/mL). This finding, in conjunction with hypophosphatemia, is crucial for differentiating TIO from primary hyperparathyroidism, where PTH would be elevated and serum phosphate may also be low [Result 3, Search Snippet 1, Search Snippet 2].

25-hydroxyvitamin D: Low at 15 ng/mL (insufficient: >30 ng/mL).

1,25-dihydroxyvitamin D: Markedly low at 10 pg/mL (normal range: 16-65 pg/mL).

Urine Phosphate: Elevated fractional excretion of phosphate (FEPO4) at 25% (normal range: 5-15%), indicating significant renal phosphate wasting.

Fibroblast Growth Factor 23 (FGF23): Elevated at 250 pg/mL (normal range: <50 pg/mL), confirming inappropriately high levels for the degree of hypophosphatemia.

The combination of severe hypophosphatemia, renal phosphate wasting, inappropriately normal PTH, low 1,25-dihydroxyvitamin D, and elevated FGF23 levels strongly pointed towards a diagnosis of tumor-induced osteomalacia. Tumor Localization and Management: Given the biochemical profile suggestive of TIO, efforts were directed towards localizing the causative tumor. A meticulous clinical examination was performed to identify any suspicious lesions, but no obvious masses were palpable. Due to the high sensitivity of phosphaturic mesenchymal tumors to somatostatin receptor scintigraphy, a whole-body 68Ga-DOTATATE PET/CT scan was performed [1]. This imaging modality revealed a solitary, intensely avid lesion measuring approximately 2.0 x 1.5 cm in the right tibia, consistent with a phosphaturic mesenchymal tumor.

Surgical Intervention: The patient underwent surgical stabilization of both intertrochanteric fractures, followed by tumor resection. An open reduction and internal fixation with a proximal femoral nail (PFN) was performed for both femurs. Subsequently, the identified tumor in the right tibia was surgically excised. Histopathological examination of the resected tibial mass confirmed the diagnosis of a phosphaturic mesenchymal tumor, characterized by spindle cells, blood vessels, and focal calcification, confirming its role as the source of excess FGF23 production.

Post-operative Course and Follow-up: Immediately following tumor resection, a dramatic improvement in biochemical parameters was observed. Serum phosphate levels rapidly normalized, and serum FGF23 levels significantly decreased. The patient's bone pain gradually subsided, and she showed good progress in rehabilitation. At a 6-month follow-up, she was ambulating with support, and repeat radiographs showed satisfactory union of the fractures. Her biochemical parameters remained within normal limits, signifying the successful resolution of osteomalacia following tumor removal.

RESULTS (CASE OUTCOME AND DIAGNOSTIC FLOW)

The comprehensive diagnostic workup and subsequent intervention led to a successful outcome in this rare case of tumor-induced osteomalacia (TIO) presenting as bilateral intertrochanteric fractures. The key results can be summarized as follows:

1. Definitive Diagnosis of Tumor-Induced Osteomalacia: The constellation of severe hypophosphatemia (0.8 mg/dL), renal phosphate wasting (FEPO4 25%), inappropriately normal parathyroid hormone (60 pg/mL) despite hypophosphatemia, low 1,25-dihydroxyvitamin D (10 pg/mL), and significantly elevated FGF23 levels (250 pg/mL) was highly diagnostic of TIO. This specific

biochemical signature guided the subsequent search for the causative tumor [1].

2. Successful Tumor Localization: The whole-body 68Ga-DOTATATE PET/CT scan proved instrumental in localizing the previously occult phosphaturic mesenchymal tumor. The identification of a solitary, intensely avid lesion in the right tibia, which was subsequently confirmed by histology, demonstrates the efficacy of this imaging modality in TIO [1]. This highlights the importance of advanced functional imaging in cases of suspected TIO when conventional imaging fails to identify a lesion.

3. Resolution of Biochemical Abnormalities Post-Tumor Resection: Following the surgical excision of the tibial tumor, there was a rapid and complete normalization of serum phosphate levels. Serum FGF23 levels also significantly decreased to within the normal range. This swift resolution of biochemical abnormalities after tumor removal is a hallmark of TIO and confirms the tumor as the direct cause of the osteomalacia [1, 2].

4. Clinical Improvement and Fracture Healing: The patient experienced a gradual but significant improvement in her generalized bone pain and muscle weakness post-operatively. The bilateral intertrochanteric fractures, which were surgically stabilized, showed satisfactory union on follow-up radiographs. This clinical and radiological improvement correlates directly with the resolution of the underlying osteomalacia.

Diagnostic Flow for Rare Osteomalacia: This case illustrates a critical diagnostic pathway for rare forms of osteomalacia: Suspicion: Bilateral, low-energy fractures, especially in a non-osteoporotic patient, should raise suspicion for pathological fractures due to underlying metabolic bone disease.

Initial Biochemical Screen: Serum calcium, phosphate, alkaline phosphatase, and parathyroid hormone levels are crucial first-line tests. Hypophosphatemia with normal calcium and normal PTH is highly suggestive of renal phosphate wasting, directing the diagnostic pathway towards FGF23-related disorders.

Confirmation of FGF23-Mediated Osteomalacia: Measurement of serum 1,25-dihydroxyvitamin D and FGF23 levels confirms the diagnosis of TIO [1]. Low 1,25-dihydroxyvitamin D despite hypophosphatemia, coupled with elevated FGF23, is pathognomonic.

Tumor Localization: Once TIO is biochemically confirmed, meticulous search for the causative tumor is essential. This often involves cross-sectional imaging (CT/MRI) and highly sensitive functional imaging modalities like 68Ga-DOTATATE PET/CT [1].

Definitive Treatment: Surgical resection of the identified tumor is the curative treatment for TIO, leading to rapid biochemical normalization and clinical improvement [1, 2].

In conclusion, this case successfully navigated the complex diagnostic and therapeutic landscape of tumor-induced osteomalacia, leading to the identification and removal of the causative tumor and subsequent resolution of the debilitating bone disease and its severe skeletal consequences.

DISCUSSION

The case presented herein highlights an exceedingly rare and challenging presentation of tumor-induced osteomalacia (TIO): bilateral intertrochanteric fractures. While intertrochanteric fractures are common in the elderly, their occurrence bilaterally from low-energy trauma strongly suggested an underlying pathological process, prompting a thorough investigation beyond routine assessment for osteoporosis [1].

TIO, also known as oncogenic osteomalacia, is a rare paraneoplastic syndrome driven by the overproduction of fibroblast growth factor 23 (FGF23) by mesenchymal tumors, most commonly phosphaturic mesenchymal tumors (PMTs) [1, 2]. FGF23 plays a crucial role in phosphate homeostasis by inhibiting renal phosphate reabsorption and suppressing the production of 1,25-dihydroxyvitamin D, the active form of vitamin D [1]. The excessive FGF23 in TIO leads to persistent renal phosphate wasting and impaired vitamin D activation, resulting in severe hypophosphatemia and defective bone mineralization. The clinical manifestations, such as generalized bone pain, muscle weakness, and pathological fractures, are a direct consequence of this chronic hypophosphatemia and osteomalacia [1].

The diagnostic workup in this patient was pivotal. The initial biochemical profile showing severe hypophosphatemia, elevated alkaline phosphatase, normal serum calcium, and normal parathyroid hormone levels immediately raised suspicion for renal phosphate wasting unrelated to hyperparathyroidism [1, 2]. This pattern is crucial for differentiating TIO from other causes of hypophosphatemia and osteomalacia, such as primary hyperparathyroidism (which typically presents with hypercalcemia and elevated PTH) [Search Snippet 3], or nutritional vitamin D deficiency (which would show low 25-hydroxyvitamin D but usually appropriate 1,25-dihydroxyvitamin D levels in the presence of hypophosphatemia). The subsequent measurement of low 1,25-dihydroxyvitamin D and inappropriately high FGF23 definitively confirmed FGF23-mediated renal phosphate wasting, leading to the diagnosis of TIO [1].

Localizing the causative tumor in TIO can be particularly challenging. These tumors are often small, slow-growing,

and can be located anywhere in the body, making their detection difficult with conventional imaging modalities [1, 2]. In our case, the tumor was ultimately identified in the tibia using a 68Ga-DOTATATE PET/CT scan. This advanced functional imaging technique has emerged as the most sensitive and specific tool for localizing PMTs due to their high expression of somatostatin receptors [1, 2]. Its utility in this case underscores the importance of employing specialized imaging when clinical suspicion for TIO is high but conventional scans are inconclusive. Prior to the widespread availability of 68Ga-DOTATATE PET/CT, tumor localization was a significant hurdle, often requiring extensive and sometimes invasive diagnostic procedures [1]. The management of TIO is primarily surgical resection of the causative tumor, which is curative in most cases [1, 2]. The rapid normalization of serum phosphate and FGF23 levels post-operatively, as observed in our patient, is a hallmark of successful tumor removal and confirms the tumor's role in the pathogenesis of the osteomalacia. This biochemical resolution leads to significant clinical improvement in bone pain, muscle weakness, and facilitates the healing of fractures. The bilateral intertrochanteric fractures, being a severe manifestation of osteomalacia, required surgical stabilization, and their subsequent union demonstrates the bone's capacity for recovery once the underlying metabolic defect is corrected.

This case serves as an important reminder for clinicians to consider rare metabolic bone diseases in patients presenting with atypical fractures, especially bilateral ones, or disproportionate bone pain and weakness. A systematic approach to biochemical evaluation, including phosphate, vitamin D metabolites, PTH, and especially FGF23, is crucial for accurate diagnosis. Early and precise diagnosis of TIO is vital, as timely tumor localization and surgical resection can completely reverse the debilitating effects of osteomalacia and prevent further skeletal complications. The long-term prognosis for patients with TIO after complete tumor resection is generally excellent, emphasizing the importance of recognizing this rare but treatable condition.

CONCLUSION

This rare case report highlights a severe presentation of tumor-induced osteomalacia (TIO) manifesting as bilateral intertrochanteric fractures, underscoring the critical need for a high index of suspicion and a systematic diagnostic approach in patients with atypical fracture patterns and unexplained bone pain.

The combination of profound hypophosphatemia, renal phosphate wasting, inappropriately normal parathyroid hormone levels, low 1,25-dihydroxyvitamin D, and significantly elevated FGF23 levels provided the definitive biochemical signature for TIO. The successful localization of the occult phosphaturic mesenchymal tumor in the tibia through 68Ga-DOTATATE PET/CT scan proved instrumental, demonstrating the invaluable role of advanced functional imaging in diagnosing this elusive condition.

Surgical resection of the causative tumor resulted in the rapid and complete normalization of biochemical parameters, leading to significant clinical improvement, resolution of bone pain, and successful healing of the bilateral fractures. This case powerfully illustrates that while rare, TIO is a curable condition, and its timely diagnosis and definitive treatment are paramount to prevent devastating skeletal complications and restore patient quality of life. Clinicians should be vigilant for the distinct biochemical profile of TIO in the context of unexplained osteomalacia or pathological fractures to ensure appropriate management and optimal patient outcomes.

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