Article published online: 2024-11-21

Phosphaturic Mesenchymal Tumor of Tibia: A Challenging Diagnosis Rendered on Percutaneous Core Needle Biopsy

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Ind J Med Paediatr Oncol

Abstract

Phosphaturic mesenchymal tumors produce excessive fibroblast growth factor 23 (FGF-23) leading to hypophosphatemia, phosphaturia, and osteomalacia. A 50-year-old male presented with pain and swelling over the anterior and medial aspect of the right leg. Imaging showed a lytic lesion in the right proximal tibia suggesting a possibility of metastasis. Though characteristic grungy calcification was not seen, a diagnosis of phosphaturic mesenchymal tumor was suggested on core biopsy. Subsequent positron emission tomography-computed tomography revealed additional fractures involving multiple sites. Further investigations showed elevated serum levels of FGF-23 and hypophosphatemia. Following excision of the tumor, phosphate levels were restored and his symptoms relieved. A diagnosis of phosphaturic mesenchymal tumors should suspected in all cases of hypophosphatemic osteomalacia. The morphology overlaps with other low-grade mesenchymal neoplasm and diagnostic difficulty enhances especially in absence of grungy calcification, as in this case. Restoration of the biochemical parameters to normal levels provide supportive evidence in establishing the diagnosis.

Keywords

- phosphaturic mesenchymal tumors
- fibroblast growth factor 23
- oncogenic osteomalacia

Introduction

Tumor-induced osteomalacia is a rare paraneoplastic syndrome caused by a morphologically and genetically distinct tumor known as phosphaturic mesenchymal tumor (PMT). It predominantly affects middle-aged adults. These tumors produce excessive fibroblast growth factor 23 (FGF-23) resulting in hypophosphatemia, phosphaturia, and osteomalacia.[1] FGF-23 has negative regulatory effects on circulating 1,25-dihydroxyvitamin D. This metabolic derangement impairs bone mineralization with reduction in osteoblastic activity leading to diffuse bone pain and multiple fragility fractures.[2] Here, in this article, we present a diagnostically challenging case of paraneoplastic hypophosphatemic

DOI https://doi.org/10.1055/s-0044-1792082.
ISSN 0971-5851.

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osteomalacia induced by PMT of bone lacking characteristic grungy calcification on histopathology.

Case History

A 50-year-old male presented with pain and swelling of the right leg since last 3 months. The pain was insidious in onset and gradually progressive in nature. He also complained of myalgia over the past 1 year. On examination, there was a 6×6 cm swelling over the anterior and medial aspect of the right leg, which was tender on palpation. There was no evidence of any sensory or neurovascular deficits. X-ray showed a lytic lesion in the right proximal tibia. Magnetic resonance imaging (MRI) showed a well-defined irregular lobulated eccentric T1 isointense, T2 short-tau inversion recovery hyperintense lesion in the diaphysis of the right tibia. The lesion extended into the adjacent soft tissue with breach in lateral cortex. The associated soft tissue component in the anterolateral aspect infiltrated the tibialis anterior muscle. These imaging findings were suggestive of a possibility of chondrosarcoma or metastasis and are depicted in ►**Fig. 1**. Core biopsy was performed which showed sheets of spindle-shaped cells with oval to elongated nuclei. The cells did not show significant nuclear pleomorphism or mitoses. Thin-walled vascular channels forming hemangiopericytomatous pattern were noted. There was no evidence of any matrix formation. Few host bony trabeculae were seen entrapped in between the lesional cells. The cells showed diffuse strong staining with vimentin and diffuse nonmembranous staining with CD99. The cells were negative for SMA, Pan CK, NKX2.2, CD34, STAT6, and S100. TLE-1 was largely negative with only weak nuclear staining in scattered cell and Ki67 labeling index was 2%. With this morphology, a possibility of low-grade mesenchymal neoplasm, most likely a PMT, was suggested and advised for estimation of serum phosphorus and FGF-23 levels. The histopathological and immunohistochemical findings are illustrated in ►**Fig. 2**. Positron emission tomography (PET)-computed tomography (CT) revealed a metabolically

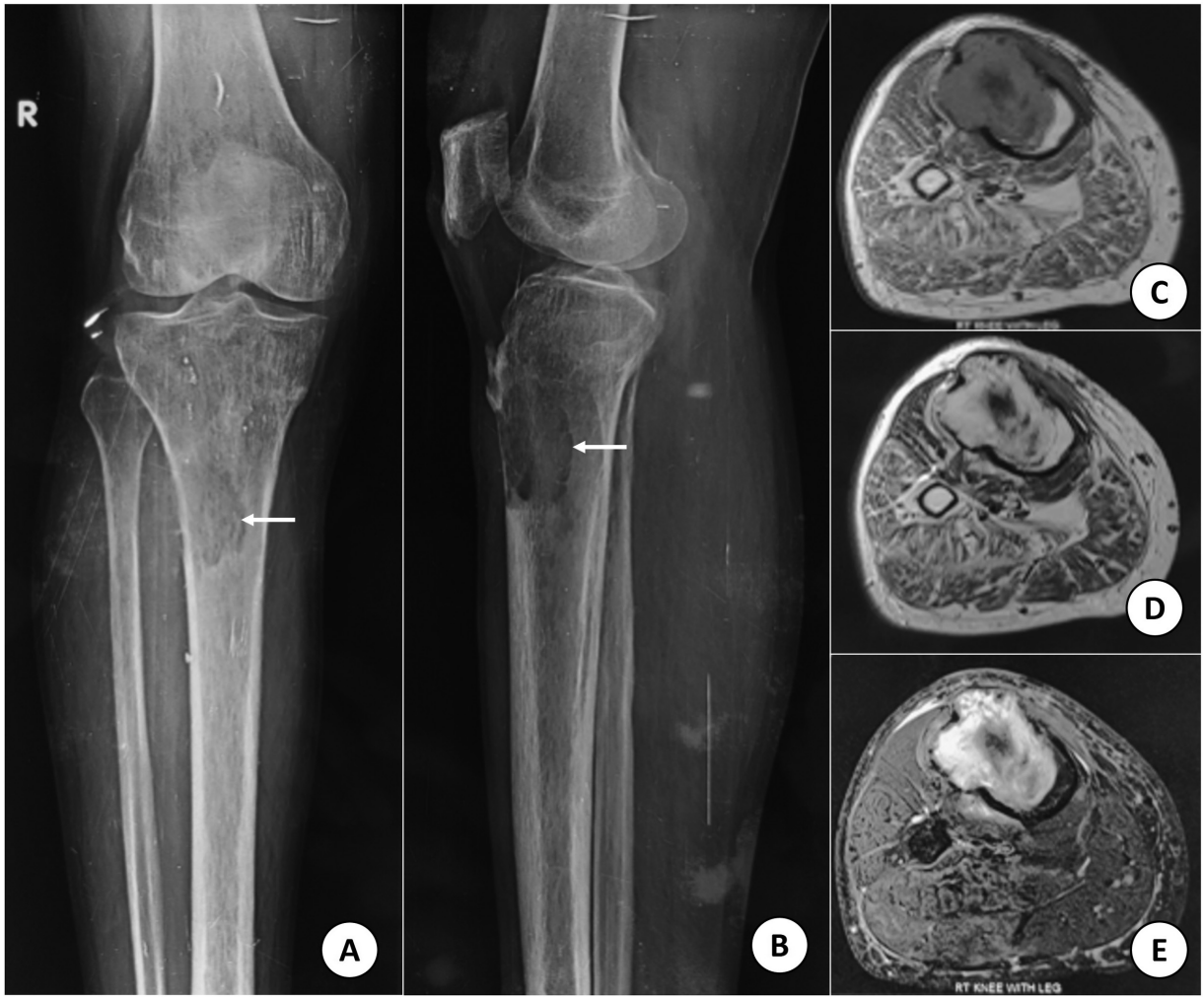

Fig. 1 (**A**) Anteroposterior and (**B**) lateral radiograph of right leg showing a well-defined eccentric lytic lesion in proximal metadiaphyseal region of the right tibia (white arrows), with cortical break along the anterior and lateral cortices. No periosteal reaction is seen. Rest of the visualized bones show diffuse decrease in density. (**C**) Axial T1-weighted, (**D**) T2-weighted, and (**E**) short-tau inversion recovery (STIR) magnetic resonance (MR) images showing a well-defined lesion along the anterolateral aspect of the right tibia, with cortical break along the anterior and lateral cortices. The lesion appears intermediate signal intensity on T1-weighted images and hyperintense on T2-weighted and STIR images. No periosteal reaction is seen. Note the fatty atrophy of the posterior compartment muscles of leg, likely due to disuse.

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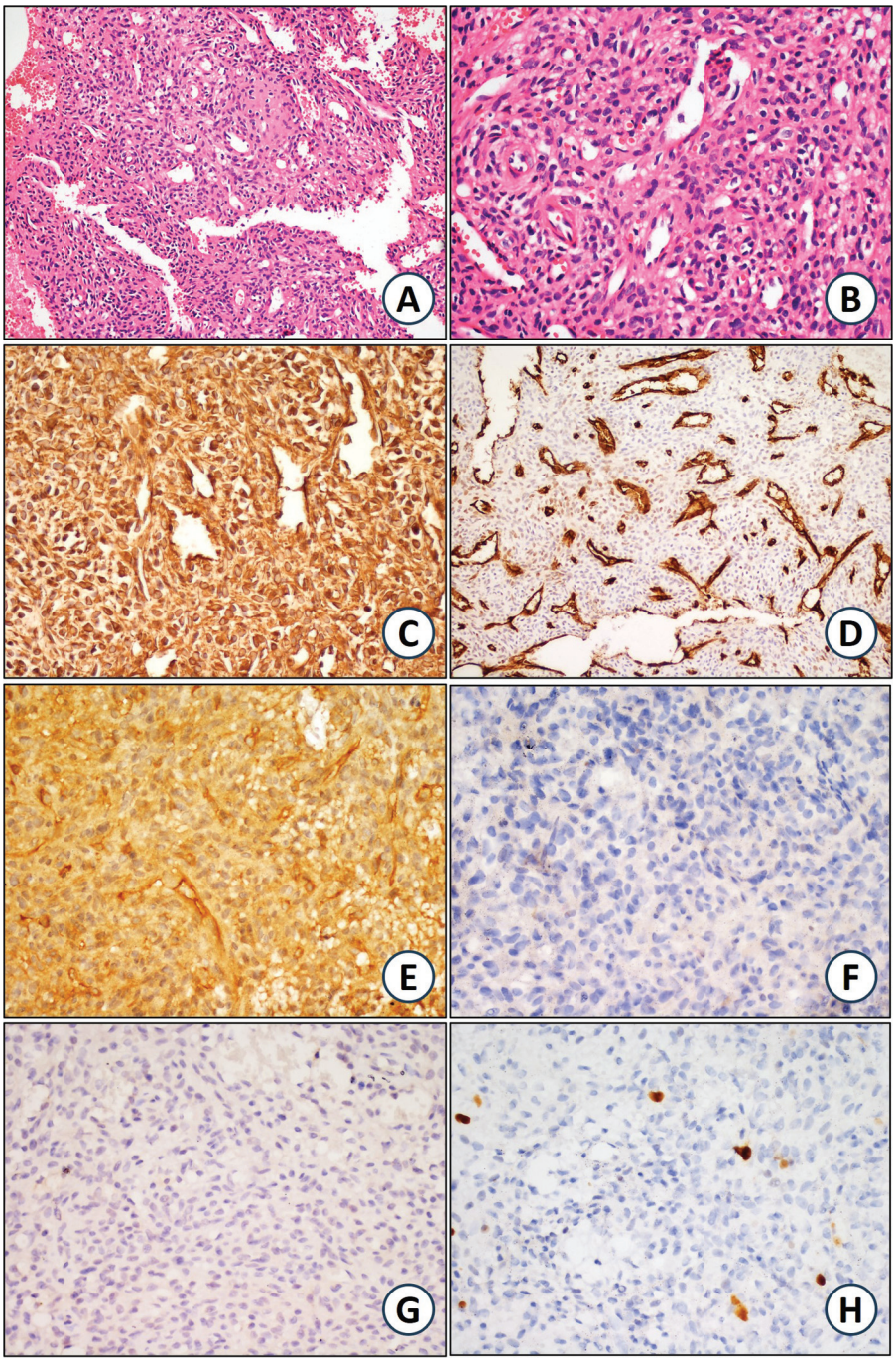

Fig. 2 (**A** and **B**) Histological sections of core biopsy showing sheets of monomorphous spindle cells with oval to elongated nuclei. Note prominent thin-walled vessels forming hemangiopericytomatous pattern (hematoxylin and eosin [H&E]; **A**, ×100 and **B**, ×200). (**C**–**H**) Immunohistochemistry findings showing diffuse positivity for vimentin (**C**), CD34 showing negative staining of tumor cells with positive staining in vascular endothelial cells (**D**), CD99 shows diffuse nonmembranous staining of tumor cells (**E**), tumor cells are negative for NKX2.2 (**F**) and TLE 1 (**G**). K_i-67 shows low labeling index (**H**) (horseradish peroxidase [HRP]-polymer; **C**, ×400, **D**, ×200, **E**, ×400, **F**, ×400, **G**, ×400, **H**, ×400).

active lytic lesion in the right proximal tibia as shown in ►**Fig. 3**. In addition, there were multiple bilateral rib fractures, insufficiency fractures involving the distal femur and the distal tibia and metabolically active pelvic nodes. The serum levels of FGF-23 were raised (288.1 RU/mL). Serum calcium and PTH levels were 8.6 mg/dL and 26.1 pg/mL, respectively. Serum phosphorus (1.2 mg/dL) and vitamin D levels (21.3 ng/mL) were low (1.4 mg/dL). Serum alkaline phosphatase was raised (410 U/L).

The patient underwent excision of tumor with extracorporeal irradiation. Reconstruction was performed with reimplantation of irradiated bone along with fibular graft and plating of proximal tibia. Excised tumor submitted for histopathology examination showed oval to spindle cells arranged in pattern-less sheets with evidence of nuclear indentations and grooves at places. There was prominent vascularity with focal areas showing multinucleated osteoclast giant cells spatially centered around thick-walled blood vessels. The

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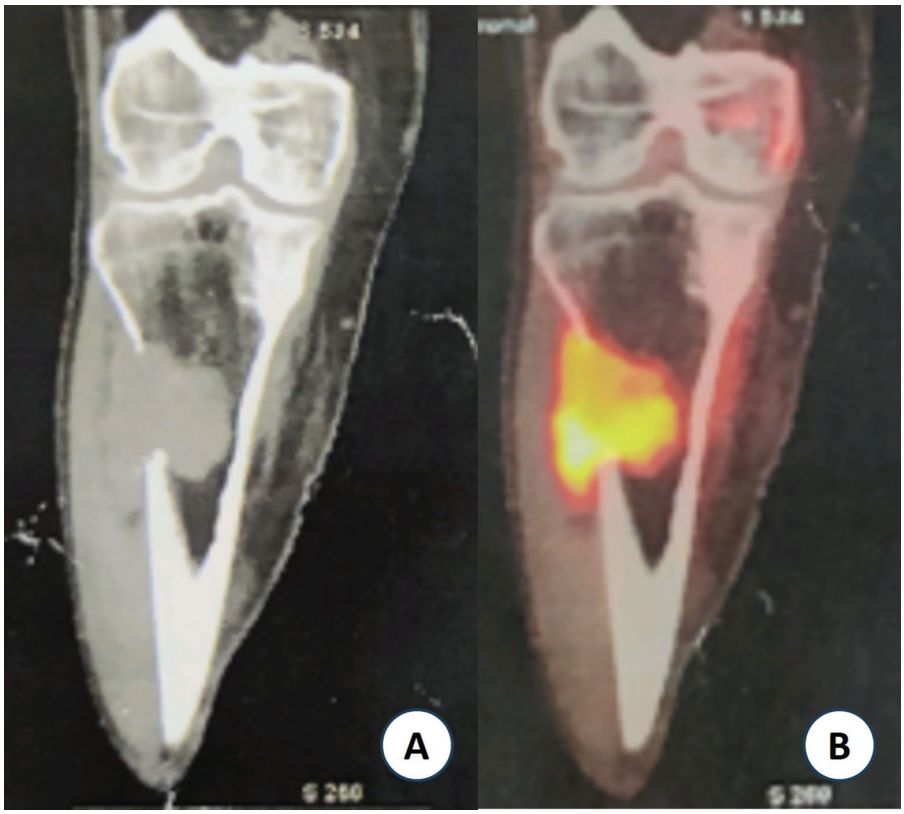

Fig. 3 Coronal reformatted (**A**) computed tomography (CT) and (**B**) positron emission tomography (PET)-fused images showing a metabolically active eccentric lytic lesion in proximal metadiaphyseal region of the right tibia, with cortical break along the lateral cortex. No periosteal reaction is seen.

lesion was seen extending from the medullary cavity through cortex into the adjacent soft tissue. The lesional cells were positive on immunohistochemistry (IHC) with SATB2 and CD56. There was weak to moderate patchy staining with ERG. The histopathological and immunohistochemical findings are shown in ►**Fig. 4**.

After surgical removal of the tumor, his phosphate level was restored to normal range (3.3 mg/dL) and symptoms were relieved. He was discharged with an advice to follow-up with a repeat FGF-23 levels done.

Discussion

Tumor-induced osteomalacia, also known as oncogenic hypophosphatemic osteomalacia, was first described in 1947 by Robert McCance, in a patient with vitamin D-resistant rickets who presented with pain, weakness, gait abnormalities, and low phosphorus levels.[3] In 1959, Andrea Prader first recognized this entity as giant cell granuloma of the rib and to be the underlying cause of osteomalacia in a young girl.[4] Though various mesenchymal tumor types have been reported over last few decades as the cause of tumor-induced osteomalacia, it is now believed that almost all cases are caused by PMT. Parameshwar et al compiled a series of 10 cases of PMT based on histopathological features and correlation with clinical, imaging, and biochemical findings. Till date, this is the first largest single institutional comprehensive study from India. Around 450 – 500 cases have been reported in the literature till date and the authors documented incidence of 0.002% in their institute with most cases manifesting in middle-aged adults.[5]

FGF-23 binds to FGF receptor in the proximal renal tubules and inhibits reabsorption of phosphate. Under physiological conditions, FGF-23 is secreted predominantly by osteogenic cells, osteoblasts, and osteocytes and subsequently undergoes degradation by proteolytic enzymes.[6] High circulating FGF-23 levels reduce the expression of type II sodium-phosphate cotransporters, leading to renal phosphate wasting. It also inhibits the hydroxylation of 25 hydroxyvitamin D resulting in decreased plasma levels of 1,25-dihydroxyvitamin D.[7] Reduction in the circulating levels of phosphorus and 1,25-dihydroxyvitamin D impairs bone mineralization.[2]

The clinical presentation includes bone pains, multiple fractures, and proximal muscle weakness mimicking osteoarticular pathology. The tumor predominantly involves the soft tissue with a minority of cases occurring in the bone. The lower extremities and craniofacial region are more commonly affected compared with pelvis and upper extremities.[1,5] The other sites like abdomen, mediastinum, and spine are rarely involved.[8]

The clinical symptoms are often vague, and the tumor may remain undetected for a long period of time. The various imaging modalities routinely used for localization of tumor are radiographs, CT, MRI, technetium bone scanning, and PET. Detection of FGF-23 overproduction by systemic venous sampling has been recently recommended.[9,10] However, the

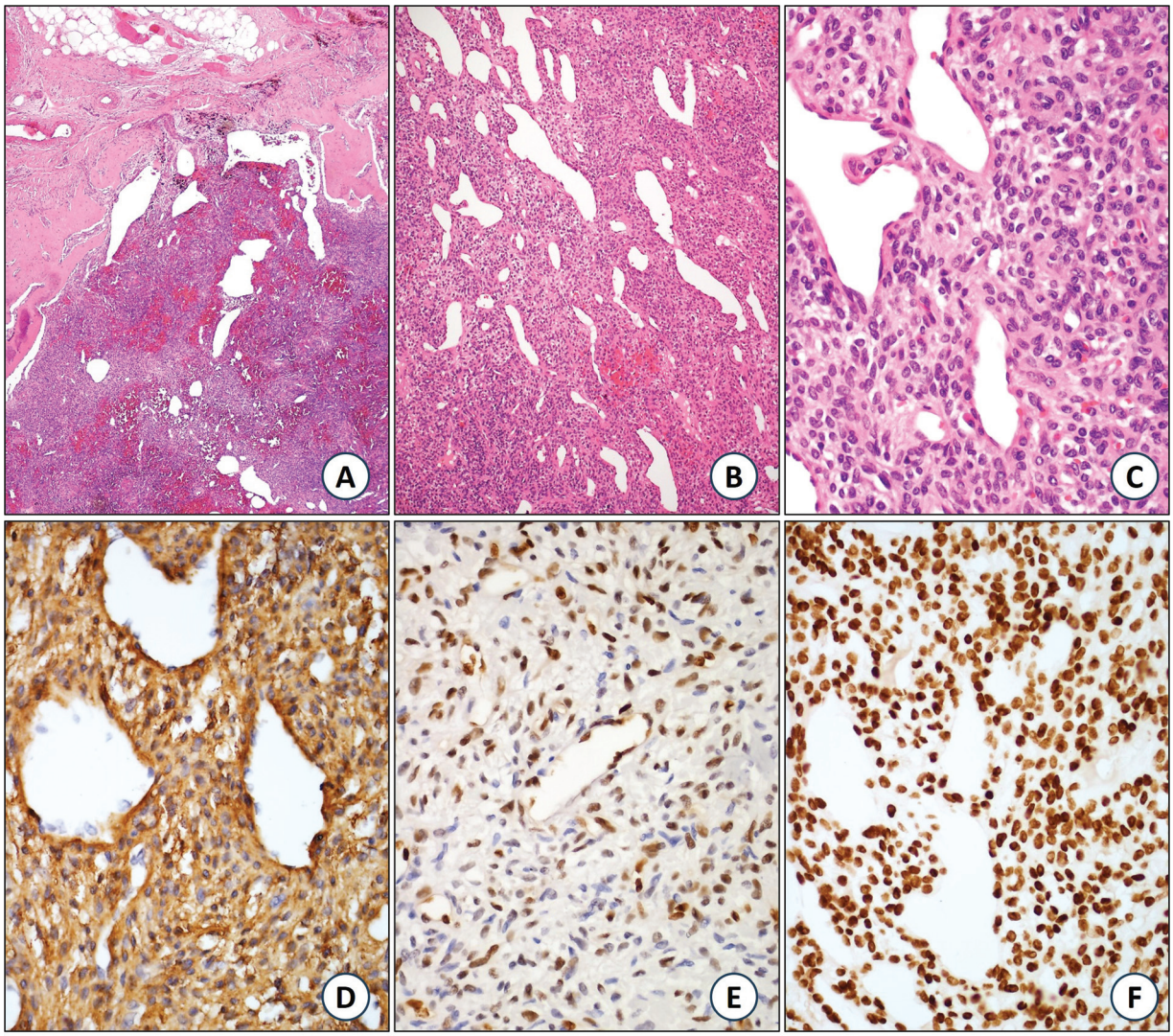

Fig. 4 (**A**–**C**) Histological sections from resected tumor showing tumor breaking through the cortical bone (**A**), tumor cells arranged in classical hemangiopericytomatous pattern (**B**), and monomorphous spindle tumor cells without any atypia or significant mitotic activity (**C**) (hematoxylin and eosin [H&E]; **A**, ×40, **B**, ×100, and **C**, ×400). (**D**–**F**) Immunohistochemistry findings showing diffuse cytoplasmic positivity of tumor cells for CD56 (**D**), patchy nuclear staining of tumor cells for ERG (**E**), and diffuse strong nuclear positivity of tumor cells for SATB2 (**F**) (horseradish peroxidase [HRP]-polymer; **D**, ×400, **E**, ×200, **F**, ×400).

use of ^{68}Gallium-conjugated somatostatin peptide analog is the most sensitive and specific for localization of tumor.[8] It is important to accurately localize the tumor as complete surgical resection is curative.

The significant laboratory findings reveal hypophosphatemia, phosphaturia, and elevated alkaline phosphatase. In addition, normal or low levels of 1,25-dihydroxyvitamin D and normal circulating levels of calcium and parathormone were also noted. Parameshwar et al reported normal serum calcium, low serum phosphorus, and elevated FGF-23 levels in all the cases wherever data was available.[5] Similar biochemical parameters ruling out calcium and vitamin D deficiency as a cause of osteomalacia were noted in the present case. Though elevated levels of serum FGF-23 support the diagnosis, it is also seen in X-linked as well as autosomal-dominant and autosomal recessive hypophosphatemic rickets.[6] The FGF-23 levels were elevated in the present case.

Histopathology reveals variable cellularity with bland spindle cells showing hemangiopericytoma-like vessels, osteoclast-like giant cells, and calcifications embedded in a chondromyxoid matrix. The morphology overlaps with solitary fibrous tumor, hemangiopericytoma/glomangiopericytoma, nonossifying fibroma, aneurysmal bone cysts, and other osteoclast giant cell-rich lesions. The presence of distinctive grungy calcification provides clue to the diagnosis. The present case did not show characteristic calcified matrix on the initial biopsy as well as resected specimen leading to diagnostic difficulty. In a case series by Parameshwar et al, hemangiopericytomatous growth pattern was seen in all the tumors. The characteristic grungy calcifications were noted in 8 out of 10 tumors. None of the tumors had shown significant mitosis or necrosis. Features associated with malignancy like high nuclear grade, increased cellularity, necrosis, and significant mitoses were not documented in any of the cases. The authors

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Author Contribution

	Name	Contribution
First Author	Dr. Monalisa Hui	data analysis, manuscript preparation, literature search
Second Author Corresponding author	Dr. Shantveer G Uppin	concept, definition of intellectual content, data analysis, manuscript review
Third Author	Dr. N Ramakrishna	data analysis, manuscript preparation, literature search
Fourth Author	Dr. B. Aravind Kumar	manuscript review,supervision
Fifth Author	Dr. K Nageshwara Rao	manuscript review,supervision
Sixth Author	Dr. Beatrice Anne	manuscript review,supervision
Seventh Author	Dr. Meher Lakshmi	manuscript review, supervision

have emphasized on the importance of histopathological diagnosis as the size of the tumors are generally very small and difficult to diagnose on clinical and radiological examination.[5] Though there are no specific IHC markers, most PMTs are known to express CD56, SATB2, and ERG as evident in this case. The role of IHC is of limited use in diagnosis.[11] Negative immunostaining for CD34, STAT6, TLE1, SMA, and S100 ruled out mesenchymal neoplasm like solitary fibrous tumor, synovial sarcoma, smooth muscle tumor, and neurogenic tumor in the present case. Immunohistochemical expression of FGF-23 have been reported in studies but have limited specificity.[12,13] Folpe et al and Houang et al reported positive staining not only in PMTs with tumor-induced osteomalacia but also other tumors like aneurysmal bone cysts and chondromyxoid fibroma.[12,13] The immunohistochemical expression of FGF-23 depends on the level of FGF-23 secreted by the tumor cells. The absence of FGF-23 gene transcript in non-PMT tumors with diffuse cytoplasmic and nuclear immunohistochemical expression confers a nonspecific staining pattern. The punctate staining pattern resulting from deposition of FGF-23 precursor molecules in the Golgi apparatus is specific. Shiba et al advocated FGF-23 as an useful immunohistochemical marker for PMT with tumor-induced osteomalacia. Though the number of samples tested were small, its utility in cases without tumor induced osteomalacia (TIO) is limited.[14] Recently, detection of FGF-23 messenger ribonucleic acid and protein expression using in situ hybridization have been studied.[15] However, these FGF-23 antibodies and probes are not widely available and was not tested in the present study.

Most of these tumors pursue a benign clinical course. Malignancy is reported rarely, and 10% tumors are known to recur.[16] Complete surgical excision results in resolution of phosphate wasting as well as restoration of vitamin D levels and FGF-23. Serum levels of FGF-23 is a good indicator to diagnose and monitor for postsurgical tumor recurrence.[1]

PMTs should be considered in the differential diagnosis in all cases of hypophosphatemic osteomalacia. The diagnosis is difficult on biopsies where characteristic grungy calcification is absent. The varied histology with morphological overlap with other low-grade mesenchymal neoplasm further adds to diagnostic dilemma. Elevated serum levels of FGF-23 at initial diagnosis with normalization of biochemical parameters and remission of symptoms following surgery may be used as supporting evidence in morphologically challenging cases.

Patient Consent

Written informed consent was obtained from all the patients and/or guardians.

Conflict of Interest

None declared.

Acknowledgment

None declared.

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