Case Report

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Pathology Section

Primary Hyperparathyroidism-Phosphaturic Mesenchymal Tumour: An Unusual Association and a Probable Syndrome

GWENDOLYN FERNANDES[1], AVANIKA[2], GLORIA KHUMANTHEM[3]

ABSTRACT

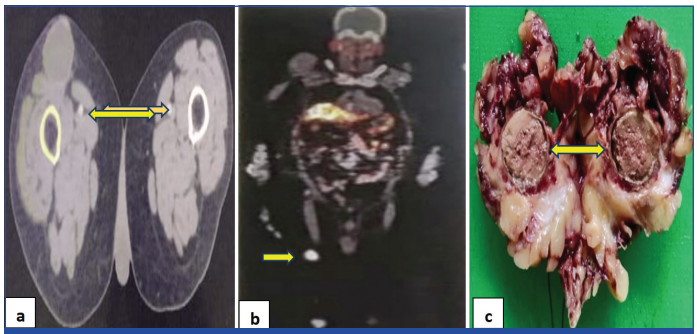
Phosphaturic Mesenchymal Tumour (PMT) is a rare and underdiagnosed tumour that causes Tumour-Induced Osteomalacia (TIO). These tumours produce Fibroblast Growth Factor-23 (FGF23), which inhibits renal tubular phosphate reabsorption, leading to hyperphosphaturia and oncogenic osteomalacia. The association of primary Hyperparathyroidism (pHPT) with PMT is extremely rare, with only two cases reported in the literature to date. A 51-year-old male presented in a bedridden state with multiple episodes of fractures throughout his skeleton over six years. Investigations revealed mild hypocalcaemia, marked hypophosphatemia, elevated serum Alkaline Phosphatase (ALP), low 25-Hydroxy Vitamin D, and persistently raised Parathormone (PTH) levels. A 68-Ga-DOTANOC 3D PET (Positron Emission Tomography) scan revealed a 4.1×3.2×2.5 cm DOTA avid mass in the right thigh. FGF23 levels were found to be 1466 pg/mL. A diagnosis of hypophosphatemic osteomalacia with pHPT was made, and the mass was subsequently excised. The thigh mass measured 3.5×2.5 cm and had a tan-brown cut surface. Microscopy revealed a benign spindle cell tumour with a vasoformative pattern and areas of grungy calcification. Immunohistochemistry demonstrated strong positivity for Vimentin, while CD34, CD68, CK, and Desmin were negative. A diagnosis of PMT, Mixed Connective Tissue type, was established. Normal phosphate, calcium, and FGF23 levels were restored after surgery, and the patient was able to walk again. This unusual case of a patient with pHPT and PMT, and the possible existence of a "pHPT-PMT syndrome", was reported in the Times of India on November 20, 2022, as "Rare phosphorus-guzzling tumour left Dongri man bedridden for three years." The exact aetiology for the association of PMT and pHPT is not known, and the hypothesis of aberrant gene expression has been implicated.

Keywords: Fractures, Fibroblast growth factor-23, Hypophosphatemia, Tumour-induced osteomalacia

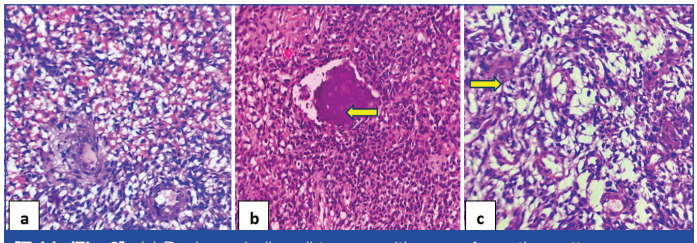
CASE REPORT

A 51-year-old male presented to the outpatient department of a tertiary care centre in a bedridden state following multiple episodes of fractures over six years. He had been bedridden for over three years and had undergone numerous orthopaedic consultations during this period. X-rays showed fractures of the right iliac bone, sacrum, bilateral neck of femur, distal tibia, subtalar joint and lumbar vertebrae. All bones exhibited marked osteopenia, and effusion of both ankle joints was also noted. Laboratory investigations revealed the following: Serum calcium: 8-8.9 mg/dL (Normal-8.5-10.2 mg/dL); Serum phosphorus: 0.8-2.0 mg/dL (Normal-2.8-4.5 mg/dL); ALP: 182-800 IU/L (Normal- 44-147 IU/L); 25-Hydroxy Vitamin D: 19.7-35.2 ng/mL (Normal- 30-50 ng/mL); PTH: 143-212 pg/mL (Normal-10-55 pg/mL); FGF23: 1466 pg/mL (Normal- <180 RU/mL). The patient's PTH levels were elevated from the beginning and continued to increase over a period of four years (2018-2022). Serum calcium remained within the range of 8-8.9 mg/dL during this time. The patient was prescribed oral calcium at a dosage of 2 g/day and Rocaltrol at a dosage of 1 g/day for this four-year period. No parathyroid adenoma was detected on Magnetic Resonance Imaging (MRI) and ultrasound of the neck. There was no renal disease, and renal function tests were normal.

A 68 Ga-DOTANOC 3D PET scan showed a 4.1×3.2×2.5 cm DOTA-avid mass in the subcutaneous tissue of the right thigh, anterior to the rectus femoris, with a Standardised Uptake Value (SUV) max of 39.1 [Table/Fig-1a,b]. Multiple healed fractures were also observed. In view of elevated PTH and FGF23, a clinical diagnosis of hypophosphatemic osteomalacia with pHPT was made. The thigh mass, which appeared non specific, had been present since the onset of symptoms and was presumed to be a lipoma until the time of the DOTA scans. It was excised and sent for histopathological examination. On gross examination, the mass was partially encapsulated, measuring 3.5×2.5 cm, with a tan-brown cut surface [Table/Fig-1c]. Microscopy revealed a benign spindle cell tumour with a vasoformative pattern [Table/Fig-2a]. Individual tumour cells were plump, spindle to ovoid in shape, with bland nuclear features and occasional cytoplasmic vacuoles. Among the tumour cells, osteoclast giant cells and a basophilic matrix with areas of "grungy calcification" were observed [Table/Fig-2b,c]. No mitoses, nuclear atypia, or necrosis were seen. Immunohistochemistry showed

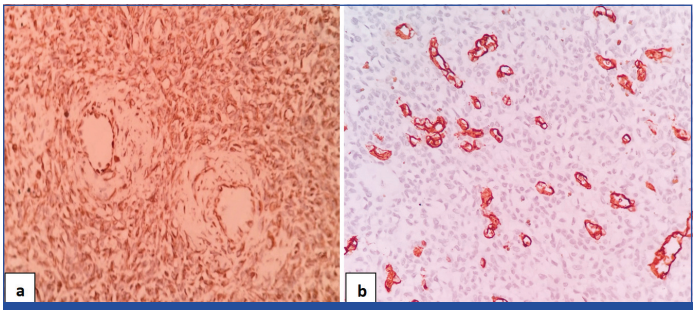


[Table/Fig-1]: (a) and (b) 68 Ga DOTANOC 3D PET scan- A 4.1×3.2×2.5 cm DOTA avid mass in the subcutaneous tissue of the right thigh, anterior to rectus femoris. SUV max 39.1; (c) Gross: 3.5×2.5 cm tumour with a tan-brown cut-surface excised from right thigh.



[Table/Fig-2]: (a) Benign spindle cell tumour with a vasoformative pattern (H&E, X400); (b) Tumour showing basophilic matrix and areas of grungy calcification (H&E, X400); (c) Osteoclast like giant cells (H&E, X400).

strong positivity for Vimentin, while CD34, CD68, CK, and Desmin were negative [Table/Fig-3a,b,4]. A diagnosis of PMT (Pleomorphic Sarcoma) - Mixed connective tissue type was given. Postsurgery, normal phosphate, calcium, FGF23 levels, and overall health were restored, allowing the patient to walk again.



[Table/Fig-3]: (a) Tumour cells showing diffuse vimentin positivity (IHC, X100); (b) Tumour cells are CD34 negative, blood vessels show strong positivity (IHC, X100).

Immunohistochemical marker	Finding
Vimentin	Positive
CD34	Negative in tumour cells
Desmin	Negative
CK Cocktail	Negative

[Table/Fig-4]: IHC markers status.

pattern, and a low mitotic index, is key to diagnosing PMTs. The immunoprofile demonstrates positive reactivity for vimentin, FGF23, smooth muscle actin, and somatostatin receptors, while desmin and factor VIII-related antigen are usually negative [1]. Good clinical and laboratory correlation is required for the diagnosis.

In a series of 10 cases of PMT reported, laboratory investigations revealed hypophosphataemia, hyperphosphaturia, elevated ALP, normal to low vitamin D levels, normal PTH levels and elevated FGF23 levels in these cases. All the patients showed normocalcemia [6]. However, index case patient exhibited pHPT and mild hypocalcaemia. Most patients with PMTs can develop secondary and even tertiary HPT due to prolonged oral phosphate therapy and inadequate calcitriol supplementation [3,7].

The association of pHPT with PMT is extremely rare, and only two cases reported in the literature could be found. Present case was compared with these two, and all three cases showed hypophosphataemia, increased levels of PTH and FGF23, with tumour sizes varying from 3.5 to 4.1 cm. The present case differs in severity, with a longer disease duration of six years and more advanced clinical deterioration. Additionally, it exhibits the most extreme hypophosphatemia and the highest FGF-23 levels. Several genes are implicated in the causation of PMT and HPT. There is a hypothesis that aberrant genes are overexpressed in PMT, which can result in hyperplasia of the parathyroid glands and autonomous

Serial no.	Age (years)/ gender	Clinical presentation and duration	Serum phosphate (2.8-4.5 mg/dL)	Serum calcium (8.5-10.2 mg/dL)	PTH (10-55 pg/mL)	FGF-23 (<180 RU/mL)	Size and site of PMT	Histopath diagnosis/ subtype
1. (Salim M et al., [2])	49, M	• Multiple fractures • Muscle weakness • Generalised bone pain • Three years	1.6 mg/dL	9.2 mg/dL	114.1 pg/mL	1330 RU/mL	3.5 cm -left lung	PMT
2. (Markou A et al., [3])	44, F	• Spontaneous fractures • Proximal muscle weakness • Generalised bone pain • Three years	1.1 mg/dL	11.1 mg/dL	284 pg/mL	1035 RU/mL	4.0 cm -left thigh	PMT-Mixed connective tissue type
3. (Present case)	51, M	• Bedridden • Multiple fractures • Generalised bone pain • Six years	0.8 mg/dL	8.6 mg/dL	143 pg/mL	1466 RU/mL	4.1 cm -right thigh	PMT-Mixed connective tissue type

[Table/Fig-5]: Comparative chart of three cases of pHPT-PMT [2,3].

DISCUSSION

The PMTs are frequently associated with TIO, a paraneoplastic syndrome that manifests as renal phosphate wasting, reduced bone mineralisation, and clinically presents with bone pain, osteomalacia, and fragility fractures. The tumour cells produce FGF23, and increased levels of this protein aid in the diagnosis [1]. PMTs are unique and underdiagnosed mesenchymal tumours of bone or soft tissue origin, and they are difficult to diagnose clinically due to their vague clinical symptoms and the small size of lesions, as well as histopathologic similarities with other mesenchymal tumours. The association of pHPT with PMT is extremely rare, with only two cases reported in the literature to date [2,3] [Table/Fig-5].

PMTs can arise from both bone and soft tissue and are generally less than 5 cm in size. In PMT-induced osteomalacia, hypophosphataemia and relative hyperphosphaturia are the most consistent laboratory findings. PMTs show a unique fusion of FN1-FGFR1, which results in high levels of FGF23 [4].

The diagnosis of PMT is challenging on histopathology due to its strong differential diagnosis with other low-grade mesenchymal tumours. Microscopically, four variants of PMTs exist: osteoblastoma-like variant, non ossifying fibroma-like variant, ossifying fibroma-like variant, and mixed connective tissue variant [5]. The most common variant is the mixed connective tissue type, as diagnosed in present case. Recognition of its unique constellation of histological features, particularly characterised by the presence of grungy, basophilic calcifications, bland normochromic spindle cells with a vasoformative

secretion of PTH. The parathyroid glands have abundant expression of FGF1 and Klotho receptors, which upregulate the expression of the PTH gene, PTH secretion, and parathyroid cell proliferation [8,9]. Furthermore, the EEF2K gene is differentially expressed in parathyroid adenomas and hyperplasia compared to normal parathyroid tissue [10]. Aberrant genes, including FGFR1, FGF1, fibronectin, and Klotho, are mechanistically involved in the HPT-PMT association [8,9].

CONCLUSION(S)

PMTs are often misdiagnosed and should be included in the differential diagnosis of TIO. Tumour-induced hypophosphatemic osteomalacia will not be missed if serum phosphorus is included in the routine biochemical investigations of patients with multiple fractures. A larger series of cases will be required to establish the exact aetiology and the basis for the mechanism of association between pHPT and PMT. A probable syndromic association of pHPT and PMT will also need to be carefully examined.

REFERENCES

[1] Goldblum JR, Folpe AL, Weiss SW. Enzinger and Weiss's Soft-tissue Tumours. 7th ed. Philadelphia: Elsevier; Philadelphia, USA; 2019. p. 1133-47.
[2] Salim M, Behairy MS, Barengolts E. TIO associated with hyperparathyroidism: A rarity, a rule, or a novel HPT-PMT syndrome—A case study with literature review. Case Reports in Endocrinology. 2021;2021:5172131.
[3] Markou A, Tsiama V, Tournis S, Papanastasiou L, Tsiavos V, Dassou A, et al. Coexistence of tumour-induced osteomalacia and primary hyperparathyroidism. Endocr Pract. 2011;17(6): e144-e148.

[4] Liu X, Yin X, Li D, Li K, Zhang H, Lu J, et al. RNA sequencing reveals novel oncogenic fusions and depicts detailed fusion transcripts of FN1-FGFR1 in phosphaturic mesenchymal tumours. Modern Pathology. 2023;36(10):100266-66.
[5] Weidner N, Santa Cruz D. Phosphaturic mesenchymal tumours. A polymorphous group causing osteomalacia or rickets. Cancer. 1987;59(8):1442-54.
[6] Parameshwar VC, Rekhi B, Duggad A, Ramadwar M. Phosphaturic mesenchymal tumour: Clinicopathological features with outcomes in 10 patients with review of literature. Indian J Pathol Microbiol. 2024;67(2):306-11.
[7] Ni X, Liu W, Zhang D, Li X, Chi Y, Feng J, et al. Hyperparathyroidism in a large cohort of Chinese patients with tumour-induced osteomalacia. J Clin Endocrinol Metab. 2023;108(5):1224-35.
[8] Baradaran A. Relationship between Klotho and parathormone. J Parathyroid Disease. 2023;11(1):e11230.
[9] Lee JC, Hsieh TH, Kao YC, Tsai CF, Huang HY, Shih CY, et al. Klotho overexpression is frequently associated with upstream rearrangements in fusion-negative phosphaturic mesenchymal tumours of bone and sinonasal tract. Modern Pathology. 2023;36(12):100336.
[10] Lu M, Kjellin H, Fotouhi O, Lee L, Nilsson IL, Haglund F, et al. Molecular profiles of oxyphilic and chief cell parathyroid adenoma. Molecular and Cellular Endocrinology. 2018;470:84-95.

PARTICULARS OF CONTRIBUTORS:
1. Professor (Additional), Department of Pathology, Seth G.S. Medical College and K.E.M. Hospital, Mumbai, Maharashtra, India.
2. Junior Resident, Department of Pathology, Seth G.S. Medical College and K.E.M. Hospital, Mumbai, Maharashtra, India.
3. Ex-fellow, Department of Uropathology, Seth G.S. Medical College and K.E.M. Hospital, Mumbai, Maharashtra, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Gwendolyn Fernandes,
B2-801 Wing, Mahindra, Vivante, Off Western Express Metro Station, Andheri (East), Mumbai-400093, Maharashtra, India.
E-mail: drgwenfern@yahoo.co.in

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