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Case Report

# Tumor-induced Osteomalacia: A Case Study of a Nasal Tumor

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## Abstract

Oncogenous osteomalacia, which is also known as tumor-induced osteomalacia, is a condition where a neoplasm is associated with systemic bone demineralization and renal phosphaturia. We report a case who presented with a bleeding nasal mass, generalized fatigue, and cramps in her leg. Excision was done, and histopathologically, it was diagnosed to be a phosphaturic mesenchymal tumor. The cramps disappeared soon after surgery and she is on regular follow-up for the past 2 years.

**Key words:** Oncogenic osteomalacia, Mesenchymal tumor, Hyperphosphaturia, Hypophosphatemia

## INTRODUCTION

Oncogenous osteomalacia (OOM) is a rare condition of a paraneoplastic syndrome[1] characterized by the association of a neoplasm with systemic bone demineralization due to renal phosphate wasting. In 1947, McCance published the first case of a patient who presented with phosphaturia which did not resolve until the tumor involving the femur was removed.[2,3] Andrea Prader, in 1959, treated an 11-year-old girl who presented with hypophosphatemia and rickets. She was operated later for a rib tumor which turned out to be a giant cell granuloma and her rickets got cured thereafter.[2]

In 1987, the term phosphaturic mesenchymal tumor (PMT) was introduced by Weidner and Santa Cruz,[3] and they described four morphological patterns, among which the most common one was a mixed connective tissue tumor variant (PMT), the others being an osteoblastoma-like tumor, a non-ossifying fibroma-like tumor, and an ossifying fibroma-like tumor.[2] PMTs can involve both bone and soft tissue.[3] 95% of these tumors involve the extremities and appendicular skeleton, with 5% involving the head and neck region.[4]

Around 50% of the PMT tumors of head and neck involve the sinonasal tract.[3] The remaining 50% are located in the mandible, floor of mouth pharynx, temporal bone, and thyroid.[4] Due to its rare presentation, PMTs are often mistaken in diagnosis for other tumors such as glomangiopericytoma and low-grade osteosarcoma,[3] chondrosarcoma, and chondroblastoma.[1]

We are reporting a case of PMT involving the nose and paranasal sinus presenting with epistaxis and bone pain. The clinical features, the pathology, and the management are described.

## CASE REPORT

A 55-year-old lady limped into the ENT OP with a 6-month history of intermittent, profuse epistaxis, and a right-sided nasal block. She also had generalized fatigue with cramps and pain in her right leg below the knee for the past 8 months. She was treated symptomatically at a local hospital and once blood had to be transfused, due to the severity of the bleed from the nose. She was found to be hypertensive and was on medication for the same. There was no remarkable family history.

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On anterior rhinoscopic and nasal endoscopic examination, a reddish, smooth, firm polypoidal mass was seen filling the right middle meatus extending anteriorly up to the middle half of the inferior turbinate [Figure 1]. Nasal septum was deviated to the left side.

Contrast-enhanced computed tomography (CT) scan revealed a well-enhancing soft tissue mass of 3 cm × 2 cm × 2 cm in the right middle meatus with extension to the right maxillary antrum [Figure 2a and b). No bony erosion was noted on the orbital walls and skull base. On T1- and T2-weighted magnetic resonance imaging (MRI) images, the soft tissue mass was heterogeneously enhancing [Figure 3a and 3b]. Blood routine and thyroid function and renal function tests were within normal limits.

Under local anesthesia, biopsy was taken and the brisk bleeding was controlled by nasal packing. The diagnosis was hemangiopericytoma-like tumor.

Following the advice of the pathologist, a battery of tests was performed, among which elevated levels of serum alkaline phosphatase (998 IU; normal < 275IU),[5] reduced levels of inorganic phosphorus (1.43 mg/dl; normal 3–4.5),[5] and 1, 25-dihydroxyvitamin $D_3$ (12.6 pg/ml; normal 25–45 pg/ml)[5] were recorded. Serum ionized calcium was 4.9 mg/dl (normal 4.3–5.6).[5]

High level of 24 h urine phosphate (1640 mg/24 h; normal 400–1300)[5] confirmed a low tubular reabsorption of phosphate.

The conclusions of the above biochemical tests were hypophosphatemia, normocalcemia, high alkaline phosphatase levels, and phosphaturia.

Radiological investigation revealed a severe osteopenia of the right femur and tibia.

Under general anesthesia, complete endoscopic excision of the mass was done [Figure 4]. The bleeding was controlled using bipolar cautery and nasal packing. The post-operative period was uneventful. The histopathology report came as a PMT. On high power microscopic view, there were small stellate cells with prominent vascular stroma in a myxoid matrix. The cells were negative for CD 34, CD 99, and S-100 and positive for vimentin. Further, analysis of fibroblast growth factor 23 (FGF23) expression by

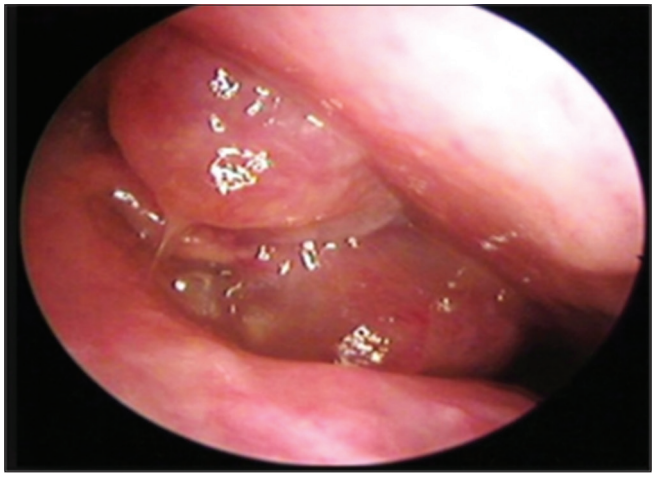

**Figure 1: 0 degree nasal endoscopy showing smooth, polypoidal mass in middle meatus**

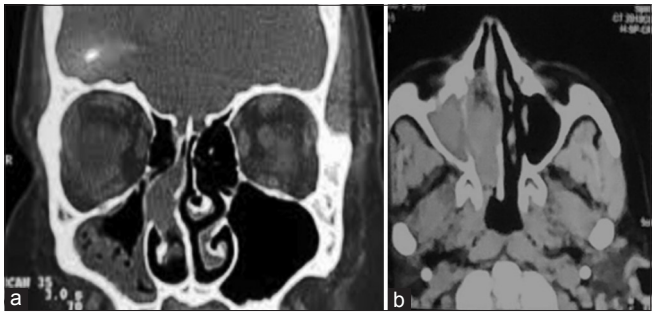


**Figure 2: (a and b) Computed tomography scan, coronal and axial views showing a moderately enhancing mass in the right nasal cavity with extension to maxillary antrum**

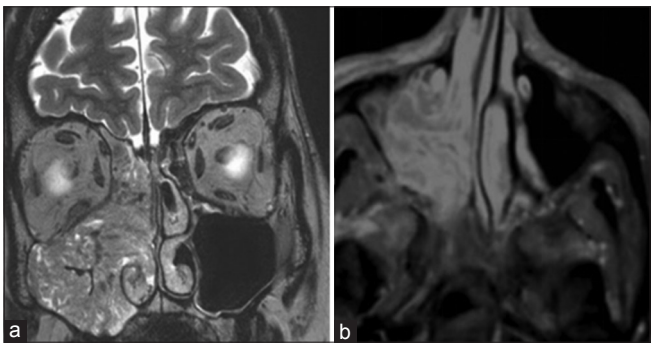


**Figure 3: (a and b) Magnetic resonance imaging scan-: Soft tissue mass in the right middle meatus extending to the right maxillary sinus shows heterogeneous enhancement on T1- and T2-weighed images**

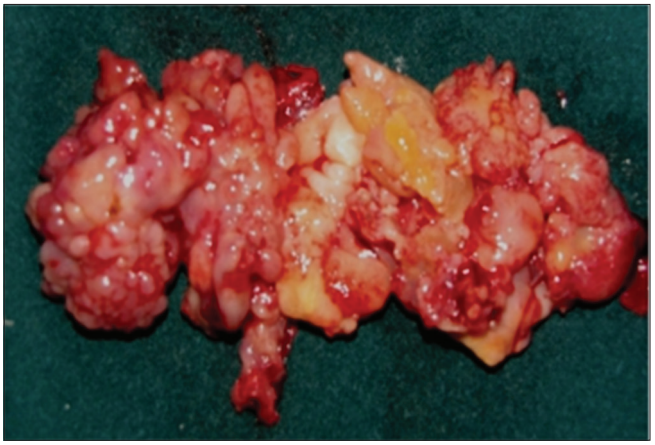

**Figure 4: Gross specimen after resection**

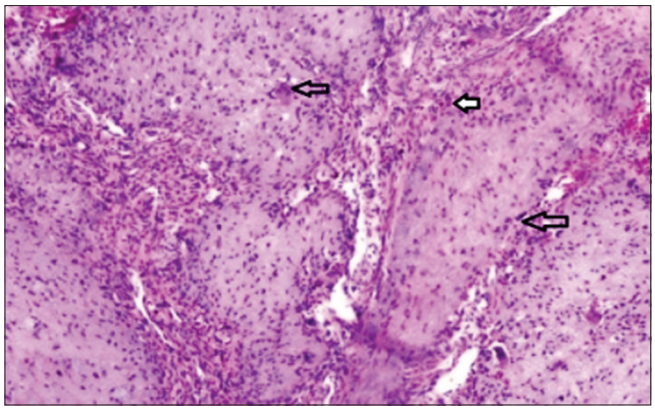

**Figure 5: Immunohistochemistry for fibroblast growth factor 23 protein staining positive under high power**

immunohistochemistry showed distinct, punctate staining in the cytoplasm of the cells [Figure 5].

The patient was given oral supplements of phosphate and Vitamin D. Within the next 2 months, her bone pain got reduced and her limp disappeared. Her serum phosphate and alkaline phosphatase levels got back to normal. Her general health improved and she is still on regular follow-up for the past 2 years. Thus, the diagnosis of osteogenic OOM was made.

## DISCUSSION

Osteomalacia means soft bones. It is a disorder in which there is demineralization resulting in weak bones and this condition occurs in adults.[6]

OOM or tumor-induced osteomalacia (TIO) is characterized by phosphaturia, hypophosphatemia, and osteomalacia with regression once these tumors are completely resected.[7]

PMTs occur commonly in extremities and paranasal sinus involvement is seen only in 6.2% of the cases.[6] As these tumors are generally small and asymptomatic, localization becomes difficult and challenging which results in delayed diagnosis, sometimes even as long as 15 years.[2,7]

PMTs are found equally in both sexes with an average age of onset at 40 years. Patients usually present with generalized musculoskeletal pain, weakness, and recurring fractures of the long bones and vertebrae.[5]

Relationship between PMT and osteomalacia was established in 1959 by Prader *et al*. PMTs secrete excess of FGF23. This physiological phosphate regulator peptide is also known as phosphatonin. FGF23 binds to the FGF receptor on the renal proximal tubules and reduces reabsorption of phosphates by inactivating the sodium-potassium pump.[5] It also inhibits 1-alpha-hydroxylase enzyme which brings down the levels of 1-alpha, 25-dihydroxyvitamin D3.[2] Thus, it is a regulatory hormone for 1-alpha, 25-dihydroxyvitamin D3. PMTs secrete FGF23 excessively leading to dysregulation of the FGF23 degradation pathway. FGF-23 in excess can lead to electrolyte imbalance with consequent damage to heart, kidneys, and brain.[1]

Serum FGF23 can be measured using C-terminal enzyme-linked immunosorbent assay, the normal range being 21 ± 11SDRU/ml.[5] Tumor expression of FGF23 can be detected by reverse transcription polymerase chain reaction on mRNA and FGF23 protein by western blotting and immunohistochemistry using FGF23 antibody.[1,8]

On histopathology, PMTs are composed of spindle-shaped or stellate cells, myxoid or myxochondroid calcified matrix with abundant microvascular supply and flocculent calcification may be seen. The osteocytes in PMTs produce FGF23 resulting in bone demineralization.[4,5] The rich microvascular stroma often misleads to a diagnosis of hemangiopericytoma.[4]

The incidence of PMT in the head and neck is probably higher as tumors in this region is frequently misdiagnosed.[3] Tumors such as osteosarcoma, mesenchymal chondrosarcoma, chondroblastoma, atypical enchondroma, spindle cell lipoma, angiolipoma, sclerosing hemangioma, hemangiopericytoma with osteoclast-like giant cells, tenosynovial giant cell tumors, and benign mesenchymal tumor are some of the differential diagnoses.[1]

Although PMTs are considered benign, histologic evidence of malignancy with multifocal or metastatic disease has been reported.[2,3]

CT scan shows a moderately enhancing soft tissue lesion, while it is isointense to diffuse enhancement to gadolinium in T1-weighted MRI and low intensity in T2-weighted MRI. MRI with short tau inversion recovery sequence, F-18 FDG-PET, whole body $^{99m}$Tc sestamibi scintigraphy, and octreotide scintigraphy is the investigations of choice in locating these lesions.[5,7] Ga-DOTANOC PET/CT is the other newer investigation modalities.[7]

Osteomalacia is not seen in all PMTs, but TIO should always be considered in patients who are being treated for musculoskeletal pain, pathological fractures, and non-familial adult-onset osteomalacia.[3]

Sinonasal PMT is a rare variant and closely resembles hemangiopericytoma histologically.[5] The positive molecular studies for FGF23 and the negative expression

of the neuronal markers such as synaptophysin and neurofilaments for PMTs are helpful in distinguishing the two.[1] Similarly, the grungy calcification noted on histopathology is seen only in PMTs.[1]

Monitoring levels of serum FGF23, 1, 25-dihydroxy D3, and phosphate levels are useful in the detection and the response to surgical outcome of TIO.[2]

Wide resection of the tumor is necessary to prevent recurrence. If the tumor is unresectable or not located, alternative medical therapy is given. Phosphate supplements such as calcitriol or alfacalcidol can be used, but complications such as hypercalcemia, renal failure, and hyperparathyroidism may result.[2]

In our case, nasal endoscopic evaluation and serum levels of inorganic phosphate and 1, 25-dihydroxyvitamin D3 are being monitored every 6 months. She has been asymptomatic ever since the surgery and has been asked to report for any further untoward symptom.

## CONCLUSION

A diagnosis of phosphaturic tumor should be kept in mind while assessing a case of osteomalacia with hypophosphatemia and imaging of the whole body can be a valuable diagnostic tool. Localization and resection of these tumors give a dramatic cure of the OOM. As PMTs are rare in the ENT field, one needs to be aware of the possibility of such a cause in the nose for a patient presenting with cramps in the leg.

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