

**Case Report:****Tumour-induced osteomalacia due to phosphaturic mesenchymal tumour of the ethmoid**

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**ABSTRACT**

Tumour-induced hypophosphatemic osteomalacia is often due to mesenchymal tumours. Surgical resection of tumour gives complete relief. We present the case of a 66-year-old male who sustained fracture of the hip after a trivial fall. After hip replacement surgery his proximal muscle weakness did not improve. On evaluation he had hypophosphatemia with hyperphosphaturia, raised fibroblast growth factor-23 levels. A gallium 68 (<sup>68</sup>Ga) - radiolabeled somatostatin analogue 1,4,7,10 – tetra azacyclododecane – N,N<sup>1</sup>, N<sup>11</sup>,N<sup>111</sup> - tetraacetic acid (DOTA) 1-NaI3 – octreotide (NOC) positron emission tomography computed tomography revealed a somatostatin receptor avid polypoidal lesion in left posterior ethmoid sinus measuring 1.5 x 1.6 cm likely representing mesenchymal tumour and retention cyst/polyp in left sphenoid sinus. Patient underwent a navigation assisted minimally invasive sinus surgery for removal of polypoidal lesion. Histopathological examination confirmed phosphaturic mesenchymal tumour.

**Key words:** *Phosphaturic mesenchymal tumor, FGF-23 levels, Hypophosphataemia, Proximal muscle weakness*

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**INTRODUCTION**

Tumour-induced osteomalacia (TIO) is a rare paraneoplastic syndrome. Hypophosphatemia with proximal muscle weakness, difficulty in walking and pathologic fractures of the long and flat bones are common manifestations of TIO.<sup>1</sup> All regions of the body are potentially affected. TIO should be suspected in a patient with hyperphosphaturia with hypophosphatemia in a non-azotemic adult in the absence of acidosis. TIO is caused by phosphaturic mesenchymal tumours. They secrete fibroblast growth factor-23 (FGF-23) which cause hyperphosphaturia. Conventional localization techniques like computed tomography (CT), magnetic resonance imaging

(MRI) [and gallium 68 (<sup>68</sup>Ga) - radiolabeled somatostatin analogue 1,4,7,10 – tetraazacyclododecane – N,N<sup>1</sup>, N<sup>11</sup>,N<sup>111</sup> - tetraacetic acid (DOTA) 1-NaI3 – octreotide (NOC) positron emission tomography computed tomography (PET-CT) Scan] (receptor imaging) help in the diagnosis. Surgical resection of the tumour provides complete relief.

**CASE REPORT**

A 66-year-old male, known to have type2 diabetes mellitus for 15 years presented with proximal muscle weakness and bone pains for six months. He could walk only with support. He had experienced a trivial trauma while crossing a road-divider and had fractured his

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left hip for which he underwent total hip replacement six months ago. Two months later, he had presented with gall bladder stones for which cholecystectomy was done. He also had coronary artery disease for which percutaneous transluminal angioplasty (PTCA) was done two years back. He was detected to have hypertension six months back.

Clinical evaluation revealed that he was of average built. Blood pressure was 150/90 mm/Hg. Biochemical evaluation revealed fasting blood sugar of 84 mg/dL, glycosylated hemoglobin (HbA<sub>1c</sub>) 7.5%, normal lipid profile, liver and thyroid functions. Arterial blood gas analysis was normal. His metabolic bone profile is shown in Table 1; salient abnormalities were hyperphosphaturia with hypophosphataemia and elevated FGF-23 levels. Bone scan (technetium<sup>99m</sup> methyl diphosphonate) showed prosthesis in left femur, and normal tracer distribution in both axial and appendicular skeleton, with visualization of both kidneys. Contrast enhanced CT of paranasal sinuses showed contrast enhanced lesion in left posterior ethmoid sinus, with inspissated secretions in sphenoid sinus (Figure 1). A <sup>68</sup>Ga DOTANOC PET-CT revealed a somatostatin receptor (SSR) - avid

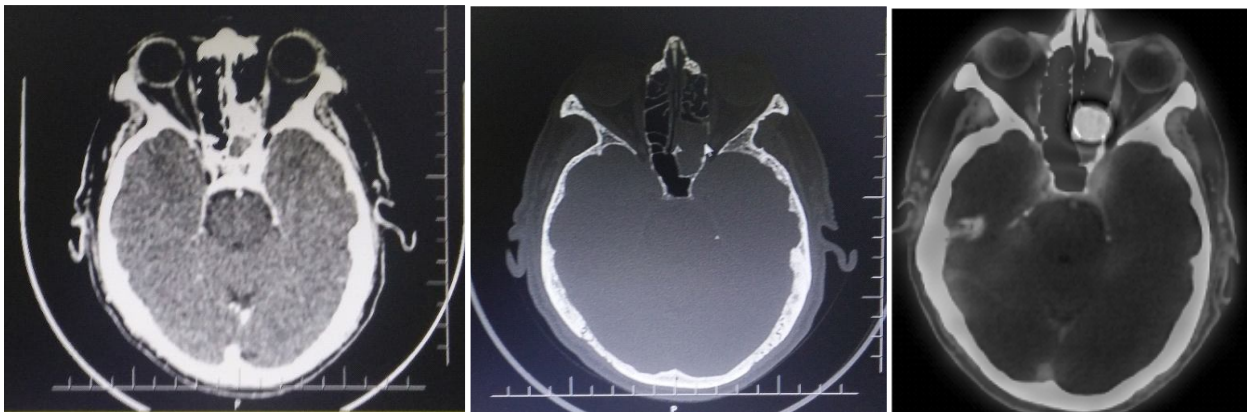
polypoidal lesion in left posterior ethmoid sinus measuring 1.5 x 1.6 cm likely to be a mesenchymal tumour and retention cyst/polyp in left sphenoid sinus. There was no evidence of parathyroid adenoma/nodule (Figure 1B).

With the biochemical parameters of hyperphosphaturia with hypophosphataemia, elevated FGF-23 levels, CT and <sup>68</sup>Ga DOTANOC PET-CT the diagnosis of phosphaturic mesenchymal tumour of the ethmoid sinus was made. Patient underwent a navigation assisted minimally invasive sinus surgery for removal of polypoidal lesion. Computer navigational assisted endoscopic approach was sought in this case as the lesion involved the posterior ethmoid sinus and sphenoid sinus due to its close proximity to the cavernous sinus, internal carotid artery and optic nerve. Also there was erosion of the lamina, which increase the chance of inadvertent entry to the orbit and the retro-orbital space. The lesion measured 1.7 x 1.4 x 0.7 cm, weighing 0.975 g, with pale grey appearance (Figure 2A). Histopathological examination showed (Figures 2B, 2C, 2D and 2E) a tumour with overlying respiratory mucosa, composed of spindle to ovoid cells, small vesicular nuclei and inconspicuous

**Table 1: Laboratory parameters**

Variable	Units	Before surgery	7 Days after surgery	6 Weeks after surgery	6 Months after surgery
Serum Creatinine	mg/dL	0.76	0.9	0.9	1.03
Serum Albumin	g/dL	4.1	3.9	3.9	3.9
Serum Calcium	mg/dL	8.9	8.8	8.9	8.9
Serum Phosphorous	mg/dL	1.8	2.79	4.4	4
Serum Alkaline Phosphate	IU/L	312	-	213	98
Serum vitamin D	ng/mL	26.8	-	39.44	31.59
Serum intact parathyroid hormone	pg/mL	152.7	-	77.25	86.79
Serum FGF	RU/mL	983	-	-	53.7
PEI		0.339	0.051	0.095	0.067
Calcium/creatinine ratio		0.007	-	0.008	-

Normal range: FGF 23 (reference Interval) = 21.6 – 91.0 RU/ml); PEI = -0.09 to +0.09; calcium/creatinine ratio <0.02  
 FGF = fibroblast growth factor; PEI = phosphate excretion index



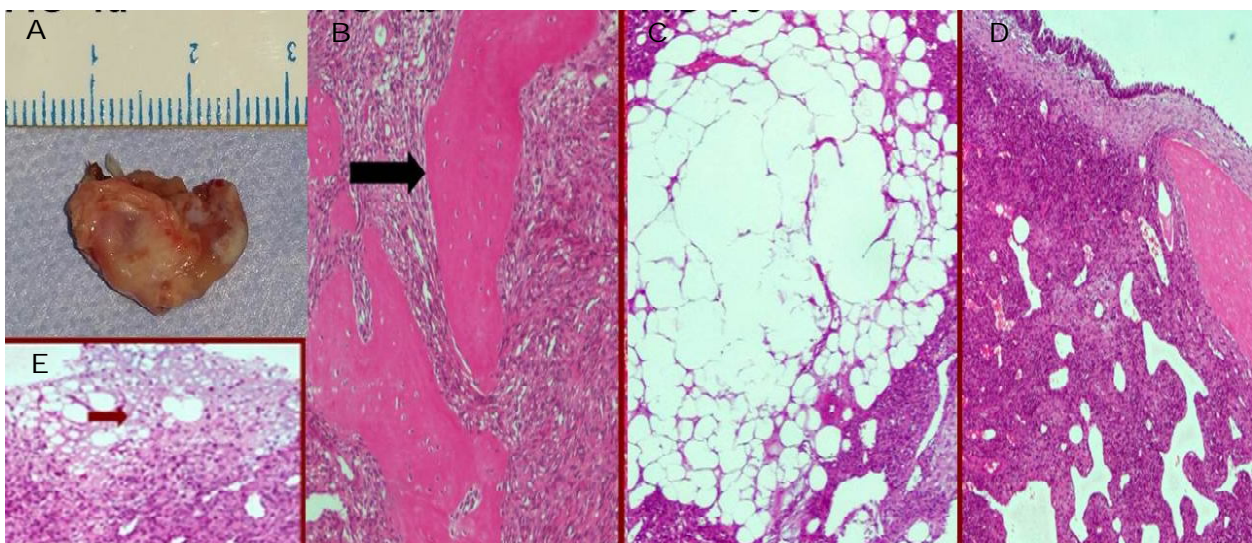
**Figure 1:** Contrast-enhanced computed tomography of paranasal sinuses showing contrast-enhanced lesion in left posterior ethmoid sinus, with inspissated secretions in sphenoid sinus

nucleoli. Tumour showed prominent intrinsic microvasculature of varying calibre of blood vessels including a few with staghorn configuration. Focal cluster of adipose tissue was seen along with presence of myxochondroid matrix and lamellar bone formation. No osteoclastic giant cell or aneurysmal bone cyst like areas were seen. Mitosis was 0-1/10 high power fields (HPF). No necrosis was seen. On immunohistochemistry occasional tumour cell showed positivity for CD34 with Ki-67 labelling index of approximately 6%-8%. Hence a final histopathological diagnosis of phosphaturic mesenchymal tumour (PMT), mixed connective tissue variant was confirmed.

Serial follow up of the biochemical parameters showed recovery as depicted by normalization of serum phosphorous levels and reduction of FGF-23 levels at the end of six months (Table 1). Symptomatically the proximal muscle weakness improved, serum phosphorous normalized and patient was able to walk without support.

### DISCUSSION

PMT is a tumour that produces FGF-23 which leads to phosphate wasting by the kidney and weakening of bones.<sup>1</sup> These tumours are rare and are commonly seen in the soft tissue and bones of the lower limbs. They are extremely rare in head and neck region. The presenting



**Figure 2:** Phosphaturic mesenchymal tumour. Macroscopic appearance of tumour (A); Photomicrograph showing lamellar bone formation (arrow) with spindle cell stromal component (B); focal presence of adipose tissue (C); overlying respiratory epithelium and stromal component with prominent vascularity (stag horn pattern) (D); and focal presence of chondromyxoid component (arrow) (E)

symptoms are fatigue, bone pains and musculoskeletal weakness. The diagnosis is elusive and medical management with vitamin D supplementation is usually ineffective which leads to delay in surgical treatment, which is the treatment of choice.<sup>1</sup>

PMT usually affect middle aged individuals with a slight female preponderance. They present with nasal obstruction or epistaxis. There is pain if there is local infiltration. Vision impairment, headache and local swelling are rare. On otorhinolaryngological examination they are frequently mistaken for inflammatory polyps.<sup>2</sup> Present patient presented with proximal muscle weakness, which is a common presenting manifestation due to phosphate loss in the urine. We had presented similar patient with proximal muscle weakness and fractures due to haemangiopericytoma of the sphenoidal bone.<sup>3</sup> The common feature in both the patients is their clinical presentation with proximal muscle weakness, fractures, hypophosphatemia, hyperphosphaturia and elevated FGF-23 levels on biochemical evaluation. Hypophosphatemia, proximal muscle weakness and elevated phosphate excretion index (PEI) should make the treating physician consider the diagnosis of PMT. The diagnosis should be confirmed by FGF-23 levels and localized by imaging modalities.

FGF-23-producing mesenchymal tumours are often benign and small size lesions. Their localization and diagnosis can be challenging.<sup>4</sup> In an effort to localize these tumors, various imaging modalities have been employed including bone scanning, MRI, CT, Indium-111 pentetreotide or octreotide scintigraphy, and PET.<sup>4</sup> Conventional CT or MRI should precede functional localization of these tumours by PET because of their varied locations.<sup>1</sup> These mesenchymal tumours express high levels of SSR. <sup>68</sup>Ga DOTANOC PET-CT is useful in documenting SSR expression. Hence, this is the imaging modality of choice to localize such

tumours.<sup>7,8</sup> PET/CT with <sup>68</sup>Ga DOTANOC PET-CT is highly sensitive (90%) and specific (82%) for the detection of neuroendocrine tumours.<sup>7,8</sup> Imaging is successful in 80% of TIO cases.<sup>5,6</sup>

Surgical resection of the tumour provides complete relief. The proximal muscle weakness disappears with rise in serum phosphate levels. Because of the hypophosphatemia and osteomalacia, these patients are to be treated with calcium and vitamin D to mineralize their bones. Computer-aided surgery (CAS) was opted as a procedure of choice. CAS technology permits a direct comparison of the intraoperative anatomy with preoperative imaging information. The use of CAS systems allows more precise dissections and fewer complications. Post-operative recovery is faster with very minimal morbidity as compared to open procedures and the patient can be discharged the very next day with normal oral intake of food, breathing through the nose and no facial sutures or deformities. Tumour resection *via* endonasal approach is the treatment of choice. Rarely they require preoperative embolization if they are vascular. Our patient did not require preoperative embolization. This is in contrast to our previous report of sphenoidal haemangiopericytoma which required preoperative embolization because of high vascularity.<sup>3</sup> Endoscopic approach offers many advantages compared to external approach – a better view of margins and surrounding tissues and accurate assessment of tumour resection, with reduced morbidity, better function and rapid recovery.

The differential diagnoses on histopathologic examination include haemangiopericytoma, aneurysmal bone cyst, meningioma, ossifying fibroma, and schwannoma. There are four distinct morphologic types of (PMTs): (i) primitive appearing mixed connective tissue tumours (PMTMCTs); (ii) osteoblastoma-like tumours; (iii) non ossifying fibroma-like

tumours; and (iv) ossifying fibroma-like tumours.<sup>7,8</sup> PMTMCTs typically show haemangiopericytoma-like and aneurysmal bone cyst-like areas. PMTMCTs are a major recognized category of TIO, characterized by a distinctive admixture of spindle cells, microcysts, osteoclast-like giant cells, cartilage-like matrix, prominent blood vessels, and metaplastic bone.<sup>9,10</sup> In this patient surgical resection led to complete relief with normalization of serum phosphorus, improvement in proximal muscle weakness, and normalization of FGF-23 levels.

PMTs result in paraneoplastic syndrome leading to unregulated FGF-23 over-secretion and an important cause of adult onset hypophosphatemia. Localization of the tumour involves functional and anatomic imaging. Endoscopically controlled endo nasal resection of sinonasal haemangiopericytomas is the modern method of therapy and cures this debilitating disease

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