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# A Case of Tumour Induced *Osteomalacia* Linked to a *Hemangiopericytoma* of the Palatine Fossa

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#### Introduction

Tumor-induced osteomalacia (TIO) - also known as oncogenic osteomalacia - is a rare paraneoplastic syndrome characterized by phosphaturic osteomalacia linked to a phosphaturic mesenchyma tumour (PMT) which may induce renal phosphate wasting by excreting phosphatonin-like factors that will inhibit phosphate renal reuptake [1]. Most frequent clinical symptoms are muscular cramping, generalized weakness, chronic fatigue, bone pain, severe bone demineralization with increased risk of fractures. The concept of mesenchymal tumors associated with TIO was first considered as a possible single distinct entity was suggested in the early 1970's by Evans, Azzopardi and Olefsky [2, 3].

This clinicopathologic entity was further codified in 1987 by Weidner and Cruz as "Phosphaturic mesenchymal tumor, mixed connective tissue variant" (PMTMCT) who described 17 TIO-associated mesenchymal tumors, all showing similar histological features [4]. More recently, Folpe and colleagues established in 2004 that most of these tumours are in fact PMTMCTs [5]. Hemangiopericytomas are subtypes of PMTMCTs and the commonest TIO-associated tumors; they are usually benign slow-growing tumours; however, less frequently, malignant osteosarcoma and fibrosarcoma have been also reported [6].

### **Case Report**

A 38 years old female patient started four years earlier to complain from persistent back pain, cramping, diffuse myalgia with progressive generalized weakness. A previous bone biopsy, showed an advanced stage of demineralization of nonspecific nature that was reported to be linked to advanced stage of osteoporosis and though, she was treated with biphosphonate derivative (alendronate), calcium oral intake and cholecalciferol (Vit D3). She denied any familial history or personal comorbidities. She was referred to our neurological department on April 2011 for chronic fatigue, progressive lower limbs motor deficit with walking impairment, swallowing difficulty and diffuses myalgia. She also complained from chronic fatigue and weight loss. Incidentally, she reported the presence of a silent slow growing mass at the upper left palatine fosse, noticed five years earlier. On physical examination she was dysphonic with nasal voice tone and hypotonic soft palate, muscle tone was reduced, tendon reflexes were absent or reduced in the four limbs, muscle strength was scored 3 out of 5 in her lower limbs bilaterally with marked walking impairment as she could walk for limited distance with assistance. There was a well-defined ovoid reddish-violate solid, renitent mass, located on the left hard palatine extended from the first premolar tooth to the second molar and 4 to 5 cm in its largest diameter (Figure 1). Laboratory findings revealed severe hypophosphatemia (0.8 mg/dL) despite high dose oral phosphorus intake (1 g/day), low serum calcium level (0.78 mg/dL), normal serum levels for alcaline phosphatase (ALP: 126 IU/L) and parathyroid hormone (PTHi 65 pg/ml); phosphaturia was abnomally high (1200 mg / 24 h) with normal calcium 94.5 mg/ 24 h, potassium (39 mMol/ 24 h), sodium 39 mMol / 24 h) levels in the urine; routine immuno-inflammatory tests were negative (ESR: 11 mm 1st hour, negative antinuclear antibodies (ANA) with normal profile screening tests, negative Anti-Neutrophil Cytoplasmic Antibody (ANCA), normal serum proteins electrophoresis with unremarkable immunoelectrophoresis profile; renal function was normal (serum creatinine 0.44 mg/dL, creatinine clearance 150 ml/min, microalbuminuria 44 mg/L). Nerve conduction study was within normal results except for overactive muscle fibres activity at rest, normal muscle fibre unit morphology ruling out any underneath myopathy. Biphosphonate was stopped; substitutive IV perfusion phosphorus therapy (0.08-0.16 mmol/kg) over 2-6

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hrs for three consecutive days) increased the phosphorus serum level to 1.2 mg/dL, followed by high dose phosphorus and calcium oral intake and calcitriol (the active form 1,25 dihydroxyvitamin D-3); myalgia was significantly reduced, however, weakness and fatigue persisted unchanged. On CT scan there was a large mass arising from the left half hard palate showing thick bony trabeculae pointing from the bone into the lesion in a sunburst pattern, whereas several foci of bony thickening and bone erosion were seen. On the MRI performed in the transversal T2, T2 TSE sagittal, coronal STIR and after gadolinium injection in the sagittal and coronal T1 SE, the lesion was 2.7  $\times$  2.2  $\times$  1.4 cm (AP  $\times$  Transverse  $\times$  cc diameter), predominantly hyperintense on T2 and STIR, extending from the left hard palate midline to the alveolar ridge, whereas the overlying mucosal lining was displaced but preserved intact borders (Figure 2). The Echo-Doppler duplex scan, confirmed the marked tumoral hypervascularity. Considering the high risk of bleeding during surgery, a superselective catheterisation of the greater palatine artery was performed showing on arteriography a tumoral blush; selective embolisation procedure was performed on the tumor using small gelfoam particles achieving successfully the complete occlusion of the tumour and arterial blood supply (Figures 3a and 3b). On the next day, a total tumour resection with hemimaxilectomy was successfully performed. The diagnosis of Hemangiopericytoma was confirmed by histopathology and immunofixation techniques (Figures 4a-4d). A dramatic improvement was observed few days after surgery as the patient recovered rapidly her muscle strength with no report of any pain or myalgia.



**Figure 1:** Solid renitent, ovoid reddish-violate mass located on the left hard palatine extended from the first premolar tooth to the second molar and 4 to 5 cm in its largest diameter.

Concomitantly, phosphatemia and urine phosphate returned to normal levels within 48 hours post-surgery. Two weeks later, she could walk independently with no limitation and without assistance. Follow up was uneventful since then and yearly CT.scan controls were also unchanged.



**Figure 2:** MRI performed in the transversal T2, T2 TSE sagittal, coronal STIR and after gadolinium injection in the sagittal and coronal T1 SE, the lesion was 2.7 × 2.2 × 1.4 cm (AP × Transverse × cc diameter), predominantly hyperintense on T2 and STIR, extending from the left hard palate midline to the alveolar ridge, whereas the overlying mucosal lining was displaced but preserved intact borders (arrow).



**Figure 3a:** Tumoral blush seen on super selective catheterization of the left greater palatine artery.

## Discussion

Symptoms of hypophosphatemia are nonspecific and with variable underlying aetiology, duration, and severity. Mild hypophosphatemia (2-2.5 mg/dL) is generally asymptomatic; symptoms alone rarely alert the physician to the possibility of hypophosphatemia. Weakness, bone pain, rhabdomyolysis, and altered mental status are the most common presenting features in symptomatic hypophosphatemic patients [7]. Severe hypophosphatemia may induce generalized weakness, chronic fatigue, diplopia, dysphagia whereas the full-blown hypophosphatemic syndrome when the plasma phosphate concentration falls to 1.0 mg/dL (0.32 mmol/L) or less, seizures, respiratory depression, confusion, delirium and congestive heart failure may occur [8].

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**Figure 3b:** Complete occlusion of the tumour arterial supply after embolization of the left great palatine artery.



**Figure 4a:** Photomicrograph x 40 showing pericytic cells with atypical mitosis around thin-wall blood vessels (Hematoxylin and eosin stain - SSH12 – 592).



**Figure 4b:** Photomicrograph x 10 showing dense perithelial arrangement of spindle and round cells, intracellular stains reticulin and oval nuclei (Hematoxylin and eosin stain - SSH12-592).



**Figure 4c:** Photomicrograph x 200 showing CD 34++ labels the vascular endothelium.



**Figure 4d:** smooth muscle actin without myofibril positivity in blood vessels wall (SSH12 – 592).

Metabolic-induced osteomalacia is usually diagnosed several years after first clinical symptoms when increased phosphaturia and low serum 1, 25 dihydroxyvitamin D levels are identified; however, in TIO, the diagnosis of phosphaturic mesenchymal tumours is more challenging and critical for the outcome and and chance for recovery. Our patient reported dysphagia as phosphatemia fell as low as 0.8 mg/dl; further delay in initiating surgery could have induced a more severe clinical presentation and a life-threatening situation. Extensive workup was performed excluding any other possible aetiology such as primary hyperparathyroidism, paraproteinemias, type II renal tubular acidosis (Fanconi syndrome) in the absence of renal glycosuria, aminoaciduria, and hypouricemia. X-linked (XLH), and Autosomal Dominant Hypophosphatemic Hypophosphatemic (ADHR) and TIO are group of diseases are which characterized by hypophosphatemia, hyperphosphaturia, without significant changes in serum concentrations of calcium, PTH, and 1,25(OH)2D3 and defective bone mineralization. XHL and ADRH were not considered in our case knowing the patient's age, the late onset of clinical symptoms and the absence of any family history. Different histological types of mesenchymal tumours can be associated with the paraneoplastic TIO; these tumours are usually benign slow-growing vascular tumours; they are associated with a variety of histologic types and are commonly mesenchymal, of both smooth muscle and endothelial cells

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origin. The diagnosis of hemangiopericytoma is made according to distinct histological patterns which have been sub-divided into 4 types: 1) phosphaturic mesenchymal tumour, mixed connective tissue type (PMTMCT); 2) osteoblastoma-like tumours; 3) ossifying fibroma-like tumours; non ossifying fibroma-like tumors and 4) [4-6]. Hemangiopericytoma is the subtype of PMTMCT that comprises approximately 70% to 80% of all tumours associated with TIO and is usually an asymptomatic slow grow, benign tumour, explaining the delay in the diagnosis making; the diagnosis lasts a mean of 4.7 years from the onset of osteomalacia [5, 9] From TIO reported cases in the literature, these tumours develop more frequently in the legs, shoulder, maxillo-facial, palate fossa, mandible, sinuses and nasal areas; rare cases are reported in the brain. Less frequently, malignant osteosarcoma and fibrosarcoma can be observed [10-20]. Phosphatonins are defined as circulating phosphaturic factors, among which the fibroblast growth factor (FGF23) is a bonederived hormone that regulates systemic phosphate homeostasis, vitamin D metabolism and inhibits renal tubular reabsorption of phosphate through mechanisms independent of PTH. Furthermore, FGF 23 interacts with the vascular endothelial growth factor (VEGF) inducing-regardless to its metabolic role - a mesodermic proliferation action by which it may act on the angiogenesis system as seen in hemangiopericytomas [21, 22]. This phosphaturic osteomalacia paraneoplastic syndrome is linked to a PMT which may excrete a phosphatonin-like factor that will inhibit phosphate renal reuptake and may induce renal phosphate wasting. Although FGF23 was not tested in our patient, the rapid normalisation of phosphatemia and phosphaturia combined with the dramatic recovery few days after surgical removal of the hemangiopericytoma highlights the probable implication of FGF23. The histological specific features showed dense perithelial arrangement of spindle and round cells, intracellular stains reticulin and oval nuclei; furthermore, CD34++ labels the vascular endothelium and smooth muscle actin (Figures 4a-4d).

## Conclusion

The association of osteomalacia and symptomatic hypophosphatemia in the absence of renal insufficiency should path the way in identifying tumour induced osteomalacia and its underlying cause. Further research in the pathophysiology of TIO would highlight the relationship with FGF23 among other phosphatonin-like factors, particularly when hemangiopaericytomas are involved.

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