

## **Case study**

### **Oncogenic Osteomalacia Secondary to Hemangiopericytoma - a case report**

#### **Abstract**

One of the rare paraneoplastic syndrome of osteomalacia is oncogenic osteomalacia or tumor induced osteomalacia (TIO) where there is phosphate depletion and abnormal vitamin metabolism caused due to small endocrine tumor that secretes phosphaturic hormone, fibroblast growth factor<sup>[1]</sup>. Phosphaturic mesenchymal tumour is very uncommon and is very difficult to diagnose. Usually it is misdiagnosed as other mesenchymal tumour due to its heterogeneity<sup>[1]</sup>. There is inappropriate FGF-23 secretion which causes low phosphate and 1,25-dihydroxyvitamin D levels<sup>[2,3]</sup>.

We are going to present a case of hypophosphatemic rickets secondary to phosphaturic mesenchymal tumour who came with complaints of proximal muscle weakness which limited his effort tolerance and activities of daily life like standing from squatting position and rib pain. His FGF-23 levels were very high above normal levels and PET CT revealed a well-defined enhancing lesion abutting femoral neurovascular bundle. After consultation with endocrinologist we have done complete excision of the mass. Post surgery all symptoms were relieved, proximal muscle strength improved gradually and serum levels of phosphorus, ALP and FGF-23 came back to normal.

Keywords :- Fibroblast growth factor-23 , Phosphaturic mesenchymal tumour, oncogenic osteomalacia.

#### **Introduction**

Osteomalacia (mollities ossium) is a metabolic bone disease which results from inadequate mineralisation of osteoid in mature bone in adults. Osteomalacia is a rare inborn error of metabolism. Oncogenic osteomalacia (OO) is a rare type of osteomalacia in which there is systemic demineralisation of bone. Common Symptoms of OO are bony pain, muscle wasting and fractures<sup>[3]</sup>. Metabolically there will be renal phosphate wasting, hypophosphatemia, decreased serum-1,25 dihydroxyvitamin levels and resistance to vitamin D supplementation.

TIO like syndrome can also be associated with some other diseases like prostate cancer, hematologic malignancies, neurofibromatosis, epidermal nevus syndrome, and polyostotic fibrous dysplasia of bone<sup>[4,5,6]</sup>. This disease was first described by Dr. Rober McCane ,he observed patient presenting with pain, weakness and abnormal gait with low phosphate levels. He tried to treat patient with high dose of vitamin D but did not succeed. The symptoms were cured by resection of tumor.

OO had association with syndromes such as neurofibromatosis and McCune-Albright syndrome and in patient with carcinomas. It has been reported that OO associated with mesenchymal tumour over expresses FGF-23. This protein inhibits renal tubular epithelial phosphate transport and this is thought to be the mechanism for most cases of OO.

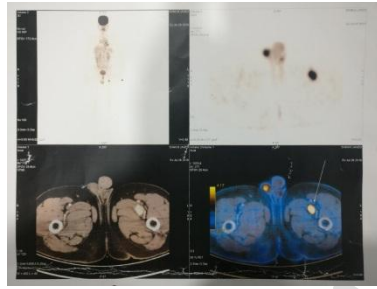
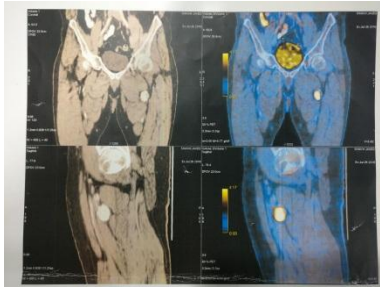
Weidner and Santa Cruz (1987) coined the term "Phosphaturic Mesenchymal Tumour, Mixed Connective Tissue variant" (PMTMCT). Histologically PMTMCT us a mixture of spindle cells, osteoclast like giant cells, prominent blood vessels, cartilage like Matrix and metaplastic bone.

### **Case Report**

A 38 yrs old male presented to neurophysician with complaint of difficulty in walking, weakness in bilateral lower limb left more than right with waddling gait and pain in ribs. All the symptoms were insidious in onset, gradually progressive limiting his daily routine activities. Patient also complained of difficulty in standing from squatting position and breathlessness after waking for 50-100 meters. Nerve conduction study was within normal limits. Laboratory parameters were Sr.Calcium- 9.47mg/dl, Sr.Phosphorus -1.48 IU/L, Alkaline Phosphatase-175.3 IU/L. Patient was treated symptomatically with phosphorus supplements but he was not relived rather his symptoms progressed. Patient was then referred to us. On further evaluation we have noticed Sr.Phosphorus – 1.46 mg % (value) and 1,25-dihydroxyvitamin value- 14.08 ng/ml and was diagnosed to have osteomalacia . X ray femur showed losers zone so patient was primarily diagnosed as hypophosphatemic rickets and started on oral calcium and vit D supplements. Symptoms of patient increased in intensity even after the treatment which pinned towards an endocrine pathology.

Endocrinologist's opinion was taken who suggested to get FGF-23 level checked. FGF-23 levels came out to be very high 1117.6 RU/ml(Normal value:-0-150RU/ml).

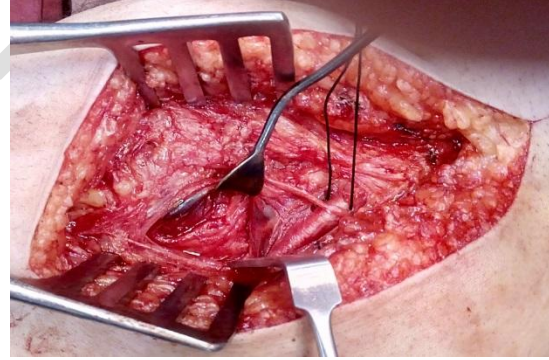
PET scan was done which further revealed well defined enhancing lesion involving medial compartment of left upper thigh abutting femoral vein suggestive of Hemangiopericytoma.



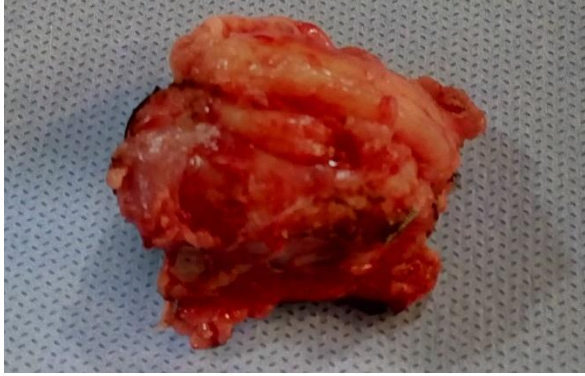
With this PET CT findings we subjected patient for excision of the mass. Intraoperatively it was found that tumour was very vascular and attached to Deep femoral vein which was excised in toto and sample was sent for histopathological examination.



EXPOSURE OF FEMORAL VESSELS VEIN



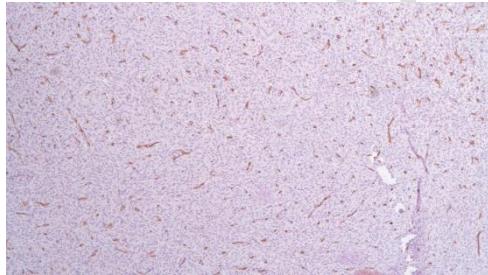
LESION ABUTTING FEMORAL



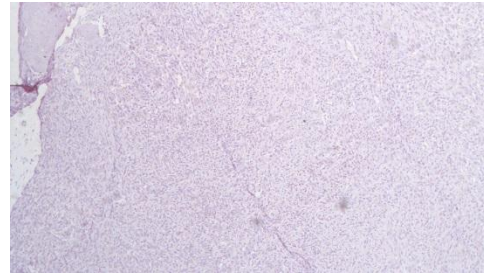
EXCISED LESION

Histologically features suggestive of mesenchymal and vascular Tumor with low grade likely to be associated with hypophosphatemic rickets IHC was also done which was positive for S-100P and KL-67 and diagnosed as benign spindle cells tumor consistent with phosphaturic mesenchymal tumour.

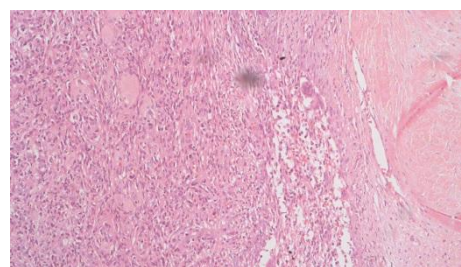
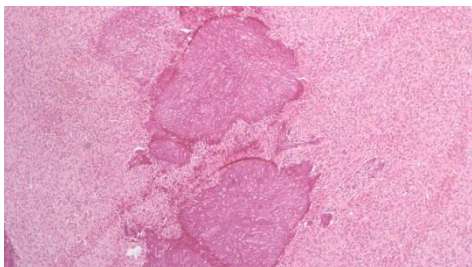
On good successive follow up all lab parameters including FGF-23 levels came within normal limits at the end of 3 weeks and patient was declared free from hypophosphatemic rickets. Patient is now symptom free and resumed his all daily activities. (FGF-23-59.3 RU/L , serum phosphorus-5.60 mg%, alkaline phosphatase -137.2mg%. Patient is not on phosphorus supplements).



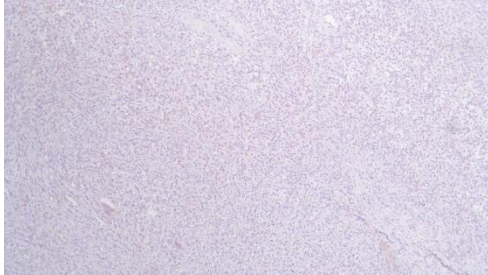
CD 34 NEGATIVE



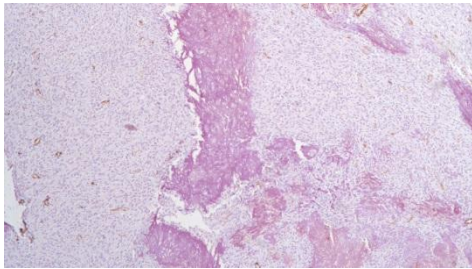
DESMIN NEGATIVE



LOW POWER FIELD - VASCULAR AND  
SHOWING  
MESENCHYMAL ELEMENTS  
PROLIFERATION



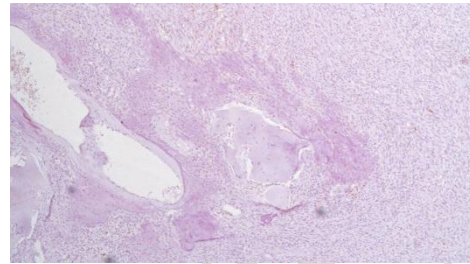
KI - 67 POSITIVE , <01%



SMOOTH MUSCLE ACTIN NEGATIVE

VASCULAR COMPONENTS

ENDOTHELIAL SPINDLE CELL



S-100 P OCCASIONAL CELLS POSITIVE

### **Discussion :-**

Tumour induced osteomalacia is a rare paraneoplastic syndrome with features of hypophosphatemia , myopathy, bone pain and fractures TIO is an acquired form of hypophosphatemia.

Ratio among male and female is 1:1. This disease presents usually at 4th and 5th decade of life. Prevalence of TIO is not known but till now 300 cases have been reported.

Almost all body regions are potentially affected by TIO. TIO presented with features ranging from weakness, difficulty in walking, loss of height, pathologic fractures in femur, vertebra, rounds pseudofractures of pubic rami and pelvic deformity. Suspicion of TIO arises when there is hypophosphatemia with hyperphosphaturia in non azotemic adult in absence of acidosis. Increased level of FGF-23 produced by the tumor, there is inhibition of tubular reabsorption of phosphate which leads to hyperphosphaturia in TIO.

Meyer et al and Nebitt et al demonstrated circulating factor that could be responsible in sets of experiments over time. Miyauchi et al supported this by transplanting human tumor in nude mice which causes hypophosphatemia<sup>[7]</sup>. There is increase in vessel size and vascular pattern which leads to increase in microvasculature in these tumors<sup>[1]</sup>. Differential diagnosis for these tumours are Hemangiopericytoma, hemangioma, sarcoma, ossifying fibroma, granuloma, giant cell tumors and osteoblastoma<sup>[1,2]</sup>. Osteocytes release FGF-23 which is a peptide and it inhibits Na-Pi-11 transporter in intestine and kidneys leading to hypophosphaturia. FGF-23 directly inhibits 1 $\alpha$  hydroxylase expression which in turn inhibits activation of 25 hydroxyvitamin D to 1,25-dihydroxyvitamin D. Decreases level of 1,25-dihydroxyvitamin D leads to decreased intestinal absorption of phosphate. In the above mentioned patient very high level of FGF-23 confirmed TIO and patient very high level of FGF-23 confirmed TIO and PET scan localised the tumor. F-18 Fluorodeoxyglucose positron emission tomography with computed tomography is most sensitive for localising TIO tumors<sup>[8]</sup>.

Mesenchymal tumour producing FGF-23 are generally benign and very small and difficult to identify. Various imaging modalities have been enjoyed to localise FGF-23 producing tumors including bone scanning, CT, MRI Indium-111 pentreotide or octreotide scintigraphy and PET. Origin of these tumor is either from bone or soft tissue where around 40% arise from bone and 55% arise from soft tissue. 31% of these tumor are found in head and 56% are found in lower extremities. Since these tumors are found in varied locations so for localisation PET scan should be done first followed by conventional CT or MRI. TIO tumors are generally small and often present within bone and are difficult to locate PET/CT with Ga 68-DOTANOC is used for detection of NET (neuroendocrine tumours) is highly sensitive(90%) and specific(82%)<sup>[9]</sup>.

Only solution of TIO to control phosphate wasting and symptoms is to resect the tumor<sup>[10]</sup>. This tumor recurs locally and can metastasize.

Phosphaturic mesenchymal tumour(PMTs) are classified into four types according to morphology 1) primitive aspirations mixed connective tissue tumor(PMTMCT) 2) osteoblastoma like tumors 3) non ossifying findings like tumors and 4) ossifying fibroma like tumors. PMTMCTs typically show Hemangiopericytoma like and aneuysmal come cyst like area.

**Conclusion** :-

TIO is a rare paraneoplastic tumor and causes hypophosphatemic osteomalacia due to over secretion of FGF-23. High index of suspicion in non responsive patients with stepwise approach involving various imaging techniques will help in successful diagnosis in 90% cases. Excision of tumor with wide margin is the treatment of choice.

### **References :-**

1 Folpe AL, Fanburg-Smith JC, Billings SD, Bisceglia M, Bertoni F, Cho JY, Econs MJ, Inwards CY, Jan de Beur SM, Mentzel T, et al. Most osteomalacia-associated mesenchymal tumors are a single histopathologic entity: an analysis of 32 cases and a comprehensive review of the literature. *American Journal of Surgical Pathology*. 2004; 28:1–30.10.1097/0000478-200401000-00001[PubMed: 14707860]

2 Drezner MK. Tumor-induced osteomalacia. *Reviews in Endocrine & Metabolic Disorders*. 2001;2:175–186.10.1023/A:1010006811394 [PubMed: 11705323]

3 Jan de Beur SM. Tumor-induced osteomalacia. *Journal of the American Medical Association*.2005;294:1260–1267.10.1001/jama.294.10.1260[PubMed: 16160135]

4 Saville PD, Nassim JR, Stevenson FH, Mulligan L, Carey M. Osteomalacia in Von Recklinghausen's neurofibromatosis; metabolic study of a case. *BMJ*. 1955; 1:1311–1313.10.1136/bmj.1.4925.1311 [PubMed: 14363873]

5 Dent CE, Gertner JM. Hypophosphataemic osteomalacia in fibrous dysplasia. *Quarterly Journal of Medicine*. 1976; 45:411–420. [PubMed: 948543]

6 Collins MT, Chebli C, Jones J, Kushner H, Consugar M, Rinaldo P, Wientroub S, Bianco P, Robey PG. Renal phosphate wasting in fibrous dysplasia of bone is part of a generalized renal tubular dysfunction similar to that seen in tumor-induced osteomalacia. *Journal of Bone and Mineral Research*. 2001; 16:806–813.10.1359/jbmr.2001.16.5.806 [PubMed: 11341325]

7 Cai Q, Hodgson SF, Kao PC, Lennon VA, Klee GG, Zinsmeister AR, Kumar R. Brief report:inhibition of renal phosphate transport by a tumor product in a patient with oncogenic osteomalacia. *New England Journal of Medicine*. 1994; 330:1645–1649.10.1056/NEJM199406093302304 [PubMed: 8177270]

8 Dupond JL, Mahammedi H, Prie D, Collin F, Gil H, Blagosklonov O, Ricbourg B, Meaux-Ruault N, Kantelip B. Oncogenic osteomalacia: diagnostic importance of fibroblast growth factor 23 and F-18 fluorodeoxyglucose PET/CT scan for the diagnosis and follow-up in one case. *Bone*. 2005b; 36:375–378.10.1016/j.bone.2005.01.001 [PubMed: 15777669]

9 Von Falck C, Rodt T, Rosenthal H, Langer F, Goesling T, Knapp WH, Galanski M. (68)Ga-DOTANOC PET/CT for the detection of a mesenchymal tumor causing oncogenic osteomalacia. *European Journal of Nuclear Medicine and Molecular Imaging*. 2008; 35:1034.10.1007/s00259-008-0755-8 [PubMed: 18369618]

10 Clunie GP, Fox PE, Stamp TC. Four cases of acquired hypophosphataemic ('oncogenic')osteomalacia. Problems of diagnosis, treatment and long-term management. *Rheumatology*. 2000;39:1415–1421.10.1093/rheumatology/39.12.1415 [PubMed: 11136887]