# “Exploring the Depths:Unraveling FGF-23 Driven- Hypophosphatemia in Shadows of Phosphaturic Tumours”


## ABSTRACT

This paper delves into the intricate realm of FGF23-induced hypophosphatemia secondary to a concealed phosphaturic tumor, shedding light on a rare yet clinically significant phenomenon. With only a limited number of reported cases worldwide, this study navigates the diagnostic challenges posed by the elusive nature of these tumors, emphasizing the importance of considering genetic etiologies.The research elucidates the pivotal role of FGF23, identified as the primary causative hormone, in orchestrating hypophosphatemia through phosphaturia. Diagnostic hurdles arising from the tumors' small size and concealed locations are addressed, with a spotlight on advanced imaging modalities such as MRI, FDG-PET scan, and 68 Ga-DOTA-TOC-PET CT scan. Recent insights into the direct impact of elevated FGF23 levels on bone health are explored, unraveling the complex interplay between FGF23, soluble Klotho, and the bone mineralization process. The study probes the ambiguity surrounding whether hypophosphatemia alone is accountable for the observed osteomalacia.This comprehensive analysis not only deepens our understanding of FGF23-induced hypophosphatemia but also underscores the necessity for heightened clinical awareness, advanced diagnostic techniques, and a multidisciplinary approach in managing patients presenting with these challenging conditions.

**Key words :** FGF23,hypophosphetemia, phosphoturic tumors, osteomalacia

## Introduction :

Hypophosphatemia is a relatively common laboratory abnormality and is often an incidental finding. The history of presenting illness will rarely indicate possible hypophosphatemia. For this reason, a clinician should have suspicion for phosphate abnormalities whenever an etiology is present that is associated with hypophosphatemia.

However, severe hypophosphatemia may have the clinical presence of altered mental status, neurological instability including seizures, and focal neurologic findings such as numbness or reflexive weakness, a cardiac manifestation of possible heart failure, muscle and bony pain, and muscular weakness and pathological fracture.

## Fibroblast growth factor and hypophsphatemia :-

We are presenting a case report of Fibroblast growth factor -23 (FGF-23) Phosphaturic mesenchymal tumor induced osteomalacia and hypophosphatemia presenting as a pathological fracture and multiple bony pain in young male. only 500 cases of FGF-23 –tumor induced osteomalacia and hypophosphatemia has been reported worldwide.(1-3) Phosphorus contributes about 1 % of total body weight. out of that , 1% in serum , 14% in cells and 85% resides in bone.

Circulating factor that could cause hypophosphatemia such idea firstly proposed by Prader (4) and was demonstrated by Meyer et al and Nesbitt et al. (5,6) Phosphaturic substance termed as 'Phosphatonin' by econs and Drezner (7). because it lowers serum phosphorus levels.Mesenchymal tumors have phosphaturic action by producing phosphatonin which leads to hypophosphatemia via decreasing renal reabsorption of phosphate. such causative hormone termed as FGF 23 which lead to Phosphaturia.(8)

The main cause of Tumor induced Hypophosphataremia (TIO) is FGF 23. (9,10). To diagnose these kinds of ( TIO ) cases always remains a challenge because of their small size and location (11), Non availability of Imaging modality for detection and confirmation of tumor. like MRI , FDG-PET scan ,68 Ga-DOTA-TOC-PET CT scan. Genetic Etiology must have to be taken under consideration because many diseases like X- linked hypophosphatemia , autosomal dominant hypophosphatemic rickets , autosomal Recessive hypophosphatemic rickets mimics like tumor induced hypophosphatemia. (12-15) Recent studies have found that FGF23 (and soluble Klotho) may directly impact bone in diseases with elevated FGF23 levels.[17-18 ]

The main function of FGF23 is to lower serum phosphate levels. which act by two ways: direct and indirect. In direct , Inhibition of phosphate reabsorption at the level of the proximal tubular cells of kidneys , and in indirect by suppression of necessary enzymes (1-α-hydroxylase) which activate vitamin D. Direct actions involve the binding of circulating FGF23 to FGF receptors (FGFRs) and coreceptor klotho on the

basolateral surface of the proximal tubular cells which supresses two sodium-phosphate co-transporters called NaPi-2a and NaPi-2c. These transporters, located on the apical surface of the proximal tubular cell, are useful for renal phosphate reabsorption. Decreased expression of NaPi-2a and NaPi-2c is therefore a direct cause of phosphaturia. (16)

Raised levels of FGF23 are responsible for impairment of bone mineralization, since serum phosphorus concentration plays an important role in the process of growth plate mineralization. What is less clear is whether or not hypophosphatemia is solely responsible for the osteomalacia.

## Case Report :-

26 years old male presented at the age of 21 years with the history of Acute progressive right hip pain and fracture of right femur neck due to minor trauma. Patient investigated for the same , (25OH) vitamin D = 19.2 ng/ml (N* - >30 ng/ml) , Serum Calcium = 8.82 mg/dl (9-11mg/dl), Serum intact PTH = 97.5 pg/ml (0-72 pg/ml), Serum phosphorus =1.6 mg/dl(3-5 mg/dl), Serum Alkaline phoshatase102.1Iu/L. [fully Automatic chemistry analyser cobas c 111]For this, patient got operated with closed reduction and internal fixation (IF) with Dynamic hip screw (DHS) and labelled as Pathological stress fracture due to Secondary Hyperparathyroidism. In this case, serum phosphorus level was too low with respect to level of 25-Hydroxy Vitamin D3 , that suggest some other hidden factor was there , which is responsible for very low level of Serum

phosphorus. Patient had advised for further investigations for Hypophosphatemia but he lost the follow up. 2-4 months after surgery and medication , patient started walking and doing daily work but still he had persistent on – off pain , some degree of limping gate , not able to do strenuous work , not able to run. Intermittently he went to local doctors and taken pain killers, but not investigated properly due to economic constraints. This continued for more than 2 yrs. After that symptoms was aggravated and he had been re-investigated , PTH intact 54.80 pg/ml(N-18.5-88pg/ml ), Sr. Creatinine 1.15 mg/dl (N-0.6-1.3mg/dl ), Sr. Phosphorus **1.5 mg/dl (N-2.4- 4.5mg/dl),** Urine creatinine 95 mg/dl( N-20-320 mg/dl ),Urine Phosphorus 38.9 mg/dl (N-70-870 mg/dl), 1-25-Hydroxy Vitamin D3 -106.92nmol/l (N- <50nmol/l).On the basis of above values Tubular reabsorption of phosphate (TRP) was calculated and found to have 69 % which is low ( Normal 95 to 100%).TmP / GFR = 1.03 which was low. On the basis of above results , serum phosphorus level is very low with low urinary reabsorption. Patient was advised further workup but he was not able to do it due to economical constraints and lost follow up again. Meanwhile Dynamic Hip Screw (DHS) was removed from Right femur neck almost after 3 years of surgery. After that patient could not able to walk properly. As screw was removed, probably there was fracture again but patient lost his all post screw removal X-rays. Patient was ambulatory with painful and restricted movements. He took pain killers in consultation with local general practitioners. Due to covid pandemic he had not undergone any investigations. 4th year of Illness , he developed intermittent aches and pains all over body (not

relieved on medication) and generalised weakness. Bony pains increased gradually and become more severe 5 years after initial presentation. Patient presented to us in our tertiary care hospital with severe aches and pains all over body, and was bedridden since 6 months. He was vitally stable. Investigation showed severe hypophosphatemia with normal calcium, vitamin D and serum PTH levels. Serum Phosphorus **1.7mg/dl (N- 2.5-4.5mg/dl)**, Serum Calcium 9.5mg/dl (N-8.4-0.2mg/dl), 1-25 OH Vitamin D3- 35 ng/ml (N-30-100ng/ml ), Serum intact PTH 69.10 pg/ml (N-12-88pg/ml ). CPK total is normal, All routine investigations like CBC, KFT,TFT, LFT except alkaline phosphatase were normal. Urine creatinine 102 mg/dl (N-20- 320mg/dl)TRP = 78% and TmP / GFR=1.32 both are low. Serum FGF23 was done and patient was started on Phosphorus rich diet with phosphate sachet 3.2gm half 6 times a day. Pain reduced within 7-8 days of phosphorus supplementation. FGF 23 level found to be high i.e 772 Ru/ml ( N= 0.00 – 300 ), which suggest us tumour induced hypophosphatemia. For localization of tumour Gadolinium 68 DOTA-TOC PET-CT SCAN done. Scan showed increased somatostatin receptor expressions noted in 13x10x16 mm sized subcutaneous soft tissue density nodule on right lower leg, seen anterior to distal end of shaft of right tibia [Image no. 1]. Contrast Enhance Magnetic Resonance Imaging (CEMRI) of Right leg was performed to localize the tumour boundaries before resection. CEMRI showed, Small relatively well defined altered signal intensity lesion measuring approximately 9x12 mm in subcutaneous plain of anterior aspect of distal 1/3rd of right leg [Image no.2] Tumour removed surgically and sent for

Histopathology. histopathological report revealed on gross examination, Unoriented, firm, brownish ,fibrous tissue piece measuring 2.3 x 1.5 x 1.3 cm, with fragile tumour measuring 1.6 x 1.5 x1 cm noted.[Image no.3] Microscopy suggestive of benign neoplasm composed of spindle cells and osteoclast type giant cells. Spindle cells are bland and arranged in sheets and fascicles with highly vascular stroma. Mitosis and necrosis was not seen with no evidence of malignancy. Which has been labelled as **Phosphaturic mesenchymal tumour**.[ Image no.4] (Bland spindles to oval neoplastic cells with intermingled osteoclasts like giant cells located by white arrow )

Patients pain reduced to 50% after 7 days of resection of tumour. His serum phosphorus level at discharge was- 2.3 mg/dl. Patient could stand with support at the time of discharge. Follow up at 3 months patient could walk with support and can do all his routine activities independently. Follow up at one year patient could walk without support. His serum phosphorus level- 3.1mg/dl. ( * : N – Normal value )

**Image 1**

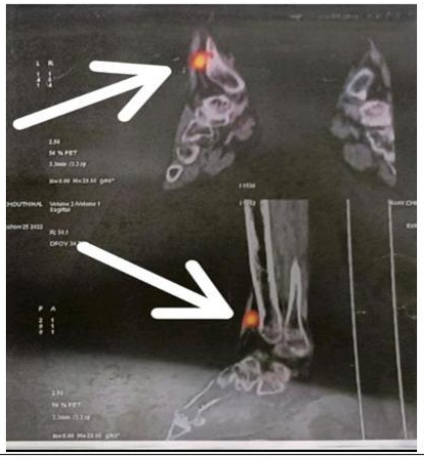


**Image 3**

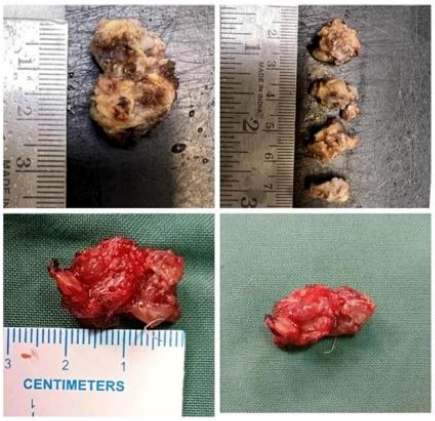



**Image 2**

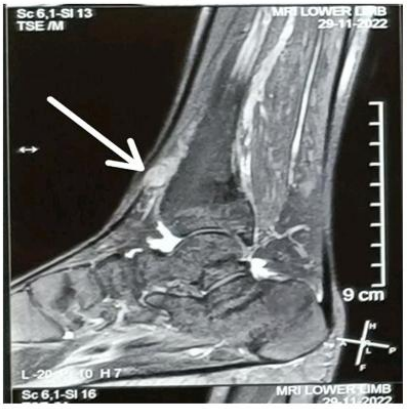
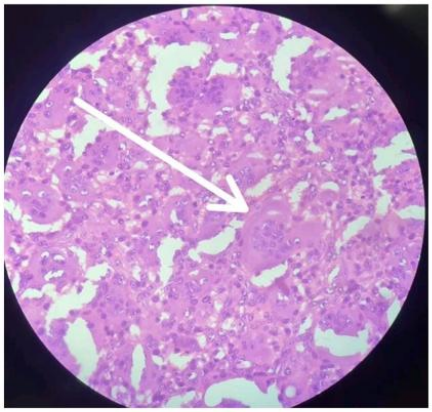



**Image 4**



## DISCUSSION :

Tumour-induced osteomalacia (TIO), also known as oncogenic osteomalacia, is a rare paraneoplastic syndrome characterized by abnormal phosphate and vitamin D metabolism, often attributed to small endocrine tumours. Diagnosis is frequently delayed for

several years due to underrecognition of condition. Patients commonly present with multiple fractures, height loss, and a generalized debilitated state, with chronic bone pain being the typical initial symptom. Confirmation of the diagnosis involves a notable improvement in symptoms and metabolic abnormalities post-complete excision of the responsible tumour.

These tumours are generally small, with elusive locations in bone or soft tissue throughout the body, exhibiting slow growth. Histologically, many are classified as phosphaturic mesenchymal tumors (PMT), characterized by spindle cells with low mitotic activity, prominent vascularity, osteoclast-like giant cells, or the presence of bony tissue. While most tumours appear benign, rare instances of malignant presentation and metastases have been reported (19–23). Infrequent metastases emphasize the importance of wide surgical margins to prevent persistence or recurrence, given the infiltration of surrounding connective tissue."

Numerous reports indicate an elevation of FGF23 in some patients with TIO, but not consistently across all cases (24-25). Tumour removal is associated with a reduction in serum FGF23 concentrations, and a temporal correlation exists between the decrease in FGF23, elevated serum phosphate, decreased renal phosphate wasting, and increased 1,25(OH)2D3 concentrations (26-27). Diagnosing TIO poses challenges due to small and elusive tumours. Various imaging techniques including bone scanning, CT (28), MRI, Indium-111 pentetreotide or octreotide scintigraphy, and PET, are employed for tumour localization (29). Advocating a stepwise approach, 99Tcm-OCT scintigraphy as the primary method to locate tumour. In

octreotide-negative cases with a strong suspicion of a tumor, FDG-PET/CT is employed, and recently, 68Ga-DOTANOC PET/CT has been explored (30). Once suspicious lesions are identified through functional imaging, confirmation through anatomical imaging (X-rays, CT, and/or MRI scans) is recommended. In our patient Ga 68 DOTA-TOC PET-CT SCAN done followed by CEMRI was done.

The treatment of choice for TIO is tumour resection with a wide margin to ensure complete removal as recurrences of tumour has been reported. (22,23,31). Postoperative intermittent monitoring is crucial. Tumour resection is almost always curative, resulting in a rapid disappearance of FGF23 from circulation and a return to normal serum phosphate levels within five days post-operation (27).

Most patients experience improvement within days to weeks after tumour removal. Bone healing begins immediately, but significant clinical improvement may take a year or more, depending on the severity of the disease. When the tumour cannot be localized nor surgically resectable, medical intervention includes phosphate supplementation and the administration of calcitriol or alfacalcidiol.

The ensuing treatment plan closely aligns with that employed for non-TIO hypophosphatemia. During the initiation of treatment, it is prudent to consistently monitor weekly laboratory results to guide the gradual adjustment of medications until treatment goals are met. Future therapeutic approaches are anticipated to benefit from an enhanced comprehension of FGF23 biology and a deeper understanding of the characteristics associated with these tumors.

This case highlights the challenges of diagnosis and management in resource-constrained settings, emphasizing the importance of timely intervention for improved outcomes.

## Conclusion :

Nonspecific symptoms like Chronic aches and pains may be presenting complaint of hypophosphatemia. Most of the time hypophosphatemia is common and incidental lab finding. Systematic approach to hypophosphatemia is needed to reach to the conclusion. Patient with multiple and recurrent fractures with unknown cause of osteomalacia needs evaluation of TIO

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