Tumor Induced Osteomalacia– Lessons Learned

Vijay P G[1], Manuel V Joseph[1], Anish Ahamed[2]

Abstract

Introduction: Tumor-induced osteomalacia(TIO) typically presents with muscle weakness, bone pain and recurrent fractures, resulting from a humoral disturbance of phosphate and vitamin D metabolism. Tumors associated with this syndrome are typically mesenchymal, and the majority constitutes a unique clinicopathological entity now known as phosphaturicmesenchymal tumors.The major humoral factor responsible is fibroblast growth factor 23 (FGF23), and measurement of this hormone has improved the clinical diagnosis of TIO. Nevertheless, even after establishing the diagnosis of TIO, localization of the causative tumor can prove difficult, expensive, and time-consuming, resulting in delayed diagnosis.Tumors secreting fibroblast growth factor 23 are often small and difficult to find with conventional imaging. Successful removal of the tumor by surgery or radiofrequency ablation leads torapid resolution of symptoms and biochemical abnormalities.

Case Report: A 32-year-old women presented to us with features of osteomalcia (5yrs duration) and subsequently with fracture shaft of femur(Rt).Another 32-year-old man presented with 11 years history of lowback ache initially,later with features of osteomalacia like subtrochanteric fractures,pelvis insufficiency fractures,multiple vertebral fracures and finally bedridden. On evaluation,both of them showed features of adult onset hypophosphatemic rickets which is most likely TIO.Serum FGF-23 level is raised in both. Conventional bone scan was negative,so we have used the utility of 68Ga-DOTA-octreotate(DOTATATE) somatostatin receptor positron emission tomography(PET)/computed tomography (CT) imaging for the anatomical localisation.Final precise localisation was done with the help of 1.5 tessla,18 channel MRI.Wide surgical excision was done. Clinically,radiologically and biochemical parameters of patients improved.Male patient developed spinal deformities and reduction in height due to malunited vertebral and subtrochanteric fractures.There is no recurrence for the last 3.5 yrs.

Conclusion: TIO should be suspected in any patient with adult onset hypophosphatemic rickets.Serum FGF 23 level helps in the diagnosis. A 68Ga-DOTA-octreotate(DOTATATE) somatostatin receptor positron emission tomography(PET)/computed tomography (CT) imagingis helpful for the anatomical localisation and 1.5 tessla MRI helps in precise localisation which is essential in surgical plannning.A wide excision if possible will cure the problem.Lack of awareness of this entity,its presentation,diagnostic modalities will cause adelay in diagnosis and hence morbidity.

Keywords: Tumor-induced osteomalacia(TIO), Fibroblast growth factor 23 (FGF23), 68Ga DOTA octreotate(DOTATATE) somatostatin receptor positron emission tomography(PET), Phosphaturicmesenchymal tumors.

Introduction

Tumor-induced osteomalacia(TIO), also known as oncogenicosteomalacia, is an acquired form of hypophosphatemiacommonly associated with benign mesenchymal tumors [1].

Tumor induced osteomalacia(TIO) typically presents with muscle weakness, bone pain and recurrent fractures, resulting

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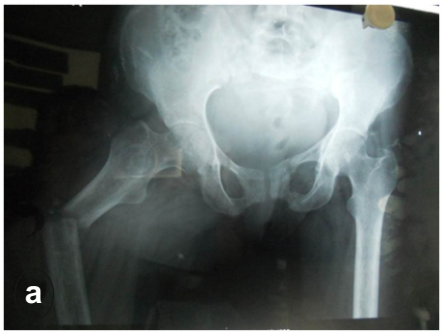

Figure 1a. Fracture shaft of femur

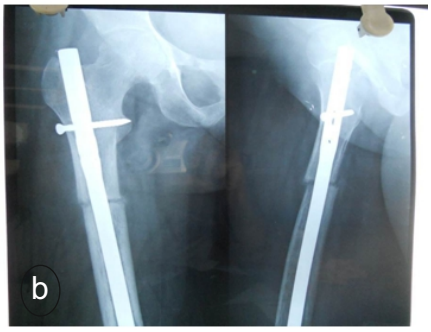

Figure 1b. ILN for fracture shaft of femur with poor healing response

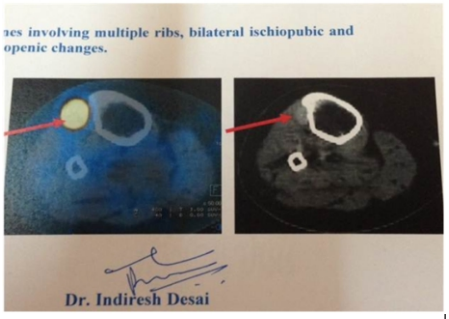

Figure 2. Ga 68 Dotanoc whole body Pet CT scan showing tumor anterolateral aspect proximal

from a humoral disturbance of phosphate and vitamin D metabolism.Successful removal of thetumor by surgery or radiofrequency ablation leads torapid resolution of symptoms and biochemical abnormalities.Tumors associated with this syndrome are typically mesenchymal, and the majority constitutes a unique clinicopathological entity now known as phosphaturicmesenchymaltumors. Most tumors which cause TIO overexpress the protein fibroblast growth factor-23 (FGF-23).This inhibits renal phosphate reabsorption in the proximal tubules acting as a phosphaturic factor[2].Measurement of FGF-23has improved the clinical diagnosis of TIO. Nevertheless, even with recognitionof TIO, localization of the causative tumor can prove difficult, expensive, and time-consuming, resulting in delayed diagnosis.Besides, tumors secreting FGF-23 are often small and difficult to find with conventional imaging.68Ga-DOTANOC PET/CT combines the specificity of octreotide scanning with the sensitivity of PET/CT.[3]. To our knowledge We describe the first 2 cases from Kerala, India, where we had used the utility of 68Ga-DOTA-octreotate(DOTATATE) somatostatin receptor positron emission tomography(PET)/computed tomography (CT) imaging and serum FGF-23 in the diagnosis of TIO.We describe the first 2 cases from Kerala, India where we combined these 2 modalities to help in the diagnosis of TIO.

Materials and Methods

The described patients havegiven consent for publication of the data and photographs.

Case Report 1

A 32-year-old purdah wearing Muslimwomen presented with difficulty in climbing stairs and getting up from squatting positionof 5 years' duration and inability to walk without support of 3 years' duration. Evaluated at multiple centers–not arrived at a diagnosis, but symptoms progressed. She was wheel chair bound. She sustained a fracture of mid shaft of right femur(Fig. 1A)after trivial fall 1year back which was surgically fixed(interlocking nail)- (Fig. 1B) She is married with 2 children. No H/O malabsorption/abdominal pain, poor sunlight exposure, consumes mixed diet, adequate calcium intake. There is proximal myopathy in lower limbs.

	Pre op	Post op
Calcium mg/dl	9.0 mg/dl	9
Phosphorous mg/dl	1.4 mg/dl	3
Albumin g/dl	4	4
Alkaline phosphatase IU/ml	370	298
Serum creatinine mg/dl	1	1
Urine calcium mg/day	171	125
Urine phosphorous mg/day	434	320
Urine creatinine mg/day	972	650
TMP GFR	2	
PTH ng/ml	35	

Investigations

25 OH vitamin D –32 ng/ml. 1,25 OH vitamin D – 16 pg/ml (normal 18-72pg/ml). THE TMP/GFR was done to acess the phospahturia using normogram[4]. In view of the low phosphorous, low TMP/ GFR, normal calcium, normal PTH a provisional diagnosis of hypophosphatemicrickets was made etiology being oncogenic osteomalacia was made. She was treated with neutral phosphorus solution 500 mg 6 hourlyand calcitriol 0.5 mcg twice daily. As her response was poor, further tests were carried out.Her FGF-23 was 396.6RU/ml (normal 0-150). Whole body Tc-99m sestamibiscan wasnormal. Ga 68 Dotanoc whole body PET CT scan showed a

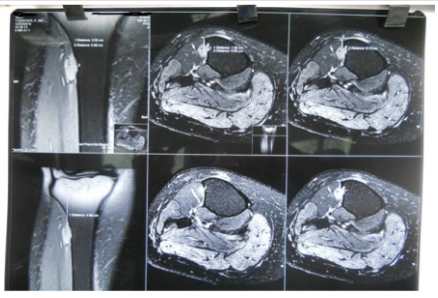

Figure 3. MRI for pinpoint localisation

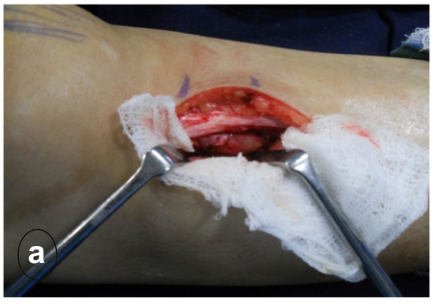

Figure 4a. Exposure of Tumor

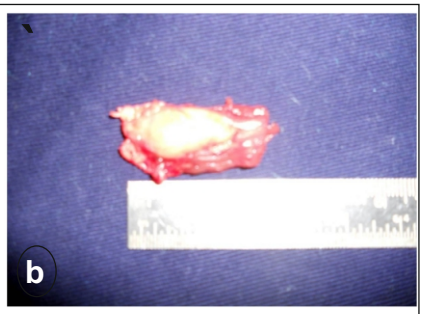

Figure 4b. Excised specimen,

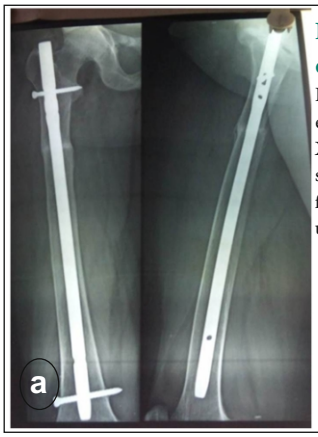

Figure 5a. Post excision X-ray showed fracture union

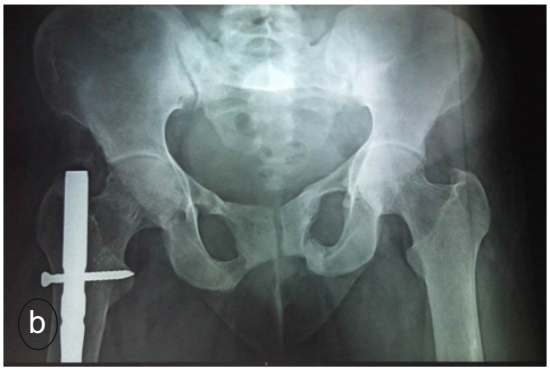

Figure 5b. Healing of loosers zone

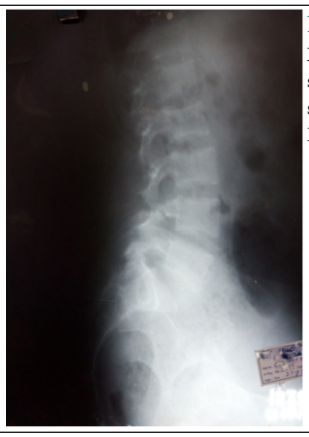

Figure 6. X-ray showing spondylolyis L4 lysis

metabolically active hypodense lesion of size1.4 x 0.9 cm soft tissue lesion noted in the lateral aspect of proximal right tibia deep to anterior muscle compartment.(Fig. 2) Multiple Looser's zoneare also seen After the tumor was identified with PET scan, it was localized by MRI(Fig3)and excised surgically. (Fig. 4A and 4B). Histopathological examination was suggestive of benign mesenchymoma. The biochemical parameters reverted to normalcy following surgery. S calcium – 9.1 mg/dl, phosphorus 3.4 mg/dl,Reversal of phosphaturia, and eventual mineralization of bone occurred.Patient improved very well after surgery, started walking, fracture healed and Looser's zone remineralized.(Fig. 5A,5B)

Case Report 2

A 32-year-old male presented with 11 year old history of low back ache-progressive, not responding to routine treatment. He was seen at different hospital and evaluated by different doctors. LBA was attributed to anx-ray(Fig. 6) and MRI finding of spondylolysis at L4 L5 and L5-S1 He developed Pathological Rt.subtrochanteric fracture femur(Fig. 7)8.5 years back.There is insufficiency fracture of pelvis on evaluation. Bone biopsy previously showed osteomalacia,all secondary causes of osteomalacia including malignancy were ruled out.USG neck and abdomen were normal.Adequate vitamin d and calcium was supplemented. Pathological fracture got malunited. Subsequently, he developed features of proximal myopathy and was bedridden with multiple pathological fractures(Fig. 8). There were multiple compression fractures in thoracic spine. Many branded it as vit d resistant rickets, subsequently lost follow up for about 6 yrs. We evaluated him as a case of suspected TIO inview of low phosphorus with normal calcium. The normal calcium, low phosphorus and low TMP/GHR were suggestive of TIO. Serum FGF-23 done by RIA is 18 RU/ml(0-150).DOTANAC PET CT identified the tumor in the right lower thigh (Fig 9). MRI showing tumor of 2.5x1.68x0.7 cm in the posteromedial aspect of femur (Fig. 10). The tumor was surgically excised(Fig.11A,11B) and histopathology was consistent with benign mesenchymoma.The patient improved well and was able to walk 6 months after surgery. Fractures consolidated in malposition (Fig.12A,12B,12C). As TIO was not suspected initially, there was a long long delay in diagnosis which resulted in deformities and loss and height(Fig. 13).

	PRE op	POST op
Serum calcium	8	9.8
Serum phosphorus	1.9	3.9
Serum albumin	4.5GM	4.9
Serum alkaline phosphatases	489	153
Serum PTH	40	
TMP/GFR	0.6ML/MT(2.5-4.51)	
25 OH VIT D	20NGM/ML	

Discussion

The term tumor-induced osteomalacia was coined in 1994 to describe a circulating phosphaturic factor which causes

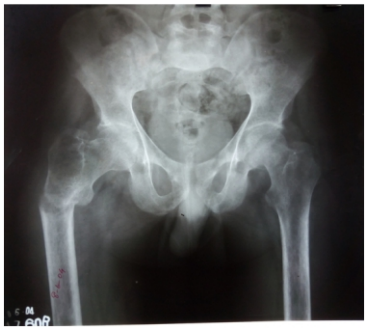

Figure 7. Rt.Subtrochanteric fracture

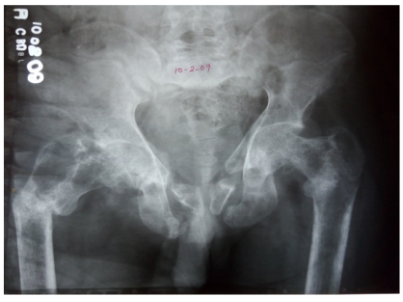

Figure 8. Multiple pathological fracures and patient is bedridden

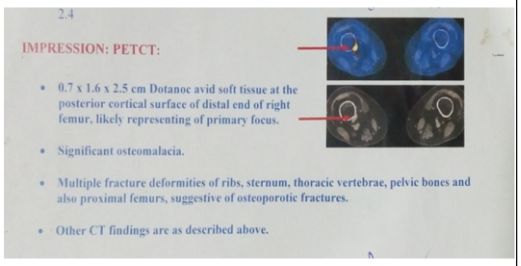

Figure 9. Ga 68 Dotanoc whole body Pet CT scan report

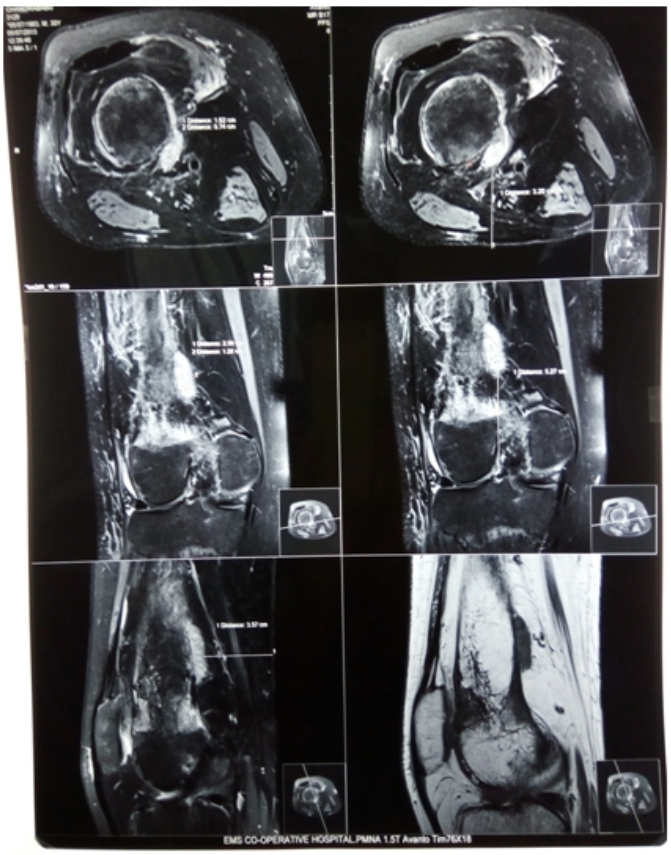

Figure 10. MRI showing tumor in popliteal region

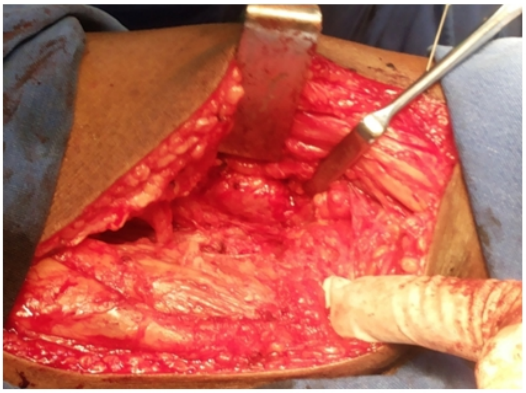

Figure 11a. Surgical exposure of tumor in popliteal fossa

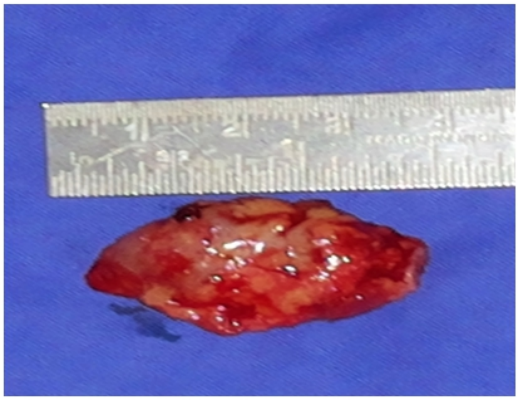

Figure 11b. Excised specimen

hypophosphatemia,renal phosphate wasting, reduced 1.25 Vitamin D and osteomalacia. FGF23 was identified as the putative phosphatonin.Other phosphatonins suggested include compounds like frizzled related protein-4, matrix extracellular phosphoglycoprotein, and FGF7 [5,6]. However, most of the data suggest that FGF23 is the primary, if not the only, clinically relevant phosphatonin [3]. Hypophosphatemia may be due to genetic and acquired causes. Genetic causes include XLH (X linked hypophosphatemic rickets), ADHR(autosomal-dominant hypophosphatemic rickets), and ARHR(autosomal-recessive hypophosphatemic rickets), which are essentially biochemical phenocopies of TIO [3]. Most of the acquired forms of hypophosphatemia are the result of direct renal tubular damage by a drug or a toxin. Although ADHR and XLHR are biochemically indistinguishable from TIO, the former two disorders typically present in childhood and are associated with lower-extremity deformities and short stature. The diagnosis of TIO was delayed very much in both our cases due to the lack of awareness of this rare disease. TIO should be suspected in adults with hypophosphatemic rickets, and should be confirmed by clinical, radiological,biochemical features, and FGF-23 measurement. Once the diagnosis of an FGF23-dependent, phosphate

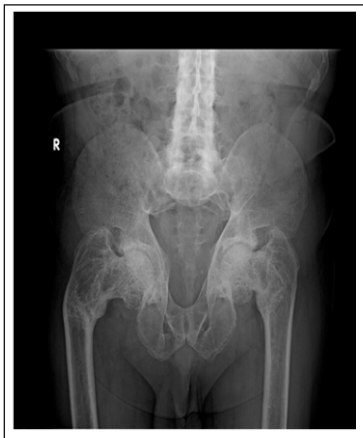

Fig. 12. A-Follow up Xrays –showing malunited, but consolidated fractures and healed loosers Zone

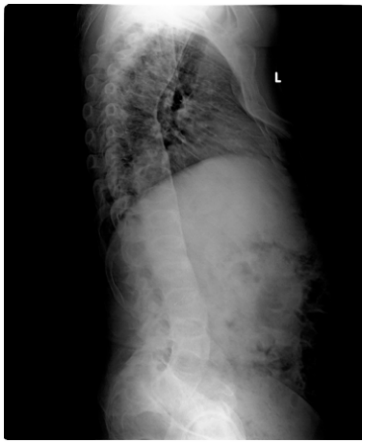

Fig. 12. B- Collapsed lumbar vertebrae fractures

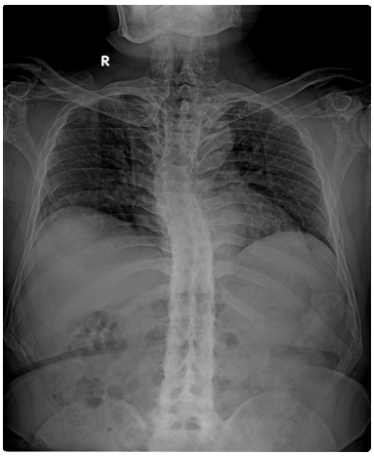

Fig. 12. C- Deformed spine after healing

Fig. 13. Lost height due to collapsed and deformed spine

wasting disorder is made, a thorough history can aid in excluding the genetic causes, such as XLH, ADHR, and ARHR. Localization studies in our cases was done with 68Ga-DOTANOC PET/CT. More recently, 68Ga DOTANOC PET/CT has been explored as a means of finding TIO tumors [7,8]. This scan combines the specificity of octreotide scanning with the sensitivity of PET/CT. It utilizes a modified octreotide molecule (DOTANOC) that has increased affinity for both somatostatin receptor 2 and 5 [9]. Labeling this compound with the positron emitter 68Ga results in a PET compound that may be more specific than FDG(F-18 fluorodeoxyglucose positron emission tomography), final localization was done with 1.5 tessla MRI. The treatment of choice for TIO is resection of the tumor with a wide margin to insure complete resection.Resection with a wide surgical margin is of utmost importance, as recurrences of these tumors have been reported [10]. Histopathology showed benign mesenchymomain both cases 3.5 yrs follow up showed no evidence of recurrence.

Conclusion

Diagnosis is commonly delayed due to the nonspecific nature of the symptoms, failure to determine or not giving importance to the serum phosphate levels during the testing of blood chemistry, lack of awareness of this rare condition, and difficulty in identifying the responsible tumor.FGF-23 is very useful in the diagnosis.68Ga-DOTANOC PET/CT can successfully localize phosphaturicmesenchymal tumors and may be a practical first step in functional imaging for this disorder. High resolution MRI helps in pin point localization of the tumor and hence surgical excision if feasible. Once diagnosed, an excellent outcome follows wide surgical excision.

Clinical message

TIO should be suspected in any patient with adult onset hypophosphatemic rickets.Serum FGF-23 level helps in the diagnosis. A 68Ga-DOTA-octreotate(DOTATATE) somatostatin receptor positron emission tomography(PET)/computed tomography (CT) imaging is helpful for the anatomical localisation and 1.5 tessla MRI helps in precise localisation which is essential in surgical plannning.A wide excision if possible will cure the problem. Lack of awareness of this entity,its presentation,diagnostic modalities will cause a delay in diagnosis and hence morbidity.

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Conflict of Interest: Nil
Source of Support: None

How to Cite this Article

Vijay P G, Joseph M V, Ahamed A.Tumor Induced Osteomalacia– Lessons Learned. International Journal of Surgical Cases 2017 Jan-Jun;3(1): 6-10.