Hypophosphatemic Rickets/ Osteomalacia: A Case Report and Review of Literature

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Abstract

Hypophosphatemic rickets/ osteomalacia comprises of a group of disorders of bone mineralization caused due to defect in renal handling of phosphorus. The group includes X linked hypophosphatemic rickets, autosomal dominant hypophosphatemic rickets and tumor induced osteomalacia. Here, we report the case of a young male who presented with mechanical low backache, muscular pains and proximal muscle weakness resulting in severe debility. He was diagnosed to have hypophosphatemic osteomalacia on the basis of hypophosphatemia, hyperphosphaturia, normal 25 hydroxy- and 1, 25 dihydroxy- vitamin D, normal intact PTH and raised serum FGF23 levels. Despite extensive search, no tumor was localized. He showed marked improvement with oral phosphate and calcitriol replacement and is under follow up.

Keywords: **Osteomalacia, Hypophosphatemic Rickets, Tumor induced osteomalacia (TIO), X linked hypophosphatemic (XLH) rickets, Autosomal dominant hypophosphatemic rickets (ADHR)**

Introduction

Hypophosphatemic osteomalacia comprises of impairment of matrix mineralization in remodeling sites of mature bones. Many syndromes causing this entity have been described namely X linked hypophosphatemic rickets (XLH), autosomal dominant hypophosphatemic rickets (ADHR) and tumor induced osteomalacia (TIO). These conditions have different etiopathogenesis, but share similar pathophysiologic mechanism i.e. reduction in phosphate reabsorption by renal tubules [1]. Main determinant of this pathophysiology is high serum levels or an increased activity of fibroblast growth factor 23 (FGF23) due to its overproduction or reduced degradation. These patients have chronic hyperphosphaturia leading to hypophosphatemia and have associated low or inappropriately normal activated vitamin D levels (1, 25 Di-hydroxy vitamin D). Here we report such a case of hypophosphatemic osteomalacia, which has shown remarkable improvement with conservative therapy and is kept under follow up.

Case Details

A 36 years old male patient presented with symptoms of mechanical type of low backache associated with pain in both the lower limbs and proximal muscle weakness of one year duration. He required support for getting up from sitting position. He also gave history of 04 cm loss of height in last one year. He was severely debilitated for last 3-4 months requiring assistance for daily living activities and was using two crutches for walking. There was no significant past medical illness and he was not on any medications previously. None of his family members were suffering from similar kind of illness. Clinical examination showed thin built male (BMI - 18.2 Kg/m^2) with pectus carinatum, reduced upper to lower segment ratio (0.8), proximal myopathy, waddling gait, normal dentition, no neurocutaneous markers, deformities, no swelling over head, neck or proximal extremities.

Initial investigations revealed normal complete blood counts, normal hepatic and renal functions. The striking feature was persistent hypophosphatemia with serum phosphate ranging between 1.6 to 2.2 mg/dl (Normal 2.5-4.8 mg/dl), normal serum calcium level (ranging between 8.8 to 9.7mg/dl) and raised serum alkaline phosphatase levels of 280 U/L (Normal 44 - 147 U/L). Tubular reabsorption

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of phosphates (TRP) [patient value: 80%; Normal 85-95%] and renal threshold phosphate concentration (Tmp/GFR) were low [patient value: 1.0mg/dl; Normal 2.8-4.4 mg/dl]. Serum levels of 25-hydroxy vitamin D 38.60 ng/ml (Normal 30- 120 ng/ml) and intact PTH (iPTH) 20 pg/ml (Normal 10-65 pg/ml) were normal respectively. The levels of FGF23 were elevated to 144 RU/ml (Expected 12.7 – 18.7 RU/ml; ELISA Immunometry) and 1,25 dihydroxy vitamin D levels were inappropriately normal at 24.40 pg/ml (Normal19.6–54.3pg/ml).

Radiographs of chest, spine and pelvis revealed Looser's zones in bilateral ribs, scapulae and femorii with fracture bilateral neck of femur (Fig 1, 2, 3). MRI spine was suggestive of multiple compression fractures lumbar vertebrae (Fig 4). Radionuclide bone scan revealed multiple insufficiency fractures consistent with osteomalacia (Fig5). Bone mineral density (DXA) showed low bone mass with T score -3.1 and Z score -3.1 at lumbar column. Whole body 18F-fluorodeoxyglucose positron emission tomography combined with computed tomography (18F- FDG PET/CT), whole body MRI scan and Gallium-68 DOTATATE PET/CT scan were carried out; however, no tumor was localized.

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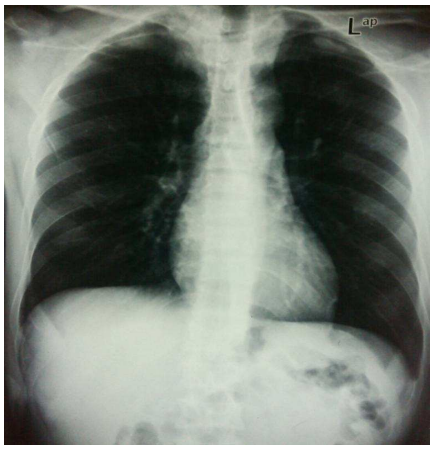

Fig.1

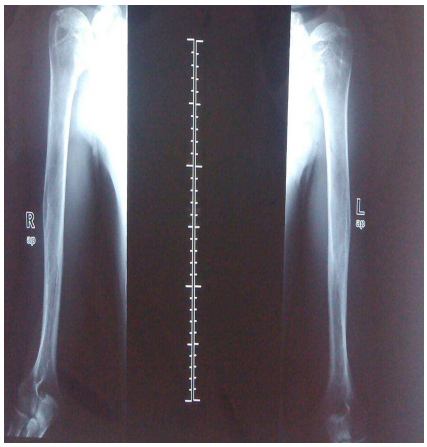

Fig.2

Fig.1. X- ray chest showing looser's zone in lower ribs.

Fig.2. X-ray Right humerus showing looser's zone.

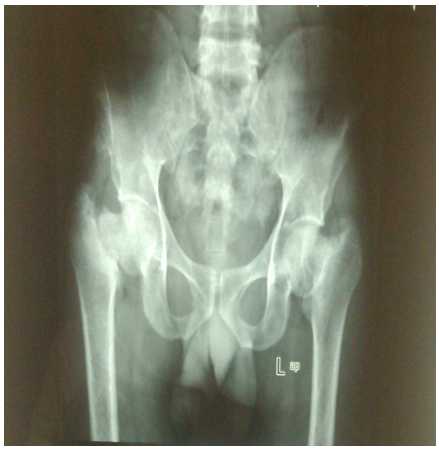

Fig.3

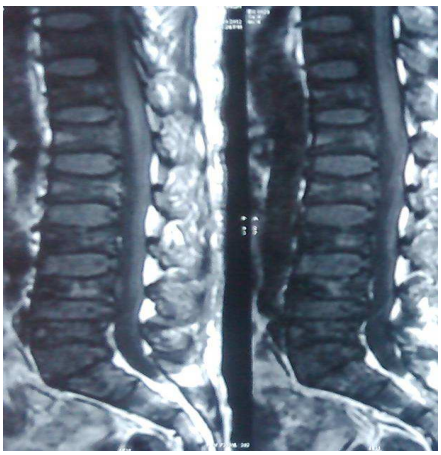

Fig.4

Fig.3. X-ray pelvis showing Fractures in both neck of femorii

Fig.4. MRI spine T1 & T2 weighted images showing diffuse loss of signal intensities in all vertebrae and multiple level mild degree vertebral collapse in lumbar region.

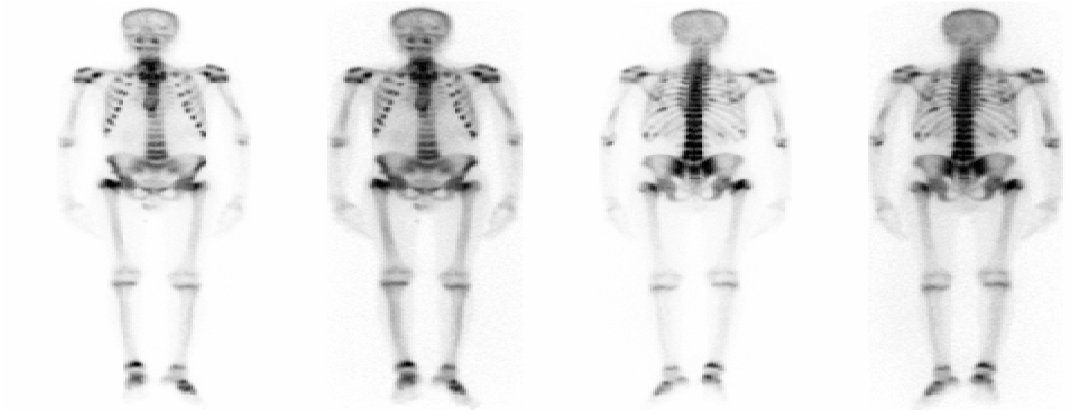

Fig.5. Radionuclide bone scan showing increased uptake in calvarium, linear uptake in shafts of both humerii and tibia, multiple foci in both shoulder joints, neck and proximal ends of both femorii, multiple vertebrae and sacrum, multiple ribs bilaterally, all costochondral and costovertebral junctions, bilateral Sacro-iliac joints and acetabulum and tarsal bones of both feet – suggestive of multiple insufficiency fractures, consistent with osteomalacia

The patient was managed with oral phosphate (1-2 gm per day in divided doses), along with 1, 25-dihydroxy vitamin D (0.25-1 µg/day) and calcium carbonate (1.5-2 g/day) supplementation. The patient showed marked symptomatic improvement within three months of therapy. Symptoms of muscle aches and backache reduced, he was able to walk without support and was able to carry out daily routine activities. Investigations at 3 months of follow up were as follows: serum calcium – 9.3 mg/dl, phosphorus – 3.3 mg/dl, Albumin – 3.8 gm/dl and alkaline phophatase – 112U/L. His doses of calcium carbonate and calcitriol were adjusted according to serum calcium and calciuria. Patient is kept under follow up and is planned for yearly evaluation for localization of tumor.

Discussion

Hypophosphatemic osteomalacia comprises of impairment of matrix mineralization in remodeling sites of mature bones. The condition is caused by pathophysiologic mechanism of reduced phosphate reabsorption by renal tubules [1]. Hypophosphatemic osteomalacia requires detection of hypophosphatemia alongwith hyperphosphaturia, hyperphosphatasia, normocalcemia, normal or reduced calciuria and low or inappropriately normal 1, 25 dihydroxy vitamin D levels. A phosphorus tubular reabsorption less than 85% is diagnostic of hyperphosphaturia [2]. FGF23 causes inhibition/or downregulation of type 2 sodium phosphate cotransporter (NaPi-IIa) in brush border membrane of proximal renal tubule leading to hyperphosphaturia and hypophosphatemia. Our patient had clinical, radiological and biochemical features suggestive of hypophosphatemic osteomalacia. As he had hyperphosphaturia (TRP80%), the causes of hypophosphatemia due to impaired intestinal absorption or cellular distribution were excluded. Primary hyperparathyroidism could easily be excluded as patient had normal serum calcium and iPTH levels.

Many syndromes causing hypophosphatemic rickets with raised FGF23 levels have been described like X linked hypophosphatemic (XLH) rickets, autosomal dominant hypophosphatemic rickets (ADHR) and tumor induced osteomalacia (TIO). XLH is X linked dominant disorder caused due to inactivating mutations in Phosphate regulating gene with Homologies to Endopeptidases on X chromosome (PHEX) leading to impaired cleavage of FGF23 by the deficient or abnormal endopeptidase. Patients present in childhood with frontal bossing, progressive limb deformities, and short stature with short limbs, dental abnormalities like abscessed noncarious teeth, enamel defect, enlarged pulp chambers and taurodontia [3]. ADHR is caused due to mutations of FGF23 at cleavage site, leading to impaired cleavage and prolonging its activity. Two subtypes of ADHR have been described, one presenting in childhood and mimics XLH and other subtype present in adolescence or adults with bony pains, muscle weakness and pseudofractures [3]. TIO is a rare

acquired paraneoplastic syndrome due to overproduction of FGF23 by slow growing mesenchymal tumor [3]. The tumors are usually benign and even in malignant tumors, metastasis is very rare. Bony pains are more severe, fractures are more common, and muscle weakness and fatigue are more prominent in TIO than other forms of osteomalacia [4]. In the present case, considering the age of onset of symptoms and raised levels of FGF23, differential diagnosis of TIO and ADHR were considered. Rapidity of onset of symptoms and negative family history of similar illness, favored tumor-induced osteomalacia as likely diagnosis, however, despite extensive search a tumor was not localized.

The greatest challenge in TIOs is to localize the tumor, as the tumor is very small, slow growing and frequently located in unusual anatomical sites. The occult nature of the tumor delays its recognition, and the average time from onset of symptoms to its recognition often exceeds 2.5 years. Once the syndrome is recognized, inability to locate the tumor further delays definitive treatment by an average of five years [5]. The conventional imaging techniques such as whole body CT or MRI may help to localize the tumor [4]. Venous sampling for FGF23 by targeting the area to study in MRI may also facilitate to locate the tumor location [6]. Nuclear imaging techniques are considered preferred modalities for localization. FDG/PET CT has been reported to be useful, but sensitivity is low considering diversity in histology and low level of proliferation of these tumors [6, 7]. As several of these tumors express somatostatin receptors (SSRs), scintigraphy with 111-Indium octreotide [7] and other SSR ligands labeled with the positron emitter 68-Gallium are the options available to localize the tumor. As described above in our case, extensive explorations including whole body MRI, FDG PET CT, Gallium -68 DOTATATE were not able to localize the tumor.

Medical therapy of hypophosphatemic osteomalacia include oral phosphate replacement (15-60 mg/kg/day in divided doses) along with calcitriol supplementation (15-60 ng/Kg/day in divided doses) to compensate its deficiency and help to increase intestinal phosphate absorption [8, 9]. Calcium prescription is also essential especially in the initial part of therapy. The best treatment of tumor-induced osteomalacia is excision of the tumor which leads to clinical and biological remission [4]. As tumors express somatostatin receptors, octreotide based therapy is an experimental approach to tackle these tumors. As many of these TIOs are derived from osteogenic cells, calcitonin has been tested with some efficacy.

Cinacalcet inhibits parathyroid hormone secretion and thus indirectly inhibits phosphate excretion and is also being proposed for tumor-induced osteomalacia [8]. Recombinant growth hormone therapy has also shown benefit in increasing the phosphate levels, growth velocity and final height, [9] but Cochrane database did not find it to be useful [10].

In our patient, hypophosphatemic osteomalacia is caused due to the excess effect of FGF23, but we are not able to localize the tumor. Patient was put on standard medical therapy with oral phosphate, calcitriol and calcium carbonate; and has shown marked clinical and biochemical improvement within three months of therapy. Patient is being planned for periodic follow up and observation for early detection of tumor, so that definitive treatment can be provided.

Conclusion

Hypophosphatemic rickets / osteo-malacia are an inherited or acquired disorder due to defective mineralization causing bony pains, muscle weakness, spontaneous fractures and significant functional disability. Syndrome combines hyperphosphaturia along with hypophophatemia and low to inappropriately normal 1, 25 dihydroxy vitamin D levels and is caused due to over expression or decreased degradation of phosphaturic agent FGF23. Medical therapy includes phosphate and calcitriol replacement and the best treatment modality for TIO is tumor excision. However, it is not always possible to localize the tumor despite of cumbersome and costly investigations. From this case report we illustrate the diagnostic approach to a case of hypophosphatemic rickets, strategies to localize the tumor in TIO and importance of medical treatment when tumor is not localized.

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