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Refractory soft tissue pains-A case report of tumor induced osteomalacia

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Abstract

Neurofibromatosis (NF1) is an autosomal-dominant genetic disorder with an incidence of 1:2600-3000. Tumor induced osteomalacia (TIO) is a metabolic disorder characterized by hypophosphatemia and inappropriately low serum levels of 1,25-OH D2. Symptoms are usually vague including chronic muscle and bone pain, weakness, and fatigue. Patients remain undiagnosed for years, often thought to have fibromyalgia. Pathogenesis of TIO involves tumor expression of Fibroblast growth factor 23 (FGF-23) causing phosphaturia. The metabolic abnormalities may be partially or completely corrected with phosphate supplementation and calcitriol. Definitive treatment requires excision of the tumoral lesions. We report case of a 32-year-old female presenting with widespread body pain and fatigue in a wheelchair bound state. Investigations showed Very low serum phosphorus, elevated FGF 23 levels and high urinary phosphorus loss, establishing the diagnosis of TIO. Phosphorus levels along with Vit D3 and calcium should be investigated in all cases of 'nonspecific' body pains.

Introduction

Tumor induced osteomalacia is a rare entity usually seen with tumors of mesenchymal origin. Sarcomas, malignant neuroma, epidermal nevus, osteoma, and neurofibromas have been associated with this syndrome [1,2].

Earliest reports were published by Gould [3] in 1918 who reported two cases of neurofibromatosis in whom postmortem study of uncalcified bone specimens demonstrated increase in osteoid: representing changes of osteomalacia. Falkson in 1958 collected 150 cases of 'phosphate diabetes' from world literature and mentioned 5 of them had neurofibromatosis. Dent in 1952 collected 67 patients with rickets and renal tubular acidosis of which two had neurofibromatosis. The osteomalacia in neurofibromatosis is characterized by later onset in adulthood, renal phosphate loss with hypophosphatemia, and multiple pseudo fractures. Hypophosphatemia results in defective mineralization of bone matrix. This is mediated via FGF23; a hormone that inhibits proximal renal tubular reabsorption of phosphate and down-regulates renal conversion of 25-hydroxyvitamin D to its active form, 1,25-dihydroxyvitamin D.

Case report

A 39-year-old lady presented to the outpatient clinic with difficulty in walking and severe widespread body pains. The pains were not relieved with rest or NSAIDs. She had been operated for neurofibroma at D4-D5 spine with intrathoracic extension 6 years back. Her previous lab investigations, a year ago, showed a low serum phosphorus (1.8mg/dl), low 25-OH-vit D3 (5.14ng/dl) and high PTH levels (90pg/ml [range 12-74pg/ml]). She had been treated with high doses of injectable Vit D3 and calcium, but showed no improvement. She had been wheelchair bound for 6 months when we saw her. On musculoskeletal examination she had severe pain in her thighs. There was no active synovitis in any of her joints. Her MRI Lumbo-sacral spine was suggestive of multiple compression fractures along the end plates and diffuse central wedging of all dorsal and lumbar vertebrae. Her present lab investigations showed normal hemogram, urine routine, renal and liver functions. Metabolic profile was as seen in Table 1.

Based on these lab reports we made a diagnosis of hypophosphatemia bone disease. Her urinary PH was acidic and serum bicarbonate levels were 24meq/litre. Her FGF-23 levels- 156 RU/ml (0-150) were elevated. She had no palpable swelling all over the body. Patient was advised a Gallium DOTATOC scan keeping in mind her history of neurofibromatosis. However due to covid-19 pandemic and difficulty in accessibility she underwent a PET-CT scan. PET CT was suggestive of hypermetabolic well circumscribed tumor in R paravertebral region medial to psoas muscle (size-3*3*3.9cm).and another similar one in left pelvic region (size-5.5*4.6 cm) likely neurofibromas.

A diagnosis of neurofibroma induced osteomalacia was made and the patient was treated with oral phosphate (3.96gm/day) and 0.5ug of 1,25-dihydroxyvitamin D. For definitive treatment she was referred to a neurosurgeon for removal of the tumors. She has been operated on for both the neurofibromas and has been doing well so far. She has

Table 1. Lab investigations showed normal hemogram, urine routine, renal and liver functions.

Investigations	Lab value	Normal range
25OH Vit D3	38.9 ng/mL	25-80 ng/mL
S.PTH	51 pg/ml	10-65pg/ml
ALP	146 IU/L	34-119IU/L
S.PO4	**1.5** mg/dL	2.5-4.5 mg/dL
Urinary po4	**137**mg/	variable
S.Ca	9.1 mg/d	8.6-10.3 mg/dL

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been discharged on high doses of oral phosphate (3.96gm sodium phosphate) and 0.25 mcg calcitriol. At 1-month post-surgery she is able to walk without help.

Discussion and conclusion

Skeletal lesions due to mesodermal dysplasia, are frequent in neurofibromatosis 1 and appear early in life, they are associated with normal serum phosphorous and calcium levels. In contrast, the osteomalacia of neurofibromatosis is very rare, presents in middle age, and is associated with marked disturbance of phosphate handling. Our patient with neurofibromatosis was symptomatic at the age of 37 years with reduced serum phosphorus levels.

Patients with progressive weakness, bone and muscle pain, and fractures should be initially evaluated for calcium, Phosphorous, alkaline phosphate, 25OH D3 and PTH levels. Serum phosphorus levels are maintained in the normal range due to complex interactions among intestinal absorption, exchange with intracellular and bone storage pools, and renal tubular reabsorption, with the kidney being the principal organ responsible for phosphorus homeostasis The presence of pseudo fractures, high alkaline phosphatase, low serum phosphate, normal 25OH Vitamin D3 and PTH in our patient pointed to the diagnosis of hypophosphatemia osteomalacia. We checked for and found a high urinary excretion of phosphorus, and fractional clearance of phosphorus (FEPi) was 17.34%. This is pointing to a phosphorus wasting state.

Excessive urinary phosphorus loss is seen in renal tubular acidosis and TIO. The presence of a normal HCO3 level, an acidic urinary PH helped exclude the diagnosis of RTA. The pathophysiology of tumor-induced osteomalacia is 2-fold: hypophosphatemia secondary to impaired proximal renal tubular reabsorption of phosphate, and inhibition of renal 25(OH)D–1-α-hydroxylase activity, which blunts the compensatory rise in serum 1,25-(OH)2-D in response to hypophosphatemia.

Among the differentials of TIO are autosomal-dominant hypophosphatemia rickets (ADHR)and X-linked hypophosphatemia rickets (XLHR). ADHR and XLHR present in childhood and are associated with lower-extremity deformities and short stature. Also, XLHR has male predominance. Both conditions, however, are biochemically similar to TIO. A definitive diagnosis can be made by commercially available genetic testing of the FGF-23 and PHEX genes, which are defective in ADHR and XLHR, respectively, but not in TIO.

Proximal myopathy and pain were particularly disabling in this patient, eventually resulting in the need for a wheelchair. It takes approximately 2.5 years from the onset of symptoms to the diagnosis of TIO [4], and the average time from diagnosis until the responsible tumor is identified is ~5 years [5]. This is likely due to small size, slow growth, and difficulties with visualization on standard imaging studies.

The tumors associated with osteomalacia may occur in either bone or soft tissue and seem to favor the extremities and craniofacial region. The medical treatment of choice for osteomalacia of neurofibromatosis and for other types of TIO is oral phosphate and active form of vitamin D3. In some patients with suspected tumor-induced osteomalacia, the tumor is never found, and continued treatment with phosphorus supplements and calcitriol is required. Permanent cure is achieved after surgical removal of the tumor which usually results in rapid correction of metabolic abnormalities because of this potential for cure, in every patient with TIO, a careful search for hidden tumors is mandatory. Patients should be instructed to examine themselves and report any unusual lumps especially in the scalp and extremities, since some of these tumors become palpable later in the course of disease. Occasionally, the tumors are multiple or in unresectable areas and their complete removal is impossible. In these patients, partial resection can lead to amelioration of clinical manifestations. The experience with this patient demonstrates that in patients with muscle pain and weakness in a known case of neurofibromatosis, an active search for metabolic abnormalities should be made [6].

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