

Debilitating Pain and Fractures: A Rare Case of Hypophosphatemic Osteomalacia with Concomitant Vitamin D Deficiency in Neurofibromatosis Type 1

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Abstract

Hypophosphatemic osteomalacia is a rare form of metabolic bone disorder in neurofibromatosis type 1 (NF1). The exact disease mechanism of this disorder in NF1 is yet to be established. We present a 44-year-old female known to have NF1, who presents with debilitating bone pain, weakness and multiple fractures. Laboratory investigations showed persistent hypophosphatemia with renal phosphate wasting suggestive of hypophosphatemic osteomalacia. She also had concomitant vitamin D deficiency which contributed to the disease severity. Medical therapy with oral phosphate and vitamin D improved her symptoms without significant changes in fracture healing or phosphate levels.

Key words: NF1, hypophosphatemia, osteomalacia, FGF23, Vitamin D deficiency

INTRODUCTION

Neurofibromatosis type 1 (NF1) is an autosomal dominant disorder resulting in mutation to the tumor suppressor gene, neurofibromin. It is associated with numerous skeletal abnormalities and disorders of the bone metabolism. Skeletal abnormalities in NF1 are common, it has been well described in literature ranging from dysplasia of the tibia and long bones, dystrophic scoliosis, chest wall deformities, sphenoid wing dysplasia and many more. In contrast, the disorders of bone metabolism in these patients are poorly understood.¹ Hypophosphatemic osteomalacia is amongst the rare disorders associated with NF1, with less than 40 cases reported to date. It usually has a later onset in adulthood with persistent hypophosphatemia, renal phosphate loss and multiple pseudofractures.²

CASE

We describe a 44-year-old female who presents with multiple long bones and axial skeleton fractures from a trivial fall in the bathroom. She was referred to the endocrine team for suspected pathological fractures with persistent hypophosphatemia. Further history revealed generalized bone pain for the last decade with progressive weakness resulting in unstable gait and frequent falls over the last two years. She was diagnosed with NF1 at the age of 17 due to pathognomonic cutaneous manifestations and positive family history. Her mother was diagnosed with NF1 in her 20's with cutaneous features, without multisystem involvement. Apart from the maternal history of NF1, there was no history of skeletal or bone metabolism disorders. She defaulted follow up subsequently, without surveillance for complications.

She had no visual or hearing impairment. There were no constitutional symptoms to suggest malignancy. She had no history of renal, liver or gastrointestinal disease. Her diet is predominantly vegetarian, with very poor appetite of late, due to debilitating pain. She spends most of her time indoors, with limited sun exposure due to restricted mobility.

Physical examination revealed a slightly built female (BMI 18) with cutaneous manifestations of NF1, café au lait patches and numerous small neurofibromas, the largest being approximately 1.5 cm predominantly over her trunk. She was found to have skeletal abnormalities of the chest wall, pectus excavatum and marked kyphoscoliosis. Neuromuscular examination was unremarkable except for proximal muscle weakness of the hip and thigh. Slit lamp examination of the eye was normal.

X-rays done showed fractures of the left 6-9th ribs, bilateral superior and inferior rami, left neck and right subtrochanteric of femur (Figure 1). Her thoracolumbar x-ray confirmed marked kyphoscoliosis with compression fracture of L1 (Figures 2 and 3). Her blood biochemistry showed a persistently low phosphate (0.31-0.56 mmol/L) with a concomitant normal calcium (2.2-2.6 mmol/L). Her other electrolytes, renal and liver function were normal except for an elevated alkaline phosphatase (300-360 U/L). Her 25-OH Vitamin D level was 25 pmol/L, suggestive of deficiency and intact Parathyroid Hormone (iPTH) was elevated at 46.4 pmol/L.

The hypophosphatemia was due to renal loss evidenced by elevated urinary fraction of phosphate excretion, 12.7% and low TMP-GFR (Ratio of Tubular Maximum



Figure 1. Pelvic x-ray showing bilateral femur fractures with diffuse osteopenia.



Figure 2. Lateral view of spine showing excessive thoracic kyphosis.

Reabsorption Rate of Phosphate to Glomerular Filtration Rate) of 0.488 (0.88-1.42). There were no abnormalities in the blood acid base balance or urinary biochemistry to suggest renal tubular dysfunction. A full body CT-scan was done to ensure an occult phosphaturic mesenchymal neoplasm resulting in tumor induced osteomalacia was not missed out. She was concluded to have hypophosphatemic osteomalacia secondary to neurofibromatosis with



Figure 3. Anteroposterior view of spine x-ray showing marked scoliosis.

concomitant vitamin D deficiency. The elevated iPTH was explained by secondary hyperparathyroidism due to vitamin D deficiency.

She was seen after 8 weeks to assess response to treatment. She reported improvement in symptoms especially bone pain and weakness despite the delay in fracture healing. There was no significant changes in her serum phosphate levels with persistent hyperphosphaturia. Unfortunately, due to the limited availability and cost of vitamin D testing, she was not able to repeat her levels. A clinical decision was made to continue the oral phosphate and to shift her to activated vitamin D, calcitriol 1 mcg a day in divided doses. Her future medical therapy will be titrated mainly based on her symptoms. She will also be monitored closely for complications of treatment with activated vitamin D such as hypercalciuria and nephrolithiasis with routine six -monthly 24 hour urine calcium/creatinine index and renal ultrasound.

DISCUSSION

This patient presented with features suggestive of renal phosphate wasting in adulthood with underlying NF1. Despite the lack of formal diagnosis, her cutaneous stigmata of NF1 preceded the onset of renal phosphate wasting by at least 20 years whereby she was well, asymptomatic till her mid 30's. Her presentation with multiple fractures and marked skeletal abnormalities with accelerated disease progression over the last few years signifies an active underlying disease pathophysiology.

As mentioned above, the association of hypophosphatemic rickets/osteomalacia with NF1 has been rarely reported in literature. These patients usually develop disease later in adulthood and often present with severe bone pain, muscle weakness and fractures.³ Their biochemistry typically reflects hypophosphatemia with normal or low calcium levels, elevated ALP, and increased urinary phosphate excretion. It is interesting to note, that despite the chronic urinary phosphate loss, the 25-OH Vitamin D, 1,25 OH Vitamin D and iPTH levels were often reported as normal.⁴ However, our patient was deficient in 25-OH Vitamin D resulting in secondary hyperparathyroidism which cannot be solely attributed due to the disease process above. It can be postulated that her vitamin D deficiency is multifactorial due to her dark skin, limited sun exposure and poor nutrition. The concomitant vitamin D deficiency could be a contributing factor to the disease severity resulting in debilitating symptoms and multiple fractures.

There have been multiple hypothesis with regard to the underlying pathophysiology of hypophosphatemic osteomalacia in NF1, however the exact mechanism of disease is yet to be established. Abdel-Wanis et al.,⁵ hypothesized in 2002 that melatonin deficiency in NF-1 may be driving the underlying mechanism of hyperphosphaturia by a complex mechanism involving decreasing the sodium-phosphate cotransport, increasing the level of cyclic adenosine monophosphate (cAMP) and the unantagonized effect of dopamine on phosphate reabsorption. Secondary hyperparathyroidism as a result of osteomalacia may augment the dopamine effect resulting in worsening phosphaturia. Melatonin deficiency also results in excess corticosteroids secretion which in turn may further inhibit melatonin secretion. This results in a vicious cycle of phosphate loss causing progressive bony deformities and osteomalacia.

In recent times, it has been suggested that excess fibroblast growth factor-23 (FGF-23) is responsible for hypophosphatemic osteomalacia in NF1.^{2,3} FGF-23 is a protein secreted by osteocytes which functions as the central regulator of phosphate metabolism. It mainly acts on the kidneys where it inhibits reabsorption of phosphate by the sodium-phosphate co-transporters in the proximal tubules. It also decreases 1,25(OH)₂Vitamin D production by suppressing the 1-alpha hydroxylase enzyme. Excess activity of FGF-23 has been proven to be responsible for various hypophosphatemic bone disorders including inherited forms of rickets and tumor induced osteomalacia.⁶ Where neurofibromatosis is concerned, there is still insufficient evidence to conclude if FGF-23 drives the pathogenesis of the disease. In a single center

study in India, it was found that only one out of three NF1 patients with persistent hypophosphatemia had marginally elevated level of plasma FGF23.⁷ In 2019, Sahoo et al.,² had reported the first unequivocally elevated FGF-23 in a NF-1 patient with skeletal dysplasia, neurofibroma and hypophosphatemia. It was initially postulated that the excess FGF-23 is produced by neurofibromas resulting in a tumor induced osteomalacia like syndrome.^{3,8} However, recent literature has disputed this theory by showing absent FGF-23 staining in histopathological examination of neurofibroma of a NF1 patient with hypophosphatemic osteomalacia who had elevated circulating levels of FGF23.² It has been proposed that the bone may be source of excess FGF-23 in NF-1 patients. This was supported by a study done on mice, where the NF1 gene deficient osteocytes in conditional knock out mice (NF1cKO) produced excess FGF-23 in their bones and exhibited an osteomalacia-like bone phenotype. This is attributed to the upregulation of PI3K intracellular signalling pathway in these neurofibromin deficient osteocytes.⁹ Unfortunately, in our patient, we were not able to send her FGF-23 levels due to logistic and financial caveats.

CONCLUSION

In conclusion, hypophosphatemic osteomalacia in NF-1 is a rare but important bone metabolism disorder. The disease process can result in debilitating pain and multiple fractures in patients, affecting their quality of life and longevity. The current consensus for treatment of this disorder is medical therapy with phosphate and activated vitamin D based on symptoms. There is no definitive therapy to treat the underlying disease itself in current practice. There has been recent interest in FGF-23 mediated hypophosphatemic rickets and osteomalacia due to the development of burosumab, a human monoclonal antibody against FGF-23. Burosumab has been proven as a novel therapeutic agent in management of both children and adults with X-linked hypophosphatemic rickets.^{10,11} An on-going open label phase 2 study using burosumab in patients with Tumor Induced Osteomalacia (TIO) syndrome and Epidermal Naevus Syndrome (ENS) has shown biochemical and symptoms improvement in these patients.¹² If the hypothesis of excess FGF-23 can be confirmed in hypophosphatemic osteomalacia in NF-1, it unlocks a possible therapeutic opportunity to use burosumab as definitive treatment in these patients.

Ethical Consideration

Patient consent was obtained before submission of the manuscript.

Statement of Authorship

All authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure

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