

Case Reports

TUMOR ASSOCIATED OSTEOMALACIA IN NEUROFIBROMATOSIS: CASE REPORT AND LITERATURE REVIEW

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ABSTRACT

The association of osteomalacia with neurofibromatosis is a very rare entity. Here a 34 year old man, a known case of neurofibromatosis, is reported who presented with bone pain, hypophosphatemia, renal phosphorus wasting, multiple Looser's pseudofractures, and low bone density. Treatment with high dose calcitriol and phosphate resulted in temporary treatment. Permanent cure was achieved after removal of two large superficial neurofibromas.

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INTRODUCTION

Tumor associated osteomalacia (TAO) is a rare entity which is seen in some patients with benign or malignant tumors. Most of these tumors are of mesenchymal origin. Sarcomas, malignant neuroma, epidermal nevus syndrome, osteoma, and neurofibromas have been associated with this syndrome.¹

Association of osteomalacia with neurofibromatosis is quite rare and from its first recognition in 1918 by Gould, fewer than 40 cases have been reported in the literature.² Hereby a known case of neurofibromatosis is described who presented with clinical and radiologic features of osteomalacia.

CASE REPORT

A 34 year old man from southern Iran referred to the endocrine clinic with progressive bone pain and difficulty in walking since 4 years ago. The patient had noticed multiple cutaneous nodules from his early adulthood and the pathologic study of one of these nodules had been reported as schwannoma. He was healthy until the age of 30 when he experienced progressive bone pain affecting his thighs, pelvis, and shins. Recently he could walk only with the help of crutches. Because of these

problems, he referred to a medical center in a neighboring county. Radiologic study revealed multiple pseudofractures and he had low plasma phosphate, normal calcium and high alkaline phosphatase levels. Despite a normal serum level of 25-(OH)- Vit D, he was given 8 injections of vitamin D₃ (totally 4.8 million IU) for 3 months and calcium supplements, but there had been no clinical improvement during the ensuing 3 months. His family history was negative for neurofibromatosis, osteomalacia, and rickets. On physical examination, there was no asymmetry or deformity of the extremities. Skin examination showed frequent cafe au lait spots throughout the body and at least 20 of them measured more than 20 mm in diameter. There were many freckles in axillary and inguinal areas. Numerous neurofibromas were present on the trunk and extremities measuring less than 1 cm in diameter but there were two large tumors one over the right knee measuring 2.5× 2.5 cm and the other one over the right ankle sized 5×5 cm (Fig. 1). According to the patient these two tumors had grown significantly during his recent illness.

Laboratory data in our center were as follows: Serum calcium was 8.6 mg/dL (normal 8.5-10.5mg/dL). Serum phosphorus was in the range of 1.2-1.4 mg/dL in 4 separate measurements (normal: 3.0-4.5 mg/dL). Alkaline phosphatase was 1800 IU/L (normal <220 IU/L)

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and gamma glutamyl transpeptidase was 42 IU/L (normal: 10-48 IU/L). 24 hour urinary excretion of calcium and phosphorus was measured three times and they were in the range of 65-88 mg/24hrs and 380-440mg/24 hrs respectively. Tubular reabsorption of phosphorus (TRP) as calculated by the formula:

$$\text{TRP(\%)} = 1 - \frac{\text{urine phosphorus} \times \text{plasma creatinine}}{\text{plasma phosphorus} \times \text{urine creatinine}}$$

was 48.5% (NL>88%).³ Renal threshold of phosphate as determined by nomogram was 0.7 mg/dL (normal >2.5 mg/dL).³ Serum PTH by IRMA method was 55 pg/mL (normal: 13-66 pg/mL), serum concentration of 25-(OH)-Vit D determined by RIA before treatment with vitamin D₃ was 35 ng/mL (NL: 10-50 ng/mL). CT scan and ultrasonography of the abdomen were normal. Radiologic bone survey showed generalized demineralization of bones and multiple symmetrical Looser's zones (pseudofractures) in bilateral fibulae and radii (Fig. 2). Bone densitometry by DEXA showed low bone mineral density. T-scores were -3.5 and -3.2 for L1 - L2 and hip respectively.

With an impression of TAO oral phosphate (2.0 gram per day in divided doses) and calcitriol (1.0 microgram per day) were started. After 2 months of treatment the patient's symptoms improved dramatically and he was able to walk without help after 4 months. At this time his serum calcium was 8.8 mg/dL, phosphorus 3.1 mg/dL and alkaline phosphatase 650 IU/L. After 5 months of treatment, the patient discontinued his medications by himself and in 2 months his symptoms recurred and he referred back to the clinic. Lab data again showed hypophosphatemia and high alkaline phosphatase. At this time, the two large tumors located on the knee and ankle were suspected to be the cause of the patient's problems. He was referred to a surgeon and these two tumors were removed. The pathology report was schwannoma. After



Fig. 1. Large neurofibromas over the ankle and knee.

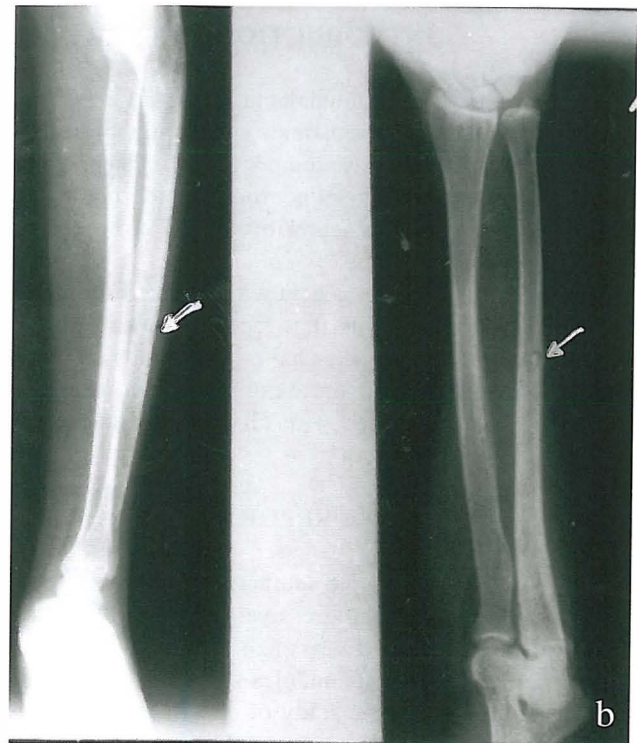


Fig. 2. Symmetrical pseudofractures in a) fibulae and b) radii.

surgery the patient had weekly measurements of serum phosphorus and calcium which showed gradual improvement. After 6 weeks his serum phosphorus was 3.4 mg/dL and serum calcium was 9.1 mg/dL. 4 months after surgery during his last visit, he was free of symptoms and lab data were all within normal limits. Tubular reabsorption of phosphorus was 86%.

DISCUSSION

TAO is thought to arise from tumors that secrete a putative circulating phosphate wasting factor referred to as phosphatonin.^{4,5} Recently it has been suggested that FGF-23, a protein with sequence homology with fibroblast growth factors (FGFs) is the phosphate wasting factor or phosphatonin.⁶ The hallmark of TAO is hypophosphatemia, high phosphate clearance and normal or near normal serum calcium levels. It has many similarities with X-linked hypophosphatemic rickets.⁷ PTH is usually normal and serum 1,25(OH)₂ vit D is low or inappropriately normal.⁸ It has been suggested that the tumor secretes products that impair 1- α hydroxylation of 25-(OH) vit D and thus produces a form of acquired vitamin D resistance.⁹

Dysplastic skeletal lesions are frequent in neurofibromatosis. These are believed to be the result of mesodermal dysplasia intrinsic to the disease and they appear early in life.¹⁰ They cause bone deformities, and are not associated with disturbances in calcium and phosphate metabolism. In contrast, the osteomalacia of neurofibromatosis is very rare, presents in middle age, and is associated with marked disturbance of phosphate handling.²

The patient presented here had no skeletal symptoms till the age of 32. The presence of multiple symmetrical Looser's pseudofractures, high alkaline phosphatase, low serum phosphate, and generalized demineralization in bone densitometry points to the diagnosis of osteomalacia. These findings have been present in other reported cases.^{2,11,12,13} The initial level of 25-(OH) vit D was normal and lack of response to treatment with high doses of vitamin D₃ rules out the possibility of vitamin D deficiency. In a review by Konishi et al,² serum phosphorus in 24 reported cases of neurofibromatosis-associated osteomalacia ranged from 1.0 to 3.0 with a mean of 1.94 \pm 0.47 mg/dL and serum calcium ranged from 7.3 to 10.0 with a mean of 9.2 \pm 0.7 mg/dL. In this regard, the present patient is similar to other cases. Serum 25-(OH) vit D level has been reported in seven similar cases and has been normal.^{2,11} We did not have the facility to measure serum 1,25-(OH)₂ vit D but the reported levels in 5 cases have been normal.² Phosphate depletion normally stimulates renal 1- α hydroxylation of vitamin D, resulting in marked elevation of serum 1,25-(OH)₂ vit D concentrations.¹⁴ Regarding profound hypophosphatemia, the

normal level of 1,25-(OH)₂ vit D in osteomalacia of neurofibromatosis should be regarded as inappropriately low.²

The patient presented here had low tubular reabsorption of phosphorus, pointing to a phosphorus wasting state and this is similar to other cases reported in the literature.^{2,11,12}

The medical treatment of choice for osteomalacia of neurofibromatosis and for other types of TAO is oral phosphate and activated vitamin D₃.² The present case responded well to this treatment, but the effect of drug therapy was temporary and the symptoms recurred after discontinuing treatment. Permanent cure is achieved after surgical removal of the tumor.^{1,13,15,16} 93 percent of patients with complete excision of the tumor are cured of osteomalacia. 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 in 57 percent of cases.¹ After complete removal of the tumor, improvement in phosphate metabolism usually changes from a debilitated state to a normal active existence.^{15,16} Because of this potential curability, in every patient with TAO, a careful search for hidden tumors is mandatory. Most of these tumors are small and usually located in the extremities and head. 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.¹ The experience with this patient demonstrates that in patients with neurofibromatosis and osteomalacia, although innumerable neurofibromas are present, it is the largest ones or those with recent growth that cause TAO and their surgical removal should be tried to achieve permanent cure.

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