



## Hypophosphataemic osteomalacia in neurofibromatosis

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**Oncogenic Osteomalacia syndrome is associated with mesenchymal tumours, caused by a protein secreted from tumours which inhibits tubular renal phosphate absorption and reduces 1,25 dihydroxy vitamin-D renal conversion. It manifests as osteomalacia with hypophosphataemia and hyperphosphaturia. Association of neurofibromatosis with oncogenic osteomalacia is unusual. We report a rare case of oncogenic osteomalacia with generalized neurofibromatosis which presented to us as pathological fracture.**

**Keywords :** oncogenic osteomalacia ; neurofibromatosis ; pathological fracture.

### INTRODUCTION

Oncogenic osteomalacia is a rare clinico-pathologic syndrome associated with mesenchymal tumours that apparently produce osteomalacia with abnormalities consisting of hypophosphataemia, normocalcaemia, and increased levels of alkaline phosphatase (1-5). Association of neurofibromatosis with oncogenic osteomalacia is unusual (1,3). We report a case of oncogenic osteomalacia with generalized neurofibromatosis which presented to us as pathological fracture.

### CASE REPORT

A 46-year-old female presented in the outpatient department with acute onset of pain in the left thigh and inability to walk for two weeks. She gave a

history of multiple nodules all over the body since childhood and generalized aches and pains for the past two years. On examination, tenderness and deformity were present in the supracondylar region of her left femur. Multiple skin nodules and café au lait spots were found all over the back and abdomen (fig 1a). She had diffuse bony tenderness. Radiographs of her left knee revealed a pathological supracondylar fracture of the left femur with osteopenia and coarse trabeculae (fig 1b). Skeletal survey revealed Looser zones in the distal fibula bilaterally (fig 1c) and in both ulnae, and resorption of multiple phalanges (acro-osteolysis) (fig 2a). A triradiate pelvis with pseudofracture of the neck of the femur and break in Shenton's arc were noted, but active straight leg raising was possible (fig 2b). Radiographs of the spine revealed a rugger jersey spine with fish mouth vertebrae (fig 2c). Laboratory investigations were : haemoglobin 11 g/dL, ESR 10 mm in first hour, CRP < 6 IU, serum calcium 8.9 mg/dL (normal values : 8.0-10.2 mg/dL), serum

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**Fig 1.** — a. Multiple skin nodules and café au lait spots over upper limbs and abdomen ; b. Pathological fracture of the femur with osteopenia, coarse trabeculae ; c. Looser zone in the distal fibula.

phosphate 1.7 mg/dL (normal values : 2.7-4.5 mg/dL), alkaline phosphatase 560 IU/L (normal values : 44-147 IU/L), urinary calcium 108 mg/24 hours (normal values : 0-300), urinary phosphate 486 mmol/24 hours (normal values : 13-42), serum PTH 70 pg/ml (normal values : 10-69 pg/ml). The patient was diagnosed as a case of von Recklinghausen disease with osteomalacia. The femoral fracture was treated with skeletal traction for six weeks, followed by a high groin cast for six weeks. This was followed with an above-knee cast brace for another three months. The patient was simultaneously put on medical therapy in the form of syrup neutral phosphate 500 mg thrice daily, oral elemental calcium 1 gram twice daily and calcitriol at 0.25 mg thrice daily. Six months later the fracture united with moderate improvement in the patient's condition and biochemical parameters. Her bone pains persisted though diminished at latest follow-up two years later.

## DISCUSSION

Oncogenic osteomalacia is a rare endocrinological paraneoplastic syndrome characterised by defective bone mineralisation from renal phosphate loss. It is an unusual condition but probably still is the most common cause for acquired hypophosphataemic osteomalacia in adult males (2).

The affected age group range is between 7 to 77 years with a M:F ratio of 1.2:1. Oncogenic osteomalacia syndrome is gradual in onset. Patients characteristically present with joint deformities, waddling gait, bone pain, muscle weakness, anorexia, fatigue, and occasionally long bone fractures. The initial clinical presentation may be mistaken for rheumatoid arthritis, muscular dystrophy, or primary neurologic disorder in some cases (4).

Oncogenic osteomalacia is almost exclusively described in patients with tumours of mesenchymal origin. The oncogenic cause of osteomalacia may



**Fig. 2.** — a. Looser zone in both ulnae and multiple phalangeal resorption (acro-osteolysis) ; b. Fracture of the neck of the femur with break in Shenton's arc and deformed pubic bones ; c. Ruggier Jersey spine and fish mouth appearance of disc indicating osteoporosis.

be unrecognized as the tumours are frequently small and asymptomatic (4). If the biochemical profile of the patient is that seen in hypophosphataemia, namely low calcium and phosphate in serum and high phosphate excretion in urine, and the patient is not responding adequately to oral calcium and vitamin D therapy, then the possibility of an underlying cause either renal or oncogenic or hereditary X-linked hypophosphatasia must be entertained. The commonest tumour described is haemangiopericytoma, but other tumour types described include fibrous dysplasia, osteosarcoma, chondroblastoma, chondromyxoid fibroma, malignant fibrous histiocytoma, giant cell tumour, haemangioma, paraganglioma, prostate cancer and oat-cell carcinoma of the lung. Neurofibromatosis is rarely associated with oncogenic osteomalacia.

Metabolic abnormalities in oncogenic osteomalacia are hypophosphataemia, hyperphosphaturia, low or normal serum calcium, raised alkaline phosphatase, low concentrations of 1,25 dihydroxylated Vitamin D, decreased tubular resorption of phosphates (2,4), normal parathormone levels and low urinary calcium. Radiographs may reveal multiple pseudo fractures, loss of trabecular structure, and non specific decrease in bone radiodensity. In case of neurofibromatosis, clinical examination and laboratory investigations clinch the diagnosis. Skeletal survey may help in localizing the lesion. Use of bone scan, octreotide scanning, extensive MR

imaging and detection of phosphate uptake inhibitory activity in serum are valuable diagnostic tools in some cases (2).

In oncogenic osteomalacia biochemical and clinical abnormalities are caused by a circulating factor phosphatonin produced by the neoplasm. Clinical removal of the tumour reverses symptoms and biochemical abnormalities. Patients with autosomal dominant hypophosphataemic rickets (ADHR) display many clinical and biological characteristics which are observed in oncogenic osteomalacia. Deficiency of melatonin is proposed as causative mechanism of osteomalacia in NF-1 (1).

The treatment of choice in oncogenic osteomalacia is tumour removal (1-5). If the tumour can be completely removed, then it leads to a dramatic improvement in the clinical course of the disease and biochemical markers and may be curative (2). The clinical resolution of symptoms and serum biochemical markers of bone turnover as osteocalcin and alkaline phosphatase activity tend to take longer to normalize. Therapy is aided by phosphate replacement and addition of vitamin D and calcium. In the event of a diffuse tumour as in our case, high doses of calcitriol and oral phosphate salts are indicated similar to that used in the treatment of X-linked hypophosphataemia (1).

In conclusion the association between hypophosphataemic osteomalacia and neurofibromatosis may be akin to the relationship between this type of

osteomalacia and mesenchymal tumours, which has been noted several times in literature.

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