



Oncogenic Osteomalacia

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Abstract

A 59 year old gentleman presented with symptoms of progressively worsening low back pain associated with difficulty in rising from a squat over a period of two years. Biochemical tests confirmed the initial clinical diagnosis of osteomalacia. Blood pool scanning revealed a focal hot spot on the site of the clinically visible swelling close to the metacarpo-phalangeal joint of the left index finger. The biopsy of the specimen obtained by excision was reported to be consistent with a phosphaturic mesenchymal tumour. The patient had complete resolution of symptoms six months following excision of the lesion. ©

INTRODUCTION

Acquired hypophosphataemic ('oncogenic') osteomalacia is a rare tumour-associated disorder, first recognized in 1947.¹ It is characterized by hypophosphataemia, phosphaturia, normocalcemia, and osteomalacia in the absence of a nutritional or drug history suggestive of vitamin D deficiency or generalized renal tubular defects. Patients typically present with bone pain and proximal muscle weakness. Tumours associated with this disorder are generally of mesenchymal origin and benign. This condition has occasionally been associated with malignant tumours. The commonest tumour described is the 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. Regardless of the origin, tumours causing oncogenic osteomalacia are often small and difficult to locate.²

CASE REPORT

A 59 year old primary school teacher presented with symptoms of progressively worsening low back pain involving the lumbar spine, sacroiliac joints and hips over a period of two years with progressive difficulty in rising from a squat and climbing stairs. At the time of presentation he could not walk without support. He was a vegetarian with an adequate intake of milk products and had adequate exposure to sunlight. There

was no history of intake of medication for seizures or tuberculosis.

On examination he had a waddling gait, was 172 cm tall and weighed 70 kg. The blood pressure was 140/90 mmHg and the pulse rate 82/min. He had extensive facial scarring of previous small pox, bony tenderness over ribs, normal joints and spine, a long standing 4x3 cm lump over his skull and a small swelling over the proximal phalanx of the left index finger which he had first noticed two years back. On systemic examination he had grade 3 power in the proximal muscles of his lower limbs and grade 4 power in the upper limb.

His investigations were as shown in Table 1. Serum FGF-23 levels were not performed.

A bone scan with technetium 99 MDP revealed multiple focal hotspots in the skull, ribs, vertebrae,

Table 1 : Details of investigations

	Values	Normal values
Fasting calcium	8.9 mg/dL	8.3 - 10.4 mg/dL
Fasting phosphate L	1.8 mg/d	3.5 - 5.0 mg/dL
Alkaline phosphatase	436 U/L	40 - 125 U/L
Serum albumin	4.3 mg/dL	
Creatinine	0.9 mg/dL	0.5 - 1.4 mg/dL
Fasting blood glucose	102 mg/dL	
Post-prandial	160 mg/dL	
Sodium	137 mg/dL	135 - 145 mg/dL
Potassium	4.4 mg/dL	3.5 - 5.0 mg/dL
Bicarbonate	25 mg/dL	22 - 29 mg/dL
Chloride	104 mg/dL	95 - 105 mg/dL
24 hour urine calcium	146 mg/24hrs	
24 hour urine phosphate	800 mg/24hr	
24 hour urine creatinine	1.3 gm /24hrs	
TMP/GFR	1.8	
25 (OH) vitamin D	52.2 ng/ml	9.0 - 57.6 ng/ml
Plasma intact PTH	46 ng/ml	8.0-74.0 ng/ml
Serum protein electrophoresis	No M band	

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Fig. 1 : Photograph of the patient's hand.

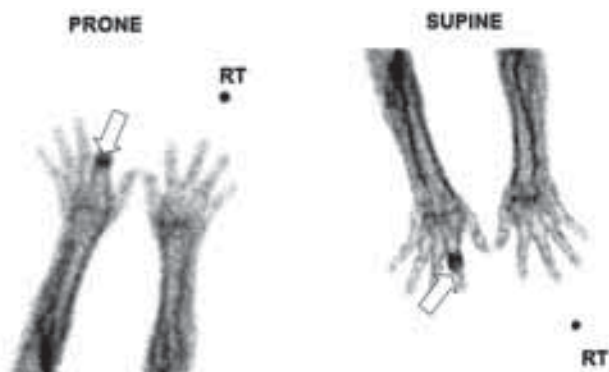


Fig. 2 : Blood pool scan of the hands showing concentration of the labeled red blood cells at the site (Arrow) of the palpable lump on the left ring finger.

humerii, clavicles, sternum and pelvic bones. Long bones of both legs showed increase in linear uptake. This was consistent with our diagnosis.

A survey for occult malignancy with abdominal imaging, stool for occult blood and chest radiography were normal. As our suspicion for a vascular tumour was high we imaged the paranasal sinuses, which was normal and undertook a blood pool scan with Technetium 99 labelled red blood cells. A focal hot spot was noted on the site of the clinically visible swelling close to the metacarpophalangeal joint of the left index finger.

Therapy with syrup neutral phosphate 500 mg thrice daily, oral elemental calcium 1 gram twice daily and alphahydroxylated vitamin D at 0.25 mg twice daily was initiated. Few days later the patient underwent excision biopsy of the lesion in his left index finger. The biopsy specimen was reported to be consistent with a phosphaturic mesenchymal tumour (Fig. 3).

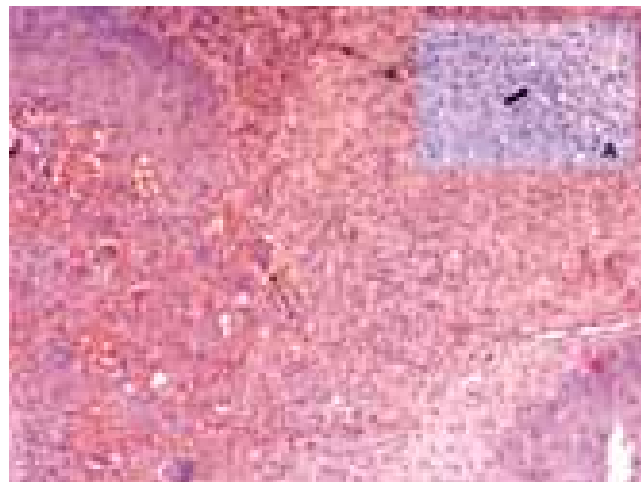


Fig. 3 : Heamatoxylin and Eosin stain of the mesenchymal tumour under 100X magnification. Arrow showing giant cells. Inset A. H & E staining at higher power showing areas of flocculant calcification. Block arrow showing area of calcification.

Six months later, he reported significant improvement in symptoms with no pain. He was able to get from the squat and had no bone tenderness. His Alkaline phosphatase was 212 U/L. His fasting serum calcium was 8.8 mg/dL and phosphate was 3.9 mmol/L (3.5 - 5.0 mmol/L). Fractional excretion of Phosphate was 0.14 with a TMP/GFR of 4.0 which implied that the phosphaturia had resolved. All treatment was stopped and he has not reported any recurrence of symptoms since.

DISCUSSION

Oncogenic osteomalacia is an unusual condition, but it probably still is the most common cause for acquired hypophosphatemic osteomalacia in adult males. The manifestations are quite similar to those of hereditary phosphate wasting disorders and the primary event is induction of severe phosphaturia by a humoral factor secreted by the tumour. The search for the possible tumour starts with a clinical examination for "lumps" especially in the region of the head and neck and the extremities.³ Evaluation of the sinuses and rectal examination of the prostate seem appropriate. Paranasal X-rays and a Skeletal survey may help in localizing the culprit lesion. Due to the vascular nature of the tumour a blood pool scan maybe helpful as was the case in our patient. Case reports of the use of octreotide scanning using In-111 labelled octreotide have been reported as a valuable diagnostic tool.⁴ Detection of phosphate uptake inhibitory activity in a blinded sample of the patient's serum using a renal cell bioassay has been suggested as the support for the diagnosis and the evidence to use an extensive MR imaging of the body to detect the lesion.

Mutations in fibroblast growth factor 23 (FGF-23) cause autosomal dominant hypophosphatemic rickets. Clinical and laboratory findings in this disorder are similar to those in oncogenic osteomalacia, in which

tumors abundantly express FGF-23 messenger RNA, and to those with X-linked hypophosphatemia, which is caused by inactivating mutations in a phosphate-regulating endopeptidase. Recombinant FGF-23 induces phosphaturia and hypophosphatemia in vivo, suggesting that it has a role in phosphate regulation. FGF-23 is readily detectable in the plasma or serum of healthy persons and can be markedly elevated in those with oncogenic osteomalacia or X-linked hypophosphatemia, suggesting that this growth factor has a role in phosphate homeostasis. FGF-23 measurements might improve the management of oncogenic osteomalacia.⁵

The treatment of choice is surgical removal of the tumour. There is a dramatic improvement in the clinical course of oncogenic osteomalacia when the offending tumour is correctly identified and completely removed. The serum phosphate level and TMP/ GFR of phosphate return to normal within hours to days after the removal of the tumor. However clinical resolution of symptoms and serum biochemical markers of bone turnover, such as the osteocalcin level and alkaline phosphatase activity, tend to take longer to normalize. Therapy may be aided by short term replacement of phosphate orally and addition of Vit D and calcium. This whole process maybe gratifying as was the case in our patient.

In the event of tumour not being found, it is recommended that vitamin D metabolites (preferably calcitriol) and oral phosphate salts be used in a manner

similar to that used in the treatment of X-linked hypophosphatemia.

A number of important questions remain. Is FGF-23 the direct mediator responsible for impaired transport of phosphate by the renal tubules? Is the bone disease simply a result of prolonged hypophosphatemia, or does FGF-23 or another tumor-derived substance have a direct effect on the skeleton?⁶

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