ONCOGENIC HYPOPHOSPHATEMIC OSTEOMALACIA ASSOCIATED WITH A GIANT CELL TUMOUR OF A TENDON SHEATH

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Abstract:
We report a case of oncogenic hypophosphatemic osteomalacia, a rare form of osteomalacia, secondary to a diffuse giant cell tumour of tendon sheath. Possible pathogenic factors are discussed in the light of previously described clinical and experimental observations. (Aust NZ J Med 1987; 17: 330-332).

Key words: Oncogenic hypophosphatemic osteomalacia, diffuse giant cell tumour.

Oncogenic hypophosphatemic osteomalacia is a rare form of osteomalacia with fewer than 50 cases reported in the literature. The syndrome is associated with mesenchymal tumours or with prostatic carcinoma. We report a case associated with diffuse giant cell tumour of a tendon sheath.

CASE REPORT

A previously well 73-year-old farmer presented with a 12 month history of diffuse musculoskeletal pain affecting his shoulders, chest wall, groin, and thighs. He had been treated with non-steroidal anti-inflammatory drugs and physiotherapy but had obtained no relief. In addition he had a soft tissue mass behind his right knee which had been present for 10 years and had not altered in size over that period. He was extremely active, was on a good diet, and was taking no medications at the time of presentation. There was no family history of bone disease or arthritis.

On examination he was tender over several ribs and both shoulders and had marked pain in the left hip on weight bearing. There was a $2 \times 3 \times 3$ cm soft tissue lesion attached to the right semitendonosis tendon. There was no obvious muscle weakness. Investigations revealed a serum calcium level of 2.08 nmol/l (normal 2.05-2.50), a serum phosphate level of 0.50 nmol/l (normal 0.8-1.6), and an alkaline phosphatase level of 120 u/l (normal <95 u/l). Hemoglobin, folate, and 24 hour fecal fat excretion were normal. His 24 hour urinary calcium excretion was 2.4 nmol/day (normal <3.75). The serum 1,25-vitamin D3 concentration was 23 nmol/l (normal 29-168) 25-vitamin D3 was 50 nmol/l (normal 22-163) and serum parathyroid hormone concentration was 0.58 ng/ml (normal <0.4 ng/ml). Renal function was normal with a serum creatinine level of 0.11 mmol/l and a creatinine clearance of 104 ml/min.

X-ray examination of the pelvis revealed a mild deformity of the left femoral neck with a healing stress fracture. The bones appeared mildly osteopenic and there was mild degenerative arthritis of the lumbar spine. A technetium bone scan demonstrated increased uptake in several areas of the ribs, shoulders, both necks of femur, and the sacrum and lower cervical vertebrae. X-ray examination of these areas showed no abnormality.

A bone biopsy showed irregular thickening of bony trabeculae with wide, non-mineralised osteoid seams, consistent with moderate osteomalacia.

In view of the clinical and laboratory findings a diagnosis of possible oncogenic osteomalacia was made, with the probable cause being a tumour of the tendon sheath. The soft tissue lesion behind the right knee was removed and consisted of firm, pale tissue with a smooth surface. Histologically, the lesion was composed of sheets of rounded and elongated cells with appearances varying from histiocytic to fibroblastic. Infrequent mitoses were noted and there was no necrosis. The cells were seen to line synovial spaces of variable sizes and numerous osteoclast-like giant cells were present. Iron pigment was plentiful and there were numerous lymphocytes. Spicules of unmineralised bone were present near the edges of the tumour and appeared to have arisen by a process of metaplasia. The appearance was thought to be that of a diffuse giant cell tumour of tendon sheath (extra-articular pigmented villonodular synovitis) (Fig. 1).

Within two days of tumour removal the serum phosphate level returned to normal (1.10 nmol/l), as did the 1,25-vitamin D3 levels (70 nmol/l), but the alkaline phosphatase and 24 hour urinary calcium and phosphate levels remained unchanged (see Table 1). Using the nomogram described by Walton and Bijvoet,[1] the renal threshold phosphate concentration increased from 0.44 mmol/l to 0.9 mmol/l when the tumour was removed. Six weeks

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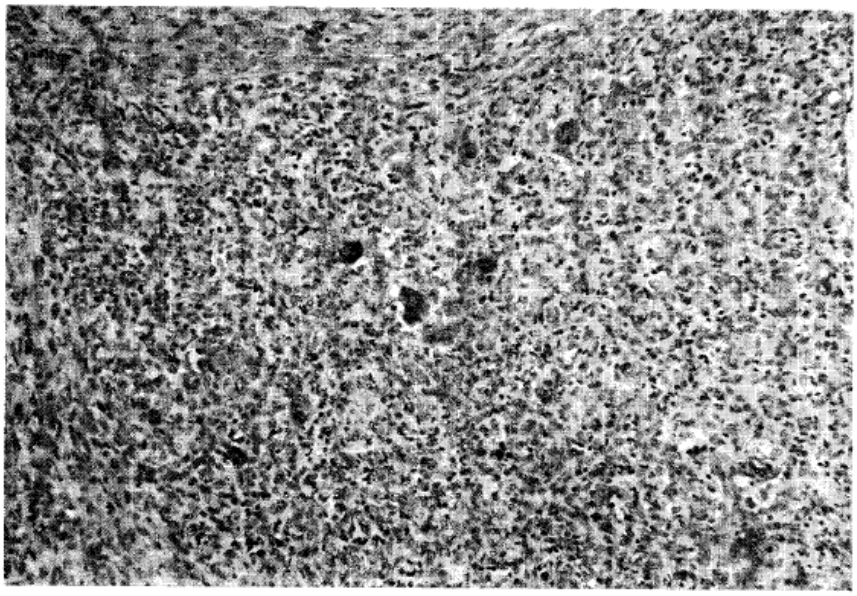

Figure 1: Microscopic appearance, showing sheets of rounded cells with histiocytic and fibroblastic features and numerous osteoclast-like giant cells.

after surgery the patient was totally asymptomatic and a repeat bone biopsy showed increased osteoblastic activity and an impressive reduction in the size of the osteoid seams. An extract of this tumour stimulated adenylate cyclase in a parathyroid hormone-responsive chick renal plasma membrane system. This stimulation was suppressed in the presence of a parathyroid hormone analogue and the data reported previously.[2]

DISCUSSION

Osteomalacia is now an uncommon form of bone disease in our community. Because of the generalised bone and joint pain, however, it is sometimes seen by rheumatologists. Osteomalacia has many causes but those associated with normocalcemia and hypophosphatemia are unusual. They include the Fanconi syndrome, X-linked hypophosphatemic rickets, adult sporadic osteomalacia, and that associated with tumours. Tumour-associated osteomalacia is rare, being recognised initially by Prader *et al.*[3] In that case, clinical and biochemical abnormalities returned to normal when the soft tissue tumour was removed. The characteristic biochemical parameters are hypophosphatemia, hyperphosphaturia, low levels of 1,25-vitamin D3, and normocalcemia usually associated with low normal levels of parathyroid hormone. The syndrome has been reported predominantly with mesenchymal tumours including hemangioma,[4,5] hemangiopericytoma,[6] fibromas, giant cell granulomas, ossifying and non-ossifying bone tumours,[7] sarcomas, and carcinoma of the prostate[8] and epidermal nevus syndrome.[9] Typically the mesenchymal tumours have prominent giant cells, spindle cells, and a high degree of vascularity and in most cases the tumour is benign.[10]

TABLE 1
Perioperative Biochemical Results

	Normal value	Pre-operative	Post-operative	
			2 days	2 months
Serum alkaline phosphatase (u/l)	20-95	120	135	215
Albumen (g/l)	40-55	40	41	40
Total serum calcium (mmol/l)	2.05-2.55	2.05	2.15	2.05
Serum phosphate (mmol/l)	0.81-1.55	0.50	1.10	1.40
24-hour urinary				
calcium (mmol/day)	<3.75	0.7	2.6	
phosphate (mmol/day)	11-31	25.2	29.2	
Serum 1,25-dihydroxyvitamin D3 (nmol/l)	29-168	23	70	
Serum 25-hydroxyvitamin D3 (nmol/l)	22-163	50	47	37
Parathyroid hormone (ng/ml)	<0.4	0.59		0.22
Nephrogenous cAMP (nmol/100 ml, GFR)	0-1.9	3.12		4.14

The pathogenesis of the syndrome is not yet clear, but several observations have been made. Saline extracts of the tumour when infused into dogs[9] and mice[11] cause phosphaturia. Prostatic tumour tissue from an affected patient transplanted into athymic nude mice caused the same biochemical abnormalities as these demonstrated in this syndrome.[12] However, Yoshikawa *et al.*[13] could not demonstrate phosphaturia when neutral buffer and methanol–chloroform extracts were injected into rats. The demonstration by Seshadri *et al.*[2] of renal adenylate cyclase stimulation by a tumour extract suggests that the tumour might be exerting its effect through a parathyroid hormone-like material. However, there has been no ultrastructural identification of secretory granules in the tumours studied.[6] In spite of this conflicting evidence, the temporal relationship between tumour removal and resolution of the biochemical abnormalities is strongly suggestive of a humoral factor. No adenylate cyclase stimulating activity was found in this patient's serum.

It has been postulated that there is defective 1-hydroxylase activity because of predominantly normal levels of 25-vitamin D3[10] and decreased levels of 1,25-vitamin D3 in the face of hypophosphatemia, which is normally a potent stimulus for the 1-hydroxylation of 25-hydroxyvitamin D3. Since 1-hydroxylation of vitamin D3 and phosphate transport both occur in the proximal tubule of the kidney it is possible that the tumour produces a humoral factor which alters the function of the proximal tubule cell, depressing 1-hydroxylase activity and causing phosphate wasting. This is consistent with the rise in renal threshold phosphate concentration observed in this patient after tumour excision. Further support for this theory is the finding of amino aciduria in eight of 25 patients tested and glycosuria in 27 patients.[10] Both of these compounds are actively resorbed in the proximal tubular cell of the kidney.

The presence of increased parathyroid hormone levels in our patient, although somewhat atypical, may represent secondary hyperparathyroidism during the healing phase of the osteomalacia. Ryan and Reiss noted that four out of 24 patients had an elevation in parathyroid hormone levels before tumour removal. However, it seems very unlikely that parathyroid hormone plays a major role in view of the low normal calcium values and the low levels of 1,25-vitamin D3.

Although these tumours of the tendon sheath are sometimes locally invasive, no recurrence has been noted two years after our patient's surgery and he remains well apart from mild osteoarthritis. Serial x-rays have showed further resolution of the osteopenia and evidence of healing of the partial femoral neck fracture.

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