Hypophosphataemic osteomalacia associated with a malignant tumour of the tibia: report of a case

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SUMMARY A case of vitamin D resistant hypophosphataemic osteomalacia with glycosuria and aminoaciduria is reported. The course of the disease was dramatically altered by the removal of a bone sarcoma which probably had been growing slowly since the onset of the patient's symptoms five years previously. The histology and electron microscopy of the tumour are described. Three years after the operation the patient remains free of symptoms.

In recent years several cases of osteomalacia with phosphaturia and hypophosphataemia have been reported in association with tumours of bone or soft tissues of uncertain histogenesis. The manner in which the tumours cause osteomalacia is uncertain, but it has been suggested that they may elaborate a humoral substance, possibly a vitamin D antagonist (Prader *et al.*, 1959).

Case report

A 44-year-old male teacher was admitted to hospital in January 1969 for surgical treatment of varicose veins. He complained of pains in the feet and difficulty on walking which persisted after the operation. In April 1970 he was readmitted with pains in the shoulders, back, left loin, and ankles. He had a waddling gait and proximal muscle weakness of the legs. An x-ray of a small lump in the right tibia was interpreted as a pseudofracture (Fig. 1), but a skeletal survey showed no other lesion or evidence of hyperparathyroidism.

Laboratory investigation disclosed hypophosphataemia: inorganic phosphorus 0.27-0.5 mmol/l (laboratory's reference range 0.7-1.4), serum calcium 2.18-2.47 mmol/l (laboratory's reference range 2.10-2.65), alkaline phosphatase 13-17 KA units with both bone and liver isoenzymes present on electrophoresis and glycosuria with a low renal threshold for glucose during an otherwise normal glucose tolerance test. Plasma proteins have been normal

Fig. 1 X-ray of lesion in right tibia, April 1970.

throughout. Urinary calcium excretion was normal (3.7-4.4 mmol/24 h) and phosphorus excretion markedly raised (31-38 mmol/24h) for the degree of hypophosphataemia. Urinary aminoacid chromatography showed excess lysine, glycine, serine, and cystine. An iliac crest biopsy showed osteomalacia without evidence of hyperparathyroidism (Fig. 2).

Nutritional factors and alimentary disease which could affect vitamin D or calcium intake were excluded by the clinical history, normal jejunal biopsy, normal faecal fat excretion and xylose absorption, normal serum proteins, and normal values in a wide range of haematological tests, including serum iron, folate, and vitamin B₁₂. The urine concentrated normally following pitressin and acidified normally following ammonium chloride. The blood urea was 5.07 mmol/l and the endogenous creatinine clearance 126 ml/min.

A diagnosis of hypophosphataemic osteomalacia due to renal tubular defect was made and the patient was discharged on 10 g of bisodium hydrogen phosphate daily. After an initial improvement bone

pain recurred and the dose of phosphate was increased by stages to a maximum of 40 g daily in May 1971. A short intense course of vitamin D was given for two weeks between June and July 1970. Vitamin D in a dose of 100 000 units daily was restarted in July 1971 and continued until shortly before the eventual removal of the tumour (Fig. 3). With this treatment urinary phosphorus excretion increased to 107 mmol/24 h and glycosuria persisted, but the patient improved and in May 1972 he felt 'the best for years'. However, in November 1972 further deterioration occurred and by July 1973 the lesion in the right tibia had become a large osteolytic tumour (Fig. 4) which on biopsy had histological features of malignancy.

A through-knee amputation was carried out in September 1973 (Mr J. Strachan) and all other treatment was discontinued. There was an immediate increase in the serum calcium and phosphate (to 2.55 mmol/l and 1.4 mmol/l respectively two weeks postoperatively) and a decrease in the serum alkaline phosphatase (Fig. 3). Plasma proteins remained in the normal range (total 75 g/l, albumin 48 g/l). The urinary calcium rose to 13.5 mmol/24 h and the phosphorus decreased to 3.1 mmol/24 h. However, the serum calcium then continued to rise, reaching 2.9 mmol/l, and the possibility of hyperparathyroidism was considered, but a skeletal survey and serum parathyroid hormone were normal. In February 1974 a hydrocortisone suppression test was carried out (40 mg 8-hourly for 10 days), the serum calcium being 2.75 mmol/l at the start, 2.80 mmol/l on the eighth day, and 2.75 mmol/l on the tenth day.

There was some uncertainty at this stage how best to proceed and an expectant policy was adopted. In subsequent months the serum calcium gradually declined to 2.50 mmol/l. However, inorganic phosphate is declining also (0.5 mmol/l by June 1976). The urinary calcium was then 4.4 mmol/24 h, the urinary phosphorus 32.0 mmol/24 h, and the serum alkaline phosphatase was normal. There was glycosuria of 4% but no aminoaciduria. The patient remains free of symptoms without any treatment.

HISTOLOGY OF THE TUMOUR

The tumour had a heterogeneous macroscopical and microscopical appearance. Most of it had the consistency of a desmoid with gritty areas, but deep within the medullary cavity there were brown soft masses and haemorrhagic cysts. Microscopically most of the tumour consisted of spindle and stellate cells separated by abundant collagen and chondroid matrix (Figs 5 and 6). In a few places there was palisading of nuclei and some osteoid. In the brown areas the tumour was very cellular; there were scattered giant cells of osteoclastic type (Fig. 7) and

Fig. 2 Undecalcified section of bone showing widened osteoid seams. Iliac crest biopsy. Toluidine blue at pH 2.8, $\times 40$.

Fig. 3 Biochemical changes and treatment from January 1970 to December 1975.

Fig. 4 X-ray of lesion in right tibia, July 1973.

Fig. 5 Area of tumour composed of scanty hyperchromatic spindle cells and abundant collagenised stroma. Haematoxylin and eosin $\times 104$.

Fig 6

Fig 7

Fig 8

Fig. 6 *Tumour composed of chondroid and fibrous matrix with few cells. H and E $\times 104$.*

Fig. 7 *Very cellular area with a few osteoclasts and island of chondroid matrix. H and E $\times 104$.*

Fig. 8 *Mitoses and nuclear pleomorphism in the cellular areas. H and E $\times 390$.*

Fig. 9 *Electron microscopical appearance of the main cell type* $\times 10\,350$.

the cellular pleomorphism and mitotic activity (Fig. 8) suggested malignancy which was otherwise confirmed by the locally aggressive behaviour and invasion of surrounding muscles. On electron microscopy the commonest cell seen was spindle or polygonal, with irregular nuclear and cytoplasmic outline (Fig. 9). The cytoplasm contained abundant rough endoplasmic reticulum, Golgi apparatus, and mitochondria. There were occasional smaller darker cells with numerous electron-dense irregular bodies in the cytoplasm. These cells were interpreted as macrophages and the bodies as ferritin bodies. No multinucleated cells were present in the material examined electron microscopically, and neurosecretory granules were not seen in multiple sections. It was concluded that the tumour was a sarcoma of unspecified type.

Discussion

The patient was at first thought to have the sporadic form of 'vitamin D resistant osteomalacia' first described by McCance (1947), and later reviewed by Dent and Stamp (1971), which is characterised by impaired tubular reabsorption of phosphate. The clinical and biochemical improvement on large doses of bisodium hydrogen phosphate initially seemed to be in accord with this view, but the recurrence of the pain and enlargement of the tibial lesion demanded fresh assessment. This lesion proved to be a sarcoma arising in bone, and its removal resulted in a rise in serum inorganic phosphate despite cessation of phosphate and vitamin D therapy.

To date at least 14 cases of vitamin D resistant osteomalacia or late onset rickets have been reported in association with tumours of bone or soft tissues (Table). In nine cases improvement or cure was observed after removal of the tumour. Eight of these cases were regarded as benign and one as possibly malignant (Massachusetts General Hospital, 1965). In a further case a probably benign tumour was not removed completely and there was no appreciable improvement after surgery (Balsan *et al.*, 1967). In three other cases the tumours were malignant and either there was no improvement after surgery or the tumours were inoperable (Hauge, 1956; Stanbury, 1972). In these three cases the patients died with disseminated metastases, and it is possible that dissemination by the time of the operation may have accounted for the failure to improve. Dent and Gertner (1976) have recently reported three further cases associated with fibrous dysplasia.

The list of histopathological diagnoses in previous cases (Table) shows a very confusing picture regard-

ing the nature of the tumours, but as critical reviews have pointed out (Massachusetts General Hospital, 1965; Evans and Azzopardi, 1972; Olefsky *et al.*, 1972; Stanbury, 1972) this may be a difference in semantics rather than a real difference in histogenesis and probably represents an attempt to classify into previously existing categories a tumour that perhaps should stand in a category of its own. In the tumour here reported there were areas which resembled giant cell tumours, fibromatoses, neurilemmomas, osteosarcomas, and chondrosarcomas. Indeed, the true malignant nature of the tumour was apparent only in small fragments of the original biopsy. This pleomorphism has been noted in previous cases. The common denominator of all these tumours is that they are mesenchymal. In some cases a cellular component with scattered osteoclasts appears to predominate, whereas in others there are variable amounts of osteoid, collagen, cartilage, and vascular elements. The name 'pleomorphic mesenchymal tumours associated with osteomalacia' appears suitable until more information becomes available. Electron microscopy confirms the mesenchymal nature of the tumour and the absence of neurosecretory granules, but there are no characteristic features in the cells which may help to elucidate their histogenesis. The recent report of the same type of osteomalacia in a patient with disseminated bone metastases from a prostatic carcinoma (Hosking *et al.*, 1975) introduces new difficulties in the interpretation of the association of hypophosphataemic osteomalacia and neoplasia, but the association in this case could be coincidental.

It is noticeable that in our case the postoperative improvement in inorganic phosphate levels was accompanied by hypercalcaemia.

The cause of this is obscure. Postoperative immobilisation was very brief and thus unlikely to have contributed. Hypervitaminosis D on stopping phosphate therapy is a possibility, but unfortunately it did not prove possible at that time to estimate the plasma 25 OH cholecalciferol. However, the calcium level was not reduced by hydrocortisone which suggests hyperparathyroidism rather than hypervitaminosis D. There was no radiological evidence of hyperparathyroidism; the serum phosphate was normal as was the serum parathyroid hormone. The serum calcium has returned to normal spontaneously, but the phosphate is now falling and it is not possible to say at this stage whether the remarkable improvement related to the operation will be permanent or whether the fall in serum phosphate heralds a recurrence of the disease. Similar hypercalcaemia has been reported after surgical excision of the tumour in Olefsky's and Pollack's cases (Olefsky *et al.*, 1972; Pollack *et al.*, 1973). In Olefsky's case

Table Reported cases of hypophosphataemic osteomalacia associated with mesenchymal tumours of bone or soft tissues

Author (Year)	Location of tumour	Histological diagnosis
Hauge (1956)	Axilla	Malignant neurilemmoma
Prader <i>et al.</i> (1959)	Rib	Reparative giant cell granuloma
Dent and Friedman (1964)	Thigh	Degenerate osteoid tissue
Yoshikawa <i>et al.</i> (1964)	Thigh	Cavernous haemangioma
Massachusetts General Hospital (1965)	Femur	Giant cell tumour (probably malignant)
Balsan <i>et al.</i> (1967)	Calvarium	Dense fibrous bony tissue
Salassa <i>et al.</i> (1970)		
Case 1	Groin	Benign sclerosing haemangioma
Case 2	Thigh	Benign sclerosing haemangioma
Evans and Azzopardi (1972)	Femur	Probably haemangiopericytoma
Stanbury (1972)		
Case 1	Fibula	Malignant mesenchymoma
Case 2	Lower leg	Malignant mesenchymoma
Olefsky <i>et al.</i> (1972)	Pharynx	Ossifying mesenchymal tumour
Pollack <i>et al.</i> (1973)	Radius	Non-ossifying fibroma
Present case	Tibia	Malignant pleomorphic mesenchymal tumour

this appeared to be due to 'tertiary' hyperparathyroidism and persisted after removal of a parathyroid 'adenoma', but hypophosphataemia did not recur after five years without treatment. In Pollack's case the follow-up was 18 months and hypercalcaemia was present for only five months after removal of the tumour. It is possible that development of tertiary hyperparathyroidism in these cases, if this is the correct interpretation, may be related to duration of the hypophosphataemia. This was 10 years in Olefsky's case, six years in our case, and three years in Pollack's case.

Rees (1975) has listed six criteria which may be used to establish ectopic hormone secretion, but only two of these, viz, an endocrine abnormality associated with the presence of the tumour and its correction upon removal of the tumour, have been demonstrated in some cases of osteomalacia. In others only the first criterion has applied. The problem is made more difficult because hypophosphataemic osteomalacia is not a sign of oversecretion of any known hormone. The syndrome is therefore not simply a consequence of ectopic hormone production, although its most likely explanation is that the tumour secretes some humoral factor which interferes with renal tubular function.

Hypophosphataemic osteomalacia is a rare disease, and fewer than 30 cases had been reported up to 1971 (Dent and Stamp, 1971). The association of some cases of this type of osteomalacia with tumours, sometimes clinically undetected for many years, makes imperative the careful search for a tumour in every case, since its removal may result in a cure.

We should like to thank Professor H. A. Sissons for help in the interpretation of the histology of this tumour, Professor P. Bordier for his opinion on the bone biopsy, Professor T. C. B. Stamp for the assay

of parathyroid hormone, and Mr J. Strachan, FRCS, for the surgical care of this patient.

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