BENIGN OSTEOBLASTOMA AS A CAUSE OF OSTEOMALACIA

A REPORT OF TWO CASES

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Two patients, a Japanese man and woman both aged eighteen, developed symptoms and signs of osteomalacia over a period of five years. Each of them had a benign osteoblastoma, one in the right fourth metacarpal and the other in the uppermost third of the right humerus. Resection of the tumours without any treatment by vitamin D resulted in rapid cure of the osteomalacia. Attempts to prove a phosphaturic humoral substance or vitamin D antagonist in the osteoblastoma of the humerus were unsuccessful, probably due to prompt excretion from the tumour cells.

There have been several reports of osteomalacia or late rickets associated with a tumour of bone or soft tissue, the removal of which resulted in either cure of the osteomalacia or improvement in its clinical course. In

CASE REPORTS

Case 1—A Japanese worker aged eighteen was admitted to our Tokyo University Branch Hospital in December 1974 with a five-year history of difficulty in walking and a swelling over

![Figure 1](image1.png)

FIG. 1

Case 1. Radiographs of the right hand. Figure 1—Showing the tumour of the fourth metacarpal. The metaphyses of the radius and the ulna show characteristic changes of late rickets. Figure 2—The appearances fifteen weeks after resection of the tumour. The transplanted third metatarsal is in good position and the new metacarpophalangeal joint is well formed. The metaphysical changes have completely healed without vitamin D treatment.

The present report two cases of osteomalacia associated with benign osteoblastoma are described. Resection of the tumours without treatment by vitamin D has established a causal relationship.

the dorsal aspect of the right hand. He had first noticed the swelling at the age of thirteen and at the same time began to feel weakness and instability of the knees when he took outdoor exercise. Over the next year the weakness progressed to such a degree that he was unable to run or to rise from the

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ground without the assistance of his hands. The symptoms gradually increased. Eighteen months before admission he developed pain in the lumbar region and knees. Abnormal radiographic appearances were found in another hospital and he was then referred to us.

On admission he was a rather thin young man, 168 centimetres in height and 47 kilograms in weight. There was a bone-hard tumour over the dorsal aspect of the right fourth metacarpal. He had a waddling gait and was unable to stand on one leg at a time, or to rise from the squatting position without using his arms.

There were no gross deformities elsewhere in the limbs or in the spine, though a rickety rosary and slight swelling of the metaphyssial regions of the long bones could be felt. The muscles such as those of the abdominal wall, the deltoid, triceps, iliopsoas and glutei were rated as only fair, while the distal muscles, such as the quadriceps, the dorsiflexors and plantar flexors of the feet, and extensors and flexors of the wrist, were rated as good. The power of grip of the right hand was 14 kilograms. The tendon reflexes were normal.

In radiographs of the hands, despite his age of eighteen
years, the epiphysial lines were widely open, showing typical changes of late rickets. The fourth right metacarpal, except for a small basal segment, had been replaced by an osteolytic bone lesion with central calcification and a ballooned and partly destroyed cortex (Fig. 1). A skeletal survey revealed a general decrease of bone density and Looser’s zones in all four pubic rami (Fig 3). There was slight ballooning of the lower lumbar discs (Fig. 5).

Laboratory findings—The serum calcium was 9.5 and 9.8 mg/100 ml; inorganic phosphorus, 1.5 and 1.4 mg/100 ml; alkaline phosphatase, 58 and 63 King-Armstrong units; serum immunoreactive parathyroid hormone (PTH), 0.7 ng/ml (normal values, 0.3–0.8); and serum 25 hydroxy D₃ was 28.5 ng/ml as measured by competitive protein-binding assay by one of us (K.O.) (Okano, Nakai, Goto and Yoshikawa 1976).
There was no albuminuria, glucosuria or aminoaciduria. The urinary excretion of calcium was 15 to 16 mg/day. The urinary excretion of phosphorus was 225 to 828 mg/day. The tubular reabsorption of phosphorus (TRP) was 58 to 83 per cent. The tubular maximum reabsorption of phosphorus (Tmp), calculated by the method of Bijvoet, was 0.66, 0.82 and 1.09 mg/min./100 ml GF. The results of creatinine clearance, Fischberg’s concentration test and the phenolsulphonephthalein excretion test were all within normal limits.

Undecalified sections from the right tenth rib revealed the presence of an excessive amount of osteoid and no tetracycline uptake (Fig. 6).

A diagnosis of Type 1 osteomalacia in Dent’s classification was made, and from the simultaneous development of the clinical signs of the osteomalacia and the bone tumour, a causal relationship was strongly suspected.

Treatment—Vitamin D treatment was deliberately withheld. On February 10, 1974 the tumour was resected and replaced by the third metatarsal and its distal articular cartilage (Fig. 2).

The improvement after operation was quite remarkable. The very next day he began to feel an increase in muscle power, and by the third day the power of grip was 27 kilograms compared with 14 kilograms before the resection. Fourteen weeks later, having completely recovered from all his previous complaints, he returned to his former work. By this time the function of the new metacarpo-phalangeal joint was excellent.

**Fig. 9**

Case 1. A histological section of the tumour, showing osteoblastic fibrous tissue in which abundant osteoid is deposited irregularly. Multinucleated giant cells are scattered between the osteoid. These features were thought to correspond with benign osteoblastoma. (Haematoxylin and eosin, × 40.)

Further investigations—The biochemical changes after operation are shown in Figure 8. The increase in serum phosphorus and the decrease in urinary phosphorus excretion were remarkable. TRP values all achieved above 90 per cent. By four weeks Tmp values were 5.33 and 4.81 mg/min./100 ml GF, serum PTH was 0.8 ng/ml, and serum 25 hydroxy D, was 12.1 ng/ml.

Biopsy specimens taken at eleven weeks showed a healing process of the osteomalacia. There was well calcified bone on the surface of osteons, still leaving uncalcified osteoid in the deeper zones. Most of these osteons took up tetracycline fluorescence, some of them showing double lines of fluorescence (Fig. 7). By fourteen weeks the radiographs showed nearly complete remineralisation and disappearance of the metaphyseal changes.

The histological diagnosis of the tumour was benign osteoblastoma (Fig. 9).

Case 2—A Japanese office girl aged eighteen was admitted in June 1975, confined to a wheel-chair. At the age of thirteen she had felt some pain in the right shoulder when she threw a ball, and this had persisted. A year later a friend noticed unsteadiness of her gait though she herself had no trouble with walking. After several months, however, she began to have difficulty in running and occasional pain in the thigh and lumbar region. By the age of seventeen the low back pain had increased and walking had become difficult. She was admitted to a local hospital where some 10 centimetres loss of height was noted but the cause of the trouble was not found. The difficulty in walking and muscle weakness progressed with a somewhat intermittent course, and early in 1975 she became unable to go out of doors.

On admission she was an obese young girl, unable to walk even with crutches. Her height was 152 centimetres and body weight 60 kilograms. There was a marked thoracic kyphosis but no deformity of the limbs apart from a bony swelling which could be felt over the antero-lateral aspect of the right upper humerus.

The spinous processes of the T.7 to 10 were tender, as were the pubic rami and the shoulders. There was marked weakness of the proximal muscles, especially in the lumbar region. On manual testing, the abdominal muscles, the
iliopsoas and glutei were rated as poor; the deltoid, biceps, quadriceps and hamstring muscles were good; and the extrinsic and intrinsic muscles of the hands and feet were normal. Thus she could stand tip-toe for a few seconds but not on one leg alone. The power of grip was 30 kilograms. The tendon reflexes were brisk.

**Laboratory findings**—The serum calcium was 9.0 mg/100 ml; inorganic phosphorus, 1.2 mg/100 ml; alkaline phosphatase, 31 King-Armstrong units; PTH, 0.5 ng/ml; and 25 hydroxy D, was 23 ng/ml. There was no albuminuria, glucosuria, or aminoaciduria. The urinary calcium excretion was 80 to 200 mg/day. The urinary phosphorus excretion was 200 to 800 mg/day. TRP was 78, 87 and 94 per cent. Tmp values were 1.5 and 1.8 mg/min./100 ml GF. Biopsy specimens from rib and ilium showed excessive osteoid and no calcification front (Fig. 14).

**Treatment**—Vitamin D was again withheld. Curettage of the tumour and bone grafting were performed in July 1975.

Radiographs showed a large osteolytic lesion situated eccentrically in the upper third of the shaft of the humerus, with an expanded and extremely thin cortex (Fig. 10). A skeletal survey revealed a general decrease in bone density and Looser's zones in the pubic rami (Fig. 12). The bodies of the lumbar vertebrae were slightly biconcave.
The clinical course was even more remarkable than in Case 1. The muscle weakness began to recover on the next day. She could walk with crutches in two weeks and without crutches by four weeks.

![Graph](image)

**Fig. 16**

Case 2. Graphs showing the biochemical response to resection of the tumour. The increase in serum phosphorus was much more marked than in Case 1 (see Fig. 8). A decrease in both serum alkaline phosphatase and urinary phosphorus excretion occurred.

![Image](image)

**Fig. 17**

Case 2. A histological section of the tumour, showing features of benign osteoblastoma as in Case 1 (see Fig. 9). There are focal nests of histiocytic foam cells. (Haematoxylin and eosin, × 100.)

Further investigations—There was a prompt increase in serum phosphorus to above the normal range within a few days. Decreases in urinary phosphorus excretion and serum alkaline phosphatase were also noted, and essentially unchanged Looser’s zones in the pubic rami were already completely recalcified (Fig. 13) and the recovery of bone atrophy was associated with the healing of the lesion in the humerus (Fig. 11). A biopsy specimen of rib taken at ten weeks showed a
normal process of bone formation with a calcification front (Fig. 15).

The histological diagnosis of the tumour was again benign osteoblastoma (Fig. 17).

**DISCUSSION**

The syndrome of tumour-induced osteomalacia was first recognised in 1959 by Prader and his associates. Linovitz and associates (1976) have reviewed thirteen cases and Morita (1976) added one further case. Because this syndrome was not recognised at the beginning of their treatment, many of these patients had large doses of vitamin D before or after operation, and this, together with other factors such as incomplete removal of the tumour or inadequate follow-up has put the proof for this syndrome somewhat into dispute.

As regards our previously reported case concerning a cavernous haemangioma in the popliteal space (Yoshikawa et al. 1964), vitamin D in a dosage of 100,000 units a day was given for three years and then discontinued owing to the development of hypercalcaemia; no recurrence has been observed as yet. The favourable course of this case might be atypical, as was suggested by Dent (1967). We are still not quite certain whether this was a case of tumour-induced osteomalacia, because we know that complete cure of adult-onset vitamin-D-resistant osteomalacia can be induced by the use of vitamin D in high dosage for a limited time, at least according to our experience (Yoshikawa 1970). In that case, a woman of twenty-six, 300,000 units of vitamin D per day were given for five months and then 100,000 units per day for two years; six years later the patient has no symptoms or signs of osteomalacia. Dent and Friedman (1964) had a similar experience.

In the present two cases, however, the immediate post-operative increase in serum inorganic phosphorus, the prompt recovery of muscle weakness, the reappearance of a calcification front and remineralisation, all occurred without vitamin D treatment over a short period of time. This, we believe, has clearly established a causal relationship between the tumour and the osteomalacia.

As for the nature of each tumour, the clinical aspects—age, localisation, benign clinical course, radiological appearance and favourable response to treatment—all correspond with the features of benign osteoblastoma.

The histological findings—fibrous vascular tissue containing abundant osteoid surrounded by osteoblast-like cells, with a few giant cells of osteoclastic type between the osteoid—also correspond to benign osteoblastoma. In Case 2 focal nests of histiocytic foam cells were thought to be of a reactive nature and of no diagnostic significance. Secretory granules and mitotic figures were not observed in either case.

The term "benign osteoblastoma" was used for the first time by Jaffe and by Lichtenstein in 1956, and according to a recent review by Marsh and his associates (1975), about 200 cases have been reported. Only twenty-one occur in the 20,000 cases registered by the Bone Tumour Committee of the Japanese Orthopaedic Association (Aoiike 1973), which indicates its infrequent occurrence.

The histological diagnosis of the tumour in this syndrome has been variously reported as giant-cell granuloma (Prader et al. 1959), cavernous haemangioma (Yoshikawa et al. 1964), malignant giant-cell tumour (Castleman and McNeeley 1965), sclerosing haemangioma (Salassa et al. 1970), an unusual type of primary bone tumour of vascular origin (Evans and Azzopardi 1972), ossifying mesenchymal tumour (Olefsky et al. 1972; Wilhoite 1975), haemangioepicytoma and angiosarcoma (Linovitz et al. 1975) and fibrous xanthoma (Morita 1976). Many of these tumours have had the nature of undifferentiated mesenchyme, making diagnosis difficult.

Hitherto no benign osteoblastoma has been reported as the tumour causing this syndrome. However, the tumour of the femur variously described by McCance (1947) as "degenerative osteoid tissue" and "ossifying mesenchymal tumour" may well have been a benign osteoblastoma, judging from the figures and text of his article.

Olefsky and his colleagues (1972) and Evans and Azzopardi (1972) have stressed the basic similarity of these tumours. However, on reviewing the histological findings of all the reported cases, we could not determine specific features that would permit a unified diagnosis. This, however, does not prevent us from realising the same functional activity of these tumours, because we know of the same hypercalcaemic action by various types of cancer cell.

The pathogenesis of the osteomalacia in this syndrome is a matter of the greatest interest. The secretion of a humoral phosphaturic substance or vitamin D antagonist has been repeatedly suggested by several authors. In our two cases the remarkable biochemical effect of the removal of the tumour on the serum phosphorus values, urinary phosphorus excretions, TRP and Tmp values, without apparent influence on the serum and urinary calcium values, strongly indicate the presence of a hyperphosphaturic substance, or more correctly a substance which affects the membrane transport of phosphate ions, as was also presumed in familial hypophosphataemic vitamin D resistant rickets.

Although we tried to find morphological evidence of a secretory function of our tumours by electron microscopy, neither endocrine granules nor other specific features were detected, which agrees with previous authors (Evans and Azzopardi 1972; Linovitz et al. 1976). Moreover we attempted to extract an active humoral substance from the tumour in Case 2.

Sixteen grams of the tissue preserved in a frozen state were used. A neutral buffer extract and a methanol-
chloroform extract were injected into rats for two weeks. Under our experimental conditions, however, these animals showed no significant differences from controls, either in serum calcium and phosphorus values or in urinary calcium and phosphorus excretion. The activity of 25 hydroxy D3-1,25-dihydroxylase of kidney mitochondria from vitamin D-deficient rats was also not inhibited by the neutral buffer extract of the tumour tissue. These experiments were performed by one of us (S. S.) and will be reported elsewhere.

In conclusion, we have not succeeded in discovering a phosphaturic or other active substance in the tumour tissue. It would appear that the tumour excretes the active substance immediately after its intracellular production, thus not allowing it to remain in detectable amount. In view of these negative results, studies on future cases should use other experimental methods such as tissue culture or transplantation.

The serum PTH values in our two cases hardly changed after the operations. In Case 2 of Salassa et al., however, the values increased from undetectable to normal.

Serum hydroxy D3 has not been measured previously in this syndrome. In the present cases a definite trend after operation was not found; in the first case it decreased, and in the second it increased. The significance of these findings is not clear but they might indicate that the active substance has an action independent of PTH or vitamin D metabolism. Further studies of the syndrome will be looked forward to with great interest.

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REFERENCES


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