Case of tumour rickets

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SUMMARY A 10-year-old boy, with widespread soft tissue tumours of bone, developed hypophosphataemic rickets due to impaired renal tubular reabsorption of phosphate. Biopsy of the largest tumour showed a nonosteogenic fibroma. We believe this boy is another example of 'tumour rickets', as other causes of rickets were excluded clinically and biochemically. Cases of rickets or osteomalacia associated with a tumour, have generally been reported to be cured by surgical removal of the tumour, implicating it as the cause of rickets or osteomalacia. Owing to the large number of tumours in this boy, surgical removal was not possible, and he required large doses of vitamin D together with oral phosphate, before his rickets healed. It is suggested that the tumour produces a phosphaturic hormone.

Although most cases of rickets are caused by dietary deficiency of vitamin D, an increasing number of non-nutritional causes have been described. Dent (1976) listed 33 in a review. One of the least common is 'tumour rickets', where hypophosphataemic rickets occurs in association with a solitary bone or soft tissue tumour. Of 16 cases described (Table 1), only 3 were in children. In most instances, rickets healed after removal of the tumour. Hypophosphataemic rickets has also been reported in association with widespread fibrous dysplasia of bone (Dent and

Gertner, 1976), and in these cases surgical removal of the bone lesions is not normally possible. We describe the medical management of a boy with hypophosphataemic rickets and multiple soft tissue tumours in bone, not amenable to surgery.

Case report

At age 7½ years this boy complained of pain in his left leg, and x-rays showed widespread osteolytic lesions mainly of the phalanges, ribs, pelvis, and long limb bones, but not of the skull. There were

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Fig. 1 Age 8½ years x-ray of knees showing large osteolytic lesions in the lower end of both femora.

Table 1 Previously reported cases of osteomalacia and rickets associated with a solitary tumour

Author	Date	Age	Sex	Nature of tumour	Medical treatment	Tumour excised	Result
McCance	1947	15	F	'Degenerating osteoid tissue' of femur	Vitamin D 500 000 units	+	Healed and vitamin D stopped
Hauge	1956	38	F	Malignant neurinoma	Vitamin D varying doses	—	Died. Disseminated malignant disease
Prader <i>et al.</i>	1959	11	F	Giant cell granuloma of rib	None	+	Healed
Yoshikawa <i>et al.</i>	1964	54	F	Cavernous haemangioma in thigh	Vitamin D 2-300 000 units	+	Healed
Castleman	1965	53	M	Giant cell sarcoma of femur	Vitamin D 50-150 000 units, 4.8 g phosphate	+	Healed. Medical treatment discontinued
Salassa <i>et al.</i>	1970	38	M	Sclerosing haemangioma of femur	Vitamin D 750 000 units, 1.7-2.7 g phosphorus	+	Healed. Medical treatment discontinued
Salassa <i>et al.</i>	1970	30	M	Sclerosing haemangioma of femur	None	+	Healed
Stanbury	1972	Adult	—	'Mesenchymoma'	Not recorded	+	Died. Disseminated malignant disease
Stanbury	1972	Adult	—	'Mesenchymoma'	Not recorded	+	Died. Disseminated malignant disease
Olefsky <i>et al.</i>	1972	40	M	Ossifying mesenchymal tumour of pharynx	Vitamin D 500 000 units, 1.9 g phosphorus	+	Healed. Medical treatment discontinued
Evans and Azzopardi	1972	45	M	Primary bone tumour possibly of vascular origin in femur	Vitamin D 200 000 units, 2.25 g phosphate	+	Incomplete healing (tumour not completely removed)
Pollack <i>et al.</i>	1973	9	M	Nonossifying fibroma radius	Vitamin D 200 000 units	+	Healed. Medical treatment discontinued
Moser and Fessel	1974	54	M	Mesenchymal tumour of big toe	Vitamin D 50 000 units, phosphate	+	Healed. Medical treatment discontinued
Wilhoite	1975	7	F	Benign ossifying mesenchymal tumour of ulnar	Vitamin D 800 units	+	Healed
Linovitz <i>et al.</i>	1976	32	M	Haemangiopericytoma of ankle	Vitamin D 50 000 units, phosphorus	+	Healed. Medical treatment discontinued (patient died 6 months later from burns)
Linovitz <i>et al.</i>	1976	51	M	Sclerosing haemangioma of knee	None	+	Healed. Recurred 1 year later as did the bone tumour. Repeat biopsy = angiosarcoma

particularly large lesions at the lower ends of both femora (Fig. 1). A diagnosis of Hand-Schueller-Christian disease was made, and he was treated with prednisone. During the next few weeks his symptoms improved, and the ESR, initially 20 mm/h, fell to 2 mm/h.

He remained symptom-free, but repeat x-rays one and 2 years later showed no change in the bony lesions, so a biopsy of the largest lesion in the right femur was performed. The tissue was composed of spindle and fusiform cells, arranged in irregular groups and interlining strands with abundant collagen formation together with numerous foci of foamy histiocytes; some multinuclear giant cells were present. The appearances were consistent with a nonosteogenic (nonossifying) fibroma (Fig. 2). Further investigation (Table 2) showed that he had hypophosphataemic rickets owing to failure of phosphate reabsorption in the kidneys, and review of the x-rays showed changes of rickets at the epiphyses. By this time he had developed genu valgum with 7 cm intermalleolar separation, and height had fallen below the 3rd centile.

Table 2 Biochemical investigations in a case of 'tumour rickets'

	December 1974 (age 10 years)		October 1975 (age 11 years)	
	(mg/100 ml)	(mmol/l)	(mg/100 ml)	(mmol/l)
Plasma calcium	10.1	2.5	9.8	2.4
phosphate	1.6	0.5	4.4	1.4
alkaline phosphatase	566 IU/l*		22 KA/100 ml†	
urea	21	3.4	15	2.5
creatinine	0.8	71 µmol/l	0.6	53 µmol/l
bicarbonate		24		26
Creatinine clearance (ml/min per 1.73 m ²)	108		—	
Plasma 25-OHD ₃ (ng/ml)	23.5		512	
Serum parathyroid hormone (pg/ml)	700 (normal <750)		—	
Phosphate reabsorption	72% filtered load		—	
Urine amino-acid chromatography	Normal		Normal	

*Normal range for a child this age - up to 200.

†Normal range age 11-12 years 12-29 KA units/100 ml.

He was treated with calciferol, starting with 1 mg daily, increasing to 4 mg daily, but his rickets did not heal, and so oral phosphate supplements were given. The serum level of phosphate rose to normal, the alkaline phosphatase fell from 556 IU/l before treatment was started to between 200 and 250 IU/l,

Fig. 2 Biopsy from tumour in femur. Nonosteogenic fibroma showing spindle and fusiform cells in irregular groups with abundant collagen formation. A multinuclear giant cell is seen near the top. (H and E $\times 330$).

and the rickets healed radiologically one year after treatment was started. At this stage, when 11 years he was admitted to University College Hospital under the care of the late Professor C. E. Dent. He was 126 cm tall (<3 rd centile) with 10 cm separation of the malleoli. His rickets had healed and the biochemical results are shown in Table 2. Surgical removal of the largest tumours from the femora was considered, but Mr E. O. G. Kirwan thought there was too great a risk of weakening these bones still further. Medical treatment was stopped, but his rickets recurred radiologically after one year and the level of alkaline phosphatase rose to 368 IU/l, so treatment with phosphate (1.5 g elemental phosphorus daily) and vitamin D (1.5 mg daily) was restarted. Details of his treatment are shown in Fig. 3, and serial x-rays in Fig. 4.

Discussion

This boy developed hypophosphataemic rickets at the age of 10 years, in association with numerous bony tumours, and needed large doses of vitamin D to induce healing. The normal plasma levels of Ca²⁺ and of 25-hydroxy-cholecalciferol, excluded dietary and intestinal causes of rickets. The normal plasma creatinine and bicarbonate concentrations and absence of aminoaciduria excluded renal causes of rickets, except for familial hypophosphataemic rickets. This is usually manifest in the 2nd year of life with florid rickets (Fraser and Salter, 1958) whereas our patient did not develop rickets until 10 years old and had no family history. Vitamin D dependent rickets (pseudodeficiency rickets) usually presents in the 2nd year of life with marked muscle weakness, low level of plasma Ca, normal or low level of plasma phosphate and aminoaciduria (Fanconi and Prader, 1969). We believe that our patient is another example of 'tumour rickets'.

Fig. 3 Biochemical changes and details of treatment in a child with 'tumour rickets'.

Fig. 4 Serial radiographs of the ankle showing (a) age 7½ years, mild changes of rickets diagnosed retrospectively; (b) age 10 years, florid rickets before treatment; (c) age 11 years, healed rickets after treatment.

The patients shown in Table 1, all of whom had a solitary bone or soft tissue tumour, were treated surgically, and their rickets were either cured or markedly improved, except for Case 3 who died of malignant disease. Surgical removal was not possible in our case owing to the large number of bone tumours; from the therapeutic point of view he resembled the cases of fibrous dysplasia described by Dent and Gertner (1976).

Medical treatment in these cases is difficult, and all forms of hypophosphataemic rickets seem relatively resistant to vitamin D. In children with familial hypophosphataemic rickets very large doses of vitamin D cause the rickets to heal (Albright *et al.*, 1937), but may cause hypercalcaemia and nephrocalcinosis (Moncrieff and Chance, 1969). Oral phosphate supplements alone were found ineffective in the case reported by Salassa *et al.* (1970). Combining oral phosphate and vitamin D in relatively small doses has been found effective in familial hypophosphataemic rickets (Glorieux *et al.*, 1972), and was the treatment used before surgery in most cases of tumour rickets.

Rickets usually precedes the appearance of the tumour, sometimes by many years (Olefsky *et al.*, 1972), and it can be seen in Table 1 that the nature of the tumour has varied considerably. Our case resembles that described by Pollack *et al.* (1973) in having a nonosteogenic fibroma, but it differs in the widespread nature of the disease.

The rickets is presumably due to hypophosphataemia resulting from failure of phosphate reabsorption in the renal tubules. This is an isolated tubular defect for there is no glycosuria, aminoaciduria, or acidosis.

After removal of the tumour, tubular reabsorption of phosphate reverts to normal, the serum phosphate level rises, and the rickets heals. All medical treatment can be stopped. This implicates the tumour as the cause of the hyperphosphaturia. It seems unlikely that this effect is mediated by parathormone for this has been normal when measured, as in our case. A possible explanation of the hypophosphataemia was offered by Pollack *et al.* (1973) and Harrison (1973), who suggested that the tumours produce a hormone which acts directly on the renal tubules inhibiting phosphate reabsorption. Such a tumour may be small and clinically unobtrusive although metabolically very active. This is illustrated by one of the patients with osteomalacia reported by Stanbury (1972) in whom a small destructive lesion in a fibula was found retrospectively in an x-ray taken 8 years before a sarcoma became clinically apparent. Thus when acquired hypophosphataemic rickets or osteomalacia is diagnosed, a very careful search for a bony or soft tissue tumour should be

made. It may be that further research will lead to the extraction of a phosphaturic agent in these tumours.

Addendum April 1978. Subsequently the rickets healed radiologically and biochemically with daily doses of phosphorus 3 g and calciferol 1.5 mg.

We thank Professor Price (Bristol) who suggested the diagnosis on the basis of the bone sections and Dr J. Cocker for reporting the biopsy. The late Professor C. Dent* also made the diagnosis on the basis of the radiographs and supervised the early treatment; we had hoped to write this paper with him.

*Charles Dent, who died on 19 September 1976, became a member of the editorial committee of the *Archives* in 1963 and from then onwards the editors were fortunate in being able to make frequent use of his unique knowledge of the metabolic disorders of bone, besides publishing many of his papers.

References

- Albright, F., Butler, A. M., and Bloomberg, E. (1937). Rickets resistant to vitamin D therapy. *American Journal of Diseases of Children*, **54**, 529-547.
- Castleman, B. (1965). Case records of the Massachusetts general hospital. Case 38-1965. *New England Journal of Medicine*, **273**, 494-504.
- Dent, C. E. (1976). Metabolic forms of rickets and osteomalacia. In *Inborn Errors of Calcium and Bone Metabolism*, pp. 124-149. Edited by H. Bickels and J. Stern. MTP Press: Lancaster.
- Dent, C. E., and Gertner, J. M. (1976). Hypophosphataemic osteomalacia in fibrous dysplasia. *Quarterly Journal of Medicine*, **45**, 411-420.
- Evans, D. J., and Azzopardi, J. G. (1972). Distinctive tumours of bone and soft tissue causing acquired vitamin D resistant osteomalacia. *Lancet*, **1**, 353-354.
- Fanconi, A., and Prader, A. (1969). Die hereditäre Pseudomangelrachitis. *Helvetica paediatrica acta*, **24**, 423-447.
- Fraser, D., and Salter, R. B. (1958). The diagnosis and management of the various types of rickets. *Pediatric Clinics of North America*, **5**, 417-441.
- Glorieux, F. H., Scriver, C. R., Reade, T. M., Goldman, H., and Roseborough, A. (1972). Use of phosphate and vitamin D to prevent dwarfism and rickets in X-linked hypophosphatemia. *New England Journal of Medicine*, **287**, 481-487.
- Harrison, H. E. (1973). Oncogenous rickets: possible elaboration by a tumour of a humoral substance inhibiting tubular reabsorption of phosphate. *Pediatrics*, **52**, 432-433.
- Hauge, B. N. (1956). Vitamin D resistant osteomalacia. *Acta medica Scandinavica*, **153**, 271-282.
- Linovitz, R. J., Resnick, D., Keissling, P., Kondon, J. J., Sekler, B., Nejdil, R. J., Rowe, J. H., and Deftos, L. J. (1976). Tumour induced osteomalacia and rickets: surgically curable syndrome. *Journal of Bone and Joint Surgery*, **58A**, 419-423.
- McCance, R. A. (1947). Osteomalacia with Looser's nodes (milkman's syndrome) due to a raised resistance to vitamin D acquired about the age of 15 years. *Quarterly Journal of Medicine*, **16**, 33-46.
- Moncrieff, M. W., and Chance, G. W. (1969). Nephrotoxic effect of vitamin D therapy in vitamin D refractory rickets. *Archives of Disease in Childhood*, **44**, 571-579.

- Moser, C. R., and Fessel, W. J. (1974). Rheumatic manifestations of hypophosphatemia. *Archives of Internal Medicine*, **134**, 674-678.
- Olefsky, J., Kempson, R., Jones, H., and Reaven, G. (1972). Tertiary hyperparathyroidism and apparent cure of vitamin D resistant rickets after removal of an ossifying mesenchymal tumour of the pharynx. *New England Journal of Medicine*, **286**, 740-745.
- Pollack, J. A., Schiller, A. L., and Crawford, J. D. (1973). Rickets and myopathy cured by removal of a non-ossifying fibroma of bone. *Pediatrics*, **52**, 364-371.
- Prader, A., Illig, R., Uehlinger, R. E., and Stadler, G. (1959). Rachitis infolge Knockentumors. *Helvetica paediatrica acta*, **14**, 554-565.
- Salassa, R. M., Towsey, J., and Arnaud, C. D. (1970). Hypophosphatemic osteomalacia associated with 'non-endocrine' tumors. *New England Journal of Medicine*, **283**, 65-70.
- Stanbury, S. W. (1972). Osteomalacia. *Clinical Endocrinology and Metabolism*, **1**, 239-266.
- Wilhoite, D. R. (1975). Acquired rickets and solitary bone tumor: the question of a causal relationship (abstract). *Clinical Orthopaedics and Related Research*, **109**, 210-211.
- Yoshikawa, S., Kawabata, M., Hatsuyama, Y., Hosokawa, O., and Fujita, T. (1964). Atypical vitamin D resistant osteomalacia. *Journal of Bone and Joint Surgery*, **46A**, 998-1007.

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