DISTINCTIVE TUMOURS OF BONE AND SOFT TISSUE CAUSING ACQUIRED VITAMIN-D-RESISTANT OSTEOMALACIA

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Summary A case of primary bone tumour associated with acquired vitamin-D-resistant osteomalacia is described. Comparison with seven other reported cases of vitamin-D-resistant osteomalacia associated with tumours suggests that it is a specific syndrome caused by a characteristic tumour.

Introduction

OVER the past twenty years there have been occasional reports of acquired vitamin-D-resistant osteomalacia associated with neoplasms. Detection of the tumours, in relation to the onset of symptoms caused by osteomalacia, has varied considerably, and the tumours have been reported under different names. As a result the syndrome is not widely recognised. Tumour ablation, if complete, can cure severe osteomalacia, so it is important that this condition be recognised and fully investigated. We have studied a personal case and the tumours from the two cases reported by Salassa et al.[1]

Case-report

The patient, aged 45 years, fractured the neck of her left femur after minor trauma. The fracture was pinned and plated. Over the next 5 months she complained of generalised weakness and pain. Investigation revealed an ununited fracture of the femoral neck as well as pseudofractures of pubic rami and of the right first metacarpal and second metatarsal bones. There was generalised bone tenderness and weakness. Hypophosphatæmia, hyperphosphaturia, and renal glycosuria were discovered with normocalcæmia, in the absence of metabolic acidosis or evidence of gastrointestinal disorder. The patient was transferred to Hammersmith Hospital, where investigation confirmed the diagnosis of hypophosphatæmic osteomalacia due to acquired vitamin-D resistance. The phosphate-excretion index (measured twice) was +0·179 and +0·48. Tubular reabsorption of phosphate was 53% (normal= 80%). Serum-calcium levels varied between 5·0 and 5·3 meq. per litre and serum-inorganic-phosphate between 0·6 and 1·1 meq. per litre (normal= 1·6–2·4 meq. per litre). Serum-alkaline-phosphatase was 23–30 King-Armstrong units per 100 ml. Renal glycosuria and hyperglycinuria were present. The patient was treated with calciferol 200,000 units a day and neutral phosphate in a dose of 2·25 g. a day. After 5 weeks' treatment bone pain had diminished and muscle power was improved; after 10 weeks bone pain had disappeared and she was sufficiently mobile to be able to climb stairs. After 4 months she walked without crutches and by 6 months she walked indoors without aid, and outside with a stick. The serum-inorganic-phosphate now varied between 1·4 and 2·1 meq. per litre. The dose of calciferol was reduced to 50,000 units a day. Over the next 9 months her condition became stationary: an expansile and lytic lesion in the region of the fractured femur was noted radiologically. All other fractures were now well healed. The serum-phosphate had again dropped to 0·6–1·2 meq. per litre, and she was readmitted for exploration of the femoral lesion. Biopsy was interpreted as an unusual type of primary bone tumour, possibly of vascular origin. The lesion was curetted and the cavity filled with bone chips. Over the next 2 months the serum-phosphate level rose to between 1·3 and 1·5 meq. per litre, and it varied over the next 12 months between 1·3 and 1·8 meq. per litre. By June, 1971 (17 months after operation), the patient's condition remained static. She is able to walk, preferably with a stick There is no sign of recalcification at the operation site, and it is considered that the tumour has probably not been completely removed.

Discussion

Eight cases of tumour-induced osteomalacia have been reported, including the present case.[1–6] These patients have in common an acquired variety of osteomalacia in the absence of nutritional deficiency or predisposing alimentary or renal disease. They have pain, deformities, and crippling weakness, to the extent of having become completely bedridden in three cases.[1,2,6] The radiological findings are those of severe osteomalacia including Looser zones. The patients are normocalcæmic and hypophosphatæmic, with a raised serum-alkaline-phosphatase. There is no hypercalciuria. Diminished tubular reabsorption of phosphate is a feature of all six cases,[1,3,5,6] including the present case, where this was studied, and a seventh was reported to show increased urinary excretion of phosphorus.[2] Parathyroid exploration in three patients was fruitless.[2–4] Negative calcium and phosphorus balances in two patients [1,4] became positive on specific treatment. Tubular reabsorption of phosphate became normal after treatment in four patients studied.[1,5,6] All eight patients had a tumour of bone or soft tissue: in one case it is not stated whether the tumour arose in bone or soft tissue. The gap between the onset of symptoms attributable to osteomalacia and tumour detection varied from 1 to 6 years, except in one case where it was 13 years.[2] In two patients with soft-tissue tumours there was a short or no interval between detection of the two disorders, as in both cases the patient himself had noticed the lump.[1] This suggests that the generally impalpable bone tumours may have been present before the onset of osteomalacia. The tumours may be as small as 3 × 2 cm.[1] The only effective therapy is vitamin D in large dosage and tumour excision. In two patients vitamin-D therapy and tumour excision coincided.[4,6] In two patients tumour excision was the only specific therapy.[1,5] These patients had as dramatic a remission as those who had vitamin-D therapy in addition. On the other hand, massive vitamin-D therapy alone (case 1 of Salassa et al.[1] and the present case) caused only a modest or temporary improvement of the biochemical abnormalities. Subsequent tumour excision in Salassa's patient [1] (case 1) caused prompt and complete remission. In Howard's patient there was improvement on vitamin-D therapy, but, following tumour removal, this therapy was no longer necessary.[3] The implication is that the tumour causes osteomalacia.

The nature of the tumours needs reassessment. Comparison of the three cases studied [1] showed a basic similarity of structure, and the detailed descriptions by Prader et al.[5] and Castleman [3] suggest that these five tumours are in the same category. The pathology of the femoral lesion in McCance's patient may be

similar.[4] In the remaining two cases the nature of the lesion is uncertain.[2,6] We believe that most or all of these tumours are a single pathological entity and are distinctive mesenchymal tumours, possibly variants of hæmangiopericytoma, but with focal, though sometimes prominent, collections of multinucleated giant-cells. The tumours are sometimes œdematous, with honeycombing of the cellular tissue to simulate angiomatous spaces. These variations have resulted in the tumours being labelled variant of giant-cell tumour of bone, reparative giant-cell granuloma, cavernous hæmangioma, sclerosing hæmangioma, and malignant neurinoma. At present we reserve judgment on the histogenesis of the tumour and its malignant potential. Some of the tumours are probably benign, but, in five of the six patients who had adequate local excision, follow-up varied from only 2½ months to 4 years. In Hauge's patient the tumour was clearly malignant.[2] In Howard's patient, Castleman regarded the tumour as probably malignant.[3]

The pathogenesis of the tumour-induced osteomalacia is uncertain. Prader[5] suggested that the tumour produced a rachitogenic substance. From what is known of hormone production by non-endocrine tumours, polypeptide hormone secretion by the tumour is a possibility, but electron microscopy failed to disclose evidence of neurosecretory granules of the type seen in polypeptide-secreting tumours. The hypothetical substance produced by the tumour must have an anti-vitamin-D-like activity, possibly inhibiting activation or acting as a competitor at the cellular level.

In conclusion, a proportion of patients with so-called idiopathic acquired vitamin-D-resistant osteomalacia have a tumour which is often difficult to detect. The removal of such a tumour can restore a bedridden person to normal life. Prospective study of cases will provide the fresh tissue needed to establish the pathogenesis of this fascinating syndrome.

We thank Prof. C. E. Dent for the urine aminoacid chromatogram, Prof. I. D. P. Wootton for the extensive biochemical investigations, Dr. A. Batty Shaw for referring the patient to Prof. O. Wrong, Dr. E. H. Soule for allowing us to study the tumours seen at the Mayo Clinic, and Dr. D. K. Peters for allowing us to study his case.

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Preliminary Communications

RELIEF OF SEVERE INTRACTABLE PAIN BY BARBOTAGE OF CEREBROSPINAL FLUID

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Summary A new method for the relief of severe intractable pain is described. The procedure consists in the aspiration and reinjection of cerebrospinal fluid through a wide-bore needle inserted into the spinal theca (barbotage). Of 14 patients treated in this way, 10 obtained relief of pain.

INTRODUCTION

REPEATED withdrawal and reinjection (barbotage) of cerebrospinal fluid (C.S.F.), introduced as a therapeutic measure by Speranski,[1] is occasionally used empirically in the treatment of various diseases, but not, so far as we know, for the relief of pain.[1,2] In experimental work on cats, Bunge et al.[3–5] have made extensive use of C.S.F. barbotage to cause peripheral demyelination of the spinal cord and brainstem. We noted a similarity between the pathological changes found by these workers in the spinal cord of the cats and those found by us at necropsy in a case of severe pain treated on several occasions by the withdrawal of C.S.F. and the intrathecal injection of ice-cold saline solution. This observation led us to begin a clinical trial of C.S.F. barbotage as a method of pain relief.

DATA ON 14 PATIENTS TREATED BY BARBOTAGE

Case no.	Sex	Age (yr.)	Site of carcinoma	Clinical details	Barbotages	Relief of pain	Known duration of relief
1	M	60	Rectum	Pain L5–S3 lt., paræsthesiæ rt. leg	1	No	..
2	M	67	Prostate	Pain lt. lower leg. Wasting and weakness lt. ant. tibial muscles. Sensory blunting L5 on lt.	1	No	..
3	F	57	Sigmoid	Rt. sciatic pain	1	Yes	1 mo.
4	F	65	Rectum	Perineal and lt. sciatic pain	1	Yes	3 wk.
5	M	63	Prostate	Pain in lt. ischium. Sensory blunting L2–3 on lt.	1	Yes	2 wk.
6	M	44	Bladder	Bilateral sciatic pain. Sensory blunting L5–S5 on lt.	2	Yes	3 mo. after 1st barbotage. 1 mo. after 2nd
7	F	56	Cervix	Bilateral lumbo-sacral pain	1	Yes	2 mo.
8	M	66	Bronchus	Lt. subcostal pain	1	Yes	1 mo.
9	F	52	Kidney	Circumferential pelvic pain	2	No	..
10	F	53	Cervix	Lumbosacral and bilateral sciatic pain	2	Yes	1 mo. after 1st barbotage. 3 wk. after 2nd
11	F	46	Rectum	Lumbosacral pain. Wasting whole rt. leg. Sensory blunting S2–S5 on rt.	4	No	..
12	M	53	Rectum	Perineal pain	1	Yes	2 days
13	M	62	Rectum	Bilateral sciatic pain	1	Yes	3 wk.
14	M	58	Bronchus	Bilateral pain C5–T1	1	Yes	1 wk.