Four cases of acquired hypophosphataemic (‘oncogenic’) osteomalacia. Problems of diagnosis, treatment and long-term management

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The insidious development of progressive bone pains and muscle weakness are well-known features of osteomalacia which may have many causes [1]. Particular diagnostic difficulties are encountered in acquired hypophosphataemia, a condition associated with increased renal phosphate clearance [2] and low circulating 1,25-dihydroxyvitamin D [1,25(OH)2D, calcitriol] [3, 4]. Many patients with this disease are shown to have benign tumours of mesenchymal origin with prominent fibrous and vascular characteristics [3, 4]. Cure is generally expected to follow surgical resection, with return of phosphate and 1,25(OH)2D levels to normal [3–5], indicating a likely causal relationship between tumour and both hypophosphataemia and 1,25(OH)2D production. Furthermore, experimental evidence supports a role for tumour products which influence both renal tubular cell phosphate transport and 1α-hydroxylase activity [6–9]. The term ‘oncogenic hypophosphataemic osteomalacia’ (OHO) is now applied to this group.

OHO was first recognized over 40 yr ago [10]. However, despite its musculoskeletal symptomology, it has only rarely been reported in the rheumatological literature [11–14]. Furthermore, most cases have been published as single case histories shortly after patients have appeared to be cured by surgery [3, 4]. Questions of diagnosis and management that have rarely been addressed include (i) the extent and methods of search for such tumours; (ii) the risk of relapse after surgery; (iii) the optimal drug treatment both in the initial stages and for long-term control; and (iv) the risk of other long-term complications. Additionally, the repeated reports of delays in diagnosis of up to 19 yr [4] suggest that the condition is poorly recognized. We therefore briefly present the case histories of four patients who have been followed for up to 23 yr, to illustrate each of these problems.

Case reports

Patient 1

A 48-yr-old Caucasian woman was first referred to the metabolic unit in 1975, 12 yr after the initial onset of widespread musculoskeletal pains. She had originally undergone intensive neurological evaluation in 1962 without diagnosis and within 3 yr had become housebound. Osteomalacia was finally diagnosed in 1965, when she fractured both arms whilst lifting her newborn baby and radiographs disclosed eight separate sites of previous fracture. She was treated with calciferol 50 000 i.u. daily and within 3 yr her symptoms had resolved. In 1970 a cystic 4-inch swelling overlying the left scapula was removed, the histology being reported as a cystic lymphangioma. She then discontinued calciferol, but in 1973 relapsed with widespread skeletal pains, weakness and fatigue.

On referral, she had a proximal myopathy, being unable to rise from a chair. A small, firm, non-tender, non-fixed periscapular mass was identified. General examination was otherwise unremarkable. Investigation showed plasma phosphorus 0.46–0.61 mmol/l (normal range 0.8–1.4); serum alkaline phosphatase (ALP) was 10.0–11.4 King–Armstrong (KA) units, within the normal range (4–12). Other normal findings included full blood count (FBC), erythrocyte sedimentation rate (ESR), liver function enzymes, fecal fat excretion, renal and bone biochemistry including calcium and parathyroid hormone (PTH), creatine phosphokinase (CPK), blood glucose and serum protein electrophoresis. There was no rheumatoid factor, anti-nuclear antibody, urinary Bence Jones protein, glycosuria or aminoaciduria. Radiographs showed osteopenia, healed left distal ulnar and right subtrochanteric fractures and typical pseudo-fractures in two metacarpal bones. Undecalcified transiliac bone biopsy revealed marked osteomalacia. Histological examination of the periscapular mass, removed incompletely under general anaesthetic, showed features similar to the original biopsy (which was recovered and re-evaluated), though it was consistent with a diagnosis of sclerosing haemangioma.
Two days after removal of the mass, the fasting serum phosphorus had risen to 0.94 mmol/l. She was treated with 25-hydroxycholecalciferol (calcidiol) 1 mg daily (kindly donated by Upjohn Co., Kalamazoo, MI, USA) during a metabolic balance study (unpublished results) and in 1 week was able to rise unaided from a chair. Within 1 month she felt recovered. Vitamin D₃ 1 mg daily was substituted and 1.5 g elemental phosphorus daily (as Phosphate Sandoz t.d.s.) added to the treatment regime. Phosphate and, later, vitamin D₃ were stopped but within 6 months her symptoms returned and the plasma phosphorus fell. Phosphate and calcidiol were recommenced but no residual tumour was identified clinically or by computed tomography (CT) from head to abdomen. Long-term treatment with 1α-hydroxycholecalciferol (alfacalcidol, 1-alpha) and phosphate was resumed. She remained generally well for 21 yr, although her musculoskeletal symptoms and biochemistry varied slightly until the dose of alfacalcidol was increased from 2 to 3 μg daily in 1987. In 1996 mild hypercalcaemia was detected after 1 yr of borderline-normal levels and within 3 months she was admitted acutely elsewhere with pyonephrosis, a staghorn renal calculus, a serum calcium of 2.77 mmol/l and a glomerular filtration rate of 27 ml/min. Medication was stopped and she underwent a nephrectomy. Normal PTH levels were subsequently demonstrated. Phosphate and alfacalcidol were restarted after she developed symptoms of osteomalacia associated with hypophosphataemia 3 months later. Her condition remains controlled.

Patient 2
A 60-yr-old woman was referred to the metabolic unit in 1979 with a 5-yr history of bilateral foot and diffuse left leg pain for which she had seen four physicians. The previous year she had undergone a lumbar discectomy for sciatica with little subsequent relief. She then developed bilateral hip, shoulder and rib pain with progressive weakness and difficulty in walking. Her diet was good, though she reported a 3 kg weight loss. Examination revealed a marked proximal myopathy and generalized bony tenderness but was otherwise unremarkable. There was no obvious tumour. Investigations showed low plasma phosphorus (0.50–0.61 mmol/l) and ALP 13–19 KA units (normal range 4–12), but other blood and urine investigations were normal, as in patient 1. Radiographs showed generalized osteopenia with multiple rib and femoral neck pseudo-fractures. Undecalcified, transiliac bone biopsy showed severe osteomalacia.

The diagnosis of acquired hypophosphataemic osteomalacia was made and she was treated initially with 10 μg alfacalcidol, 8 g Ossopan daily and Phosphate Sandoz q.d.s. Her symptoms improved within days. Within 1 month they had largely resolved. A metabolic balance study confirming the need for phosphate supplements during this phase has been reported previously [15]. Phosphate Sandoz was then reduced to t.d.s., alfacalcidol to 2 μg daily and later to 1 μg daily, and she remained well with normophosphataemia for 2 yr. She then began to relapse with associated hypophosphataemia (0.66–0.82 mmol/l). In 1992 she underwent CT examination from head to pelvis and a mass was demonstrated in the ethmoid sinus. Histology of the excised tumour revealed a haemangiopericytoma. All medication was then stopped and for 4 yr her clinical condition, although characterized by occasional musculoskeletal symptoms, remained stable with normal serum phosphorus and ALP. In 1986 she relapsed again and bone biopsy again confirmed osteomalacia: she was again hypophosphataemic (0.53 mmol/l) but CT showed no apparent tumour. Treatment was resumed, this time with calcitriol 0.5 μg daily, and Phosphate Sandoz. She then became depressed and anxious (though not hypercalcaemic). In 1998 her bowel habit altered. Colonic carcinoma was diagnosed elsewhere and, although bowel resection appeared initially successful, she died of metastatic disease in 1989.
Oncogenic hypophosphataemic osteomalacia

The right femur and also of L4 was confirmed; however, disseminated malignancy was also suspected because of his generally poor condition, weakness and widespread musculoskeletal pain associated with multiple truncal, rib and appendicular skeletal abnormalities reported on a $^{99m}$Tc-MDP (methylene diphosphonate) scan (Fig. 2). Investigations including serum protein electrophoresis, urinalysis for Bence Jones protein, liver function, prostate-specific antigen, abdominal ultrasound and CT were normal. Biopsy of bone marrow and iliac crest bone (decalcified) failed to demonstrate malignancy. It was nevertheless concluded that the most likely diagnosis was metastatic cancer from an unknown primary tumour and he was treated with non-opioid analgesia and calcitonin for bone pain. Late in 1996 he returned to Iran. However, his weakness, mobility and pain slowly

the serum phosphate rose to 1.56 mmol/l. The relationship between her various biochemical indices at this time has been reported briefly [16]. Calcitriol was reduced further and finally stopped 5 months after surgery. However, within 1 month the ALP had risen and phosphate and $1,25(OH)_{2}D$ fallen to 0.7 mmol/l and 15 pg/ml respectively. Treatment with phosphate and calcitriol was recommenced and after 8 yr of follow-up she has remained well, although handicapped by kyphosis, on maintenance doses of Phosphate Sandoz t.d.s. and calcitriol 0.5 µg daily. Attempts to reduce the phosphate and calcitriol dose further have been associated with falls in serum phosphate and $1,25(OH)_{2}D$. She has declined further surgery to her perineum.

**Patient 4**

A 61-yr-old Iranian man was referred to the metabolic unit in 1997 with a 5-yr history of progressively worsening widespread pain and weakness.

In Iran in 1995 he was shown to have typical radiographic features of Paget’s disease in the right femur, which had been confirmed on bone biopsy, following which he came to Britain for specialist orthopaedic and rheumatology consultation elsewhere. Paget’s disease of

**Fig. 1.** Multiple thoracic vertebral fractures in a 59-yr-old woman with a 10-yr history consistent with a diagnosis of osteomalacia, ultimately diagnosed as oncogenic hypophosphataemic osteomalacia associated with a vulval haemangio-pericytoma (patient 3).

**Fig. 2.** Whole-body $^{99m}$Tc-MDP images in hypophosphataemic osteomalacia (patient 4). The scan shows multiple areas of discrete tracer localization. The areas which are radiographically consistent with a diagnosis of Paget’s disease are represented by tracer uptake in the right femur and L4.
deteriorated. He then returned to Britain and was referred to our unit in January 1997.

Owing to pain and weakness, he had become entirely dependent on his family to complete all his domestic activities. He was cachectic, had a severe proximal myopathy, was unable to rise from a chair and could mobilize only with crutches. He had widespread vitiligo. Examination was otherwise unremarkable and no tumour was found. Review of all medical records prior to referral revealed raised ALP and persistent hypophosphataemia (0.39–0.69 mmol/l). Abnormal investigations in our unit were plasma phosphorus 0.36 mmol/l (normal range 0.7–1.5), ALP 345 IU/l (normal range 35–115), plasma 25(OH)D 247 nmol/l (normal range 20–195) and 1,25(OH)2D < 1 pmol/l (normal range 25–150). Apart from evidence for Paget’s disease of the right femur and L4 and general osteopenia, there were no additional radiological signs, particularly no pseudo-fractures. A diagnosis of acquired hypophosphataemic osteomalacia was made. He was treated with 4 μg calcitriol daily (reduced after 4 days to 3 μg). Phosphate Sandoz t.d.s. and, initially, 1500 mg calcium daily in divided doses. A noticeable improvement in muscle strength occurred within 3 weeks and was associated with normalization of his plasma phosphorus. Within 6 weeks he was able to walk without using a stick. Plasma phosphorus and calcium stabilized in the normal range on 3 tablets Phosphate Sandoz and 2 μg calcitriol daily. After 4 months, his pains had virtually resolved and he had become freely mobile; however, he still had low back pain and an elevated ALP, presumed secondary to Paget’s disease. This was treated with intravenous pamidronate before his return to Iran on long-term medication. After 2 yr he remains well on a maintenance dose of calcitriol 0.75 μg daily.

All measurements of PTH and 1,25(OH)2D in our hands have been carefully validated with respect to normal ranges and reproducibility [17].

Discussion

Diagnosis of acquired hypophosphataemic osteomalacia requires recognition of the typical clinical and radiological features of osteomalacia in association with hypophosphataemia [5]. Other conditions associated with hypophosphataemia should be excluded (Table 1). The diagnosis of OHO became evident in the first three patients after disclosure of a tumour which, after removal, resulted in improvement of symptoms and biochemical indices. A diagnosis of OHO remains possible in the fourth patient. Although acquired hypophosphataemic osteomalacia is a rare condition, these four cases illustrate the wholly disproportionate toll that its lack of recognition exacts.

Delay in diagnosis of OHO and the search for tumours

Despite over 100 cases of acquired hypophosphataemic osteomalacia and OHO in the literature [13], the diagnosis continues to be easily missed. Common to all our cases was consultation of a number of physicians, a delay in correct diagnosis (3–12 yr) and prolonged morbidity. At worst, as with patient 4, and as previously reported [18], patients may be mistakenly thought to have neoplasia with secondary skeletal metastases. In the fourth case, the presence of Paget’s disease deflected attention from the possibility of osteomalacia, although clearly the significance of hypophosphataemia was unrecognized and the possibility of osteomalacia was not raised in the radiologist’s bone scan report.

Having recognized hypophosphataemic osteomalacia, the next question is the extent to which an associated tumour should be sought. As the first three cases illustrate, tumours are often small, difficult to locate and in obscure areas. This is consistent with most other cases [3, 13]. In two of our patients the tumours were superficial (subcutaneous), though easy enough to overlook. Tumours may predate the onset of osteomalacia or become evident after the diagnosis of hypophosphataemic osteomalacia has been made [19]. The question remains, with regard to patient 4, as to whether, and what kind of, investigations should be undertaken in a further search for a tumour.

If the patient is unaware of any odd lump, and if a thorough clinical examination fails to identify one, then imaging studies should be done. The optimum imaging modality is not known but, as the majority of tumours are in a limb and many in bone [13], bone scintigraphy may be helpful [20], though it will be difficult to interpret in the presence of osteomalacia and/or other bone diseases. Because tumours have prominent vasculature in approximately 50% of cases [13], both scintigraphy with radiopharmaceuticals which have a prominent blood pool phase and angiography [21, 22] should also be considered. We would also recommend, as have others [3], that investigation of the head and neck may be rewarding. There are no data comparing the performance of CT and magnetic resonance imaging in a search for tumours.

Management of acquired hypophosphataemic osteomalacia and OHO

Acquired hypophosphataemic osteomalacia will always respond to large doses of vitamin D, or its potent derivatives and phosphate supplements [2, 5]. Although it has been stated that the presence of an appropriate tumour prevents complete resolution of osteomalacia [4], it is clear from the present report that patients may be maintained in good health for years on medical treatment alone. While the search for a tumour is important, as its complete resection commonly effects a
## Table 1. Biochemical findings in the major acquired conditions characterized by hypophosphataemia and musculoskeletal symptoms (from Reference 34, abridged)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Plasma indices</th>
<th>Urinary indices</th>
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<tbody>
<tr>
<td>Nutritional osteomalacia</td>
<td>Calcium ↓ or low/normal</td>
<td>Calcium ↓</td>
</tr>
<tr>
<td></td>
<td>25 hydroxyvitamin D ↓</td>
<td>Phosphate normal a</td>
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<td></td>
<td>1.25 dihydroxyvitamin D ↓, normal or ↑ b</td>
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<tr>
<td></td>
<td>PTH ↑</td>
<td></td>
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<td></td>
<td>ALP ↑</td>
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<tr>
<td>Oncogenic osteomalacia</td>
<td>Calcium normal</td>
<td>Calcium normal</td>
</tr>
<tr>
<td></td>
<td>25 hydroxyvitamin D normal</td>
<td>Phosphate normal a</td>
</tr>
<tr>
<td></td>
<td>1.25 dihydroxyvitamin D ↓</td>
<td>Occasional aminoaciduria</td>
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<tr>
<td></td>
<td>PTH normal or ↑</td>
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<td></td>
<td>ALP ↑</td>
<td></td>
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<tr>
<td>Acidotic forms of osteomalacia^c</td>
<td>Calcium normal or ↓</td>
<td>Calcium normal or ↑</td>
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<tr>
<td></td>
<td>25 hydroxyvitamin D normal</td>
<td>Phosphate normal a</td>
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<td></td>
<td>1.25 dihydroxyvitamin D normal or ↓</td>
<td>Aminoaciduria</td>
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<td></td>
<td>PTH normal or ↑</td>
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<td></td>
<td>ALP ↑</td>
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<tr>
<td>Primary hyperparathyroidism</td>
<td>Calcium ↑</td>
<td>Calcium normal a</td>
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<tr>
<td></td>
<td>25 hydroxyvitamin D normal</td>
<td>Phosphate normal a</td>
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<td></td>
<td>1.25 dihydroxyvitamin D normal or ↑</td>
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<td></td>
<td>PTH ↑</td>
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<td></td>
<td>ALP normal or ↑</td>
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<tr>
<td>Humoral hypercalcaemia of</td>
<td>Calcium ↑</td>
<td>Calcium ↑</td>
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<tr>
<td>malignancy (PTHrP)</td>
<td>25 hydroxyvitamin D normal</td>
<td>Phosphate normal a</td>
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<tr>
<td></td>
<td>1.25 dihydroxyvitamin D normal or ↓</td>
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<td></td>
<td>PTH normal or ↓</td>
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<td></td>
<td>ALP normal</td>
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^aRelated to seasonal variation.
^bDepends on any recent exposure to vitamin D.
^cOccasionally within normal limits.
^dBut renal phosphate clearance always high.
^eIncludes renal tubular acidosis and the Fanconi syndromes.
^fDepending on the presence of bone disease (osteitis fibrosa).
^gOwing to increased renal tubular reabsorption.
^hEffects mediated by PTH-related peptide. Differences between the condition and primary hyperparathyroidism broadly reflect the effects of relative end organ resistance to PTHrP compared with PTH.

cure [3–5], it is also clear from our report that relapse may be equally common if patients are followed for long enough. Moreover, these tumours are not encapsulated and complete resection may be problematical. Either way, it is clear that big doses of calcitriol or alfalcaldiol and phosphate supplements rapidly relieve symptoms in the early stages [3, 4, 23] and will speed recovery whether or not a tumour has been successfully resected. Metabolic balance studies have shown the additional effect of calcium supplements in the first 4–6 months of healing [2]. Our experience suggests that only when patients have recovered clinically should calcitriol be discontinued to determine whether a cure has indeed been effected.

**Relapse of osteomalacia**

While reported ‘cures’ suggest that treatment be safely discontinued after clinical and biochemical recovery following tumour resection, it is clear from the present report that the frequency of relapse has been inadequately emphasized in the literature. Incomplete resection, as in our first and third patients, is one obvious reason. Multicentric tumours are another possibility [20, 24, 25]. The cause of relapse in our second patient, 4 yr after treatment withdrawal, is obscure as CT did not identify a tumour recurrence at the original site. Her ultimate colonic carcinoma is a possible candidate, and anecdotal reference has been made to hypophosphatemia among patients with metastatic disease [3, 4]. Generally, long-term follow-up appears a prudent measure.

**Long-term pharmacological management**

All four of these cases illustrate that pharmacological therapy may be necessary in the long term. Experience from the present cases, other cases in our experience (T.C.B. Stamp, unpublished findings) and those in the literature suggests patients can be maintained on 0.5–1 µg calcitriol or 2–3 µg alfalcaldiol together with a supplement of 1500 mg phosphorus daily. We are unaware of any studies which suggest an optimal diurnal timing of supplementation. The importance of regular renal monitoring in order to forestall progressive calcification is only too well illustrated by the first case, although a purely infective aetiology cannot be excluded. Finally, ‘tertiary’ hyperparathyroidism has been stated to occur in 5% of OHO cases [4]. This may be an underestimate as it was observed in two of an original series of nine patients with acquired hypophosphataemia [5]. Its aetiology has been debated [4, 14, 26, 27], though it may simply be a complication of long-term phosphate supplementation, reducing calcium levels and
inducing parathyroid hyperplasia, as in X-linked hypophosphataemic rickets [28].

**Tumours in OHO**

The tumours occurring in OHO have been variously described as sclerosing angioma, benign angiofibroma, haemangiopericytoma, chondrosarcoma, primitive mesenchymal tumour and giant cell tumour of bone [3, 4]. The commonest morphological pattern is characterized by stromal cells growing in poorly defined sheets, osteoclast-like cells, islands of cartilage and prominent vascularity [29]. Acquired hypophosphataemic osteomalacia may also be associated with a variety of carcinomas of epidermal and endodermal origin [30], multiple myeloma and chronic lymphocytic leukaemia [31]. It is also associated with fibrous dysplasia of bone [32] and neurofibromatosis [3, 33].

The exact way in which tumours are associated with the biochemical and renal abnormalities in OHO is unknown. There is some evidence to suggest that, in many cases, effects on renal phosphate handling and 1,25(OH)₂D production may be due to tumour-produced humoral factor (or factors) acting on renal tubular cells. First, tumour extracts may induce phosphaturic activity when infused into dogs [6]; secondly, tumour transplanted into athymic nude mice can induce hypophosphataemia and phosphaturia [7, 8]; and thirdly, tumour extracts have been shown to inhibit 25-hydroxyvitamin D-1α-hydroxylase activity in cultures of renal tubular cells [7]. More recently, two candidate proteins (~56–58 kDa) have been identified in tumour-conditioned media obtained from cultured tumour cells from a patient with OHO which, the authors conclude, may be associated with alteration of sodium-dependent phosphate cotransport and 1α-hydroxylase activity in kidney cells, as shown in vitro [9].

**Concluding remarks**

These cases confirm that slow recognition of acquired hypophosphataemic osteomalacia and OHO amongst physicians continues to result in unnecessary and prolonged morbidity. The cases emphasize that osteomalacia may predate the discovery of a tumour and illustrate that the site and nature of tumours and their complete resection is often difficult to confirm. Importantly, even after apparently complete resection of the tumour and recovery of the patient, relapses may occur and long-term pharmacological treatment may be necessary. Finally, serious complications of long-term treatment may develop.

We would, therefore, advocate maintaining a high index of suspicion for OHO in patients with persistent unexplained pain and weakness associated with biochemical features suggestive of hypophosphataemic osteomalacia (Table 1). Assiduous follow-up with surveillance for tumour recurrence, biochemical monitoring and regular renal investigations are important for all patients in whom OHO has either been diagnosed or is a likely diagnosis.

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**References**

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