CASE REPORT

Diagnosis of a patient with oncogenic osteomalacia using a phosphate uptake bioassay of serum and magnetic resonance imaging

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Abstract

A previously healthy man with no family history of fractures presented with muscle pain, back pain and height loss. Investigations revealed hypophosphataemia, phosphaturia, undetectable serum 1,25-dihydroxyvitamin D and severe osteomalacia on bone biopsy, suggestive of a diagnosis of oncogenic osteomalacia. Thorough physical examination did not locate a tumour. Support for the diagnosis was obtained by detection of phosphate uptake inhibitory activity in a blinded sample of the patient’s serum using a renal cell bioassay. On the basis of detection of this bioactivity, a total body magnetic resonance (MR) examination was performed. A small tumour was located in the right leg. Removal of the tumour resulted in the rapid reversal of symptoms and the abnormal biochemistry typical of oncogenic osteomalacia. Inhibitory activity was also demonstrated using the bioassay in serum from two other patients with confirmed or presumptive oncogenic osteomalacia, but not in serum from two patients with hypophosphataemia of other origin. This is the first case to be reported in which the diagnosis of oncogenic osteomalacia was assisted by demonstration of inhibitory activity of the patient’s serum in a renal cell phosphate bioassay that provided an impetus for total body MR imaging.

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Introduction

Oncogenic osteomalacia is a condition that is often difficult to diagnose and to manage (reviewed in (1–3)). Patients frequently present with vague symptoms of bone and muscle pain and muscle weakness. The typical biochemical findings are hypophosphataemia, renal phosphate wasting, low serum concentration of 1,25-dihydroxyvitamin D (1,25(OH)2D) and frequently increased serum alkaline phosphatase. Impaired mineralisation of bone presents as rickets or osteomalacia, as indicated by bone biopsy, and patients may have recurrent fractures. The tumour responsible for the symptoms and signs of oncogenic osteomalacia may be located in almost any part of the body, with a large proportion occurring in the upper and lower extremities and around the head. The tumours are often small and slowly growing. They are of a wide variety of histological types and are mostly benign and of mesenchymal origin (reviewed in (4)).

Location of the tumour is often difficult, and the diagnosis cannot be confirmed until the tumour is located and removed. If it can be located and completely removed, there is usually rapid reversal of the abnormal biochemistry and alleviation of symptoms. The search for the tumour usually starts with a very thorough physical examination, then radiographic survey and bone scans. Computed tomography (CT) and magnetic resonance (MR) examinations of any clinically suspicious areas have also been used (5–8).

In the case reported here, a patient presented with symptoms and signs suggestive of oncogenic osteomalacia; however, no tumour could be located by physical examination. A renal cell phosphate uptake bioassay, with which we have previously demonstrated inhibition of renal phosphate uptake by conditioned media from cultured oncogenic osteomalacia tumour cells (9), was used to test a blinded sample of the patient’s serum against age- and sex-matched controls. Detection of phosphate uptake inhibitory activity in the patient’s serum provided the impetus for carrying out a whole-body MR examination.

The renal phosphate uptake assay was also used to test sera from other patients with hypophosphataemia,
with or without other symptoms and signs of oncogenic osteomalacia, to determine its usefulness in assisting in the diagnosis of this condition.

**Case reports**

**Patient 1**

Patient 1 presented in 1993 at age 26 years with muscle pain. He was a previously healthy man, a part-time body-builder, with no family history of fractures. X-ray examination in 1994 detected no vertebral fractures. Over the next 2 years, the patient also suffered muscle ache, generalised stiffness and severe back pain and he lost 8 cm in height between 1995 and 1996. Multiple vertebral fractures were shown by X-ray examination in February 1996.

In June 1996, he was seen after referral to the clinic at Uppsala. Biochemical investigations indicated low serum phosphate concentration of 0.43 mmol/l (normal range 0.76–1.44 mmol/l), high urinary phosphate clearance of 32.7 ml/min (normal range 4–12 ml/min), low tubular phosphate reabsorption of 69% (normal range 87–94%), undetectable 1,25(OH)2D and increased alkaline phosphatase of 26 ukat/l (normal range 0.8–4.8 ukat/l). The serum concentrations of 25-hydroxyvitamin D (27 nmol/l; normal range 25–105 nmol/l), parathyroid hormone (PTH) (33 ng/l; normal range 12–55 ng/l) and calcium (2.34 mmol/l; normal range 2.20–2.60 mmol/l), and other biochemical measurements were all within normal ranges. There was no evidence of aminoaciduria or skeletal dysmorphism. The patient had a severe myopathy. Bone biopsy indicated severe osteomalacia. The patient's history and physical findings were suggestive of a diagnosis of oncogenic osteomalacia, though no tumour could be located on physical examination. The patient was treated from June 1996 with phosphate and 1,25(OH)2D, which relieved his symptoms.

In 1997, a sample of the patient's serum and sera from two age- and sex-matched normal controls were tested in a blinded manner, in the phosphate uptake assay. Phosphate uptake inhibitory activity was detected in the serum from patient 1 compared with the control sera in the renal cell bioassay. Detection of this activity was further evidence that the patient's symptoms were due to oncogenic osteomalacia. On the basis of this evidence, a further search for the tumour was carried out using a whole-body MR examination. In that examination a small, subcutaneous, highly vascularised tumour was detected in the right leg 20 cm proximal to the knee.

The tumour was removed in January 1998 and was classified histologically as angiodyplasia. Serum phosphate returned to within the normal range 10 h after the operation, and the serum concentration of 1,25(OH)2D also normalised. The patient had full mobility within 3 days after operation and had no pain or stiffness. His myopathy, which had been only partially improved by treatment, vanished within 2 days. He returned to full-time work, and at follow-up after 1 year he remained well. The changes in biochemistry are summarised in Table 1.

**Patient 2**

Patient 2 has been reported previously (10). In this patient, the diagnosis of oncogenic osteomalacia was confirmed by clinical improvement after removal of a prostate adenocarcinoma. Serum was collected from patient 2 before and after surgical removal of the tumour.

**Patient 3**

This female patient first presented in 1985 at age 36 years with generalised bone and muscle pain, hypophosphataemia (0.4 mmol/l, normal range 0.8–1.5 mmol/l), low serum concentration of 1,25(OH)2D

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**Table 1 Changes in biochemical measurements from patient 1 before treatment and after surgical removal of tumour.**

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Serum phosphate (0.76–1.44 mmol/l)</td>
<td>0.43 mmol/l</td>
<td>0.55 mmol/l</td>
<td>0.91 mmol/l</td>
<td>1.36 mmol/l</td>
</tr>
<tr>
<td>Phosphate clearance (4–12 ml/min)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tubular phosphate reabsorption (87–94%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1,25(OH)2D (40–130 pmol/l)</td>
<td>ND</td>
<td>51 pmol/l (treated with 1,25(OH)2D 2 µg/day)</td>
<td>107 pmol/l</td>
<td></td>
</tr>
<tr>
<td>25(OH)D (NR 25–105 nmol/l)</td>
<td>27 nmol/l</td>
<td>23 nmol/l</td>
<td>31 nmol/l</td>
<td></td>
</tr>
</tbody>
</table>

Biochemical measurements for patient 1 are summarized before treatment in June 1996, immediately before surgery to remove the tumour in January 1998, after surgery, and at follow-up in May 1998. The normal range for each measurement is shown in the first column, except for 25(OH)D, for which the laboratory normal range changed in 1997 and the relevant values (NR) are shown for each time of measurement. ND, not detectable.
and osteomalacia on bone biopsy. Careful physical examinations and bone scans have failed to locate a causative tumour and she has been treated since 1985 with phosphate and 1,25(OH)2D, which alleviate her symptoms. If treatment is interrupted, symptoms of muscle pain recur after only a few days. The patient was unwilling to undergo MR examination. In 1999, octreotide scintigraphy was carried out using the somatostatin receptor analog octreotide, which has been used to locate other tumours in patients with oncogenic osteomalacia (11). No tumour was located.

**Materials and methods**

**Materials**

The OK 3B2 cells were kindly provided by Professor H Murer, Zurich, Switzerland. Tissue culture media and additives were obtained from Gibco BRL Life Technologies (Gaithersburg, MD, USA) and Trace Biosciences (Melbourne, Victoria, Australia). The isotopes [32P]orthophosphoric acid was obtained from Gene-Works, Adelaide, Australia and Norit A charcoal from ICN, Cleveland, Ohio, USA. All other chemicals were obtained from Sigma Chemical Co, St Louis, MO, USA.

**Phosphate uptake assay**

A renal phosphate uptake assay was used (9) in which we have previously detected inhibitory activity in conditioned media from oncogenic osteomalacia tumour cells, using OK 3B2 cells, which are particularly sensitive to PTH. Phosphate uptake was measured as previously described (9) in cells grown to confluence in 24-well plates; they were changed to serum-free medium 24 h before the uptake assay. Patients’ serum samples were tested compared with serum samples from two age- and sex-matched controls each. The serum samples were heat-inactivated at 56°C for 30 min to overcome the cytotoxic effects of unheated serum, then diluted to 5–20% v/v in serum-free DMEM medium. The OK 3B2 cells were preincubated with the diluted serum samples for 20 h, the preincubation time for maximal inhibitory activity with conditioned medium (12). Uptake of [32P]orthophosphate was then measured after incubation with 32P-uptake solution for 15 min. The total protein per well was measured using the Bio-Rad protein assay (Bio-Rad Laboratories, Hercules, CA, USA).

**Charcoal extraction of serum**

Serum samples were charcoal extracted by a method based on that described by Lajeunesse et al. (13). The patients’ and control serum samples were first heat inactivated and then 5 ml serum was added to 0.5 g washed charcoal. After mixing, the charcoal was recovered by centrifugation and eluted in 750 μl 1 mol/l acetic acid. The eluants were then diluted with serum-free DMEM medium with bovine serum albumin added to a final concentration of 0.1%, then tested in the phosphate uptake bioassay.

**Magnetic resonance imaging**

The MR examinations were carried out on a 0.5T scanner (Gyrosan T5-NT, Philips, Best, The Netherlands). Fat-suppressed T2-weighted STIR images (repetition time (TR) 2500 ms, echo time (TE) 120 ms, Inversion time (TI) 120 ms, matrix 203−256/256) with a field of view of 275−450 cm and a slice thickness of 6−8 mm, gap 0.8−1.6 mm, were obtained in the frontal plane at the following locations: neck, thorax and upper abdomen, pelvis and proximal part of the upper leg, distal part of the upper leg and proximal part of lower leg, distal part of the lower leg and the foot. Complementary T2-STIR and T1-weighted sequences in the axial and frontal plane were performed in areas suspected of containing the tumour. Contrast-enhanced (20 ml of 0.5 mmol/kg gadolinium diethylene triamine pentacetic acid-bismethylamide (GdDTP A)-BMA) T1-weighted images were obtained in the tumour area of the upper leg.

**Statistical analysis**

The results are expressed as the mean±s.d. Significant differences between means were determined using Student’s two sample t-test, assuming equal variance.

**Results**

**Testing of patients’ sera in renal phosphate uptake bioassay**

A sample of serum from patient 1 with blinded identity was tested in the phosphate uptake assay at 5−20% v/v dilutions compared with sera from two age- and sex-matched controls. Significant inhibition of renal phosphate uptake was detected in the patient 1 serum (Table 2). The activity detected in the blinded sample was small (from 3% to 9% inhibition of control uptake) but significant (P < 0.05) and detected in three different assays.

Significant inhibitory activity was also detected in serum from patient 2, in whom the diagnosis of oncogenic osteomalacia was subsequently confirmed by the clinical improvement that occurred after removal of a prostate adenocarcinoma. Significant inhibition of phosphate uptake compared with control was detected in the preoperative serum – up to 24% inhibition of control at 20% v/v dilution (Table 2) – but no significant inhibition was detected in postoperative serum.

Significant inhibitory activity was also detected in serum from patient 3 (Fig. 1) with symptoms and signs
typical of oncogenic osteomalacia, but in whom no tumour has been located. Significant inhibitory activity up to 32% inhibition of control has been detected in serum from this patient (Table 2). Similar significant inhibitory activity has been demonstrated in three different serum samples collected from her over a 2-year period.

Sera from two other patients with hypophosphataemia, but without other signs of oncogenic osteomalacia, were also tested in the bioassay. Patient 4 is a 36-year old man with hypophosphataemia, but normal serum 1,25(OH)2D concentration, no muscle pain and no evidence of osteomalacia or rickets. His hypophosphataemia is as yet unexplained. Patient 5 is a 12-year old girl with hypophosphataemia and rickets, with an increased serum 1,25(OH)2D concentration and hypercalciuria. Her clinical presentation is consistent with a diagnosis of hereditary hypophosphataemic rickets (14), and there are two other affected family members. No inhibition of phosphate uptake was detected in sera from these two patients compared with control sera at dilutions of 5–20% v/v (Table 2). Some stimulation of phosphate uptake compared with control sera was detected in sera from these patients, up to 1.4-fold control by the serum of patient 5.

**Charcoal extraction of serum**

After determining that phosphate uptake inhibitory activity was present in sera of patients with proven or presumptive oncogenic osteomalacia, the sera were next tested to determine whether the activity could be extracted with charcoal and eluted with acetic acid, as described with the inhibitory activity in sera from Hyp mice (13). This was shown to be the case for serum from patients 1 and 3. There was insufficient pre-operative serum available from Patient 2 for charcoal extraction. Acetic acid eluants of charcoal extracts from patients 1 and 3 both significantly inhibited phosphate uptake compared with eluants from control sera (Table 3).

**MR imaging**

In patient 1 an oval area (10 × 8 × 5 mm) with very high signal intensity, located subcutaneously approximately 20 cm proximal to the knee joint, was seen on the

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**Table 2** Effect of patient serum on renal phosphate uptake by OK 3B2 cells.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Serum dilution (% v/v)</th>
<th>Phosphate uptake (c.p.m./mg protein×10³)</th>
<th>Inhibition by patient serum compared with control serum (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Patient serum</td>
<td>Control serum</td>
</tr>
<tr>
<td>Patients with diagnosis of OOM confirmed by tumour removal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient 1</td>
<td>15</td>
<td>1792±33</td>
<td>1963±55</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>2035±46</td>
<td>2098±10</td>
</tr>
<tr>
<td>Patient 2</td>
<td>10</td>
<td>3177±48</td>
<td>3991±98</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>2492±24</td>
<td>3282±35</td>
</tr>
<tr>
<td>Patient with symptoms and signs of OOM but diagnosis not confirmed</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient 3</td>
<td>15</td>
<td>1198±87</td>
<td>1451±56</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>823±54</td>
<td>1205±200</td>
</tr>
<tr>
<td>Patients with hypophosphataemia of other origin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient 4</td>
<td>10</td>
<td>1424±174</td>
<td>1289±42</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>1377±125</td>
<td>1092±83</td>
</tr>
<tr>
<td>Patient 5</td>
<td>10</td>
<td>1537±287</td>
<td>1500±78</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>1541±108</td>
<td>1200±36</td>
</tr>
</tbody>
</table>

Phosphate uptake was measured in triplicate in confluent OK 3B2 cells that had been incubated with heat-inactivated serum at 10–20% v/v dilution for 20 h. OOM, oncogenic osteomalacia.

*Significantly different from control (P < 0.05).
T2-weighted STIR images in the frontal plane (Fig. 2A). Complementary axial T2-weighted STIR images and pre- and post-contrast T1-weighted images (Fig. 2B–D) confirmed this finding and the signal intensity pattern corresponded to a highly vascularised tumour.

**Discussion**

This case report describes the use of a renal phosphate uptake bioassay of serum and whole-body MR imaging for the diagnosis of oncogenic osteomalacia and localisation of the tumour. The patient presented with increasing muscle ache and pain, and had demonstrated hypophosphataemia, high urinary phosphate excretion, undetectable serum 1,25(OH)2D and severe osteomalacia typical of oncogenic osteomalacia. No tumour, however, could be located. Localising the tumour, which is needed for a definite diagnosis, is commonly a problem in patients presenting with clinical signs and symptoms suggestive of oncogenic osteomalacia. The tumours responsible for the condition can be located in almost any part of the body and are often small and slowly growing (reviewed, (3, 4)). Difficulty in locating the tumour may result in delays of several years between the original presentation and definitive diagnosis, and treatment by removal of the tumour, which is needed for a definite diagnosis, is often a problem in patients presenting with clinical signs consistent with oncogenic osteomalacia. No tumour, however, could be located. Localising the tumour, which is needed for a definite diagnosis, is commonly a problem in patients presenting with clinical signs and symptoms suggestive of oncogenic osteomalacia. The tumours responsible for the condition can be located in almost any part of the body and are often small and slowly growing (reviewed, (3, 4)).

In the studies presented here, a sample of serum from patient 1 was first tested in a blinded manner in a renal phosphate uptake bioassay, in which we have shown inhibition of renal phosphate uptake by conditioned medium from cultured oncogenic osteomalacia tumour cells (9). Detection of phosphate uptake inhibition in the patient’s serum compared with control serum in this assay provided further evidence for the diagnosis of oncogenic osteomalacia, and on this basis a whole-body MR scan was carried out. As most tumours have a high signal intensity on T2-weighted images because of high water content, we used the highly water-sensitive fat-suppressed T2-weighted STIR sequence in this patient. With a large field of view (450 cm) it is possible to get an overview and screen for tumours, using only this sequence with relatively few investigated areas, even if, as in our patient, the tumour location is completely unknown. MR imaging was successful in identifying a small subcutaneous tumour in the right leg. Surgical removal of the tumour resulted in normalisation of the abnormal biochemistry and resolution of the patient’s symptoms.

There has been one previous report of testing serum from a patient with oncogenic osteomalacia; the serum was shown in fact to stimulate phosphate uptake by the PTH-sensitive OK/E cell line to a greater extent than control serum after incubation for 4 h (21). As discussed by the authors, their inability to detect inhibitory activity may have been due to the short time course used. In the studies reported here, the OK 3B2 cells were incubated with diluted serum for 20 h – the time course we have used with conditioned media (12) – before measurement of phosphate uptake.

Inhibition of phosphate uptake compared with control serum was also demonstrated in our studies by serum from a second patient in whom the diagnosis was subsequently confirmed by removal of the tumour, and in a third patient with clinical signs consistent with oncogenic osteomalacia and biopsy-proven osteomalacia, but in whom no tumour has yet been located. In the latter patient, inhibitory activity up to 32% inhibition of control at 20% v/v dilution was demonstrated in several samples collected over a 2-year interval. The lower percentage inhibition in response to patient 1 serum compared with serum from patients 2 and 3 (Table 2) was most probably attributable to the inherent variability of a bioassay system. In this study, the sera were each compared with age- and sex-matched controls and there was also variability in the

<table>
<thead>
<tr>
<th>Patient</th>
<th>Serum dilution (% v/v)</th>
<th>Phosphate uptake (c.p.m./mg protein × 10^3)</th>
<th>Inhibition by patient serum compared with control serum (%)</th>
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<tbody>
<tr>
<td>Patient 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unextracted serum</td>
<td>20</td>
<td>4019±47</td>
<td>4131±65</td>
</tr>
<tr>
<td>Charcoal-extracted serum eluant</td>
<td>5</td>
<td>2338±63</td>
<td>2576±139</td>
</tr>
<tr>
<td>Patient 3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unextracted serum</td>
<td>20</td>
<td>823±54</td>
<td>1205±200</td>
</tr>
<tr>
<td>Charcoal-extracted serum eluant</td>
<td>10</td>
<td>687±46</td>
<td>1162±267</td>
</tr>
</tbody>
</table>

Phosphate uptake was measured in triplicate in confluent OK 3B2 cells that had been incubated with heat-inactivated serum or acetic acid eluants of charcoal extracts of serum at 10–20% v/v dilution for 20 h.

*SSignificantly different from control (P < 0.05).*
baseline responses. Therefore, the responses were evaluated on an intra-assay basis, which reproducibly showed significant inhibitory activity of serum from patients 1, 2 and 3 compared with their appropriate controls. We also tested sera from two other patients with clinical features suggestive of oncogenic osteomalacia, but who were not included in this report because they did not have biopsy-proven osteomalacia. Sera from these patients did not inhibit phosphate uptake compared with control serum samples.

Lajeunesse et al. (23) have studied renal phosphate uptake inhibitory activity in serum from Hyp mice, the mouse model of X-linked hypophosphataemic rickets. The clinical similarities between oncogenic osteomalacia and the inherited condition, X-linked hypophosphataemic rickets, and evidence for the involvement of a humoral factor in both, have led to proposals that similar mechanisms may be involved in the two conditions (2, 24). Lajeunesse et al. (23) reported a maximal effect of inhibition of renal phosphate uptake by serum from Hyp mice with a longer time course of...
24 h of incubation, similar to the time course used in this study. The phosphate uptake inhibitory activity of serum from patients with oncogenic osteomalacia was also extracted by charcoal and was recovered by elution in acetic acid in this study, in a manner similar to that described by Lajeunesse et al. (13) with Hyp mice serum. The similarity in properties of the phosphate uptake inhibitory activity between the oncogenic osteomalacia patient serum and Hyp mice serum, in time course and after charcoal extraction, supports the hypothesis of a common phosphate regulating factor in the two conditions.

In conclusion, this case report describes the first patient in whom detection of phosphate uptake inhibitory activity in the serum assisted in the diagnosis and prompted subsequent localisation of the tumour by whole-body MR imaging. Although some candidate genes for oncogenic osteomalacia have recently been described (25, 26) the causative circulating factor has not yet been identified and there is not yet available a definitive diagnostic serum test for the presence of this factor. The final diagnosis of oncogenic osteomalacia is dependent on the localisation of the tumour, which is also essential for the successful management of the patient. Localisation can present a clinical problem, however, if the tumour is not found by routine investigations and more sophisticated tests have to be considered. In this case, the advantage of the bioassay result was the confirmation of the provisional diagnosis, which then prompted the whole-body MR scan. The diagnosis was finally confirmed when the tumour, located by the MR scan, was removed and the patient’s symptoms and signs were normalised.

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