Spontaneous healing of osteitis fibrosa cystica in primary hyperparathyroidism

CJ Gibbs, JGB Millar, J Smith

Summary
A 24-year-old man with primary hyperparathyroidism and osteitis fibrosa cystica developed acute hypocalcaemia. Spontaneous healing of his bone disease was confirmed radiographically and by correction of the serum alkaline phosphatase. Hypercalcaemia associated with a raised serum parathyroid hormone recurred 90 weeks after the initial presentation. During the fourth neck exploration a parathyroid adenoma was removed, resulting in resolution of his condition. Haemorrhagic infarction of an adenoma was the most likely cause of the acute hypocalcaemic episode.

Keywords: primary hyperparathyroidism, osteitis fibrosa cystica, hypercalcaemia

A 24-year-old man presented with a painless swelling of the right mandible, lethargy, anorexia, thirst and lower backache. Examination was normal apart from the mandibular swelling. Radiographs showed a large translucency in the right mandibular body (figure 1A). Subperiosteal erosion and distal phalangeal tuft resorption were present in the hands (figure 2A). Intravenous urography showed localised medullary sponge kidney of the upper pole of the left kidney with nephrocalcinosis. Serum biochemistry showed hypercalcaemia and an elevated parathyroid hormone concentration (table).

Ten days after the initial consultation the patient was admitted with paraesthesiae in the hands, feet and face, and dyspnoea from a feeling of pressure on his chest. Serum biochemistry showed hypocalcaemia (table).

He was treated with oral calcium supplements 1200 mg daily (without vitamin D) and discharged home. A biopsy of the mandibular swelling one month later showed a ‘brown tumour’ due to hyperparathyroid bone disease. There was fibrous replacement of the marrow space (osteitis fibrosa cystica). Osteoclasts were numerous and osteoblastic new bone formation was increased at the margins of the lesion.

His backache gradually improved; by 30 weeks the serum calcium returned to normal and the serum alkaline phosphatase fell to just above the upper reference limit (figure 3). He remained well on no treatment until he presented again with the original symptoms 90 weeks after the first consultation. Serum biochemistry showed hypercalcaemia, hypophosphataemia, elevated parathyroid hormone, but normal alkaline phosphatase (table). Radiographs showed improvement in the mandibular translucency and resolution of the phalangeal tuft resorption and subperiosteal erosion (figures 1B, 2B). Thallium scan of the neck showed no evidence of parathyroid activity and neck exploration failed to reveal any parathyroid tissue. Venous sampling showed no step-up in parathyroid hormone concentration in the neck or chest. Selective angiography suggested a parathyroid adenoma behind the right clavicle but two further explorations revealed only one normal parathyroid gland. Computed tomography (CT) of the neck showed a low attenuation, non-enhancing mass in the right lower pole of the thyroid gland. Ultrasonography confirmed a hypo-echoic mass 1.5 x 0.5 cm in the right lobe of the thyroid.

Removal of the right lobe of the thyroid during the fourth neck exploration, five years after the first presentation, was successful and histology confirmed a parathyroid adenoma 1.4 x 1.0 x 0.8 cm within the excised thyroid tissue. The patient became hypocalcaemic and required maintenance oral calcitriol treatment for hypoparathyroidism, but he remained well two years later on calcitriol 6 μg/day with a serum calcium in the normal range.

Discussion
This is the first well-documented report of a spontaneous cure of osteitis fibrosa cystica in proven primary hyperparathyroidism. The acute hypocalcaemia that heralded the event was most probably due to haemorrhagic infarction of a parathyroid adenoma, which could be termed parathyroid apoplexy. Similar crises are well known in other endocrine adenomas, for example, pituitary apoplexy. We could not justify urgent surgical exploration to prove the presence of a necrotic parathyroid adenoma and at that date urgent CT, ultrasound or magnetic resonance imaging of the neck to demonstrate a haemorrhagic mass were not available at the unit where he presented. When hyperparathyroidism recurred and a parathyroid adenoma was excised, no infarcted parathyroid tissue was found, but this is not surprising in view of the interval of five years. A previous pathological study has shown that severe acute hypocalcaemia in a patient with a suspected parathyroid

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Spontaneous cure of osteitis fibrosa cystica

Figure 1 Radiographs of the mandible (A) on presentation, (B) 10 months later and (C) five years later, showing spontaneous resolution of osteitis fibrosa cystica. Note the translucency due to a brown tumour eroding the cusps of the adjacent molar (A). Healing is apparent in (B) with new bone formation within the defect. In (C) the lesion has reduced in size and sclerotic is apparent in the posterior half of the brown tumour. A dense sclerotic rim is extending into the lesion from the margins.

Figure 2 Radiographs of the hand showing distal phalangeal tuft resorption and subperiosteal resorption along the radial borders of the phalanges (A) and spontaneous resolution after two years (B).
Table

Serum and urine biochemistry in a patient with a parathyroid adenoma to show spontaneous changes over 90 weeks

<table>
<thead>
<tr>
<th>Weeks:</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>12</th>
<th>30</th>
<th>90</th>
<th>Normal range</th>
</tr>
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<tbody>
<tr>
<td>Serum calcium (adjusted) (mmol/l)</td>
<td>3.94</td>
<td>3.71</td>
<td>1.78</td>
<td>2.05</td>
<td>2.23</td>
<td>3.25</td>
<td>2.20-2.60</td>
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<tr>
<td>Serum phosphate (mmol/l)</td>
<td>0.94</td>
<td>0.85</td>
<td>0.59</td>
<td>1.07</td>
<td>1.37</td>
<td>0.56</td>
<td>0.80-1.5</td>
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<tr>
<td>Serum magnesium (mmol/l)</td>
<td>1041</td>
<td>73</td>
<td>8.6</td>
<td>6.1</td>
<td>7.0</td>
<td>5.1</td>
<td>2.0-6.5</td>
</tr>
<tr>
<td>Serum alkaline phosphatase (IU/l)</td>
<td>269</td>
<td>298</td>
<td>328</td>
<td>269</td>
<td>298</td>
<td>269</td>
<td>80-280</td>
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<tr>
<td>Serum creatinine (mmol/l)</td>
<td>-</td>
<td>121</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>120</td>
<td>60-130</td>
</tr>
<tr>
<td>Serum N-terminal parathyroid hormone (ng/ml)</td>
<td>-</td>
<td>-</td>
<td>3.4</td>
<td>0.7</td>
<td>-</td>
<td>-</td>
<td>&lt;0.6</td>
</tr>
<tr>
<td>Serum intact parathyroid hormone (pmol/l)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>13.8</td>
<td>-</td>
<td>0.8-8.5</td>
</tr>
<tr>
<td>Serum 250H-cholecalciferol (ng/ml)</td>
<td>-</td>
<td>-</td>
<td>8.0</td>
<td>-</td>
<td>13.8</td>
<td>-</td>
<td>8-50</td>
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<td>Urine calcium excretion (mmol/24 h)</td>
<td>-</td>
<td>-</td>
<td>3.4</td>
<td>-</td>
<td>-</td>
<td>23</td>
<td>16-32</td>
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<tr>
<td>Urine phosphate excretion (mmol/24 h)</td>
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<td>-</td>
<td>-</td>
<td>11.4</td>
<td>9-17</td>
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<tr>
<td>Urine creatinine excretion (mmol/24 h)</td>
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<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

Figure 3 Serum calcium and serum alkaline phosphatase in a patient with a parathyroid adenoma followed for 250 weeks. The first hypocalcaemic episode was spontaneous, the second was after parathyroidectomy.

Summary/learning points

- after parathyroidectomy hungry bone disease may occur, causing prolonged hypocalcaemia while the skeleton takes up mineral to fill resorption cavities
- brown tumours heal by dense sclerosis over 12 months

The heightened activity of the osteoclasts up to the time of involution of the adenoma would lead to numerous resorption cavities. The time taken for osteoblasts to fill these cavities with new bone is three to four months in normal bone, but may be longer in osteitis fibrosa cystica despite the high bone turnover. The bone formation marker, alkaline phosphatase, took over 30 weeks to return to normal in our case. The mandibular defect healed as would be expected for a brown tumour which typically undergoes dense sclerosis within 12 months, in contrast to bone cysts which do not remineralise. Complete sclerosis did not occur, probably because of recurrent hyperparathyroidism after 30 weeks.

After parathyroidectomy the skeleton's avid requirement for calcium and phosphate to mineralise new bone (hungry bone disease) may last for months. The prolonged hypocalcaemia in our patient was probably due to this, compounded by suppression of the remaining parathyroid glands by previous chronic hypercalcemia, as demonstrated by an inadequate parathyroid hormone response (0.7 ng/ml) during the hypocalcaemic crisis.

There was difficulty in localising the adenoma because of its size and position. Small and ectopic parathyroid glands are poorly visualised by thallium subtraction imaging because of the low energy of the emitted photon.

Finally, hypocalcaemia in a patient with known primary hyperparathyroidism should lead one to consider acute pancreatitis and vitamin D deficiency, which are known complications of primary hyperparathyroidism and more common causes of hypocalcaemia than necrosis of an adenoma.

We acknowledge the assistance given by Professor JHL O'Riordan, Mr EJG Milroy and Dr HWP Rooke.
Cefuroxime-induced thrombocytopenia?

Peter Aitken, SMN Zaidi

Summary
We present the case of a 77-year-old man who became thrombocytopenic whilst treated parenterally with cefuroxime in the absence of proven infection and recovered when the cefuroxime was discontinued.

Keywords: cefuroxime, thrombocytopenia

Since 1966 there have been a number of case reports suggesting a link between cephalosporin therapy and blood dyscrasias, especially thrombocytopenia. In each case the causal link remains unproven because of the presence of confounding variables and the ethical position that precludes re-exposure of the sensitive individual to confirm the cause and effect. An immunological mechanism has been described in cefotetan-induced thrombocytopenia where potent IgG-cefotetan-dependent antplatelet antibodies were detected in the patient's serum. An animal model in the dog has also been described.

Case report
A 77-year-old man known to suffer from mild Alzheimer's disease and recurrent depressive disorder was admitted with a 10-day history of increasing anxiety and agitation and worsening depression. Examination revealed marked psychomotor agitation, perseverations and verbal stereotypes. His cognitive functioning had deteriorated. He appeared physically ill with a fluctuating conscious level, tachycardia, tachypnoea and profuse sweating. He remained apyrexial.

We diagnosed acute confusional state (delirium ICD 10) superimposed on mild dementia precipitating a relapse of his depressive disorder. We started haloperidol 5 mg bid on admission. Investigations included full blood count, erythrocyte sedimentation rate, mid-stream urine and urinary electrolytes, liver function tests, calcium, glucose, thyroid function tests, VDRL/TPA, three sets of blood cultures, malarial parasites, a chest X-ray and an electrocardiogram.

The significant preliminary result was growth of a Staphylococcus species (unspecified) in one blood culture bottle. We commenced cefuroxime 750 mg tid parenterally. We repeated the full blood count on days one and three of cefuroxime therapy and noted the platelet count to have fallen to 92 x 10^9/L. We considered this to be due to presumed infection or a side-effect of medication. On day five of cefuroxime therapy we received the final microbiological report on the blood culture identifying the organism as Staphylococcus epidermidis, a contaminant skin commensal. We stopped cefuroxime and repeated the full blood count days later, finding that the platelet count had risen to 164 x 10^9/L. Nine days later it was 325 x 10^9/L. The diagnosis was now a severe depressive episode. A course of electroconvulsive therapy was started on the day after

Side-effects of cefuroxime

- hypersensitivity reactions
- overgrowth of susceptible organisms
- gastrointestinal disturbance
- pseudomembranous colitis
- haematological parameters altered, including decreased haemoglobin concentration, leucopenia, neutropenia
- positive Coombs test
- transient rise in liver function tests
- pain at injection site
- very rare reports of thrombocytopenia

Box 1

References

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