Case Report;

Disabling Bone Pain after Long-term Kidney Transplantation.

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Case Report

A 77 year-old man who had received a renal transplant 13 years before was referred to the renal metabolic bone clinic at Westmead Hospital. He had an 8 week history of bilateral shin pain, which he first noticed in the right and then the left mid tibial regions. The pain developed shortly after a change from low dose cyclosporine to tacrolimus because of worsening chronic tophaceous gout. However there was no improvement when he was changed back to cyclosporine for one week, and he resumed taking tacrolimus. He described the pain as a continuous, dull ache, constant throughout the day and not improving with simple analgesia. He required walking sticks to move about, whereas 2 months before he had been walking without difficulty. Intercurrently he had noticed some loss of appetite but no weight loss or other constitutional symptoms, and he had not had any injury.

His chronic kidney disease was secondary to IgA nephropathy and creatinine levels had been stable at around 90 mcmol/L since his kidney transplant. A focal adenocarcinoma of the prostate had been diagnosed 6 years before this presentation, and had been managed by local treatment with no recurrences and a stable PSA. Five years before presentation a cryptococcal lung infection had been treated and a left posterior auricular squamous cell carcinoma (SCC) had been excised, followed by a left neck dissection, subtotal parotidectomy and radiotherapy. SCCs had also been excised from the left hand and forearm, with no recurrences. He had been treated for osteoporosis with alendronate 70 mg weekly for 2 years; the alendronate having been stopped 2 weeks after the pain began.

The patient was a pensioner and lived with his wife. He rarely drank alcohol, did not smoke tobacco or use illicit drugs or herbal supplements and at presentation his daily medications were allopurinol 300 mg, aspirin 100 mg, simvastatin 40 mg, prednisolone 10 mg and tacrolimus 2 mg twice daily.

On examination his temperature was 36.6°C, blood pressure 110/60 mm Hg, pulse 78 beats/minute, respiratory rate 20/minute, weight 60 kg and oxygen saturation 98% on room air. He was euvolaemic. There were gouty tophi at the elbow, wrist, ankle and first metatarsal joints. There was marked bilateral tibial tenderness, but the skin was not inflamed. Neurological examination was normal and pedal pulses were present. The remainder of the examination, including the neck, lymph nodes and rectal examination of the prostate was normal. There was no digital clubbing.

Initial outpatient investigations are listed in Table 1

Table 1. PSA: prostate specific antigen, ALP: alkaline phosphatase
<table>
<thead>
<tr>
<th></th>
<th>Value</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tacrolimus (trough level)</td>
<td>6 microgram/L</td>
<td>Within therapeutic range</td>
</tr>
<tr>
<td>Total PSA (µg/L)</td>
<td>1.1</td>
<td>0.30 - 7.5</td>
</tr>
<tr>
<td>Corrected calcium (mmol/L)</td>
<td>2.44</td>
<td>2.15 - 2.55</td>
</tr>
<tr>
<td>Phosphate (mmol/L)</td>
<td>1.0</td>
<td>0.8 - 1.5</td>
</tr>
<tr>
<td>ALP (U/L)</td>
<td>103</td>
<td>35 - 110</td>
</tr>
<tr>
<td>25-OH Vitamin D</td>
<td>74 nmol/L</td>
<td>51 - 140</td>
</tr>
<tr>
<td>Intact-PTH (pmol/L)</td>
<td>7.9</td>
<td>1.6 - 6.9</td>
</tr>
<tr>
<td>Bone specific ALP (µg/L)</td>
<td>22.0</td>
<td>3.7 - 20.9</td>
</tr>
<tr>
<td>Urine deoxypyridinoline/creatinine ratio (nmol/mmol)</td>
<td>7.2</td>
<td>2.3 - 5.4 (males)</td>
</tr>
<tr>
<td>C-reactive protein (mg/L)</td>
<td>8</td>
<td>&lt;5</td>
</tr>
<tr>
<td>Serum uric acid (mmol/L)</td>
<td>0.57</td>
<td>0.20 - 0.45</td>
</tr>
<tr>
<td>Serum and urine protein immunoelectrophoresis</td>
<td>No paraprotein detected</td>
<td></td>
</tr>
</tbody>
</table>

A chest X-ray was reported normal, as were tibial x-rays (Figure 1) although there was possible mild cortical thickening. On magnetic resonance imaging (MRI) there was marrow oedema and a prominent periosteal reaction involving the tibiae and left femur (Figure 2) together with a clinically silent lesion affecting the left femoral shaft. A radionuclide bone scan showed symmetrical, linear increased uptake in both tibiae and the left femur, and in addition, uptake was noted in both clinically asymptomatic humeri.

He was admitted to hospital unable to walk; with intractable mid tibial bone pain requiring oxycodone hydrochloride and gabapentin for relief. A further diagnostic test was performed.

**Differential diagnosis**
The prominent clinical feature in this case was severe and disabling bilateral mid-tibial pain. Non-articular bone pain is a relatively uncommon symptom, and the differential diagnoses generally encompass osteomalacia, atypical fracture, metastatic bone disease, Paget’s disease of bone, a periosteal reaction (periostitis) or, in patients taking calcineurin inhibitors, a flare of bone pain termed the calcineurin inhibitor-induced pain syndrome (CIPS). In determining the most likely diagnosis, it is important to correlate the clinical features with the investigation findings.

This patient’s history contained several factors that might contribute to adverse bone health, including a renal transplant with long-term glucocorticoid and calcineurin inhibitor therapy. Osteoporosis, possibly due to glucocorticoid use, was also present, and the patient had received alendronate for 2 years. There was a history of cancer, and in particular the left posterior auricular SCC had required extensive therapy. Laboratory investigations showed evidence of mild hyperparathyroidism and bone turnover; evidenced by increased values of bone-specific alkaline phosphatase, an osteoblast marker that is not influenced by diurnal variation or renal function, and of the bone resorption marker deoxypyridinoline/creatinine.

A number of diagnoses could be reasonably excluded. There was no evidence of vitamin D deficiency or hypophosphataemia that might support a diagnosis of osteomalacia and although CIPS affects the distal extremities and can cause severe, symmetrical bone pain, it generally occurs within the first months after transplantation (1,2). Vitamin C is essential for normal collagen synthesis and although rare, scurvy may present with bone and joint pain, subperiosteal haemorrhages and restriction of movement. Scurvy can occur in older people with restrictive diets, but was not considered likely in this case. On the other hand, the development of atypical fractures was not so readily excluded. Prodromal pain occurs in over 70% of patients with atypical femur fractures (3), usually felt in the upper femur or groin. Although most commonly located in the subtrochanteric region of the femur, recent case reports have described fractures affecting the humerus (4) and tibia. These are reported to have similar morphology to atypical femoral fractures, with local cortical thickening, transverse or oblique configuration and a medial cortical spike. This patient had some clinical factors associated with atypical fractures, including bisphosphonate and glucocorticoid use, increased bone resorption markers and periosteal change. However, the 2 years of bisphosphonate treatment is shorter than exposure times generally associated with atypical fractures.

With a periosteal reaction demonstrated at a number of skeletal sites, another uncommon cause of bone pain should also be considered; hypertrophic osteoarthropathy (HOA). This condition is characterized by a symmetrical periostitis of tubular bones, less frequently arthralgias and sympathetic effusions of distal, large joints, hypertrophic skin changes (pachydermia) and digital
clubbing (5). It may be inherited with the clinical features resulting from mutations in the gene responsible for encoding the prostaglandin degradation enzyme 15-hydroxyprostaglandin dehydrogenase, which leads to an accumulation of prostaglandin E2 (6,7). However, neurological, hormonal and immune mechanisms have also been suggested. Secondary forms may be caused by parenchymal lung disease (particularly adenocarcinoma), cardiac disease such as right-to-left shunts and occasionally gastrointestinal diseases or haematological malignancies such as Hodgkin lymphoma.

A secondary form of periostitis due to a cancer would appear to be the most likely cause of the findings in this case. As to the mechanism, the role of the pulmonary endothelium in clearing a variety of circulating substances was recognised several decades ago. Normally, megacaryocytes fragment in the lung circulation, but in secondary HOA they bypass the pulmonary vascular network through arteriovenous anastomoses and reach peripheral capillaries to release platelet-derived growth factors (PDGF) from alpha granules (8). This promotes angiogenesis, vascular proliferation, oedema and osteoblast activation. Other substances such as bradykinin, slow-reacting substance of anaphylaxis and transforming growth factor-β 1 are also released from platelet alpha granules, and can promote angiogenesis, neo-osteogenesis and oedema. Lung cancers may also produce PDGF (9). Vascular endothelial growth factor (VEGF) has similar bone and vascular effects to PDGF and levels are reported to decline following lung cancer resection (10).

Subperiosteal neo-osteogenesis may present radiologically as symmetrical, linear periosteal thickening (11). On radionuclide bone scans or magnetic resonance imaging, these linear periosteal changes are most commonly detected involving distal long bones and less commonly the humerii and femora; producing a ‘tram line’ appearance on bone scintigraphy (12). Bisphosphonates may have a role in the symptomatic treatment of hypertrophic osteoarthropathy (13), possibly due to inhibition of bone turnover and reducing VEGF levels.

**Diagnosis**

A bone biopsy was performed at one of the sites of tibial pain. This disclosed small deposits of poorly differentiated metastatic cancer, predominantly within vascular spaces, with hyperchromatic nuclei and increased nuclear to cytoplasmic ratio but no squamous differentiation, keratinization or glandular formation. Although the chest x-ray was normal at presentation, a subsequent chest CT revealed a left lung lesion extending into the adjacent mediastinum anterior to the ascending aorta, with no lymphadenopathy and no abnormality of soft tissue structures of neck. The most likely diagnosis was therefore primary lung cancer with metastatic disease to bone, and an associated
hypertrophic pulmonary osteoarthropathy. The patient was treated with an infusion of zoledronic
acid, but decided against further investigations or treatment and was referred for palliative care.

**Conclusion**

The longevity of organ transplant recipients comes at a price; the risk of developing a malignancy.
For patients requiring long term immunosuppression, this risk is 3 - 4 times greater than that of the
general population. Bone pain may certainly indicate the presence of bone metastases, but the
linear, symmetrical periostitis involving tibiae and humerii in this case supported an additional
diagnosis of HOA. In fact, HOA is a more likely cause of bone pain than metastatic disease (14).
Interestingly, neither wrist tenderness nor digital clubbing was identified in this case.

**Figure 1.** X-Ray of the tibia and fibula; X-Rays of the pelvis, both femora and the humeri were
reported normal. However subtle periosteal thickening may be present.

**Figure 2.** MRI of lower limbs showing prominent marrow signal change bilaterally in the mid tibiae
with prominent periosteal reaction.

**Figure 3.** CT chest showing left lung lesion extending into adjacent mediastinum.
References:


