Osteoporos Int (2014) 25:769–772
DOI 10.1007/s00198-013-2425-3

CASE REPORT

A case report of disabling bone pain after long-term kidney transplantation

T. M. M. Myint · M. Vucak-Dzumhur · P. R. Ebeling · G. J. Elder

Received: 9 April 2013 / Accepted: 3 June 2013 / Published online: 26 June 2013

Abstract A 77-year-old man, who received a renal transplant 13 years before for IgA glomerulonephritis, was referred after he developed bilateral mid-tibial aching pain that did not improve with simple analgesia. He had recently been changed from low-dose cyclosporine to tacrolimus, but the pain did not improve when this was reversed. He had a history of focal prostatic adenocarcinoma, cryptococcal lung infection, osteoporosis treated with alendronate for 2 years and multiple squamous cell carcinomas, including one requiring left neck dissection and radiotherapy. Upon physical examination, he had gouty tophi and marked bilateral tibial tenderness but had no other clinical findings. Laboratory investigations included an elevated intact parathyroid hormone value of 7.9 pmol/L (1.6 to 6.9), bone specific alkaline phosphatase of 22 μg/L (3.7 to 20.9), urinary deoxypyridinoline/creatinine ratio of 7.2 nmol/mmol (2.5 to 5.4) and C-reactive protein. Chest X-ray and tibial X-rays were normal, but there was marrow oedema and a prominent periosteal reaction on magnetic resonance imaging. A radionuclide bone scan showed increased symmetrical, linear uptake in both tibiae and the left femur, and uptake was also noted in both clinically asymptomatic humeri. Tibial bone biopsy disclosed small deposits of poorly differentiated metastatic cancer and a follow-up chest CT revealed a lung lesion. It was concluded that the bone pain and periostitis was caused by primary lung cancer with metastatic disease to bone, and an associated hypertrophic osteoarthropathy.

Keyword Kidney transplantation · Bone pain · Hypertrophic osteoarthropathy

T. M. M. Myint · M. Vucak-Dzumhur · G. J. Elder
Department of Renal Medicine, Westmead Hospital, Westmead, NSW, Australia

P. R. Ebeling
The University of Melbourne, NorthWest Academic Centre, Melbourne, Victoria, Australia

G. J. Elder (✉)
Osteoporosis and Bone Biology Division, Garvan Institute of Medical Research, Sydney, NSW, Australia
e-mail: g.elder@garvan.org.au

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 1 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 μmol/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 prostate-specific antigen (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

Table 1 Initial outpatient laboratory test results

Diagnostic test	Value	Range
Tacrolimus (trough level)	6 μg/L	Within therapeutic range
Total PSA (μg/L)	1.1	0.30–7.5
Corrected calcium (mmol/L)	2.44	2.15–2.55
Phosphate (mmol/L)	1.0	0.8–1.5
ALP (U/L)	103	35–110
25-OH Vitamin D	74 nmol/L	51–140
Intact-PTH (pmol/L)	7.9	1.6–6.9
Bone-specific ALP (μg/L)	22.0	3.7–20.9
Urine deoxypyridinoline/ creatinine ratio (nmol/mmol)	7.2	2.3–5.4 (males)
C-reactive protein (mg/L)	8	<5
Serum uric acid (mmol/L)	0.57	0.20–0.45
Serum and urine protein immunoelectrophoresis	No paraprotein detected	

PSA, prostate-specific antigen, *ALP* alkaline phosphatase

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 was 110/60 mm Hg, pulse was 78 beats/min, respiratory rate was 20 cycles/min, weight was 60 kg and oxygen saturation was 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.

A chest X-ray was reported normal, as were tibial X-rays (Fig. 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 (Fig. 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 the 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.

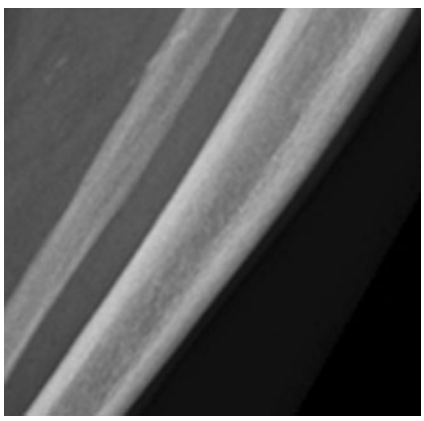

Fig. 1 X-ray of the tibia and fibula was reported normal, as were X-rays of the pelvis, both femora and the humeri. However, subtle periosteal thickening may be present

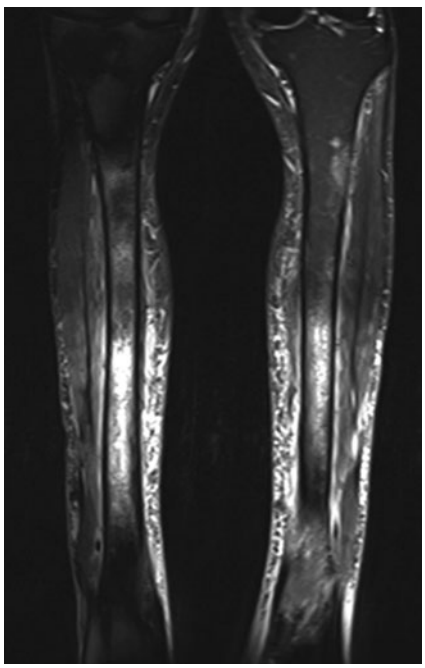

Fig. 2 MRI of lower limbs showing prominent marrow signal change bilaterally in the mid-tibiae with prominent periosteal reaction

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 be 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 characterised by a symmetrical periostitis of tubular bones, less frequent 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's 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, megakaryocytes 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 humeri 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 the 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, subsequent chest computed tomography (CT)

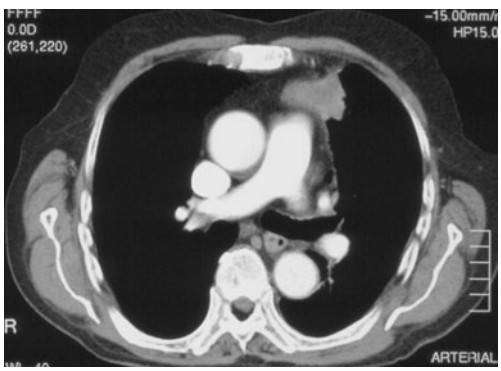

Fig. 3 Chest CT showing left lung lesion extending into adjacent mediastinum

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 the neck (Fig. 3). The most likely diagnosis was therefore primary lung cancer with metastatic disease to bone and an associated hypertrophic 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 humeri 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.

Conflicts of interest None.

References

1. Grotz WH, Breitenfeldt MK, Braune SW, Allmann KH, Krause TM et al (2001) Calcineurin-inhibitor induced pain syndrome (CIPS): a severe disabling complication after organ transplantation. Transpl Int 14(1):16–23
2. Elder GJ (2006) From marrow oedema to osteonecrosis: common paths in the development of post-transplant bone pain. Nephrology (Carlton) 11(6):560–567
3. Shane E, Burr D, Ebeling PR et al (2010) Atypical subtrochanteric and diaphyseal femoral fractures: report of a task force of the American Society for Bone and Mineral Research. J Bone Miner Res 25(11):2267–2294
4. Yavropoulou MP, Giusti A, Ramautar SD, Dijkstra S, Hamdy NAT et al (2012) Low-energy fractures of the humeral shaft and bisphosphonate use. J Bone Miner Res 27(6):1425–1431
5. Martinez-Lavin M, Matucci-Cerinic M, Jajic I et al (1993) Hypertrophic osteoarthropathy: consensus on its definition, classification, assessment and diagnostic criteria. J Rheumatol 20:1386–1387
6. Castory M, Sinibaldi L, Mingarelli R, Lachman RS, Rimoin DL et al (2005) Pachydermoperiostosis: an update. Clin Genet 68:477–486
7. Martinez-Ferrer, Peris P, Alos L, Morales-Ruiz M, Guanabens N (2009) Prostaglandin E2 and bone turnover markers in the evaluation of Primary hypertrophic osteoarthropathy (pachydermoperiostosis): a case report. Clin Rheumatol 28(10):1229–1233
8. Silveri F, De Angelis R, Argentari F et al (1996) Hypertrophic osteoarthropathy: endothelium and platelet function. Clin Rheumatol 15:435–439
9. Kawai T, Hiroi S, Torikata C (1997) Expression in lung carcinoma of platelet-derived growth factor and its receptors. Lab Invest 77:431–436
10. Silveira LH, Martinez-Lavin M, Pineda C et al (2000) Vascular endothelial growth factor and Hypertrophic osteoarthropathy. Clin Exp Rheumatol 18:57–62
11. Pineda C (1992) Diagnostic imaging in hypertrophic osteoarthropathy. Clin Exp Rheumatol 10(Suppl 7):27–33
12. Russo R, Lee A, Mansberg R, Emmett L (2009) Hypertrophic pulmonary osteoarthropathy demonstrated on SPECT/CT. Clin Nucl Med 34(9):628–631
13. King MM, Nelson DA (2008) Hypertrophic osteoarthropathy effectively treated with zolnedronic acid. Clin Lung Cancer 9(3):179–182
14. Saeed H, Massarweh S (2012) Images in clinical medicine. Hypertrophic pulmonary osteoarthropathy and tripe palms. N Engl J Med 366(4):360