Acute renal failure and hypercalcaemia in a man from Guyana: what is the link?

Case

A 51-year old Guyanese businessman presented with a 5-week history of increasing lethargy, thirst, polyuria and diffuse symmetrical pain in both small and large joints. His own doctor prescribed diclofenac for the arthralgia, and atenolol and bendrofluazide for hypertension. He had migrated to the UK at the age of 18 and had no clinical history of note. His mother had died aged 57 of unknown cause. On examination, he was afebrile and clinically hypovolaemic. There was diffuse small joint tenderness but no other significant clinical findings. Laboratory tests revealed: leukocytosis of $21.9 \times 10^9/l$ (neutrophils $12.3 \times 10^9/l$, lymphocytes $6.8 \times 10^9/l$), marked hypercalcemia [calcium adjusted for albumin concentration (ACa) $5.12 \text{ mmol/l}$], phosphate $1.7 \text{ mmol/l}$, serum albumin $35 \text{ g/l}$ and renal dysfunction [urea $17.9 \text{ mmol/l}$, creatinine $206 \mu \text{mol/l}$ ($2.34 \text{ mg/dl}$)]. One month earlier, his urea had been $4.9 \text{ mmol/l}$ and creatinine $82 \mu \text{mol/l}$ ($0.93 \text{ mg/dl}$). His 24 h urine volume was 6 litres with a protein excretion of $0.4 \text{ g/24 h}$ and creatinine clearance $47 \text{ ml/min}$. Blood film showed a lymphocytosis with pleomorphic morphology, but bone marrow trephine showed only hypercellular marrow with reactive non-specific changes. All medication was stopped on admission and he was fluid resuscitated. Pamidronate ($60–90 \text{ mg}$) was administered on six occasions over a period of 1 month. Though renal function improved [urea $5.5 \text{ mmol/l}$, creatinine ($92 \mu \text{mol/l}$, $1.04 \text{ mg/dl}$)], ACa remained consistently $>3.00 \text{ mmol/l}$.

Our patient’s resistant hypercalcaemia was investigated and a number of hormones and cytokines involved in calcium homeostasis were measured using standard chemistry assays (Roche, Lewes, UK) and commercial immunoassays (Nichols, San Juan Capistrano, USA, R & D Systems, UK, Biomedica, GmbH): parathyroid hormone (PTH) $0.3 \text{ pmol/l}$ ($0.5–5.5$), 25-OH-vitamin D $29 \text{ nmol/l}$ ($>50$), 1,25-(OH)$_2$-vitamin D $38 \text{ nmol/l}$ ($43–144$), PTH-related peptide (PTHrP) $6.3 \text{ pmol/l}$ ($<1.8$), interleukin-6 (IL-6) $4.6 \text{ pg/ml}$ ($<3$), receptor activator of nuclear factor-κB ligand (RANKL) $1.3 \text{ pmol/l}$ ($0.7–1.2$), osteoprotegerin (OPG) $8.3 \text{ pmol/l}$ ($2.7–3.2$), tumour necrosis factor-α (TNF-α) $2.9 \text{ pg/ml}$ ($<15.6$) and soluble TNF receptor-1 (sTNFR-1) $3787 \text{ pg/ml}$ ($512–1739$).

Radiographs of the sites of bony tenderness were taken (Figure 1). An isotope scan of the parathyroids was normal, and computed tomography (CT) scan of his neck, thorax and abdomen showed a non-obstructing right renal calculus but no other abnormalities.

Questions

(i) What does the X-ray show?
(ii) What serological test would be useful?
(iii) What is the diagnosis?
Answer to the quiz on the preceding page

The radiograph shows both subperiosteal bone resorption and widespread discrete 1–2 mm diameter foci of cortical loss. X-rays of the distal forearm bones showed similar changes. Subperiosteal erosions, especially on the radial aspect of the middle phalanx of the middle and index fingers, are pathognomonic of hyperparathyroidism. Furthermore, in hyperparathyroidism, there can be intra-cortical bone loss in the form of ‘brown’ tumours. However, in our patient, the radiologically discrete areas of cortical loss are far too small to be considered to be ‘brown’ tumours. In addition, the apparently normal bone density on the X-ray and the extensive involvement of the metacarpal bones rules out hyperparathyroidism. There are a number of other causes of bone resorption. In myeloma, the lesions are ‘punched out’ and rarely affect the peripheral skeleton. Sarcoidosis produces a lace-like pattern of bone loss unlike the appearances in Figure 1. The sparing of the joints in our patient also excludes erosive arthropathies such as osteoarthritis and rheumatoid arthritis. Clearly, in our patient, the priority was to exclude a neoplastic cause for his bone disease.

In view of the patient’s country of origin, antibodies to human lymphotropic T-cell virus type 1 (HTLV-1) were sought; they were positive. A diagnosis of acute adult T-cell leukaemia/lymphoma (ATLL) was made; immunophenotyping (CD2⁺/HLA-DR⁺ = 85%) was diagnostic of HTLV-1 infection. Our patient’s illness, therefore, was a clear example of ATLL-related humoral hypercalcaemia of malignancy (HHM).

Prognosis of patients with ATLL is poor. The median survival is 8 months, and the 4-year survival is only 12% even when treated optimally. Our patient had a particularly aggressive and resistant form of the disease and he underwent multiple regimens of chemotherapy including CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone), PitMiCEBO (mitoxantrone, cyclophosphamide, etoposide, bleomycin, vincristine, prednisolone), DHAP (dexamethasone, cisplatin, cytarabine) and EMI (epirubicin, etoposide, ifosfamide, mesna). He was also given CAMPATH (CD52 monoclonal antibody), and a combination of interferon-α with combivir (zidovudine and lamivudine), the latter regimen having been shown to be beneficial in recent studies. Sadly, our patient failed to improve and died 3 months after presentation.

Hypercalcaemia is common in certain haematological malignancies and occurs in up to 80% of cases of ATLL, a condition closely associated with HTLV-1 infection [1]. This virus is endemic in the southern Caribbean (where our patient was born) and Japan. It can be transmitted both sexually and through blood contamination, but in our patient vertical transmission, during pregnancy or breast-feeding [2], is most likely. In patients acquiring HTLV-1 infection at an early age, there is a 2–4% lifetime risk of developing ATLL [3]. The fact that our patient was
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completely well until presentation is consistent with the known latent period of at least 20 years between infection and disease manifestation [4].

HHM is a consequence of calcium release secondary to accelerated widespread bone resorption [5]. A number of cytokines, also expressed by ATLL cells, can induce proliferation of the bone-resorbing osteoclast, but until recently it was not clear which ones were responsible for directly initiating osteoclastogenesis. Osteogenic factors previously postulated include IL-1, IL-2, IL-6, TNF-α, macrophage colony-stimulating factor (M-CSF) and PTHrP [6,7]. It is now clear that the elusive osteoclastic differentiation factor is the well-known ligand, RANKL [8]. Expressed by pre-osteoblastic and stromal cells, RANKL binds to its receptor RANK on the surface of pre-osteoclast lineage cells and pre-fusion osteoclasts to initiate differentiation to osteoclasts. The process is moderated by OPG (a soluble protein secreted by osteoblasts), which acts as a decoy receptor for RANKL [9].

PTH can be low in HHM, whereas PTHrP, which has a partially identical sequence (13 amino acids) in the active domain to PTH and shares the same receptor (PTH1-R), can be significantly elevated [10]. This was the case in our patient. In vivo, PTHrP increases bone resorption and renal tubular reabsorption of calcium. In addition, cytokines such as IL-6, IL-1 and TNF have been shown to have a synergistic action with PTHrP [11,12]. However, PTHrP alone does not appear to increase the numbers of osteoclasts and it has not been shown convincingly that osteoclasts express PTH receptors; hence, direct osteoclast activation by PTHrP is unlikely.

Circulating IL-6, TNF-α and PTHrP were increased in our patient, and the overall synergistic effect could explain the extreme hypercalcaemia observed. Surprisingly, for such severe hypercalcaemia, both RANKL and TNF-α levels were not significantly elevated in the presence of high OPG and sTNFR-1 levels. However, since each assay measures only the free fraction of the molecule, it is possible that the bound (unmeasured) portion of RANKL/TNF-α was high. The significance and role of sTNFR-1 in osteoclastogenesis have yet to be defined.

We did not check for the presence of tax, a viral gene product that is expressed in tumour cells transformed by HTLV-I in vivo. Tax, although it induces the expression of a wide range of host cell gene products—including cytokines, transcription factors and membrane proteins and receptors—is not associated with the expression of the RANKL gene [13].

Although some patients with ATLL have elevated levels of 1,25-(OH)2-vitamin D as a result of increased 1α-hydroxylase activity, the majority, like our patient, have suppressed 1,25-(OH)2-vitamin D levels. Elevation of 1,25-(OH)2-vitamin D levels, therefore, is not a contributory factor in the hypercalcaemia.

This case highlights the complexity of the pathophysiology of HHM and the advances that have been made in its understanding. It should be mentioned that OPG has shown promising therapeutic effects in malignant, rheumatic and post-menopausal bone disease and also in inhibiting the apoptosis of myeloma and cancer cells in vitro.

Our patient is unusual in presenting with symptoms secondary to hypercalcaemia but with no obvious clinical features of ATLL—lymphadenopathy, skin lesions or organomegaly; also, there were no constitutional symptoms of lymphoma. The important clue in making the correct diagnosis was his country of origin. This case underlines the importance of considering all aspects of a patient’s history. It also illustrates the paradox of having a very long period of asymptomatic HTLV-1 infection culminating in a short fulminating final phase of acute ATLL.

Several questions are raised by this patient’s case. Since HTLV-1 is sexually transmitted, should his wife be screened? Indeed, should individuals at risk, including the newborn, be screened routinely? Currently in the UK, there is no widespread screening of individuals from endemic areas. However, in August 2002, HTLV-1 screening was introduced by the National Blood Service for all donations of blood products, and for certain donor tissue—cornea, skin, bone and heart valves [14,15]. Yet, for solid organs, neither the UK nor Eurotransplant tests for HTLV-1 infection. Should they not now be doing so?

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References


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