Correspondence

Hypercalcemia: A Manifestation of Immune Reconstitution Complicating Tuberculosis in an HIV-Infected Person

Sir—In the report by Jenny-Avital and Abadi [1], we read with interest that, among a series of HIV-1–infected patients who developed antiretroviral treatment (ART)–induced immune reconstitution cryptococcosis, 1 patient also developed hypercalcemia. Restoration of the host’s granulomatous response to cryptococcal antigen in the mediastinal lymph nodes was postulated as being a source of increased 1,25-dihydroxy-vitamin-D3 [1,25(OH)2D3]. Herein, we report a similar phenomenon that occurred in a patient with tuberculosis (TB) that supports this conclusion.

A 44-year-old African man was admitted to the hospital with widespread smear-positive pulmonary TB; culture yielded fully susceptible Mycobacterium tuberculosis. HIV-1 infection, AIDS, and HIV nephropathy were also diagnosed, and the initial CD4 lymphocyte count was 8 × 106 cells/L. Clinical improvement during the intensive phase of standard, quadruple anti-TB treatment was paralleled by marked amelioration of the pulmonary radiographic appearances. The patient also received prophylaxis against pneumocystis pneumonia, and, in the third month of TB treatment, ART involving 3 agents was commenced.

Four weeks after ART was started, the patient developed increasing breathlessness and was found to have recurrent bilateral upper zone pulmonary radiographic shadowing and associated hypoxia. Marked hypercalcemia was also noted; the albumin-corrected serum calcium level increased to 3.07 mmol/L (normal range, 2.20–2.52 mmol/L) from a pre-ART level of 2.39 mmol/L. He denied taking calcium or vitamin D supplements. Serum concentrations of phosphate and alkaline phosphatase and the findings of a bone scan were normal. The serum creatinine level was elevated (197 mmol/L; normal range, 60–110 mmol/L), and the serum parathyroid hormone level was low (0.4 pmol/L; normal range, 1.1–6.9 pmol/L). The serum 25-hydroxycholecalciferol level was very low (<17 pmol/L; normal >25 pmol/L), in keeping with marked malnutrition. In contrast, serum levels of 1,25(OH)2D3 were paradoxically normal (84 pmol/L; normal range, 40–150 pmol/L), despite significant renal impairment. A bronchoalveolar lavage fluid specimen was found to contain abundant alveolar macrophages, but it tested negative for acid-fast bacilli and Pneumocystis carinii and was sterile on culture.

At this time, after 4 weeks of ART, the plasma HIV load had decreased to 451 copies/mL from 456,778 copies/mL, and his CD4 count had rapidly increased to 110 × 106 cells/L from 8 × 106 cells/L. A diagnosis of immune reconstitution alveolitis complicated by hypercalcemia was made. After addition of prednisolone (40 mg q.d. once daily) to the treatment regimen, the patient’s respiratory symptoms markedly improved, and the serum calcium level returned to the normal range within 1 week.

Hypercalcemia is a recognized complication of granulomatous lung disease, including sarcoidosis [2], TB [3, 4], and fungal disease [5, 6]. Extra-renal production of physiologically active 1,25(OH)2D3 due to the 1α-hydroxylase activity of alveolar macrophages is the underlying mechanism [2]. The host granulomatous response is markedly impaired in patients with advanced HIV-induced immunodeficiency [7]. However, we suggest that restoration of the granulomatous host response during ART led to increased synthesis of 1,25(OH)2D3 in this patient, which caused hypercalcemia. An alternative diagnosis of drug-induced hypercalcemia was considered but has not previously been reported in association with the drugs administered in this case. Granuloma formation and 1α-hydroxylase activity are suppressed by corticosteroids [2], and, indeed, the patient’s serum calcium level normalized rapidly while he was receiving prednisolone. Clinicians should be alert to the possibility of hypercalcemia in immune reconstitution syndromes.

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References

Use of Veterinary Vaccines Associated with Illness in a Man

Sir—We read with interest the articles by Berkelman [1] and Weil et al. [2], and we wish to report a case of human illness associated with the use of vaccine strain *Brucella mellitensis* REV 1. The patient was a 76-year-old man. His medical history included arterial hypertension, herpes zoster, nonsteroidal anti-inflammatory drug–induced digestive hemorrhages, and a total knee replacement, which was performed 5 years before his current visit.

The patient presented with inflammatory prosthetic knee pain associated with swelling of the joint. No other local or general syndrome involving fever was present. A nonspecific, self-limited episode of fever syndrome lasting for 1 week had occurred 45 days before presentation. The patient later reported that he had handled, sacrificed, and eviscerated 2 lambs at his farm, which is located in an area where brucellosis is endemic.

Initial examination had been performed at another hospital and revealed a globular sedimentation rate (GSR) of 73 mm/h (normal value, \( \leq 20 \) mm/h), a C-reactive protein (CRP) level of 39.9 g/dL (normal value, \( \leq 10 \) g/dL). The *Brucella* titer was found to be 1:320 by agglutination testing and 1:640 by Coombs testing. No treatable arterial hypertension, herpes zoster, nonsteroidal anti-inflammatory drug–induced digestive hemorrhages, and a total knee replacement, which was performed 5 years before his current visit.

The patient was initially treated with linezolid, amoxicillin–clavulanate, and levofloxacin, together with surgical cleansing.

The patient was asymptomatic at the time of communication, 2 years later, and had a good prosthetic function. Antibiotic treatment for a 6-month period was effective. The use of modified germs for the treatment of cattle may cause certain agents to enter into the human cycle and lead to pathology. We have no experience in this field, and such situations are unknown to us.

This is an example of transmissions that could occur when live germs are used in animal vaccines. The drug susceptibility characteristics for such events are anomalous. We should remain alert and be prepared for potentially similar cases in the future.

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References

Delayed Discovery of Linezolid-Resistant, Vancomycin-Resistant *Enterococcus faecium*: Lessons Learned

Sir—In reference to the study by Rahim et al. [1], we report what we believe to be yet another case of infection with linezolid-resistant, vancomycin-resistant *Enterococcus faecium* (LRVREF) in the United States in which the patient did not have prior exposure to linezolid, along with a cautionary note about revisiting the microbiology data reporting practices.

Our patient was an 81-year-old woman with multiple serious medical comorbidities. She had been treated several months earlier with a 6-week course of intravenous vancomycin for methicillin-resistant *Staphylococcus aureus* (MRSA) septic arthritis, and she was readmitted for “general decline and further decrease from baseline.” At admission, joint aspirate cultures yielded MRSA, and urine cultures yielded vancomycin-resistant *E. faecium*. The patient was initially treated with linezolid; she continued receiving this therapy because she refused placement of intravenous lines. Shortly thereafter, the patient died after being classified as “comfort care only,” in accordance with her and her family’s wishes. Unfortunately, we serendipitously “discovered” this resistant isolate after the fact during the preparation of our annual antibiogram. Although the LRVREF isolate did not change the eventual outcome for our patient (several urine cultures were negative for LRVREF), this provided an opportunity for the microbiology, infection control, and pharmacy sections at our institutions to learn several lessons.