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Inappropriate secretion of antidiuretic hormone as the initial sign of central nervous system progression of nocardiosis in a patient with chronic lymphocytic leukemia

Sir,

Nocardiosis is a relatively rare infection caused by aerobic actinomycetes of the genus *Nocardia*. Nocardiosis occurs mainly in immunocompromised hosts as an opportunistic infection; pulmonary infection is the general form of presentation.¹ The infection, however, frequently disseminates to distant sites, especially the central nervous system (CNS) but the onset of CNS invasion can be silent for months or even years.^{1,2}

A 52-year old woman was diagnosed in early 1993 as having Binet stage II classic B-cell chronic lymphocytic leukemia (CLL). She was treated with chlorambucil and prednisone for six months. CLL progressed very slowly, but she refused further therapy. In July 1998 she was admitted to hospital because of a four-day history of dyspnea and fever. Physical examinations and chest X-rays revealed a massive right pleural effusion with bilateral alveolar condensation. An aerobic actinomycetes later identified as *N. asteroides* was isolated from her sputum. No antimicrobial susceptibility tests were performed and treatment with imipenem (500 mg every 6 hours) plus amikacin (500 mg every 12 hours) was started. A thoracic CT scan showed a solid alveolar condensation in the right upper lobe of the lung with signs of extensive central cavitation (Figure 1). Within five days her clinical condition dramatically improved. However, twenty-five days later the patient developed drowsiness, a change in character and visual hallucinations. Her blood chemistry showed plasma sodium of 120 meq/L (normal >138 meq/L); plasma osmolarity

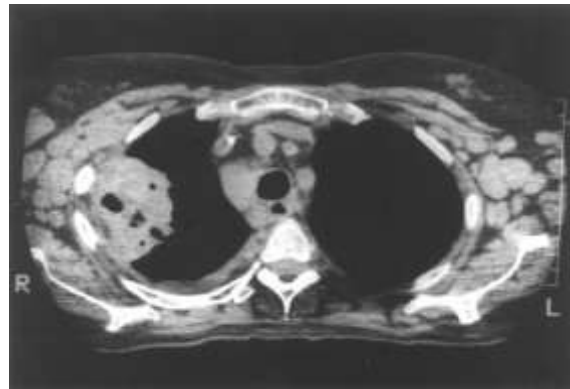


Figure 1. Thoracic CT scan shows an alveolar infiltrate in the right upper lobe with various areas of cavitation.

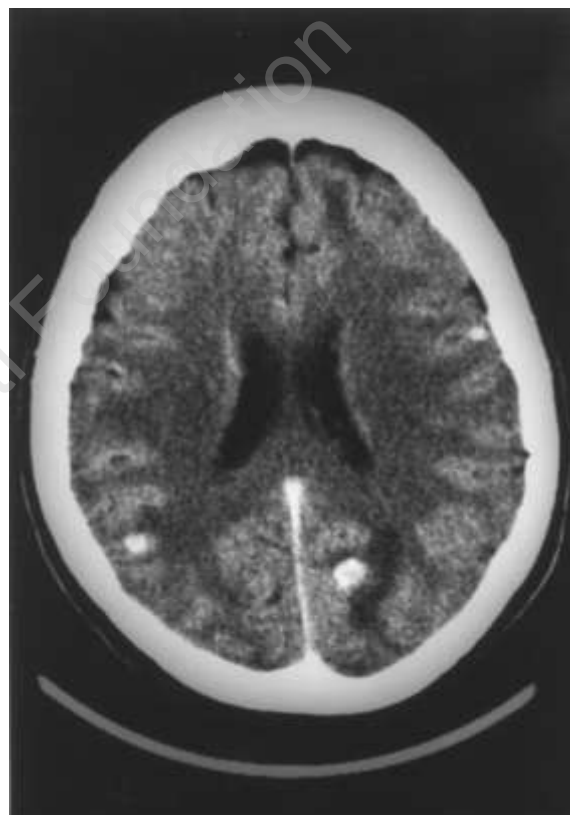


Figure 2. Brain CT scan shows several nodular lesions suggestive of brain abscesses.

was 259 mosm/L (normal >300 mosm/L) with concomitant high urinary osmolarity of 347 mosm/L. These findings were consistent with the diagnosis of inappropriate secretion of antidiuretic hormone (SIADH); pharmacological causes of this syndrome were excluded. A cranial CT scan showed multiple bilateral hypodense lesions with ring-shaped enhancement following the administration of intravenous contrast (Figure 2) highly suggestive of intracranial abscesses. The antibiotic treatment was changed to meropenem

(1 g every 8 hours) because of its greater ability to cross the blood brain-barrier, trimethoprim/sulphamethoxazole (160/800 mg every 8 hours) and amikacin (500 mg every 12 hours). The patient's clinical condition slowly deteriorated and the patient died 73 days after the start of the antibiotic treatment. Post-mortem examination confirmed the diagnosis of CNS and pulmonary nocardiosis.

Infection remains a major cause of significant morbidity and mortality in patients with advanced CLL.³ *N. asteroides* is the most frequent species of *Nocardia* involved in human infection. Although there are rare descriptions of this infection being one of the emerging infectious complications of purine analog-based therapy for CLL and low-grade lymphoma,³ there have been no previous reports of it occurring in patients treated with chlorambucil. The most interesting thing to learn from our case is, however, that CNS involvement can be silent and elusive; in fact, the CNS may have been involved from the onset of the disease but the poor passage of imipenem and amikacin across the blood-brain barrier may have allowed its progression. Clinically, however the first sign of this complication was SIADH which constitutes an interesting and previously undescribed association. In a recently described case a patient who attained apparent control of the infection was later found at autopsy to have an active *N. asteroides* cerebral abscess.⁴

Some authors have recommended routine cranial CT scanning in all patients diagnosed as having a nocardial pulmonary infection and no neurologic signs or symptoms;² in patients with hematologic malignancies, this recommendation should be given even more consideration. Finally, since nocardiosis is prone to relapse following initially successful therapy,¹⁻³ these patients should receive long-term secondary prophylaxis during subsequent courses of chemotherapy.⁵

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Graft-versus-lymphoma effect in a patient with a refractory low-grade lymphoma

Sir,

Allogeneic bone marrow transplantation (BMT) reduces the risk of relapse in non-Hodgkin's lymphoma (NHL) by approximately half as compared to autografting.¹ The lower risk of relapse following allograft is mainly attributed to the immunologic graft versus NHL (GvNHL) effect.^{2,3} The discontinuation of immunosuppressive therapy, with or without donor lymphocyte infusion (DLI), has been recently proposed as an effective approach to induce GvNHL in patients relapsed after allogeneic BMT.^{3,4}

We describe the case of a patient with stage IV follicular NHL in whom a GvNHL effect was induced after allogeneic BMT by cyclosporin A (CSA) withdrawal. In January 1993, a 34-year old man presented with enlargement of axillary, inguinal and lateral cervical lymph nodes. Enlargement of abdominal and mediastinal lymph nodes was also documented. A lymph node biopsy was diagnostic for follicular NHL and iliac crest biopsy demonstrated bone marrow involvement. Cytogenetics and bcl-2 gene rearrangement analysis were not performed. The patient failed to achieve durable responses after several lines of chemotherapy, i.e. anthracycline-containing regimens, α -interferon and fludarabine. In March 1997 he underwent allogeneic BMT from an HLA-identical sibling donor. Pre-transplant re-evaluation of the disease status revealed general enlargement of both mediastinal and abdominal lymph nodes and bone marrow involvement. The conditioning regimen consisted of busulfan and cyclophosphamide, while CSA and short-course methotrexate were administered for graft-versus-host disease (GvHD) prophylaxis. He developed grade I GvHD on day +45 after transplant and methylprednisone 0.5 mg/kg/die was administered. The patient attained complete response as documented by total body CT scan and bone marrow biopsy. On day +248 bilateral cervical lymph nodes appeared with biopsy-confirmed recurrence of follicular NHL, while total body CT scan did not reveal further lymph node enlargement. CSA was immediately withdrawn in order to induce a GvNHL effect and,