Cryptococcal Immune Reconstitution Inflammatory Syndrome following Alemtuzumab Therapy

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Alemtuzumab is a lymphocyte ablative agent that may cause susceptibility to severe opportunistic infections similar to those seen in AIDS. Pathogen-specific immune reconstitution syndromes can complicate antiretroviral therapy and immune recovery in HIV-infected patients. We present the first reported case of immune reconstitution syndrome associated with T lymphocyte recovery after alemtuzumab therapy.

A 55-year-old white man received a diagnosis of T cell prolymphocytic leukemia in December 2003. The patient’s peripheral blood lymphocyte count was \(191 \times 10^9\) cells/L (reference range, 1.2–4.0 \(\times 10^9\) cells/L), with a clonal population of T cells expressing the cell surface markers CD2, CD3, CD4, CD5, and CD7. Sequential treatment with fludarabine and cyclophosphamide failed to achieve disease remission. The results of serological tests for HIV type 1 and type 2 and human T lymphotropic virus type 1 and type 11 were negative.

Twenty-six doses of a planned 36 doses of thrice-weekly alemtuzumab (Campath-1H; Genzyme) were administered as salvage therapy, together with prophylactic cotrimoxazole and valaciclovir. Alemtuzumab is a humanized anti-CD52 monoclonal antibody that causes profound T and B lymphocyte depletion and moderate neutropenia; following administration of alemtuzumab, recovery of CD4+ T cells may take \(>1\) year [1]. Profound lymphopenia and neutropenia ensued, with nadir cell counts of 0.007 \(\times 10^9\) cells/L and 0.5 \(\times 10^9\) cells/L (reference range, 2.0–7.5 \(\times 10^9\) cells/L), respectively. Analysis of a bone marrow sample obtained by trephine biopsy 4 months after stopping alemtuzumab therapy showed complete disease remission.

In March 2004, the patient presented with a 3-week history of neck stiffness, headache, nausea, vomiting, photophobia, reduced visual acuity, and increasing dyspnoea. The patient’s CD4+ T cell count at admission to the hospital was 0.007 \(\times 10^9\) cells/L (reference range, 0.5–1.4 \(\times 10^9\) cells/L), representing 1% of total blood lymphocytes, and the patient’s neutrophil count was 0.7 \(\times 10^9\) cells/L. Within 48 h after admission, the patient developed acute renal, respiratory, and circulatory failure and was transferred to the intensive care unit for ventilatory support, inotrope support, and renal dialysis. Chest radiographs revealed diffuse bilateral interstitial pulmonary shadowing. Lumbar puncture yielded clear acellular CSF with an opening pressure of 28 cm H\(_2\)O, a protein level of 3.3 g/L, and a glucose level of 0.29 mmol/L. India ink stain demonstrated abundant encapsulated yeast cells, and culture grew \textit{Cryptococcus neoformans}. The cryptococcal antigen titer was \(>1:4096\) in blood and \(>1:2048\) in CSF. \textit{C. neoformans} was also cultured from blood and urine samples, and yeast-like cells were seen on microscopic examination of sputum and bone marrow samples. Investigations for other opportunistic pathogens, including \textit{Pneumocystis jiroveci}, had negative results.

Treatment with intravenous liposomal amphotericin (3 mg/kg), which was started 1 day after admission to the hospital, was continued for 6 weeks. Fluconazole was not given because of its potentially toxic impact on bone marrow function, especially in the presence of renal failure. CSF, blood, and urine cultures had positive results for 37, 21, and 22 days, respectively. Intravenous fluconazole (administered at a dosage of 400 mg per day) was added to the treatment regimen 14 days after hospital admission because of the poor response to therapy. Repeated lumbar punctures and, subsequently, insertion of a ventricular-peritoneal shunt were required because of persistently elevated intracranial pressure. With the exception of persistent impairment of renal function (serum creatinine levels of \(\sim 300\) \(\mu\)mol/L; reference range, 30–115 \(\mu\)mol/L), the patient eventually made a good recovery, and he was discharged in June 2004 with a prescription for oral fluconazole (200 mg administered once per day).

The patient was readmitted to the hospital in January 2005—10 months after the acute presentation reported above—with a 2-week history of fever, dry cough, headache, and rash on the lower extremities. He had continued taking maintenance oral fluconazole (200 mg once per day) since discharge from the hospital 7 months earlier. On physical examination, the...
patient was febrile and tachypnoeic, but he was not hypoxic at rest. There was a painful, blanching maculopapular rash on the lower extremities that subsequently became confluent. The findings of respiratory and neurological examinations were normal, and there was no meningism. Diffuse interstitial shadowing was seen on a chest radiograph, and a high-resolution CT of the lungs showed ground glass opacities consistent with alveolar inflammation. Examination of CSF samples revealed a WBC count of <1 × 10^6 cells/mL and normal protein and glucose levels; microscopic examination and culture of CSF samples had negative results. The patient's CSF cryptococcal antigen titer had decreased to 1:128, and the serum titer had decreased to 1:1024. Serum C-reactive protein levels peaked at 250 mg/L (normal value, <5 mg/L), and the patient experienced neutrophil leucocytosis, with an increase in neutrophil count from 0.8 × 10^9 cells/L prior to onset of symptoms to 10.1 × 10^9 cells/L. The patient's CD4^+ T cell count 2 weeks after presentation was 0.134 × 10^9 cells/L (16% of total lymphocytes), having been 0.042 × 10^9 cells/L (3% of total lymphocytes) 3 months earlier. Further evaluation for opportunistic infection was unrevealing, and a bone marrow aspirate sample showed no evidence of leukemia relapse. Examination of a skin biopsy sample revealed granulomatous small vessel vasculitis (figure 1A) and multiple yeast-like cells on periodic acid–Schiff (figure 1B) and Grocott (figure 1C) stains. Cultures of biopsy tissue were not performed.

The patient's fever and respiratory symptoms resolved within 2 weeks with no additional therapy, and the rash gradually resolved over the course of the following month. The patient was admitted to the hospital again 3 months later with a generalized pruritic papulo-pustular rash, pleural effusion, acute renal deterioration, and moderate hypercalcemia, with a corrected serum calcium concentration of 2.97 mmol/L (reference range, 2.15–2.60 mmol/L). He had continued taking oral fluconazole throughout this period. Pleural fluid showed a lymphocyte count of 0.54 × 10^9 cells/L, with mixed phenotype on flow cytometry and negative fungal and bacterial culture results. The patient's CD4^+ T cell count had increased to 0.278 × 10^9 cells/L (22% of total lymphocytes). Histopathological examination of a biopsied skin lesion revealed a mixed inflammatory cell infiltrate and scattered fungal cells. Cultures of the biopsied tissue were not performed. With the exception of a persistent pruritic rash that was treated with topical corticosteroids, the patient's symptoms gradually resolved over the following 3 weeks. Six months later, the patient remained well, receiving fluconazole maintenance therapy (200 mg once per day) with no evidence of disease recurrence, but with a persistent serum cryptococcal antigen titer of 1:1024.

Our patient initially presented with fulminant disseminated cryptococcosis in the context of profound cellular immunodeficiency. Subsequent presentations several months after recovery from this illness are likely explained by a C. neoformans–specific immune reconstitution inflammatory response, which has heretofore not been described following alemtuzumab therapy. Given that neither skin biopsy sample was submitted for culture, strict criteria for immune reconstitution syndrome (IRS) were not satisfied in our patient, but key clinical and laboratory features that have previously been described were present, and no viable organisms were isolated from any of the tissues examined.

Fever, pleuropulmonary involvement, and hypercalcemia with granulomatous inflammation have all been observed in cryptococcal IRS following HAART [2], which may occur in up to 30% of HIV-infected patients with a history of cryptococcal meningitis [3]. Subcutaneous abscesses have also been described in these patients [4], but cutaneous involvement—as in our patient, who had microscopically evident cryptococcal cells and granulomatous inflammation characteristic of IRS in the dermis—has not, to our knowledge, been described. In the context of HIV-related immunodeficiency and HAART, risk factors for IRS include a low CD4^+ T cell nadir, short time between onset of a clinically recognized opportunistic infection and immune recovery, and high antigenic load at the time of immune recovery [3, 5, 6]. Although the interval between the

Figure 1. Histopathological findings of skin biopsy samples obtained in January 2005, showing a necrotizing granulomatous vasculitis (A; hematoxylin and eosin stain; original magnification, ×400) and Cryptococcal yeast cells in dermis by periodic acid–Schiff stain (B; original magnification, ×1000) and Grocott stain (C; original magnification, ×1000).
initial presentation and the onset of IRS was 10 months in our case, the CD4+ T cell count had recovered from a prolonged low nadir while there was still a high tissue antigenic load, as revealed by examination of a skin biopsy sample. Similarly delayed presentations with C. neoformans–related IRS have been reported following the initiation of HAART [2].

Our case highlights some of the difficulties in the diagnosis of IRS, which is complicated by heterogeneous presentation and lack of specific diagnostic laboratory tests. A positive diagnosis usually relies on the demonstration of a sterile inflammatory syndrome in the context of immune restoration, while the specific organism against which the response is directed may be demonstrated histopathologically [7]. As in our patient, primary cryptococcal infection in the severely immunocompromised host is characterized by an abundance of yeast cells and histiocytes with relatively little acute inflammatory response [8], while C. neoformans–related IRS exhibits focal granulomatous inflammation and often morphologically compatible organisms that can usually not be cultured [2, 7]. Diagnostic criteria have been proposed for IRS following HAART [6] but have not been proposed for other contexts.

We believe this to be the first description of IRS following treatment with alemtuzumab, a potent T cell lympholytic agent that is increasingly used for the treatment of refractory hematological malignancies and autoimmune conditions. Opportunistic infections are well-recognized complications of treatment with alemtuzumab [1, 9], and IRS following immune recovery may become an important cause of morbidity. Recent reports suggest that cryptococcal IRS may also occur in patients undergoing solid-organ transplantation [10]. Recognition of IRS with recovery from iatrogenic suppression of immunity is likely to become increasingly important to avoid unnecessary investigation and to prompt consideration of antiinflammatory therapy [11].

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References