A cryptic cause of cryptococcal meningitis

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Abstract

Cryptococcus neoformans commonly causes opportunistic infection in immunocompromised patients, especially in patients with AIDS. The CD4+ T-lymphocyte count is measured in patients with HIV infection, because it signals an increased risk of opportunistic infection and a decline in immunological function. We report a case of cryptococcal meningitis in a patient with persistently low CD4+ cell counts without evidence of HIV infection. The patient's underlying immunocompromised state was attributed to idiopathic CD4+ T-lymphocytopenia (ICL), a recently described syndrome characterized by depletions in the CD4+ T-cell subsets without evidence of HIV infection. Immunodeficiency can exist in the absence of laboratory evidence of HIV infection, highlighting the importance of evaluating T-cell subsets in patients who present with unusual infections.

Case

A previously healthy 42-year-old man was admitted to hospital with a history of headache and fever for 2 weeks in February 2000. One week before admission, he had been evaluated at another hospital, where the results of a brain CT study were normal, and a lumbar puncture revealed possible budding yeast cells.

The patient was married and had been monogamous. There was no history of same-sex intercourse, blood transfusion, injection drug use or recent travel. The patient did not have a history of frequent illness or infection, thrush, fever or weight loss. There was no shortness of breath, cough or hemoptysis before admission. The results of an HIV test, obtained for life insurance purposes in 1997, were negative. The family kept a large birdhouse on their property, which the patient had recently cleaned.

The patient presented initially with an ictal episode and recovered spontaneously. His temperature was 36.7°C. Meningismus was present. Funduscopic examination did not reveal any lesions or papilledema. The oropharynx was clear of any obvious lesions.

Examination showed the cardiovascular and respiratory systems to be normal. There were no skin lesions, lymphadenopathy or splenomegaly. Rectal examination revealed a normal, nontender prostate.

Laboratory tests revealed a leukocyte count of 12.6×10^9/L (neutrophils 10.9×10^9/L, lymphocytes 0.7×10^9/L). The findings from a chest radiograph were normal. A lumbar puncture revealed an opening pressure of 55 mm H_20 and a leukocyte count of 13 (normally 0–5) $\times 10^6$/L, with 85% neutrophils and 15% monocytes. There were no erythrocytes. Cerebrospinal fluid (CSF) and serum cryptococcal antigen were positive with significant titres (1:256 and > 1:512 respectively). India ink staining revealed encapsulated budding yeast cells consistent with *Cryptococcus neoformans* meningitis. CSF fungal culture confirmed the diagnosis of cryptococcal meningitis.

Treatment with phenytoin, amphotericin B (0.5 mg/kg daily) and flucytosine (100 mg/kg daily) was initiated. A CD4+ T-lymphocyte count was significantly depressed (90×10^6/L), and was presumed to reflect an underlying HIV infection. However, on day 10 of the patient's stay in hospital, HIV-1 and HIV-2 antibodies were negative as determined by both enzyme-linked immunosorbent assay (ELISA) and Western blot. Antibodies to human T-cell lymphotropic-virus-1 (HTLV-I) and HTLV-II were not detected. The patient's immunoglobulin profile was within the normal range. His condition improved during his stay in hospital, and he was discharged on day 16 on fluconazole (400 mg/d).

After 23 months of follow-up, the patient continued to have a depleted CD4+ cell count (80×10^6/L). Serial serum cryptococcal antigen measurements continued to improve (> 1:8). The results of a repeat HIV test were negative. Fungal culture of repeated CSF samples was negative beginning 2 weeks after initiation of treatment. The patient was otherwise well and continued fluconazole treatment.

Comments

C. neoformans infection is common in immunocompromised patients, especially in patients with AIDS.[1] The CD4+ T-lymphocyte count is measured in HIV infection, because it signals an increased risk of opportunistic infection and a decline in immunological function. Physicians sometimes use the CD4+ count as a surrogate marker for HIV infection, especially in patients who present with unusual infections.[2] Over the last decade, cases of severely low CD4+ T-lymphocyte counts in the absence of HIV infection have been reported.[3,4] The US Centers for Disease Control and Prevention designated this new syndrome idiopathic CD4+ T-lymphocytopenia (ICL).[5] Patients with ICL typically have CD4+ T-lymphocyte depletion, no serological evidence of HIV infection, and no defined immunodeficiency or therapy associated with T-cell depletion.[5] The patient described here fulfills the criteria for ICL presenting with cryptoccocal meningitis.

In patients with depressed CD4+ T-lymphocyte counts, other causes should be considered besides HIV infection. Common variable immunodeficiency can present with low

CD4+ counts and opportunistic infections but is associated with generally low levels of immunoglobulins,[6] differentiating this condition from ICL, in which immunoglobulin levels are usually in the normal range. It is possible that in the case described here cryptococcal infection may have led to the decline in CD4+ cells. It has been suggested that cryptococcal antigens may block cell-mediated immunity through suppressor T-cell functions.[7,8] However, whether a specific decline in CD4+ levels may be due to cryptococcal antigens has not been reported previously. Other variables that influence CD4+ T-cell counts have been reviewed and include circadian rhythm, corticosteroid administration, severe physical and psychological stress,[9] and advanced age.[10] A recent study of critically ill patients admitted to a medical intensive care unit found 17% of patients with CD4+ T-cell counts lower than 200×10^6/L.[11] Our patient had persistently depressed CD4+ T-cell counts in the absence of clinically evident ongoing infection; the observed immunodeficiency in this case is most probably explained by the ICL syndrome.

Previous cases of patients with ICL have been reported since 1983, which were probably associated with the time when routine T-cell subset testing was performed in patients with HIV infection. Reported cases have exhibited a variety of opportunistic infections and include patients with a wide range of ages and geographic distribution.[3] Cryptococcal infections, as in immunocompetent patients, have had protean manifestations in patients with ICL; presentations of meningitis,[4] pulmonary involvement,[4] and invasive[12] and disseminated infections[13] have been noted. Although the literature is limited and follow-up has generally been short, the prognosis for patients with ICL appears encouraging; most patients remain clinically stable, without the ongoing deterioration characteristic of patients with HIV infection.[3]

There are several interesting features to this patient's presentation that warrant mention. Despite ongoing treatment, our patient was noted to have persistent, yet declining, cryptococcal antigenemia. Although serum cryptococcal capsular antigen is a sensitive and specific serological test for acute cryptococcal meningitis, ongoing monitoring of antigen during suppressive therapy is not predictive of relapse in patients with HIV.[14] This may not be generalizable to patients with ICL. More importantly, in our patient, there was no clinical or CSF evidence of persistent cryptococcal meningitis. Our patient continues to receive fluconazole suppressive therapy. Ongoing maintenance therapy (i.e., secondary prophylaxis) for cryptococcal meningitis in patients with AIDS may be beneficial[1] and is recommended to prevent relapse.[6,15] Whether this holds for patients with ICL is unknown. Finally, we speculate that our patient may have acquired his cryptococcal infection when he cleaned his birdhouse 3–4 weeks before becoming ill. Birds, and their droppings, have been shown to harbour *Cryptococcus* and act as a reservoir for its transmission.[16]

This case illustrates that other conditions, aside from HIV infection, can result in the depletion of the CD4+ T-lymphocyte cell population, and the consequent immunocompromise. Physicians should avoid the assumption that a decreased CD4+ count represents an undiagnosed HIV infection and should not use the test as a surrogate for HIV serological testing. Immunodeficiency can exist in the absence of laboratory evidence of HIV infection, highlighting the importance of evaluating T-cell subsets in patients who present with unusual infections.

This article has been peer reviewed.

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Competing interests: None declared.

Contributors: Drs. Cheung, Rachlis and Shumak were the primary physicians involved in the care of the patient during his initial presentation at the hospital. Dr. Rachlis continues to supervise the outpatient follow-up of the patient, provided patient data, and contributed to, reviewed and revised the manuscript. Dr. Cheung was primarily responsible for collecting data and writing the manuscript. Dr. Shumak conceptualized the format of the case report and contributed to, reviewed and revised the manuscript.

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