Cryptococcus neoformans commonly causes opportunistic infections in immunocompromised patients, especially in patients with AIDS. CD4+ T-lymphocytopenia in AIDS indicates an increased risk of opportunistic infection and a decline in immunological function. Idiopathic CD4 T-lymphocytopenia (ICL) is 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, and T-cell subsets should be evaluated in patients who present with unusual opportunistic infections. We report a case of pulmonary cryptococcosis and lung cancer in a patient with persistently low CD4+ cell counts, without evidence of HIV infection.

**Key Words:** Idiopathic CD4 T-lymphocytopenia, cryptococcosis, lung cancer

**INTRODUCTION**

Idiopathic CD4 T-lymphocytopenia (ICL) is a rare condition. The Centers for Disease Control and Prevention defines this condition as a CD4+ count < 300 cells/mm$^3$, or, alternatively, a CD4+ cell count that is less than 20% of the total T-cell count on two occasions, with no evidence of human immunodeficiency virus (HIV) infection on testing, and the absence of any defined immunodeficiency or therapy which could depress CD4+ T-cell levels. There have been reports of ICL occurring along with a variety of opportunistic or nonopportunistic infections.

**CASE REPORT**

A 73 year-old-man was admitted to the hospital with general weakness and poor appetite, which had persisted for 2 months. He also complained of mild dyspnea on exertion, and cough. One week before admission, he had been evaluated at another hospital, where chest X-rays showed multiple cavitary lung lesions.

The patient had no history of blood transfusion, IV drug use, same-sex intercourse, or recent travel. The patient had a 2-year history of diabetes mellitus and hypertension. He had a 70 pack-year smoking history and social alcohol drinking. He had no history of frequent illness, fever or weight loss. On admission, his blood pressure was 110/90 mmHg, pulse rate 94 beats/min, respiratory rate 22/min and body temperature 36.2°C. On physical examination, coarse crackles were audible in both lower lung fields. There were no skin lesions, lymphadenopathy, or splenomegaly.

Laboratory studies showed whole blood cells 7,300/mm$^3$ (neutrophil 86.4%, lymphocyte 7%, monocyte 5.2%, eosinophil 1.0%, basophil 0.4%), hemoglobin 11.5 g/dl, platelet count 464,000/mm$^3$, blood glucose 109 mg/dl, total bilirubin 0.5 mg/dl, aspartate aminotransferase (AST) 19 IU/L, alanin aminotransferase (ALT) 25 IU/L, lactate dehydrogenase (LDH) 448 IU/L, HbA1C 6.4%. Urinalysis and microscopic examinations were normal.

A sputum gram stain and bacterial culture revealed no organisms. Direct examinations and
sputum culture were negative for acid-fast organisms. Multiple thick-walled cavitary lesions, with nodules and consolidations in both lungs, were noted on chest radiography (Fig. 1). Multiple patch consolidations and multiple large pulmonary nodules with cavitary formations and severe wall thickening of subsegmental bronchi in the whole lung field were noted on the chest CT scan (Fig. 2). Fiberoptic bronchoscopy with transbronchial lung biopsy was performed for purposes of identification of any possible causative pathogen. On bronchoscopy, there were white exudate-covered nodules in the orifice of the anterior segment of the right upper lobe. An endobronchial biopsy was also performed. Histologic findings of the endobronchial biopsy showed moderately differentiated squamous cell carcinoma. Histologically, the transbronchial lung biopsy revealed multinodular peribronchial granulomas with central necrosis. Percutaneous needle aspiration cytology revealed yeast-form fungi, consistent with cryptococci (Fig. 3). A cerebrospinal fluid (CSF) cryptococcal antigen test, an India ink staining, and a fungal culture were all negative. Serum cryptococcal antigen was positive (1:16 titer).

Although the patient's CD4+ T-lymphocyte count had significantly decreased (127 × 10^6/L), HIV antibodies were negative according to both enzyme-linked immunosorbent assay (ELISA) and western blot tests. Also, HIV antigen (P24 Ag) was not detectable. His immunoglobulin electrophoresis profile was within the normal range. Initially, amphotericin B (0.5 mg/Kg/day) was infused for 15 days. After switching from intravenous amphotericin to oral fluconazole, the patient was discharged on day 32, and remained on fluconazole (400 mg/day). After 4 weeks of fluconazole therapy, coughing and dyspnea had lessened, and chest radiography showed decreased consolidations and multiple lung cavitary nodules. In order to treat the lung cancer, a right upper lobectomy was performed. The pathologic staging was IA (T1 N0 M0). He was discharged, receiving fluconazole. After a 10-month follow-up, the patient continued to have a decreased CD4+
T-lymphocyte count \((172 \times 10^6/\text{L})\). An additional HIV test proved to be negative. The patient was otherwise well, and continued fluconazole treatment.

**DISCUSSION**

Idiopathic CD4 T-lymphocytopenia (ICL) is a rare disease, associated with progressive loss of CD4+ T lymphocytes, accompanied by opportunistic infections characteristic of AIDS, in the absence of any known condition.\(^1\,^2\) This patient fulfills the criteria for ICL, presenting with pulmonary cryptococcosis and non-small cell lung cancer. The etiology of this syndrome is unclear and will almost certainly prove to be multifarious, given the lack of risk factors for acquisition of bloodborne infections in most individuals, absence of a clear epidemiologic pattern, and the transient nature of many cases. Lymphopenia may be related either to blood lymphocyte emigration to, or sequestration within, lymphoid tissue or other infected organs. Progressive T-cell loss may, additionally, become lymphopenia in both lymphoid tissue and blood. In one series of ICL, apoptotic T-cell loss of unknown cause, leading to complications associated with immune deficiency, was documented in 7 of 8 patients, and involved either the CD4+, or both the CD4+ and CD8+ T-cell subsets.\(^3\) Transient apoptotic T-cell loss in vivo has previously been suspected to be a consequence of viral infections, such as Epstein-Barr virus infection in humans.\(^4\)

Previous cases of patients with ICL have been reported since 1983. This is due less to a sudden appearance of ICL in the population, than to the inception of routine T-cell subset testing as a generalized protocol in patients with HIV infection. Reported cases have exhibited a variety of opportunistic infections, and include patients encompassing a wide range of ages and geographical distribution.\(^5\) Cryptococcal infections have had variable manifestations in patients with ICL; presentations of pulmonary involvement, meningitis, and invasive and disseminated infections have been noted.\(^6\,^7\) 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 HIV patients.\(^5\)

Fluconazole maintenance therapy for secondary prophylaxis may be beneficial for cryptococcal infection in patients with AIDS, and is recommended for prevention of relapses.\(^8\,^9\) However, it remains unknown whether or not fluconazole suppression is beneficial in patients with ICL.

There is no gold standard for the treatment of pulmonary cryptococcosis, due to the absence of controlled trials, and treatment should be guided by severity of illness and underlying disease. Fluconazole is adequate therapy for most patients with infections that are limited to the lungs.\(^10\) In this case, which involves immune deficiency and CD4+ lymphocytopenia, the patient will undergo fluconazole maintenance until the disappearance of his lung lesions.

Immunodeficiency can exist in the absence of HIV infection. It is important to evaluate T-cell subsets in patients who present with unusual infections.

**REFERENCES**

1. Centers for Disease Control and Prevention. Unexplained CD4+ T lymphocyte depletion in persons without evident HIV infection. MMWR 1992;41:541-5.
2. Smith DK, Neal JJ, Holmberg DS. Unexplained opportunistic infections and CD4+ T lymphocytopenia without HIV infection. N Engl J Med 1993;328:373-9.
3. Laurence J, Mitra D, Steiner M, Lynch DH, Siegal FP, Staiano-Coico L. Apoptotic depletion of CD4+ T cells in idiopathic CD4+ T lymphocytopenia. J Clin Invest 1996;97:672-80.
4. Uehara T, Miyawaki T, Ohta K, Tamaru Y, Yokoi T, Nakamura S, et al. Apoptotic cell death of primed CD45RO+ T lymphocytes in Epstein-Barr virus-induced infectious mononucleosis. Blood 1992;80:452-8.
5. Fauci AS. CD4+ T-lymphocytopenia without HIV infection: no lights, no camera, just facts. N Engl J Med 1993;328:429-31.
6. Yinnon AM, Rudensky B, Sagi E, Breuer G, Brautbar C, Polacheck I, et al. Invasive cryptococcosis in a family with epidermodysplasia verruciformis and idiopathic CD4 cell depletion. Clin Infect Dis 1997;25:1252-3.
7. Menon BS, Shuaib IL, Zamani M, Haq JA, Aiyar S, Noh LM. Idiopathic CD4+ T-lymphocytopenia in a child with disseminated cryptococcosis. Ann Trop Pediatr 1998;18:45-8.
neoformans in the acquired immunodeficiency syndrome. N Engl J Med 1989;321:794-9.

9. 1999 USPHS/IDSA guideline for the prevention of opportunistic infections in persons infected with human immunodeficiency virus. MMWR Morb Mortal Wkly Rep 1999;48:1-65.

10. Pappas PG, Perfect JR, Cloud GA, Larsen RA, Pankey GA, Lancaster DJ, et al. Cryptococcosis in human immunodeficiency virus-negative patients in the era of effective azole therapy. Clin Infect Dis 2001;33:690-9.