

# Disseminated Cryptococcosis in a Patient With Idiopathic CD4+ T-Lymphocytopenia

Alaa Muslimani, MD<sup>1</sup>

Neelamkavil S. Francis, MD<sup>1</sup>

K. V. Gopalakrishna, MD, FACP, FIDSA<sup>2</sup>

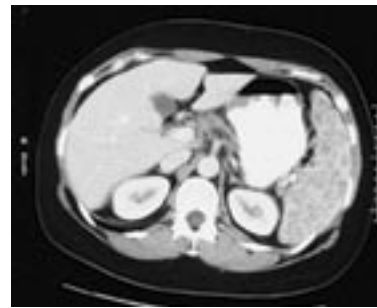
Hamed A. Daw, MD<sup>3,4</sup>

<sup>1</sup>Section of Internal Medicine, <sup>2</sup>Section of Infectious Disease, <sup>3</sup>Section of Hematology & Oncology, <sup>4</sup>Department of Pathology; Fairview Hospital, Cleveland Clinic Health System; Cleveland, Ohio

A reduced number of CD4+ cells leads to deterioration in cellular immunity and a predisposition to develop opportunistic infections. The most common cause of low CD4+ cell count is HIV infection. However, acute glucocorticoid treatment,<sup>1</sup> severe physical stress and acute myocardial infarction,<sup>2</sup> and infections, such as tuberculosis, hepatitis B, Epstein Barr virus–associated mononucleosis, and cytomegalovirus, may cause a transient depression in CD4+ count. Few case reports have described patients with CD4 T-lymphopenia in the absence of serologic or virologic evidence of HIV-1 infection or any other risk factors.<sup>3,4</sup> Those cases were classified as idiopathic CD4+ T-lymphocytopenia (ICL). A variety of acute and chronic infections may be associated with ICL; however, cryptococcal infections secondary to ICL have been rarely reported. We report a rare case of disseminated cryptococcal infection involving spleen, breast, and soft tissue in a female patient diagnosed with ICL.

## Case Report

A previously healthy 42-year-old woman presented with two erythematous sore lumps, one in the left breast and one in the left thigh. Both progressed over a period of 3 weeks. She had been married for 21 years and had no risk factors for HIV infection. There was no significant past medical history, fever, or weight loss. On physical exam there were two lumps (breast, thigh), but no palpable lymphadenopathy. The abdominal examination showed 3-cm splenomegaly below the left costal margin. Laboratory studies showed a white blood cell (WBC) count of 6,700/ $\mu$ L with 86.4% neutrophils, 3.6% lymphocytes, 1.7% basophils, 6.4% monocytes, and 1.9% eosinophils. Hemoglobin was 14.2 g/dL and platelet count was 325,000/ $\mu$ L. The immunoglobulin (Ig) electrophoresis



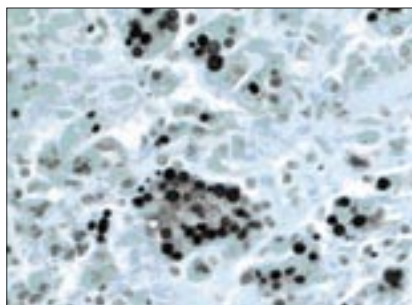
**Figure 1.** Multiple hypodense splenic lesions consistent with microabscess/metastasis.

profile showed serum levels of IgG, IgA, and IgM within the normal range.

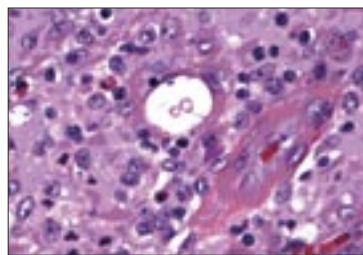
A computed tomography (CT) scan of the chest and abdomen disclosed mild mediastinal lymphadenopathy, as well as multiple hypodense lesions in the spleen consistent with abscesses (Figure 1). Ultrasound of the breast lump showed two complex cysts. Purulent material was aspirated from the breast and thigh lesion, and splenectomy was performed. Cytology and histology from the breast, thigh, and spleen revealed yeast-form fungi consistent with *Cryptococcus* (Figures 2 and 3). Culture was positive for *Cryptococcus neoformans*. Serum cryptococcal antigen was positive (titer 1:215), CD4+ T-lymphocyte count was decreased to 173 cells/mL (normal range, 500–1,500), and HIV antibodies were negative by enzyme-linked immunosorbent assay (ELISA) and Western blot tests. The patient was started on liposomal amphotericin B 5 mg/kg daily for a total of 5 weeks, followed by oral fluconazole 400 mg/day for another 4 weeks. Two years later the patient continued to display a decreased CD4+ T-lymphocyte count (154 cells/ $\mu$ L), but without further opportunistic infection.

Address correspondence to:

Hamed A. Daw, MD, Cleveland Clinic Cancer Center (Moll Pavilion)  
18200 Lorain Ave, Cleveland, OH, 44111; Phone: 216-476-7606;  
Fax: 216-476-6967; E-mail: dawh@ccf.org.



**Figure 2.** Breast biopsy. Budding yeast (*Cryptococcus*): the dark black structures in the center (GMS stain, original magnification  $\times 100$ ).



**Figure 3.** Breast biopsy. Encapsulated yeast with cell walls positive for mucin, characteristic of *Cryptococcus* (Mucin stain, original magnification  $\times 100$ ).

## Discussion

Idiopathic CD4+ T-lymphocytopenia is defined as a CD4+ cell count less than 300 cells/ $\mu$ L, or alternatively, a CD4+ cell count that is less than 20% of the total T-cell count on two occasions, with no evidence of HIV on testing, and the absence of any defined immunodeficiency or therapy that could depress CD4+ T-cell level.<sup>5</sup> The etiology of this syndrome is unclear, with a lack of risk factors for acquisition of bloodborne infection in most individuals and an absence of a clear epidemiologic pattern.

ICL is a rare disease, with an incidence of 0.25% among blood donors.<sup>6</sup> Smith and colleagues reviewed 230,179 cases of AIDS patients from the AIDS reporting system, and only two cases fit the definition of ICL.<sup>7</sup> Cryptococcal infections have had variable manifestations in patients with ICL, including pulmonary involvement, meningitis,<sup>7</sup> and invasive<sup>8</sup> and disseminated<sup>9</sup> infections.

*C. neoformans* is an encapsulated yeast that has become an increasingly prevalent pathogen in immunocompromised patients. It produces infection following inhalation through the respiratory tract. The organism disseminates hematogenously and has a propensity to localize to the central nervous system. The most common manifestation of *C. neoformans* infection is meningitis followed by pulmonary involvement.<sup>10</sup> It has rarely been reported to cause adrenal insufficiency.<sup>11,12</sup>

The optimal treatment of this infection is dependent upon whether or not the patient has coexisting HIV infection. Cryptococcal infection cannot be eradicated in patients with AIDS unless the immune status improves following antiretroviral therapy. Fluconazole maintenance therapy for secondary prophylaxis may be beneficial for cryptococcal infection in patients with AIDS and recommended to prevent relapse.<sup>13</sup>

In comparison, non-HIV-infected patients do not require chronic suppressive therapy, as complete

eradication of the organism can be accomplished in the absence of rapidly fatal underlying diseases, such as some malignancies.

Whether ongoing antifungal or retroviral maintenance therapy should be given to patients with ICL is unknown. In our case, the patient was free of any infections in the absence of treatment for almost 2 years of follow-up. It is possible to argue that the cryptococcal infection may have led to a decline in CD4+ cells, as there was no measured antecedent CD4+ cell count. However, the CD4+ cell count was still low 2 years after the patient was totally cured from the infection. To our knowledge, a transient decline in the CD4 level due to cryptococcal infection has not been reported. It remains unknown whether or not fluconazole suppression is beneficial in patients with ICL. Our patient received fluconazole maintenance for 4 weeks until the disappearance of lesions.

The prognosis for patients with ICL appears encouraging, as most patients remain clinically stable, inconsistent with ongoing deterioration characteristic of HIV patients.<sup>14</sup>

## Conclusion

Cryptococcal infections demonstrate variable manifestations in patients with ICL and may be treated by liposomal amphotericin and oral fluconazole, with or without surgery. Further prophylactic treatment might not be needed unless the patient experiences opportunistic infections or relapse of the original infection. Finally, CD4+ cell counts should be part of the assessment of any patient with unusual opportunistic infections.

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## Review

### Cryptococcosis in HIV-negative Immunodeficiency

Klaus Warnatz, MD

*Division of Rheumatology and Clinical Immunology  
University Clinic Freiburg  
Freiburg, Germany*

The report presented by Muslimani and colleagues<sup>1</sup> describes the unusual case of a previously healthy 42-year-old woman with disseminated cryptococcosis. Diagnostic evaluation of the HIV-negative patient revealed an underlying idiopathic CD4+ T-cell lymphocytopenia (ICL). ICL is a rare immunodeficiency in adults.<sup>2</sup> It was first defined in July 1992 by the Centers for Disease Control and Prevention to include HIV-1 and -2–negative patients with numbers of circulating CD4+ T lymphocytes below 300 cells/ $\mu$ L or less than 20% of total T cells on more than one occasion. In addition, any defined immunodeficiency or therapy associated with depressed levels of CD4+ T cells have to be excluded. This review addresses two aspects of this case report. Although the detection of opportunistic infections like cryptococcosis almost always triggers the search for an underlying immunodeficiency, the differential diagnosis

of this immunodeficiency after exclusion of HIV infection remains rather diffuse in adult patients. Therefore, after discussing cryptococcosis in HIV-negative patients the differential diagnosis of ICL is reviewed.

#### Differential Diagnosis of Cryptococcosis in HIV-negative Patients

Cryptococcosis is an invasive fungal infection caused by the yeast *Cryptococcus neoformans*. This ubiquitous pathogen rarely causes disseminated infection in healthy individuals. In immunocompetent hosts *Cryptococcus gattii* infections have caused focal, central nervous system (CNS) and pulmonary disease.<sup>3</sup> Among the HIV-negative population, transplantation,<sup>4</sup> prolonged steroid treatment,<sup>5</sup> sarcoidosis,<sup>6,7</sup> and malignancy<sup>8,9</sup> have been identified as the main preconditions. Disseminated cryptococcosis has been described in over 20 patients with ICL by Walker and colleagues<sup>10</sup> and others, underlining the central role of T cells in the defense against cryptococcal infection. Several reports depict cryptococcosis in patients with genetically defined CD40L deficiency.<sup>11,12</sup> The activation of monocytes/macrophages via CD40<sup>13</sup> is the affected important defense mechanism against this fungal infection,<sup>14,15</sup> which is independent of the CD4+ cell count. Mouse models suggest only a minor role of the humoral defense,<sup>16</sup> which is shown by the lack of case reports on cryptococcosis in common variable immune deficiency patients and only one report in a patient with Bruton agammaglobulinemia.<sup>17</sup>

In HIV patients, cryptococcosis is one of the major AIDS-defining secondary infections. Approximately 10–15% of AIDS patients develop disseminated cryptococcosis, and the risk increases at CD4+ cell counts below 100 cells/ $\mu$ L.<sup>18</sup>

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Address correspondence to:

Klaus Warnatz MD, Division of Rheumatology and Clinical Immunology,  
Freiburg University Hospital, Hugstetterstr. 55, D-79106 Freiburg, Germany;  
Phone: +49-761-2703695; Fax: +49-761-2703306;  
E-mail: klaus.warnatz@uniklinik-freiburg.de.

(Clinical Case Study Review, continued from page 448)

The most common clinical manifestation of cryptococcosis is meningoencephalitis. The mastitis, splenitis, and skin infection reported by Muslimani and colleagues represent an unusual clinical presentation. The involvement of the CNS must be excluded in all patients with cryptococcosis due to the tropism of the pathogen. In immune-compromised patients who present with signs of fever and headache, cryptococcosis is one of the major differential diagnoses. In more than 50% of cases a spinal tap allows for direct microscopic diagnosis by India ink staining, and almost all cerebrospinal fluid (CSF) samples are positive in culture. CSF cell counts are usually only slightly elevated, partly corresponding to the extent of the underlying cellular immunodeficiency. Additionally, a fast screening test can be performed by enzyme-linked immunosorbent assay for circulating cryptococcal antigen in the serum of patients,<sup>19</sup> as reported in the case of Muslimani and colleagues. In immune-compromised patients, a concomitant antigenemia is almost always present.

The therapy for this disease usually consists of a combination of amphotericin B and either flucytosin or fluconazole, which has been shown to be superior to monotherapy with amphotericin B.<sup>20</sup> This combination therapy is given for 14 days. If good clinical and serologic response (antigenemia or antigen in CSF) is achieved, the combination therapy is followed by oral therapy with fluconazole (400 mg/day). The duration of this secondary prophylaxis is undetermined and, as stated by the authors, no recommendations exist for HIV-negative patients. The patient described in the current case had an excellent response to treatment, with no signs of relapse during 2 years of follow-up. Based on the HIV literature<sup>21</sup> 3 months of oral fluconazole therapy and a confirmation of a negative serum cryptococcal antigen test is suggested before discontinuation.

Even though there are no guidelines available for repeated cryptococcal antigen testing, patients should be screened for relapse after discontinuing therapy especially in case of a new onset of clinical symptoms compatible with cryptococcosis. The absence of relapse in the described patient, despite the persistently low CD4+ cell count, which has also been reported for several other patients, demonstrates that the experience with HIV-infected patients serves only as a guideline and demonstrates that ICL has a different and usually less progressive course of disease.

### Differential Diagnosis of CD4+ T-cell Lymphopenia in Adult HIV-negative Patients

HIV infection is obviously the most important differential diagnosis in adults and must be unambiguously excluded.

After exclusion of HIV infection, the differential diagnosis includes malignancy (especially lymphoma),<sup>22</sup> autoimmune disease (especially systemic lupus erythematosus), other connective tissue diseases,<sup>23</sup> rare primary immunodeficiency disorders with late onset (eg, adenosine deaminase deficiency),<sup>24</sup> drug-induced lymphopenia (especially by chemotherapy and immunosuppressive therapy),<sup>25</sup> radiation,<sup>26</sup> and parainfectious as well as postinfectious CD4 lymphopenia. Therefore, a careful medical history and examination is crucial.

The evaluation for malignancy should include a chest radiograph, ultrasound of the abdomen, gynecologic examination, and a bone marrow biopsy in otherwise healthy people. Extended examinations, including computed tomography scan and gastroscopy, for mucosa-associated lymphoid tissue lymphoma may be required in patients with increased risk or symptoms of malignant disease. Autoimmune diseases should be excluded by the medical history and serologic screening for autoantibodies.

Drug-induced lymphopenia is probable in patients currently on or after long-term steroid therapy, chemotherapy, or immunosuppressive therapy. CD4+ lymphocytes recover with a slower rate than CD8+ lymphocytes<sup>27</sup> after discontinuation of therapy. Severe drug-induced CD4 lymphopenia may be associated with an increased infection rate<sup>25</sup>; thus, monitoring of CD4+ lymphocytes in lymphopenic patients was suggested by Gluck and colleagues.

Radiation-induced lymphopenia<sup>26</sup> affects almost three quarters of patients who receive pelvic irradiation. Although all lymphocyte populations are reduced initially, the decline in natural killer and CD8 cells is limited to the first 2–3 weeks. The CD4 cells recover much more slowly.

Infection-induced CD4 lymphopenia sometimes generates a diagnostic dilemma, as opportunistic infections may be a cause or effect of CD4 lymphopenia. The most commonly described infections inducing CD4 lymphopenia, apart from HIV, are extrapulmonary tuberculosis,<sup>28–31</sup> cytomegalovirus,<sup>32</sup> human T-lymphotropic virus II,<sup>33</sup> Epstein Barr virus, and other viral and fungal infections,<sup>32,34</sup> including cryptococcosis.<sup>35</sup> In most cases of parainfectious CD4 lymphopenia, the CD4:CD8 ratio does not invert and as described in tuberculosis, usually normalizes after therapy.<sup>31</sup> Muslimani and colleagues conclude correctly that the persistence of CD4 lymphopenia after successful therapy of the cryptococcosis suggests underlying ICL, rather than infection-induced CD4 lymphopenia. This, however, is not always conclusive because in cases of pre-existing immunodeficiency, the lymphocytopenia often becomes more pronounced during the infection and the recovery of CD4+ lymphocytes after infection in otherwise healthy individuals is not always

complete. It is remarkable that many patients with idiopathic CD4 lymphopenia suffer from recurrent infection rather than a variety of different opportunistic infections.

The presented case adds to the growing number of case reports of opportunistic infections in patients with ICL. However, ICL itself remains a conundrum. It most likely describes a very heterogeneous syndrome. Given the estimation that 0.25–0.4% of blood donors fulfill the criteria of ICL,<sup>36,37</sup> a large part of this population remains clinically asymptomatic. The example of CD40L deficiency demonstrates that not only the number of T cells, but also certain functional deficits, strongly affect the susceptibility to cryptococcal infection. A future task will be to examine the underlying defects causing CD4 lymphopenia in ICL and more importantly to determine the risk factors, other than low CD4+ cell count, for increased susceptibility to opportunistic infection in this patient population.

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