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# *Cryptococcus neoformans* Meningoencephalitis in a Patient with Idiopathic CD4<sup>+</sup> T Lymphocytopenia

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## ABSTRACT

*Cryptococcus neoformans* is a leading cause of invasive cryptococcal infections which include meningitis/meningoencephalitis, cerebral cryptococcoma, invasive pulmonary and mediastinal infection. Invasive infection is mainly diagnosed in immunocompromised patients, especially in HIV-infected individuals. There is a rising number of patients with invasive cryptococcal infections in immunocompromised patients who are HIV-negative. Among several primary immunodeficiency syndromes, considered as possible reasons for these invasive infections, idiopathic CD4<sup>+</sup> T lymphocytopenia (ICL) is most frequently diagnosed. The pathogenesis of this rare syndrome is still unknown, while its clinical spectrum ranges from an asymptomatic laboratory abnormality to life-threatening opportunistic infections. Here we present an HIV-negative young man suffering from cryptococcal meningoencephalitis in whom ICL was diagnosed.

**Key words:** Cryptococcal meningoencephalitis, CD4<sup>+</sup> T cell immunodeficiency, HIV

## Introduction

*Cryptococcus* is a worldwide-spread encapsulated yeast (Basidiomycetes) which can be isolated from animals and animal-based food, pigeon droppings and fruit<sup>1–3</sup>. Cryptococci are normal human colonizers, while infection with this yeast is usually seen in immunocompromised individuals<sup>4</sup>. *Cryptococcus neoformans* is the leading cause of invasive cryptococcal infection worldwide. This fungus, as mentioned before, usually causes infections in immunocompromised patients, especially in HIV-infected individuals<sup>5</sup>. Following the emergence of the HIV-related immunodeficiency syndrome, *Cryptococcus neoformans* meningitis was rapidly recognized among the most frequent opportunistic infections in both the United States and rest of the world<sup>5–7</sup>. Invasive cryptococcal infections besides meningitis or meningoencephalitis, otherwise include cerebral cryptococcoma, invasive pulmonary and mediastinal infection and prostate infection in males. Although the literature in general refers to the meningeal syndrome as cryptococcal meningitis, the correct histopathologic term for this condition would be meningoencephalitis, because in most autopsied cases there is a

clear evidence of both involvement of the meninges and the underlying brain parenchyma<sup>8</sup>. Invasive neural infection is usually caused by species complex *C. neoformans* var *grubii* (serotype A), or *C. neoformans* var *neoformans* (serotype D). *Cryptococcus gatii* (serotypes B and C) is recognized as a species distinct from *C. neoformans* and almost always affects individuals with no identifiable immune impairment in whom pulmonary and brain mass lesions are common<sup>9</sup>. Predominance of different serotypes may depend on the presence or absence of an underlying condition (immunocompetent versus immunocompetent hosts) and geographic distribution<sup>10</sup>. Other non-*neoformans* cryptococcal species responsible for invasive fungal disease include *Cryptococcus laurentii* (recently reclassified as *Cryptococcus flavescens*) and *Cryptococcus albidus*, but these fungi are infrequently found in humans and do not have a selective tropism for the central nervous system (CNS) as *C. neoformans*<sup>11</sup>. Moreover, infection with these cryptococcal species is usually seen in patients following antifungal treatment<sup>12</sup>.

Following inhalation, cryptococcal spores are deposited into the pulmonary alveoli and meningitis occurs from hematogenous dissemination of the fungus from the lungs. The disease is often difficult to diagnose. Headache and fever are prominent symptoms at the onset of CNS involvement, other symptoms of meningitis may arise subsequently (vomiting, photophobia, meningismus). The headache, intermittent at the onset, is mostly localized in the frontal and temporal regions, but with disease progression it becomes continuous and progressively severe. Visual disturbances such as diplopia and photophobia are also early symptoms of the disease. Other ocular disorders include strabismus, nystagmus, anisocoria, ptosis, neuroretinitis, retinal hemorrhages, optic nerve atrophy and ophthalmoplegia. Papilledema is present in half of active cases, due to increased spinal fluid pressure<sup>13</sup>.

The CD4<sup>+</sup> T lymphocyte count in HIV-infected patients determines the rate of immunological function of patients and the susceptibility to opportunistic infections. Although not generally accepted, some physicians still use the number of CD4<sup>+</sup> T cells as a surrogate marker for HIV infection, mostly in patients who present with unusual infections<sup>14</sup>. Invasive cryptococcal infections occur in HIV-infected individuals especially when the HIV-associated immunodeficiency is severe, as expressed by a CD4<sup>+</sup> T lymphocyte count below 50–100 cells/ $\mu$ L<sup>5,15,16</sup>.

In recent years there is a rising number of reports of opportunistic infections, including cryptococcal infections in immunocompromised individuals who are HIV-uninfected. Several primary immunodeficiency syndromes are also considered as a possible underlying condition for cryptococcal infections, among which idiopathic CD4<sup>+</sup> T lymphocytopenia (ICL) is most frequently diagnosed. Patients suffering from ICL have low numbers of CD4<sup>+</sup> T cells, without serologic confirmation of HIV infection and no history of previous immunodeficiency or therapy associated with depletion of T cells<sup>17,18</sup>. ICL is a rare disease and still described as an occasional result in analyzing the pathogenesis of immunodeficiency in HIV-negative patients<sup>19</sup>. Pathogenesis of this immunodeficiency is still not elucidated and several mechanisms of the disease are proposed: defective generation of CD4<sup>+</sup> T cell precursors in patients presented with low levels of CD34<sup>+</sup>CD38<sup>-</sup>DR<sup>+</sup> hematopoietic stem cells<sup>20</sup>, insufficient production of IL-2 and TNF- $\alpha$  necessary for T cell proliferation<sup>21</sup>, increased apoptosis of CD4<sup>+</sup> T cells<sup>21</sup>, and most recent, impaired expression of CXCR4 receptor on the surface of CD4<sup>+</sup> T cells, necessary for IL-2 mediated induction of CD4<sup>+</sup> T cell proliferation<sup>22</sup>.

## Case Report

A previously healthy 28 year old man was admitted to the Clinic of Infectious Diseases at the Clinical Hospital Center Rijeka in December 2005 with a 3-day history of mild fever (up to 38 °C) and intermittent headache. Several hours before admission the patient vomited, noticed

tremor and experienced speech difficulties (slurred speech followed by complete aphonia). The patient was in a steady monogamous heterosexual relationship. There was no history of blood transfusion, injection drug use or recent travel. He owned a pet dog and has been occasionally visiting a countryside farmstead where his relatives kept poultry. The patient did not have a history of frequent infections, thrush, fever or weight loss. There was no shortness of breath, cough or hemoptysis before admission.

Physical examination on admission revealed that the patient was mildly dehydrated, psychically disorientated and restless. He had normal cardiovascular and respiratory function, reactive mydriasis, negative signs of meningeal involvement and no evident focal neurological deficit. There were no skin lesions, and lymphadenopathy or splenomegaly were also not present.

Laboratory tests revealed a leukocyte count of  $8.9 \times 10^9/L$  (granulocytes  $7.1 \times 10^9/L$ , lymphocytes  $1.6 \times 10^9/L$ ), and a normal red blood cell and thrombocyte count. The serum C-reactive protein was 11 mg/L, the plasma sodium and potassium levels were 131 mmol/L and 3.0 mmol/L respectively. A chest radiograph revealed scar tissue in the upper left pulmonary lobe. Brain computer tomography (CT) was normal. A lumbar puncture revealed pleocytosis in the cerebrospinal fluid (CSF) with a leukocyte count of  $478 \times 10^6/L$  (88% of neutrophils, 9% of lymphocytes and 3% of monocytes), proteinorachia of 1.38 g/L, mildly increased lactate levels of 2.23 mmol/L, decreased chloride levels of 113 mmol/L and a normal serum/CSF glucose ratio (6.4/3.7 mmol/L). The patient was initially treated with acyclovir ( $3 \times 10$  mg/kg i.v.). Additional lumbar punctures were performed with similar CSF cell counts; the leukocyte count range was from 177 to  $320 \times 10^6/L$  cells (mononuclear cells: 51–60%). The CSF glucose level was low (down to 0.8 mmol/L) and the protein levels were somewhat more increased as compared to the initial CSF analysis (1.86 g/L). Antituberculosis drugs were given in view of these CSF findings. The patient occasionally complained of vertigo, blurred vision and diplopia. CSF cultures revealed no bacteria, including *Mycobacterium tuberculosis* (TB) in any of the samples tested. However, India ink staining of the last two CSF samples (of five) revealed encapsulated budding yeast cells consistent with *Cryptococcus neoformans*. This result was confirmed with CSF fungal culture. *C. neoformans* was sensitive to amphotericin B, fluconazole, itraconazole and 5-fluorocytosine. Antituberculous drugs were discontinued and the patient initially received treatment with amphotericin B (0.35 mg/kg daily for two days, followed with 0.7 mg/kg daily) for four weeks. Eight days after antifungal treatment was initiated, the patient was transferred to University Hospital of Infectious Diseases »Dr. Fran Mihaljević« in Zagreb, Croatia for additional diagnostic procedures, further treatment and follow up. During the course of treatment papilledema was also observed; it lasted for one month. He was discharged from the hospital in a good general condition and further treatment with oral fluconazole (400 mg/day) was recommended for additional eight weeks.

Immunocytological analysis of the patient blood samples revealed significantly decreased CD4<sup>+</sup> T lymphocyte count ( $236 \times 10^6/L$ ) which indicated the possibility of underlying HIV infection. However, HIV 1 and HIV 2 antibodies were negative as determined by both enzyme linked immunosorbent assay (ELISA) and Western blot. Furthermore, we performed polymerase chain reaction (PCR) analysis for HIV RNA, which was also negative. The patient's CD8<sup>+</sup> T cell, B cell, NK cell count and immunoglobulin profile were within the normal range. Patient was HBsAg, anti-HCV, tuberculin test, TPHA and VDRL negative.

During 34 months of follow-up we observed no disease relapse. The patient continued to have a depleted CD4<sup>+</sup> T cell count ( $139\text{--}193 \times 10^6/L$ ) and increased levels of CD3-CD56<sup>+</sup> cells (35–54%; normal to 15%) but with no signs of myeloproliferation or isolated NK-cell proliferation, and normal phagocyte function of both monocytes and granulocytes. Immunological tests were all negative showing existence of no autoantibodies or any collagen disease. The results of a repeat HIV testing were negative. ELISA analysis showed the patient to be IgM anti-CMV and anti-EBV negative, IgG anti-CMV and anti-EBV positive. PCR analysis detected EBV DNA but not CMV DNA in the serum. Repeated ELISA testing showed persistence of IgG EBV VCA antibodies, IgG EBNA antibodies and IgG EBV EA antibodies. IgM EBV VCA antibodies were not detected, however, EBV viremia persisted suggesting chronic EBV infection.

Fungal cultures of repeated CSF samples were negative from 2 weeks after the initiation of treatment with amphotericin B. However, in CSF, serum and urine samples cryptococcal antigen was positive by latex agglutination in the next 6 months. Fluconazole treatment (400 mg daily) was given for a total of 9 months. At the end of treatment the patient's CSF findings were normal, fungal cultures were negative and no cryptococcal antigen was detected. Antifungal prophylaxis with 100 mg of oral fluconazole daily and *Pneumocystis carinii* prophylaxis (PCP) with oral trimethoprim-sulfamethoxazole 960 mg every second day was given. A follow-up brain CT scan was also normal. The patient decided to stop PCP and antifungal prophylaxis treatment after 24 months.

## Discussion and Conclusion

We report a patient with meningoencephalitis caused by *Cryptococcus neoformans*. The patient was not HIV infected and had no apparent underlying immunodeficiency at presentation. During his follow-up it became clear that he had persistently depressed CD4<sup>+</sup> T cell counts in the absence of other underlying condition; therefore the observed immunodeficiency in this case is most probably explained by the idiopathic CD4<sup>+</sup> T lymphocytopenia (ICL) syndrome.

Confirmed chronic EBV infection in our patient required further follow-up since ICL can precede, and may indicate the presence of several malignant diseases, among which Burkitt's lymphoma is associated with EBV in-

fection<sup>23</sup>. However, persistent EBV viremia can not explain CD4<sup>+</sup> T cell immunodeficiency since CD4<sup>+</sup> T cells are normally preserved and completely functional in latent EBV infection and EBV-infected healthy donors<sup>24</sup>.

Increasing number of cases with decreased or severely low CD4<sup>+</sup> T lymphocyte counts in the absence of HIV infection, or other apparent underlying immunodeficiency have been recently reported. The US Centers for Disease Control and Prevention designated this new syndrome as idiopathic CD4<sup>+</sup> T lymphocytopenia<sup>18</sup>. Other immunodeficiency syndromes can also present with low CD4<sup>+</sup> T cell count. Among primary immunodeficiency syndromes patients with common variable immunodeficiency have low CD4<sup>+</sup> T cell counts but these patients have generally low levels of immunoglobulins which differences them from ICL where immunoglobulin levels are usually in the normal range<sup>25</sup>. Circadian rhythm, corticosteroid administration, severe physical and psychological stress and advanced age are also been considered to influence the CD4<sup>+</sup> T cell count<sup>26,27</sup>. Interestingly, cryptococcal infection by itself may induce CD4<sup>+</sup> T cell deficiency through blocking the cell-mediated immunity through suppressor T cell functions<sup>28</sup>. Although not completely elucidated, ICL is considered to have a good long-term prognosis, the patients are usually clinically stable, without ongoing immunological deterioration<sup>19</sup>. A variety of opportunistic infections is described in patients suffering from ICL among which cryptococcal infection presents with meningitis, pulmonary involvement and invasive or disseminated infections<sup>29–31</sup>.

*Cryptococcus neoformans* infection is common in immunocompromised patients, especially in patients with acquired immunodeficiency syndrome (AIDS)<sup>5</sup>. The disease is sometimes difficult to diagnose and can be misdiagnosed with other infectious causes of meningitis (fungal, mycobacterial, bacterial, viral), syphilis, lymphoma, mass lesions, intoxication, HIV encephalopathy, trauma, epilepsy, schizophrenia or even bipolar disorder<sup>32</sup>. Serum cryptococcal capsular antigen is a sensitive and specific serological test for acute cryptococcal meningitis. However, in HIV-positive patients ongoing monitoring of antigen presence during suppressive therapy is not predictive of disease relapse. This phenomenon may not be attributable to patients with ICL since several cases of cryptococcal meningitis in patients with this syndrome show persistent cryptococcal antigenemia without signs of meningitis<sup>28</sup>. It is worth mentioning that in our case serum cryptococcal antigenemia was low from the onset of the disease although there was a clear evidence of meningitis.

Prolonged secondary prophylaxis of cryptococcal infection in HIV-infected patients today is overcome by successful highly active antiretroviral therapy (HAART) induced immune reconstitution, and presently is considered unnecessary in patients with CD4<sup>+</sup> T cell count over  $200/\mu L$ <sup>9,33,34</sup>. Immune reconstitution inflammatory syndrome is also described in patients showing improvement in CD4<sup>+</sup> T cell counts following HAART and is characterized by atypical manifestation of opportunistic



infections, including cryptococcal pulmonary disease, meningitis or lymphadenitis<sup>35</sup>. In ICL patients, until recently, there were no formal recommendation on secondary prophylaxis and, as in our case, patients mainly received antifungal prophylaxis for a prolonged time period. It is worth to point out that in the current Infectious Diseases Society of America issued Clinical practice guidelines for the management of cryptococcal disease ICL is not specifically addressed, however, in non-HIV-infected and non-transplant hosts maintenance therapy with fluconazole for 6 to 12 months is recommended<sup>36</sup>.

In conclusion, we described a patient with the idiopathic CD4<sup>+</sup> T cell immunodeficiency syndrome and cryptococcal meningitis. This case highlights the fact that CD4<sup>+</sup> T cell immunodeficiency can exist in the absence of laboratory evidence of HIV infection. Finally, HIV negative patients who present with CNS cryptococcosis without an apparent immunodeficiency should be evaluated for the presence of CD4<sup>+</sup> T cell immunodeficiency.

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## **MENINGOENCEFALITIS UZROKOVAN CRYPTOCOCCUS NEOFORMANS-OM U BOLESNIKA S IDIOPATSKOM CD4<sup>+</sup> T LIMFOCITOPENIJOM**

### **S A Ž E T A K**

*Cryptococcus neoformans* najučestaliji je uzročnik invazivnih kriptokokoza koje uključuju kriptokokni meningoencefalitis, moždane apscese (tzv. moždane kriptokokome), kriptokokozu pluća i infekciju medijastinuma. Invazivne kriptokokne infekcije uglavnom pogađaju bolesnike s oštećenom imunosti, posebice osobe inficirane HIV-om. Ipak, opisani su brojni slučajevi invazivnih kriptokoknih infekcija u osoba s nedostatnom imunošću koji nemaju dokazanu HIV infekciju. Među nekoliko primarnih sindroma imunodeficijencije koji bi mogli biti razlogom invazivne kriptokokne infekcije, sve učestalije se opisuje idiopatska CD4<sup>+</sup> T limfocitna imunodeficijencija. Patogeneza ove bolesti nije do kraja razjašnjena, a klinička slika u oboljelih varira od asimptomatske, laboratorijski potvrđene bolesti do teških oportunističkih infekcija. U ovom radu smo prikazali slučaj imunodeficijentne HIV-negativne osobe oboljele od kriptokoknog meningoencefalitisa uzrokovanog gljivom *Cryptococcus neoformans*. Kod bolesnika je dokazana idiopatska CD4<sup>+</sup> T limfocitna imunodeficijencija.