

# A case of severe meningoencephalitis co-infection due to *Cryptococcus neoformans* and *Treponema pallidum* in an HIV-positive patient

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## Abstract

Cryptococcal meningitis and neurosyphilis are rare diseases in Europe. Coinfection of the nervous system by two distinct non-viral organisms is uncommon and frequently undiagnosed. Differential diagnosis suggests that a single pathologic process should be sought. However, in the presence of severe immunodeficiency, this approach may not be accurate. In the literature, there have been described only one case of *Cryptococcus neoformans* and *Treponema pallidum* coinfection affecting nervous system. We report a case of 30-years-old man admitted to a local hospital due to symptoms of meningitis. On admission, the immunological and viral status of the patient was unknown. It led to delayed diagnosis, as cerebrospinal fluid (CSF) results were unspecific. Eventually, *Cryptococcus neoformans* was detected in CSF. He was referred to Department of Infectious Diseases of Poznan University of Medical Sciences, where a full panel of tests was performed and confirmed HIV infection, cryptococcal meningitis, and neurosyphilis. The patient was put on antiretroviral therapy (ART), ceftriaxone, and amphotericin B. Magnetic resonance imaging revealed an encephalitis. After an aggressive therapy, patient has become stable, and on a frequent follow-up schedule in the outpatient setting.

The reported case is extremely rare. Diagnosed coinfection shows the importance of considering many etiologic possibilities, when an immunocompromised patient presents to an emergency room. Clinicians need to consider *Cryptococcus neoformans* and syphilis in the differential diagnosis of neurological disorders, particularly aseptic meningitis, as early diagnosis and treatment lead to a better prognosis.

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**Key words:** *Cryptococcus neoformans*, co-infection, *Treponema pallidum*, meningoencephalitis.

## Introduction

Highly active antiretroviral therapy (HAART) introduced in 1996 is a significant factor ameliorating human immunodeficiency virus (HIV)-positive patients' lives. However,

according to Sactor *et al.* research, 70% of them still experience or are likely to experience one of neurological complications during their lifespan [1]. These could either present as primary or secondary conditions. The primary is directly caused by the HIV, whereas the secondary is a result of immu-

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nosuppression, and is represented mostly by opportunistic infections [2].

Despite the high frequency and wide spectrum of pathogens of neurological complications in HIV-positive patients, it is very unlikely to diagnose a patient with a co-infection caused by two distinct non-viral organisms, as we present in this study. To our knowledge, there has been only one case report of cryptococcal meningitis and neurosyphilis co-infection described in English literature [3].

As a separate entity, meningitis caused by *Cryptococcus neoformans* is a rare disease in healthy population, but at the same time, is the most common opportunistic infection of central nervous system in HIV-positive population, occurring when CD4 T-cell count drops below 100 cells/mm<sup>3</sup>. On the other hand, neurosyphilis that has been thought to be an almost eradicated disease, not only increases in prevalence, but also presents atypical and more aggressive form in immunocompromised patients [1].

## Case report

A 30-year-old male presented to the regional hospital with an 8-day history of head and neck pain and upper respiratory tract infection symptoms including fever of 38.5°C. Neurological examination revealed neck stiffness, positive Kernig's sign, absence of patellar and Achilles tendon reflexes, and instability in Romberg test. Results of cerebrospinal fluid (CSF) analysis were inconclusive (WBC count: 28/μl; glucose: 33 mg/dl; protein: 62 mg/dl, CSF culture was negative). Head computed tomography (CT) revealed no changes. Empirical treatment with acyclovir and ceftriaxone was implemented, however, it turned out ineffective. Eventually, 7 days after admission, India ink staining in CSF culture confirmed *Cryptococcus neoformans* infection. Secondary to the diagnosis of an extrapulmonary cryptococcosis, he was referred to the Department of Infectious Diseases of Poznan University of Medical Sciences.

On admission, patient reported strong headache, vertigo, dry cough, periodic diarrhea, dysuria, polyuria, vision deterioration ("hazy picture"), and periodic deterioration of hearing. Physical examination revealed insufficient weight, anxiety, neck stiffness, enlargement of lymph nodes, and hepatomegaly. Funduscopic examination (no sign of optic nerve edema), head CT, and CSF results (CSF pressure: 180 mmH<sub>2</sub>O) excluded the possibility of increased intracranial pressure (ICP) on admission. HIV tests were performed and confirmed HIV infection. At that point, his CD4 count was 41 cells/mm<sup>3</sup>, CD8 count 805 cells/mm<sup>3</sup>, and viral load 299,000 copies/ml. Patient's epidemiological history suggests multiple risky sexual behaviors such as belonging to MSM (men who have sex with men) group, multiple casual sexual partners within last year, and repetitive unprotected sex. Based on these findings, syphilis serology in serum and CSF was performed. All of them were conclusive for *Treponema pallidum* infection – serum: *Treponema pallidum* hemagglutination assay (TPHA) 1 : 2560; fluorescent treponemal antibody (FTA) 1 : 200; CSF : TPHA 1 : 10; FTA 1 : 50). CSF

fungal tests confirmed presence of *Cryptococcus neoformans*. Clinicians observed neurocognitive impairment, which was assessed in MMSE (Mini-Mental State Examination). The patient scored 18 points out of 30, and consequently a mild dementia was diagnosed. Head magnetic resonance imaging (MRI) corresponded with the neurocognitive state of patients, as it revealed encephalitis with small ischemic foci.

As a part of antifungal treatment in accordance with the current guidelines, patient was treated with 250 mg amphotericin B in a lipid complex formulation and 1,250 mg flucytosine 4 times a day for 28 days, and with 400 mg fluconazole subsequently. ART, consisting of tenofovir, lamivudine, and lopinavir/ritonavir was implemented immediately. Neurosyphilis was treated with aqueous crystalline penicillin G, 24 million units per day, intravenously for 14 days. Lumbar puncture (LP) was done 14 and 28 days after treatment initiation. At day 14, CSF results were within normal range; however, CSF culture revealed singular yeast like cells. At day 28, CSF results and CSF culture confirmed full resolution.

Even though after 28 days, a significant improvement of clinical state neurocognitive functions was observed (patient scored 30 points out of 30 in MMSE), a radiological follow-up (head MRI) revealed deterioration. The enlargement of previously founded ischemic lesions and extension of ventricular system were observed.

Patient was discharged home in a good condition with 400 mg dose of fluconazole prescribed as *Cryptococcus neoformans* secondary prophylaxis (to be continued for the period of one year), and remains on a frequent follow up schedule in the outpatient setting. His immunological state after 3 months of ARV therapy improved reaching CD4 and CD8 count 145/mm<sup>3</sup> and 1,491/mm<sup>3</sup>, respectively. Viral load fell under 50 copies/ml. The neurocognitive functions after 3 months showed no deterioration. Patient's neurosyphilis follow-up was planned to involve regular clinical monitoring, with serum RPR levels at 6 and 12 months after discharge.

## Discussion

HIV should be considered in all acute neurological syndromes (aseptic meningitis, GB syndrome, cerebrovascular accident, mass lesions, etc.), and urgently confirmed with an HIV antibody test. Early recognition is essential and so is the introduction of appropriate treatment, investigation, as well as ART.

A delay in diagnosis of cryptococcal meningitis may be a result of a low prevalence of this infection in Europe, even in HIV-positive population. According to Antinori *et al.*, hardly 2.2% of HIV-positive patients were diagnosed with *Cryptococcus neoformans* infection in European population [4], whereas in Africa, it represents the predominant cause of meningitis [5].

Katchanov *et al.* suggest that improvement in differential may be achieved by considering underlying HIV infection in all patients presenting with aseptic meningitis, testing for HIV in patients from HIV high-risk groups, and testing for

*Cryptococcus neoformans* in HIV-positive patients irrespective of their neurological symptoms or CSF results [6].

An average time-to-diagnosis delay for cryptococcal meningitis is quantified to be 5 days [6]. In the presented case, the final diagnosis was confirmed within 7 days, which might be due to the fact that HIV status of the patient was unknown at the time, the regional hospital he was admitted to had a limited experience with HIV opportunistic infections, and the patient's neurological manifestation was unusually severe for cryptococcal meningitis.

*Cryptococcus neoformans* infection forces to transfer the patients to a higher-level referral hospital, where a more thorough diagnostic process is implemented. ID department at Poznan University of Medical sciences confirmed HIV-induced severe immunosuppression (C3), syphilis with CNS involvement, and severe encephalitis suggested in MRI as a result of coinfection.

As neurosyphilis is a highly unexpected finding; however, with a rising prevalence of syphilis, it is mandatory to consider a possible etiology of neurological symptoms. Its incidence in pre-HAART era was proved to 9% in HIV-positive patients. However, no data after HAART implementation was gathered for comparison [7]. Nowadays, a widespread of HAART and antibiotic use makes the diagnosis even more challenging, as the neurological manifestation is often atypical or even asymptomatic. Nevertheless, as this study highlights, even with such clinical features it may lead to severe neurocognitive impairment. Therefore, the screening for this reemerging disease should be a crucial part of diagnostics in immunocompromised patients.

Even though HAART provides suppression of HIV replication in plasma, CNS acts as a "sanctuary site" for the virus, where it can mutate independently. This chronic process is thought to cause persistent neuroinflammation and influence neurocognitive abilities [8].

MMSE was carried out on the admission of the patient, showing a significant decrease in neurocognitive function (with 18/30 points). Introduction of the treatment led to visible clinical improvement (with a repeated MMSE 30 days later, resulting in 30/30 points), even though the radiologic findings suggested progression of his condition.

There is no data on prognosis for *Cryptococcus neoformans* and neurosyphilis coinfecting patients. Although the treatment turned out to be successful, the long-term effects of severe encephalitis the patient experienced, remain unknown.

## Conclusions

Clinicians need to consider *Cryptococcus neoformans* and syphilis in the differential diagnosis of neurological disorders, particularly aseptic meningitis, as early diagnosis and treatment lead to a better prognosis. Still, even though there is a specific treatment, the prognosis remains unclear. The diagnosed co-infection shows the importance of considering many etiologic possibilities when an immunocompromised patient presents to emergency room.

## Conflict of interest

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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