Case Report

First HIV Diagnosis in a Patient with Cryptococcus Neoformans Meningitis : A Case Report

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Abstract

Cryptococcal meningitis is a life-threatening infection in HIV-positive patients. It usually presents with symptoms of lethargy, personality changes, memory disorders and cognitive decline. Fever is a common symptom, while specific meningeal signs such as headache, neck stiffness, and photophobia appear in 25 to 33% of patients. However, these symptoms are non-specific and unreliable in advanced HIV infection where the inflammatory response is impaired. Treatment in HIV-infected patients includes a combination of appropriate antifungal therapy, medical interventions aiming at the reduction of elevated intracranial pressure, and initiation of antiretroviral therapy at the appropriate time to avoid immune reconstitution syndrome (IRIS). We present a case of a patient diagnosed with cryptococcal meningitis and newly diagnosed HIV infection in the Department of Internal Medicine at KAT General Hospital.

Key words: Meningitis, Cryptococcus neoformans, Human Immunodeficiency Virus

Introduction

Cryptococcal meningitis is one of the most common causes of meningitis in patients with HIV/AIDS, especially in developing countries (Spec & Powderly 1918a). It is a life-threatening infection in HIV-positive patients, and mortality ranges between 7 and 15%, globally (Spec & Powderly 1995). Usually, it presents with symptoms of lethargy, personality changes, memory disorders and cognitive decline. Fever is a common symptom while specific meningeal signs such as headache, neck stiffness, photophobia occur in 25-33% of patients. However, these symptoms are non-specific and unreliable in advanced HIV cases where the immune response is impaired. Other symptoms include visual disturbances, and even blindness due to increased intracranial pressure, adhesive arachnoiditis or direct nerve damage. In rare cases, deafness and dementia have been reported as complications of cryptococcal meningitis (Spec & Powderly 1918b).

The fungus Cryptococcus neoformans is classified into 4 serotypes based on the capsular polysaccharide glucuronoxymannan (GXM). The capsular types A to D correspond to the certain species (Warkentien, Crum-Cianflone 2010). Specifically capsular type A corresponds to C. neoformans var. grubii, B and C capsular types to C. neoformans var gattii and, capsular type D to C. neoformans var. neoformans. Recently, C. gattii has been classified as a separate species, as it has been shown that it is genetically different from C. neoformans. High concentrations of Cryptococcus are present in bird feces, particularly in pigeons and hens (Warkentien, Crum-Cianflone 2010). However, human

infection usually occurs without a history of direct contact with birds (Warkentien, Crum-Cianflone 2010). Human infection appears to be associated with inhalation of the fungus (Sukroongreung et al., 199. Remarkably, C. neoformans has been isolated from the nasopharynx of 50% of HIV infected patients with cryptococcosis, whereas no C. neoformans has been isolated from HIV infected patients without cryptococcosis (Mitchell & Perfect 1999) This evidence strongly supports the fact that inhalation is the main way of fungus' invasion into the human body (Mitchell & Perfect 1999)

Cryptococcal meningitis is fatal if the appropriate treatment is delayed. The treatment being provided to HIV positive patients involves a combination of appropriate antimicrobial therapy, as well as medical approaches that aim at reducing the elevated intracranial pressure and initiating antiretroviral therapy at the appropriate time (Spec & Powderly 1918c). Guidelines recommend that antifungal treatment should be divided into an induction phase of at least two weeks, a stabilization phase of at least 10 weeks and a maintenance phase that could be extended for lifelong (Spec & Powderly 1918c).

The recommended initial treatment for cryptococcal meningitis in HIV infected individuals includes the combination of amphotericin B, in a dose of 0.7-1 mg/kg/day and flucytosine 100 mg/kg/day. Alternatively, amphotericin B and fluconazole could be given for two weeks followed by fluconazole 400mg per day for 8 or more weeks.

The initiation of HAART in cryptococcal meningitis should be delayed for at least 2 weeks or even longer following the onset of antifungal treatment (Warkentien & Crum-Cianflone 2010). This may reduce the risk of progression into an immunological state known as immune reconstitution inflammatory syndrome (IRIS), which is associated with increased mortality rates (Warkentien & Crum-Cianflone 2010).

Clinical case

A 34-year-old male of Ukrainian origin was admitted to the emergency department of KAT General Hospital of Athens Greece, after he has been found semi-consciousness lying on the floor under unclear circumstances. During the clinical examination, the patient was disoriented and febrile up to 40^{o}C. During the neurological evaluation, the patient was responding partially on commands, and localizing to painful stimuli, while he was having incomprehensible speech. Moreover, a significant clinical sign that was found was neck stiffness. The rest of the physical examination did not reveal any other pathological findings. A complete blood count test was obtained which showed normal white blood cell count, slight increase of c-reactive protein (CRP) levels, and hyponatremia. The head computed tomography showed no pathological lesions in the brain parenchyma, and no abnormal calcification was observed. The sulcus and gyrus were found to be normal. Also, there was no midline deviation. A chest X-ray was performed which did not depict any lesions relevant to active lung disease. An immediate lumbar puncture (LP) was performed because of his persistent neurological status. The complete CSF examination revealed 85/μl leukocytes with 58% polymorphonuclear cells and 42% lymphocytes. In addition, biochemical analysis of CSF showed increased protein (345. 3 mg/dl) and low glucose (21 mg/dl) levels. Empiric broad therapy including acyclovir, ampicillin, vancomycin, ceftriaxone, and fluconazole, was immediately started.

Further CSF tests were ordered including CSF culture, CSF Gram stain, a complete CSF testing to detect proteins, antigens, and antibodies produced in certain infectious diseases, as well as molecular CSF testing. Based on the results of CSF tests, Cryptococcus Ag was found to be positive. Acyclovir was discontinued and was replaced by amphotericin B. No modification was done on the rest of the initial therapeutic scheme given to the patient, till the completion of the remaining CSF tests. Cryptococcus was also isolated from the CSF culture, so ampicillin and ceftriaxone were discontinued. The results of the remaining CSF tests were negative.

Even though there was a gradual improvement in his level of consciousness during his hospitalization, he reported several episodes of headache, photophobia, and short-

term memory impairment.

Furthermore, HIV testing was done which was positive for HIV antibodies. The CD4 lymphocyte count was 56 cells/mm3. Furthermore, no pathogen was isolated neither from the blood cultures nor the urine cultures.

Finally, the patient's neurological status was improved gradually, reaching to an excellent level of consciousness, but the short-term memory impairment was remained till the day of his discharge. After … days of hospitalization, the patient was transferred to … Hospital in Infectious Diseases Unit.

Discussion

Cryptococcus neoformans is considered one of the most prevalent opportunistic infections and accounts for significant life-threatening complications in HIV infected individuals (Salami et al., 2009). Nowadays, an important rise in the incidence of cryptococcal meningitis in HIV infected patients has been observed globally (Salami et al.,). In the contrary, there is a reduction in its prevalence as it can be diagnosed in early disease stage (Spec & Powderly 2018c).

Commonly, Cryptococcal meningitis become apparent as chronic meningitis (Kumar et al., 2008). It frequently appears when the CD4+ T cell count is below 100 cells/ µl. It initially presents in the form of cryptococcal meningitis, followed by pulmonary cryptococcosis and lastly by cutaneous cryptococcosis (Salami et al., 2009). In our case, the measured CD4+ count was 56 cells/mm3 and the cryptococcal meningitis was considered a result of HIV – related manifestation. In these patients, low CSF cell counts and glucose levels, reduced level of consciousness, increased intracranial pressure are among the factors with the poorest prognosis (Diamond & Bennett 1974).

A major diagnostic technique used in many cases of CNS infection is the imaging of the central nervous system (Xie et al., 2021) However, the definitive diagnostic method for meningitis is the CSF testing and its culture for bacteria, as well as blood cultures (Xie et al., 2021). To be mentioned, in cryptococcal meningitis the cellular and chemical alterations of CSF are commonly similar to tuberculous meningitis, thus the culture and isolation of the microbe in CSF specimen is necessary for the definitive diagnosis (Murphy et al., 2020).

The identification of cryptococcal antigen in CFS has been proven to have high sensitivity and specificity, ranging between 93-100% and 93-98% respectively (Kumar et al., 2008, (Murphy et al., 2020). There is a low percentage of false positive results ranging from 0-0.4% (Bicanic & Harrison 2005)

Our case report presents an acute clinical presentation of newly diagnosed cryptococcal meningitis in a patient with HIV infection. The patient had typical clinical signs of meningitis including fever and headache. The induction therapeutic scheme given to the patient included amphotericin B, ampicillin, vancomycin, ceftriaxone, and fluconazole. The response to therapy was acceptable with significant clinical improvement of the patient.

Conclusion

In summary, cryptococcal meningitis is a major cause of both morbidity and mortality in HIV-positive patients. Cryptococcal meningitis should be considered in the differential diagnosis especially in patients with both typical and atypical symptoms as well as signs of meningeal infections. There is clear evidence that the combination of early and appropriate therapeutic approach is vital for the survival of these patients.

References

Bicanic T, Harrison TS. (2005). Cryptococcal meningitis. Br Med Bull.; 72:99-118. doi: 10.1093/bmb/ldh043. PMID: 15838017.

Diamond RD, Bennett JE. (1974). Prognosticostic factors in cryptococcal meningitis: A study in 111 cases. Ann Intern Med , 80, 176-81, doi: 10.7326/0003-4819-80-2-176. PMID: 4811791.

Kumar S, Wanchu A, Chakrabarti A, Sharma A, Bambery P, Singh S. (2008). Cryptococcal meningitis in HIV infected: experience from a North Indian tertiary center. Neurol India. 56(4):444-449.

Mitchell, T.G. and Perfect, J.R. (1995) Cryptococcosis in the era of AIDS – 100yrs after the discovery of Cryptococcus neoformans. *Clin Microbiol Rev*, 8(4) 515–548

Murphy LS, Lacy AJ, Smith AT, Shah KS. (2020). Cryptococcal meningitis in an immunocompetent patient. Am J Emerg Med. 38(11):2492.e1-2492.e3. doi:

10.1016/j.ajem.2020.05.115. Epub 2020 Jun 6. PMID: 32534877.

Salami AK, Ogunmodele JA, Fowotade A, Nwabuisi C, Wahab KW, Desalu OO, Fadeyi A. (2009). Cryptococcal meningitis in a newly diagnosed AIDS patient: a case report. West Afr J Med.;28(5):343-6. doi: 10.4314/wajm.v28i5.55944. PMID: 20383842.

Spec A., & Powderly WG. (1918a). Chapter 11 - Cryptococcal meningitis in AIDS,» Handbook of Clinical Neurology, 139-150.

Spec A, Powderly WG. (2018b) Cryptococcal meningitis in AIDS. Handb Clin Neurol; 152:139-150. doi: 10.1016/B978-0-444-63849-6.00011

Spec A, Powderly WG. (2018c). Cryptococcal meningitis. Division of Infectious Diseases, Department of Medicine, Washington University School of Medicine, St. Louis, MO, United States.

Spec A, Powderly WG. (1995). «Clinical & host differences between infections with the two varieties of Cryptococcus neoformans.,» *Clin Infect Dis.*, 21, 1, 28 – 36

Sukroongreung S, Eampokalap B, Tansuphaswadikul S, Nilakul C, Tantimavanich S. (1999). Recovery of Cryptococcus neoformans from the nasopharynx of AIDS patients. Mycopathologia. 1998-1999; 143(3):131-4. doi: 10.1023/a:1006909532185. PMID: 10353208.

Warkentien T, Crum-Cianflone NF. (2010). An update on Cryptococcus among HIV-infected patients. Int J STD AIDS. 2010 Oct;21(10):679-84. doi: 10.1258/ijsa.2010.010182. PMID: 21139145; PMCID: PMC3134968.

Xie Y, Ruan B, Lang G, Zhu B. (2021). Case Report: Streptococcus Suis Meningitis Diagnosed in a HIV-Infected Patient With Cryptococcal Meningitis Using Next-Generation Sequencing. Front Med (Lausanne) ;8:736064. doi: 10.3389/fmed.2021.736064. PMID: 34778300; PMCID: PMC8581154.