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Cryptococcal Meningitis in HIV Patients and Its Management

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ABSTRACT

Cryptococcal meningitis is infectious disease and has emerged as a number one reason for infectious morbidity and mortality in patients with AIDS. Among the human immunological disorder virus (HIV)-seropositive subjects, cryptococcal infectious disease is that the second commonest cause of opportunistic neuro-infection. Cryptococcal infectious disease happens in non-HIV patients who are immunodeficient due to diabetes, cancer, solid organ transplants, chemotherapeutic drugs, hematological malignancies etc and rarely in healthy individuals with no obvious predisposing factors.
Diagnosis of cryptococcal infectious disease is fairly simple once the diagnosing is considered in the differential diagnosis of chronic infectious disease. Treatment of a patient with cryptococcal infection is a challenge for both the physician and the patient, but rewarding, as many would recover with timely and adequate antifungal therapy.

Key words: Cryptococcal meningitis, HIV, AIDS

INTRODUCTION

Many microorganisms can cause chronic meningitis. The incidence of infections caused by the encapsulated yeast *Cryptococcus neoformans* has risen markedly over the past 25 years as a result of the HIV epidemic and increasing the use of immunosuppressive therapies. [1] Cryptococcal infectious disease has emerged as a leading reason behind infectious of morbidity and mortality in patients with AIDS. [2] Among the HIV seropositive subjects, cryptococcal infection is the second most because opportunistic neuro-infection and frequently occurred in advanced HIV disease. [3] In a study from a major Italian HIV centre cryptococcosis was diagnosed in 2.2% of all HIV-infected in-patients in the post-HAART era 1997–2006. It is one of the AIDS-defining illnesses in up to 69% of patients with HIV infection. [4] Cryptococcal meningitis is one of the AIDS-defining illnesses. [5] Cryptococcal infectious occurred in non-HIV patients who are immunodeficient due to cancer, solid organ transplants, chemotherapeutical medicine, diabetes, hematological malignancies etc and rarely in healthy people with no obvious predisposing factors. Mirza *et al*.[6] conducted a population-based surveillance during 1992-2000 in two areas of USA and found 1491 cases of cryptococcal infection, 11% of the total cohort in non-HIV patients. Diagnosis of cryptococcal infectious disease is fairly easy once the diagnosis is considered in the differential diagnosis of chronic infectious disease. Treatment of a patient with cryptococcal infection is a challenge for both the physician and the patient, but rewarding, as many would recover with timely and adequate antifungal therapy. Cryptococcal infectious disease is the commonest form of fungal infectious disease and is caused by Cryptococcus neoformans. *C. neoformans* is an encapsulated heterobasidiomycetous fungus & first identified as human pathogen in 1894, when it was isolated from tibia of a patient in Germany by Buese and Buschke. [7] In the same year, it was also isolated from peach juice by Sanfelice. The first description of *Cryptococcal meningitis* was published in 1905 by Van Han Semann, although a case of chronic meningitis described in 1861 by Zenker, prior to pathogen isolation, was probably the first

case history. [8] Cryptococcosis caused by the C. neoformans varieties occur mostly in individuals with AIDS and other form of impaired immunity. In contrast, C. gatti-related disease is not associated with specific immune deficit and often occurs in immunocompetent individuals. [9] Individual at high risk for cryptococcal infection include patient with haematological malignancy, recipients of solid organ transplants who require ongoing immunosuppressive therapy, persons whose medical conditions necessitate glucocorticoids therapy, patients with advanced HIV infection and CD4+ T lymphocyte count of < 200/ µL. [9]

Pathophysiology:

C. neoformans spreads hematogenously to the central nervous system (CNS) from pulmonary foci, which can be subclinical. For one, cryptococcal capsule antigens might have limited ability to induce an inflammatory response in the cerebrospinal fluid. Furthermore, the alternative pathway of complement is absent in the CSF. By contrast, Cerebrospinal fluid (CSF) is good growth medium for the organism in culture, probably as a result of trophic properties of dopamine and alternative neurotransmitters within the CSF and the absence of cryptococcus-toxic proteins. Cryptococcal infection develops only CD4+ lymph cell counts fall below one hundred cells/µL.

At this stage, macrophage function also is impaired. Immune reconstitution inflammatory syndrome is occurred in some patients after treatment with highly active antiretroviral therapy (HAART). This syndrome is paradoxical deterioration in the clinical status despite satisfactory management of microorganism replication associated improvement of CD4+ counts as a result of an exuberant inflammatory response toward previously diagnosed or latent opportunistic pathogens. [10]

Epidemiology:

Cryptococcus is ubiquitous in the environment. Among HIV-infected patients in the US, the annual incidence of cryptococcosis is 2-7 cases per one thousand with up to 89% occurring as a CNS manifestation. [11] It is the 4th most common cause of opportunistic infections and CNS manifestations (66–89%) are by far more common than manifestations in other organs. Its incidence has declined recently because of widespread use of antifungal and antiretroviral agents. [12] CNS cryptococcosis is rare in children with AIDS.

Diagnosis:

The diagnosis of cryptococcosis is most often made by the latex agglutination test for capsular polysaccharide antigen. This antigen can be obtained from either cerebrospinal fluid (CSF) or serum, and when present in CSF, is over 90% sensitive and specific for the diagnosis of cryptococcal meningitis. [13] India ink stains are less sensitive than the capsular antigen. [14] In one study of HIV-negative adults with cryptococcosis, India ink was 51% sensitive and CSF culture 89% sensitive among the 157 patients with meningitis. In contrast, the antigen test had a sensitivity of 97% and 87% from the CNS and blood, respectively. [15] In a study involving both HIV positive and negative patients, the India ink stain was positive in 80% (48/60) of patients with cryptococcal meningitis. [16] If isolated from culture, *Cryptococcus* appears as singular, narrow-based budding yeast that is urease negative and can be distinguished by its preferential growth on birdseed agar.

Treatment:

The nature and duration of treatment for cryptococcal infection is based on the immunity of the host and anatomic sites of involvement. For immunocompetent persons with cryptococcal meningitis, the standard treatment consists of amphotericin B 0.7-1.0 mg/kg/day along with 5-flucytosine 100 mg/kg/day for 6-10 weeks. An alternate to this regimen is amphotericin B 0.7-1.0 mg/kg/day plus 5-flucytosine 100 mg/kg/day for two weeks, followed by fluconazole 400mg/day for a minimum of ten weeks. Fluconazole "consolidation" treatment may be constant for as long as 6-12 months, depending on the clinical status

of the patient. For patients with HIV infection and cryptococcal infection, induction treatment with amphotericin B 0.7-1.0 mg/kg/day plus 5-flucytosine 100 mg/kg/day is given for 2 weeks, followed by fluconazole 400mg/day for ten weeks. After 10 weeks of treatment period, the fluconazole dosage may be reduced to 200 mg/day, depending on the clinical grade of the patient. [17] Fluconazole should be continued for lifetime or at least up to the time the CD4+ count reaches 350/cmm. Flucytosine is not regularly used in India due to shortage of availability and the high cost. Observing of serum creatinine and potassium levels should be done frequently (once a week) when amphotericin B is administered. Itraconazole albeit less effective, may be a suitable another for patients intolerant to fluconazole. [18] If cryptococcus is still grown from CSF, then acute treatment should be continued considering probable dose changes to the present therapy or addition of other antifungal agents.

Antiretroviral treatment is usually started when the clinical condition of the patient is moderately stable particularly in those with very low CD4+ (<100 cells/cmm) counts. Patients with cryptococcal IRIS can present as meningitis, intracranial mass lesions, pulmonary cavitation or lymphadenitis. [19] It usually occurs after a few weeks or a few months and is treated with steroids or nonsteroidal, antiinflammatory drugs. [20] Bilateral blindness has also been stated after starting antiretroviral therapy in a patient with cryptococcal meningitis. [21]

CONCLUSION

Cryptococcal meningitis is the most common, opportunistic, fungal infection of the nervous system in immunocompromised individuals. A high index of suspicion is needed for early diagnosis and it is a good clinical practice to use India ink stain and the cryptococcal antigen assay in all cases of meningitis. Early diagnosis and adequate treatment may save the lives of these unfortunate patients. With the advent of antiretroviral therapy, the incidence of opportunistic infections is on a decline in developed countries. In developing countries also, as in India, the incidence of cryptococcal infections may decline in the future with increasing access to antiretroviral therapy. [22]

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