AJMHR
Asian Journal of Medical and Health Research
Journal home page: www.ajmhr.com

Cryptococcal Meningitis In HIV Patients

Suhas Dabhade, Rahul Yeole*
Dr. Hedgewar Rugnalaya, Garkheda, Aurangabad - 431005

ABSTRACT

Cryptococcal meningitis has emerged as a leading cause of infectious morbidity and mortality in patients with AIDS. Among the human immunodeficiency virus (HIV)-seropositive subjects, cryptococcal meningitis is the second most common cause of opportunistic neuro-infection. Cryptococcal meningitis occurs in non-HIV patients who are immune deficient 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 meningitis is fairly straightforward once the diagnosis is considered in the differential diagnosis of chronic meningitis. 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.

Keywords: Human Immunodeficiency Virus, Cryptococcal Infection

Received 17 April 2019, Accepted 01 May 2019

Please cite this article as: Yeole R *et al*., Cryptococcal Meningitis In HIV Patients. Asian Journal of Medical and Health Research 2019.

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 meningitis has emerged as a leading cause of infectious morbidity and mortality in patients with AIDS[2]. Among the human immunodeficiency virus (HIV)-seropositive subjects, cryptococcal meningitis is the second most common cause of opportunistic neuro-infection and usually occurs 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 meningitis occurs in non-HIV patients who are immuno deficient due to diabetes, cancer, solid organ transplants, chemotherapeutic drugs, haematological malignancies etc and rarely in healthy individuals 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 meningitis is fairly straightforward once the diagnosis is considered in the differential diagnosis of chronic meningitis. 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 meningitis is the most common form of fungal meningitis 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 contrasat , C. gatti-related disease is not associated with specific immune deficit and often occurs in immunocompetent individuals[9]. Individual at high risk for cryotococcal 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:

Cryptococcus neoformans spreads hematogenously to the CNS from pulmonary foci, which may be subclinical. For one, cryptococcal capsule antigens may 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, CSF is a good growth medium for the organism in culture, possibly because of trophic properties of dopamine and other neurotransmitters in the CSF and the absence of cryptococcus-toxic proteins. Cryptococcal disease usually develops only when CD4+ lymphocyte counts fall below 100 cells/μL. At this stage, macrophage function also is impaired. Immune reconstitution inflammatory syndrome occurs in some patients after treatment with highly active antiretroviral therapy (HAART). This syndrome is a paradoxical deterioration in the clinical status despite satisfactory control of viral replication and 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 United States, the annual incidence of cryptococcosis is 2–7 cases per 1000, with up to 89% occurring as a CNS manifestation.[11] It is the fourth most common cause of opportunistic infections (after *Pneumocystis jiroveci,* cytomegalovirus [CMV], and mycobacteria), 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 individuals with cryptococcal

meningitis, the standard therapy consists of amphotericin B 0.7-1.0 mg/kg/day along with 5-flucytosine 100 mg/kg/day for 6-10 weeks. An alternative 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" therapy may be continued for as long as 6-12 months, depending on the clinical status of the patient. For patients with HIV infection and cryptococcal meningitis, induction therapy with amphotericin B 0.7-1.0 mg/kg/day plus 5-flucytosine 100 mg/kg/day is given for two weeks, followed by fluconazole 400mg/day for a minimum of ten weeks. After ten weeks of therapy, the fluconazole dosage may be reduced to 200 mg/day, depending on the clinical status of the patient[17]. Fluconazole should be continued for life or at least up to the time the CD4+ count reaches 350/cmm. Flucytosine is not routinely used in India due to lack of availability and the high cost. Monitoring of serum creatinine and potassium levels should be done frequently (once a week) when amphotericin B is administered. traconazole albeit less effective, may be a suitable alternative for patients intolerant to fluconazole[18]. If cryptococcus is still grown from CSF, then acute treatment should be continued considering possible dose changes to the existing therapy or addition of other antifungal agents.

Antiretroviral therapy is usually started when the clinical condition of the patient is relatively stable especially 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, anti-inflammatory drugs[20]. Bilateral blindness has also been reported 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]

REFERENCES:

1. Bicanic T, Harrison TS. Cryptococcal meningitis. Br Med Bull. 2005; 72:99–118

2. Mitchell TG, Perfect JR. Cryptococcosis in the era of AIDS-100 years after the discovery of Cryptococcus neoformans . Clin Microbiol Rev 1995;8:515-4
3. Currie BP, Casadevall A. Estimation of the prevalence of cryptococcal infection among patients infected with the human immunodeficiency virus in New York City. Clin Infect Dis 1994;19:1029-33.
4. .Pyrgos V, Seitz AE, Steiner CA, Prevots DR, Williamson PR. Epidemiology of cryptococcal meningitis in the US: 1997-2009. PLoS One. 2013;8:e56269.
5. Clark RA, Greer D, Atkinson W, Valainis GT, Hyslop N. Spectrum of Cryptococcus neoformans infection in 68 patients infected with human immunodeficiency virus. Rev Infect Dis 1990;12:768-77.
6. Mirza SA, Phelan M, Rimland D, Graviss E, Hamill R, Brandt ME, et al. The changing epidemiology of cryptococcosis: An update from population-based active surveillance in 2 large metropolitan areas, 1992-2000. Clin Infect Dis 2003; 36:789-94.
7. Chander J. 1st ed. New Delhi: Interprint; 1996. A textbook of Medical Mycology; pp. 83–9
8. Mitchell TG, Perfect JR. Cryptococcosis in the era of AIDS- 100 years after discovery of Cryptoccus neoformans. Clin Microbiol Rev. 1995;8:515–48.
9. Arturo casadevall, infectious disease fungal infections, cryptococcosis harrisons principle of internal medicine , 18 th edition , page no. 1646.
10. https://emedicine.medscape.com/article/1167389-overview#a2. Felicia J Gliksman. CNS Cryptococcosis in HIV. Updated: Nov 27, 2017. Retrived: 16 Mar 19.
11. Hajjeh RA; Conn LA; Stephens DS, et.al. Cryptococcosis: population-based multistate active surveillance and risk factors in human immunodeficiency virus-infected persons. Cryptococcal Active Surveillance Group. J Infect Dis. 1999; 179(2):449-54
12. Mirza SA; Phelan M; Rimland D, et.al. The changing epidemiology of cryptococcosis: an update from population-based active surveillance in 2 large metropolitan areas, 1992-2000. Clin Infect Dis. 2003; 36(6):789-94
13. Satischandra P, Mathew T, Gadre G, Nagarathna S, Chandramukhi A, Mahadevan A, Shankar SK. Cryptococcal meningitis: Clinical, diagnostic and therapeutic overviews. Neurol India. 2007; 55:226–232.
14. Hajjeh RA, Brandt ME, Pinner RW. Emergence of cryptococcal disease: Epidemiologic perspectives 100 years after its discovery. Epidemiol Rev. 1995; 17:303–320.

15. Pappas P, Perfect JR, Cloud GA, Larsen RA, Pankey GA, Lancaster DJ, Henderson H, et al. Cryptococcosis in human immunodeficiency virus-negative patients in the era of effective azole therapy. Clin Infect Dis. 2001;33:690–699.
16. Khanna N, Chandramuki A, Desai A, Ravi V. Cryptococcal infections of the central nervous system: an analysis of predisposing factors, laboratory findings and outcomes in patients from South India with special reference to HIV infection. J Med Microb. 1996;45:376–379.
17. Saag MS, Graybill RJ, Larsen RA, Pappas PG, Perfect JR, Powderly WG, et al . Practice guidelines for the management of Cryptococcal disease. Clin Infect Dis 2000;30:710-8.
18. van der Horst CM, Saag MS, Cloud GA, Hamill RJ, Graybill JR, Sobel JD, et al . Treatment of cryptococcal meningitis associated with the acquired immunodeficiency syndrome. N Engl J Med 1997; 337:15-21.
19. Jenny-Avital ER, Abadi M. Immune reconstitution cryptococcosis after initiation of successful highly active antiretroviral therapy. Clin Infect Dis 2002;35:e128-33.
20. Skiest DJ, Hester LJ, Hardy RD. Cryptococcal immune reconstitution inflammatory syndrome: Report of four cases in three patients and review of the literature. J Infect 2005;51:e289-97.
21. De Schacht C, Smets RM, Callens S, Colebunders R. Bilateral blindness after starting highly active antiretroviral treatment in a patient with HIV infection and cryptococcal meningitis. Acta Clin Belg 2005;60:10-2.
22. Cornell SH, Jacoby CG. The varied computed tomographic appearance of intracranial cryptococcosis. Radiology 1982;143:703-7