

Prevalence and clinical presentation of *Cryptococcal meningitis* among HIV seropositive patients

Vasant Baradkar, M. Mathur, A. De, S. Kumar, M. Rathi

Department of Microbiology, Lokmanya Tilak Municipal Medical College and General Hospital, Sion, Mumbai - 400 002, India

Address for correspondence:

Dr. Vasant Baradkar, Department of Microbiology, L. T. M. M. C and L. T. M. G. H, Sion, Mumbai - 400 022, India.

E-mail: vasantbaradkar@yahoo.com

Abstract

A total of 573 HIV seropositive and clinically suspected cases of *Cryptococcal meningitis* were included in the study, from January 2006 to January 2007. CSF samples were processed by negative staining with 10% Nigrosin, cultured on Sabouraud's dextrose agar, biochemical tests, such as urease test and brownish growth in Niger seed agar. The prevalence of *Cryptococcal meningitis* was found to be 2.79%. The most common signs and symptoms were: fever (100%), headache (100%), altered sensorium (100%), and neck stiffness (90%). All the patients responded to intravenous Amphotericin B treatment.

Key words: *Cryptococcal meningitis*, HIV

INTRODUCTION

Cryptococcal meningitis is an opportunistic fungal infection in HIV seropositive patients.^[1] It is one of the presenting manifestations of acquired immune deficiency syndrome (AIDS).^[2] It is the most common lethal fungal infection in patients with AIDS worldwide.^[3-5] Recent data indicates that the incidence of cryptococcal infection is high in the developing countries such as India.^[6,7] The clinical signs and symptoms of *Cryptococcus neoformans* are indistinguishable from those of many other causes of meningitis.^[8] A retrospective study was undertaken in our institute with the purpose of describing clinical and laboratory characteristics of CNS cryptococcosis in HIV reactive patients with meningeal signs and to find the prevalence of *Cryptococcal meningitis* in the HIV-infected patients.

MATERIALS AND METHODS

The study was conducted in the Department of Microbiology, LTMMC and LTMGH, Sion, Mumbai, from January 2006 to July 2007. A total of 573 HIV seropositive, suspected of *Cryptococcal meningitis*,

were include in the study. Medical records of these patients were reviewed and data was collected clinically. The cerebrospinal fluid (CSF) samples were processed for fungal culture after preliminary microscopic examination, comprising wet mount, negative staining with 10% Nigrosin and Gram's staining. The sample was inoculated on two sets of Sabouraud's Dextrose agar (SDA), one incubated at 37°C and another at 24°C, in special biological oxygen demand (BOD) incubator. Fungal cultures were observed for growth, and were followed for four weeks. The colony morphology was noted. *Cryptococcus neoformans* was identified base on yeast like mucoid colony on SDA, urease test and L-Dopa test. Subculture of colony from SDA was done on Niger seed agar, which was incubated at 37C and observed for appearance of brownish colonies suggestive of *Cryptococcus neoformans*^[9] [Figure 1].

RESULTS

Out of 573 processed samples, 19 yielded growth of *Cryptococcus neoformans* with prevalence of 2.79%; out of these, ten were male (52.63%) and six were

How to cite this article:

Baradkar V, Mathur M, De A, Kumar S, Rathi M. Prevalence and clinical presentation of *Cryptococcal meningitis* among HIV seropositive patients. Indian J Sex Transm Dis 2009;30:19-22.

DOI: 10.4103/0253-7184.55474



Figure 1: Growth of *Cryptococcus neoformans* on Niger seed agar showing brownish colonies. (Note: *Candida albicans* showing white colonies is used as negative controls)

females (47.37%). All the positive patients were in the age group of 20 to 40 years (78.95%). Out of the 19 patients, only four were aware of their HIV status prior to admission and the rest were diagnosed only after admission; these patients were on antiretroviral therapy.

The clinical presentation was almost same in most of the patients with few exceptions. Fever (100%), headache since a month (100%), altered sensorium (100%), and terminal neck stiffness (90%) were present in the individuals. Vomiting was present in 10 cases (52.63%). Out of 19 patients, three were suffering from pulmonary tuberculosis and were on antitubercular treatment; 10 (52.63%) had oral candidiasis. The CSF counts and WBC counts were nonspecific. The CD₄ counts of all these cases were <100 cells/ μ l.

These patients were given Amphotericin B, all the patients responded to this regimen.

DISCUSSION

Cryptococcus neoformans is one of the most common opportunistic infection in AIDS.^[1]

The genus *Cryptococcus* contains at least 39 species of yeasts, but few are able to cause disease in human beings. Even those that cause infection are not primarily pathogens, they have so called 'readymade virulence' as a side effect of their adaptation to their environments. Most human infections are due to *Cryptococcus neoformans*. Disease has very rarely been attributed to other species such as *C. flavescens* (formerly *laurentii*). *Cryptococcus neoformans* is an encapsulated yeast first identified as human pathogen in 1894, when

it was isolated from tibia of a patient in Germany by Buese and Buschke.^[10] 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.^[11] *Cryptococcus neoformans* exists in asexual or sexual forms. The asexual form is characterized by oval to spherical budding yeast cells with a polysaccharide capsule, while the sexual or perfect stage is characterized by the presence of basidiospores. The sexual form has not been described in association with clinical specimens and is observed only during mating. The asexual form with capsule is frequently seen in clinical specimens.^[11]

Virulence is due to oxidase, protease enzymes and carbohydrate capsule, which can be demonstrated by negative staining with 10% Nigrosin or India Ink. Noncapsular mutant forms lack pathogenicity. Dioxide concentration favors capsule bioformation. Infections occur through inhalation of yeast cells in respiratory pathogens, then remain dormant depending on the host in immune system. Dissemination is due to serious defects in host immune system. The risk factors include, advanced HIV stage, corticosteroid use, lymphomas, sarcoidosis, lymphoproliferative disorders, hypogammaglobulinemia, systemic lupus erythematosus, cirrhosis and peritoneal dialysis.^[9-11]

Although, cryptococcosis is an established disease, worldwide prevalence, was low before AIDS era.^[9-11] The HIV pandemic has a profound impact on the prevalence of cryptococcal disease. In India, HIV infection is wide spread and it was estimated that approximately 2.5 million were HIV-infected in 2006.^[12] Correspondingly, *Cryptococcal meningitis* has emerged as an important opportunistic pathogen in these patients.

Cryptococcosis, one of the AIDS defining infections, considered as "sleeping disease" became an "awakening giant" within a couple of years and has been now been predicted as the "Mycosis of the future," with a predilection that for every million patients with AIDS, 50,000–100,000 will contract cryptococcosis.^[12,13] Its prevalence varies from place to place. In our study, the prevalence observed was 2.79, this is comparable with the recent report from India,^[2] which showed prevalence rate of 2.09%, varying between 19.8–45.8%.^[9] Other studies show higher prevalence. A study conducted at Department of Medicine, Choithram Hospital and Research

Centre, Manik Bagh showed low prevalence of 3.1%.^[14] A review report of 2001,^[14] on the status of cryptococcosis in India, strangely reveals more cases from Northern parts, where HIV prevalence is low compared to high HIV prevalent states in the Southern or Western India. Since then over all scenario has not changed much. The discrepancy probably is due to under reporting and misdiagnosis of cases.^[15]

Over the years, three successive studies spanning over a period of 12 years(1992-2004), in AIIMS, it revealed that parallel to increase in number of HIV cases; HIV cryptococcosis co-infection increased from 20% in 1992-1996 to 30%, 1996-2000, 37% and 49% in 2000-2004^[16] but no such increase in prevalence over two years was observed in this study.

In our study, it was observed that males were involved slightly more than females, which may reflect a difference of exposure rather than a difference in host susceptibility, as it was noted earlier.^[16] Though children are less commonly affected, now there is increase in the prevalence of *Cryptococcal meningitis* observed in HIV-infected children.^[14,16]

Meningitis in cryptococcosis is the most common central nervous system manifestation. It would be more accurate to describe the syndrome as meningoencephalitis, since histopathological examination demonstrates that along with the subarachnoid space, the brain parenchyma is usually involved. The presentation varies, it may present as subacute (presentation over 2–4 weeks). However, the organisms can also cause acute meningitis occurring over a few days to a week, and true chronic meningitis. In all our cases, the presentation was almost similar to subacute, because history of headache was present since a month.^[11–16]

The clinical manifestations observed in the present study were—headache (100%), altered sensorium (100%), fever (100%), terminal neck stiffness (90%); vomiting was present in 10 cases. Prasad *et al.*,^[17] noted—headache in 89.5% cases, fever in 78.9%, altered sensorium in 23.7%, neck rigidity in 13.2%, and seizures in 10.5%. whereas, Lakshmi V *et al.*,^[2] noted—headache in 31–92% cases, fever in 49–79%, altered sensorium in 71–79%, and neck stiffness in 66.66%. Our findings are comparable with above studies in India.

Other manifestations mentioned by other workers are lethargy, stupor, coma, papilloedema and cranial nerve palsies. Also, complications noted are motor defects, changes in mentation and symptoms of raised

intracranial tension,^[9] but no such complications were observed in the present study.

Out of 19 patients suffering from *Cryptococcal meningitis* in the present study, three had concurrent pulmonary tuberculosis and ten had lesions suggestive of oral candidiasis. Lakshmi *et al.*,^[2] noted concurrent pulmonary tuberculosis in 28.21% cases and lesions suggestive of oral candidiasis in 17.9%.

All the 19 patients in our study responded to induction therapy to IV Amphotericin B (1mg/kg daily) for 2 weeks, followed by Fluconazole 400 mg daily for two months. No relapse was observed in any of these patients.

Infection with HIV continues to be more important risk factor for development of CNS cryptococcosis and is an important contributor to morbidity and mortality in HIV-infected patients. As clinical picture may be confusing with viral or tubercular meningitis, a high index of suspicion and routine mycological surveillance is required to help in an early diagnosis and appropriate therapy, as majority of patients responded to therapy.

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Source of Support: Nil, **Conflict of Interest:** None declared.