

Meningitis caused by *Cryptococcus neoformans* and Herpes simplex virus: Dual infection in an immunocompetent patient

Poesy Payal, Uma Sekar¹, Sujatha S², Anupma Jyoti Kindo¹

Department of Microbiology, Sri Ramachandra University, ¹Department of Microbiology, Sri Ramachandra Medical College and Research Institute, Chennai, ²Department of Medicine, Karpaga Vinayaga Institute of Medical Sciences and Research Institute, Kanchipuram, Tamil Nadu, India

ABSTRACT

Cryptococcus neoformans and Herpes simplex virus (HSV) are known agents of fungal and viral meningitis, respectively, in immunocompromised patients but rarely seen in immunocompetent patients. The present report is of an immunocompetent patient, engineer by profession, who was diagnosed to have meningitis with two organisms. The patient presented with fever, chills and headache for 25 days, altered sensorium for four days and altered speech for two days. Lumbar puncture was done, cerebrospinal fluid was sent for serology and culture was positive for budding yeast cells with capsule in India ink preparation. Culture yielded mucoid, cream-coloured colonies, and latex agglutination for *Cryptococcus* antigen was positive. Polymerase chain reaction on CSF was positive for HSV-1. The patient was treated with Ceftriaxone, Doxycycline, Acyclovir, injection Mannitol and Amphotericin B.

Key words: *Cryptococcus neoformans*, herpes simplex virus, immunocompetent

INTRODUCTION

The incidence of infections caused by the encapsulated yeast *Cryptococcus neoformans* has risen markedly over the past 20 years as a result of the HIV epidemic and increasing usage of immunosuppressive therapy.^[1] Cryptococcal meningitis is a common opportunistic infection and AIDS-defining illness in patients with late-stage HIV infection, particularly in Southeast Asia and South and East Africa.^[2,3] Cryptococcal meningitis also occurs in patients with other forms of immunosuppression. However, with the start of antiretroviral therapy, there has been a decline in the incidence. Cryptococcal meningitis is rarely seen in immunocompetent patients. Herpes simplex virus (HSV) is also known to cause viral meningitis and encephalitis. Although HSV-1 typically causes encephalitis and HSV-2 meningitis, this distinction is not absolute, and several series have noted a small percentage of crossover examples, with encephalitis caused by HSV-2 and meningitis caused by HSV-1. This is a case report of cryptococcal and HSV-1

meningitis in an otherwise healthy immunocompetent individual.

CASE REPORT

A 47-year-old male, engineer by profession from South India, was admitted to the Intensive Care Unit of a tertiary care centre on February 2016. He presented with fever, chills and headache for 25 days, altered sensorium for four days and altered speech for two days. There was no history of vomiting, seizure, weakness of limbs or loose stool. The patient had a previous history of tuberculous lymphadenitis, for which antituberculous treatment was given. The patient had undergone cholecystectomy in the

Address for correspondence: Dr. Anupma Jyoti Kindo,
E-mail: anupmalakra@gmail.com

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How to cite this article: Payal P, Sekar U, Sujatha S, Kindo AJ. Meningitis caused by *Cryptococcus neoformans* and Herpes simplex virus: Dual infection in an immunocompetent patient. J Acad Clin Microbiol 2016;18:114-6.

Access this article online

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DOI:
10.4103/0972-1282.194942

past. He was also an alcoholic. On examination, the patient was febrile and unconscious, with a Glasgow Coma Scale of 9t/15 (E₃M₃V₁). Neck rigidity and Kernig's sign were positive. Pupillary response was bilaterally sluggish, plantars were bilaterally extensor and all deep tendon reflexes were diminished. A sensory and motor system examination could not be performed as the patient was drowsy, arousable but not responding to verbal commands. Examination of other systems revealed no obvious abnormality.

Laboratory investigations revealed a total count of 11,400, packed cell volume of 42, platelet count of 3.50, international normalized ratio of 0.99 and partial thromboplastin time normal. Serum electrolytes, renal function tests and liver function tests were within normal limits. Chest X-ray, an ultrasonography and computerised tomography scan of the head were done which showed no abnormality. Ophthalmological examination revealed bilateral papilloedema, hence neurological referral was also sought. On doing magnetic resonance imaging, multiple hypodense areas involving bilateral thalami, left hippocampus, cerebral vermis and right cerebral peduncle were seen. Increased intracranial pressure was noted.

The patient was intubated and started on Ceftriaxone, Doxycycline and Acyclovir. For bilateral papilloedema, parenteral Mannitol was given. Later, tracheostomy was done. Guarded lumbar puncture was done, and cerebrospinal fluid (CSF) sample was sent for laboratory investigation.

On examination, the sample revealed white blood cell count of 3 cells/cumm, red blood cell count of 25 cells/cumm, protein of 46 mg/dl and glucose of 23 mg/dl.

CSF was clear. Gram stain showed pus cell, plenty of large, spherical budding yeast cells suggestive of *Cryptococcus*. India ink preparation showed capsulated yeast cells. Cryptococcal latex agglutination test was positive. Cultures were performed on duplicate in Sabouraud's dextrose agar and incubated at 25°C and 37°C. After two days of incubation, it yielded smooth, moist colonies. When the growth was subcultured on sunflower seed husk medium and kept at 25°C and 37°C, it showed brownish pigmentation suggestive of melanin production. Urease test was positive; VITEK2 Compaq was used to identify the organism along with sensitivity pattern.

At the same time, the sample was run in qualitative real-time polymerase chain reaction (ABI 7900) using ARGENE Kit for HSV-1, HSV-2 and Varicella-zoster virus and it showed to be positive for HSV-1.

The patient was tested for antibodies to HIV and found to be nonreactive for HIV-1 and HIV-2. His immunoglobulin

levels (IgG, IgA and IgM), complement levels and CD3 and CD4 cell counts were found to be within normal limits, thus ruling out any immunodeficiency.

Treatment was started with conventional Amphotericin B at 1 mg/kg per day as an intravenous infusion along with intravenous fluids and Mannitol. Serum electrolytes and renal functions were monitored on a daily basis. The patient succumbed to the infection on the 16th day, after starting treatment.

DISCUSSION

We report a rare case of dual infection caused by *C. neoformans* and HSV. Our patient had no instance of going to any forest or living close to it, any contact with birds and also had no previous history of orolabial or genital herpes. According to Chau *et al.*, 2010, cryptococcal meningitis is rare in immunocompetent patients and its treatment guidelines are based largely on evidence from trials in patients with HIV infection.^[4] Cryptococcal meningitis has been sporadically reported in HIV-negative patients with immunosuppression caused by organ transplant and cancer chemotherapy, reticuloendothelial malignancies, corticosteroid therapy and sarcoidosis.^[5,6] The clinical course of cryptococcal meningitis is indolent with a median time to diagnosis from onset of symptoms being 44 days with a range of seven days to one year.

In patients with an intact immune system, cryptococcal meningitis usually presents with the typical signs and symptoms of meningitis, fever, neck stiffness and headache, which was seen in our patient along with altered sensorium and sluggish/incoherent speech, no obvious underlying cause can be detected in such cases.^[7,8] HSV-1 also is known to cause viral encephalitis and rarely viral meningitis. HSV-2 meningitis has also been identified as a significant cause of morbidity and mortality in immunocompromised patients,^[9] but its occurrence in an immunocompetent patient without any history of orolabial ulcer in childhood or any genital herpes in the recent past is rare.

Current practices of anti-cryptococcal therapy in India for immunocompetent patients generally include Amphotericin B alone or with Flucytosine (5-fluorocytosine), and sometimes followed by Fluconazole.^[10] Our patient was given only one antifungal agent, namely Amphotericin B.

The patient might have survived if he had been diagnosed with meningitis due to dual organisms earlier in the course of the disease. This report aims to make clinicians aware that rarely two aetiological agents can simultaneously cause

meningitis and only proper investigation done promptly will help to start effective and specific treatment.

CONCLUSION

Meningitis due to dual infection in patients is possible even if the patient is immunocompetent, and proper laboratory investigation is needed to start early and appropriate treatment.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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