

CASE REPORT

AFRICAN JOURNAL OF CLINICAL AND EXPERIMENTAL MICROBIOLOGY
AJCEM/2004035/2542
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SEPTEMBER 2005

ISSN 1595-689X VOL 6 NO 3
<http://www.ajol.info/journals/ajcem>

CRYPTOCOCCAL MENINGITIS IN PATIENTS WITH HUMAN IMMUNODEFICIENCY VIRUS INFECTION: REPORT OF THREE CASES

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Although *Cryptococcus* is an infrequent pathogen in patients without AIDS, it is known to be a major cause of meningitis in those with the disease. In recent times, the incidence of cryptococcal meningitis in patients infected with HIV has increased worldwide mainly because of the increased awareness by both the physicians and clinical microbiologists. We report here three cases of cryptococcal meningitis in HIV patients treated at the Port-of Spain General Hospital in one year. The clinical manifestations in these patients included prolonged and severe headache, neck stiffness and blurring of vision. The patients were treated with amphotericin B. Two patients died a few days after receiving the drug while one patient survived. We suggest that any HIV patient with prolonged headache should be promptly investigated for cryptococcal meningitis

INTRODUCTION

Cryptococcus is one of the most common community acquired opportunistic fungal agents causing serious infections (1). Cryptococcal disease is the most frequent life threatening and third most common fungal infections in patients with AIDS (1, 2). The incidence of cryptococcal infection in AIDS ranges from between 6% to 10% in the United States and 15% to 30% in sub-Sahara Africa (2, 3). *Cryptococcus neoformans* var *neoformans* is the most frequent species affecting the central nervous system and meningitis is most commonly observed (1, 2, 4-7).

The clinical manifestations of cryptococcosis have been extensively reviewed both in patients with or without AIDS, and there is practically no difference in presentation (8). Amphotericin B, with or without 5-fluorocytosine, remains the drug of choice (1, 4). The effective dose and duration of treatment with these drugs has been the subject of controversy and some

authors have recommended lifelong therapy (9, 10).

We present the clinical features and course of cryptococcal meningitis in three HIV infected patients diagnosed in the course of one year at the Port.-of-Spain General Hospital, Trinidad and Tobago, West Indies.

CASE REPORTS

Case 1 (R.S., POSGH No. 624006)

A 22 year old male of African descent presented with headache of two months duration with progressive worsening during the two weeks to admission. This was associated with intermittent fever, vomiting and weight loss after receiving treatment from his doctor. On the day of admission, he had suffered a brief period of loss of consciousness, which prompted him to seek medical attention. History of HIV seropositivity was also obtained and confirmed at the sexually transmitted diseases clinic.

Examination revealed febrile patient with generalized body wasting. He had neck stiffness and positive Kernig's sign. There were

no lateralizing signs. Haemoglobin was 102 gm/L, WBC $0.9 \times 10^9/L$, platelet $89 \times 10^9/L$, Basal Urea Nitrogen (BUN) 4.67 mg/L, creatinine $109.09 \mu\text{mol}/L$, sodium 132 mmol/L and potassium 3.7 mmol/L. Lumbar puncture yielded clear and colourless CSF with no cells, protein level of 4 mg/L and glucose concentration of 2.11 mmol/L (simultaneous blood glucose level was 6.22 mmol/L). An India ink preparation was positive for *Cryptococcus*.

Despite treatment with combined intravenous amphotericin B and oral fluconazole, he deteriorated progressively and died 6 days after admission.

Case 2 (L.F., POSGH No. 13672)

A 32 year old male of African descent who received treatment from a health center was admitted with weight loss, progressive worsening headache, intermittent vomiting and blurring of vision of two months duration.

On admission, he was wasted and febrile, with oral candidiasis, axillary lymphadenopathy and mild neck stiffness. Ophthalmoscopy showed slightly blurred disc margins and mild retinal venous distension. No localizing signs were evident on neurological examination. Haemoglobin was 93 gm/L, WBC $5.4 \times 10^9/L$ and platelets $155 \times 10^9/L$. BUN was 2.5 mg/L, creatinine $90.91 \mu\text{mol}/L$, sodium 131 mmol/L and potassium 5.1 mmol/L.

Lumbar puncture yielded turbid CSF containing no white cell but numerous yeast cells. CSF protein was 0.306 mmol/L and CSF glucose was 0.167 mmol/L (simultaneous blood glucose was 7.67 mmol/L). CSF India ink stain was positive and cryptococcal antigen titre was reported as $> 1/1256$. On culture, *Cryptococcus neoformans* was isolated. Serological testing for HIV antibodies was positive by ELISA and Western blot method.

Patient was treated with intravenous amphotericin B (660 mg over 13 days) followed by oral fluconazole 400 mg on day 15 and 200mg daily thereafter. There was slow improvement during the period of hospitalization and he was discharged after 17 days on admission. A follow up appointment at the STD clinic was continued with further supply of oral fluconazole.

Case 3 (D. K., POSGH No. 987902)

A 27 year old man of East Indian descent, treated by a general practitioner was referred to Port-of-Spain General Hospital because of persistent night sweats, cough, weight loss, fever and severe headache of three months duration.

Physical examination revealed a dehydrated, wasted male patient with fever (temperature 38.2°C), generalized lymphadenopathy, oral candidiasis and mild neck stiffness. Haemoglobin was 89 gm/L, WBC $3.4 \times 10^9/L$, BUN 9.17 mg/L, creatinine $118.18 \mu\text{mol}/L$, sodium 125 mmol/L and potassium 4.1 mmol/L. The CSF was cloudy and contained numerous yeast cells but no white cells, protein concentration was 60 mg/L and glucose level was 2.78 mmol/L (simultaneous blood glucose was 5.22 mmol/L). CSF India ink stain was positive and culture yielded *Cryptococcus*. Cryptococcal antigen titre in the CSF was 1/256. A positive HIV test on his blood was confirmed by the Public Health Laboratory.

Treatment with intravenous amphotericin B daily was begun but the patient deteriorated rapidly and died six days after admission.

DISCUSSION

Cryptococcus neoformans is an opportunistic fungus that causes life threatening infections in human but especially

in immuno-compromised patients (8, 11). The infection is the most commonly diagnosed fungal infection of the CNS with meningitis being the most common manifestation (12). It ranked third among infectious agents causing neurological disease in AIDS patients (1, 7). Cryptococcal disease is common in patients with HIV (4) and in the United States of America and the countries of the sub-Saharan Africa, the incidence ranges from between 6-10% and 15-30% respectively (2, 3).

In the three cases presented, which were seen in the year 1996 at the Port-of-Spain General Hospital, several features associated with poor prognosis in cryptococcal meningitis as previously reported by Diamond and Bennet (14), were seen. These include severe leucopaenia, demonstration of the organism on India ink stain, high titre of cryptococcal antigen in the CSF, hyponatraemia and prior treatment with corticosteroid.

High mortality has also been reported in patients with cryptococcal meningitis who were diagnosed very late (8, 15), and the high mortality in our series was therefore not unexpected as they presented after 8-12 weeks of symptoms. Also, as cryptococcosis is an insidious and slow infection, asymptomatic infection could occur and the actual period of the infection before treatment might have been longer (16). The prognostic factors associated with high mortality may also be obscure in some cases (9) as was the case in the one patient who survived in our series.

As previously demonstrated by others (17, 18), our cases showed that cryptococcal infection in AIDS patients is associated with high mortality even when treated with amphotericin B with or without flucytosine, the drugs of choice (19). The effective dose and duration of treatment with these drugs has

been subject of much controversy and some authors have advocated life-long therapy (9, 10).

The only patient who survived in our series received several antimicrobial agents from private doctors before reporting to the hospital. He was transfused two units of whole blood after receiving amphotericin B for 6 days and was found to improve clinically with the haemoglobin rising to 6 mg/dl. The antifungal drugs and fresh whole blood received could have helped to reduce the severity of infection and also improve the immune system in this patient as Liss and Rimland (20) have reported that both neutrophil and cell mediated immunity are important host defenses for this infection in AIDS (16).

From the cases reported, we suggest that sexually active individuals with fever and prolonged headache, especially those who are immuno-compromised or at high risk of contacting HIV infection, be promptly investigated for meningitis, as early diagnosis still offers the best chance for successful treatment.

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