

Management of AIDS Related Cryptococcus Neoformans Meningitis in a Rural Hospital Setting

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Abstract Background: Cryptococcal meningitis is an opportunistic infection caused by *Cryptococcus neoformans* or *Cryptococcus gattii*. Case Presentation: This case describes a 34 year-old Indonesian female who presented with fever associated with vomiting, headache, photophobia and neck stiffness. On physical examination she had high grade pyrexia with obvious signs of meningism. Lumbar puncture revealed intracranial hypertension of 90cmH₂O. Cerebrospinal fluid (CSF) analysis detected the presence of cryptococcal antigen which was later confirmed as *Cryptococcus neoformans* on species identification testing using polymerase chain reaction (PCR) method. India Ink tested positive. The CECT and MRI of the brain were normal. Her HIV ELISA analysis was reactive with a low CD4 count of 38cells/mm³. The HIV viral load was 500,000 copies/ ml. She was treated with intravenous Amphotericin B and oral flucytosine for 4 weeks. She underwent repeated lumbar punctures until her CSF pressure normalized. Repeated CSF analysis post treatment showed complete clearance of *Cryptococcus neoformans*. Conclusion: Its effective management of *Cryptococcus neoformans* meningitis relies on quick identification of the organism, relief of intracranial pressure and commencement of antibiotic treatment.

Keywords: meningitis, fever, cryptococcus, antibiotic, vomiting

Cite This Article: Lai Nai Kiat Sean, Cynthia Sandanamsamy, Chan Weng Kit, Naganathan, and Ganesh Kasinathan, "Management of AIDS Related Cryptococcus Neoformans Meningitis in a Rural Hospital Setting." *American Journal of Epidemiology and Infectious Disease*, vol. 3, no. 4 (2015): 80-83. doi: 10.12691/ajeid-3-4-2.

1. Introduction

Cryptococcus meningitis is an opportunistic fungal infection caused by the organism *Cryptococcus neoformans* or *Cryptococcus gattii*. [1] It is more common in immunocompromised patients such as in Acquired Immune Deficiency Syndrome (AIDS) patients and has a high mortality rate in developing countries where access to highly active antiretroviral therapy (HAART) is limited. [2] The estimated global deaths are around 600,000 with sub-Saharan Africa reporting highest number of cases (720,000 cases) followed by Asia and South East Asia (120,000 cases). [2, 3] Common symptoms of cryptococcal meningitis are fever (50%), malaise, headache, neck stiffness and personality changes. [2] We report a case of AIDS related cryptococcal meningitis which was successfully treated with antifungals in a rural hospital setting which has limited resources.

2. Case Presentation

A 34 year-old Indonesian female with a known history of Acquired Immunodeficiency Syndrome (AIDS) presented with frontal headache, high grade fever, vomiting, and neck stiffness for four days associated with poor oral intake. One month prior to this admission, she had Pneumocystis Jiroveci Pneumonia in which she

required non-invasive ventilation. She was discharged from the hospital well after completion of trimethoprim-sulfamethoxazole. She married thrice and her previous husband was sexually promiscuous. She denied any intravenous drug usage. She did not have any seizures, unilateral body weakness, altered vision, or photophobia. She did not complain of diplopia or hearing loss. She has no significant family history. She is a homemaker. She is non-smoker and a teetotaler. Her husband was tested positive for retroviral disease for which he is currently on treatment. Physical examination revealed a lethargic obese woman. Her BMI was 35 kg/m². She was febrile to touch with a temperature of 39.2°C. She was clinically dehydrated with a blood pressure of 140/96 mmHg. She was tachycardic with a pulse rate of 106 beats per minute. Her neck was stiff and rigid. Kernig's and Brudzinski's signs were present. Lungs were clear with normal heart sounds. On examination of the abdomen, her liver and spleen were not palpable. She had no skin rash or palpable lymph nodes. Fundoscopy was normal. All 12 pairs of cranial nerves were intact. There was no other obvious neurological deficits.

Her full blood count, liver function, renal function tests and HIV parameters are as shown in Table 1. Blood cultures did not grow any organisms. HepB_sAg, AntiHep C and Venereal Disease Research Laboratory test /Treponema Pallidum Haemagglutination (VDRL/TPHA) screening were all not reactive. Contrast Enhanced Computed Tomography (CECT) and Magnetic Resonance

Imaging (MRI) of the brain showed no abnormalities. Cerebral spinal fluid (CSF) analysis revealed a high opening pressure of 90cmH₂O. CSF analysis results are as shown in Table 2. A sample of CSF (Figure 2) was sent to Institute of Medical Research (IMR) for species identification which confirmed *Cryptococcus neoformans* on PCR analysis. Chest radiography showed clear lung fields.

Table 1. Serum Biomarkers

Serum Biomarkers	Values (Normal range)
Hemoglobin	10.2 g/dL (11.5-18.0)
White Blood Cell Count	5.3 x10 ⁹ /L (4-11.0)
Platelet	415 x10 ⁹ /L (150-400)
Sodium	133mmol/L (130-145)
Potassium	3.48 mmol/L (3.3-5.1)
Serum creatinine	56.0 umol/L (40-80)
Total bilirubin	7.3 umol/L (0-21)
Total protein	75.1 g/L (66-87)
Albumin	31.0 g/L (39.7-49.4)
Random Blood Sugar	5.6 mmol/L (4 – 7.8)
ALP	47.0 U/L (40-129)
ALT	18.2 U/L (0-41)
AST	20.3 U/L (0-40)
Creatinine Kinase	26.0 U/L (39-308)
CRP	37.11 mg/L (<5)
HIV ELISA	Reactive
CD4 count	38 cells/mm ³ (500 – 1600)
HIV Viral Load	500,000 copies/ ml



Figure 1. CECT of the Brain

Table 2. Cerebrospinal Fluid Analysis (CSF analysis)

CSF Parameters	Values (Normal range)
Appearance	Clear/ Colorless
Total Protein	0.70 g/L (0.1- 0.4)
Glucose	<50% of blood glucose (>60% of blood glucose)
Cell count	Predominant lymphocytes
Acid fast bacilli PCR (Polymerase Chain Reaction)	Not detected
India Ink	Negative
Bacterial Latex Agglutination	Present
Cryptococcus Antigen Titer	1:8000
Species Identification Test (PCR)	<i>Cryptococcus neoformans</i>
Fungal Culture and Sensitivity (C&S)	<i>Cryptococcus neoformans</i>



Figure 2. CSF (Before treatment)

A diagnosis of *Cryptococcus neoformans* meningitis was made. The patient was started on IV Amphotericin B (0.7mg/kg/day) once daily and oral Flucytosine (25mg/kg/dose) four times daily. Flucytosine was obtained from a tertiary hospital due to its unavailability in our hospital. She completed four weeks of treatment in the ward. Subsequent repeated lumbar punctures showed normalization of CSF pressures and clearance of *Cryptococcus neoformans*. She was discharged with fluconazole maintenance 400mg/day for eight weeks. On subsequent follow up at the specialist clinic, she was clinically well with no new symptoms.

3. Discussion

Cryptococcus neoformans is capable of infecting any organs but more common sites of infection usually in the lungs and central nervous system. [1] *Cryptococcus neoformans* infection can either progress as asymptomatic or lead to respiratory failure among immunocompromised individuals especially HIV-infected patients.[1] Three other common sites of infection with clinical significance include the skin, eye and prostate. In HIV-infected patients, pulmonary and CNS manifestations are more common together with higher positivity rates of Indian ink

tests. [4] They also present with higher polysaccharide antigen titres and more positive blood cultures of *Cryptococcus*. [4] The gold standard investigation for the diagnosis of *Cryptococcus meningitis* is cerebrospinal fluid examination. [6] In patients with HIV, white blood cell counts in the CSF might be normal. [5] Examination of CSF can be done using India ink which carries a relative sensitivity of 75% in a centrifuged sample. [6] However, a concentration of yeasts less than 10^4 colony forming units (CFU) is unlikely to be detected on India ink, and therefore all patients should have CSF fungal culture and cryptococcal antigen testing if resources allow. [6] *Cryptococcus* antigen testing is an alternative to the India ink for the diagnosis of cryptococcal meningitis. [7] *Cryptococcus* antigen testing has a sensitivity of 99% in subjects with antigen titer of 1:2048. [7] Fungal culture carries a sensitivity of 90% in the diagnosis of cryptococcal meningitis. [7] *Cryptococcus neoformans* and *Candida albicans* are morphologically similar when viewed under direct microscope. Hence differentiation between the two yeasts is made based on clinical and other laboratory test such as by the detection of candida antigen testing via enzyme linked immunosorbent assay (ELISA) and radioimmunoassay. [5] *Cryptococcus neoformans* have been identified using different PCR based methods such as nested PCR, multiplex PCR and real time PCR in which the PCR assays primers target on specific DNA sequences. [5] Studies have shown that PCR yields highest sensitivity (92.9%) when compared with culture (85.5%) and India ink test (76.8%) in terms of molecular diagnosis of *Cryptococcus*. [5] Clinical features of candidiasis may manifest as oropharyngeal, esophageal or vulvovaginal infections with oropharyngeal being one of the initial presentations. [5] In immunocompromised host, *Candida* species usually causes acute neutrophilic meningitis as compared to *Cryptococcus neoformans* which results in chronic lymphocytic meningitis. [5] Computed tomography (CT) of the brain is of limited diagnostic value in Cryptococcal Meningitis. It is shown to be normal in almost 50% of the cases. [7] Despite of its limited diagnostic value, it is routinely carried out in patients to exclude any mass lesions or HIV-related pathologies like Toxoplasmosis or CNS lymphoma. [7] In this case, the patient's CT and MRI were normal and did not reveal any focal brain lesions, midline shift or hydrocephalus. Management of *Cryptococcus neoformans* meningitis focuses mainly on the antifungal drugs namely Amphotericin B, flucytosine and azoles. Amphotericin B is the fundamental drug of choice in the treatment for *Cryptococcus neoformans* Meningitis [7]. The Infectious Disease Society of America recommended a 3 step treatment approach for Cryptococcal Meningitis which includes an induction of 2 weeks with Amphotericin B (0.7mg/kg/day) and flucytosine (100mg/kg/day) followed by a consolidation phase of 8 weeks with fluconazole (400mg/day) and lastly a maintenance with fluconazole (200mg/day) for life. [7] A systematic review and meta-analysis was carried to determine the efficacy of Amphotericin B with flucytosine versus Amphotericin B monotherapy. Results of the analysis revealed a higher proportion of CSF sterilization at 14 days in the combination group (RR 0.81 95%CI: 0.68 to 0.98) as compared to Amphotericin B monotherapy. [7] However, no significant difference in the mortality rate between the

two intervention groups was noted.[7] Mortality was lower in patients with the combination therapy of Amphotericin B and flucytosine at 2 weeks point with the overall reduction of mortality of 44% (RR 0.56, 95%CI 0.33-0.95 p= 0.03). [8] Early fungicidal activity (EFA) which is the time to fungal clearance was significantly shorter in people receiving Amphotericin B and flucytosine rather than Amphotericin B and fluconazole. [8] Increased intracranial pressure is common with cryptococcal meningitis. An opening pressure of more than 250mm/H₂O and those with symptoms related to increased intracranial pressure warranted a therapeutic lumbar puncture. [9] A survival rate of 69% was observed with therapeutic lumbar punctures. [9]

4. Conclusion

In conclusion, cryptococcal meningitis is a common form of meningitis that is more prevalent in HIV/AIDS population. The respiratory tract is usually the primary source of the infection before it spreads hematogenously to the CNS. Its effective management relies on quick identification of the organism, relief of intracranial pressure and commencement of antibiotic treatment. This case highlights the successful management of cryptococcal meningitis in a rural setting where resources are limited.

Acknowledgement

We would like to acknowledge with much appreciation the crucial roles of Dr. Sirajudeen Rowther, the Head of Department, Department of Medicine, Segamat Hospital for the motivation and guidance during the production of this case study.

Statement of Competing Interest

None.

List of Abbreviations

Non standard abbreviations – None.

Informed Consent

Informed consent was obtained from the patient for the publication of this study.

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