Cryptococcal meningitis in a HIV positive patient

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Introduction

Cryptococcal meningitis is a major opportunistic infection and a leading cause of mortality in patients infected with HIV in most of the developing world¹. Clinical presentation is usually sub-acute and typical features of inflammation like fever may be absent. Once the cryptococcal meningitis is suspected, the diagnosis is straight forward in most patients due to the availability of highly sensitive and specific tests¹. Amphotericin B is a toxic drug even though highly active against cryptococci. Toxic effects of amphotericin B can be minimized by close monitoring of the patient and adopting certain precautionary measures.

Clinical Synopsis

A 38 year old farmer who had been detected HIV sero-positive one year ago, presented with headache of 15 days duration and change in behaviour for the last three days. He had not been receiving ART or cotrimoxazole prophylaxis. Headache was holocranial, throbbing, constant and did not respond to paracetamol. He vomited 3 – 4 times when headache was very severe and unbearable. There was no visual disturbance or photophobia, nor history of fever. He became irritable and abusive during previous three days. There was no deviation of mouth, slurring of speech or weakness of limbs. He did not have cough or shortness of breath. He had been treated for pulmonary tuberculosis, 6 months ago. At presentation, he was not receiving any medication. He had multiple sexual exposures with women of unknown serostatus 10 – 12 years earlier but never used narcotic drugs. He was married and his wife was tested negative for HIV infection.

On examination, the patient was wasted, pale but and afebrile. There was no oral thrush or skin lesions. Pulse rate was 90 beats per minute, respiratory rate was 18 breaths per minute and blood pressure was

110/70 mmHg. He was conscious but disoriented. Neck stiffness was present. Pupils reacted to light equally in both sides. No apparent cranial nerve palsies existed. Patient moved all four limbs while muscle tone, deep tendon reflexes and plantar reflex were normal. Examination of cardiovascular system, respiratory system and abdomen were unremarkable.

Laboratory studies revealed haemoglobin of 8 g/dl, MCV of 70 fL, white cell count of 4500/ul, and platelet count of 225,000/ul. CD4 cell count was 40/ul. Serum transaminase levels were normal. Serum creatinine level was 0.8 mg/dl while serum - sodium, potassium, magnesium and calcium levels were within normal range. Chest radiograph and computed tomographic (CT) scan of brain were normal. Cerebrospinal fluid (CSF) examination showed cryptococci in India ink staining and cryptococcal antigen was positive. Protein level was 50 mg/dl and sugar of 60 mg/dl (capillary blood sugar – 95 mg/dl). Gram stain of CSF did not show any micro organisms or cells and acid fast bacilli were not seen.

As CSF findings were consistent with cryptococcal meningitis, treatment with amphotericin B 0.7 mg/kg IV infusion, once daily was initiated. The patient was hydrated well using normal saline and pretreated with hydrocortisone and chlorpheniramine to minimize infusion related side effects. Full blood count, serum levels of creatinine, potassium, magnesium and calcium were closely monitored. Five days after commencing amphotericin B therapy, serum levels of potassium and magnesium started to decline but creatinine and other electrolyte levels remained normal. Hypokalaemia and hypomagnesaemia were corrected with appropriate supplement therapy. Amphotericin B therapy was switched over to oral fluconazole 400 mg/daily dose, after 14 days. Patient completely recovered at this time and antiretroviral therapy (stavudine + lamivudine + nevirapine) was started.

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Comment

Cryptococcal meningitis is the first differential diagnosis to be considered in a of HIV positive patient presenting with severe headache and features of meningism. As this patient had a past history of tuberculosis, the possibility of tuberculous meningitis was also high. The other considerations being bacterial meningitis and viral meningo-encephalitis. Meningeal infiltration of lymphomas may present in a similar way. Absence of fever does not exclude infection in an immunocompromised patient. Neck stiffness which is a typical feature of meningeal inflammation may be absent in HIV positives. Therefore, high degree of suspicion is essential for correct and timely diagnosis.

Cryptococcosis is one of the most common fungal infections of the central nervous system among AIDS patients and present as meningitis, meningo-encephalitis or space occupying lesion. *Cryptococcus neoformans* var *neoformans* and *Cryptococcus neoformans* var *grubii* are responsible for 98% of all Cryptococcal infections in patients with AIDS and is found in aged pigeon feces. Cryptococcal disease usually develops when CD4 cell count decline below 100 cells/ul. At this stage macrophage function, which is important in combating fungal infections, is also impaired. The fungus enters the lungs by inhalation and disseminates haematogenously to the central nervous system (CNS) and other organs like skin, bones and genitourinary tract. But CNS is the preferred site^{2,3}.

Onset of cryptococcal meningitis is usually insidious. Patients often present with severe headache with or without fever. Headache occurs in 73 – 81% of patients and fever in 62 – 88%. Other clinical features include malaise (38 – 76%), nausea and vomiting (8 – 42%), visual disturbances (30%), nuchal rigidity (22 – 44%), altered mental status (18 – 28%), photophobia (19%), papilloedema (10%) and cranial neuropathies (6%)^{1,4}.

A lumbar puncture is the diagnostic procedure of choice and is carried out in all cases of suspected cryptococcal meningitis. The sensitivity of India ink

staining of CSF is 75% while sensitivity of cryptococcal culture and antigen are more than 95%. Cryptococcal antigen titer represents the organism load in CSF. Mononuclear pleocytosis (>20 cells/ul) occurs in 13 – 31% and protein levels exceed 45 mg/dl in 35 – 65% of patients. Computed tomographic (CT) scan or magnetic resonance imaging (MRI) scan of the brain is usually normal but may reveal meningeal enhancement, diffuse brain atrophy, cerebral oedema or in minority of cases cryptococcomas. Commonly, ventricles are normal in patients with raised intracranial pressure. Neuro imaging is warranted prior to lumbar puncture when focal signs are present^{4,5}.

Untreated Cryptococcal meningitis is fatal. Several studies have reported acute mortality rates of 6 – 14%. A minority of patients die within the first 6 weeks after diagnosis, despite treatment. In addition the rate of relapse after treatment is about 30 – 50%⁴.

Amphotericin B is the drug of choice for cryptococcal meningitis because of its rapid onset of action. In high doses it is fungicidal as it damages the fungal cytoplasmic membrane. Amphotericin B, 0.7 – 1 mg/kg day intravenously is given for 2 weeks as induction therapy followed by oral fluconazole 400mg daily for 8 – 10 weeks. Maintenance therapy should be continued with fluconazole 200mg/day for life or till immune reconstitution occurs, following antiretroviral therapy. Resistance to amphotericin B and fluconazole is rare⁶.

Side effects of amphotericin B include nephrotoxicity, electrolyte imbalances, infusion related reactions, anaemia, thrombophlebitis, hypotension, nausea, vomiting and headache. While on amphotericin therapy; patients should be closely monitored for nephrotoxicity, electrolyte imbalances and anaemia. Mild to moderate elevation of serum creatinine levels are common and reversible. Renal dysfunction is dose dependant and can be managed by adjusting doses. Serum potassium, magnesium and calcium levels should be monitored carefully as the common electrolyte imbalances are hypokalaemia, hypomagnesaemia and hypocalcaemia. Once the electrolyte imbalances are detected, they should be corrected immediately with supplements⁷.

Nephrotoxicity can be reduced by adequate hydration and salt loading with infusing 500ml normal saline before and after amphotericin dose. Concomitant use of nephrotoxic drugs such as foscarnet, cidofovir and aminoglycosides should be avoided as much as possible. Lipid formulations of amphotericin are less toxic but they are expensive and action is less reliable in cryptococcal meningitis. Infusion related adverse reactions can be ameliorated by pre treating with corticosteroids approximately 30 min before infusion⁷.

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