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Cryptococcal Meningitis and Its Optimal Antifungal Therapy

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ABSTRACT

Cryptococcal meningitis is the major life threatening opportunistic infection and is caused by Cryptococcus neoformans. Severe headache and with or without fever is the characteristic feature in patients with cryptococcal meningitis. Headache is seen in > 75% while Fever is seen in only 65% of the patients. For the diagnosis of cryptococcal infection neuroimaging of the brain, India ink, cerebrospinal fluid (CSF) culture is considered. We report a case of cryptococcal meningitis who's cryptococcal antigen testing was positive and India ink examination showed the cells resembling cryptococcus and he was treated with antifungal drugs mainly the combination therapy showed better outcome.

Key Words: Cryptococcal meningitis, Amphotericin B, Cerebrospinal fluid (CSF)

INTRODUCTION

Cryptococcosis is a subacute or chronic meningeal infection caused by the yeast-like fungus Cryptococcus neoformans. It is reproduced by budding and is an encapsulated, yeast-like fungus. It is a saprophyte in nature, with a world-wide distribution rather than any defined endemic area. [1] Because the organism is omnipresence it is presumed that exposure to C.neoformans is common. Headache and fever are the most common symptoms associated with cryptococcal meningitis. Cryptococcal meningitis is often unrecognized for several days and weeks and may manifest as pyrexia of unknown origin. [2] Nausea, vomiting, and neck stiffness are the less common symptoms and cryptococcal meningitis are asymptomatic in some patients. [3,4,1]

Cryptococcal infection of the central nervous system is nearly always detected by abnormalities in the cerebrospinal fluid. Cryptococcal meningitis may cause progressive visual disturbances such as decreased visual acuity, increased blind spot, papilloedema, optic atrophy. With the enhancement of the relevance ratio and recognition of its life-threatening effect, more and more clinicians' attention should be needed for cryptococcal meningitis. According to the official statistics approximately one million new cases each year worldwide and the lethality is more than 50 percent [5,6]. However the azole anti-fungal group has shown excellent results in the treatment of cryptococcal meningitis. Combination of flucytosine and amphotericin B is the best present induction therapy for Cryptococcal infection.

CASE REPORT

The patient was a 11year-old who was previously well and first presented to a private pediatrician with a complaint of occasional headache and they suspected case of? Meningitic sequelae with OCT (Optical coherence tomography) showing

increased RNFL (Retinal nerve fiber layer) and early thinning of Ganglion cell layer for Paediatric neurology opinion and further management.

Child presented with gradual painless loss of vision initially with blurring of vision, increasing scotoma and progressively worsening loss of vision. Mild perception of light in right eye present. Left eye – absent. History of ?seizures preceded by aura – past 4 days, bilateral upper limb jerky movements with awareness of surroundings, lasting for few seconds, post ictal drowsiness lasts for 10 minutes. Currently 3-4 episodes per day. Was seizure free for 25 days prior, on good compliance with anti-epileptic drugs.

The child was admitted for the above complaints. On admission , under aseptic precautions, lumbar puncture was done and CSF was sent for analysis - cell count, biochemistry, cultures, India ink stain and Xpert MTB on consultation with Infectious disease specialist.

CSF cell counts: WBC 6.21 $10^3/mm^3$, RBC-3400 cells/mm3, Glucose - 57, Protein - 35.6g/dl, Chloride -125mmol/l. No AFB seen on AFB (acid-fast bacillus) stain, Gene Xpert MTB - negative.India ink stain for Cryptococcus revealed that moderate capsulated budding yeast like cells resembling cryptococcus and cryptococcal antigen testing was positive. Infectious disease specialist opined as non-responsive (Amphotericin given for 7 days in previous hospital admission) cryptococcal meningitis in apparently immunocompetent host and advises re-introduction with Liposomal amphotericin B and 5-flucytosine for 4 weeks with regular monitoring of serum K and creatinine. Primary immunodeficiency workup was done which was unremarkable. Ophthal opinion was sought on the advice of I.D specialist :Fundus - Disc edema + pallor + tortuousity of vessels + media clear,ocular movements full, visual axis clear. No evidence of chorioretinitis or vitritis noted. Opined as Disc edema due to secondary ICT changes. Advised for VEP (visual evoked potential) of both eyes.

Due to the need of long term iv medication, PICC (peripherally inserted central catheter) line was inserted in the right cubital fossa on under aseptic precautions. Pre and post procedure were normal and functioning well.

The child was treated with oral antiepileptics and antifungals. There was a mild decreased in potassium levels from 5.meq/l to 3.4meq/l for which he was given oral potassium supplememts with stat dose of i.m MGSO4. He had nausea with intermittent abdominal pain for which he was given oral emeset and Liver function tests were done on the advice of Infectious disease specialist and his Ambisome dose was re-adjusted (100->75mg iv OD).

He had mild painful swelling in his lower lumbar spine, for which USG at lumbar puncture site was done - which revealed focal subcutaneous soft tissue inflammation seen at the lumbar puncture site. No collection present. Hence he was advised to start on oral amoxicillin.

Infectious disease consultant also advised for repeat cell count, biochemistry, fungal culture (only) and India ink stain to check for response to treatment of meningitis. Parents were counselled for long term therapy with anti-fungal and he is being discharged on the following advice. He is advised for ophthalmic assessment and to reassess his visual status. Regular monitoring of serum K, Cr, mg is required to manage toxicity.

DISCUSSION

The majority of the patients with cryptococcal meningitis get better with adequate therapy. Morbidity is unusual while mortality is seen in about 10% of the cases.

Headache, fever, neck pain are the nonspecific clinical manifestations of Cryptococcal meningitis. In this patient he was suffering with fever, headache occasional and also have vision related problems. Initially they were suspecting meningitis, further India ink stain for Cryptococcus revealed that moderate

capsulated budding yeast like cells resembling cryptococcus and Cryptococcal antigen testing was positive. It is important to diagnosis early of cryptococcal infection for better outcomes. Usually cryptococcal infection has been diagnosed by India ink microscopy on cerebrospinal fluid (CSF), culture or latex agglutination for cryptococcal antigenaemia. [7]

Amphotericin B is the important drug of choice (DOC) for initial therapy in CNS cryptococcosis. It is used based on condition either used alone or in combination with flucytosine. Studies shows that compare to intravenous or oral fluconazole, Amphotericin B often leads to clinical improvement more rapidly and has a rapid onset of action. Monitor renal function carefully throughout its administration, because amphotericin B is nephrotoxic. However Amphotericin B administered over a 6- to 8-hour period have more chances of nephrotoxicity, instead of that administered as a continuous infusion over 24 hours appears to have significantly less nephrotoxicity. For this patient initially infectious disease specialist opined as non-responsive (Amphotericin given for 7 days in previous hospital admission) cryptococcal meningitis in apparently immunocompetent host and advise to start Liposomal amphotericin B.

Other preparations of amphotericin B include amphotericin B cholesteryl complex (Amphotec), liposomal amphotericin B (AmBisome), amphotericin B lipid complex (Abelcet), and amphotericin B colloidal dispersion (Amphocin). As they all cost much more, It remains unclear if these alternative forms of amphotericin B are superior to standard nonlipid amphotericin B. The lipid preparations may have an advantage in sparing renal function compare with amphotericin B desoxycholate, but they may be associated with higher relapse rates. Elevations in serum creatinine and BUN level associated with amphotericin B usually return to normal after therapy is completed. Amphotericin B administering as a continuous drip over 24 hours reduces the frequency and severity of renal toxicity. [8]

For this patient after he was confirmed with cryptococcal meningitis from the side of infection control team he started to receive the intravenous Liposomal amphotericin B 100 mg OD and tablet 5-flucytosine 500 mg thrice a day for 4 weeks with regular monitoring of serum K and creatinine. Electrolyte disturbances are common in amphotericin therapy. In this patient during hospital stay there was a mild decrease in potassium level and it was corrected by potassium supplement and readjusted the dose of inj.amphotericinB 75 mg OD.

Flucytosine should be administered in conjunction with amphotericin B since it is unreliable if used alone, and resistance develops rapidly in cryptococcal disease. Data on the use of fluconazole plus flucytosine are limited because of this combination have less effectiveness but amphotericin B plus flucytosine are more effective and for the better outcome patient was advised to receive long term therapy with antifungal drugs and monitoring of Serum K,Creatinine, Mg levels once in 2-3 days.

CONCLUSION

In conclusion, cryptococcal meningitis is the most opportunistic, fungal infection of the nervous system. Early diagnosis and proactive antifungal therapy may save the lives of the patients. Our patient showed a good clinical and laboratory response to the combination therapy of intravenous Liposomal amphotericin B and oral flucytosine.

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