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Cryptococcal Meningitis in a Patient with Pure Red Cell Aplasia: A Challenge Too Far

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ABSTRACT

Cryptococcal meningitis is a life threatening fungal infection primarily occurring in immunocompromised patients. Here we present a case of a 64 years old lady, known diabetic and hypertensive with pure red cell aplasia on steroids and cyclosporine who initially presented with clinical features suggestive of hyponatremia. However her blood culture showed growth of *Cryptococcus neoformans*. Lumbar puncture showed the presence of *Cryptococcal* meningitis. Conventional therapy for *Cryptococcal* meningitis involves Liposomal Amphotericin B and Flucytosine. However, Flucytosine has been associated with bone marrow suppression and hence could not be used here due to the background of red cell aplasia. Instead we started therapy with Liposomal Amphotericin B and high dose Fluconazole. However, Fluconazole had to be stopped due to hepatotoxicity and Posaconazole was given instead but there was failure to respond to antifungal therapy with persistence of *Cryptococcus* in CSF India ink preparation. She developed a secondary urinary tract infection and eventually succumbed due to immune paralysis.

INTRODUCTION

Cryptococcal meningitis is a life-threatening fungal infection, predominantly caused by the encapsulated yeast *Cryptococcal neoformans*. This opportunistic pathogen primarily targets immunocompromised individuals. The incidence of *cryptococcal* meningitis has been on the rise in recent years[1]. The treatment regimen for cryptococcal meningitis involves an induction phase with the use of amphotericin B and flucytosine followed by consolidation and maintenance phase with fluconazole. Flucytosine is however notorious for causing bone marrow suppression and it has to be used in caution in haematological disorders like pure red cell aplasia.

Case report-our patient, a 64 years old lady, known diabetic and hypertensive, diagnosed with pure red cell aplasia a few months ago for which she was on cyclosporine as well as prednisolone. She was admitted with drowsiness, headache and loose stools for the past 4 days. She was found to have serum sodium of 124 meq L^{-1} with a urine spot sodium of 79 meq L^{-1}. A provisional diagnosis of hyponatremia due to SIADH was made which was being evaluated and treated. Blood cultures were sent on admission due to a possibility of sepsis. She was shifted to the ward and was planned for discharge but kept complaining of persistent headache and sleepiness. MRI brain showed minor focal microbleeds in the cerebellum and chronic ischaemic changes in both cerebral hemispheres. On the 5th day of admission, her blood cultures showed the growth of *Cryptococcus neoformans* which was sensitive to all antifungals including fluconazole (VITEK2). She was shifted back to the ICU and an urgent lumbar puncture was done which showed a high opening pressure, increased proteins (99.7 mg dL^{-1}), normal glucose (75 mg dL^{-1}) and an India ink suggestive of budding yeast cells. This was sufficient to make a diagnosis of Cryptococcal meningitis and she was started on a modified induction therapy involving Liposomal Amphotericin B (3 mg kg^{-1}) and high dose Fluconazole (1200 mg). CSF cultures showed the growth of *Cryptococcus* which was resistant to fluconazole (by VITEK2). Therapeutic drainage of CSF was initially being done on alternate days with monitoring of the opening pressure and checking for the persistence of yeast cells on India ink, as we did not have the facilities for *Cryptococcal* Antigen titres available at our institute (lateral flow assay was only available). CSF was drained at each setting till the CSF pressure decreased to less than 20 cm H_2O. Renal function tests were being monitored routinely to rule out Amphotericin induced nephrotoxicity and serial liver function tests were being checked to rule out hepatotoxicity secondary to Fluconazole. Prednisolone was rapidly tapered and 50 mg of Hydrocortisone daily was continued. She developed transaminitis after 6 days of starting high dose Fluconazole and hence had to be stopped. Dose of Liposomal Amphotericin B was increased to 200 mg daily (4 mg kg^{-1}) from 150 mg (3 mg kg^{-1}). Repeat CSF samples showed persistence of cryptococcal antigen on India ink with a high CSF protein and low glucose. As Fluconazole could not be used, Posaconazole was added to Amphotericin B at a dose of 300 mg once daily. Her urine culture showed growth of *Pseudomonas aeruginosa* which was treated with appropriate antibiotics. However, her drowsiness and headache did not subside and she developed gasping respiration along with desaturation for which she had to be mechanically ventilated. Following this another attempt at CSF drainage was taken but showed a bloody tap, even though CT brain did not show any haemorrhage. Her sensorium however did not improve and she developed AKI for which she had to be dialysed. Eventually her hypotension worsened and she expired due to septic shock and multi-organ dysfunction.

DISCUSSIONS

Initially the non-specific symptoms of headache and drowsiness were attributed to hyponatremia but cultures were sent with the possibility of sepsis with the immunosuppressed background of the patient. Cryptococcal meningitis is associated with a higher mortality in the non-HIV population as compared to the HIV population[2]. The universally accepted treatment regimen for cryptococcal meningitis is the one recommended by the IDSA, involving an induction phase of at least 2 weeks using Liposomal Amphotericin B and Flucytosine[3]. In 2022, the WHO updated its 2018 guidelines for the treatment of cryptococcal meningitis in HIV-infected patients. They recommend that treatment should be given in three distinct phases: 'induction' therapy, with combination of Liposomal Amphotericin B at 10 mg kg^{-1} single dose with Flucytosine 25 mg kg^{-1} 6th hourly and Fluconazole 800 mg kg^{-1} in the first 2 weeks of treatment, "consolidation" with Fluconazole 800 mg^{-1} day for 8 weeks and then fluconazole "maintenance" therapy at 200 mg^{-1} day for 1 year to prevent relapse until immune recovery occurs. The regimen in non-HIV patients involves an induction phase of Liposomal Amphotericin B at 3-5 mg kg^{-1} and Flucytosine at 100 mg kg^{-1} day in 4 divided doses, consolidation phase with fluconazole at 400-800 mg once daily and a maintenance phase with 200 mg daily fluconazole[4]. The treatment of *Cryptococcal* meningitis in non-HIV patients is more challenging than in HIV patients due to a variety of reasons. Delayed diagnosis, higher fungal burden and a lower rate of response include a few.

Flucytosine however can precipitate bone marrow suppression and would have been a risky option with the background of pure red cell aplasia[5]. WHO recommends the use of Amphotericin B with 1200 mg^{-1} day Fluconazole in cases where Flucytosine in not available or cannot be used[6]. Hepatoxicity is a common problem with Fluconazole and hence liver function tests were monitored serially. As current guidelines strongly recommend aggressive therapeutic CSF drainage and maintaining the opening pressure below 25 cm H_2O we attempted to do the same and despite multiple attempts at the same the opening pressure continued to remain high. Posaconazole has proven to be of success with Cryptococcal meningitis and Pitisuttithum *et al*.[7] was able to show a 48% success with the same. Therefore Posaconazole was used as a third option in our case. Intrathecal Amphotericin B was shown to have good efficacy in treated Cryptococcal meningitis by Yuchong *et al*.[8] but was not considered in our case due to the increased probability of a secondary infection. She eventually succumbed to the invasive fungal infection and a secondary hospital acquired infection.

CONCLUSION

Flucytosine has been associated with bone marrow suppression and worsening of haematological conditions, though we could not find any data specific to pure red cell aplasia. We chose not to use Flucytosine though the combination of the same with amphotericin was found to be associated with a faster rate of yeast clearance as compared to a combination of amphotericin B and fluconazole. The use of Flucytosine after balancing the risk and benefits could have led to a positive outcome faster in our patient.

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