ORIGINAL RESEARCH PAPER

General Medicine

CRYPTOCOCCAL MENINGITIS IN AIHA – ONE OF ITS KIND

KEY WORD: Cryptococcal meningitis, Autoimmune haemolytic anaemia

Ashok Sunder* Head Of The Department, Department Of Medicine, Tata Main Hospital, Jamshedpur.*Corresponding Author

Manish Kumar Specialist Department Of Medicine, Tata Main Hospital, Jamshedpur

Sudip Saha Senior Registrar, Department Of Medicine, Tata Main Hospital, Jamshedpur

ABSTRACT

Cryptococcal Meningitis is a life threatening fungal disease which occurs mainly in patients with immunocompromised conditions, such as HIV infection, solid organ transplants, autoimmune diseases like Autoimmune haemolytic anaemia (AIHA), use of steroids and other immunosuppressants but it has also been described in previously healthy individuals[1]. Cryptococcal infection can occur in 2.8-8.0 % of solid organ transplants and ranks third after Candida and Aspergillus, but its association with haematological conditions is very rare (0.07% only).

Anaemia, long-term use of steroids and splenectomy are the risk factors for AIHA complicated with Cryptococcal infection. In India, though isolated cases of *Cryptococcus* have been reported from different centres, [2,3,4,5] no case has been reported from in and around Jharkhand. Thus, we are reporting a case of Cryptococcal Meningitis for the first time in a patient of Autoimmune Haemolytic Anaemia from Tata Main Hospital, Jamshedpur, Jharkhand.

INTRODUCTION:

Cryptococcal Meningitis is a central nervous system infection, caused by *Cryptococcus Neoformans* (*C. neoformans*), an encapsulated yeast like fungus, round to oval with a large polysaccharide capsule ranging from 1 to 30 microns when cultivated in lab [6] and in natural environment, it is smaller and poorly encapsulated. There are four capsular types A, B, C and D. Pigeon droppings commonly contain serotypes A or D and has been isolated from a litter of the species Eucalyptus Camaldulesis, whereas serotype B has been isolated from E. Tereticornis and is the only pathogenic species in humans.

CNS invasion is secondary to haematogenous infection or may represent reactivation of the disease. The time of onset of symptoms for diagnosis ranges from days to months [7]. Infection usually presents as a sub-acute process. Headache, fever and nausea are the common symptoms. The early features lack specificity which may delay diagnosis.

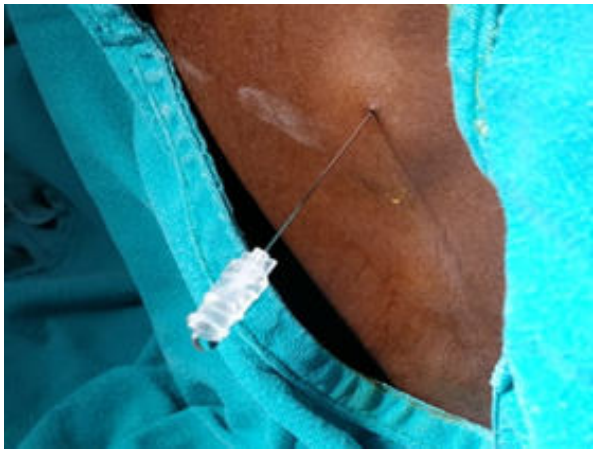
In recent years, it has been reported as a major life threatening opportunistic infection associated with HIV with a leading cause of mortality ranging from 7 – 15 % around the world and 6% in the United States of America [8]. Amongst the survivors 40% have significant neurological disorders like loss of vision, decreased mental function, hydrocephalus, cranial nerve palsies with relapse occurring in 25% of cases [9]. One should suspect Cryptococcus in a patient of fever with headache and a background of AIDS with CD4 cell count less than 200 cells / microliter, Hodgkin's disease, Diabetes and in patients receiving corticosteroids or immunosuppressants. We report a case of Cryptococcal Meningitis in a patient of Autoimmune haemolytic anaemia who was on steroids and immunosuppressants.

The Case:

A 55 years old gentleman got admitted in our hospital with a two-week history of fever, headache and burning micturition. He had a history of Cold agglutinin type autoimmune haemolytic anaemia for which he was on Tab Azathioprine, Prednisolone and Folic acid.

On admission, he had mild pallor with a GCS of 15/15. His vitals and systemic examination were normal including the CNS. Based on the above history a provisional diagnosis of urinary tract infection was made and he was started on broadspectrum antibiotics including steroid and Azathioprine. Initial investigation showed Haemoglobin of 7.9 gm%, CRP - 4.55, Low serum protein (5.4gm%) and albumin (2.89 gm%). Indirect Coombs test was negative whereas the direct coombs test was positive. Urine routine showed pus cells 4-6 /HPF. All other reports including TLC, LFT, RFT and TFT were within normal limits. Gene Xpert test for Tuberculosis, Viral serology, Blood cultures, Dengue and Malaria were negative.

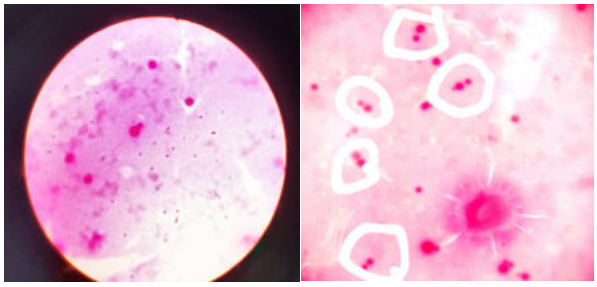
In view of persisting high grade fever, Echocardiography, MRI Brain, CECT Thorax and Abdomen done. CECT thorax showed small fibrotic lesions with mild bronchiectasis right upper lobe and left upper lobe. CT abdomen was unremarkable. MRI brain showed mild diffuse cerebral atrophy with chronic ischemic changes and Echocardiography showed normal size cardiac chambers, normal ejection fraction, and there was no evidence of vegetations.



Picture 1 – LP underway showing clear fluid

During treatment, he had two episodes of focal convulsions for which intravenous Levetiracetam was started. In view of persistent headache, focal convulsion and fever, lumbar puncture and CSF analysis done which showed ADA-3.8 U/L, Protein-53.8 mg/dl, sugar-29mg/dl, WBC-2/cumm.

Microscopic study showed fair number of round to ovoid structures with peripheral halo and budding yeast cells, typical of *C. Neoformans* which was confirmed by the India ink stain.



CSF Analysis - Encapsulated yeast suggestive of Cryptococcal Neoformans

So, based on the above findings a diagnosis of Cryptococcal Meningitis was made and he was started on a combination of intravenous liposomal Amphotericin-B 40 mg/day and Cap Flucytosine 1250mg QID for 14 days. Two units of packed cells were transfused and the Hb levels reached 10 gms%. The patient's clinical condition significantly improved after 5 days of medication. In a repeat lumbar puncture on the 8th day of therapy, the CSF showed presence of round to ovoid structures with peripheral halo and budding yeast cells, typical of *C. Neoformans* but the numbers were much less and after 15 days of therapy, CSF study was negative for Cryptococcus on India ink staining. The patient was discharged after 25 days of hospitalisation, on oral Fluconazole (400 mg per day) for a further 12 weeks.

In his follow up visits, he remained free of fever and any neurological symptoms or signs. Later on, about 12 months later, we were told he died due to severe haemolysis following blood transfusion along with nosocomial sepsis and multi organ dysfunction. This was rather unfortunate, given the fact that he recovered from Cryptococcal Meningitis, a potentially lethal disease and had left the hospital alive and healthy.

DISCUSSION:

Herewith, we wrote about our experience with Cryptococcal Meningitis in an immuno compromised patient. Due to increase use of extensive broad-spectrum antibiotics, corticosteroids, immunosuppressive drugs, the incidence of Cryptococcosis in the susceptible population is high. It also occurs in HIV positive patients and organ transplant recipients. AIHA is an immune mediated disorder where antibodies are directed towards the RBC of our own body, leading to their destruction. Hence, these patients usually need long-term treatment with immunosuppressive agents, corticosteroids or splenectomy, which eventually inhibits the body's immune response, thus increasing the possibility of infection by opportunistic infections like Cryptococcus Neoformans.

Whilst reviewing the literature we discovered the following points:

1. Cryptococcal manifestations lack specificity and is thus confused with chronic infections like Tuberculosis and Urinary tract infections.
2. The main symptoms are headache, nausea, vomiting and fever, others being coma, epilepsy, hearing loss, blurred vision and blindness.
3. The diagnosis is usually delayed and signs of meningeal irritation may appear late too.
4. MRI Brain, may, at times show multiple abnormal signals, but is usually normal.
5. CSF examination and biochemical examination including cell count, protein and glucose are usually in the normal range.

Delayed diagnosis leads to progression of disease and eventually death. Treatment in non-transplant cases is with Injection Amphotericin B plus Flucytosine for at least 2 weeks as induction therapy, which can be extended to 6 weeks in case of neurological complications. This is followed by a period of consolidation with oral Fluconazole for a minimum of 10 – 12 weeks.

CONCLUSION:

Cryptococcal infection is usually uncommon in patients with haematological diseases and so can be easily misdiagnosed. Cryptococcal Meningitis is a serious infection and the clinical course of AIHA on immunosuppressants may get complicated by infection with C. neoformans. One should have a high index of suspicion for Cryptococcal Meningitis in patients of AIHA on immunosuppressants with complaints of unexplained fever and headache. Its clinical presentation can be subacute and deceptive; therefore, its diagnosis requires a proper evaluation of both clinical and laboratory findings.

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