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Case Report

Fatal cryptococcal meningitis in a patient with uncontrolled diabetes mellitus: A case report

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Abstract

Cryptococcal meningitis (CM) is an opportunistic yeast infection which necessitates prudent diagnostic & treatment protocols. This opportunistic fungus is universal in distribution and acquired through inhalation. Literature highlights the association of CM with deficient T- cell mediated immunity. We report a case of non-Human Immunodeficiency Virus (HIV) associated CM in a young adult male patient with Type 2 Diabetes mellitus (T2DM) who presented with repeated episodes of headaches terminating in loss of consciousness and finally succumbing to death despite perceptive treatment efforts. This case report emphasises the importance of considering CM as a differential diagnosis among non-HIV infected, patients with T2DM & the grim outcome associated with it.

Keywords: Cryptococcal, Meningitis, Diabetes mellitus, Type-II, India INK, Immunochromatography.

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1. Introduction

Cryptococcus is an invasive basidiomycetous yeast. This opportunistic fungus is worldwide in distribution and acquired via inhalation. Several species of this genus survive abundantly in eucalyptus trees, almond tree barks and olive trees of the tropics.[1] Pigeon droppings which are a rich source of nitrogen and creatinine[2] harbour a homely niche for cryptococcal yeast. Given the scenario of overpopulous pigeon menace in urban areas of tropical Low and Middle Income Countries (LMICs), the likelihood of exposure to cryptococci from the inhalation of infectious propagules (presumed to be either spores or desiccated yeasts) by adulthood is inevitable. Immunocompromised status associated with solid organ transplant, diabetes, HIV/Acquired immunodeficiency syndrome (AIDS) and the use of immunosuppressive drugs are key risk factors for expression and reactivation of the nascent infection.[3]

LMICs are seeing a progressive increase in the number of lifestyle associated disorders. India houses the second largest number of adults with T2DM globally, which is an imminent danger to the quality of working population in the country.[4] The impact of early onset T2DM in urban India is significant given the escalating prevalence due to lifestyle metamorphosis, unplanned healthcare expenses in the backing of a strong genetic component.[5,6] Individuals with inadequate glycaemic control are prone to infections due to the glucose-rich blood serving as an excellent growth media for opportunistic pathogens in the backdrop of immune dysregulation.[3,7] Opportunistic CM is one such sporadically reported condition with grave outcome among non-HIV affected individuals with T2DM. Literature backs varied clinical presentation and diagnosis is usually steadfast with cerebrospinal fluid (CSF) India Ink microscopy, culture & antigen testing. Parenteral amphotericin-based therapy combined with flucytosine are currently the preferred options

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for induction therapy of cryptococcal meningitis.[8] However the associated mortality rates remain extremely high even in the recent times. We report one such case of a young adult person with T2DM who succumbed to CM induced vasculitis.

2. Case Report

A 29 year old male patient with uncontrolled Type 2 diabetes mellitus (T2DM) presented with history of altered sensorium of 3 days duration, repeated episodes of projectile vomiting and four generalised seizure episodes with post ictal confusion. Upon probing the past history of the patient it was found that he had repeated episodes of headaches for a duration of 5 months for which the patient was placed on acute & preventive anti-migraine pharmacological drugs apart from being on anti-diabetic medication for T2DM. Psychosocial history given by immediate family members revealed the patient was a chronic alcoholic for the past 10 years. The patient did not have any pet pigeons and was not a bird breeder by occupation. No significant genetic history noted. The Timeline of symptoms is described in **Figure 1**.

On admission the patient was found to be drowsy & disoriented to time, place & person. Bilateral pitting oedema was present. The blood pressure was found to be 120/80mmHG with a pulse of 107 beats per minute. Patient recorded an SPO2 of 98% at room air. Systemic examination revealed a mute bilateral plantar response, 1+ Reflexes with the patient obeying commands and moving all 4 limbs despite documented drowsiness.

Blood Investigations revealed a total leucocyte count of 10,110 cells/cumm. The differential picture revealed a neutrophil count of 76.6% & lymphocyte count of 14%. Erythrocyte Sedimentation Rate (ESR) was found to be 15mm in 1 hour with a 36.1% packed cell volume. Platelets remained normal at 3.37 Lakh/cumm. The renal and liver function tests were within normal limits. Random blood glucose was deranged at 339 mg/dl and HbA1c (glycated haemoglobin) stood at 7.6%. The patient was seronegative for HIV, Hepatis B surface Antigen (HBsAg) & anti hepatitis C virus IgM by chemiluminescence immunoassay. The urine microscopy was well within normal limits. Indirect immunofluorescence for antinuclear antibodies was found to be negative. Blood electrolyte picture showed a mild hyponatremia with sodium at 131mEq/L. Potassium and chloride were within normal limits. The Procalcitonin was documented to be 23.21ngm/ml. C - reactive protein was documented at 131.23mg/l.

Magnetic resonance imaging (MRI) of brain with contrast showed diffuse sulcal FLAIR hyperintensities with leptomeningeal enhancement in bilateral parieto-temporal occipital lobes suggestive of meningitis. Multifocal acute infarcts in bilateral frontal & occipital lobes with foci of blooming in right lentiform nucleus suggestive of haemorrhagic transformation secondary to vasculitis. Cerebrospinal fluid (CSF) was tapped and analysed. The CSF glucose was reduced and the observed value was 54.90 (Serum blood sugar = 339mg/dl). The CSF protein was increased at 230mg/dl and the CSF chloride level was normal at 118.8mEq/L.CSF showed increased lymphocytes with encapsulated broad based budding yeasts on India Ink examination (**Figure 2**). CSF Genexpert real-time Polymerase chain reaction (PCR) for *Mycobacterium tuberculosis* was negative. The CSF lateral flow immunoassay for cryptococcal antigen was found to be positive (**Figure 3**). The diagnostic challenges faced were negative result of the serum cryptococcal antigen and CSF fungal culture negativity despite collecting the sample prior to initiation of antifungal therapy.

With the above investigations on hand, a working diagnosis of CM with multifocal infarcts was made and the patient was placed in the Intensive care unit (ICU) in view of poor GCS score. Patient was started on insulin infusion to achieve glycaemic control. ABG showed compensated metabolic acidosis. Patient was bridged and changed to subcutaneous insulin after achieving glycaemic control.

Due to the challenges associated with inaccessibility of liposomal amphotericin B and anticipated adverse effects attributed to difficulty of monitoring Intravenous (IV) amphotericin B therapy a low dose of 0.5mg/kg slow IV over 4-6 hours twice daily along with oral fluconazole 400 mg twice daily was started as depicted **Figure 4**. This is a preferred regimen in LMICs given its lower cost, safety profile and availability. Despite 7 days of antifungal therapy, a repeat CSF tapped showed the presence of Cryptococci upon India Ink examination which failed to grow on culture. CSF Cryptococcal antigen was positive by lateral flow assay. *Interferon-Gamma (IFN γ)* adjunct therapy was suggested which the patient did not receive due to non-affordability. Despite aggressive treatment the patient sadly succumbed to his condition.

3. Discussion

Invasive fungal diseases (IFD) remain underappreciated causes of death among diabetic patients.[7] The invasion of the cryptococcal microbiota into the human mucosa via inhalation or rarely direct inoculation results in colonisation and dissemination of the acquired fungus which remains latent awaiting the right opportunity to thrive and slay the human host. The presence of yeast ligand specific receptors in the human Central nervous system (CNS) and the high dopamine levels augment the virulence of this neurotropic yeast.[9] Parallelly the attributable host factors of dysregulated immune response, exaggerated pro-inflammatory cytokines and sugar rich hyperglycaemic milieu serves as a rich growth media for this opportunistic fungus.[3,9]

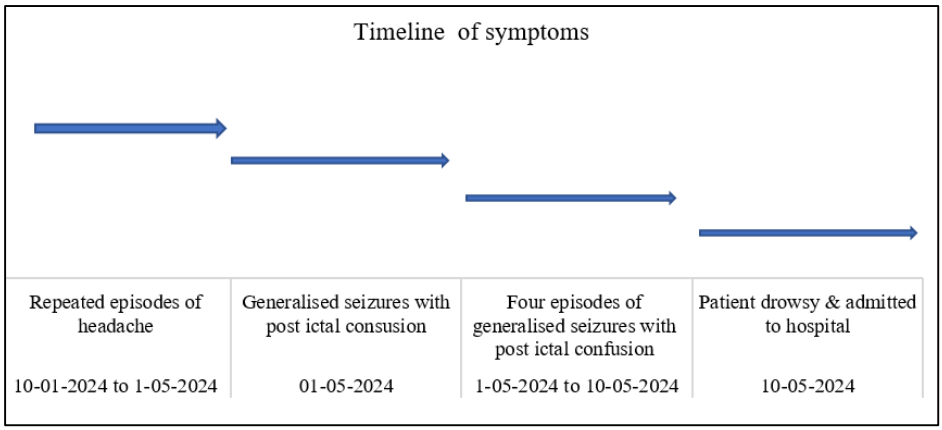

Figure 1: Timeline of symptoms

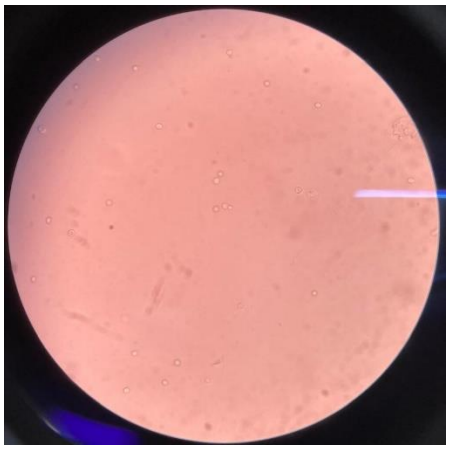

Figure 2: CSF showing lymphocytes with encapsulated broad based budding yeasts on India Ink examination

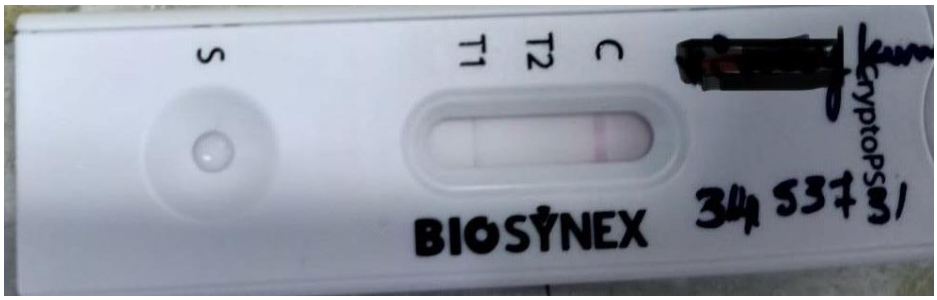

Figure 3: The CSF lateral flow immunoassay showing positive result for cryptococcal antigen

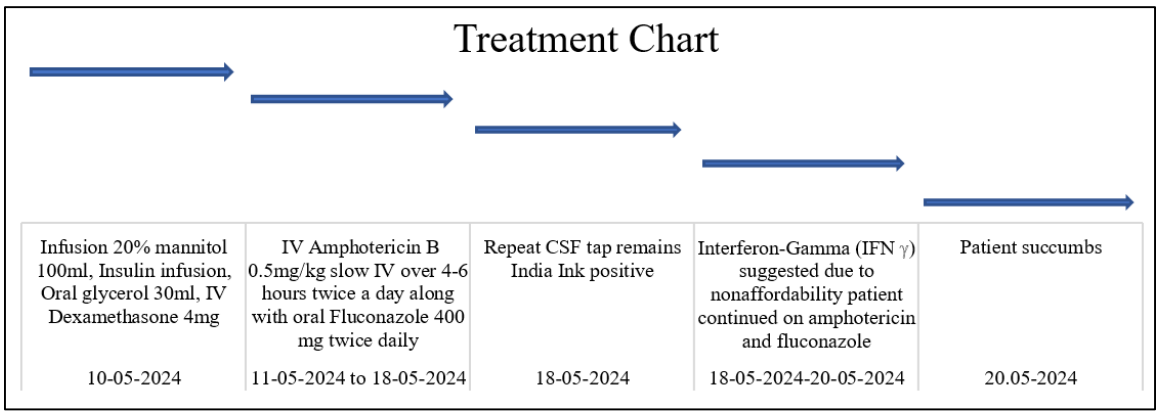

Figure 4: Treatment chart

The host immune response and not the disease severity decides the clinical manifestation of cryptococcal IFD to a great extent, thereby clinching the diagnosis requires a high degree of clinical vigil. An interesting finding in the above case report is the elevation of acute phase markers PCT & CRP. The elevation could be explained due to immune dysregulation considering the fact that these biomarkers have limited ability to distinguish sepsis from other inflammatory and non-inflammatory states.[10] Literature backs with evidence the utility of these markers in distinctive differentiation of viral meningitis but, they do not find a good utility to distinguish fungal from bacterial meningitis.[10,1] According to standard criteria, an invasive or systemic fungal disease is proven when tissue damage due to fungal elements is observed by histopathologic examination and/or when the aetiologic agent is isolated by culture from clinical sterile samples such as blood, tissue or CSF.[12] The traditional diagnostic paradigm relies on CSF culture as the gold standard for diagnosis of CM. The availability of non-culture based diagnostics have helped in diagnosing culture sterile CM due to the varying degree of fungal burden.[13] Similar to the present case report literature documents an unexpected higher mortality among the cases of culture sterile CM.[13] This could be attributed to the higher pro inflammatory cytokines resulting in the paradoxical immune reconstitution inflammatory syndrome (IRIS).[14] The analytic detection range of the Cryptococcal antigen (CrAg) lateral flow immuno-chromatographic assay is consistently reliable with a few instances of cross reaction with Aspergillus species, Paracoccidioides species and Rheumatoid factor (RF) protein.[15] In such situations the simple yet pertinent India Ink examination coupled with the CSF CrAg assay can serve to augment the diagnostic specificity as highlighted in our case-report.

Induction treatment with liposomal amphotericin B alongside flucytosine is the first line treatment for the management of CM followed by strict adherence to consolidation and maintenance therapy.[8,16] The use of adjunct high-dose dexamethasone, sertraline and tamoxifen have proved ineffective and harmful.[16] Newer molecules such as *Miltefosine, AR-12, T-2307* have been explored for the purpose of fungal clearance.[17] The utility of adjunctive therapy with newer molecules and drug re-purposing is gaining pace in management of CM. Adjunctive exogenous IFN- γ has supporting evidence of faster clearance of yeasts from the CSF.[8,16] However on a contradictory note, a few clinicians have observed that despite improved fungal clearance a possibility of failed protection from patient mortality clearly exists.[17]

A Noteworthy limitation in the case reported is the use of low dose amphotericin-B and fluconazole. This regimen is favoured in LMICs due to advantages of accessibility, drug safety and cost incurred. Augmenting the regimen dilemma is the fact that fungal clearance does not equilibrate to reduced patient mortality thereby obscuring the utility of adjunctive therapy. As per WHO recommendation AMBITION-cm is the preferred antifungal therapy for cryptococcal infections among the individuals with HIV.[16] However the utility of this regimen is not time tested among non-HIV infected population. The 2024 guidelines for cryptococcosis[16] advocates the use of high dose liposomal amphotericin B 3-4mg/kg daily alongside with adjunctive flucytosine 25mg/kg four times daily by incorporating data from contemporary clinical trials. The inaccessibility to the high dose regimens and the adjunctive agents scamped the grim chances of survival as in the case of the above mentioned patient who succumbed to CM.

4. Conclusion

To conclude, our case of overwhelming CSF culture sterile CM in a young diabetic, non-HIV infected patient highlights the amalgamatory role of a clinician & his laboratory counterpart towards clinching the accurate diagnosis. The presence of uncontrolled hyperglycaemia and sterile CSF cultures associated with CSF CrAg positivity are red flags which pave way towards mortality.

The neurotropism expressed by cryptococcus, encompassed by the numerous virulence factors in addition to the host desynchronized pro-inflammatory cytokines are responsible for the heightened mortality risk in diabetic patients with CM. The exogenous anti-cytokine therapy needs further exploration as a supplement therapeutic modality to compliment the available antimicrobial agents.

5. Patient Perspective

The patient was drowsy and disoriented to time place & person at the time of hospital admission. Hence the patient could not express his perspective.

6. Declaration of Patient Consent

Ethical clearance/ Declaration of patient consent: The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

7. Availability of Supporting Data

Not disclosable as per the Hospital Policy.

8. Financial Support and Sponsorship

Nil.

9. Conflicts of Interest

All the authors declare no conflict of interest.

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