CASE REPORT

CRYPTOCOCCAL MENINGITIS IN IMMUNOCOMPETENT PATIENT

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Cryptococcal meningitis (CM) is life threatening fungal infection of central nervous system (CNS). Although it is commonly associated with immunosuppression but rarely it can occur in immune competent patient. We report a case of 21 year old non HIV infected girl. Based on initial diagnoses of tuberculosis Bacillus meningitis (TBM), she was started on anti-tuberculosis treatment (ATT). However failure to respond to treatment prompted a quest for alternative diagnosis. A final Diagnosis of CM was confirmed on latex agglutination antigen detection on cerebrospinal fluid (CSF) analysis. The patient responded well to antifungal treatment. Initially diagnosis was missed due to common occurrence of tuberculosis infection in Pakistan and resemblance of its symptomatology and magnetic resonance imaging (MRI) findings with CNS cryptoccocal infection.

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INTRODUCTION

Cryptococcus neoformans (*C. neoforman s*) is encapsulated fungus which is inhaled from environment. There are two varieties of *C. neoforman s*, named as "neoformans variety" and "gatti variety" which are pathogenic to humans. Infection in immunocompromised patients is caused by *C. neoforman* variety neoformans through bird's droppings mainly pigeon. *C. neoforman* variety *gatti* is found around eucalyptus tree and cause infection in immunocompetent patients.[1] It is mostly found in tropical and subtropical regions. CNS involvement is in the form of meningitis, meningoencephalitis and cryptococcoma. This infection spreads by haematogenous route to brain from initial site of infection in lungs.[2] Symptomatic involvements of other organs like eyes, skin and prostate can also occur.[3]

CASE REPORT

A 21 year old female presented with diagnosis of demyelinating disease of CNS. She was referred for plasmapheresis. Initially six month ago, she developed headache, weight loss and low grade fever. Headache was bilateral, progressive in nature with nocturnal worsening. It used to aggravate on straining and coughing but relieved on taking painkillers. Fever was intermittent with mostly nocturnal spikes. History of seizures, focal neurological deficit, visual defects, faecal or urinary incontinence, polyarthralgia, and skin rash was unremarkable. History of blood transfusion, dialysis or any kind of drugs including steroid was not present.

Patient was afebrile with regular pulse of 72 beats/min, blood pressure of 110/60 mmHg in sitting position, respirations 20/min and 35 Kg weight. She looked pale and emaciated. Systemic examination including meningeal signs and fundoscopy were unremarkable. At our hospital baseline investigations including complete blood picture, liver function test, renal function test and ESR were normal except for Hg 9.3 gm/dl. Serological tests for HBV, HCV, HIV, Syphilis and Brucella were unremarkable. Autoimmune screen including ANA and ENA was normal. Chest X ray and ultrasound abdomen did not reveal any abnormality. Lumber puncture showed opening pressure of 250mmH_2O. CSF analysis revealed proteins 1.5g/L (0.2 to 0.45 g/L), Glucose 3.8mmol/L (3.4 to 4.4mmol/L) and only few lymphocytes. CSF did not showed any organism on Zeihl-Neelson and India Ink staining for acid fast bacteria (AFB) and Cryptococcus respectively. PCR for mycobacterium and VDRL for syphilis were negative in CSF.

MRI brain showed discrete bilateral lesions in centrum semiovale and periventricular white matter, as well as internal capsule and lentiform nucleus. These lesions were hypo intense on T1W1 but hyper intense on T2W1 and FLAIR sequences. These lesions showed facilitated diffusion on DWI/ADC mapping. Except for the lesion of left internal capsule which showed nodular contrast enhancement, none of the other lesions showed significant contrast enhancement on T1W1 CE sequences. GRE was unremarkable. Bilateral mild dilatation of temporal horns of lateral ventricle was present which suggested communicating hydrocephalus. Leptomeningeal enhancement was seen with extension into sulci. MRA was unremarkable except for the mild contour irregularities. Based on history, lab findings and radiological study, patient was started on ATT along with high dose steroids. Initial response to treatment was quite satisfactory as headache and fever settled. But after 6 weeks when steroids were tapered off, the frequency & intensity of headache increased and fever reoccurred with night sweats. At this point multidisciplinary approach was used and case discussed with Radiologist, Microbiologist and Neurologist. MRI brain and CSF analysis were repeated. MRI findings were exactly same but cryptococcal antigen was positive which resulted to definitive diagnosis of cryptococcal meningoencephalitis.

Patient was started on combination therapy of Amphotercin B and fluconazole along with high dose steroids. After 6 weeks Amphotericin B was stopped and steroids were tapered off. Fluconazole was continued for 6 months. Patient condition improved gradually and repeat MRI brain showed reduction in lesion size. Presently Patient, nine months after stopping treatment is asymptomatic.

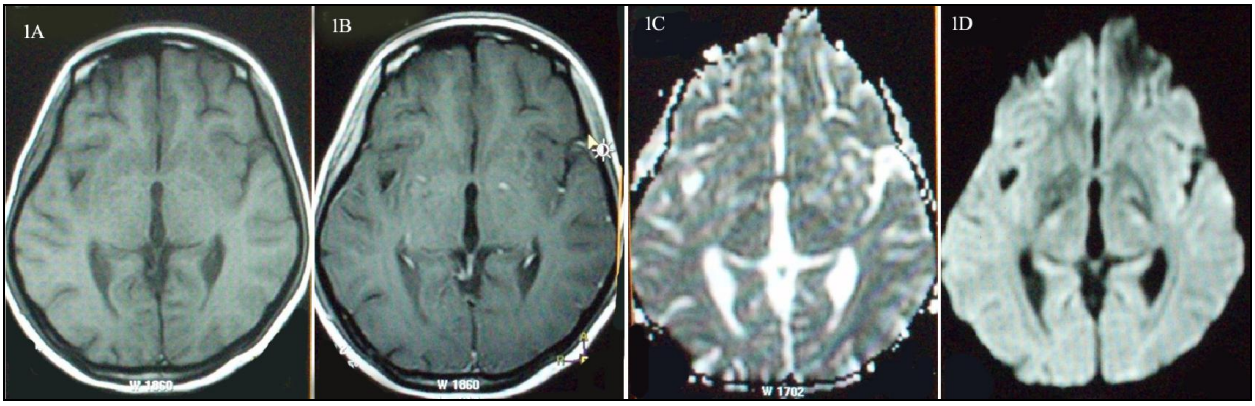

Figure-1: Axial images of brain including T1WI, DWI/ADC & T1W1CE. Hypo intense lesions are visible on T1W1 sequence (1A), without significant contrast enhancement on T1W1 CE sequence (1B). These lesions show facilitated diffusion on DWI/ADC mapping (1C&1D)

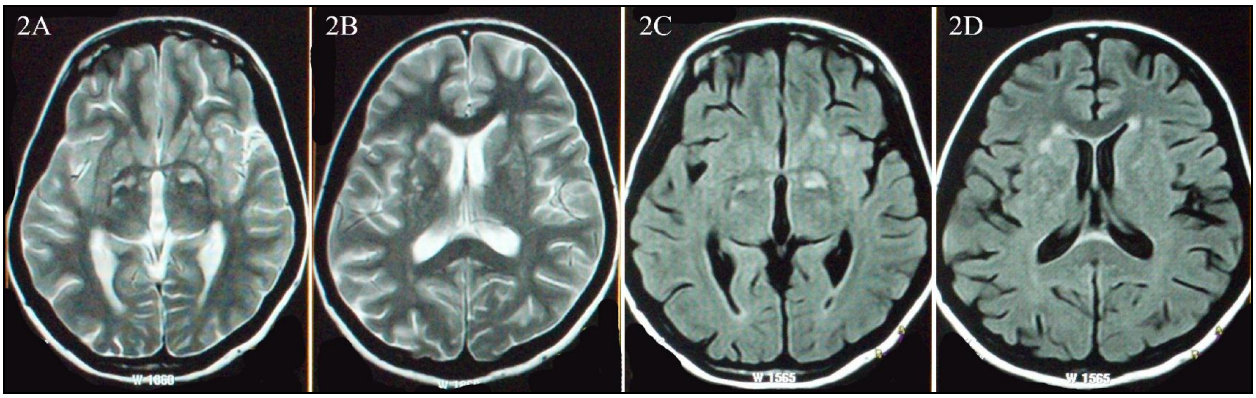

Figure-2: Axial images of brain including T2W1& FLAIR. Hyper intense lesions are visible in centrum semiovale and periventricular white matter, as well as internal capsule and lentiform nucleus on T2W1 (2A&2B) sequences and FLAIR (2C&2D) sequences

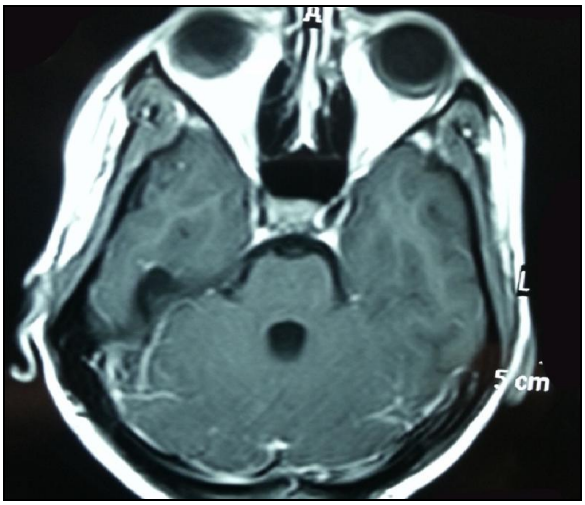

Figure-3A: Axial section at brain stem level shows leptomeningeal enhancement

DISCUSION

Cyptococcal meningitis is an opportunistic infection well recognized and common in HIV patients.[4] In our medical setup this falls in agreement and it is rare to find Cryptococcal meningitis in non-immune compromised patients. In our country due to common symptomatology and proportional increment in TB infection, the provisional diagnosis is often used and treatment is established accordingly. The state of immune suppression can be due to high dose chronic steroid use[5] but our patient with her history, had no such event leading to steroid use before in her clinical course. A study conducted in a hospital in China showed 154 non-HIV-infected patients with cryptococcal meningitis who presented in a period of 10 years[6] in comparison to our hospital where this was the first case to be documented. This might be just the manifestation of poor data collection and

record keeping still prevalent in our medical setup.[7] Study showed the main initial clinical presentations to be headache, vomiting and fever. Our patient presented with headache, fever and weight loss in addition. Cause of Cryptococcal meningitis in a 21 year old female does raise questions regarding other conditions as reported by Rovest M. *et al*.[8] Our baseline test and elaborate initial investigations however revealed nothing of such nature, leading to the only convenient diagnosis and treatment option of TB meningitis. Cryptococcal meningitis in HIV patients, present with high antigen and fungal titers[9] but it is safe to assume due to our initial tests that our patient was in no immunocompromised state such as HIV. Having established that and the fact that steroids along with Anti TB were started after the initial presentation, the patient had cryptococcal meningitis at the time of presentation in a immune-competent state, making it a unique and dilemmatic scenario.

Leptomeningeal enhancement and intra-ventricular cystic lesions were more common than intraparenchymal findings[10] showed in study conducted on crypotococcal meningitis patients in un-immunocompromised state which agreed with our MRI findings in this patient. Majority of patients diagnosed require only medical treatment[11] with Amhotericin B and Fluconazole for 6 weeks as proven and administered successfully in our patient with significant improvement. As mentioned by Tripathi S[12] further studies on neuronal-astroglial-microglial interaction will offer deeper insight into the pathogenesis and immune mechanisms in the cellular and patho-morphological evolution of tuberculous and cryptococcal infections. This will ensure in our setup a more early diagnosis of the culprit and break the monotony of Anti TB treatment in our meningitis patients. Canteros CE[13] conducted a study, to study the 123 serotypes of culprit Cryptococcus causing meningitis. Our aim however should be to effectively differentially diagnose and treat respectively before proceeding to such advancements.

CONCLUSION

Clinical and radiological presentation of CM in immunocompetent patients is almost similar to TBM so CM is always a differential diagnosis of TBM. It can only be diagnosed with low threshold for cryptoccocal agglutination test in CSF, in settings of patients presenting with clinical picture of TBM.

AUTHOR'S CONTRIBUTION

SA: Study concept, design, data analysis and interpretation. KG: Study design and data acquisition. MWW: Data analysis and critical revision of the manuscript for important intellectual content. HM: Literature review, formatting and data analysis.

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