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Diagnostic Challenge of Tuberculous Meningitis with Tuberculoma in a Newly Diagnosed HIV Infected Patient ART Naïve

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Abstract

Tuberculous meningitis is a subacute disease with symptoms that may persist for several weeks before diagnosis. It can clinically present similarly to other forms of meningitis and this often leads to a delay in treatment. Detection of Mycobacteria Tuberculosis in cerebral spinal fluid remains the gold standard. However, there is low positive rate of mycobacterial detection. Treatment should be initiated as soon as clinical suspicion is supported by initial CSF findings after excluding other causes such as bacteria and fungus.

Keywords: Tuberculoma • Ring enhancing lesion

Abbreviations: HIV: Human Immunodeficiency Virus • VI: Sixth • CNS: Central Nervous System • CSF: Cerebra Spinal Fluid • X-PERT: Gene xpert • MTB: Mycobacteria Tuberculosis • OP: opening pressure • RIF: Rifampicin • MRI: Magnetic Resonance Imaging • IgG: Immunoglobilin G • IgM: Immunoglobulin M • TBM: Tuberculous Meningitis • TB: Tuberculosis • ZN: Ziehl Neelsen

Introduction

Approximately 1% of patients infected with Mycobacterium Tuberculosis (MTB) develop CNS involvement. CNS tuberculosis may manifest as tuberculous meningitis (TBM), intracranial tuberculoma or tuberculous abscess [1]. TBM is the most common and accounts for more than 100,000 new cases every year [2]. Diagnosis of TBM is difficult as it can clinically present similarly to other forms of meningitis. This leads to a delay in treatment resulting in mortality or lifelong sequelae. The microbiologic diagnosis of TBM requires the isolation of Mycobacterium tuberculosis (MTB) from the cerebrospinal fluid (CSF) of an infected patient. Many cases of TBM cannot be confirmed as isolation of MTB is difficult therefore, the diagnosis of TBM continues to be challenging for clinicians. Cerebrospinal fluid (CSF) smear microscopy with Ziehl–Neelsen staining for acid-fast bacilli is the most widely available test for TBM diagnosis, but the test is insensitive [3]. Culture takes long time 2-8 weeks to give out results therefore too slow for immediate treatment decision. Xpert ultra has improved sensitivity, but has insufficient negative predictive value to exclude TBM when the result is negative [4]. Clinicians must be cautious when ruling out TBM with Xpert Ultra when the result is negative. This case shows the challenges faced in the diagnosis of TBM.

Case Summary

A 34-years-old patient was admitted to our hospital due to persistent worsening headache and confusion. He had been attending neurology clinic for 6 months due to raised intracranial pressure. He was a newly diagnosed HIV positive ART naïve, CD4 count was 118 cells/μl. On examination he was confused and had left VI cranial nerve palsy. Based on these findings, cryptococcal meningitis, tuberculous meningitis, CNS lymphoma and toxoplasmosis were considered to be differential diagnoses. Cerebral spinal fluid OP was 60 cm H_2O clear fluid, CSF microbiology was unremarkable. CSF cell count showed lymphocyte predominance, Low CSF glucose 2.44 mmol/l, high CSF protein 1.07 g/l compatible with TB meningitis. CSF Xpert MTB/RIF and Xpert MTB/RIF ultra-results revealed no mycobacteria tuberculosis. Toxoplasma serology IgG and IgM were negative. A chest x-ray was normal and contrast enhanced brain MRI showed ring enhancement in the left basal ganglia region with non-restricting capsule, significant peri-lesion oedema and midline shift to contralateral side compatible with tuberculoma (Figure 1).

Discussion

Mycobacterium Tuberculosis is one of the most challenging causes of meningitis to diagnose because of the difficulties in rapidly identifying the organism in the CSF samples. This often leads to a delay in treatment and subsequent mortality or lifelong disability. It has a subacute clinical course, and demonstrates no specific symptoms other than those observed in patients with other forms of meningitis [5]. Patients can present with fever, headache and stiff neck along with focal neurological deficits, behavioural

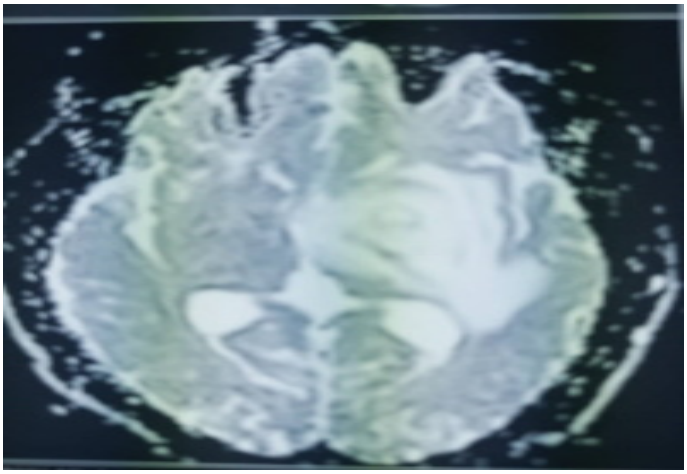

Figure 1. Contrast enhanced brain MRI showing ring enhancement in the left basal ganglia region with non-restricting capsule, significant peri-lesion oedema and midline shift to contralateral side compatible with tuberculoma.

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changes, and alterations in consciousness [6]. It is important to note that when evaluating common complaints such as headache, a broad differential diagnosis should be considered. Since the diagnosis is difficult it requires a high degree of clinical suspicion. TBM has been reported to have a high mortality of more than 60% in HIV infected patients [7,8]. Tuberculoma needs to be considered in patients who present with a brain mass even if they are not known to have pulmonary tuberculosis. Advances of magnetic resonance imaging has emerged as a quality tool aiding in the diagnostic evaluation of tuberculomas and to differentiate it from other single hyperdense intracranial lesions [9,10]. This has led to an earlier and successful medical treatment of the disease. MRI is capable of recognising range of patterns in the diagnosis of tuberculous meningitis [10]. The most common findings are meningeal enhancement, hydrocephalus, basal exudates, infarcts, and tuberculomas. Microbiological confirmation of TBM is still the gold standard; however detection of Mycobacteria Tuberculosis in the CSF remains challenging due to its pauci-bacillary nature [11].

Several MTB detection tests are available but each test has advantages and limitations. ZN smear microscopy can be performed quickly and is widely available but has low sensitivity ranging from 10-50% and rarely higher, modified ZN stain does not improve diagnosis of TBM [3]. Mycobacteria culture has improved sensitivity though still poor and growth takes several weeks therefore too late to guide for early anti TB treatment. Studies have shown that Gene Xpert MTB/RIF ultra has improved sensitivity for TBM diagnosis but it has insufficient negative predictive value to exclude TBM when the result is negative [12]. Cresswell F et al. found a negative predictive value of 93% concluding that xpert ultra MTB/RIF cannot be used as a rule out test(4). This indicates that clinical judgement is essential, and, in some cases, empirical therapy may be needed like in the present case report. Some authors have reported that multiple lumbar punctures with large volume CSF may be needed for the diagnosis of tuberculous meningitis [13]. Large volume CSF are important for optimal test performance. More organisms are likely to be present when a larger CSF volume is used for the test [14]. Volume of more than 6 ml may maximize the number of MTB bacteria in the sample and hence improving the chances of confirming a diagnosis of TBM [15]. Also, centrifuging CSF at 3000g for 15 minutes concentrates MTB and improves diagnostic sensitivity [15]. Repeat lumbar puncture for large CSF volume could not be done to our patient due to the mass effect. TBM with tuberculoma was the more likely diagnosis even though it was not able to confirm the aetiology histologically. A trial with first line anti tuberculous drugs led to a significant clinical and radiological improvement which indirectly confirmed the diagnosis (Figure 2). The anti-tuberculous treatment was given following the recommendation of the Tanzanian TB national guideline. He received adjunctive corticosteroid therapy prednisolone 1 mg/kg for 6 weeks followed by a tapering course over 2 weeks. The duration of anti-tuberculous treatment was 12 months. There was an initial phase which constituted of four drug regimens (Isoniazid, Rifampicin, Ethambutol and pyrazinamide) for 2 months and the continuation phase with Isoniazid and Rifampicin which were extended for 10 months in order to complete 12 months of therapy. ART was started after approximately 8 weeks of anti-tuberculosis treatment to minimise the risk of IRIS. Bahr N et al. have recommended deferring ART to 4-6 weeks after beginning of anti TB medication [16]. Follow up at 9 months of antituberculosis treatment contrast enhanced brain MRI showed complete resolution of the tuberculoma, only basal cisterns patchy meningeal enhancement is observed which might represent inflammation (Figure 3). However, patients with acquired immunodeficiency syndrome may show minimal meningeal enhancement due to lack of immune response [17]. Response to anti TB treatment was good despite of the presence of large lesion.

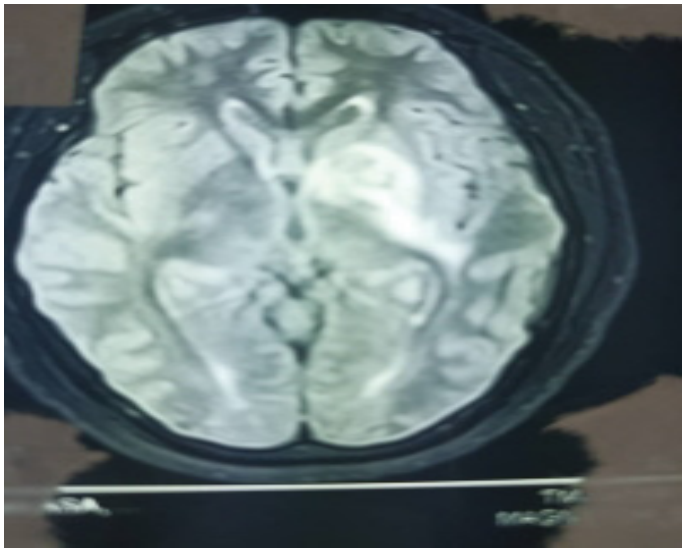

Figure 2. Brain MRI showing significant radiological improvement i.e., reduced size of the lesion.

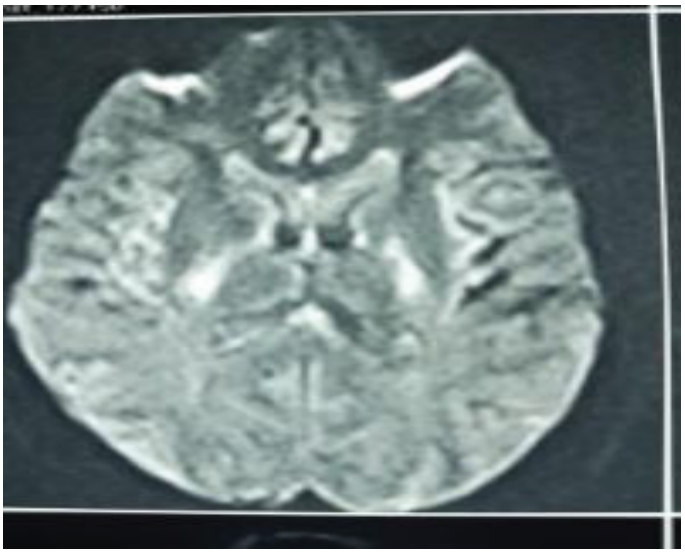

Figure 3. Contrast enhanced brain MRI showing complete resolution of the tuberculoma, only basal cisterns patchy meningeal enhancement is observed.

Conclusion

TB meningitis is difficult to diagnose. Treatment should be initiated as soon as clinical suspicion is supported by initial CSF findings after excluding other causes such as bacteria and fungus. Clinical presentation, CSF findings and neuroimaging should be used conjunctively for TBM diagnosis and most often empirical therapy is needed. Early treatment will lead to better outcome of tuberculous meningitis reducing mortality and morbidity.

Acknowledgment

The authors acknowledge medical ward staff who assisted in the care of this patient throughout his stay in Amana Regional Referral hospital.

Consent to Publish

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Authors' Contributions

RHS reviewed the patient prior to treatment, follow up during treatment, wrote the initial draft of manuscript and reviewed several drafts of the manuscript. FM wrote the initial draft of manuscript and revised several drafts of the manuscript. SK reviewed several drafts of the manuscript. SM reviewed several drafts of the manuscript. All authors read and approved the final manuscript.

Conflict of Interest

All authors declare that they have no competing interest with the subject matter or materials discussed in the manuscript.

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