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Pediatric Imaging *Case Report*

Lessons learned from a fatal case of tuberculous meningitis with a rapid decline in an infant

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ABSTRACT

Tuberculous meningitis is a highly lethal, often underrecognized disease with characteristic clinical and imaging features which can be cured if the diagnosis and subsequent treatment are begun at early stages. Frequently, there is a delayed diagnosis of this condition due to unfamiliarity of clinicians in non-endemic areas about its presentation and diagnostic workup. This article presents a case of rapid decline and fatality due to tuberculous meningitis in an 11-month-old child from a non-TB-endemic area and describes the characteristic clinical presentation, imaging findings, and diagnostic pitfalls associated with this condition.

Keywords: Tuberculous meningitis, Central nervous system tuberculosis, Tuberculosis, Basal meningitis

INTRODUCTION

Tuberculous meningitis is associated with high morbidity and mortality. Its clinical and imaging presentation may be mistaken for other infectious and non-infectious etiologies which lead to delayed treatment increasing its lethality. Due to its low incidence in many affluent countries, there is a general lack of familiarity with and misconceptions about how isolated central nervous system (CNS) tuberculosis presents resulting in delayed diagnosis and treatment with poor outcomes. This case report aims to highlight the classic clinical presentation, imaging findings, and diagnostic pitfalls in the diagnosis of tuberculous meningitis.

CASE REPORT

A previously healthy 11-month-old female was sent to the children's hospital from her pediatrician's office for a 10-day history of persistent fever and vomiting. She was treated by her pediatrician for presumed right lower lobe pneumonia based on a chest X-ray (CXR) read by a general radiologist from an outside facility 3 days before presenting to our hospital. In the emergency department, the patient was febrile, but generally well appearing. A CXR revealed a normal cardiac silhouette without mediastinal or hilar adenopathy and a questionable hazy opacity in the right lung base, concerning atelectasis. Thus, the previously obtained CXR was determined to be a false positive for pneumonia. Antibiotics were not continued due to low clinical suspicion for pneumonia. She was admitted to the general pediatric ward for dehydration.

She remained febrile, especially overnight, and a sepsis workup was obtained for persistent fevers. WBC and differential, complete metabolic panel, C-reactive protein (CRP), erythrocyte sedimentation rate, urinalysis, urine culture, and blood cultures were all within normal limits. A follow-up CXR repeated 1 day later showed complete resolution of previously questioned hazy right basilar opacity, likely an area of resolved atelectasis. An infectious disease subspecialty consult was obtained on day 2 of admission for persistent fevers of unknown origin. The working differential included tularemia (known history of exposure to wild hare), malignancy, and multisystem inflammatory syndrome in children.

On day 3 of hospitalization, the patient exhibited a new sluggish right pupillary response to light. A computed tomography (CT) of the head [Figure 1] was done and demonstrated a well-circumscribed right thalamic hypodensity, concerning infarction of indeterminate age. A brain magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA) with contrast were performed which showed three focal punctate areas of restricted diffusion involving the right thalamus, right temporal periventricular white matter, and the left inferior frontal lobe concerning multifocal brain infarctions with extensive basilar predominant leptomeningeal enhancement and thick enhancement of basilar cisterns concerning for basilar meningitis [Figures 2 and 3]. MRA of the brain was normal at this time [Figure 4]. Since the patient had a normal CXR, tuberculous meningitis was not seriously considered in the initial differential diagnosis. However, the finding of multifocal brain infarctions spanning several arterial territories raised concern for embolic phenomenon from entities such as cardiac vegetations or underlying intracardiac or vascular shunts.

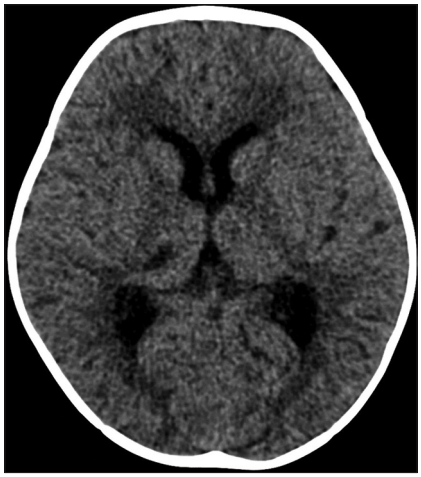

Figure 1: Eleven months old with fever and new-onset sluggish right pupillary light reflex response. Axial image from non-contrast CT of the head shows a well-circumscribed lucent lesion in the right thalamus.

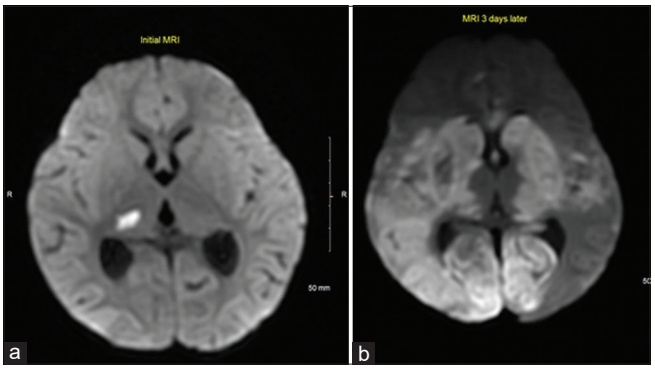

Figure 2: Eleven months old with fever and progressive neurological symptoms. Selected axial DWI image from the initial MRI brain (a) shows a focal punctate area of restricted diffusion, likely small infarctions involving the right thalamus. Follow-up MRI 3 days later (b) at the same level reveals marked progressively restricted diffusion of both cerebral hemispheres and bilateral deep gray nuclei (caudate, thalami, and lentiform nuclei).

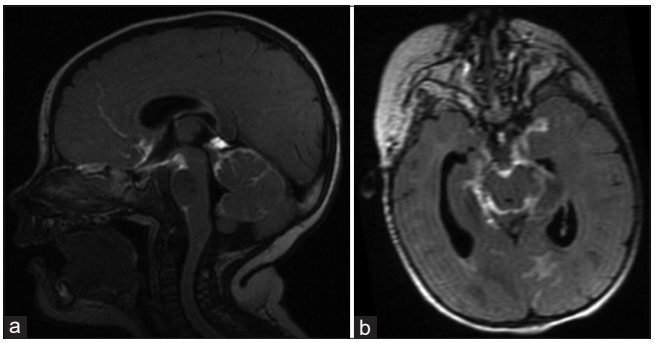

Figure 3: Eleven months old with fever and progressive neurological symptoms. Midline sagittal cube FLAIR post-contrast image of the brain (a) from the initial MRI demonstrates marked meningeal enhancement of the inferior frontal lobes, brainstem, and cerebellum with a thick enhancement of the basal cisterns. Axial post-contrast T1-FLAIR image (b) at the level of the basal cisterns shows characteristic encasement by thick enhancing exudates lining these cisterns.

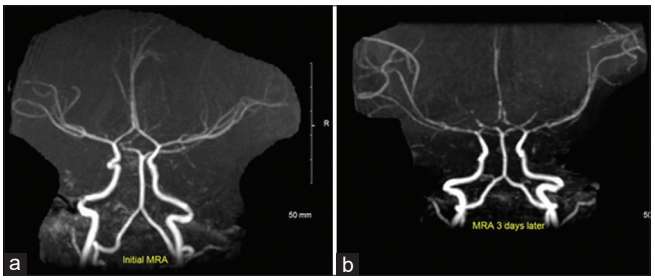

Figure 4: Eleven months old with fever and progressive neurological symptoms. Initial MRA (a) is within normal limits. Follow-up MRA (b) performed 3 days later reveals progressive areas of proximal narrowing and irregularity of A1, M1, and P1 segments of the ACA, MCA, and PCA, respectively.

Transthoracic and transesophageal echocardiograms are within normal limits without cardiac vegetations. Cerebrospinal fluid (CSF) analysis shows WBC of 23/mm^3 with 88% lymphocytes, glucose 36 mg/dL, and protein 105 mg/dL. The patient was empirically begun on vancomycin, ceftriaxone, acyclovir, and doxycycline. A complete infectious workup was obtained, including purified protein derivative (PPD), interferon-gamma release assay (IGRA), and testing for rickettsia, toxoplasmosis, histoplasmosis, *Bartonella*, Ehrlichia, lymphocytic choriomeningitis virus, Epstein–Barr virus, cytomegalovirus, human immunodeficiency virus, and syphilis.

Over the next 24 h, the patient rapidly deteriorated, with clinical posturing and concern for new-onset seizure activity, requiring transfer to the intensive care unit and subsequent intubation. The following day, the patient rapidly declined with obvious facial droop and posturing, hydrocephalus on imaging requiring external ventricular drain placement. On day 6 of hospitalization, a follow-up MRI and MRA of the head without contrast revealed progressively restricted diffusion throughout both cerebral hemispheres, deep gray nuclei, brainstem, and cerebellum concerning for extensive progressive multifocal infarctions with new marked irregular narrowing of multiple cerebral arteries raising concern for CNS vasculitis [Figures 2 and 4]. Tuberculosis was not considered in the differential given normal PPD and normal CXR.

On day 7 of hospitalization, IGRA returned positive, leading to a diagnosis of tuberculous meningitis. Four drugs TB treatment therapy with steroids was scheduled to be started. However, due to the extensive neurologic injuries, the family decided to withdraw care, and the patient passed away the following day.

DISCUSSION

Our patient was an 11-month-old Caucasian female without reported TB exposure who lived in a non-endemic area but presented in the early prodromal stage of tuberculous meningitis (TBM) and rapidly progressed through the next two stages. Initial brain MRI findings of leptomeningeal enhancement, hydrocephalus, basal exudates, and infarcts were consistent with TBM. CSF analysis showed pleocytosis, elevated protein, and low glucose. Although these findings were suggestive of TBM, there were several factors leading away from considering TBM as the primary etiology. Most notably, the patient lived in a non-endemic area with no history of TB exposure, and her initial laboratory and diagnostic workup were negative, with a normal serum WBC, CRP, chest radiograph, and negative PPD. This delayed suspicion for TBM prevented early initiation of treatment in her disease course which could have altered her outcome.

CNS tuberculosis has a varied presentation including TBM, parenchymal tuberculosis ranging from cerebritis, brain abscess, tuberculoma, to miliary tuberculosis, and spinal or calvarial involvement, with TBM being the most common.[1,2] TBM is rare in the United States with 100–150 cases reported annually, accounting for <3% of bacterial meningitis.[3]

TBM can be the sole manifestation of TB and does not require prior pulmonary or extrapulmonary disease.[4] A large percentage of children and infants with TBM have no radiographic evidence for TB on CXRs.[5] The clinical manifestations of TBM arise from basilar meningeal fibrosis and vascular inflammation.[3] It is a smoldering subacute disease with symptoms progressing over several days (median of 10 days).[3] TBM typically progresses through the following three phases: Early prodromal, meningitis, and paralytic.[6] The early prodromal phase typically presents with low-grade fevers, malaise, and personality changes.[6] The meningitis phase follows, presenting with lethargy and vomiting.[6] Classic meningeal signs, including stiff neck, headaches, and fever, are not always present, which can skew the clinical picture.[7] During this phase, cranial nerve palsies, in particular, affecting the oculomotor, trochlear, and abducens nerves, are common.[2,4] The final paralytic phase consists of hemiparesis, paraparesis, seizures, coma, and death.[4,6]

If CNS TB is suspected, CSF analysis, neuroimaging with MRI and laboratory testing for TB should be obtained. Neuroimaging most commonly shows meningeal enhancement, hydrocephalus, basal exudates, infarcts, and tuberculomas.[1-4,7] Vasculitis with superimposed vasospasm causing ischemia can affect multiple intracranial arteries commonly involving the perforating branches of the lateral lenticulostriate arteries, the posterior cerebral artery/basilar artery, and the medial lenticulostriate arteries can lead to extensive infarcts, with potential for brain herniation.[7] MRI and MRA of the brain with contrast are the preferred screening imaging modalities due to the increased sensitivity of MRI for the various manifestations of CNS tuberculosis.[8]

Meningeal enhancement seen in up to 90% of cases is the most sensitive feature of TBM.[1,2] Enhancing exudates in the basilar cisterns are a common and specific imaging feature of TBM on both contrast-enhanced CT and MRI.[1,2] On non-enhanced CT, basal cistern obliteration by isodense to mildly hyperdense exudates is commonly seen with TBM.[2] Subpial exudates are another feature of TBM, primarily located along the surface of the inferomedial frontal and anteromedial surface of the temporal lobes as well as a superior aspect of the cerebellum, and floor of the third ventricle with potential for extension to suprasellar and basilar cisterns from these sites.[2] These exudates are made of a mixture of neutrophils, mononuclear cells, erythrocytes, and bacilli.[2]

Strokes are a common feature of TBM and can be identified on MRI in up to 57% of TBM patients and identified on

autopsy in 22–56% of cases with the prevalence of strokes being greater in the pediatric population compared to adults.[9,10] Multiple bilateral infarcts involving the basal ganglia are common with TBM, portending a poor prognosis with the reported mortality rate being 3 times higher in TBM patients with strokes compared to TBM patients without infarctions.[9,10] Most strokes with TBM are due to abnormalities involving the cortical branches and the perforator vessels from both the anterior and posterior circulation rather than being in a particular ischemic prone TB zone as previously thought.[7,11]

Our patient had abnormal enhancement of the basilar cisterns, basilar predominant meningeal enhancement, rapidly progressive multifocal brain infarctions spanning several arterial territories, extensive narrowing, and irregularity of multiple arteries of the circle of Willis likely a combination of vasculitis and vasospasm, with late presentation of hydrocephalus requiring drain placement. The initial presentation of multifocal brain infarctions spanning multiple arterial territories is a feature of TBM that can be misinterpreted as arising from an embolic phenomenon as in our scenario.

PPD and IGRA should be performed. However, PPD may yield false-negative results with an overwhelming disease burden as seen in our patient.[12] IGRA is not similarly impacted, so it serves as confirmatory testing. However, IGRA results take a few days. If there is any suspicion for TBM, empiric therapy should be started due to the high potential for rapid decline which can be mitigated with early treatment. TBM in children is treated with isoniazid, rifampin, pyrazinamide, and ethambutol with the addition of systemic steroids.[3] The initial four-drug regimen duration is 2 months followed by isoniazid and rifampin for 7 months.[3] The prognosis is based on the neurologic status at the time of presentation and the time to initiation of treatment.[3] Delay in the initiation of these medications leads to worsened morbidity and mortality and so empiric TBM therapy should be started at the earliest suspicion even without immediate confirmatory laboratory findings because there is less harm caused by starting treatment than not treated early.

CONCLUSION

TBM should be considered in patients with fever and vomiting and signs of cranial nerve involvement regardless of a normal CXR, normal laboratory values, or the absence of TB exposure history. MRI and MRA of the brain with contrast are the best diagnostic imaging study and will commonly show meningeal enhancement, hydrocephalus, basal exudates, multifocal infarctions, and tuberculomas. A normal chest radiograph and non-reactive tuberculin skin test do not mean that TBM can be excluded from the differential when clinical and brain MRI findings raise concern.

Declaration of patient consent

Patient consent is not required as the patient's identity is not disclosed or compromised.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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