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CASE REPORT

The Challenges of Diagnosing Tuberculous Meningitis and Importance of Early Intervention

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Abstract

Background: **Reported is a patient found to have miliary TB seeding the lungs and brain with CNS involvement resulting in tuberculous meningitis (TBM). False security in laboratory studies that lack adequate sensitivity resulted in delay of therapy which may have negatively impacted the patient's outcome. This case report aims to emphasize the importance of early initiation of therapy when clinical suspicion remains high despite initially negative diagnostic studies.**

Case presentation: **52 year old female originally from Guatemala presented headache, neck pain, vomiting and photophobia. CT of the chest showed numerous submillimeter sized bilateral lung nodules, with scattered calcifications. IGRA of the serum, sputum Acid Fast Bacillus (AFB) stain and culture and CSF AFB stain and culture were obtained and were all initially negative. Clinical suspicion for tuberculous meningitis remained high and RIPE therapy and methylprednisolone were started. CSF AFB culture was found positive for MTB. Despite therapy, patient continued to clinically decline with poor overall prognosis.**

Conclusion: **Early diagnosis and initiation of therapy is paramount in improving outcomes in TBM. Unfortunately, the available diagnostic tests lack adequate sensitivity to confidently rule out disease. False negative results can delay therapy and worsen clinical outcomes. Early identification often relies on history, evaluation of risk factors, in conjunction with corresponding labs and imaging findings. If clinical suspicion is high, empiric therapy should be initiated early. Infectious disease consultation is often indicated to further assist with diagnosis and management.**

Keywords: Tuberculous meningitis, Tuberculosis, Meningitis

1. Background

Tuberculosis (TB) remains one of the leading causes of death from an infectious agent worldwide with tuberculous meningitis (TBM) being one of the most deadly forms of the disease.[1,2] Given the relatively rapid progression and significant mortality of TBM, early recognition and treatment is essential. TBM can be difficult to diagnose as confirmatory laboratory testing lacks reliable sensitivity and specificity to guide management. Early identification often relies on a comprehensive history, evaluation of risk factors and a high suspicion of disease based on the corresponding clinical picture. Initiation of therapy should not be withheld while awaiting confirmatory testing. Here we discuss a case of TBM that emphasizes the clinical importance of early recognition, appropriate testing and empiric therapy.

2. Case presentation

A 52-year-old female born in Guatemala presented with complaints of diffuse headache, right-sided neck pain, vomiting and photophobia which started 3 days prior to presentation. She denied any recent travel or illness but confirmed that her spouse had multiple incarcerations. On presentation she was found afebrile and hemodynamically stable. She complained of paravertebral and upper thoracic spine discomfort with negative Kernig and Brudzinski signs on examination. Initial CBC showed no evidence of anemia or leukocytosis. Initial CT of the

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head showed no evidence of intracranial hemorrhage, mass-effect, hydrocephalus or midline shift. CT of the chest showed numerous submillimeter sized bilateral lung nodules, with scattered calcifications (Fig. 1). The chemistry panel was within normal range. The lumbar puncture performed on admission revealed colorless clear fluid with a white blood cell count 278/mm3, red blood cell count 35/mm3, glucose 26 mg/dL (ref 40–70 mg/dL) and protein 147 mg/dL (ref 15–45 mg/dL). Manual differentiation of the CSF revealed lymphocytes 48%, neutrophils 47% and mononuclear cells 3%. An MRI of the brain with contrast demonstrated greater than 40 submillimeter, similar in size to the lesions seen in the lungs, enhancing foci in the supratentorial brain, infratentorial brain and brainstem along with dural enhancement suggestive of a meningoencephalitis (Fig. 2). The patient was initially started on vancomycin, ceftriaxone, ampicillin and acyclovir although these were discontinued as PCR for typical viral and bacterial meningeal infectious etiologies was negative. IGRA of the serum was negative revealing Nil .03 IU/mL, Mitogen-Nil 9.50 IU/mL, TB1-Nil .01 IU/mL and TB2-Nil .01 IU/mL. Sputum Acid Fast Bacillus (AFB) stain and culture and CSF AFB stain and culture were also obtained and were all initially negative. CSF fungal cultures resulted negative. A sample of the initial CSF was sent to pathology for further review. Unfortunately, adenosine deaminase (ADA) was not recorded from the initial sample. During her hospital stay, she continued to experience progressive encephalopathy and agitation eventually requiring intubation and mechanical ventilation. Repeat CT of the head on hospital day 5 revealed dilated lateral and 3rd ventricles requiring extra ventricular drain placement by neurosurgery. Given high clinical suspicion for tb, despite negative testing to date, she was started on rifampin, isoniazid, pyrazinamide, ethambutol (RIPE) and methylprednisolone 40 mg every 8 h in addition to vancomycin and cefepime.

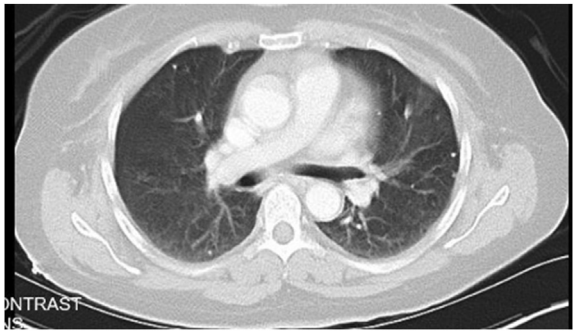

Fig. 1. CT of the chest without contrast-demonstrated numerous submillimeter sized bilateral lung nodules, with scattered calcifications.

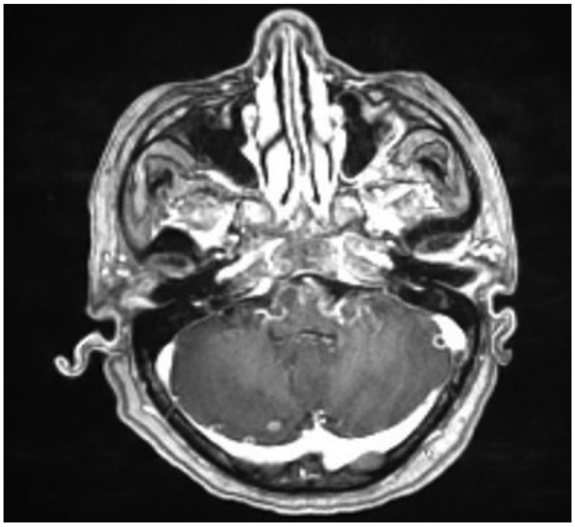

Fig. 2. MRI of the brain with contrast-demonstrated submillimeter enhancing foci in the supratentorial brain, infratentorial brain and brainstem.

The next day, pathology from the initial CSF sample revealed findings suggestive of granulomatous inflammation potentially consistent with TB. On hospital day 19 initial CSF AFB culture returned positive and was sent for confirmatory testing which revealed *Mycobacterium tuberculosis* complex. Unfortunately despite initiation of RIPE therapy and corticosteroids, she continued to exhibit significant neurologic decline. She eventually required tracheostomy and percutaneous endoscopic gastrostomy tube placement and is evidencing an overall poor prognosis.

3. Discussion

Tuberculosis remains one of the leading causes of death worldwide secondary to an infectious disease.[1] TBM is one of the deadliest forms of tuberculosis and accounts for roughly 5% of extrapulmonary TB cases.[3,4] This patient was found to have miliary TB seeding the lungs and brain with CNS involvement resulting in tuberculous meningitis (TBM). Miliary TB can develop at the time of the primary infection or can occur later secondary to reactivation of dormant disease. Miliary TB develops from a lymphohematogenous dissemination of TB from a pulmonary extrapulmonary focus with embolization to the vasculature of various organs including the nervous system. Miliary TB has a mortality rate ranging from 25% to 30% although those estimates are often higher in individuals with CNS involvement.[5] Early diagnosis and treatment is critical as delays in therapy are associated with worsened prognosis.

Early diagnosis depends on high clinical suspicion. Workup begins with a thorough history and evaluation of underlying risk factors which would increase the probability of disease. In this case, birth in a country with a moderate to high incidence of TB and history of exposure to an incarcerated family member placed her at increased risk of being infected with TB. Other significant risk factors include persons in close contact with an individual infected with TB, homelessness, injection drug use, alcoholism, HIV and individuals who work with people who are at high risk for TB such as healthcare and correctional facilities (CDC). Medications that suppress the immune system such as tumor necrosis factor alpha inhibitors can also increase risk of TB[6]

With suspicion for meningitis, prompt lumbar puncture and imaging of the brain should be obtained. The CSF in patients with TBM and military TB typically reveals lymphocytic-predominant pleocytosis, elevated protein levels and low glucose.[7] Further CSF studies including cytology, pathology, AFB smear, AFB culture, ADA and IGRA should also be obtained to support the diagnosis. Viral, bacterial and fungal panels should be obtained to rule out alternative etiologies. MRI of the brain is often nonspecific revealing basal meningeal enhancement and hydrocephalus.[6,7] In instances of miliary TB, MRI of the brain reveals numerous, round, small, homogenous, ring enhancing lesions usually 2–3 mm in diameter often with meningeal involvement.[8] These lesions are often radiographically similar to the lung nodules given the hematogenous dissemination. Due to the inadequate sensitivity of confirmatory testing, a suspicious history along with clinically correlating CSF and radiologic findings should prompt early initiation of therapy.

TBM is paucibacillary when caused by miliary disease which significantly decreases the efficacy of standard diagnostic testing.[6] IGRA of the serum only has a sensitivity and specificity of 74% and 78% respectively when diagnosing TBM.[4] CSF studies also lack sensitivity with AFB smear of 20–40%, culture 40–80% and IGRA of about 80%.[6,7,9] CSF culture and smear are heavily dependent on sample quantity with significant reductions in sensitivity if the sample is less than 6 ml.[10] Obtaining multiple CSF samples has been shown to significantly improve sensitivity.[7] Despite inadequate sensitivities, mycobacterial culture remains the gold standard for diagnosis of TBM but can take up to 8 weeks for a final result.[11] Adenosine deaminase activity quantification in the CSF may also play a role in the diagnosis of TBM, although the specificity is questionable.[6] This was not performed in the case above. Promising results are being seen with nucleic acid amplification techniques and biomarker based diagnostic approaches although further research is needed before adopting them into clinical practice.[2]

This case illustrates the importance of guiding the management of TBM based on clinical suspicion to prevent delay in therapy based on negative results from non-sensitive testing. If clinical suspicion remains high, negative diagnostic testing does not adequately rule out the diagnosis. Given the relatively rapid progression of TBM, early initiation of RIPE and immunosuppressive therapy is essential to overall prognosis.[12] Involvement of infectious disease specialist is often necessary due to the complexity of the diagnosis.

4. Conclusion

TBM is rapidly progressing and has a mortality of up to 65%.[7] Early diagnosis and initiation of therapy is paramount in improving outcomes. Unfortunately, the available diagnostic tests lack adequate sensitivity to confidently rule out disease. False negative results can delay therapy and worsen clinical outcomes. Early identification often relies on history, evaluation of risk factors, in conjunction with corresponding labs and imaging findings. If clinical suspicion is high, empiric therapy should be initiated early. Typical management includes RIPE and immunosuppressive therapy. Infectious disease consultation is often indicated to further assist with diagnosis and management. Multiple novel diagnostic studies show promise but require further research prior to being adopted into clinical practice.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Acquired.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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Authors' contributions

AA reviewed existing literature regarding tuberculous meningitis and was the major contributing author to the manuscript. DL provided further expertise in the subject matter and was coauthor to the manuscript.

Conflict of interest

The authors declare that they have no competing interests.

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Not applicable.

List of abbreviations

TB	Tuberculosis
TBM	Tuberculous meningitis
CSF	Cerebral spinal fluid
AFB	Acid Fast Bacillus
IGRA	Interferon Gamma Release Assay
RIPE	Rifampin, Isoniazid, Pyrazinamide, Ethambutol

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