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Case Report

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Missed Window, Lost Life: The Deadly Course of TB Meningitis in a Pregnant Woman

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Abstract

Tuberculosis meningitis is the most severe form of extrapulmonary TB. TB meningitis has an insidious onset and atypical clinical manifestation. Thus, it is usually in its advanced stage when it is diagnosed resulting in poor therapeutic efficacy and often causing severe extrapulmonary tuberculosis with high mortality. Despite the presence of different diagnostic and treatment modalities, mortality remains unacceptably high. A pregnant female patient was referred to our hospital emergency with suspected meningitis with a history of fever and recurrent vomiting. She was being managed conservatively and several tests were done (Complete Hemogram, Metabolic Profile, and Infection Panel). After various neurological investigations, CT scan of the brain revealed a lesion, suspicious of TB meningitis, though not confirmed. She gave birth to a baby girl, after which she felt drowsy. ATT was initiated 5 days post admission, on the day following her delivery. Her condition was still deteriorating. The patient died at last, following which the final diagnosis of TB meningitis came. The following case illustrates the clinical presentation and diagnostic approach in a pregnant lady. Tubercular Meningitis (TBM) diagnosis has many intricacies though the disease is completely curable.

INTRODUCTION

Tuberculosis is one of the leading causes of mortality among women of reproductive age and high-risk pregnancies in India. Various factors, including hormonal changes throughout the months, socioeconomic status, and underlying health conditions, play a crucial role in disease prevalence and presentation among women.

Pregnancy can obscure the symptoms of TB which may delay the diagnosis, leading to increased mortality and long-term disability. Thus, early but reasonable suspicion and prompt exclusion of strong evidence are key contributors to timely diagnosis and treatment.

CASE REPORT

A 23 years old G_2P_1 Indian woman, with a previous cesarean section, was admitted at 34 weeks of gestation with complaints of fever and intermittent vomiting for 1.5 months. Her past medical history was not significant, and her past surgical history included a left-sided fimbrial cystectomy 5 years prior. Her family history revealed TB in her father.

Her vitals were stable, while her fever profile was negative for Malaria Parasite, Dengue IgM, Widal Test, and Scrub Typhus, and she received Inj. Ceftriaxone. She was referred to a tertiary center hospital, and upon examination, she was found to be conscious but restless with neck rigidity. A provisional diagnosis of meningitis during pregnancy was made. Later, examination findings were drowsy, left lateral rectus palsy with left upper limb weakness, and she was managed conservatively with Inf. ceftriaxone and azithromycin. The patient was then referred to our hospital for MRI and effective supervision.

On admission, the patient was immediately transferred to the ICU. Her GCS was $E_4V_3M_4$, BP: 112/98 mmHg, Pulse rate:78/min and Temperature: 98.2°F, CBG: 126 mg/dl. On examination,

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neck rigidity was present, the angle of mouth deviated to the right, plantar reflex was normal, mild pallor was present, and the chest was clear bilaterally. No cyanosis, clubbing, icterus, or edema was noted. Abdominal examination revealed a uterine height of 34 weeks, an FHS of 130 bpm, no scar tenderness, and a midline vertical incision below the umbilicus. Per vaginal examination revealed Os-Parous, cervix-tubular, show present with active dribbling. Inj. Dexamethasone and Inj. Ceftriaxone was then administered.

On the next day, blood report showed the following results: Hb: 11.5 g/dl, Hct: 37%, WBC: 17,000/mm3, Platelet: 3.26 lakh/mm3, Urea: 16mg/dl, Creatinine: 0.75, Total bilirubin: 1.24 mg/dl, AST: 270 U/L, ALT: 134 U/L, ALP: 158 U/L, total protein: 5.2 g/dl, albumin: 3.4 g/dl, Sodium: 135mEq/L, potassium: 4.4mEq/L, FBS: 92mg/dl, PT: 14s, INR: 1.04, ESR: 10mm/hr, MPDA and Widal were negative with Urine RE/ME showing 12-14 pus cells/hpf.

Though MRI was indicated, that could not be done. CT scan of the brain revealed a hypodense lesion at the right basal ganglia and internal capsule suggestive of brain abscess or acute infarction. T. aspirin 75 mg OD and Inf. Mannitol 100 ml TDS for 3 days. Routine investigations were repeated daily. TSH: 295, FT4: 1.10, WBC: 16000/mm3 and deranged liver enzymes, AST: 235 IU/L, AST: 545 IU/L, Dengue NS1 and IgM negative. Urine culture showed no growth.

On the next day, the patient had the first episode of fever since admission of 102°F which was managed with Inf. PCM and thereafter, fever recurred every 10-12 hours. An Anesthesia referral was given for lumbar puncture and a CSF sample was collected and sent for analysis. CSF sample had a turbid white appearance with cell count 6/mm3 of which 60% lymphocytes, 40% polymorphs, no RBC noted with low glucose: 9.0 mg/dL (normal: 20-40 mg/dL), raised protein: 107.5 mg/dL (normal: 15-45 mg/dL), ADA:11.0 U/L (cut off value: 10 IU/L). Her head CT scan revealed hypodensity areas in the right temporal and basal ganglia regions with the right more than the left. There is a mass effect of compression of the right lateral ventricle, cortical sulci and cisterns are partially effaced.

The following evening, the patient was restless, drowsy, and in labor. A baby girl weighing 2650 grams was delivered vaginally. Post-delivery, the patient remained drowsy.

A neurology review was conducted on next morning with a CT scan and CSF analysis, raising a suspicion of Tubercular meningitis with tubercular arteritis. Since her liver enzymes were deranged, a referral to the DOTS center was made for a preferred regimen of Antitubercular Therapy (ATT). After 5 days of admission, the patient was initiated on ATT. The center started her on a regimen consisting of Inj. Streptomycin (1g) I.M., T. Levofloxacin (1000 mg) OD, and T. Ethambutol (1200 mg) OD. Injection Dexamethasone (8 mg) TDS was added. Reports collected in the evening showed hypernatremia with Na^+: 150 mEq/L, K^+: 3.4 mEq/L, and improvement in liver enzymes (AST: 142 U/L, ALT: 209 U/L, ALP: 163 U/L). The CSF study for ZN stain, Gram stain, and culture reports were all negative. Blood culture showed growth of Methicillin-Resistant Staphylococcus aureus (MRSA), which was sensitive to Ciprofloxacin, Clindamycin, Linezolid, and Vancomycin. Inj. Linezolid and Inj. Meropenem was added as per their opinion.

In the evening, the patient became extremely drowsy, with vitals recorded as BP: 134/90 mmHg, PR: 96/min, SpO_2: 97% on room air, and a temperature of 102°F. Chest auscultation revealed bilateral crepitations. An ABG was performed, and referrals were sent to the RP Medicine and Anesthesia teams. Based on their advice, regular suctioning was carried out, and moist oxygen inhalation via NRBM was administered. Despite PCM infusion and cold sponging overnight, the patient's temperature remained consistently elevated, reaching 105°F.

The next morning, the patient was found to be unresponsive and the vitals continued to deteriorate. BP: 80/40 mmHg, PR: 64/min, and SpO_2: 94% were recorded while the patient was on moist oxygen via NRBM at 8 L/min. An urgent Anesthesia call was booked, and CPR was initiated following the ACLS protocol. Injection Atropine and Injection Adrenaline were administered. Despite three cycles of CPR, there was no return of spontaneous circulation, and the patient was declared clinically dead on the same day at 9:45 AM.

A posthumous CSF study for CBNAAT revealed the presence of Rifampicin-Indeterminate Mycobacterium tuberculosis.

The cause of death was determined to be tubercular meningitis in an antenatal mother at 34 weeks of pregnancy, preceded by vaginal delivery.

DISCUSSION

Tuberculosis (TB) primarily affects the lower respiratory tract but can also cause extrapulmonary tuberculosis (EPTB), with tubercular meningitis being the most severe form. This condition occurs in 1-2% of active TB cases and arises from hematogenous spread to the meninges or brain, where it may remain dormant before rupturing into the subarachnoid space. The resulting inflammation can lead to complications such as hydrocephalus and coma. The early understanding of TB meningitis pathogenesis was established in 1933 by Rich and McCordock through animal studies, which demonstrated that TBM could develop after a primary infection with M. tuberculosis under certain conditions. Epidemiologically, TBM is more prevalent in areas with high TB incidence, closely linked to socioeconomic factors.

Initial clinical manifestations include severe headache, fever, and malaise, with progression leading to neurological deficits and possible coma or death. Diagnosing TB meningitis is challenging due to non-specific clinical symptoms and a lack of sensitive detection methods. Additionally, pregnancy can obscure symptomatology, leading to misdiagnosis and delayed treatment.[1] TB can adversely affect pregnancy outcomes, including prematurity and increased perinatal mortality.

As already mentioned, CSF studies for TBM in our patient were negative. Even in high-resource settings, no single test can rule out the disease. Therefore, doctors should not exclude the possibility of TB meningitis even when the tests are negative.

Although culture remains the gold standard for diagnosis, the WHO recommends Xpert MTB/RIF as the initial test, despite its low sensitivity of 71.1% for CSF analysis.[2] When positive, Xpert MTB/RIF

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has a sensitivity of 71.1% and a specificity of 96.9% compared to a composite reference standard. However, a negative result does not exclude TB meningitis.[3] The goal for an ideal diagnosis is to demonstrate the presence of Mycobacterium tuberculosis bacilli in the CSF. However, the smear microscopy of CSF is generally insensitive as it only tests positive in 5%–30% of patients, and culture methods are tedious and lengthy.[4] Currently, the use of PCR technology for detecting Mycobacterium tuberculosis DNA is widely accepted. However, this method exhibits a variable sensitivity and specificity that depends on the types of PCR tests used. A meta-analysis showed that commercial nucleic acid amplification tests have a sensitivity of 56% and a specificity of 96%.[5] The low sensitivity of this PCR test was attributed to the utilization of a single target for amplification, resulting in false negative results. Newer PCR tests, called Multiplex PCRs, allow for the amplification of several target genes (IS6110, protein b, and MPB64) simultaneously, and this has helped to increase sensitivity to a level of 85–95% and specificity to 100%.[6]

In a low-income country like India which has a high burden of TB, physicians must be cautious not to miss a chance of diagnosing the disease. A combination of clinical features alongside radiological and microbiological investigations should be utilized.

Therefore, patients with the infection should have:

- Radiological imaging: Chest and brain radiographs
- Culture of CSF
- Immunological tests: IGRA
- Molecular tests: PCR of CSF sample
- Any other test to look for TB bacteria elsewhere in the body

BCG vaccination is included in birth dose of the National Immunization Schedule. Therefore, PPD positivity is not confirmatory in the diagnosis of TB itself.

A study investigating TBM's prognostic factors and developing strategies to improve clinical efficacy found that advanced age is one of the most important prognostic factors. Others include consciousness disturbance, concomitant hematogenous disseminated TB at other sites (bone TB, abdominal TB, TB lymph node), hydrocephalus, and low Glasgow coma scale score. Factors predicting good prognosis include timely anti-tubercular therapy and rational use of steroids. Results suggested that the use of steroids markedly improved the outcomes. However, prednisolone ≥ 120 mg/day had increased side effects than therapeutic outcomes. The use of surgery has a controversial effect on prognosis.[7]

The ADA isoenzyme is a major contributor to increased ADA activity in the CSF of patients with TB meningitis, probably reflecting the monocyte-macrophage origin of ADA. Study shows that measurement of the ADA isoenzymes could help distinguish between bacterial and TB infections in the CSF. ADA has been considered a marker of cell mediated immunity and its activity has been observed in various infections including TBM. As it plays a role in both cell mediated and humoral immunity, the varying levels of ADA in CSF may help differentiate TBM from non-TBM infectious meningitis and non-infectious neurological disorders, and this has been discussed earlier by various workers. Various workers have reported the reliability of CSF ADA activity in TBM patients using different cut-off values. Pettersson et al. reported sensitivity of 100% and specificity of 99% when a cut-off value of 20 U/L/min was used, but in that study, there were only three enrolled tuberculous meningitis patients.[8] Baro et al. proposed a cut-off value of 6.5 U/L/min and showed a sensitivity of 83.3% and specificity of 85.3%.[9] However, this study used only 12 cases of TBM patients, and pyogenic and viral meningitis was not distinguished from the group with other central nervous system diseases. Similarly increased CSF ADA levels have been reported in childhood TBM with adverse neurological outcomes. However, Gambhir et al reported a low sensitivity of 44% and specificity of 75% for ADA test with a cut-off value of 8 IU/L/min, which showed overlap between TBM and non-TBM patients, especially for infectious neurological disorders like pyogenic meningitis.[10] In another recent study, an ADA cut-off value of 11.39 U/L/min in CSF has been calculated for the diagnosis of TBM infection. Using that, a sensitivity of 96% and 78% have been demonstrated in the CSF of culture-positive and clinically diagnosed TBM patients, respectively. False positive results were noted in 24% of pyogenic meningitis cases.[11]

In various studies, it was shown that there was better outcome with early diagnosis and Antitubercular therapy. Pulmonary and extrapulmonary disease should be treated with the same regimens. Some experts recommend 9–12 months of treatment for TB meningitis, given the serious risk of disability and mortality. In tubercular meningitis, Ethambutol should be replaced by Streptomycin. The traditional treatment for pulmonary TB has been standardized to the RIPE (Rifampin, Isoniazid, Pyrazinamide, Ethambutol) therapy for 2 months, followed by Rifampin and Isoniazid for 10 months. The empirical treatment for TBM remains the same as the treatment for pulmonary TB; the empirical treatment is warranted when clinical features and CSF findings suggest TBM, even before microbiologic confirmation, since timely treatment dramatically improves the outcome of TBM.[12] In a review of TBM in 160 adults, each case was treated with at least four drug ATT regimens, and an early and long treatment strategy was administered (12-18 months). Treatment was started within the first 3 days following hospitalization in 76%, out of them 10% died, and the rest showed improvement. 2.5% died before treatment could be started, and 1.25% died among whom initiation of therapy was delayed. Therefore, poor prognostic factors other than delay in treatment also play some part in patient mortality.[13] Unless drug resistance is suspected, adjuvant corticosteroid treatment is recommended for TB meningitis. Presentation of a rare outcome of TB that occurred during pregnancy makes this case one of the few cases of complicated tuberculosis with atypical presentation.

LIMITATIONS

This case has potential limitations. Firstly, despite immense efforts, our patient could not be saved. Secondly, the diagnosis was delayed. This feature is not a limitation per se but rather acknowledgment that no single method exists to diagnose this condition.

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CONCLUSION

This study highlights the difficulty in diagnosis of this disease. In low and middle-income countries, tuberculosis is the result of undernourished health made worse by improper healthcare services. The rising magnitude of health problems by tuberculosis requires special attention. Recognizing the distinct aspects of tubercular meningitis is essential for understanding its clinical manifestations, diagnostic difficulties, and treatment outcomes.

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