Case Report

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Diagnostic challenges in tuberculous meningitis: a case report with negative genexpert result

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Introduction: Tuberculous meningitis (TBM) is a severe form of tuberculosis affecting the meninges, primarily caused by *Mycobacterium tuberculosis*. Diagnosis of TBM poses numerous challenges due to its nonspecific clinical presentation and the limitations of diagnostic tests like GeneXpert.

Case presentation: The authors report a case of a 22-year-old female from Eastern Nepal presenting with acute-onset fever, headache, vomiting, and neck pain. Cerebrospinal fluid (CSF) analysis showed lymphocytic pleocytosis, elevated protein, low glucose levels, and cobweb coagulum indicative of TBM. However, the GeneXpert test revealed negative results.

Discussion: In resource-limited settings like Nepal, where access to GeneXpert MTB/Rif is limited, CSF analysis and clinical algorithms play a crucial role in diagnosing TBM. Relying solely on GeneXpert results may lead to false negatives, so a high level of suspicion based on patient risk factors is essential. Prompt initiation of empirical antitubercular therapy is vital for a favorable outcome in TBM cases.

Conclusion: Negative MTB PCR results from CSF can be misleading in diagnosis of tubercular meningitis. Therefore, comprehensive evaluations, including detailed patient history, physical examination, and CSF fluid analysis, are crucial in high tuberculous prevalence countries to ensure accurate and timely diagnosis.

Keywords: adenosine deaminase, genexpert, lumbar puncture, lymphocytic pleocytosis, tubercular meningitis

Introduction

Tuberculous meningitis (TBM) is an extrapulmonary form of tuberculosis (TB) caused by *Mycobacterium tuberculosis* infecting the meninges. The primary infection usually starts in the lungs and then spreads to the lymph nodes. In TBM, the bacteria form collections in the brain called Rich foci, leading to an intense inflammatory response and meningitis symptoms[1]. Children aged 0–4 years are more susceptible, especially in regions with higher TB prevalence. In developed countries, TBM is more commonly seen in adults due to TB reactivation or underlying immunocompromised conditions like chronic steroid use, diabetes, or alcoholism[2]. TBM generally accounts for about 1% of all extrapulmonary TB cases and varies in prevalence based on regional TB rates. HIV-positive individuals, especially those with low CD4 counts, are more susceptible to CNS involvement and disseminated TB[3,4]. The diagnostic procedure involves the examination of cerebrospinal fluid (CSF), which typically shows low glucose levels, elevated protein levels, and a higher count of white blood cells, predominantly lymphocytes[4]. GeneXpert test does not exclude TBM. GeneXpert should be used in combination with other diagnostic tests, clinical findings, and when possible, radiologic data to inform their overall suspicion for TBM[5]. First-line antitubercular treatments have good penetration into the CSF so used as the primary regimen for the treatment of TBM. Treatment may be adjusted based on drug sensitivity results received later[6].

HIGHLIGHTS

- Tuberculous meningitis (TBM) is challenging to diagnose due to nonspecific symptoms and low sensitivity of GeneXpert MTB/RIF test.
- Acute symptoms in TBM can be misdiagnosed or cause delays in treatment, leading to neurological complications and poor outcomes.
- Cerebrospinal fluid analysis and clinical presentation are crucial for TBM diagnosis when GeneXpert results are inconclusive in resource-limited settings.
- TBM requires a high index of suspicion, especially in tuberculous-endemic areas, to ensure early detection and treatment.

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In our case report, we presented the challenging diagnosis of TBM in a 22-year-old female from Eastern Nepal. The case report emphasizes the difficulties encountered when the result of GeneXpert testing came back negative, leading to uncertainties in the diagnostic process in TB endemic countries with low-resource settings. This case report is in line with the CARE reporting checklist[7].

Case presentation

A 22-year-old female from Eastern Nepal presented to the emergency department with an acute-onset fever of 103°F and agitation that had persisted for 2 days. She also complained of earache, severe headache, nausea, vomiting, dizziness, and neck pain. She had no chest pain, palpitations, shortness of breath, hemoptysis, weight loss, or night sweating. The patient had no known comorbidities and had not experienced similar symptoms in the past.

Physical examination revealed a blood pressure of 130/80 mm Hg, temperature of 103°F, pulse rate of 96 beats per minute, respiratory rate of 22 breaths per minute, and oxygen saturation of 99% on ambient air. Clinically, she appeared irritable and ill-looking, but there were no signs of pallor, icterus, cyanosis, clubbing, lymphadenopathy, edema, or dehydration. Upon further examination, the patient exhibited neck stiffness, and both Kernig's and Brudzinski's signs were positive.

Given the presenting symptoms and clinical findings, a differential diagnosis of meningitis and encephalitis were considered. Laboratory tests revealed raised erythrocyte sedimentation rate, low hemoglobin level (10.4 g/dl), increased white blood cell count of 23 500/mm^3, neutrophilia (90%, normal range: 40–70%), lymphocytopenia (7%), low packed cell volume, mean cell volume, and mean cell hemoglobin, respectively, as shown in Table 1. The patient had hypomagnesemia, hyponatremia, and hypocalcemia but normal blood urea, serum creatinine, random blood sugar, and potassium levels (Table 1). HIV, Hepatitis B surface antigen, Hepatitis C Virus, and Venereal Disease Research Laboratory/ Rapid plasma reagin testing were non-reactive. The serological tests for dengue fever were negative. The sputum sample was examined for presence of any acid-fast bacilli (AFB) and found to be AFB negative. The patient has normal noncontrast computed tomography scan of the brain and normal chest radiography findings as shown in Figures 1 and 2, respectively. She had albuminuria of 2+ on the dipstick test but no bacterial growth on the urine culture.

Initially, the patient had presented to primary health center, where she was suspected as a case of bacterial or viral meningitis based on acute clinical presentation and negative sputum for AFB. The patient was treated there with intravenous ampicillin along with other empiric treatment prior to transfer to our teaching hospital. Then on presentation to our teaching hospital, she was admitted to the ICU and was given empiric intravenous antibiotics, namely ceftriaxone and vancomycin and empiric intravenous acyclovir therapy, respectively, while awaiting the CSF analysis reports. A lumbar puncture was performed under an aseptic condition and CSF analysis showed clear, light yellow fluid with cobweb coagulum (Fig. 3). The total cell count in CSF was 195/μl with lymphocyte predominance (90% lymphocytes and 10% neutrophils) (Table 1). CSF glucose level was low while albumin level was significantly elevated (Table 1). The adenosine deaminase (ADA) enzyme level in CSF fluid was high (12 IU/l). CSF GeneXpert test was negative but qualitative serum C-reactive protein was positive in the patient. The serological test for Japanese Encephalitis (anti-JE IgM in serum and CSF) was also negative.

Table 1

Laboratory findings of the patient at the time of presentation

Laboratory parameters	Results	Units	Reference range
Complete blood cell count			
Hemoglobin	10.2	g/dl	12–15
WBC count	23 500	/mm^3	4000–11 000
Platelet count	286 000	/mm^3	150 000–450 000
Differential count			
Neutrophils	90	%	40–70
Lymphocytes	7	%	20–40
Eosinophils	1	%	1–6
Monocytes	2	%	2–10
Packed cell volume	32	%	36–42
Mean cell volume	77	fl	80–100
Mean cell hemoglobin	26	pg	27–32
Mean cell hemoglobin concentration	32	g/dl	30–35
Erythrocyte sedimentation rate	58	mm/h	0–20
Serum electrolyte levels			
Serum Na+	133	mmol/l	135–145
Serum K+	3.8	mmol/l	3.5–5.5
Serum calcium	8.0	mg/dl	8.6–10.3
Serum magnesium	1.2	mg/dl	1.6–2.5
Cerebrospinal fluid analysis			
Total leukocyte count	195	/μL	0–5
Glucose	23	mg/dl	40–70
Albumin	200	mg/dl	15 –45

WBC, white blood cell.

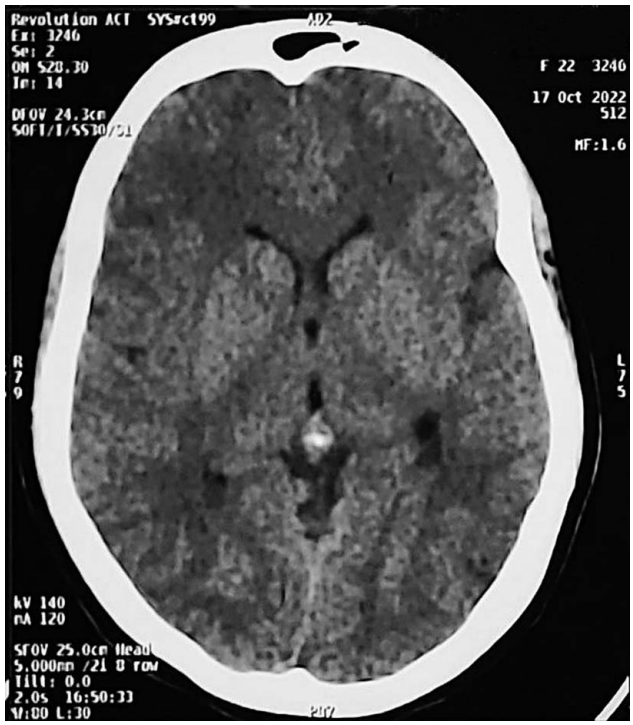

Figure 1. Normal noncontrast computed tomography of the brain.

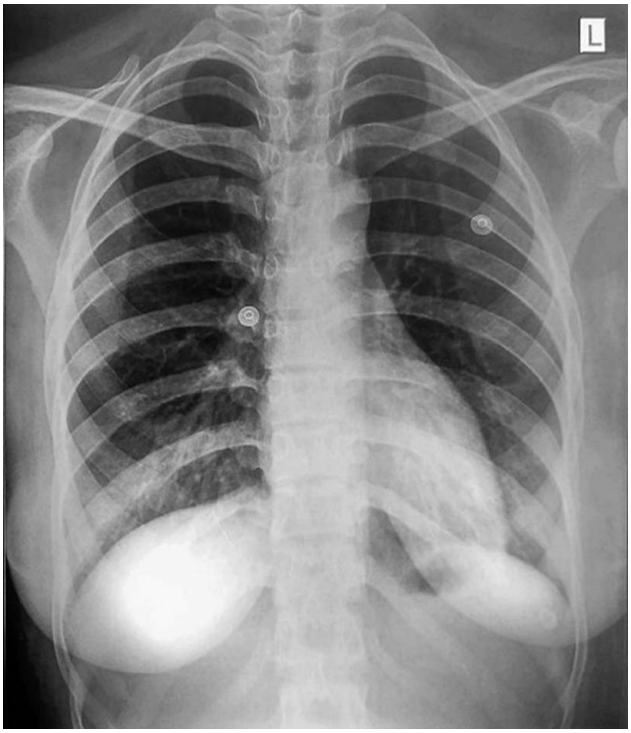

Figure 2. Normal chest radiography findings.

Considering the clinical history, examination, and relevant investigations, bacterial and viral meningitis/encephalitis were ruled out and thus based on the CSF analysis reports, a diagnosis of tubercular meningitis was established. Despite the empirical treatment, as there was no improvement in the patient's condition, antitubercular therapy was started on second day of admission as per the National Tuberculosis Management Guidelines 2019. She was initiated on intensive phase treatment of 2 months, consisting of isoniazid, rifampicin, pyrazinamide, and ethambutol along with dexamethasone in the dose of 0.4 mg/kg/day for 2 weeks. Within 2 days of initiation of therapy, her health condition markedly improved with resolution of symptoms and laboratory abnormalities and all the empirical therapy were stopped. The patient was shifted to ward and eventually discharged in good health on 10th day of admission. Following the initial 2 weeks, the oral dexamethasone was tapered at a rate of 0.1 mg/kg/week until reaching a maintenance dose of 0.1 mg/kg/day. Thereafter, the dose was reduced to 4 mg/day and gradually tapered by 1 mg/week until it was eventually discontinued, with the total duration of dexamethasone treatment spanning 10 weeks. Intensive phase treatment was followed by continuation phase with isoniazid, rifampicin, and ethambutol for an additional 7 months. Throughout the treatment period, the patient showed a steady recovery. Follow-up examinations indicated no neurological deficits, and the patient remained asymptomatic at subsequent visits.

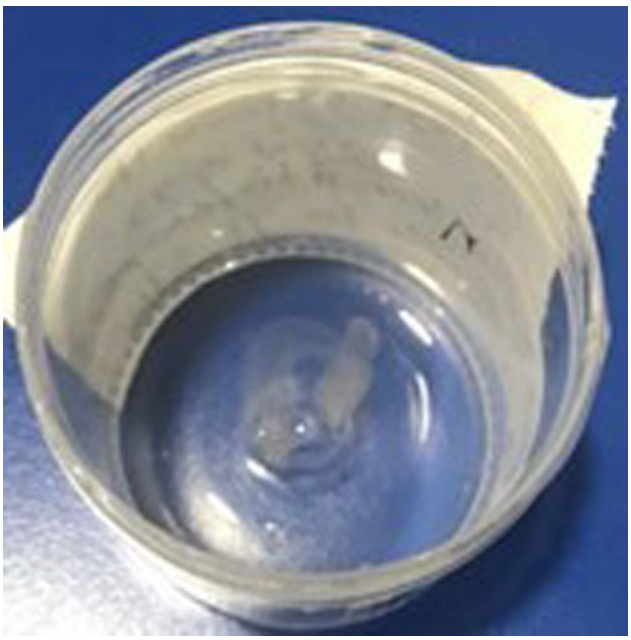

Figure 3. Gross cerebrospinal fluid finding showing clear light yellow fluid with cobweb coagulum.

Discussion

TB can affect any organ system of the body including the central nervous system[8]. About one-third of the world's population is assumed to have MTB infection[1]. CNS is involved in 1–2% of all TB cases and 7–8% of all Extra-pulmonary tuberculosis cases among immunocompetent patients[9]. In Nepal, TB has an annual incidence of 245 cases per 100 000 people in the population[10,11]. The National Tuberculosis Programme (NTP) registered 37 861 all forms of TB cases in Fiscal year 2021/2022 out of which 28% were extrapulmonary TB cases[12]. Although, the exact prevalence of TBM cases is not yet determined, a study conducted by Bhatta *et al.*[13] revealed that 16% of 585 TB cases within their study population were diagnosed with TBM. The frequency of TBM has been influenced by several factors including the global burden of TB, the prevalence of HIV, and age-related aspects[14]. In developed countries, tubercular meningitis accounts for 6% of all meningitis cases, while in developing countries, it makes up one-third to one-half of all bacterial meningitis cases[1]. Tubercular meningitis is the most severe clinical manifestation of extrapulmonary TB[9] characterized by subacute or chronic inflammation of the meninges enveloping the brain and spinal cord resulting from the invasion of *Mycobacterium tuberculosis* in the subarachnoid space[1,15].

Recognition of TBM is frequently difficult in routine clinical practice due to its nonspecific presentation[16]. The clinical features of TBM resemble those of other bacterial meningitis, characterized by symptoms such as fever, headache, vomiting, altered mental status, and neck stiffness[16,17]. A history of latent TB or prior TB exposure is found in 10% of TBM cases[16]. So, it is important to know TB status, particularly in developing countries with low socioeconomic status to facilitate the diagnosis and management of CNS complications, such as tubercular meningitis[18]. TBM has further imposed challenges in diagnosis compared to the other forms of bacterial meningitis due to its slower onset of symptoms and the paucibacillary nature of the infection, making it harder to detect in CSF[9,19]. The acute onset of symptoms in our patient closely resembles bacterial or viral

meningitis, leading to difficulties in making a definitive diagnosis[20]. Based on acute clinical presentation and negative AFB sputum, the patient was given antibiotics and antiviral therapy but the lack of the patient's response to medications for bacterial or viral meningitis has further complicated the diagnostic challenges. The presentation of TBM may resemble that of meningoencephalitis, and its diagnosis requires a high level of clinical suspicion, especially in a country with a high burden of TB[21]. The negative result of the serological testing excludes the possibility of Japanese Encephalitis in the patient.

Timely detection and proper treatment are essential in minimizing morbidity and mortality associated with TBM[22]. A conclusive diagnosis depends on the integration of clinical, radiological, and laboratory findings[14]. Laboratory diagnostic procedures for TBM primarily rely on the identification of acid-fast bacilli in CSF smear or isolation of MTB in either solid or liquid culture media[9,14]. Ziehl–Neelsen staining provides rapid results but has lower sensitivity of 10–20% while culture is more sensitive (60–70%) but takes greater than or equal to 2 weeks to produce observable bacterial replication which is too slow to aid in clinical diagnosis[5]. Thus, clinicians must not wait for culture results and should initiate empirical therapy promptly as death can occur[9]. Rapid diagnostic tests with higher sensitivity and specificity are necessary to support the presumptive diagnosis[22]. Genotypic methods have now emerged to address the need for rapid diagnosis of TBM[9]. PCR-based assays have been reported to have 56% sensitivity and 90% specificity with GeneXpert sensitivity ranging from 50 to 80%[14]. In 2013, WHO approved the GeneXpert MTB/RIF assay as the preferred initial test over conventional microscopy and culture for diagnosing TBM in low-resource settings like Nepal[3,9,14]. However, PCR testing of CSF for TBM diagnosis has significant limitations[5]. The patient of our case shows negative results to PCR despite having positive gross CSF findings. The lower sensitivity of GeneXpert in TBM diagnosis may be attributed to the very low bacillary load in the CSF sample to reach the detection threshold limit as detection is possible only when the required threshold limit is reached[5]. It could be due to the presence of PCR inhibitors such as erythrocytes in the CSF sample that causes errors in the result[9] or due to the low volume of the sample tested[5]. The absence of the target gene in TB isolates can also result in a false negative result[6]. Additionally, failure of the procedure to capture and lyse the bacilli may lead to an inaccurate outcome as the accuracy of the GeneXpert assay primarily depends on the effective capture of intact bacilli from the specimen within the cartridge[9]. Brain imaging can be a valuable tool in aiding the diagnosis of TBM but is not sufficient on its own to confirm the diagnosis[16]. Thus, normal brain imaging does not exclude the diagnosis. As per the WHO guidelines, when patients are suspected of having TBM but show negative results on GeneXpert assay, additional diagnostic studies are recommended for further evaluation[19].

Lumbar puncture is important in differentiating between various types of meningitis. In the case of TBM, CSF analysis reveals lymphocytic pleocytosis, elevated protein levels, and low glucose levels[16]. The findings in our patient are consistent with TBM as observed in CSF analysis. Viral meningitis may show similar CSF findings[1,4]. However, it is of utmost importance to consider TBM as part of differential diagnosis for patients who came from TB endemic areas and present with unclear meningitis, particularly when lymphocytic pleocytosis is observed[16]. Determination of ADA levels in CSF adds a diagnostic value in distinguishing TBM from nontubercular meningitis in immunocompetent patients due to its higher sensitivity (75–94%) and specificity (86–97%)[18]. CSF ADA levels are elevated in TBM as compared to non-TBM like viral meningitis[23]. A study by Solari *et al.*[24] highlighted the significance of CSF parameters like protein, glucose, chloride, and ADA levels, along with lymphocytic pleocytosis, in early TBM diagnosis. In a study by Ghosh *et al.*[18], it was found that the CSF ADA level cutoff point of 8.5 IU/l is indicative of a diagnosis of TBM which further adds a diagnostic value to our case. It is more sensitive than AFB smear and culture and can be suggestive of the diagnosis of TBM[22]. In addition, this diagnostic tool is simple, rapid, inexpensive, easily accessible and can be performed even with minimal training, making it particularly beneficial in areas with limited resources[25]. It can facilitate clinicians in decision making process soon after admission and enables timely antitubercular therapy to prevent complications associated with disability and morbidity[24]. For this reason, lumbar puncture and CSF ADA estimation need to find a place as a routine investigation in a resource-limited country like ours where there is high prevalence of TB and TBM.

If there arise any difficulties in differentiating TBM from other forms of meningitis based on the initial CSF test or GeneXpert, empirical antitubercular therapy should be considered[4]. Delays in diagnosis and treatment have resulted in poor prognosis[4]. The mortality rate in TBM is influenced by the patient's age, clinical condition at admission, length of delay in initiating therapy, and the specific treatment approach employed[4]. Although tubercular meningitis has an insidious onset of symptom ranging from 1 day to 9 months before diagnosis, but when a patient presenting with acute symptoms is either misdiagnosed or have delayed diagnosis, it may lead to tuberculoma formation and long-term neurological sequelae, including mental retardation, hydrocephalus, cranial nerve palsy, sensorineural hearing loss, stroke-related lateralizing neurological deficits, seizures, coma, and even death[6]. Hence, a favorable outcome in TBM is only possible if early diagnosis and treatment are done before the condition advances to later stages[4].

In the resource-limited settings of Nepal, access to the GeneXpert MTB/Rif test may be limited[26,27]. In such cases, alternative diagnostic tests like CSF analysis become important[16]. The use of diagnostic algorithms based on CSF values and patient clinical presentation can be helpful to differentiate it from other forms of meningitis[1]. So, relying solely on GeneXpert MTB/Rif results is not enough. Instead, doctors should maintain a high level of suspicion for TB meningitis based on patient risk factors to make an accurate diagnosis, especially in endemic countries with low-resource settings[1].

Considering the CSF analysis and raised ADA level, the decision was made to shift the treatment from antibiotics to antitubercular therapy adhering to National Tuberculosis Management Guidelines 2019 promptly. She was put under intensive phase therapy for 2 months, consisting of rifampicin, isoniazid, pyrazinamide, and ethambutol followed by continuation phase with isoniazid, rifampicin, and ethambutol for an additional 7 months[26]. After the initiation of therapy, there was a significant improvement in the health of the patient.

Conclusion

It is important to note that negative MTB PCR results from CSF can be misleading. Thus, in cases like ours, where no improvement is

seen within 2 days; TBM should remain a significant consideration until it is ruled out through lumbar puncture and CSF analysis even if the GeneXpert result is negative. Lumbar puncture is mandatory and can be the main modality for doctors to get a more accurate diagnosis of TB meningitis in limited health facilities. Comprehensive and clear guidance is essential for establishing the investigative pathway for TBM. The detailed history of the patient, thorough physical examination, and CSF fluid analysis can greatly aid in the diagnosis of TBM, particularly in patients living in countries with a higher prevalence of TB like Nepal. Prompt action, timely diagnosis and appropriate therapy help in substantial improvement in patients with TBM.

Ethical approval

None.

Consent

Written informed consent was obtained from the parents for the 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 on request.

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Author contribution

B.G., I.T., and J.Y. wrote the original manuscript, reviewed, and edited the original manuscript. S.B., M.B.P., N.M., S.B., Y.R.A., S.S., and M.B. reviewed and edited the original manuscript.

Conflicts of interest

Authors have no conflict of interest to declare.

Research registration

1. Name of the registry: none.
2. Unique identifying number or registration ID: none.
3. Hyperlink to your specific registration (must be publicly accessible and will be checked): none.

Guarantor

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Data availability statement

All available data are within the manuscript itself.

Provenance and peer review

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