Complex Tuberculous Meningitis: A Case Series Highlighting Rare Co-infections and Severe Complications

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Abstract

This case series presents two complex cases of tuberculous meningitis (TBM) with different complications, illustrating the diverse clinical presentations and management challenges of this disease. Case 1 involves an 18-year-old female with TBM complicated by cryptococcal co-infection, while Case 2 describes a 64-year-old female with TBM complicated by obstructive hydrocephalus and secondary bacterial infections. Both patients had been on anti-tubercular therapy before presentation. Diagnostic approaches included cerebrospinal fluid analysis, cultures, and molecular testing. Management strategies varied based on complications, involving antifungal therapy in Case 1 and neurosurgical intervention in Case 2. Outcomes differed significantly, with Case 1 showing complete symptom resolution and Case 2 resulting in mortality despite aggressive treatment. These cases underscore the importance of maintaining high suspicion for TBM, even in patients on anti-tubercular therapy, and the need for comprehensive diagnostic approaches and tailored treatment strategies. They highlight the potential for severe complications and the complexity of managing TBM.

Keywords: Tuberculous, meningitis, complications,co-infection,treatment

Background

Tuberculous meningitis (TBM) remains a significant global health challenge, particularly in tuberculosis-endemic regions. It is one of the most severe forms of extrapulmonary tuberculosis, accounting for approximately 1-5% of all tuberculosis cases [1]. TBM is characterized by inflammation of the meninges due to Mycobacterium tuberculosis infection and is associated with high morbidity and mortality rates, especially when diagnosis and treatment are delayed [2]. The diagnosis and management of TBM are complicated by its nonspecific clinical presentation, the need for specialized diagnostic tests, and the potential for severe complications. These complications can include hydrocephalus, cerebral infarction, and secondary infections, which further contribute to the poor outcomes often associated with TBM [3].

This case series presents two complex cases of TBM with different complications, highlighting the varied clinical presentations, diagnostic challenges, and management strategies in TBM patients. This case series presents two complex cases of TBM with different complications, highlighting the diverse clinical presentations, diagnostic challenges, and management strategies. By examining these cases, we aim to contribute to the understanding of TBM's complex nature and emphasize the need for comprehensive, tailored approaches to diagnosis and treatment.

Case Presentations

Case 1:

An 18-year-old female presented to the emergency department with severe headache, backache, vertigo, and vomiting persisting for 7 days. The patient had a known history of Pott's spine and had been on Anti-Tuberculosis Therapy (ATT) for the past 4 months. She had no history of surgeries and her immunization history was unknown. The patient did not have any history of smoking or known allergies and followed a non-vegetarian diet.

The patient's vital signs were as follows: pulse rate 80/min, respiratory rate 18/min, blood pressure 140/70 mm Hg. She measured 5 feet in height and weighed 36 kg. The patient appeared drowsy but was arousable. Physical examination revealed pallor, but no clubbing, edema, jaundice, or cyanosis was observed. A neurological examination showed that the patient was drowsy but able to obey commands. Her pupils were bilaterally reactive at 2 mm, and a right upper motor neuron facial palsy was noted. Deep tendon reflexes showed normal tone, and both upper and lower limb power was 5/5. Importantly, neck rigidity and Kernig's sign were present, strongly suggesting meningeal irritation. Respiratory, cardiovascular, gastrointestinal, and abdominal examinations were within normal limits.

Case 2:

A 64-year-old female was admitted to the emergency ward with a history of severe headache, drowsiness, and weakness lasting seven days. She also reported blinking and twitching of her left eye, difficulty swallowing, and an inability to walk, coupled with generalised body

weakness and knee pain. The patient had no known history of hypertension or diabetes mellitus but had been diagnosed with tubercular meningitis at a local hospital six months earlier and was on Anti-tubercular drugs (ATDs). She had no history of surgeries, smoking, alcohol use, or allergies and followed a vegetarian diet. Her immunization history was unknown.

Upon admission, her vital signs were as follows: pulse rate of 105 beats per minute, respiratory rate of 16 breaths per minute, and blood pressure of 110/70 mmHg. She was 155 cm tall and weighed 50 kg. A general physical examination revealed pallor but no signs of clubbing, edema, jaundice, or cyanosis. Neurological examination showed that the patient was drowsy yet arousable and able to follow commands, with a Glasgow Coma Scale (GCS) score of E3V3M3. Her pupils were bilaterally reactive at 2 mm. The left side of her face exhibited twitching with blinking in the left eye. Deep tendon reflexes showed normal tone, and both upper and lower limb power was 5/5. Notably, signs of meningeal irritation including neck rigidity, Kernig's sign, and Brudzinski's sign were all positive. Respiratory, cardiovascular, gastrointestinal, and abdominal examinations were within normal limits.

Clinical and Laboratory Findings

Case 1 Specific Findings: The cerebrospinal fluid (CSF) analysis revealed the presence of Cryptococcus neoformans, confirmed by India ink staining and culture. Truenat PCR detected Mycobacterium tuberculosis (MTB) Complex DNA at very low levels, with no rifampicin resistance detected.

Case 2 Specific Findings: CSF culture identified Stenotrophomonas maltophilia, sensitive to levofloxacin, minocycline, and trimethoprim-sulfamethoxazole. Endotracheal tube culture yielded Klebsiella pneumoniae and Pseudomonas aeruginosa. The patient was diagnosed with obstructive hydrocephalus and neuro-tuberculoma based on neuroimaging.

Comparison of clinical findings and laboratory findings of case 1 and case 2 are shown in table 1 and 2.

Table 1: Comparison of Clinical Findings

Clinical Feature	Case 1	Case 2
Age	18 years	64 years
Gender	Female	Female
Duration of Symptoms	7 days	7 days
Primary Complaints	Headache, backache, vertigo, vomiting	Headache, drowsiness, left eye twitching, difficulty swallowing
ATT History	4 months	6 months
Consciousness	Drowsy but arousable	Drowsy, GCS E3V3M3
Neck Rigidity	Present	Present
Kernig's Sign	Present	Present
Brudzinski's Sign	Not reported	Present
Focal Neurological Deficit	Right UMN facial palsy	Twitching in the left side of face

Hydrocephalus	Not reported	Present (Obstructive)
Neuro-tuberculoma	Not reported	Present

Table 2: Comparison of Laboratory Findings

Parameter	Case 1	Case 2	Reference Range
CSF Appearance	Clear, colorless	Clear, colorless	-
CSF Volume	3 mL	15 mL	-
CSF WBC Count	10 cells/cmm	05 cells/cmm	0-5 cells/cmm
CSF Glucose	11.0 mg/dL	52.2 mg/dL	70-110 mg/dL
CSF Protein	115.04 mg/dL	70.3 mg/dL	<50 mg/dL
Blood WBC Count	16,500/cmm	4,100/cmm	4,000-10,000/cmm
Hemoglobin	Not reported	11.5 g/dL	12.0-15.0 g/dL
Truenat PCR for MTB	Detected at very low levels	Not detected	-
India Ink Preparation	Positive for C. neoformans	Negative	-
CSF Culture	C. neoformans	S. maltophilia	-
ET Tube Culture	Not applicable	K. pneumoniae, P. aeruginosa	-

Management and Outcomes

The patient was initially on ATT, which was continued. Antifungal therapy with amphotericin B and fluconazole was initiated upon cryptococcal co-infection diagnosis. Follow-up at three weeks and two months showed significant clinical improvement and complete resolution of symptoms, respectively in Case 1. The patient's treatment was adjusted based on culture sensitivity, including cotrimoxazole, minocycline, and ceftazidime-avibactam in Case 2. She underwent surgery for obstructive hydrocephalus. Despite aggressive management, the patient's condition deteriorated, and she expired on 01/07/2024.

Discussion

This case series highlights the complex and varied presentations of tuberculous meningitis (TBM), emphasizing the challenges in diagnosis and management, particularly when complicated by co-infections or secondary infections. Both cases demonstrate the importance of maintaining a high index of suspicion for TBM in endemic areas, even in patients already on anti-tubercular therapy (ATT).

The first case, involving an 18-year-old female, is notable for the co-infection of TBM with Cryptococcus neoformans. This combination is extremely rare, with only a handful of cases reported in the literature [6]. The detection of both pathogens underscores the importance of comprehensive microbiological testing in TBM cases, especially when clinical presentation or response to treatment is atypical. The successful outcome in this case can be attributed to

early detection and appropriate management of both infections. The cryptococcal co-infection in Case 1 raises important considerations about the immune status of patients with TBM. While cryptococcal meningitis is often associated with immunocompromised states, particularly HIV infection, this patient had no known immunodeficiency [7]. This suggests that TBM itself, or perhaps the anti-tubercular treatment, may have created a state of local immunosuppression in the central nervous system, allowing for opportunistic cryptococcal infection. This hypothesis aligns with recent research indicating that M. tuberculosis can modulate host immune responses, potentially increasing susceptibility to other pathogens [8].

The second case, a 64-year-old female, presents a more complex clinical picture with TBM complicated by obstructive hydrocephalus and secondary bacterial infections. The isolation of Stenotrophomonas maltophilia from the CSF is particularly concerning, as this opportunistic pathogen is known for its intrinsic resistance to multiple antibiotics [9]. S. maltophilia infections are increasingly recognized as a significant challenge in healthcare settings, particularly in critically ill or immunocompromised patients [10]. The additional isolation of Klebsiella pneumoniae and Pseudomonas aeruginosa from the endotracheal tube culture further complicates the clinical scenario, highlighting the risk of nosocomial infections in critically ill TBM patients. The development of hydrocephalus in Case 2 is a well-recognized complication of TBM, occurring in up to 85% of cases in some series [11]. Hydrocephalus in TBM can be communicating or non-communicating, with the former being more common and often manageable with medical therapy alone. However, obstructive hydrocephalus, as seen in this case, typically requires neurosurgical intervention [12]. The presence of hydrocephalus is a poor prognostic indicator in TBM, associated with higher rates of mortality and neurological sequelae [13].

Both cases demonstrate the variability in CSF findings in TBM. While Case 1 showed classical TBM findings of low CSF glucose and high protein, Case 2 had relatively normal CSF parameters. This variability emphasizes the need for a high degree of clinical suspicion and the use of multiple diagnostic modalities in suspected TBM cases [14]. The British Infection Society guidelines suggest that a CSF:plasma glucose ratio of less than 0.5 is suggestive of TBM, but normal CSF biochemistry does not exclude the diagnosis [15].

The role of molecular diagnostic techniques in TBM diagnosis is highlighted in these cases. In Case 1, Truenat PCR detected MTB Complex DNA at very low levels, proving crucial in confirming the diagnosis. However, in Case 2, the PCR was negative, possibly due to the long duration of ATT prior to testing. This underscores the limitations of molecular tests in treated cases and the need for clinical correlation [16]. The sensitivity of PCR-based tests for TBM can vary widely, ranging from 32% to 87%, depending on the specific assay and the CSF volume used [17]. The World Health Organization now recommends Xpert MTB/RIF Ultra as the initial diagnostic test for TBM, given its improved sensitivity over conventional PCR methods [18]. The management of TBM with complications requires a multidisciplinary approach. In Case 1, the addition of antifungal therapy to the ATT regimen led to a favorable outcome. The choice of amphotericin B and fluconazole aligns with current guidelines for the treatment of cryptococcal meningitis [19]. However, Case 2 illustrates the challenges in managing TBM with multiple complications. Despite aggressive antimicrobial therapy and neurosurgical intervention for hydrocephalus, the patient's condition deteriorated, likely due to the combination of advanced TBM and multidrug-resistant nosocomial infections [20].

These cases also highlight the importance of drug susceptibility testing in guiding therapy. In Case 2, the antibiotic regimen was tailored based on the susceptibility profile of S. maltophilia. However, the presence of multiple drug-resistant organisms posed a significant challenge to effective treatment [21]. The emergence of drug-resistant pathogens in the context of TBM is a growing concern, particularly in settings where empiric broad-spectrum antibiotics are frequently used [22]. The contrasting outcomes in these cases reflect the spectrum of prognosis in complicated TBM. While early diagnosis and appropriate management can lead to favorable outcomes, as seen in Case 1, advanced disease with multiple complications can have poor outcomes despite aggressive treatment, as demonstrated in Case 2 [23]. Prognostic factors in TBM include the stage of disease at presentation, age, HIV status, and the development of complications such as hydrocephalus or stroke [24].

The role of corticosteroids in the management of TBM is well-established, with studies showing improved survival and reduced morbidity [25]. Both cases in this series received dexamethasone as part of their treatment regimen, aligning with current treatment guidelines. A landmark study by Thwaites et al. demonstrated that dexamethasone was associated with reduced mortality in TBM patients, particularly in those with more severe disease [26]. These cases also raise important considerations about the duration of ATT in TBM. Both patients developed complications while on ATT, suggesting that the optimal duration of treatment may need to be individualized based on clinical and radiological response [27]. Current guidelines recommend a minimum of 9-12 months of ATT for TBM, but some experts suggest that longer durations may be necessary in complicated cases or those with poor initial response [28].

The occurrence of secondary infections in Case 2 highlights the importance of infection control measures in the management of TBM patients, particularly those requiring prolonged hospitalization or invasive procedures. Strategies to prevent nosocomial infections should be an integral part of TBM management protocols [29]. From a public health perspective, these cases underscore the ongoing challenges in tuberculosis control and the need for improved strategies for early diagnosis and treatment of TBM. The WHO's End TB Strategy aims to reduce TB incidence by 90% and TB deaths by 95% between 2015 and 2035 [30]. Achieving these goals will require not only advances in diagnostic and therapeutic modalities but also improvements in healthcare delivery systems and public health interventions.

Finally, these cases emphasize the need for further research in several areas of TBM management. These include the development of more sensitive and specific diagnostic tests, optimization of treatment regimens (including the role of newer anti-tubercular drugs), strategies for managing drug-resistant TB, and approaches to prevent and treat the complications of TBM [31].

Conclusion

This case series illustrates the complex nature of TBM and its management, particularly when complicated by co-infections or nosocomial infections. It emphasizes the need for a high index of suspicion, comprehensive diagnostic approaches, and individualized treatment strategies. The cases highlight the potential for both favorable and poor outcomes in TBM, depending on various factors including timing of diagnosis, presence of complications, and emergence of drug-resistant pathogens. Future research should focus on developing more sensitive and specific diagnostic tools, optimizing treatment regimens, and strategies to

prevent and manage complications in TBM. Continued efforts in these areas, along with improved public health measures, will be crucial in reducing the global burden of this devastating disease.

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