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Case Report

Tuberculous Meningoencephalitis In Lost To Follow-Up Pulmonary Tuberculosis Patient: A Case Report

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ABSTRACT

Background: Tuberculous meningoencephalitis (TBME) is a rare extrapulmonary TB that accounted for less than 1-2% with high mortality and morbidity rate. Loss of follow-up (LTFU) TB cases are also associated with worse prognosis, treatment failure, drug-resistant cases, decompensations, and complications. The objective of this study is to present a TBME case in LTFU patient as both conditions are correlated with worse outcomes for the patient.

Case report: A 20-year-old man with a history of discontinued TB therapy presented to the emergency room (ER) with complaints of depressed consciousness, absence seizure, fever, shivers, nausea, vomiting, and holo-cranial headache. The diagnosis of TBME was confirmed by contrast-enhanced radiological findings, detection of M. tuberculosis in sputum, and blood investigations. Early initiation of anti-tuberculous drugs was given and showed marked clinical improvement followed by complete relief after a month follow-up.

Conclusion: TBME should be considered in patients living in high-rate TB countries with presumptive symptoms and signs supported by laboratory investigations as well as radiological findings to initiate prompt treatment. LTFU patients should be monitored with family or social group support while optimizing TB regimens in healthcare facilities

INTRODUCTION

Tuberculosis (TB) is one of the mainstay problems in Indonesia. Indonesia accounts for almost 10% of the global cases of Tuberculosis and is ranked second following India. The latest World Health Organization (WHO) 2021 report of the TB incidence rate in Indonesia is 354/100.000, but a recent study found the incidence rate is to be as high as 759.1/100,000 in 2021.(1,2) Mortality in untreated TB patients is 50-60% hence the Public Private Mix (PPM) approach was introduced by the WHO to increase the efficacy of TB diagnosis, detection, and

treatment. The priorities of PPM implementation in Indonesia are the completed treatment, successful treatment, and cure rate. [1,3,4]

In 2019, a study conducted by the Indonesian Ministry of Health revealed that as many as 62% of tuberculosis (TB) cases remain unreported and undetected. These include the patients who did receive treatment for at least a month and discontinued the treatment for at least two months in a row or loss of follow-up (LTFU) patients. The incidence of LTFU cases rose to 7.2% in 2022 from 6.8% in 2021.[4,5] An early termination of anti-tuberculous treatment increases the risk of a worse prognosis, treatment failure, drug-resistant cases, decompensations, and complications such as extra-pulmonary Tuberculosis infections.[6–8] Increased occurrences of extra-pulmonary Tuberculosis have been observed in the past two years. By late 2022, 10% of TB cases in Indonesia were diagnosed with extra-pulmonary TB.

Extra-pulmonary Tuberculosis infection of the central nervous system may involve the meninges, the brain tissue, or both. Tuberculous meningoencephalitis (TBME) is an extra-pulmonary complication affecting both the meninges and brain tissue that occurs in less than 1% of TB patients.[9,10] TBME is the underlying etiology of 6% of bacterial meningoencephalitis cases. It's correlated with high mortality and morbidity.[9–11] In children younger than 15 years old, the reported mortality rate is 15-29% and 20-50% in adults.[7,10] The rapid progression of the central nervous system (CNS) deterioration is related to a 70% increase in mortality in late treatment initiation and risk of virus transmission.[6,10,12] A permanent neurological damage is associated with late treatment in neurotuberculosis.[12,13] Hence, an early diagnosis of TB is needed, although due to the atypical features presented in most cases, delayed diagnosis of TBME is common.[9] We report a 20-year-old male lost to follow-up (LTFU) patient with tuberculous meningoencephalitis..

CASE REPORT

A 20-year-old man was presented to the emergency room of Ciawi Regional Hospital with complaints of a progressive deterioration of consciousness for the last three days. An episode of absence seizure that lasted for 10 minutes, a day before admission was reported. The complaints were associated with a high-grade fever, an episode of shivers, nausea, and a holo-cranial headache The patient had a history of productive cough for the past four months and had initiated category one tuberculosis treatment four months ago, but discontinued it prematurely two months after starting the therapy. The patient stated that he stopped taking the 4FDC because he is in a boarding school which limited his time for his routine outpatient follow-up. The patient is a heavy smoker; >12 cigarettes/day, and the habit persisted even after being diagnosed with TBC.

Physical examination revealed that the patient was somnolent with a Glasgow Coma Scale (GCS) of 11/15 (E3M5V3), impaired orientation as well as positive neck rigidity and meningeal irritation signs, classified as a TBME grade II. Rhonchi can be auscultated in both lungs; otherwise, there are no lateralization, hemiparesis, and cranial nerve palsy found, the other systemic examinations were within normal limits. The patient was under-weight at 53 kg and 167 cm tall. Initial investigation showed a marked elevation of the erythrocyte sedimentation rate (ESR) at 110 mm, leukocytosis, and hyponatremia with negative HIV polymerase chain reaction (PCR) test results. The chest X-ray revealed a bilateral patchy infiltrate in the apex and suprahilar region, a typical lung tuberculosis finding, with prominent bronchovascular markings. (**Figure 1**).

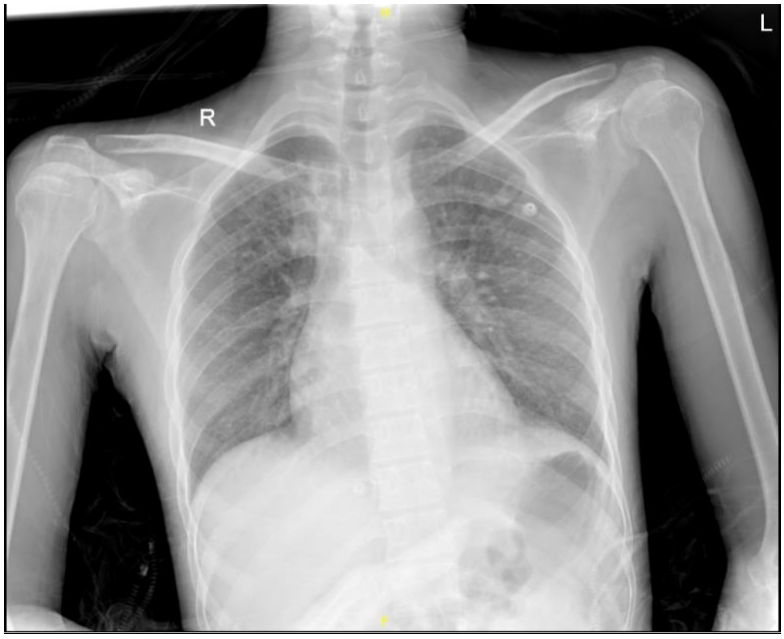

Figure 1. Patient Chest X-ray in AP (anteroposterior) view showed suprahilar and apex patchy infiltrate and prominent bronchovascular markings in both lungs

The contrast-enhanced head computed tomography (CECT) findings suggested a probability of viral meningoencephalitis with leptomeningeal and basal parenchymal enhancement, no signs of hydrocephalus. Further evaluation of magnetic resonance imaging (MRI) was not performed. (**Figure 2**). The patient was hospitalized for seven days and received intravenous dexamethasone at a dosage of 0,4 mg/kg/day, starting on the second day in response to the loss of consciousness. The dosage was then tapered off by the fifth day to 0,3 mg/kg/day. Additionally, intravenous ceftriaxone was administered at a dose of 2 grams/day, along with the initiation of neuroprotective agents. The rapid tuberculosis molecular test using Gene X-pert detected rifampicin-sensitive Mycobacterium tuberculosis (MTB). Intravenous administration of levofloxacin at a dose of 750 mg/day was initiated as part of the anti-tuberculosis treatment regimen. Three tablets of fixed-dose combination (FDC) therapy were commenced on the third day once the patient had regained alertness and consciousness. Hyponatremia was corrected with 0.9% normal saline. No treatment side effects have been reported. Upon discharge, the patient exhibited slight dizziness, resulting in a modified Rankin Scale (MRS) score of 1. The diagnosis of tuberculous meningoencephalitis was established based on the patient's symptoms and medical history, findings from contrast-enhanced computed tomography (CECT), positive MTB detection in the rapid test, and complete clinical improvement following anti-tuberculosis therapy during the one-month hospitalization period. No new occurrences of seizures or neurological complications were reported. The patient will receive anti-tuberculosis medication for one year, along with oral dexamethasone starting at a dosage of 4 mg/day. The dosage will be tapered off each week over the course of one month. Scheduled routine outpatient follow-up appointments are arranged.

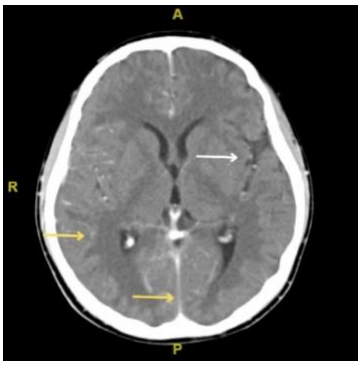

Figure 2. Head contrast-enhanced computed tomography (CECT) axial view showed bilateral enhancement in the sylvian fissure and ambient cistern (white arrows), as well as leptomeningeal enhancement (yellow arrow)

DISCUSSION

The involvement of the CNS accounted for 1-2% of pulmonary TB cases compared to the reported rate of 30% in miliary TB.[6,14] At an early stage, TBME is generally presented with suggestive symptoms of pulmonary TB in addition to the typical meningitis signs; headache, neck pain, vomiting, fever, and positive meningeal signs which are present in this patient. The clinical findings correlate with TBME pathogenesis.[9,10] In some cases, inflammation of the arachnoid layers, pia mater, and choroid plexus may manifest as brain edema due to increased production and malabsorption of CSF. Other profound neurological manifestations that occur later as the disease progresses are attributed to direct nerve invasion, host-impaired immune response, intracerebral vessel occlusion, vasculitis and tuberculous granuloma or abscess formation.[9,10,15] Some literature discussed the common CNS regions that are commonly involved in TBME, the 'tuberculosis area', which includes the oculomotor and abducens nerve, as well as brain regions supplied by the medial columnar artery and thalamic perforating artery.[9,16,17]

According to the TBME grading system by the British Medical Research Council (MRC), the patient is classified as grade II TBME. The following classifications are (1) Grade I, with intact consciousness (GCS score 15) and no evident focal neurologic signs; (2) Grade II, with intact consciousness (GCS score 15) and no evident focal neurologic signs or GCS score between 11 to 14; (3) Grade III, with GCS score below 10 (Table 1).[18,19]

Table 1. Tuberculous meningitis grading system by the British Medical Research Council (MRC)

TBM Grade	Diagnostic Criteria
Grade I	GCS 15, no focal neurologic signs
Grade II	GCS 15 with focal neurologic signs or GCS 11-14
Grade III	GCS ≤10

GCS=Glasgow coma scale

The standard of TBME diagnosis tests are microscopic findings of M. tuberculosis and Lowenstein Jensen (LJ) culture of the cerebrospinal fluid (CSF) that has to be observed daily for 6-8 weeks.[13,20] However, previous studies reported a sensitivity below 10% for the microscopic acid-fast bacilli (AFB) smear and 8,7-30% for LJ culture.[(9,13)] Extrapulmonary lesions have less MTB density; and paucibacillary, hence the low sensitivity found.[(14)] In a medical emergency, both of these tests are

specific yet not applicable and should not relied solely on diagnosing TBME. CSF analysis may show lymphocytic pleocytosis, decreased CSF glucose, and increased CSF protein but is unspecific in ruling out other CNS infections, including neurosarcoidosis and cryptococcal meningitis.[21] Hyponatremia was found in this patient's electrolyte panel and is seen in 35-71% of TBME patients due to non-neurological etiology such as vomitus. Other etiologies are syndrome of inappropriate antidiuretic hormone (SIADH), adrenal insufficiency, cerebral salt-wasting syndrome (CSWS). There is no significant correlation between hyponatremia and increased mortality rate reported in previous literature, however, hyponatremia seen in patients with longer hospitalization duration.[9,22,23]

Chest radiography should be taken as 50% of TBME patients presented with active pulmonary TB.[(9)] A confirmation of TB infection supports TBME diagnosis confirmation. Common findings in neuroimaging of TBME include (1) parenchymal and leptomeningeal enhancement as the most common findings accounted for 38-80%; (2) hydrocephalus or brain edema in 58-71% cases; (3) tuberculoma in 46-70%; (4) cerebral infarction accounted for 13-35%; (5) vasculitis/vasospasm in 11.1-37,2% TBME patients.[17,24,25] In rare cases, high-density enhancement in the basal cistern indicating a formation of thick exudates may be found. The sensitivity of the CECT scan is as high as 88% in detecting meningoencephalitis yet it is unspecific for MTB etiology due to similar presentation with other viral meningoencephalitis infections.[17] MRI is superior compared to CECT in the early stage of TBME with similar sensitivity reported (89%).[17,24,25]

Throughout the year, there are several diagnostic criteria developed and tested. The diagnostic criteria used in this case are based on Table 2. The TBME was classified as definite, probable, and possible in adults.[19] Positive clinical meningitis signs, TB infection suggestive chest X-ray, and meningoencephalitis findings in head-contrast CT scan, the TBME in this case is probable TBME; there are no further examinations of the CSF done.

Table 2. Tuberculous meningitis diagnostic criteria the British Medical Research Council (MRC) used in clinical trials

Classification	Diagnostic Criteria
Definite TBME	Clinical meningitis signs plus acid-fast bacilli seen in the CSF or
Probable TBME	Clinical meningitis signs plus 1 of the following: - Radiographic evidence of pulmonary TB - Acid-fast bacilli seen in sputum or gastric fluid - Evidence of extrapulmonary tuberculosis - CT scan or MRI brain scan features consistent with TBME
Possible TBME	Clinical meningitis signs plus ≥2 of the following: - History of previous TB infection - Illness duration >5 days - GCS <15 - Focal neurologic signs - and ≥2 of the following: - Yellow CSF - >50% lymphocytes in the CSF - - CSF glucose <50% blood glucose

TTBME=tuberculous meningoencephalitis; CSF=cerebrospinal fluid; CT=computed tomography; MRI=magnetic resonance imaging; GCS=Glasgow coma scale

In this case, the patient was given an early initiation of anti-tuberculosis to improve clinical state and to help rule out other possible etiologies. However, 1st line anti-tuberculous regimens have a poor blood-brain barrier (BBB) and blood-cerebrospinal fluid-barrier (BCSFB) penetration.[9,26] Hence levofloxacin, a 2nd line anti-tuberculosis drug, is added in this case due to its high concentration in the CSF compared to other quinolones (70%), in-vitro bactericidal activity, and efficacy in MDR TBME with minimal hepatotoxicity as well as nephrotoxicity.[26–29] The recommended duration of levofloxacin administration according to previous studies ranged from 1 to 8 weeks of TB treatment at 20 mg per kilogram per day, in this case, the levofloxacin was given at 1 week intravenously.[19,26]

According to WHO, starting in 2021 LTFU patients without isoniazid or rifampicin-resistant MTB and positive BTA findings in sputum will start over their 1st line anti-tuberculous regimens for 9 to 12 months.[30] Three FDC tablets were given after the patient had regained consciousness and could swallow. The FDC tablets were given according to the patient's weight, in this case, 3 tablets as the patient weighed 53 kg (**Table 3**). In the first 56 days, the patient will be given 4FDC tablets, each tablet consists of rifampicin (150 mg), isoniazid (75 mg), pyrazinamide (400 mg), and ethambutol (275 mg). For the next 7 to 10 months, 2FDC tablets will be given daily which consists of rifampicin and isoniazid, both 150 mg each.

Table 3. Recommended fixed-dose combination (FDC) dose according to weight

Weight	4FDC 2 months, daily dose	Weight 7-10 months, daily dose
30-37 kg	2 tablets	2 tablets
39-54 kg	3 tablets	3 tablets
55-70 kg	4 tablets	4 tablets
≥ 71 kg	5 tablets	5 tablets

FDC=fixed-dose combination

Intravenous corticosteroid's role in TBME is to reduce the mortality rate and clinical deterioration upon anti-tuberculosis therapy contributable to an impaired inflammatory response to dead bacteria.[18,31–33] Early treatment administration, less than 72 hours, is recommended as delayed treatment increases the mortality rate up to 70% associated with severe neurological sequelae and permanent disabilities.[12] The complete resolution of neurological symptoms and shorter hospitalization duration in this case is in line with high GCS score, absent cerebral infarction or intracranial tuberculoma formation, and early initiation of anti-tuberculous drugs, without MDR as well as HIV co-infection. Dexamethasone dose and route in TBME were given according to MRC grade (Table 4). In this patient, a Grade II TBME, the intravenous dexamethasone wasn't given for 4 weeks. We administer IV dexamethasone only in the first week of treatment because of the patient's limited resources and compliance. The reported CNS tuberculoma findings in LTFU patients are as high as 25,8%.[6] However, currently, no multi-center studies of tuberculous meningoencephalitis prevalence in LTFU patients. Previous literature stated that LTFU may place the patient at a higher risk of rifampicin-resistant MTB infection and reported multidrug resistance (MDR) outbreaks.[6,34] The findings of drug or rifampicin resistance in new cases are ranged

from 0.71% to 3.4% compared to 11.8 to 18% in patients who had treated before.[35] Osman et al reported the mortality rate in LTFU patients is as high as 69.7% in 30 days of diagnosis.[36] As discussed in the previous paragraph, 2FDC tablet administration in LTFU patients was recommended to be taken daily in contrast to thrice weekly administration in category one patients.

Table 4. Recommended Dexamethasone treatment in TBME patients

	Grade I TBME	Grade II and III TBME
Week 1	0.3 mg/kg IV	0.4 mg/kg IV
Week 2	0.2 mg/kg IV	0.3 mg/kg IV
Week 3	0.1 mg/kg IV	0.2 mg/kg IV
Week 4	3 mg total/day PO	0.1 mg/kg IV
Week 5	2 mg total/day PO	4 mg total/day PO
Week 6	1 mg total/day PO	3 mg total/day PO
Week 7		2 mg total/day PO
Week 8		1 mg total/day PO

IV=intravenous; PO= peroral

The reported CNS tuberculoma findings in LTFU patients are as high as 25,8%.(6) However, currently, no multi-center studies of tuberculous meningoencephalitis prevalence in LTFU patients. Previous literature stated that LTFU may place the patient at a higher risk of rifampicin-resistant MTB infection and reported multidrug resistance (MDR) outbreaks.[6,34] The findings of drug or rifampicin resistance in new cases are ranged from 0.71% to 3.4% compared to 11.8 to 18% in patients who had treated before.(35) Osman et al reported the mortality rate in LTFU patients is as high as 69.7% in 30 days of diagnosis.[36] As discussed in the previous paragraph, 2FDC tablet administration in LTFU patients was recommended to be taken daily in contrast to thrice weekly administration in category one patients.

In 2012, Rodrigo et al developed a strategic instrument to predict high-risk LTFU patients. Risk factors for treatment noncompliance include immigration status, living conditions, substance addiction, age, HIV co-infection, limited comprehension of tuberculosis, employment or financial circumstances, and prior anti-tuberculosis treatment (Table 5). Patients scoring ≥2 exhibit a higher LTFU probability.[37] A previous study conducted in Indonesia reported similar external and internal factors contributing to LTFU findings with additions of treatment termination due to adverse effects, smoking habits, and economic status.[38] In this present case, the patient is living in an institution (1 point) and had a poor patient understanding (1 point) with a total score of 2. This observation aligns with the LTFU status of this patient.

Currently, there are no specific targeted preventive measures for TBME in patients with Pulmonary Tuberculosis who are lost to follow-up (LTFU) in Indonesia. Direct observed therapy short course (DOTS) is introduced by WHO as a strategy to increase the success rate of TB treatment. In LTFU cases, Supervisor for Drug Swallowing (SWS) strategy implementation is important. [4,39] The SWS is commonly a person who lives with the patient and willingly to help the patient. Previous studies showed improved treatment effectivity and compliance in patient with SWS compared to those who didn't.[40] Hence, in this case, his mother was trained to be the SWS of this patient despite not living in the same house.

Table 5. A predictive scoring instrument for loss to follow-up outcome in TB patients

LTFU risk	Score
Immigration	1
Living alone	1
Living in an institution	2
Previous anti-TB treatment	2
Poor patient understanding	2
Intravenous drug use	4
Unknown Intravenous drug use status	1

LTFU=loss to follow-up

The evident limitations in this case are the limited resources, patient compliance and the patient's housing circumstances. The treatment in this reported case was also sub-optimal as the intravenous dexamethasone administration was not given for 4 weeks. Eventually improving the provided information or patient education, implementation of direct observed therapy short course (DOTS), utilizing systems or tools, the access of diagnostic tools, increasing TB service quality, community-based therapy, and collaborations of health organization and institutions, Social Health Insurance Administration Body, training health workers to an end goal of decrease LTFU cases with the help of early prediction tools. A specific intervention and regimens to ensure TB eradication, especially in developing countries with a high burden of TB.

CONCLUSION

The diagnosis of TBME should be considered in patients with presumptive meningoencephalitis symptoms and signs in regions with high TB infection rates. It is recommended to initiate anti-tuberculosis therapy promptly in patients with strong suspicion of TBME according to the evidence obtained through a multidimensional assessment while considering the resources limitation and the availability of diagnostic tools. Treatment compliance and associated complications should be monitored while ensuring a comprehensive understanding of TBC, enhancing family or social support awareness and optimizing the implementation of current TB regimens to decrease LTFU cases within healthcare facilitiese.

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