International Research Journal of Medical and Pharmaceutical Sciences
Volume.9, Number 4; October-December, 2024;
ISSN: 2836-8207 | Impact Factor: 6.62
https://zapjournals.com/Journals/index.php/Pharmaceutical
Published By: Zendo Academic Publishing

DELAYED DIAGNOSIS OF TUBERCULOUS LEPTOMENINGITIS COMPLICATED BY MULTISYSTEMIC MORBIDITIES IN A KENYAN HOSPITAL

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Article Info
Keywords: Tuberculous meningitis, TBM, TB Leptomeningitis, TBM diagnostics, Xpert/MTB/Rif, Kenya.
DOI
10.5281/zenodo.13889663

Abstract
Tuberculous meningitis (TBM) is the most severe and uniformly fatal form of extrapulmonary tuberculosis without treatment. HIV co-infection is the most serious risk factor of TBM in sub-Saharan Africa. The diagnosis of TBM is fraught with many patient and health system challenges, leading to treatment delays and serious TBM-related morbidity and mortality. These include a lack of resources for adequate TB diagnostics, lack of adequate knowledge on typical and atypical TB presentations, over-reliance on bacteriological methods to confirm TB diagnosis, and failure to consider TB in the absence of available diagnostic methods in the face of compatible clinical characteristics. The World Health Organization (WHO) recommended the use of Xpert/MTB/Rif as the initial diagnostic test for TBM in 2013, but the sensitivity rates for cerebrospinal fluid diagnosis of TBM vary from 59% to 72% depending on the methodology used. In this study, we report on the case of a young high school student in rural Kenya whose TBM diagnosis and treatment were delayed by 2 years, leading to significant disease-related morbidity. Her subsequent presumptive diagnosis of TBM and treatment with anti-TB drugs, adjunctive corticosteroids, and supportive care led to the resolution of almost all her complications. We emphasize the need for empirical TBM treatment in appropriate clinical circumstances.

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INTRODUCTION

The 2022 global tuberculosis (TB) report showed that approximately 10·6 million people became ill with TB in 2021, compared with 10·1 million in 2020, and 1·6 million people died from tuberculosis in 2021 compared with 1·5 million in 2020. Furthermore, the incidence rate of tuberculosis increased by 3.6% in 2021 relative to 2020 (Bagcchi, 2023). Sub-Saharan Africa bears the highest burden of the global TB figures, with over half of all TB cases being coinfected with HIV (Zumla et al., 2015). Kenya is ranked among countries with high TB burden, with an incidence rate of 251/100,000 population in 2021. Of these cases, 24% were HIV-coinfected ((CDC), 2021). A 2016 TB prevalence survey study in Kenya showed that the burden of TB is higher in the urban populations than in the rural populations, with up to 86% of the TB cases found in HIV-negative people (Enos et al., 2018). Tuberculous meningitis (TBM) is the most severe and lethal form of extrapulmonary tuberculosis, with up to 100,000 new cases occurring annually (Wilkinson et al., 2017). It is characterized by hematogenous seeding of the subarachnoid space with the bacilli of *M. tuberculosis*, leading to subacute or chronic meningitis (Seddon et al., 2019; Wilkinson et al., 2017). HIV co-infection is the most common and serious risk factor for TBM, especially in sub-Saharan Africa (Navasardyan et al., 2023; Veltman et al., 2014). Patients with TBM present with severe headaches, fever, night sweats, lethargy, altered mental status, convulsions, features of elevated intracranial pressure, and complications like cranial neuropathies, stroke, tuberculoma, etc. (Marx & Chan, 2011). The diagnosis of TBM is based on a compatible clinical history, cerebrospinal fluid (CSF) showing predominant lymphocytic pleocytosis, elevated proteins (usually between 100 and 500 mg/dl), and low glucose (usually less than 45 mg/dl). CSF may also show acid-fast bacilli during microscopy, culture, or polymerase chain reaction (PCR), e.g., the Xpert/MTB/Rif, albeit with varying levels of sensitivity and specificity (Marx & Chan, 2011). Classic neuroimaging features of TBM include basal leptomeningeal enhancement and hydrocephalus (Marx & Chan, 2011). Without treatment, TBM is uniformly fatal, whereas delayed treatment can lead to serious chronic systemic and neurological disabilities (Anderson et al., 2010). Timely treatment dramatically improves patient outcomes in TBM and is thus warranted when the clinical picture and CSF findings suggest TBM even without bacteriological confirmation. Unfortunately, many patient and health system factors lead to delays in the diagnosis and management of TB, resulting in significant morbidity and mortality. These include a lack of adequate knowledge on typical and atypical TB presentations, a long chain of care-seeking through multiple health providers, perceived stigma, financial constraints, poor access to health care, lack of resources for adequate TB diagnostics, over-reliance on bacteriological methods to confirm TB diagnosis, failure to consider TB anyway when the available diagnostic methods return a negative TB test results in the face of compatible clinical characteristics, etc. (Paramasivam et al., 2017; Teo et al., 2021). Treatment for drug-sensitive TBM with antimicrobials generally includes 2 months of daily rifampicin, isoniazid, pyrazinamide, and ethambutol, followed by 7-10 months of rifampicin and isoniazid. Adjunctive corticosteroids are included as per various treatment protocols to reduce morbidity and mortality of TBM. (Prasad et al., 2016; Thwaites et al., 2004; "Treatment of tuberculosis," 2003; "WHO Guidelines Approved by the Guidelines Review Committee," 2010).

CASE SUMMARY

Clinical history and physical examination

A 19-year-old female high school student from Narok, Kenya, the fifth born among 10 siblings from a polygamous family, first presented to us in October 2023 with recurrent generalized tonic-clonic (GTC) convulsions, fever to peak temperatures of 41.6^0C, drenching night sweats, and altered mental status (she was confused and having active visual hallucinations). She was well until September 2021, when she developed recurrent fever, occasional drenching night sweats but no cough, and painful bilateral nodular swellings on her face and anterior tibial regions (the latter lasted about 1 month). This was associated with left upper and lower

limb twitches for about a week, which were then followed by GTC seizures, each lasting about 10-20 minutes with post-ictal sleep and occurring about 2-3 times per month. She was seen at local health centers and placed on an unknown dosage of oral phenobarbitone to control the seizures. By February-March 2022, the convulsions had worsened to 2-4 episodes daily, and she stopped attending school. She was admitted to the regional hospital three times over a 4-month period. A computed tomography (CT) scan of the brain performed in September 2022 (images not available) revealed a left frontoparietal vasogenic edema likely secondary to an underlying space-occupying lesion. A follow-up magnetic resonance imaging (MRI) of the brain (images not available) revealed a left parietal lobe wedge-shaped area of brain edema with a thick pachy-leptomeningeal enhancement over this region with a mild mass effect effacing the overlying sulci, but no mass lesion was noted. The differential diagnosis included focal pachy-leptomeningitis versus left parietal lobe middle cerebral artery territory ischemic infarct. An electroencephalogram (EEG) revealed abnormal awake EEG findings with seizure foci noted in the frontotemporal cortical regions bilaterally with secondary generalization suggestive of complex partial seizures. (See figure 1). No lumbar puncture was performed at that time.

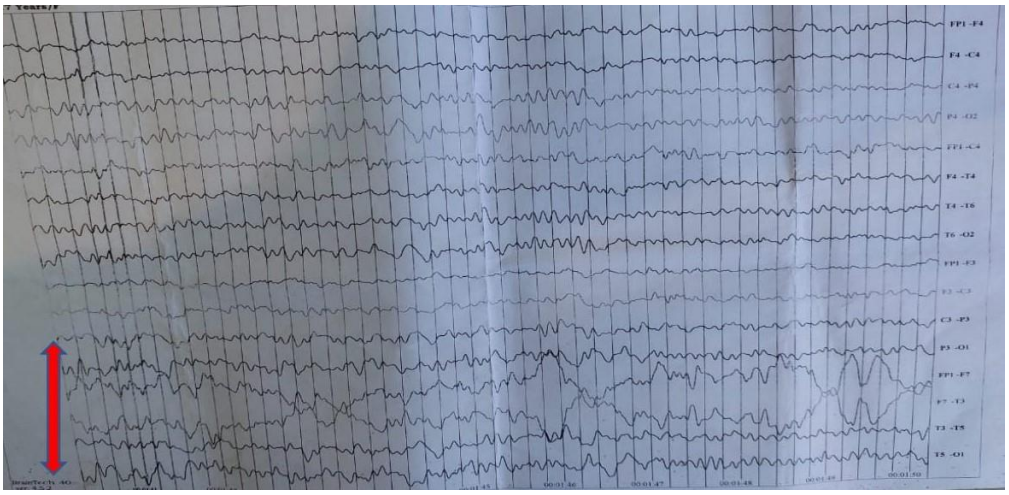

Figure 1: Awake EEG showing sharp wave epileptiform discharges (in the region marked with the double arrowhead) over the frontotemporal cortical regions bilaterally.

The patient was treated for bacterial meningitis and atypical pneumonia with intravenous ceftriaxone for 5 days only. Multiple sputum evaluations using Xpert/MTB/Rif and Ziehl-Neelsen staining for tuberculosis were negative. The convulsions were poorly controlled on carbamazepine because of poor medication adherence. She was also administered aspirin and a statin for presumed secondary prevention of stroke. 6 months prior to her current presentation, she had become bed-bound due to progressive lower limb weakness which was worse on the left side. By then she had defaulted on all her medications.

At the first admission, she was in status epilepticus, which was aborted with intravenous diazepam and a loading dose of intravenous phenytoin in saline, followed by an oral maintenance dose. She also underwent successful, comprehensive resuscitation. Clinically, she appeared sick-looking with a GCS after 1 day of 12/15; pupils were equally reactive bilaterally to light at about 4 mm size, but she had reduced visual acuity in the left eye with significant meningismus, peripheral features of an upper motor neuron lesion with power of grade 3/5 in the left and 4/5 in the right lower limbs, respectively, and an intact sensory examination with no sensory level. She had coarse bilateral transmitted sounds due to airway secretions; normal, regular heart sounds; marked epigastric tenderness; grade 1 bed sores in the bi-trochanteric regions; and early flexion contractures in both knees and elbows.

Workup and management

A chest X-ray (CXR) revealed non-specific bilateral hilar infiltrates but no obvious perihilar adenopathy. (See figure 2). A computed tomography scan of the brain at admission showed left frontoparietal lobe vasogenic edema without an obvious mass lesion. (See figure 3). Subsequent MRI showed features of diffuse leptomeningitis with associated left parietal focal cerebritis; consider tuberculosis. (See figure 4).

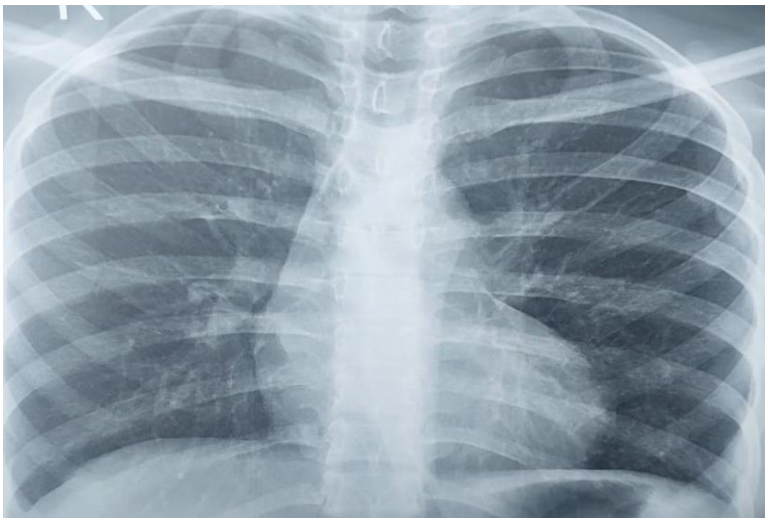

Figure 2: CXR showing non-specific bi-hilar infiltrates without any obvious perihilar adenopathy.

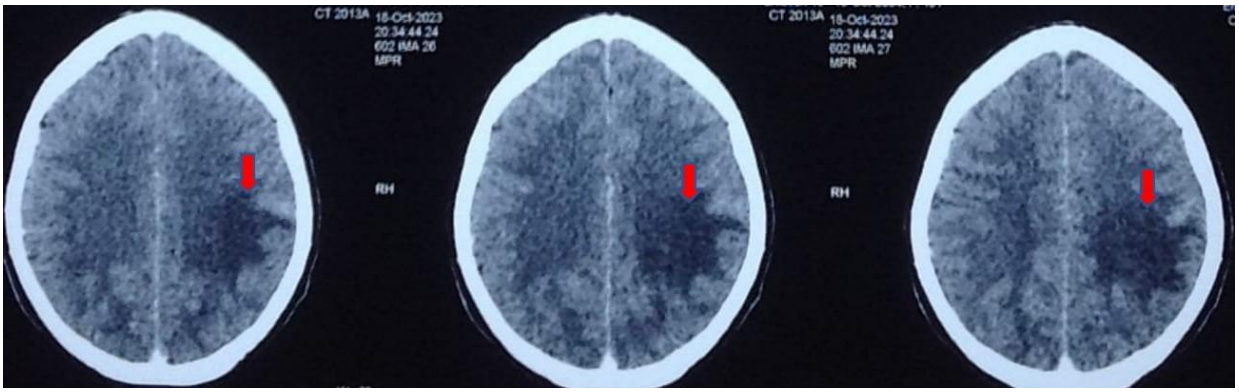

Figure 3: Computed tomography scan of the brain showing a focal area of vasogenic edema in the left frontoparietal lobe (marked with red arrows) without any obvious mass lesion.

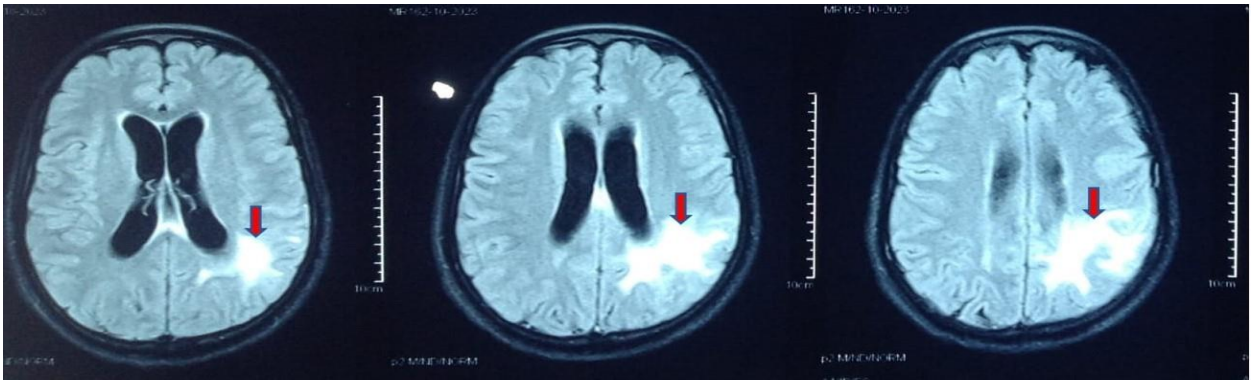

Figure 4: Magnetic resonance imaging of the brain showing subcortical and deep vasogenic edema involving the left parietal lobe (marked with red arrows), with effacement of the overlying sulci and diffuse overlying leptomeningeal enhancement most marked in the basal cisterns.

A lumbar puncture done showed cloudy cerebrospinal fluid (CSF) under pressure with neutrophilic pleocytosis (numerous leucocytes with 77% neutrophils and 19% lymphocytes), elevated proteins at 96 mg/dl, low glucose at 40 mg/dl (serum glucose was 148 mg/dl), negative CSF VDRL and cryptococcal antigen tests, and negative CSF for acid-fast bacilli and Xpert/MTB/Rif for tuberculosis. The erythrocyte sedimentation rate (ESR) was 65 mm/hr. Other laboratory tests included a normal complete blood count, normal renal, liver, and electrolyte panels, normal urinalysis with a negative pregnancy test, and a negative HIV test. In view of her clinical presentation and these findings, we immediately started treatment for both bacterial and tuberculous meningoencephalitis with intravenous ceftriaxone (2 g twice daily for 7 days) and RHZE (rifampicin, isoniazid, pyrazinamide, and ethambutol) with pyridoxine (to forestall isoniazid-induced peripheral neuropathy), intravenous dexamethasone, and later on de-escalated to tapered-dose oral prednisone (with gastroprotection using omeprazole and osteoprotection using vitamin D-calcium combo tablets), phenytoin, and comprehensive supportive therapy. She had a tumultuous inpatient course characterized by florid psychosis requiring antipsychotic therapy with short course olanzapine and physical restraints, acute kidney injury, recurrent urine retention requiring Foley catheter management, severe hyponatremia requiring hypertonic saline infusion, breakthrough GTC convulsions, and severe psychosocial issues requiring counseling. TB therapy was provided for 9 months (i.e., 2 months of intensive phase with the RHZE, followed by 7 months of continuation phase with RH), as per local guidelines.

Clinical progress and follow-up

Following her index admission, she recovered enough to be discharged on a wheelchair after 2 weeks with ongoing TB therapy, steroids, outpatient physiotherapy, psychological counseling, and supportive care. In the 4th week of treatment, she experienced worsening reduction in visual acuity in her left eye, which was noted at admission. The patient had a formal ophthalmology review, which raised concerns regarding the possible role of ethambutol in worsening her visual acuity, with a recommendation to stop it completely. However, we considered the need to eradicate TB to supersede this concern and continued ethambutol until the end of the intensive phase of the TB treatment. By then, her visual acuity had declined to the mere perception of light. In the 5th week of TB therapy, the patient developed an episode of acute hepatitis A characterized by a severe cholestatic phase of the disease with deep jaundice and hepatocellular dysfunction (the transaminases rose 5-fold). She eventually developed coagulopathy, sepsis, and grade 3 hepatic encephalopathy. This was successfully managed in the wards with bed rest, vitamin K supplementation, laxatives, antibiotics, and supportive care. We withdrew her RHZE for 13 days and bridged it with a more liver-friendly regimen comprising levofloxacin (there was no moxifloxacin available) and ethambutol. We could not give aminoglycoside because she had an acute kidney injury. She recovered fully and was put back on RHZE, and the treatment duration was adjusted accordingly. She developed severe sensorimotor peripheral neuropathy in both legs in the 6th month of treatment, which resolved with the addition of pregabalin. By the 7th month of treatment, she could ambulate with minor assistance. By the 8th month, she was walking on her own without assistance. It has been almost 3 months since she finished her TB treatment. She has gained weight from a nadir of 41 kg to a current 55 kg; her visual acuity in her left eye has improved to near-normal; she walks independently; she has had no further convulsions; and she has resumed schooling. The patient has ongoing outpatient follow-up and psychosocial support in a multidisciplinary team.

DISCUSSION

Leptomeningitis is a radiological term that describes the post-contrast enhancement of the pia and arachnoid layers of the meninges, whereas pachymeningitis refers to enhancement of the dura mater (Kioumehr et al., 1995). Leptomeningitis is the most common complication, especially in infections, and is commonly called meningitis or arachnoiditis (Mace, 2008). Tuberculous leptomeningitis, simply called tuberculous meningitis (TBM), still poses significant diagnostic challenges, especially due to difficulties in identifying tuberculous bacilli in CSF

samples (Chin, 2014). CSF smear microscopy staining for acid-fast bacilli only has a sensitivity of about 15%, whereas mycobacterial culture takes about 42 days, which is too slow to be helpful in a sick-patient situation (Bahr & Boulware, 2014). The World Health Organization (WHO) recommended the use of Xpert/MTB/Rif as the initial diagnostic test for TBM in 2013 ("WHO Guidelines Approved by the Guidelines Review Committee," 2013). The sensitivity and specificity of the Xpert/MTB/Rif assay for the diagnosis of TBM vary widely in the literature and seem to be principally affected by the methodology of performing the tests, including the volume of the CSF and centrifugation techniques. Patel *et al*.(2023) found a 67% sensitivity for TBM with Xpert/MTB/Rif in microbiologically proven TBM (Patel et al., 2013). However, Nhu *et al.* (2014) found that Xpert/MTB/Rif had 59% sensitivity and 99% specificity for TBM using consensus clinical criteria as the reference standard (Nhu et al., 2014). In resource-limited clinical settings, the diagnostic challenges are further compounded by a lack of resources, poor access to health care, and inadequate knowledge about typical and atypical TB presentations, among other delays (Paramasivam et al., 2017; Teo et al., 2021). Our patient should have been diagnosed with TB at the very early stage. She lived in a high-TB-burden country and presented with recurrent fever, drenching night sweats, anorexia, altered mental and neurological status, and weight loss. These symptoms are compatible with TB and TBM (Marx & Chan, 2011). The painful nodular swellings on her face and bilateral anterior tibial regions were most consistent with erythema nodosum, which is a skin manifestation of TB, although the typical site is the shins, ankles, and knees (Laborada & Cohen, 2021). For our patient, the factors that seemed to have contributed to the delays in her diagnosis and treatment for TBM included failure to have been assessed by experienced physicians earlier, failure to have done a lumbar puncture earlier, failure to consider TBM as a top differential from the very onset of her illness along the chain of health facilities she visited, failure to consider TB when the sputum studies for TB returned a negative verdict, and lack of a comprehensive follow-up plan. TBM must be considered in any patient presenting with clinical features of meningitis in a high-TB-burden country like Kenya or in high-risk persons in low-TB-burden regions (Chin, 2014). Even in the face of a negative laboratory work-up for TB (be it sputum or CSF for acid fast bacilli or Xpert/MTB/Rif assay), empirical treatment of TBM with anti-TB drugs and adjunctive corticosteroids as per the WHO and local guidelines remains the standard of care (Prasad et al., 2016; "WHO Guidelines Approved by the Guidelines Review Committee," 2010). Fortunately, our patient has remarkably improved over a full course of TBM treatment, albeit at the cost of significant TBM-related morbidity caused by significant diagnostic and therapeutic delays.

CONCLUSION

TBM poses significant diagnostic challenges, particularly in resource-limited clinical settings. Multiple patient and health system-related factors can delay the diagnosis and treatment of TBM and cause unnecessary and unacceptable TBM-related morbidity and mortality. Empirical treatment of TBM with anti-TB drugs and adjunctive corticosteroids is the standard of care for patients with features of meningitis in high-TB-burden populations even when the diagnosis has not been confirmed bacteriologically.

ACKNOWLEDGEMENT

The authors acknowledge Dan Kahinga (physiotherapist), Juliana and Collette (psychological counselors), Silas Odhiambo (patient attendant), Seth Manera, Steve Nyagah, and Rose Makanga (administration), the nursing staff in the female wards and TB clinic of St. Joseph Rift Valley Hospital, Gilgil, for their help in managing the patient.

Ethical Consideration

Informed consent was obtained from the patient for this case.

Conflict of interest

The authors declare no conflicts of interest.

Funding information
The authors declare that they have no funding sources.

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