Disseminated *Mycobacterium bovis* infection complicated by meningitis and stroke: a case report

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Abstract—We describe a case of a 19-year-old female presenting with *Mycobacterium bovis* meningitis, a rarely encountered infection. We discuss the use of pyrosequencing to aid in prompt diagnosis of *M. bovis* infection, as well as treatment strategies and challenges given the organism’s intrinsic resistance to pyrazinamide.

**Keywords:** tuberculosis, bovis, meningitis
Introduction

Despite advances in antituberculous chemotherapy, tuberculous meningitis (TBM) remains associated with significant morbidity and mortality.\textsuperscript{1,2} Although most commonly associated with \textit{Mycobacterium tuberculosis} (Mtb), other members of the Mtb complex can cause CNS disease. Indeed, in the early 20\textsuperscript{th} century, \textit{Mycobacterium bovis} (\textit{M. bovis}) caused approximately 25\% of cases of TBM\textsuperscript{3} and was particularly a concern for young children.\textsuperscript{4} As \textit{M. bovis} infection is largely attributed to transmission from cattle and consumption of unpasteurized milk, its incidence has dramatically decreased in developed countries following implementation of milk pasteurization and bovine tuberculosis surveillance. However these improvements have not been universal, and substantial rates of \textit{M. bovis} disease have been noted in immigrant communities.\textsuperscript{5,6} Rarely, cases of meningitis with \textit{M. bovis} BCG have been reported complicating BCG vaccination.\textsuperscript{7}

There remain significant gaps in our understanding of \textit{M. bovis} disease and its management. While \textit{M bovis} has been associated with a higher proportion of extrapulmonary manifestations than Mtb,\textsuperscript{8} rates of CNS disease might be similar.\textsuperscript{5} Published experience in the management of CNS \textit{M bovis} however is limited to individual case reports and small series,\textsuperscript{5,9–12} and there are no major treatment guidelines available.

We report a case of a young female presenting with disseminated \textit{M. bovis} infection complicated by meningitis and stroke secondary to TB vasculitis, managed with the addition of corticosteroids, aspirin, and levofloxacin to her TB regimen.
Case Presentation

A 19-year-old female with past medical history of cerebral palsy, developmental delay, and prior seizures presented to an outside hospital with nausea, vomiting, abdominal distension, and fevers. She was found to have bilateral tubo-ovarian abscesses (TOA) and was treated for presumed pelvic inflammatory disease with ampicillin-sulbactam, metronidazole, and doxycycline. Following discharge, she continued to have worsening abdominal distension, nausea, anorexia, and weight loss. She presented again to an outside hospital about six months later.

Computed tomography (CT) imaging of the abdomen and pelvis at that time was notable for bilateral TOA, mesenteric and omental nodularity, and bilateral pulmonary nodules. Drainage from her TOA and tissue from a retroperitoneal lymph node biopsy were both smear-negative for acid fast bacilli (AFB). However, both samples were positive for *M. tuberculosis* complex on molecular testing (TOA fluid via real-time PCR at Quest Diagnostics, San Juan Capistrano, CA and lymph node tissue via Cepheid Xpert® MTB/RIF assay). She was diagnosed with tuberculosis with peritoneal and pulmonary involvement and was transferred to our hospital for ongoing management.

Developmental history was notable for premature birth and being non-verbal at baseline. Social history was notable for prior residence on a farm in Mexico where she lived in close proximity to cattle. She was not known to be immunocompromised, and 4th generation HIV ELISA was negative. She had no prior history of treatment for active or latent tuberculosis, and no known TB contacts.

On presentation to our hospital, she was noted to have nuchal rigidity and ongoing nausea and vomiting. A head CT scan demonstrated multiple small ring-enhancing parenchymal
lesions in the left frontal lobe and left cerebellar vermis, along with bilateral supratentorial sulcal enhancement, concerning for CNS tuberculosis with tuberculomas and meningitis (Figure 1).

Treatment for tuberculosis was initiated with rifampin 600mg/day (15 mg/kg) (patient weight 38 kg), isoniazid 300mg/day, pyrazinamide 750 mg/day, and ethambutol 600 mg/day and she was started on adjunctive dexamethasone 0.4 mg/kg IV daily, using the tapered regimen reported by Thwaites and colleagues. Cerebrospinal fluid (CSF) testing showed a white blood cell count of 115 cells/mcL (56% lymphocytes), protein 98 mg/dL, and glucose 20 mg/dL. AFB smear was negative, but CSF cultures were ultimately positive for M. tuberculosis complex. Culture from her TOA fluid also grew M. tuberculosis complex, whereas culture from her retroperitoneal lymph node biopsy was negative.

After two days of treatment, ethambutol was discontinued due to concern for difficulty monitoring potential ocular toxicity given her cognitive impairment, and levofloxacin 750mg/day was started. On day five of hospitalization, she was noted to have new left-sided hemiplegia, and MRI brain was consistent with acute infarct likely secondary to TB vasculitis (Figure 2). Aspirin 162mg daily was initiated due to its potential benefit in stroke reduction in TBM. Once a sample of pelvic abscess fluid yielded growth of acid fast bacilli, the sample was sent by clinician request to the California Department of Public Health for pyrosequencing and showed that her disease was actually due to M. bovis, based on pncA sequencing. Pyrazinamide was discontinued given the organism’s intrinsic resistance, and she was started on linezolid 600mg/day in order to provide an additional agent with good CNS penetration pending full drug susceptibility test results. Phenotypic susceptibility testing performed via MGIT on isolates from pelvic fluid and CSF showed that her M. bovis was resistant to pyrazinamide, but susceptible to
isoniazid, rifampin, ethambutol and streptomycin. Additional susceptibility testing for her CSF isolate was performed at National Jewish Health via the indirect proportion method on 7H11 agar and showed susceptibility to all tested drugs (amikacin, capreomycin, ethionamide, levofloxacin, moxifloxacin, PAS, and rifabutin). Pyrosequencing also did not detect any resistance-associated mutations for INH, rifampin, quinolones, amikacin, kanamycin, or capreomycin. Linezolid was stopped after 1 month due to induced anemia (nadir hemoglobin 9.3 g/dL from 12.7 g/dL). The patient continued treatment with isoniazid, rifampin, levofloxacin, and aspirin; and dexamethasone taper was initiated. She remained stable on this regimen, with anticipated total treatment duration of 12 months. There has been no clinical evidence of recurrent infarcts or new neurological sequelae on follow-up several months later.

Conclusions

This case highlights some of the clinical challenges that arise in the management of M. bovis meningitis, a rarely encountered infection. There was a significant lag in diagnosis likely related to difficulties with history and exam given her developmental delay. Unfortunately, even when these communication barriers are not present, the diagnosis of TBM may not be initially considered due to nonspecific symptoms such as fever, headache, vomiting, anorexia, and failure to thrive. Delayed diagnosis in TBM remains a major concern given the poor prognosis associated with more advanced disease.\textsuperscript{1,9,16} The availability of rapid molecular diagnostic tools such as the Cepheid Xpert\textsuperscript{®} MTB/RIF assay has the potential to allow for more timely diagnosis of TB, as in the case reported here where initial body fluid samples were all smear-negative. However, despite the potential utility of Xpert for the diagnosis of extra-pulmonary TB,\textsuperscript{17} its use
on non-respiratory specimens is considered off-label by the US Food and Drug Administration, and testing of such specimens may not be widely available due to need for laboratory validation.

While the prompt recognition of TBM is important for clinical management, working with the clinical laboratory to speciate the mycobacterium may also be helpful, particularly before phenotypic antimicrobial susceptibility results are available. *M. bovis* is intrinsically resistant to pyrazinamide, so its identification allows this potentially hepatotoxic therapy to be discontinued at an earlier point. In this case, we were fortunate to have access to rapid molecular testing through the California Department of Public Health’s Microbial Diseases Laboratory. The lab’s pyrosequencing assay screens for and reports resistance-associated mutations in multiple bacterial genes associated with drug resistance (i.e. *rpoB* for rifampin); *M. bovis* is differentiated from *M. tuberculosis* based on pyrosequencing of the *pncA* gene.

What are the therapeutic implications if pyrazinamide cannot be used in the treatment of TB meningitis? Despite its potential toxicities, pyrazinamide is appealing as a part of CNS TB treatment given its good CNS penetration. The impact of omitting pyrazinamide is not entirely clear in the context of 9-12 months of TB meningitis therapy, though its use has been associated with improved outcomes. In our case, identification of *M. bovis* through pyrosequencing prompted modification of her treatment regimen to include linezolid, an alternative drug with good CNS penetration, although limited published experience in TBM. Additional TB drugs known to have good CNS penetration include isoniazid and fluoroquinolones, both of which were included in her treatment, along with the more poorly-tolerated second-line drugs cycloserine and ethionamide. The role for newer TB drugs such as bedaquiline and delamanid in TB meningitis remains to be defined, though CSF concentrations may be low for both. Despite promising initial studies, the addition of a fluoroquinolone has not been shown to
confer a mortality benefit in TBM.\textsuperscript{27–29} Whether there is a benefit to incorporating a fluoroquinolone or an alternative agent with good CNS penetration into TB treatment regimens when pyrazinamide cannot be used remains uncertain.

In addition to drug choice, drug dosing remains an important consideration in the management of TB meningitis.\textsuperscript{30} Rifampin has garnered the greatest attention in this regard\textsuperscript{31} based on animal models suggesting greater efficacy with higher rifampin dosing. Although Ruslami and colleagues found that a two week course of intravenous rifampin (13 mg/kg) was associated with reduced mortality compared to standard dosing of oral rifampin (10mg/kg),\textsuperscript{29} a similar mortality benefit was not seen with higher dose oral rifampin (15mg/kg) in Vietnam.\textsuperscript{27} However, there is ongoing interest in studying even larger doses of rifampin for both pulmonary and meningeal TB.\textsuperscript{32,33}

The optimal duration of therapy for pan-susceptible TB meningitis remains a matter of debate, with current US guidelines recommending 9-12 months duration.\textsuperscript{34} This uncertainty is reflected by the variation observed in clinical practice globally; for example, nearly half of clinicians in one Indian study preferred to treat for 18 months.\textsuperscript{35} It is uncertain whether treatment beyond 12 months has a role in the setting of pyrazinamide mono-resistance.

Despite the availability of effective antimicrobial agents, patients with TB meningitis remain at risk for paradoxical worsening on therapy\textsuperscript{36} (labeled as IRIS or immune-reconstitution inflammatory syndrome in HIV+ patients) and severe complications such as vasculitis leading to ischemic stroke, which may be driven by a pathologic immune response.\textsuperscript{37} Consequently there has been considerable interest in the use of adjunctive host-directed therapies in tuberculosis.\textsuperscript{38} Corticosteroids have been shown to improve mortality,\textsuperscript{13} whereas aspirin may reduce the risk of stroke.\textsuperscript{14,15} The optimal dosing of aspirin remains uncertain and is an area of ongoing study;\textsuperscript{39} we
chose to treat the case patient with 162 mg/day of aspirin to approximate the 150mg/day dosing used by Misra and colleagues. It is not clear whether corticosteroids and aspirin have similar benefit in cases of CNS *M. bovis* infection, though it seems reasonable to consider their use as is more generally recommended in TB meningitis.

In one retrospective case series conducted in Mexico, CNS *M. bovis* infection was associated with worse outcomes compared to *M. tuberculosis*, including increased frequency of tuberculomas and neurological sequelae. Whether these differences in outcomes are due to differences in species virulence or immune response, or instead reflect antimicrobial regimens of differing potency is not clear. While our patient’s disseminated *M. bovis* infection was complicated by meningitis, tuberculomas, and stroke, to date she has not had additional neurologic complications in the context of a treatment strategy employing drugs with good CNS penetration such as linezolid and levofloxacin, as well as adjunctive corticosteroids and aspirin. Further study is needed to clarify optimal therapy for *M bovis* and pyrazinamide-resistant TBM more generally.
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K.C. and J.S. participated in the literature review and production of the manuscript.

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Conflicts of Interest

No author has any potential conflict of interest related to this article.

Patient Consent Statement

Our article does not include factors necessitating patient’s written consent. No human subjects experiments were conducted related to this case report, therefore approval by local ethical committees was not indicated.
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Figure 1 Legend:

Contrast-enhanced CT imaging on presentation demonstrating tuberculomas (arrows) in the left frontal lobe and left cerebellar vermis.

Figure 2 Legend:

Diffusion-weighted image (DWI) MRI sequence demonstrating acute ischemic infarct affecting the right basal ganglia. Areas of restricted diffusion were visualized in the right corona radiata, posterior limb of the internal capsule, and putamen, as well as left anterior centrum semiovale.
Figure 2