Successful Treatment of a Child With Extensively Drug-Resistant Tuberculous Meningitis

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Unlike in pulmonary multidrug-resistant (MDR) tuberculosis, the clinical outcome of MDR tuberculous meningitis (TBM) in children, including extensively drug-resistant tuberculosis, is poor and management is challenging. We report the successful treatment of a case of extensively drug-resistant TBM in a 4-year-old girl, and we discuss implications for tuberculosis diagnosis and chemotherapy.

Key words. extensively drug-resistant; linezolid; treatment; tuberculous meningitis; Western Cape.

BACKGROUND

The World Health Organization (WHO) estimated 480,000 incident cases of multidrug-resistant (MDR) tuberculosis (TB) (ie, resistant to both isoniazid and rifampin) worldwide in 2013; 9% of these were estimated to be extensively drug-resistant (XDR-TB; ie, MDR with additional fluoroquinolone and second-line injectable resistance) [1]. Tuberculous meningitis (TBM), a serious form of extrapulmonary TB in young children, is associated with high morbidity and mortality; therefore, early effective treatment is essential. Among children with TBM, MDR is associated with increased risk of unfavorable outcome, including death [2]. We report a child successfully treated for XDR-TBM.

CASE

In 2011, a 4-year-old girl presented to her primary healthcare clinic with a 3-week history of fever, abdominal discomfort, worsening headache, periorbital edema, and vomiting. Her past medical history was unremarkable; she was human immunodeficiency virus-uninfected and had been vaccinated with bacille Calmette-Guerin. No TB exposure was identified. After transfer to a tertiary hospital, she developed left-sided weakness and left facial palsy. On examination, she was drowsy, had neck stiffness, and had a left hemiparesis. Cerebrospinal fluid (CSF) sampling showed lymphocytes 100/mm3, polymorphonuclear cells 40/mm3, protein 2.2 g/L, and glucose 1.8 mmol/L. A computed tomography (CT) scan showed meningeal enhancement, multiple ring-enhancing lesions, multiple infarcts in the right basal ganglia, and hydrocephalus. An air encephalogram showed communicating hydrocephalus; therefore, a ventriculoperitoneal shunt was not placed. Mantoux tuberculin skin test measured 20 mm induration, chest radiography was normal, and 2 gastric aspirates and CSF were negative for acid-fast bacilli (AFB) on smear microscopy and culture-negative for Mycobacterium tuberculosis (M tuberculosis). Xpert MTB/RIF was not available at the time. The diagnosis of probable TBM was made, and TB treatment started with intended dosages (approximated due to tablet size) of 20 mg/kg isoniazid (INH), 20 mg/kg rifampin (RIF), 40 mg/kg pyrazinamide (PZA), and 20 mg/kg ethionamide (ETO). A total of 2 mg/kg prednisolone was given for 4 weeks and then tapered over 2 weeks. Figure 1 summarizes the chemotherapy throughout the course of treatment. She was transferred to a local TB hospital for long-term management.

Two months after commencing TB treatment, raised liver enzymes were noted with an alanine aminotransferase
peak serum concentration of 244 U/L. Hepatitis A serology was negative. In view of presumed drug-induced hepatitis, INH, RIF, PZA, and ETO were stopped and a more liver-friendly regimen was started, consisting of approximated dosages of ofloxacin (OFX) 20 mg/kg, terizidone (TZD) 20 mg/kg, amikacin (AMK) 20 mg/kg, and ethambutol (EMB) 20 mg/kg. Ofloxacin was the only fluoroquinolone available through the TB program at the time.

A few days later, the patient developed vomiting and ataxia. A CT scan of the brain showed progressive meningeal enhancement and worsening hydrocephalus; a ventriculoperitoneal shunt was inserted. By this time, ALT (44 U/L) had normalized; the initial TBM regimen was re-started excluding PZA, and liver-friendly anti-TB medications apart from TZD were discontinued (Figure 1).

In the following months, the patient improved clinically, with steady weight gain and resolving left hemiparesis, but she had persistent ataxia. Five months after treatment initiation, she was transferred to a convalescent center to complete treatment. Treatment was directly observed in hospital throughout the entire course. After completing a total of 7 months of chemotherapy, the patient was discharged home in good clinical condition.

Three weeks after discharge, she presented again with a 2-week history of headache and abdominal distension. On clinical examination she was pale, had abdominal distension, hepatosplenomegaly, aphasia, and was unable to walk due to recurring left hemiparesis. A repeat CT scan of the brain showed progression of the hydrocephalus and new lesions suggestive of tuberculomas in the brain stem. Cerebrospinal fluid changes were again suggestive of TBM: white blood cells of 15/mm³, protein 3 g/L, and glucose 2.3 mmol/L. Abdominal ultrasound showed loculated ascites with fibrinous strands. The ventriculoperitoneal shunt was removed and replaced by a ventriculopleural shunt. Cerebrospinal fluid, induced sputum, gastric aspirates, and ascitic fluid were sent for culture. The ascitic fluid sample was AFB-positive on microscopy and culture-positive for M tuberculosis. Drug susceptibility testing (DST) with line probe assay (GenoType MTBDRplus; Hain Lifescience, Nehren, Germany) revealed resistance to RIF and INH, the latter with both inhA promoter region and katG gene mutations. The patient was initially started on MDR-TBM treatment with intended dosages (approximated) of 40 mg/kg PZA, 25 mg/kg EMB, 20 mg/kg ETO, 20 mg/kg AMK, 20 mg/kg OFX, 20 mg/kg TZD, and 150 mg/kg para-aminosalicylic acid (PAS) given once daily. One month later, phenotypic DST results showed resistance to AMK, OFX, EMB, and streptomycin, but susceptibility to ETO.

Subsequently, AMK was replaced by capreomycin 20 mg/kg and OFX was replaced by levofloxacin 20 mg/kg.
EMB concentrations would likely have been low [3], and have achieved effective concentrations, but AMK and drug penetration. Ofl oxacin and TZD could possibly have achieved effective concentrations, but AMK and EMB concentrations would likely have been low [3], and TZD alone may not have been sufficient to protect OFX from acquiring resistance. Extensively DR-TB bacilli from CSF could potentially have passed through the ventriculoperitoneal shunt causing abdominal TB, where XDR M tuberculosis was cultured from the ascitic fluid.

Regardless of the actual source of her XDR-TB, this case demonstrates the importance of obtaining bacteriologic confirmation of M tuberculosis to allow for DST, particularly in settings with a high burden of DR-TB. Although confirming a diagnosis is challenging in children who frequently have paucibacillary disease, sampling multiple sites, as in this case, can increase the yield. If a culture is obtained, DST should be done; if first-line drug resistance is found, second-line DST should be done when possible. Without culture confirmation of XDR-TB, this child may have had a poor outcome, because she had no known XDR-TB exposure and therefore the diagnosis was not suspected. Linezolid has good anti-TB action and penetrates the CSF well. Although linezolid was the most important component of her treatment, it would not have been used empirically because of cost in this setting. Therefore, she would likely have failed treatment with a standard MDR treatment regimen in the absence of linezolid.

The outcomes of MDR-TBM described in the literature are poor [2]. Management of DR-TBM should consider the CSF penetration of anti-TB drugs. The aminoglycosides and EMB have poor CSF penetration [3]. Ethionamide has good CSF penetration, but it may be ineffective in M tuberculosis isolates with inhA promoter region mutations. Fluoroquinolones have good bactericidal activity and moderate CSF penetration, but they may not be effective in XDR-TB. Terizidone or cycloserine, although only bacteriostatic, have good CSF penetration and no known cross-resistance with other TB drugs and are therefore an attractive option in the treatment of DR-TBM [3]. Para-aminosalicylic acid may be important in DR-TBM if given as single, daily high-dose treatment to achieve reasonable CSF concentration.

Despite the prolonged treatment course and large number of medications, including WHO Group 5 drugs linezolid and clofazimine, this patient’s adverse effects were few, mild, and reversible. Notably, linezolid given twice daily for 18 months at 10 mg/kg per dose was well tolerated with the exception of mild anemia, possibly related to linezolid. Previous studies have shown that linezolid is associated with a good clinical outcome in difficult-to-treat cases of DR-TB in children [4]. We believe it was key to the successful treatment of this child. Linezolid is likely the most effective drug available in MDR-TBM cases also resistant to the fluoroquinolones and should be included in the regimen when this diagnosis is confirmed or suspected [4]. The clinical experience with clofazimine in childhood TB is limited; however, studies in adults...
suggest that treatment-limiting adverse effects are uncommon and treatment outcome in pulmonary XDR-TB is improved [5].

CONCLUSIONS
In conclusion, our case showed that with aggressive individualized treatment and close supportive care, children with XDR-TBM can be successfully treated.

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References