Case Report: Congenital Transmission of Multidrug-Resistant Tuberculosis

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Abstract. This article presents a case of multidrug-resistant tuberculosis (TB) in a Peruvian infant. His mother was diagnosed with disseminated TB, and treatment commenced 11 days postpartum. The infant was diagnosed with TB after 40 days and died at 2 months and 2 days of age. Congenital transmission of TB to the infant was suspected, because direct postpartum transmission was considered unlikely; also, thorough screening of contacts for TB was negative. Spoligotyping confirmed that both mother and baby were infected with identical strains of the Beijing family (SIT1).

INTRODUCTION

Tuberculosis is relatively common in pregnant women, and although rare, vertical transmission carries a poor prognosis, especially where multi-drug resistant tuberculosis (MDR-TB) is involved. Diagnosis is challenging because of non-specific manifestations and clinical overlap with common neonatal conditions, and diagnostic delays are common. A high index of suspicion and prompt treatment are, therefore, critical.

Pregnancy creates a state of physiological immunosuppression, and tuberculosis (TB) in pregnant women is relatively common.^{1,2} The placenta forms an effective barrier to bacterial penetration, and vertical transmission of TB to the infant is rare, with postpartum transmission occurring far more frequently.³ However, when vertical transmission of TB does occur, prognosis is poor, with reported mortality rates of 50% and 22% in untreated and treated infants, respectively.⁴ Initiation of treatment is recommended immediately after diagnosis is suspected without waiting for laboratory confirmation. Non-specific clinical manifestations in neonates and asymptomatic or undiagnosed maternal infection can, however, lead to significant diagnostic delays, and such delays have been associated with worse clinical outcomes. A high index of suspicion is, therefore, critical.

We present a case of probable congenitally acquired multidrug-resistant TB in a Peruvian infant and explore the challenges in diagnosis and management of congenital TB in settings with high rates of circulating multidrug resistance in the community.

CLINICAL CASE PRESENTATION

A 22-year-old woman with no significant past medical history presented during her first pregnancy. She had attended four of six routine antenatal appointments recommended by national guidelines. In the final month of pregnancy, she had experienced some dyspnea on moderate exertion, which she attributed to the pregnancy; there had been no other complications. Her son was born by vaginal delivery at full term, weighing 3.140 kg. The baby did not receive a Bacillus Calmette–Guérin (BCG) vaccine. He remained hospitalized

with bronchopneumonia, which was treated with amikacin and ampicillin, and was discharged after 7 days.

The mother was initially discharged home but presented to the hospital 2 days after delivery complaining of cough and epigastric and retrosternal pain of moderate severity. She was pyrexial at 40°C, and breath sounds were reduced in the left lung base. Chest radiography showed bilateral infiltrates consistent with military TB and a left-sided pleural effusion (Figure 1). Three sputum samples were negative for acid and alcohol fast bacilli (AAFBs). Abdominal ultrasound showed multiple gallstones, and she was treated empirically for cholangitis with ampicillin and gentamicin. However, she failed to adequately respond, and on day 11 post-delivery, she commenced standard first-line anti-TB chemotherapy comprising rifampin, isoniazid, pyrazinamide, and ethambutol. She was discharged home on day 15 but returned two days later with dyspnea on moderate exertion. A human immunodeficiency virus (HIV) test was negative, and AAFBs were not detected from feces or urine; however, sputum microscopy was positive for TB (paucibacillary: 2 AAFBs seen), and sputum culture was also later positive (two colonies detected). There was insufficient growth for drug susceptibility testing to be performed. She was commenced on steroids, and anti-TB treatment was continued. Despite this treatment, she remained febrile, and on day 28, she developed deranged liver function tests (Gamma GT 740 U/L, ALT 375 U/L, ALP 454 U/L). An adverse drug reaction was suspected, and her treatment regimen was modified to ciprofloxacin, cycloserine, streptomycin, and ethambutol. On day 36, ciprofloxacin was changed to levofloxacin, and a rifampin challenge was initiated.

The baby, meanwhile, had been at home with his father and grandmother, and he developed rhinorrhea, cough, fever, and difficulty in breathing. He joined his mother in the hospital at age 40 days, and he had a respiratory rate of 64 breaths/minute, prolonged expiration, wheeze on chest auscultation, and a distended abdomen with hepatomegaly (6 cm liver edge). Weight was 3.930 kg. Blood tests showed a leukocytosis (white blood cell [WBC] = $13.200 \times \text{millimeter}^3$, neutrophils = 43%, band neutrophils = 14%) and elevated C-reactive protein (348 mg/L). Chest X-ray showed bilateral pulmonary opacification with right-sided predominance, causing partial obscuration of the pericardiac border with a negative cardiac silhouette sign (Figure 2). Cerebrospinal fluid (CSF) analysis revealed elevated leukocytes (60 cells/mm^3 , 39% mononuclear cells, 61% neutrophils; reference range for infants born at term⁵ = 0–22 WBCs/mm³), mildly elevated

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FIGURE 1. Chest X-ray of the mother on readmission 2 days post-delivery.

protein (196 mg/dL; reference range = 20–170 mg/dL), normal glucose (48 mg/dL; reference range = 34–119 mg/dL), and elevated adenosine deaminase (ADA; 13.5 U/L; reference range = 0–9 U/L). The CSF was negative for AAFBs. Microscopy for AAFBs in urine, stool, and gastric aspirate was positive (++), which prompted initiation of first-line anti-TB therapy with rifampin, isoniazid, pyrazinamide, and ethambutol in addition to ceftriaxone, salbutamol, and prednisone. Ethambutol was substituted with streptomycin after 2 days. The abdominal distension increased, and an abdominal ultrasound scan showed distended bowel loops and ascites. A sample of gastric fluid was sent for rifampin and isoniazid sensitivity testing using the Microscopic Observation Drug Susceptibility (MODS) assay. On day 9, a mucopurulent ear discharge was noted, which was also AAFB-positive (+++). The infant became increasingly dyspnoeic and distressed, and oxygen saturations fell to 84% on air. Vancomycin and meropenem were commenced to cover for bacterial sepsis; however, the baby died at 2 months and 2 days of age. The

FIGURE 2. Chest X-ray of the infant at age 40 days showing bilateral pulmonary opacification with right-sided predominance, causing partial obscuration of the pericardiac border with a negative cardiac silhouette sign.

MODS assay result was reported on the day of the baby's death (12 days after the sample had been sent) as TB resistant to both isoniazid (0.4 µg/mL) and rifampin (1.0 µg/mL).

The mother remained hospitalized with a diagnosis of disseminated TB: in addition to miliary TB in the lungs, TB choroiditis was detected on fundoscopy, and intestinal TB was diagnosed after abdominal ultrasound. After MDR-TB had been detected in her baby, she was commenced on para-aminosalicylic acid (PAS), ethambutol, cycloserine, levofloxacin, and kanamycin, and sputum was processed using the MODS assay, which confirmed resistance to isoniazid (0.4 µg/mL) and rifampin (1.0 µg/mL). At day 66, she complained of headache and a tingling sensation in the right side of her body. A lumbar puncture was performed, and CSF examination was compatible with TB meningoencephalitis. The patient's headache worsened, and she required placement of a ventriculoperitoneal shunt for hydrocephalus.

Thorough intradomestic contact, screening for TB was performed. None of the contacts reported any clinical symptoms consistent with TB, including fever, cough, or night sweats. The baby had been living with his father and grandmother, who underwent sputum microscopy and chest X-rays, which were negative. The baby's aunt and her three sons, all under the age of 10 years, had visited frequently and were also screened. The aunt had a normal chest X-ray, and her sons underwent para-aminosalicylic acid (PPD) testing, of which one son was positive and two sons were negative. Additional questioning elicited that, 2 years previously, the mother's ex-partner had a close friend who had been diagnosed with pulmonary TB; there had been no known contact with persons with proven or suspected TB since that time.

Spoligotyping was performed using the initial strains obtained from both the mother and baby, which showed that both were infected with genetically identical strains of the Beijing family (SIT1). The baby's strain underwent additional testing for sensitivity to second-line drugs, showing additional resistance to streptomycin, kanamycin, and capreomycin. Susceptibility testing to second-line drugs had not been possible for the mother's initial strain, because there had been insufficient growth; however, as described, testing of a later sputum specimen using the MODS assay showed rifampin and isoniazid resistance.

DISCUSSION

Congenital TB occurs when there is maternal TB bacteremia or disseminated TB involving the genital tract and/or placenta. Infants are believed to be infected by hematogenous spread through the umbilical vein or after fetal ingestion or aspiration of infected amniotic fluid.⁶ Diagnostic criteria were initially described in 1935⁷ and updated in 1994.⁶ These criteria require proven TB lesions in the infant plus one or more of (1) lesions occurring in the first week of life, (2) a primary hepatic complex, (3) maternal genital tract or placental TB, and/or (4) exclusion of post-natal transmission by thorough investigation of contacts.

Differentiating congenitally from neonatally acquired TB can be difficult. In this case, TB was isolated from both the infant and his mother, and both had been symptomatic in the week after delivery. The mother's infection was disseminated, involving several organ systems, and thus, it plausibly also included the genital tract or placenta, presenting a possible

mode of infection. Because serial sputum microscopy had been negative and her first positive specimen taken more than 2 weeks later had been paucibacillary, airborne transmission from the mother to the baby is unlikely. In addition, mother and baby had spent very little time together after the birth, the neonate had no known contact with other persons with TB, and thorough contact screening had been negative. Therefore, the likelihood of him acquiring and developing active TB in such a short time interval is low, and vertical transmission is probable.

We were unable to find any published reports of congenitally acquired MDR-TB. This case highlights the importance of maintaining a high index of suspicion for TB. It commenced with symptoms of isolated mild dyspnea on exertion during an uneventful pregnancy in an apparently healthy 22-year-old woman and ended with multiorgan complications requiring intense treatment regimens with second-line agents and neurosurgical intervention as well as the death of her baby at 2 months of age. Whereas the mother's TB treatment was initiated fairly early in the course of her disease after chest X-ray changes, diagnosis in the infant took much longer; TB treatment was not initiated until multiorgan involvement and atypical X-ray changes had developed and AAFBs had been observed, despite the mother having already received TB treatment for 3 weeks by the time that she was hospitalized.

Treatment of TB during pregnancy acts as a preventative measure and is widely recommended, because the risks of teratogenicity are considered to be outweighed by the benefit of treatment to both the mother and the child. Current recommendations are that pregnant women are treated with non-teratogenic drugs where possible. Peruvian guidelines state that first-line drugs should be used throughout pregnancy and that second-line injectables can be used from the second trimester or even before after a risk-benefit evaluation and the patient's informed consent.

Diagnostic delays in pregnant women can occur because of late presentation to antenatal services; the non-specificity of symptoms, which, as in this case, can be confused for the normal physiological state of pregnancy; poor prenatal care; and delays in obtaining radiographic studies.⁸⁻¹⁰ Of pregnant women with TB, 17% are diagnosed in the first trimester, 31% are diagnosed in the second trimester, 3% are diagnosed in the third trimester, and 22% are diagnosed after delivery.¹¹

Diagnosis of TB in the neonate can be even more challenging. Clinical manifestations are non-specific and often mistaken for signs of more common conditions that can present in the neonatal period, including sepsis and other infections.¹² In addition to systemic symptoms, manifestations can include ascites, isolated otitis, lymphadenitis, facial nerve palsy, and TB of the spine.¹³⁻¹⁷ Infected mothers are often undiagnosed at presentation, and diagnosis of the newborn often prompts a search for the illness in the mother rather than the reverse: in a review of 32 cases of congenital TB, 24 of the mothers were asymptomatic.¹⁸ Diagnostic delays are such that there have been reports of diagnosis occurring up to 3 months post-delivery,¹⁹ and in a review that included 300 cases of congenital TB, the median age at diagnosis was 24 days (range = 1-84 days).¹

Because it is so rare, there have been no therapeutic trials to determine the optimal treatment of congenitally acquired TB, and it is recommended that these infants receive the same treatment as infants infected after birth. Treatment in chil-

dren is similar to treatment of adults, comprising an intensive phase followed by a continuation phase, with MDR-TB cases falling under Diagnostic Category IV and requiring second-line drugs.²⁰ Although the optimal duration of therapy has not been established, many experts treat infants with congenitally or post-natally acquired TB for 9-12 months because of the low immunologic capability of young infants.²¹

The outcomes in this case may have been particularly poor, because the neonate's symptoms at birth were initially attributed to bronchopneumonia and treated with amikacin, a bactericidal agent that is used against *Mycobacterium tuberculosis*, which could have masked the natural progression of the disease. In addition, as in adults, the presence of a multidrug-resistant strain of TB is a poor prognostic indicator. In a cohort of 27 pregnant women who received treatment for TB, 16 women had drug-resistant disease, and rates of adverse outcomes were higher among children born to the women with MDR-TB than the children born to the women with drug-susceptible strains (6 of 16 children and 2 of 11 children, respectively).²² Even when MDR-TB is detected in the mother before or during pregnancy, its treatment may be suboptimal or delayed. Although aggressive treatment is recommended in pansusceptible TB, because the benefit of treatment is considered to outweigh the risk of fetal damage, in MDR-TB, fear of teratogenicity associated with second-line drugs can lead physicians to err on the side of caution and undertreat pregnant patients, despite this fear being largely based on insufficiency of data rather than compelling evidence of toxicity. A case series²³ of seven pregnant women with MDR-TB, also in Lima, reported modified treatment regimens in six patients; the seventh woman was on an individualized regimen for treatment failure at the time of pregnancy. In this series, all babies were born were term, and there were no peripartum or neonatal complications. Drobac and others²⁴ found no significant evidence of toxicity in six children, with an average age of 3.7 years, who had been exposed to second-line agents *in utero*. In a 10-year retrospective cohort of 38 women treated for MDR-TB,²⁵ 61% of the mothers were cured, 13% of the mothers died, 5% of the mothers had treatment failure, 13% of the mothers discontinued treatment, and 5% of the mothers remained on treatment. Clinical deterioration of TB during pregnancy occurred in four women, five pregnancies ended in spontaneous abortion, and one child was stillborn; among the live births, three children were born with low birth weight, one child was born pre-maturely, and one child suffered fetal distress. The study concluded by advocating continuation of treatment of MDR-TB throughout pregnancy.²⁵ In the case presented above, if the mother had been diagnosed and treated for MDR-TB during pregnancy, she may not have experienced systemic dissemination and complications from her TB, and the baby would have had a better chance of survival.

Because a congenitally infected infant will harbor the same strain as the mother, treatment of MDR-TB should be commenced when the mother is known or suspected to have MDR-TB based on either personal risk factors or being in settings of high levels of circulating resistant strains. Peru has the third highest incidence of TB in the Americas after Haiti and Bolivia,²⁶ with 32,477 cases diagnosed in 2010, giving an incidence of 96.1 cases per 100,000 people; 908 of these cases were in children 0-9 years old, and 226 of these cases were in pregnant women. There were 1,094 cases of multidrug-resistant

TB (3.4%), including 315 cases of extensively resistant TB (1.0%).²⁷ It would, therefore, be reasonable in this setting to have a high index of suspicion for MDR-TB in the infant. Testing for MDR-TB is not widely performed, and there is likely to be significant underreporting, meaning that cases of congenital MDR-TB may be going unnoticed. It is imperative to screen pregnant women for TB, treat those women found to be infected, and evaluate babies born to infected mothers for the possibility of congenitally acquired TB. Susceptibility testing should be performed as part of the universal screening for MDR-TB, and contact tracing is vital, not only intradomestic but also within the community.

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