CONGENITAL TRANSMISSION OF MULTIDRUG-RESISTANT TUBERCULOSIS: CASE REPORT

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ABSTRACT
This article presents a case of multi drug-resistant congenital tuberculosis (TB) in an infant. His mother was diagnosed with disseminated TB and treatment commenced 26 days postpartum. The infant was diagnosed with TB after 46 days and died at 2 months and 16 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. The importance of early diagnosis and treatment is crucial in considering non specific nature of presentation and high mortality associated with it.

Keywords: Multidrug-Resistant Tuberculosis

INTRODUCTION
Tuberculosis (TB) is a global public health problem, India and China together account for almost 40 per cent of the world’s TB (Global tuberculosis Report, 2012). Congenital infection by vertical transmission is rare with only 358 cases reported till 1995 and another 18 cases reported from 2001 to 2005 (Hassang et al., 2006). High neonatal mortality (up to 60%) and morbidity warrant early diagnosis and treatment of newborns suffering from TB. Existing guidelines for management of the newborns delivered to mothers with TB are variable and have no uniform consensus.

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 (Ormerod, 2001; Margono et al., 1994). 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 (Hassan et al., 2006). 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 (Patel and DeSantis, 2008). 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 an infant and explore the challenges in diagnosis and management of congenital TB in settings with high rates of circulating multi drug resistance in the community.

CASES
A 46 day old male infant was admitted in PBM hospital Bikaner, Rajasthan on 29 March, 2016 with a history of difficulty in respiration, fever, cough, poor feeding, and suck rest cycle during feeding, excessive cry, abdominal distension and failure to gain weight since 15-16 days. He was born at 38 weeks of gestation at private hospital, Ganganagar, Rajasthan to a 23-year-old primi mother. His birth weight was 2.5 kg. The infant was immunized and partially breast fed since birth, but on top milk since 20 days in view of her mother’s admission for extensive tubercular bronchopneumonia. On examination, he was pale, lethargic and weighed 2.8 kg. He had respiratory distress with chest recessions, bilateral crepitations...
and hepatosplenomegaly and dextrocardia. Other systems were essentially normal. Investigations revealed hemoglobin of 9.4 gm%, total leucocyte counts of 17,300/cumm with 46% polymorphs, 40% lymphocytes, ESR -07, CRP positive, and peripheral smear was suggestive of normocytic normochromic anaemia. Chest radiograph showed severe bronchopneumonic changes suggesting military mottling of both the lungs and dextrocardia. Mantoux test was positive (15mm) and gastric aspirates for AFB was positive. Ultrasound revealed hepatosplenomegaly with multiple hypoechoic hepatic foci and enlarged portal lymph nodes. CBNAAT (cartridge based nucleic acid amplification technique) was positive of both mother and child and showed rifampicin resistance. Both mother and infant were anti-HIV antibody negative. Two consecutive sputum tests of mother were negative for AFB smear and culture. A diagnosis of congenital tuberculosis was implied and he was started on isoniazid, rifampicin, pyrazinamide, streptomycin and meropenam along with vancomycin. He continued to deteriorate rapidly and additional management included injection aminophylline, furosemide and digoxin. Result of CBNAAT was positive in both mother and child, so 2nd line drugs of ATT were started, and never the less he expired after 1 month of admission. Biopsy from endometrium of mother showed typical tubercul granuloma confirming the source of infection and perinatal onset of this disease in the neonate. Now his mother is on 2nd line drugs of ATT and there is improvement in her condition, she is on regular follow up in TB and Chest department of our hospital.

DISCUSSION

Congenital TB occurs when there is maternal TB bacteremiaor 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 (Cantwell et al., 1994). Diagnostic criteria were initially described in 1935 (Beitzki, 1935) and updated in 1994 (Cantwell et al., 1994). 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 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 so airborne transmission from the mother to the baby is unlikely. In addition, 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.

Infection in such cases can be acquired through three different modes; transplacentally with primary complex in the liver, aspiration of infected amniotic fluid during passage through birth canal when lungs are primary focus and ingestion of infected material where the primary focus is in the gut. An infant infected intrauterino will present with hepatic or more disseminated disease while those infected during birth may present with pulmonary or miliary disease. Pathologically, the striking fact about the tubercular lesion is the lack of host response due to which most infants do not develop tuberculin sensitivity throughout their illness. Congenital tuberculosis is particularly difficult to diagnose since the non-specific presenting signs and symptoms (because of lack of host response). Infertility, poor reproductive performance, recurrent abortions, still births, premature rupture of membranes and preterm labour are known effects of tuberculosis in pregnancy. The foetus may have intrauterine growth retardation, low birth weight, and has increased risk of mortality. The median age of presentation of congenital TB is 24 days (range, 1 to 84 days). Clinical manifestations are non-specific and include poor feeding, fever, irritability, failure to thrive, cough, and respiratory distress. Examination reveals hepatosplenomegaly and abdominal distension. Lymphadenopathy lethargy, meningitis, septicemia, unresolving or recurrent pneumonia, disseminated intravascular coagulation, jaundice, ascitis, otitis media with or without mastoiditis, parotitis, osteomyelitis, paravertebral abscess, cold abscess, and papular or pustular skin lesions are other
known features. Apnea, vomiting, cyanosis, jaundice, seizures and petechiae have been reported in less than 10 per cent of cases (Bate et al., 1986). Clinical manifestations in neonates masquerade sepsis, prematurity, viral infections or other acute or chronic intrauterine infections and hence diagnosis is difficult and may be missed. Therefore, in the setting of poor response to antibiotics and supportive therapy, and negative results of microbiological evaluation and serological tests for acute and chronic intrauterine infections, TB should be suspected. Specimens from the neonate suitable for microscopy and culture include gastric aspirates, sputum (induced), tracheal aspirates (if mechanically ventilated), skin lesions, ear discharge, ascitic fluid, cerebrospinal fluid (CSF) and, pleural fluid (if present) for acid fast bacilli and cultured on standard egg based media for 12 wk. Bronchoalveolar lavage (BAL) is an important investigation and detection of Mycobacterium tuberculosis DNA in BAL fluid by polymerase chain reaction (PCR) is diagnostic in newborn. Liver or lymph node biopsy may be undertaken for histology and culture. Postmortem biopsies (e.g. liver, lung, nodes, and skin lesions) can also be done. Conventional light microscopy (Ziehl-Neelsen or Kinyoun stain) or fluorescence microscopy (auramine stain) are used for detection of mycobacterium. Chest radiography and computed tomography may show the presence of scattered infiltrates, bronchopneumonia, consolidation or periportal hypodensity which are non -specific. Mantoux test if possible is supportive evidence, but negative results do not rule out disease. Multiple and repeated investigations may be done in view of high suspicion. Newer methods: Slow and tedious conventional methods have been recently replaced by quicker methods. The WHO has accredited LED (light emitting diode) fluorescence microscopy and liquid based mycobacteria growth indicator tube (MGIT) in developed countries for fast results. Indirect methods include rapid interferon gamma assays, QuantiFERON-TB Gold assay and T-SPOT using antigens ESAT-6, CFP-10 and TB7 but have shown inconsistent results in newborn. Large trials using Gene Xpert (real time PCR) in children have been useful for rapid diagnosis in communities with a high burden of TB including multiple drug resistant (MDR) tuberculosis. Other mycobacteriophage-based assays like Fast Plaque TB-Rif, molecular line probe assays (LPAs) such as GenoType MTBDR plus assay and the Inno-LiPA Rif TB assay are costly and with only a few studies in newborns.

Maternal disease and therapy- Extra pulmonary, miliary and meningeal TB in mother are high risk factors for congenital TB in neonates. Vertical transmission from mothers with tubercular pleural effusion or generalized adenopathy does not occur. However, there is a lack of scientific literature regarding increased risk of congenital TB if mothers have resistant TB or concurrent HIV infection. Mothers who have completed anti tubercular treatment (ATT) before delivery or have received ATT for at least two weeks duration before delivery are less likely to transmit the disease to the newborn as compared to untreated mothers. Anti -tubercular drugs are found to be safe in pregnancy except streptomycin in the first trimester. No literature is available regarding the safety of second line anti-tubercular drugs used for resistant TB in pregnancy.

In case of maternal sickness or if mother is smear positive at the time of delivery or mothers with MDR TB, when breast feeding may not be possible, expressed breast milk feeding is an alternative, with personal hygiene. AAP recommends continued feeding with expressed milk in mothers with pulmonary TB who are contagious, untreated or treated (< 3 week) with isolation. WHO recommends feeding under all circumstances; however, close contact with the baby should be reduced. No specific treatment regimens for congenital tuberculosis are advised. Treatment includes isoniazid, rifampicin, ethambutol and kanamycin or amikacin for the first two months followed by isoniazid and rifampicin for 6-12 months or similar to miliary tuberculosis or isoniazid, rifampicin and pyrazinamide along with streptomycin and kanamycin for 9 to 12 months. Follow up - Neonates diagnosed and treated for congenital tuberculosis should be monitored while on therapy, but no details regarding the timing or the modes of monitoring exist. DOTS recommends chest X-ray at the end of treatment. American academy of Pediatrics suggested that infants receiving prophylaxis should have clinical surveillance (Snider and Bloch, 1984). Bacillus Calmettee Guerin (BCG) vaccination protects against the dissemination of tuberculosis and severe disease. In neonates with congenital tuberculosis there is no utility of BCG vaccine.
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Pediatrics advises BCG vaccination at birth to all neonates after excluding congenital tuberculosis even if chemoprophylaxis is planned.

Management of multidrug-resistant tuberculosis (MDRTB) in pregnancy is like a double-edged sword. On one hand, second line anti-tubercular drugs used for the treatment are potentially teratogenic, less effective, and more noxious; on the other hand, suboptimal treatment of such patients may be hazardous. Therefore, management of these patients involves multidisciplinary approach with the team comprising obstetrician, neonatologist, pulmonologist, and public health experts. Treatment regimens and duration of therapy for such patients need individualization in accordance with susceptibility pattern of infective strain. Therapy is usually delayed until second trimester in order to avoid teratogenic effect of the drugs unless patient is HIV positive or in critical condition. Favorable regimens for MDR-TB outside pregnancy are ethionamide, pyrazinamide, kanamycin, levofloxacin, ethambutol, and cycloserine during 6–9 months of the intensive phase and 4 drugs, levofloxacin, ethionamide, ethambutol, and cycloserine, during the 18–24 months of the continuation phase.

Conclusion

It concluded that infant had congenital tuberculosis based on the following: all of the contact were healthy and had negative screening tests, mother had tubercular granuloma in endometrial tissues and negative sputum smear for AFB. These factors exclude possibility of postnatal transmission and demonstrate in utero transmission. The frequency of congenital tuberculosis is probably under estimated. The clinician should be aware that congenital tuberculosis might present with unusual features. An improved screening of women at risk and sensitization of medical community is necessary. Hence, diagnosis of tuberculosis in mother is very important. However, extra pulmonary tuberculosis in child bearing women is associated with a high incidence of infertility due to genital tuberculosis and is said to be one of the reasons for low incidence of congenital tuberculosis.

REFERENCES