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ORIGINAL PAPER

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Connatal tuberculosis in an extremely low birth weight infant: case report and management of exposure to tuberculosis in a neonatal intensive care unit

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Abstract A case of connatal tuberculosis in an extremely low birth weight infant is reported. The patient was a female with a birth weight of 973 g born in the 27th week of pregnancy. She developed respiratory distress and signs of infection immediately after birth, which did not respond to mechanical ventilation, antibiotics, and corticosteroid therapy. Connatal tuberculosis was confirmed at 48 days of age by isolation of *Mycobacterium tuberculosis* from the infant's tracheal aspirate and the mother's menstrual discharge. The infant died of respiratory failure at 90 days of age. Mantoux tuberculin skin tests (TST) were performed on 99 infants, 144 medical staff members, and two family members. TST conversion occurred in three medical staff members, and preventive therapy with isoniazid was initiated. Eight exposed infants had normal chest X-rays and negative gastric aspirates for acid-fast bacilli and all received preventive isoniazid therapy. No case of tuberculosis developed during the 2-year follow-up period.

Conclusion Connatal tuberculosis should be considered in neonatal respiratory infection resistant to antibiotics. Prevention of transmission of tuberculosis on the neonatal intensive care unit by chemoprophylaxis is important.

Key words Extremely low-birth weight infant · Neonatal intensive care unit · Neonatal tuberculosis · Respiratory distress

Abbreviations *IMV* intermittent mandatory ventilation · *NICU* neonatal intensive care unit · *TST* tuberculin skin test

Introduction

Signs of tuberculosis in neonates are non-specific and the mothers of such infants are often asymptomatic. This may result in a delayed diagnosis, leading to long periods of bacterial shedding without treatment or management to prevent secondary transmission. On the neonatal intensive care unit (NICU), an outbreak of tuberculosis may result in transmission not only to other infants and medical staff, but also to housekeeping and other personnel who enter the room or have contact with infant secretions. In an extremely low birth weight infant, connatal tuberculosis was diagnosed at 48 days of age; the infant died of respiratory failure despite antituberculosis chemotherapy.

Case report

A Japanese woman aged 27 years, gravida 1, para 0, developed fever, diagnosed as interstitial pneumonia in the 8th week of pregnancy. The Mantoux tuberculin skin test (TST) with 2.5 tuberculin units of purified protein derivative was negative. Both culture and PCR for *Mycobacterium tuberculosis* in her sputum were negative. Since pulmonary tuberculosis was ruled out, corticosteroid pulse therapy was initiated. In the 27th week of preg-

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nancy, an emergency caesarean section was performed because of fetal distress. The infant was a female with a birth weight of 973 g; the Apgar scores were 2 and 5. Neither the liver nor the spleen were enlarged. Because of grunting, retraction, and cyanosis, an endotracheal tube was inserted, assisted ventilation was begun, and the infant was admitted to the NICU. Laboratory examination revealed leucocytosis (26400/μl), but the CRP was normal. A diagnosis of respiratory distress syndrome was made based on a chest X-ray.

At 4 days of age, artificial ventilation was discontinued. However, because of recurrent apnoea intermittent mandatory ventilation (IMV) was reinitiated at 13 days of age; antibiotics were given because of elevation of the CRP to 2.3 mg/dl. Despite several courses of antibiotic therapy, the patient's respiratory status deteriorated and increasing respiratory support became necessary. The chest radiograph revealed severely decreased lung volumes (Fig. 1). These findings suggested bronchopulmonary dysplasia and administration of dexamethasone (0.5 mg/kg per day) was started at 40 days of age. However, the patient's respiratory status continued to decline and the CRP reached 20 mg/dl at 48 days of age. Congenital syphilis, cytomegalovirus infection and human immunodeficiency virus infection were ruled out by serological tests. Smear samples from tracheal and gastric aspirates at 48 days of age revealed Ziehl-Neelsen-stained acid-fast bacilli. *M. tuberculosis* was identified by PCR and culture of the same samples. The strain was sensitive to isoniazid, rifampicin, streptomycin, pyrazinamide, and ethambutol. There were no abnormal findings in the CSF with negative culture for *M. tuberculosis*. The Mantoux TST with 2.5 tuberculin units of purifed protein derivative was negative. Dexamethasone was discontinued and oral isoniazid (15 mg/kg per day), rifampicin (15 mg/kg per day), and pyrazinamide (20 mg/kg per day), and intramuscular injection of streptomycin (30 mg/kg every other day) were started. Although the CRP decreased to 4 mg/dl at 60 days of age, smear samples from tracheal aspirates consistently showed acid-fast bacilli until the end of the clinical course. At 75 days of age, the chest X-ray revealed giant bullae. The patient developed respiratory failure which was resistant to 100% oxygen, IMV, and high-frequency oscillation and died of respiratory failure at 90 days of age. All TST performed during the clinical course were negative.

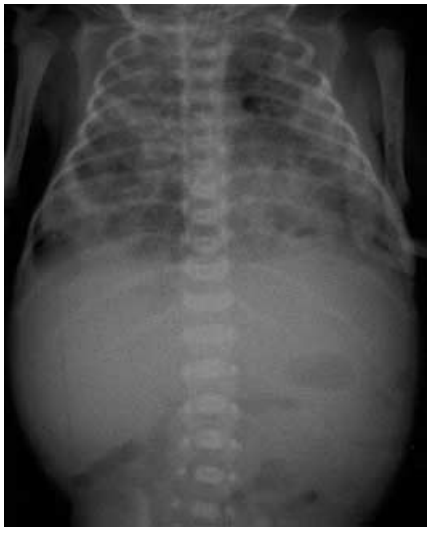

Fig. 1 Chest X-ray film taken at 40 days of age

Management of exposure to tuberculosis

After *M. tuberculosis* was detected, the patient was isolated in a single room equipped with an independent air conditioning system and negative air pressure. Medical staff and the patient's family wore special masks and disposable gowns for prevention of secondary infection with hand washing with povidone iodine and 70% ethanol before entry and after leaving the room. There were eight infants in closed incubators on the NICU during the period of hospitalisation of the patient. TST were negative and chest radiographs were normal in all infants. Preventive therapy with isoniazid was started. After 3 months of prophylaxis, TST and chest radiology were performed; no abnormal findings were obtained. *M. tuberculosis* was not isolated from gastric aspirates in any of the infants. Two months later, additional TSTs were again negative. There were 91 infants in the continuing care unit adjacent to the NICU. This unit had an independent air conditioning system. Of the 91 infants, 90 underwent TST at our hospital 1 month after exposure and at regional health care centres 4 months after birth. The one remaining infant underwent TST at a regional health care centre 4 months after birth. All test results were negative. All the infants on the NICU were followed for development, growth, and physical findings, as were all the infants in the continuing care unit. In the 2-year period following exposure, no patients developed tuberculosis. All 144 medical staff members involved in this case, including doctors, nurses, aides, sales representatives, medical students, and nursing students, underwent chest X-rays and TST. No abnormal findings were revealed on chest X-ray films. On TST, three staff members became positive after contact with the patient and received isoniazid. In the 2-year period following exposure, no medical staff members developed tuberculosis.

PCR and culture for *M. tuberculosis* from the tracheal aspirate of the patient's mother at 2 and 3 months after delivery were negative. However, *M. tuberculosis* was found in her menstrual discharge 2 months after delivery. The strain was sensitive to isoniazid, rifampicin, streptomycin, pyrazinamide, and ethambutol. These results suggested tuberculous endometritis with vertical transmission to the fetus via the amniotic fluid. The father's TST was negative, and chest X-ray film was normal.

Discussion

More than 300 cases of neonatal tuberculosis have been reported [8]. The main routes of infection are via the umbilical cord and amniotic fluid [7]. In the latter, the fetus inhales and/or ingests infected fluid, resulting in respiratory and gastrointestinal tract infection. Symptoms in neonates with tuberculosis are often nonspecific. Respiratory distress, fever, hepatosplenomegaly, poor feeding, and lethargy are common [7]. In our case,

apnoeic spells and elevation of the CRP led to the diagnosis of bacterial infection. Since the patient was an extremely low birth weight infant, severe bronchopulmonary dysplasia was considered responsible for her chest X-ray findings and respiratory status. Corticosteroids were administered because of respiratory failure, perhaps causing dissemination of tuberculosis.

On the NICU, secondary tuberculosis infection via aspirates from the respiratory or digestive tracts is more likely than via coughing [4]. Some reports have evaluated prevention of secondary infection of neonates who have been exposed to tuberculosis. Light et al. [5] and Stewart et al. [9] recommended preventive therapy with isoniazid for 3 months and 8 weeks, respectively. The American Thoracic Society and the Center for Disease Control have recommended that tuberculin-negative children and adolescents who are in close contact with infectious persons within the past 3 months, should receive preventive therapy until a repeat tuberculin-negative skin test is observed 12 weeks after the last infectious contact [1]. Neonates younger than 6 weeks of age who are infected with *M. tuberculosis* often do not react to TST because their immune system is immature [3]. We therefore gave chemoprophylaxis for infants on the NICU for 3 months despite negative TST. For infants on the continuing care unit, we conducted repeated TST without preventive therapy. Three medical staff members converted to positive after contact with the patient, presumably because of infectious particles from the respiratory and digestive tract of the index case.

In Japan, the number of newly registered patients with tuberculosis was 42,000 in 1997; the incidence rates per 100,000 population were 33.8 in the overall population and 2.1 below 4 years of age [6]. Most tuberculosis patients are elderly, but recently the number of younger patients has increased, including patients of childbearing age. Infected infants may be encountered on the NICU. The mother is often diagnosed with tuberculosis after the infant's diagnosis is made. We emphasise that examination for connatal tuberculosis is necessary for refractory neonatal respiratory distress or infection resistant to antibiotics; prevention of nosocomial transmission of tuberculosis in the NICU by appropriate management must follow.

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