Case Report

Fatal congenital tuberculosis due to a Beijing strain in a premature neonate

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Congenital tuberculosis (TB) remains a rare disease but is fatal if untreated. Early detection is difficult because of the non-specific nature of the symptoms in TB during pregnancy and infancy. This report summarizes a case of congenital TB in a very premature infant, born at 25 weeks gestation. Miliary TB was diagnosed in the mother when the neonate was 20 days old. Antituberculous therapy allowed a rapid improvement in the mother. The infant died at 27 days old. A Beijing genotype strain of *Mycobacterium tuberculosis* was isolated both in the mother, from pulmonary and urine specimens, and in the infant, from peritoneal fluid.

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Introduction

Transmission of *Mycobacterium tuberculosis* during pregnancy is rare, but is often fatal for the infant if it is premature and if infection is not treated in a timely manner. Early diagnosis is essential. However, the clinical presentation of tuberculosis (TB) during pregnancy and infancy is often non-specific, making recognition difficult (Hassan *et al.*, 2006; Ormerod, 2001). This report concerns a very low birth weight premature infant whose TB was suspected only 3 weeks after birth when diagnosis was made in the mother. The isolated strain of *M. tuberculosis* belonged to the Beijing family, known for its particular virulence (Lillebaek *et al.*, 2003).

Case report

A 29-year-old woman from Zambia who had been living in London for several years, presented at the Maternity Department, University Morvan Hospital in Brest, France, with a 2 week history of weight loss, asthenia and high

fever, precipitating an emergency vaginal delivery at 25 weeks gestation. On the day first post-partum, her temperature rose to 40 °C. No abnormality explaining the fever was found. Investigations revealed a white blood cell count of 12 000 cells mm⁻³ and a C-reactive protein level of 169 mg l⁻¹. Serological testing for human immunodeficiency virus, and bacterial cultures of blood, urine and endocervical swabs were negative. Amoxicillin plus clavulanic acid was begun as antibiotherapy for possible chorioamnionitis. Ten days after delivery, her fever continued; therefore, a computed tomography scan of the chest, abdomen and pelvis was carried out. It revealed subcarinal adenopathy and bilateral nodular shadows throughout both lung fields suggestive of a miliary TB. A urine sample and two sputum samples were negative for acid-fast bacilli (AFB) using Ziehl–Neelsen staining and for the *M. tuberculosis* complex by DNA PCR assay (Amplicor *M. tuberculosis* PCR assay; Roche). A bronchoalveolar lavage was also negative for AFB but positive for *M. tuberculosis* complex by PCR. Treatment with rifampicin, isoniazid, ethambutol and pyrazinamide was immediately instituted, and the patient gradually improved over the subsequent weeks. Cultures from the sputum, urine and bronchoalveolar lavage specimens yielded *M. tuberculosis* within 18 days in an MGIT (mycobacteria growth

Abbreviations: AFB, acid-fast bacilli; MIRU, mycobacterial interspersed repetitive unit; TB, tuberculosis; VNTR, variable number of tandem repeats.

indicator tube) (Becton Dickinson). Susceptibility of the isolate to rifampicin, isoniazid, ethambutol and pyrazinamide was evaluated on solid medium using the proportion method (Bio-Rad). It was susceptible to the four antituberculous drugs. The spoligotyping technique showed that the isolate belonged to the Beijing family. Retrospectively, the placenta was analysed by real-time PCR (*M. tuberculosis* LC PCR kit; Qiagen) and was positive for *M. tuberculosis* complex. However, culturing for mycobacteria could not be done, because of the fixation of the samples in formaldehyde and its inclusion in paraffin. Evaluation of the patient's family members for possible contagious TB revealed that she had been in contact 3 months before the beginning of her pregnancy with her sister, living in Zambia, but who was hospitalized for pulmonary TB when she came to visit her in London. However, no familial tracking of TB was arranged.

The infant was an 840 g female. She was transferred to the Neonatal Intensive Care Unit (Pediatrics Department, University Morvan Hospital, Brest, France). A preventive treatment with cefotaxime and amoxicillin was initiated because of the maternal fever. The infant was clinically stable until the fifth day, when she presented suddenly with an abdominal distension and progressive respiratory distress requiring mechanical ventilation. Her white blood cell count was $36\,700\text{ cells mm}^{-3}$ and her C-reactive protein level was 30 mg l^{-1} . A chest and abdominal X-ray showed a bronchopulmonary dysplasia and a pneumoperitoneum. The initial antibiotherapy was then replaced with a combination of cefotaxime, vancomycin and metronidazole. Bacterial cultures of peritoneal fluid were negative at day 6 and 13. As maternal TB was diagnosed at 3 weeks post-partum with PCR, a work up for TB in the infant was performed on peritoneal fluid at day 22. It was negative for AFB, but cultures yielded *M. tuberculosis* 3 weeks later. Unfortunately, the infant died at 27 days of age.

The *M. tuberculosis* strains isolated in the mother and infant were fingerprinted using the 12-loci MIRU (mycobacterial interspersed repetitive unit)-VNTR (variable number of tandem repeats) method (Mazars *et al.*, 2001), which revealed identical molecular patterns of 2, 2, 3, 3, 2, 5, 1, 7, 3, 5, 3, and four repeats for loci MIRU 2, 4, 10, 16, 20, 23, 24, 26, 27, 31, 39 and 40. This molecular pattern was entered in MIRU-VNTRplus (<http://www.miru-vntrplus.org>), a freely accessible web application for the assignment of *M. tuberculosis* lineages by comparison with reference strains. The constructed phylogenetic tree based on MIRU-VNTR patterns confirmed that the strains belonged to the Beijing family.

Discussion

Congenital TB remains a rare manifestation of a common infectious disease. Only about 300 cases had been reported worldwide until 1989. Since then, over 80 additional cases have been described. China, India, Africa and Latin America have the highest overall TB infection rates (Pal & Ghosh, 2008; Patel & DeSantis, 2008). Most of the

literature consists of individual case reports, case series and reviews (Pal & Ghosh, 2008; Cantwell *et al.*, 1994; Stähelin-Massik *et al.*, 2002; Berk & Sylvester, 2004; Chang *et al.*, 2005). The mortality rate is very high, nearly 50 %, which is often due to delayed diagnosis (Patel & DeSantis, 2008).

In this case report, it is unfortunate that the mother did not have a follow-up for latent TB at the beginning of her pregnancy because of the contact with her sister who had a pulmonary TB. The diagnosis of TB was delayed before and after delivery because of the non-specific symptoms. The use of molecular techniques, such as the PCR method, is an interesting possibility for reducing the delay in diagnosis.

A timely diagnosis of congenital TB is difficult because signs and symptoms in neonates are often initially attributed to other causes, such as prematurity, bacterial sepsis or other congenital infections (Hassan *et al.*, 2006). Moreover, in pregnant women, diagnosis of TB may be delayed by the non-specific nature of early symptoms and the frequency of malaise and fatigue (Ormerod, 2001). Maternal history, an important clue for rapid diagnosis, may be absent. Typically, infected infants are born prematurely, their non-specific symptoms begin in the second or third week of life, and include above all hepatosplenomegaly, respiratory distress, lymphadenopathy and abdominal distension (Ormerod, 2001).

Congenital TB is defined as TB occurring in infants as a result of maternal TB when the illness involves the genital track or the placenta. It should be distinguished from the more frequently acquired neonatal TB in which the infant is infected after birth by an adult with a pulmonary disease. TB bacilli are introduced into the fetus either haematologically via the umbilical vein, and the primary focus is often in the fetal liver, or via infected amniotic fluid that is ingested or aspirated *in utero* or at birth. In 1935, Beitzke first suggested diagnostic criteria mainly for distinguishing congenital TB from postnatally acquired disease based on post-mortem findings (Beitzke, 1935).

Revised diagnostic criteria are proven TB lesions in the infant plus one of the following: (a) lesions occurring in the first week of life, (b) a primary hepatic complex, (c) maternal genital tract or placental TB, or (d) exclusion of postnatal transmission by thorough investigation of contacts (Cantwell *et al.*, 1994). On the basis of these considerations, this case report fulfils the diagnostic criteria for congenital TB.

M. tuberculosis Beijing genotype strains are reported to be highly prevalent throughout Asia and in the countries of the former Soviet Union. They are increasingly reported in other areas of the world, and are frequently associated with large outbreaks of TB, increased virulence and drug resistance (Lillebaek *et al.*, 2003). A 7 year study was described in Malawi where 4.3 % of patients with TB were infected with a Beijing strain (Glynn *et al.*, 2002). Among these patients, four came from Zambia. In our report, the mother had been in contact with her sister who was living in Zambia. The isolates from both mother and infant

belonged to the Beijing family. They did not have any specific phenotypic features. Identification of the Beijing strain had been carried out first with spoligotyping of the mother's isolate, then confirmation with MIRU-VNTR both on the mother's and the newborn's isolate. However, contrary to many Beijing strains, the isolate was susceptible to the major antituberculous drugs. Beijing strains are rare in France. To know the real incidence of these strains, it would be interesting to fingerprint the *M. tuberculosis* isolates from patients coming from countries where prevalence is high. In conclusion, early diagnosis requires clinical awareness of congenital TB, especially in neonates born of immigrant groups in which TB is known to be prevalent, with or without knowledge of maternal illness.

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