

Atypical Presentation of Congenital Tuberculosis in a Preterm Infant

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Abstract Hong Kong is endemic for tuberculosis but congenital or perinatal tuberculosis is a rare entity. We describe a case of congenital tuberculosis in a premature infant with atypical presentation both in the mother and the baby.

Key words Congenital tuberculosis

Case Report

A female infant was born at 30 weeks with birth weight of 1285 grams. The mother suffered from primary infertility due to tuboperitoneal factor. *In-vitro* fertilisation was performed with embryo transfer which produced a single fetus. She developed threatened abortion at the first trimester and membrane ruptured at 15 weeks followed by recurrent vaginal spotting. Serial ultrasound showed normal fetal growth despite decreased liquor volume. She developed fever at 18 weeks and endocervical swab yielded *Escherichia coli*. A course of antibiotics including Ampicillin, Sulbactam and Metronidazole was given and fever settled. Fetal growth remained satisfactory with normal fetal heart tracing. Vaginal bleeding increased at 30 weeks and the baby was delivered by emergency LSCS for suspected fetal distress. Antenatal steroid and intravenous Augmentin was given prior to delivery.

The baby was apnoeic and flaccid at birth but responded promptly to resuscitation. Apgar score was 5 at 1 and 9 at 5 minutes. There was no significant respiratory distress after

birth but she was ventilated for recurrent apnoea. Chest radiograph revealed increased lung markings and intravenous Penicillin and Cefotaxime were started to cover for presumptive pneumonia. Gastric aspirate, eye swabs, ear swabs, blood and cerebrospinal fluid for cultures were all negative. Placenta weighed 500 grams and histological examination was initially reported as normal. Toxoplasmosis, rubella, cytomegalovirus and herpes titres were not elevated. Peripheral blood count and liver function were also normal. The baby became dependent on nasal continuous positive airway pressure due to refractory apnoea which was treated as apnoea of prematurity. Feeding was not tolerated with moderate abdominal distension. Bilateral pulmonary infiltrate and nonspecific bowel dilatation was shown on radiograph. A few courses of antibiotics were given but no pathogens were identified. At 6th week of life, she was noted to have erythematous skin papules and pustules over the neck. A solitary red nodule was also noted at right foot plantar (Figure 1).

The mother developed fever since day 2 postpartum. There was no localising signs or symptoms. Several courses of antibiotics were given with no response. Cultures from blood, midstream urine and endocervical swabs were negative. Other investigations including autoimmune markers, widal test, malaria, HIV status, Mantoux test and ESR were all normal. Chest radiograph was normal and ultrasound pelvis with Doppler showed no abnormality. At around 7 weeks postpartum, she suddenly developed right eye ptosis followed by left hemiparesis and soon lapsed into coma. Lumbar puncture revealed marked increased protein, low glucose and raised white cell count with

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predominant lymphocytes in cerebrospinal fluid. Acid fast bacilli (AFB) were seen by smear and polymerase chain reaction (PCR) for TB was positive. TB meningitis was then diagnosed and magnetic resonance imaging showed hypodense area over right basal ganglia and right temporal meningeal enhancement. Cerebrospinal fluid culture subsequently confirmed growth of *Mycobacterium tuberculosis*. Retrospective review of placental histology revealed presence of Langhans' giant cell and positive Ziehl-Neelson (ZN) staining for AFB (Figure 2). Histology of the endometrial biopsy taken prior to in-vitro fertilisation during workup for subfertility was also reviewed which



Figure 1 a) Cutaneous lesion over neck; b) Erythematous nodule at foot plantar.

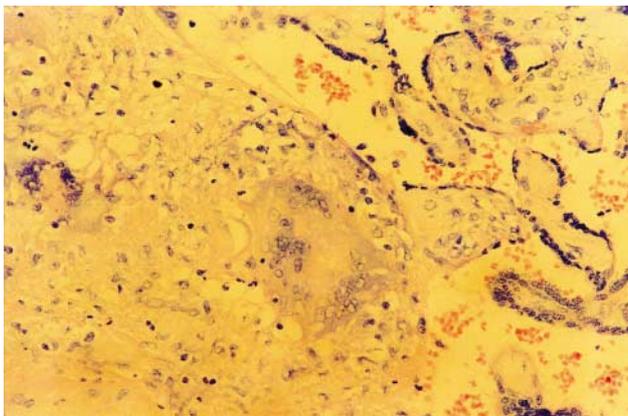


Figure 2 Section from placental tissue: Langhans' type giant cells with acid fast bacilli demonstrated by Ziehl-Neelsen stain.

showed granulomatous endometritis and positive staining for AFB.

Eventually as maternal tuberculosis was diagnosed at 7 weeks postpartum, workup for TB in the baby was performed. Gastric aspirate was positive for AFB smear and TB PCR. Examination of urine and cerebrospinal fluid was negative. She was then treated with oral isoniazid, rifampicin, pyrazinamide and intravenous amikacin. Apnoea decreased and CPAP was weaned off. Feeding was better tolerated with satisfactory weight gain and amikacin was stopped after 3 weeks. Right foot nodule and lymphadenopathy over right axillary and bilateral inguinal region became larger. Hepatosplenomegaly became prominent. Ultrasound showed multiple hypoechoic lesions in liver and spleen. Incision and drainage was performed for the right foot abscess and the pus was positive for AFB smear and culture. Amikacin was resumed and continued for total of 10 weeks. Skin lesions and lymphadenopathy gradually resolved and she was discharged at postnatal age of 5 months. Rifampicin and isoniazid was given for 1 year.

Discussion

Congenital tuberculosis was rare despite tuberculosis itself is the leading cause of death from a single infectious disease in many parts of the world. Hong Kong is endemic for tuberculosis with annual incidence of more than 100 cases per 100,000 population but congenital tuberculosis is rarely reported. Apart from the diagnostic difficulty and under-reporting, the rarity of the condition is contributed by the fact that tuberculous endometritis commonly results in subfertility and hence diminishes the likelihood of congenital tuberculosis from occurring.¹ However with the advance in assisted reproduction technology, women with tuberculous endometritis can still give birth to babies. This case illustrates the importance of having a high index of suspicion for tuberculosis in infertile women due to tuboperitoneal factors especially in endemic areas. Histological features of tuberculous endometritis were unfortunately missed prior to *in-vitro* fertilisation in our case and led to subsequent disseminated tuberculous infection in the mother and the infant.

In utero infection of *Mycobacterium tuberculosis* is most commonly caused by haematogenous spread from the mother causing placental seeding. The organisms reach the fetus via the umbilical vein and the primary focus is often in the fetal liver. Another route of infection is by direct

ingestion or aspiration of infected amniotic fluid if the caseous lesion in the placenta ruptures directly into the amniotic cavity. Since our infant had no liver involvement initially and presented with respiratory and intestinal symptoms, the latter route of infection seemed more likely.

The original diagnostic criteria laid down by Beitzke in 1935 require that the infant have proved tuberculosis disease plus one of the following: lesion in the first few days of life, a primary hepatic complex or exclusion of postnatal transmission by separation of infants and mothers at birth.² These criteria have become difficult to apply in current practice. Thus a revised criteria was proposed by Cantwell et al in 1994 requiring documentation of tuberculosis lesions in the infant and one of the following: (1) lesions in the first week of life; (2) a primary hepatic complex or caseating hepatic granulomas; (3) tuberculous infection of the placenta or maternal genital tract; or (4) exclusion of extra-uterine infection by investigation of contacts.³

Since Cantwell's report of 29 cases using the new diagnostic criteria, around 50 more cases of congenital tuberculosis were reported in English literatures. Cases continue to be reported from developing countries where tuberculosis is prevalent.⁴⁻⁶ The largest case series of congenital tuberculosis was reported from Thailand.⁴ Nine cases were detected from 1979 to 1998 with fatality rate of 33.3%. In developed countries most cases were contributed by new immigrants from endemic region.^{7,8} A surge of perinatal tuberculosis in infants is associated with increased tuberculosis infection in HIV positive mothers.⁹ Six cases of congenital tuberculosis that fulfilled the Cantwell's criteria were identified within one year period in a province in South Africa with epidemics of both tuberculosis and HIV infection.¹⁰ Four out of six of these mothers had tuberculosis and HIV coinfection.

According to Cantwell's review, hepatomegaly, fever and respiratory distress are the most frequent clinical features.³ As highlighted by our case and other recent reports, early signs and symptoms are often nonspecific and confused with those due to prematurity or mimic more common neonatal disease such as bacterial sepsis.^{11,12} Tuberculosis should be considered in an ill neonate with a poor response to conventional antibiotics therapy especially in endemic areas for tuberculosis or if the mother has risk factors for tuberculosis. Symptoms may be present at birth but typical features of congenital tuberculosis may evolve in a few weeks. Our patient presented atypically with cutaneous lesion as the first sign of tuberculosis when the typical features of fever, hepatosplenomegaly and respiratory

distress had not developed. The erythematous papules over the neck and the foot nodule were nonspecific in morphology but occurred in atypical sites of cellulitis or skin sepsis. Other reported uncommon manifestations of congenital tuberculosis included isolated otitis, facial nerve palsy and TB spine.¹³⁻¹⁵

By the time the clinical manifestations of congenital tuberculosis become florid, smear and culture for mycobacterium from gastric aspirate or endotracheal aspirate or other biopsy specimen are often positive. For early diagnosis, histologic examination of the placenta provides a useful and non-invasive tool. However, it was only done in a few cases.^{16,17} In the present case, the initial histologic examination of the placenta was reported as normal and only subsequent review of the placental section with proper staining finally revealed the pathology. Thus, histologic examination of the placenta is mandatory for the evaluation of unexplained maternal fever or other features suggestive of intrauterine infection. The pathologist should be informed of the clinical suspicion so that proper staining can be done.

Our patient was treated with isoniazid, rifampicin, pyrazinamide and an aminoglycoside which is the suggested regimen by Red Book 2006.¹⁸ Intravenous amikacin was used instead of intramuscular Streptomycin to avoid daily puncture of the skin and a prolonged course of 10 weeks was given subsequently for TB abscess.

In summary, congenital tuberculosis is still a rare disease even in endemic area like Hong Kong. Routine screening of tuberculosis of pregnant mother is probably not cost effective. However investigations for tuberculosis including placental histology with AFB staining should be initiated in the presence of unexplained maternal fever, past history of maternal TB or features suggestive of intrauterine infection. With greater vigilance in looking for the disease and adequate chemotherapy, the infant and maternal mortality of perinatal tuberculosis should be much reduced even in areas where tuberculosis is prevalent.

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