Name of Journal: World Journal of Clinical Cases

Manuscript NO: 74356

Manuscript Type: CASE REPORT

Congenital tuberculosis with tuberculous meningitis, and situs inversus totalis: A case report

case report

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Abstract

BACKGROUND
Congenital tuberculosis (TB), tuberculous meningitis, and situs inversus totalis (SIT) are rare diseases. We here report a patient who simultaneously suffered from these three rare diseases. There is currently no such report in the literature. Congenital tuberculosis is easily misdiagnosed and has a high case fatality rate. Timely anti-tuberculosis treatment is required.

CASE SUMMARY
A 19-day-old male newborn was admitted to hospital due to a fever for 6 h. His blood tests and chest X-rays suggested infection, and he was initially considered to have neonatal pneumonia and sepsis. He did not respond to conventional anti-infective treatment. Finally, *Mycobacterium tuberculosis* was found in sputum lavage fluid on the 10th day after admission. In addition, the mother's tuberculin skin test was positive, with an induration of 22 mm, and her pelvic computed tomography scan suggested the possibility of tuberculous pelvic inflammatory disease. The child was diagnosed with congenital tuberculosis and immediately managed with anti-tuberculosis therapy and symptomatic supportive treatment. However, the infant's condition gradually worsened and he developed severe tuberculous pneumonia and tuberculous meningitis, and eventually died of respiratory failure.

CONCLUSION
If conventional anti-infective treatment is ineffective in neonatal pneumonia, anti-tuberculosis treatment should be considered.

Key Words: Tuberculosis; Congenital; Situs Inversus; Newborn; Infant; Case Report

**Core Tip:** Congenital tuberculosis is rare in the clinic, and early diagnosis is challenging. The disease develops rapidly, and the mortality rate is exceptionally high. In the present case, the infant's condition worsened due to delays in diagnosis and anti-tuberculosis treatment, and he developed severe tuberculous pneumonia and tuberculous meningitis, and eventually died of respiratory failure. Early screening of tuberculosis infection and anti-tuberculosis treatment are essential to reduce mortality and improve the prognosis in children who do not respond to conventional anti-infective therapy.

**INTRODUCTION**

Congenital tuberculosis (TB) refers to an infection due to contact between the baby and the tuberculosis bacillus in the uterus or during delivery. Maternal tuberculosis can be transmitted to the fetus through the placenta or by inhalation of infected amniotic fluid. The former forms primary complexes in the liver of infants, and the latter forms primary lesions in the lungs or gastrointestinal tract.[1] Congenital tuberculosis is very rare, and the mortality rate is exceptionally high.[2, 3] Respiratory failure is the most common cause of death.[2, 4, 5] Intracranial infection is one of the most severe complications, seriously affecting the prognosis.[3] Misdiagnosis and untimely treatment are the main reasons for aggravation of the condition. Situs inversus totalis is a rare congenital malformation, and some patients may also suffer from defective ciliary motility.[6] The ciliary immobility is involved in the absence of mucociliary transport in the respiratory epithelia,[7] which may induce lung infections. We here report a patient who suffered from rare congenital tuberculosis, tuberculous meningitis, and total visceral reversal. Congenital tuberculosis complicated with situs inversus totalis was not found from the Google Scholar and PubMed databases.

**CASE PRESENTATION**

*Chief complaints*
A 19-day-old male newborn was admitted to the hospital with a fever for 6 h.

**History of present illness**

The child was born at 41 wk of gestation and was delivered smoothly. The birth weight was 2.925 kg, breathing 50 breaths/min, weight 3.93 kg, heart rate 150 beats/min, no intrauterine distress, no premature rupture of fetal membranes. Fever occurred 6 h before admission, and the highest body temperature was 38.2°C.

**History of past illness**

The baby was delivered normally without a history of allergies.

**Personal and family history**

His mother had a history of miscarriage. Both parents denied a history of tuberculosis, but his grandmother had tuberculosis when she was young.

**Physical examination**

Breath sounds were rough in both lungs, with an increased breathing rate and wet rales could be heard.

**Laboratory examinations**

The following parameters were observed in serum: C reactive protein (CRP) 46.3 mg/L (reference range ≤6.0 mg/L), procalcitonin 1.23 μg/L (reference range <0.054 μg/L), white blood cells (WBC) 22.92×10^9/L (reference range 15-20×10^9/L), neutrophils 0.701, total bilirubin 87.9 μmol/L (reference range <26.0 μmol/L), indirect bilirubin 81.2 μmol/L (reference range <14.0 μmol/L). Cerebrospinal fluid (CSF) was cloudy, with a chloride ion level of 117.5 mmol/L (reference range 120.0-132.0 mmol/L), protein concentration 0.92 g/L (reference range 0.08-0.43 g/L), glucose 3.15 mmol/L (reference range 3.9-5.0 mmol/L), adenosine deaminase 0.2 U/L, and WBC 35×10^6/L (reference range <30×10^6/L). Bacterial testing showed Gram-positive cocci on smears, acid-fast
bacilli were found on acid-fast staining, and the tuberculin-\(\gamma\)-interferon release test was positive. Microbial genetic testing detected the \textit{Mycobacterium tuberculosis} complex.

\textbf{Imaging examinations}

Chest radiography showed increased texture and thickening of the lungs, scattered with patchy high-density shadows. In addition, the apex of the heart and gastric bobble was on the right, and the liver was on the left (Figure 1A, B). Chest computed tomography (CT) showed multiple nodules in both lungs, and hilar lymph nodes were enlarged (Figure 2A, B). The heart, liver, and spleen were also completely reversed, showing mirror-like changes (Figure 2B, C).

\textbf{FINAL DIAGNOSIS}

The baby was finally diagnosed with congenital tuberculosis with tuberculous meningitis and situs inversus totalis.

\textbf{TREATMENT}

Following admission, the patient underwent repeated tests for viruses and bacteria, including \textit{Mycobacterium tuberculosis} and other pathogens. The test samples included blood, sputum, gastric juice, and CSF. The test results in the first ten days were all negative. Amoxicillin and Clavulanate Potassium were given on the day of admission. Potassium retinoic acid (0.117 g IV q8h), was discontinued the next day and changed to oseltamivir phosphate granules (10 mg oral qd), and ceftazidime (0.19 g IV q8h). Vancomycin (58 mg IV q8h) was administered and the blood concentration of vancomycin was controlled at 7.4 \(\mu\)g/mL (effective range 7-10 \(\mu\)g/mL). Meropenem (0.15 g IV q8h) was added on the 4th day after admission. However, these anti-infective treatments were ineffective, lung exudation was aggravated, and regular blood oxygen saturation could not be maintained. Invasive ventilation was then used to support the patient's breathing. Neurological symptoms such as epilepsy and irritability were also observed. On the 10th day after admission, acid-fast bacilli were found in the patient's
sputum following acid-fast staining. Microbial genetic tests confirmed *Mycobacterium tuberculosis* complex. Vancomycin, oseltamivir phosphate particles, and ceftazidime were then stopped, and anti-tuberculosis treatment was started with niacin injection (0.057 g IV qd); pyrazinamide tablets (0.13 g gastric tube injection qd), and rifampicin injection (0.057 g IV qd). After seven days of anti-tuberculosis treatment, the patient’s chest radiography showed improvement in lung exudation (Figure 1A, B). The child was kept alive through invasive ventilation, but eventually died of respiratory failure due to the worsening of the disease.

**OUTCOME AND FOLLOW-UP**

The newborn was undergoing anti-tuberculosis treatment, due to delays in diagnosis and treatment, and his condition continued to deteriorate and he eventually developed severe pneumonia and tuberculous meningitis, and died of respiratory failure at 38 days.

**DISCUSSION**

Congenital tuberculosis is a rare disease. In 2005, fewer than 376 cases were reported worldwide.[2] Cantwell *et al.[1]* proposed the classic diagnostic criteria for congenital tuberculosis, where infants were confirmed to have tuberculosis if they had at least one of the followings: symptoms in the first week after birth, primary liver tuberculosis complex, maternal genital tract or placental tuberculosis, and postpartum transmission was ruled out by thorough investigation of contacts. In this case, the mother’s tuberculin skin test was positive, and pelvic CT suggested possible tuberculous peritonitis. Moreover, *Mycobacterium tuberculosis* was found in the baby’s sputum, and chest radiography indicated progressive and disseminated tuberculosis. Therefore, our case met these diagnostic criteria.

The clinical manifestations of congenital tuberculosis are non-specific, making early diagnosis difficult.[1, 5] The most common clinical symptoms are loss of appetite, fever, restlessness, hypoplasia, weight loss, cough, respiratory distress, hepatosplenomegaly,
spleenomegaly, lymphadenopathy, and abdominal distension.\textsuperscript{[2, 8]} Generally, congenital tuberculosis is easily misdiagnosed as pneumonia, sepsis, and purulent meningitis.\textsuperscript{[3]} Conventional antibiotic treatment is ineffective and the disease may progress to serious complications such as miliary tuberculosis and tuberculous meningitis. These serious complications may be related to the infant's immature innate immunity.\textsuperscript{[9]} The clinical symptoms of the child, in this case, were mainly fever, loss of appetite, restlessness, and respiratory distress. These symptoms are non-specific. \textit{Mycobacterium tuberculosis} was not detected in the baby in the first ten days after admission. The mother had no symptoms of tuberculosis infection before and after childbirth. Therefore, tuberculosis infection could not be diagnosed early.

Laboratory tests for congenital tuberculosis are generally non-characteristic and easily confused with acute infections due to other pathogens.\textsuperscript{[10]} The most common reaction is an increase in the number of WBC and inflammatory indicators. Identifying the presence of tubercle bacilli by fluid body cultures, acid-fast staining, or tissue biopsy is the gold standard for the diagnosis of tuberculosis.\textsuperscript{[11]} In our case, bacteria and viruses were tested immediately after admission, and the results were negative. In addition, repeated acid-fast staining of sputum and gastric juice was negative, and tubercle bacilli were not found in the sputum until the 10th day after admission. Delayed diagnosis is a crucial cause of disease aggravation.

The imaging manifestations of congenital tuberculosis have specific characteristics. Early imaging of lesions may include interstitial pneumonia,\textsuperscript{[12]} and miliary pneumonia and multiple pulmonary nodules may appear when the condition worsens. Multiple pulmonary nodules are considered disease progression.\textsuperscript{[12]} Peng \textit{et al} \textsuperscript{[3]} suggested that miliary tuberculosis on chest imaging four weeks postpartum should be used as one of the diagnostic criteria for congenital tuberculosis, which can provide a timely basis for diagnosis and treatment. If \textit{Mycobacterium tuberculosis} spreads to the liver and spleen \textit{via} the blood, it can form a primary complex. Abdominal CT showed hepatosplenomegaly, and multiple low-density primary complexes were also seen. In our case, the baby's chest radiography and chest CT showed scattered high-density nodules in both lungs,
thickened lung texture, enlarged hilar lymph nodes, and normal size and density of liver and spleen. In addition, the dextrocardia and internal organs were reversed (Figures 1, 2). Therefore, we believe that the cause in this case was the infant inhaling or ingesting amniotic fluid contaminated by Mycobacterium tuberculosis.

In recent decades, neonatal tuberculous meningitis has rarely been reported.\textsuperscript{[13-15]} Common neurological symptoms and signs include drowsiness, meningeal irritation, cranial nerve palsy, epilepsy, hemiplegia, alteration of consciousness, coma, etc.\textsuperscript{[16]} About half of all tuberculous meningitis infections cause severe disability or death.\textsuperscript{[17]} When tuberculosis meningitis is suspected, magnetic resonance imaging (MRI) should be selected, as it is unique in assessing early and late disease and is effective in children with suspected tuberculosis meningitis.\textsuperscript{[18, 19]} In this case, the infant's neurological symptoms were irritability, convulsions, and poor response. The number of WBCs and protein concentrations in the CSF were increased, and the concentrations of glucose and chloride ions were decreased. Combined with the detection of tuberculosis and multiple pulmonary nodules following sputum analysis, this was consistent with the diagnostic criteria for tuberculous meningitis.\textsuperscript{[20]} Unfortunately, head MRI was not performed at that time.

Inborn anomalies of organ placement are rare developmental abnormalities with an incidence of about 1/8000,\textsuperscript{[21]} which can be divided into situs inversus totalis (SIT) and incomplete situs inversus (ISI).\textsuperscript{[22]} However, in 20-25% of SIT cases, they also have Kartagener syndrome (KS) (bronchial immobility, bronchiectasis, chronic sinusitis, male infertility).\textsuperscript{[23, 24]} KS is also known as ciliary immobility syndrome, which can lead to obstruction of mucus drainage from the respiratory tract, which increases the possibility of lung infection. However, we cannot confirm whether the baby has KS and whether KS will increase the prevalence of congenital tuberculosis.

The mortality rate of congenital tuberculosis is very high, close to 50%, usually due to delayed diagnosis and treatment.\textsuperscript{[5]} The clinical manifestations do not improve after antibiotic treatment, and the condition of 96% of children may worsen.\textsuperscript{[5]} Early diagnosis and timely antituberculosis treatment can significantly reduce infant
mortality and improve prognosis.[3] Newborns with congenital tuberculosis should receive isoniazid (10-15 mg/kg/day), rifampicin (10-20 mg/kg/day), pyrazinamide (20-40 mg/kg/day), and streptomycin (20-40 mg/kg/day) intravenously for 2 months; isoniazid and rifampicin should be continued for 6 months.[25] Our patient only started anti-tuberculosis treatment on the 10th day after admission, but his condition continued to deteriorate, and he eventually developed severe pneumonia and tuberculous meningitis and died of respiratory failure at 38 days.

CONCLUSION
Congenital tuberculosis is very rare, and concurrent tuberculous meningitis and congenital situs inversus totalis have not been reported. It is not clear whether they are related or not. The clinical manifestations of congenital tuberculosis are non-specific, the detection of pathogenic bacteria is difficult, it is easily misdiagnosed, the fatality rate of the disease is high, and it can progress to severe tuberculous meningitis. Early diagnosis and anti-tuberculosis treatment are the keys to reducing mortality and improving infant prognosis. For infants with a high suspicion of tuberculosis infection, empirical anti-tuberculosis treatment should be administered.
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