Successful treatment of two extremely premature infants with perinatal tuberculosis and severe sepsis

Lam Van Nguyen | Nam Huu Dao | Thuy Phuong Dang | Hung Viet Pham

Abstract
Perinatal tuberculosis (TB) is a rare disease with severe clinical conditions that may spread to several organs. Early diagnosis to initiate an anti-TB regimen is key to saving patients. We report the successful treatment of two preterm babies with perinatal TB and sepsis at the National Children’s Hospital (NCH), Vietnam.

KEYWORDS
children, perinatal, premature, tuberculosis

1 | INTRODUCTION

According to the World Health Organization (WHO), in 2020, a total of 1.2 million children were infected with tuberculosis (TB) worldwide. Although the field of management and treatment of pediatric TB has significantly improved, several challenges in the early detection and prevention of TB, especially in neonates, still exist. Perinatal TB includes infection of mycobacterium tuberculosis (MTB) in utero, intrapartum, or soon after birth and has replaced the terminology of congenital TB. Our report aims to provide beneficial information on two preterm neonates with TB infection and discuss challenges in the diagnosis and treatment of perinatal TB.

2 | CASE DESCRIPTION

2.1 | First case

The first case is a boy, first child, 26 weeks of gestational age (GA), 900 g at birth. The mother had in vitro fertilization (IVF) with twin fetuses, a natural onset of labor, and normal delivery.

2.1.1 | Child’s condition at admission

The child had severe condition and needed mechanical ventilation with high index: SIMV, FiO2 100%, PIP
24, PEEP 5, f = 35 breaths/min, spO2 88%–90%, normal heart rate, f = 150 times/min, refill 2 s, arterial pressure, 58/27 (40) mmHg. Bilateral crackles were noted upon examination.

Clinical examination revealed normal abdominal tension and a normal liver and spleen. The child showed weak primitive reflexes and temperature at 36.7°C; convulsions, edema, and purpura were not observed.

Subclinical investigation showed tracheal aspirate and cerebrospinal fluid (CSF) were collected for MTB diagnosis and isolation of other bacteria. Blood was collected for bacterial culture and serological assays for toxoplasma IgM/IgG, CMV IgM/IgG, rubella IgM/IgG, HSV1 and 2 IgM/IgG, and HIV.

2.1.2 | Findings

Cerebrospinal fluid was negative for MTB; however, MTB was detected in the tracheal aspirate through AFB staining, real-time polymerase chain reaction (PCR), and Xpert MTB/RIF assay. The Xpert MTB/RIF assay showed that MTB had no rifampicin resistance, similar to that of the mother. Bacterial isolation from the tracheal aspirate revealed antibiotic-resistant *Klebsiella pneumoniae*. The minimum inhibitory concentration antibiogram showed resistance to amoxicillin/clavulanic acid, ampicillin/sulbactam, and all cephalosporin generations. However, the bacterial strain was susceptible to carbapenems, amikacin, and trimethoprim/sulfamethoxazole. Other findings were not significant; the detailed results are shown in Table 1.

*Clinical imaging:* An in-bed chest radiograph showed opacity of the left lower lobe and nodular lesion concentrated in the right hilum (Figure 1). Fontanel ultrasound was normal, but cranial magnetic resonance imaging (MRI) findings showed an 11 × 8 mm lesion in the right temporal lobes; the border had absorption with a contrast agent, edema was noted in the surrounding brain, and the ventricles were normal.

*Intensive care:* The child’s management comprised of mechanical ventilation, vital recovery, vasoregulation, antibiotics for *Klebsiella pneumoniae* (meropenem, colistin, amikacin), and anti-TB drugs: 2 months of isoniazid, rifampicin, pyrazinamide, and ethambutol (2RHZE), with dexamethasone for meningitis. The regimen was prescribed according to the hospital’s guidelines and in accordance with the WHO recommendation for pediatric TB.4

*Other support:* Due to long-term mechanical ventilation and prematurity with pulmonary dysplasia, diuretic drugs furosemide (2 mg/kg/day), aldactone (2 mg/kg/day), and sildenafil (4 mg/kg/day) for 2 months were indicated for the control of pulmonary hypertension.

2.1.3 | Treatment monitoring and response

After 5 days of treatment, the child’s respiratory condition improved, with a reduction in the index for mechanical ventilation. After 17 days of anti-TB regimen, mechanical ventilation was discontinued, and the child was switched to oxygenation via nasal cannula. After 2RHZE, the child could self-breathe and drink. He had no pulmonary crackles, but chest radiography revealed pulmonary dysplasia. The gastric aspirate showed negative results for AFB.

Laboratory findings at discharge revealed normal white blood cell and C-reactive protein (CRP) levels, and hepatic and renal function were normal. Natriuretic peptide tests showed normal NT-proBNP levels.

The child was discharged with continuous rifampicin and isoniazid for 4 months (4HR). By September 2021, the child was 7.5 months old, ending the anti-TB regimen, with good development, and weighed 6.5 kg. The child was continually followed up at our hospital and the National Lung Hospital. A detailed examination of the child at 6, 7, and 9 months old is described in Table 2.

2.2 | Second case

The second case is a boy, 26 weeks of GA, born through normal delivery, weighing 850 g at birth. The mother had an IVF single fetus. He had respiratory failure immediately after birth, was in intensive care, and was indicated continuous positive airway pressure therapy. Afterward, the child had pneumonia and severe sepsis and was intubated and administered antibiotics without improvement. When he was 2 months old, he was transferred to NCH from Hanoi Obstetrics and Gynecology Hospital.

The laboratory findings at Hanoi Obstetrics and Gynecology Hospital indicated that bacterial isolation in tracheal aspirate showed *E. coli* (9 days), *K. pneumoniae* (17 days), *S. maltophilia* (25 days), and *C. albicans* (45 days); thereafter, the child was treated with imipenem, amikacin, and amphotericin B.

*Maternal history:* The mother had two miscarriages and one stillbirth at 21 weeks of gestation. At this time of pregnancy, the mother was likely healthy, with no fever or cough and no vaginal inflammation. Prenatal care recorded a low-lying placenta. At 25 weeks of gestation, bleeding occurred, and the gestation was terminated.

When the child stayed in NCH (after 2 weeks), the mother developed backache and persistent fever and was then examined and defined as having spinal TB. There were no records of TB among other family members.
### TABLE 1  Clinical profile and investigations of patients

| Characteristics            | First case                  | Second case                  |
|---------------------------|-----------------------------|------------------------------|
|                           | Admission | Discharge | Admission | Discharge |
| Gestational age           | 26 weeks, BW = 900 g        | 26 weeks, BW = 850 g        |
| Suspected source of TB    | Mother     | Mother     |
| Time of TB detection      | 35 days    | 81 days    |
| Markers of infection      |            |            |
| WBC (G/L)                 | 31.5       | 6.06       | 8.14      | 15.26     |
| Neut, %                   | 78.3       | 28.9       | 49.7      | 29.9      |
| Lym, %                    | 10.5       | 38.3       | 35.3      | 55.5      |
| PLT (G/L)                 | 19         | 304        | 114       | 497       |
| CRP (mg/L)                | 113        | 1.12       | 91.23     | PCT: 0.17 |
| Arterial blood gas        |            |            |
| pH                        | 7.08       | NA         | 7.27      | NA        |
| PCO₂ (mmHg)               | 111        | NA         | 53        | NA        |
| pO₂ (mmHg)                | 54         | NA         | 66        | NA        |
| HCO₃ (mmol/L)             | 32.9       | NA         | 22.5      | NA        |
| BE (mmol/L)               | 0.1        | NA         | −2.9      | NA        |
| Lactat (mmol/L)           | 1.4        | NA         | 4.0       | NA        |
| Blood biochemistry        |            |            |
| Ure (mmol/L)              | 3.09       | 3.3        | 0.9       | 4.4       |
| Creatinine (mmol/L)       | 56.4       | 38.8       | 27.3      | 33        |
| GOT (U/L)                 | 45.7       | 37.4       | 64.7      | 30.7      |
| GPT (U/L)                 | 15.8       | 13.3       | 20.3      | 19.6      |
| Glucose (mmol/L)          | 6.8        | NA         | 4.79      | NA        |
| Na/K/Cl (mmol/L)          | 134.6/4.33/106 | 135/5.4/103 | 139/3.2/109 | 135/4.9/98 |
| NT-proBNP (pmol/L)        | 6024       | 43.5       | 241       |            |
| CSF characteristics       |            |            |
| Cells/ml                  | 04         | 22 (Neu 49%, Lym 28%, Mono 23%) |
| Protein (g/L)             | 1.32       | 1.48       |
| Clo (mmol/L)              | 117        |            |
| Glucose (mmol/L)          | 3.39       | 3.11       |
| Real-time PCR for TB      | neg in CSF | neg in CSF |
| Xpert MTB/RIF assay       | neg in CSF | neg in CSF |
| Microbiological assays<sup>a</sup> | | |
| Tracheal aspirate         |            |            |
| AFB                       | pos        | neg in gastric aspirate | neg | NA |
| Real-time PCR for TB      | pos        | NA         | neg       | NA        |
| Xpert MTB/RIF             | pos        | NA         | pos       | NA        |
| Bacterial culture         | K. pneumoniae | neg       | neg       | NA        |
| CMV in aspirate (copies/ml) | NA     | NA         | 1 × 10⁶     | 2.8 × 10⁴ |
| CMV in plasma (copies/ml) | NA         | NA         | 1.8 × 10⁵   | neg       |
| Serological assays        |            |            |
| Anti-HIV ELISA            | neg        | neg        |

(Continues)
2.2.1 | Child’s condition at admission

The child had severe pneumonia and septic shock, underwent mechanical ventilation with a high index (spO2 86%–90%), and had bilateral crackles. Hemodynamics was unstable, which was vasoregulated with adrenaline and dopamine. Laboratory findings revealed thrombocytopenia and elevated CRP levels, and blood gas test results showed uncompensated acidosis.

Clinical examination revealed lethargy, weak primitive reflexes, flat fontanel, mild abdominal tension, normal liver, and spleen.

Clinical imaging through in-bed chest X-ray showed severe pulmonary lesion with diffuse bilateral reticulonodular infiltrates (Figure 2).

Subclinical investigation was carried out upon admission. Blood and tracheal aspirates were collected for bacterial isolation. Blood was collected for serological assays to detect toxoplasma IgG/IgM, CMV IgM/IgG, rubella IgM/IgG, HSV1 and 2 IgM/IgG, and HIV.

After 2 weeks of treatment, with information from the mother, tracheal aspirate and CSF were collected for MTB diagnosis.

2.2.2 | Findings

None of the pathogenic bacteria or fungi were detected in the blood or tracheal aspirate. The viral load of CMV was $1.8 \times 10^5$ copies/ml in plasma and $10 \times 10^6$ copies/ml in the tracheal aspirate, and anti-CMV IgM/IgG was positive.

MTB was detected in the tracheal aspirate through the Xpert MTB/RIF assay, with no rifampicin resistance. CSF was negative for MTB, although the laboratory characteristics of CSF have changed. Details of all findings are presented in Table 1.
Antibiotic at intensive care: Upon admission, the prescribed antibiotics included colistin, meropenem, and amphotericin B, in combination with ganciclovir.

Two weeks after admission, anti-TB drugs (2RHZE) and dexamethasone were initiated.

Other support: The child underwent nutrition therapy, pulmonary hypertension was controlled, and diuretics were administered.

2.2.3 | Treatment monitoring and response

Two weeks after admission, the patient's condition slowly improved; he still had vast lung damage (Figure 2) and received mechanical ventilation with a high index.

After 1 week of anti-TB regimen, the patient's condition improved, with a reduction in the ventilator index. He was switched to noninvasive oxygen therapy via nasal cannula after 2 weeks of the anti-TB regimen. Chest X-ray images showed healing of the pulmonary lesions (Figure 3). At the end of the 2RHZE treatment, the child could self-breathe and suck milk, and he continuously received 4HR. Upon discharge, the child was 4 months old, weighing 3.7 kg. The child was continually followed up at our hospital and the National Lung Hospital. Detailed examination of the child at 6 and 7 months old is shown in Table 2.

### Table 2 Medical records of the two cases at follow-up

| Time point | First case                                      | Second case                                      |
|------------|-------------------------------------------------|-------------------------------------------------|
| 1st visit  | 6 months old, W = 5.6 kg, H = 65 cm              | 6 months old, W = 4.8 kg, H = 63.5 cm           |
|            | Cognitive: response to communication            | Cognitive: response to communication            |
|            | Development: starts rolling over and holds head up | Development: starts rolling over and holds head up |
|            | Ophthalmology findings: good response to ROP treatment | Ophthalmology findings: good response to ROP treatment |
|            | Cardiology findings: normal, no pulmonary hypertension | Cardiology findings: normal, no pulmonary hypertension |
| 2nd visit  | 7.5 months old, 6.5 kg                          | 7.0 months old, W = 5.2 kg, H = 65 cm (end of November 2021) |
|            | Examined at National Lung Hospital, finished anti-TB therapy | Examined at National Lung Hospital, 2nd month of anti-TB continuation phase |
|            | Chest X-ray findings: normal                    | Chest X-ray findings: normal                    |
|            | Laboratory findings: stable                     | Laboratory findings: stable                     |
| 3rd visit  | 9 months old, W = 6.7 kg, H = 70 cm             | Pending                                         |
|            | Development: satisfactorily rolls over, holds on to furniture to stand up | Development: satisfactory rolls over, holds on to furniture to stand up |
|            | Ophthalmology and cardiology findings: stable   | Ophthalmology and cardiology findings: stable   |
|            | Got vaccinated through the nationwide vaccine program | Got vaccinated through the nationwide vaccine program |

Abbreviations: H, height; ROP, retinopathy of prematurity; W, weight.
There are two forms of TB infection in newborns: congenital TB and TB acquired after birth. The three routes of transmission are as follows: The first is bacteremia through the umbilical vein, creating primary lesions in the liver or lungs; the second is by swallowing or aspirating TB-contaminated amniotic fluid in utero, with primary lesions in the lungs or gastrointestinal tract (congenital TB); and the third is postpartum infection (acquired TB) through inhalation of tubercle bacilli or ingestion of infected breast milk. Congenital TB is defined as the case in which an infant has TB due to infection in utero or before passing the mother’s genital tract. The diagnostic criteria for congenital TB were established by Beitzke in 1935. It was later edited by Cantwell in 1994. Infants were categorized as having TB lesions and at least one of the following conditions:

- TB lesions appear in the first week after birth.
- Primary granulomatous or complex liver lesions.
- Detecting TB in the mother’s genital tract or placenta.
- Exclusion of the possibility of postnatal transmission by thoroughly investigating the routes of transmission, including medical staff caring for the baby.

However, the symptoms, diagnosis, management, and prognosis are similar due to the difficulty in determining the exact timing and circumstances of infection. As a result, the term perinatal TB has been widely used to describe both conditions. It includes TB acquired in utero, during birth, or in early infancy and has replaced the term congenital TB.

The disease is often difficult to diagnose because of its nonspecific clinical manifestations. Newborns infected with TB are often premature births. In 2017, Samedi et al. described a congenital TB case with IVF, 24 weeks GA, birthweight of 590 g. Due to the lack of host immune response, it was usually classified as generalized TB, manifesting in the lungs, pleura, meninges, kidneys, liver, and adrenal glands. Hepatosplenomegaly may occur in over 65%, respiratory failure >70%, fever >50%, and lymphadenopathy in 38% of perinatal TB cases. It may also manifest as sepsis, jaundice, ascites, disseminated intravascular coagulation, otitis media, osteomyelitis, and vertebral abscess. Other nonspecific symptoms include lethargy, poor feeding, irritability, abdominal distension, and growth retardation. Symptoms may appear soon after birth but are usually detected between the second and fourth week postpartum. According to the literature, the average age when TB manifests in reported cases was 24 days (ranging from 1 to 84 days). In our cases, it was difficult to determine the exact time the child presented with TB. They were transferred to our hospital at 35 days and 60 days of age, with manifestation of sepsis and respiratory failure that was associated with extremely preterm birth, without definitive TB infection in advance.

The symptoms of perinatal TB in neonates are easily confused with other diseases such as sepsis, pneumonia, meningitis, or other congenital infections, such as ToRCH, HIV, and syphilis, but respond poorly to antibiotics and standard therapies. A report from Thailand showed a case that was first admitted with omphalitis and sepsis, without responding to cefotaxime and amikacin. Other cases from Romania presented clinical features of peritonitis, before a definitive diagnosis of miliary perinatal TB.

As described above, TB should always be suspected, especially in children from endemic areas with high TB prevalence, whose mothers or family members have a history of TB. Even if the source of infection is unknown, TB cannot be excluded. In our report, the patients had been receiving prolonged antibiotic treatment, combined with supportive therapy, without improvement. After a careful investigation of the mother’s medical history, a suspicious diagnosis was established, and MTB testing was immediately performed.

In addition to confirming TB infection through microbiological assays, clinical imaging is an indispensable tool in the diagnosis of perinatal TB. Chest radiography usually shows miliary TB lung lesions (accounting for nearly 50%
of cases), in addition to nodular lesions, lobar pneumonia, or bronchopneumonia.\textsuperscript{10,11} Abdominal ultrasound often shows hepatosplenomegaly, or localized hepatic lesions, and retroperitoneal lymph nodes.\textsuperscript{12} In the case reported by Samedi et al., brain MRI findings showed multiple small ring-enhancing cerebral and cerebellar lesions. This case had no confirmation of MTB from the child’s samples, but the mother was diagnosed with pulmonary TB. Both AFB placental pathology and PCR for MTB in placental tissue were positive.\textsuperscript{6} In our report, only the second patient had suspected miliary TB. However, he had no hepatosplenomegaly or liver damage on both clinical examination and abdominal ultrasound.

Hematological assays of perinatal TB infants can be confused with a pyogenic bacterial infection, with an increase in white blood cell count, especially in neutrophils. Elevation of neutrophils is the child’s first defense barrier.\textsuperscript{13} In biochemistry, the level of CRP is also elevated. The reason is the children’s response to MTB as vigorously as to pyogenic bacteria, which is different from adult TB. In our first patient, the white blood cell count was up to 31.5 G/L, of which neutrophils accounted for 78%. The patient’s white blood cell count was consistently high, even with the long-term use of broad-spectrum antibiotics, and only decreased when anti-TB drugs were prescribed. In 2001, Mazade et al. reported a patient who showed clinical features of sepsis, with 21,000 white blood cells/mm\textsuperscript{3} on admission and had leukopenia (1580 leukocytes/mm\textsuperscript{3}) by the third hospital day.\textsuperscript{14}

Age at onset, white blood cell count, and treatment with anti-TB drugs are factors related to the prognosis of perinatal TB. Peng et al. showed that at the age of onset of >3 weeks postpartum, blood leukocyte count >12 G/L had a better prognosis than early-onset cases of leukopenia. Timely diagnosis is key, and patients should be treated with appropriate anti-TB medicine, significantly reducing the patient’s mortality rate.\textsuperscript{15}

4 | CONCLUSION

The diagnosis of perinatal TB is very complicated; therefore, it is necessary to carefully examine the mother’s medical history, together with the clinical signs, assess the child’s response to the diagnosis, treat the disease promptly, and save the patient’s life. In our two cases, the definitive diagnosis was perinatal TB. The combination of anti-TB drugs with other antibiotics and antiviral therapy successfully saved the patients and provided a good long-term outcome.

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CONFICT OF INTEREST

None.

AUTHOR CONTRIBUTIONS

Lam Van Nguyen involved in treatment, conceptualization, investigation, editing of the manuscript, and final approval of the manuscript. Nam Huu Dao involved in treatment, conceptualization, data collection, and writing of the manuscript. Thuy Phuong Dang involved in treatment, data collection, and writing of the manuscript. Hung Viet Pham involved in conceptualization and design, summary and interpretation of data, revision of the manuscript, and submission of the manuscript.

ETHICAL APPROVAL

Institutional Review Board does not require the authors submit ethical approval for writing manuscript of clinical case report.

CONSENT

Written patient consent was sent to the children’s parents and approved and signed before submission.

DATA AVAILABILITY STATEMENT

Data are available on request due to privacy/ethical restrictions.

ORCID

Hung Viet Pham © https://orcid.org/0000-0002-8622-9935

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