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Case Presentation : Congenital Tuberculosis in A Premature Infant Presented with Miliary Tuberculosis

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Abstract

Congenital tuberculosis (TB) is a rare neonatal infection resulting from vertical transmission of Mycobacterium tuberculosis from mother to infant. Fewer than 500 cases have been reported worldwide, with a high mortality rate up to 40%. Diagnosis is challenging due to its nonspecific presentation and resemblance to neonatal sepsis. We report a case of a 1-month-old preterm infant admitted with worsening respiratory distress, fever, and cough. Chest X-ray revealed a "snow storm appearance" consistent with miliary tuberculosis. The infant's mother had a history of chronic cough prior to pregnancy and later tested positive for Mycobacterium tuberculosis by sputum PCR. The sputum PCR test in the infant also returned positive. Laboratory findings included leukocytosis with neutrophil predominance and elevated transaminases. The infant was given respiratory support with CPAP and treated with a standard four-drug antitubercular regimen (2HRZE/10HR) and corticosteroids due to severe respiratory involvement. The clinical course was favorable, with resolution of respiratory symptoms and radiologic improvement, allowing discharge after 16 days of hospitalization. The diagnosis of congenital tuberculosis in this patient was confirmed based on the mother's history of suspected pulmonary tuberculosis prior to pregnancy, along with the confirmed diagnosis of tuberculosis through a positive sputum PCR test in the mother and the infant. Liver biopsy which is gold standard of diagnosis could not be performed due to the patient's unstable condition and the consideration of the benefit invasive procedure.Awareness of maternal risk factor for TB plays a pivotal role in suspected congenital tuberculosis, enables early diagnosis and prompt treatment, reducing mortality and long-term sequelae.

Keywords: Congenital Tuberculosis, Miliary Tuberculosis, Sputum PCR, Vertical Transmission, Neonate

Abstrak

Tuberkulosis kongenital merupakan infeksi neonatus yang terjadi akibat transmisi vertikal Mycobacterium tuberculosis dari ibu ke bayi. Tuberkulosis kongenital merupakan kasus yang jarang, kurang dari 500 kasus telah dilaporkan di seluruh dunia dengan angka mortalitas mencapai 40%. Diagnosis sering kali sulit ditegakkan karena manifestasi klinis yang tidak spesifik dan menyerupai sepsis neonatorum. Kami melaporkan kasus seorang bayi prematur berusia 1 bulan yang dirawat dengan keluhan distress nafas progresif, demam, dan batuk. Foto toraks menunjukkan gambaran "snow storm appearance" yang sesuai dengan tuberkulosis milier. Ibu pasien memiliki riwayat batuk kronis sebelum kehamilan dan kemudian terkonfirmasi positif Mycobacterium tuberculosis melalui pemeriksaan PCR sputum. Hasil PCR sputum pada bayi juga menunjukkan hasil positif. Pemeriksaan laboratorium menunjukkan leukositosis dengan dominasi neutrofil serta peningkatan kadar transaminase. Pasien menggunakan alat bantu nafas CPAP dan diberikan terapi antituberkulosis (2HRZE/10HR) disertai kortikosteroid karena keterlibatan respirasi yang berat. Selamat rawatan pasien mengalami perbaikan klinis dan perbaikan radiologis sehingga pasien dapat dipulangkan setelah 16 hari perawatan. Diagnosis tuberkulosis kongenital pada pasien ini ditegakkan berdasarkan riwayat dugaan tuberkulosis paru pada ibu sebelum kehamilan, serta terkonfirmasi melalui hasil PCR sputum yang positif pada ibu dan bayi. Biopsi hati yang merupakan golden standar diagnosis tidak dapat dilakukan karena kondisi pasien yang tidak stabil dan pertimbangan manfaat prosedur invasif. Kesadaran terhadap faktor risiko tuberkulosis pada ibu berperan penting dalam kecurigaan kasus tuberkulosis kongenital, memungkinkan diagnosis dini serta pemberian terapi tepat waktu sehingga dapat menurunkan angka kematian dan mencegah komplikasi jangka panjang.

***Kata kunci** : Tuberkulosis Kongenital, Tuberkulosis Milier, PCR Sputum, Transmisi Vertikal, Neonatus*

I. BACKGROUND

Congenital tuberculosis (TB) is a rare neonatal infection resulting from vertical transmission of Mycobacterium tuberculosis from mother to fetus. The condition often goes unrecognized due to its non-specific clinical presentation and rarity. Fewer than 500 cases documented worldwide.[1,2] However, even with appropriate treatment Congenital TB is associated with a high mortality rate of up to 40%, and the disease fatal without treatment [2,3,4]

Most cases of Congenital Tuberculosis occurring in settings of high maternal TB prevalence, immunosuppression, or late maternal diagnosis. The disease poses diagnostic challenges due to its resemblance to other neonatal infections and sepsis-like syndrome.[5] It is difficult to differentiate between true Congenital TB and those acquired postnataly, in general, clinical presentation and management remain the same between those group.[3,6]

Perinatal Transmission of Congenital Tuberculosis most commonly associated with disseminated infection in mother. There are two theories has been conduct, Hematogenous transmission through placenta and Aspiration or Ingestion of Infected Amniotic Fluid.[7]

1. Transplacental Transmission

In mothers with miliary TB or active pulmonary TB accompanied by bacteremia, M. tuberculosis may invade the intervillous space of the placenta. Bacilli penetrate the syncytiotrophoblasts and enter the fetal circulation through the umbilical vein. The liver is usually the first organ affected, functioning as the primary filter of blood from the umbilical vein, leading to the formation of a primary hepatic complex. From there, hematogenous dissemination may spread to other fetal organs such as the spleen, lungs, kidneys, and brain.[3,6,7]

2. Aspiration of Infected Amniotic Fluid

In cases of genital or placental TB, rupture of tuberculous lesions into the amniotic fluid may occur. The fetus subsequently aspirates or swallows the infected fluid, leading to primary infection in the lungs or gastrointestinal tract, followed by systemic dissemination.[5,6,8]

In neonates and infants, the immune system is still immature. CD4 T-cell production of IFN-γ is lower in children aged 0–3 years compared to adults.[9,10] Phagocyte function (macrophages, neutrophils) and cytokine production (such as IL-12, TNF-α) are also not fully developed, resulting in inadequate granuloma formation to control M. tuberculosis. Consequently, hematogenous spread is more likely to occur. [5,9,11]

Clinical symptoms often manifest within the first 2 - 4 weeks of life, The clinical presentation is highly non-specific, making diagnosis particularly difficult. Common symptoms may include poor feeding, inadequate weight gain, lethargy, irritability, coughing, respiratory distress, fever, vomiting, abdominal bloating, and seizures. On physical examination, hepatosplenomegaly and lymphadenopathy are frequently observed.[4,6]

Assessment of maternal risk factor for TB is important in suspected congenital tuberculosis. It occurs only when the mother develops active disease during pregnancy, more frequent in miliary and genital forms of TB. Although the maternal TB can be asymptomatic (especially in cases of genital TB) or manifest after childbirth.[7]

Cantwell's criteria aid diagnosis and require at least one of the following: lesions present within the first week of life, primary hepatic complex or liver granulomas, maternal genital tract or placental TB, or exclusion of postnatal sources.[4] This criteria is difficult to fulfill and has several limitation.[6] The only pathognomonic lesion in congenital TB is

the presence of a primary hepatic complex with caseating granulomas.[7]

Polymerase chain reaction (PCR) testing of bronchoalveolar lavage fluid has proven effective as a diagnostic tool in neonates. Cerebrospinal fluid (CSF) analysis is also important, as tuberculous meningitis occurs in approximately one-third of congenital TB cases. The Mantoux test is often negative in neonates at the initial stage, but may become positive within a few months. Liver biopsy is 100% sensitive in the diagnosis of congenital tuberculosis.[5,12]

According to recommendations from the American Academy of Pediatrics (AAP), the initial intensive phase of treatment consists of a four-drug regimen for the first two months, including isoniazid (INH), rifampisin (RIF), pyrazinamide (PZA), and either ethambutol (EMB) or an aminoglycoside such as amikacin. Following the intensive phase, the continuation phase typically involves 7 to 10 months of isoniazid and rifampisin therapy, bringing the total treatment duration to approximately 9 to 12 months.[5,6,13] In cases with suspected tuberculous meningitis, adjunctive corticosteroid therapy (prednisone) at a dose of 2 mg/kg/day for 4–6 weeks, tapered gradually, is recommended.[5,12]

Despite treatment, congenital TB remains associated with a high mortality rate of up to 40%, primarily due to its nonspecific clinical manifestations, which often delay diagnosis.[11]

II. CASE REPORT

A preterm infant born at 36 weeks of gestation, currently with a corrected age of 4 days and a chronological age of 1 month and 4 days, was admitted to Andalas University Hospital with the chief complaint of worsening shortness of breath since one day prior to admission. Shortness of breath had been going on for 5 days. The respiratory distress was preceded by a productive cough that began five days prior to admission, described as wet with coarse breath sounds.

The infant also developed a fluctuating, low-grade fever. There was no history of seizures.

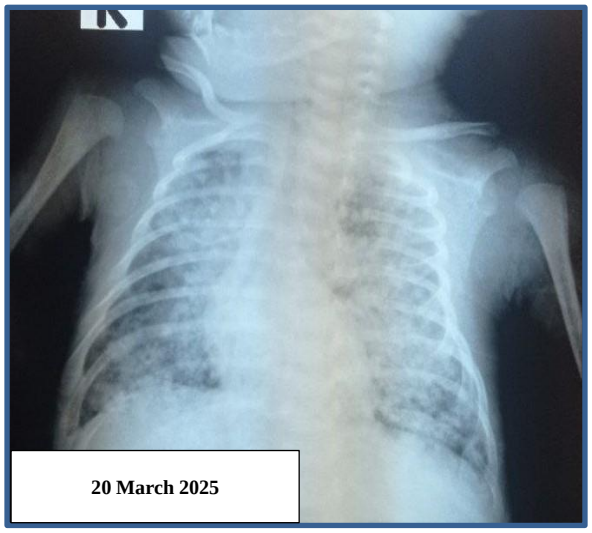
The patient is the fifth child, born via spontaneous vaginal delivery attended by a general practitioner, at a gestational age of 36 weeks. Birth weight was 2 kg. The infant cried vigorously at birth, showed no signs of respiratory depression, and had no cyanosis. There is no history of resuscitation at birth. The Patient had not received BCG immunization. Patient also appeared malnourished, with a body weight of 2,7 kg and a body length of 52 cm (WHZ < -3SD).

The patient's mother sought medical attention at regional hospital 1 month prior to pregnancy for a suspected tuberculosis due to prolonged history of cough. Sputum examination was performed with negative results, and no anti-tuberculosis treatment was initiated.

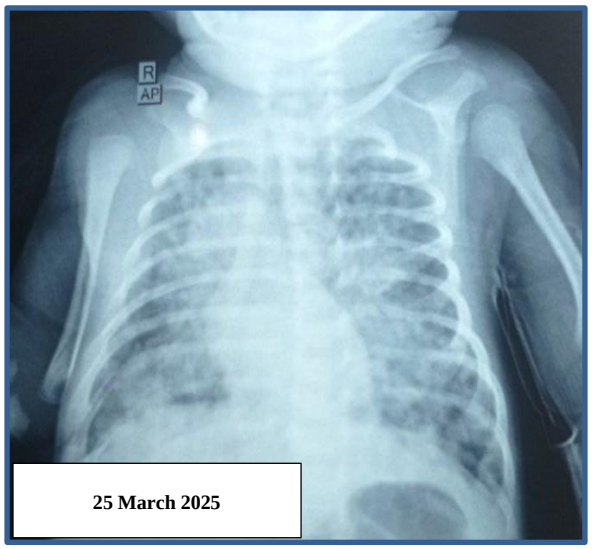
Upon admission the patient appeared severely ill but was fully conscious and cried vigorously. The child was visibly agitated and in severe respiratory distress. Respiratory rate was 50–60 breaths per minute. Heart rate was 180 beats per minute, with a strong palpable pulse. Oxygen saturation on room air was 84%. After given CPAP (Continuous Airway Positive Pressue) therapy (PEEP 7 cmH_2O, FiO_2 40%), oxygen saturation improved to 92–94%, with S/F ratio 235. The patient was febrile with a body temperature of 38,2°C. On respiratory examination, there was marked epigastric and intercostal retraction. Auscultation revealed prominent fine crackles across all lung fields. No wheezing was noted. Cardiovascular examination showed regular heart sounds without audible murmurs. Abdominal examination revealed a soft and non-distended abdomen, with normal bowel

sounds. The liver and spleen were not palpable. Extremities were warm, with a capillary refill time of less than 2 seconds. No pallor, mottling, or peripheral cyanosis was observed.

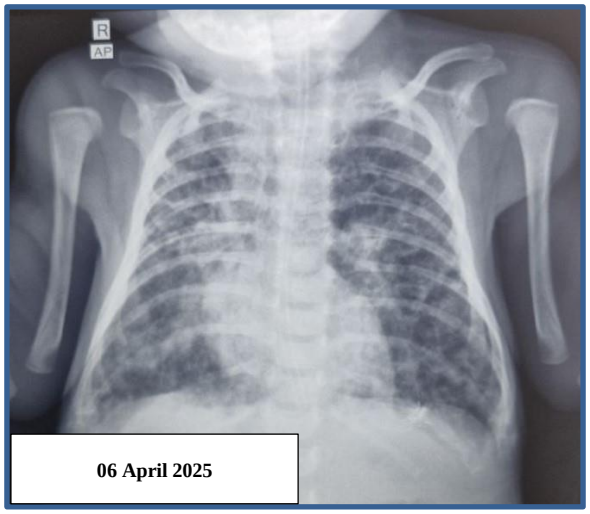
Patient's chest X-ray revealed numerous small nodular opacities diffusely distributed across both lung fields symmetrically, consistent with a “Snowstorm appearance”. Thus, the patient was suspected to have congenital tuberculosis.



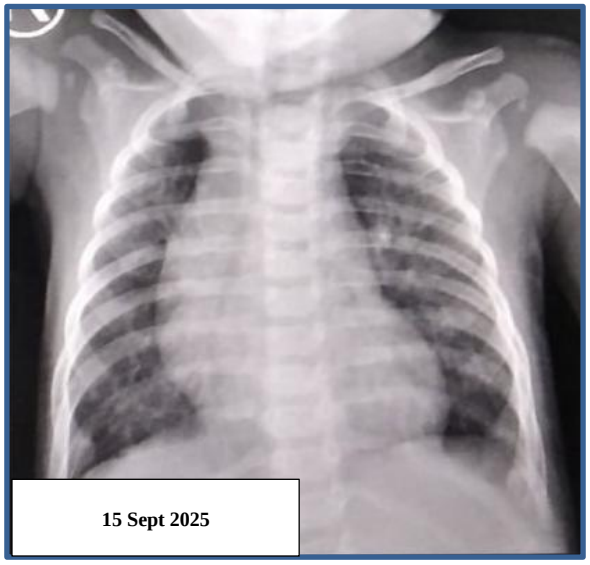
Picture 1. X-Ray Upon Admission



Picture 2. X-Ray On 5th Day Of Treatment



Picture 3. X-Ray Upon Discharge



Picture 4. Follow Up X-Ray At Polyclinic

On laboratory finding, Haemoglobin 11.5 mg/dl, Leucocyte count 19,7 x 109 /L (neutrophils 85%, lymphocytes 10%, monocyte 3%), and Platelets 193 x 109 /L.

Blood gas analysis result in metabolic acidosis, Lac 2.4 /pH 7.38 /pCO2 26 /pO2 152 /HCO3- 15.4 /BE -8.8 /SpO2 99. Liver function tests showed a twofold elevation in AST (142 U/L) and a 3.3-fold increase in ALT (110 U/L). Mantoux test was not reactives.

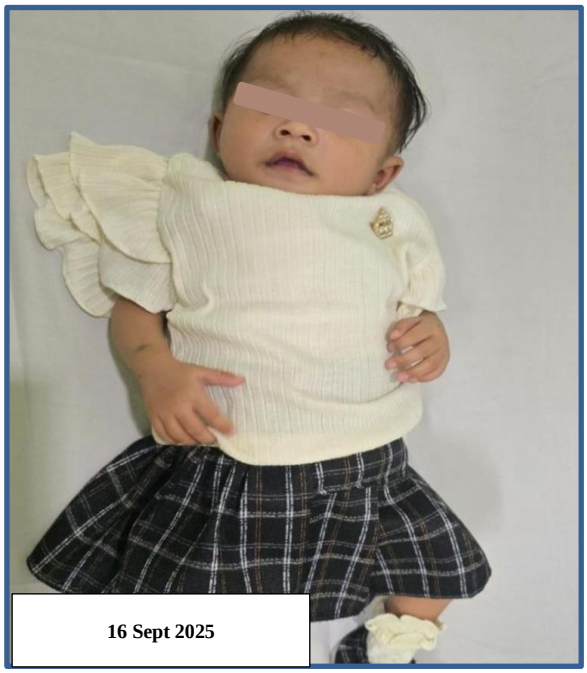
While the infant was hospitalized, the mother also reported persistent fatigue and a prolonged cough, which remained prominent. She was subsequently advised to

be admitted for further evaluation. During her hospitalization, given the clinical suspicion of tuberculosis, a sputum PCR test using the Xpert MTB/RIF assay was performed, and the result showed Mycobacterium tuberculosis (MTB) detected. The infant's sputum PCR examination also showed MTB detected . In infants with miliary tuberculosis, central nervous system involvement in the form of meningitis must be ruled out. A lumbar puncture was subsequently performed on the patient, and the cerebrospinal fluid analysis revealed normal results. Thus ruled out tuberculous meningitis.

Based on the mother's history of suspected pulmonary tuberculosis prior to pregnancy, along with the confirmed diagnosis of tuberculosis through a positive sputum PCR test in the mother and the infant, a diagnosis of congenital tuberculosis was established. The Patient was initiated on anti-tuberculosis therapy 2HRZE / 10 HR, [Isoniazid 10mg/kg (H), Rifampicin 15mg/kg (R), Pyrazinamid 35 mg/kg (Z), Ethambutol 20 mg/kg (E)]. In cases of miliary tuberculosis with severe respiratory distress, prednisone was administered at a dose of 2 mg/kg and tapered off. Patient also received treatment for malnutrition, along with a high calorie formula, initiated at 50% of the recommended dietary allowance (RDA) and gradually increased according to patient's tolerance. The patient showed a good response and symptoms resolves. Repeat chest

radiograph revealed resolution . Patient no longer need oxygen support. The patient was discharged after 16 days of hospitalization. Patient then continued follow-up at polyclinic with monitoring of therapeutic response, medication adherence, and nutritional status. At six months of anti-tuberculosis therapy, patient gained 5.3 kg in body weight and reached a body length of 60 cm. The nutritional status showed improvement, with the conclusion of good nutrition and normal stature. The patient no longer exhibited respiratory symptoms. Follow-up chest radiography demonstrated further improvement.

Picture 4. Clinical Photo Upon Admission



Picture 4. Clinical Photo After 6 Months Of Therapy

III. DISCUSSION

Congenital TB should be suspected in any newborn of a mother with a history of disseminated or extrapulmonary TB during pregnancy or with active disease during

labour or the postpartum period, even if the physical examination at birth is normal.[7]

In newborns and infants, the immune response is immature. The IFN-γ and CD4 T cells are key to M. tuberculosis control. T cells (CD4+) specific for M. Tuberculosis is lower in younger children (0–3 years old), which are essential for controlling intracellular pathogens like M. tuberculosis.[9,10] Phagocyte (macrophages, neutrophils) function and cytokines production (e.g IL-12, TNF-alfa) are underdeveloped, intercellular killing is inadequate. This immature immunity results in inadequate granuloma formation to control M. tuberculosis. This promoted hematogenous dissemination, and congenital TB often presents as disseminated/miliary TB.[4] M. tuberculosis tends to grow uncontrolled, Mycobacteria can spread, leading to meningitis or miliary disease forms. This occurs more often in infants and young children than in immune-competent adults.[5,9,11]

This patient did not receive BCG immunization. BCG vaccination has been demonstrated to provide protection against M. tuberculosis infection and progression to active TB disease.[14] This effect is mediated through the activation of Mycobacteria-specific CD4+ and CD8+ T cells as well as B cells, leading to the development of memory and plasma cells and the production of antigen-specific antibodies that respond to TB antigens.[15]

Diagnosing neonatal TB requires a high degree of suspicion, as the clinical presentation tends to be atypical and it carries a high morbidity and mortality.[16] This case describes an infant presenting with respiratory distress, characterized by fever and shortness of breath, preceded by a productive cough.

Chest radiographic examination revealed multiple small nodules distributed throughout the lung, consistent with the characteristic “snowstorm appearance” of miliary tuberculosis. A strong suspicion of maternal tuberculosis transmission was supported by positive sputum PCR test in mother, thereby confirming active pulmonary TB. Mantoux test result for the infant was non-reactive.

Mantoux test in neonates often negative in initial stage but frequently becomes positive within a few months. The infant's sputum examination using the PCR also revealed the presence of MTB detected. PCR gastric and tracheal aspirates are far more sensitive than the Mantoux test. Gastric and tracheal aspirates are positive in 80% whereas, Mantoux is positive in less than 15% of cases.[5]

The only pathognomonic lesion in congenital TB is the presence of a primary hepatic complex with caseating granulomas.[7] Abdominal examination revealed that liver and spleen were not palpable. Liver function tests showed a twofold elevation in AST (142 U/L) and a 3.3-fold increase in ALT (110 U/L). In this patient, a liver biopsy could not be performed due to the patient's unstable condition and the consideration of the benefit invasive procedure. The diagnosis of congenital tuberculosis confirmed based on the mother's history of suspected pulmonary tuberculosis prior to pregnancy, along with the confirmed diagnosis of tuberculosis through a positive sputum PCR test in the mother and the infant.

In this patient, despite the absence of clinical signs of central nervous system involvement, a lumbar puncture was performed and yielded normal results. M. tuberculosis tends to grow uncontrolled in infant due to immature immunes response. Mycobacteria can spread, leading to meningitis or miliary disease forms. Cerebrospinal fluid analysis for suspected central nervous system involvement is very essential because

tubercular meningitis occurs in 1/3 rd cases of congenital TB.[5,9]

Congenital TB is treatable if diagnosed and treated early.[17] The patient received comprehensive treatment, including respiratory distress management with CPAP support, definitive therapy with anti-tuberculosis drugs and treatment for malnutrition. In cases of miliary tuberculosis with severe respiratory distress, prednisone was also administered. The patient showed a good response to the administered therapy, with improvement in respiratory effort, resolution of fever, and no further need for oxygen support. Repeat chest radiograph revealed resolution. The patient was discharged after 16 days of hospitalization.

At admission, the patient presented with malnutrition. After six months of therapy, the patient showed weight gain and improvement in nutritional status to well-nourished. Children with malnutrition have a twofold higher risk of developing tuberculosis. Studies have also demonstrated that malnutrition contributes to more severe disease manifestations and prolonged hospital stays.[18,19] Malnutrition is a common comorbidity that can exacerbate disease progression. Tuberculosis infection may result in loss of appetite, leading to reduced dietary intake and subsequent malnutrition.[20] In addition, TB infection increases the body's metabolic demands, thereby elevating the requirements for calories and nutrients, resulting in further depletion of nutrient stores. This increase nutrient requirement is largely driven by the immune response to infection. Therefore , the management of malnutrition to support immune response is mandatory in treatment of tuberculosis patients.[20,21]

IV. CONCULUSION

Congenital TB is the result of complex interactions between maternal infection, placental pathology, and neonatal immunodeficiency. The primary mechanisms include hematogenous transplacental dissemination and aspiration of infected amniotic fluid. Due to the immature immune response in neonates, the infection can rapidly disseminate, affecting multiple organs. Awareness of maternal risk factor for TB plays a pivotal role in suspected congenital tuberculosis, in conjunction with positive PCR test, enables early diagnosis and prompt treatment, reducing mortality and long-term sequelae.[3]

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