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Case Study

A Case of Perinatal Tuberculosis with Adverse Reaction to Antituberculous Drugs and Hypercalcemia: An Underestimated Enemy

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Abstract

The clinical presentation of perinatal tuberculosis (PTB) is highly variable. It can range from an asymptomatic condition to nonspecific symptoms such as lethargy, fever, feeding difficulties, poor weight gain, respiratory distress, hepatosplenomegaly, lymphadenopathy, abdominal distension with ascites, or a clinical picture resembling "neonatal sepsis". Its approach involves using tools to establish differential diagnoses with other infectious diseases and the immediate study of household contacts. Complications, sequelae, and high mortality rates are often recorded, depending on the form of presentation and the time elapsed until diagnosis and treatment, making it a true medical challenge. The objective of this report is to present a case of PTB with multisystem failure, hepatic adverse reaction to anti-TB drugs (ADR) and hypercalcemia.

Keywords: *Tuberculosis; Perinatal Tuberculosis; Hypercalcemia; Disseminated Tuberculosis; Adverse Reactions to Antituberculous Drugs*

Introduction

Perinatal tuberculosis (PTB) is a severe form of tuberculosis. Its incidence is unknown because many children die before the diagnosis is established, contributing to underreporting of this condition. PTB includes: a) congenital TB, which usually originates from a mother with TB who infects the child through intrauterine or birth canal infection during childbirth, and b) neonatal TB, acquired through airborne transmission from the mother or other sources of infection in the first days of life. Differentiating congenital TB from neonatal TB has epidemiological significance, as identifying the contagious source helps to treat it and prevent transmission.

The immaturity of the child's immune system, especially in premature babies, plays an important role in the pathogenesis of this infection. This is due to the decreased specific response of Th1 helper lymphocytes, which reduces the ability to effectively respond to *Mycobacterium tuberculosis* (*M.T*) infection.

PTB often presents with nonspecific signs. Differential diagnoses with other causes of neonatal sepsis are required. Due to its high mortality, the prognosis depends on timely diagnosis and treatment to prevent the development of severe complications.

Clinical Case

A 2-month-old eutrophic girl of Creole ethnicity, born from a controlled pregnancy with oligohydramnios and delivered by cesarean section due to premature rupture of membranes (PROM). She was full-term with appropriate weight for gestational age. Personal history includes hospitalization at one month of age for bronchiolitis with hypoxemia, requiring oxygen therapy via nasal cannula for 2 days. Chest X-ray showed bilateral interstitial infiltrates. No nasopharyngeal swab test was performed.

Presenting complaints included fever, respiratory difficulty, and cough for 4 days. At physical examination, the patient was in poor general condition: tachycardic, tachypneic, distressed, with abdominal distension (ascites), and poorly perfused. She was febrile (38.5°C/101.3°F) with no visible B.C.G (Bacillus Calmette-Guerin) scar. She was admitted to the Pediatric Intensive Care Unit with a presumed diagnosis of multiorgan failure due to septic shock.

Admission laboratory data: leukocytosis (32,200/mm^3), anemia (hemoglobin 8.8 g/dl), C-reactive protein (CRP) 10.2 mg/dl, urea 0.83 g/l, lactate dehydrogenase (LDH) 6741 IU/l, aspartate aminotransferase (AST) 7430 IU/l, alanine aminotransferase (ALT) 1284 IU/l, gamma-glutamyl transpeptidase (GGT) 154 IU/l, creatinine 1.3 mg/dl.

Treatment included ceftriaxone 100 mg/kg/day, amikacin 15 mg/kg/day, and corticosteroids (dexamethasone 0.6 mg/kg/day). She required inotropic support for 14 days, peritoneal dialysis for 4 days, mechanical ventilatory assistance (MVA) for 21 days, non-invasive ventilation (NIV) for 2 days, and remained dependent on oxygen via nasal cannula. She received multiple transfusions of red blood cells and platelets.

A consultation was made with the Pediatric Pulmonology Service. Due to the patient's critical condition and the miliary pattern observed in radiology, the condition was assumed to be sepsis of possible tuberculous etiology. The following tests were requested:

a) Tracheal aspirate for Ziehl-Neelsen (ZN) staining and culture (C).

b) Blood cultures positive for *M. tuberculosis* (*MT*) (MGIT™ 960), sensitive to H/R.

c) Cerebrospinal fluid (CSF) and peritoneal fluid cultures negative for common germs and MT. Gene Xpert® (*MT*/RIF) could not be performed. Omental biopsy showed mature adipose tissue and brown fat with a mild diffuse nonspecific mononuclear lymphoplasmacytic inflammatory process.

d) Serologies for human immunodeficiency virus (HIV), hepatitis (A, B, C), toxoplasmosis, herpes simplex, syphilis (VDRL), and Chagas disease, as well as Mycoplasma pneumoniae, were negative.

e) Imaging studies: Chest X-ray showed a bilateral interstitial infiltrate with a miliary pattern. High-resolution computed tomography of the chest (HRCT) was performed later due to the critical condition of the patient, revealing areas of increased density with a consolidative aspect associated with bronchogram, peribronchovascular involvement in the middle lobe, lingula, and posterior basal segments of both lower lobes. Ground-glass and micronodular patterns with a tendency to consolidation were observed in both upper lobes (Figure 1 and 2). Pleural ultrasound showed bilateral pleural effusion (right 8 mm^3, left 3 mm^3). Abdominal ultrasound revealed free fluid in the cavity and homogeneous hepatomegaly. Brain ultrasound was normal.

f) Cardiac evaluation: Electrocardiogram was normal. Echocardiogram showed a patent foramen ovale (PFO) without hemodynamic impact, with the rest being normal.

g) Fundus examination ruled out the presence of choroidal tubercles.

h) Epidemiological study of the source: A non-cohabiting sister had a history of bacillary TB and completed treatment. A paternal uncle with bacillary TB was diagnosed following the child's illness. TB was ruled out in the rest of the contacts, and chemoprophylaxis was indicated for those who needed it.

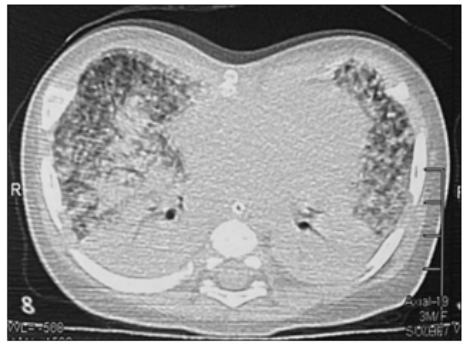

Figure 1: *Chest CT scan shows areas of increased density with a consolidative appearance, associated with peribronchovascular air bronchograms in the middle lobe, lingula, and posterior basal segments of both lower lobes. Areas of ground-glass opacity and micronodular infiltrates are noted in the upper lobe.*

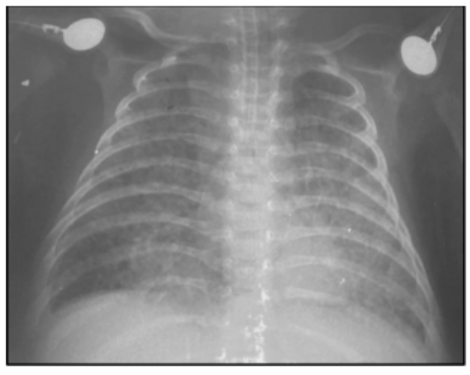

Figure 2: *Chest X-ray (PA view) reveals miliary disease. Multiple, uniform, and disseminated micronodules (2 - 4 mm) are present in both hemithoraces, compatible with a diffuse miliary interstitial pattern.*

The results confirmed the diagnosis of tuberculous sepsis.

Evolution: Due to liver and kidney failure, second-line anti-TB treatment was initiated with the following drugs: ethambutol (E) 20 mg/kg/day, meropenem 10 mg/kg/day, levofloxacin (Lfx) 15 mg/kg/day, streptomycin (S) 20 mg/kg/day, and linezolid (Lzd) 10 mg/kg/day.

The patient remained in intensive care for 25 days. She was then transferred to the general ward with oxygen therapy via nasal cannula, anti-TB drugs, and gradually decreasing corticosteroids, coinciding with clinical and radiological deterioration. Analytical studies showed hypercalcemia and decreased parathyroid hormone levels. Evaluated jointly with endocrinology and nephrology, it was assumed

to be hypercalcemia secondary to granulomatous disease. Hyperhydration and meprednisone at 3 mg/kg/day were prescribed, leading to marked improvement.

A month and a half after starting treatment, liver enzymes normalized. First-line drugs were then gradually introduced: rifampicin (R) 15 mg/kg/day, isoniazid (H) 15 mg/kg/day, pyrazinamide (Z) 25 mg/kg/day, progressively until full doses were reached, along with pyridoxine 10 mg. One month later, the patient developed a hepatic adverse drug reaction (ADR) and was switched to streptomycin, levofloxacin, and ethambutol. This resolved within 9 days, and first-line drugs were gradually reintroduced with good progress.

After 4 and a half months of hospitalization, the patient was in good general condition with adequate weight gain, normal analytical controls, and improved chest X-rays. She was discharged from the hospital with isoniazid (H), rifampicin (R), pyridoxine (vitamin B6), and oxygen therapy via nasal cannula (until 9 months of age). She completed 12 months of anti-TB treatment. Audiological and ophthalmological evaluations were normal. Chest X-ray was normal.

Discussion

Perinatal tuberculosis (PTB) includes both prenatal or congenital TB and postnatal or neonatal TB [1,2]. The increase in the incidence of PTB is likely due to delays in the early detection of TB during pregnancy. This can result from physiological and immunological changes that make women more susceptible to reactivating latent TB or acquiring TB through infection. Additionally, the lack of epidemiological studies in symptomatic respiratory patients contributes to this rise. Its frequency is not well determined [3-5].

Congenital TB is acquired through several pathophysiological mechanisms: a) Koch's bacilli reach the fetus via the umbilical vessels, creating a primary focus in the liver and periportal lymph nodes, which was not observed in our patient. The bacilli can then reach the fetal lungs through the bloodstream, b) Aspiration of amniotic fluid containing Koch's bacilli results in the formation of primary complexes at the hilar level, leading to pulmonary forms, which were not found in our case, c) Deglutition of infected amniotic fluid, leading to intestinal TB, d) Penetration through the Eustachian tube, causing tuberculous otitis, e) Infection in the maternal genitourinary tract, potentially contaminating the newborn during delivery.

Regardless of the pathophysiology, dissemination can occur in 25-35% of cases through the lymphatic or hematogenous route, affecting multiple organs.

In postnatal or neonatal TB, the inhalation route is common across all forms of presentation.

In our case, the epidemiological study ruled out maternal TB but identified TB in the family environment, confirming the diagnosis of PTB.

In both congenital and postnatal forms, the immaturity of the child's immune system plays a significant role, especially due to the decreased specific response of Th1 helper lymphocytes, which reduces the ability to effectively respond to Mycobacterium tuberculosis infection [6,7].

Clinically, in congenital TB, signs and symptoms usually appear in the second or third week of life. The most common include stagnant weight curve, food refusal or increased residuals, fever (48%), lethargy, irritability, seizures, meningitis (21 - 50%), unexplained neurological focality, especially cranial nerve palsies, respiratory difficulty, and apneas (72%). Persistent otorrhea without tympanic membrane perforation, often accompanied by preauricular and retromandibular adenomegaly (17%), may also raise suspicion. Hepatosplenomegaly (76%), sometimes accompanied by jaundice due to the compression of extrahepatic bile ducts by hilar adenomegalies, is common. Peripheral adenomegaly (38%) and abdominal distension, vomiting, or ascites of unknown etiology are also frequently observed [8-10].

Diagnosing congenital TB requires a high index of suspicion. It was initially based on Beitzki's criteria (1935), which required liver biopsy to demonstrate granulomas. These criteria were later modified by Cantwell and colleagues (1994), who defined the condition when one or more of the following conditions were met: 1) lesion in the first week of life, 2) hepatic primary complex with caseating granulomas, 3) confirmation of TB in the placenta or maternal genital tract (uterus or adnexa), and 4) exclusion of postnatal exposure to a bacillary source, including hospital staff. Currently, the latter concept is included in postnatal or neonatal TB [2,8,11-14].

The diagnostic tests for congenital and neonatal TB are similar and are based on the microbiological detection of the bacillus, as was the case in our patient with positive blood cultures and tracheal aspirates for Koch's bacillus. They recognize two levels:

1. 1st level: a) Biochemistry: Leukocytosis with neutrophilia, anemia, and thrombocytopenia are often seen, along with hypertransaminasemia and elevated C-reactive protein, b) Tuberculin test: Negative in most cases due to impaired specific T-helper lymphocyte response. It was not performed in our case; the test should be repeated after 3 months, c) Fundus examination: Choroidal tubercles may be seen, which were not present in our patient, d) Interferon gamma release assay (IGRA): Few data are available on the diagnostic yield of IGRA in neonates, e) Chest X-ray: Shows different patterns depending on the route of infection. In aspirative forms, nodular elements confluent in some areas and zones of air trapping in both lung fields are usually observed. When infection occurs via the umbilical route, bilateral, diffuse micronodular lesions are seen, covering both lung fields from apex to base, resembling true miliary dissemination, as observed in our case. Lam Van Nguyen and colleagues report this pattern in about 50% of cases, f) Abdominal ultrasound: The only pathognomonic neonatal lesion of congenital TB is the presence of a primary complex in the hepatic hilum, g) If there is a history of gestational tuberculosis, histopathological and microbiological studies of the placenta and amniotic fluid should be performed, h) Gastric lavage: Shows 70 - 80% positivity, i) Epidemiological focus study: Positive in this case.
2. 2nd level: a) Cerebrospinal fluid (CSF): Cytochemistry, PCR, BK, and culture. Our patient had a negative culture for Koch's bacillus. If the central nervous system is affected, neuroimaging such as contrast-enhanced CT scan, ultrasound, or brain MRI is requested, b) Other invasive tests: Bronchoscopy with bronchial wash, liver, transbronchial or lymph node biopsy, performed if previous studies are inconclusive and there is a strong clinical suspicion, c) If there is pleural effusion, a pleural puncture with adenosine deaminase (ADA) study should be considered, d) Molecular diagnostic techniques by PCR: Allow early diagnosis and simultaneous detection of resistance mutations [8,14-17].

Suspicion of PTB is based on the lack of response to traditional antibiotic treatment, especially in children of mothers with risk factors or tuberculosis infection. Differential diagnoses include sepsis, pneumonia (viral, bacterial, *Candida*, *P. jirovecii*), and vertically transmitted infections (toxoplasmosis, *cytomegalovirus* (CMV), rubella, herpes virus, HIV).

The treatment of PTB (congenital and neonatal) is the same and should be initiated based on the probability of TB, even before bacteriological confirmation is received. According to the World Health Organization (WHO) and national guidelines, it consists of H, R, Z, and E in the initial phase, followed by R and H. Due to the high bacillary load, respiratory isolation is necessary. The total duration of therapy should be at least 12 months [18].

As our patient experienced a hepatic adverse drug reaction (ADR), second-line anti-TB drugs were used according to national guidelines. These drugs are less effective, more toxic, require prolonged use, and should be managed by TB experts. Once liver enzymes normalized, first-line drugs were reintroduced.

An ADR is any unexpected and undesired event following the administration of anti-TB drugs at the usual dose and route during treatment. ADRs are classified as: a) Intolerance manifestations (most common), b) Toxic reactions (usually dose-dependent), c) Based on

the drug dose: Type I: Dose-dependent, and Type II: Dose-independent, d) Based on severity: mild: minor clinical manifestations managed symptomatically without discontinuing drugs, moderate: Significant manifestations not life-threatening but requiring therapeutic measures and/or temporary or permanent drug suspension and severe: Life-threatening manifestations causing permanent disability, requiring hospitalization, congenital anomalies, malignancies, or death.

Most cases involve mild, asymptomatic, and transient transaminase elevations, where treatment should not be interrupted as they resolve spontaneously. If transaminases increase more than five times the upper normal limit without symptoms or more than three times with symptoms, or if bilirubin increases, drug suspension is necessary. The management approach includes waiting for hepatogram normalization or administering at least three non-hepatotoxic drugs.

Genetic variability is possibly the most important risk factor for hepatotoxicity, as genetic polymorphism strongly influences the metabolism of drugs and foreign substances in the body. A higher incidence of hepatic alterations is observed in the study of the genotype and phenotype of N-acetyltransferase 2 (NAT2), which reveals different alleles associated with the speed of acetylation, either rapid or slow. This is seen in children under 3 years old, as in our case, and in the presence of the major histocompatibility complex, HLA-DQ.

Our patient experienced a moderate hepatic ADR with transaminase levels increasing more than five times the normal values, requiring the replacement of first-line anti-TB drugs until normalization, after which progressive reintroduction was initiated. Administering medication under direct observation allows early detection of any symptoms or warning signs of imminent ADRs. In our case, aminoglycosides were used, with strict laboratory monitoring due to renal failure. Additionally, it is necessary to monitor ototoxicity with auditory function tests. Ethambutol requires strict controls due to the potential for optic neuritis, which our patient did not develop.

Similar to what is described by R. Pece, our case presented with hypercalcemia [19]. This is observed in granulomatous diseases, including sarcoidosis and TB. The primary abnormality results from an increase in intestinal calcium absorption. It is described as being associated with high concentrations of calcitriol produced in the granulomatous tissue, along with other contributing factors. The absence of suppression of calcitriol synthesis in granulomatous processes is due to the extrarenal production of calcitriol, independent of PTH, from 25(OH) D3 by activated mononuclear cells (primarily macrophages) in the lungs and lymph nodes. The treatment of hypercalcemia in these cases should be aimed at reducing intestinal calcium absorption and calcitriol synthesis. This can be achieved by reducing calcium intake, hyperhydration, and administering low doses of steroids, as occurred in our case.

The first-line drugs and dosages are the same as those for treating tuberculosis in other pediatric ages. The dosages of the drugs must consider body weight and weight gain, which can be very rapid in young infants. Pharmacokinetic studies of anti-TB drugs in newborns, especially premature neonates, are currently very limited. The duration of treatment depends on the clinical form. Vitamin B6 should be added. Respiratory isolation measures should be taken for those who present a positive bacilloscopy in gastric juice or tracheal aspirate, as in our patient.

The prognosis of perinatal tuberculosis (TBP) depends on the diagnostic suspicion in the neonate or infant and the early administration of treatment, which guarantees a cure and prevents fatal disseminated forms or sequelae. The therapeutic response is determined by the regression of clinical symptoms. The literature reports a high mortality rate.

Upon discharge, patients should receive regular monthly check-ups until treatment completion to monitor clinical progress, treatment adherence, and drug toxicity. Follow-up should continue for two years after treatment completion.

Our diagnosis of TBP was based on a high index of clinical suspicion in a girl who was admitted with septic shock, respiratory focus, and multi-organ failure, coupled with the exclusion of sepsis from other etiologies, radiological findings compatible with a miliary pattern, the absence of maternal TB, a positive epidemiological environment, and positive bacilloscopy with recovery of *M. tuberculosis*.

Conclusion

TBP is often underdiagnosed due to its broad clinical variability. It should be suspected particularly in developing countries, where there is a high prevalence of TB, in a newborn or infant presenting with nonspecific symptoms, multisystem involvement, and a lack of response to initial empirical antibiotic treatment. All means should be exhausted to achieve a timely diagnosis, allowing for the initiation of treatment and therapeutic success, with strict follow-up to detect complications. Adverse reactions to anti-TB drugs must be monitored. The presentation of hypercalcemia is interesting and uncommon. An epidemiological study of the source should always be conducted. The best way to prevent TBP is through the proper treatment and prevention of TB in pregnant women, especially those from endemic regions.

Conflicts of Interest

The authors declare having no conflicts of interest.

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