

Congenital Tuberculosis: A Diagnostic Challenge that Stems from the Mother

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Abstract

Tuberculosis (TB) is an age-old disease with a high prevalence worldwide; however, congenital presentation is infrequent and is rarely described in the literature. The incidence of congenital TB is not well-established, with fewer than 400 cases published in scientific literature. Fetal transmission rates can vary between 0 - 16%, with transmission being exceptional with maternal pulmonary TB, especially when the mother has received appropriate treatment, while more common from genital or miliary/disseminated TB. We present the case of a 31-week preterm newborn with a mother's history of miliary TB with meningeal involvement diagnosed before delivery but with poor adherence to pharmacological treatment. Congenital TB was diagnosed as early as the second day of life, leading to a prompt initiation of therapy.

Keywords

Congenital Tuberculosis, Newborn, Transmission

1. Introduction

Tuberculosis is an ancient disease with a high prevalence worldwide; however, congenital presentation is not frequent and is little reported in the literature. It is acquired in utero by transplacental passage through the umbilical vein, by aspiration and ingestion of contaminated amniotic fluid, or by direct contact with maternal genital lesions. Diagnosis is often challenging, and neonates, in particular, represent a vulnerable population at high risk of developing severe acute disseminated disease. They usually present with nonspecific clinical manifestations; hence, the epidemiological history is critical for diagnostic suspicion [1].

In most previous case reports, the diagnosis of the neonate was not known until the onset of symptoms in the third week of life; however, due to the history of

mycobacteremia in the mother in the 29th week of gestation and poor adherence to treatment, the patient was at high risk of vertical transmission; therefore, the diagnosis was made on the third day of life with evidence of Mycobacteria in the second gastric juice sample despite being asymptomatic, taking into account that the gold standard for the diagnosis of this pathology is the anatomopathological study of the placenta, however, unfortunately, the sample was not available. In Colombia, as in other parts of the world, there are very few reported cases [2].

2. Case Presentation

2.1. Maternal Outcome

It is a 20-year-old, previously healthy, migrant woman on her second pregnancy, with late admission to prenatal care and negative screening for maternal infectious diseases, previously diagnosed with IUGR type 1. She was admitted to the hospital at 28 weeks of gestation with a one-month history of productive cough, dyspnea, nocturnal diaphoresis, subjective fever, and hemoptysis. On admission, she was in poor general condition, with altered consciousness, hemodynamic instability, and severe respiratory distress. She was transferred to the intensive care unit with pulmonary sepsis. She was started on supportive measures, including mechanical ventilation, antibiotic treatment with piperacillin/tazobactam 4.5 grams every 8 hours for 3 days, and two doses of betamethasone for pulmonary maturation. Chest X-ray (**Figure 1**) revealed diffuse interstitial opacities. A chest tomography (**Figure 2**) showed calcifications, nodules, and generalized micronodules with a “budding tree” appearance associated with bibasal cavitations. Subsequently, a tracheal aspirate sample was positive for molecular detection of *Mycobacterium tuberculosis* without resistance to Rifampin. Later, the central nervous system was also demonstrated. Miliary TB was confirmed. Therefore, a 2-month intensive phase of isoniazid (INH), rifampin (RIF), pyrazinamide (PZA), and ethambutol (EMB) was proposed and initiated, followed by a 4-month continuation phase of INH and RIF, with the following doses respectively, 100 mg, 150 mg, 1000 mg, and 800 mg daily in addition to Pyridoxine for risk of polyneuropathy [1]. She was hospitalized for fifteen days, and a week after discharge, she started labor, which is the reason why she reconsulted.

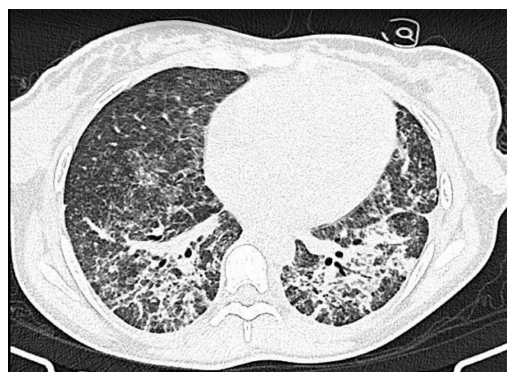


Figure 1. Chest computed tomography.

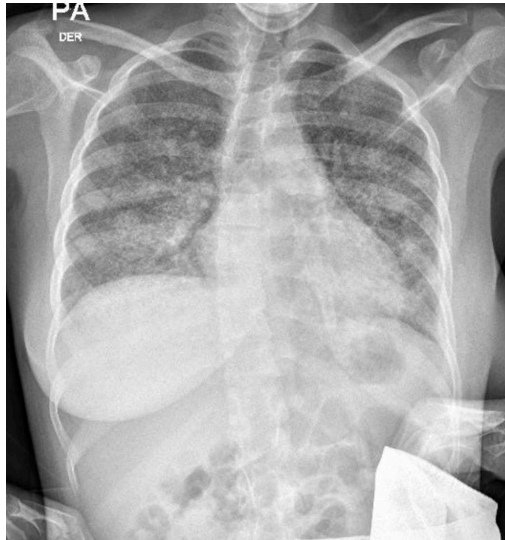


Figure 2. Chest xray.

2.2. Neonatal Outcome

Approximately three weeks later, a 31-week-old patient was born by spontaneous vertex delivery, with adequate weight for gestational age; he was born with respiratory distress and need for conducted neonatal adaptation, so he was transferred to the neonatal intensive care unit (NICU). His mother reported poor adherence to antituberculous treatment since discharge. During his stay in the NICU, a tuberculin test, chest X-ray, total abdominal ultrasound, transfontanelar ultrasound, and serial smear microscopy of gastric aspirate were ordered (**Table 1**). A molecular test in gastric aspirate was positive for *M. tuberculosis*, and treatment was started with Isoniazid, Rifampin, Pyrazinamide, and Ethambutol with adequate tolerance. Extended imaging examinations (chest X-ray, ultrasound of the abdomen, and MRI of the central nervous system) were unrevealing. The patient was finally discharged after one month of life without requiring supplemental oxygen, asymptomatic, and with no alterations on physical examination; the patient was planned to be managed with an antituberculosis regimen for 12 months and close monitoring. Unfortunately, there is no data available on their follow-up since they never attended their medical check-ups and were planning to return to their country of origin, contributing to the main challenge, which is the immigration of unvaccinated people with risk factors for contracting the disease, increasing the prevalence of the disease in the country of residence. Another important challenge to take into account is that since they are low-income immigrants, they do not initially have health insurance, which decreases access to therapy and, therefore, adherence.

Table 1. Newborn's diagnostic studies.

Patient's age	Laboratory tests	Results
First 24 hours of life	Blood type	O+
	Blood culture	No growth of microorganisms

Continued

	Bilirubin	Conjugated: 0; Indirect: 5.1
	Ionogram	Na: 134.2; K: 4.7; Ca: 8.1
	Transaminases	ASAT: 43.3; ALAT: 11.3
	Hemoleukogram	Hb: 16.3; Ht: 46; MCV: 102.2; MCH: 36; EDA: 16.1; Leukocytes: 12500; Neutrophils: 66% (8250); Lymphocytes: 27%(3370); Monocytes: 6%(750); Eosinophils: 1% (120); Basophils: 0
The second day of life	Bacilloscopy #1 in gastric juice	Negative
	PCR for Mycobacterium tuberculosis in gastric juice #1	Trace
	Culture #1 for Mycobacterium Tuberculosis	Negative
	CSF cytochemistry	Proteins: 295; Glucose: 45; No erythrocyte, leukocyte, PMN, mononuclear cell count by clotted test—gram staining: no microorganisms observed.
The third day of life	Bacilloscopy #2 in gastric juice	Negative
	PCR for Mycobacterium tuberculosis in gastric juice #2	Not detected
	Culture #2 for Mycobacterium Tuberculosis	Negative
The fourth day of life	Bacilloscopy #3 in gastric juice	Negative
	PCR for Mycobacterium tuberculosis in gastric juice #3	Not detected
	Culture #3 for Mycobacterium Tuberculosis	Negative

3. Discussion

TB is one of the principal infectious diseases worldwide; it is caused by the microorganism *Mycobacterium tuberculosis*, which belongs to the *Mycobacterium* family. It is a gram-positive, slow-growing, non-motile, non-spore-forming, strictly aerobic, acid-alcohol-resistant bacteria. The transmission is usually by airborne particles and, to a lesser extent, by vertical transmission [3]-[5].

Congenital tuberculosis is defined by the intrauterine or intrapartum acquisition of *Mycobacterium tuberculosis*. It is infrequent but largely undetected. Even though tuberculosis is a medium-incidence disease worldwide (130 cases/100,000

inhabitants), there is global concern about the disease during pregnancy, as it is not routinely screened.

In low-incidence countries, the estimated prevalence of TB in pregnant women reaches 10 to 20 cases per 100,000 individuals, which increases to 60 per 100,000 in high-incidence countries. The incidence of congenital TB remains unknown, with less than 400 published cases in the scientific literature [6]; however, it is known that the fetal transmission rate ranges between 0 - 16%, being exceptional when the mother has received adequate treatment for pulmonary TB. Delay in diagnosis is the most significant contributor to mortality by congenital TB, which varies between 44 - 50%.

Intrauterine transmission occurs by hematogenous dissemination, usually from the rupture of a placental tubercle, and then transmitted to the fetus via the umbilical vein or from aspiration or ingestion of infected amniotic fluid or blood. As a result, the bacteria can seed into the liver or lungs and form multiple primary complexes [7] [8].

On the other side, perinatal TB is acquired in the immediate postpartum period, in which microorganisms are transmitted to the neonate either by ingestion or inhalation of the infected droplets from the mother or by direct contact with the infected genital tract, injured skin, mucous membranes or with other infected people [9].

The kidneys and liver are the main organs affected in congenital TB; however, the clinical manifestations are generally nonspecific and may vary according to the inoculum, involved site, and size of caseous lesions.

Some clinical findings reported in the literature include hepatomegaly with/without splenomegaly, respiratory distress, lymphadenopathy, fever, irritability, and lethargy (Table 2). Our patient only presented respiratory distress, which could have been related to prematurity. It is essential to consider other differential diagnoses, such as transient tachypnea of the newborn, respiratory distress syndrome, meconium aspiration syndrome, pneumonia, sepsis, pneumothorax, persistent pulmonary hypertension of the newborn, and even delayed transition. However, the mother's medical history was highly relevant, making it necessary to confirm or rule out congenital tuberculosis.

The clinical, social, and infectious profile of the mother should be considered. Beitzke criteria were classically described in 1935 and consequently reviewed by Cantwell in 1994, yet its usefulness is currently debated, considering that studies of the placenta are only sometimes available and that imaging findings may appear late [10]. Initial diagnostic evaluation of the infant includes a complete blood count, PCR, tuberculin test and/or interferon-gamma release assay, acid-fast smears, culture and molecular testing of respiratory specimens, blood cultures, and cerebrospinal fluid analysis. Organ involvement must be ruled out by cerebral and abdominal ultrasound, chest x-rays/tomography, and eye examination [3] [11]. Additionally, the anatomopathological and microbiological study of the placenta holds significant importance, with granulomas serving as a critical finding and constitute the starting point to guide the diagnosis [5] [9] [12].

Table 2. Symptoms of congenital tuberculosis.

Unspecified	Fever
	Respiratory distress
	Pallness
	Jaundice
	Lymphadenopathy
	Hepatosplenomegaly
Respiratory	Tachypnea
	Apnea
	Cyanosis
	Cough
	Wheezing
Neurological	Lethargy
	Irritability
	Meningitis
	Seizures
Gastrointestinal	Oral intolerance
	Failure to thrive
	Abdominal distension
	Vomit
Others	Rash
	Otorrhea
	Facial paralysis
	Bone deformity

In previous case reports, the newborn's diagnosis remained elusive until symptoms emerged in the second-third week of life. However, in our case, owing to the mother's history of disseminated TB infection at week 29 of gestation and poor adherence to treatment, the patient was at high risk of vertical transmission. Therefore, despite the absence of symptoms, diagnostic tests, including microbiological studies, were ordered early, leading to a diagnosis on the second day of

life. Unfortunately, obtaining the anatomopathological study of the placenta was impossible, which would have provided invaluable findings for the current case.

Treatment of congenital TB is similar to other forms of TB regardless of the transmission route [9] [13] Two-month intensive phase followed by ten months of the second phase since these patients have a high risk of presenting miliary TB and involvement of the central nervous system, is recommended. To date, there are no formal clinical trials focused on perinatal TB; however, current data has shown neonates have equal tolerance to regimens used in older patients [2] [14].

4. Conclusion

Congenital TB continues to be a diagnostic challenge at present. We present the case of a patient with a diagnosis of congenital tuberculosis that could be made early thanks to the clinical suspicion due to maternal history and later by microbiological studies. This allowed the initiation of treatment before the presentation of clinical signs and symptoms and, therefore, a better outcome for the patient. The importance of keeping the diagnostic suspicion present is therefore emphasized, especially in tuberculosis-endemic countries, where this pathology should remain on the list of differential diagnoses in neonates with nonspecific clinical manifestations with no response to the usual treatment, especially if they have a suggestive maternal clinical history.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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