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Congenital Tuberculosis: Case Report, Imaging and Review of the Literature

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Abstract
Background: *Tuberculosis is a menace facing developing world. In India it is not unusual for pregnant women to get affected by tuberculosis. Since many of these pregnant women are asymptomatic or have non-specific symptoms the diagnosis is often delayed or even missed. An infected mother may transmit the infection to the fetus causing congenital tuberculosis which is even more challenging to diagnose not only because of its rarity but also due to non-specific signs and symptoms in neonate. We present here a case of A 37 days old infant who presented with respiratory distress, hepatosplenomegaly and refusal to feed.*
Case Report: *A 37 days old infant presented with high spikes of fever, cough and refusal for feeds for past 15 days and had no response to antibiotics. He was not immunized. On examination infant was having hepatosplenomegaly and respiratory distress. On auscultation bilateral crepitations were present. On computed tomography extensive nodules in bilateral lung parenchyma with extensive mediastinal and bilateral hilar lymphadenopathy. In view of imaging features and the fact that the child didn't respond to IV antibiotics a diagnosis of Koch's was considered and investigations were done. Diagnosis of Koch's was confirmed on the basis of investigations such as gastric aspirate for AFB, M. Tuberculosis DNA-GeneXpert and by polymerase chain reaction (PCR).*
Conclusion: *The diagnosis of congenital tuberculosis requires a high index of suspicion and thorough evaluation of both mother and infant. Because of non-specific symptomatology in neonates the diagnosis may be delayed leading to complications.*
Keywords: *Neonatal tuberculosis, Imaging, Diagnosis, Management.*

Introduction

Tuberculosis is one of the leading infectious diseases worldwide and is still a serious public health problem in many countries. World Health Organization (WHO) estimates that in many parts of the developing world one-third of the population is infected with tuberculosis and the infection rate increases nearly 1% per year[1]. Tuberculosis is more common in pregnant women and the prevalence of active tuberculosis in pregnant and postpartum women from high burden countries is upper to 60 cases per 100 000 population per year and from low burden tuberculosis countries, the prevalence is lower to

20 cases per 100 000 population per year or it is lower about 10 cases in total. The pregnancy is known to be a state of physiological immunosuppression and hence there are increased chances of reactivation of tuberculosis in pregnant women. Although rare, vertical transmission carries a poor prognosis. The incidence of congenital tuberculosis is low; however, its significance lays on a mortality rate of up to 50%. The high mortality in part is also due to delayed diagnosis because of non-specific symptomatology of tuberculosis in newborns[2].

The incidence of tuberculosis on pregnancy is increasing in countries with limited socioeconomic resources. In most of these countries, increased incidence is associated with increased prevalence of tuberculosis in the population of women of childbearing age[3]. Latent pattern tuberculosis in pregnancy are correlated with a high risk of progression to active pattern that increases the risk of transmission from infected mother to child in the first 3 weeks of life. Congenital tuberculosis is caused by Mycobacterium tuberculosis acquired either in utero or at delivery[4]. The disease is a rare complication of in utero tubercular infection due to maternal hematogenous spread. In the second or third week after childbirth, the symptoms usually emerge and precocious diagnosis is essential. However, as already mentioned the clinical presentation of tuberculosis during pregnancy and infancy is often nonspecific, making diagnosis difficult. Even though, tuberculosis among pregnant women is not uncommon, documented cases of congenital tuberculosis are conspicuous by their rarity. It is because placenta forms a protective barrier against the invasion of the fetus by the tuberculous organisms[5].

Congenital tuberculosis is difficult to diagnose not only because it's uncommon but also because it presents with nonspecific signs and there are no pathognomic features which could be considered as diagnostic of congenital tuberculosis[6]. The clinical presentation may differ in different neonates depending upon whether they were infected in-utero or during birth. The neonates who were infected in utero are more likely to present hepatic or disseminated foci of infection unlike neonates infected during birth who are more likely to present with pulmonary form or miliary koch's[7]. The common clinical signs seen in neonates with congenital tuberculosis may include poor feeding, respiratory distress, organomegaly, jaundice, fever, lymphadenopathy and lethargy. In fulminant cases meningitis, neonatal seizures and respiratory failure may quickly ensue[8]. Since all these signs are also common in any other infections it is important to elicit the history of tuberculosis in mother[9]. A high index of suspicion, early diagnosis and prompt antikoch's treatment is essential not only to prevent mortality but also in preventing devastating complications such a hydrocephalus[10].

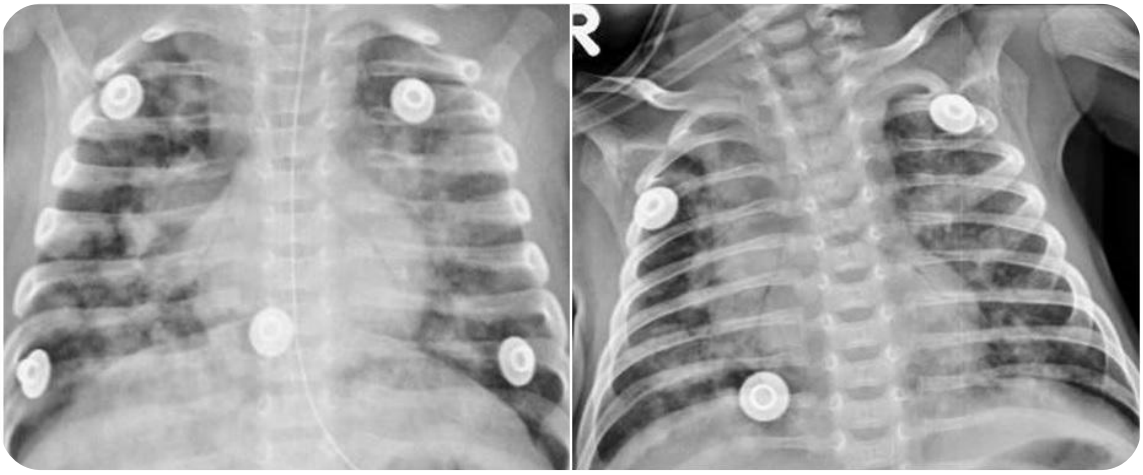
Case Report

A 37 days old infant presented with high spikes of fever, cough and refusal to take feeds for past 15 days. He already received intravenous antibiotics but didn't respond to it. The natal and immediate postnatal history showed that he was born to a primi gravida mother at 34 weeks of gestation by cesarean section, with normal Apgar scores at 1 and 5 minutes, clear amniotic fluid, and a grossly normal placenta. The birth weight was 2.75 kg. Antenatal period was supervised and uncomplicated. He was given BCG at birth and was exclusively breast-fed.

On general examination, his weight was 2.9 kg with length of 49 cm and head circumference of 37 cm. There was evidence of respiratory distress in the form of tachypnea (respiratory rate was 74 per minute) with subcostal and intercostal retractions. The child had mild pallor, no icterus or superficial lymphadenopathy. Despite history of BCG vaccination at birth BCG scar was absent. Systemic examination revealed bilateral lung crepitations with mild hepatosplenomegaly. Laboratory evaluation showed hemoglobin of 8.8 g/dL, total leucocyte count of 12,800/mm3 with

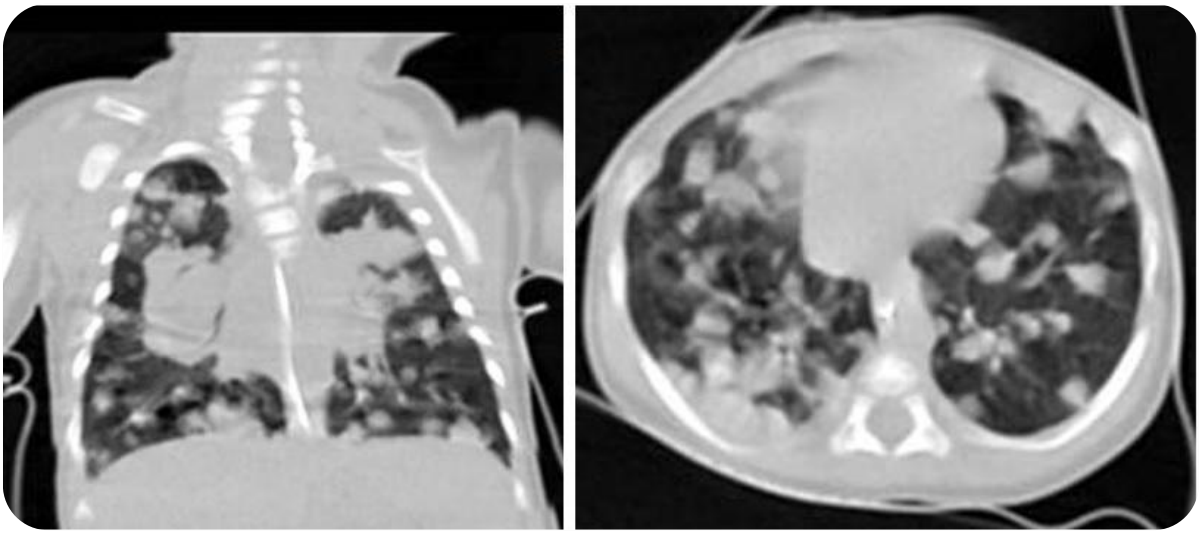
70% neutrophils, the white-cell count was 26,000 per cubic millimeter, with 51 percent polymorphonuclear cells, 7 percent band forms, 26 percent lymphocytes, and 16 percent monocytes. Erythrocyte sedimentation rate was 12mm/hr. Liver function tests were abnormal with total bilirubin of 3 mg/dL (direct 1.8 mg/dL) and elevated liver enzymes (alanine aminotransferase was 168 U per liter, and aspartate aminotransferase was 176 U per liter). Cerebrospinal fluid analysis was normal.

Imaging studies were done. A chest radiograph showed bilateral infiltrates. Abdominal ultrasonography (US) showed hepatosplen-omegaly, however, no focal lesions were identified in liver.



Chest radiograph AP view shows- Patchy haziness in bilateral lungs, predominantly in perihilar and para-cardiac region

High resolution CT chest was performed which showed extensive nodules in bilateral lung parenchyma with extensive mediastinal and bilateral hilar lymphadenopathy and mild bronchial compression seen by hilar lymphadenopathy.



Plain CT scan of thorax shows extensive nodular opacities of varying sizes (5 - 13mm) with irregular margin seen dispersed in bilateral lung parenchyma- probably infective nodules. Extensive enlarged mediastinal and bilateral hilar lymph nodes noted encasing the tracheo-bronchial tree causing compression on bilateral main bronchi (right > left).

In view of imaging finding congenital koch's was suspected and hence montoux test was done which turned out to be positive. Gastric aspirate for AFB was found to be containing acid fast bacilli s/o koch's. Culture and sensitivity of aspirated fluid was also positive for acid fast bacilli. The

diagnosis was confirmed by M Tuberculosis DNA-GeneXpert and Bronchoalveolar lavage (BAL) showing acid fast bacilli. Lastly DNA in BAL fluid by polymerase chain reaction (PCR) was found to be positive for Mycobacterium tuberculosis proteins. A final diagnosis of congenital tuberculosis was hence confirmed. Maternal montoux also turned out to be strongly positive with an in duration of 22mm. The baby was started on antikoch's treatment and responded well to the treatment.

Discussion

Congenital tuberculosis is a very rare condition. Only 300 cases were reported in the literature till 1989; subsequently, 58 cases were reviewed by Abughali N *et al* in 1994[11], and from 2001 to December 2005, 18 more cases have been reported. Tuberculosis remains a major public health scourge. Congenital tuberculosis is estimated at 2% in countries with high tuberculosis endemic. It is lower in developed countries, making it an unknown disease and difficult to evoke. The mortality rate is very important and high, nearly 50%, which is often due to delayed diagnosis followed to delayed treatment, and 22% among patients receiving chemotherapy. Furthermore, newborn infants who suffer from congenital tuberculosis after 4 weeks of age have a 77% existence rate compared with 44% survival in those who suffer before 4 weeks[12].

Even though, tuberculosis among pregnant women is not uncommon, documented cases of congenital tuberculosis are conspicuous by their rarity. It is because placenta forms a protective barrier against the invasion of the fetus by the tuberculous organisms. It is assumed that the infection has been acquired in utero, because of: (i) the age of the infant, (ii) absence of any known contact with an open case of tuberculosis, and (iii) generalized dissemination of the disease. The World Health Organization reported that, in 2010, tuberculosis led to the death of half a million women and, at least, 64 000 children. There were also some 10 million children orphaned by tuberculosis[13].

According to the 2012 report on the situation of tuberculosis in Turkey, overall tuberculosis mortality was 3.1% (525 deaths out of 17 148 cases). Congenital tuberculosis has been frequently reported in regions with a high tuberculosis prevalence among adults. The high rate of tuberculosis among women of childbearing potential in developing countries is also related to a higher risk of congenital tuberculosis[14].

Modes of transmission of congenital tuberculosis is thought to be acquired in three ways: transplacentally, where primary complex is in liver, aspiration of infected amniotic fluid during birth, when lungs are primary focus and ingestion of infected material where the primary is in the gut. Many authors have inferred that infection of the placenta or the maternal genital tract is necessary for congenital transmission. Female genital tuberculosis is uncommon, with an average annual incidence of 0.036 cases per 100,000 women of childbearing age in the United States from 1985 through 1991[15].

Beitzke in 1935, established a criterion for differentiating congenital tuberculosis from postnatally acquired tuberculosis, and it included:

1. Isolation of M. tuberculosis from the infant,
2. Demonstration of the primary complex in the liver,
3. In the absence of primary complex in the liver-
    - a) Evidence of tuberculosis within days after birth.
    - b) Absence of contact with a case of tuberculosis after birth.

However, Beitzke criteria were developed from autopsy series and were rigid. Cantwell revised these criteria in 1994, and they include:

Proven tuberculosis lesions in the infant plus one of the following:

i. Lesions occurring in the first week of life,
ii. A primary hepatic complex,

iii. Maternal genital tract or placental tuberculosis,
iv. Exclusion of postnatal transmission by thorough investigation of contacts.

Our case met the Cantwell's criteria as it is a proven case of tuberculosis in a neonate. Signs and symptoms are usually non-specific and include respiratory distress, fever, and hepatosplenomegaly. Congenital tuberculosis has a very high mortality rate, and those presenting before 4 weeks have mortality up to 50%. Our case too presented approximately by 4 weeks, thus stressing on the need for high index of suspicion, early diagnosis and prompt treatment. Clinical presentation of tuberculosis in the neonatal period is identical if the acquisition of the disease is congenital or postnatal. Furthermore, known effects of tuberculosis in pregnancy are marked with the problems like infertility, poor reproductive performance, repeated abortions, stillbirths, preterm labor, and premature rupture of membranes. Fetus may have intrauterine growth retardation and low birth weight and has increased risk of mortality. The average age of manifestation of congenital tuberculosis is 24 days (ranges from 1 to 84 days)[18].

There have been cases of late onset up to 3 months of life or over, as the case study by Vogel et al. has shown, describing the appearance of congenital tuberculosis manifestation at 154 days after birth. And another study reported the case on day 112. The clinical features comprise hepatosplenomegaly with liver and spleen lesion, abdominal distension, lymphadenopathy, and ascites; pneumonia with respiratory distress, military, nodular, or lymphadenopathy in imaging finding, and no improvement in spite of use of broad-spectrum antibiotic treatment; meningitis with involvement of cranial pairs of facial nerve, lymphocytosis, and decrease of biological levels of glucose and protein in cerebrospinal fluid; and sepsis and finally other banal signs. But none of them is pathognomonic of congenital tuberculosis. Several authors demonstrated that the complication of delay diagnostic of congenital tuberculosis incorporates military, meningitis tuberculosis, and otitis media, resulting in seizures, deafness, and death. The last complication is common, proven in most cases we have seen[19].

The knowledge of a potential latent or active Mycobacterium tuberculosis infection during pregnancy is crucial. As described by many authors including Tomar et al the screening of mother is an essential component. A recent study by Peng et al. establishes that 162 mothers had open tuberculosis throughout pregnancy or postpartum period[20]. Of them, 121 had no past history of tuberculosis before getting pregnant and were diagnosed through pregnancy. In a review of 32 cases of congenital tuberculosis, 24 of the mothers were asymptomatic[21].

Furthermore, Singh et al. described another opportunity to make the diagnosis of congenital tuberculosis. They reported clinical and laboratory findings for tuberculosis investigation. It includes newborn infant mainly from endemic areas unresponsive to conventional treatment for worsening pneumonia, if the mother was labelled to have tuberculosis and baby has no exact symptoms, when the cerebrospinal fluid was discovered to have a high lymphocyte count in the nonexistence of any identifiable bacterial pathogen and in manifestation of fever and hepatic and splenic enlargement[22].

Investigation includes tuberculin test, early morning gastric aspirate for acid fast bacilli, and Mycobacterium culture in all body fluid and biopsy swab from lymph node and liver. The histology and culture of placental biopsy sample should be performed and evaluated. The tuberculin test is generally negative in newborn infants at first manifestation, while a study conducted by Bor et al. suggests that TST reaction was positive (16 mm). Frequently, the TST converts to a positive result months later after the first negativity result. Correspondingly in another study of 9 infants with congenital tuberculosis, only 2 presented the positive reactions (>10 mm). Tuberculin skin testing is positive in less than

15% of cases of congenital tuberculosis while gastric or tracheal aspirates are positive for tuberculosis in 80% of cases. A recent report proved the value of bronchoalveolar lavage as a technique of isolating the mycobacteria in perinatal tuberculosis. Liver biopsy is really possible because it can have a very high diagnosis sensibility, which is 100%[23].

Recently, interferon-gamma (IFN-γ) release assays have not been authenticated in children younger than the age of 5 years. They may be accepted in combination with TST but should not be utilized as a substitution. In contrast, Zheng et al. attested T-spot assay in their case, based on IFN-γ release assays (IGRAs) from specific T cells in vitro in response to stimulation of Mycobacterium tuberculosis antigens and which has objectified a positive result in a premature newborn, conceived by in vitro fertilization[24].

Sometimes radiographic finding in some of cases is uneventful at the onset, but if diagnosis and treatment are delayed, radiographic progression will be poor very quickly. In 143 cases of congenital tuberculosis, chest radiographical findings reviewed by Peng et al. which are 46.8% represented a miliary pattern. Also, given the case reports we have analyzed, hepatosplenomegaly dominates the imaging abdominal finding associated with multiple focal lesions, as were the cases presented by Raj and Sarin, Lee et al[25].

Endometrial biopsy and histological examination of placenta are useful. Several studies followed this method, but sometimes mother declines to carry out it. No precise treatment regimens for management of congenital tuberculosis are recommended. Treatment contains isoniazid, rifampicin, ethambutol, and kanamycin or amikacin for the first two months followed by isoniazid and rifampicin for 6–12 months or similar to miliary tuberculosis or isoniazid, rifampicin, and pyrazinamide along with streptomycin and kanamycin for 9 to 12 months. Some also advise using corticosteroids for tuberculosis meningitis to reduce both mortality rates and neurologic sequelae. The use of corticosteroids in other severe patterns of congenital tuberculosis infection, such as endobronchial and miliary disease, can also be accepted. Doctors use the treatment scheme for 9 to 12 months as long as there is low immunologic ability in infants. Timely identification and proper treatment regimens for congenital TUBERCUL-OSIS highly correlated with upgraded outcomes. According to the institution criteria by Cantwell et al[17] in 1994, mortality rates from published cases were about 45%. Several experts evoke and emphasize the improvement in mortality rate after the implementation of previously elucidated criterion. It is mandatory to investigate the antenatal history of the mother to best use these criteria and immediately institute the treatment under high suspicion. The risk of untreated tuberculous disease in newborn infant is higher than the side effects with antitubercular therapies. So, it is always beneficial to treat the condition rather than leaving it untreated.

Conclusion

Congenital tuberculosis is a rare entity. Its diagnosis is usually delayed due to nonspecific signs. A high index of suspicion, early diagnosis and prompt antitubercular management is essential as delayed diagnosis is associated with mortality and devastating complications such as hydrocephalus.

Conflict of Interest: None.

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