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Case Report Open Access

Pulmonary Tuberculosis with Hematogenous Spread Associated with Hemaphagocytic Syndrome and Multiple Pulmonary Pneumatoceles

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Abstract

Background: The association between tuberculosis, multiple bilateral pulmonary pneumatoceles and secondary hemophagocytic syndrome is uncommon. With this case, we would like to highlight the importance of an early and correct diagnosis of tuberculosis to prevent such complications.

Case presentation: We report the case of a 2 months-old infant diagnosed with pulmonary tuberculosis with hematogenous spread and multiorgan involvement that developed multiple bilateral pulmonary pneumatoceles and secondary hemophagocytic syndrome.

Conclusions: Tuberculosis is an important global health issue, with an increased risk to present disseminated forms in the infant. An adequate epidemiological study of an infected patient is essential to prevent the spread of contacts and establish an early treatment to avoid the occurrence of secondary complications that may be lifethreatening.

Keywords: Tuberculosis; Pneumatoceles; Hemophagocytic

Abbreviation:

BIPAP: Biphasic Positive Airway Pressure; CPAP: Continuous Positive Airway Pressure; CPR: Cardiopulmonary Resuscitation; CT: Computed Tomography; HIV: Human Immunodeficiency Virus; PCR: Protein C Reactive; PCR: Polymerase Chain Reaction; PCT: Procalcitonin; PICU: Pediatric Intensive Care Unit; RSV: Respiratory Sincitial Virus; TB: Tuberculosis.

Introduction

Tuberculosis (TB) is the most common cause of infection-related death worldwide. In 1993, the World Health Organization (WHO) declared tuberculosis to be a global public health emergency. Although pulmonary tuberculosis is the commonest type of TB in children, extrapulmonary tuberculosis can be present in a wide variety of anatomical sites. The association between tuberculosis, multiple bilateral pulmonary pneumatoceles and secondary hemophagocytic syndrome had been scarcely reported in the literature. We would like to highlight the importance of a correct diagnosis of tuberculosis disease and proper study and tracking contacts of the index case, to avoid microepidemics and these complications.

Case Presentation

We present a case of a bolivian 2 months-old boy, without relevant antecedents and with a correct vaccination schedule, who was referred to our hospital with a history of fever, cough, vomiting and irritability in the last two weeks.

On examination, the patient presented hypoventilation and bilateral rales in pulmonary auscultation, hepatomegaly (3 cm) and splenomegaly (2 cm) and irritability. Laboratory tests showed leukocytosis with neutrophilia (17900 leukocytes, neutrophils 59%) with increased reactants (PCR 15.10 mg/dl and PCT 3.34 ng/ml), urinalysis (intense pyuria, bacteriuria, negative urine culture), nasopharyngeal RSV and influenza test (negative) and chest radiography with bronchopneumonia (Figure 1). He was admitted to a hospital with a diagnosis of pneumonia and suspected urinary tract infection, beginning empirical antibiotic therapy with intravenous cefotaxime and gentamicin. PCR for common respiratory viruses in nasopharyngeal exudate were negative and serology (epstein-barr virus, HIV, treponema pallidum, mycoplasma pneumoniae and chlamydia pneumoniae) were negative.

A severe clinical deterioration was observed in the next 24 h, with higher fever and an important respiratory distress that required supplemental oxygen therapy. Chest radiography showed bilateral pulmonary infiltrates and consolidation in right lung. A complementary medical history was taken from his mother, revealing a two weeks history of asthenia and anorexia with productive cough. In addition, she referred poor weight gain during the last quarter of her pregnancy and an episode of catarrhal symptoms and chest pain. The mother received broad-spectrum antibiotic treatment, as in a respiratory infection, with apparent remission. Inquiring again about family history, she explained that they both live with eigth more

people, including one maternal uncle who had been diagnosed of bacilliferous pulmonary tuberculosis sensitive to isoniazid a year before the birth of our patient. Then, the entire family unit was studied, with normal results in their tuberculin tests and chest X-rays with the mother exception: her chest radiography showed an image compatible with miliary tuberculosis with positive smear and left pleural effusion. She was admitted for quadruple antituberculous therapy, subsequently withdrawing ethambutol as soon as sputum sensitivity revealed no resistance. Endometrial biopsy and PCR for *M. tuberculosis* were negative. The two girls in school age residing in the house were treated with primary prophylaxis for 3 months.

Due to the increasing and progressive respiratory requirements (high flow oxygen therapy to 10 bpm and FiO_2 40%), our patient was transferred to our Pediatric Intensive Care Unit (PICU). With the suspected diagnosis based on family history, a chest computerized tomography was performed, demonstrating bilateral and nodular infiltrates, some of them cavitated, associated to a bilateral pleural effusion predominantly in right base. Hypoechoic liver and spleen nodules were found in the abdominal CT, suggesting a septic emboli, as well as axillary, mediastinal, mesenteric, retroperitoneal and inguinal lymphadenopathy. These finding are consistent with miliary tuberculosis with hematogenous spread (Figure 2). A PPD was requested (0 mm) and Ziehl-Neelsen test in urine, bacterial and mycobacteria urine culture were negative. Lumbar puncture and serial blood cultures were sterile. Treatment with isoniazid, rifampicin, ethambutol, pyrazinamide and methylprednisolone started when consecutive three days gastric aspirates were obtained. In the first gastric aspirate, acid-alcohol-resistant bacilli sensitive to isoniazid and rifampicin were identified. Therefore, ethambutol was suspended and our patient continued triple therapy with initially favorable evolution. Control lumbar puncture remained sterile and no choroidal tuberculomas were present on funduscopy.

In serial controls, the patient presented bicytopenia (minimum hemoglobin 7.2 g/dl, requiring blood transfusion, and 28000 platelets without bleeding), hypertriglyceridemia (maximum of 564 mg/dl), hyperferritinemia (maximum 600 ng/dl) and hypofibrinogenaemia (<100 mg/dl). Bone marrow aspirate was required and showed a slight increase of histiocytes with haemophagocytosis phenomena in some of them, with sterile culture. Immunological study showed normal population quantity and phenotype of NK cells in peripheral blood, with normal cytotoxic activity and degranulation. These findings were consistent with hemophagocytic syndrome, probably secondary to pulmonary tuberculosis, with hematogenous spread.

Initial methylprednisolone was replaced by dexamethasone for 4 days, presenting favorable analytical and clinical course, without any respiratory support to continue treatment. However, 48 h later, the patient presented new respiratory progressive deterioration. New chest X-ray and CT revealed multiple bilateral cavitations with pneumatoceles, the biggest one of 4 cm in maximum diameter in the left upper lobe, and multiple areas of bilateral alveolar consolidation (Figure 3). The patient was readmitted to PICU with progressive rising in respiratory support: high flow oxygen therapy and noninvasive ventilation mode continuous positive airway pressure (CPAP) and biphasic positive airway pressure (BiPAP). Finally, on the 9th day of PICU readmission, intubation and conventional mechanic ventilation was required. After 24 h, the patient presented sudden respiratory worsening with cardiopulmonary arrest. Suspecting pneumatoceles rupture, air drainage tap was performed, escaping abundant air from the right hemithorax and less from the left one. At the end, after CPR maneuvers, the patient finally died. Necropsy was not allowed. Table 1 resumes clinical, radiological and analytic parameters found during the hospital admission.

Hemophagocytic Syndrome	**Our patient**
Molecular diagnosis compatible	No molecular diagnosis
Fever	Fever
Splenomegaly	Splenomegaly
Peripheral blood cytopenia in at least 2 of 3 series: -Hemoglobin <9 g/dl -Platelets <100 × 10^9/L -Neutrophils <1 × 10^9/l	Peripheral blood cytopenia in at least 2 of 3 series: -Minimum hemoglobin 7.2 g/dl -Thrombocytopenia (minimum 28000 platelets)
Hypertriglyceridemia (>265 mg/dl) and hipofibrinogenemia (fibrinogen <150 mg/dl)	Hypertriglyceridemia (maximum of 564 mg/dl), hyperferritinemia and hypofibrinogenaemia (<100 mgdl).
Haemophagocytosis phenomena in bone narrow, lymphadenopathy or spleen	Haemophagocytosis phenomena in bone narrow
Additional criteria: -Hyperferritinemia (>500 ng/ml). -Cytotoxic activity of natural killer cells decreased or absent -Elevation of soluble receptor of interleukin 2 > 2,400 U/ml (not determined in our patient	Additional criteria: -NK cells normal population quantity and phenotype with appropriate cytotoxic activity and degranulation. -Hyperferritinemia (maxinum 600 ng/dl). -sIL-2R not studied.

Table 1: Clinical, radiological and analytic parameters.

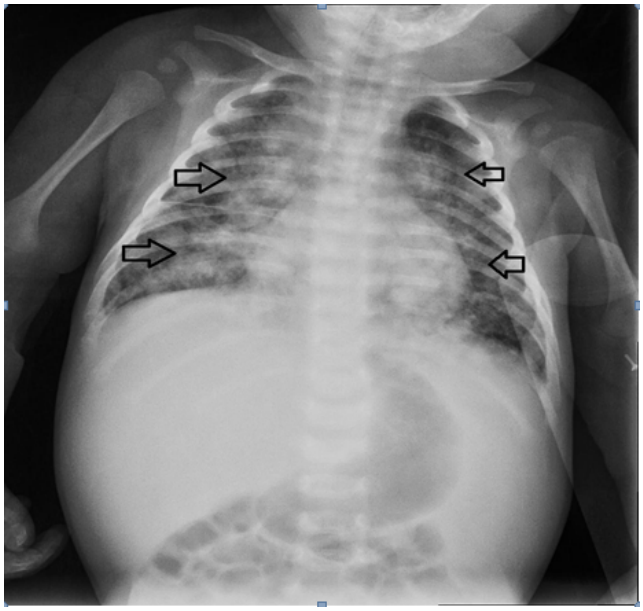

Figure 1: Chest X-ray image showing bilateral alveolar consolidations and bronchogram compatible with bronchopneumonia.

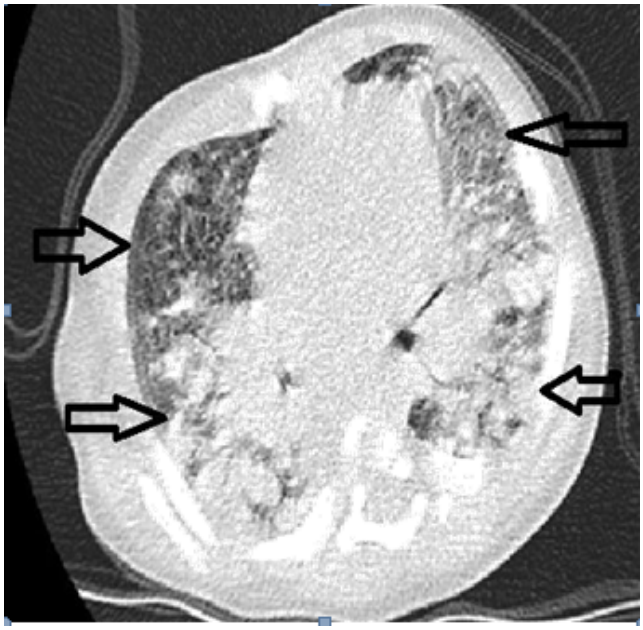

Figure 2: CT image showing bilateral nodular infiltrates, bilateral pleural effusion predominantly in the right base, spleen and liver nodules and axillary, mediastinal, mesenteric, retroperitoneal and inguinal lymphadenopathy.

About the study contact, patient's uncle was interpreted as index case. He voluntarily discontinued treatment within two months and restarted it during admission of our case. Our patient´s mother had negative tuberculin test in the study of contacts but she did not receive prophylaxis and she was diagnosed of miliary tuberculosis smear-positive during admission of our case. The mother was probably our patient´s source of infection by respiratory route, because congenital tuberculosis was excluded as the patient did not fulfilled Cadtwell ´s criterial.

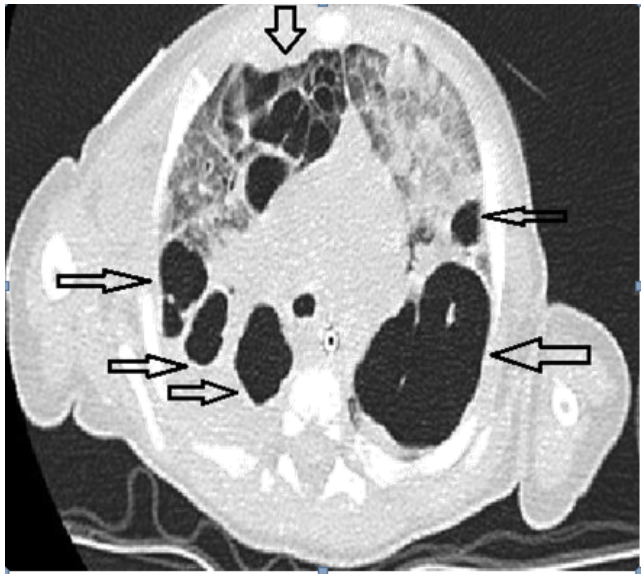

Figure 3: CT image showing multiple pneumatoceles and multiple areas of bilateral alveolar consolidation in the parenchyma not cavitated.

Initial valoration	Fever, caugh, irritability. Bilateral rales in pulmonary auscultation, hepatomegaly and splenomegaly.
	Chest X-Ray: bronchopneumonia.
	Urinanalisys: intense pyuria.
	Analitic parameters: leukocytosis with neutrophilia.
	Treatment: cefotaxime and gentamicin.
24 h before	Higher fever and severe respiratory distress.
	Bilateral pulmonary infiltrates and consolidation in right lung (Figure 1)
	Mother diagnosis of tuberculosis.
Pediatric Intensive Care Unit	CT: bilateral and nodular infiltrates, some of them cavitated, bilateral pleural effusion hypoechoic liver and spleen nodules; and disseminated lymphadenopathy.
	Bicytopenia (hemoglobin 7.2 g /dl; 28000 platelets), hypertriglyceridemia (564 mg/dl), hyperferritinemia (600 ng/dl), hypofibrinogenaemia (<100 mg dl).
	First gastric aspirate: acid-alcohol-resistant bacilli sensitive to isoniazid and rifampicin.

	Bone marrow aspirate: slight increase of histiocytes with haemophagocytosis phenomena in some of them, with sterile culture.
	Immunological study: normal CK cells population quantity and phenotype and normal cytotoxic activity and degranulation.
	Treatment: quadruple therapy and methylprednisolone initially (ethambutol suspended and methylprednisolone replaced by dexamethasone).
Readmission to ward	Clinical deterioration 48 after. Chest X-ray and CT revealed multiple bilateral cavitations with pneumatoceles, and multiple areas of bilateral alveolar consolidation.
Readmission to PICU	Progressive clinical deterioration. Pneumothorax.Cardiopulmonary arrest and death.

Table 2: Diagnostic criteria of hemophagocytic syndrome and those observed in our patient.

Discussion

Tuberculosis is a worldwide problem with high mortality, especially in developing countries. In childhood, risk of spreading and complications that can seriously compromise life is significantly higher [1]. Therefore, a comprehensive epidemiological study is essential in order to achieve an accurate diagnosis, early and correct treatment and to prevent infection of contacts.

Pneumatoceles are usually associated with bacterial pneumonias (*S. aureus*, *S. pneumoniae*, *H influenzae*, *Klebsiella*, *E. coli*) [2,3], but they have also been described in *P. jirovecci* in HIV-infected patients 4 or caused by chest trauma. The association with TB disease is unusual and has seldom been described [4-9], even more rarely in childhood [10-13]. Pathogenesis of these lesions remains unclear. Pneumatoceles may be formed from caverns whose content has been emptied by TB treatment. Furthermore, they may appear in areas without parenchymal pulmonary involvement. This last mechanism is favored by the appearance of atelectasis and the effect of rise valve collapse.

Chest CT evaluates size, location and wall thickness, relationship with adjacent structures, underlying complications and value indication and type of treatment. In asymptomatic patients and pneumatoceles smaller than 50% of hemithorax, a conservative approach can be adopted with serial radiological controls. Usually, they resolve spontaneously, although it could be a slow process that lasts long after the resolution of primary process. In our case, we opted for a conservative management and radiological surveillance of pneumatoceles at the beginning, as the patient initially responded to antituberculous treatment and criteria for drainage aspiration or surgical treatment were not applicable in that moment (symptomatic patients or those with unstable situation, or in whom the size is not reduced or increases after starting appropriate treatment for a prolonged period of time, thickened wall, presence of bronchopulmonary fistula, or atelectasis pulmonary) [14].

Hemophagocytic lymphohistiocytosis is a systemic hyperinflammation reaction due to an exaggerated and ineffective immune response triggered by an antigen, leading to hyperactivation of cytotoxic T lymphocytes and NK cells, cytokines hyperproduction and hyperresponsiveness macrophage infiltrating vital issues [15,16]. Initial symptoms can be confused with sepsis or multiple organ failure. For this reason, diagnosis requires a high index of suspicion. It is characterized by persistent fever, hepatosplenomegaly, lymphadenopathy, rash, edema, jaundice, hypoalbuminemia, hyponatremia, altered coagulation and neurological symptoms (irritability, altered level of consciousness). All of these findings were present in our case.

The diagnosis is confirmed by the International Histiocyte Society criteria 16: genetic confirmation (not done in our case) and/or at least 5 of the following criteria: fever, splenomegaly, bicytopenia (hemoglobin <9 g/dl, platelet count $<100 \times 10^9$/L or neutrophils $<1 \times 10^9$/l), hypertriglyceridemia (>265 mg/dl) and / or hipofibrinogenemia (fibrinogen <150 mg/dl) and haemophagocytosis phenomena in bone marrow, lymph node or spleen. We could find all criteria present in our patient. Additional criteria are: hyperferritinemia (>500 ng/ml), cytotoxic activity of natural killer cells decreased or absent (although it may be normal in secondary forms, as in our case), and soluble receptor of interleukin 2 elevation >2,400 U/ml (not determined in our patient). Table 2, summarizes the diagnostic criteria of hemophagocytic syndrome and those observed in our patient. The association between tuberculosis and hemophagocytic syndrome in children has been scarcely reported in the literature [17-22]. As sometimes the symptoms are non-specific and radiological findings do not help to guide the diagnosis, this entity should be considered in patients with prolonged fever, pancytopenia and splenomegaly.

Congenital tuberculosis is a rare entity [23-29] but it should be discarded in infected neonates or infants. The diagnosis is based on Cantwell criteria, but our patient did not fulfill the criteria. First of all, maternal endometrial biopsy was not compatible. Secondly, *M. tuberculosis* culture was not obtained in the first week of life. Thirdly, his mother had not referred previously contact with a tuberculosis patient. Also, neither our patient or his mother presented suspicious symptoms. Finally, primary liver caseating granuloma complex was not obtained by histopathological study, due to high invasiveness of the process in the context of our patient instability condition. In addition, there was a likely postnatal infection from his mother, who was smear-positive.

Conclusions

In conclusion, we would like to highlight the presence of hemophagocytic syndrome secondary to disseminated pulmonary tuberculosis as an entity that requires a high index of suspicion and early treatment to avoid poor prognosis. Also, notice the exceptional nature of the evolution to multiple pneumatoceles, even after the initial apparent clinical and radiological patient improvement. In addition, we consider that a correct diagnosis of tuberculosis disease and a proper study and tracking contacts of the index case are of utmost importance in order to avoid microepidemics and prophylactic treatment in contacts, where an appropriate intervention in the epidemiological chain could have prevented the spread of the disease and fatal outcome of our patient.

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