Case report

Miliary Tuberculosis with Cutaneous Affectations and SARS-CoV-2 Coinfection in Pediatric Patient: Case Report in Mexico

ABSTRACT

Aims: To describe a case of miliary tuberculosis with cutaneous affectations and SARS-CoV-2 coinfection in pediatric patient in Mexico.
Presentation of case: 10 month old male patient, with incomplete vaccination. Low socioeconomic level. The parents indicated, that began with a single small, erythematous, non-pruritic, papule-type skin lesion in the infralabial region, with no other symptoms. During the following three months, the lesions became generalized. On June 23, 2020, he was admitted to the "Hospital para el Niño Poblano" in emergency area with mild malnutrition, lethargic state, fluid and electrolyte imbalance, metabolic acidosis, oral candidiasis, and septic shock, requiring endotracheal intubation. Besides, innumerable acid fast bacilli with diagnosis cutaneous TB was, identified. Primary immunodeficiency and total depletion of T lymphocytes. RT-PCR was performed for SARS-CoV-2 in bronchial aspirate, with a positive result. On June 25, 2020 died of cardiorespiratory arrest, secondary to septic shock and cutaneous tuberculosis.
Discussion: Miliary tuberculosis with cutaneous affectations is difficult to diagnose due to its clinical manifestations that can be confused with various diseases, and downplay others, generating inappropriate and delayed treatment. Additionally, SARS-CoV-2 can intensify the clinical manifestations of miliary tuberculosis and be unnoticed in their care, and directly influencing the mortality of this type of patients.
Conclusion: The case described is valuable due to its infrequency, which reveals the importance to perform a differentiated diagnosis, considering socioeconomic and epidemiological context mainly in the first level of care. It is recommended to continue with research in order to generate information on the possible clinical pictures.

Keywords: clinical microbiology, COVID-19, immunodeficiency, Mycobacterium tuberculosis.

1. INTRODUCTION

Tuberculosis (TB) is the infectious disease with the highest global mortality, causing 1.5 million deaths during 2018 [1]. Mycobacterium tuberculosis complex has the ability to grow within host cells and to be transmitted directly from one host to another [2]. The usual classification of TB is infiltrative, focal, tuberculoma, miliary, and fibrocavernous [3]. Miliary tuberculosis is a lethal form of TB with massive lymphohaematogenous spread from a Mycobacterium tuberculosis laden focus [4] being rare the cutaneous manifestations [5]. Socioeconomic status may influence the pathogenesis of TB because, the risk of exposure is directly associated with the burden of the underlying disease and mortality. Once the

infection has occurred, there is greater susceptibility in people with comorbidities such as, human infection virus (HIV), diabetes, silicosis or rheumatoid arthritis and other chronic or immunosuppressive diseases [6]. SARS-CoV-2 appears to induce cytokine storm, and therefore, generate immunomodulatory or immunosuppressive effects. Different studies have shown, TB status could influence the development, but not the mortality of severe acute respiratory syndrome in coinfection by SARS-CoV-2, finding a risk of 2.1 times greater for critical illness owing to COVID-19; contributing to worsen the prognosis and increase the mortality of TB patients [7]. The objective of this paper is to describe a case of miliary tuberculosis with cutaneous affectations and SARS-CoV-2 coinfection in a pediatric patient in Mexico.

2. PRESENTATION OF CASE

10 month old male patient, native and resident from Central Region of the state of Puebla, Mexico. Weight at birth of 2.5 kg and 50 cm in height. Breastfeeding for six months. Incomplete national vaccination schedule for age (administered BCG). Without significant family and personal antecedents. Low socioeconomic level, with overcrowding. The parents indicated that during the last week of February 2020, he began with a single, small, erythematous, non-pruritic, papule-type skin lesion in the infralabial region, no other symptoms. For the next three months, the lesions became generalized (face, neck, anterior and posterior thorax, abdomen and upper extremities), increasing in size, being confluent, pustular, non-suppurative, with an erythematous base, as well as, color changes to violaceous from the center to the peripheral and painful. He received, exclusively topical treatment with betamethasone for four weeks.

On June 11, 2020, he started a persistent and continuous febrile picture of 38.5ºC with nightly predominance, he improved with paracetamol (unknown dose), accompanied by a non-productive cough and in accesses, presenting mainly in the mornings, being taken to private medical services, begining treatment with ambroxol and ceftriaxone (dose unknown). On June 21, 2020, he presented a productive cough in short accesses, with hyaline expectoration in moderate quantity, adding respiratory difficulty with nasal flaring, expiratory whimper and intercostal drawing, in addition, the skin lesions are disseminated, type punched ulcers, suppurative, so that, he is admitted to private medical services (unknown treatment). For lack of improvement, the parents request voluntary discharge.

On June 23, 2020, he was admitted to the “Hospital para el Niño Poblano” in the Emergency Area with mild malnutrition, lethargic state, fluid and electrolyte imbalance, metabolic acidosis, oral candidiasis, and septic shock, requiring endotracheal intubation (Fig. 1). He was treated with antibiotics based on meropenem (40 mg / kg / 24 h) and vancomycin (15 mg / 24 h), in addition to fluconazole (6 mg / kg / 24 h) and erythrocyte transfusion. He was transferred to the Pediatric Intensive Care Area. He was assessed by pediatric infectology, with a probable diagnosis of ecthyma gangrenosum vs staphylococcal toxic shock, adjusting the doses of antibiotics (meropenem 120 mg / kg / 24 h; vancomycin 60 mg / kg / 24 h) already established, adding clindamycin (40 mg / kg / 24 h), and coverage with liposomal amphotericin B (1 mg / kg / 24 h), due to suspected superinfection by fungal agents according to the time of evolution.

On June 25, 2020, the Pediatric Dermatology Area performed a skin biopsy with histopathological results, recognizing tiny fragments of corneal material, without giant cells or granuloma formation (Fig. 2). In the Zihel-Neelsen stain, innumerable acid-fast bacilli (AFB) with a diagnosis of cutaneous TB, were identified (Fig. 3). Periodic Acid-Schiff and Gram stains were negative.

On the same date, a real-time Reverse Transcriptase Polymerase Chain Reaction assay was indicated to Mycobacterium tuberculosis Complex, (RT-PCR-RT, Xpert MTB / RIF system) in skin biopsy samples and bronchial aspirate, with a compatible result, without detection of mutation in the rpoB gene associated by resistance to rifampicin. The Ziehl-Neelsen staining technique showed positive AFB smear microscopy (+++), skin culture (+++) (Fig. 4), and bronchial aspirate (+).

In addition, Löwenstein-Jensen culture medium, in skin biopsy and bronchial aspirate showed growth in 34 days. In the first, abundant, rough, pale yellow colonies were identified. In the second, smooth yellow confluent colonies were observed, contrasted by the color of the culture medium (Fig. 5). Identification and confirmation of Mycobacterium tuberculosis was carried out through molecular methods.

Table 1 shows the evolution of the blood count parameters and acute phase reactants and coagulation factors, during the length of stay. Progressive secondary cytopenias to infectious process and elevated levels of acute phase reactants and protocalcitonin were observed. A diagnostic approach was realized for primary immunodeficiency, finding evidence of hypogammaglobulinemia (A, M and E), and total depletion of T lymphocytes, with normal production of B and NK. In high school, there was no detectable viral load to HIV.

Additionally, the Culture of mycobacteria was performed on a solid Löwestein-Jensen medium, with a positive result (+++) of abundant and uncountable AFB colonies by skin biopsy sample; and a positive result (+) of confluent colonies of AFB in number <100, at bronchial aspirate sample. Antifimic management was started through isoniazid, rifampin, pyrazinamide, and ethambutol. On June 25, 2020 considering these results and as the COVID-19 pandemic continues, RT-PCR was performed to SARS-CoV-2 by means of bronchial aspirate, with a positive result. This day, he died of cardiorespiratory arrest, secondary to septic shock and cutaneous TB.

The patient presented an inappropriate clinical evolution, by septic refractory shock to inotropics, requiring an increase in the mechanical ventilation parameters. Chest radiographs showed a consolidation in the entire left hemithorax, with loss of cardiac silhouette contour and ipsilateral costo-diaphragmatic angle (Fig. 6).

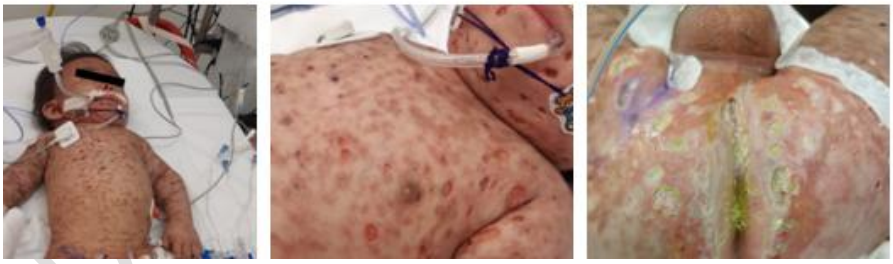

Fig. 1. Clinical appearance of ulcerative, punched-out, suppurative and disseminated dermal lesions upon admission.

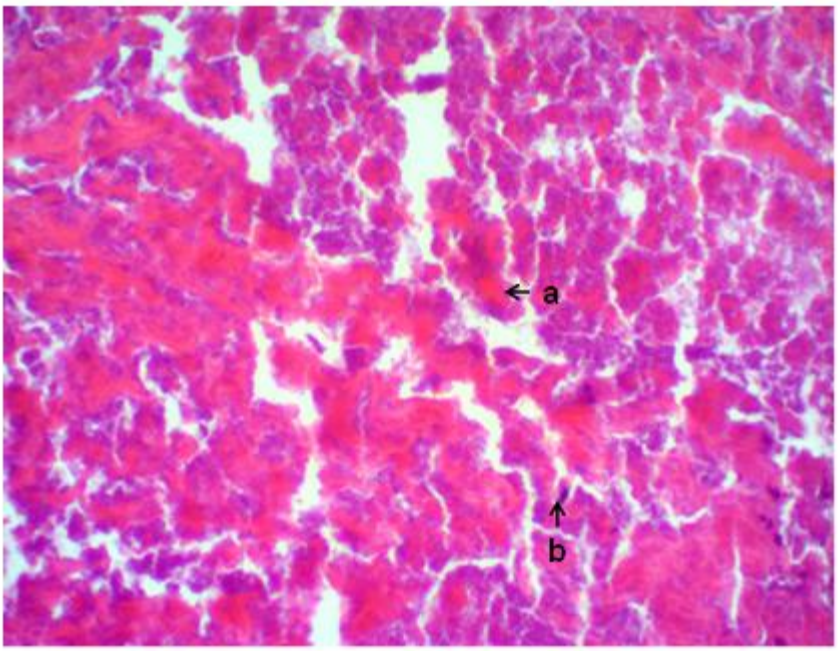

Fig. 2. Skin biopsy. Simple light microscopy. Objective magnification 40x. Hematoxylin and eosin staining technique. Tissue showing total loss of skin histology, replaced by cellular debris with granular cytoplasm (a) and polymorphonuclear leukocytes (acute inflammation) (b).

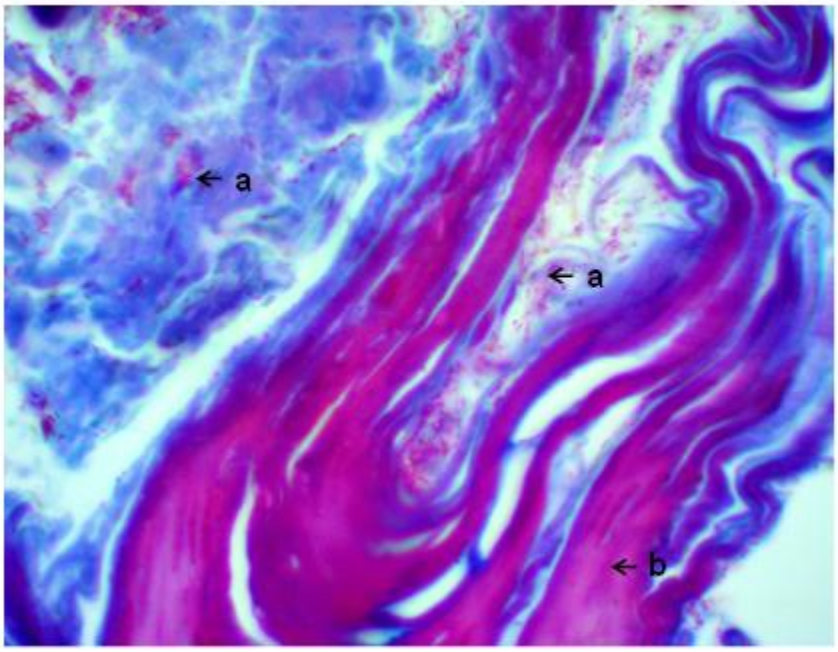

Fig. 3.Skin biopsy. Simple light microscopy, Zihel-Neelsen technique, 100x objective. Visualization of the bacilli of the Mycobacterium tuberculosis complex in red (a);

contrasting with the cellular detritus and laminated keratin of the stratum corneum of the skin (b).

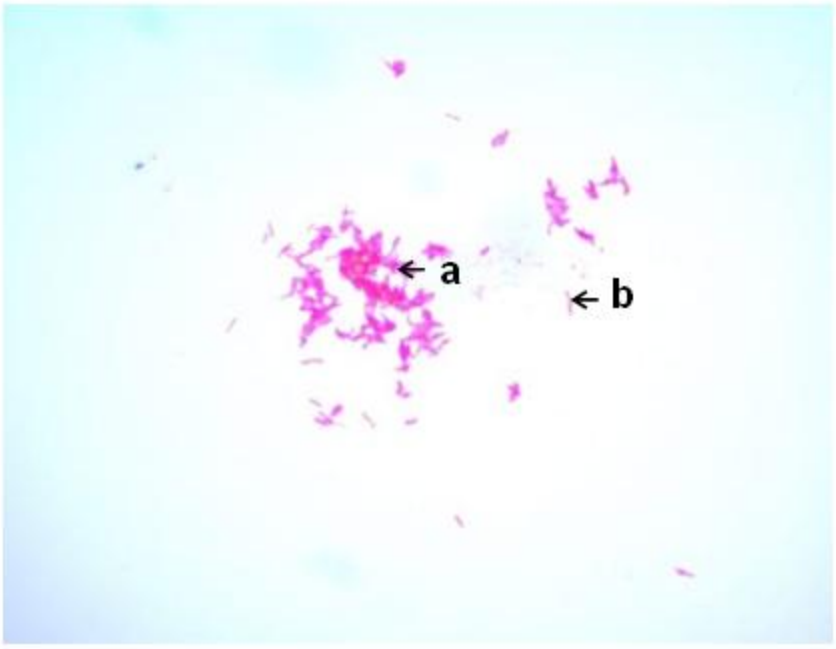

Fig. 4. Skin biopsy culture. Simple light microscopy in an immersion objective, magnification 100 x. Zihel-Neelsen staining technique. Large conglomerates of AFB are observed in a "bead effect" exhibiting a spotty appearance (a). The AFB isolated, show a slight curvature in their morphology (b).

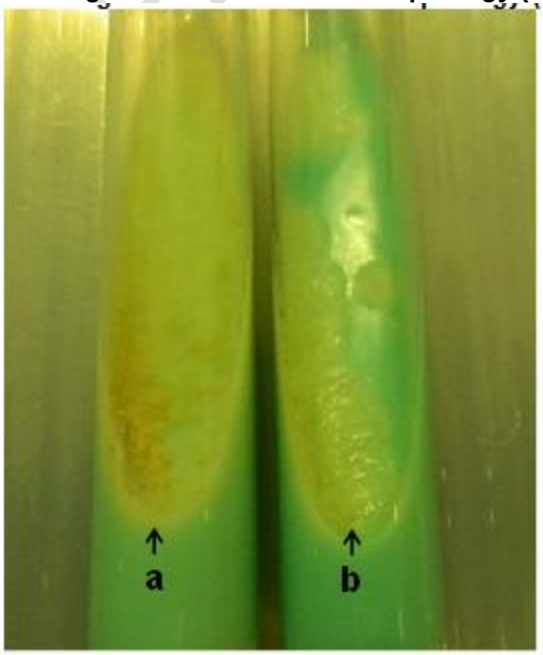

Figure 5. Skin cultures and bronchial aspirate. Löwestein – Jensen culture medium. Growth rate in 34 days. Incubation conditions: 37 ° C temperature in ambient atmosphere. Skin biopsy culture: abundant, confluent, rough, faint yellow colonies (a). Culture of bronchial aspirate: confluent, smooth, pale yellow colonies (b).

Table 1. Evolution of blood count parameters and acute phase reactants and coagulation factors.

	Date of sampling			
Parameter	23-06-2020	24-06-2020	25-06-2020	26-06-2020
Hemoglobin (g/dL)	5.40	6.60	-	7.80
Hematocrit (%)	18.60	21.50	-	25.30
Leukocytes (10^3/µL)	7.21	0.45	-	1.95
Neutrophils (10^3/µL)	6.49	0.36	-	1.35
Band (10^3/µL)	3.76	0.12	-	0.04
Lymphocytes (10^3/µL)	0.72	0.08	-	0.29
Eosinophils (10^3/µL)	-	0.0045	-	0.058
Platelets (mm^3)	84,000	4,000	-	9,000
ESR* (mm/h)	-	2	-	-
CRP** (mg/L)	-	>96	-	-
Procalcitonin (ng/mL)	-	-	242.7	-
Ferritin (ng/mL)	-	1207.27	-	-
D-dimer (ng/mL)	2578	3723	-	-
Fibrinogen(mg/dL)	553	300	-	-

*ESR: erythrocyte sedimentation rate; **CRP: C-reactive protein

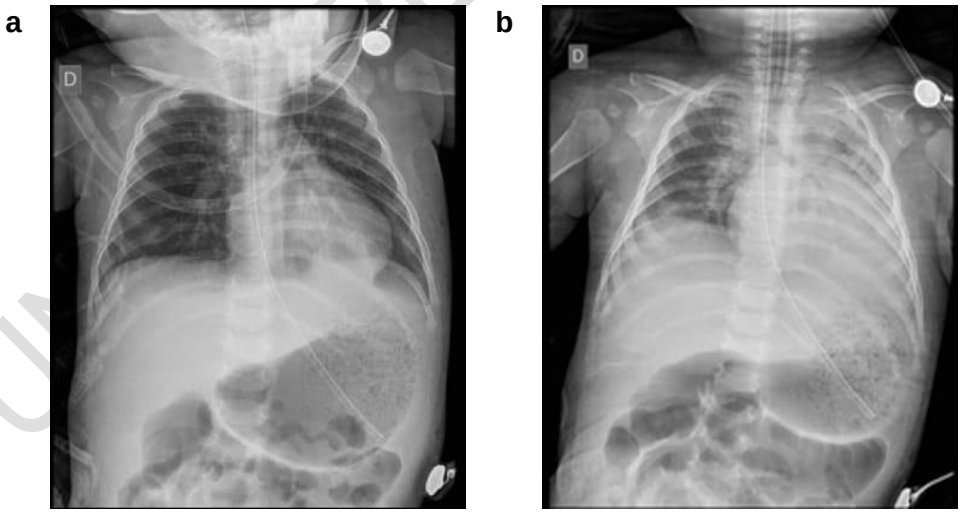

Fig. 6. Plain anteroposterior chest radiographs. X-ray on admission, observing right parahilar infiltrates with air bronchogram (a). Chest X-ray 48 hours after admission, with consolidation in the entire left hemithorax, loss of the contour of the cardiac silhouette and the ipsilateral costo-diaphragmatic angle (b).

3. DISCUSSION

The reported case shows how significant, is social protection (food, health, education and housing) to prevention, diagnosis and adequate management of TB in all its variants, and hence, its future incidence [8]. In this sense, exposure to TB is intensified in collective living environments, homes of people with active tuberculosis and crowded places, overwhile these factors, are associated with poverty [9]. The host's immune system stops the progression of TB, with immunodeficient conditions and malnutrition being important risk factors for developing its active form. Active TB is responsible nearly half of deaths in untreated people, so that early diagnosis and effective treatment crucial is determinant [10].

TB is usually acquired through the lungs and intestines however, cutaneous TB being a manifestation of systemic involvement. The etiologic agents are generally Mycobacterium tuberculosis, Mycobacterium bovis, and the Calmette-Guérin bacillus [11]. Cutaneous TB represents a small proportion of all TB cases, classified by the type of dissemination (exogenous and endogenous), route of infection (autoinoculation, direct inoculation, hematogenous, lymphatic, BCG vaccine), as well as, by the bacterial load (multibacillary , paucibacillary, without localization of mycobacteria to direct visualization or cultures). The clinical manifestations in exogenous infection can be Tuberculous chancre, Tuberculosis verrucosa cutis, and Lupus vulgaris (uncommon). In exogenous Lupus vulgaris (most cases), Scrofuloderma, Miliary tuberculosis, orificial tuberculosis, tuberculosis abscess and papulonecrotic tuberculosis [12,13].

Currently, the human availability, material and technological resources is essential to detection and identification of microorganisms, that cause coinfections, and even more so in those see the respiratory tract. They represent clinical dilemmas, and diagnostic and therapeutic challenges, as the case report presented [14]. Co-infections of any origin during COVID-19 pandemic need an effective strategy in the diagnostic and therapeutic approach, and even more in miliary TB with skin affectations, due to their clinical manifestations they may represent an obstacle in the prioritization of the medical care [15]. The co-infection of miliary TB with skin involvement and SARS-CoV-2, mainly in first-time patients, probably results in the lack of identification of either disease, due to nonspecific clinical characteristics of both, coupled with scarcity of clinical resources. [14, 15].

COVID-19 in moderate, severe and critical stages, immunodeficiency or the use of immunomodulators can lead to the reactivation and intensification of TB, which in turn can be a predisposing factor to manifestations of SARS-CoV -2 [16,17]. Miliary tuberculosis with cutaneous affectations is difficult to diagnose because, its clinical manifestations can be confused with various diseases, and downplay others, generating inappropriate and delayed treatment. SARS-CoV-2 can intensify the clinical manifestations of miliary tuberculosis and be unnoticed their care, directly influencing the mortality of this type of patients [18]. In the current epidemiological context, the suspicion of co-infections with TB in addition to COVID-19 in patients with respiratory tract infections, nonspecific clinical characteristics and an unexplained or prolonged clinical course must be contemplated [14].

4. CONCLUSION

The case study described is outstanding, due to, its infrequency, because it reveals the differentiated diagnosis importance, based on the socioeconomic and epidemiological context, mainly in the first level of care, from human, material and technological resources which are usually insufficient, reflecting a lower quality and opportunity in medical services, and resulting in higher morbidity and mortality in this type of patients. Finally, it is

recommended to continue with this research, in order to generate information about possible clinical pictures of miliary tuberculosis and co-infection by SARS-CoV-2.

CONSENT

All authors declare that written informed consent was obtained from the parents patient for publication of this case report and accompanying images.

ETHICAL APPROVAL

The research work was examined and approved by the hospital research and ethics committee.

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