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Case Report

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Prolonged Cholestasis as an Initial Presentation of Miliary Tuberculosis in a Pediatric Patient

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Abstract

Miliary tuberculosis is a severe form of tuberculosis resulting from hematogenous dissemination of *Mycobacterium tuberculosis* and may cause respiratory failure and multiorgan involvement in infants. Hepatic involvement is uncommon and may present as prolonged cholestasis and granulomatous hepatitis, making the diagnosis particularly challenging. We report an infant with miliary tuberculosis presenting with infantile cholestasis and acute respiratory failure. A 2-month-old infant presented with persistent cholestasis developed at 6 weeks of age and acute respiratory failure requiring noninvasive mechanical ventilation. Initial evaluation, including intraoperative cholangiography, excluded biliary atresia, and an extensive infectious, metabolic, autoimmune, immunologic, and genetic evaluation did not identify an alternative cause. Chest computed tomography demonstrated bilateral ground-glass opacities and peripheral micronodules in a miliary pattern. Liver biopsy showed granulomatous hepatitis with focal central necrosis and multinucleated giant cells. The diagnosis of *Mycobacterium tuberculosis* was confirmed by sputum polymerase chain reaction and acid-fast bacilli culture. A four-drug anti-tuberculosis regimen led to complete clinical, radiological, and biochemical resolution, with full recovery by 4 months of age. Miliary tuberculosis should be considered in infants presenting with severe respiratory failure, prolonged neonatal cholestasis, and granulomatous hepatitis, particularly in endemic regions. Early recognition of miliary pulmonary patterns on imaging and prompt initiation of targeted anti-tuberculosis therapy is critical to improve outcomes and ensure a favorable prognosis.

Keywords: Miliary tuberculosis; Granulomatous hepatitis; Neonatal cholestasis; Respiratory failure; Infant

Introduction

Tuberculosis continues to be one of the leading causes of childhood morbidity and mortality worldwide, with an increasing incidence in recent years [1]. Although pulmonary involvement is the most common manifestation, miliary tuberculosis represents a severe form of the disease with high morbidity and mortality if not promptly diagnosed and treated, due to hematogenous and lymphatic dissemination of *Mycobacterium tuberculosis* (*M. tuberculosis*) to multiple organs; however, hepatic involvement remains an exceptional presentation, with a clinical incidence of less than 1% [2]. Within this range, tuberculous hepatitis is a rare condition in children, presenting with diverse and generally nonspecific symptoms like constitutional disturbances, prolonged fever, and sometimes jaundice [3].

Diagnosis is challenging because the clinical manifestations of miliary tuberculosis in infants are often nonspecific and may overlap with more common neonatal and infant conditions. In particular, prolonged cholestasis may initially direct the diagnostic evaluation toward biliary, metabolic, genetic, or autoimmune disorders, while respiratory manifestations may appear later in the disease course [4]. Microbiological confirmation can also be difficult in infants because of the paucibacillary nature of pediatric tuberculosis and the challenges associated with obtaining respiratory specimens. Therefore, recognition of extrapulmonary clues, including hepatic granulomatous inflammation, characteristic thoracic imaging findings, and epidemiological exposure, may be critical for establishing the diagnosis [5]. Initiating standard anti-tuberculosis treatment promptly is essential for achieving high rates of recovery and preventing complications [3]. Here, we report a case of an infant who had respiratory fail-

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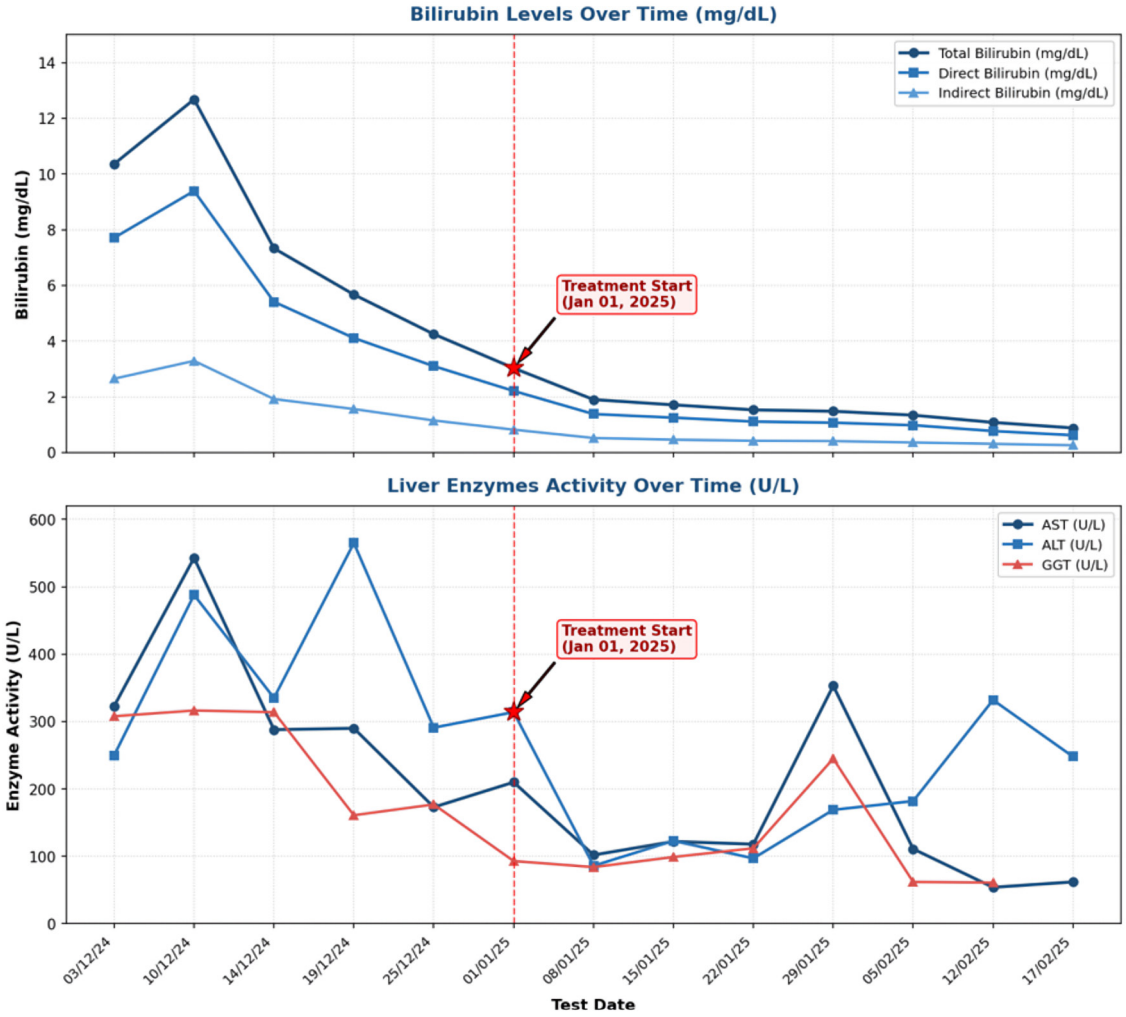


Figure 1. Liver biochemical profile with elevated aminotransferases and cholestatic enzymes. AST: aspartate aminotransferase; ALT: alanine aminotransferase; GGT: gamma-glutamyl transferase.

ure and prolonged cholestatic jaundice due to granulomatous hepatitis caused by *M. tuberculosis*.

Case Report

A 2-month-old male infant with no perinatal or family history, on mixed feeding, developed jaundice at 6 weeks. The jaundice worsened, leading to hospitalization. Initial laboratory evaluation demonstrated leukopenia (white blood cell count, 3,390/mm^3), hemoglobin 10.8 g/dL, hematocrit 32%, and thrombocytosis (platelet count, 522,000/mm^3). Liver biochemistry showed marked hepatocellular and cholestatic abnormalities, with an aspartate aminotransferase level of 323.2 U/L, alanine aminotransferase level of 250 U/L, gamma-glutamyl transferase level of 307.9 U/L, total bilirubin of 12.45 mg/dL, direct bilirubin of 10.51 mg/dL, and indirect bilirubin of 1.94 mg/dL (Fig. 1). An ultrasound failed to visualize the gallbladder, prompting a cholangiogram and intraoperative cholangiography that ultimately ruled out biliary atresia. Subsequently, the patient experienced worsening respiratory function, advancing to acute respiratory failure that necessitates noninvasive mechanical ventilation; an initial chest radiograph showed bilateral perihilar bronchial wall thickening, pulmonary consolidations predominantly involving the left upper lobe, and areas of increased opacity with a tendency toward consolidation in the right lung. No characteristic miliary pattern was identified on the initial radiograph. During hospitalization, a workup for cholestatic hepatitis was conducted (Table 1), which included infectious, metabolic (including thyroid profile), autoimmune, and genetic immunological assessments. While in the intensive care unit, chest computed tomography (CT) demonstrated peripheral micronodules in the right upper and middle lobes and diffuse ground-glass opacities (Fig. 2). Parents report that his grandfather has a chronic condition, a cough. Additionally, a liver biopsy showed periportal predominant granulomatous inflammation with focal central necrosis associated with interface hepatitis (Fig. 3). Based on these findings, a suspicion of tuberculosis was raised, leading to a purified protein derivative (PPD) test, sputum polymerase chain reaction (PCR), induced

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Table 1. Approach to Prolonged Neonatal Cholestasis in a 2-Month-Old Infant

Diagnostic study	Result
First line studies	
Intraoperative cholangiography	Negative for biliary atresia
Infectious disease screening	Negative: hepatitis A, B, CMV, EBV, HIV, COVID, Toxoplasma, rubella, HSV, adenovirus
Alpha-1 antitrypsin level	288 mg/dL (90–200), normal
Thyroid profile	TSH 6.45 µU/mL; free T4 1.83 ng/dL
Alagille syndrome workup	No butterfly vertebrae, no cardiopathy, no ocular alteration, no dysmorphic facies, no renal involvement
Second line studies	
Immunologic workup	Normal immunoglobulins, normal neutrophil burst
Metabolic workup	Qualitative amino acids in urine: normal; very long-chain fatty acids: elevated C26:1-hexacosenoic (elevated in malnutrition); blood gases: normal; ammonia 68.8 µg/dL
Autoimmune hepatitis and vasculitis workup	Negative ANAs, negative anti-smooth muscle antibody, negative anti-LKM1, immunoglobulin G 917 mg/dL, negative ANCA
Total bile acids	140.99 µmol/L, elevated
Iontophoresis with pilocarpine stimulation	First: 52 mEq/L (indeterminate); Second: 31 mEq/L (associated with probable malnutrition)
Genetic study	Whole-exome sequencing (WES) and mitochondrial genome single-copy number variant screening: negative

CMV: cytomegalovirus; EBV: Epstein–Barr virus; HIV: human immunodeficiency virus; COVID: coronavirus disease; TSH: thyroid-stimulating hormone; T4: thyroxine; ANAs: antinuclear antibodies; anti-LKM1: anti-liver-kidney microsomal type 1 antibody; ANCA: antineutrophil cytoplasmic antibodies.

sputum bacilloscopy with bronchoalveolar lavage culture, and GeneXpert was requested. Serial bacilloscopy was positive in two out of three samples; the PCR for *M. tuberculosis* in sputum was also positive, along with the culture; rifampicin resistance was ruled out. Tests were performed on the parents, with the father testing positive for *M. tuberculosis*. Our patient received antitubercular treatment (rifampicin, isoniazid, pyrazinamide, and ethambutol) using individually compounded liquid formulations prepared for pediatric administration, with doses adjusted according to the patient's body weight. The patient showed significant respiratory and cholestatic improvement. Despite being hepatotoxic, there was no deterioration in his liver function. After 4 months, he was discharged with outpatient multidisciplinary follow-up so far without any sequelae.

Discussion

Granulomatous hepatitis in the pediatric population is a rare entity with a heterogeneous and frequently nonspecific clinical

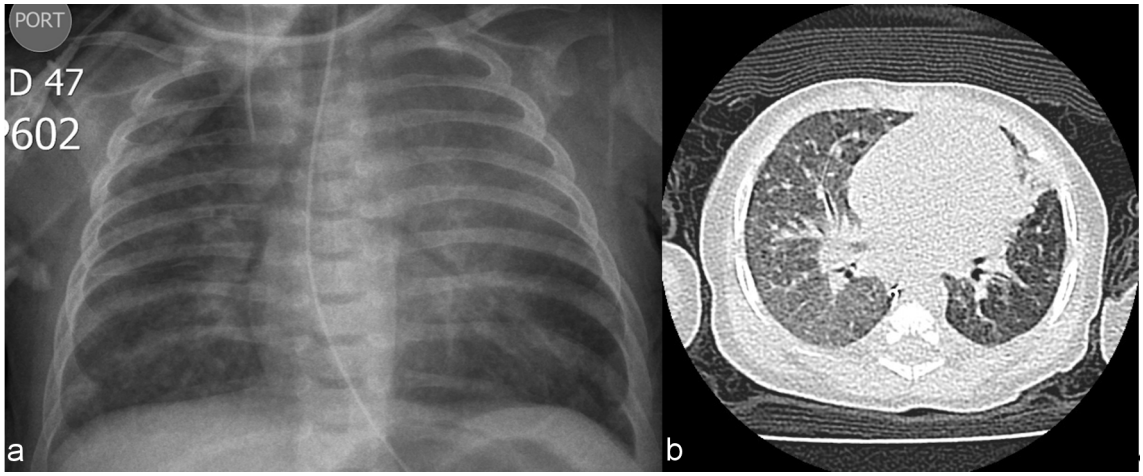


Figure 2. Baseline chest X-ray and CT. (a) Bilateral thickening of the peribronchovascular parahilar interstitium with consolidation in the upper lobe and lingula. (b) Chest computed tomography with multilobar involvement characterized by bilateral ground-glass opacities, peripheral micronodules, and alveolar filling regions. CT: computed tomography.

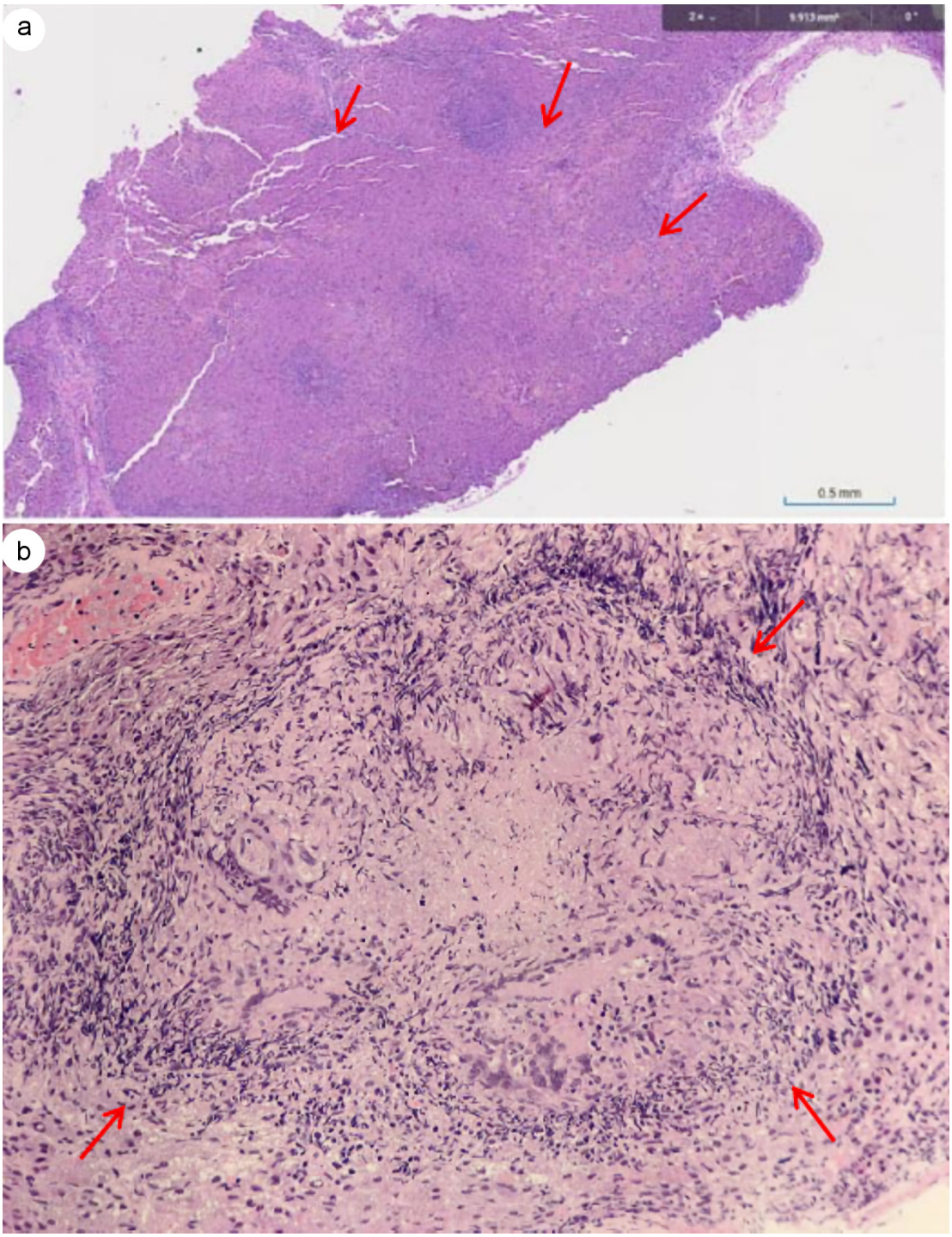


Figure 3. Liver biopsy (a) Multiple granulomas in the liver parenchyma (arrows, H&E, × 10). (b) Granuloma with peripheral halo of lymphocytes, central necrosis, and presence of multinucleated giant cells (arrows, H&E, × 40). H&E: hematoxylin and eosin stain.

presentation, typically characterized by prolonged fever, hepatomegaly, and abnormalities in liver function tests. Its reported prevalence has declined over time, from approximately 4% in earlier cohorts to less than 0.6% in more recent series [6]. Within this framework, miliary tuberculosis in infants constitutes an uncommon yet highly severe form of disease, driven by extensive hematogenous dissemination of *M. tuberculosis*. Although it represents only 1–7% of pediatric tuberculosis cases, it carries a disproportionately high mortality risk and is often characterized by a subacute course with failure to thrive, hepatosplenomegaly, and progressive respiratory compromise [7–9].

This case is notable for its initial presentation as prolonged

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neonatal cholestasis, which obscured the underlying pulmonary involvement until the onset of acute respiratory failure. Although the lungs constitute the primary site of miliary dissemination—supported by the characteristic CT findings of diffuse micronodules and ground-glass opacities reflecting alveolar and interstitial inflammation due to hematogenous spread—our patient remained previously healthy, without evidence of immunodeficiency or typical features such as prolonged fever or constitutional symptoms [10, 11]. Remarkably, cholestasis, defined by a significant elevation of conjugated bilirubin (> 1.0 mg/dL) [12], represented the sole manifestation of hepatic involvement. During the initial evaluation, the most common infectious etiologies for this age group were systematically excluded, and there was no history of perinatal exposure or maternal active tuberculosis [10]. In this context, histopathological findings on liver biopsy were pivotal in raising suspicion for tuberculosis, which was subsequently supported by microbiological confirmation and the identification of active tuberculosis in the patient's father as the likely source of exposure.

Hepatic granulomas are found in 2–15% of liver biopsies, with more than 60% secondary to systemic processes; in developing countries, infectious etiologies have a higher incidence. However, tuberculous etiology in this context is uncommon, and most cases reported in the literature have been identified in patients with human immunodeficiency virus (HIV) or other states of immunosuppression [11, 13]. Tuberculous granulomas are characterized by central caseous necrosis and prominent peripheral inflammatory infiltrate, distinguishing them from sarcoid, suppurative, foreign body, and xanthomatous granulomas. The immune response involves the activation of macrophages and helper T lymphocytes toward Th1, Th2, Th17, or T-regulatory subpopulations [11].

The treatment should follow the recommendations established by the World Health Organization, ensuring full compliance with the anti-tuberculosis regimen [14]. Patients with hepatitis secondary to tuberculosis have shown an excellent therapeutic response, with resolution of liver lesions and significant clinical improvement.

Conclusions

Disseminated tuberculosis should be considered in infants with unexplained prolonged cholestasis or granulomatous hepatitis, particularly when respiratory deterioration, characteristic pulmonary imaging findings, or a potential household tuberculosis exposure is present. In this setting, integrating hepatic histopathology with thoracic imaging and microbiological testing may facilitate early recognition of miliary tuberculosis. Prompt initiation of appropriate antituberculosis therapy is essential to prevent progression of disseminated disease and improve clinical outcomes.

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Conflict of Interest

The authors declare that they have no conflict of interest.

Informed Consent

Written informed consent was obtained from the patient's legal guardian for the publication of this case report, in accordance with the institutional guidelines of Fundacion Santa Fe de Bogota. Patient anonymity and confidentiality have been strictly maintained.

Author Contributions

CZP and JFVC conceived and designed the case report. CZ, MJRB, JCM, MAS, KG, and SDRA contributed to patient management, investigation, and data collection. RLP and KG contributed to histopathological evaluation and interpretation. JFVC and OPP provided clinical supervision and contributed to the interpretation of the findings. MJRB and CZ performed the literature review and drafted the manuscript. All authors contributed to the critical revision of the manuscript, approved the final version, and agreed to be accountable for all aspects of the work.

Data Availability

Any inquiries regarding supporting data availability of this study should be directed to the corresponding author.

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