Case Report
Volume 8:1, 2024

Clinical and Medical Case Reports

ISSN: 2684-4915 Open Access

Acute Miliary Tuberculosis with Diffuse Ground-glass Change as the First Imaging Manifestation: A Case Report

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Abstract

Introduction: To investigate the clinical and chest imaging features of acute military tuberculosis with diffuse ground-glass opacities.

Methods: A case of acute military tuberculosis with diffuse ground-glass opacities was reported.

Results: The patient, a 52-year-old male, was hospitalized for 10 days with fever, and his body temperature fluctuated between 37.8 °C and 40 °C. The patient had a medical history of nephrotic syndrome for 20 years, lymph node tuberculosis for 10 years and viral hepatitis C for 3 years. There were no findings with Chest CT, and all 5 times of blood culture were negative during the first 12 days of the disease course. Metagenomic Next-Generation Sequencing (mNGS) was employed, revealing the detection of 13 specific reads belonging to *M. tuberculosis* complex, indicating the drug treatment on day 13. After receiving treatment with isoniazid, rifampicin, pyrazinamide and ethambutol, the highest body temperature of the patient decreased to 38.5 °C on day 17. A follow-up chest CT scan showed diffuse ground-glass opacities, and mNGS data analysis revealed 27 specific reads of *M. tuberculosis* complex in Bronchoalveolar Lavage Fluid (BALF) on day 17. The highest body temperature of the patient decreased to 38 °C on day 20. On day 33 of the disease course, a follow-up chest CT scan demonstrated typical imaging changes of miliary tuberculosis, and the body temperature of the patient returned to normal.

Conclusion: The imaging features of immunocompromised patients with acute miliary tuberculosis may manifest as diffuse ground glass opacities. mNGS with high sensitivity is valuable for early and accurate diagnosis, particularly in immunocompromised patients presenting with diffuse ground-glass opacities indicative of acute miliary tuberculosis.

Keywords: Pulmonary tuberculosis • *Mycobacterium tuberculosis* • Metagenome • Case report • Imaging

Introduction

Tuberculosis remains the leading cause of mortality among infectious diseases worldwide. According to statistics, there were approximately 10 million newly diagnosed cases and 1.4 million fatalities worldwide in 2019. The incidence of tuberculosis in China is the highest among all infectious diseases nationwide and ranks second globally in terms of morbidity and mortality [1]. Given its highly contagious nature, early diagnosis and treatment are crucial. In recent years, the increasing prevalence of underlying diseases, such as diabetes and immunodeficiency disorders, as well as the widespread use of immunosuppressive drugs, has led to a rise in tuberculosis incidence and a diversity of changes in tuberculosis imaging. Specifically, atypical pulmonary tuberculosis with predominantly ground-glass changes but no typical clinical symptoms is often misdiagnosed as other diseases that exhibit similar imaging manifestations, such as viral pneumonia, allergic pneumonia, and pneumocystis pneumonia. This situation not only brings huge challenge to the correct diagnosis and treatment of tuberculosis, but also increases the economic and mental burden of patients. In this paper, we report a case of hematogenous pulmonary tuberculosis with diffuse ground-glass opacities on imaging to improve the understanding of this disease and reducing misdiagnosis as well as underdiagnosis.

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Received: 02 January, 2024, Manuscript No. cmcr-24-124226; **Editor assigned:** 03 January, 2024, Pre QC No. P-124226; **Reviewed:** 12 January, 2024, QC No. Q-124226; **Revised:** 20 January, 2024, Manuscript No. R-124226; **Published:** 29 January, 2024, DOI: 10.37421/2684-4915.2024.8.288

Case Presentation

A 52-year-old male presented with a fever of 38 °C after catching a cold 10 days before admission. The patient's temperature normalized after taking anti-fever medication, but spiked to 40 °C again within 4-5 hours. He has a history of nephrotic syndrome for over 20 years and was treated with prednisone for 6 months before discontinuing treatment. Additionally, he has had left axillary lymph node tuberculosis for 10 years and took anti-tuberculosis drugs for 2 months before stopping due to abnormal liver function. He also suffers from a 2-year history of hepatitis C with cirrhosis and underwent closed chest drainage for pleural effusion in another hospital. His laboratory evaluation on admission showed a leucocyte count of 3.24 × 109/L, with 71.6% neutrophils, 20.4% lymphocytes, hemoglobin level of 88g/L, platelet count of 131 × 109/L, C-reactive protein level of 126.67mg/L. Chest radiography revealed increased lung parenchymal markings, patchy opacities with indistinct margins in the right lung, and thickening of the right interlobular septa.

The patient was initially diagnosed with pneumonia and treated empirically with moxifloxacin combined with cefoperazone sulbactam. On day 12, chest CT scan (Figure 1 (1-3)) demonstrated multiple nodules in the upper lobe of the right lung and localized ground-glass opacities in both lungs. The patient had a persistent high fever with a maximum temperature of 41 °C, and then was transferred to the ICU due to severe illness. After being transferred, routine blood test was performed: a leucocyte count of 1.26 × 109/L, lymphocytes count of 0.18 × 109/L, hemoglobin level of 54g/L, platelet count of 56 × 109/L. Due to the severe infection-related trilineage reduction and critically illness of patient, the anti-infective therapy was adjusted to moxifloxacin and intravenous

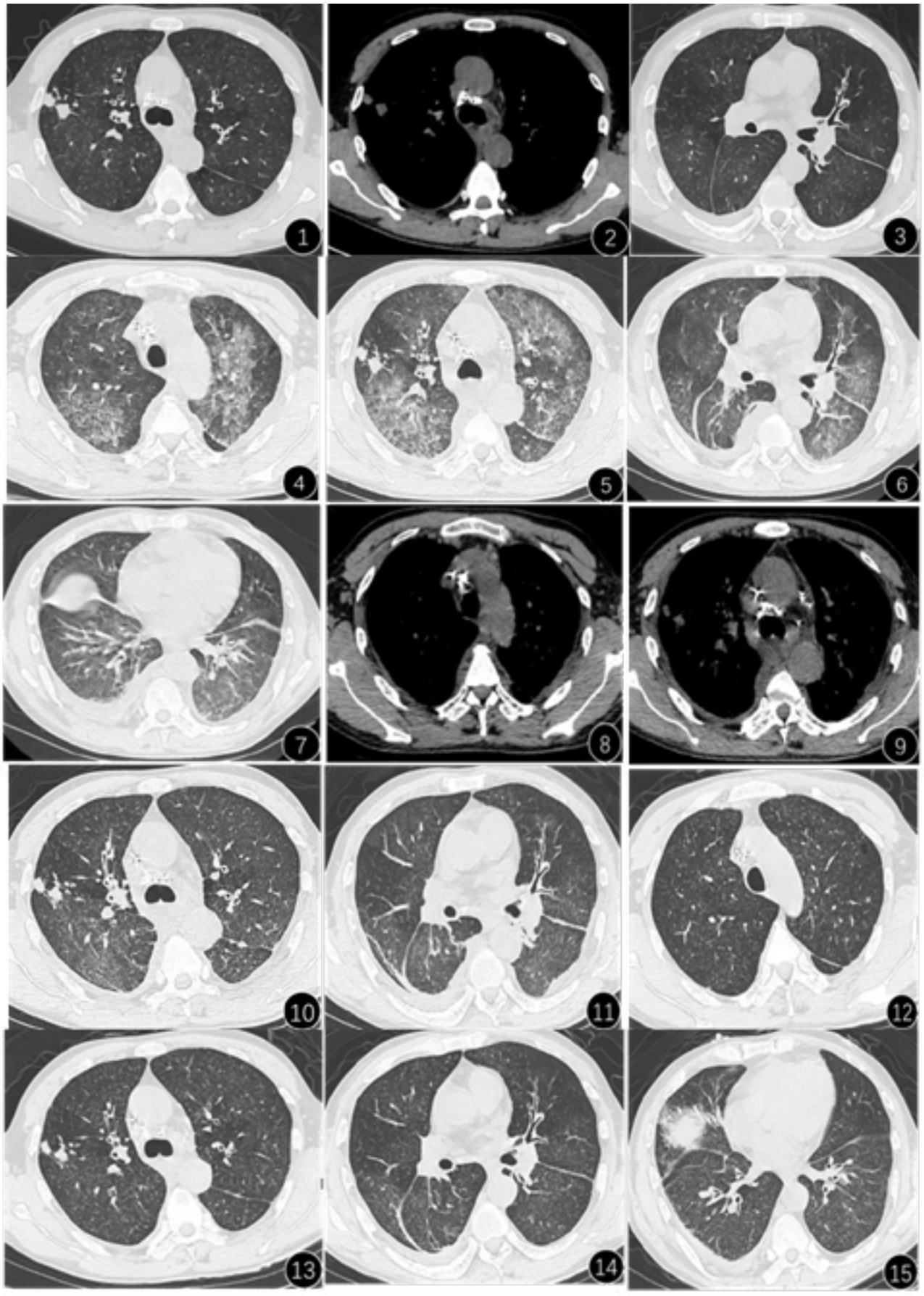

Figure 1. Chest CT scans of the patient at different 121 stages of disease.

drip of meropenem. Bacterial culture and mNGS of blood were performed due to persistent high fever and rigor after transfer to the ICU. TB tests yielded normal results except for a positive T-SPOT test for TB in blood. Bacterial blood cultures were continually negative for 5 times. On day 13, blood mNGS reported no pathogen was detected in plasma, but *M. tuberculosis* complex was detected in blood cells (13 specific reads, positive reference range ≥2) (Table 1).

For clinically important and difficult-to-detect pathogenic such as Mycobacterium tuberculosis, the detection of 1 specific sequence can be determined as positive [2]. Based on the patient's symptoms, signs, disease process and other clinical manifestation, the possibility of *M. tuberculosis* infection was considered, leading to the addition of anti-tuberculosis treatment (isoniazid, rifampin, pyrazinamide, streptomycin) to the previous regimen. The patient's temperature decreased, but wheezing and dyspnoea symptoms were evident. Blood gas analysis showed type I respiratory failure, while a chest CT scan on day 17 (Figure 1 (4-9)) demonstrated diffuse ground-glass opacities in both lungs. BNP parameters were within normal limits to exclude cardiogenic factors. Bronchoalveolar Lavage Fluid (BALF) was collected from the lingual lobe of the left lung for culture, acid-fast stain, G and GM tests, all of which yielded negative results. *M. tuberculosis* complex (27 specific reads, positive reference range ≥ 2), Corynebacterium striatum (28 specific reads, positive reference range ≥ 20), Hepacivirus C (1 specific read, positive reference range ≥ 3) and Enterococcus faecalis (3 specific reads, positive reference range ≥ 20) (Table 1) was detected by mNGS data analysis. In line with the patient's symptoms and other laboratory tests, Corynebacterium striatus [3] and Enterococcus faecalis [4] are clinically considered to be colonizers of the respiratory tract with low pathogenicity.

Since the patient has a history of Hepacivirus C, and the result of GeneXpert was positive, anti-tuberculosis therapy was continued while discontinuous veno-venous hemofiltration (CVVH) was performed. After 7 days of treatment, the patient's maximum body temperature decreased to 38 °C. A follow-up chest CT scan (Figure 1 (10,11)) revealed partial resolution of the ground-glass opacities and a faint military shadow. Subsequently, there was gradual improvement in temperature, inflammatory markers, respiratory function and overall clinical status. On day 33, a follow-up chest CT scan (Figure 1 (12-15)) demonstrated miliary shadows in both lungs that were evenly distributed, dense and of equal size. At the same time, the BALF test revealed a positive culture result for *M. tuberculosis*. Based on these findings, the diagnosis of acute hematogenous disseminated pulmonary tuberculosis was ultimately confirmed. The patient was discharged with medication in the third week of treatment due to personal reasons. Follow-up after discharge revealed that the patient remained generally well, with a normal temperature and no significant abnormalities on repeat chest radiographs.

Results and Discussion

Most hematogenous disseminated pulmonary tuberculosis occurs after primary pulmonary tuberculosis and is more common in children. In adults, it is typically caused by the entry of *M. tuberculosis* bacteria into the bloodstream from latent foci following primary infection, and occasionally by secondary active TB foci in the lungs or other organs eroding the adjacent lymphatic or circulatory system. Typical imaging presented as relatively evenly distributed, miliary shadows of similar density and size diffusing in both lungs. In general, clinical diagnosis is not challenging; however, due to the significant increase in the number of immunocompromised individuals caused by disease or medication in recent years, the clinical presentation has become diverse and atypical [5,6]. According to literature, diffuse ground glass opacity (GGO) incidence in patients with hematogenous disseminated pulmonary tuberculosis/ Miliary Tuberculosis (MT) ranges from 64% to 92% [7-9]. Studies [9] have indicated that patients with a degree of GGO exceeding 50% exhibit more pronounced acute symptoms, experience significant changes in the levels of biomarkers such as CRP and albumin during the acute phase of inflammation, and may progress to ARDS in some cases. These findings suggest that MT patients with extensive GGO develop the disease at a faster rate. Differences in the degree of GGO in MT patients may be related to individual differences in the inflammatory response of disseminated M. tuberculosis, which may depend on the interaction between mycobacteria virulence and host immunity [10]. The model of hematogenously disseminated pulmonary TB with diffuse GGO can be divided into two types based on the presence or absence of miliary nodules: predominantly diffuse GGO presentation and diffuse GGO with miliary nodules. Diffuse GGO occurs mainly in cases of hematogenously disseminated TB combined with Diffuse Alveolar Damage (DAD), which is a high-risk factor for Acute Respiratory Distress Syndrome (ARDS), indicating a poor prognosis. The diffuse GGO model is mainly due to impaired host immune function resulting in poor or no nodule formation. Due to the lack of typical signs, diffuse GGO in pulmonary TB is often misdiagnosed as viral pneumonia, PJP, or interstitial pneumonia, etc., which can easily lead to delayed diagnosis/treatment and death. Methods for improving differential diagnosis include the utilization of image reconstruction techniques to optimize detection of military nodules against a ground-glass opacity background, as well as careful attention to features such as nodules, solid lesions, calcified foci, and cavities that suggest the diagnosis. Active pathogenetic testing for *M. tuberculosis* should also be performed in order to confirm the diagnosis. In this case report, no evidence of other pathogens was found in multiple bloods or BALF cultures, cardiogenic factors were excluded, and the patient's underlying disease suggested that he was an immunocompromised individual. On analysis of the chest CT, the diffuse ground-glass opacity in this case, as in the case in the literature review, was due to diffuse alveolar damage caused by the acute tuberculosis infection resulting in the failure of typical intact tuberculous nodule formation. The shortcoming of this case was the lack of histopathological evidence.

Tuberculosis is caused by the *M. tuberculosis* complex and usually requires bacteriological evidence to confirm the diagnosis. Traditionally, a positive acid-fast stain or culture of respiratory specimens has been considered the "gold standard" for the diagnosis of tuberculosis, while blood culture has not been routinely used, nor has the obtaining of pathogenic evidence from blood been considered in clinical diagnosis. In this case report, tuberculosis was initially diagnosed by mNGS of blood, and further BALF testing was performed to confirm the diagnosis of tuberculosis.

With the gradual rise of the AIDS epidemic, it has been found that HIV-associated TB is prone to concomitant with *M. tuberculosis* bacteraemia. A meta-analysis included 23 studies and 5751 patients with HIV TB, in which the mean incidence of *M. tuberculosis* bacteraemia was 38% and the incidence of bacteraemia was negatively correlated with CD4+ lymphocyte count, when the CD4+ lymphocyte count was 74/μL, the incidence of bacteraemia can be up to 45% [7]. Blood culture of *M. tuberculosis* takes 6-12 days, although it is significantly shorter than solid culture, which takes 8-12 weeks, it still affects timely treatment of patients. With the rapid development of molecular diagnostic methods, rapid detection of the target pathogen has become possible [8]. In patients with confirmed HIV TB, rapid detection of *M. tuberculosis* genomic DNA in mononuclear cells from blood was possible by polymerase chain reaction (PCR) [9], PCR (82.0%) has a significantly higher positive rate than blood culture (12.5%), and the similar situation also occurs in patients without confirmed HIV TB (33.0% *vs.* 5.5%) [10]. The breakthrough of *M. tuberculosis* from infected alveoli into the blood stream and the achievement of a certain number of viable bacteria is an important condition for a positive blood culture. If the number of viable bacteria is too low or *M. tuberculosis* is phagocytosed by monocytes or granulocytes and then enters the blood circulation, the blood culture can be negative when the *M. tuberculosis* PCR of blood monocytes is positive, thus making the *M. tuberculosis* PCR of blood mononuclear cells

Table 1. BALF, bronchoalveolar lavage fluid; mNGS, metagenomic next-generation sequencing.

Date	05/03/2021	28/02/2021
Sample	BALF	Blood
Pathogen	reads	reads
Mycobacterium tuberculosis complex	27	13
Hepacivirus C	1	-
Corynebacterium striatum	28	-
Enterococcus faecalis	3	-

more sensitive for the diagnosis of tuberculosis than the blood culture [11]. Subsequent clinical studies have also confirmed that in non-HIV tuberculosis patients, the PCR positivity of *M. tuberculosis* genomic DNA in blood mononuclear cells is 40%, and the higher the amount of acid-fast bacilli on sputum smears, the higher the PCR positivity rate, up to 87.5% in patients with grade 4 sputum acid-fast bacilli [11,12]. In patients with active tuberculosis, *M. tuberculosis* may be present in the bloodstream as live or intracellular bacteria in monocytes or as cell-free DNA (cfDNA) in plasma. cfDNA is a nucleic acid fragment that is released during the death and degradation of *M. tuberculosis* or its host cell, unlike genomic DNA, where 70% of cfDNA is less than 300 bp, with an average of 170 bp in blood [13]. In patients with active tuberculosis, the plasma levels of *M. tuberculosis* cell-free DNA (cfDNA) may exceed those of its genomic DNA due to cfDNA's susceptibility to degradation and clearance. Although the kinetics of *M. tuberculosis* cfDNA metabolism remain unclear, there may be a window period for measuring cfDNA; however, once detected, it can serve as an indicator of active infection and reflect the patient's disease activity status [14]. In a study of 118 confirmed TB patients with aetiological methods, real-time PCR had higher sensitivity than GeneXpert (61.01% *vs*. 79.70%) and similar specificity (96.72% *vs*. 95.10%) for cfDNA detection [14], digital PCR had higher sensitivity and specificity than real-time PCR, with specificity up to 100% [13].

The detection technology represented by GeneXpert, which is based on qPCR, amplifies the specific sequence of the rpoB gene and the core region associated with rifampicin resistance of *M. tuberculosis* for detection, but PCR technology requires the presence of a specific target pathogen, which is its limitation [15]. In contrast, metagenomic Next Generation Sequencing (mNGS) can directly sequence all nucleic acids in a sample without bias to detect possible pathogenic sequences contained in the sample. In addition, due to its rapidity, efficiency and high resolution of mutated genes, several recent expert consensuses in China have recommended that mNGS be used as an adjunct to routine testing in difficult-to-diagnose, critically ill, treatment-resistant and immunosuppressed patients [16-19]. However, looking back at the original mNGS detection data, it is often possible to detect the sequences of many other pathogens while detecting MTB. This is the advantage of NGS compared to Xpert and other targeted detections that only detect MTB when used to detect difficult infections. But it also brings difficulties to the interpretation of the final report.

Moreover, compared with other pathogens, the number of detected sequences in samples of MTB infection may are lower [20], and these issues need to be resolved in larger studies.

The target of mNGS is nucleic acids not surviving pathogens. Given the potential for DNA degradation *in vivo* over time, it is crucial to accurately identify the responsible DNA in common bacterial infections [21]. There are no clinical studies of blood mNGS for the diagnosis of tuberculosis. In this case, no *M. tuberculosis* complex DNA was detected in the plasma, while the blood cells were positive; suggesting that *M. tuberculosis* complex DNA is more likely to originate from monocytes. At the same time, mNGS analysis of BALF also detected DNA of *M. tuberculosis* complex, confirming a diagnosis of pulmonary tuberculosis without evidence of extrapulmonary involvement. The response to treatment further supported this diagnosis [18]. Additionally, mNGS has 100% specificity in detecting DNA from co-infecting pathogens and can identify pathogen DNA even when culture or GeneXpert results are negative. When used in combination with other tests, mNGS can achieve a pathogen detection rate of nearly 80% [2]. mNGS outperforms GeneXpert in detecting extrapulmonary tuberculosis [22,23]. In patients with severe pneumonia, both blood and BALF mNGS were performed, the common etiology test can help 50% of patients to confirm pathogen, whereas the rate in BALF can be up to 85%. The concordance rate between blood mNGS and BALF mNGS is up to 60%, with a consistent trend observed during treatment. However, the number of pathogen sequences detected by blood mNGS is significantly lower than that of BALF at the same time point, which is consistent with our patient's results [24]. Performing mNGS of plasma, blood cell layer and BALF alongside routine testing can reduce missdiagnosis of TB, shorten the delay in diagnosis and improve prognosis. mNGS is a useful and non-substitutable addition to routine clinical testing.

Conclusion

The imaging features of immunocompromised patients with acute miliary tuberculosis may manifest as diffuse ground glass opacities. mNGS with high sensitivity is valuable for early and accurate diagnosis, particularly in immunocompromised patients presenting with diffuse ground-glass opacities indicative of acute miliary tuberculosis.

Data Availability

The patient data used to support the findings of this study are included within the article.

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Author Contributions

Xin Yu contributed to the manuscript preparation, Yahui Huang reviewed and edited the original work of Xin Yu, Yin Zhang and Xianglong Cai prepared clinical info of the patient, Liangliang Liu and Na Zhang contributed on the treatment, Jingzhi Zhu, and Xiaotong Xi were responsible for the collection of clinical specimens and information and data analysis. Ran Ding contributed to review this manuscript. Guoqiang Li contributed to the study design and review of the manuscript. All authors contributed to the article and approved the submitted version.

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How to cite this article: Yu, Xin, Yahui Huang, Yin Zhang and Xianglong Cai, et al. "Acute Miliary Tuberculosis with Diffuse Ground-Glass Change as the First Imaging Manifestation: A Case Report." *Clin Med Case Rep* 8 (2024): 288.