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CASE REPORT

Disseminated Pyrazinamide-Resistant Mycobacterium Bovis in an AIDS Patient: The Role of Molecular Diagnosis and Optimized Therapy

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Abstract: Disseminated Mycobacterium bovis (M. bovis) infection is a rare but serious complication in immunocompromised individuals, particularly in those with advanced HIV/AIDS. Diagnosis is often delayed owing to overlapping clinical features with those of other mycobacterial infections. We report a case of disseminated M. bovis infection in a severely immunocompromised patient with AIDS. Rapid identification was achieved using molecular diagnostic techniques, specifically fluorescent PCR melting curve analysis, which enabled timely adjustments to antimicrobial therapy. The patient showed significant clinical improvement and resolution of symptoms. This case underscores the importance of early molecular diagnostics and tailored therapeutic strategies for managing opportunistic infections, such as M. bovis, in patients with HIV/AIDS. These findings highlight the need for broader implementation of advanced diagnostic tools to improve outcomes and mitigate the risks of treatment failure and drug resistance in vulnerable populations.

Keywords: M. bovis, PZA-resistant, AIDS, opportunistic infection, co-infection

Background

In resource-limited countries with high tuberculosis (TB) prevalence, up to 60% of extrapulmonary TB cases are observed in HIV-infected individuals, especially when the $CD4^+$ T lymphocyte count is < 300 cells/μL.[1,2] Mycobacterium bovis (M. bovis) belongs to the Mycobacterium tuberculosis complex (MTBC) and is primarily transmitted through contact with infected cattle or their products such as unpasteurized dairy.[3–5] Although M. bovis infection in humans is rare, especially in HIV-positive patients, this case underscores the growing need for early molecular diagnosis to prevent severe outcomes in immunocompromised populations. Here, we report a case of disseminated M. bovis infection in a Chinese AIDS patient. This report discusses the patient's clinical presentation, diagnostic workup, and treatment process to enhance the recognition of disseminated M. bovis infection in AIDS patients and to summarize the experience.

Case Presentation

A 34-year-old Mongolian male patient with a 32-year history of hepatitis B was diagnosed with an HIV infection in 2022. His $CD4^+$ T lymphocyte count was 228 cells/μL at that time, with an unknown HIV RNA viral load. He was started on bictegravir/emtricitabine/tenofovir alafenamide as antiretroviral therapy, and has remained on this regimen. In early July 2023, the patient developed a fever with a maximum temperature of 38°C, accompanied by chills, dizziness,

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abdominal distension, and loose stools. Abdominal computed tomography (CT) performed at a local hospital revealed significant ascites. The patient presented to our hospital on July 26, 2023, for further evaluation and management. He denied consumption of unpasteurized milk or raw meat, although he regularly consumed mutton and resided in urban Inner Mongolia.

On physical examination, the patient was obese with palpable, tender, and mobile lymph nodes in the neck, axillae, and groin. Abdominal examination revealed distension with positive rebound tenderness and shifting dullness, but no palpable masses. Hepatosplenomegaly and peripheral edema were not observed.

Laboratory tests showed a white blood cell count of 7.04×10^9/L with a monocyte percentage of 10.8%. The HIV RNA load was undetectable, and the $CD4^+$ T cell count dropped to 71 cells/μL. Imaging studies included enhanced abdominal CT that showed peritoneal thickening, ascites, and enlarged lymph nodes in the abdominal cavity and retroperitoneum with multiple low-density splenic lesions suggestive of an infectious process. Positron emission tomography-CT findings indicated (1) diffuse peritonitis with lymph node involvement, suggestive of TB or another special infection, (2) a potential indolent lymphoma with mature B-cell differentiation, and (3) the possibility of an occult gastrointestinal malignancy with peritoneal and lymphatic metastases (Figure 1A). Multisite biopsy of the peritoneum and axillary lymph nodes, along with ascitic fluid cytology, is recommended.

On admission, the patient underwent abdominal paracentesis with catheter drainage, which revealed hemorrhagic exudative ascites. Ascitic fluid was negative for next-generation sequencing (NGS), culture, TB DNA, acid-fast staining, and cytology. Ultrasonography confirmed lymphadenopathy in the neck and axillae, and biopsy of the left axillary lymph nodes was performed. Histopathology revealed necrotizing granulomatous lymphadenitis with negative acid-fast staining, although TB could not be excluded (Figure 1B). Results of the TB Xpert test were negative. Capsule endoscopy revealed small-bowel inflammation and lymphangiectasia (Figure 1C). Colonoscopy revealed congested mucosa with segmental erosions and ulcers, predominantly in the ascending and transverse colon. Biopsies were obtained from these sites (Figure 1D). Histopathology of the ileocecal valve showed chronic inflammation with epithelioid granulomas. Acid-fast staining was positive (Figure 1E), although TB Xpert staining remained negative.

Given the positive acid-fast staining in the ileocecal biopsy, a mycobacterial infection was confirmed. Owing to the patient's severe immunodeficiency, both TB and non-tuberculous mycobacterial (NTM) infections were considered possible. Therefore, the patient was started on a combination therapy of azithromycin (0.5 g daily), moxifloxacin (0.4 g daily), isoniazid (0.3 g daily), ethambutol (1 g daily), and linezolid (0.6 g twice daily) to target mycobacterial infections, with a planned treatment duration of 9–12 months. Two months after discharge, follow-up colonoscopy revealed significant improvement in the erosions and ulcers in the colorectal mucosa. Repeat enhanced abdominal CT tomography revealed decreased lymph node enlargement and peritoneal thickening.

In May 2024, our hospital initiated a new project for identifying Mycobacterium species using fluorescent PCR melting curve analysis. We tested the patient's ileocecal biopsy samples obtained on August 11, 2023, and confirmed that the infection was caused by M. bovis, ruling out NTM. Azithromycin was initially included in the empiric regimen to provide coverage against possible non-tuberculous mycobacterial (NTM) infections, given the patient's severe immunosuppression and the uncertainty of the pathogen at the time. After M. bovis was confirmed by molecular testing and NTM infection was excluded, azithromycin was discontinued as it is not indicated for treatment of M. bovis or other MTBC members. Consequently, the regimen was adjusted to moxifloxacin (0.4 g daily), isoniazid (0.3 g daily), ethambutol (1 g daily), clofazimine (0.1 g daily), and linezolid (0.6 g daily). By August 2024, follow-up colonoscopy showed complete resolution of prior lesions, and enhanced CT revealed further reduction in lymphadenopathy.

Discussion and Conclusions

To our knowledge, this is one of the few reported cases of disseminated M. bovis infection in an AIDS patient with intestinal involvement. Unlike most previously reported cases that focus on pulmonary or localized extrapulmonary manifestations, this case highlights the diagnostic challenges of widespread disease involving the gastrointestinal tract. Additionally, we utilized fluorescent PCR melting curve analysis on archival biopsy samples, providing a practical example of how retrospective molecular diagnostics can refine treatment strategies. These aspects underscore the case's novelty and relevance for clinical practice.

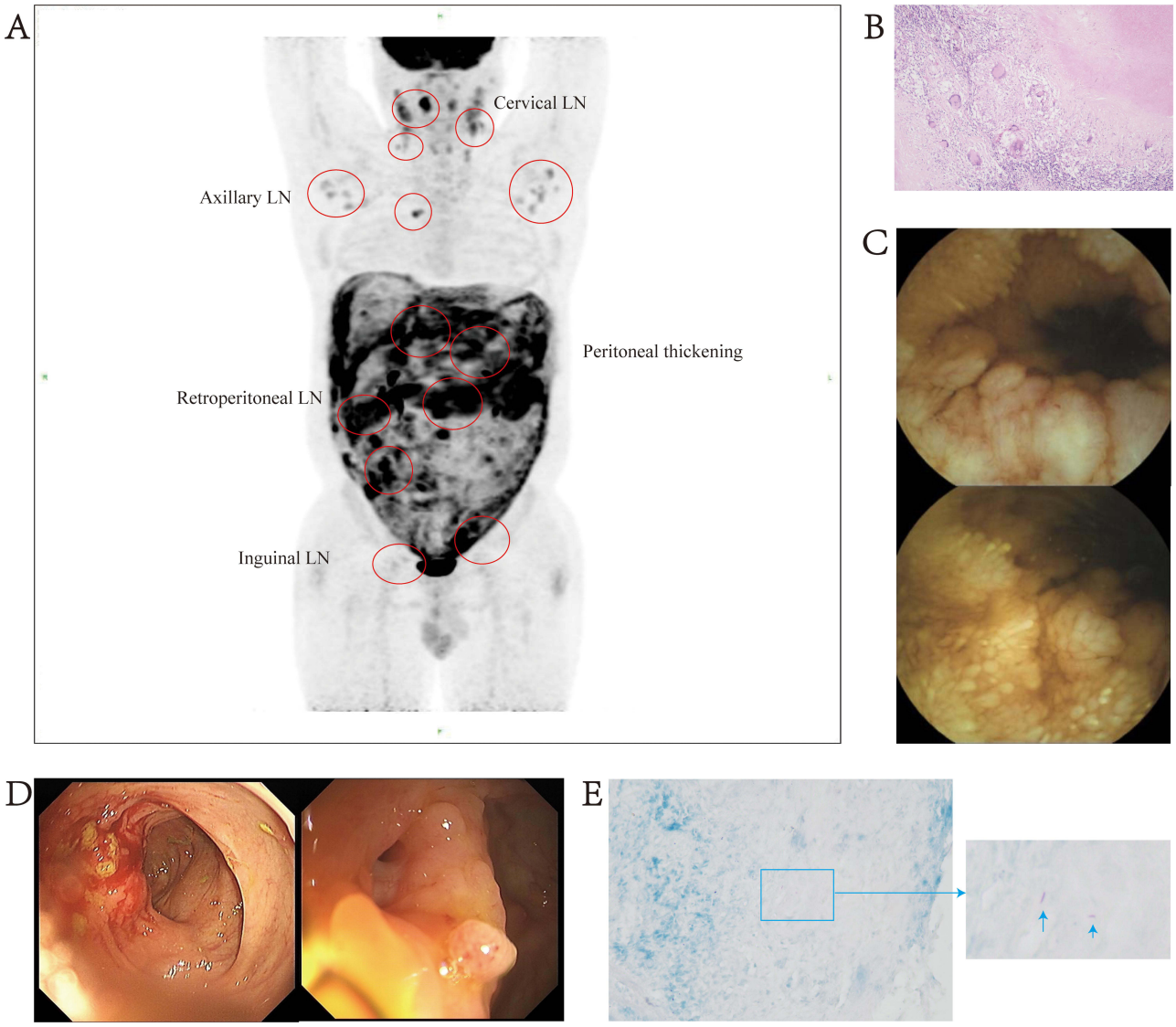

Figure 1 Comprehensive Diagnostic Imaging and Pathology Findings in an AIDS Patient with Disseminated Mycobacterium bovis Infection. (**A**) Brain and body ^18F-FDG PET-CT images; PET-CT showing multiple FDG-avid lymph nodes in the bilateral cervical and axillary regions; additional FDG-avid lymph nodes are present in the right internal mammary region, cardiophrenic angle, and costophrenic angle. The peritoneum, omentum, and mesentery appear thickened and hyperdense, with diffusely increased FDG uptake. Red circles indicate representative anatomical regions Mildly FDG-avid lymph nodes are also observed in the retroperitoneum and bilateral inguinal regions. (**B**) Axillary lymph node pathology (HE stain, 100x magnification): multinucleated giant cell infiltration and necrosis; (**C**) Capsule endoscopy showing small bowel inflammation and lymphangiectasia; (**D**) Colonoscopic findings at the ileocecal valve and transverse colon; (**E**) Ileocecal pathology (400x magnification): positive acid-fast bacilli staining. Blue arrows indicate positively stained acid-fast bacilli. All images have been anonymized to remove any identifying patient information.
Abbreviation: LN, lymph nodes.

Epidemiology

M. bovis is a member of the MTBC, which causes TB in cattle and other mammals, including humans. It is estimated that M. bovis accounts for less than 1.5% of all human TB cases outside Africa and 2.8% in African regions.[6] Despite its relatively low incidence, M. bovis poses a significant threat to public health, particularly in immunocompromised individuals. HIV infection increases both the overall incidence of TB and the proportion of disseminated, miliary, and extrapulmonary TB.

Although M. bovis is primarily associated with zoonotic transmission through unpasteurized dairy, other routes such as consumption of undercooked meat, exposure to contaminated surfaces, or airborne transmission from infected animals or handlers may occur, even in urban environments.[7,8] In this case, although the patient resided in an urban area and denied dairy exposure, his habitual mutton consumption and potential indirect contact with contaminated sources may

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represent plausible transmission pathways. Such cases emphasize the need to consider atypical exposures when evaluating TB etiology in immunocompromised hosts.

Diagnostic Considerations

In this case, we achieved the molecular diagnosis of M. bovis using fluorescent PCR melting curve analysis, which amplified the target DNA and analyzed the melting curve to distinguish M. bovis from other mycobacteria. Traditional TB diagnostics like culture and GeneXpert have limitations in detecting M. bovis. Culture is time-consuming and often yields false negatives in extrapulmonary or low-burden infections, while GeneXpert cannot differentiate M. bovis from M. tuberculosis. In contrast, molecular methods such as fluorescent PCR melting curve analysis enable rapid, species-level identification with higher sensitivity, especially in smear-negative or tissue-based samples.[9] Fluorescent PCR melting curve analysis identifies mycobacterial species by analyzing DNA dissociation characteristics after amplification. Each species within the MTBC has a unique melting profile, allowing differentiation without the need for sequencing. This technique is particularly useful for formalin-fixed paraffin-embedded samples. These advantages make them valuable tools for timely and accurate diagnosis in immunocompromised patients. However, its diagnostic yield may decrease in specimens with low bacterial burden, and false negatives can occur if DNA quality is poor. Moreover, it requires specialized instruments and trained personnel, limiting its availability in resource-constrained settings. Additionally, we integrated the patient's previous pathological specimens with this cutting-edge molecular diagnostic technology to ensure precise pathogen identification. This approach significantly enhances the efficiency and accuracy of diagnosis, providing strong support for the overall management of cases.

Therapeutic Implications

The prognosis of M. bovis TB in HIV-infected individuals may be worse than that of M. tuberculosis–TB. A cohort study of 86 HIV-positive TB patients in San Diego, California found a higher mortality rate in the M. bovis group than in the M. tuberculosis group (10% vs 3.6%).[10] Another report involving 19 HIV-positive patients with primary multidrug-resistant M. bovis TB reported a 100% mortality rate.[11] This could be due to delayed diagnosis, inadequate treatment in the context of pyrazinamide resistance, older patient age (following reactivation of latent infections from past livestock exposure), or increased virulence of M. bovis.

The intrinsic resistance of M. bovis to pyrazinamide is a key diagnostic differentiator from M. tuberculosis. This resistance is attributed to a naturally occurring mutation or deletion in the *pncA* gene, which encodes pyrazinamidase—an enzyme required to convert PZA into its active form, pyrazinoic acid.[12] In contrast, PZA resistance in M. tuberculosis is usually acquired through specific *pncA* mutations after drug exposure. Beyond PZA, there is growing evidence of emerging resistance to other first-line drugs in M. bovis. Surveillance data from endemic regions have reported increasing resistance rates to isoniazid, rifampicin, and streptomycin, particularly in treatment-experienced or previously exposed individuals.[13] A study from Mexico City between 2000 and 2014 found that M. bovis strains isolated from treatment-naïve patients exhibited higher resistance to isoniazid, rifampicin, and streptomycin than M. tuberculosis strains (10.9% vs 3.4%).[14–17] Resistance rates to isoniazid and rifampicin were 38.5% and 34.4%, respectively, in treatment-experienced patients.[18] As isoniazid, rifampicin, and pyrazinamide are the first-line TB drugs, rapid pathogen identification is crucial for improving patient outcomes. In this case, drug susceptibility testing beyond pyrazinamide was not performed because the available biopsy material was limited and only sufficient for species-level identification using formalin-fixed paraffin-embedded tissue. Nonetheless, the patient showed significant clinical improvement with the modified treatment regimen, and no signs of resistance or treatment failure were observed during follow-up.

Limitations

This report has several limitations. First, molecular confirmation of M. bovis was made retrospectively, after treatment had already been initiated, highlighting the need for earlier species-level diagnostics in similar cases. Second, the exact source of infection remains uncertain, as the patient denied high-risk exposures such as unpasteurized dairy, suggesting the need for more comprehensive zoonotic exposure assessments. Third, as a single case study, the generalizability of our findings is limited, and larger studies are needed to validate the utility of molecular diagnostics and treatment strategies in

broader HIV/AIDS populations. Lastly, while the patient responded well to therapy, long-term follow-up data on resistance development is lacking, underscoring the importance of post-treatment monitoring.

Conclusion

The successful diagnosis and management of this case not only provides valuable insights for similar cases in the future but also highlights the importance of early molecular diagnosis in reducing treatment failure and the spread of drug-resistant TB. Further research on the clinical manifestations and optimal treatment strategies for M. bovis infection in immunocompromised patients is warranted.

Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of Beijing Youan Hospital, Capital Medical University (2022/069). Institutional approval was obtained from Beijing Youan Hospital, Capital Medical University for the publication of this case report and its related details. Written informed consent was obtained from the patient for the publication of all case details and accompanying images.

Consent for Publication

Written informed consent for publication of this case report and any accompanying images was obtained from the patient. A copy of the written consent form is available for review by the editor of the journal.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests for this work.

References

1. Society CMAAGot ID, Society AGotTMaP. Expert consensus on the diagnosis and treatment of hiv co-infected with Mycobacterium tuberculosis. *Chin J Clin Infectious Dis*. 2017;10(2):81–90.
2. Naing C, Mak JW, Maung M, Wong SF, Kassim AI. Meta-analysis: the association between HIV infection and extrapulmonary tuberculosis. *Lung*. 2013;191(1):27–34. doi:10.1007/s00408-012-9440-6
3. Cordova E, Gonzalo X, Boschi A, et al. Human Mycobacterium bovis infection in Buenos Aires: epidemiology, microbiology and clinical presentation. *Int J Tuberculosis Lung Dis*. 2012;16(3):415–417. doi:10.5588/ijtld.10.0605
4. Gan SH, Ang MLT, Lim AJ, Sng LH, Chee CBE. Pulmonary tuberculosis due to Mycobacterium bovis: a case in Singapore. *Singapore Med J*. 2023. doi:10.4103/singaporemedj.SMJ-2021-310
5. Petel D, Waters V, Kitai I. Disseminated Mycobacterium bovis infection presenting with cervical lymphadenitis in a 15-year-old girl. *CMAJ*. 2023;195(34):E1155–e6. doi:10.1503/cmaj.230700
6. Müller B, Dürr S, Alonso S, et al. Zoonotic Mycobacterium bovis-induced tuberculosis in humans. *Emerg Infect Dis*. 2013;19(6):899–908. doi:10.3201/eid1906.120543

7. Silva MR, Rocha ADS, Araújo FR, et al. Risk factors for human Mycobacterium bovis infections in an urban area of Brazil. *Memorias Do Instituto Oswaldo Cruz*. 2018;113(8):e170445. doi:10.1590/0074-02760170445
8. BaoYing Z, XiaoJun L, HaiQun B, Fan L, LiuBo Z. Contamination and transmission of Mycobacteria in indoor environments of public buildings. *Central Eur J Public Health*. 2022;30(1):26–31. doi:10.21101/cejph.a5198
9. Lorente-Leal V, Liandris E, Castellanos E, et al. Validation of a real-time PCR for the detection of Mycobacterium tuberculosis complex members in bovine tissue samples. *Front Vet Sci*. 2019;6:61. doi:10.3389/fvets.2019.00061
10. Dronda F, Chaves F, González López A, Catalán S, Fernández González F. Bacteremia due to Mycobacterium tuberculosis in patients coinfected with the human immunodeficiency virus. *Med clinica*. 1993;101(14):534–537.
11. Ramdas KE, Lyashchenko KP, Greenwald R, Robbe-Austerman S, McManis C, Waters WR. Mycobacterium bovis infection in humans and cats in same household, Texas, USA, 2012. *Emerg Infect Dis*. 2015;21(3):480–483. doi:10.3201/eid2103.140715
12. Kim NY, Kim DY, Chu J, Jung SH. pncA large deletion is the characteristic of pyrazinamide-resistant mycobacterium tuberculosis belonging to the east asian lineage. *Infection Chemother*. 2023;55(2):247–256. doi:10.3947/ic.2023.0037
13. Franco MMJ, Ribeiro MG, Pavan FR, et al. Genotyping and rifampicin and isoniazid resistance in Mycobacterium bovis strains isolated from the lymph nodes of slaughtered cattle. *Tuberculosis*. 2017;104:30–37. doi:10.1016/j.tube.2017.02.006
14. de la Hoz RE, Waycott S, Garcia D, Melendez R, Bia FJ. Initial screening for antituberculous drug resistance at an inpatient facility in Leon, Nicaragua. *American JTrop Med Hyg*. 1997;56(1):24–26. doi:10.4269/ajtmh.1997.56.24
15. Rivero A, Márquez M, Santos J, et al. High rate of tuberculosis reinfection during a nosocomial outbreak of multidrug-resistant tuberculosis caused by Mycobacterium bovis strain B. *Clin Infect Dis*. 2001;32(1):159–161. doi:10.1086/317547
16. Bouvet E, Casalino E, Mendoza-Sassi G, et al. A nosocomial outbreak of multidrug-resistant Mycobacterium bovis among HIV-infected patients. A case-control study. *AIDS*. 1993;7(11):1453–1460. doi:10.1097/00002030-199311000-00008
17. Guerrero A, Cobo J, Fortún J, et al. Nosocomial transmission of Mycobacterium bovis resistant to 11 drugs in people with advanced HIV-1 infection. *Lancet*. 1997;350(9093):1738–1742. doi:10.1016/S0140-6736(97)07567-3
18. Valle M B-D, Torres-González P, Cervera-Hernández ME, et al. Trends of Mycobacterium bovis Isolation and first-line anti-tuberculosis drug susceptibility profile: a fifteen-year laboratory-based surveillance. *PLoS Negl Trop Dis*. 2015;9(9):e0004124. doi:10.1371/journal.pntd.0004124