The Emergence of Drug Resistance in Extrapulmonary Tuberculosis: A Case Series

Herikurniawan*, Aziza Harris, Mira Yulianti, Ni Nyoman Indirawati Kusuma, Cleopas Martin Rumende

Division of Respirology and Critical Illness, Department of Internal Medicine, Faculty of Medicine, Universitas Indonesia – Cipto Mangunkusumo Hospital, Jakarta, Indonesia.

Corresponding Author:
Herikurniawan, MD. Division of Respirology and Critical Care, Department of Internal Medicine, Faculty of Medicine, Universitas Indonesia - Dr. Cipto Mangunkusumo Hospital. Jl. Diponegoro no. 71, Jakarta 10430, Indonesia. Email: herikurniawan.md@gmail.com

ABSTRACT

Drug-resistant extrapulmonary tuberculosis (DR-EPTB) represents an escalating global health challenge, complicated by rising rates of rifampicin-resistant (RR-TB) and multidrug-resistant tuberculosis (MDR-TB). Despite growing awareness, DR-EPTB remains underdiagnosed and underreported, often due to presumptive assumptions of drug sensitivity. This case series describes three distinct cases of DR-EPTB: a 34-year-old woman diagnosed with primary MDR-TB involving the lungs and colon; a 41-year-old man with RR-TB-associated arthritis of the elbow joint, following a previous history of pulmonary TB; and a 63-year-old immunosuppressed woman presenting with primary laryngeal and pulmonary RR-TB. These cases highlight the diagnostic complexities and emphasize the necessity of prompt and precise diagnosis facilitated by molecular diagnostics, particularly GeneXpert MTB/RIF. Increased awareness and vigilance for DR-EPTB among clinicians are critical for early detection, effective management, and curbing the spread of drug-resistant strains.

Keywords: *tuberculosis, multidrug-resistant; extrapulmonary; rifampin resistance; molecular diagnostic techniques; drug resistance, bacterial.*

INTRODUCTION

Tuberculosis (TB), caused by *Mycobacterium tuberculosis*, remains a significant global health concern, affecting approximately 25% of the worldwide population. Among TB cases, 8-24% manifest as extrapulmonary TB (EPTB).[1] While recognition of EPTB has increased, drug-resistant EPTB (DR-EPTB) continues to be underreported.[2] Accurate diagnosis often relies on histopathological examination.[3] However, integrating molecular diagnostic techniques significantly improves diagnostic accuracy and treatment outcomes.[4] This case series presents rare DR-EPTB cases: colorectal TB (11% of gastrointestinal TB)[5], elbow joint TB arthritis (<5% of musculoskeletal TB[6], and laryngeal TB (<1%)[7], emphasizing the importance of early detection and personalized therapeutic strategies to improve outcomes.

CASE ILLUSTRATION

Case 1

A 34-year-old woman with no prior TB risk factors presented with persistent epigastric pain, non-bloody diarrhea, non-productive cough, and night sweats within the last three months. Physical examination was unremarkable, but laboratory findings revealed anemia (Hb: 8.5 g/dL). Initial chest X-ray demonstrated ring-like opacities and reticulonodular consolidations (**Figure 1**). Colonoscopy revealed multiple ulcers and inflamed mucosa extending from the colon to the terminal ileum. Biopsies

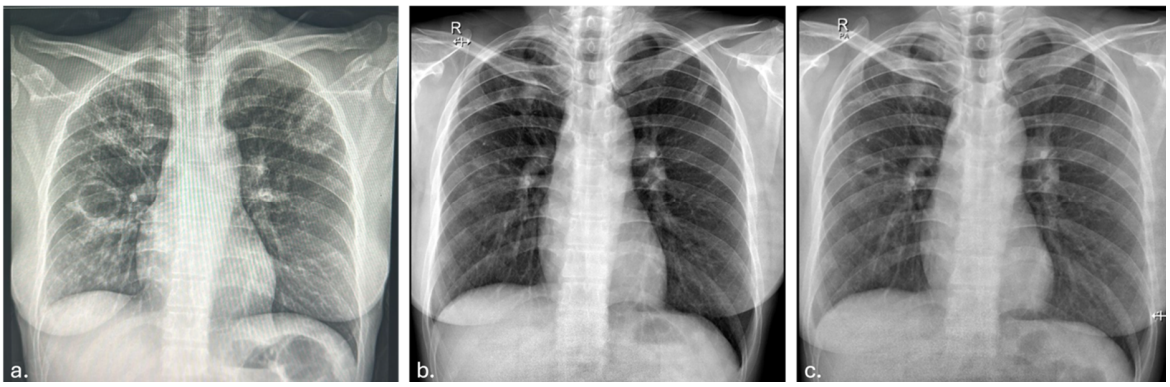

Figure 1. Serial chest X-rays: (a) Two months before treatment, (b) Three months after treatment, (c) Five months after treatment

were obtained from these sites and tested via GeneXpert MTB/RIF, ultimately yielding rifampicin-resistant TB (RR-TB). Subsequent sputum analyses using GeneXpert indicated resistance to rifampicin, and sputum culture revealed resistance to isoniazid, consistent with a diagnosis of multidrug-resistant TB (MDR-TB) with pulmonary and gastrointestinal involvement. The patient completed a 26-week regimen of bedaquiline, linezolid, pretomanid, and moxifloxacin, with significant symptom improvement and resolution of TB on follow-up sputum tests after six months.

Case 2

A 41-year-old man with a two-year prior history of pulmonary TB treatment presented with painful right elbow swelling, fatigue, night sweats, and 13 kg weight loss over six months. Physical examination revealed significant elbow swelling with limited range of motion, while chest X-ray indicated multiple lung cavitary lesions suggestive of pulmonary TB, and right forearm X-ray showed fluid collection and cortical erosions consistent with TB arthritis (**Figure 2**). GeneXpert testing confirmed RR-TB from both sputum and elbow synovial fluid samples. The patient was initiated on a 20-week regimen of bedaquiline, levofloxacin, linezolid, clofazimine, and ethambutol. Despite initial improvement, including weight gain and increased physical strength, the patient succumbed to pneumonia-related complications two months into treatment.

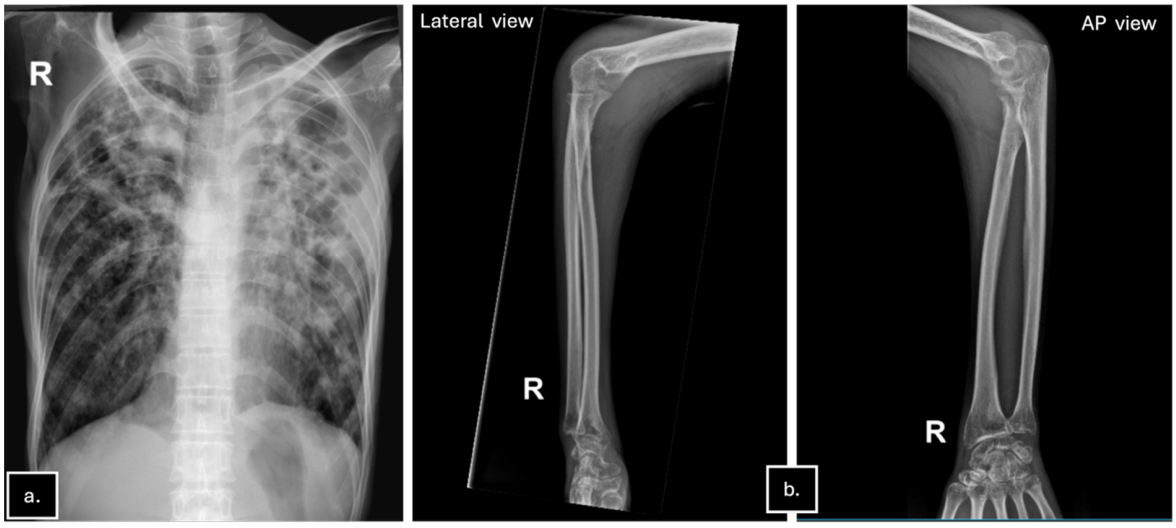

Figure 2. Imaging before treatment (a) Chest X-Ray; (b) X-Ray of right forearm

Case 3

A 63-year-old immunosuppressed woman with systemic lupus erythematosus (SLE) and rheumatoid arthritis presented with progressive hoarseness and intermittent dry cough over three months. Chest CT scan identified nodular opacities and tree-in-bud patterns suggestive of pulmonary TB (**Figure 3**). Rhino-pharyngo-laryngoscopy revealed a rough epiglottic mass, and biopsy confirmed chronic granulomatous inflammation positive for rifampicin-resistant *Mycobacterium tuberculosis* via GeneXpert. Although two sputum acid-fast bacilli (AFB) tests were negative, the clinical and histological findings supported the diagnosis of laryngeal RR-TB. The patient received an 11-month regimen of bedaquiline, levofloxacin, clofazimine, ethambutol, ethionamide, isoniazid, and pyrazinamide, with significant symptom improvement and weight gain. Follow-up sputum tests after 11 months were negative.

DISCUSSION

This case series highlights the significant challenges encountered in diagnosing and managing DR-EPTB, particularly in atypical clinical presentations. RR-TB and MDR-TB represent severe global health threats further complicated by extrapulmonary involvement. Diagnosing EPTB frequently necessitates invasive diagnostic procedures and advanced molecular tools such as GeneXpert MTB/RIF, particularly in resource-limited settings.[3] Additionally, immunosuppressive conditions or prior TB treatments increase the risk of reactivation or the development of drug-resistant forms, complicating disease management.[8,9]

In Case 1, an unusual presentation of primary MDR-TB involving both pulmonary and gastrointestinal sites was diagnosed through integrated diagnostic approaches, including colonoscopic biopsy and sputum analysis. This underscores the critical role of comprehensive diagnostic strategies in identifying complex presentations of TB. Case 2 highlights the clinical complexity of managing TB arthritis alongside active pulmonary TB in a patient previously treated for TB. This scenario illustrates the necessity for heightened vigilance regarding recurrence and drug resistance, especially among high-risk individuals. Case 3 describes a rare instance of primary laryngeal TB in an immunosuppressed patient with systemic autoimmune diseases, emphasizing the diagnostic challenges in atypical TB manifestations.

The significance of these cases lies primarily in their diagnostic and therapeutic implications. They reinforce the essential role of molecular diagnostics like GeneXpert MTB/RIF, especially for confirming TB and detecting drug resistance in extrapulmonary sites where conventional methods may prove inadequate.[3] Additionally, these cases illustrate the efficacy of newer DR-TB treatment regimens, including bedaquiline-containing combinations, even in complex and atypical clinical scenarios.[9,10] Furthermore, these cases emphasize the need for multidisciplinary and tailored management strategies, especially

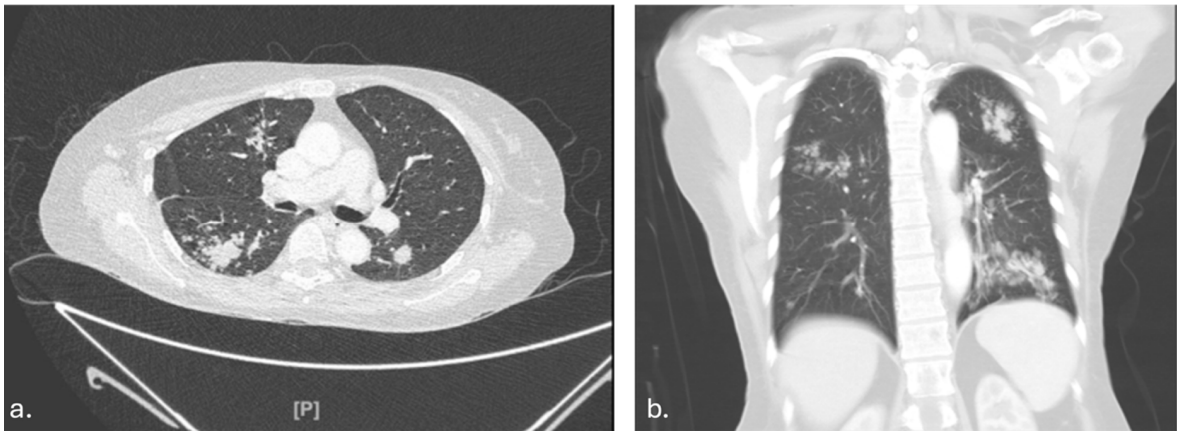

Figure 3. Chest CT scan with contrast before treatment: (a) Axial plane, (b) Coronal plane

in patients with comorbidities or prior TB treatment.

The outcomes of these cases support the conclusion that integrating advanced diagnostic tools with personalized treatment strategies can yield favorable clinical results, even in challenging drug-resistant and extrapulmonary TB cases. In Case 1, nonspecific symptoms initially obscured the diagnosis of gastrointestinal TB, but molecular testing via GeneXpert on biopsy specimens identified rifampicin resistance promptly, facilitating the timely initiation of targeted treatment. Conversely, Case 2 highlights ongoing diagnostic and management challenges inherent in TB arthritis with systemic involvement, complicated further by the patient's prior TB history and multiple comorbidities, ultimately resulting in an unfavorable outcome despite appropriate DR-TB therapy. Finally, in Case 3, the rare presentation of laryngeal TB in an immunosuppressed patient underlines the importance of heightened clinical suspicion and the utility of histopathology combined with molecular diagnostics in atypical TB. Early detection enabled effective management with a short-course DR-TB regimen, leading to a favorable outcome.[3,10]

Collectively, these cases emphasize the importance of clinical vigilance, timely diagnostics, and tailored therapeutic regimens in managing DR-TB. Advanced molecular diagnostic tools, such as GeneXpert MTB/RIF, and innovative therapeutic options have significantly revolutionized TB care, providing opportunities for improved patient outcomes even in complex and drug-resistant scenarios. Nonetheless, challenges, including delayed diagnosis, patient adherence issues, and systemic involvement, underline the continuing need for innovation and a comprehensive, multidisciplinary approach to TB management.

CONCLUSION

These cases highlight the diagnostic complexities and emphasize the necessity of prompt and precise diagnosis facilitated by molecular diagnostics, particularly GeneXpert MTB/RIF. Increased awareness and vigilance for DR-EPTB among clinicians are critical for early detection, effective management, and curbing the spread of drug-resistant strains.

CONFLICT OF INTERESTS

The authors declare no conflict of interest.

REFERENCES

1. Global Tuberculosis Report 2019. Geneva: World Health Organization; 2019. p. 283.
2. Miiro E, Olum R, Baluku JB. Clinical features, resistance patterns and treatment outcomes of drug-resistant extra-pulmonary tuberculosis: A scoping review. Journal of Clinical Tuberculosis and Other Mycobacterial Diseases. 2023;33.
3. Lee JY. Diagnosis and treatment of extrapulmonary tuberculosis. Tuberculosis and Respiratory Diseases. 2015;78:47–55.
4. Nguyen TNA, Berre VA Le, Bañuls AL, Nguyen TVA. Molecular diagnosis of drug-resistant tuberculosis; A literature review. Front Microbiol. 2019;10(Mar).
5. Gharbi G, Mahmoudi M, Yakoubi M, et al. Colonic tuberculosis: A case report. Future Sci OA. 2022 Dec 1;8(10).
6. Khetpal N, Khalid S, Kumar R, et al. Tuberculous arthritis of the elbow joint: An uncommon location with a diagnostic dilemma. Cureus. 2018 (Apr 11).
7. Migliorelli A, Mazzocco T, Bonsembiante A, et al. Laryngeal tuberculosis: a case report with focus on voice assessment and review of the literature. Acta Otorhinolaryngologica Italica. 2022;42:407–14.
8. Viana LA, Cristelli MP, Santos DW, et al. Influence of epidemiology, immunosuppressive regimens, clinical presentation, and treatment on kidney transplant outcomes of patients diagnosed with tuberculosis: A retrospective cohort analysis. American Journal of Transplantation. 2019 May 1;19(5):1421–31.
9. WHO consolidated guidelines on drug-resistant tuberculosis treatment. World Health Organization; 2019. p. 99.
10. Gopalaswamy R, Dusthackeer VNA, Kannayan S, Subbian S. Extrapulmonary tuberculosis: An update on the diagnosis, treatment and drug resistance. Journal of Respiration. 2021 May 26;1(2):141–64.