

Diagnosis and Therapeutic Challenges of Drug-Resistant Tuberculosis Infection After Kidney Transplantation: A Rare Case Report

Chang Song^{1,2,*}, Chun-Yan Zhao^{1,2,*}, Xue-Wen Huang^{1,2,*}, Chang-Jiang Mo², Hang-Biao Qiang¹, Xiao-Shi Lin², Zhen-Tao Huang², Zhou-Hua Xie¹, Qing-Dong Zhu¹

¹Department of Tuberculosis, The Fourth People's Hospital of Nanning, Nanning, Guangxi, 530023, People's Republic of China; ²Clinical Medical School, Guangxi Medical University, Nanning, Guangxi, 530021, People's Republic of China

*These authors contributed equally to this work

Correspondence: Qing-Dong Zhu; Zhou-Hua Xie, Department of Tuberculosis, The Fourth People's Hospital of Nanning, Nanning, Guangxi, 530023, People's Republic of China, Email zhuqingdong2003@163.com; 1491348066@qq.com

Background: Kidney transplant recipients are at high risk for tuberculosis (TB), particularly drug-resistant forms, due to prolonged immunosuppressive therapy. The diagnosis and treatment of TB in this population pose unique challenges, including infection control, graft protection, and drug interactions.

Case Presentation: We report the case of a 28-year-old male kidney transplant recipient was diagnosed with pulmonary TB four months post-transplantation. The patient self-discontinued initial anti-TB therapy after one month, leading to relapse nine months later, with confirmed rifampicin resistant. Following three months of treatment with a second-line regimen including linezolid, he developed disseminated skeletal TB, with drug susceptibility testing indicating linezolid resistance. The treatment was adjusted to an all-oral regimen including isoniazid, moxifloxacin, clofazimine, cycloserine, and bedaquiline, resulting in significant clinical and radiological improvement.

Discussion: In the present case, the patient's non-adherence to the medication regimen resulted in initial treatment failure. Against the backdrop of immunosuppression, rifampicin resistance emerged rapidly. Although the subsequent linezolid-containing regimen was administered for a short duration, it likely triggered ribosomal target mutations—leading to linezolid resistance and hematogenous dissemination to the bone—driven by both drug selection pressure and the history of irregular treatment. Confronted with dual resistance and disseminated disease, the therapeutic strategy pivoted to a bedaquiline-based regimen. This shift highlights the clinical management art of finely balancing treatment efficacy with the risk of rejection through the optimized adjustment of immunosuppressants guided by therapeutic drug monitoring.

Conclusion: The management of drug-resistant tuberculosis in kidney transplant recipients necessitates a flexible and comprehensive strategy. This encompasses early clinical suspicion, the prompt performance of molecular and phenotypic drug susceptibility testing to guide therapeutic decisions, rigorous management of treatment adherence, and the real-time adjustment of therapeutic regimens based on evolving resistance profiles and clinical responses. Multidisciplinary collaboration is essential for balancing anti-tuberculosis efficacy with graft survival. Although novel agents such as bedaquiline offer promising options for salvage therapy, their administration in transplant recipients requires intensified monitoring for drug-drug interactions and adverse events.

Keywords: kidney transplantation, drug-resistant tuberculosis, bedaquiline

Introduction

Kidney transplantation is the most effective treatment for end-stage renal disease, significantly improving both survival and quality of life. However, long-term or lifelong immunosuppressive therapy, essential for preventing graft rejection, inevitably induces a state of persistent immunodeficiency. This iatrogenic immunosuppression disrupts the balance between host and pathogen, making opportunistic infections a leading cause of morbidity and a significant threat to long-

term graft and patient survival.¹ Among these infections, tuberculosis (TB) a particular risk due to its insidious onset, atypical clinical manifestations, diagnostic challenges, complex treatment regimens, and high mortality rate.^{2,3} The global burden of TB remains substantial. According to the World Health Organization's latest report, TB continues to rank among the leading causes of death from infectious disease, with over 1.2 million deaths and approximately 10.7 million new cases reported in 2024.⁴ Drug-resistant TB, particularly multidrug-resistant TB (MDR-TB, resistant to at least isoniazid and rifampicin) and extensively drug-resistant TB (XDR-TB, resistant to fluoroquinolones and at least one second-line injectable agent in addition to MDR-TB), represents a major challenge in TB control.⁵ Even in immunocompetent individuals, MDR-TB treatment is highly demanding, often requiring regimens lasting up to 24 months, carrying a high risk of adverse drug reactions, and achieving significantly lower cure rates compared to drug-susceptible TB.^{6,7} Despite established general guidelines, the management of MDR-TB in the unique context of kidney transplantation remains poorly characterized, necessitating a deeper examination of specific clinical encounters to bridge this knowledge gap.

In transplant recipients, the emergence of drug-resistant TB introduces further complexity, creating a clinical paradox. On one hand, successful treatment requires the prolonged and combined use of multiple second-line anti-TB agents. On the other, many of these drugs, including linezolid, bedaquiline, delamanid, aminoglycosides (eg, amikacin), and fluoroquinolones, carry substantial toxicity risks (eg, bone marrow suppression, QT interval prolongation, hepatotoxicity, nephrotoxicity, ototoxicity, peripheral neuropathy).^{8–10} Moreover, several of these agents have significant and potentially life-threatening interactions with immunosuppressants such as tacrolimus, which are critical for graft preservation.⁹ Given the scarcity of existing literature and the absence of standardized protocols for this specific population, analyzing real-world cases is essential to refine therapeutic strategies and improve clinical outcomes.

To address this need, this report presents a detailed case of MDR-TB following kidney transplantation. We trace the clinical course from early suspicion and diagnosis through complex treatment adjustments, offering practical insights into the diagnostic dilemmas and therapeutic challenges encountered. By elucidating the specific management hurdles in this case, we aim to provide actionable evidence to enhance clinical awareness and guide future decision-making for drug-resistant TB in kidney transplant recipients.

Case Report

Phase I: October 2022 – Secondary Pulmonary Tuberculosis and Premature Discontinuation of First-Line Therapy

A 28-year-old male with end-stage renal disease (CKD5) underwent allogeneic kidney transplantation in June 2022. Postoperatively, he received standard immunosuppressive therapy including tacrolimus, mycophenolate mofetil, and prednisone, along with glutathione for hepatoprotection and Bailing capsules for renal support. In early October 2022, the patient developed exertional dyspnea, which progressed over a week and was accompanied by paroxysmal cough, white sticky sputum, and fever with a maximum temperature of 39.8°C. He also reported fatigue and poor appetite, with no chills, night sweats, weight loss, chest tightness, palpitations, abdominal pain, or diarrhea. He was admitted on October 17, 2022. Next-generation sequencing (NGS) of bronchoalveolar lavage fluid (BALF) detected a high sequence count of *Mycobacterium tuberculosis* (MTB). Acid-fast bacilli (AFB) staining of BALF and sputum samples was strongly positive (3+ and 4+, respectively). MTB DNA was detected in BALF, and the Xpert MTB/RIF assay indicated a high bacterial load. A diagnosis of secondary pulmonary tuberculosis (retreatment) was made. The patient had a history of childhood TB, though details of treatment were unavailable and adherence had been incomplete. Chest CT revealed: (1) secondary pulmonary TB involving the upper, middle, and lower lobes bilaterally; (2) bilateral pleural thickening and calcification, with small encapsulated pleural effusions (Figure 1A).

Initial laboratory tests showed mild respiratory alkalosis (pH 7.47, pCO₂ 35 mmHg), adequate oxygenation (pO₂ 104 mmHg, oxygenation index 358.62 mmHg), leukocytosis (10.9×10⁹/L), hemoglobin 122 g/L, platelets 175×10⁹/L, mildly elevated procalcitonin (0.83 ng/mL), prolonged prothrombin time (17.1 s, INR 1.4), prolonged activated partial thromboplastin time (46.6 s), and reduced fibrinogen (1.81 g/L). Liver and kidney function, electrolytes, and cardiac enzymes were within normal limits. A standard retreatment regimen, isoniazid, rifampicin, ethambutol, moxifloxacin

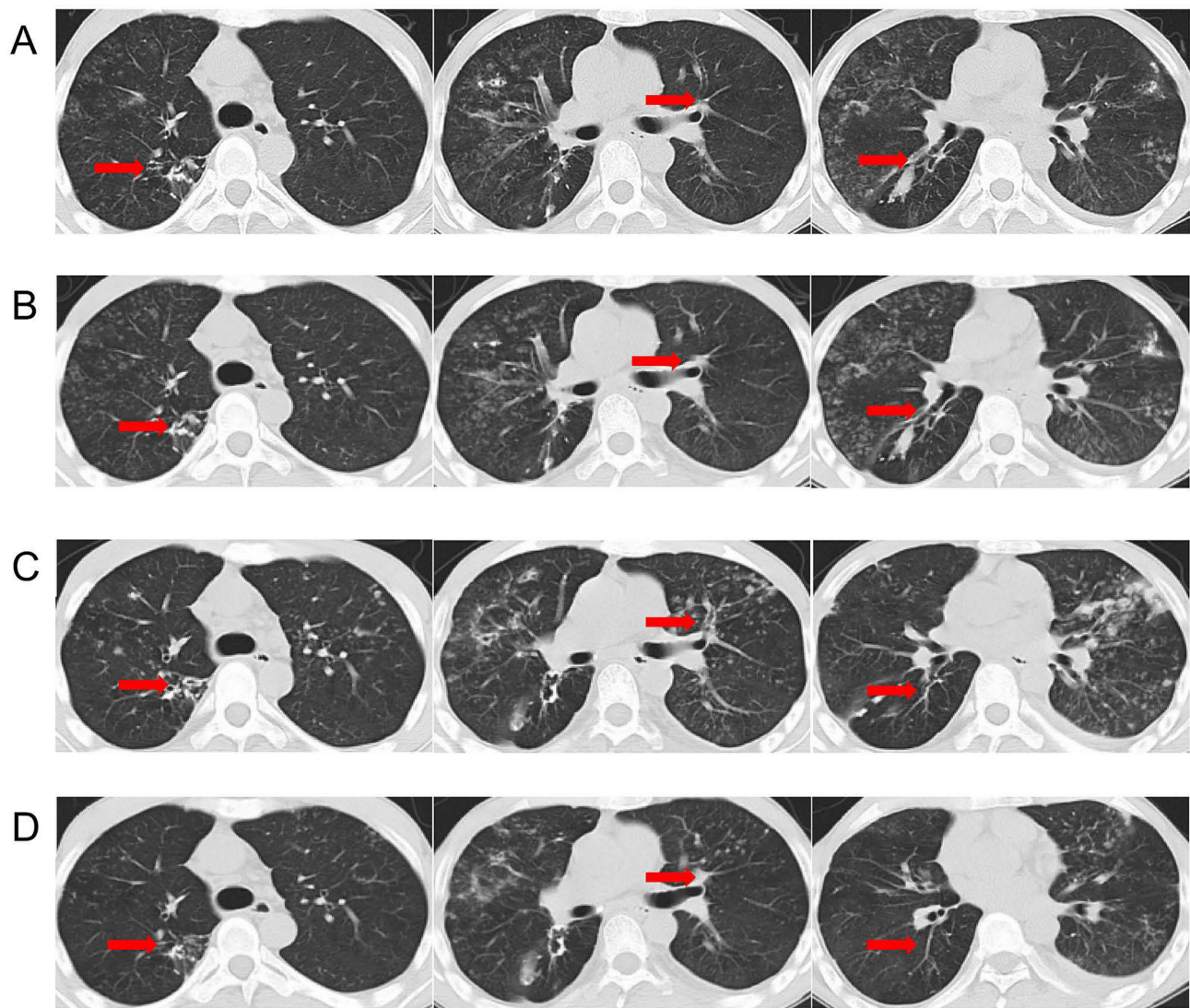


Figure 1 Patient's lung CT examination. ((A). First hospitalization: Multiple bronchiectasis in both lungs, bilateral pleural thickening and calcification, and enlarged mediastinal lymph nodes; (B) Second hospitalization: The lesions increased; (C) Third hospitalization: The lesions further increased; (D) Fourth hospitalization: The lesions absorbed and decreased).

Note: The bronchiectasis lesion is indicated by the red arrow.

(2HREMfx/10HRE) was initiated along with hepatoprotective and supportive care. After approximately nine days of treatment, the patient's symptoms improved, and he was discharged with instructions to continue therapy. However, he self-discontinued all anti-TB medications in January 2023.

Phase 2: October 2023 – Relapse with Drug Resistance and Initiation of MDR-TB Regimen (Mfx-Lzd-Cfz-Cs-H)

Nine months after discontinuation, the patient was readmitted on October 14, 2023, with cough and sputum production. Chest CT showed significant progression of pulmonary lesions (Figure 1B). Sputum AFB staining was 3+, MTB DNA was again detected in BALF. The Xpert MTB/RIF assay revealed rifampicin resistance (*rpoB* mutation), while melt curve PCR confirmed susceptibility to isoniazid and fluoroquinolones. A diagnosis of rifampicin-resistant tuberculosis (RR-TB) was made. The treatment regimen was adjusted to include moxifloxacin, linezolid, clofazimine, cycloserine, and high-dose isoniazid (6Mfx-Lzd-Cfz-Cs-Hh/12Mfx-Cfz-Cs-Hh), and the patient was discharged on this MDR-TB regimen.

Approximately 3 months later, he was readmitted for left-sided back pain. Phenotypic drug susceptibility testing (DST) from prior cultures confirmed resistance to rifampicin, rifabutin, and linezolid. Chest CT revealed new periosteal reactions involving the left 8th-12th ribs, surrounding soft tissue hypodensity with abscess formation, and a left-sided encapsulated hydropneumothorax, alongside worsening pulmonary lesions. Ultrasound-guided aspiration of paraspinal abscess yielded purulent fluid positive for *M. tuberculosis* DNA, confirming osseous TB with abscess formation. The diagnosis was updated to rifampicin- and linezolid-resistant pulmonary TB, with associated tuberculous pleurisy and skeletal TB. With resistance to linezolid, a core second-line drug, and evidence of disease dissemination, the treatment approach became increasingly complex.

Phase 3: January 2024 – Regimen Modification with Bedaquiline and Subsequent Clinical Improvement

Following multidisciplinary consultation and shared decision-making with the patient, a novel all-oral regimen including bedaquiline was initiated on January 17, 2024. The revised regimen consisted of isoniazid, moxifloxacin, clofazimine, cycloserine, and bedaquiline fumarate (H-Mfx-Cfz-Cs-Bdq). Following this adjustment, the patient experienced gradual relief of back pain, decreased inflammatory markers, and radiological improvement, including absorption of pulmonary lesions and resolution of the left hydropneumothorax (Figure 1C). He was briefly hospitalized in February and March 2024 for cough, dizziness, and fatigue but continued on the revised regimen. Immunosuppressive therapy (eg, tacrolimus) was closely monitored and adjusted throughout treatment. Hepatoprotective and renal supportive therapies were maintained. Laboratory data showed hemoglobin recovery to 140 g/L and stable serum creatinine around 129 $\mu\text{mol/L}$, consistent with baseline renal impairment. Chest CT scans continued to demonstrate gradual resolution of lesions (Figure 1D). A comprehensive summary of microbiological, renal, hematologic, and hepatic parameters during hospitalization is presented in Table 1. No severe adverse drug reactions were observed. During subsequent regular outpatient

Table 1 Patient Characteristics

Date	First Hospitalization	Second Hospitalization	Third Hospitalization	Fourth Hospitalization	Fifth Hospitalization
Sputum Culture	+	+	–	–	–
Sputum Smear	+	+	–	–	–
Creatinine ($\mu\text{mol/L}$)	91.8	136	161	115	129
Urea (mmol/L)	18.6	10.64	13.53	11.9	15.31
Uric Acid ($\mu\text{mol/L}$)	363	372	357	396	459
Endogenous Creatinine Clearance Rate (mL/min)	26	32	24	33	31
Prothrombin Time (sec)	17.1	15.1	15.6	14.8	13.8
Prothrombin Time Activity (%)	61	65	71	80	74
Activated Partial Thromboplastin Time (sec)	46.6	53.2	49.9	48.1	46.8
Fibrinogen (g/L)	1.81	5.81	5.78	5.33	5.42
White Blood Cells ($10^9/\text{L}$)	4.2	6.7	16.3	4.7	5
Red Blood Cells ($10^{12}/\text{L}$)	3.73	3.81	3.9	3.6	4.6
Hemoglobin (g/L)	107	144	117	107	140

(Continued)

Table 1 (Continued).

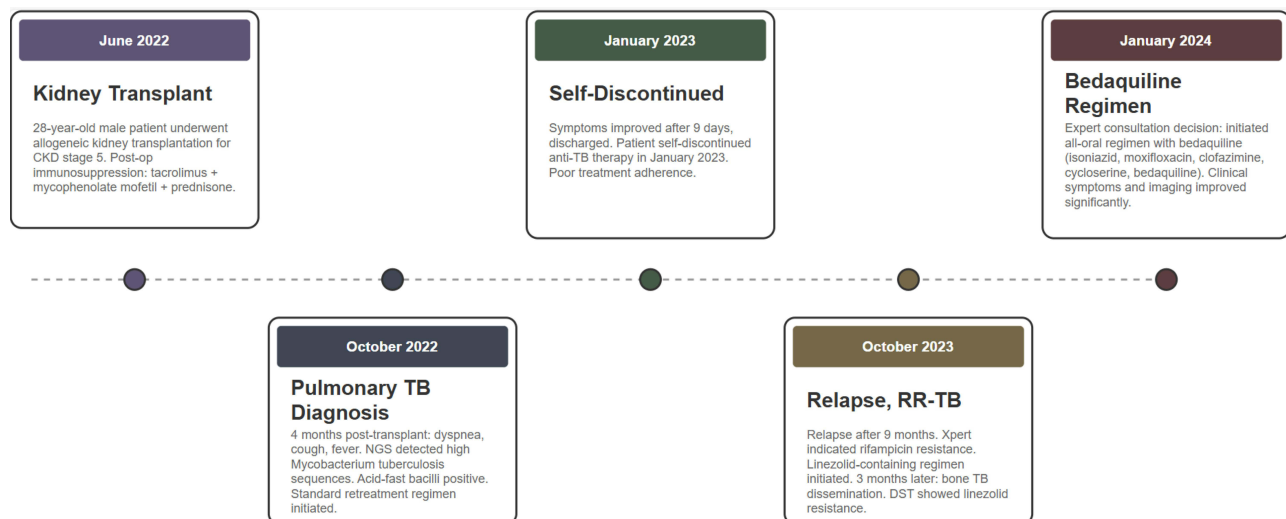
Date	First Hospitalization	Second Hospitalization	Third Hospitalization	Fourth Hospitalization	Fifth Hospitalization
Aspartate Aminotransferase (U/L)	8.6	10	12	13	14
Alanine Aminotransferase (U/L)	7.5	11	3	5	6
Total Bilirubin (μmol/L)	11	10.5	3.1	4.3	5.4
Direct Bilirubin (μmol/L)	6	5.8	1.6	2.4	4.8
Albumin (g/L)	31.4	37.4	35.9	39.8	32

follow-up, the patient reported a significant improvement in overall health and a marked alleviation of treatment-related anxiety following the transition to the new regimen. The treatment flowchart of the patient is shown in [Figure 2](#).

Discussion

Kidney transplant recipients, as a special population under long-term iatrogenic immunosuppression, present significant challenges in the management of opportunistic infections. This case involved a patient who developed PTB shortly after kidney transplantation and experienced a complex clinical course, including premature discontinuation of initial therapy, relapse, the emergence of rifampicin resistance and subsequent linezolid resistance, and extrapulmonary dissemination to the skeletal system. Disease control was ultimately achieved through an individualized, all-oral regimen centered on bedaquiline.

Due to chronic immunosuppression, kidney transplant recipients are at markedly elevated risk for TB. Published literature indicates that the incidence of post-transplant TB is 20 to 74 times higher than in the general population, with a predilection for extrapulmonary and disseminated forms, often accompanied by atypical imaging features.¹¹ The underlying mechanism involves the profound suppression of T-cell proliferation and function, especially CD4⁺ T cells, by immunosuppressive agents such as calcineurin inhibitors, which are essential for graft survival.¹² In this case, the onset of pulmonary TB occurred four months post-transplantation, consistent with the reported peak incidence within the first year.¹³ Most cases of post-transplant TB result from reactivation of latent infections rather than *de novo* exposure.¹³ The patient's childhood history of incompletely treated TB likely served as the source of reactivation and contributed to

**Figure 2** Patient's treatment flowchart.

the development of drug resistance. Immunosuppression not only increases the risk of reactivation but may also alter the disease's natural history, resulting in atypical or rapidly progressive clinical progressions.^{8,14}

From a diagnostic standpoint, this case illustrates the essential role of molecular techniques in the early detection and characterization of TB in transplant recipients. During the first hospitalization, rapid confirmation of MTB infection and identification of rifampicin resistance were achieved using NGS and the Xpert MTB/RIF assay, consistent with current guideline-recommended strategies.⁴ NGS provides comprehensive pathogen profiling, including strain identification and detection of resistance-conferring mutations, which is invaluable in tailoring individualized therapy.^{15,16} Although NGS and Xpert MTB/RIF provided critical evidence for rapid diagnosis and early detection of rifampicin resistance in the present case, their application faces multiple practical challenges. While NGS offers comprehensive profiling of pathogens and resistance genes, its utility is hindered by high costs, complex data analysis, and limited accessibility in resource-limited settings.^{17,18} Although the Xpert platform is relatively rapid and user-friendly, its sensitivity may be compromised when processing extrapulmonary specimens or samples with low bacillary loads, and it is unable to detect extensive drug resistance beyond rifampicin.¹⁹ Therefore, in clinical practice, it is essential to prudently select and integrate these tools by considering local epidemiology, resource availability, and individual patient characteristics, while continuing to rely on traditional culture and phenotypic drug susceptibility testing as the gold standard and a necessary supplement. While drug resistance was promptly identified during the relapse through a combination of smear microscopy, molecular assays, and drug susceptibility testing (DST), the diagnosis of skeletal TB relied on ultrasound-guided aspiration. This highlights the importance of a multimodal diagnostic approach that integrates imaging, microbiological, and molecular modalities. CT findings including periosteal reaction and soft tissue abscess, combined with positive MTB DNA from aspirated material, confirmed disseminated disease and underscore the need to consider extrapulmonary TB in transplant recipients presenting with musculoskeletal symptoms.

The patient's self-discontinuation of anti-TB therapy after one month underscores the considerable challenges associated with treatment adherence in this population. The patient's poor treatment adherence is primarily attributed to the following complex and interrelated factors: Firstly, long-term administration of immunosuppressants and anti-rejection drugs constitutes a complex therapeutic regimen; the addition of anti-tuberculosis medications significantly increases this complexity, thereby predisposing patients to missed or incorrect dosing. Secondly, common adverse effects of anti-tuberculosis drugs, such as hepatorenal impairment and gastrointestinal reactions, overlap with the side effects of immunosuppressants, markedly exacerbating patient discomfort and diminishing the willingness to persist with treatment. Furthermore, the necessity for frequent monitoring—including repeated imaging, blood tests, and therapeutic drug monitoring—imposes a considerable psychological burden on the patient. The patient reported reduced anxiety and enhanced confidence in treatment following the transition to an all-oral regimen, suggesting that regimen simplification and effective physician-patient communication are crucial for improving the patient experience. Consequently, a multidisciplinary support system integrating pharmaceutical consultation, nursing support, psychological counseling, and social worker intervention is of paramount significance for enhancing long-term treatment adherence and improving overall patient outcomes.

Upon diagnosis of rifampicin-resistant TB, a linezolid-containing second-line regimen was initiated. However, within three months, linezolid resistance emerged, and the disease disseminated to the bones. Rifampicin resistance is primarily caused by specific mutations in the *rpoB* gene of MTB (such as Ser531Leu and His526Tyr). These mutations induce structural alterations in the β -subunit of RNA polymerase, significantly reducing its binding affinity to rifampicin and thereby resulting in drug resistance.²⁰ Linezolid is a core drug for drug-resistant tuberculosis; however, its adverse effects—including myelosuppression, peripheral neuropathy, optic neuritis, and gastrointestinal reactions—are equally prominent.²¹ Transplant recipients are at a higher risk for poor adherence due to these side effects. The emergence of linezolid resistance represents a critical warning. Its mechanism is primarily associated with mutations in bacterial genes encoding ribosomal components, such as the 23S rRNA gene and the *rplC* locus.^{22–24} These mutations reduce the affinity of linezolid for its ribosomal target. The rapid development of resistance may be attributed to two key factors: First, a history of irregular prior treatment. The patient's initial self-discontinuation of medication led to exposure at subtherapeutic concentrations. This failed to completely eradicate the pathogen and instead imposed persistent selective pressure on the bacterial population, favoring the survival and expansion of pre-existing resistant mutant strains. Second,

the synergistic impact of the immunosuppressed state. The impaired cellular immunity in transplant recipients (particularly the insufficiency of CD4⁺ T cell function) undermined the host's fundamental capacity to clear bacteria. Consequently, even under pharmacological treatment, low-level resistant mutant strains were more prone to evading clearance. Under the selective pressure of second-line agents such as linezolid, following the failure of first-line drugs, these strains rapidly became the dominant population, ultimately leading to clinical treatment failure and disease dissemination. In the face of dual resistance and dissemination, a novel, fully oral regimen incorporating bedaquiline was initiated. Clinical improvement, including symptom resolution, declining inflammatory markers, and radiological recovery, was observed following the switch. Bedaquiline is a novel diarylquinoline drug targeting the ATP synthase of MTB. It exerts unique bactericidal and sterilizing activity by inhibiting bacterial energy generation and demonstrates potent efficacy against *Mycobacterium tuberculosis* including multidrug-resistant strains.²⁵ In this case, it proved to be a pivotal component of salvage therapy following linezolid resistance. While the patient did not experience significant adverse effects such as QT prolongation, close electrocardiographic monitoring remains essential, particularly in transplant recipients, where drug interactions and cumulative toxicities must be carefully managed. The successful use of bedaquiline in this case offers cautious optimism for its role in transplant populations. New anti-TB agents such as bedaquiline and delamanid are reshaping the global treatment landscape for drug-resistant TB, facilitating shorter, all-oral, and more tolerable regimens.²⁶ These advances have been incorporated into recent World Health Organization guidelines, which endorse bedaquiline-containing regimens as part of standardized MDR-TB treatment protocols.²⁷ However, it must be soberly recognized that although bedaquiline demonstrated significant efficacy as salvage therapy in this case, its application in transplant recipients still requires a prudent approach. First, drug interactions pose a potential challenge: as a CYP3A4 substrate, bedaquiline exhibits complex pharmacokinetic interactions with calcineurin inhibitors commonly used in clinical practice.²⁸ Therefore, rigorous therapeutic drug monitoring (TDM) is essential to optimize dosage and avoid the risks of immunosuppression inadequacy or excess. Second, long-term safety data regarding this drug in immunosuppressed populations remain scarce, and the long-term risks of adverse events such as QT interval prolongation and hepatic dysfunction have yet to be fully elucidated. Furthermore, in the context of profound immunosuppression, whether monotherapy or bedaquiline-containing regimens can effectively prevent long-term recurrence remains to be confirmed by prospective studies with larger sample sizes and longer follow-up periods. In summary, bedaquiline should be regarded as a potent therapeutic intervention requiring strict monitoring rather than a routine, risk-free option. This case highlights the severe challenge of sequential drug resistance in immunosuppressed hosts; particularly when adherence is poor, the immune status accelerates the selection of resistant strains, increasing the burden of refractory tuberculosis and the risk of community transmission. This underscores the importance of rigorous pre-transplant screening for latent infection and postoperative education, as well as the necessity of utilizing rapid molecular diagnostics and drug susceptibility testing to guide early treatment. Clinicians should maintain a high degree of vigilance for high-risk patients and consider empiric coverage of resistant bacteria.

This case underscores the complexity of managing drug-resistant TB in kidney transplant recipients and highlights the importance of precision diagnostics, dynamic treatment modification, close monitoring, and multidisciplinary collaboration. Continuously improving the understanding of such complex infections and refining clinical management pathways is of immeasurable value for ensuring the long-term success of kidney transplantation as a major therapeutic achievement and for improving the quality of life of recipients. There is an urgent need for future multicenter studies to focus on the following directions: clarifying the long-term safety and pharmacokinetic profiles of novel anti-tuberculosis drugs (such as bedaquiline and delamanid) in solid organ transplant recipients; establishing precise immunosuppressive regulation strategies based on immune monitoring and therapeutic drug monitoring; and formulating guidelines for the prevention, screening, and early intervention of drug-resistant tuberculosis tailored to the transplant population. The findings from these research efforts will lay a solid foundation for the evidence-based management of this special population.

Data Sharing Statement

The datasets analyzed during the current study are available from the corresponding author on reasonable request (Qing-Dong Zhu: zhuqingdong2003@163.com).

Ethical Statement

The study protocol was approved by the Ethics Committee of The Fourth People's Hospital of Nanning (Ethical Approval Number: [2025]52), no institutional approval is needed to publish the details of this case. This study obtained the informed consent for publication of patient details and accompanying images. This study is in accordance with the Declaration of Helsinki and adhere to CARE guidelines (<https://www.care-statement.org/>) in order to ensure all key details about the case are reported.

Consent for Publication

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. Written consent is available by request.

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.

Funding

This work was supported by the Guangxi Key Research and Development Plan Project (Guike AB25069097) and Guangxi Health Commission Self-Funded Research Project (Z-A20231211).

Disclosure

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.

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