

DELAYED-ONSET LINEZOLID-INDUCED SEVERE ANEMIA IN A YOUNG PATIENT WITH SPINAL RIFAMPICIN-RESISTANT TUBERCULOSIS

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ABSTRACT

Background: Linezolid is a core drug in regimens for multidrug-resistant and rifampicin-resistant tuberculosis (MDR/RR-TB) due to its potent intracellular activity against *Mycobacterium tuberculosis*. However, prolonged use is associated with cumulative hematologic toxicity, which can develop insidiously during extended treatment.

Case Presentation: We present the case of a 20-year-old female with spinal RR-TB who developed severe anemia after 11 months on a linezolid-containing regimen, following an initially stable hematologic profile. Laboratory monitoring revealed progressive anemia (hemoglobin 5.9 g/dL) and leukopenia (white blood cell count 1,790/mm³). Bone marrow suppression secondary to linezolid toxicity was suspected. Discontinuation of linezolid and transfusion support led to gradual hematologic recovery.

Conclusion: This case highlights the potential for delayed-onset, yet reversible, hematologic toxicity during long-term linezolid therapy, even in young patients without traditional risk factors. Sustained hematologic monitoring throughout the entire treatment course is essential to ensure patient safety and optimize outcomes in RR-TB management.

Keywords: Linezolid, Bicytopenia, Rifampicin-Resistant Tuberculosis, Hematologic Toxicity, Long-Term Monitoring, Case Report

ABSTRAK

Latar Belakang: Linezolid merupakan salah satu obat utama dalam rejimen pengobatan tuberkulosis multidrug resistant dan resisten rifampisin (MDR/RR-TB) karena aktivitas intraselulernya yang kuat terhadap *Mycobacterium tuberculosis*. Namun, penggunaan jangka panjang linezolid dikaitkan dengan toksisitas hematologis kumulatif yang dapat berkembang secara perlahan selama pengobatan berkepanjangan.

Presentasi Kasus: Kami melaporkan kasus seorang perempuan usia 20 tahun dengan tuberkulosis RR pada tulang belakang yang mengalami anemia berat setelah 11 bulan menjalani pengobatan dengan rejimen yang mengandung linezolid, meskipun sebelumnya profil hematologisnya stabil. Pemantauan laboratorium menunjukkan anemia progresif (hemoglobin 5,9 g/dL) dan leukopenia (jumlah leukosit 1.790/mm³). Supresi sumsum tulang akibat toksisitas linezolid dicurigai sebagai penyebabnya. Penghentian linezolid dan pemberian transfusi mendukung pemulihan hematologis secara bertahap.

Kesimpulan: Kasus ini menyoroti potensi toksisitas hematologis dengan onset tertunda namun reversibel selama

terapi linezolid jangka panjang, bahkan pada pasien muda tanpa faktor risiko tradisional. Pemantauan hematologis yang berkelanjutan sepanjang durasi pengobatan sangat penting untuk menjaga keselamatan pasien dan mengoptimalkan hasil terapi pada kasus RR-TB.

Kata Kunci: linezolid, bisitopenia, tuberkulosis resisten rifampisin, toksisitas hematologis, pemantauan jangka panjang, laporan kasus

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INTRODUCTION

Drug-resistant tuberculosis (DR-TB), particularly rifampicin-resistant (RR) and multidrug-resistant (MDR) forms, continues to pose a major challenge to global TB control, with significant clinical and public health implications.^{1,2} Among recent therapeutic advances, the incorporation of linezolid has improved outcomes in patients with DR-TB, largely due to its potent activity against *Mycobacterium tuberculosis*.³

However, the use of linezolid carries a substantial risk of toxicity, and its optimal dose and duration remain undefined.⁴ While short-course use (less than 28 days) for non-TB infections is generally safe and well tolerated, prolonged treatment in cases such as MDR/XDR-TB, which typically lasts six months or more, is associated with frequent and serious adverse effects. These toxicities are often dose- and duration-dependent and include anemia, neutropenia, thrombocytopenia, peripheral neuropathy, and, less commonly, optic neuropathy, lactic acidosis, pancreatitis, and rhabdomyolysis.⁵ Such adverse effects often necessitate early dose reduction or discontinuation, potentially compromising the therapeutic efficacy of linezolid.^{4,5}

Although early hematologic monitoring is commonly performed, continued surveillance throughout prolonged therapy is often lacking, especially in high-burden settings with limited laboratory access. Most existing reports focus on early-onset cytopenias or patients with comorbidities, with limited data on delayed hematologic toxicity in young, otherwise healthy individuals. To our knowledge, this is among the few documented cases of delayed-onset linezolid-induced bicytopenia in such a population. This case highlights the potential for insidious, yet reversible, hematologic toxicity and the need for sustained monitoring throughout the treatment course.

CASE ILLUSTRATION

A 20-year-old female, previously healthy, presented to our national referral hospital with progressive mid-thoracic

swelling and ascending paresthesia in both lower limbs that had developed over the past year. Initially ambulatory, her symptoms worsened after six months when she experienced acute bilateral lower limb paralysis following a motorcycle accident.

Spinal imaging revealed a severe compression fracture of the T8 vertebral body, narrowing of the T7–T8 intervertebral disc space, and an associated gibbus deformity. Lumbar imaging demonstrated destruction of the anterior portion of the L5 vertebral body, along with a prevertebral soft tissue mass at the L4–L5 level, and spondylodiscitis at L5–S1. Based on these findings, spinal imaging and clinical evaluation at a secondary care facility suggested thoracic tuberculous spondylitis. The patient was started on anti-tuberculosis therapy and subsequently completed a 7-month course. However, despite completing the treatment, there was no improvement, and the patient was referred to our hospital for further evaluation and management.

Upon referral to our center for definitive management, the patient underwent thoracic laminectomy and surgical debridement at the T8 level. Intraoperative tissue analysis using the Xpert MTB/RIF assay confirmed the presence of *Mycobacterium tuberculosis* with rifampicin resistance. Histopathological examination of a biopsy from the T8–T9 vertebral body revealed granulomatous inflammation, consistent with tuberculous spondylitis.

Chest radiography showed fibrosis in the middle zone of the right lung, spondylodiscitis at the T7–T8 level with a paravertebral abscess, and posterior spinal stabilization with a rod and multiple screws in place. Additional spinal imaging demonstrated a severe compression fracture of the T8 vertebral body, with narrowing of the T7–T8 disc space and adjacent gibbus deformity, as well as destruction of the anterior aspect of the L5 vertebral body and a soft tissue mass at the prevertebral L4–L5 level, with spondylodiscitis at L5–S1 (Fig. 1). The patient was started on the WHO-recommended regimen for rifampicin-resistant tuberculosis,

including bedaquiline, levofloxacin, linezolid, clofazimine, and cycloserine for the intensive phase (6 months), followed by a continuation phase of 14 months without bedaquiline.



Figure 1. Chest radiography

Throughout treatment, the patient underwent regular hematologic monitoring. Serial laboratory assessments showed an initially stable hematologic profile, with slight declines in hemoglobin, white blood cell, and platelet counts over time. By the 11th month, she developed symptomatic bicytopenia with severe anemia (hemoglobin level of 5.9 g/dL), a white blood cell count of 1,790/mm³, and mild thrombocytopenia (platelet count of 127,000/mm³). Peripheral smear showed normocytic-normochromic anemia with low reticulocyte count. After discontinuing linezolid and with transfusion support, her hematologic parameters improved, confirming that the marrow suppression was temporally related to linezolid therapy.

Table 1. Serial Hematologic Parameters During Linezolid-Based Treatment for Rifampicin-Resistant Tuberculosis

Follow-up (Month)	Hb (g/dL)	Ht (%)	RBC (10 ¹² /μL)	MCV (fL)	MCH (pg)	MCHC (g/dL)	WBC (10 ³ /μL)	Platelets (10 ³ /μL)	Notes
Baseline	10.7	32.9	4.22	78.0	25.4	32.5	8.69	265	Before treatment
2	9.6	29.8	3.91	76.2	24.6	32.2	7.16	413	
5	10.5	31.8	3.82	83.2	27.5	33.0	6.10	303	
7	9.9	29.7	3.06	97.1	32.4	33.3	4.36	270	
8	9.5	27.8	2.86	97.2	33.2	34.2	4.21	282	
10	8.8	25.6	2.69	95.2	32.7	34.4	3.62	277	
11	5.9	16.4	1.85	88.6	31.9	36.0	1.79	127	Linezolid discontinued
11*	9.1	26.6	2.95	90.2	30.8	34.2	1.94	107	ANC 1.260×10 ³ /μL
12	11.8	35.5	4.16	85.3	28.4	33.2	4.33	279	
13	12.0	33.4	4.46	74.9	26.9	35.9	5.17	305	
14	11.5	32.8	4.36	75.2	26.4	35.1	3.41	257	
15	12.0	34.8	4.51	77.2	26.6	34.5	4.24	261	

Abbreviations. Hb: Hemoglobin; Ht: Hematocrit; RBC: red blood cell; WBC: white blood cell; MCV: mean corpuscular volume; MCH: mean corpuscular hemoglobin; MCHC: mean corpuscular hemoglobin concentration; ANC: absolute neutrophil count.
*Hematologic improvement observed after packed red blood cell transfusion and cessation of linezolid therapy.

DISCUSSION

Linezolid has become a cornerstone in WHO-recommended regimens for multidrug-resistant and rifampicin-resistant tuberculosis (MDR/RR-TB), due to its proven efficacy in improving culture conversion and treatment success rates in MDR/XDR-TB patients.² Its favorable pharmacokinetic profile, including excellent oral bioavailability, high tissue penetration, and reliable bone concentration, makes it an effective option for prolonged treatment, especially in skeletal infections.^{5,6} Despite these advantages, linezolid's clinical utility is limited by significant hematologic toxicity—most commonly anemia, thrombocytopenia, and neutropenia—which

are often cumulative, dose- and duration-dependent, and may affect up to 58.9% of patients on high-dose regimens.^{5,7} This toxicity is mechanistically linked to inhibition of mitochondrial protein synthesis, which impairs mitochondrial function in hematopoietic precursors and suppresses bone marrow activity.^{5,8,9}

Our patient demonstrated a gradual but continuous decline in hemoglobin and white cell counts over several months, culminating in severe bicytopenia after 11 months of linezolid-based therapy. Notably, the patient maintained a relatively stable hematologic profile during the early phases of treatment, and no other identifiable causes—such as

nutritional deficiencies, active infections, or infiltrative marrow pathology—were found to account for the decline. Hematologic recovery after linezolid discontinuation further supports the diagnosis of cumulative drug-induced bone marrow suppression.⁷

This clinical course is consistent with reports of delayed-onset cytopenias associated with prolonged linezolid use. While hematologic toxicity is often reported to emerge within the first few weeks of therapy,⁹ bone marrow suppression—including anemia and thrombocytopenia—typically occurs within the first 1–2 months, particularly at doses ≥ 600 mg/day.¹⁰ However, our patient's late-onset presentation highlights that toxicity may accumulate silently over time despite an initial period of tolerance. Anemia is a common complication of linezolid therapy, with a reported incidence as high as 38.1% among MDR- and XDR-TB patients treated for a median duration of 300 days (range: 140–690 days).⁵

Although bone marrow biopsy was not performed in this case, the temporal relationship between linezolid use and hematologic decline, followed by recovery upon drug discontinuation, supports a causal link. This limitation should be acknowledged, yet does not negate the clinical relevance of the case.

Linezolid has a half-life of 5 to 7 hours, and approximately 35% of the drug is excreted unchanged in the urine. It is metabolized via non-enzymatic oxidation into two major metabolites—PNU-142300 and PNU-142586—which are primarily excreted renally. While clearance of linezolid is relatively unaffected by renal function, these metabolites can accumulate to higher levels in patients with renal impairment.¹¹ Although the direct contribution of these metabolites to bone marrow toxicity has not been fully elucidated, prolonged exposure is thought to heighten hematologic risk.^{11,12} Importantly, our patient had preserved renal function and lacked conventional risk factors, yet still developed delayed-onset bicytopenia. This

supports the notion that cumulative mitochondrial injury from sustained linezolid exposure alone may be sufficient to induce bone marrow suppression—even in individuals with intact metabolite clearance.^{11,12}

The underlying mechanism of toxicity is believed to involve mitochondrial dysfunction. Linezolid inhibits mitochondrial protein synthesis by binding to the mitochondrial ribosome, which shares structural similarities with its bacterial counterpart.⁸ This impairment disrupts erythroid and myeloid progenitor activity in the bone marrow, ultimately leading to reversible myelosuppression. Histologic features such as vacuolated erythroblasts and reduced erythroid precursors have been reported in similar cases, paralleling the marrow effects of other mitochondrial toxins like chloramphenicol.^{5,6}

Although known risk factors for linezolid-induced toxicity include renal impairment, advanced age, and pre-existing anemia, this case illustrates that cumulative exposure alone can lead to hematologic complications even in young, otherwise healthy individuals. The prolonged exposure (over 300 days) and absence of early warning signs underscore that serious toxicity can evolve insidiously, reinforcing the need for vigilance throughout the treatment course.

Preventive strategies remain limited. Supplementation with iron, folate, vitamins, or erythropoietin has shown inconsistent efficacy. Empirical dose reduction to 300–600 mg/day, including off-label use of 300 mg in select cases may help mitigate toxicity, though these approaches are not standardized and are often implemented without pharmacokinetic guidance.^{1,6}

A review of three similar published cases (Yang et al. 2022; Lan et al. 2023; Mo et al. 2024) reveals early-onset cytopenia (within 1–3 months) in older adults with comorbidities. In contrast, our patient, a young individual with no prior risk factors, developed toxicity after nearly one year, underscoring the role of cumulative exposure rather than host factors alone. These

comparisons support the unique nature of our case in terms of patient demographic, timing of onset, and reversibility of hematologic suppression.

Therapeutic drug monitoring (TDM) is increasingly recommended to optimize linezolid exposure and minimize toxicity. Expert consensus suggests maintaining a trough concentration within 2–8 mg/L, with a narrower range of 2–6.3 mg/L providing the best balance of efficacy and safety.¹³ Trough levels ≥ 2 mg/L have been associated with an increased risk of anemia, thrombocytopenia, and peripheral neuropathy, reinforcing the need for careful dose adjustment.¹⁴ Additionally, achieving an AUC/MIC ratio >100 has been linked to therapeutic success, underscoring the importance of balancing drug exposure and treatment duration.^{14,15} While TDM offers a practical means of personalizing dosing to individual pharmacokinetic profiles—especially in patients with risk factors such as renal dysfunction, advanced age, or pre-existing anemia—access to TDM remains limited in many high-burden TB settings.^{7,13–15}

This case aligns with emerging evidence that the risk of anemia associated with linezolid is not confined to the early phase of treatment. In one cohort of 221 patients receiving linezolid, nearly 48% of those who developed anemia did so after just 14 days of therapy, with the projected cumulative risk reaching 50% by day 72.¹⁶ In our patient, the development of severe bicytopenia after more than 300 days of therapy underscores that hematologic toxicity can evolve insidiously, even in the absence of conventional risk factors. These findings highlight the critical importance of ongoing hematologic surveillance throughout the entire course of linezolid therapy, not just in the early phase. Incorporating structured toxicity monitoring and, where feasible, therapeutic drug monitoring may enable early detection and timely dose adjustments, reducing the risk of irreversible complications.

CONCLUSION

This case contributes to the underreported body of evidence documenting delayed hematologic toxicity associated with prolonged linezolid therapy. It underscores the importance of structured toxicity monitoring protocols, including predefined thresholds for dose adjustment and interruption, even in patients without conventional risk factors. As linezolid continues to play a central role in MDR/RR-TB treatment, optimizing its use through individualized monitoring and evidence-based dosing strategies is essential to balancing therapeutic efficacy with patient safety. Future research is needed to establish early biomarkers of mitochondrial injury and refine treatment algorithms based on real-world pharmacovigilance data.

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