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# Severe Rifampicin-Induced Immune Thrombocytopenia During Treatment of Cavitary Pulmonary Tuberculosis: A Case Report

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## ABSTRACT

Rifampicin is first-line therapy for drug-susceptible tuberculosis (TB) but rarely causes severe immune-mediated thrombocytopenia, which may be overlooked amid multiple concomitant medications. A 49-year-old man with cavitary pulmonary TB developed severe thrombocytopenia nine days after starting rifampicin-containing therapy; platelets fell abruptly from 311,000/µL to 9,000/µL. He also received prophylactic heparin, vancomycin, and other antimicrobials. The 4Ts score indicated low probability of heparin-induced thrombocytopenia, and peripheral smear excluded microangiopathic processes. Rifampicin-induced immune thrombocytopenia (RIT) was diagnosed based on temporal association, exclusion of major alternatives, and rapid platelet recovery after rifampicin discontinuation. RIT should be considered in acute severe thrombocytopenia during TB treatment, even with other thrombocytopenia-associated drugs. Early recognition and prompt withdrawal of the offending agent are essential to reduce bleeding risk and permit continuation of effective TB therapy with an alternative regimen.

## Introduction

Rifampicin is a cornerstone of first-line therapy for drug-susceptible tuberculosis (TB), essential for shortening treatment duration and improving cure rates. Although generally well tolerated, it can cause uncommon but significant adverse reactions, including hepatotoxicity, hypersensitivity, and hematologic complications [1]. Rifampicin-induced thrombocytopenia (RIT) is rare but potentially life-threatening. Mechanisms include immune-mediated platelet destruction via rifampicin-dependent antiplatelet antibodies, often triggered by intermittent dosing, treatment interruption, or re-exposure; however, cases during continuous daily therapy have been documented [2].

RIT diagnosis is challenging, especially in hospitalized patients receiving multiple thrombocytopenia-associated medications. The differential includes heparin-induced thrombocytopenia (HIT), sepsis-

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related coagulopathy, disseminated intravascular coagulation (DIC), and drug-induced immune thrombocytopenia from agents such as vancomycin or β-lactams. Prompt diagnosis is critical: rifampicin discontinuation typically leads to rapid platelet recovery, whereas delayed intervention may cause severe bleeding [3].

Here, we present a case of severe thrombocytopenia developing early during first-line TB treatment in a patient with cavitary pulmonary TB, with a focused literature review highlighting clinical clues for timely identification and management of this rare but important adverse drug reaction.

## Case Presentation

A 49-year-old man (178 cm, 79 kg; 30 pack-years smoking) was admitted with one month of progressive weakness, malaise, and productive non-bloody cough worsening over the prior week, plus orthopnea and exertional dyspnea. He had bilateral total hip arthroplasty and remote appendectomy; no other significant medical, family, or medication history.

On admission, he appeared ill but was alert, oriented, and hemodynamically stable (BP 108/71 mmHg; HR 87/min; RR 18/min; T 37.5°C; SpO2 96% on room air). Examination showed mild coarse inspiratory crackles over upper lung fields, epigastric tenderness, and bilateral 2+ pitting lower-extremity edema; no pallor or jaundice.

Baseline labs showed hyponatremia, hypocalcemia, elevated inflammatory markers, and leukocytosis; hemoglobin, platelets, and coagulation studies were normal (Table 1). Color Doppler excluded DVT. Contrast-enhanced chest CT showed cavitary lesions highly suggestive of active TB.

Prophylactic subcutaneous heparin 5,000 units twice daily and first-line anti-TB therapy (rifampicin, isoniazid, pyrazinamide,ethambutol) were started. For suspected concomitant pneumonia, vancomycin 1 g IV twice daily, cefepime,and levofloxacin were added, with pantoprazole for gastroprotection.

Platelet counts fluctuated mildly early (Table 1). On Day 10, they fell to 15,000/µL, reaching 9,000/µL on Day 11. After 10 units of platelets on Day 11, counts rose to 38,000/µL on Day 12. This episode occurred 9 days after starting rifampicin, whereas heparin dosing was unchanged since admission, favoring rifampicin-induced immune thrombocytopenia.

Counts later recovered to 311,000/µL. On Day 30 , another precipitous decline occurred,from 363, 000/µL to 9,000/µL within 24 hours. With ongoing rifampicin and unchanged heparin, recurrence at a consistent interval after rifampicin exposure further supported a rifampicin-mediated reaction rather than HIT (Table 2).

Thrombocytopenia was isolated and abrupt, without anemia progression, coagulopathy, hemolysis, or peripheral smear findings of thrombotic microangiopathy, supporting peripheral immune-mediated platelet destruction rather than marrow suppression or consumptive thrombocytopenia.

Peripheral blood smear, reviewed by hematology,

**Table 1.** Admission laboratory finding.

| Laboratory parameter | Result | Status/interpretation |
|---|---|---|
| Sodium (mmol/l) | 129 | Low (hyponatremia) |
| Calcium (mg/dl) | 7.8 | Low (hypocalcemia) |
| CRP (mg/l) | 131 | Elevated (increased) |
| ESR (mm/hr) | 44 | Elevated (increased) |
| WBC (/µl) | 11,600 | Elevated (leukocytosis) |
| Hb (g/dl) | 12.2 | Normal |
| Platelet count (/µl) | 363,000 | Normal (initial value) |
| Coagulation studies | Within normal limits | Normal |

CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; Hb: Hemoglobin; WBC: White blood cell

**Table 2.** Serial platelet counts during hospitalization.

| Day | Day 1 | Day2 | Day3 | Day5 | Day6 | Day7 | Day8 | Day10 | Day11 | Day12 |
|---|---|---|---|---|---|---|---|---|---|---|
| **Platelet count (/µl)** | 363,000 | 266,000 | 304,000 | 293,000 | 335,000 | 231,000 | 311,000 | 15,000 | 9,000 (Nadir) Received 10 units platelets | 38,000 |

**Table 3.** Naranjo adverse drug reaction probability scale.

| Question | Yes | No | Not known Or not done | Score of our case |
|---|---|---|---|---|
| 1. Are there previous conclusive reports on this reaction? | +1 | 0 | 0 | 0 |
| 2. Did adverse event appear after the suspected drug was given? | +2 | -1 | 0 | +2 |
| 3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was given? | +1 | 0 | 0 | +1 |
| 4. Did the adverse reaction appear when the drug was re-administered? | +2 | -1 | 0 | 0 |
| 5. Are there alternative causes that could have caused the reaction? | -1 | +2 | 0 | -1 |
| 6. Did the reaction reappear when a placebo was given? | -1 | +1 | 0 | 0 |
| 7. Was the drug detected in any body fluid in toxic concentrations? | +1 | 0 | 0 | 0 |
| 8. Was the reaction more severe when the dose was increased, or less severe when the dose was decreased? | +1 | 0 | 0 | 0 |
| 9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure? | +1 | 0 | 0 | 0 |
| 10. Was the adverse event confirmed by any objective evidence? | +1 | 0 | 0 | +1 |

Total score:3

The Naranjo scale categorizes causality as doubtful (<2), possible (2–4), probable (5–8), and definite (≥9). Possible denotes a temporal and recognized pattern but alternative disease explanation; probable denotes logical timing, recognized response, improvement on withdrawal, and no better explanation (challenge not required); definite requires recurrence on re-challenge or confirmed toxic drug level.

showed no schistocytes, hemolysis, or immature cells, excluding thrombotic microangiopathy (TTP/HUS) and marrow infiltration. Coagulation studies—fibrinogen 412 mg/dL, D-dimer 1.33 µg/mL, and fibrin degradation products (FDP) 5 µg/mL—argued against overt disseminated intravascular coagulation (DIC) or primary fibrinolysis. Isolated profound thrombocytopenia with intact coagulation and normal erythrocyte morphology favored peripheral immune-mediated platelet destruction over consumptive or microangiopathic causes.

The patient received 10 units of pooled platelets, with a modest rise to 38,000/µL by Day 12. A repeat peripheral blood smear showed no schistocytes, blasts, or features of thrombotic microangiopathy or leukemia. Systematic evaluation included a 4Ts score of 3 (low pretest probability for HIT), with no skin lesions. Given the strong temporal association, onset nine days after therapy initiation, and exclusion of HIT, rifampicin was considered the most probable cause. Vancomycin and β-lactams were recognized alternatives but deemed less likely given the classic timing, severity of platelet decline, and recovery after rifampicin withdrawal. The Naranjo scale score was 3 (possible adverse drug reaction), reflecting a reasonable temporal sequence, recognized response, improvement after withdrawal, and no more likely explanation; no re-exposure was performed (Table 3).

In consultation with the infectious disease and pharmacotherapy services, the first-line TB regimen was discontinued on October 5th. A rifampicin-sparing, second-line regimen was instituted, consisting of isoniazid (300 mg daily), pyrazinamide (1500 mg), ethambutol (1400 mg daily), and levofloxacin (750 mg daily) for 18 months.

Rapid hematologic recovery followed rifampicin withdrawal: within 24 hours, platelet count rose to 59,000/µL without further transfusion, strongly supporting RIT. The patient continued to improve on a rifampicin-sparing regimen (isoniazid 300 mg daily, pyrazinamide 1500 mg, ethambutol 1400 mg daily, and levofloxacin 750 mg daily for 18 months). He was discharged with pulmonary TB and resolved thrombocytopenia on this rifampicin-free regimen.

## Discussion

We describe severe immune-mediated thrombocytopenia due to rifampicin, supported by onset after 9 days, exclusion of HIT and other causes, and rapid platelet normalization after withdrawal [3]. Although drug-dependent platelet antibody testing was unavailable, the clinical course was consistent with rifampicin-induced immune thrombocytopenia.

RIT occurs after intermittent or continuous rifampicin, though intermittent exposure and treatment interruption increase risk. Cases present with abrupt, severe thrombocytopenia, requiring immediate drug discontinuation and alternative anti-TB therapy [14].

Rifampicin is essential for standard 6-month first-line anti-TB regimens in drug-susceptible

TB [11]. Permanent withdrawal due to immune thrombocytopenia requires prolonged second-line regimens (9–20 months), increasing toxicity, non-adherence, cost, relapse, and resistance risk [11, 12].

RIT is mediated by drug-dependent IgG antibodies binding platelet membrane glycoproteins, causing opsonization and accelerated reticuloendothelial clearance [4]. It can occur on first exposure (typically within a week) or more rapidly upon re-exposure. Intermittent or interrupted regimens, especially high intermittent doses (e.g., 1200 mg two or three times weekly), are associated with higher thrombocytopenia incidence than continuous daily dosing. This suggests uninterrupted daily therapy may induce immunological tolerance, whereas interruptions favor sensitization and overt immune-mediated thrombocytopenia upon rifampicin reintroduction [5, 6].

Host and immunologic factors, not demographics, drive RIT susceptibility, with no consistent epidemiologic predictors across ages, sexes, or autoimmune status [6]. The key determinant is idiosyncratic formation of rifampicin-dependent IgG antiplatelet antibodies against platelet glycoproteins, causing opsonization and reticuloendothelial clearance [5, 7]. These antibodies can persist for years, explaining abrupt severe thrombocytopenia on re-exposure despite prior tolerance [5, 7]. Although TB may modulate immunity, no specific infectious profile increases risk, and most rifampicin recipients never develop RIT, underscoring its idiosyncratic nature [5, 6].

Rifampicin toxicity is schedule-dependent rather than linearly dose-dependent. High single or intermittent high-dose regimens (e.g., 1200 mg two or three times weekly) predominate in RIT reports, suggesting elevated antigenic load per exposure promotes immune-mediated platelet destruction in sensitized patients. Continuous daily standard dosing carries very low incidence, possibly due to immunological tolerance or efficient immune complex clearance [5, 6]. Concomitant thrombocytopenia-inducing drugs (e.g., heparin, β-lactams) complicate causality but lack evidence of synergy with rifampicin; polypharmacy may nonetheless delay diagnosis and prolong exposure, increasing bleeding risk [3, 8].

Rifampicin reintroduction is contraindicated because persistent drug-dependent antibodies confer high recurrence risk, with case reports of abrupt severe platelet drops within hours to days of re-challenge; guidelines recommend permanent avoidance and rifampicin-free alternatives to prevent life-threatening hemorrhage [10, 13].

This case is instructive for three reasons: HIT was a natural initial suspect, underscoring the need for broad differential diagnosis; the severity (nadir <10,000/μL) highlights rifampicin's potential for life-threatening complications; and successful transition to a fluoroquinolone-based regimen demonstrates effective alternatives that ensure continuity of anti-TB treatment. RIT typically presents with abrupt platelet drops below $20\times10^9$/L, mucocutaneous or visceral bleeding within 5–10 days of initial exposure, or hours upon re-exposure [6, 9, 10]. Delayed diagnosis and continued rifampicin predict life-threatening hemorrhage [3, 8]. Rapid platelet recovery within 48–72 hours, normalizing in about one week after withdrawal, supports an immune-mediated mechanism and differentiates RIT from DIC or HIT, particularly with detectable drug-dependent antibodies [3, 5, 6, 8].

This report has some limitations. Drug-dependent platelet antibody testing was not performed; diagnosis relied on clinical assessment, exclusion of alternatives, and response to withdrawal. Because multiple thrombocytopenia-associated medications were given, complete exclusion of other drug contributions is not possible. Nevertheless, the temporal relationship and clinical course strongly supported rifampicin as the most likely offending agent.

## Conclusions

Rifampicin-induced immune thrombocytopenia is rare but life-threatening. Clinicians should consider rifampicin as a cause of abrupt severe thrombocytopenia, even with other thrombocytopenia-associated drugs. Early identification, drug withdrawal, and an alternative TB regimen are essential to prevent bleeding and maintain effective treatment.

## Authors' Contributions

**ES**: Data curation, Investigation, writing – original draft, Writing – review & editing.
**FA**: Writing – review & editing.
**BS**: Conceptualization, Project administration, Supervision, Validation, Writing – review & editing
All authors reviewed the manuscript, approved the final version, and agreed to be accountable for all aspects of the work.

## Ethical Considerations

### Availability of data and material

Available from the corresponding author upon request.

### Ethics approval and consent to participate

This report complied with the Declaration of Helsinki. Written informed consent was obtained from the patient for participation and publication of clinical information.

### Consent for publication

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

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### Conflict of Interests

The authors declare no competing financial or personal interests that could have influenced this work. All additional tests were funded independently by the authors.

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