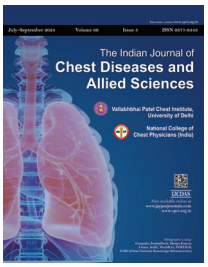
CASE SERIES

Case Series on Rifampicin-induced Thrombocytopenia with Daily Regimen: Clinical Insights and Management Strategies



Eshutosh Chandra[1], Amitesh Gupta[2], Shipra Anand[3], Irshad Ahmad[4], Pooja Narwal[5], Naresh Kumar[6]

This article is available on www.vpci.org.in

Received on: 11 September 2024; *Accepted on:* 30 October 2024; *Published on:* 19 November 2024

Abstract

Thrombocytopenia, a rare but serious complication of rifampicin treatment, underscores the importance of timely intervention to prevent adverse outcomes. This article offers a detailed exploration of rifampicin-induced thrombocytopenia, shedding light on its causes, symptoms, diagnosis, and treatment options. Through a blend of research insights and real-life cases, we emphasize the crucial role of healthcare providers in recognizing and addressing this condition promptly. By advocating for increased awareness and vigilant monitoring, we aim to ensure the safety and well-being of patients undergoing anti-tuberculosis treatment.

Keywords: Adverse effect, Immune-mediated reaction, Rifampicin, Thrombocytopenia, Tuberculosis.

The Indian Journal of Chest Diseases and Allied Sciences (2024): 10.5005/jp-journals-11007-0126

Abbreviations Used in this Article

AFB = Acid-fast bacilli; APTT = Activated partial thromboplastin time; ATT = Anti-tubercular therapy; BT = Bleeding time; CBC = Complete blood count; CECT = Contrast-enhanced computed tomography; CT = Clotting time; CT = Computed tomography; CXR = Chest X-ray; FDC = Fixed-dose combination; GM-CSF = Granulocyte-macrophage colony-stimulating factor; Hb = Hemoglobin; INR = International normalized ratio; IVIG = Intravenous immunoglobulin; L = Lymphocytes; LFT = Liver function tests; N = Neutrophil; PRBC = Packed red blood cells; PT = Prothrombin time; RE = Routine examination; RIT = Rifampicin-induced thrombocytopenia; SOB = Shortness of breath; TLC = Total leukocytes count.

Introduction

Rifampicin, a key anti-tubercular drug that inhibits bacterial DNA-dependent RNA polymerase, can cause gastrointestinal (nausea, vomiting, hepatitis), dermatological (rashes, pruritus, flushing), and hematological (thrombocytopenia, neutropenia, hemolytic anemia) side effects. Rifampicin-induced thrombocytopenia, an immune-mediated reaction, typically appears within 5–7 days but may occur rapidly in individuals with pre-existing antibodies, leading to potentially life-threatening platelet destruction.

We present a series of four cases of rifampicin induced thrombocytopenia presenting to our department and their management (Table 1).

Discussion

Tuberculosis (TB), a chronic granulomatous infection caused by Mycobacterium tuberculosis, primarily manifests as pulmonary disease. Despite a declining incidence, India reported around 25% of the 10.6 million global TB cases in 2021 (Global TB Report 2023), highlighting its ongoing public health significance.[1] Newly diagnosed tuberculosis patients are initially treated with an effective regimen comprising four drugs: isoniazid, rifampicin, pyrazinamide, and ethambutol. None of the antitubercular drugs are devoid of risk, and the World Health Organization (WHO) advocates for the monitoring and reporting of suspected or confirmed adverse drug reactions associated with these medications.

Effective chemotherapy is essential for tuberculosis management, but first-line drugs such as isoniazid, rifampicin, ethambutol, and pyrazinamide can cause side effects like hepatotoxicity, nausea, vomiting, rashes, allergies, peripheral neuropathy, and optic neuritis. Anti-tubercular therapy (ATT) may also lead to various hematological abnormalities. Rifampicin, in particular, can cause gastrointestinal issues, drug-induced hepatitis, rash, flushing, flu-like syndrome, and blood disorders like thrombocytopenia, neutropenia, and hemolytic anemia.

The introduction of rifampicin in 1965 revolutionized TB treatment by initiating the era of short-course chemotherapy. This breakthrough drastically reduced the duration of anti-TB therapy from 12–24 months to just 6 months.[2] Despite advancements, TB treatment remains a challenging endeavor for physicians due to the

[1]Department Respiratory Medicine, Santosh Medical College and Hospital, Ghaziabad, Uttar Pradesh, India

[2–6]Department of Pulmonary Medicine, Maulana Azad Medical College and Associated Lok Nayak Hospital, New Delhi, India

Corresponding Author: Amitesh Gupta, Department of Pulmonary Medicine, Maulana Azad Medical College and Associated Lok Nayak Hospital, New Delhi, India, Phone: +91 8826687283, e-mail: amiteshami@gmail.com

How to cite this article: Chandra E, Gupta A, Anand S, *et al*. Case Series on Rifampicin-induced Thrombocytopenia with Daily Regimen: Clinical Insights and Management Strategies. Indian J Chest Dis Allied Sci 2024;66(3):106–109.

Source of support: Nil

Conflict of interest: None

Table 1: Detailed tabular presentation for the four cases

Case	*Patient demographics*	*Presenting symptoms*	*Initial findings*	*Investigations*	*Treatment and response*	*Outcome*
1	53-year-old male, non-diabetic, non-hypertensive	- Fever for 2.5 months - Weight loss - Loss of appetite - Generalized weakness - No cough, expectoration, chest pain, or SOB	- Hb: 9.8 gm/dL - TC: 10,000/µL (N74%, L18%) - Platelets: 110 × 10^3µL - Urine RE: 2–3 pus cells, no RBCs or casts - Blood cultures: no growth	- CECT thorax and abdomen: Multiple lymph nodes (pre/para tracheal, right hilar) with necrosis; hepatomegaly - EBUS TBNA suggested but initially refused; Gene expert: MTB detected, RIF resistance: not detected; Cytology: Granulomatous lymphadenitis, AFB seen	- Started on ATT (initially refused EBUS TBNA); after 9–10 days, developed petechial rashes, severe thrombocytopenia (platelets 15 × 10^3/µL); ATT stopped, supportive care (IVIG, GM-CSF) - Bone marrow: Hypercellular with increased mature megakaryocytes	- Resumed ATT with alternative regimen (excluding Rifampicin); Recovered with no recurrence of rashes; repeat CBC: Hb: 10 gm/dL, TLC: 4,000/µL, Platelets: 227 × 10^3/µL
2	65-year-old male, diabetic, hypertensive	- Low-grade fever for 20 days - Weight loss - Loss of appetite - Cough and SOB	- Hb: 11.2 gm/dL - TLC: 10,500/µL (N72%, L23%) - Platelets: 140 × 10^3/µL - Urinalysis: No significant abnormalities	- CXR: Consolidation in right upper lobe - Sputum: AFB positive - LFT: Elevated transaminases (SGPT: 80 U/L, SGOT: 45 U/L) -Coagulation profile: prolonged PT and APTT	- Started on standard ATT; developed petechial rash, mucosal bleeding (platelets 8 × 10^3/µL); ATT stopped, supportive care (PRBC and platelet transfusions, IVIG, GM-CSF) - Reintroduced ATT excluding Rifampicin	-Recovered with alternative ATT regimen; CBC normalized with Hb: 8.5 gm/dL, TLC: 6,000/µL, Platelets: 8 × 10^3/µL; Close monitoring during follow-up
3	37-year-old female, previously healthy	- Persistent cough for 2 months - Low-grade fever - Night sweats - Weight loss (~5 kg)	- Hb: 10.2 gm/dL - TC: 11,600/ µL - Platelets: 17 × 10^3/µL	- Sputum: AFB positive - Dengue serology: IgM positive - LFT: Mild elevations, not detailed	- Started on FDC ATT; developed generalized hyperpigmented rash, lichenoid dermatitis (platelets 17 × 10^3/µL); ATT stopped, managed for dengue (supportive care, platelet transfusions) - Systematic drug re-challenge identified Rifampicin as the cause of adverse reactions	- Recovered with alternative ATT regimen (excluding Rifampicin); Platelets increased to 550 × 10^3/µL; gradual improvement and normalization of clinical condition
4	38-year-old female, homemaker	- Fever for 3 months - Productive cough - Decreased appetite - Heavy vaginal bleeding for 4 days - Hemoptysis - Sudden onset of skin eruptions	- Hb: 5.9 gm/dL - Platelets: 47 × 10^3/µL (dropped to 7 × 10^3/µL) - Bleeding Time: 2′ 9″ - Clotting Time: 5′ 28″ - PT: 3.8′ - INR: 1.27	- Sputum: AFB positive - Hematological investigations: Abnormal BT, CT, prolonged PT and INR; no Dengue markers - LFT: Not detailed, likely mild elevations	- ATT stopped due to extensive purpura and thrombocytopenia; supportive care (platelet and blood transfusions) - Subsequent re-challenge indicated Rifampicin-induced thrombocytopenia; recovered with Ethambutol, Pyrazinamide, and Isoniazid	- Discharged on alternative ATT regimen (excluding Rifampicin); Platelets increased to 170 × 10^3/µL; significant clinical improvement with planned close follow-up

AFB, acid-fast bacilli; APTT, activated partial thromboplastin time; ATT, anti-tubercular therapy; BT, bleeding time; CBC, complete blood count; CECT, contrast-enhanced computed tomography; CT, computed tomography; CT, clotting time; CXR, chest X-Ray; FDC, fixed-dose combination; GM-CSF, granulocyte-macrophage colony-stimulating factor; Hb, hemoglobin; INR, International normalized ratio; IVIG, intravenous immunoglobulin; L, lymphocytes; LFT, liver function tests; N, neutrophil; PRBC, packed red blood cells; PT, prothrombin time; RE, routine examination; SOB, shortness of breath; TLC, total leucocytes count

prolonged treatment duration, adverse drug effects, suboptimal medication adherence, and emergence of drug resistance.

Thrombocytopenia, often defined as a platelet count below 150×10^9/L, is more clinically significant below 100×10^9/L. Causes include viral infections, autoimmune diseases, lymphoproliferative disorders, and various medications.

Rifampicin-induced thrombocytopenia (RIT), first reported by Blajchman et al. in 1970, is a reversible condition if detected early.[3] It involves anti-rifampicin antibodies (ARA), mainly IgM, forming immune complexes with rifampicin, leading to platelet destruction via complement fixation (type III hypersensitivity) and the production of antiplatelet and anti-erythrocyte antibodies (type II hypersensitivity). Discontinuation of rifampicin usually normalizes blood counts. Other drugs causing thrombocytopenia include quinine, chloroquine, sulfonamides, and aspirin. Adverse reactions to first-line antituberculous drugs vary widely, from 8.0 to 85%, but are usually mild. Rifampicin-induced thrombocytopenia, though rare, is a potentially life-threatening complication of anti-tuberculosis therapy, often associated with high-dose intermittent regimens (1,200 mg twice-weekly). Daily treatment or cases following therapy interruptions are infrequent. The TB Research Center in Chennai reported only one case in over 8,000 patients treated over 30 years.[4] Thrombocytopenia can arise with any of the primary antitubercular medications.

Prior to diagnosing thrombocytopenia, it's essential to exclude pseudothrombocytopenia, which may arise from factors such as inadequate anticoagulation in blood tubes, thrombocyte aggregation, or the use of abciximab. George et al. conducted a comprehensive collection of case reports concerning drug-induced thrombocytopenia, establishing standard criteria to elucidate the association between drugs and thrombocytopenia (Table 2).[5]

If the suspected drug fulfils all criteria, the level of evidence is considered definite. Meeting the first three criteria denotes a probable association, while fulfilling only the first criterion indicates a possible link. Failure to meet the first criterion suggests an unlikely causative relationship.

Epidemiological data on drug-induced immune thrombocytopenia (DITP) are limited, with an estimated incidence of about 10 cases per 1,000,000 people annually, likely an underestimate. DITP arises from two mechanisms: suppression of platelet production and platelet destruction. Destruction occurs via hapten-dependent antibodies, platelet-reactive autoantibodies, and drug-dependent antibodies (DDabs). Pool et al. found a strong link between rifampicin-dependent antibodies and adverse reactions, especially with a 1,200 mg twice-weekly regimen.[6] According to WHO-UMC Causality Categories, rifampicin is a "Probable/Likely" cause of this adverse drug reaction. Ferguson and the Hong Kong trial reported thrombocytopenia even with daily rifampicin, occurring from the first to the fourteenth month of therapy.[7,8] A literature search identified around 35 cases of rifampicin-induced thrombocytopenia, including 15 case reports. Larbaoui et al. noted a patient with generalized purpura after four months of therapy.[9] Doyle et al. found adverse effects, including fever, in 28 of 74 patients on high-dose rifampicin (1,800 mg) twice-weekly.[10] Bansal et al. reported thrombocytopenia following re-exposure to rifampicin a decade later, indicating long-lasting drug sensitivity.[11] Mehta et al. documented three cases of rifampicin-induced thrombocytopenia with antiplatelet antibodies showing increased binding in the presence of rifampicin, indicating it as the causative agent.[12] Despite its rarity, rifampicin-induced thrombocytopenia is potentially fatal. Banu Rekha VV et al. reported only one case among 8,000 patients treated over 30 years at the Tuberculosis Research Centre.[4]

Diagnosing drug-induced thrombocytopenia is primarily based on exclusion. Immune thrombocytopenia and secondary forms often occur with various immune disorders. Direct assays for platelet-bound antibodies have a sensitivity of 49–66%, specificity of 78–92%, and a positive predictive value of 80–83%. However, a negative result does not conclusively exclude the diagnosis. Diagnosing drug-induced immune thrombocytopenia involves clinical assessment of bruising, petechiae, and bleeding, along with reviewing the suspected drug. Essential tests include total blood count and peripheral blood smear to rule out pseudothrombocytopenia, and platelet serology tests. Thrombocytopenia can occur up to 14 months after starting treatment and is less frequent with daily regimens due to continuous drug presence of neutralizing antibodies. Intermittent therapy allows antibody accumulation during drug-free periods, intensifying reactions upon reinitiation, though daily regimens can still result in thrombocytopenia.

Corticosteroids have been employed in cases where thrombocytopenia arises from an immune-mediated mechanism, although their efficacy remains unproven. Platelet transfusion is warranted in instances of severe thrombocytopenia or wet purpura due to the heightened risk of intracranial hemorrhage. Plasmapheresis and intravenous immunoglobulin (IVIG) have been employed in the management of drug-induced thrombocytopenia. However, the efficacy of these interventions remains contentious. The immediate cessation of the offending drug is considered the paramount step in treatment.

After stopping the causative drug, platelet counts typically normalize within 7–10 days, often without needing further treatment. Platelet transfusion may be required if counts fall below 20,000/mm^3. Reintroducing rifampicin must be strictly avoided to prevent immune reactions, even in small doses, following purpura onset. Immediate cessation of rifampicin and avoiding re-administration are critical.

In our experience, these cases underscore a rare complication of daily rifampicin therapy, which exhibited a favorable response to discontinuation of the implicated drug alongside supportive measures, resulting in gradual amelioration of symptoms and

Table 2: Four diagnostic criteria established by George et al.[5]

Criterion	*Description*
1. Drug timing and recovery	The suspected drug preceded the onset of thrombocytopenia, and complete and sustained recovery occurred following drug withdrawal.
2. Drug exclusivity	The suspected drug was the sole medication used prior to thrombocytopenia onset, or other drugs were continued or reintroduced after discontinuation of the suspected drug, resulting in sustained normalization of platelet counts.
3. Exclusion of alternative causes	Alternative causes of thrombocytopenia were ruled out.
4. Re-exposure response	Re-exposure to the suspected drug led to recurrent thrombocytopenia.

normalization of blood cell counts. Patients are currently managed on alternative regimens comprising isoniazid, ethambutol, pyrazinamide, and levofloxacin, with diligent monitoring of complete blood counts (CBCs) to ensure therapeutic efficacy and safety.

Conclusion

Thrombocytopenia, although uncommon with rifampicin, can range from minor bleeding to severe complications such as gastrointestinal hemorrhage or acute subdural hematoma. It can occur even without prior rifampicin exposure. Regular monitoring for blood and liver abnormalities is essential during tuberculosis treatment. Immediate discontinuation of rifampicin upon suspicion is crucial. Patients should avoid using rifampicin again to prevent recurrence, as re-introduction poses risks in cases of rifampicin-induced thrombocytopenia.

References

1. World Health Organization. World Health Organization Global Tuberculosis Report 2020. [online] Available from: https://www.who.int/publications/i/item/9789240013131. [Last accessed October, 2024].
2. Aquinas M. Short-course therapy for tuberculosis. Drugs 1982;24(2):118–132. DOI: 10.2165/00003495-198224020-00002.
3. Blajchman MA, Lowry RC, Petil JE, et al. Rifampicin induced thrombocytopenia. Br Med J 1970;3(5713):24–26. DOI: 10.1136/bmj.3.5713.24.
4. BanuRekha VV, Adhilakshmi AR, Jawahar MS. Rifampicin-induced acute thrombocytopenia. Lung India 2005;22(4):122–124. Available from: http://eprints.nirt.res.in/id/eprint/683.
5. George JN, Raskob GE, Shah SR, et al. Drug induced thrombocytopenia a systematic review of published case reports. Ann Intern Med 1998;129(11):886–890. DOI: 10.7326/0003-4819-129-11_part_1-199812010-00009.
6. Pool G, Stradling P, Worlledge S. Potentially serious side effects of high dose twice weekly rifampicin. Br Med J 1971;3(5770):343–347. DOI: 10.1136/bmj.3.5770.343.
7. Ferguson GC. Rifampicin and thrombocytopenia. Br Med J 1971;3(5775):638. DOI: 10.1136/bmj.3.5775.638.
8. George JN, Raskob GE, Shah SR, et al. Drug induced thrombocytopenia a systematic review of published case reports. Ann Intern Med 1998;129(11):886–890. DOI: 10.7326/0003-4819-129-11_part_1-199812010-00009.
9. Larbaoui D, Chaulet P, Grosset J, et al. Intermittent treatment of "intractable chronic tuberculosis" by combined rifampicin-ethambutol: Preliminary results of a controlled survey made in Algeria. Rev Tuberc Pneumol (Paris) 1970;34(4):559–566. PMID: 4928583.
10. Doyle JA. In XX International Tuberculosis Conference, New York. New York: Excerpta Medica; 1969; p. 25.
11. Bansal R, Sharma PK, Sharma A. A case of thrombocytopenia caused by rifampicin and pyrazinamide. Indian J Pharmacol 2013;45(4):405–407. DOI: 10.4103/0253-7613.114998.
12. Mehta YS, Jijina FF, Badakere SS, et al. Rifampicin-induced immune thrombocytopenia. Tuber Lung Dis 1996;77(6):558–562. DOI: 10.1016/s0962-8479(96)90056-8.