IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 25, Issue 9 Ser. 2 (September. 2026), PP 05-10
www.iosrjournals.org

Early and Delayed Onset Rifampicin-Induced Thrombocytopenia During Daily Antituberculosis Therapy: A Report of Two Cases

Serghini N, Kasmi F, Kilali R, Reguig N, Aharmim M, Bourkadi JE
Department of Pulmonology and Phthisiology, Moulay Youssef Hospital, Salé, Morocco
Corresponding author: Serghini N., Department of Pulmonology and Phthisiology, Moulay Youssef Hospital, Salé, Morocco.

Abstract
Background: *Thrombocytopenia is a rare but potentially life-threatening adverse reaction to rifampicin, a cornerstone of first-line antituberculosis therapy. It is attributed to drug-dependent antibodies that bind platelet membrane glycoproteins in the presence of the drug and cause accelerated platelet destruction. It has classically been described with intermittent or interrupted regimens, and is less well characterised during continuous daily therapy.*
Case presentation: *We report two men treated with a daily fixed-dose combination of isoniazid, rifampicin, ethambutol and pyrazinamide for bacteriologically confirmed pulmonary tuberculosis, who developed severe thrombocytopenia with bleeding at very different points in their treatment. The first, aged 49 years, presented on day 3 with epistaxis, generalised purpura and buccal petechiae, with a platelet count of 23,000/mm³. The second, aged 47 years, presented on day 140 of uninterrupted daily treatment with mild haemoptysis and epistaxis, with a platelet count of 2,000/mm³. Antituberculosis therapy was stopped immediately in both patients and platelets were transfused. The first recovered within 48 hours; the second required 13 units of platelets and corticosteroids at 1 mg/kg for two weeks, with recovery over 20 days. Causality was assessed as probable using the WHO–UMC criteria in both cases. Neither patient had recurrent thrombocytopenia on rifampicin-free regimens.*
Conclusion: *These cases show that rifampicin-induced thrombocytopenia can arise within days of the first dose or after months of uneventful daily therapy, and that daily administration does not eliminate the risk. Any unexplained thrombocytopenia or new bleeding during rifampicin therapy should prompt an immediate platelet count, withdrawal of the drug, and permanent avoidance of re-exposure.*
Keywords: *Rifampicin; Drug-induced thrombocytopenia; Tuberculosis; Purpura; Case report*

Date of Submission: 04-09-2026 Date of Acceptance: 14-09-2026

I. Introduction

Drug-induced immune thrombocytopenia is a well-recognised entity in which drug-dependent antibodies bind platelet surface antigens in the presence of the offending drug and accelerate platelet clearance [1,2]. More than a hundred drugs have been implicated, and the diagnosis rests largely on clinical criteria because confirmatory antibody testing is unavailable in most laboratories [3].

Rifampicin has been implicated since 1970 [4]. Its haematological toxicity was subsequently characterised in patients receiving high-dose intermittent regimens, in whom purpura and thrombocytopenia occurred with a frequency clearly related to dose interval [5,6]. The mechanism involves rifampicin-dependent antibodies, usually of the IgG or IgM class, which bind platelet membrane glycoproteins — principally the glycoprotein Ib/IX complex — only in the presence of the drug [7–10]. Because sensitisation persists, re-exposure may provoke a faster and more severe reaction than the index episode.

With the near-universal adoption of daily fixed-dose combination therapy, this complication has become uncommon, and severe thrombocytopenia arising during continuous daily treatment is less well characterised, although several recent series have described it [11–14]. We report two patients treated with a daily fixed-dose combination who developed severe thrombocytopenia with bleeding at markedly different times — on day 3 and on day 140 of treatment — and discuss the implications for surveillance during rifampicin-containing therapy.

II. Case Presentation

Case 1

A 49-year-old man with no known drug allergy and no known previous exposure to rifampicin was diagnosed with pulmonary tuberculosis, confirmed on sputum by the Xpert MTB/RIF assay. Rifampicin resistance was not detected. HIV serology was negative.

Daily first-line therapy was started with a fixed-dose combination containing rifampicin 150 mg, isoniazid 75 mg, ethambutol 275 mg and pyrazinamide 400 mg per tablet, given as five tablets daily for a body weight of 70 kg in accordance with the weight bands of the current Moroccan national tuberculosis programme guidelines [17]. This corresponded to a rifampicin dose of 750 mg daily, or approximately 10.7 mg/kg per day.

On day 3, the patient developed epistaxis, generalised purpura and petechiae of the buccal mucosa, with no fever, no systemic symptoms and no organomegaly. Investigations showed isolated severe thrombocytopenia with a platelet count of 23,000/mm³ (23×10^9/L), a haemoglobin level of 15 g/dL and a prothrombin index of 85%. No pre-treatment platelet count was available.

A chest radiograph obtained at the time of the bleeding episode showed an opacity of the upper third of the left hemithorax, consistent with the known pulmonary tuberculosis, with no radiographic evidence of alveolar haemorrhage (Figure 1A).

All antituberculosis drugs were stopped immediately and platelets were transfused. Clinical and haematological improvement was rapid, with normalisation of the platelet count within 48 hours and no further bleeding.

Rifampicin was considered the most likely offending drug and was permanently withdrawn. A rifampicin-free regimen combining isoniazid, ethambutol, pyrazinamide and levofloxacin was then introduced. The reintroduction of the three companion drugs was not followed by any fall in the platelet count, which supported rifampicin as the causative agent. Using the WHO–UMC criteria, the adverse reaction was classified as probable. The subsequent course was favourable, with no recurrence of thrombocytopenia.

Case 2

A 47-year-old man with a 30 pack-year smoking history, occasional alcohol use and cannabis use stopped three months before presentation, and no other relevant medical history, was diagnosed with pulmonary tuberculosis confirmed on sputum by the Xpert MTB/RIF assay. Rifampicin resistance was not detected. HIV serology was negative.

He received the same daily fixed-dose combination, given as three tablets daily for a body weight of 47 kg in accordance with the national weight bands [17], corresponding to a rifampicin dose of 450 mg daily or approximately 9.6 mg/kg per day. Treatment was supervised and taken regularly, with no documented interruption. Sputum smear microscopy nevertheless remained positive at four months of treatment.

On day 140, the patient presented with mild haemoptysis and epistaxis. Auscultation revealed rhonchi over the left hemithorax. Laboratory testing showed severe thrombocytopenia with a platelet count of 2,000/mm³ (2×10^9/L) and a haemoglobin level of 11 g/dL. Ethylenediaminetetraacetic acid (EDTA)-induced pseudothrombocytopenia was excluded on peripheral blood smear. No pre-treatment platelet count was available.

A chest radiograph on admission showed bilateral lesions predominating on the left with cavitary lucencies, and no radiographic evidence of alveolar haemorrhage (Figure 1B).

All antituberculosis drugs were stopped immediately. Given the depth of the thrombocytopenia and the active bleeding, the patient received 13 units of platelets and corticosteroid therapy at 1 mg/kg per day for two weeks. The platelet count recovered progressively over 20 days. Causality was assessed as probable using the WHO–UMC criteria and rifampicin was permanently withdrawn.

Two problems therefore had to be addressed simultaneously. Rifampicin had to be permanently withdrawn because of the adverse reaction, and sputum smears had remained positive at four months despite documented adherence to a correctly dosed regimen. Rifampicin resistance had not been detected on the initial molecular test, but the Xpert MTB/RIF assay interrogates only the rpoB gene and therefore gives no information on susceptibility to isoniazid, pyrazinamide or ethambutol; sputum culture and phenotypic drug susceptibility testing were not performed, so resistance to the companion drugs could be neither confirmed nor excluded. After haematological recovery, an individualised regimen combining amikacin, ethambutol, levofloxacin and linezolid was therefore started empirically, on the hypothesis of undetected resistance to one or more first-line drugs. Ethambutol was thus given again, without recurrence of thrombocytopenia. The subsequent course was favourable, with clinical improvement and a platelet count that remained normal. Both patients were still receiving antituberculosis treatment at the time of writing, with sustained normal platelet counts and no recurrence of thrombocytopenia.

Table 1. Comparative summary of the two cases

Feature	Case 1	Case 2
Age / sex	49 years / male	47 years / male
Relevant history	No known drug allergy; no known previous rifampicin exposure	30 pack-year smoking; occasional alcohol; cannabis stopped 3 months earlier
HIV serology	Negative	Negative
Diagnosis	Pulmonary TB; Xpert MTB/RIF positive on sputum, rifampicin resistance not detected	Pulmonary TB; Xpert MTB/RIF positive on sputum, rifampicin resistance not detected
Body weight / FDC dose	70 kg / 5 tablets daily (rifampicin 750 mg, ≈ 10.7 mg/kg/day)	47 kg / 3 tablets daily (rifampicin 450 mg, ≈ 9.6 mg/kg/day)
Time to onset	Day 3 of treatment	Day 140 of daily uninterrupted treatment
Sputum status at event	Not applicable	Smear positive at 4 months
Bleeding manifestations	Epistaxis, generalised purpura, buccal petechiae	Mild haemoptysis, epistaxis
Platelet count at onset	23,000/mm³ (23 × 10⁹/L)	2,000/mm³ (2 × 10⁹/L)
Haemoglobin	15 g/dL	11 g/dL
WHO–UMC causality	Probable	Probable
Immediate management	All antituberculosis drugs stopped; platelet transfusion	All antituberculosis drugs stopped; 13 units of platelets; prednisone 1 mg/kg for 2 weeks
Time to platelet recovery	48 hours	20 days
Subsequent regimen	Isoniazid + ethambutol + pyrazinamide + levofloxacin	Amikacin + ethambutol + levofloxacin + linezolid, chosen empirically for persistent smear positivity
Rifampicin re-exposure	Permanently avoided	Permanently avoided
Outcome	Favourable; no recurrence	Favourable; no recurrence

FDC: fixed-dose combination; TB: tuberculosis; WHO–UMC: World Health Organization–Uppsala Monitoring Centre.

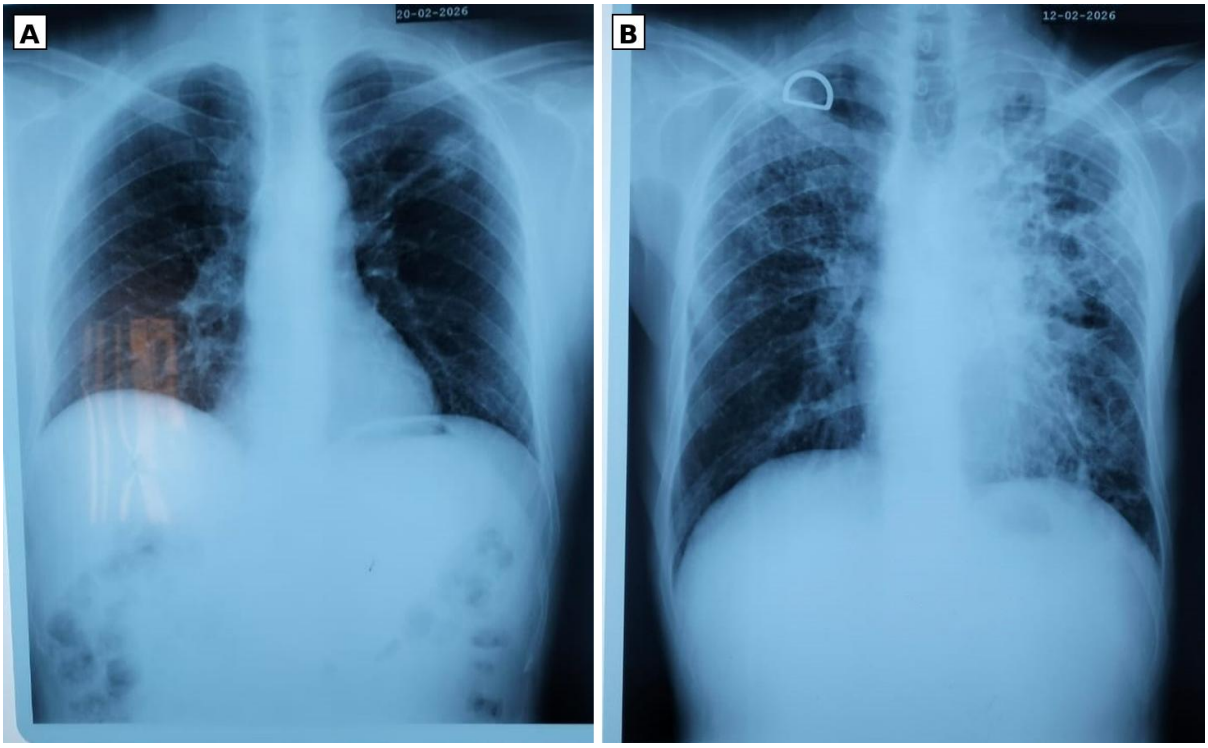

Figure 1. (A) Case 1: chest radiograph at the time of the day-3 bleeding episode, showing an opacity of the upper third of the left hemithorax and no radiographic evidence of alveolar haemorrhage. (B) Case 2: chest radiograph on admission with haemoptysis and epistaxis on day 140 of treatment, showing bilateral lesions predominating on the left with cavitary lucencies and no radiographic evidence of alveolar haemorrhage.

III. Discussion

Rifampicin-induced thrombocytopenia is uncommon but potentially serious. It was first reported in 1970 [4] and was characterised soon afterwards in patients receiving high-dose intermittent regimens, in whom purpura was clearly related to the dose interval and the dose size [5,6]. Its true incidence is unknown and is probably underestimated, both because reporting is not systematic and because confirmatory antibody testing is unavailable in routine practice. Reports nonetheless continue to appear in contemporary treatment settings [11–14].

The mechanism is immunological. Rifampicin-dependent antibodies, typically IgG or IgM, bind platelet membrane antigens only in the presence of the drug and cause accelerated clearance [1,2,7,8]. The glycoprotein Ib/IX complex has been identified as the principal target, and rifampicin-dependent antibodies appear to bind an epitope on glycoprotein IX similar to that recognised by quinine-dependent antibodies [9,10]. Rifampicin does not bind platelets directly; the drug–antibody complex is thought to attach to the platelet surface, so that platelet destruction stops rapidly once the drug is cleared. In our two patients, rifampicin-dependent platelet antibodies could not be sought because the assay was not available.

Immune sensitisation has classically been linked to intermittent administration or to interruption and resumption of treatment [5,8], and daily continuous therapy is generally regarded as carrying a lower risk. Both of our patients were nevertheless on a strictly daily fixed-dose combination, as were the patients in several recent series [12–14]. Daily administration therefore reduces, but does not abolish, the risk.

The timing in our two patients was strikingly different. The onset on day 3 in Case 1 is early for a first exposure, since primary sensitisation usually requires several days to a week; Nakane et al. reported severe thrombocytopenia on day 7 in a patient without previous exposure [12]. Two explanations are possible. Either sensitisation occurred unusually rapidly, or the patient had an unrecognised previous exposure to rifampicin — a plausible scenario given its use outside tuberculosis, and one described by Chandramouli, whose patients had been treated years earlier [13]. Both remain speculative in the absence of antibody testing, and the early onset should be interpreted with that caution.

The onset on day 140 in Case 2, after more than four months of uninterrupted daily therapy, is equally instructive. There was no documented interruption that could have favoured sensitisation, and the reaction was profound, with a platelet count of 2,000/mm³. The practical message is that a long period of good tolerance does not exclude the diagnosis, and that this reaction should be considered at any point during rifampicin-containing treatment.

The diagnosis of drug-induced thrombocytopenia remains clinical. The criteria proposed by George et al. require that the thrombocytopenia occurs during exposure to the drug, that other causes are excluded, that it resolves after withdrawal, and, ideally, that it recurs on re-exposure [3]. The first three were satisfied in both of our patients; re-exposure was neither performed nor justifiable. Attribution to rifampicin specifically is limited by the fact that all four drugs were withdrawn together, so that dechallenge does not by itself identify the culprit. It is supported, however, by the subsequent course: in Case 1 isoniazid, ethambutol and pyrazinamide were all reintroduced without recurrence, which amounts to a rechallenge of the three companion drugs, and in Case 2 ethambutol was given again without recurrence. Taken with the prior probability derived from the published literature, rifampicin remains by far the most likely cause in both patients.

Alternative causes of severe thrombocytopenia in a patient receiving antituberculosis treatment should nonetheless be considered systematically: HIV-associated thrombocytopenia, tuberculosis itself, disseminated intravascular coagulation, thrombotic microangiopathy, hypersplenism, primary bone marrow disorders, immune thrombocytopenic purpura, and thrombocytopenia caused by other drugs — including isoniazid, ethambutol and pyrazinamide, each of which has been implicated. Pseudothrombocytopenia due to EDTA-induced platelet clumping was excluded on blood smear in Case 2. In both patients the thrombocytopenia was isolated, with no fever, sepsis, organomegaly or anaemia sufficient to suggest a consumptive or microangiopathic process, and it resolved after drug withdrawal; disseminated intravascular coagulation and thrombotic microangiopathy were therefore considered unlikely on clinical grounds, although they were not formally excluded by coagulation testing or by measurement of schistocytes. The absence of a pre-treatment platelet count in both patients is a further limitation, since it prevents formal confirmation that the count was normal before exposure.

Management rests on immediate withdrawal of the drug. Platelet transfusion is indicated when thrombocytopenia is severe or bleeding is active, as in both of our patients. The value of corticosteroids is debated, since recovery after withdrawal is usually spontaneous and rapid; they are often given when the distinction from immune thrombocytopenic purpura is not immediately clear, as in Case 2. The two courses observed here illustrate the range: the platelet count normalised within 48 hours in Case 1, whereas recovery took 20 days in Case 2 despite platelet transfusion and corticosteroids. The reason for this difference cannot be established from the available data; it may reflect the depth of the thrombocytopenia, differences in antibody titre or kinetics, or individual variability. In the absence of antibody testing, no firm conclusion can be drawn.

Rifampicin was permanently withdrawn in both patients and neither had a recurrence on a rifampicin-free regimen. Re-exposure after a probable episode should generally be avoided, because the recurrence may be

more rapid and more severe than the index reaction [15]; cautious reintroduction has occasionally been reported [16], but it cannot be recommended after severe bleeding of the kind described here. The loss of rifampicin is a genuine therapeutic problem, since it substantially prolongs treatment and reduces its sterilising activity.

The regimen in Case 2 was modified for two converging reasons, and the distinction matters. Rifampicin had to be abandoned because of the adverse reaction, which by itself dictated a rifampicin-free regimen. Independently, sputum smears remained positive at four months despite documented adherence and correct dosing. Persistent bacteriological positivity at that stage raises the question of drug resistance, and it should be remembered that a negative Xpert MTB/RIF result excludes only rifampicin resistance: mutations conferring resistance to isoniazid, pyrazinamide or ethambutol are not detected by this assay, and smear microscopy cannot distinguish viable from non-viable bacilli. In the absence of culture and phenotypic drug susceptibility testing, the choice of an individualised second-line regimen was empirical, guided by the hypothesis of undetected resistance in a patient who had already lost the most active sterilising drug in the regimen. Where culture and susceptibility testing are available, they should be obtained before such a decision, and this case illustrates the practical difficulty of managing a patient who loses rifampicin to an adverse reaction while the bacteriological response is also unsatisfactory.

This report has several limitations. It concerns only two patients. Rifampicin-dependent platelet antibody testing, the reference method for confirming the diagnosis, was not available in our setting — a constraint common to many high-burden, resource-limited settings and one that probably contributes to the under-recognition of this reaction. Pre-treatment platelet counts were not available, and the retrospective nature of the data meant that a full coagulation profile could not be documented. All four drugs were withdrawn simultaneously, so that dechallenge alone does not identify the culprit. Finally, in Case 2, culture and phenotypic drug susceptibility testing were not performed, so the hypothesis of undetected resistance to a companion drug could not be verified.

IV. Key Clinical Messages

- Rifampicin-induced thrombocytopenia may occur within days of the first dose or after several months of uninterrupted daily therapy; a long period of good tolerance does not exclude it.
- Any new bleeding or unexplained thrombocytopenia in a patient taking rifampicin warrants an immediate platelet count and examination of the blood smear.
- Immediate withdrawal of rifampicin is the cornerstone of management; platelet transfusion is indicated for severe thrombocytopenia or active bleeding, whereas the role of corticosteroids is not established.
- Recovery is usually rapid after withdrawal but may take several weeks in severe cases.
- Rifampicin should not be reintroduced after a probable episode, because recurrence may be more rapid and more severe.
- The other drugs may be continued or reintroduced once alternative causes have been considered, and their uneventful reintroduction supports the attribution to rifampicin.

V. Conclusion

Rifampicin-induced thrombocytopenia is a rare but potentially life-threatening complication of antituberculosis therapy that may arise at very different stages of treatment, including after prolonged and previously uneventful daily exposure. The two patients reported here developed severe thrombocytopenia on day 3 and on day 140 of a daily fixed-dose combination regimen, with platelet counts of 23,000/mm³ and 2,000/mm³ and recovery times of 48 hours and 20 days respectively. Clinicians should therefore maintain a high index of suspicion throughout rifampicin-containing treatment. Early recognition, immediate withdrawal of the drug, appropriate management of bleeding and permanent avoidance of re-exposure are the determinants of a favourable outcome. Further work is needed to clarify the mechanisms of this reaction during daily therapy and to identify the patients at risk.

VI. Declarations

Consent for publication

Consent for treatment and for the publication of this case report and the accompanying clinical images was obtained from both patients. A written copy of the consent is available for review by the Editor-in-Chief on request.

Ethical approval

This report describes the routine clinical care of individual patients and, in accordance with institutional policy, did not require separate approval from a formal ethics committee. The care described was provided in accordance with the ethical principles of the Declaration of Helsinki.

Authors' contributions

Concept and design: Serghini N, Reguig N. Acquisition, analysis or interpretation of data: Serghini N, Kasmi F, Kilali R, Reguig N. Drafting of the manuscript: Serghini N. Critical review of the manuscript for important

intellectual content: Reguig N, Bourkadi JE. All authors have reviewed the final version to be published and agree to be accountable for all aspects of the work.

Conflict of interest

The authors declare that they have no conflict of interest.

Funding

No funding was received for this work.

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