Rifampicin-Induced Thrombocytopenia: A Case Report

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ABSTRACT

INTRODUCTION: The worldwide prevalence of adverse drug reactions (ADR) to anti-TB medication ranges from 8% to 85%. Major adverse reactions include hepatic, renal, and hematologic disorders of which, Rifampicin-induced thrombocytopenia is one of these rare complications.

CASE: A 58-year-old Filipino male developed respiratory and gastrointestinal bleeding with a severe drop in platelet count after several days of anti-tuberculosis (anti-TB) medications. The patient had oral mucosal petechiae, blood-streaked sputum, and epistaxis. The symptoms progressed to the formation of small adherent clots beneath the tongue, gum bleeding, melena, massive epistaxis, and hemoptysis with continued intake of the anti-TB drugs. The patient had anemia, normal WBC and differential count, and thrombocytopenia of 3 x 10^3/uL, a drop from 235 x 10^3/uL five days prior. The bleeding resolved with the discontinuation of the drugs. A slow graded oral challenge to each of the drugs was done to identify the culprit medication. There was a recurrence of bleeding and a decrease in the platelet count after administration of rifampicin. The anti-TB medications were modified not to include rifampicin. The patient was discharged with no signs of bleeding and a normal complete blood count.

CONCLUSION: TB is a prevalent disease in our country, and its medications can cause adverse drug reactions. Rifampicin-induced thrombocytopenia is a rare and life-threatening condition that physicians must be aware of and able to recognize promptly and treat properly to prevent recurrence of similar cases in the future. The patient should be forewarned not to take rifampicin and any fixed-dose combination drugs containing rifampicin.

Keywords: *Rifampicin, Thrombocytopenia, Platelet, Tuberculosis*

INTRODUCTION

Tuberculosis is a major health problem and the sixth leading cause of death and illness in the Philippines.[21] Filipinos are given the first line anti-tuberculosis (TB) medications. However, there are adverse drug reactions (ADR) associated with these multidrug regimens that may cause a delay in treatment, drug resistance, and treatment failure, as well as increases in morbidity and mortality rates.

The worldwide prevalence of ADR to anti-TB drugs ranges from 8% to 85% in various studies.[23] Major adverse reactions include hepatic, renal, and hematologic disorders[25]. Hematologic reactions to first-line anti-TB treatment occur in only 0.1-0.7%.[23]

Rifampicin-induced thrombocytopenia is one of the rare complications of anti-TB medications. Its clinical manifestations can be benign to life-threatening, presenting as petechiae, bruising, and epistaxis to gastrointestinal or genitourinary mucosal bleeding, or even intracranial hemorrhage resulting in death. Only a few cases have been reported worldwide, and none published locally.[1-20, 25]

The early recognition of the ADR, identification of the offending drug, and appropriate management of both the illness and the ADR may be challenging to many physicians. Likewise, the search for alternative medications can become a burden to both physicians and patients, given the burden of TB in our country and the widespread use of rifampicin as one of the components of fixed-drug combination therapy.

CASE REPORT

A 58-year-old male, Filipino, came into our institution due to respiratory and gastrointestinal mucosal bleeding.

Two months prior to admission, the patient experienced a productive cough with purulent sputum associated with night sweats and weight loss of approximately 20%. He self-medicated with herbal concoctions made with turmeric and lemongrass and cotrimoxazole 800/160 mg/tab, one tab OD for seven days without relief of symptoms.

Fifteen days prior to admission, he sought consultation with a private physician and was diagnosed bacteriologically with pulmonary tuberculosis. He was referred to the Tuberculosis-Directly Observed Treatment, Short Course (TB-DOTS) Center for anti-TB medications treatment.

Twelve days before admission, the patient was started on fixed-dose combination HRZE tablets (isoniazid 75mg, rifampicin 150mg, pyrazinamide 400mg, ethambutol 275mg) 4 tablets once a day with good compliance. There were no adverse reactions noted until seven days before admission when he started to have body malaise associated with the appearance of oral mucosal petechiae, blood-streaked sputum and repeated epistaxis. A day later, a consultation was done, and a complete blood count (CBC) showed anemia of 106, normal WBC and differential counts, and normal platelet count of 235 x 10^3/uL (*Table I*). He was discharged after 12 hours with tranexamic acid and butamirate citrate tablets with no recurrence of bleeding. The HRZE tablets were continued.

Four days prior to admission, the patient noted small adherent clots beneath the tongue and gum bleeding. He also had a passage of tarry stools. This was followed

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Table I. Results of Diagnostic Tests

Laboratory Parameter	Result
Occult Blood	Positive
Dengue NS1, IgM, IgG	Negative
HBsAg	Non-Reactive
HIV Rapid	Non-Reactive
Reticulocyte	4.2% (Elevated)
Albumin (g/L)	32.2 (Decreased)
Total Bilirubin (umiol/L)	17.8 (Normal)
Direct Bilirubin (umol/L)	6.4 (Normal)
LDH (U/L)	934.1 (Elevated)
SGPT (U/L)	83.17 (Normal)
SGOT (U/L)	47.8 (Normal)
BUN (mmol/L)	7.02 (Normal)
Creatinine (umol/L)	85.7 (Normal)
PT INR	1.17 (Normal)
APTT	37.2 (Normal)
APTT Control	28.1 (Normal)

Urinalysis	
Appearance	Clear
Color	Dark Yellow
Protein	Negative
pH	5.5
SG	1.016
Glucose	Negative
Microalbumin	1+
Urine bilirubin	Negative
Red cells	56
Pus cells	5
Epithelial cells	2
Bacteria	1

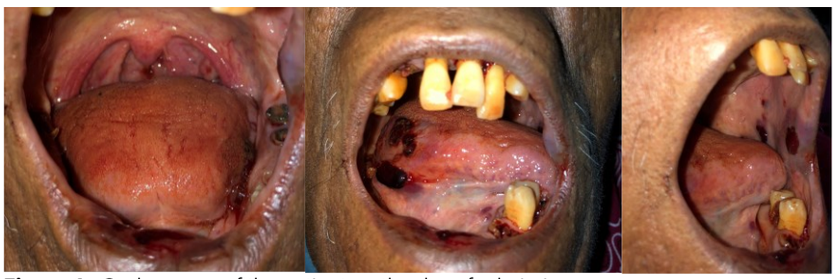

Figure 1. Oral mucosa of the patient on the day of admission

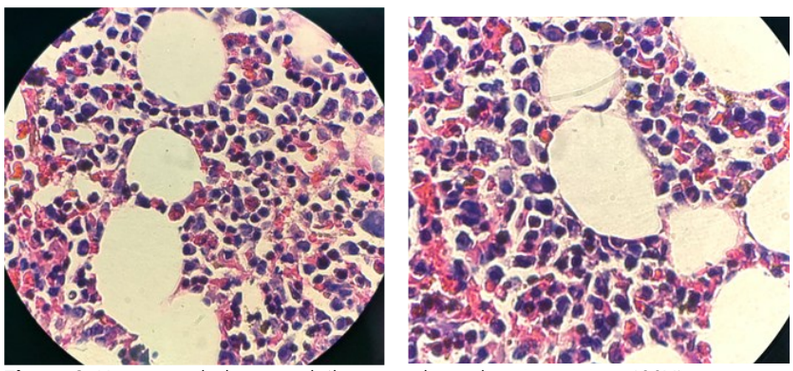

Figure 2. Hematopathology result (hematoxylin and eosin staining, 400X). Sections showed increased bone marrow cellularity (80%), megakaryocytes, and marrow fat. There were no atypical cells present.

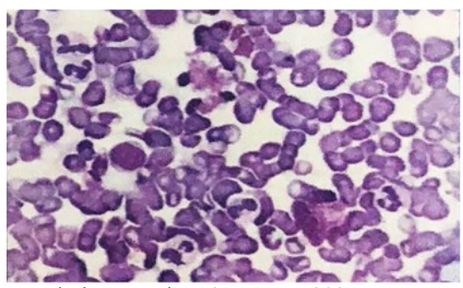

Figure 3. Hematopathology result (H & E stain, 1000x). Bone marrow smears showed normal cellularity and hematopoietic cells in different stages of maturation. No atypical cells were present.

by episodes of epistaxis approximately 100cc and hemoptysis of approximately 200cc in 24 hours which prompted him to seek admission.

The patient had no previous history of anemia, thrombocytopenia, easy bruising, rash, jaundice, abdominal pain, headache, hoarseness of voice, dyspnea, chest pain, palpitations, edema, dysuria, gross hematuria, and vomiting.

The past medical history was unremarkable. There was no previous history of tuberculosis. He had no history of food and drug allergies. He was a previous 35-pack years smoker and a previous alcoholic beverage drinker. There was no family history of malignancy and blood dyscrasia.

The patient was examined in the emergency room, awake, wheelchair-bound, oriented to the three spheres, and with stable vital signs at the emergency room. He was well-groomed but with a note of bloodstains on his shirt and hand towel. The patient had a body mass index of 23.11 kg/m^2.

On physical examination, there were no ecchymosis, hematomas, and petechiae on the skin. The patient, however, had pale palpebral conjunctiva. The oral mucosa showed petechiae and gum bleeding with adherent blood clots on the tongue (*Figure 1*). There were no cervical lymphadenopathies. Fine crackles were heard on the left basal lung field. The abdomen was flat, soft, and non-tender with no organomegaly. Direct rectal exam revealed smooth rectal mucosa but with tarry stool on the examining finger.

The CBC showed anemia of 109 g/L, normal WBC of 4.27 x 10^9/ul, and thrombocytopenia of 3 x 10^3/uL. This showed a dramatic decline from 235 x 10^3/uL taken five days prior. Anti-TB medications (HRZE) were temporarily withheld while the cause of thrombocytopenia was being investigated.

The melena approximately 100ml per day, gum bleeding, and oral mucosal petechiae persisted, leading to progressive anemia of 80 g/L. A total of thirteen units of platelet concentrate and two units of packed RBC were transfused, which raised the platelet count to 39 x 10^3/uL and raised the hemoglobin to 87 g/L (*Figure 7*).

Further investigations showed positive fecal occult blood tests and microscopic hematuria. The liver and renal function tests were normal. Dengue viral markers, HIV, Hepatitis B, and Coomb's test for hemolysis were also negative (*Table I*). The ultrasound of the whole abdomen revealed hepatosplenic calcifications, which may result from granulomatous infectious disease.

Peripheral blood smear showed normochromic normocytic anemia with severe thrombocytopenia and absence of platelet clumping (pseudo-thrombocytopenia). Bone marrow aspiration and biopsy results revealed myeloid hyperplasia and hypercellular marrow, respectively (*Figures 2 and 3*). Bone marrow differential count disclosed an erythrocytic and

granulocytic series in all stages of development with an orderly maturation pattern and normal morphologic appearance. Megakaryocytes were seen 0-1/LPF with adequate platelet formation. These findings were consistent with thrombocytopenia due to increased peripheral platelet destruction. However, a confirmatory test for the specific drug causing thrombocytopenia is not available in our institution.

The patient was referred to the Allergy and immunology service. The HRZE medications were withheld temporarily with control of bleeding after four days of discontinuation. At this point, drug-induced thrombocytopenia was considered due to the temporal association between the decreasing platelet count and the drug exposure. The patient's presentation was "certainly" and "definitely" associated with rifampicin using the WHO-UMC Causality Categories and Naranjo ADR probability scale, respectively (*Tables I and II*).[32]

After temporarily withholding the HRZE medications, there was a cessation of bleeding after four days. A slow graded oral challenge to each HRZE was planned due to the lack of equally potent alternative first-line anti-TB drugs. A graded challenge's objective is to verify that the patient will not experience an immediate adverse reaction to a given drug. It involves fewer doses, shorter duration, and does not induce drug tolerance. Since there may be a risk of recurrence of thrombocytopenia, full informed consent was obtained and performed under close observation and a controlled environment.

Each drug was reintroduced starting with ¼ of the total dose and gradually increased at regular intervals until the full dose was reached. The latest platelet count before the challenge was 406 x10^3/uL. (Please see *Figure 7* for the schedule of medication titration.)

However, when rifampicin (450mg once a day) was reintroduced, oral mucosal petechiae, gum bleeding, and petechiae on bilateral inner thighs reappeared after 10 hours of intake (*Figure 4*). Repeat CBC revealed a drop of platelet count from 271 to 32 x 10^3/uL a day after.

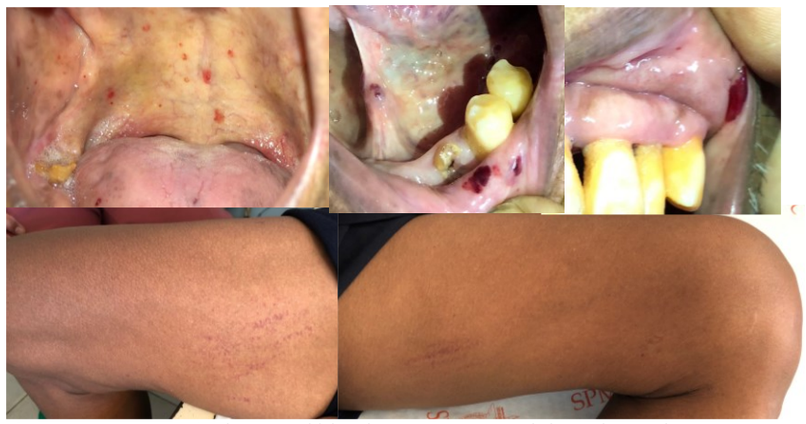

Figure 4. Top row: Oral mucosal bleeding Bottom row: bilateral petechiae inner thighs (black arrows) a day after one dose of rifampicin.

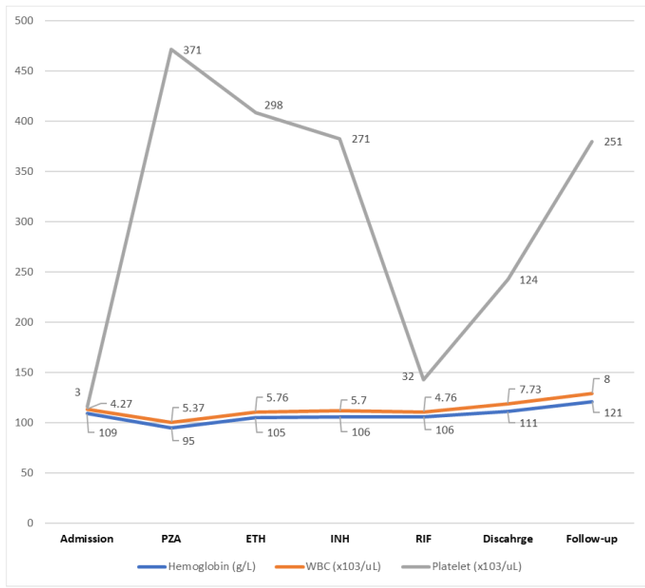

Figure 5. Complete blood count (hemoglobin, white blood cell count and platelet count) during the course of admission

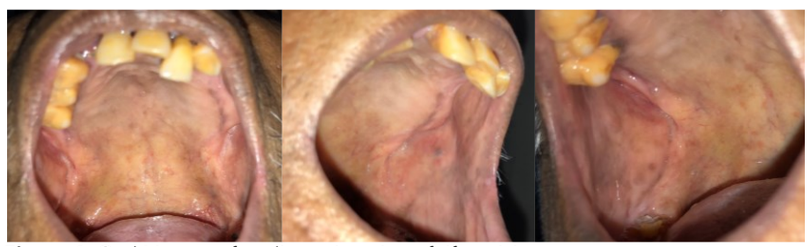

Figure 6. Oral Mucosa after discontinuation of rifampicin.

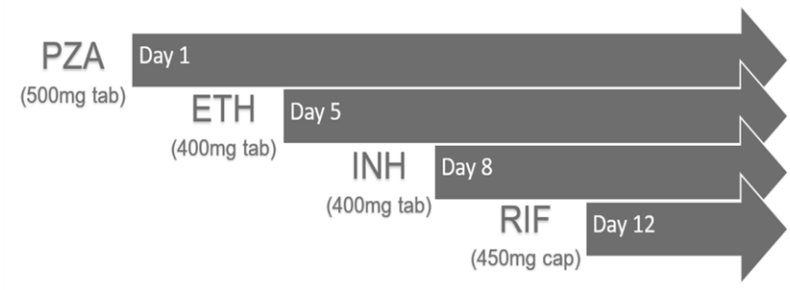

Figure 7. Slow-graded Oral Challenge to anti-TB medications schedule

Rifampicin tablet was immediately stopped while the other anti-Koch's medications were continued. He was also given a short course of oral prednisone at 20mg BID for five days. Platelet concentrate was requested in case of persistence and progression of bleeding. The platelet counts gradually rose from 32 to 124 x 10^3/uL after the last prednisone dose was taken (*Figure 5*). There was a resolution of bleeding in all locations (*Figure 6*).

The pulmonology service advised the following anti TB regimen: pyrazinamide 500mg/tablet, 3 tablets OD, ethambutol 400mg/tablet, 2 tablets OD, isoniazid 400mg/tablet, 1 tablet OD for 2 months for the intensive phase and ethambutol 400mg/tablet, 2 tablets OD, isoniazid 400mg/tablet, 1 tablet OD for 10 months during the maintenance phase.

The patient was discharged with no signs of bleeding and with normal CBC and platelet count. He was advised not to take rifampicin or any fixed-dose combination medications containing this drug. Aside from bleeding, the patient was also educated on the other major adverse effects to watch out for on the remaining drugs. He was seen on follow-up after one week with normal CBC results and no signs of bleeding (*Figure 5*).

DISCUSSION

The case presented a Filipino male with pulmonary tuberculosis who developed respiratory and gastrointestinal bleeding with a severe drop in platelet count after several days of fixed-dose anti-TB medications. A graded oral challenge to each of the drugs identified rifampicin as the culprit medication.

One of the many challenges clinicians face is identifying and managing the adverse reactions (ADR) of appropriately administered medications. ADRs account for about 2-6% of hospital admissions.[27] This has led to delayed treatment, prolonged hospital stays, and decreased quality of life.

Adverse drug reaction is classified into Type A and Type B.[27,28] Type A reactions occur in about 80% of adverse reactions. They are predictable and related to the toxicity of the drug. These reactions are easily reversed by reduction or withdrawal of the drug. Type B reactions, which include hypersensitivity reactions, are less common and affect only predisposed individuals. Most ADRs due to anti-TB medications belong to type B reactions. They are further classified into immune-mediated and non-immune mediated reactions.[27] Immune-mediated reactions include the four types of hypersensitivity reactions.

Rifampicin plays an essential role in the treatment of tuberculosis. The addition of rifampicin to previous regimens has markedly shortened the course of TB treatment. Adverse reactions to rifampicin include flu-like syndrome, gastrointestinal upset, and occasional hepatotoxicity.[29] Rarely, life-threatening adverse reactions can also occur, as in our patient who presented with mucosal bleeding and severe thrombocytopenia.

There is limited data on rifampicin-induced thrombocytopenia. A thorough and extensive literature search resulted in only 26 cases in 20 published papers worldwide.[1-20] Most of these cases used rifampicin for the treatment of pulmonary tuberculosis. Other reported cases used rifampicin as a treatment for TB meningitis, leprosy, TB lymphadenitis, and brucellosis. Like the reported cases, confirmation of drug-induced thrombocytopenia may not be available at the time of presentation, but after stabilizing and rechallenge the drugs, antiplatelet IgG and IgM antibodies appeared after giving rifampicin. In our patient's case, laboratory confirmation is not available in the institution.

In general, drug-induced thrombocytopenia presents with petechiae, bruising, and epistaxis[30]. Wet purpura is blood blisters at the oral mucosa that denotes an increased risk for life-threatening hemorrhage.[31] Platelet count can range from 40 x 10^3/uL to as low as 2 x 10^3/uL. Severe thrombocytopenia can present with gastrointestinal or genitourinary mucosal bleeding or even intracranial hemorrhage resulting in death.[30] The purpura and gastrointestinal bleeding were found in our patient days after taking HRZE medications.

Rifampicin-induced thrombocytopenia is a type II hypersensitivity reaction. This involves IgG- or IgM-mediated cytotoxicity directed to the membranes of erythrocytes, leukocytes, and in this case, the platelets. Destruction of these cells can occur through complement-mediated cell lysis, antibody-dependent cell-mediated cytotoxicity, or opsonization.[27] Investigations have been done to establish the specific antigen to which rifampicin-specific antiplatelet antibodies react.[6,12,19]

Confirmatory laboratory tests for rifampicin-induced thrombocytopenia are available but can be expensive and time-consuming. Immunofluorescence by flow cytometry is a sensitive method for detecting drug-specific platelet antibodies. One study detected positive fluorescence when the patient's serum was premixed with rifampicin while absent in the control serum.[6,12,16] Another study also demonstrated high titers of anti-rifampicin antibodies through passive hemagglutinin assay compared to the control group.[14]

Drug-induced thrombocytopenia remains a diagnosis of exclusion. Awareness and a high index of suspicion are necessary for its early detection. In the absence of confirmatory laboratories, it can be supported and confirmed by a recurrence of thrombocytopenia after reintroduction and resolution of bleeding and correction of thrombocytopenia after discontinuation of the suspected drug. Standardized assessments to recognize ADR have been developed to objectively assess and establish the relationship between the drug and the adverse event. The WHO-UMC Causality Categories and Naranjo ADR probability scale used in the case presented are the most widely accepted methods that help evaluate the proper relationship between drug exposure and the occurrence of adverse drug reaction.[32]

Fixed-dose combination therapy has been extensively used to improve compliance in multidrug regimens like anti TB. However, the guideline requires all drugs to be discontinued when major adverse reactions occur. This leaves the patient without treatment for tuberculosis.[24] There is no effective alternative first-line treatments for TB. Therefore, a slow-graded oral challenge to each of the anti-TB medications was done to identify the specific medication responsible for the adverse events. The treatment of rifampicin-induced thrombocytopenia is principally discontinuing the offending drug. After rifampicin reintroduction and its resolution after rifampicin discontinuation, recurrence of the thrombocytopenia was noted in our patient, hence, confirming our diagnosis.

CONCLUSION

Adverse drug reactions are common occurrences with anti-TB medications. However, hematologic reactions are very rare complications. Drug-induced thrombocytopenia due to rifampicin may be benign, but in a few, it can cause severe thrombocytopenia resulting in life-threatening bleeding. Early recognition is vital since most cases are simply resolved with the discontinuation of the drug.

The era of fixed drug combination therapy for TB has complicated the process of identifying the culprit medication. All medications become suspect when ADRs occur. The age-old practice of slow graded challenge can systematically identify and confirm the culprit drug in the absence of specialized laboratory workups.

TB is a major health burden in our country. The use of our first-line medications may inevitably result in some ADRs. However, there are instances when we need to look beyond hepatitis and skin manifestations as the only ADRs to our TB meds. Like in our patient who experienced life-threatening thrombocytopenia, intake of rifampicin should also be taken into consideration to give an immediate and appropriate treatment that could be life-saving.

Conflict of Interest: None

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