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Case Report

A case report of rifampicin-induced dual adverse drug reaction: pancytopenia and hyperpigmentation

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ABSTRACT

Rifampicin is a first-line anti-tuberculosis (TB) drug widely used for its potent bactericidal activity. Although generally well tolerated, it can occasionally lead to uncommon adverse drug reactions (ADRs). Among these, pancytopenia and hyperpigmentation are extremely rare and may complicate therapy or cause unnecessary medication non-compliance. We report a case of a middle-aged female receiving anti-TB therapy (ATT) for past one week. She developed pancytopenia and brown patchy hyperpigmentation following rifampicin single regimen re-administration. Rifampicin was promptly withdrawn, and supportive management was provided. Progressive improvement in both hematological parameters and cutaneous pigmentation was observed after discontinuation. Rifampicin-induced pancytopenia results primarily from idiosyncratic or immune-mediated marrow suppression, whereas hyperpigmentation is believed to occur due to increased melanin production or dermal drug deposition. The visible change in the skin caused considerable distress and fear of continuing treatment, necessitating empathy and appropriate counseling to gain the individual's trust. Health-care professionals should maintain a high index of suspicion for rare rifampicin-induced reactions presenting with simultaneous hematologic and dermatologic features. Early recognition, prompt drug withdrawal, and empathetic patient counseling are vital for favorable outcomes. Reporting even minor adverse effects contributes to pharmacovigilance and enhances awareness of such uncommon presentations.

Keywords: Rifampicin, Hyperpigmentation, Pancytopenia, Pharmacovigilance, Case report

INTRODUCTION

Tuberculosis (TB) remains a formidable threat to the human population. The world health organization (WHO) states that TB is the second leading cause of death worldwide, next to acquired immunodeficiency syndrome (AIDS). Though rifampicin, an anti-TB drug, is a mainstay treatment for ATT during both the intensive and continuation phases of the treatment, it is not devoid of ADRs.[1] Two such rare, yet clinically significant ADRs are pancytopenia and hyperpigmentation.[2,3] The challenge intensifies when this patient, on ATT, is newly diagnosed with AIDS, complicating the differential diagnosis of these cutaneous and hematological reactions. Such sudden visual and blood changes can alarm patients, causing therapy discontinuation and complicating outcomes. This case highlights the delicate balance between life-saving ATT and life-threatening adverse reactions, emphasizing real-world clinical complexities.

CASE REPORT

A 41-year-old female was admitted to the thoracic ward with chief complaints of intermittent fever, diarrhea and vomiting for three days. The patient had been diagnosed with pulmonary TB (PTB) one week prior, without

evidence of drug resistance, and was prescribed a fixed-dose combination, rifampicin 150 mg, isoniazid 75 mg, pyrazinamide 400 mg, and ethambutol 275 mg, four tablets in the morning. Patient ignored the feeling of itching that emerged after the administration of the fixed-dose combination ATT tablet.

Before initiating the treatment for current complaints, a complete blood count was tested. The patient's laboratory report showed pancytopenia on the day of admission, whereas a better hematological count was ensured before the start of ATT. Suspicion of ATT-induced pancytopenia arose. Peripheral smear test confirmed normocytic normochromic anemia with leukopenia and thrombocytopenia. A bone marrow biopsy couldn't be done due to the limited resource setting in a rural hospital. Patient's financial distress also added to the inability to test bone marrow suppression. Reticulocyte count was 1.4%. The values of liver function test and thyroid function tests were normal.

Symptomatic management for fever and gastrointestinal complaints was initiated, and tablet form of cetrizine 10 mg (Antihistamine) was prescribed for itching; however, no improvement was observed over three days.

Suspecting a potential ATT-related ADR, the treating physician split the regimen and reintroduced only Tab. Isoniazid 300 mg and Tab. Pyridoxine 50 mg for two days, which the patient tolerated well. Split regimen of tablet rifampicin 600 mg was then reintroduced, and within 24 hours, patchy, non-scaly hyperpigmentation appeared on both upper limbs, extending up to the breasts (Figure 1 and 2). The physician diagnosed rifampicin-induced hyperpigmentation, a rare but significant ADR, and discontinued the drug.

During hospitalization, the patient was also confirmed human immunodeficiency virus (HIV) positive. Anti-retroviral therapy (ART) was initially deferred as the patient was non-cooperative with additional medications, and the physician aimed to stabilize ATT first. Tab. Pyrazinamide 150 mg and Tab. Ethambutol 800 mg were sequentially reintroduced at two-day intervals, accompanied by thorough counseling. Rifampicin was excluded from the regimen, and a Bedaquiline-based regimen was initiated after psychiatric consultation.

Laboratory monitoring (Table 1) revealed gradually improving hematological parameters, supporting rifampicin-induced pancytopenia. The patient was discharged once no further progression of hyperpigmentation was observed, and she tolerated the modified ATT regimen. Plans for initiating ART were made following stabilization.

Decline in the values of all three blood components, white blood cells, red blood cells and platelets is seen after one week of the ATT therapy (on the day of hospital admission). Six days after discontinuation of rifampicin (on the day of discharge), improvement in these values is noted.

Table 1: Comparison of laboratory values.

Tests	Before starting ATT	Day of admission	Date of discharge
WBC	$4.8\times10^3/\mu l$	$1.9\times10^3/\mu l$	$3.3\times10^3/\mu l$
RBC	$3.58\times10^6/\mu l$	$3.52\times10^6/\mu l$	$3.54\times10^6/\mu l$
Hb	10.1 g/dl	7.2 g/dl	9.8 g/dl
Platelets	$124\times10^3/\mu l$	$80\times10^3/\mu l$	$100\times10^3/\mu l$

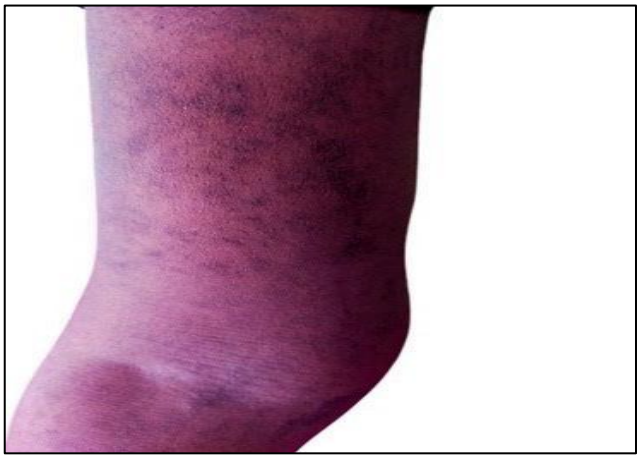

Figure 1: Hyperpigmentation on right upper limb.

Scattered patches of brown-black, non-scaly hyperpigmentation observed in the left upper limb.

Figure 2: Hyperpigmentation on left upper limb.

Scattered patches of brown-black, non-scaly hyperpigmentation observed in the right upper limb.

DISCUSSION

The burden of TB remains a major public health concern. 40% of global TB cases are reported in Africa, Asia, India and China collectively.[4] Though there are reports that have accused rifampicin of causing ADRs, either pancytopenia or hyperpigmentation, this is the first case documenting dual ADR burden (Pancytopenia and hyperpigmentation) in an individual administering rifampicin.

Rifampicin induced pancytopenia

Drug-induced hematological disorders encompass a wide spectrum, depressing the three major cell lines, RBC, WBC and platelets, either one or more.

The underlying mechanism involves various pathways like immune-mediated reactions, enzymatic pathway interference, direct inhibition of bone marrow, increased cellular lysis, malabsorption and idiosyncratic reactions.[2,4]

Reports from Japan have described leucopenia associated with rifampicin and isoniazid. Malaysian studies identified normocytic normochromic anemia as the most frequent hematological abnormality associated with ATT. Thrombocytopenia has also been observed among 24% of the Indian ATT population.[4]

A rare ADR, rifampicin-induced pancytopenia, has also been reported earlier.[2]

Rifampicin induced hyperpigmentation

Explanation on rifampicin-induced hyperpigmentation is limited due to scarce literature availability. Among the very few previous reports, one described generalized hyperpigmentation in a 74-year-old man receiving ATT with rifampicin and isoniazid for 4 months, and other one described hyperpigmentation on a 40-year-old female who was on leprosy treatment with rifampicin for 2 months.[3,5]

Though hyperpigmentation tends to develop gradually from 2-4 months, there are supportive studies that confirm hyperpigmentation can also develop within 1 week.[6]

The pathogenesis of drug-induced hyperpigmentation is multifactorial. It may result from melanin accumulation secondary to stimulation of epidermal melanocytes, non-specific inflammation caused by the drug or direct deposition of the drug or its metabolites within dermal macrophages and connective tissue.

Rifampicin commonly causes reddish discolouration of the skin and bodily fluids. However, the present case is an unusual demonstration of brown-black patchy hyperpigmentation.

Causality and severity assessment

Causality for both rifampicin-induced pancytopenia and hyperpigmentation was assessed using Naranjo's ADR probability scale. Pancytopenia was classified as a 'possible' ADR, whereas hyperpigmentation was considered a 'probable' ADR (Table 2).[7]

The severity of both these ADRs was classified as level 4 severity (moderate severity) using Hartwig's severity assessment scale.[8]

The core treatment for ADRs includes withdrawal of the causative drug. Likewise, improvement in pancytopenia and non-progressive hyperpigmentation was achieved after the withdrawal of rifampicin.

In this case, the sudden appearance of brown patchy hyperpigmentation caused considerable fear and anxiety in the patient, leading to apprehension about continuing therapy.

Patient counseling played a crucial role in addressing the participant's fears, reassuring her that the reaction was drug-related and reversible after withdrawal, and reinforcing the importance of adherence to modified therapy under supervision. For pancytopenia, prompt identification and discontinuation of rifampicin were essential to prevent life-threatening complications, with gradual hematological recovery following cessation.

This case also emphasizes the importance of early recognition and reporting of even seemingly minor or transient adverse effects, such as itching. Encouraging patients to promptly communicate any new symptoms and fostering a strong clinician-patient partnership are key to preventing morbidity and ensuring safer pharmacotherapy.

The lack of resource in the rural hospital to perform a bone marrow biopsy, financial restraints of the participant and lack of long-term follow-up are limitations of this study.

Table 2: Naranjo ADR probability scale.[7]

Questions	Score assessing pancytopenia	Score assessing hyperpigmentation
Prior, similar reports	+1	+1
ADR occurrence after drug administration	+2	+2
ADR improved after drug withdrawal	+1	+1
ADR reappearance when the drug was re-administered?	0	+2
Alternative causes that could have caused the reaction	-1	-1
Placebo reaction seen	0	0
Toxic concentrations of drug in body fluids?	0	0
Did severity of ADR change with dose?	0	0
Similar drug-ADR reactions in the past?	0	+1
Objective evidence availability	+1	+1
Score	4 (Possible)	7 (Probable)

The causality score of both the ADRs was calculated individually using the Naranjo ADR probability scale. Rifampicin-induced pancytopenia was classified into the 'possible' category with a score of 4. Rifampicin-induced hyperpigmentation was classified into the 'probable' category with a score of 7.

CONCLUSION

Rifampicin remains a cornerstone in TB management, yet it's potential to cause rare but serious adverse reactions such as pancytopenia and hyperpigmentation warrants clinical vigilance. The present case underscores the importance of early recognition, causality assessment, and timely management to prevent complications. Cutaneous changes often cause anxiety and risk of non-adherence, emphasizing the critical role of patient counselling and reassurance. Individualized therapy, continuous monitoring, and patient education about possible adverse effects during long-term treatment are essential to minimize harm and sustain therapeutic success. This case highlights the need for a patient-centered approach in managing life-saving yet potentially toxic therapies, particularly in those with additional vulnerabilities such as HIV co-infection.

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