WWW.IJRPR.COM

International Journal of Research Publication and Reviews

Journal homepage: www.ijrpr.com ISSN 2582-7421

Rifampicin Induced Cutaneous Adverse Drug Reaction: A Case Report

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DOI: https://doi.org/10.55248/gengpi.5.0124.0115

ABSTRACT:

The treatment of drug-sensitive tuberculosis involves a combination of four drugs, including Rifampicin, Isoniazid, Pyrazinamide, and Ethambutol. Managing adverse skin reactions to these anti-tubercular drugs poses a dilemma, balancing the risk of drug-resistant tuberculosis with the potential worsening of adverse reactions. Adverse reactions, especially skin manifestations, are more prevalent in individuals co-infected with HIV and tuberculosis. An 11-year-old HIV-positive male with Pulmonary Tuberculosis (PTB) presented with vomiting, loose stools, and a high-grade intermittent fever. Having received Anti-Tuberculosis Treatment (ATT) for a week, the patient developed an erythematous rash progressing to hyperpigmented patches, conjunctivitis, and oral lesions. Dermatology diagnosed it as an Exanthematous Drug Eruption, leading to discontinuation of ATT. Rechallenge with ATT drugs identified Rifampicin as the causative agent, resulting in whole-body pruritus. The manifestation of Rifampicin-induced Cutaneous Adverse Drug Reaction (CADR) deviating from conventional patterns highlights the need for individualized approaches. Early detection, careful observation, and judicious management are crucial in preventing adverse outcomes. The case falls under the 'certain' category on the WHO-UMC Causality Assessment scale, emphasizing the importance of vigilant monitoring and prompt intervention in such challenging scenarios.

Keywords: Tuberculosis, Cutaneous Adverse Drug Reaction (CADR), WHO-UMC, Exanthematous, Hyperpigmentation, Drug eruption, Lichenoid Drug eruption, DRESS syndrome.

1. Introduction:

According to the World Health Organization (WHO), a Drug Hypersensitivity Reaction (DHR) is classified as a significant adverse drug reaction (ADR) characterized by "objectively reproducible symptoms or signs that arise following exposure to a specific stimulus at a dose that is typically well-tolerated by individuals without hypersensitivity" [2]

Presently, a treatment regimen for drug-sensitive tuberculosis involves a combination of four drugs, including Rifampicin, Isoniazid, Pyrazinamide, and Ethambutol. Managing adverse skin reactions to these anti-tubercular drugs poses a dilemma. On one side, discontinuing the treatment increases the chances of developing widespread and drug-resistant tuberculosis. On the other side, persisting with the treatment may result in the ongoing or worsening of the adverse drug reaction. [2, 3]

Mild liver dysfunction stands out as the most frequent adverse reaction induced by first-line anti-tuberculosis drugs, with severe effects such as liver failure or mortality being exceedingly rare. Additionally, these drugs may elicit other adverse reactions, including skin rashes localized or covering the entire body, with the maculopapular type being the most prevalent. [1]

Dealing with the co-infection of HIV and tuberculosis presents numerous management challenges, particularly in handling adverse drug reactions. Both first-line and second-line drug reactions are more prevalent in individuals infected with HIV. [4, 5]

The clinical spectrum consists of Morbilliform (measles-like) Drug Eruption (MDE), commonly known as maculopapular eruption, Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN), Drug Rash with Eosinophilia and Systemic Symptoms (DRESS syndrome), Lichenoid Drug Eruption (LDE), and Fixed Drug Eruptions (FDE).[2, 3, 4]

In our case, careful observation and confirmation through the steps of stopping and restarting medication clearly point to rifampicin as the cause of the skin reactions. This differs from the usual pattern from current literature10, 2 and highlights the special nature of our case compared to what is typically seen in existing studies. Our goal is to share this unique situation, providing a simpler and clearer view of how rifampicin can affect the skin in pediatric tuberculosis co infected with IDV.

2. Case presentation:

An 11-year-old male child was admitted to the hospital with complaints of vomiting and loose stools (6 episodes/day) for the past 2 days, accompanied by a high-grade intermittent fever without chills and rigors. The patient had a history of being HIV positive and having Pulmonary Tuberculosis (PTB), diagnosed a month ago. The child had been on Anti-Tuberculosis Treatment (ATT) for a week but had not started Antiretroviral Therapy (ART). The patient's mother was also HIV positive, but her elder sister was HIV negative. There was no history of tuberculosis, asthma, or epilepsy in the family, and the child did not have any developmental delays. The child's immunizations were up-to-date according to the National Immunization Schedule (NIS).

On physical examination, the pulse rate was 162 bpm, respiratory rate 48 cpm, SpO2 97% on room air, blood pressure 100/60 mm Hg with pallor, and no signs of icterus, clubbing, cyanosis, or lymphadenopathy. Systemic examination revealed abdominal distension with a centrally located umbilicus, flanks not full, local rise of temperature, soft abdomen, and hepatomegaly (4cm RCM). Percussion indicated a tympanic note over the abdomen, bowel sounds were audible, and respiratory examination showed bilateral non-vascular breath sounds, added breath sounds, and crepitations. Cardiovascular examination revealed regular heart sounds with no murmurs, and the central nervous system examination indicated drowsiness with equal and reactive pupils, without any focal neurological deficits.

Laboratory investigations and chest radiograph revealed bilateral pneumonia. The patient developed an erythematous rash starting from the forearms, cheeks, and face, which spread slowly to the neck, lower and upper extremities, abdomen, and the entire body, turning into blackish patches - hyperpigmented rashes. The patient also had redness of the eyes, watery discharge (conjunctivitis), and erosion over the lower lip, and a strawberry-type tongue. Dermatology diagnosed it as an Exanthematous Drug Eruption and recommended discontinuing ATT. To confirm ATT-induced reaction, rechallenge with ATT drugs was suggested sequentially at one-week intervals, starting with the least to the highest risk drugs, as a single drug challenge. The dermatology department recommended Calamine lotion, Zinc oxide cream, multivitamin supplements, and sun protection.

Table 1: Laboratory parameter

Parameter	Results	Reference range
Hemoglobin	11.6	14-18 g/dl
WBC-Total Count	3410	4500-11000 cells/cumm
PCV	38	39-49%
Sodium	134	135-145 mEq/L
Potassium	3.7	3.5-5.0 mEq/L
Chloride	112	97-107 mEq/L
S.Creatinine	0.5	0.6-1.2 mg/dl
S.Urea	20	20-50 mg/dl
AST	111	0-35 U/L
ALT	124	0-35 U/L
ALP	583	30-120 U/L
Total Bilirubin	0.3	0.1-1 mg/dl
S.Folic Acid	4.83	2-520 ng/ml
Vitamin B12	751.7	211-911 pg/ml
CD45 Lymphocyte gated	475	1000-3000 /c.mm
CD 3 T-cells	344	1200-2600 cells/ L
CD 4 Helper T-cells	64	650-1500 cells/ L
CD 8 Suppressor T-cells	279	370-1100 cells/ L
CD4/CD8 ratio	0.23	=> 1.0

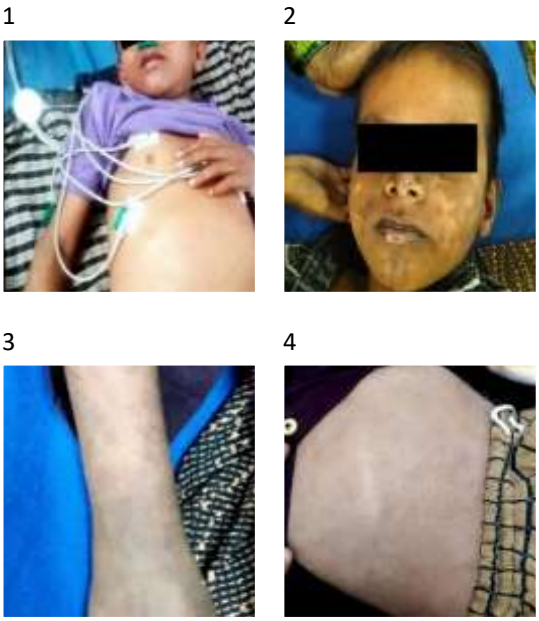

Figure 1: Skin showing generalized eruption and hyperpigmented due to Rifampicin (1, 2). Skin showing exfoliation and patches after stopping Rifampicin for (3, 4)

Toxic Shock Syndrome was ruled out as the blood pressure was not below the 5th centile for individuals under 16 years of age. The final diagnosis was a known case of HIV positivity with Pulmonary Tuberculosis, ATT-induced Gastroenteritis, and Drug-Induced Eruption.

Symptomatic treatment was initiated with medications, including IV fluids, Inj. CEFTRIAXONE 600mg BD, Inj. PIPZO 1.2gm TID, Inj. VANCOMYCIN 200mg TID, Inj. PANTOPRAZOLE 20mg BD, Tab. ACETAMINOPHEN 250mg BD, Tab. PYRIDOXINE 50mg 0-0-1, Tab. Sulfamethoxazole+Trimethoprim 150mg BD, Inj. CIPROFLOXACIN 100mg BD, Tab. FLUCONAZOLE 100mg OD, Inj. ONDANSETRON 0.8cc BD, Inj. LINEZOLID 160mg TID. ATT was stopped after 2 days of admission due to a drug reaction.

From the 10th day of admission, rechallenge with Tab. ETHAMBUTOL 400mg 1-0-0 was started and continued for 12-13 days with no reaction. Subsequently, Tab. RIFAMPICIN 300mg 1-0-0 was administered on the 18th day, resulting in whole-body pruritus after one day. CHLORPHENIRAMINE was given as a stat dose, and Tab. RIFAMPICIN was stopped, confirming it as RIFAMPICIN-induced Cutaneous Adverse Drug Reaction (CADR). The patient's condition worsened, necessitating a transfer from the general ward to the PICU due to respiratory distress, ultimately resulting in the patient's demise. According to the WHO-UMC Causality Assessment scale, this case falls under the 'certain' category.

3. Discussion:

Tuberculosis is the ninth leading cause of death worldwide and affects approximately 10 million people each year. The management of HIV tuberculosis co-infection is challenging, given issues such as Adverse Drug Reactions (ADR), complex drug interactions, overlapping toxicities, and tuberculosis-associated immune reconstitution inflammatory syndrome [4]. After the introduction of fixed-dose combination (FDC) antituberculosis therapy (ATT) in India in 2016, involving a switch from intermittent therapy to a daily regimen tailored to the patient's body weight, there was a slight increase in the incidence of drug reactions. This could be attributed to factors such as an enhanced rate of tuberculosis detection, improved treatment adherence, early detection of cutaneous adverse drug reactions (CADRs), or potentially the increased dosage of drugs administered daily compared to the previous thrice-weekly regimen. [2]

The spectrum of tuberculosis-associated ADR ranges from minor to life-threatening, including delayed-type Cutaneous Adverse Drug Reactions (CADR), immediate-type hypersensitivity reactions, drug-induced liver injury, nausea and vomiting, arthralgia, peripheral neuropathy, vertigo, and psychosis [4].The severity of clinical presentations associated with Drug Hypersensitivity Reactions (DHRs) can range from mild, such as urticaria, to severe conditions like Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome or Stevens-Johnson Syndrome (SJS)/Toxic Epidermal Necrolysis (TEN) Adverse Drug Reactions (ADRs). Fixed Drug Eruption, including Drug Hypersensitivity Reactions (DHRs) to highly effective first-line anti-TB drugs, carries significance due to its potential to restrict the use of these medications, leading to increased loss to follow-up, treatment failure, and relapse[2].

Earlier research has established a correlation between genetic variations of the CYP2C19 and CYP2C9 genes and the development of skin rash induced by first-line antituberculosis drugs. The reported incidence of cutaneous adverse drug reactions (CADRs) in patients undergoing antitubercular therapy is 5.7%. It ranks third among adverse effects associated with ATT after impaired liver function and gastrointestinal disorders. However, it is important to

note that all first-line drugs have the potential to cause cutaneous adverse drug reactions (CADRs), and there are no comprehensive studies available to quantify the contribution of each individual drug [2].

Various risk factors associated are genetic susceptibility, elderly age group, female gender, diabetes, organ failure, polypharmacy, infections such as HIV, EBV, autoimmune diseases (rheumatoid arthritis, Sjogren's disease, SLE), malignancy especially hematological, and fixed-dose combinations of ATT. The elderly age group is prone to adverse reactions due to polypharmacy, reduced renal excretion, variable drug absorption, and metabolism by the liver. CADRs are relatively less common in males due to the potential microsomal-inducing effects of androgens. Additionally, females, in comparison to males, typically have lower body weight, smaller organ size, higher body fat percentage, different gastric motility, and a decreased glomerular filtration rate. These physiological differences can alter the pharmacokinetics and pharmacodynamics of drugs. Smoking, on the other hand, impacts the metabolic process by functioning as a liver enzyme inducer, specifically affecting hepatic cytochrome P450 enzymes [2].

Table 2: The degree and severity of allergic skin reactions with ATT Drugs [2]

Severity	Clinical symptoms
1st degree	Moderate itching or reddish rash
2nd degree	Maculopapular rash with or without itching
3rd degree	Papular, vesicular, wet rashes, purpura, skin or mucosal ulcer
4th degree	Bullous lesions (Steven Johnson Syndrome), Febrile erythroderma, Skin necrosis (Toxic Epidermal Necrolysis)

There is limited data on the efficacy of in-vitro tests to identify offending antituberculosis drugs. They are technically demanding, require expensive equipment and sterile cultures. The role of patch, skin prick, and intradermal testing is yet to be fully determined for antituberculosis drug-associated CADR. It has recently been shown that in HIV-infected persons, patch and skin prick tests to antituberculosis drugs resulted in systemic reactions rather than localized reactions. These tests had low sensitivity. This suggests that in HIV-tuberculosis co-infection, cutaneous tests may not be beneficial in reducing the risk of rechallenge reactions [4].

Discontinuing ATT increases the risk of disseminated disease and drug-resistant tuberculosis. Therefore, re-challenge should be initiated as early as possible considering it is relatively safe. Re-challenge is defined as a controlled administration of a drug to diagnose drug hypersensitivity reactions. Tuberculosis outcomes are better if a re-challenge is undertaken, and only the offending drug is removed from the treatment regimen [2]. There are no clear guidelines regarding re-challenge and only limited studies in the literature [10].

Learning points:

- While administering fixed dose ATT, caution has to be taken to observe for hypersensitivity reactions.
- Combination therapy has to be stopped, and second-line ATT (Fluoroquinolones/Linezolid) has to be started to bridge the gap of first-line antitubercular therapy.
- The drug with the least potential to cause adverse reactions to be started at the lowest dose and gradually escalated each day till the appropriate dose, followed by the next drug with a higher potential than the former. From least to the highest, the risk for hypersensitivity is Isoniazid, Rifampicin, Pyrazinamide, and Ethambutol.
- Care has to be taken to observe for any hypersensitivity reaction, and the availability of emergency drugs to manage anaphylaxis and anaphylactic shock is to be ensured [2]
- Prompt resolution of the lesions after withdrawal of the ATT and treatment with oral antihistamines, corticosteroids, and emollients. Patients must be advised to avoid scratching, avoid precipitating factors, and must be treated for the underlying cause and complications [3]

In our case patient had K/C/O HIV positive and Pulmonary Tuberculosis since 1-month, was on ATT first-line regimen from 1-week and not on ART. Then complained of gastroenteritis symptoms, fever, erythematosus rash, itching all over the body, conjunctivitis then started symptomatic treatment such as emollient, antibiotics, IV Fluids, antipyretics & had stopped ATT drugs. Then they had decided to start rechallenge of ATT drugs, initially with ETHAMBUTOL & then RIFAMPICIN. The patient had no reaction with ETHAMBUTOL but had a reaction with RIFAMPICIN. Therefore, by this, they had confirmed it as RIFAMPICIN induced Cutaneous Adverse Drug Reaction (CADR). Based on WHO-UMC Causality Assessment scale, this case falls under the 'certain' category.

But here patient was not adhered to ART and could have provided corticosteroids & antihistamines also along with emollients for the skin reaction.

4. Conclusion

In summary, a patient diagnosed with HIV-positive and Pulmonary Tuberculosis commenced treatment with first-line Anti-Tuberculosis Drugs (ATT) for one week but did not initiate Antiretroviral Therapy (ART). The patient presented with complaints of an exanthematous rash and hyperpigmentation throughout the body. Temporary suspension of ATT and administration of symptomatic therapy were implemented. Subsequently, a rechallenge was conducted to identify the causative drug, confirming it as a RIFAMPICIN-induced Cutaneous Adverse Drug Reaction among the first-line ATT drugs.

Early detection to avoid triggers and potential complications, along with a judicious approach, may prove life-saving in patients experiencing this type of Adverse Drug Reaction (ADR). Standard treatment for any Cutaneous Adverse Drug Reactions (CADRs) involves the use of antihistamines, steroids, and topical emollients to maintain skin moisture. Exploring novel strategies such as immunomodulatory therapies is crucial, considering that CADRs are ultimately linked to a malfunctioning immune system. Regular monitoring of liver and kidney functions, especially in comorbid patients and those on polydrug therapy, is essential to prevent drug toxicity and reduce the incidence of CADRs due to impaired metabolism or drug elimination

Consent of the patient

Written informed consent was obtained from the patients for publications of this case report and accompanying images.

Author agreement statement

This is an original work done and we solemnly declare that the manuscript has not been published before in any other journals.

We also confirm that all the mentioned authors are aware of all the declarations and agree to them.

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