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Case Series

Dermatology Section

Drug Rechallenge in Adverse Cutaneous Drug Reactions to Antitubercular Therapy: A Case Series

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ABSTRACT

Adverse Cutaneous Drug Reactions (CADRs) to Anti-Tubercular Therapy (ATT) range from mild pruritus to severe reactions such as Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), often leading to treatment interruption. Rechallenge is particularly challenging as reactions commonly occur during the intensive phase involving multiple drugs. In this case series of seven patients, structured inpatient rechallenge protocols enabled the identification of culprit drugs and the successful completion of ATT in all cases. Rifampicin was tolerated in all patients, while isoniazid and pyrazinamide were most frequently implicated. All patients were followed for 6-12 months without recurrence. This series highlights that supervised rechallenge, with careful monitoring, can optimise treatment completion while ensuring patient safety.

Keywords: Adverse reactions, Hypersensitivity, Skin, Tuberculosis treatment

INTRODUCTION

Tuberculosis (TB) is a major global public health problem, particularly in developing countries such as India. Standard first-line ATT includes isoniazid (H), rifampicin (R), pyrazinamide (Z), and ethambutol (E) during the intensive phase, followed by continuation therapy with HRE. Adverse Drug Reactions (ADRs) to ATT are reported in 8-85% of patients worldwide, while Indian studies report a prevalence of 2.3-17% [1], with higher incidence during the intensive phase and daily regimens. Cutaneous ADRs (CADRs) are relatively uncommon, accounting for 2-6% [2].

Among first-line drugs, the commonest implicated drug was found to be ethambutol (E) in 18 (45%) patients followed by pyrazinamide (Z) in 8 (20%), isoniazid (H) in 7 (17.5%), rifampicin (R) in 6 (15%) patients [3]. CADRs represent a wide immunological spectrum, predominantly type IV hypersensitivity reactions, including maculopapular rash, lichenoid eruptions, erythema multiforme, DRESS, and rarely Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis (SJS/TEN) [3]. The proposed mechanisms for these reactions include the activation of drug-specific T-cells, the formation of reactive metabolites, and genetic susceptibility, which may involve specific Human Leukocyte Antigen (HLA) associations. Risk factors contributing to the likelihood of experiencing CADRs include Human Immunodeficiency Virus (HIV) infection, polypharmacy, liver dysfunction, and advanced age [2,3].

Despite the clinical relevance of ATT-induced CADRs, universally accepted rechallenge guidelines are lacking, resulting in wide variation in clinical practice. The present case study is a series of seven patients with ATT-induced CADRs who underwent supervised inpatient rechallenge and completed treatment using individualised regimens.

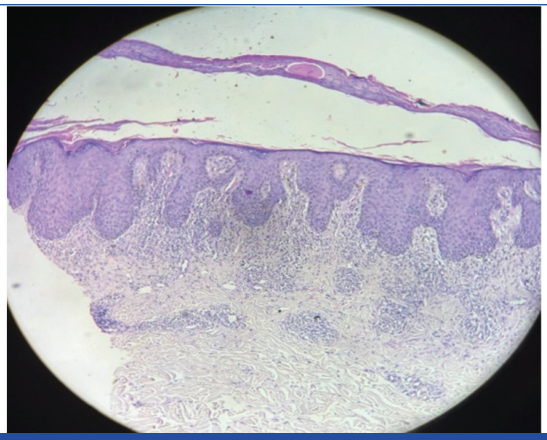
Rechallenge was performed inpatient after complete resolution of cutaneous and systemic features, with daily clinical monitoring and Complete Blood Count (CBC) (eosinophils) and Liver Function Test (LFT)/ Renal Function Test (RFT) at baseline and every 48 hours. Rechallenge was stopped on occurrence of pruritus, rash, facial oedema, mucosal involvement, eosinophilia>10%, or ≥2 fold transaminase elevation. Drugs were reintroduced sequentially at 24-hour intervals using graded dose escalation (¼, ½, full dose).

CASE SERIES

Case 1

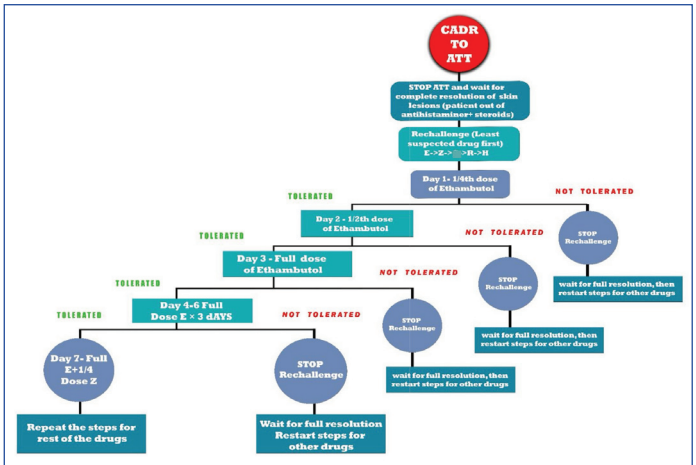
A 56-year-old male with smear-positive, drug-sensitive pulmonary TB (first episode) was started on weight-based Category I ATT (HRZE) under the National Tuberculosis Elimination Programme. He had no co-morbidities, and HIV and viral hepatitis serology were negative. After six weeks, he developed generalized hyperpigmented exfoliating plaques [Table/Fig-1] with eosinophilia (18%) and transaminitis {Aspartate Aminotransferase (AST) 132 IU/L, Alanine Aminotransferase (ALT) 148 IU/L}. Skin biopsy showed lichenoid interface dermatitis with eosinophils [Table/Fig-2]. Based on above findings, ATT-induced DRESS was diagnosed. The ATT therapy was stopped, and oral prednisolone at a dose of 1 mg/kg/day was initiated, leading to complete clinical and laboratory resolution within three weeks.

[Table/Fig-1]: Case 1: a) Exfoliative hyperpigmented plaques over back at presentation; b) Post-treatment residual hyperpigmentation.



[Table/Fig-2]: Skin biopsy showing lichenoid interface dermatitis.
Haematoxylin and Eosin (H&E),10x

Sequential inpatient rechallenge [Table/Fig-3] was undertaken. On day 2, ethambutol (600 mg) caused erythema, pruritus, eosinophilia (8%), and mild transaminitis (AST 62 IU/L, ALT 70 IU/L) and was withdrawn and treated with prednisolone 0.5 mg/kg/day, which was tapered over two weeks. Pyrazinamide re-challenge with 400 mg on day 1 led to pruritus and transaminitis, and was stopped and managed accordingly. Isoniazid (75 mg) was then introduced. Twelve hours later, he developed a severe rash worse than the index reaction with eosinophilia (15%) and marked transaminitis (AST 245 IU/L, ALT 245 IU/L). Isoniazid was stopped and prednisolone 1 mg/kg/day was tapered over four weeks. At three weeks, there was complete clinical resolution and normalisation of laboratory parameters.

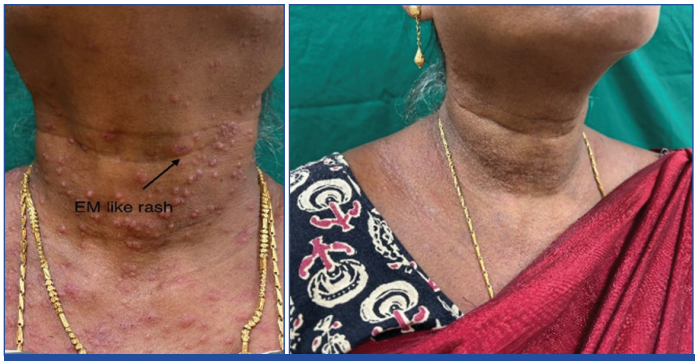


[Table/Fig-3]: ATT rechallenge schedule with dose escalation.

Rifampicin was successfully reintroduced at 150 mg and tolerated. Due to intolerance to multiple first-line drugs, he completed six months of rifampicin and ofloxacin. He remained relapse-free at 12 months follow-up with improvement [Table/Fig-1b].

Case 2

A 30-year-old female with extrapulmonary tubercular cervical lymphadenitis (first episode, drug sensitive, Tissue smear positive for Acid Fast Bacillus (AFB) developed multiple erythematous annular plaques with central necrosis [Table/Fig-4], two weeks after starting Category I ATT (HRZE). She had no co-morbidities. The laboratory investigations showed mild eosinophilia (9%). A diagnosis of ATT-induced erythema multiforme-like reaction was made. Skin biopsy was not performed due to classical clinical morphology. Symptoms resolved with oral antihistamines and short-course oral prednisolone (0.5 mg/kg), tapered over two weeks [Table/Fig-5]. Inpatient rechallenge with drug and dosage schedule as per [Table/Fig-3] was undertaken. Ethambutol, pyrazinamide, and isoniazid individually caused pruritic maculopapular rash with mild eosinophilia (6%) within 24 hours of introduction and so were withheld. Rifampicin was

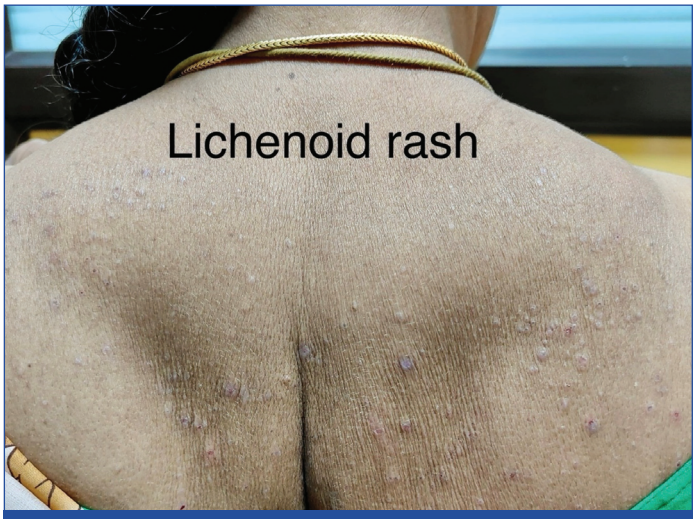


[Table/Fig-4]: Case 2: Targetoid lesions over chest and neck.
[Table/Fig-5]: Case 2: Post resolution of targetoid lesions.

tolerated, and she completed nine months of rifampicin, ofloxacin, and streptomycin without recurrence of symptoms.

Cases 3,4

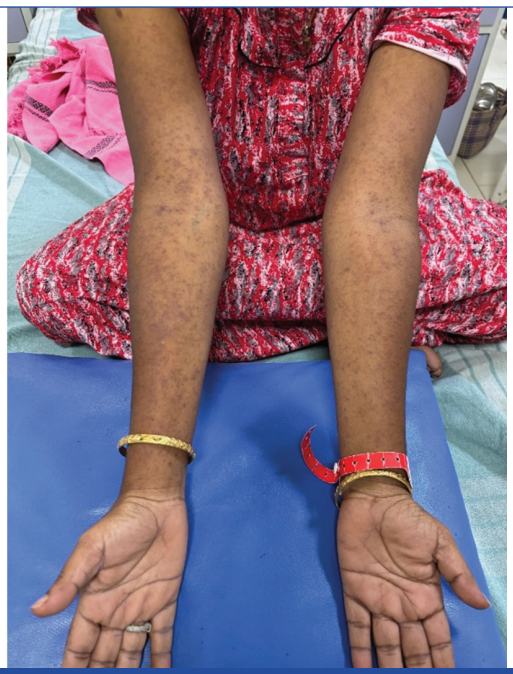
Two females, 32-year-old and 48-year-old, respectively, with extrapulmonary tubercular cervical lymphadenitis (first episode, drug sensitive, Tissue smear AFB positive) developed violaceous lichenoid papules four weeks after initiating HRZE [Table/Fig-6]. They had no co-morbidities. Investigations were normal. Lesions resolved with oral levocetirizine 10 mg OD and topical mometasone Furoate 0.1% within ten days. Rechallenge was conducted with the sequence and dose as outlined in [Table/Fig-3], which elicited a pruritic rash within 24 hours of isoniazid and pyrazinamide. These medications were subsequently withdrawn, and the rash was managed with topical mometasone furoate 0.1% for a week. The reaction being mild without systemic involvement in both cases; they had complete resolution within a week and further rechallenge was continued. Both tolerated rifampicin and ethambutol and were continued on rifampicin, ethambutol, and ofloxacin without recurrence for six months.



[Table/Fig-6]: Case 3: Violaceous lichenoid papules over upper back.

Cases 5-7

Three patients 32-year-old female, 45-year-old male and 29-year-old male with smear-positive pulmonary Tuberculosis (TB) (first episode, drug sensitive) with no co-morbidities, developed maculopapular rash [Table/Fig-7] within 7-10 days of HRZE initiation. Symptoms resolved with ATT withdrawal and managed with oral levocetirizine 10 mg OD for one week. Rechallenge was done with drug dose and duration as per [Table/Fig-3]. Within 24 hours of ethambutol introduction, they developed pruritus without rash recurrence. CBC and LFT remained normal. In view of only mild pruritis without rash recurrence and no systemic symptoms, no drug was withheld and all three patients tolerated ATT well without recurrence. At two-month follow-up, chest radiographs were normal, sputum smears were negative, and they were continued on the HRE continuation phase.



[Table/Fig-7]: Case 5 (Maculopapular rash): Erythematous papules over forearms.

DISCUSSION

The reported incidence of CADRs in patients undergoing ATT is 5.7% [4], ranking third among adverse effects after liver dysfunction and gastrointestinal disorders. Gupta G et al., recorded that all first-line ATTs can cause rashes, with incidence rates of 2.38% for pyrazinamide, 1.45% for streptomycin, 1.44% for ethambutol, 1.23% for rifampicin, and 0.98% for isoniazid [5]. Drugs like pyrazinamide can be converted by Amidase/Xanthine oxidase to reactive metabolites that act as haptens, which bind to host proteins, triggering a reaction. Genetic variations in CYP2C19 and CYP2C9, as well as ABCC2 haplotypes, increase the risk of ATT-induced skin rash. The common risk factors include old age, HIV infection, autoimmune diseases, liver or kidney dysfunction, and polypharmacy [6,7].

This series achieved a 100% ATT completion rate, comparable to the 92% reported by Modi B and Modha J [7]. Rifampicin was consistently tolerated, while isoniazid and pyrazinamide were most commonly implicated comparable to the findings of Gupta G et al., [5]. Severe reactions such as SJS/TEN remain absolute contraindications due to its high mortality rate for rechallenge and alternate regimens are mandatory; none of our patients experienced these. Rechallenge was preferred over desensitisation, as reactions were delayed-type, non IgE mediated [7], and second-line drugs were readily available. It was performed inpatient after the complete resolution of symptoms, with daily monitoring. The rechallenge was stopped if pruritus, rash, facial oedema, mucosal involvement, eosinophilia over 10%, or a two-fold increase in transaminase levels occurred. Drugs were reintroduced sequentially at 24 hours using a graded dose escalation.

Second-line therapy for drug-resistant TB primarily uses all-oral regimens, including BPaLM (bedaquiline, pretomanid, linezolid, moxifloxacin) for six months; longer individualised regimens may include fluoroquinolones, linezolid, clofazimine, cycloserine, ethionamide, and injectables [8]. Most patients had CADRs to multiple first-line drugs except rifampicin, so a rifampicin-based alternate regimen with ofloxacin [9] was chosen based on availability. Rechallenge protocol and monitoring corresponded to Sharma RK et al., highlighting its safety in ATT-related CADRs [3].

Further research is needed to develop a fail-safe rechallenge schedule. Future studies should focus on developing standardised, evidence-based rechallenge protocols with defined sequencing and monitoring parameters. This case series did not include any genetic analysis.

CONCLUSION(S)

Supervised inpatient rechallenges with structured dose escalation and close monitoring allows safe identification of culprit drugs and successful ATT completion in most CADRs, excluding life-threatening reactions. Standardised protocols are urgently needed to address this issue.

REFERENCES

[1] Spalgais S, Ahmed M, Mrigpuri P, Kumar R. Exfoliated dermatitis and hepatitis to first-line ATT with treatment of drug-sensitive TB with second-line ATT: A roller coaster ride. Chest Dis Rep. 2024;12:e12626. Doi: 10.4081/cdr.12.12626.

[2] Lehloenya RJ, Dheda K. Cutaneous adverse drug reactions to anti-tuberculosis drugs: State of the art and into the future. Expert Rev Anti Infect Ther. 2012;10(4):475-86. Doi: 10.1586/eri.12.13.

[3] Sharma RK, Verma GK, Tegta GR, Sood S, Rattan R, Gupta M. Spectrum of cutaneous adverse drug reactions to antitubercular drugs and safe therapy after rechallenge: A retrospective study. Indian Dermatol Online J. 2020;11(2):177-81.

[4] Tan WC, Ong CK, Kang SC, Razak MA. Two years review of cutaneous adverse drug reaction from first line anti-tuberculous drugs. Med J Malaysia. 2007;62(2):143-46. PMID: 18705448.

[5] Gupta G, Das AK, Kirtana J, Baitha U, Sinha S. Drug-induced hypersensitivity reaction and re-introduction of anti-tubercular drugs (ATT): A case report and review of literature. J Drug Deliv Ther. 2023;13(6):01-05.

[6] Kim SH, Jee YK, Lee JH, Lee BH, Kim YS, Park JS, et al. ABCC2 haplotype is associated with antituberculosis drug-induced maculopapular eruption. Allergy Asthma Immunol Res. 2011;4(6):362-66. Doi: 10.4168/aair.2012.4.6.362.

[7] Modi B, Modha J. Spectrum of anti-tubercular therapy-induced cutaneous adverse drug reactions and its management through rechallenge: A prospective study at a tertiary care centre. Indian J Tuberc. 2022;69(4):470-75.

[8] Rikhotso MC, Ledwaba SE, Ngandu JP, Mavumengwana V, Kinnear CJ, Warren R, et al. Favourable outcomes in RR-TB patients using BPaL and other WHO-recommended second-line anti-TB drugs. Int J Tuberc Lung Dis. 2023;27(8):599-605. Doi: 10.5588/ijtld.22.0649.

[9] Kohno S, Koga H, Kaku M, Maesaki S, Hara K. Prospective comparative study of ofloxacin or ethambutol for the treatment of pulmonary tuberculosis. Chest. 1992;102(6):1815-18. Doi: 10.1378/chest.102.6.1815.

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